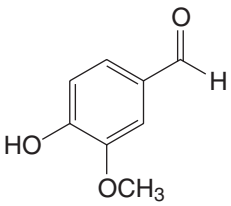
16

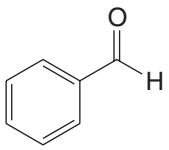
Aldehydes and Ketones

Nucleophilic Addition to the Carbonyl Group

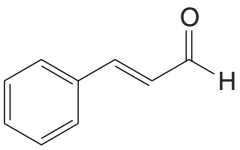
Everyone has at least some first-hand sensory knowledge of aldehydes and ketones. Some aldehydes are responsible for very pleasant tastes and odors, such as vanillin from vanilla beans, benzaldehyde from almonds, and cinnamaldehyde from cinnamon (shown above). On the other hand, acetaldehyde (ethanal) causes the unpleasant "hangover" feeling that can result from consuming alcoholic beverages, and formaldehyde (methanal) is highly toxic and has a very pungent odor, as do many other aldehydes.



Vanillin

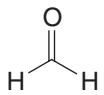


Benzaldehyde



Cinnamaldehyde

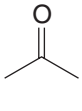
Acetaldehyde



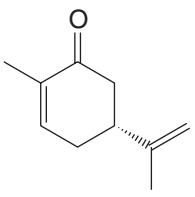
Formaldehyde

Structurally, the difference between the chemical cause of hangovers and the taste of vanilla ice cream is simply a methyl group versus a substituted phenyl group. But, what a difference this switch makes! Lovers of vanilla ice cream would not be pleased if the vanillin in their dessert were replaced by acetaldehyde!

The family of ketones has similar variation in properties. Acetone, for example, is a solvent with a sharp odor, whereas (*R*)-carvone is a natural oil that has the odor of spearmint.



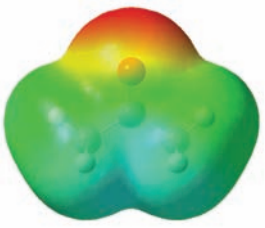
Acetone



(*R*)-Carvone

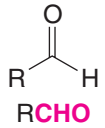
Openmirrors.com

16.1 Introduction



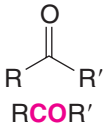
Acetone

- Aldehydes have a **carbonyl group** bonded to a carbon atom on one side and a hydrogen atom on the other side. (Formaldehyde is an exception because it has hydrogen atoms on both sides.)
- Ketones have a carbonyl group bonded to carbon atoms on both sides.



RCHO

General formulas for an aldehyde



RCOR′

General formulas for a ketone

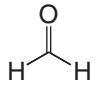
Although earlier chapters have given us some insight into the chemistry of carbonyl compounds, we shall now consider their chemistry in detail. The reason: The chemistry of the carbonyl group is central to the chemistry of most of the chapters that follow.

In this chapter we focus our attention on the preparation of aldehydes and ketones, their physical properties, and especially *nucleophilic addition reactions at their carbonyl groups*.

16.2 Nomenclature of Aldehydes and Ketones

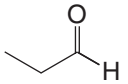
- Aliphatic aldehydes are named substitutively in the IUPAC system by replacing the final **-e** of the name of the corresponding alkane with **-al.**

Since the aldehyde group must be at an end of the carbon chain, there is no need to indicate its position. When other substituents are present the carbonyl group carbon is assigned position 1. Many aldehydes also have common names; these are given below in parentheses. These common names are derived from the common names for the corresponding carboxylic acids (Section 17.2A), and some of them are retained by the IUPAC as acceptable names.

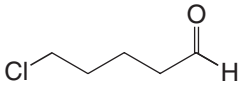


Methanal (formaldehyde)

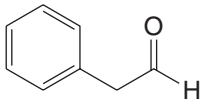
Ethanal (acetaldehyde)



Propanal (propionaldehyde)

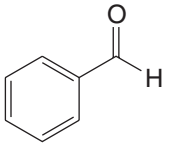


5-Chloropentanal

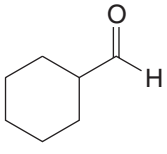


Phenylethanal (phenylacetaldehyde)

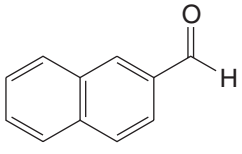
- Aldehydes in which the —CHO group is attached to a ring system are named substitutively by adding the suffix **carbaldehyde**. Several examples follow:



Benzenecarbaldehyde (benzaldehyde)



Cyclohexanecarbaldehyde

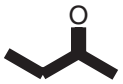


2-Naphthalenecarbaldehyde

The common name *benzaldehyde* is far more frequently used than benzenecarbaldehyde for C_6H_5CHO, and it is the name we shall use in this text.

- Aliphatic ketones are named substitutively by replacing the final **-e** of the name of the corresponding alkane with **-one.**

The chain is then numbered in the way that gives the carbonyl carbon atom the lower possible number, and this number is used to designate its position.



Butanone
(ethyl methyl ketone)

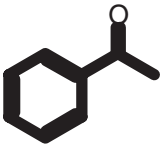
2-Pentanone
(methyl propyl ketone)

Pent-4-en-2-one
(not 1-penten-4-one)
(allyl methyl ketone)

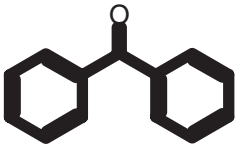
Common functional group names for ketones (in parentheses above) are obtained simply by separately naming the two groups attached to the carbonyl group and adding the word **ketone** as a separate word.

Some ketones have common names that are retained in the IUPAC system:

Acetone
(propanone)

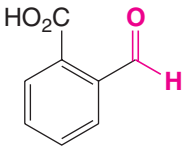


Acetophenone
(1-phenylethanone
or methyl phenyl ketone)

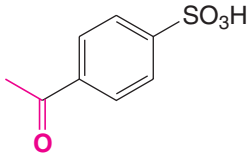


Benzophenone
(diphenylmethanone
or diphenyl ketone)

When it is necessary to name the  group as a prefix, it is the **methanoyl** or **formyl group.** The  group is called the **ethanoyl** or **acetyl group** (often abbreviated as Ac). When  groups are named as substituents, they are called **alkanoyl** or **acyl groups.**



2-Methanoylbenzoic acid
(*o*-formylbenzoic acid)

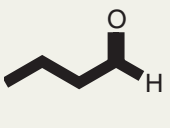


4-Ethanoylbenzenesulfonic acid
(*p*-acetylbenzenesulfonic acid)

Solved Problem 16.1

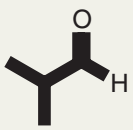
Write bond-line formulas for three isomeric compounds that contain a carbonyl group and have the molecular formula C_4H_8O. Then give their IUPAC names.

STRATEGY AND ANSWER Write the formulas and then name the compounds.



Butanal

Butanone



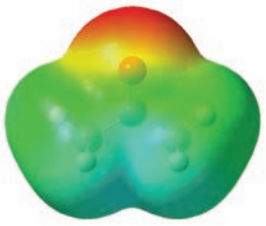
2-Methylpropanal

Openmirrors.com

Review Problem 16.1

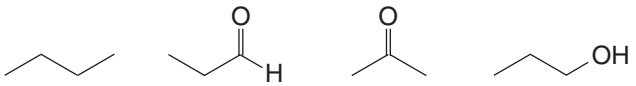
(a) Give IUPAC substitutive names for the seven isomeric aldehydes and ketones with the formula $C_5H_{10}O$. **(b)** Give structures and names (common or IUPAC substitutive names) for all the aldehydes and ketones that contain a benzene ring and have the formula C_8H_8O.

16.3 Physical Properties



A map of electrostatic potential for acetone shows the polarity of the carbonyl C═O bond.

The carbonyl group is a polar group; therefore, aldehydes and ketones have higher boiling points than hydrocarbons of the same molecular weight. However, since aldehydes and ketones cannot have strong hydrogen bonds *between their molecules*, they have lower boiling points than the corresponding alcohols. The following compounds that have similar molecular weights exemplify this trend:



Butane bp −0.5°C (MW = 58) | **Propanal** bp 49°C (MW = 58) | **Acetone** bp 56.1°C (MW = 58) | **1-Propanol** bp 97.2°C (MW = 60)

Review Problem 16.2

Which compound in each of the following pairs has the higher boiling point? (Answer this problem without consulting tables.)

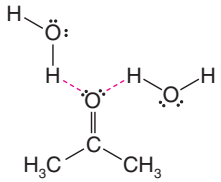
(a) Pentanal or 1-pentanol

(b) 2-Pentanone or 2-pentanol

(c) Pentane or pentanal

(d) Acetophenone or 2-phenylethanol

(e) Benzaldehyde or benzyl alcohol



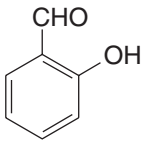
Hydrogen bonding (shown in red) between water molecules and acetone

The carbonyl oxygen atom allows molecules of aldehydes and ketones to form strong hydrogen bonds to molecules of water. As a result, low-molecular-weight aldehydes and ketones show appreciable solubilities in water. Acetone and acetaldehyde are soluble in water in all proportions.

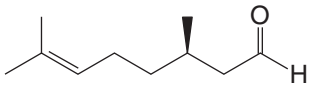
TABLE 16.1 Physical Properties of Aldehydes and Ketones

Formula	Name	mp (°C)	bp (°C)	Solubility in Water
HCHO	Formaldehyde	−92	−21	Very soluble
CH_3CHO	Acetaldehyde	−125	21	∞
CH_3CH_2CHO	Propanal	−81	49	Very soluble
$CH_3(CH_2)_2CHO$	Butanal	−99	76	Soluble
$CH_3(CH_2)_3CHO$	Pentanal	−91.5	102	Slightly soluble
$CH_3(CH_2)_4CHO$	Hexanal	−51	131	Slightly soluble
C_6H_5CHO	Benzaldehyde	−26	178	Slightly soluble
$C_6H_5CH_2CHO$	Phenylacetaldehyde	33	193	Slightly soluble
CH_3COCH_3	Acetone	−95	56.1	∞
$CH_3COCH_2CH_3$	Butanone	−86	79.6	Very soluble
$CH_3COCH_2CH_2CH_3$	2-Pentanone	−78	102	Soluble
$CH_3CH_2COCH_2CH_3$	3-Pentanone	−39	102	Soluble
$C_6H_5COCH_3$	Acetophenone	21	202	Insoluble
$C_6H_5COC_6H_5$	Benzophenone	48	306	Insoluble

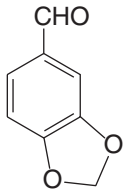
Table 16.1 lists the physical properties of a number of common aldehydes and ketones. Some aldehydes obtained from natural sources have very pleasant fragrances. The following are some in addition to those we mentioned at the beginning of this chapter.



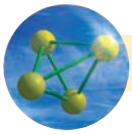
Salicylaldehyde (from meadowsweet)



Citronellal (the scent of lemon in certain plants)



Piperonal (made from safrole; odor of heliotrope)



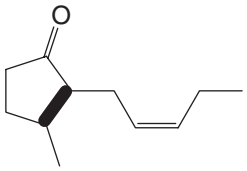
THE CHEMISTRY OF . . .

Aldehydes and Ketones in Perfumes

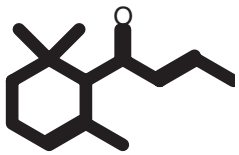
Many aldehydes and ketones have pleasant fragrances and, because of this, they have found use in perfumes. Originally, the ingredients for perfumes came from natural sources such as essential oils (Section 23.3), but with the development of synthetic organic chemistry in the nineteenth century, many ingredients now used in perfumes result from the creativity of laboratory chemists.

Practitioners of the perfumer's art, those who blend perfumes, talk of their ingredients in a language derived from music. The cabinet that holds the bottles containing the compounds that the perfumer blends is called an "organ." The ingredients themselves are described as having certain "notes." For example, highly volatile substances are said to display "head notes," those less volatile and usually associated with flowers are said to have "heart notes," and the least volatile ingredients, usually with woody, balsamic, or musklike aromas, are described as "base notes."*

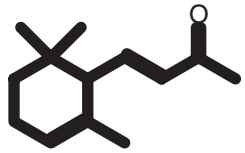
(*Z*)-Jasmone (with the odor of jasmine) and α-damascone (odor of roses) have "heart notes," as do the ionones (with the odor of violets). All of these ketones can be obtained from natural sources.



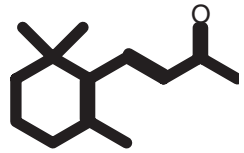
***Z*-Jasmone**



α-Damascone

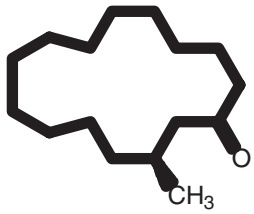


α-Ionone



β-Ionone

Two ketones from exotic natural sources are muscone (from the Himalayan musk deer) and civetone (from the African civet cat).



Muscone

Civetone

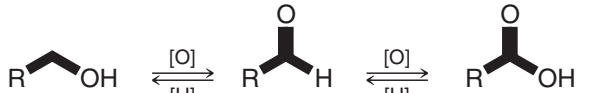
Stereochemistry has a marked influence on odors. For example, the (*R*)-enantiomer of muscone (depicted above) is described as having a "rich and powerful musk," whereas the (*S*)-enantiomer is described as being "poor and less strong." The (*R*)-enantiomer of α-damascone has a rose petal odor with more apple and fruitier notes than the (*S*)-enantiomer.

*For an in-depth discussion of the perfume industry, see Fortineau, A.-D. "Chemistry Perfumes Your Daily Life," *J. Chem. Educ.*, **2004**, *81*, 45–50.

16.4 Synthesis of Aldehydes

16.4A Aldehydes by Oxidation of 1° Alcohols

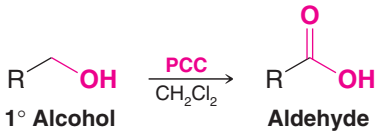
- The oxidation state of an aldehyde lies between that of a 1° alcohol and a carboxylic acid (Section 12.4A).



1° Alcohol **Aldehyde** **Carboxylic acid**

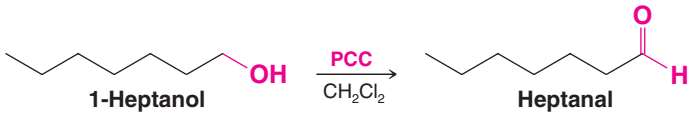
Openmirrors.com

Aldehydes can be prepared from 1° alcohols by oxidation with pyridinium chlorochromate ($C_5H_5NH^+CrO_3Cl^-$, or PCC):



1° Alcohol **Aldehyde**

An example of the use of PCC in the synthesis of an aldehyde is the oxidation of 1-heptanol to heptanal:

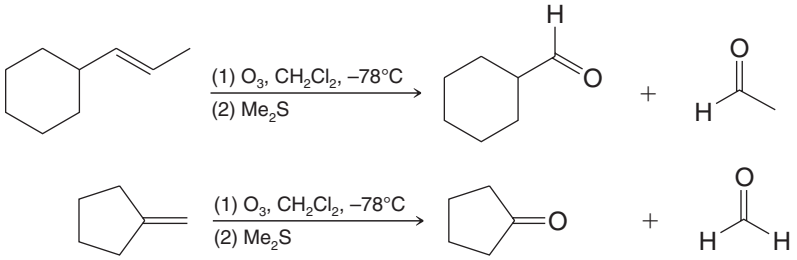


1-Heptanol **Heptanal (93%)**

16.4B Aldehydes by Ozonolysis of Alkenes

- Alkenes can be cleaved by ozonolysis of their double bond (Section 8.17B). The products are aldehydes and ketones.

In Chapter 8 we also saw how this procedure has utility in structure determination. The following examples illustrate the synthesis of aldehydes by ozonolysis of alkenes.

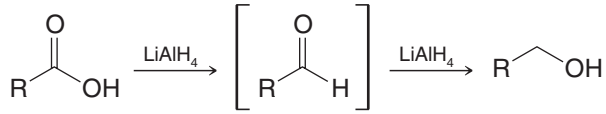


16.4C Aldehydes by Reduction of Acyl Chlorides, Esters, and Nitriles

Theoretically, it ought to be possible to prepare aldehydes by reduction of carboxylic acids. In practice, this is not possible with the reagent normally used to reduce a carboxylic acid, lithium aluminum hydride ($LiAlH_4$ or LAH).

- When any carboxylic acid is treated with LAH, it is reduced all the way to the 1° alcohol.
- This happens because LAH is a very powerful reducing agent and aldehydes are very easily reduced.

Any aldehyde that might be formed in the reaction mixture is immediately reduced by LAH to the 1° alcohol. (It does not help to use a stoichiometric amount of LAH, because as soon as the first few molecules of aldehyde are formed in the mixture, there will still be much unreacted LAH present and it will reduce the aldehyde.)



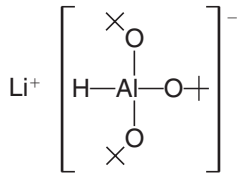
Carboxylic acid **Aldehyde** **1° Alcohol**

The secret to success here is not to use a carboxylic acid itself, but to use a derivative of a carboxylic acid that is more easily reduced, and an aluminum hydride derivative that is less reactive than LAH.

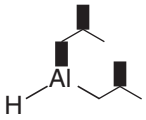
- Acyl chlorides ($RCOCl$), esters (RCO_2R'), and nitriles (RCN) are all easily prepared from carboxylic acids (Chapter 17), and they all are more easily reduced.

(Acyl chlorides, esters, and nitriles all also have the same oxidation state as carboxylic acids. Convince yourself of this by applying the principles that you learned in Section 12.2A).

- Two derivatives of aluminum hydride that are less reactive than LAH, in part because they are much more sterically hindered, are **lithium tri-*tert*-butoxyaluminum hydride** and **diisobutylaluminum hydride (DIBAL-H)**:

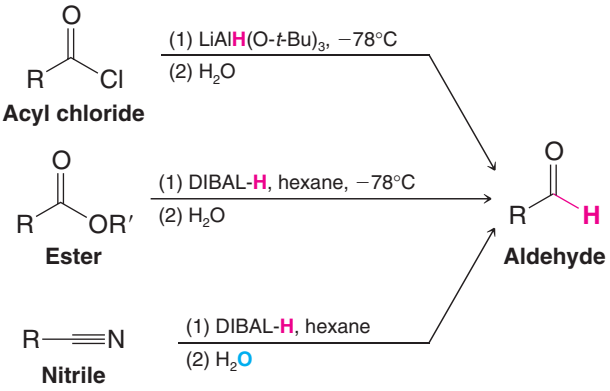


Lithium tri-*tert*-butoxyaluminum hydride



Diisobutylaluminum hydride (abbreviated *i*-Bu$_2$AlH or DIBAL-H)

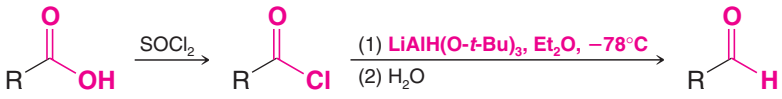
- The following scheme summarizes how lithium tri-*tert*-butoxyaluminum hydride and DIBAL-H can be used to synthesize aldehydes from acid derivatives:



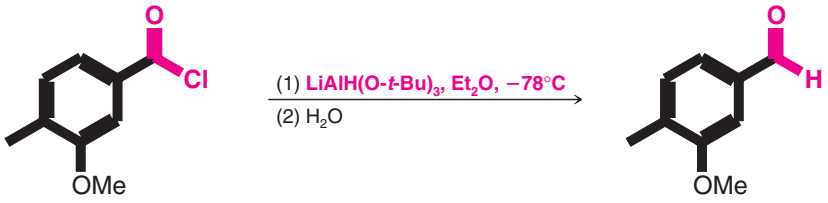
We now examine each of these aldehyde syntheses in more detail.

Aldehydes from Acyl Chlorides: RCOCl → RCHO

- Acyl chlorides can be reduced to aldehydes by treating them with LiAlH[OC(CH$_3$)$_3$]$_3$, lithium tri-*tert*-butoxyaluminum hydride, at −78°C.
- Carboxylic acids can be converted to acyl chlorides by using $SOCl_2$ (see Section 15.7).



The following is a specific example:



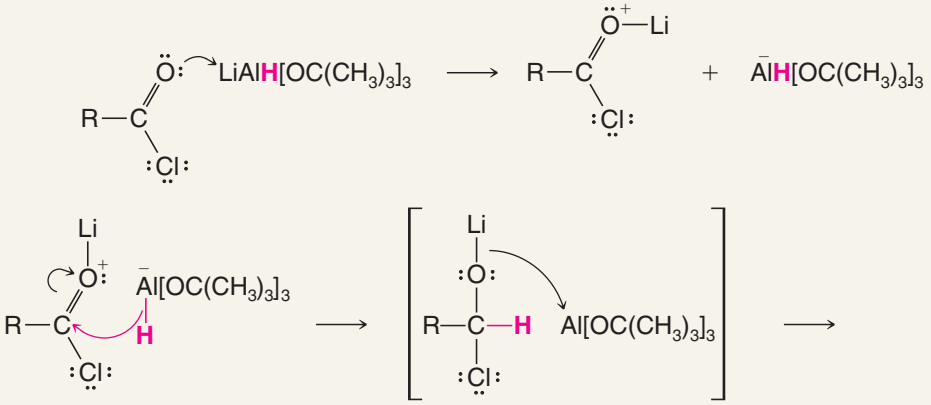
3-Methoxy-4-methylbenzoyl chloride **3-Methoxy-4-methylbenzaldehyde**

Mechanistically, the reduction is brought about by the transfer of a hydride ion from the aluminum atom to the carbonyl carbon of the acyl chloride (see Section 12.3). Subsequent hydrolysis frees the aldehyde.

Openmirrors.com

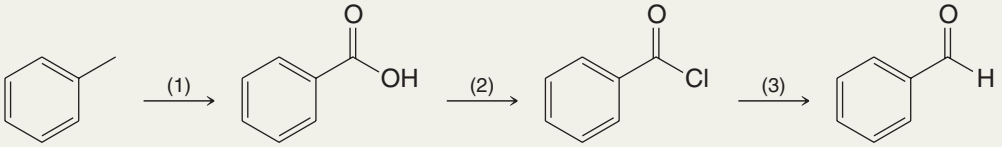
A MECHANISM FOR THE REACTION

Reduction of an Acyl Chloride to an Aldehyde



Solved Problem 16.2

Provide the reagents for transformations (1), (2), and (3).



STRATEGY AND ANSWER In (1), we must oxidize methylbenzene to benzoic acid. To do this we use hot potassium permanganate in a basic solution followed by an acidic workup (see Section 15.13C). For (2), we must convert a carboxylic acid to an acid chloride. For this transformation we use thionyl chloride or phosphorus pentachloride (see Section 15.7). For (3), we must reduce an acid chloride to an aldehyde. For this we use lithium tri-*tert*-butoxyaluminum hydride (see above).

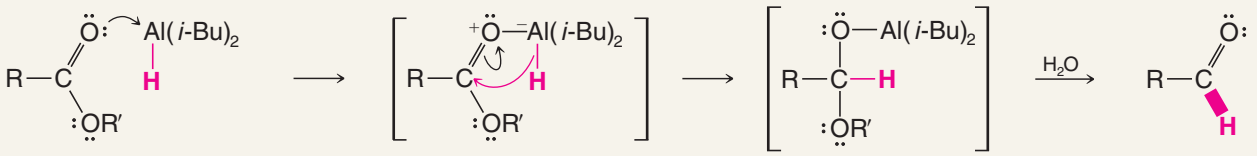
Aldehydes from Esters and Nitriles: $RCO_2R' \rightarrow RCHO$ and $RC{\equiv}N \rightarrow RCHO$

- Both esters and nitriles can be reduced to aldehydes by DIBAL-H.

Carefully controlled amounts of DIBAL-H must be used to avoid overreduction, and the ester reduction must be carried out at low temperatures. Both reductions result in the formation of a relatively stable intermediate by the addition of a hydride ion to the carbonyl carbon of the ester or to the carbon of the —C≡N group of the nitrile. Hydrolysis of the intermediate liberates the aldehyde. Schematically, the reactions can be viewed in the following way.

A MECHANISM FOR THE REACTION

Reduction of an Ester to an Aldehyde



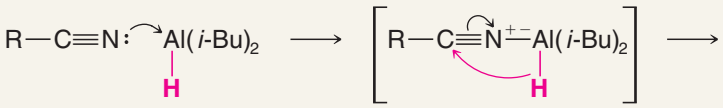
The aluminum atom accepts an electron pair from the carbonyl oxygen atom in a Lewis acid-base reaction.

Transfer of a hydride ion to the carbonyl carbon brings about its reduction.

Addition of water at the end of the reaction hydrolyzes the aluminum complex and produces the aldehyde.

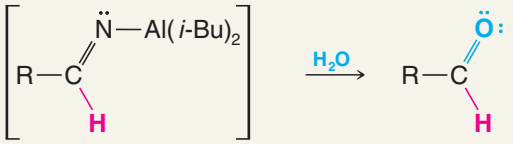
A MECHANISM FOR THE REACTION

Reduction of a Nitrile to an Aldehyde



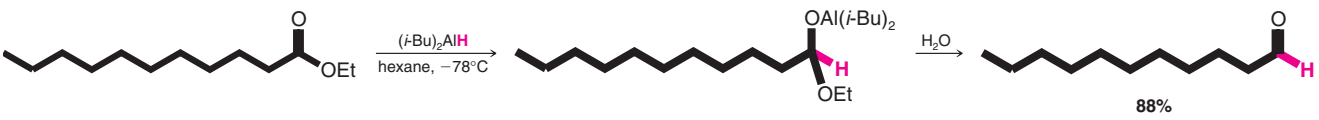
The aluminum atom accepts an electron pair from the nitrile in a Lewis acid-base reaction.

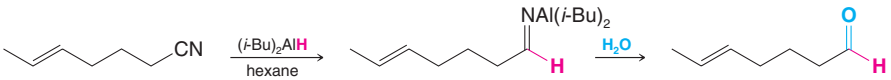
Transfer of a hydride ion to the nitrile carbon brings about its reduction.



Addition of water at the end of the reaction hydrolyzes the aluminum complex and produces the aldehyde. (Several steps are involved. See Section 16.8 relating to imines.)

The following specific examples illustrate these syntheses:

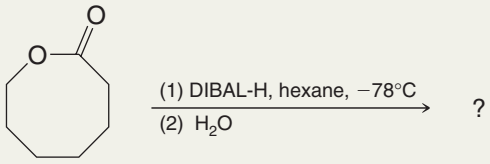




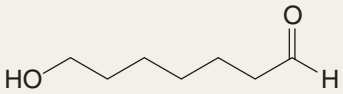
Openmirrors.com

Solved Problem 16.3

What is the product of the following reaction?

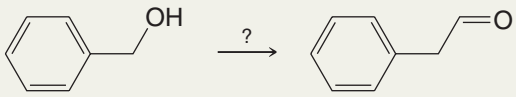


STRATEGY AND ANSWER The starting compound is a cyclic ester, so the product would be an aldehyde that also contains an alcohol hydroxyl group.

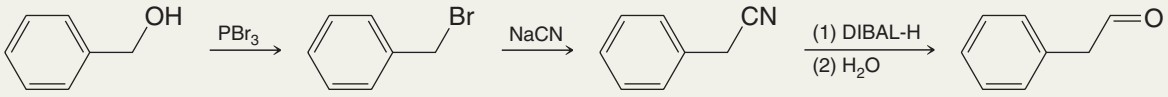


Solved Problem 16.4

Starting with benzyl alcohol, outline a synthesis of phenylethanal.



STRATEGY AND ANSWER Convert the benzyl alcohol to benzyl bromide with PBr_3, then replace the bromine by cyanide in an S_N2 reaction. Lastly, reduce the nitrile to phenylethanal.



Review Problem 16.3

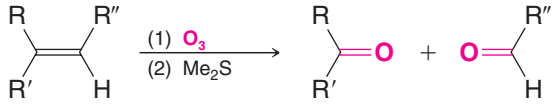
Show how you would synthesize propanal from each of the following: **(a)** 1-propanol and **(b)** propanoic acid ($CH_3CH_2CO_2H$).

16.5 Synthesis of Ketones

16.5A Ketones from Alkenes, Arenes, and 2° Alcohols

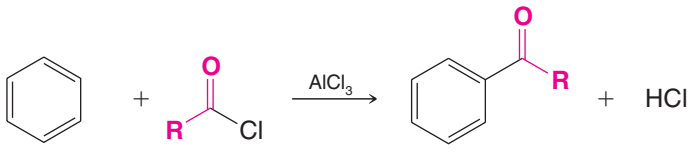
We have seen three laboratory methods for the preparation of ketones in earlier chapters:

1. Ketones (and aldehydes) by ozonolysis of alkenes (discussed in Section 8.17B).



Ketone **Aldehyde**

2. Ketones from arenes by Friedel–Crafts acylations (discussed in Section 15.7). For example:

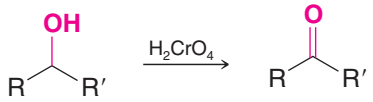


An alkyl aryl ketone

Alternatively,

A diaryl ketone

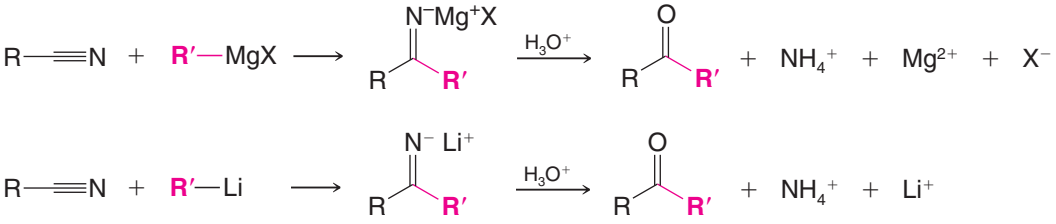
3. Ketones from secondary alcohols by oxidation (discussed in Section 12.4):



16.5B Ketones from Nitriles

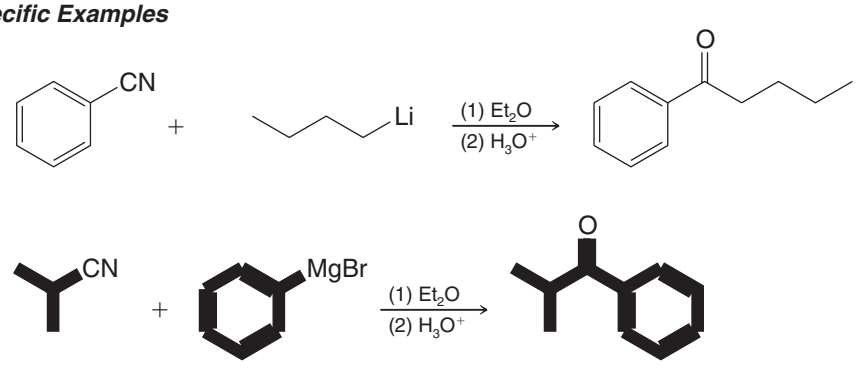
Treating a nitrile (R—C≡N) with either a Grignard reagent or an organolithium reagent followed by hydrolysis yields a ketone.

General Reactions



The mechanism for the acidic hydrolysis step is the reverse of one that we shall study for imine formation in Section 16.8A.

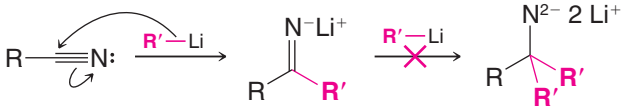
Specific Examples



2-Cyanopropane

2-Methyl-1-phenylpropanone (isopropyl phenyl ketone)

Even though a nitrile has a triple bond, addition of the Grignard or lithium reagent takes place only once. The reason: If addition took place twice, this would place a double negative charge on the nitrogen.



(The dianion does not form.)

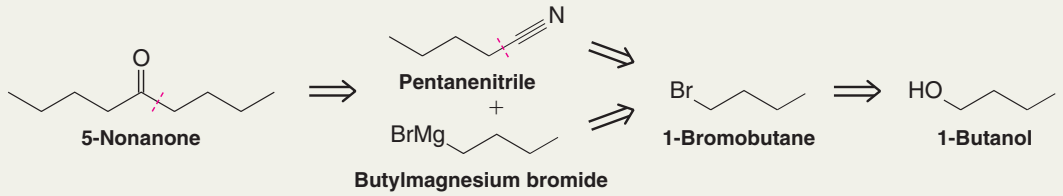
Openmirrors.com

Solved Problem 16.5

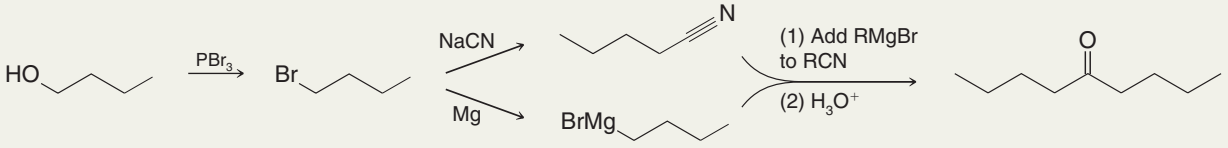
ILLUSTRATING A MULTISTEP SYNTHESIS With 1-butanol as your only organic starting compound, devise a synthesis of 5-nonanone. Begin by writing a retrosynthetic analysis.

ANSWER Retrosynthetic disconnection of 5-nonanone suggests butylmagnesium bromide and pentanenitrile as immediate precursors. Butylmagnesium bromide can, in turn, be synthesized from 1-bromobutane. Pentanenitrile can also be synthesized from 1-bromobutane, via S_N2 reaction of 1-bromobutane with cyanide. To begin the synthesis, 1-bromobutane can be prepared from 1-butanol by reaction with phosphorus tribromide.

Retrosynthetic Analysis



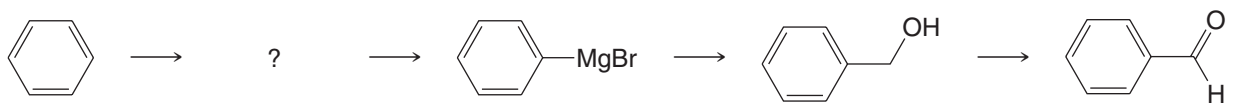
Synthesis



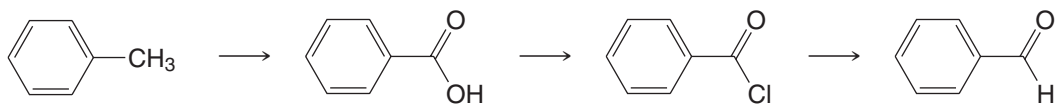
Review Problem 16.4

Provide the reagents and indicated intermediates in each of the following syntheses.

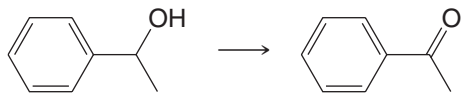
(a)



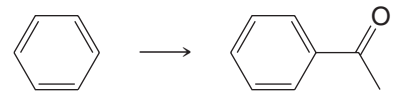
(b)



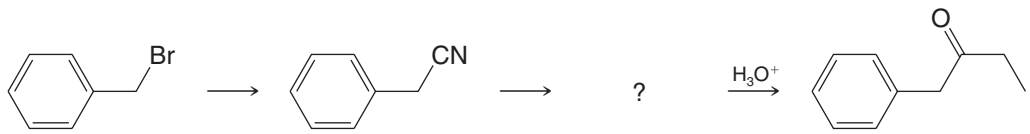
(c)



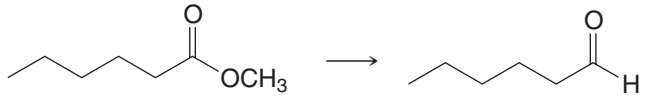
(d)



(e)



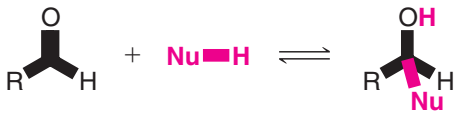
(f)



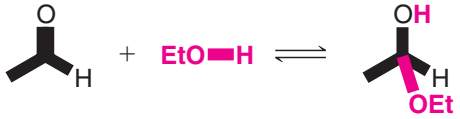
16.6 Nucleophilic Addition to the Carbon–Oxygen Double Bond

- The most characteristic reaction of aldehydes and ketones is *nucleophilic addition* to the carbon–oxygen double bond.

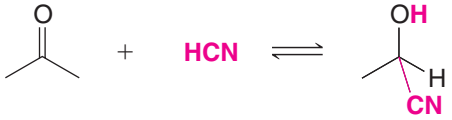
General Reaction



Specific Examples

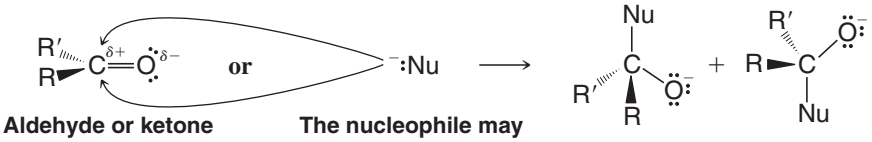


A hemiacetal (see Section 16.7)



A cyanohydrin (see Section 16.9)

Aldehydes and ketones are especially susceptible to nucleophilic addition because of the structural features that we discussed in Section 12.1 and which are shown below.



Aldehyde or ketone (R or R′ may be H) **The nucleophile may attack from above or below.**

- The trigonal planar arrangement of groups around the carbonyl carbon atom means that the carbonyl carbon atom is relatively open to attack from above or below the plane of the carbonyl group (see above).
- The positive charge on the carbonyl carbon atom means that it is especially susceptible to attack by a nucleophile.
- The negative charge on the carbonyl oxygen atom means that nucleophilic addition is susceptible to acid catalysis.

Nucleophilic addition to the carbon–oxygen double bond occurs, therefore, in either of two general ways.

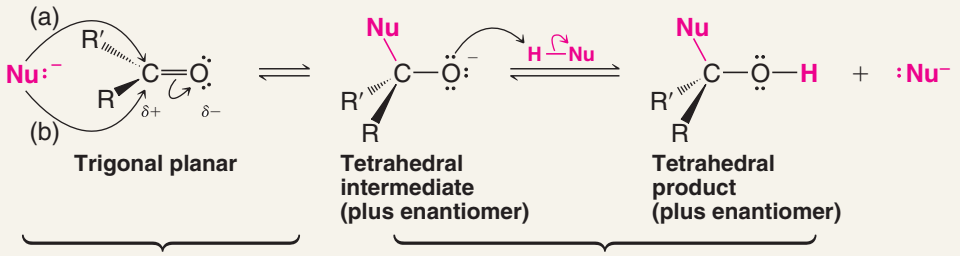
1. **When the reagent is a strong nucleophile (Nu:$^-$),** addition usually takes place in the following way (see the mechanism box on the following page), converting the trigonal planar aldehyde or ketone into a tetrahedral product.

   In this type of addition the nucleophile uses its electron pair to form a bond to the carbonyl carbon atom. As this happens the electron pair of the carbon–oxygen π bond shifts out to the electronegative carbonyl oxygen atom and the hybridization state of both the carbon and the oxygen changes from sp^2 to sp^3. ***The important aspect of this step is the ability of the carbonyl oxygen atom to accommodate the electron pair of the carbon–oxygen double bond.***

Openmirrors.com

A MECHANISM FOR THE REACTION

Addition of a Strong Nucleophile to an Aldehyde or Ketone



In this step the nucleophile forms a bond to the carbon by donating an electron pair to the top or bottom face of the carbonyl group [path (a) or (b)]. An electron pair shifts out to the oxygen.

In the second step the alkoxide oxygen, because it is strongly basic, removes a proton from H—Nu or some other acid.

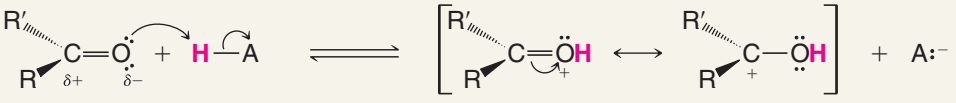
In the second step the oxygen atom accepts a proton. This happens because the oxygen atom is now much more basic; it carries a full negative charge as an alkoxide anion.

2. **When an acid catalyst is present and the nucleophile is weak**, reaction of the carbonyl oxygen with the acid enhances electrophilicity of the carbonyl group.

A MECHANISM FOR THE REACTION

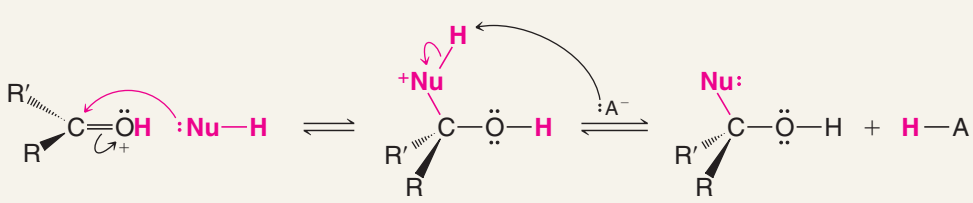
Acid-Catalyzed Nucleophilic Addition to an Aldehyde or Ketone

Step 1

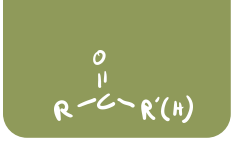


In this step an electron pair of the carbonyl oxygen accepts a proton from the acid (or associates with a Lewis acid), producing an oxonium cation. The carbon of the oxonium cation is more susceptible to nucleophilic attack than the carbonyl of the starting ketone.

Step 2



In the first of these two steps, the oxonium cation accepts the electron pair of the nucleophile. In the second step, a base removes a proton from the positively charged atom, regenerating the acid.



This mechanism operates when carbonyl compounds are treated with *strong acids* in the presence of *weak nucleophiles*. In the first step the acid donates a proton to an electron pair of the carbonyl oxygen atom. The resulting protonated carbonyl compound, an **oxonium cation**, is highly reactive toward nucleophilic attack at the carbonyl carbon atom because the carbonyl carbon atom carries more positive charge than it does in the unprotonated compound.

Helpful Hint

Any compound containing a positively charged oxygen atom that forms three covalent bonds is an *oxonium cation.*

16.6A Reversibility of Nucleophilic Additions to the Carbon–Oxygen Double Bond

- Many nucleophilic additions to carbon–oxygen double bonds are reversible; the overall results of these reactions depend, therefore, on the position of an equilibrium.

This contrasts markedly with most electrophilic additions to carbon–carbon double bonds and with nucleophilic substitutions at saturated carbon atoms. The latter reactions are essentially irreversible, and overall results are a function of relative reaction rates.

16.6B Relative Reactivity: Aldehydes versus Ketones

- In general, aldehydes are more reactive in nucleophilic additions than are ketones. Both steric and electronic factors favor aldehydes.

Steric Factors In aldehydes, where one group is a hydrogen atom, the central carbon of the tetrahedral product formed from the aldehyde is less crowded and the product is more stable. Formation of the product, therefore, is favored at equilibrium. With ketones, the two alkyl substituents at the carbonyl carbon cause greater steric crowding in the tetrahedral product and make it less stable. Therefore, a smaller concentration of the product is present at equilibrium.

Electronic Factors Because alkyl groups are electron releasing, aldehydes are more reactive on electronic grounds as well. Aldehydes have only one electron-releasing group to partially neutralize, and thereby stabilize, the positive charge at their carbonyl carbon atom. Ketones have two electron-releasing groups and are stabilized more. Greater stabilization of the ketone (the reactant) relative to its product means that the equilibrium constant for the formation of the tetrahedral product from a ketone is smaller and the reaction is less favorable:

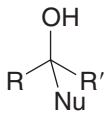
Aldehyde **Ketone**

The Ketone carbonyl carbon is less positive because it has two electron-releasing alkyl groups.

On the other hand, electron-withdrawing substituents (e.g., $—CF_3$ or $—CCl_3$ groups) cause the carbonyl carbon to be more positive (and the starting compound to become less stable), causing the addition reaction to be more favorable.

16.6C Addition Products Can Undergo Further Reactions

Nucleophilic addition to a carbonyl group may lead to a product that is stable under the reaction conditions that we employ. If this is the case we are then able to isolate products with the following general structure:



Openmirrors.com

In other reactions the product formed initially may be unstable and may spontaneously undergo subsequent reactions. One common subsequent reaction is an *elimination reaction*, especially *dehydration*. Even if the initial addition product is stable, we may deliberately bring about a subsequent reaction by our choice of reaction conditions.

Review Problem 16.5 The reaction of an aldehyde or ketone with a Grignard reagent (Section 12.8) is a nucleophilic addition to the carbon–oxygen double bond. **(a)** What is the nucleophile? **(b)** The magnesium portion of the Grignard reagent plays an important part in this reaction. What is its function? **(c)** What product is formed initially? **(d)** What product forms when water is added?

Review Problem 16.6 The reactions of aldehydes and ketones with $LiAlH_4$ and $NaBH_4$ (Section 12.3) are nucleophilic additions to the carbonyl group. What is the nucleophile in these reactions?

16.7 The Addition of Alcohols: Hemiacetals and Acetals

- Aldehydes and ketones react with alcohols to form **hemiacetals** and **acetals** by an equilibrium reaction.

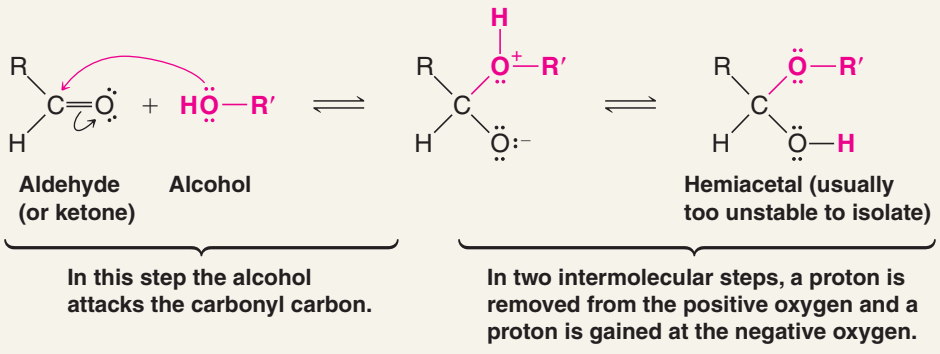
16.7A Hemiacetals

- The essential structural features of a **hemiacetal** are an —OH and an —OR group attached to the same carbon atom.

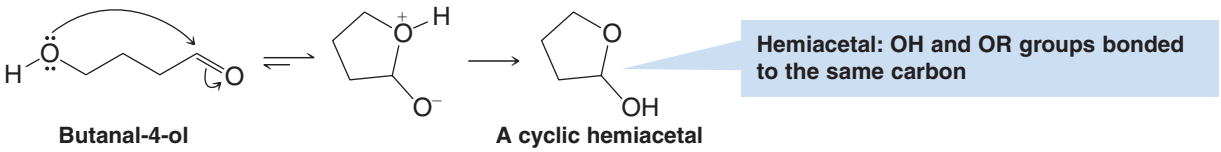
The hemiacetal results by nucleophilic addition of an alcohol oxygen to the carbonyl carbon of an aldehyde or ketone.

A MECHANISM FOR THE REACTION

Hemiacetal Formation

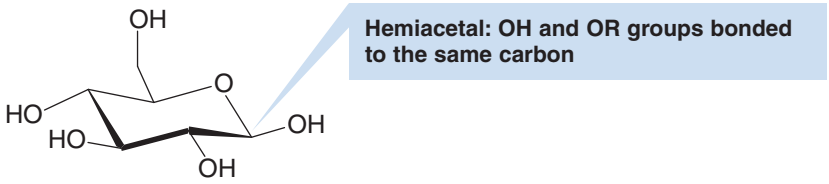


- Most open-chain hemiacetals are not sufficiently stable to allow their isolation. Cyclic hemiacetals with five- or six-membered rings, however, are usually much more stable.



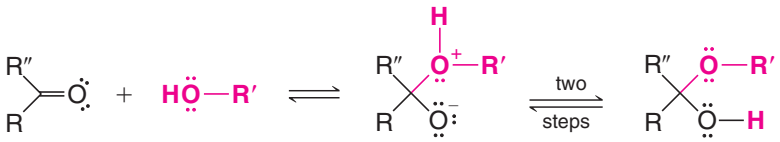
Butanal-4-ol **A cyclic hemiacetal**

Most simple sugars (Chapter 22) exist primarily in a cyclic hemiacetal form. Glucose is an example:



(+)-Glucose
(a cyclic hemiacetal)

Whether the carbonyl reactant is an aldehyde or a ketone, the product with an —OH and an —OR group is called a **hemiacetal**.

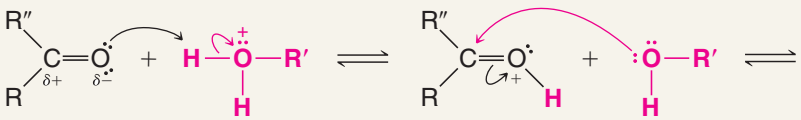


Ketone **Hemiacetal**

- The formation of hemiacetals is catalyzed by acids and bases.

A MECHANISM FOR THE REACTION

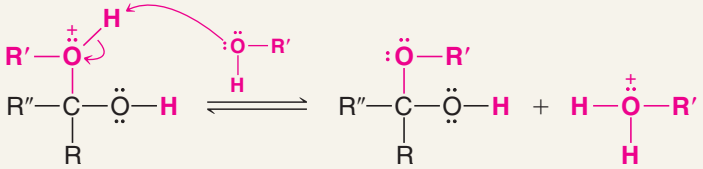
Acid-Catalyzed Hemiacetal Formation



(R″ may be H)

Protonation of the aldehyde or ketone oxygen atom makes the carbonyl carbon more susceptible to nucleophilic attack. [The protonated alcohol results from reaction of the alcohol (present in excess) with the acid catalyst, e.g., gaseous (anhydrous) HCl.]

An alcohol molecule adds to the carbon of the oxonium cation.

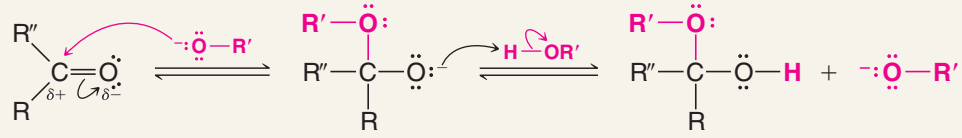


The transfer of a proton from the positive oxygen to another molecule of the alcohol leads to the hemiacetal.

Openmirrors.com

A MECHANISM FOR THE REACTION

Base-Catalyzed Hemiacetal Formation



(R″ may be H)

An alkoxide anion acting as a nucleophile attacks the carbonyl carbon atom. An electron pair shifts onto the oxygen atom, producing a new alkoxide anion.

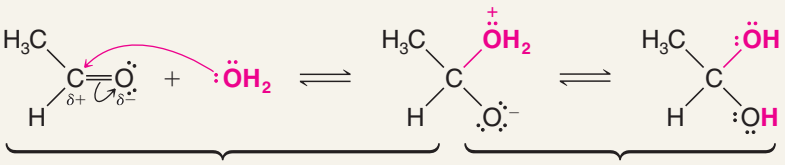
The alkoxide anion abstracts a proton from an alcohol molecule to produce the hemiacetal and regenerates an alkoxide anion.

Aldehyde Hydrates: *gem*-Diols Dissolving an aldehyde such as acetaldehyde in water causes the establishment of an equilibrium between the aldehyde and its **hydrate**. This hydrate is in actuality a 1,1-diol, called a geminal diol (or simply a *gem*-diol).

The *gem*-diol results from a nucleophilic addition of water to the carbonyl group of the aldehyde.

A MECHANISM FOR THE REACTION

Hydrate Formation

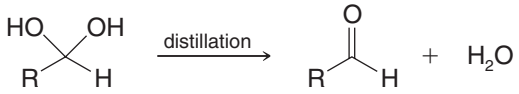


In this step water attacks the carbonyl carbon atom.

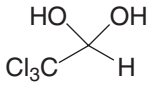
In two intermolecular steps a proton is lost from the positive oxygen atom and a proton is gained at the negative oxygen atom.

The equilibrium for the addition of water to most ketones is unfavorable, whereas some aldehydes (e.g., formaldehyde) exist primarily as the *gem*-diol in aqueous solution.

It is not possible to isolate most *gem*-diols from the aqueous solutions in which they are formed. Evaporation of the water, for example, simply displaces the overall equilibrium to the right and the *gem*-diol (or hydrate) reverts to the carbonyl compound:



Compounds with strong electron-withdrawing groups attached to the carbonyl group can form stable *gem*-diols. An example is the compound called chloral hydrate:



Chloral hydrate

Review Problem 16.7

Dissolving formaldehyde in water leads to a solution containing primarily the *gem*-diol $CH_2(OH)_2$. Show the steps in its formation from formaldehyde.

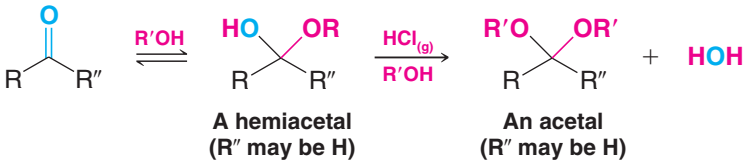
Review Problem 16.8

When acetone is dissolved in water containing ^{18}O instead of ordinary ^{16}O (i.e., $H_2{}^{18}O$ instead of $H_2{}^{16}O$), the acetone soon begins to acquire ^{18}O and becomes $CH_3C(=\,^{18}O)CH_3$. The formation of this oxygen-labeled acetone is catalyzed by traces of strong acids and by strong bases (e.g., OH^-). Show the steps that explain both the acid-catalyzed reaction and the base-catalyzed reaction.

16.7B Acetals

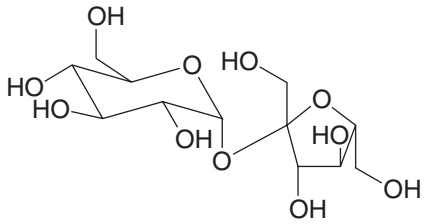
- An **acetal** has two —OR groups attached to the same carbon atom.

If we take an alcohol solution of an aldehyde (or ketone) and pass into it a small amount of gaseous HCl, a hemiacetal forms, and then the hemiacetal reacts with a second molar equivalent of the alcohol to produce an **acetal**.



Review Problem 16.9

Shown below is the structural formula for sucrose (table sugar). Sucrose has two acetal groupings. Identify these.



- The mechanism for acetal formation involves acid-catalyzed formation of the hemiacetal, then an acid-catalyzed elimination of water, followed by a second *addition* of the alcohol and loss of a proton.
- All steps in the formation of an acetal from an aldehyde are reversible.

If we dissolve an aldehyde in a large excess of an anhydrous alcohol and add a small amount of an anhydrous acid (e.g., gaseous HCl or concentrated H_2SO_4), the equilibrium will strongly favor the formation of an acetal. After the equilibrium is established, we can isolate the acetal by neutralizing the acid and evaporating the excess alcohol.

If we then place the acetal in water and add a catalytic amount of acid, all of the steps reverse. Under these conditions (an excess of water), the equilibrium favors the formation of the aldehyde. The acetal undergoes ***hydrolysis***:

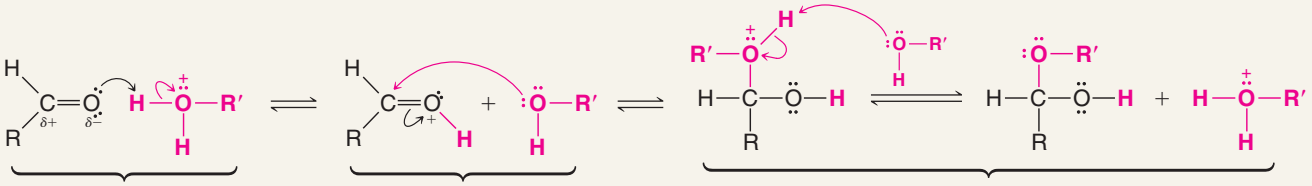
Helpful Hint

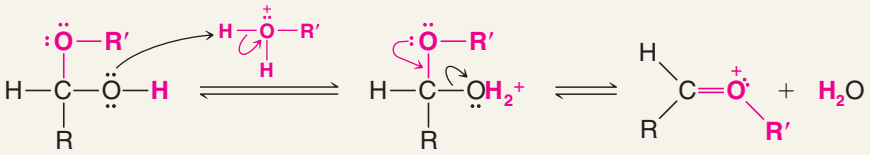
Equilibrium conditions govern the formation and hydrolysis of hemiacetals and acetals.

Openmirrors.com

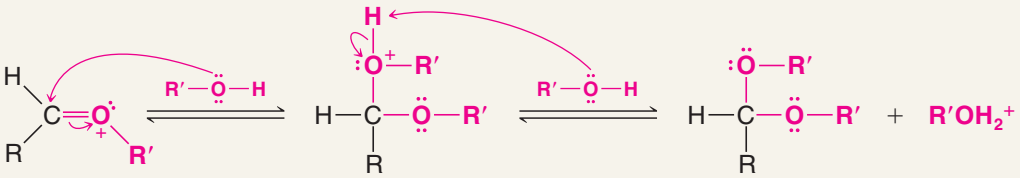
A MECHANISM FOR THE REACTION

Acid-Catalyzed Acetal Formation





Protonation of the hydroxyl group leads to elimination of water and formation of a highly reactive oxonium cation.

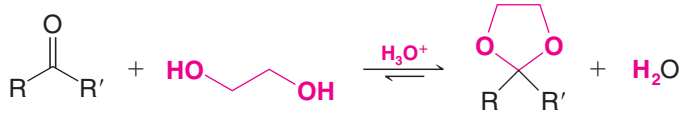


Attack on the carbon of the oxonium ion by a second molecule of the alcohol, followed by removal of a proton, leads to the acetal.

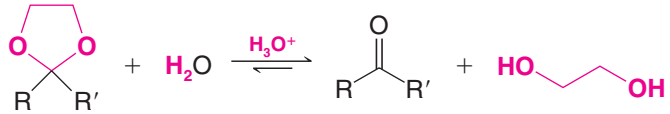
Review Problem 16.10 Write a detailed mechanism for the formation of an acetal from benzaldehyde and methanol in the presence of an acid catalyst.

Cyclic Acetals

- Cyclic acetal formation is favored when a ketone or an aldehyde is treated with an excess of a 1,2-diol and a trace of acid:



This reaction, too, can be reversed by treating the acetal with aqueous acid:



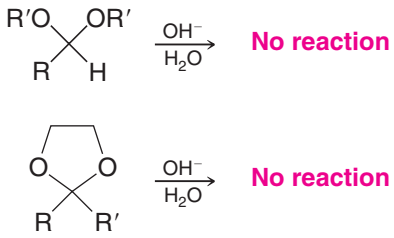
Acetal formation is not favored when ketones are treated with simple alcohols and gaseous HCl.

Outline all steps in the mechanism for the formation of a cyclic acetal from acetone and ethylene glycol (1,2-ethanediol) in the presence of gaseous HCl.

Review Problem 16.11

16.7C Acetals Are Used as Protecting Groups

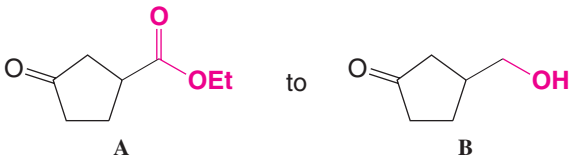
- Although acetals are hydrolyzed to aldehydes and ketones in aqueous acid, ***acetals are stable in basic solutions***:



- Acetals are used to protect aldehydes and ketones from undesired reactions in basic solutions.

We can convert an aldehyde or ketone to an acetal, carry out a reaction on some other part of the molecule, and then hydrolyze the acetal with aqueous acid.

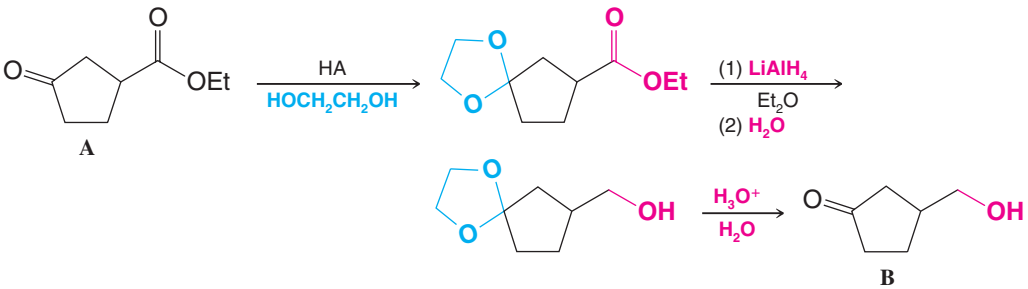
As an example, let us consider the problem of converting



Helpful Hint

Protecting groups are strategic tools for synthesis. See Sections 11.11D, 11.11E, and 12.9 also.

Keto groups are more easily reduced than ester groups. Any reducing agent (e.g., $LiAlH_4$ or H_2/Ni) that can reduce the ester group of **A** reduces the keto group as well. But if we "protect" the keto group by converting it to a cyclic acetal (the ester group does not react), we can reduce the ester group in basic solution without affecting the cyclic acetal. After we finish the ester reduction, we can hydrolyze the cyclic acetal and obtain our desired product, **B**:



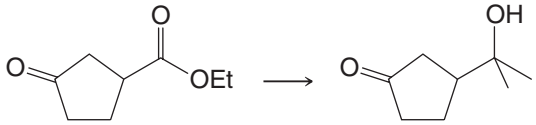
What product would be obtained if **A** were treated with lithium aluminum hydride without first converting it to a cyclic acetal?

Review Problem 16.12

Openmirrors.com

Review Problem 16.13

(a) Show how you might use a cyclic acetal in carrying out the following transformation:

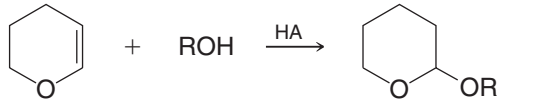


A **C**

(b) Why would a direct addition of methylmagnesium bromide to **A** fail to give **C**?

Review Problem 16.14

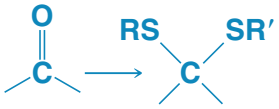
Dihydropyran reacts readily with an alcohol in the presence of a trace of anhydrous HCl or H_2SO_4 to form a tetrahydropyranyl (THP) ether:



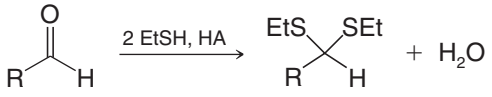
Dihydropyran **Tetrahydropyranyl ether**

(a) Write a plausible mechanism for this reaction. **(b)** Tetrahydropyranyl ethers are stable in aqueous base but hydrolyze rapidly in aqueous acid to yield the original alcohol and another compound. Explain. (What is the other compound?) **(c)** The tetrahydropyranyl group can be used as a protecting group for alcohols and phenols. Show how you might use it in a synthesis of 5-methyl-1,5-hexanediol starting with 4-chloro-1-butanol.

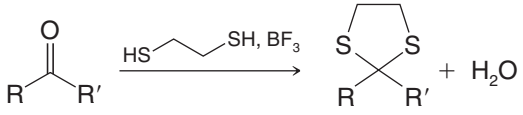
16.7D Thioacetals



- Aldehydes and ketones react with thiols to form *thioacetals*:



Thioacetal



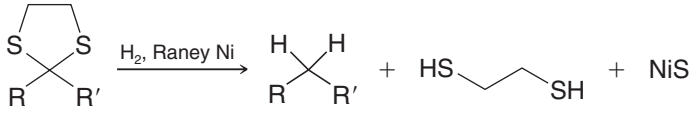
Cyclic thioacetal

Helpful Hint

A method for reducing the carbonyl group of aldehydes and ketones to —CH_2— groups.

Thioacetals are important in organic synthesis because they react with hydrogen and Raney nickel to yield hydrocarbons. Raney nickel is a special nickel catalyst that contains adsorbed hydrogen.

- Thioacetal formation with subsequent "desulfurization" with hydrogen and Raney nickel gives us an additional method for converting carbonyl groups of aldehydes and ketones to —CH_2— groups:



The other method we have studied is the **Clemmensen reduction** (Section 15.9).

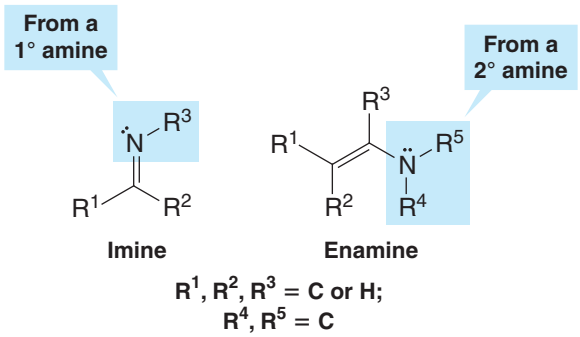
Review Problem 16.15

Show how you might use thioacetal formation and Raney nickel desulfurization to convert: **(a)** cyclohexanone to cyclohexane and **(b)** benzaldehyde to toluene.

16.8 The Addition of Primary and Secondary Amines

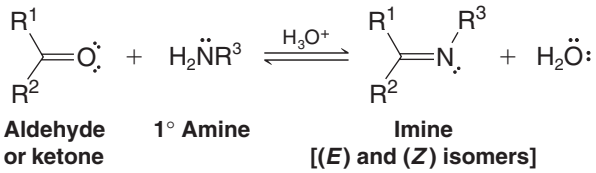
- Aldehydes and ketones react with primary amines to form **imines** and with secondary amines to form **enamines**.

Imines have a carbon–nitrogen double bond. Enamines have an amino group joined to a carbon–carbon double bond (they are alk*eneamines*).



16.8A Imines

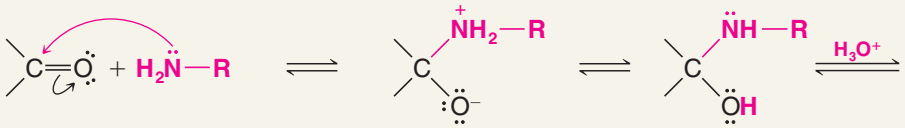
A general equation for the formation of an imine from a primary amine and an aldehyde or ketone is shown here. Imine formation is acid catalyzed, and the product can form as a mixture of (*E*) and (*Z*) isomers:



Imine formation generally takes place fastest between pH 4 and 5 and is slow at very low or very high pH. We can understand why an acid catalyst is necessary if we consider the mechanism that has been proposed for imine formation. The important step is the step in which the protonated aminoalcohol loses a molecule of water to become an iminium ion. By protonating the alcohol group, the acid converts a poor leaving group (an —OH group) into a good one (an $—OH_2^+$ group).

A MECHANISM FOR THE REACTION

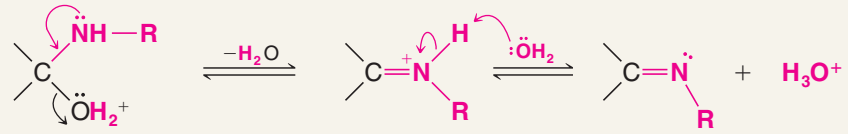
Imine Formation



The amine adds to the carbonyl group to form a dipolar tetrahedral intermediate.

Intermolecular proton transfer from nitrogen to oxygen produces an aminoalcohol.

Openmirrors.com



Protonated aminoalcohol | **Iminium ion** | **Imine [(*E*) and (*Z*) isomers]**

Protonation of the oxygen produces a good leaving group. Loss of a molecule of water yields an iminium ion.

Transfer of a proton to water produces the imine and regenerates the catalytic hydronium ion.

The reaction proceeds more slowly if the hydronium ion concentration is too high, because protonation of the amine itself takes place to a considerable extent; this has the effect of decreasing the concentration of the nucleophile needed in the first step. If the concentration of the hydronium ion is too low, the reaction becomes slower because the concentration of the protonated aminoalcohol becomes lower. A pH between pH 4 and pH 5 is an effective compromise.

Imine formation occurs in many biochemical reactions because enzymes often use an $—NH_2$ group to react with an aldehyde or ketone. An imine linkage is important in the biochemistry of pyridoxal phosphate (which is related to vitamin B_6; see "The Chemistry of . . ." box on the next page), and in one step of the reactions that take place during the visual process (see "The Photochemistry of Vision," Section 13.9).

Helpful Hint

See "The Chemistry of . . . A Very Versatile Vitamine, Pyridoxine (Vitamin B_6)" on the next page, and "The Chemistry of... Pyridoxal Phosphate" in *WileyPLUS*.

Imines are also formed as intermediates in a useful laboratory synthesis of amines that we shall study in Section 20.4.

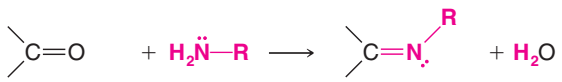
16.8B Oximes and Hydrazones

- Compounds such as hydroxylamine (NH_2OH), hydrazine (NH_2NH_2), and substituted hydrazines such as phenylhydrazine ($C_6H_5NHNH_2$) and 2,4-dinitrophenylhydrazine, form C═N derivatives of aldehydes and ketones.

These derivatives are called oximes, hydrazones, phenylhydrazones, and 2,4-dinitrophenylhydrazones, respectively. The mechanisms by which these C═N derivatives form are similar to the mechanism for imine formation from a primary amine. As with imines, the formation of (*E*) and (*Z*) isomers is possible. Table 16.2 shows general examples of these reactions.

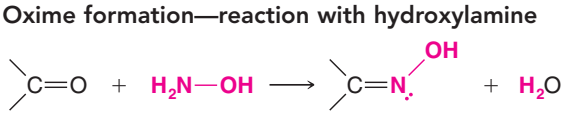
TABLE 16.2 Reactions of Aldehydes and Ketones with Derivatives of Ammonia

1. Imine formation—reaction with a primary amine



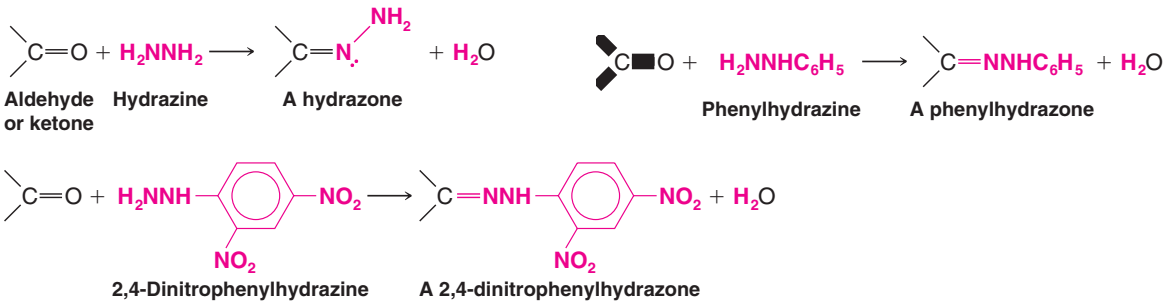
Aldehyde or ketone | **A 1° amine** | **An imine [(*E*) and (*Z*) isomers]**

2. Oxime formation—reaction with hydroxylamine

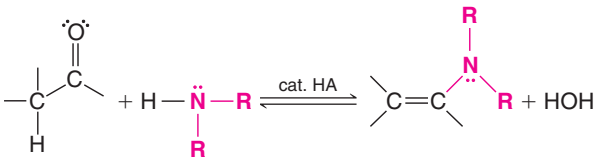


Aldehyde or ketone | **Hydroxylamine** | **An oxime [(*E*) and (*Z*) isomers]**

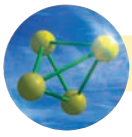
3. Hydrazone and substituted hydrazone formation—reactions with hydrazine, phenylhydrazine, and 2,4-dinitrophenylhydrazine [each derivative can form as an (*E*) or (*Z*) isomer]



4. Enamine formation—reaction with a secondary amine

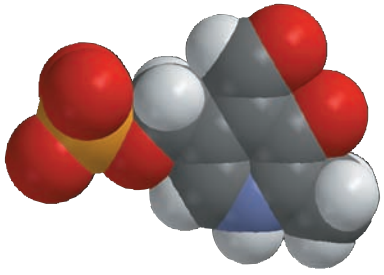


Oximes and the various **hydrazone** derivatives of aldehydes and ketones are sometimes used to identify unknown aldehydes and ketones. These derivatives are usually relatively insoluble solids that have sharp, characteristic melting points. The melting point of the derivative of an unknown compound can be compared with the melting point for the same derivative of a known compound or with data found in a reference table, and on this basis one can propose an identity for the unknown compound. Most laboratory textbooks for organic chemistry include extensive tables of derivative melting points. The method of comparing melting points is only useful, however, for compounds that have derivative melting points previously reported in the literature. Spectroscopic methods (especially IR, NMR, and mass spectrometry) are more generally applicable to identification of unknown compounds (Section 16.13).



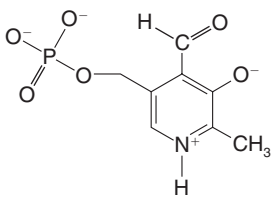
THE CHEMISTRY OF . . .

A Very Versatile Vitamin, Pyridoxine (Vitamin B_6)

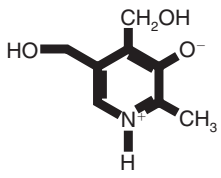


Pyridoxal phosphate (vitamin B_6).

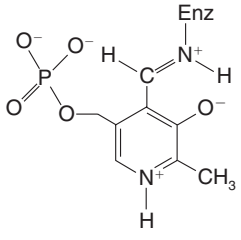
Pyridoxal phosphate (PLP) is at the heart of chemistry conducted by a number of enzymes. Many of us know the coenzyme pyridoxal phosphate by the closely related vitamin from which it is derived in our diet—pyridoxine, or vitamin B_6. Wheat is a good dietary source of vitamin B_6. Although pyridoxal phosphate (see below and the model) is a member of the aldehyde family, when it is involved in biological chemistry, it often contains the closely related functional group with a carbon–nitrogen double bond, the imine group.



Pyridoxal phosphate (PLP)



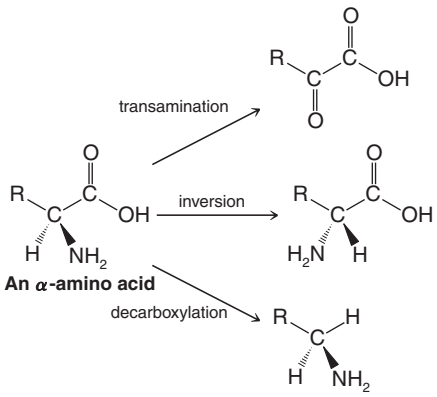
Pyridoxine



PLP with an imine group

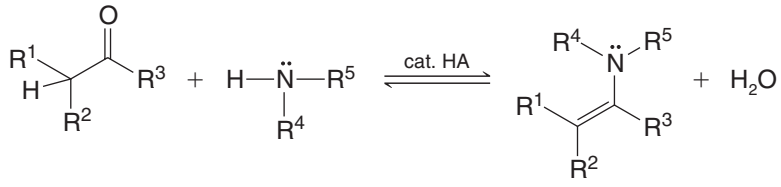
Openmirrors.com

Some enzymatic reactions that involve PLP include *transaminations*, which convert amino acids to ketones for use in the citric acid cycle and other pathways; *decarboxylation* of amino acids for biosynthesis of neurotransmitters such as histamine, dopamine, and serotonin; and *inversion* of amino acid chirality centers, such as required for the biosynthesis of cell walls in bacteria.



16.8C Enamines

Aldehydes and ketones react with secondary amines to form enamines. The following is a general equation for enamine formation:



Secondary amine **Enamine**

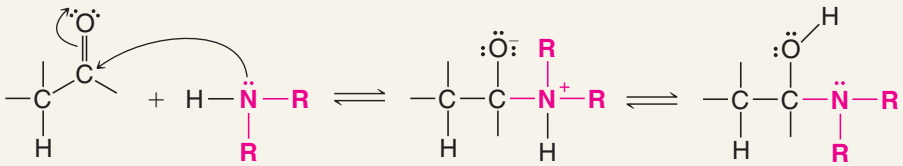
A mechanism for the reaction is given in the box below. Note the difference between the previously described mechanism for imine formation and this mechanism for enamine formation. In enamine formation, which involves a secondary amine, there is no proton for removal from the nitrogen in the iminium cation intermediate. Hence, a neutral imine cannot be formed. A proton is removed from a carbon adjacent to the former carbonyl group instead, resulting in an enamine. We shall see in Chapter 18 that enamines are very useful for carbon–carbon bond formation (Section 18.9).

Tertiary amines do not form stable addition products with aldehydes and ketones because, on forming the tetrahedral intermediate, the resulting formal positive charge cannot be neutralized by loss of a proton.

A MECHANISM FOR THE REACTION

Enamine Formation

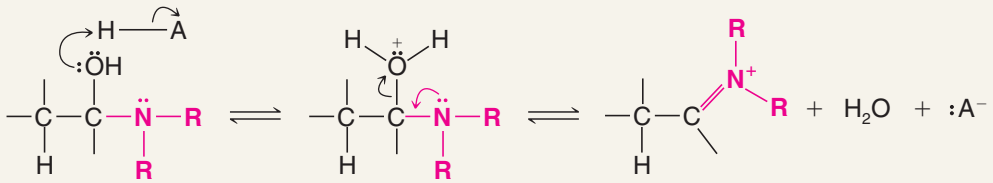
Step 1



Aldehyde or ketone **Secondary amine** **Aminoalcohol intermediate**

The amine adds to the ketone or aldehyde carbonyl to form a tetrahedral adduct. Intermolecular proton transfer leads to the aminoalcohol intermediate.

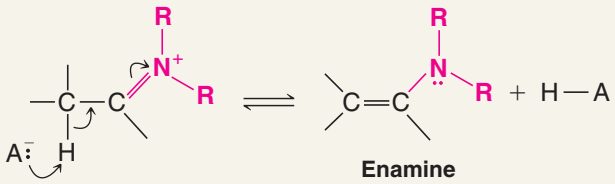
Step 2



Aminoalcohol intermediate **Iminium ion intermediate**

The aminoalcohol intermediate is protonated by the catalytic acid. Contribution of an unshared electron pair from the nitrogen atom and departure of a water molecule lead to an iminium cation intermediate.

Step 3

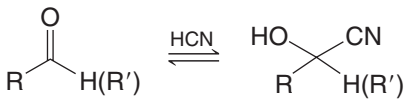


Enamine

A proton is removed from the carbon adjacent to the iminium group. Proton removal occurs from the carbon because there is no proton to remove from the nitrogen of the iminium cation (as there would have been if a primary amine had been used). This step forms the enamine, neutralizes the formal charge, and regenerates the catalytic acid. (If there had been a proton to remove from the nitrogen of the iminium cation, the final product would have been an imine.)

16.9 The Addition of Hydrogen Cyanide: Cyanohydrins

- Hydrogen cyanide adds to the carbonyl groups of aldehydes and most ketones to form compounds called **cyanohydrins**. (Ketones in which the carbonyl group is highly hindered do not undergo this reaction.)

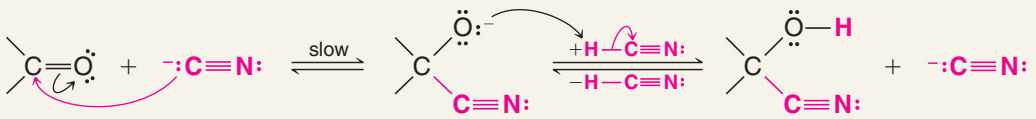


A cyanohydrin

Cyanohydrins form fastest under conditions where cyanide anions are present to act as the nucleophile. Use of potassium cyanide, or any base that can generate cyanide anions from HCN, increases the reaction rate as compared to the use of HCN alone. The addition of hydrogen cyanide itself to a carbonyl group is slow because the weak acidity of HCN ($pK_a \sim 9$) provides only a small concentration of the nucleophilic cyanide anion. The following is a mechanism for formation of a cyanohydrin.

A MECHANISM FOR THE REACTION

Cyanohydrin Formation



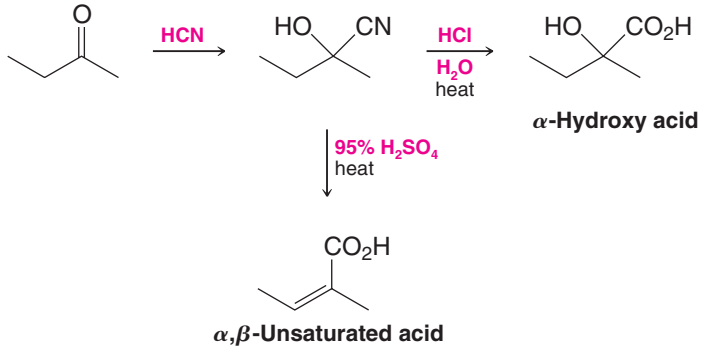
Great care must be taken when working with hydrogen cyanide due to its high toxicity and volatility. Reactions involving HCN must be conducted in an efficient fume hood.

Openmirrors.com

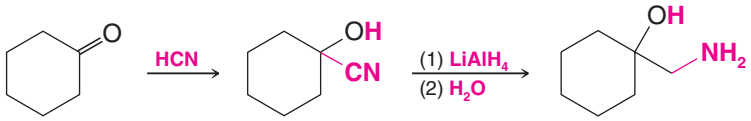
Cyanohydrins are useful intermediates in organic synthesis because they can be converted to several other functional groups.

- Acidic hydrolysis converts cyanohydrins to α-hydroxy acids or to α,β-unsaturated acids.

The mechanism for this hydrolysis is discussed in Section 17.8H. The preparation of α-hydroxy acids from cyanohydrins is part of the Kiliani–Fischer synthesis of simple sugars (Section 22.9A):

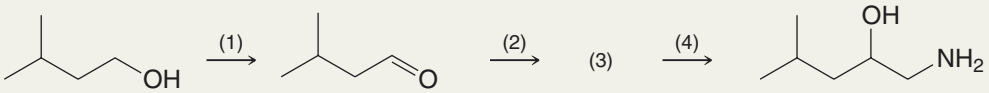


- Reduction of a cyanohydrin with lithium aluminum hydride gives a β-aminoalcohol:

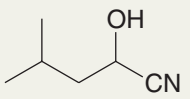


Solved Problem 16.6

Provide the missing reagents and intermediate in the following synthesis.

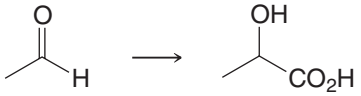


STRATEGY AND ANSWER Step (1) requires oxidation of a primary alcohol to an aldehyde; use PCC (Section 12.4). To reach the final product from the aldehyde we need to add a carbon atom to the chain and introduce a primary amine. This combination suggests use of a nitrile, which we know can be reduced to a primary amine. Thus, adding HCN to the aldehyde in step (2) forms the cyanohydrin (3), shown below. This step also affords the alcohol group present in the final product. In step (4) we reduce the nitrile to a primary amine using $LiAlH_4$.



Review Problem 16.16

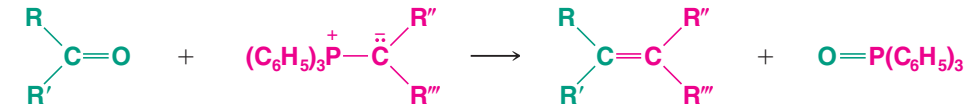
(a) Show how you might prepare lactic acid from acetaldehyde through a cyanohydrin intermediate. **(b)** What stereoisomeric form of lactic acid would you expect to obtain?



16.10 The Addition of Ylides: The Wittig Reaction

- Aldehydes and ketones react with phosphorus ylides to yield alkenes and triphenylphosphine oxide (a by-product). This reaction is known as the **Wittig reaction**.

The Wittig reaction has proved to be a valuable method for synthesizing alkenes. The **ylide** required for the reaction is a molecule with no net charge but which has a negative carbon atom adjacent to a positive heteroatom, which in the Wittig reaction is a phosphorus atom. Phosphorus ylides are also called phosphoranes.

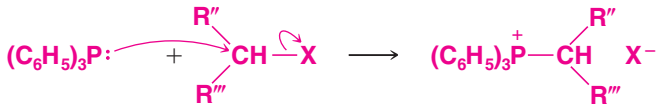


The Wittig reaction is applicable to a wide variety of compounds, and although a mixture of (*E*) and (*Z*) isomers may result, the Wittig reaction offers a great advantage over most other alkene syntheses in that *no ambiguity exists as to the location of the double bond in the product*. (This is in contrast to E1 eliminations, which may yield multiple alkene products by rearrangement to more stable carbocation intermediates, and both E1 and E2 elimination reactions, which may produce multiple products when different β hydrogens are available for removal.)

Phosphorus ylides are easily prepared from triphenylphosphine and primary or secondary alkyl halides. Their preparation involves two reactions:

General Reaction

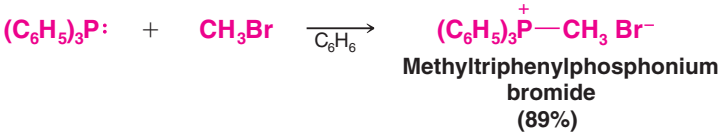
Reaction 1



Reaction 2

Specific Example

Reaction 1

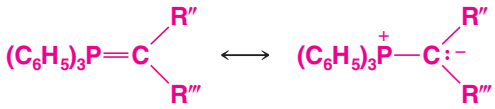


Reaction 2

The first reaction is a nucleophilic substitution reaction. Triphenylphosphine is an excellent nucleophile and a weak base. It reacts readily with 1° and 2° alkyl halides by an S_N2 mechanism to displace a halide ion from the alkyl halide to give an alkyltriphenylphosphonium salt. **The second reaction is an acid–base reaction**. A strong base (usually an alkyllithium or phenyllithium) removes a proton from the carbon that is attached to phosphorus to give the ylide.

Openmirrors.com

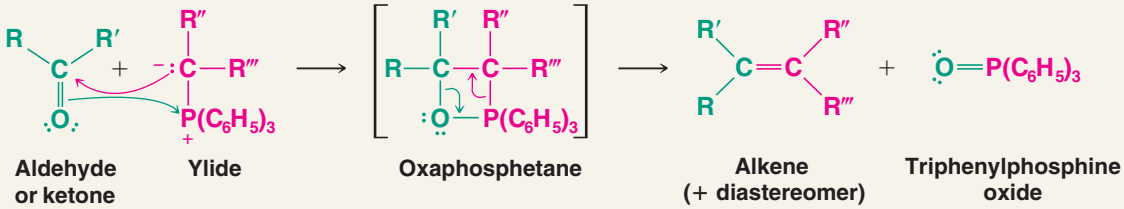
Phosphorus ylides can be represented as a hybrid of the two resonance structures shown here. Quantum mechanical calculations indicate that the contribution made by the first structure is relatively unimportant.



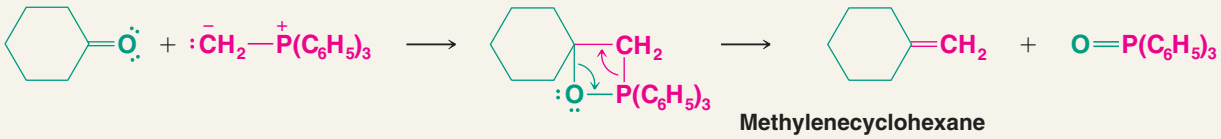
Studies by E. Vedejs (University of Michigan) indicate that the Wittig reaction takes place in two steps. In the first step (below), the aldehyde or ketone combines with the ylide in a cycloaddition reaction to form the four-membered ring of an oxaphosphetane. Then in a second step, the oxaphosphetane decomposes to form the alkene and triphenylphosphine oxide. The driving force for the reaction is the formation of the very strong ($DH° =$ 540 kJ mol^{-1}) phosphorus–oxygen bond in triphenylphosphine oxide.

A MECHANISM FOR THE REACTION

The Wittig Reaction

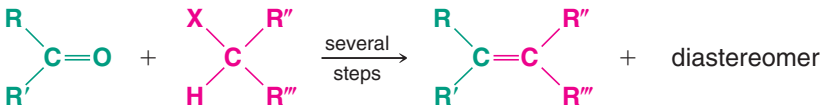


Specific Example



While Wittig syntheses may appear to be complicated, in practice they are easy to carry out. Most of the steps can be carried out in the same reaction vessel, and the entire synthesis can be accomplished in a matter of hours.

The overall result of a Wittig synthesis is



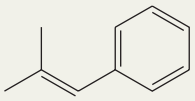
16.10A How to Plan a Wittig Synthesis

Planning a Wittig synthesis begins with recognizing in the desired alkene what can be the aldehyde or ketone component and what can be the halide component. Any or all of the R groups may be hydrogen, although yields are generally better when at least one group is hydrogen. The halide component must be a primary, secondary, or methyl halide.

Solved Problem 16.7

Synthesize 2-methyl-1-phenylprop-1-ene using a Wittig reaction. Begin by writing a retrosynthetic analysis.

STRATEGY AND ANSWER We examine the structure of the compound, paying attention to the groups on each side of the double bond:

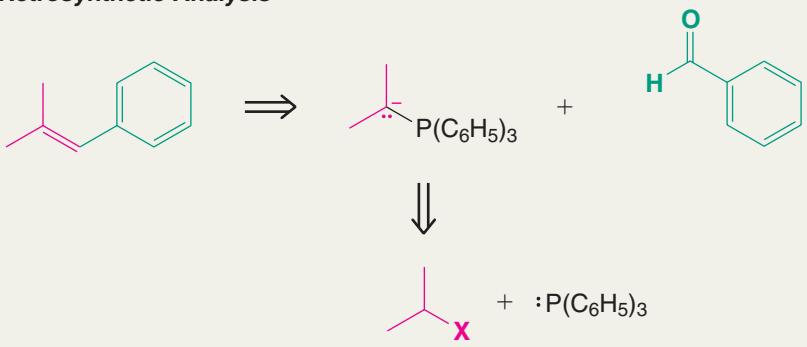


2-Methyl-1-phenylprop-1-ene

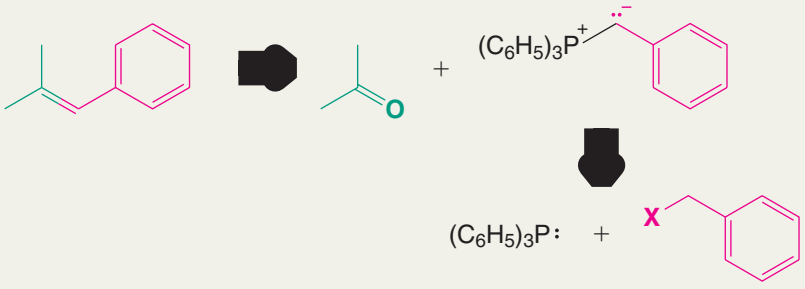
We see that two retrosynthetic analyses are possible.

Retrosynthetic Analysis

(a)



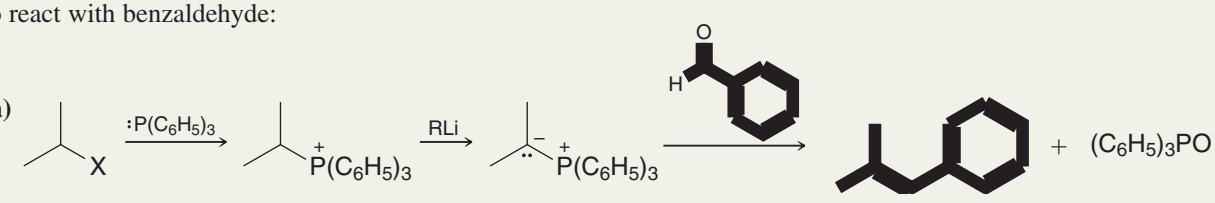
(b)



Synthesis

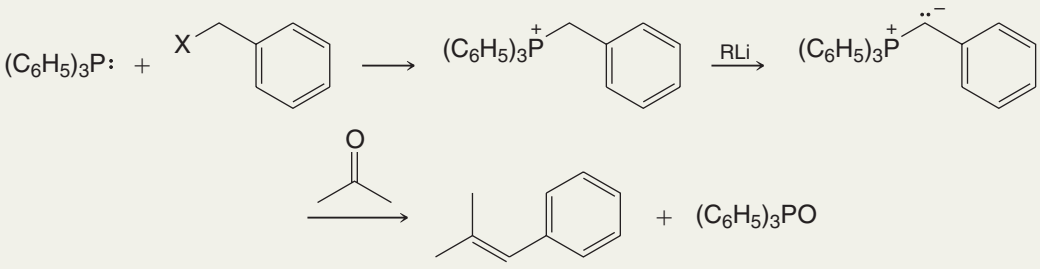
Following retrosynthetic analysis (a), we begin by making the ylide from a 2-halopropane and then allow the ylide to react with benzaldehyde:

(a)



Following retrosynthetic analysis (b), we make the ylide from a benzyl halide and allow it to react with acetone:

(b)



Openmirrors.com

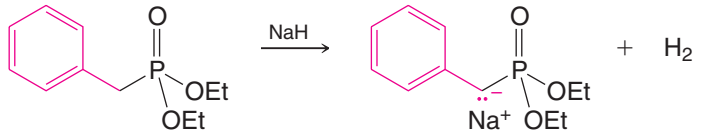
16.10B The Horner–Wadsworth–Emmons Reaction: A Modification of the Wittig Reaction

A widely used variation of the Wittig reaction is the **Horner–Wadsworth–Emmons** modification.

- The Horner–Wadsworth–Emmons reaction involves use of a phosphonate ester instead of a triphenylphosphonium salt. The major product is usually the (*E*)-alkene isomer.

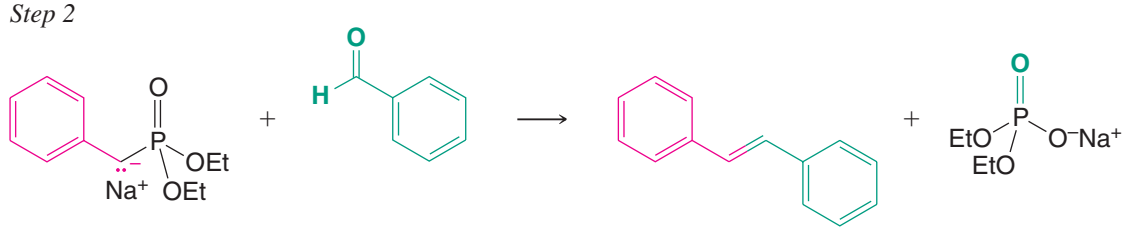
Some bases that are typically used to form the phosphonate ester carbanion include sodium hydride, potassium *tert*-butoxide, and butyllithium. The following reaction sequence is an example:

Step 1



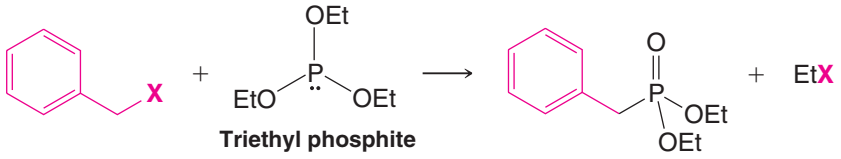
A phosphonate ester

Step 2



84%

The phosphonate ester is prepared by reaction of a trialkyl phosphite [$(RO)_3P$] with an appropriate halide (a process called the Arbuzov reaction). The following is an example:

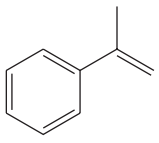


Triethyl phosphite

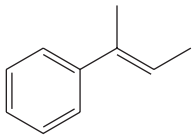
Review Problem 16.17

In addition to triphenylphosphine, assume that you have available as starting materials any necessary aldehydes, ketones, and organic halides. Show how you might synthesize each of the following alkenes using the Wittig reaction:

(a)

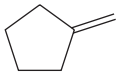


(b)

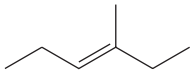


(c)

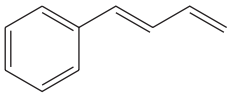
(d)



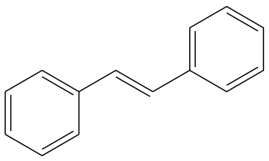
(e)



(f)

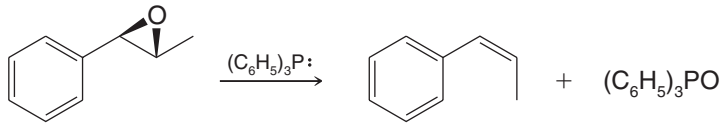


(g)



Triphenylphosphine can be used to convert epoxides to alkenes, for example,

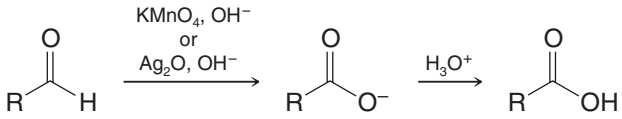
Review Problem 16.18



Propose a likely mechanism for this reaction.

16.11 Oxidation of Aldehydes

Aldehydes are much more easily oxidized than ketones. Aldehydes are readily oxidized by strong oxidizing agents such as potassium permanganate, and they are also oxidized by such mild oxidizing agents as silver oxide:



Notice that in these oxidations aldehydes lose the hydrogen that is attached to the carbonyl carbon atom. Because ketones lack this hydrogen, they are more resistant to oxidation. Aldehydes undergo slow oxidation by oxygen in the air, and thus stored samples of aldehydes often contain the corresponding carboxylic acid as an impurity.

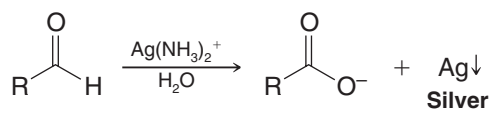
16.12 Chemical Analyses for Aldehydes and Ketones

16.12A Derivatives of Aldehydes and Ketones

Aldehydes and ketones can be differentiated from noncarbonyl compounds through their reactions with derivatives of ammonia (Section 16.8B). 2,4-Dinitrophenylhydrazine and hydroxylamine react with aldehydes and ketones to form precipitates. Oximes are usually colorless, whereas 2,4-dinitrophenylhydrazones are usually orange. The melting points of these derivatives can also be used in identifying specific aldehydes and ketones.

16.12B Tollens' Test (Silver Mirror Test)

The ease with which aldehydes undergo oxidation differentiates them from most ketones. Mixing aqueous silver nitrate with aqueous ammonia produces a solution known as Tollens' reagent. The reagent contains the diamminosilver(I) ion, $Ag(NH_3)_2^+$. Although this ion is a very weak oxidizing agent, it oxidizes aldehydes to carboxylate anions. As it does this, silver is reduced from the +1 oxidation state [of $Ag(NH_3)_2^+$] to metallic silver. If the rate of reaction is slow and the walls of the vessel are clean, metallic silver deposits on the walls of the test tube as a mirror; if not, it deposits as a gray-to-black precipitate. Tollens' reagent gives a negative result with all ketones except α-hydroxy ketones:



Openmirrors.com

16.13 Spectroscopic Properties of Aldehydes and Ketones

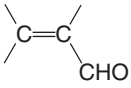
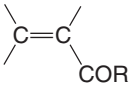
16.13A IR Spectra of Aldehydes and Ketones

- Carbonyl groups of aldehydes and ketones give rise to very strong C=O stretching absorption bands in the 1665–1780-cm^{-1} region.

The exact location of the carbonyl IR absorption (Table 16.3) depends on the structure of the aldehyde or ketone and is one of the most useful and characteristic absorptions in the IR spectrum.

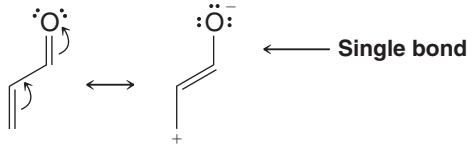
- Saturated acyclic aldehydes typically absorb near 1730 cm^{-1}; similar ketones absorb near 1715 cm^{-1}.

TABLE 16.3 IR Carbonyl Stretching Bands of Aldehydes and Ketones

C=O Stretching Frequencies			
Compound	**Range (cm^{-1})**	**Compound**	**Range (cm^{-1})**
R—CHO	1720–1740	RCOR	1705–1720
Ar—CHO	1695–1715	ArCOR	1680–1700
	1680–1690		1665–1680
		Cyclohexanone	1715
		Cyclopentanone	1751
		Cyclobutanone	1785

- Conjugation of the carbonyl group with a double bond or a benzene ring shifts the C=O absorption to lower frequencies by about 40 cm^{-1}.

This shift to lower frequencies occurs because the carbonyl double bond of a conjugated compound has more single-bond character (see the resonance structures below), and single bonds are easier to stretch than double bonds.



The location of the carbonyl absorption of cyclic ketones depends on the size of the ring (compare the cyclic compounds in Table 16.3). *As the ring grows smaller, the* C=O *stretching peak is shifted to higher frequencies.*

Vibrations of the C—H bond of the CHO group of aldehydes also give two weak bands in the 2700–2775- and 2820–2900-cm^{-1} regions that are easily identified.

Figure 16.1 shows the IR spectrum of phenylethanal.

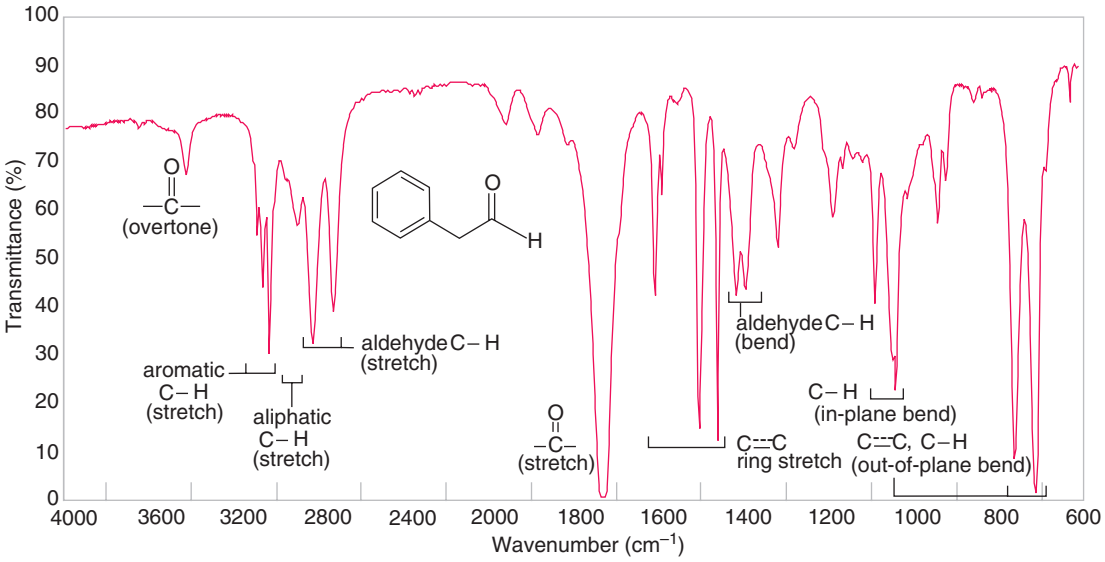


Figure 16.1 The infrared spectrum of phenylethanal.

16.13B NMR Spectra of Aldehydes and Ketones

^{13}C NMR Spectra

- The carbonyl carbon of an aldehyde or ketone gives characteristic NMR signals in the δ 180–220 region of ^{13}C spectra.

Since almost no other signals occur in this region, *the presence of a signal in this region (near δ 200) strongly suggests the presence of a carbonyl group*.

^{1}H NMR Spectra

- An aldehyde proton gives a distinct ^{1}H NMR signal downfield in the δ 9–12 region where almost no other protons absorb; therefore, it is easily identified.

The aldehyde proton of an aliphatic aldehyde shows spin–spin coupling with protons on the adjacent α carbon, and the splitting pattern reveals the degree of substitution of the α carbon. For example, in acetaldehyde (CH_3CHO) the aldehyde proton signal is split into a quartet by the three methyl protons, and the methyl proton signal is split into a doublet by the aldehyde proton. The coupling constant is small, however (about 3 Hz, as compared with typical vicinal splitting of about 7 Hz).

- Protons on the α carbon are deshielded by the carbonyl group, and their signals generally appear in the δ 2.0–2.3 region.
- Methyl ketones show a characteristic (3H) singlet near δ 2.1.

Figures 16.2 and 16.3 show annotated ^{1}H and ^{13}C spectra of phenylethanal.

Openmirrors.com

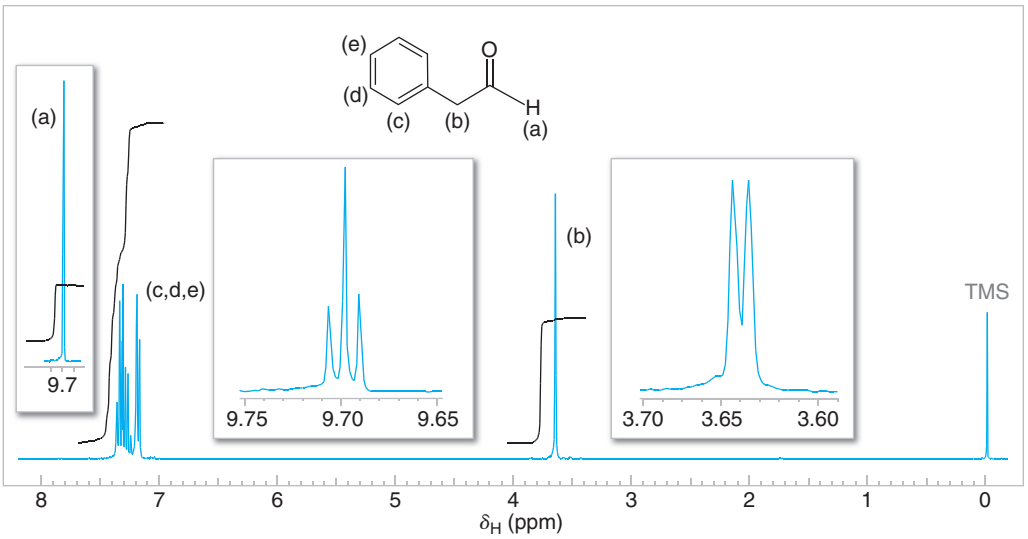


Figure 16.2 The 300-MHz ^{1}H NMR spectrum of phenylethanal. The small coupling between the aldehyde and methylene protons (2.6 Hz) is shown in the expanded offset plots.

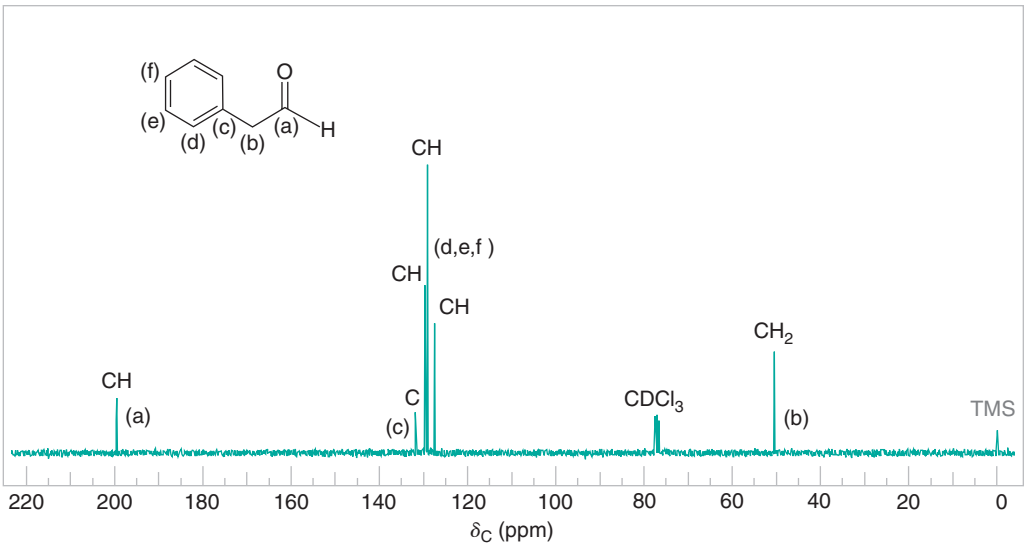


Figure 16.3 The broadband proton-decoupled ^{13}C NMR spectrum of phenylethanal. DEPT ^{13}C NMR information and carbon assignments are shown near each peak.

16.13C Mass Spectra of Aldehydes and Ketones

The mass spectra of ketones usually show a peak corresponding to the molecular ion. Aldehydes typically produce a prominent $M.^{+} - 1$ peak in their mass spectra from cleavage of the aldehyde hydrogen. Ketones usually undergo cleavage on either side of the carbonyl group to produce acylium ions, $RC{\equiv}O:^{+}$, where R can be the alkyl group from either side of the ketone carbonyl. Cleavage via the McLafferty rearrangement (Section 9.16D) is also possible in many aldehydes and ketones.

16.13D UV Spectra

The carbonyl groups of saturated aldehydes and ketones give a weak absorption band in the UV region between 270 and 300 nm. This band is shifted to longer wavelengths (300–350 nm) when the carbonyl group is conjugated with a double bond.

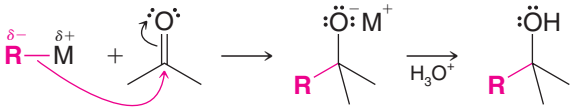
16.14 Summary of Aldehyde and Ketone Addition Reactions

The nucleophilic addition reactions of aldehydes and ketones occurring at the carbonyl carbon atom that we have studied so far are summarized below. In Chapters 18 and 19 we shall see other examples.

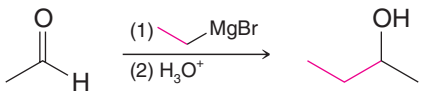
Nucleophilic Addition Reactions of Aldehydes and Ketones

1. ***Addition of Organometallic Compounds*** **(Section 12.7C)**

General Reaction



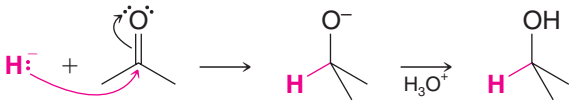
Specific Example Using a Grignard Reagent **(Section 12.7C)**



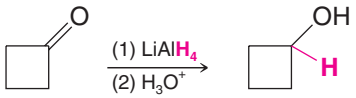
67%

2. ***Addition of Hydride Ion*** **(Section 12.3)**

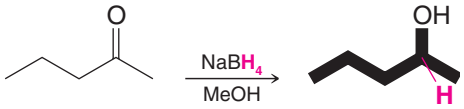
General Reaction



Specific Examples Using Metal Hydrides **(Section 12.3)**



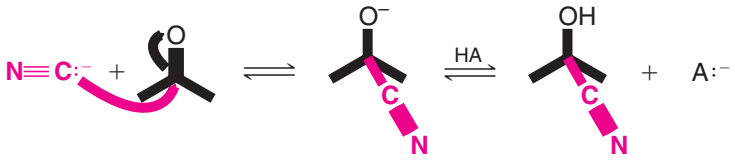
(90%)



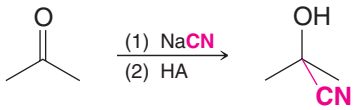
(100%)

3. ***Addition of Hydrogen Cyanide*** **(Section 16.9)**

General Reaction



Specific Example

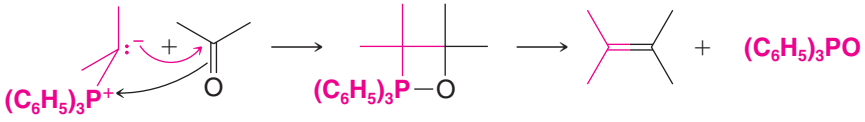


Acetone cyanohydrin
(78%)

Openmirrors.com

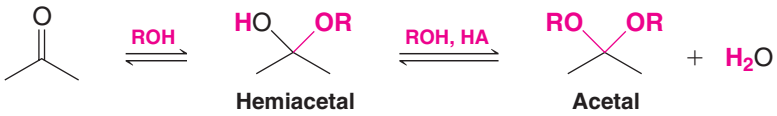
4. *Addition of Ylides* (Section 16.10)

The Wittig Reaction

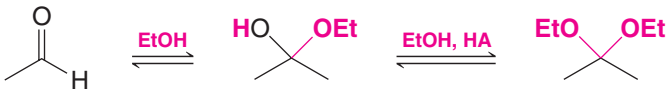


5. *Addition of Alcohols* (Section 16.7)

General Reaction

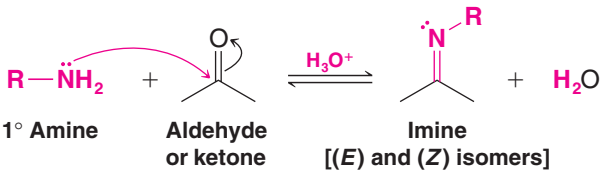


Specific Example

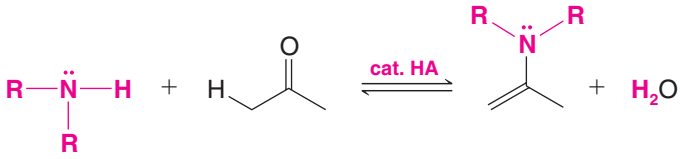


6. *Addition of Derivatives of Ammonia* (Section 16.8)

Imines



Enamines



Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Problems

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

REACTIONS AND NOMENCLATURE

16.19 Give a structural formula and another acceptable name for each of the following compounds:

(a) Formaldehyde
(b) Acetaldehyde
(c) Phenylacetaldehyde
(d) Acetone
(e) Ethyl methyl ketone
(f) Acetophenone
(g) Benzophenone
(h) Salicylaldehyde
(i) Vanillin
(j) Diethyl ketone
(k) Ethyl isopropyl ketone
(l) Diisopropyl ketone
(m) Dibutyl ketone
(n) Dipropyl ketone
(o) Cinnamaldehyde

16.20 Write structural formulas for the products formed when propanal reacts with each of the following reagents:

(a) $NaBH_4$ in aqueous NaOH

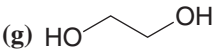
(b) C_6H_5MgBr, then H_3O^+

(c) $LiAlH_4$, then H_2O

(d) Ag_2O, OH^-

(e) $(C_6H_5)_3\overset{+}{P}{=}\ddot{\overline{C}}H_2$

(f) H_2 and Pt

(g)  and HA

(h) $CH_3\ddot{\overline{C}}H{-}\overset{+}{P}(C_6H_5)_3$

(i) $Ag(NH_3)_2^+$

(j) Hydroxylamine

(k) Phenylhydrazine

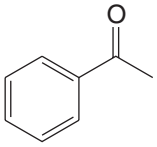
(l) Cold dilute $KMnO_4$

(m)  , HA

(n)  , HA, then Raney nickel

16.21 Give structural formulas for the products formed (if any) from the reaction of acetone with each reagent in Exercise 16.20.

16.22 What products would be obtained when acetophenone reacts under each of the following conditions?


Acetophenone

(a) Acetophenone + $HNO_3 \xrightarrow[H_2SO_4]{}$

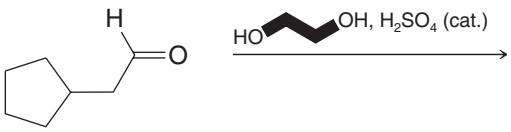
(b) Acetophenone + $C_6H_5NHNH_2 \xrightarrow{HA}$

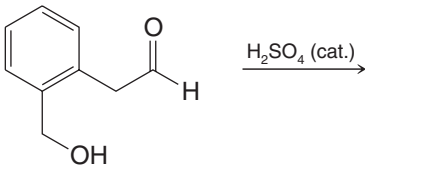
(c) Acetophenone + $^-{:}CH_2{-}\overset{+}{P}(C_6H_5)_3 \longrightarrow$

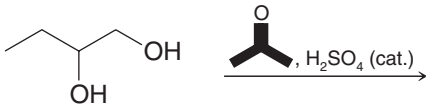
(d) Acetophenone + $NaBH_4 \xrightarrow[OH^-]{H_2O}$

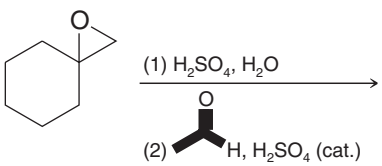
(e) Acetophenone + $C_6H_5MgBr \xrightarrow[(2)\ NH_4Cl]{}$

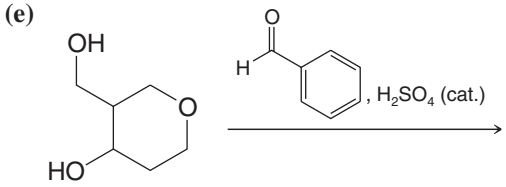
16.23 Predict the major organic product from each of the following reactions.

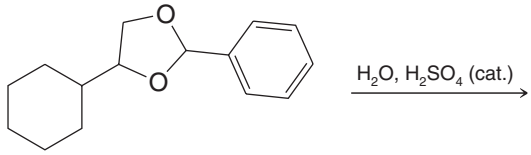
(a) 

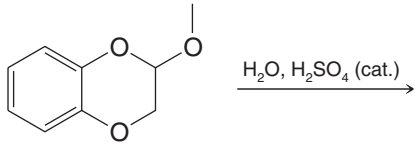
(b) 

(c) 

(d) 

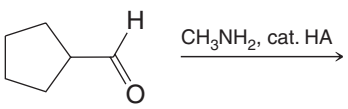
(e) 

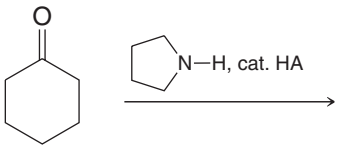
(f) 

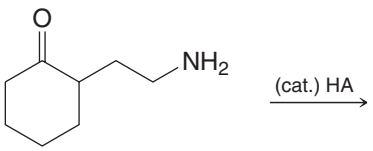
(g) 

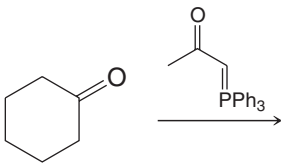
Openmirrors.com

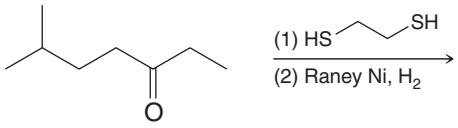
16.24 Predict the major product from each of the following reactions.

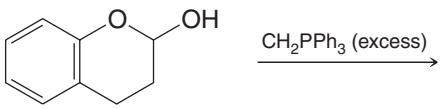
(a)


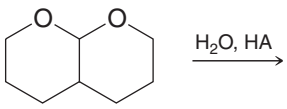
(b)


(c)


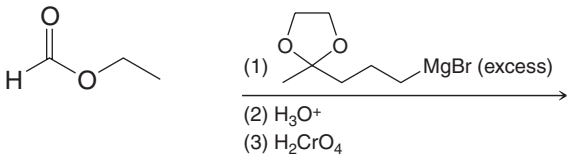
(d)


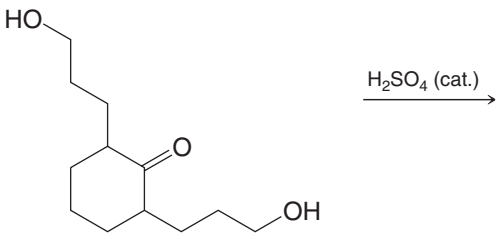
(e)


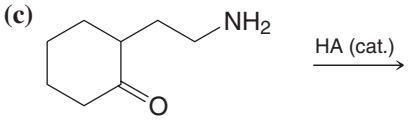
(f)


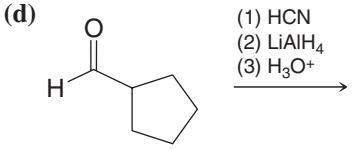
(g)


16.25 Predict the major product from each of the following reactions.

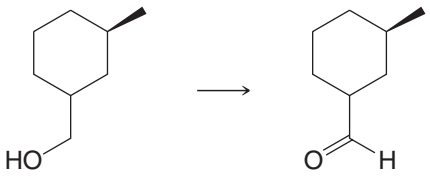
(a)


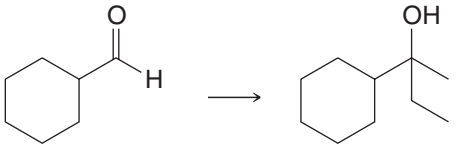
(b)


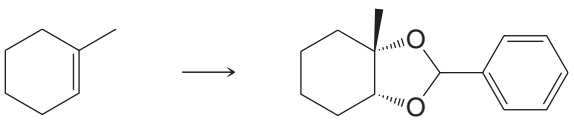
(c)


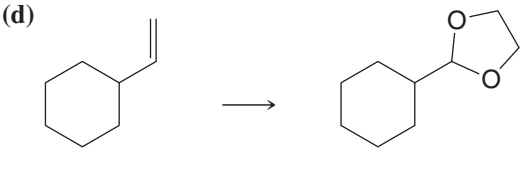
(d)


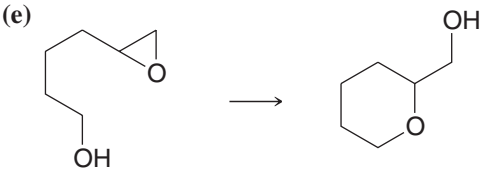
16.26 Provide the reagents needed to accomplish each of the following transformations.

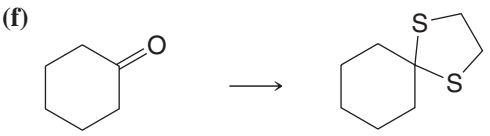
(a)


(b)


(c)


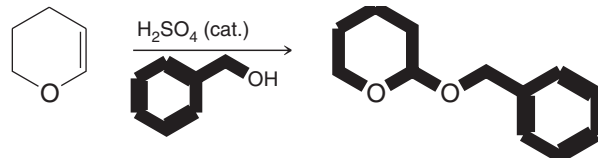
(d)


(e)


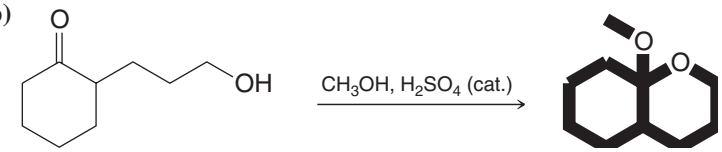
(f)


16.27 Write detailed mechanisms for each of the following reactions.

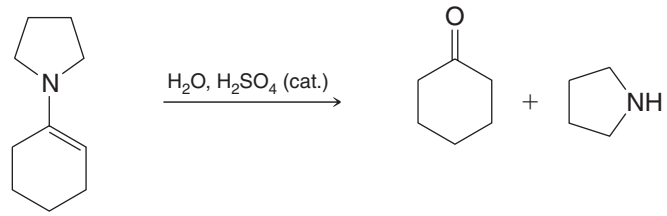
(a)



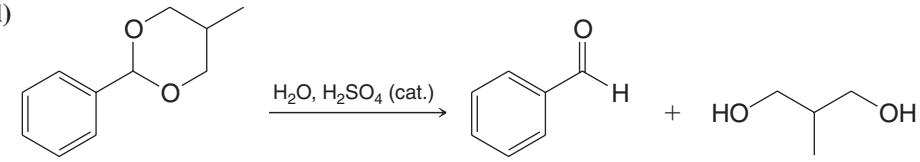
(b)



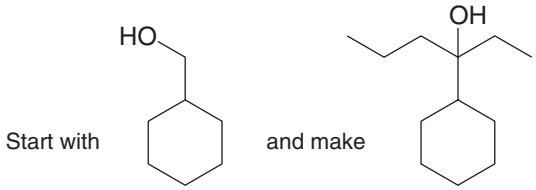
(c)



(d)



16.28 Provide the reagents necessary for the following synthesis.



SYNTHESIS

16.29 **(a)** Synthesize phenyl propyl ketone from benzene and any other needed reagents.

(b) Give two methods for transforming phenyl propyl ketone into butylbenzene.

16.30 Show how you would convert benzaldehyde into each of the following. You may use any other needed reagents, and more than one step may be required.

(a) Benzyl alcohol
(b) Benzoic acid
(c) Benzoyl chloride
(d) Benzophenone
(e) 1-Phenylethanol
(f) 3-Methyl-1-phenyl-1-butanol
(g) Benzyl bromide
(h) Toluene
(i) $C_6H_5CH(OCH_3)_2$
(j) $C_6H_5CH^{18}O$
(k) C_6H_5CHDOH
(l) $C_6H_5CH(OH)CN$
(m) $C_6H_5CH{=}NOH$
(n) $C_6H_5CH{=}NNHC_6H_5$
(o) $C_6H_5CH{=}CHCH{=}CH_2$

16.31 Show how ethyl phenyl ketone ($C_6H_5COCH_2CH_3$) could be synthesized from each of the following:

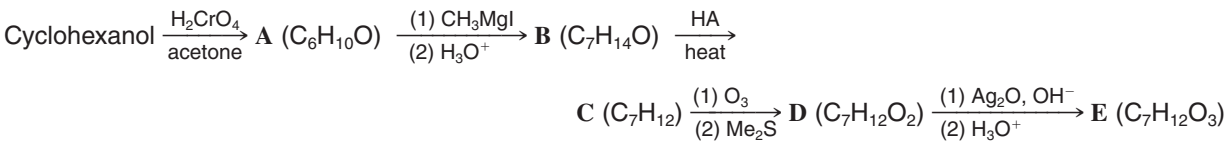
(a) Benzene
(b) Benzonitrile, C_6H_5CN
(c) Benzaldehyde

16.32 Show how benzaldehyde could be synthesized from each of the following:

(a) Benzyl alcohol
(b) Benzoic acid
(c) Phenylethyne
(d) Phenylethene (styrene)
(e) $C_6H_5CO_2CH_3$
(f) $C_6H_5C{\equiv}N$

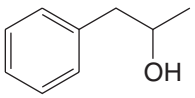
Openmirrors.com

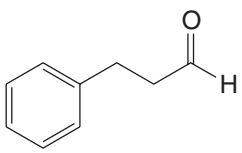
16.33 Give structures for compounds **A–E**.

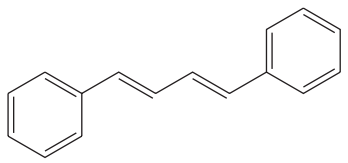


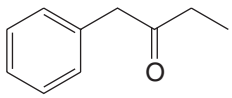
16.34 Warming piperonal (Section 16.3) with dilute aqueous HCl converts it to a compound with the formula $C_7H_6O_3$. What is this compound, and what type of reaction is involved?

16.35 Starting with benzyl bromide, show how you would synthesize each of the following:

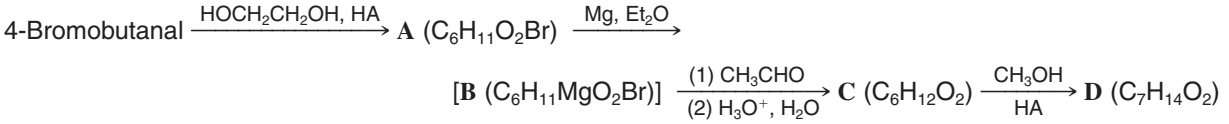
(a) 

(b) 

(c) 

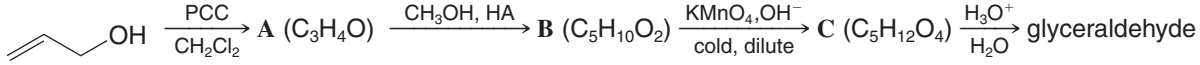
(d) 

16.36 Compounds **A** and **D** do not give positive Tollens' tests; however, compound **C** does. Give structures for **A–D**.



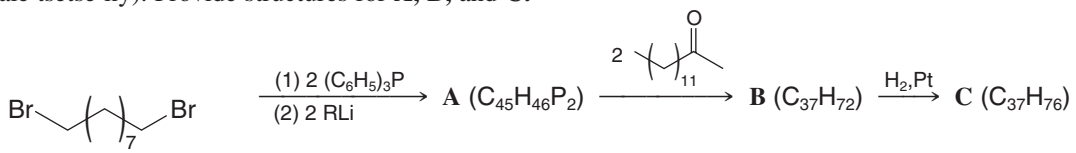
16.37 Dianeackerone is a volatile natural product isolated from secretory glands of the adult African dwarf crocodile. The compound is believed to be a pheromone associated with nesting and mating. Dianeackerone is named after Diane Ackerman, an author in the field of natural history and champion of the importance of preserving biodiversity. The IUPAC name of dianeackerone is 3,7-diethyl-9-phenylnonan-2-one, and it is found as both the (3*S*,7*S*) and (3*S*,7*R*) stereoisomers. Draw structures for both stereoisomers of dianeackerone.

16.38 Outlined here is a synthesis of glyceraldehyde (Section 5.15A). What are the intermediates **A–C** and what stereoisomeric form of glyceraldehyde would you expect to obtain?



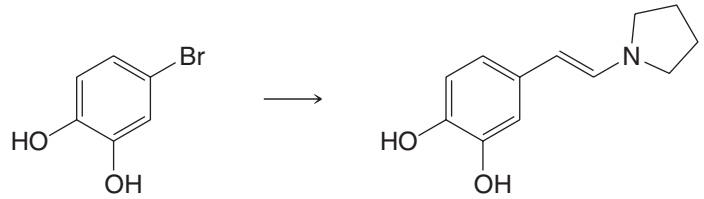
16.39 Consider the reduction of (*R*)-3-phenyl-2-pentanone by sodium borohydride. After the reduction is complete, the mixture is separated by chromatography into two fractions. These fractions contain isomeric compounds, and each isomer is optically active. What are these two isomers and what is the stereoisomeric relationship between them?

16.40 The structure of the sex pheromone (attractant) of the female tsetse fly has been confirmed by the following synthesis. Compound **C** appears to be identical to the natural pheromone in all respects (including the response of the male tsetse fly). Provide structures for **A, B,** and **C.**

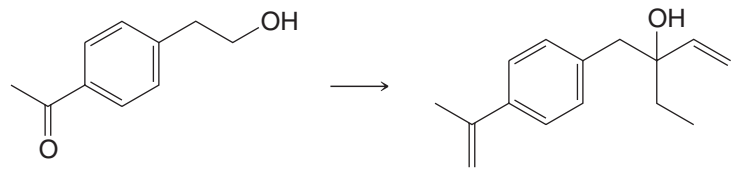


16.41 Provide reagents that would accomplish each of the following syntheses. Begin by writing a retrosynthetic analysis.

(a)

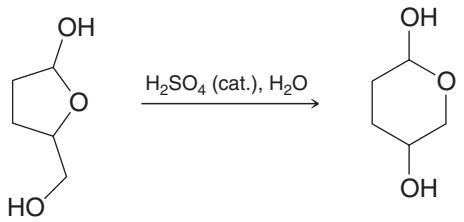


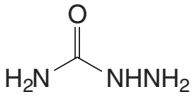
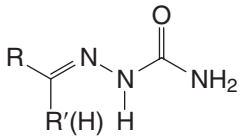
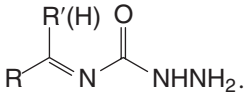
(b)



MECHANISMS AND STRUCTURE ELUCIDATION

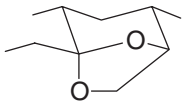
16.42 Write a detailed mechanism for the following reaction.



16.43 When  (semicarbazide) reacts with a ketone (or an aldehyde) to form a derivative known as a semicarbazone, only one nitrogen atom of semicarbazide acts as a nucleophile and attacks the carbonyl carbon atom of the ketone. The product of the reaction, consequently, is  rather than  .

What factor accounts for the fact that two nitrogen atoms of semicarbazide are relatively non-nucleophilic?

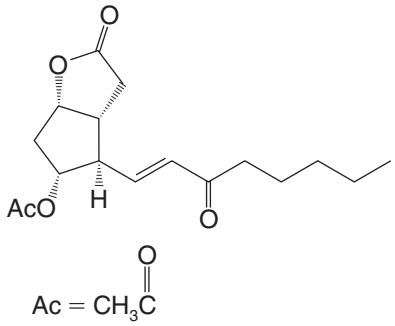
16.44 Dutch elm disease is caused by a fungus transmitted to elm trees by the elm bark beetle. The female beetle, when she has located an attractive elm tree, releases several pheromones, including multistriatin, below. These pheromones attract male beetles, which bring with them the deadly fungus.



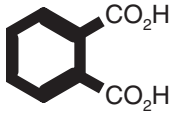
Multistriatin

Treating multistriatin with dilute aqueous acid at room temperature leads to the formation of a product, $C_{10}H_{20}O_3$, which shows a strong infrared peak near 1715 cm^{-1}. Propose a structure for this product.

16.45 The following structure is an intermediate in a synthesis of prostaglandins $F_{2\alpha}$ and E_2 by E. J. Corey (Harvard University). A Horner–Wadsworth–Emmons reaction was used to form the (*E*)-alkene. Write structures for the phosphonate ester and carbonyl reactant that were used in this process. (*Note*: The carbonyl component of the reaction included the cyclopentyl group.)



16.46 Compounds **W** and **X** are isomers; they have the molecular formula C_9H_8O. The IR spectrum of each compound shows a strong absorption band near 1715 cm^{-1}. Oxidation of either compound with hot, basic potassium permanganate followed by acidification yields phthalic acid. The ^1H NMR spectrum of **W** shows a multiplet at δ 7.3 and a singlet at δ 3.4. The ^1H NMR spectrum of **X** shows a multiplet at δ 7.5, a triplet at δ 3.1, and a triplet at δ 2.5. Propose structures for **W** and **X**.



Phthalic acid

Openmirrors.com

16.47 Compounds **Y** and **Z** are isomers with the molecular formula $C_{10}H_{12}O$. The IR spectrum of each compound shows a strong absorption band near 1710 cm^{-1}. The ^1H NMR spectra of **Y** and **Z** are given in Figs. 16.4 and 16.5. Propose structures for **Y** and **Z**.

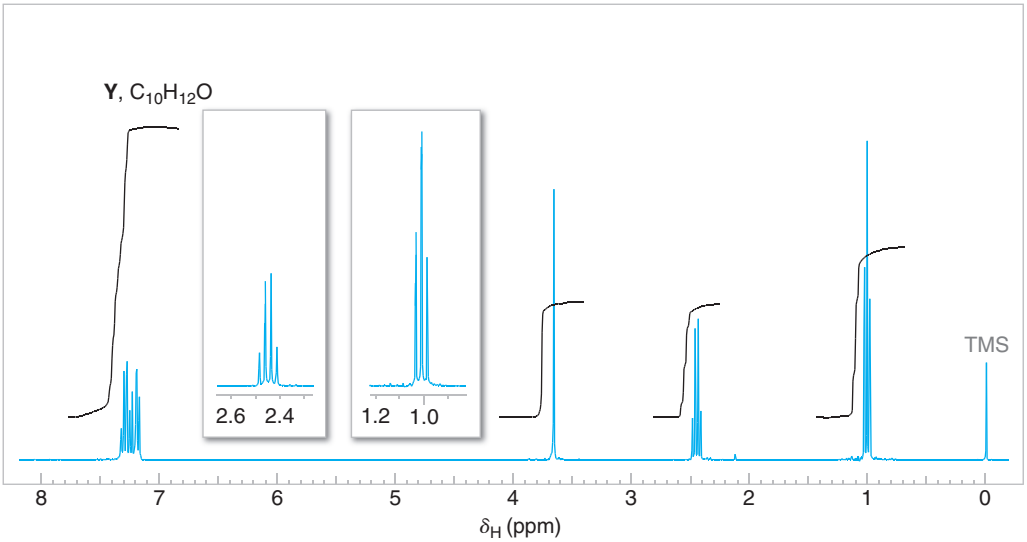


Figure 16.4 The 300-MHz ^1H NMR spectrum of compound **Y**, Problem 16.47. Expansions of the signals are shown in the offset plots.

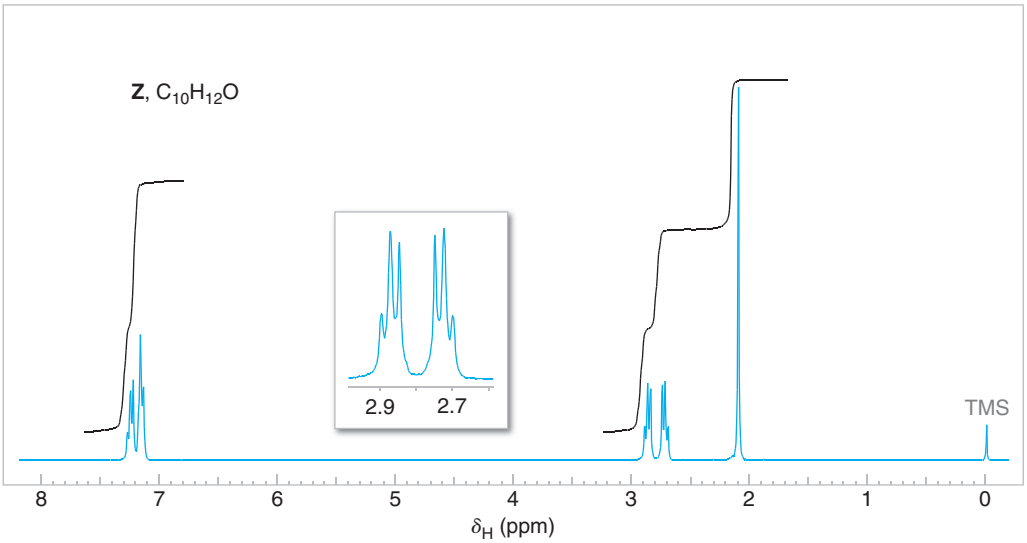


Figure 16.5 The 300-MHz ^1H NMR spectrum of compound **Z**, Problem 16.47. Expansions of the signals are shown in the offset plots.

16.48 Compound **A** ($C_9H_{18}O$) forms a phenylhydrazone, but it gives a negative Tollens' test. The IR spectrum of **A** has a strong band near 1710 cm^{-1}. The broadband proton-decoupled ^{13}C NMR spectrum of **A** is given in Fig. 16.6. Propose a structure for **A**.

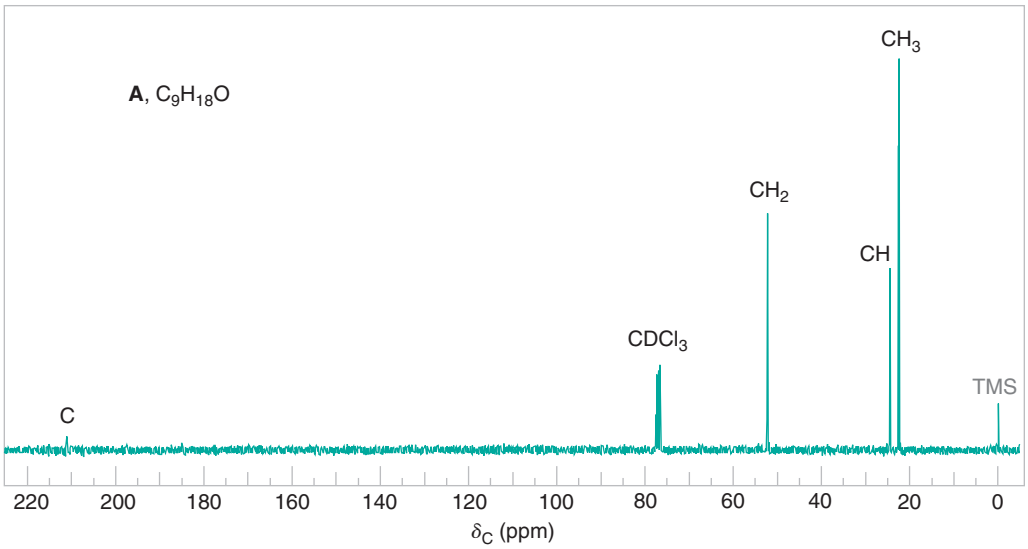


Figure 16.6 The broadband proton-decoupled ^{13}C NMR spectrum of compound A, Problem 16.48. Information from the DEPT ^{13}C NMR spectra is given above the peaks.

16.49 Compound **B** ($C_8H_{12}O_2$) shows a strong carbonyl absorption in its IR spectrum. The broadband proton-decoupled ^{13}C NMR spectrum of **B** has only three signals, at δ 19 (CH_3), 71 (C), and 216 (C). Propose a structure for **B**.

Challenge Problems

16.50 **(a)** What would be the frequencies of the two absorption bands expected to be most prominent in the infrared spectrum of 4-hydroxycycloheptanone **(C)**?

(b) In reality, the lower frequency band of these two is very weak. Draw the structure of an isomer that would exist in equilibrium with **C** and that explains this observation.

16.51 One of the important reactions of benzylic alcohols, ethers, and esters is the ease of cleavage of the benzyl–oxygen bond during hydrogenation. This is another example of "hydrogenolysis," the cleavage of a bond by hydrogen. It is facilitated by the presence of acid. Hydrogenolysis can also occur with strained-ring compounds.

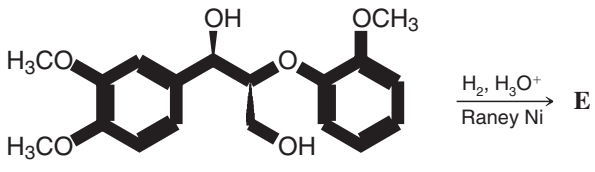
On hydrogenation of compound **D** (see below) using Raney nickel catalyst in a dilute solution of hydrogen chloride in dioxane and water, most products have a 3,4-dimethoxyphenyl group attached to a side chain. Among these, an interesting product is **E**, whose formation illustrates not only hydrogenolysis but also the migratory aptitude of phenyl groups. For product **E**, these are key spectral data:

MS (*m/z*): 196.1084 ($M^{\cdot+}$, at high resolution), 178

IR (cm^{-1}): 3400 (broad), 3050, 2850 (CH_3—O stretch)

^{1}H NMR (δ, in $CDCl_3$): 1.21 (d, 3H, J = 7 Hz), 2.25 (s, 1H), 2.83 (m, 1H), 3.58 (d, 2H, J = 7 Hz), 3.82 (s, 6H), 6.70 (s, 3H).

What is the structure of compound **E**?



D

Openmirrors.com

Learning Group Problems

A synthesis of ascorbic acid (vitamin C, **1**) starting from D-(+)-galactose (**2**) is shown below (Haworth, W.N., et al., *J. Chem. Soc*., **1933,** 1419–1423). Consider the following questions about the design and reactions used in this synthesis:

(a) Why did Haworth and co-workers introduce the acetal functional groups in **3**?

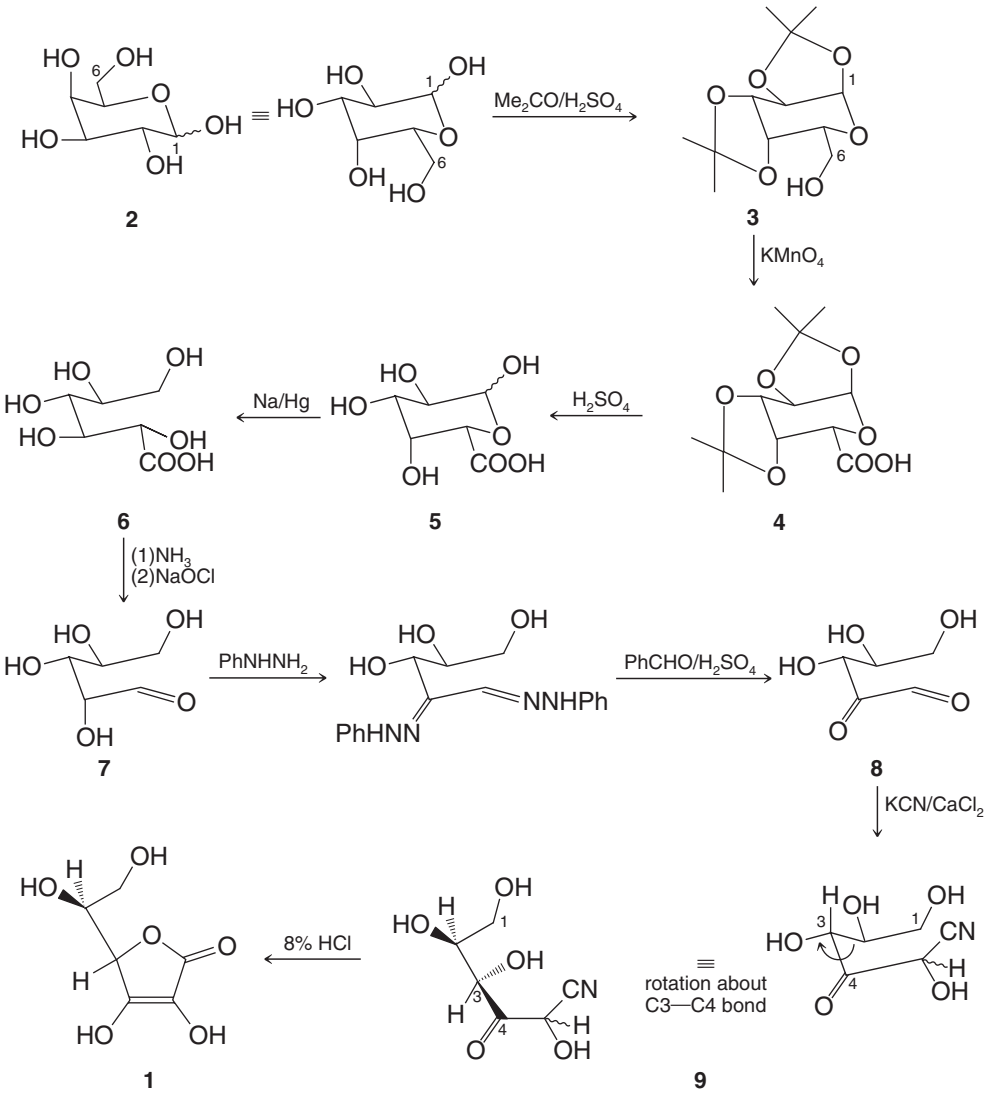
(b) Write a mechanism for the formation of one of the acetals.

(c) Write a mechanism for the hydrolysis of one of the acetals (**4** to **5**). Assume that water was present in the reaction mixture.

(d) In the reaction from **5** to **6** you can assume that there was acid (e.g., HCl) present with the sodium amalgam. What reaction occurred here and from what functional group did that reaction actually proceed?

(e) Write a mechanism for the formation of a phenylhydrazone from the aldehyde carbonyl of **7**. [Do not be concerned about the phenylhydrazone group at C2. We shall study the formation of bishydrazones of this type (called an osazone) in Chapter 22.]

(f) What reaction was used to add the carbon atom that ultimately became the lactone carbonyl carbon in ascorbic acid (**1**)?



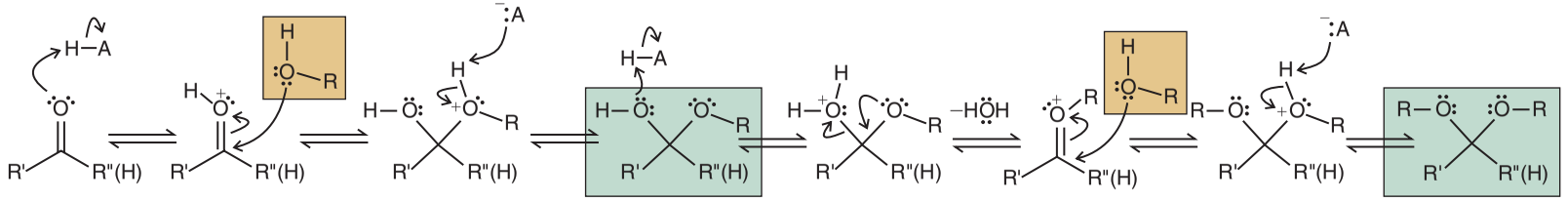
Openmirrors.com

SUMMARY OF MECHANISMS

Acetals, Imines, and Enamines: Common Mechanistic Themes in Their Acid-catalyzed Formation from Aldehydes and Ketones

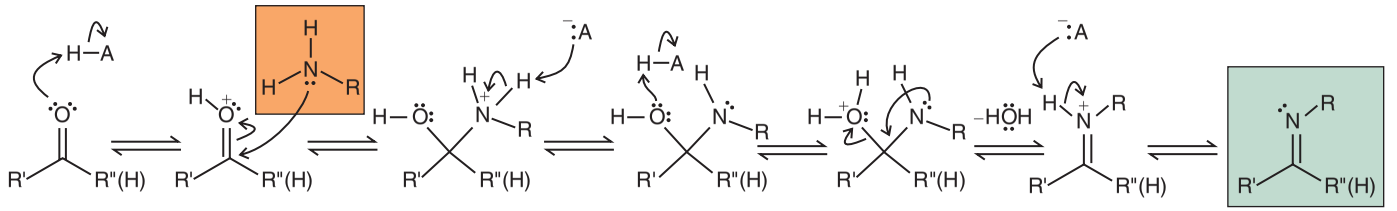
Many steps are nearly the same in acid-catalyzed reactions of aldehydes and ketones with alcohols and amines. Compare the mechanisms vertically to see the similarities and differences. Note differences in completion of the mechanism for each type of product.

I. Hemiacetal and acetal formation: reaction with alcohols



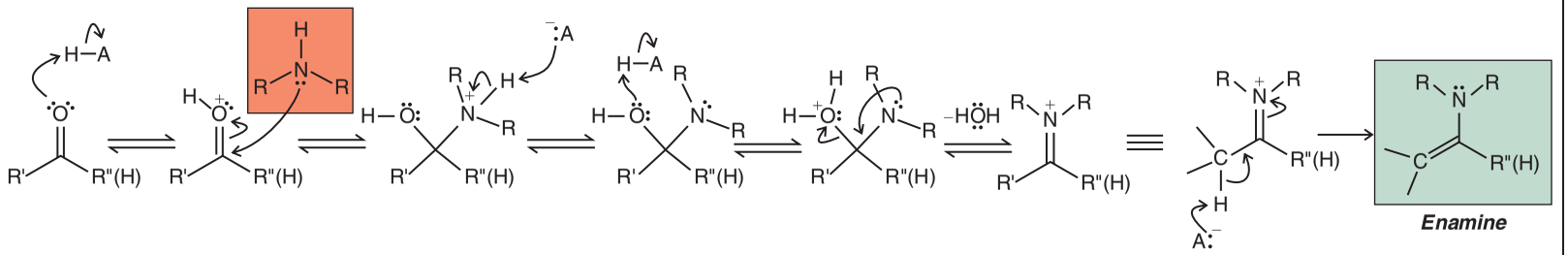
*In **acetal** formation, the oxonium ion is attacked by a second alcohol molecule.*

II. Imine formation: reaction with primary amines



*In **imine** formation, the proton on the initial iminium ion is removed, leading to the stable imine product.*

III. Enamine formation: reaction with secondary amines

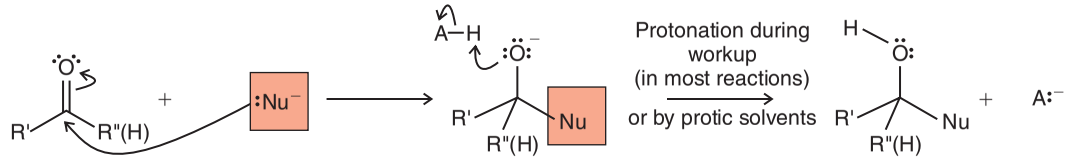


*In **enamine** formation, a proton is removed from a carbon adjacent to the iminium carbon (because no proton is available for removal from the nitrogen).*

SUMMARY OF MECHANISMS

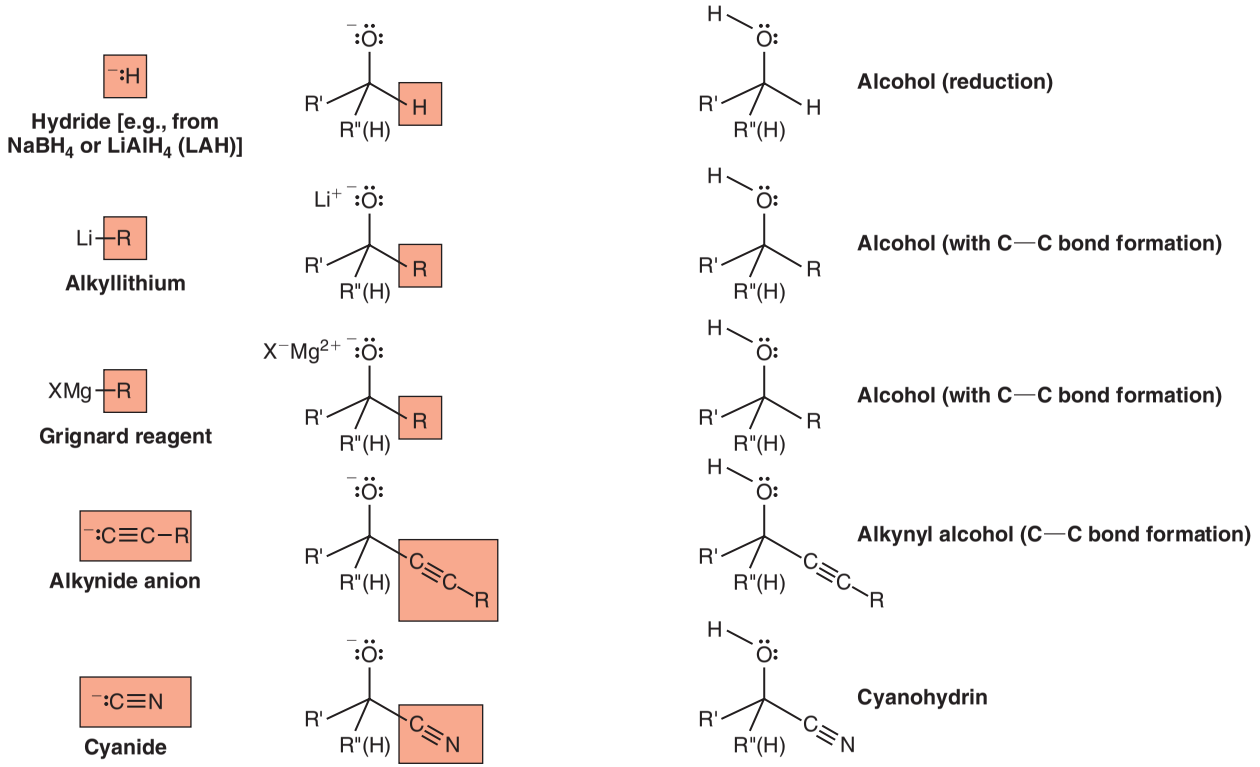
Nucleophilic Addition to Aldehydes and Ketones Under Basic Conditions

Generalized nucleophilic addition to an aldehyde or ketone:



Aldehyde or ketone | Nucleophile | Tetrahedral intermediate | Product

Examples:

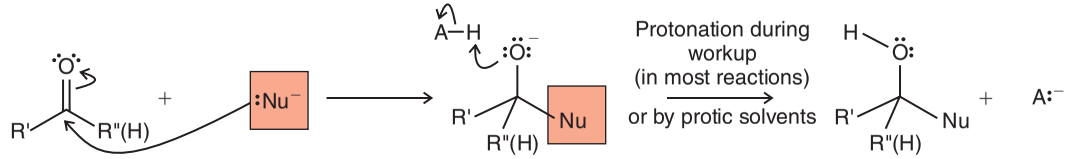


Openmirrors.com

SUMMARY OF MECHANISMS

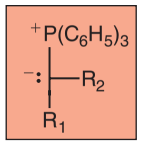
Nucleophilic Addition to Aldehydes and Ketones Under Basic Conditions

Generalized nucleophilic addition to an aldehyde or ketone:

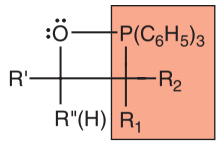


Aldehyde or ketone | Nucleophile | Tetrahedral Intermediate | Product

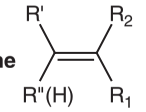
Examples (continued):



Phosphorus ylide

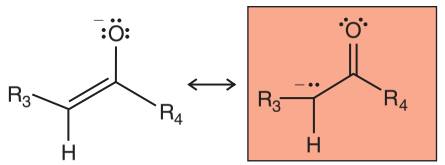


Oxaphosphetane intermediate

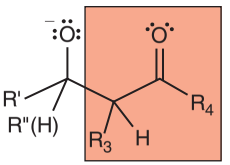


(plus diastereomer)

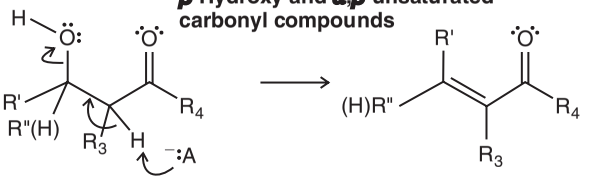
Wittig preparation of alkenes (with loss of triphenylphosphine oxide [$(C_6H_5)_3PO$])



Enolate (see Chapter 18)



β-Hydroxy and α,β-unsaturated carbonyl compounds



Synthetic Connections

Some Synthetic Connections of Aldehydes, Ketones, and Other Functional Groups

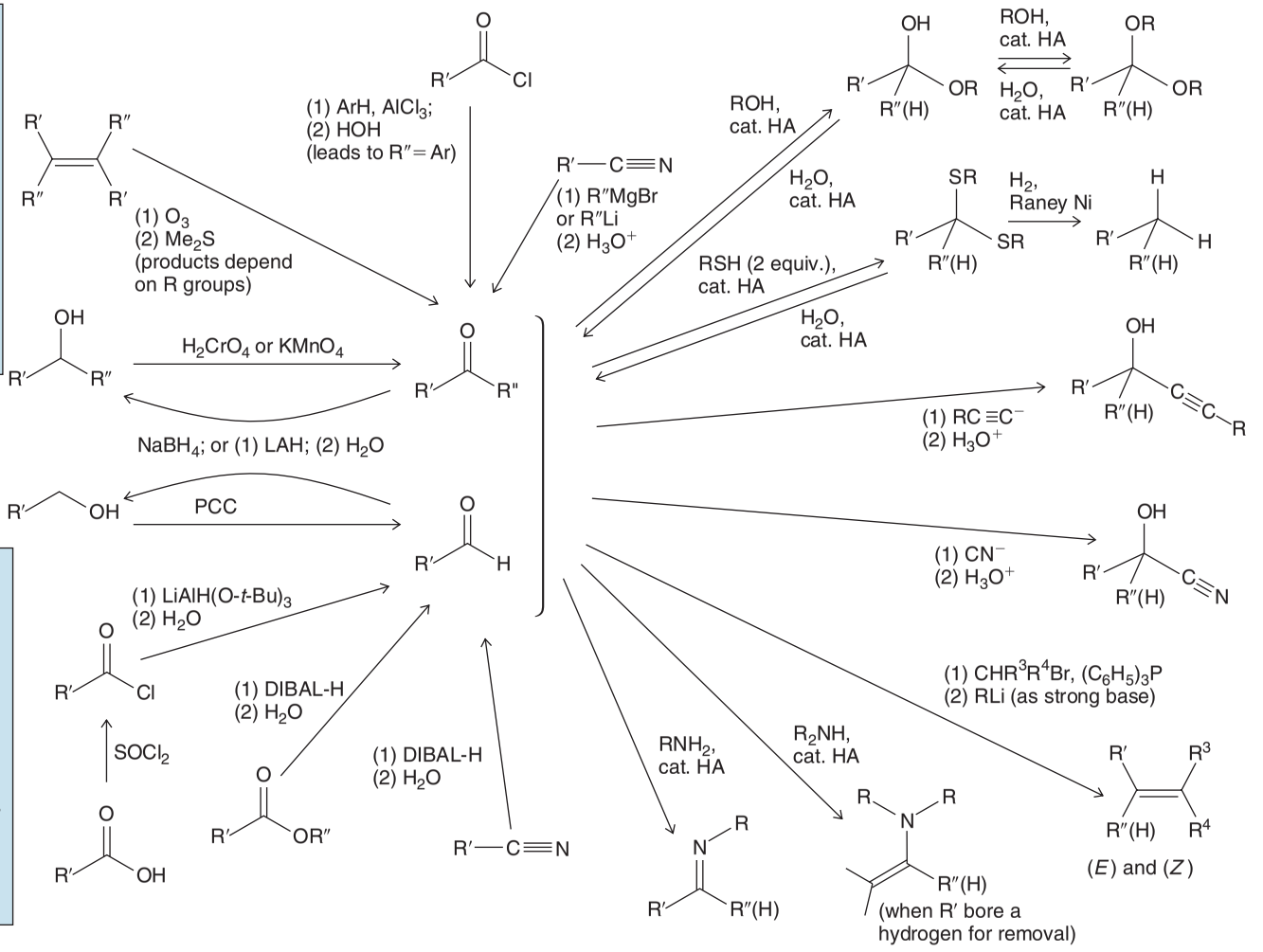
Clockwise from center, bottom:

I. Preparation of aldehydes and ketones:

- Nitrile, ester, acyl halide reduction
- Alcohol oxidation
- Ozonolysis
- Friedel–Crafts acylation
- Grignard with nitrile
- Acetal and hemiacetal hydrolysis

II. Reactions of aldehydes and ketones:

- Hemiacetal and acetal formation
- Thioacetal formation and reduction
- Alkynide anion addition
- Nitrile addition (cyanohydrin formation)
- Wittig synthesis of alkenes
- Enamine synthesis
- Imine synthesis
- Reduction to alcohols (left, center)



17

Carboxylic Acids and Their Derivatives

Nucleophilic Addition–Elimination at the Acyl Carbon

A portion of nylon 6,6, a polyamide.

Polyesters, nylon, and many biological molecules share a common aspect of bond formation during their synthesis. This process is called acyl substitution, and it involves creation of a bond by nucleophilic addition and elimination at a carbonyl group. Acyl substitution reactions occur every moment of every day in our bodies as we biosynthesize proteins, fats, precursors to steroids, and other molecules and as we degrade food molecules to provide energy and biosynthetic raw materials. Acyl substitution reactions are used virtually nonstop in industry as well. Approximately 3 billion pounds of nylon and 4 billion pounds of polyester fibers are made by acyl substitution reactions every year. The molecular graphic above is a portion of a nylon 6,6 polymer.

The functional groups of acyl substitution reactions all relate to carboxylic acids. They include acyl chlorides, anhydrides, esters, amides, thioesters, carboxylic acids themselves, and others that we shall study in this chapter. In Special Topic C we shall see how acyl substitution reactions are used to synthesize polymers such as nylon and Mylar. In Special Topic E we shall consider the biosynthesis of fatty acids and other biological molecules by acyl substitution reactions. Although many functional groups participate in acyl substitution reactions, their reactions are all readily understandable because of the common mechanistic theme that unites them: nucleophilic addition–elimination at an acyl carbon.

Openmirrors.com

17.1 Introduction

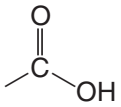
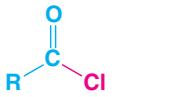
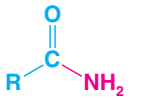
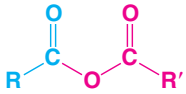
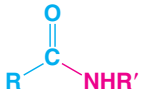
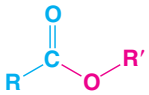
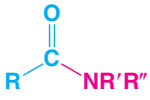
The carboxyl group,  (abbreviated —CO_2H or —COOH), is one of the most widely occurring functional groups in chemistry and biochemistry. Not only are carboxylic acids themselves important, but the carboxyl group is the parent group of a large family of related compounds called **acyl compounds** or **carboxylic acid derivatives**, shown in Table 17.1.

TABLE 17.1 Carboxylic Acid Derivatives

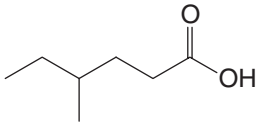
Structure	Name	Structure	Name
	Acyl (or acid) chloride		Amide
	Acid anhydride		
	Ester		
	Nitrile		

17.2 Nomenclature and Physical Properties

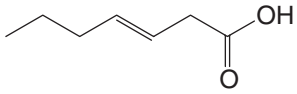
17.2A Carboxylic Acids

- Systematic or substitutive names for carboxylic acids are obtained by dropping the final *-e* of the name of the alkane corresponding to the longest chain in the acid and by adding *-oic acid*. The carboxyl carbon atom is assigned number 1.

The following examples show how this is done:



4-Methylhexanoic acid

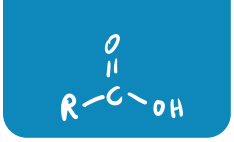


(*E*)-3-Heptenoic acid [or (*E*)-hept-3-enoic acid]

Valerian is a source of valeric acid.

Many carboxylic acids have common names that are derived from Latin or Greek words that indicate one of their natural sources. Methanoic acid is called formic acid (*formica*, Latin: ant). Ethanoic acid is called acetic acid (*acetum*, Latin: vinegar). Butanoic acid is one compound responsible for the odor of rancid butter, so its common name is butyric acid (*butyrum*, Latin: butter). Pentanoic acid, as a result of its occurrence in valerian, a perennial herb, is named valeric acid. Hexanoic acid is one compound associated with the odor of goats, hence its common name, caproic acid (*caper*, Latin: goat). Octadecanoic acid takes its common name, stearic acid, from the Greek word *stear*, for tallow.

Most of these common names have been used for a long time and some are likely to remain in common usage, so it is helpful to be familiar with them. In this text we shall refer to methanoic acid and ethanoic acid as formic acid and acetic acid, respectively. However, in almost all other instances we shall use IUPAC systematic or substitutive names.



Carboxylic acids are polar substances. Their molecules can form strong hydrogen bonds with each other and with water. As a result, carboxylic acids generally have high boiling points, and low-molecular-weight carboxylic acids show appreciable solubility in water. As the length of the carbon chain increases, water solubility declines.

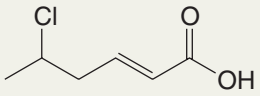
17.2B Carboxylate Salts

Salts of carboxylic acids are named as *-ates*; in both common and systematic names, *-ate* replaces *-ic acid*. The name of the cation precedes that of the carboxylate anion. Thus, CH_3CO_2Na is sodium acetate or sodium ethanoate.

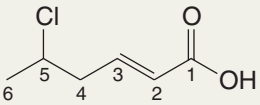
Sodium and potassium salts of most carboxylic acids are readily soluble in water. This is true even of the long-chain carboxylic acids. Sodium or potassium salts of long-chain carboxylic acids are the major ingredients of soap (see Section 23.2C).

Solved Problem 17.1

Give an IUPAC systematic name for the following compound.



STRATEGY AND ANSWER First we number the chain beginning with the carbon of the carboxylic acid group.

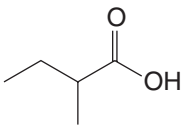


This chain contains six carbons with one double bond, so the base name is **hexenoic acid**. Then we give the position of the double bond and its stereochemistry, and the position and name of the substituent. The name, therefore, is (*E*)-5-chloro-2-hexenoic acid.

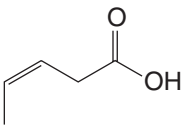
Review Problem 17.1

Give an IUPAC systematic name for each of the following:

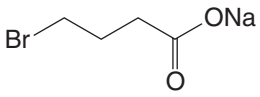
(a)



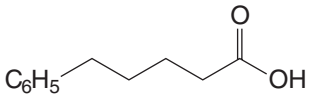
(b)



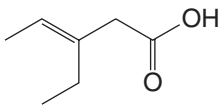
(c)



(d)



(e)



Review Problem 17.2

Experiments show that the molecular weight of acetic acid in the vapor state (just above its boiling point) is approximately 120. Explain the discrepancy between this experimental value and the true value of approximately 60.

17.2C Acidity of Carboxylic Acids

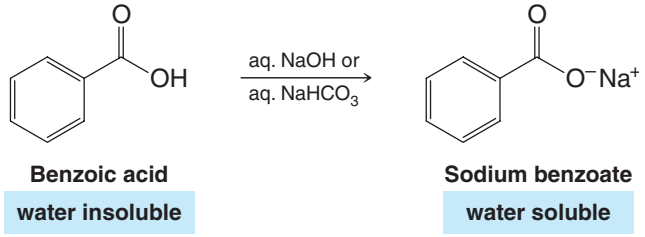
Most unsubstituted carboxylic acids have K_a values in the range of 10^{-4}–10^{-5} (pK_a = 4–5). The pK_a of water is about 16, and the apparent pK_a of H_2CO_3 is about 7. These relative acidities mean that carboxylic acids react readily with aqueous solutions of sodium hydroxide and sodium bicarbonate to form soluble sodium salts. We can use solubility tests, therefore, to distinguish water-insoluble carboxylic acids from water-insoluble phenols (Chapter 21) and alcohols.

Helpful Hint

Solubility tests such as these are rapid and useful ways to classify unknown compounds.

Openmirrors.com

- Water-insoluble carboxylic acids dissolve in either aqueous sodium hydroxide or aqueous sodium bicarbonate.

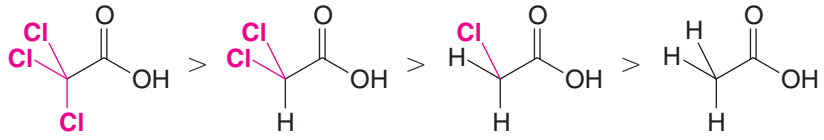


Benzoic acid — **water insoluble**

Sodium benzoate — **water soluble**

- Water-insoluble phenols (Section 21.5) dissolve in aqueous sodium hydroxide but (except for some nitrophenols) do not dissolve in aqueous sodium bicarbonate.
- Water-insoluble alcohols do not dissolve in either aqueous sodium hydroxide or sodium bicarbonate.

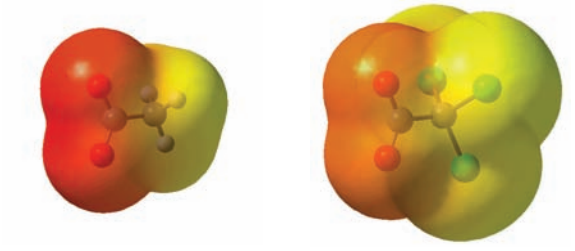
Carboxylic acids having electron-withdrawing groups are stronger than unsubstituted acids. The chloroacetic acids, for example, show the following order of acidities:



pK_a 0.70 1.48 2.86 4.76

As we saw in Section 3.11, this acid-strengthening effect of electron-withdrawing groups arises from a combination of inductive effects and entropy effects. We can visualize inductive charge delocalization when we compare the electrostatic potential maps for carboxylate anions of acetic acid and trichloroacetetic acid in Fig. 17.1. The maps show more negative charge localized near the acetate carboxyl group than the trichloroacetate carboxyl group. Delocalization of the negative charge in trichloroacetate by the electron-withdrawing effect of its three chlorine atoms contributes to its being a stronger acid than acetic acid.

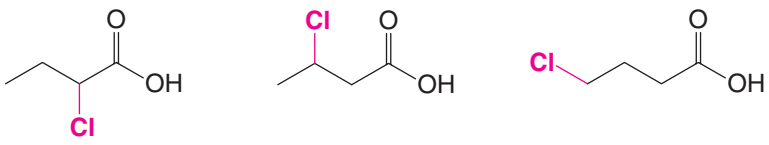
- In general, the more delocalization of charge in the conjugate base, the more stable is the anion, and the stronger the acid.



(*a*) (*b*)

Figure 17.1 Electrostatic potential maps for the carboxylate anions of *(a)* acetic acid and *(b)* trichloroacetic acid. There is greater delocalization of negative charge in trichloroacetate than acetate due to the inductive electron-withdrawing effect of the three chlorine atoms in trichloroacetate.

Since inductive effects are not transmitted very effectively through covalent bonds, the acid-strengthening effect decreases as the distance between the electron-withdrawing group and the carboxyl group increases. Of the chlorobutanoic acids that follow, the strongest acid is 2-chlorobutanoic acid:



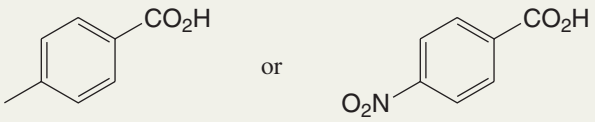
2-Chlorobutanoic acid (pK_a = 2.85)

3-Chlorobutanoic acid (pK_a = 4.05)

4-Chlorobutanoic acid (pK_a = 4.50)

Solved Problem 17.2

Which carboxylic acid would you expect to be stronger, **A** or **B**?



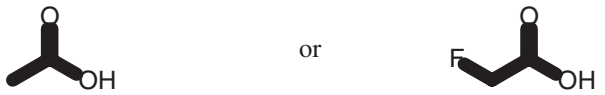
A **B**

STRATEGY AND ANSWER The electron-withdrawing effect of the nitro group would help stabilize the conjugate base of **B**, whereas the electron-donating effect of the methyl group in **A** would destabilize its conjugate base. Therefore, **B** is expected to be the stronger acid.

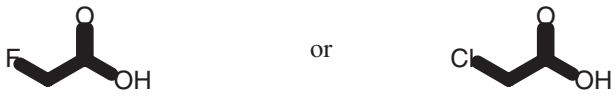
Review Problem 17.3

Which acid of each pair shown here would you expect to be stronger?

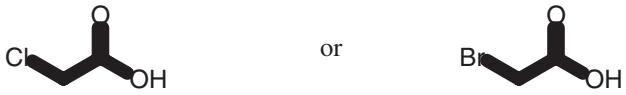
(a)



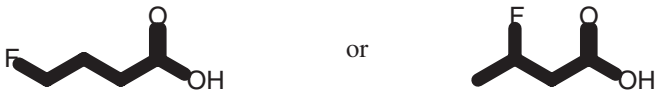
(b)



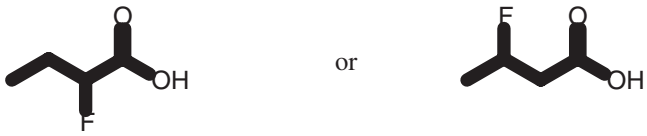
(c)



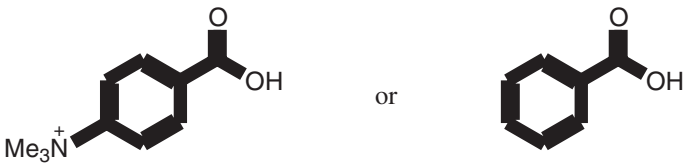
(d)



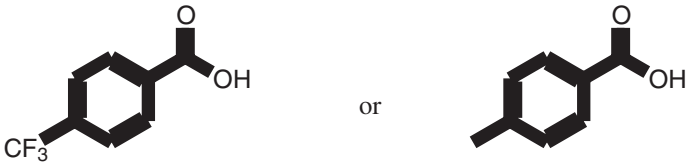
(e)



(f)



(g)



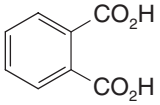
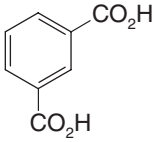
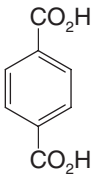
17.2D Dicarboxylic Acids

Dicarboxylic acids are named as **alkanedioic acids** in the IUPAC systematic or substitutive system. Most simple dicarboxylic acids have common names (Table 17.2).

Openmirrors.com

TABLE 17.2 Dicarboxylic Acids

Succinic and fumaric acids are key metabolites in the citric acid pathway. Adipic acid is used in the synthesis of nylon. The isomers of phthalic acid are used in making polyesters. See Special Topic C for further information on polymers.

Structure	Common Name	mp (°C)	pK_a (at 25°C)	
			pK_{a1}	pK_{a2}
$HO_2C—CO_2H$	Oxalic acid	189 dec	1.2	4.2
$HO_2CCH_2CO_2H$	Malonic acid	136	2.9	5.7
$HO_2C(CH_2)_2CO_2H$	Succinic acid	187	4.2	5.6
$HO_2C(CH_2)_3CO_2H$	Glutaric acid	98	4.3	5.4
$HO_2C(CH_2)_4CO_2H$	Adipic acid	153	4.4	5.6
cis-$HO_2C—CH{=}CH—CO_2H$	Maleic acid	131	1.9	6.1
trans-$HO_2C—CH{=}CH—CO_2H$	Fumaric acid	287	3.0	4.4
	Phthalic acid	206–208 dec	2.9	5.4
	Isophthalic acid	345–348	3.5	4.6
	Terephthalic acid	Sublimes	3.5	4.8

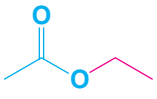
Solved Problem 17.3

Suggest explanations for the following. (**a**) The pK_{a1} for all of the dicarboxylic acids in Table 17.2 is smaller than the pK_a for a monocarboxylic acid with the same number of carbon atoms. (**b**) The difference between pK_{a1} and pK_{a2} for dicarboxylic acids of the type $HO_2C(CH_2)_nCO_2H$ decreases as n increases.

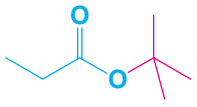
STRATEGY AND ANSWER (**a**) The carboxyl group is electron-withdrawing; thus, in a dicarboxylic acid such as those in Table 17.2, one carboxylic acid group increases the acidity of the other. (**b**) As the distance between the carboxyl groups increases, the acid-strengthening, inductive effect decreases.

17.2E Esters

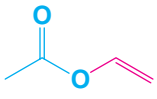
The names of esters are derived from the names of the alcohol (with the ending **-yl**) and the acid (with the ending **-ate** or **-oate**). The portion of the name derived from the alcohol comes first:



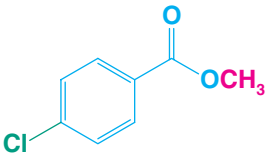
Ethyl acetate or **ethyl ethanoate**



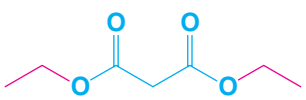
***tert*-Butyl propanoate**



Vinyl acetate or **ethenyl ethanoate**



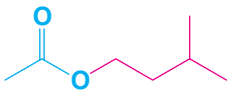
Methyl *p*-chlorobenzoate



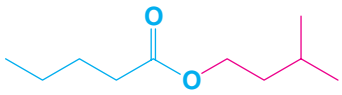
Diethyl malonate

Esters are polar compounds, but, lacking a hydrogen attached to oxygen, their molecules cannot form strong hydrogen bonds to each other. As a result, esters have boiling points that are lower than those of acids and alcohols of comparable molecular weight. The boiling points of esters are about the same as those of comparable aldehydes and ketones.

Unlike the low-molecular-weight acids, esters usually have pleasant odors, some resembling those of fruits, and these are used in the manufacture of synthetic flavors:



Isopentyl acetate
(used in synthetic banana flavor)



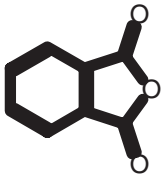
Isopentyl pentanoate
(used in synthetic apple flavor)

17.2F Carboxylic Anhydrides

Most anhydrides are named by dropping the word **acid** from the name of the carboxylic acid and then adding the word **anhydride:**

Acetic anhydride
(ethanoic anhydride)
mp –73°C

Succinic anhydride
mp 121°C

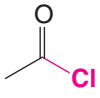


Phthalic anhydride
mp 131°C

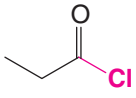
Maleic anhydride
mp 53°C

17.2G Acyl Chlorides

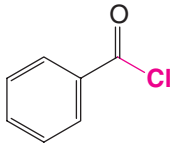
Acyl chlorides are also called **acid chlorides.** They are named by dropping **-ic acid** from the name of the acid and then adding **-yl chloride.** Examples are



Acetyl chloride
(ethanoyl chloride)
mp −112°C; bp 51°C



Propanoyl chloride
mp −94°C; bp 80°C

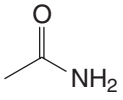


Benzoyl chloride
mp −1°C; bp 197°C

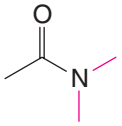
Acyl chlorides and carboxylic anhydrides have boiling points in the same range as esters of comparable molecular weight.

17.2H Amides

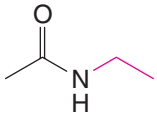
Amides that have no substituent on nitrogen are named by dropping **-ic acid** from the common name of the acid (or *-oic acid* from the substitutive name) and then adding **-amide.** Alkyl groups on the nitrogen atom of amides are named as substituents, and the named substituent is prefaced by *N*- or *N,N*-. Examples are



Acetamide
(ethanamide)
mp 82°C; bp 221°C

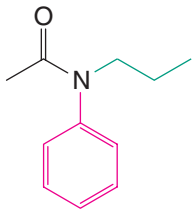


***N,N*-Dimethylacetamide**
mp −20°C; bp 166°C

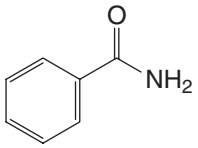


***N*-Ethylacetamide**
bp 205°C

Openmirrors.com



***N*-Phenyl-*N*-propylacetamide**
mp 49°C; bp 266°C at 712 torr



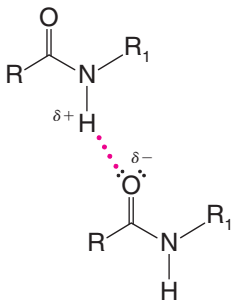
Benzamide
mp 130°C; bp 290°C

- Amides with nitrogen atoms bearing one or two hydrogen atoms are able to form strong hydrogen bonds to each other.

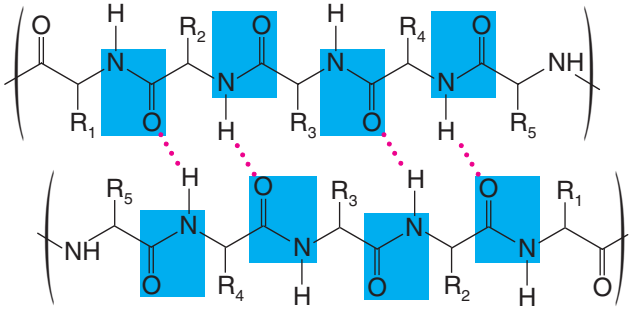
Such amides have high melting points and boiling points. On the other hand, molecules of *N,N*-disubstituted amides cannot form strong hydrogen bonds to each other, and they have lower melting points and boiling points. The melting and boiling data given above illustrate this trend.

- Hydrogen bonding between amide groups plays a key role in the way proteins and peptides fold to achieve their overall shape (Chapter 24).

Proteins and peptides (short proteins) are polymers of amino acids joined by amide groups. One feature common to the structure of many proteins is the β sheet, shown below:



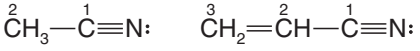
Hydrogen bonding (red dots) between amide molecules



Hydrogen bonding between amide groups of peptide chains. This interaction between chains (called a β sheet) is important to the structure of many proteins.

17.2I Nitriles

Carboxylic acids can be converted to nitriles and vice versa. In IUPAC substitutive nomenclature, acyclic nitriles are named by adding the suffix *-nitrile* to the name of the corresponding hydrocarbon. The carbon atom of the —C≡N group is assigned number 1. Additional examples of nitriles were presented in Section 2.11 with other functional groups of organic molecules. The name acetonitrile is an acceptable common name for CH_3CN, and acrylonitrile is an acceptable common name for $CH_2{=}CHCN$:



Ethanenitrile (acetonitrile)

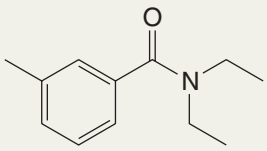
Propenenitrile (acrylonitrile)

Solved Problem 17.4

N,N-Diethyl-3-methylbenzamide (also called *N,N*-diethyl-*m*-toluamide, or DEET) is used in many insect repellants. Write its structure.

(see next page for the answer)

ANSWER



DEET

Review Problem 17.4

Write structural formulas for the following:

(a) Methyl propanoate
(b) Ethyl *p*-nitrobenzoate
(c) Dimethyl malonate
(d) *N,N*-Dimethylbenzamide
(e) Pentanenitrile
(f) Dimethyl phthalate
(g) Dipropyl maleate
(h) *N,N*-Dimethylformamide
(i) 2-Bromopropanoyl bromide
(j) Diethyl succinate

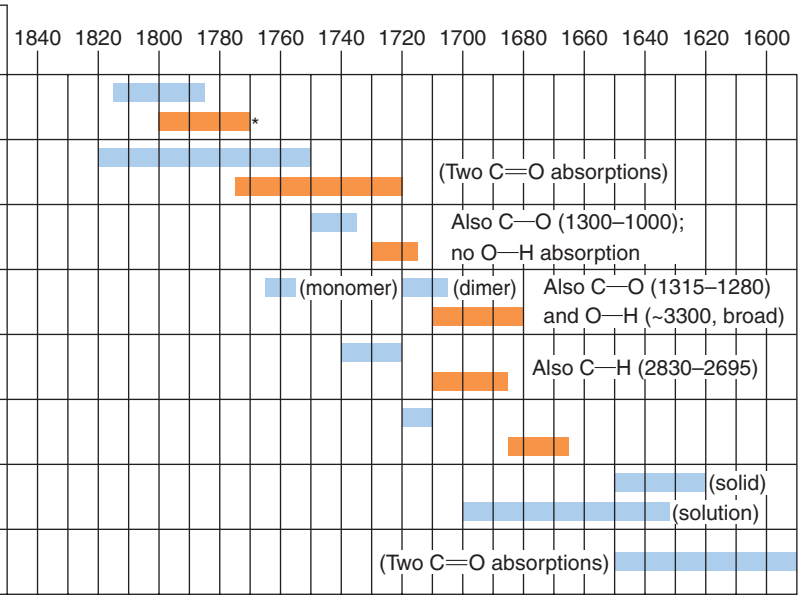
17.2J Spectroscopic Properties of Acyl Compounds

Helpful Hint
Infrared spectroscopy is useful for classifying acyl compounds.

IR Spectra Infrared spectroscopy is of considerable importance in identifying carboxylic acids and their derivatives. The C═O stretching band is one of the most prominent in their IR spectra since it is always a strong band. Figure 17.2 gives the location of this band for most acyl compounds.

- The C═O stretching band occurs at different frequencies for acids, esters, and amides, and its precise location is often helpful in structure determination.
- Conjugation and electron-donating groups bonded to the carbonyl shift the location of the C═O absorption to lower frequencies.

Functional Group	Approximate Frequency Range (cm^{-1})
Acid chloride	1815–1785 1800–1770 (conj.)
Acid anhydride	1820–1750 1775–1720 (conj.)
Ester/lactone	1750–1735 1730–1715 (conj.)
Carboxylic acid	~1760 or 1720–1705 1710–1680 (conj.)
Aldehyde	1740–1720 1710–1685 (conj.)
Ketone	1720–1710 1685–1665 (conj.)
Amide/lactam	1700–1620
Carboxylate salt	1650–1550



*Orange bars represent absorption ranges for conjugated species.

Figure 17.2 Approximate carbonyl IR absorption frequencies. (Frequency ranges based on Silverstein and Webster, reprinted with permission of John Wiley & Sons, Inc. from Silverstein, R. and Webster, F. X., *Spectrometric Identification of Organic Compounds, Sixth Edition*. Copyright 1998.)

Openmirrors.com

- Electron-withdrawing groups bonded to the carbonyl shift the C=O absorption to higher frequencies.
- The hydroxyl groups of carboxylic acids also give rise to a broad peak in the 2500–3100-cm^{-1} region arising from O—H stretching vibrations.
- The N—H stretching vibrations of amides absorb between 3140 and 3500 cm^{-1}.

Presence or absence of an O—H or N—H absorption can be an important clue as to which carbonyl functional group is present in an unknown compound.

Figure 17.3 shows an annotated spectrum of propanoic acid. Nitriles show an intense and characteristic infrared absorption band near 2250 cm^{-1} that arises from stretching of the carbon–nitrogen triple bond.

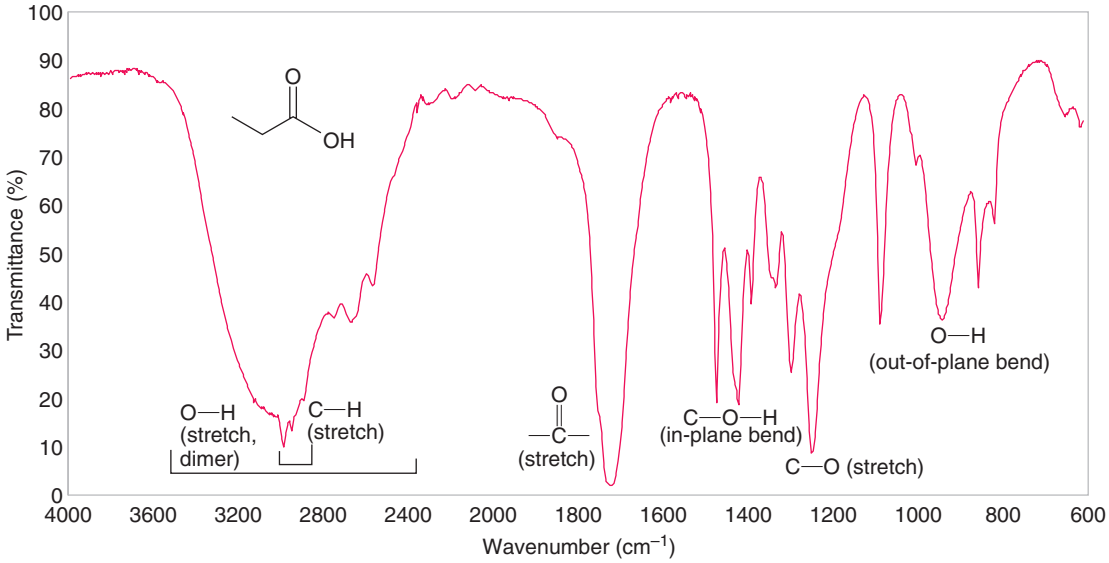


Figure 17.3 The infrared spectrum of propanoic acid.

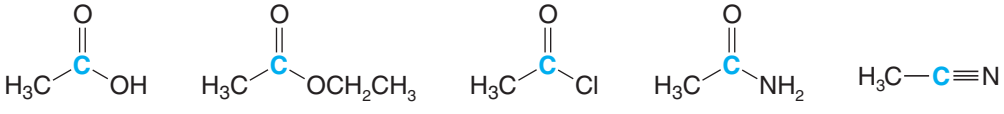
^{1}H NMR Spectra

- The acidic protons of carboxylic acids are highly deshielded and absorb far downfield in the δ 10–12 region.
- The protons of the α carbon of carboxylic acids absorb in the δ 2.0–2.5 region.

Figure 17.4 gives an annotated ^{1}H NMR spectrum of an ester, methyl propanoate; it shows the normal splitting pattern (quartet and triplet) of an ethyl group, and, as we would expect, it shows an unsplit methyl group.

^{13}C NMR Spectra

- The carbonyl carbon of carboxylic acids and their derivatives occurs downfield in the δ 160–180 region (see the following examples), but not as far downfield as for aldehydes and ketones (δ 180–220).
- The nitrile carbon is not shifted so far downfield and absorbs in the δ 115–120 region.



^{13}C NMR chemical shifts for the carbonyl or nitrile carbon atom

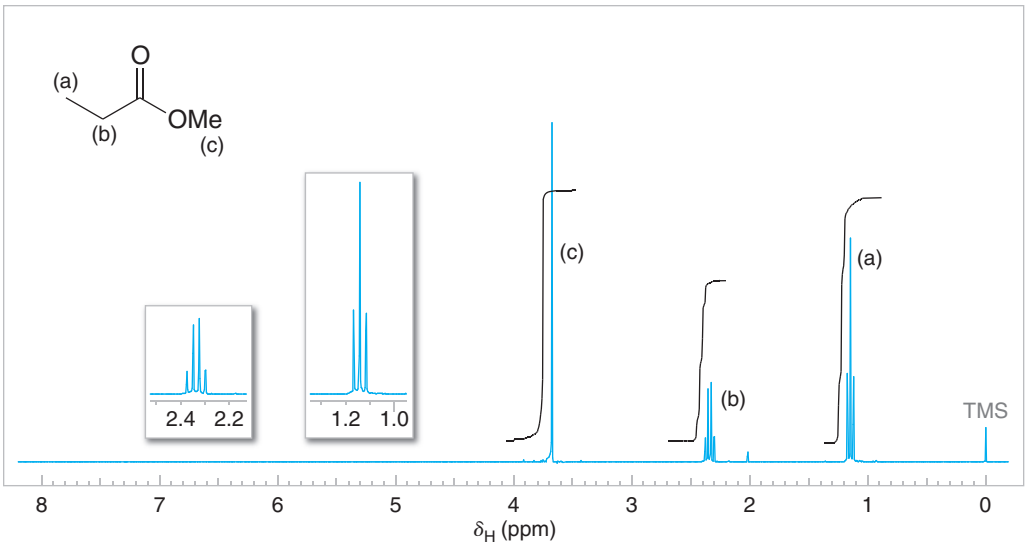
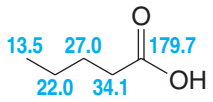


Figure 17.4 The 300-MHz ^{1}H NMR spectrum of methyl propanoate. Expansions of the signals are shown in the offset plots.

The carbon atoms of the alkyl groups of carboxylic acids and their derivatives have ^{13}C chemical shifts much further upfield. The chemical shifts for each carbon of pentanoic acid are as follows:

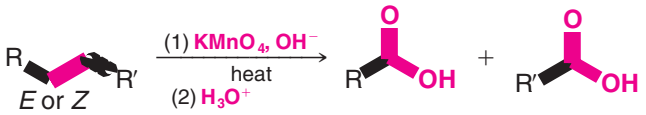


^{13}C NMR chemical shifts (δ)

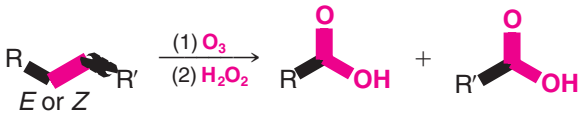
17.3 *Preparation of Carboxylic Acids*

Most of the methods for the preparation of carboxylic acids have been presented previously:

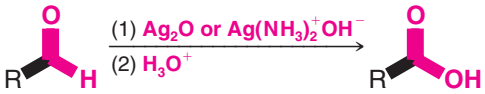
1. **By oxidation of alkenes.** We learned in Section 8.17A that alkenes can be oxidized to carboxylic acids with hot alkaline $KMnO_4$:



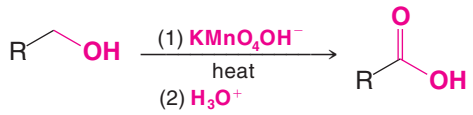
Alternatively, ozonides (Section 8.17B) can be subjected to an oxidative workup that yields carboxylic acids:

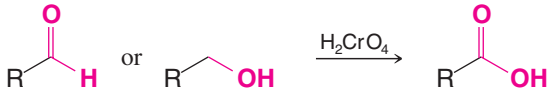


2. **By oxidation of aldehydes and primary alcohols.** Aldehydes can be oxidized to carboxylic acids with mild oxidizing agents such as $Ag(NH_3)_2^+OH^-$ (Section 16.12B). Primary alcohols can be oxidized with $KMnO_4$. Aldehydes and primary alcohols are oxidized to carboxylic acids with chromic acid (H_2CrO_4) in aqueous acetone (the Jones oxidation; Section 12.4C).

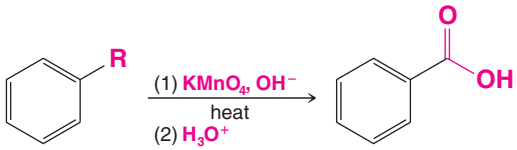


Openmirrors.com

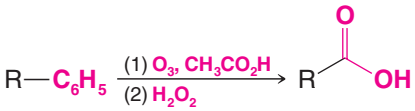




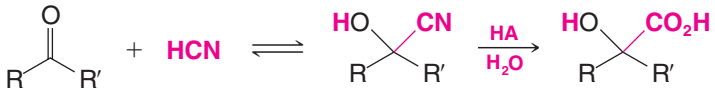
3. **By oxidation of alkylbenzenes.** Primary and secondary alkyl groups (but not 3° groups) directly attached to a benzene ring are oxidized by $KMnO_4$ to a $—CO_2H$ group (Section 15.13C):



4. **By oxidation of the benzene ring.** The benzene ring of an alkylbenzene can be converted to a carboxyl group by ozonolysis, followed by treatment with hydrogen peroxide (Section 15.13D):

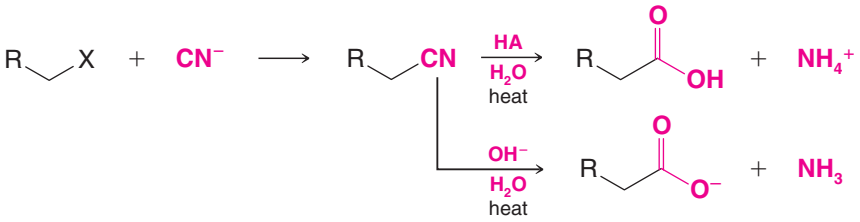


5. **By hydrolysis of cyanohydrins and other nitriles.** We saw, in Section 16.9, that aldehydes and ketones can be converted to **cyanohydrins** and that these can be hydrolyzed to α-hydroxy acids. In the hydrolysis the —CN group is converted to a $—CO_2H$ group. The mechanism of nitrile hydrolysis is discussed in Section 17.8H:

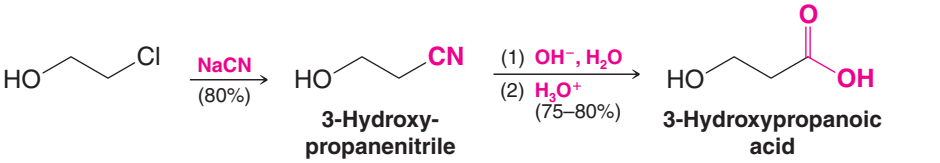


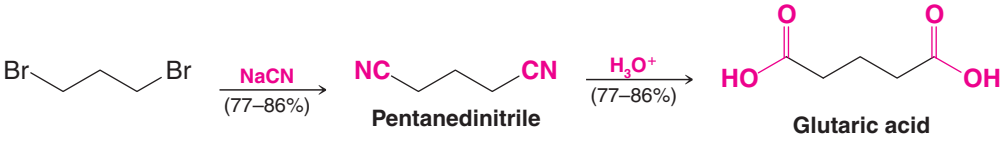
Nitriles can also be prepared by nucleophilic substitution reactions of alkyl halides with sodium cyanide. Hydrolysis of the nitrile yields a carboxylic acid *with a chain one carbon atom longer* than the original alkyl halide:

General Reaction



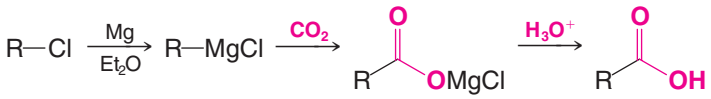
Specific Examples



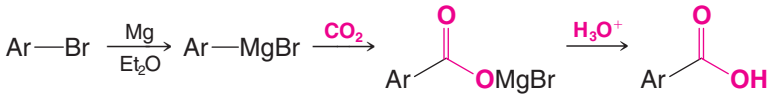


This synthetic method is generally limited to the use of *primary alkyl halides*. The cyanide ion is a relatively strong base, and the use of a secondary or tertiary alkyl halide leads primarily to an alkene (through E2 elimination) rather than to a nitrile (through S_N2 substitution). Aryl halides (except for those with ortho and para nitro groups) do not react with sodium cyanide.

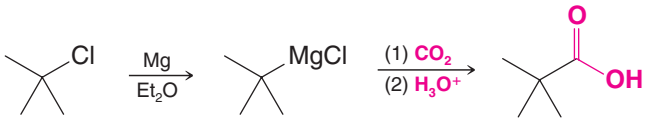
6. By carbonation of Grignard reagents. Grignard reagents react with carbon dioxide to yield magnesium carboxylates. Acidification produces carboxylic acids:



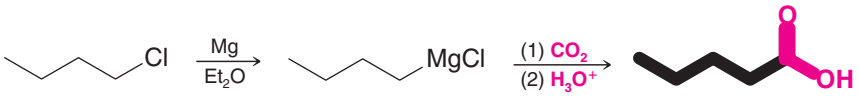
or



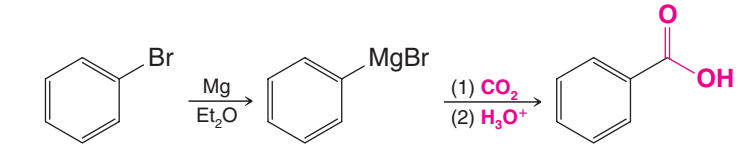
This synthesis of carboxylic acids is applicable to primary, secondary, tertiary, allyl, benzyl, and aryl halides, provided they have no groups incompatible with a Grignard reaction (see Section 12.8B):



***tert*-Butyl chloride** — **2,2-Dimethylpropanoic acid (79–80% overall)**

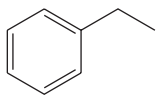
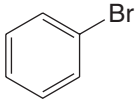
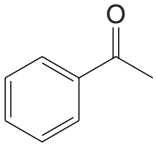
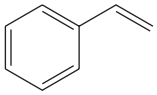


Butyl chloride — **Pentanoic acid (80% overall)**



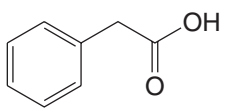
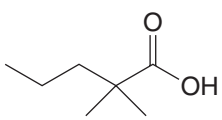
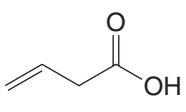
Bromobenzene — **Benzoic acid (85%)**

Show how each of the following compounds could be converted to benzoic acid: *Review Problem 17.5*

(a)  **(b)**  **(c)**  **(d)** 

(e) Benzyl alcohol **(f)** Benzaldehyde

Show how you would prepare each of the following carboxylic acids through a Grignard synthesis: *Review Problem 17.6*

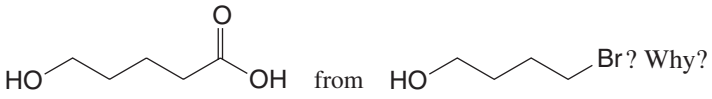
(a)  **(b)**  **(c)** 

(d) 4-Methylbenzoic acid **(e)** Hexanoic acid

Openmirrors.com

Review Problem 17.7

(a) Which of the carboxylic acids in Review Problem 17.6 could be prepared by a nitrile synthesis as well? **(b)** Which synthesis, Grignard or nitrile, would you choose to prepare

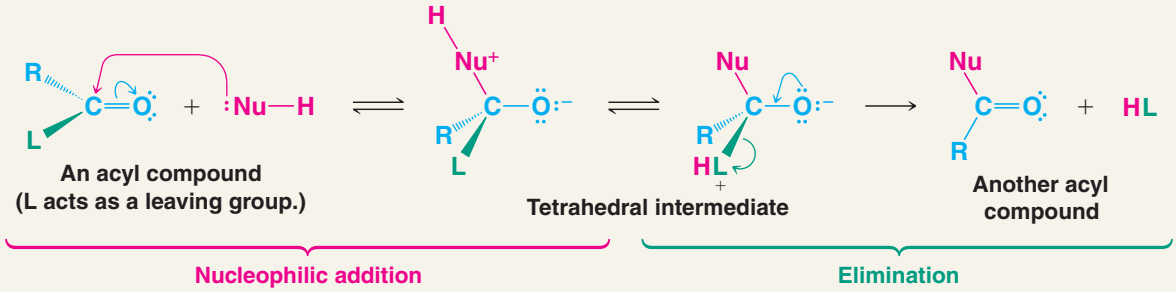


17.4 *Acyl Substitution: Nucleophilic Addition–Elimination at the Acyl Carbon*

The reactions of carboxylic acids and their derivatives are characterized by **nucleophilic addition–elimination** at their acyl (carbonyl) carbon atoms. The result is a substitution at the acyl carbon. Key to this mechanism is formation of a **tetrahedral intermediate** that returns to a carbonyl group after the elimination of a leaving group. We shall encounter many reactions of this general type, as shown in the following box.

A MECHANISM FOR THE REACTION

Acyl Substitution by Nucleophilic Addition–Elimination



Helpful Hint

If you bear in mind the general mechanism for acyl substitution, you will see the common theme among reactions in this chapter.

Many reactions like this occur in living organisms, and biochemists call them **acyl transfer reactions.** Acetyl-coenzyme A, discussed in Special Topic E, often serves as a biochemical acyl transfer agent. Acyl substitution reactions are of tremendous importance in industry as well, as described in the chapter opening essay and Special Topic C.

- The initial step in an acyl substitution reaction is nucleophilic addition at the carbonyl carbon atom. This step is facilitated by the relative steric openness of the carbonyl carbon atom and the ability of the carbonyl oxygen atom to accommodate an electron pair of the carbon–oxygen double bond.
- In the second step the tetrahedral intermediate eliminates a leaving group (**L** in the mechanism above); this **elimination** leads to regeneration of the carbon–oxygen double bond and to a substitution product.

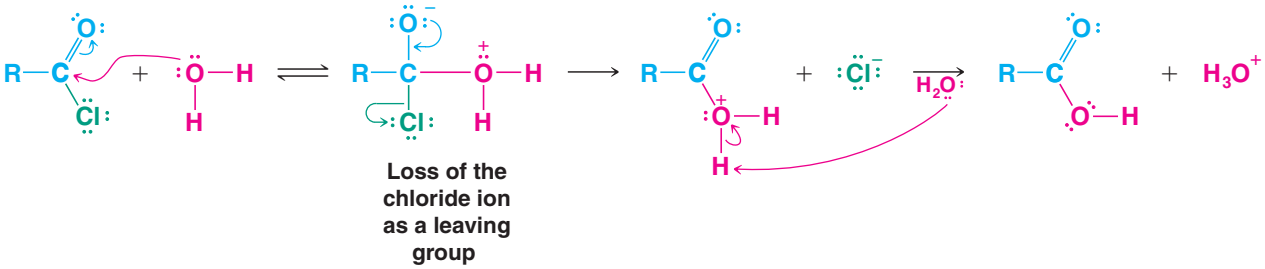
The overall process, therefore, is **acyl substitution** by a **nucleophilic addition–elimination** mechanism.

Acyl compounds react as they do because they all have good, or reasonably good, leaving groups (or they can be protonated to form good leaving groups) attached to the carbonyl carbon atom.

- Acyl substitution requires a leaving group at the carbonyl carbon.

An acyl chloride, for example, generally reacts by losing *a chloride ion*—a very weak base and thus a very good leaving group. The reaction of an acyl chloride with water is an example.

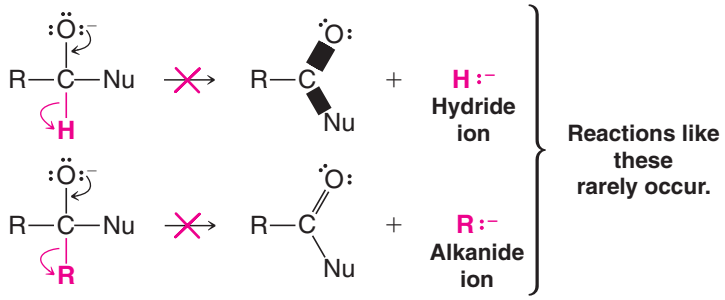
Specific Example



An acid anhydride generally reacts by losing *a carboxylate anion* or a molecule of a *carboxylic acid*—both are weak bases and good leaving groups.

As we shall see later, esters generally undergo nucleophilic addition–elimination by losing a molecule of an *alcohol* (Section 17.7B), acids react by losing a molecule of *water* (Section 17.7A), and amides react by losing a molecule of *ammonia* or of an *amine* (Section 17.8F). All of the molecules lost in these reactions are weak bases and are reasonably good leaving groups.

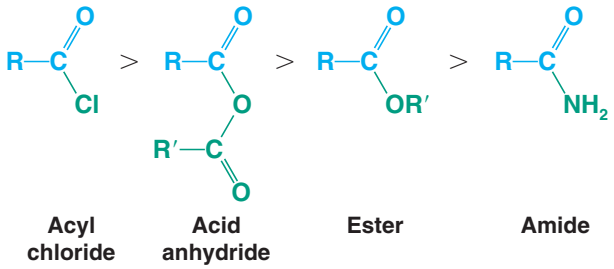
For an aldehyde or ketone to react by nucleophilic addition–elimination, the tetrahedral intermediate would need to eject a hydride ion ($H:^-$) or an alkanide ion ($R:^-$). Both are *very powerful bases*, and both are therefore *very poor leaving groups*:



[The haloform reaction (Section 18.3C) is one of the rare instances in which an alkanide anion can act as a leaving group, but then only, as we shall see, because the leaving group is a weakly basic trihalomethyl anion.]

17.4A Relative Reactivity of Acyl Compounds

Of the acid derivatives that we study in this chapter, acyl chlorides are the most reactive toward nucleophilic addition–elimination, and amides are the least reactive. In general, the overall order of reactivity is



The green groups in the structures above can be related to the green **L** group in the Mechanism for the Reaction box at the beginning of Section 17.4.

Openmirrors.com

- The general order of reactivity of acid derivatives can be explained by taking into account the basicity of the leaving groups.

When acyl chlorides react, the leaving group is a *chloride ion*. When acid anhydrides react, the leaving group is a carboxylic acid or a carboxylate ion. When esters react, the leaving group is an alcohol, and when amides react, the leaving group is an amine (or ammonia). Of all of these bases, chloride ions are the *weakest bases* and acyl chlorides are the *most reactive* acyl compounds. Amines (or ammonia) are the *strongest bases* and so amides are the *least reactive* acyl compounds.

17.4B Synthesis of Acid Derivatives

As we begin now to explore the syntheses of carboxylic acid derivatives, we shall find that in many instances one acid derivative can be synthesized through a nucleophilic addition–elimination reaction of another. The order of reactivities that we have presented gives us a clue as to which syntheses are practical and which are not. In general, ***less reactive acyl compounds can be synthesized from more reactive ones, but the reverse is usually difficult and, when possible, requires special reagents.***

- Synthesis of acid derivatives by acyl substitution requires that the reactant have a better leaving group at the acyl carbon than the product.

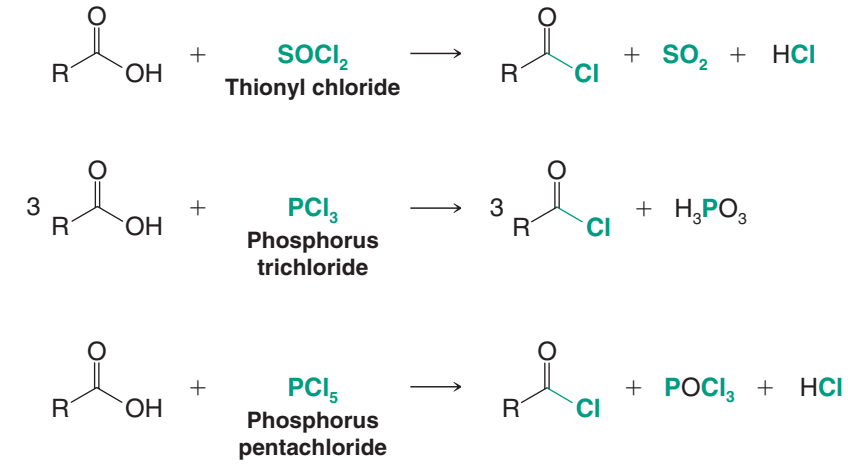
17.5 Acyl Chlorides

17.5A Synthesis of Acyl Chlorides

Since acyl chlorides are the most reactive of the acid derivatives, we must use special reagents to prepare them. We use other acid chlorides, *the acid chlorides of inorganic acids*: We use PCl_5 (an acid chloride of phosphoric acid), PCl_3 (an acid chloride of phosphorous acid), and $SOCl_2$ (an acid chloride of sulfurous acid).

All of these reagents react with carboxylic acids to give acyl chlorides in good yield:

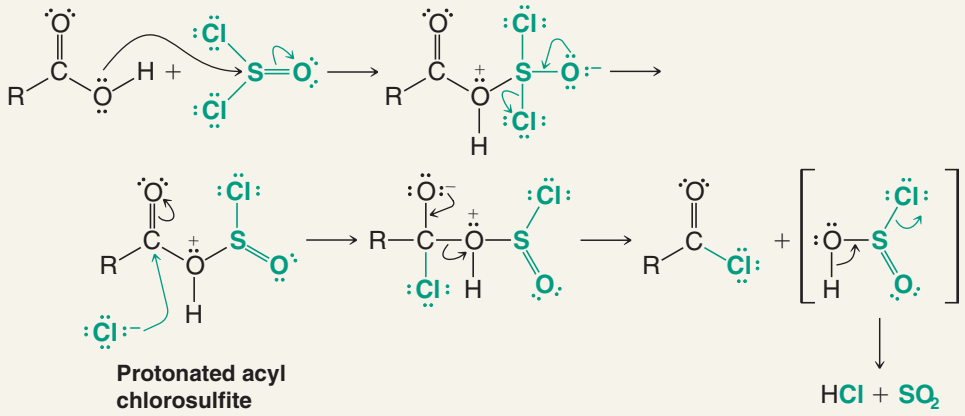
General Reactions



These reactions all involve nucleophilic addition–elimination by a chloride ion on a highly reactive intermediate: a protonated acyl chlorosulfite, a protonated acyl chlorophosphite, or a protonated acyl chlorophosphate. These intermediates contain even better acyl leaving groups than the acyl chloride product. Thionyl chloride, for example, reacts with a carboxylic acid in the following way.

A MECHANISM FOR THE REACTION

Synthesis of Acyl Chlorides Using Thionyl Chloride



17.5B Reactions of Acyl Chlorides

Because acyl chlorides are the most reactive of the acyl derivatives, they are easily converted to less reactive ones.

- Often the best synthetic route to an anhydride, an ester, or an amide is synthesis of an acyl chloride from the carboxylic acid and then conversion of the acyl chloride to the desired acyl derivative.

The scheme given in Fig. 17.5 illustrates how this can be done. We examine these reactions in detail in Sections 17.6–17.8.

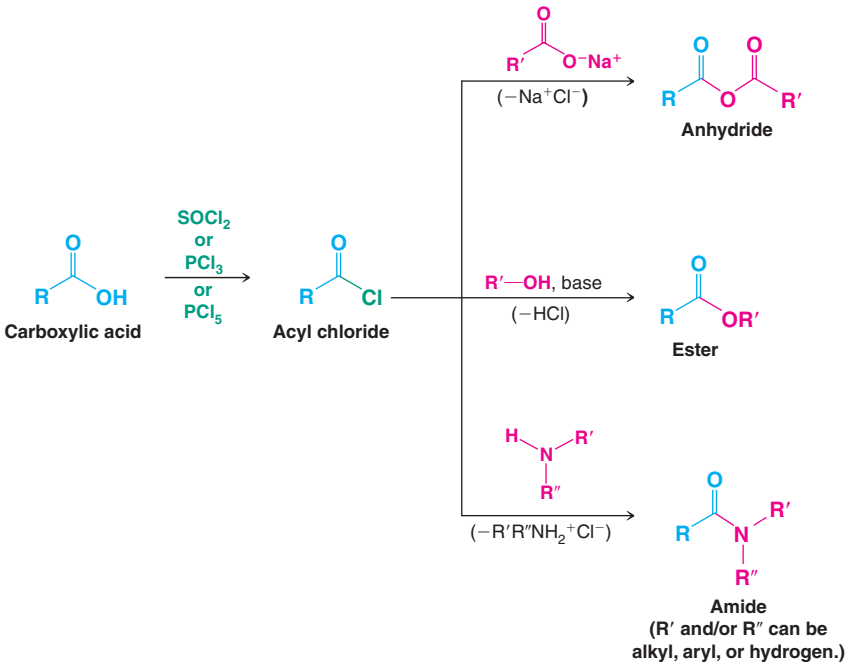
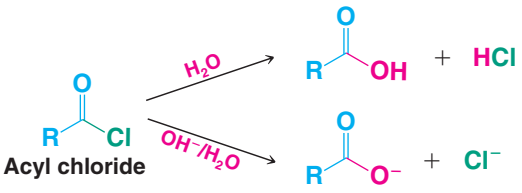


Figure 17.5 Preparation of an acyl chloride and reactions of acyl chlorides.

Openmirrors.com

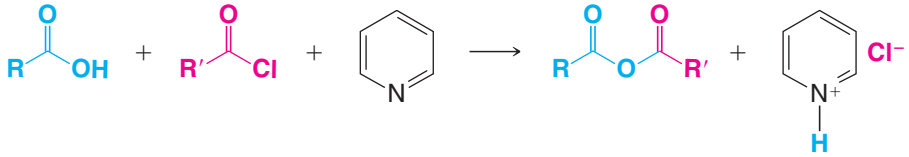
Acyl chlorides also react with water and (even more rapidly) with aqueous base, but these reactions are usually not carried out deliberately because they destroy the useful acyl chloride reactant by regenerating either the carboxylic acid or its salt:



17.6 Carboxylic Acid Anhydrides

17.6A Synthesis of Carboxylic Acid Anhydrides

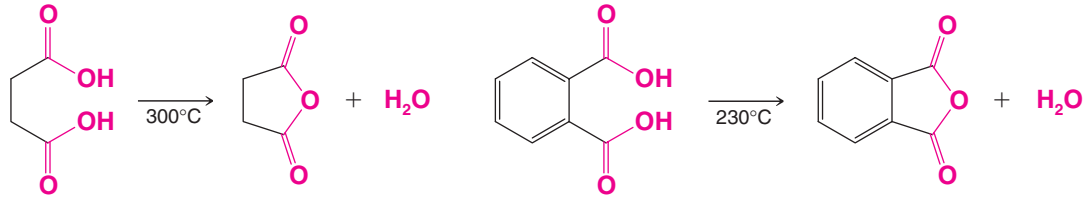
Carboxylic acids react with acyl chlorides in the presence of pyridine to give carboxylic acid anhydrides. Pyridine deprotonates the carboxylic acid, enhancing its nucleophilicity.



This method is frequently used in the laboratory for the preparation of anhydrides. The method is quite general and can be used to prepare mixed anhydrides ($R \neq R'$) or symmetric anhydrides ($R = R'$).

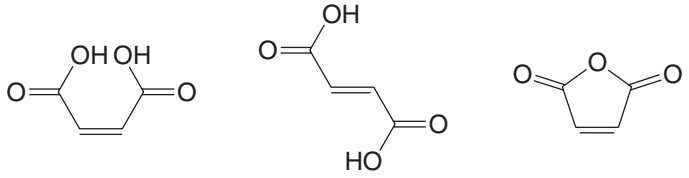
Sodium salts of carboxylic acids also react with acyl chlorides to give anhydrides:

Cyclic anhydrides can sometimes be prepared simply by heating the appropriate dicarboxylic acid. This method succeeds, however, only when anhydride formation leads to a five- or six-membered ring:



Review Problem 17.8

When maleic acid is heated to 200°C, it loses water and becomes maleic anhydride. Fumaric acid, a diastereomer of maleic acid, requires a much higher temperature before it dehydrates; when it does, it also yields maleic anhydride. Provide an explanation for these observations.



17.6B Reactions of Carboxylic Acid Anhydrides

Because carboxylic acid anhydrides are highly reactive, they can be used to prepare esters and amides (Fig. 17.6). We study these reactions in detail in Sections 17.7 and 17.8.

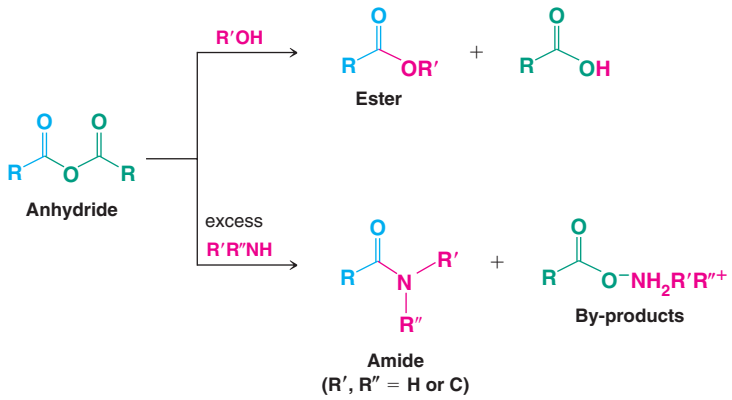
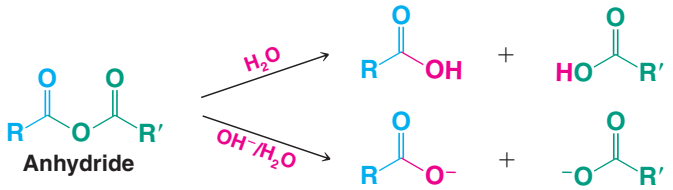


Figure 17.6 Reactions of carboxylic acid anhydrides.

Carboxylic acid anhydrides also undergo hydrolysis:

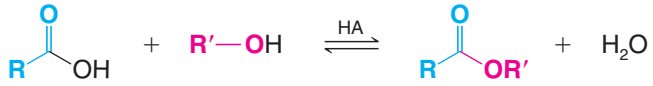


17.7 Esters

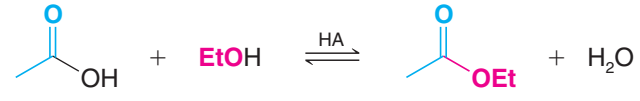
17.7A Synthesis of Esters: Esterification

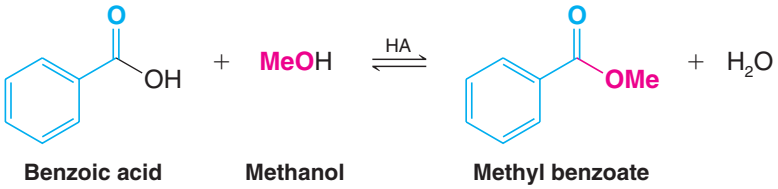
Carboxylic acids react with alcohols to form esters through a condensation reaction known as **esterification**:

General Reaction



Specific Examples





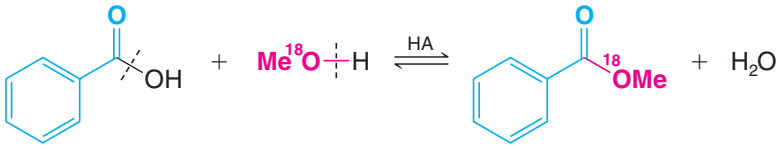
- Acid-catalyzed esterifications, such as these examples, are called Fischer esterifications.

Fischer esterifications proceed very slowly in the absence of strong acids, but they reach equilibrium within a matter of a few hours when an acid and an alcohol are refluxed with a small amount of concentrated sulfuric acid or hydrogen chloride. Since the position of

Openmirrors.com

equilibrium controls the amount of the ester formed, the use of an excess of either the carboxylic acid or the alcohol increases the yield based on the limiting reagent. Just which component we choose to use in excess will depend on its availability and cost. The yield of an esterification reaction can also be increased by removing water from the reaction mixture as it is formed.

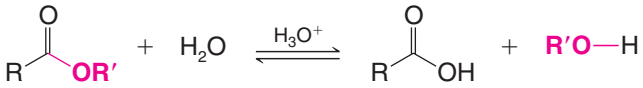
When benzoic acid reacts with methanol that has been labeled with ^{18}O, the labeled oxygen appears in the ester. This result reveals just which bonds break in the esterification:



The results of the labeling experiment and the fact that esterifications are acid catalyzed are both consistent with the mechanism that follows. This mechanism is typical of acid-catalyzed nucleophilic addition–elimination reactions at acyl carbon atoms.

If we follow the forward reactions in this mechanism, we have the mechanism for the *acid-catalyzed esterification of an acid*. If, however, we follow the reverse reactions, we have the mechanism for the *acid-catalyzed hydrolysis of an ester*:

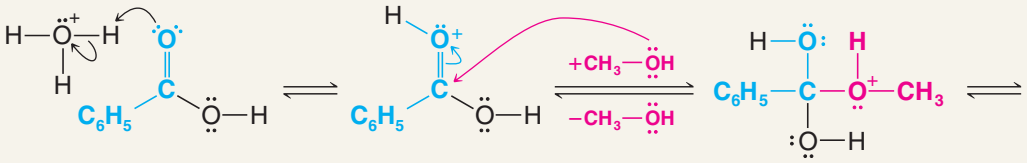
Acid-Catalyzed Ester Hydrolysis



Which result we obtain will depend on the conditions we choose. If we want to esterify an acid, we use an excess of the alcohol and, if possible, remove the water as it is formed. If we want to hydrolyze an ester, we use a large excess of water; that is, we reflux the ester with dilute aqueous HCl or dilute aqueous H_2SO_4.

A MECHANISM FOR THE REACTION

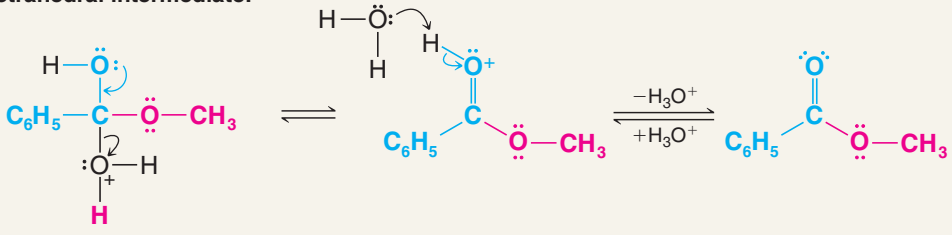
Acid-Catalyzed Esterification



The carboxylic acid accepts a proton from the strong acid catalyst.

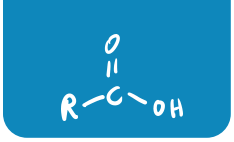
The alcohol attacks the protonated carbonyl group to give a tetrahedral intermediate.

A proton is lost at one oxygen atom and gained at another.



Loss of a molecule of water gives a protonated ester.

Transfer of a proton to a base leads to the ester.



Review Problem 17.9

Where would you expect to find the labeled oxygen if you carried out an acid-catalyzed hydrolysis of methyl benzoate in ^{18}O-labeled water? Write a detailed mechanism to support your answer.

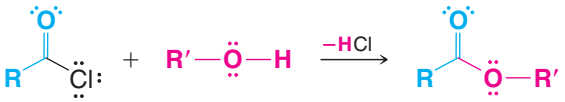
Steric factors strongly affect the rates of acid-catalyzed hydrolyses of esters. Large groups near the reaction site, whether in the alcohol component or the acid component, slow both reactions markedly. Tertiary alcohols, for example, react so slowly in acid-catalyzed esterifications that they usually undergo elimination instead. However, they can be converted to esters safely through the use of acyl chlorides and anhydrides in the ways that follow.

Esters from Acyl Chlorides

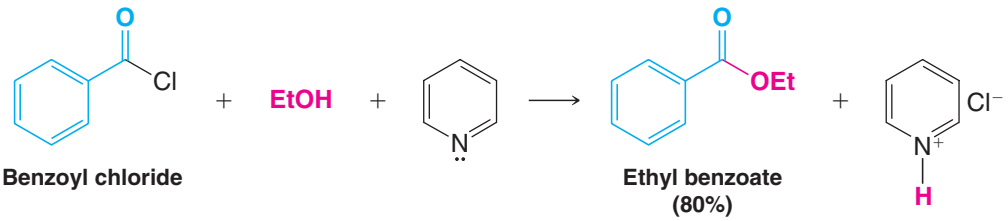
- The reaction of acyl chlorides with alcohols is one of the best ways to synthesize an ester.

The reaction of an acyl chloride with an alcohol to form an ester occurs rapidly and does not require an acid catalyst. Pyridine is often added to the reaction mixture to react with the HCl that forms. (Pyridine may also react with the acyl chloride to form an acylpyridinium ion, an intermediate that is even more reactive toward the nucleophile than the acyl chloride is.)

General Reaction



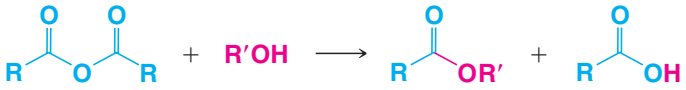
Specific Example



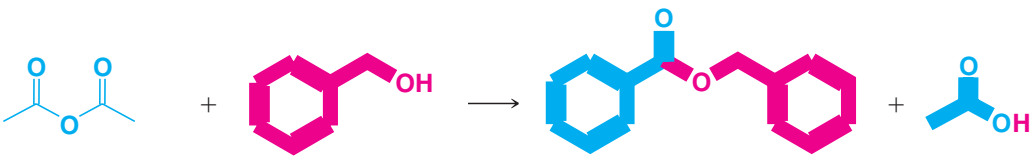
Benzoyl chloride **Ethyl benzoate (80%)**

Esters from Carboxylic Acid Anhydrides Carboxylic acid anhydrides also react with alcohols to form esters in the absence of an acid catalyst.

General Reaction



Specific Example

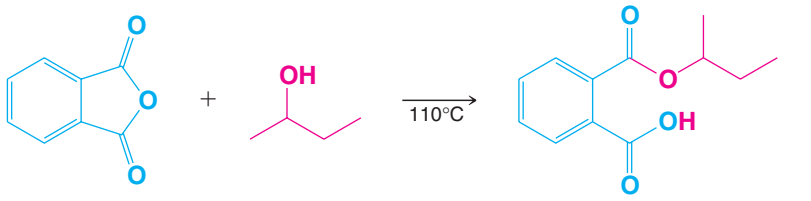


Acetic anhydride **Benzyl alcohol** **Benzyl acetate**

- Ester synthesis is often accomplished best by the reaction of an alcohol with an acyl chloride or anhydride. These reagents avoid the use of a strong acid, as is needed for acid-catalyzed esterification. A strong acid may cause side reactions depending on what other functional groups are present.

Openmirrors.com

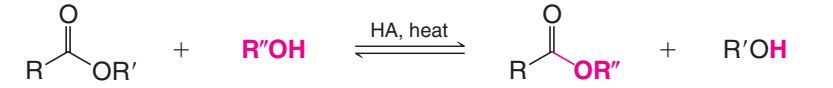
Cyclic anhydrides react with one molar equivalent of an alcohol to form compounds that are *both esters and acids*:



Phthalic anhydride + **sec-Butyl alcohol** → **sec-Butyl hydrogen phthalate (97%)**

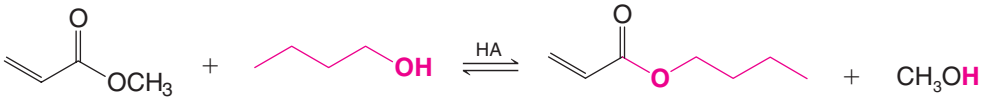
Review Problem 17.10

Esters can also be synthesized by **transesterification**:



High-boiling ester + **High-boiling alcohol** ⇌ **Higher boiling ester** + **Lower boiling alcohol**

In this procedure we shift the equilibrium to the right by allowing the low-boiling alcohol to distill from the reaction mixture. The mechanism for transesterification is similar to that for an acid-catalyzed esterification (or an acid-catalyzed ester hydrolysis). Write a detailed mechanism for the following transesterification:

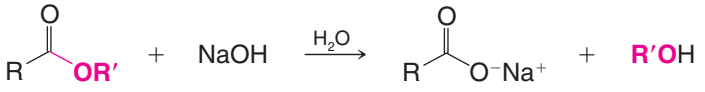


Methyl acrylate + **Butyl alcohol** ⇌ **Butyl acrylate (94%)** + **Methanol**

17.7B Base-Promoted Hydrolysis of Esters: Saponification

- Esters undergo *base-promoted hydrolysis* as well as acid hydrolysis.

Base-promoted hydrolysis is called **saponification**, from the Latin word *sapo*, soap (see Section 23.2C). Refluxing an ester with aqueous sodium hydroxide, for example, produces an alcohol and the sodium salt of the acid:



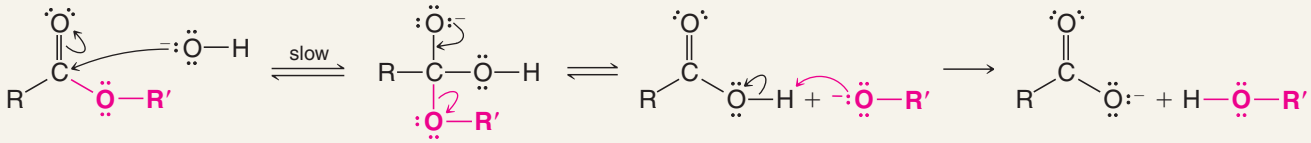
Ester + NaOH → **Sodium carboxylate** + **Alcohol**

The carboxylate ion is very unreactive toward nucleophilic substitution because it is negatively charged. Base-promoted hydrolysis of an ester, as a result, is an essentially irreversible reaction.

The mechanism for base-promoted hydrolysis of an ester also involves a nucleophilic addition–elimination at the acyl carbon.

A MECHANISM FOR THE REACTION

Base-Promoted Hydrolysis of an Ester

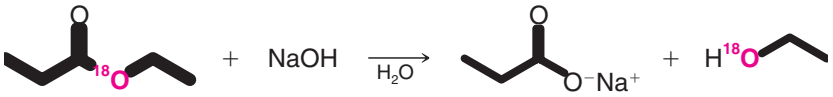


A hydroxide ion attacks the carbonyl carbon atom.

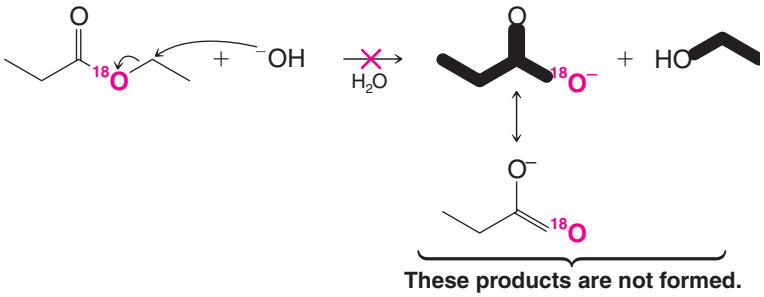
The tetrahedral intermediate expels an alkoxide ion.

Transfer of a proton leads to the products of the reaction.

Evidence for this mechanism comes from studies done with isotopically labeled esters. When ethyl propanoate labeled with ^{18}O in the ether-type oxygen of the ester (below) is subjected to hydrolysis with aqueous NaOH, all of the ^{18}O shows up in the ethanol that is produced. None of the ^{18}O appears in the propanoate ion:

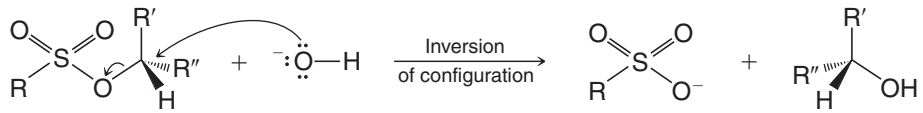


This labeling result is completely consistent with the mechanism given above (outline the steps for yourself and follow the labeled oxygen through to the products). If the hydroxide ion had attacked the alkyl carbon instead of the acyl carbon, the alcohol obtained would not have been labeled. Attack at the alkyl carbon is almost never observed. (For one exception see Review Problem 17.12.)



These products are not formed.

Although nucleophilic attack at the alkyl carbon seldom occurs with esters of carboxylic acids, it is the preferred mode of attack with esters of sulfonic acids (e.g., tosylates, mesylates, and triflates; Section 11.10).



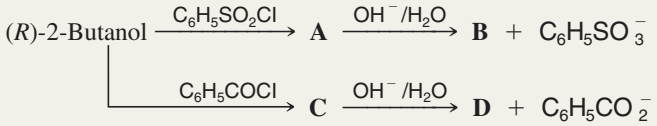
An alkyl sulfonate

This mechanism is preferred with alkyl sulfonates.

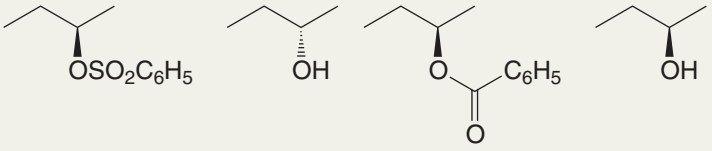
Openmirrors.com

Solved Problem 17.5

Give stereochemical formulas for **A–D**. [*Hint*: **B** and **D** are enantiomers of each other.]



STRATEGY AND ANSWER Compound **A** is a benzenesulfonate ester, which forms with retention of configuration from (*R*)-2-butanol. **B** is the S_N2 product formed by reaction with hydroxide, which occurs with **inversion** of configuration. **C** is a benzoate ester, formation of which does not affect the configuration at the chirality center. Saponification of **C** to form **D** does not affect the chirality center either, since it is an acyl substitution reaction.



A **B** **C** **D**

Review Problem 17.11

(a) Write stereochemical formulas for compounds **A–F:**

1. *cis*-3-Methylcyclopentanol + $C_6H_5SO_2Cl$ ⟶ **A** $\xrightarrow[\text{heat}]{OH^-}$ **B** + $C_6H_5SO_3^-$

2. *cis*-3-Methylcyclopentanol + $C_6H_5C(=O)Cl$ ⟶ **C** $\xrightarrow[\text{reflux}]{OH^-}$ **D** + $C_6H_5CO_2^-$

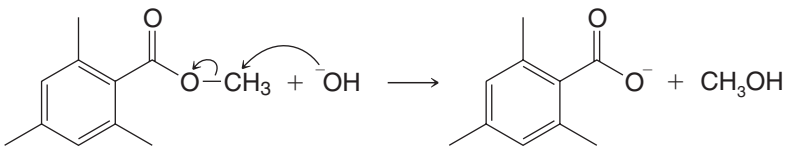
3. (*R*)-2-Bromooctane + $CH_3CO_2^-Na^+$ ⟶ **E** + NaBr $\xrightarrow[\text{(reflux)}]{OH^-,\ H_2O}$ **F**

4. (*R*)-2-Bromooctane + OH^- $\xrightarrow[\text{acetone}]{}$ **F** + Br^-

(b) Which of the last two methods, **3** or **4**, would you expect to give a higher yield of **F**? Why?

Review Problem 17.12

Base-promoted hydrolysis of methyl mesitoate occurs through an attack on the alcohol carbon instead of the acyl carbon:

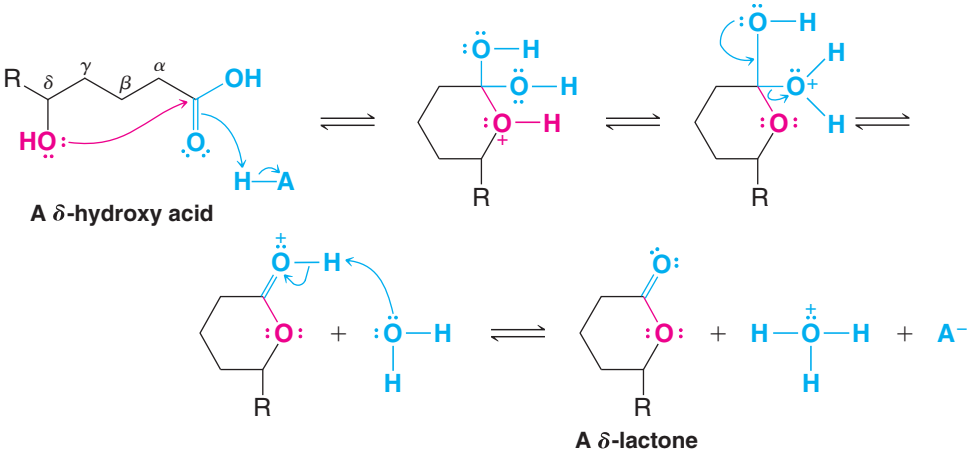


Methyl mesitoate

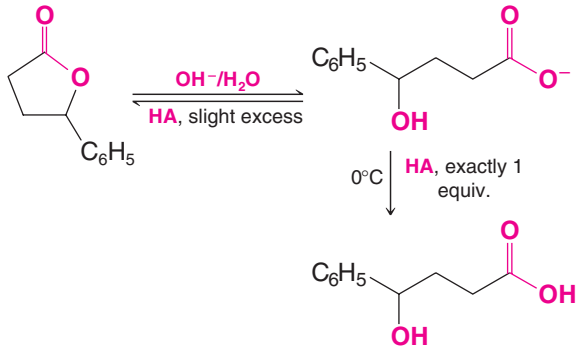
(a) Can you suggest a reason that accounts for this unusual behavior? **(b)** Suggest an experiment with labeled compounds that would confirm this mode of attack.

17.7C Lactones

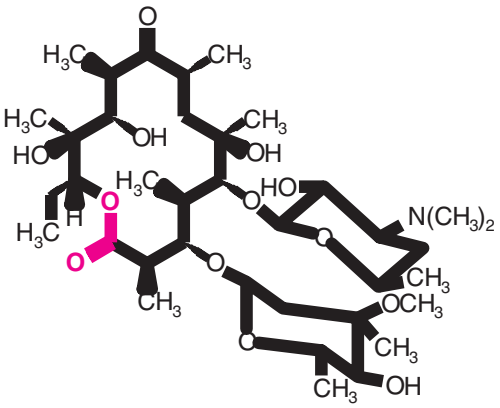
Carboxylic acids whose molecules have a hydroxyl group on a γ or δ carbon undergo an intramolecular esterification to give cyclic esters known as γ- or δ-*lactones*. The reaction is acid catalyzed:

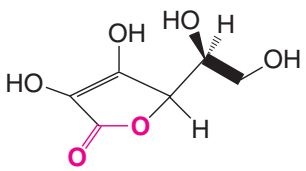


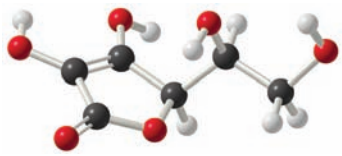
Lactones are hydrolyzed by aqueous base just as other esters are. Acidification of the sodium salt, however, may lead spontaneously back to the γ- or δ-lactone, particularly if excess acid is used:



Many lactones occur in nature. Vitamin C (below), for example, is a γ-lactone. Some antibiotics, such as erythromycin and nonactin (Section 11.16), are lactones with very large rings (called macrocyclic lactones), but most naturally occurring lactones are γ- or δ-lactones; that is, most contain five- or six-membered rings.

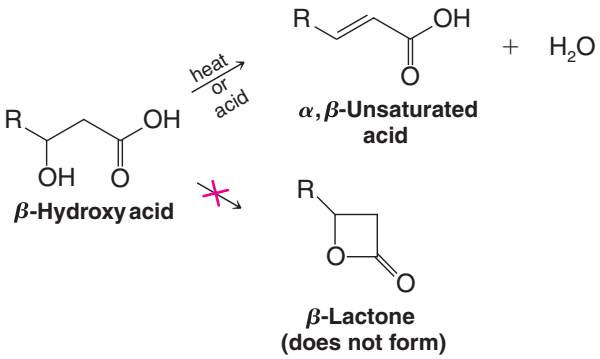

Erythromycin A


Vitamin C
(ascorbic acid)



β-Lactones (lactones with four-membered rings) have been detected as intermediates in some reactions, and several have been isolated. They are highly reactive, however. If one attempts to prepare a β-lactone from a β-hydroxy acid, β elimination usually occurs instead:

Openmirrors.com



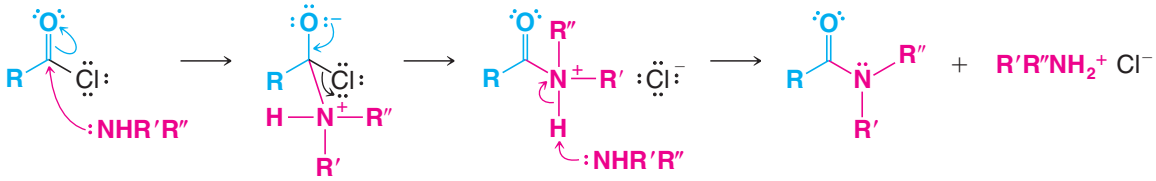
17.8 Amides

17.8A Synthesis of Amides

Amides can be prepared in a variety of ways, starting with acyl chlorides, acid anhydrides, esters, carboxylic acids, and carboxylate salts. All of these methods involve nucleophilic addition–elimination reactions by ammonia or an amine at an acyl carbon. As we might expect, acid chlorides are the most reactive and carboxylate anions are the least.

17.8B Amides from Acyl Chlorides

Primary amines, secondary amines, and ammonia all react rapidly with acid chlorides to form amides. An excess of ammonia or amine is used to neutralize the HCl that would be formed otherwise:



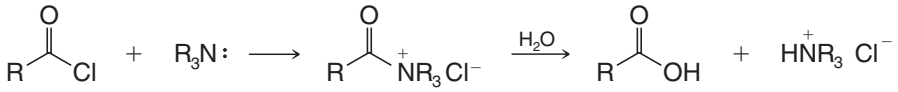
Reactant
Ammonia; R′, R″ = H
1° Amine; R′ = H, R″ = alkyl, aryl
2° Amine; R′, R″ = alkyl, aryl

Product
Unsubstituted amide; R′, R″ = H
***N*-Substituted amide; R′ = H, R″ = alkyl, aryl**
***N,N*-Disubstituted amide; R′, R″ = alkyl, aryl**

- The reaction of an amine with an acyl chloride is one of the most widely used laboratory methods for the synthesis of amides, because acyl chlorides are themselves easily prepared from carboxylic acids.

The reaction between an acyl chloride and an amine (or ammonia) usually takes place at room temperature (or below) and produces the amide in high yield.

Acyl chlorides also react with tertiary amines by a nucleophilic addition–elimination reaction. The acylammonium ion that forms, however, is not stable in the presence of water or any hydroxylic solvent:

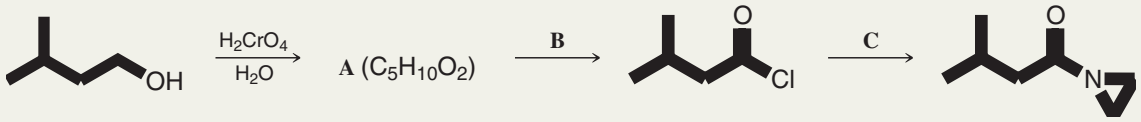


Acyl chloride **3° Amine** **Acylammonium chloride**

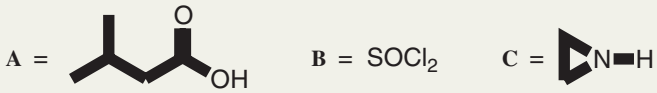
Acylpyridinium ions are probably involved as intermediates in those reactions of acyl chlorides that are carried out in the presence of pyridine.

Solved Problem 17.6

Provide the missing compounds, **A–C**, in the following synthesis.

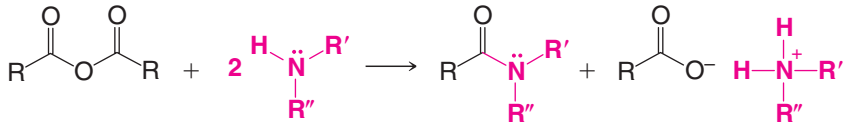


STRATEGY AND ANSWER The first reaction is a chromic acid oxidation, leading to $C_5H_{10}O_2$, which is consistent with the carboxylic acid derived from 3-methyl-1-butanol. **B** must be a reagent by which we can prepare an acid chloride. The final product is an amide, thus **C** must be the appropriate amine. Compounds **A–C**, therefore, are as follows:



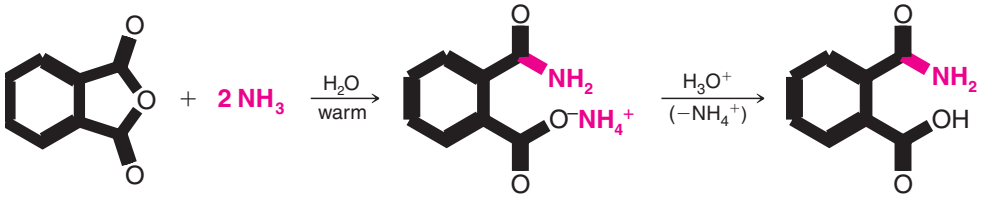
17.8C Amides from Carboxylic Anhydrides

Acid anhydrides react with ammonia and with primary and secondary amines to form amides through reactions that are analogous to those of acyl chlorides:



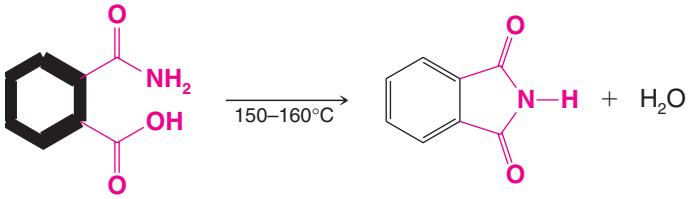
R′, R″ can be H, alkyl, or aryl.

Cyclic anhydrides react with ammonia or an amine in the same general way as acyclic anhydrides; however, the reaction yields a product that is both an amide and an ammonium salt. Acidifying the ammonium salt gives a compound that is both an amide and an acid:



Phthalic anhydride | **Ammonium phthalamate (94%)** | **Phthalamic acid (81%)**

Heating the amide acid causes dehydration to occur and gives an *imide*. Imides contain the linkage —C(=O)—NH—C(=O)—.

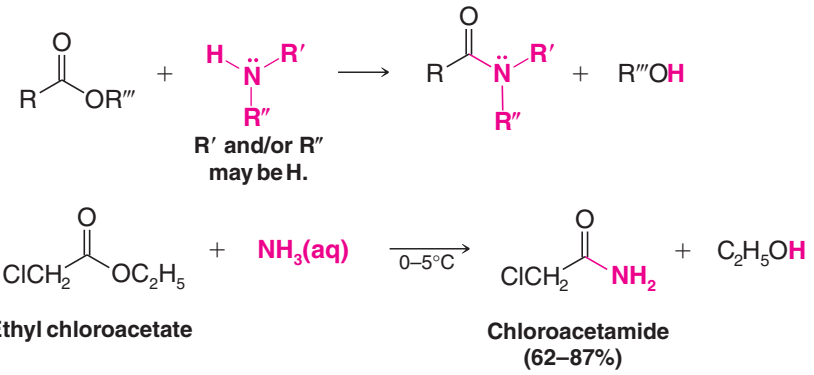


Phthalamic acid | **Phthalimide (~100%)**

Openmirrors.com

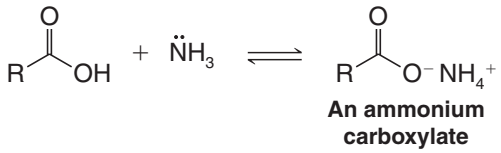
17.8D Amides from Esters

Esters undergo nucleophilic addition–elimination at their acyl carbon atoms when they are treated with ammonia (called *ammonolysis*) or with primary and secondary amines. These reactions take place much more slowly than those of acyl chlorides and anhydrides, but they can still be synthetically useful:

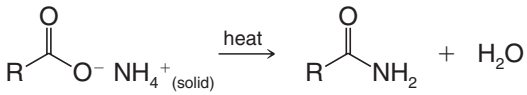


17.8E Amides from Carboxylic Acids and Ammonium Carboxylates

Carboxylic acids react with aqueous ammonia to form ammonium salts:



Because of the low reactivity of the carboxylate ion toward nucleophilic addition–elimination, further reaction does not usually take place in aqueous solution. However, if we evaporate the water and subsequently heat the dry salt, dehydration produces an amide:

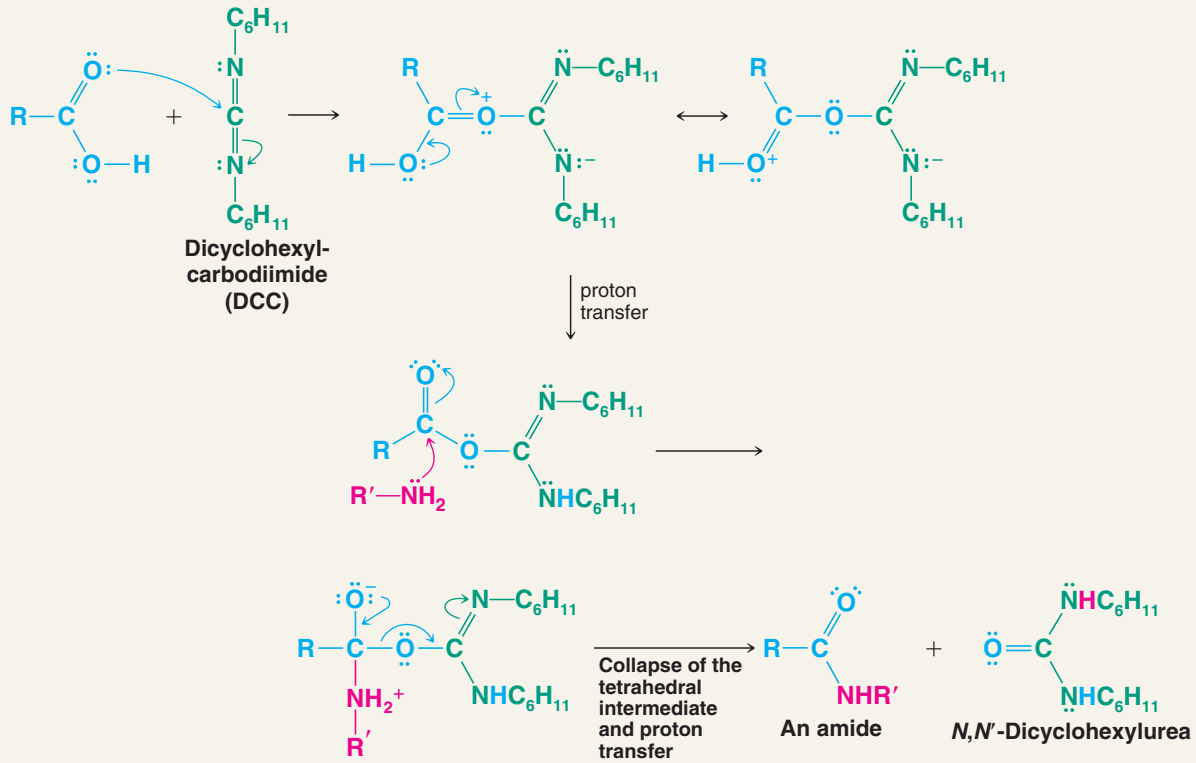


This is generally a poor method for preparing amides. A much better method is to convert the acid to an acyl chloride and then treat the acyl chloride with ammonia or an amine (Section 17.8B).

Amides are of great importance in biochemistry. The linkages that join individual amino acids together to form proteins are primarily amide linkages. As a consequence, much research has been done to find convenient and mild ways for amide synthesis. Dialkylcarbodiimides (R—N═C═N—R), such as diisopropylcarbodiimide and dicyclohexylcarbodiimide (DCC), are especially useful reagents for amide synthesis. Dialkylcarbodiimides promote amide formation by reacting with the carboxyl group of an acid and activating it toward nucleophilic addition–elimination.

A MECHANISM FOR THE REACTION

DCC-Promoted Amide Synthesis

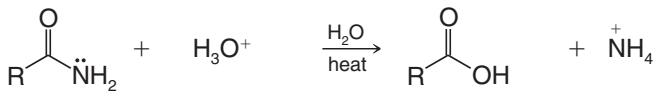


The intermediate in this synthesis does not need to be isolated, and both steps take place at room temperature. Amides are produced in very high yield. In Chapter 24 we shall see how diisopropylcarbodiimide is used in an automated synthesis of peptides.

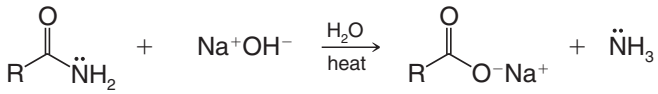
17.8F Hydrolysis of Amides

- Amides undergo hydrolysis when they are heated with aqueous acid or aqueous base.

Acidic Hydrolysis



Basic Hydrolysis



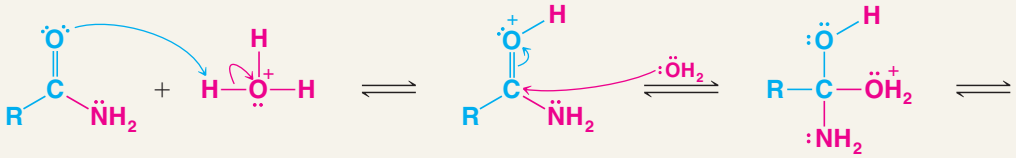
Openmirrors.com

N-Substituted amides and *N*,*N*-disubstituted amides also undergo hydrolysis in aqueous acid or base. Amide hydrolysis by either method takes place more slowly than the corresponding hydrolysis of an ester. Thus, amide hydrolyses generally require the forcing conditions of heat and strong acid or base.

The mechanism for acid hydrolysis of an amide is similar to that given in Section 17.7A for the acid hydrolysis of an ester. Water acts as a nucleophile and attacks the protonated amide. The leaving group in the acidic hydrolysis of an amide is ammonia (or an amine).

A MECHANISM FOR THE REACTION

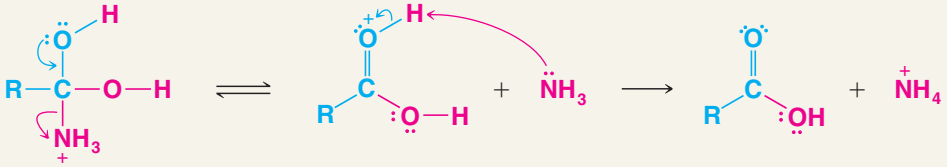
Acidic Hydrolysis of an Amide



The amide carbonyl accepts a proton from the aqueous acid.

A water molecule attacks the protonated carbonyl to give a tetrahedral intermediate.

A proton is lost at one oxygen and gained at the nitrogen.



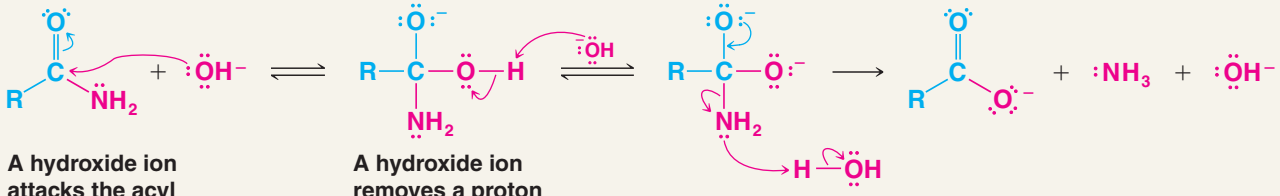
Loss of a molecule of ammonia gives a protonated carboxylic acid.

Transfer of a proton to ammonia leads to the carboxylic acid and an ammonium ion.

There is evidence that in basic hydrolyses of amides, hydroxide ions act both as nucleophiles and as bases.

A MECHANISM FOR THE REACTION

Basic Hydrolysis of an Amide



A hydroxide ion attacks the acyl carbon of the amide.

A hydroxide ion removes a proton to give a dianion.

The dianion loses a molecule of ammonia (or an amine); this step is synchronized with a proton transfer from water due to the basicity of NH_2^-.

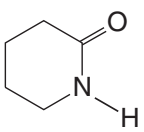
Hydrolysis of amides by enzymes is central to the digestion of proteins. The mechanism for protein hydrolysis by the enzyme chymotrypsin is presented in Section 24.11.

Review Problem 17.13

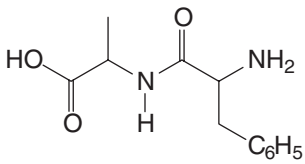
What products would you obtain from acidic and basic hydrolysis of each of the following amides?

(a) *N*,*N*-Diethylbenzamide

(b)



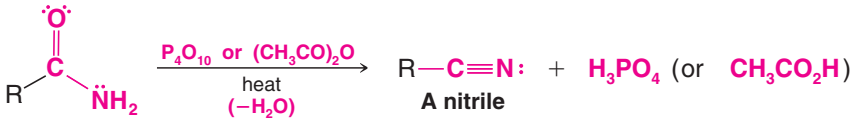
(c)



(a dipeptide)

17.8G Nitriles from the Dehydration of Amides

Amides react with P_4O_{10} (a compound that is often called phosphorus pentoxide and written P_2O_5) or with boiling acetic anhydride to form nitriles:

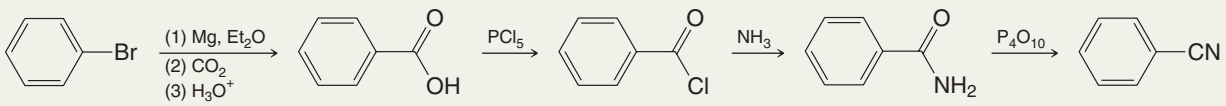


This is a useful synthetic method for preparing nitriles that are not available by nucleophilic substitution reactions between alkyl halides and cyanide ion.

Solved Problem 17.7

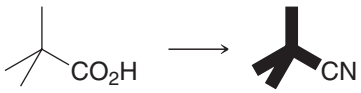
At first glance the conversion of bromobenzene to benzenenitrile looks simple—just carry out a nucleophilic substitution using cyanide ion as the nucleophile. Then we remember that bromobenzene does not undergo either an S_N1 or an S_N2 reaction (Section 6.14A). The conversion can be accomplished, however, though it involves several steps. Outline possible steps.

ANSWER

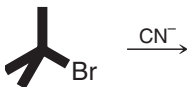


Review Problem 17.14

(a) Provide the reagents required to accomplish the following transformation.

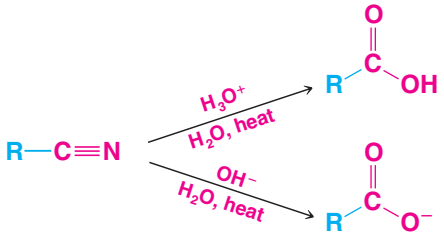


(b) What product would you likely obtain if you attempted to synthesize the nitrile above by the following method?



17.8H Hydrolysis of Nitriles

- Nitriles are related to carboxylic acids because complete hydrolysis of a nitrile produces a carboxylic acid or a carboxylate anion (Sections 16.9 and 17.3):



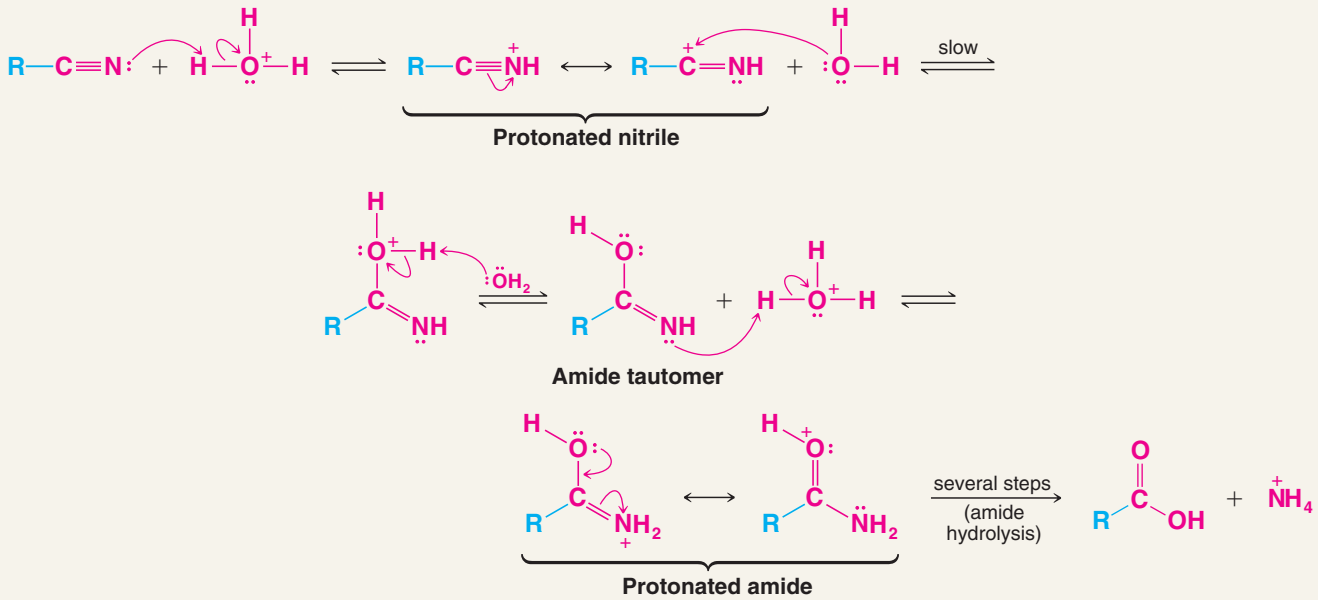
Openmirrors.com

The mechanisms for these hydrolyses are related to those for the acidic and basic hydrolyses of amides.

In **acidic hydrolysis** of a nitrile the first step is protonation of the nitrogen atom. This protonation (in the following sequence) enhances polarization of the nitrile group and makes the carbon atom more susceptible to nucleophilic attack by the weak nucleophile, water. The loss of a proton from the oxygen atom then produces a tautomeric form of an amide. Gain of a proton at the nitrogen atom gives a **protonated amide**, and from this point on the steps are the same as those given for the acidic hydrolysis of an amide in Section 17.8F. (In concentrated H_2SO_4 the reaction stops at the protonated amide, and this is a useful way of making amides from nitriles.)

A MECHANISM FOR THE REACTION

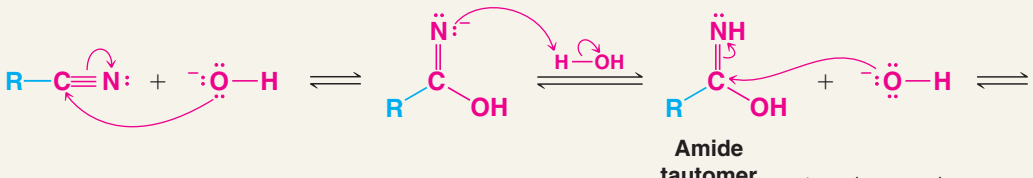
Acidic Hydrolysis of a Nitrile



In **basic hydrolysis,** a hydroxide ion attacks the nitrile carbon atom, and subsequent protonation leads to the amide tautomer. Further attack by the hydroxide ion leads to hydrolysis in a manner analogous to that for the basic hydrolysis of an amide (Section 17.8F). (Under the appropriate conditions, amides can be isolated when nitriles are hydrolyzed.)

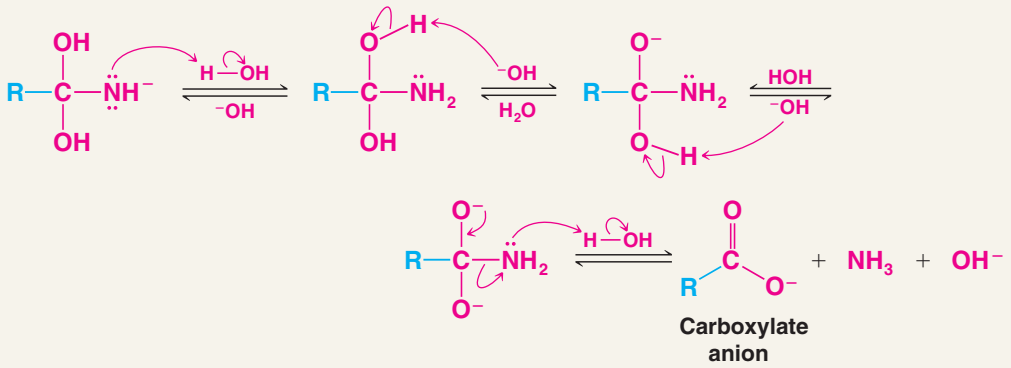
A MECHANISM FOR THE REACTION

Basic Hydrolysis of a Nitrile



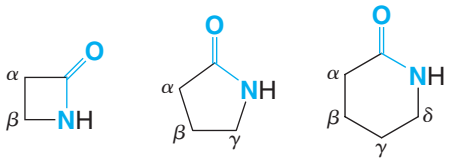
(mechanism box continues on the next page)

(continued from the previous page)



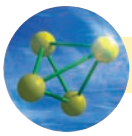
17.8I Lactams

Cyclic amides are called **lactams**. The size of the lactam ring is designated by Greek letters in a way that is analogous to lactone nomenclature (Section 17.7C):



A β-lactam **A γ-lactam** **A δ-lactam**

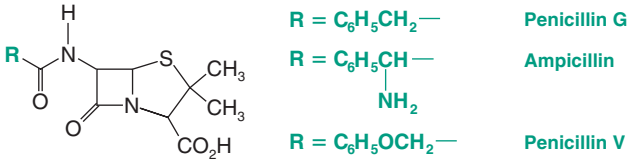
γ-Lactams and δ-lactams often form spontaneously from γ- and δ-amino acids. β-Lactams, however, are highly reactive; their strained four-membered rings open easily in the presence of nucleophilic reagents.



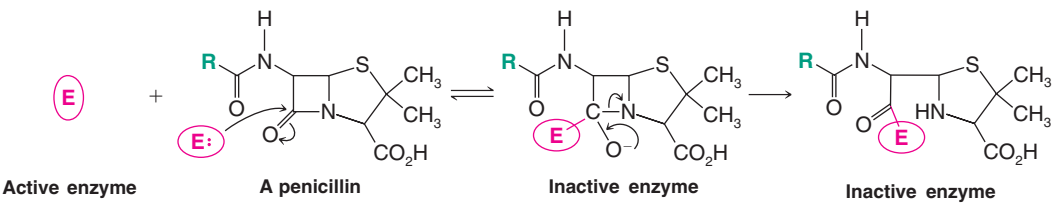
THE CHEMISTRY OF . . .

Penicillins

The penicillin antibiotics (see the following structures) contain a β-lactam ring:

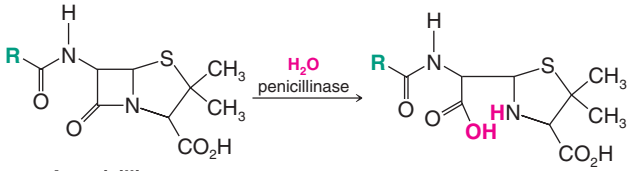


The penicillins apparently act by interfering with the synthesis of bacterial cell walls. It is thought that they do this by reacting with an amino group of an essential enzyme of the cell wall biosynthetic pathway. This reaction involves ring opening of the β-lactam and acylation of the enzyme, inactivating it.



Openmirrors.com

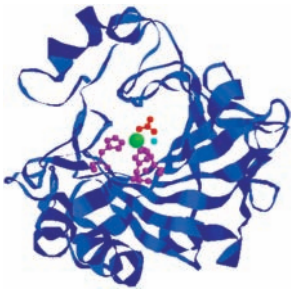
Bacterial resistance to the penicillin antibiotics is a serious problem for the treatment of infections. Bacteria that have developed resistance to penicillin produce an enzyme called penicillinase. Penicillinase hydrolyzes the β-lactam ring of penicillin, resulting in penicilloic acid. Because penicilloic acid cannot act as an acylating agent, it is incapable of blocking bacterial cell wall synthesis by the mechanism shown above.



A penicillin **Penicilloic acid**

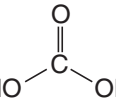
An industrial-scale reactor for preparation of an antibiotic.

17.9 Derivatives of Carbonic Acid



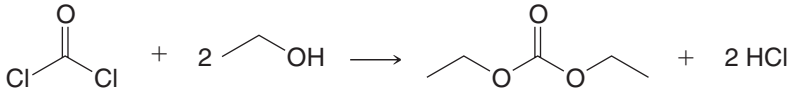
Carbonic anhydrase

Carbonic anhydrase is an enzyme that interconverts water and carbon dioxide with carbonic acid. A carbonate dianion is shown in red within the structure of carbonic anhydrase above.



Carbonic acid, HO–C(=O)–OH, is an unstable compound that decomposes spontaneously to produce carbon dioxide and water and, therefore, cannot be isolated. However, many acyl chlorides, esters, and amides that are derived from carbonic acid are stable compounds that have important applications.

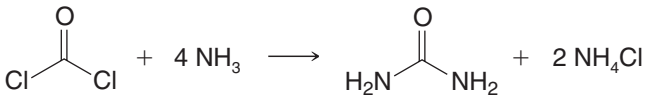
Carbonyl dichloride (ClCOCl), a highly toxic compound that is also called *phosgene*, can be thought of as the diacyl chloride of carbonic acid. Carbonyl dichloride reacts by nucleophilic addition–elimination with two molar equivalents of an alcohol to yield a **dialkyl carbonate:**



Carbonyl dichloride **Diethyl carbonate**

A tertiary amine is usually added to the reaction to neutralize the hydrogen chloride that is produced.

Carbonyl dichloride reacts with ammonia to yield **urea** (Section 1.1A):



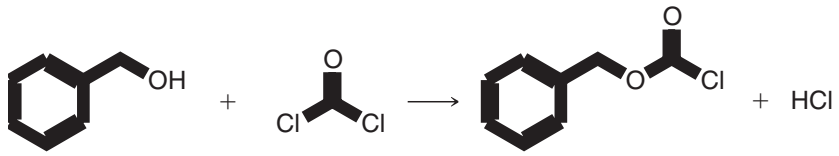
Urea is the end product of the metabolism of nitrogen-containing compounds in most mammals and is excreted in the urine.

17.9A Alkyl Chloroformates and Carbamates (Urethanes)

Treating carbonyl dichloride with one molar equivalent of an alcohol leads to the formation of an alkyl chloroformate:

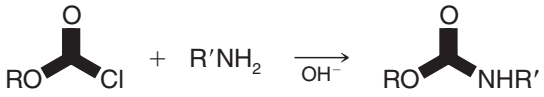
Alkyl chloroformate

Specific Example



Benzyl chloroformate

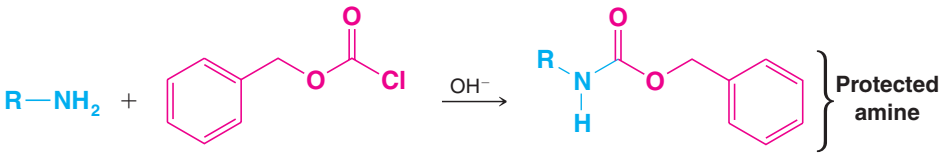
Alkyl chloroformates react with ammonia or amines to yield compounds called *carbamates* or *urethanes*:



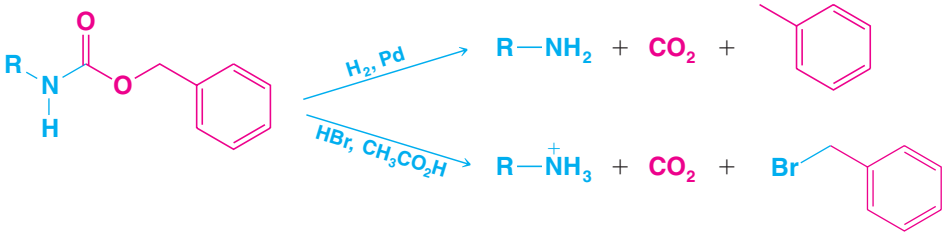
A carbamate (or urethane)

Benzyl chloroformate is used to install an amino protecting (blocking) group called the benzyloxycarbonyl group. We shall see in Section 24.7A how this protecting group is used in the synthesis of peptides and proteins. One advantage of the benzyloxycarbonyl group is that it can be removed under mild conditions. Treating the benzyloxycarbonyl derivative with hydrogen and a catalyst or with cold HBr in acetic acid removes the protecting group:

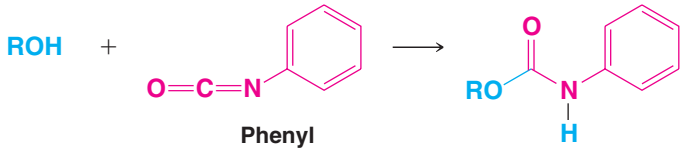
Protection



Deprotection

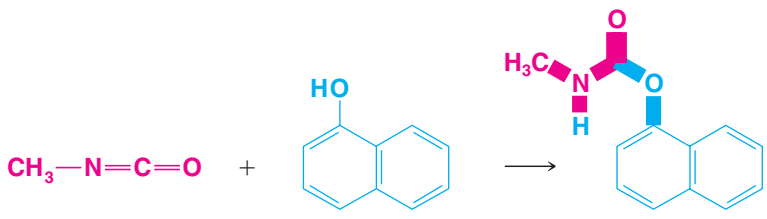


Carbamates can also be synthesized by allowing an alcohol to react with an isocyanate, R—N═C═O. (Carbamates tend to be nicely crystalline solids and are useful derivatives for identifying alcohols.) The reaction is an example of nucleophilic addition to the acyl carbon:



Phenyl isocyanate

The insecticide called *Sevin* is a carbamate made by allowing 1-naphthol to react with methyl isocyanate:



Methyl isocyanate **1-Naphthol** **Sevin**

Openmirrors.com

A tragic accident that occurred at Bhopal, India, in 1984 was caused by leakage of methyl isocyanate from a manufacturing plant. Methyl isocyanate is a highly toxic gas, and more than 1800 people living near the plant lost their lives.

Review Problem 17.15

Write structures for the products of the following reactions:

(a) $C_6H_5CH_2OH + C_6H_5N{=}C{=}O \longrightarrow$

(b) $ClCOCl$ + excess $CH_3NH_2 \longrightarrow$

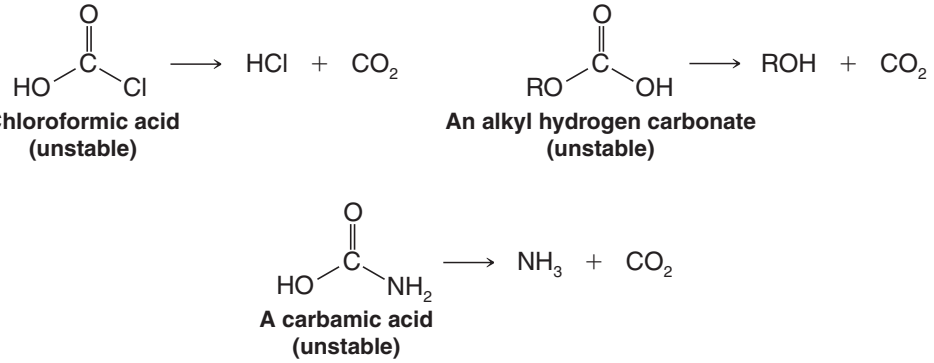
(c) Glycine ($H_3\overset{+}{N}CH_2CO_2^-$) + $C_6H_5CH_2OCOCl \xrightarrow{OH^-}$

(d) Product of (c) + H_2, Pd $\longrightarrow$

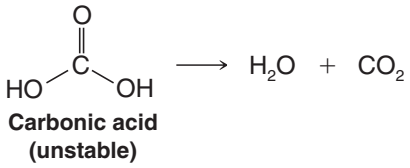
(e) Product of (c) + cold HBr, $CH_3CO_2H \longrightarrow$

(f) Urea + OH^-, H_2O, heat

Although alkyl chloroformates (ROCOCl), dialkyl carbonates (ROCOOR), and carbamates ($ROCONH_2$, ROCONHR, etc.) are stable, chloroformic acid (HOCOCl), alkyl hydrogen carbonates (ROCOOH), and carbamic acid ($HOCONH_2$) are not. These latter compounds decompose spontaneously to liberate carbon dioxide:

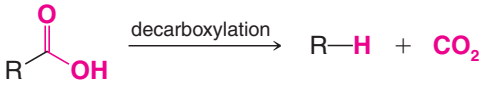


This instability is a characteristic that these compounds share with their functional parent, carbonic acid:



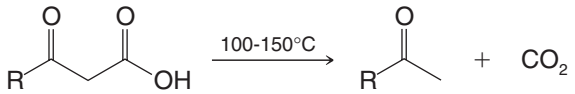
17.10 Decarboxylation of Carboxylic Acids

The reaction whereby a carboxylic acid loses CO_2 is called a **decarboxylation**:



Although the unusual stability of carbon dioxide means that decarboxylation of most acids is exothermic, in practice the reaction is not always easy to carry out because the reaction is very slow. Special groups usually have to be present in the molecule for decarboxylation to be rapid enough to be synthetically useful.

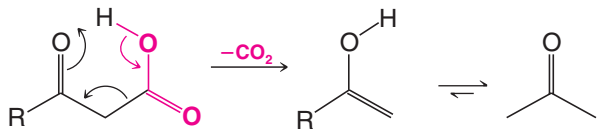
- Carboxylic acids that have a carbonyl group one carbon removed from the carboxylic acid group, called **β-keto acids,** decarboxylate readily when they are heated to 100–150°C. Some β-keto acids even decarboxylate slowly at room temperature.



A β-keto acid

There are two reasons for this ease of decarboxylation:

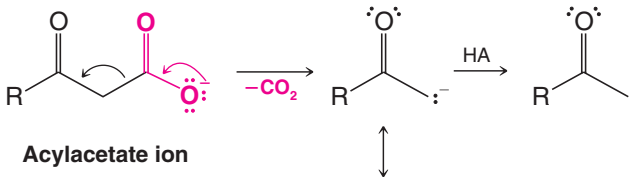
1. When the acid itself decarboxylates, it can do so through a six-membered cyclic transition state:



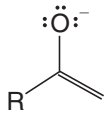
β-Keto acid **Enol** **Ketone**

This reaction produces an enol directly and avoids an anionic intermediate. The enol then tautomerizes to a methyl ketone.

2. When the carboxylate anion decarboxylates, it forms a resonance-stabilized anion:



Acylacetate ion

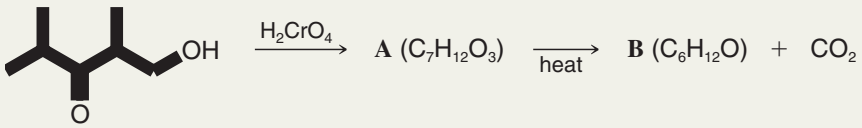


Resonance-stabilized anion

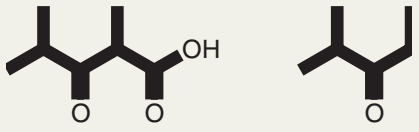
This type of anion, which we shall study further in chapter 19, is much more stable than simply $RCH_2:^-$, the anion that would have been produced by decarboxylation in the absence of a β-carbonyl group.

Solved Problem 17.8

Provide structures for **A** and **B**.



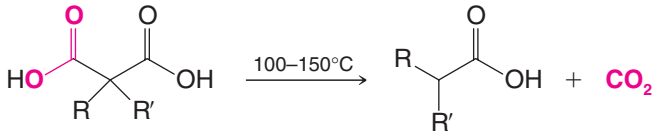
STRATEGY AND ANSWER H_2CrO_4 oxidizes a primary alcohol to a carboxylic acid, which is consistent with the formula provided for **A**. Because **A** is a β-ketocarboxylic acid, it decarboxylates on heating to form **B**.



A **B**

Openmirrors.com

β-Dicarboxylic acids (1,3-dicarboxylic acids, also called malonic acids) decarboxylate readily for reasons similar to β-keto acids.



A β-dicarboxylic acid

β-Dicarboxylic acids undergo decarboxylation so readily that they do not form cyclic anhydrides (Section 17.6A).

We shall see in Sections 18.6 and 18.7 how decarboxylation of β-keto acids and malonic acids is synthetically useful.

17.10A Decarboxylation of Carboxyl Radicals

Although the carboxylate ions (RCO_2^-) of simple aliphatic acids do not decarboxylate readily, carboxyl radicals ($RCO_2\cdot$) do. They decarboxylate by losing CO_2 and producing alkyl radicals:

$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$

Review Problem 17.16

Using decarboxylation reactions, outline a synthesis of each of the following from appropriate starting materials:

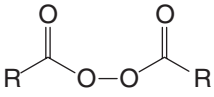
(a) 2-Hexanone

(b) 2-Methylbutanoic acid

(c) Cyclohexanone

(d) Pentanoic acid

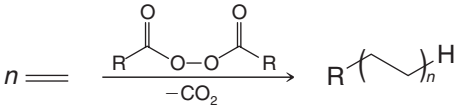
Review Problem 17.17

Diacyl peroxides,  , decompose readily when heated.

(a) What factor accounts for this instability?

(b) The decomposition of a diacyl peroxide produces CO_2. How is it formed?

(c) Diacyl peroxides are often used to initiate radical reactions, for example, the polymerization of an alkene:



Show the steps involved.

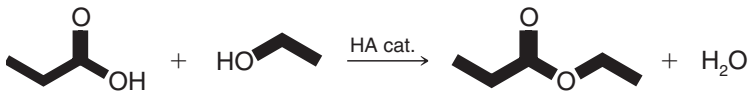
17.11 Chemical Tests for Acyl Compounds

Carboxylic acids are weak acids, and their acidity helps us to detect them.

- Aqueous solutions of water-soluble carboxylic acids give an acid test with blue litmus paper.
- Water-insoluble carboxylic acids dissolve in aqueous sodium hydroxide and aqueous sodium bicarbonate (see Section 17.2C).
- Sodium bicarbonate helps us distinguish carboxylic acids from most phenols. Except for the di- and trinitrophenols, phenols do not dissolve in aqueous sodium bicarbonate. When carboxylic acids dissolve in aqueous sodium bicarbonate, they also cause the evolution of carbon dioxide.

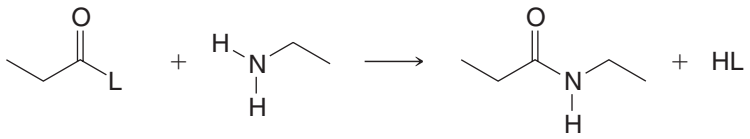
17.12 Polyesters and Polyamides: Step-Growth Polymers

We have seen in Section 17.7A that carboxylic acids react with alcohols to form esters.



Carboxylic acid **Alcohol** **Ester**

In a similar way carboxylic acid derivatives (L is a leaving group) react with amines (Sect. 17.8) to form amides.

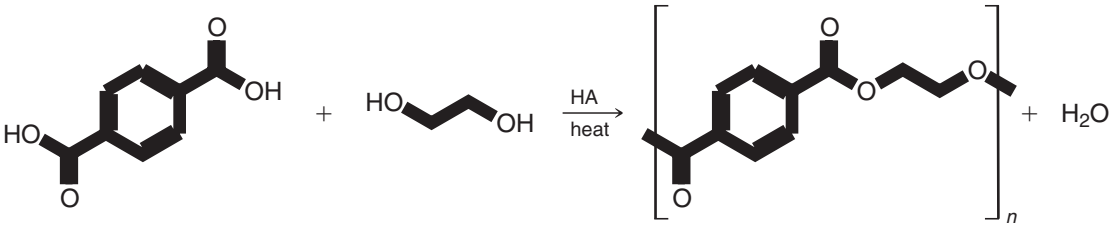


Carboxylic acid derivative **Amine** **Amide**

In each reaction the two reactants become joined and a small molecule is lost. Such reactions are often called **condensation reactions.**

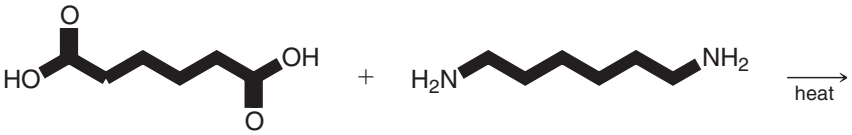
Similar condensation reactions beginning with dicarboxylic acids and either diols or diamines can be used to form polymers that are either **polyesters** or **polyamides.** These polymers are called *step-growth polymers*. [Recall that in Section 10.10 and Special Topic B, we studied another group of polymers called *chain-growth polymers* (also called *addition polymers*), which are formed by radicals undergoing chain-reactions.]

- **Polyesters**. When a dicarboxylic acid reacts with a diol under the appropriate conditions, the product is a polyester. For example, the reaction of 1,4-benzenedicarboxylic acid (terephthalic acid) with 1,2-ethanediol leads to the formation of the familiar polyesters called Dacron, Terelene or Mylar, and systemically called poly(ethylene terephthalate).



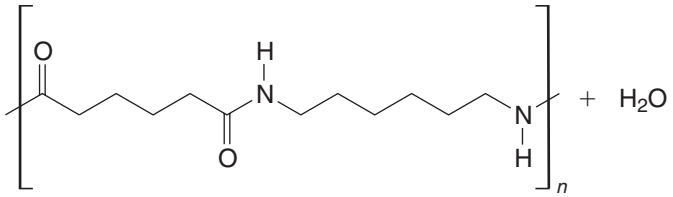
Terephthalic acid **1,2-Ethanediol** **Poly(ethylene terephthalate) (a polyester)**

- **Polyamides**. When a dicarboxylic acid or acid chloride or anhydride reacts with a diamine under the appropriate conditions, the product is a polyamide. For example, 1,6-hexanedioic acid (adipic acid) can react with 1,6-hexanediamine with heat in an industrial process to form a familiar polyamide called Nylon. This example of nylon is called nylon 6,6 because both components of the polymer have six carbon atoms. Other nylons can be made in a similar way.



1,6-Hexanedioic acid **1,6-Hexanediamine**

Openmirrors.com



Nylon 6,6
(A polyamide)

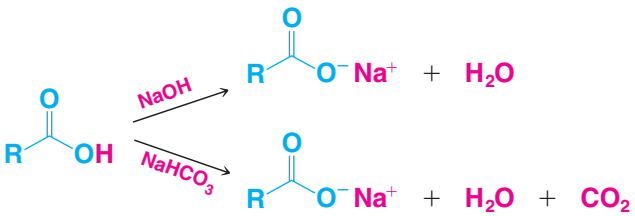
Special Topic C continues our discussion of Step-Growth Polymers.

17.13 *Summary of the Reactions of Carboxylic Acids and Their Derivatives*

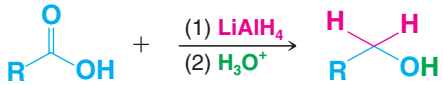
The reactions of carboxylic acids and their derivatives are summarized here. Many (but not all) of the reactions in this summary are acyl substitution reactions (they are principally the reactions referenced to Sections 17.5 and beyond). As you use this summary, you will find it helpful to also review Section 17.4, which presents the general nucleophilic addition–elimination mechanism for acyl substitution. It is instructive to relate aspects of the specific acyl substitution reactions below to this general mechanism. In some cases proton transfer steps are also involved, such as to make a leaving group more suitable by prior protonation or to transfer a proton to a stronger base at some point in a reaction, but in all acyl substitution the essential nucleophilic addition–elimination steps are identifiable.

Reactions of Carboxylic Acids

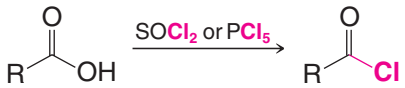
1. As acids (discussed in Sections 3.11 and 17.2C):



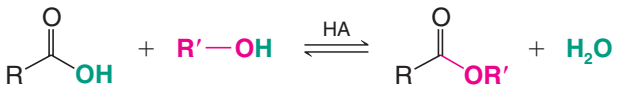
2. Reduction (discussed in Section 12.3):



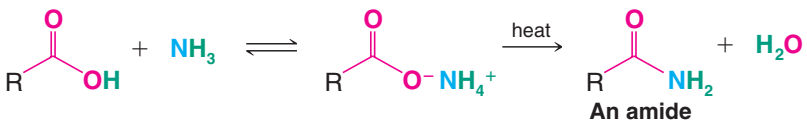
3. Conversion to acyl chlorides (discussed in Section 17.5):



4. Conversion to esters (Fischer esterification) or lactones (discussed in Section 17.7A):

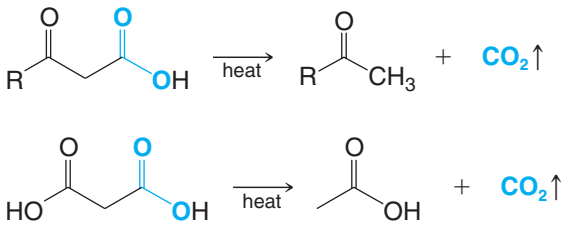


5. Conversion to amides (discussed in Section 17.8E):



An amide

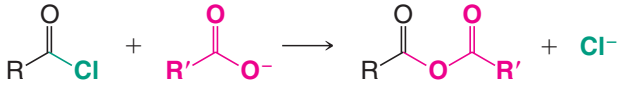
6. Decarboxylation (discussed in Section 17.10):



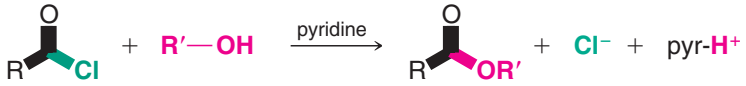
Reactions of Acyl Chlorides

1. Conversion (hydrolysis) to acids (discussed in Section 17.5B):

2. Conversion to anhydrides (discussed in Section 17.6A):



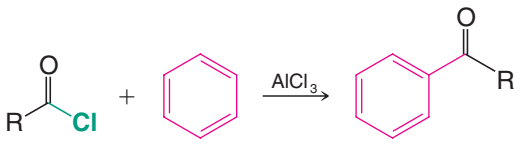
3. Conversion to esters (discussed in Section 17.7A):



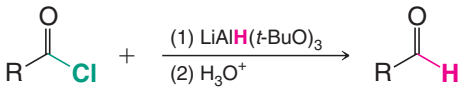
4. Conversion to amides (discussed in Section 17.8B):

R′ and/or R″ may be H.

5. Conversion to ketones (Friedel–Crafts acylation, Section 15.7–15.9):

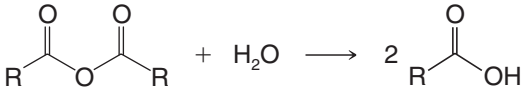


6. Conversion to aldehydes (discussed in Section 16.4C):



Reactions of Acid Anhydrides

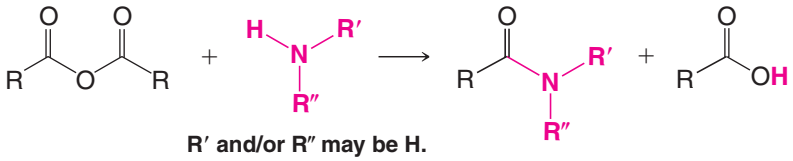
1. Conversion (hydrolysis) to acids (discussed in Section 17.6B):



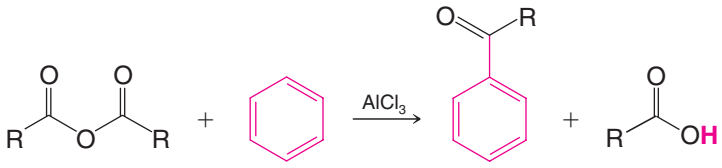
2. Conversion to esters (discussed in Sections 17.6B and 17.7A):

Openmirrors.com

3. Conversion to amides (discussed in Section 17.8C):

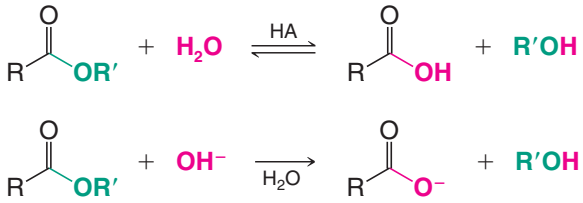


4. Conversion to aryl ketones (Friedel–Crafts acylation, Sections 15.7–15.9):

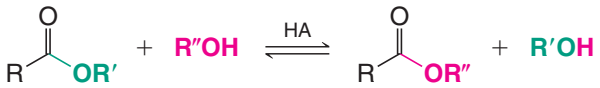


Reactions of Esters

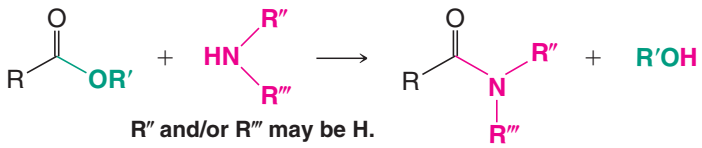
1. Hydrolysis (discussed in Section 17.7B):



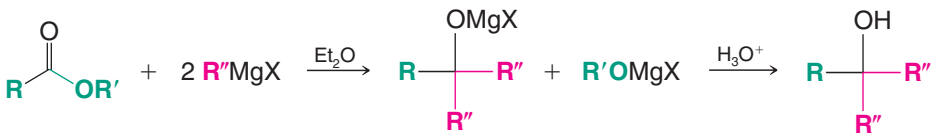
2. Conversion to other esters: transesterification (discussed in Review Problem 17.10):



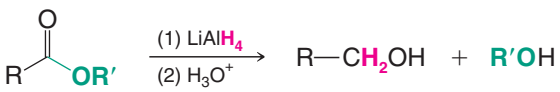
3. Conversion to amides (discussed in Section 17.8D):



4. Reaction with Grignard reagents (discussed in Section 12.8):

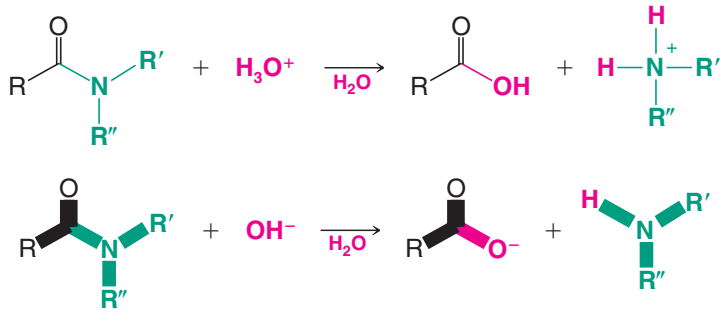


5. Reduction (discussed in Section 12.3):



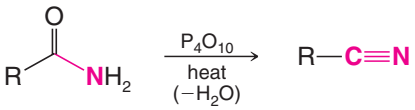
Reactions of Amides

1. Hydrolysis (discussed in Section 17.8F):



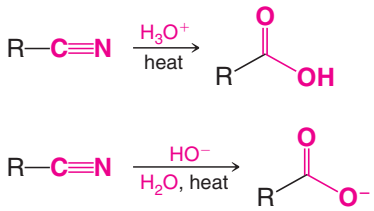
R, R′, and/or R″ may be H.

2. Conversion to nitriles: dehydration (discussed in Section 17.8G):

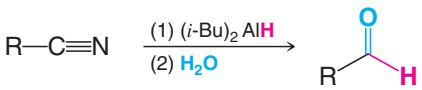


Reactions of Nitriles

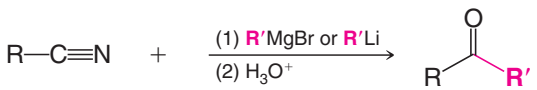
1. Hydrolysis to a carboxylic acid or carboxylate anion (Section 17.8H):



2. Reduction to an aldehyde with $(i\text{-Bu})_2$AlH (DIBAL-H, Section 16.4C):



3. Conversion to a ketone by a Grignard or organolithium reagent (Section 16.5B):



Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Openmirrors.com

Problems

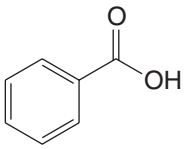
Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

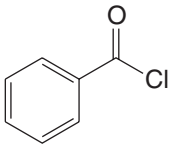
STRUCTURE AND NOMENCLATURE

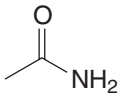
17.18 Write a structural formula for each of the following compounds:

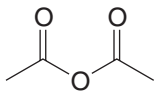
(a) Octanoic acid
(b) Propanamide
(c) *N,N*-Diethylhexanamide
(d) 2-Methyl-4-hexenoic acid
(e) Butanedioic acid
(f) 1,2-Benzenedioc acid (phthalic acid)
(g) 1,4-Benzenedioic acid (terephthalic acid)
(h) Acetic anhydride
(i) Isobutyl propanoate
(j) Benzyl acetate
(k) Ethanoyl chloride (acetyl chloride)
(l) 2-Methylpropanenitrile
(m) Ethyl 3-oxobutanoate (ethyl acetoacetate)
(n) Diethyl propanedioate (diethyl malonate)

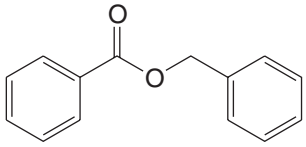
17.19 Give an IUPAC systematic or common name for each of the following compounds:

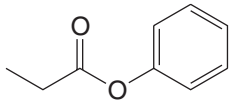
(a) 

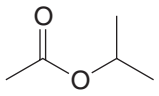
(b) 

(c) 

(d) 

(e) 

(f) 

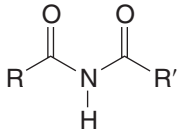
(g) 

(h) CH_3CN

17.20 Amides are weaker bases than corresponding amines. For example, most water-insoluble amines (RNH_2) will dissolve in dilute aqueous acids (aqueous HCl, H_2SO_4, etc.) by forming water-soluble alkylaminium salts ($RNH_3^+X^-$). Corresponding amides ($RCONH_2$) *do not dissolve in dilute aqueous acids*, however. Propose an explanation for the much lower basicity of amides when compared to amines.

17.21 While amides are much less basic than amines, they are much stronger acids. Amides have pK_a values in the range 14–16, whereas for amines, pK_a = 33–35.

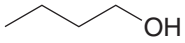
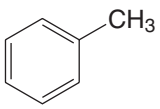
(a) What factor accounts for the much greater acidity of amides?

(b) Imides, that is, compounds with the structure  , are even stronger acids than amides.

For imides, pK_a = 9–10, and as a consequence, water-insoluble imides dissolve in aqueous NaOH by forming soluble sodium salts. What extra factor accounts for the greater acidity of imides?

FUNCTIONAL GROUP TRANSFORMATIONS

17.22 What major organic product would you expect to obtain when acetyl chloride reacts with each of the following?

(a) H_2O
(b) BuLi (excess)
(c)  and pyridine
(d) NH_3 (excess)
(e)  and $AlCl_3$
(f) $LiAlH(t\text{-}BuO)_3$
(g) $NaOH/H_2O$
(h) CH_3NH_2 (excess)
(i) $(CH_3)_2NH$ (excess)
(j) EtOH and pyridine
(k) $CH_3CO_2^-Na^+$
(l) CH_3CO_2H and pyridine

17.23 What major organic product would you expect to obtain when acetic anhydride reacts with each of the following?

(a) NH_3 (excess) **(c)** $CH_3CH_2CH_2OH$ **(e)** $CH_3CH_2NH_2$ (excess)

(b) H_2O **(d)** $C_6H_6 + AlCl_3$ **(f)** $(CH_3CH_2)_2NH$ (excess)

17.24 What major organic product would you expect to obtain when succinic anhydride reacts with each of the reagents given in Problem 17.23?

17.25 What products would you expect to obtain when ethyl propanoate reacts with each of the following?

(a) H_3O^+, H_2O **(c)** 1-Octanol, HCl **(e)** $LiAlH_4$, then H_2O

(b) OH^-, H_2O **(d)** CH_3NH_2 **(f)** Excess C_6H_5MgBr, then H_2O, NH_4Cl

17.26 What products would you expect to obtain when propanamide reacts with each of the following?

(a) H_3O^+, H_2O **(b)** OH^-, H_2O **(c)** P_4O_{10} and heat

17.27 What products would you expect to obtain when each of the following compounds is heated?

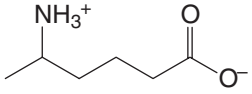
(a) 4-Hydroxybutanoic acid

(b) 3-Hydroxybutanoic acid

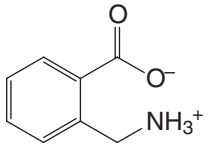
(c) 2-Hydroxybutanoic acid

(d) Glutaric acid

(e)



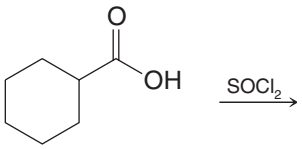
(f)



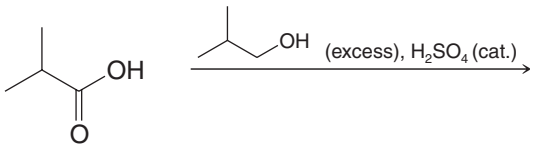
GENERAL PROBLEMS

17.28 Write structural formulas for the major organic products from each of the following reactions.

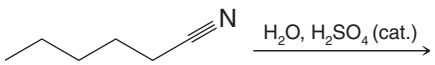
(a)



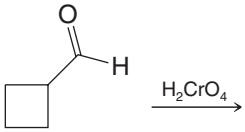
(b)



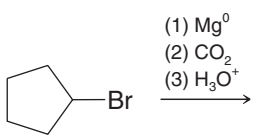
(c)



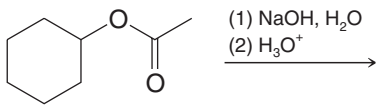
(d)



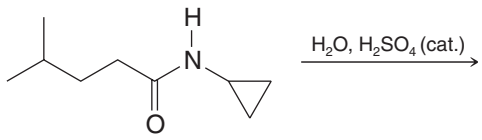
(e)



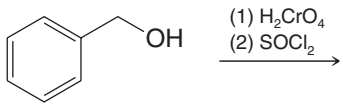
(f)



(g)

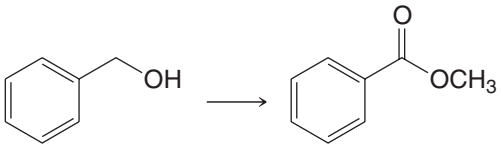


(h)

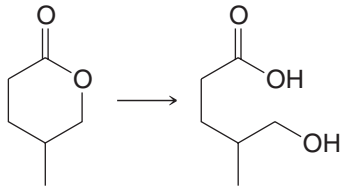


17.29 Indicate reagents that would accomplish each of following transformations. More than one reaction may be necessary in some cases.

(a)

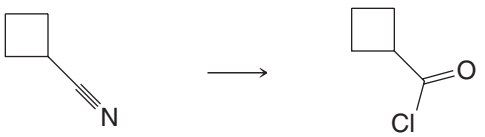


(b)



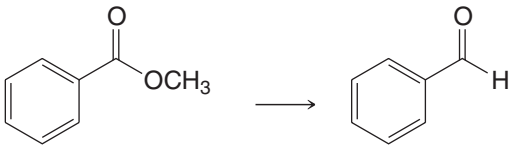
Openmirrors.com

(c)

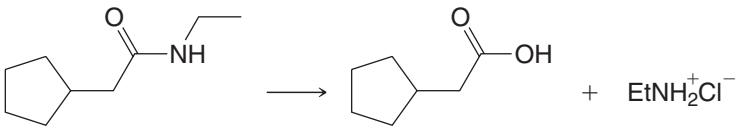


(d)

(e)

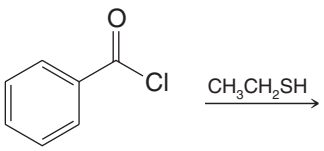


(f)

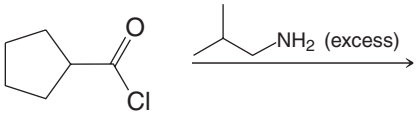


17.30 Write structural formulas for the major organic products from each of the following reactions.

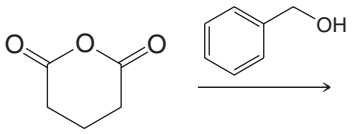
(a)



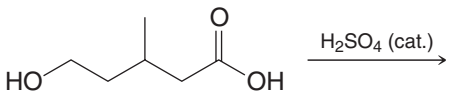
(b)



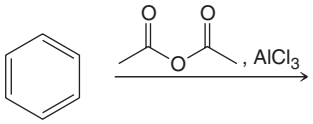
(c)



(d)

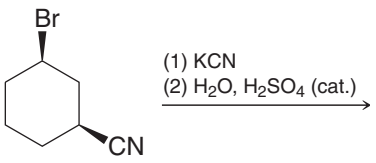


(e)

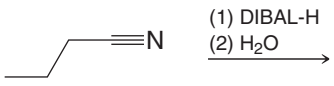


17.31 Write structural formulas for the major organic products from each of the following reactions.

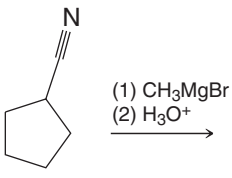
(a)



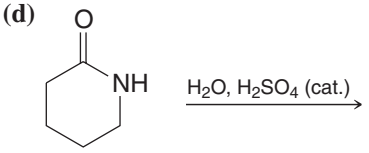
(b)



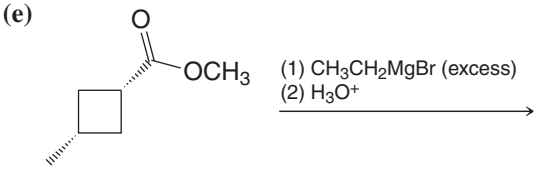
(c)



(d)



(e)

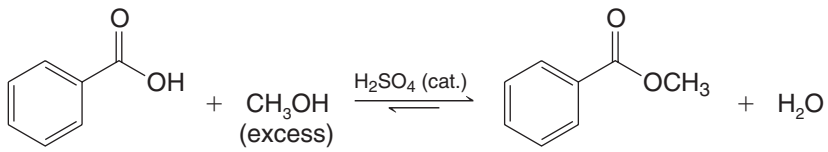


MECHANISMS

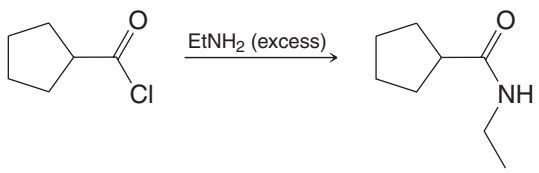
17.32 Write detailed mechanisms for the acidic and basic hydrolysis of propanamide.

17.33 Provide a detailed mechanism for each of the following reactions.

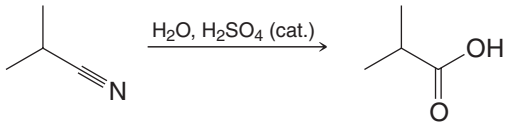
(a)



(b)



(c)



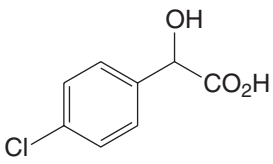
17.34 On heating, *cis*-4-hydroxycyclohexanecarboxylic acid forms a lactone but *trans*-4-hydroxycyclohexanecarboxylic acid does not. Explain.

SYNTHESIS

17.35 Show how *p*-chlorotoluene could be converted to each of the following:

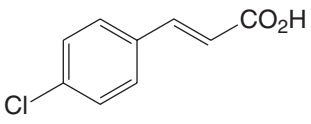
(a) *p*-Chlorobenzoic acid

(b)



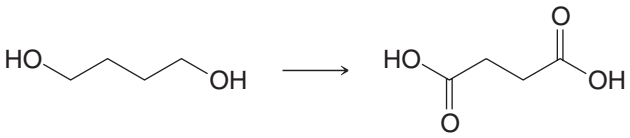
(c) *p*-Chlorophenylacetic acid

(d)

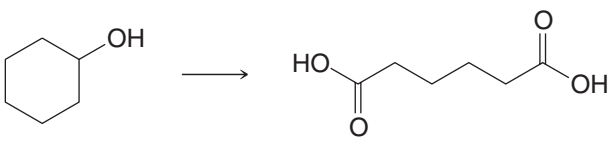


17.36 Indicate the reagents needed for each of the following syntheses. More than one step may be needed.

(a)



(b)



17.37 Show how pentanoic acid can be prepared from each of the following:

(a) 1-Pentanol

(b) 1-Bromobutane (two ways)

(c) 5-Decene

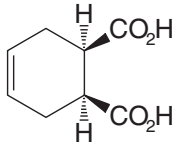
(d) Pentanal

17.38 The active ingredient of the insect repellent Off is *N*,*N*-diethyl-*m*-toluamide, *m*-$CH_3C_6H_4CON(CH_2CH_3)_2$. Outline a synthesis of this compound starting with 3-methylbenzoic acid (*m*-toluic acid).

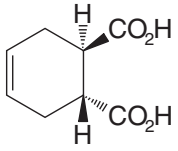
17.39 Starting with benzene and succinic anhydride and using any other needed reagents, outline a synthesis of 1-phenylnaphthalene.

17.40 Starting with either *cis*- or *trans*-$HO_2C—CH=CH—CO_2H$ (i.e., either maleic or fumaric acid) and using any other needed compounds, outline syntheses of each of the following:

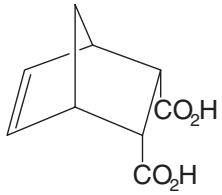
(a)



(b)



(c)



Openmirrors.com

17.41 Give stereochemical formulas for compounds **A–Q**:

(a) (*R*)-(−)-2-Butanol $\xrightarrow[\text{pyridine}]{\text{p-toluenesulfonyl chloride (TsCl)}}$ **A** $\xrightarrow{CN^-}$ **B** (C_5H_9N) $\xrightarrow[H_2O]{H_2SO_4}$

(+)-**C** ($C_5H_{10}O_2$) $\xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4}$ (−)-**D** ($C_5H_{12}O$)

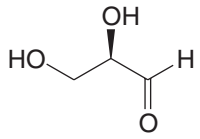
(b) (*R*)-(−)-2-Butanol $\xrightarrow[\text{pyridine}]{PBr_3}$ **E** (C_4H_9Br) $\xrightarrow{CN^-}$ **F** (C_5H_9N) $\xrightarrow[H_2O]{H_2SO_4}$

(−)-**C** ($C_5H_{10}O_2$) $\xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4}$ (+)-**D** ($C_5H_{12}O$)

(c) **A** $\xrightarrow{CH_3CO_2^-}$ **G** ($C_6H_{12}O_2$) $\xrightarrow{OH^-}$ (+)-**H** ($C_4H_{10}O$) + $CH_3CO_2^-$

(d) (−)-**D** $\xrightarrow{PBr_3}$ **J** ($C_5H_{11}Br$) $\xrightarrow[Et_2O]{Mg}$ **K** ($C_5H_{11}MgBr$) $\xrightarrow[(2)\ H_3O^+]{(1)\ CO_2}$ **L** ($C_6H_{12}O_2$)

(e)



(*R*)-(+)-Glyceraldehyde

$\xrightarrow{HCN}$ **M** ($C_4H_7NO_3$) + **N** ($C_4H_7NO_3$)

Diastereomers, separated by fractional crystallization

(f) **M** $\xrightarrow[H_2O]{H_2SO_4}$ **P** ($C_4H_8O_5$) $\xrightarrow[HNO_3]{[O]}$ *meso*-tartaric acid

(g) **N** $\xrightarrow[H_2O]{H_2SO_4}$ **Q** ($C_4H_8O_5$) $\xrightarrow[HNO_3]{[O]}$ (−)-tartaric acid

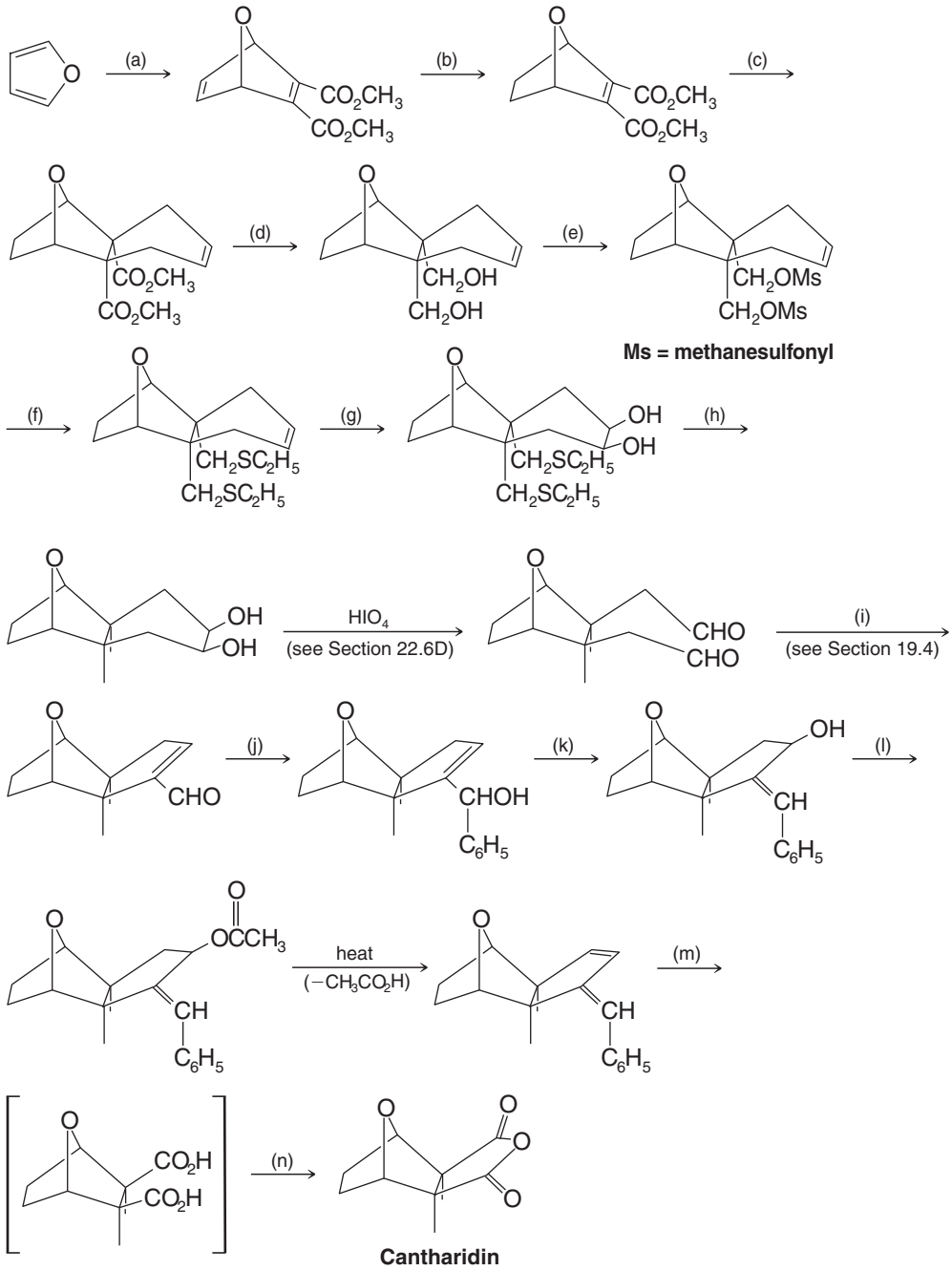
17.42 (*R*)-(+)-Glyceraldehyde can be transformed into (+)-malic acid by the following synthetic route. Give stereochemical structures for the products of each step.

(*R*)-(+)-Glyceraldehyde $\xrightarrow[\text{oxidation}]{Br_2,\ H_2O}$ (−)-glyceric acid $\xrightarrow{PBr_3}$

(−)-3-bromo-2-hydroxypropanoic acid $\xrightarrow{NaCN}$ $C_4H_5NO_3$ $\xrightarrow[\text{heat}]{H_3O^+}$ (+)-malic acid

17.43 (*R*)-(+)-Glyceraldehyde can also be transformed into (−)-malic acid. This synthesis begins with the conversion of (*R*)-(+)-glyceraldehyde into (−)-tartaric acid, as shown in Problem 17.41, parts (e) and (g). Then (−)-tartaric acid is allowed to react with phosphorus tribromide in order to replace one alcoholic —OH group with —Br. This step takes place with inversion of configuration at the carbon that undergoes attack. Treating the product of this reaction with dimethyl sulfide produces (−)-malic acid. **(a)** Outline all steps in this synthesis by writing stereochemical structures for each intermediate. **(b)** The step in which (−)-tartaric acid is treated with phosphorus tribromide produces only one stereoisomer, even though there are two replaceable —OH groups. How is this possible? **(c)** Suppose that the step in which (−)-tartaric acid is treated with phosphorus tribromide had taken place with "mixed" stereochemistry, that is, with both inversion and retention at the carbon under attack. How many stereoisomers would have been produced? **(d)** What difference would this have made to the overall outcome of the synthesis?

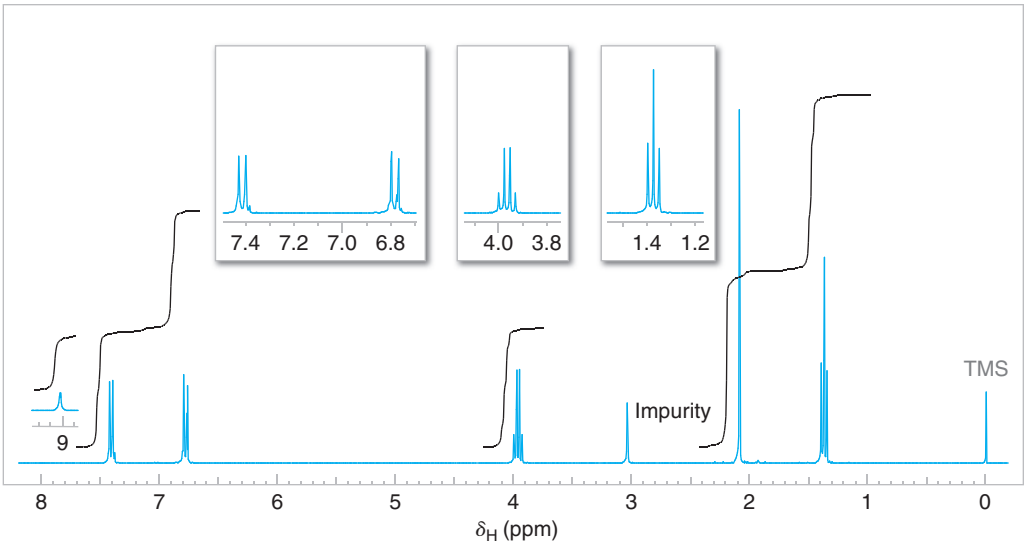
17.44 Cantharidin is a powerful vesicant that can be isolated from dried beetles (*Cantharis vesicatoria*, or "Spanish fly"). Outlined here is the stereospecific synthesis of cantharidin reported by Gilbert Stork (Columbia University). Supply the missing reagents (a)–(n).



SPECTROSCOPY

17.45 The IR and ^1H NMR spectra of phenacetin ($C_{10}H_{13}NO_2$) are given in Fig. 17.7. Phenacetin is an analgesic and antipyretic compound and was the P of A–P–C tablets (**a**spirin–**p**henacetin–**c**affeine). (Because of its toxicity, phenacetin is no longer used medically.) When phenacetin is heated with aqueous sodium hydroxide, it yields phenetidine ($C_8H_{11}NO$) and sodium acetate. Propose structures for phenacetin and phenetidine.

Openmirrors.com



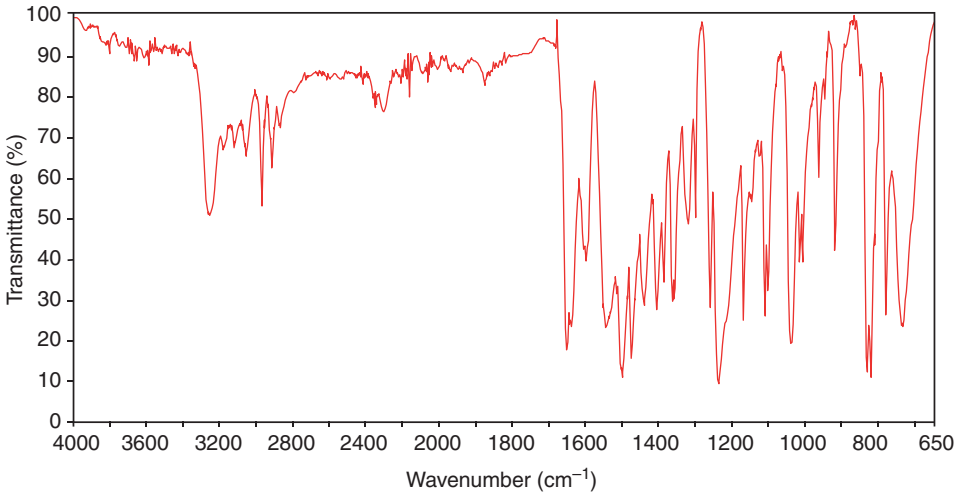


Figure 17.7 The 300-MHz ^{1}H NMR and IR spectra of phenacetin. Expansions of the ^{1}H NMR signals are shown in the offset plots.

17.46 Given here are the ^{1}H NMR spectra and carbonyl IR absorption peaks of five acyl compounds. Propose a structure for each.

(a) $C_8H_{14}O_4$	^{1}H NMR Spectrum		IR Spectrum
	Triplet	δ 1.2 (6H)	1740 cm^{-1}
	Singlet	δ 2.5 (4H)	
	Quartet	δ 4.1 (4H)	
(b) $C_{11}H_{14}O_2$	^{1}H NMR Spectrum		IR Spectrum
	Doublet	δ 1.0 (6H)	1720 cm^{-1}
	Multiplet	δ 2.1 (1H)	
	Doublet	δ 4.1 (2H)	
	Multiplet	δ 7.8 (5H)	
(c) $C_{10}H_{12}O_2$	^{1}H NMR Spectrum		IR Spectrum
	Triplet	δ 1.2 (3H)	1740 cm^{-1}
	Singlet	δ 3.5 (2H)	
	Quartet	δ 4.1 (2H)	
	Multiplet	δ 7.3 (5H)	
(d) $C_2H_2Cl_2O_2$	^{1}H NMR Spectrum		IR Spectrum
	Singlet	δ 6.0	Broad peak 2500–2700 cm^{-1}
	Singlet	δ 11.70	1705 cm^{-1}

(e) $C_4H_7ClO_2$	^{1}H NMR Spectrum		IR Spectrum
	Triplet	δ 1.3	1745 cm^{-1}
	Singlet	δ 4.0	
	Quartet	δ 4.2	

17.47 Compound **X** ($C_7H_{12}O_4$) is insoluble in aqueous sodium bicarbonate. The IR spectrum of **X** has a strong absorption peak near 1740 cm^{-1}, and its broadband proton-decoupled ^{13}C spectrum is given in Fig. 17.8. Propose a structure for **X.**

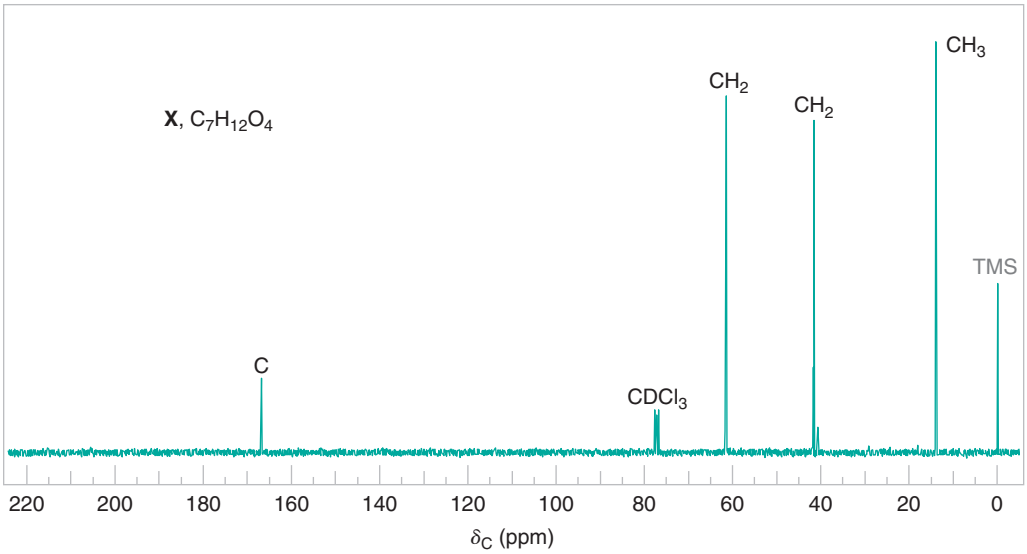


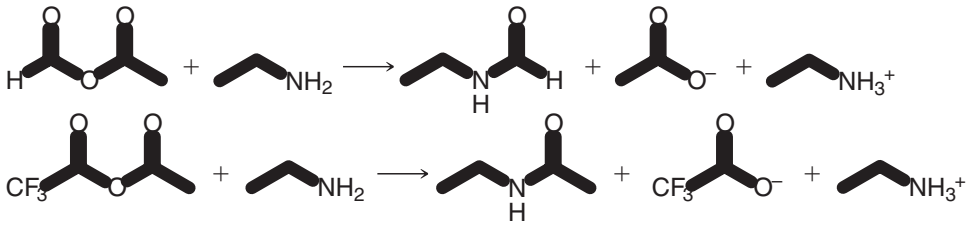
Figure 17.8 Broadband proton-decoupled ^{13}C NMR spectrum of compound **X**, Problem 17.47. Information from the DEPT ^{13}C NMR spectra is given above each peak.

17.48 Compound **Y** ($C_8H_4O_3$) dissolves slowly when warmed with aqueous sodium bicarbonate. The IR spectrum of **Y** has strong peaks at 1779 and at 1854 cm^{-1}. The broadband proton-decoupled ^{13}C spectrum of **Y** exhibits signals at δ 125 (CH), 130 (C), 136 (CH), and 162 (C). Acidification of the bicarbonate solution of **Y** gave compound **Z**. The proton-decoupled ^{13}C NMR spectrum of **Z** showed four signals. When **Y** was warmed in ethanol, a compound **AA** was produced. The ^{13}C NMR spectrum of **AA** displayed 10 signals. Propose structures for **Y, Z,** and **AA.**

Challenge Problems

17.49 Ketene, $H_2C{=}C{=}O$, is an important industrial chemical. Predict the products that would be formed when ketene reacts with **(a)** ethanol, **(b)** acetic acid, and **(c)** ethylamine. [*Hint*: Markovnikov addition occurs.]

17.50 Two unsymmetrical anhydrides react with ethylamine as follows:



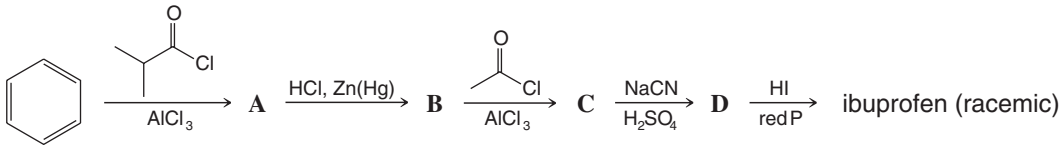
Explain the factors that might account for the formation of the products in each reaction.

17.51 Starting with 1-naphthol, suggest an alternative synthesis of the insecticide Sevin to the one given in Section 17.9A.

17.52 Suggest a synthesis of ibuprofen (Section 5.11) from benzene, employing **chloromethylation** as one step. Chloromethylation is a special case of the Friedel–Crafts reaction in which a mixture of HCHO and HCl, in the presence of $ZnCl_2$, introduces a $-CH_2Cl$ group into an aromatic ring.

Openmirrors.com

17.53 An alternative synthesis of ibuprofen is given below. Supply the structural formulas for compounds **A–D**:



17.54 As a method for the synthesis of cinnamaldehyde (3-phenyl-2-propenal), a chemist treated 3-phenyl-2-propen-1-ol with $K_2Cr_2O_7$ in sulfuric acid. The product obtained from the reaction gave a signal at δ 164.5 in its ^{13}C NMR spectrum. Alternatively, when the chemist treated 3-phenyl-2-propen-1-ol with PCC in CH_2Cl_2, the ^{13}C NMR spectrum of the product displayed a signal at δ 193.8. (All other signals in the spectra of both compounds appeared at similar chemical shifts.) **(a)** Which reaction produced cinnamaldehyde? **(b)** What was the other product?

Learning Group Problems

The Chemical Synthesis of Peptides Carboxylic acids and acyl derivatives of the carboxyl functional group are very important in biochemistry. For example, the carboxylic acid functional group is present in the family of lipids called fatty acids. Lipids called glycerides contain the ester functional group, a derivative of carboxylic acids. Furthermore, the entire class of biopolymers called proteins contain repeating amide functional group linkages. Amides are also derivatives of carboxylic acids. Both laboratory and biochemical syntheses of proteins require reactions that involve substitution at activated acyl carbons.

This Learning Group Problem focuses on the chemical synthesis of small proteins, called peptides. The essence of peptide or protein synthesis is formation of the amide functional group by reaction of an activated carboxylic acid derivative with an amine.

First we shall consider reactions for traditional chemical synthesis of peptides and then we look at reactions used in automated solid-phase peptide synthesis. The method for solid-phase peptide synthesis was invented by R. B. Merrifield (Rockefeller University), for which he earned the 1984 Nobel Prize in Chemistry. Solid-phase peptide synthesis reactions are so reliable that they have been incorporated into machines called peptide synthesizers (Section 24.7D).

1. The first step in peptide synthesis is blocking (protection) of the amine functional group of an amino acid (a compound that contains both amine and carboxylic acid functional groups). Such a reaction is shown in Section 24.7C in the reaction between Ala (alanine) and benzyl chloroformate. The functional group formed in the structure labeled Z-Ala is called a carbamate (or urethane). (Z is a benzyloxycarbonyl group, $C_6H_5CH_2OC(=O)-$).

(a) Write a detailed mechanism for formation of Z-Ala from Ala and benzyl chloroformate in the presence of hydroxide.

(b) In the reaction of part (a), why does the amino group act as the nucleophile preferentially over the carboxylate anion?

(c) Another widely used amino protecting group is the 9-fluorenylmethoxycarbonyl (Fmoc) group. Fmoc is the protecting group most often used in automated solid-phase peptide synthesis (see part 4 below). Write a detailed mechanism for formation of an Fmoc-protected amino acid under the conditions given in Section 24.7A.

2. The second step in the reactions of Section 24.7C is the formation of a mixed anhydride. Write a detailed mechanism for the reaction between Z-Ala and ethyl chloroformate ($ClCO_2C_2H_5$) in the presence of triethylamine to form the mixed anhydride. What is the purpose of this step?

3. The third step in the sequence of reactions in Section 24.7C is the one that actually joins the new amino acid (in this case leucine, abbreviated Leu) by another amide functional group. Write a detailed mechanism for this step (from the mixed anhydride of Z-Ala to Z-Ala-Leu). Show how CO_2 and ethanol are formed in the course of this mechanism.

4. A sequence of reactions commonly used for solid-phase peptide synthesis is shown in Section 24.7D.

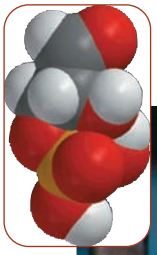
(a) Write a detailed mechanism for step 1, in which diisopropylcarbodiimide is used to join the carboxyl group of the first amino acid (in Fmoc-protected form) to a hydroxyl group on the polymer solid support.

(b) Step 3 of the automated synthesis involves removal of the Fmoc group by reaction with piperidine (a reaction also shown in Section 24.7A). Write a detailed mechanism for this step.

18

Reactions at the α Carbon of Carbonyl Compounds

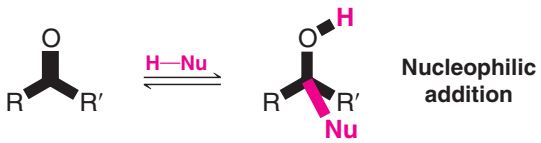
Enols and Enolates



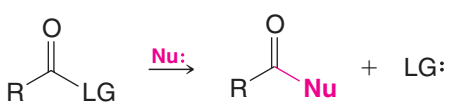
Glyceraldehyde-3-phosphate (GAP).

When we exercise vigorously, our bodies rely heavily on the metabolic process of glycolysis to derive energy from glucose. Glycolysis splits glucose into two three-carbon molecules. Only one of these three-carbon molecules (glyceraldehyde-3-phosphate, GAP, shown above) is directly capable of going further in the glycolytic pathway. The other three-carbon molecule (dihydroxyacetone-3-phosphate, DHAP) is not wasted, however. It is converted to a second molecule of GAP, via a type of intermediate that is key to our studies in this chapter—an enol (so named because the intermediate is an alk**en**e alcoh**ol**). We shall learn about enols and enolates, their conjugate bases, in this chapter.

In Chapter 16, we saw how aldehydes and ketones can undergo nucleophilic addition at their carbonyl groups. For example:



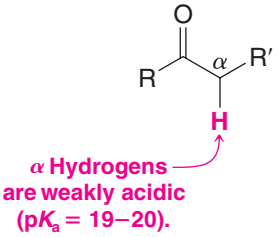
In Chapter 17 we saw how substitution could occur at a carbonyl group if a suitable leaving group is present. This type of reaction is called acyl substitution. For example:



(Proton transfer steps are involved in some nucleophilic addition and acyl substitution reactions, as detailed in Chapters 16 and 17.)

Openmirrors.com

In this chapter we shall discuss reactions that derive from the weak acidity of hydrogen atoms on carbon atoms adjacent to α carbonyl group. These hydrogen atoms are called the **α hydrogens**, and the carbon to which they are attached is called the **α carbon**.



18.1 *The Acidity of the α Hydrogens of Carbonyl Compounds: Enolate Anions*

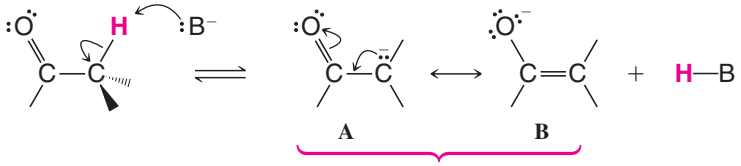
When we say that the α hydrogens of carbonyl compounds are acidic, *we mean that they are unusually acidic for hydrogen atoms attached to carbon.*

- The pK_a values for the α hydrogens of most simple aldehydes or ketones are of the order of 19–20.

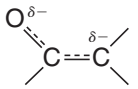
This means that they are more acidic than hydrogen atoms of ethyne, $pK_a = 25$, and are far more acidic than the hydrogens of ethene ($pK_a = 44$) or of ethane ($pK_a = 50$).

The reasons for the unusual acidity of the α hydrogens of carbonyl compounds are straightforward.

- The carbonyl group is strongly electron withdrawing, and when a carbonyl compound loses an α proton, the anion that is produced, called an **enolate**, is stabilized by delocalization.

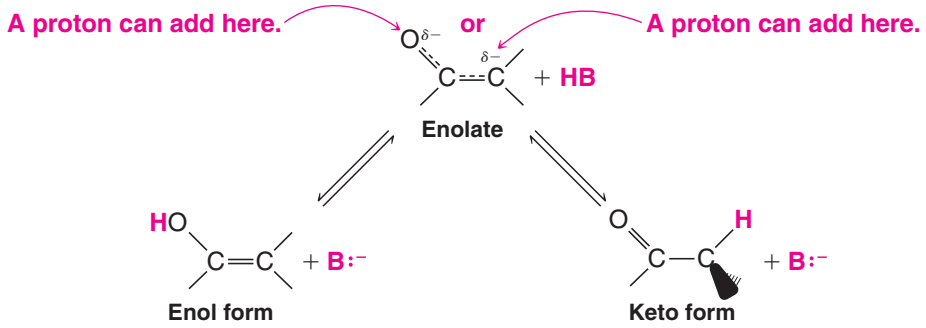


Two resonance structures, **A** and **B**, can be written for the enolate. In structure **A** the negative charge is on carbon, and in structure **B** the negative charge is on oxygen. Both structures contribute to the hybrid. Although structure **A** is favored by the strength of its carbon–oxygen π bond relative to the weaker carbon–carbon π bond of **B**, structure **B** makes a greater contribution to the hybrid because oxygen, being highly electronegative, is better able to accommodate the negative charge. We can depict the enolate hybrid in the following way:



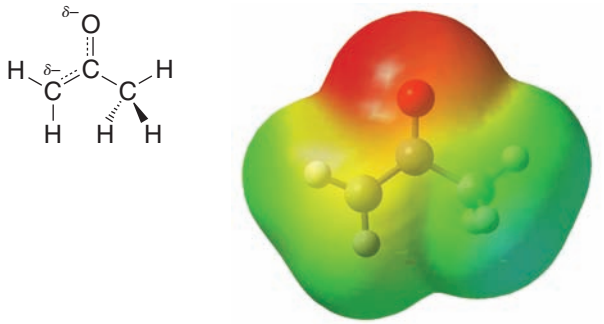
When this resonance-stabilized enolate accepts a proton, it can do so in either of two ways: It can accept the proton at carbon to form the original carbonyl compound in what is called the **keto form** or it may accept the proton at oxygen to form an **enol** (alk**en**e alco**hol**).

- The enolate is the conjugate base of both the enol and keto forms.



Both of these reactions are reversible.

A calculated electrostatic potential map for the enolate of acetone is shown below. The map indicates approximately the outermost extent of electron density (the van der Waals surface) of the acetone enolate. Red color near the oxygen is consistent with oxygen being better able to stabilize the excess negative charge of the anion. Yellow at the carbon where the α hydrogen was removed indicates that some of the excess negative charge is localized there as well. These implications are parallel with the conclusions above about charge distribution in the hybrid based on delocalization and electronegativity effects.



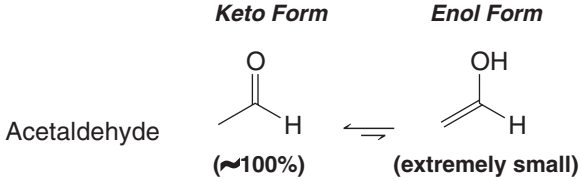
Acetone enolate

18.2 Keto and Enol Tautomers

The keto and enol forms of carbonyl compounds are constitutional isomers, but of a special type. Because they are easily interconverted in the presence of traces of acids and bases, chemists use a special term to describe this type of constitutional isomerism.

- Interconvertible keto and enol forms are called **tautomers**, and their interconversion is called **tautomerization**.

Under most circumstances, we encounter keto–enol tautomers in a state of equilibrium. (The surfaces of ordinary laboratory glassware are able to catalyze the interconversion and establish the equilibrium.) For simple monocarbonyl compounds such as acetone and acetaldehyde, the amount of the enol form present at equilibrium is *very small*. In acetone it is much less than 1%; in acetaldehyde the enol concentration is too small to be detected. The greater stability of the following keto forms of monocarbonyl compounds can be related to the greater strength of the carbon–oxygen π bond compared to the carbon–carbon π bond (~364 versus ~250 kJ mol^{-1}):



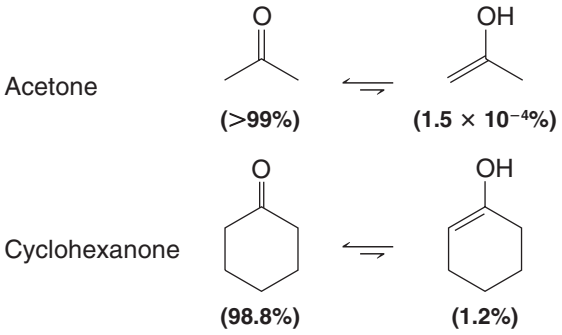
Helpful Hint

Keto–enol tautomers are not resonance structures. They are constitutional isomers in equilibrium (generally favoring the keto form).

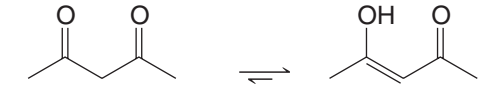
Openmirrors.com

Helpful Hint

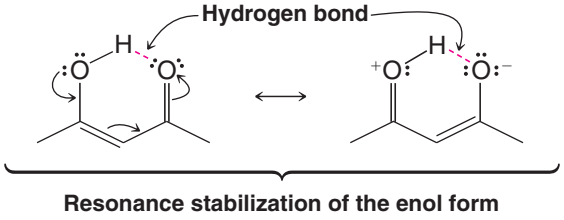
See "The Chemistry of... TIM (Triose Phosphate Isomerase) Recycles Carbon via an Enol" in *WileyPLUS* for more information relating to this chapter's opener about an important energy-yielding biochemical process.



In compounds whose molecules have two carbonyl groups separated by one carbon atom (called β-dicarbonyl compounds), the amount of enol present at equilibrium is far higher. For example, pentane-2,4-dione exists in the enol form to an extent of 76%:



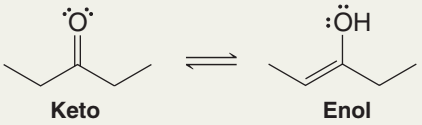
- The greater stability of the enol form of β-dicarbonyl compounds can be attributed to resonance stabilization of the conjugated double bonds and (in a cyclic form) through hydrogen bonding.



Solved Problem 18.1

Write bond-line structures for the keto and enol forms of 3-pentanone.

ANSWER



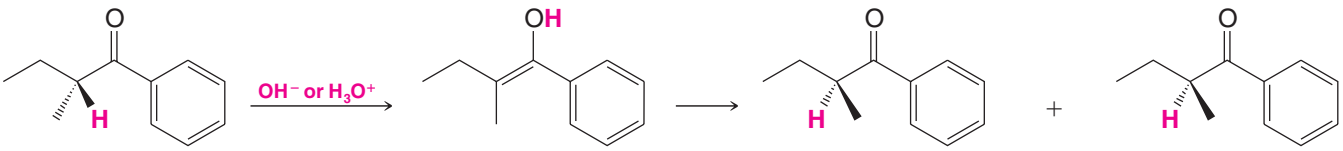
Review Problem 18.1

For all practical purposes, the compound cyclohexa-2,4-dien-1-one exists totally in its enol form. Write the structure of cyclohexa-2,4-dien-1-one and of its enol form. What special factor accounts for the stability of the enol form?

18.3 Reactions via Enols and Enolates

18.3A Racemization

When a solution of (*R*)-(+)-2-methyl-1-phenylbutan-1-one (see the following reaction) in aqueous ethanol is treated with either acids or bases, the solution gradually loses its optical activity. After a time, isolation of the ketone shows that it has been completely racemized. The (+) form of the ketone has been converted to an equimolar mixture of its enantiomers through its enol form.



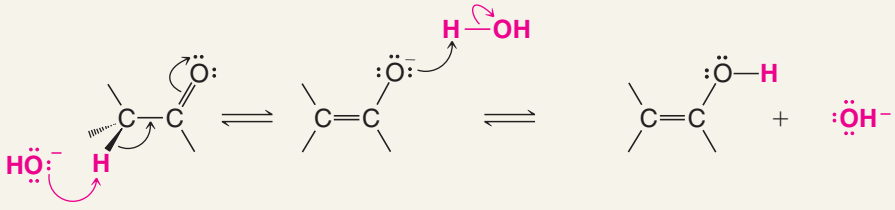
(*R*)-(+)-2-Methyl-1-phenylbutan-1-one | Enol (achiral) | (±)-2-Methyl-1-phenylbutan-1-one (racemic form)

- Racemization at an α carbon takes place in the presence of acids or bases because the keto form slowly but reversibly changes to its enol *and the enol is achiral*. When the enol reverts to the keto form, it can produce equal amounts of the two enantiomers.

A base catalyzes the formation of an enol through the intermediate formation of an enolate anion.

A MECHANISM FOR THE REACTION

Base-Catalyzed Enolization

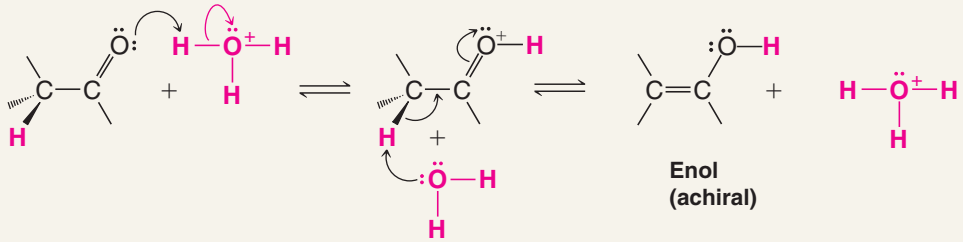


Enolate (achiral) | Enol (achiral)

An acid can catalyze enolization in the following way.

A MECHANISM FOR THE REACTION

Acid-Catalyzed Enolization

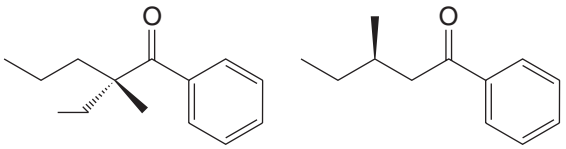


Openmirrors.com

In acyclic ketones, the enol or enolate formed can be (*E*) or (*Z*). Protonation on one face of the (*E*) isomer and protonation on the same face of the (*Z*) isomer produces enantiomers.

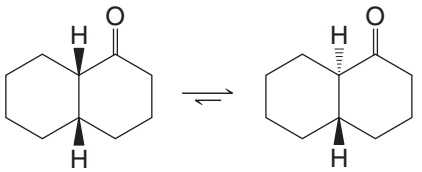
Review Problem 18.2

Would optically active ketones such as the following undergo acid- or base-catalyzed racemization? Explain your answer.



- Diastereomers that differ in configuration at only one of several chirality centers are sometimes called **epimers**.

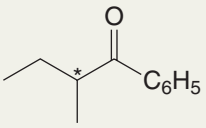
Keto–enol tautomerization can sometimes be used to convert a less stable epimer to a more stable one. This equilibration process is an example of **epimerization**. An example is the epimerization of *cis*-decalone to *trans*-decalone:



***cis*-Decalone** ⇌ ***trans*-Decalone**

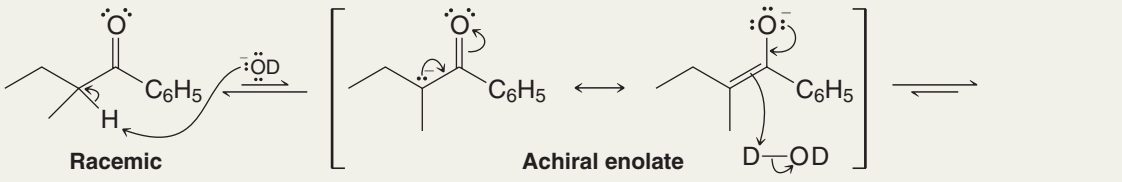
Solved Problem 18.2

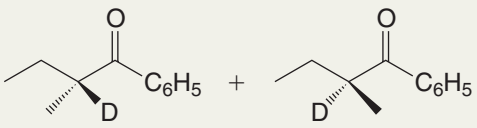
Treating racemic 2-methyl-1-phenylbutan-1-one with NaOD in the presence of D_2O produces a deuterium-labeled compound as a racemic form. Write a mechanism that explains this result.



Racemic

STRATEGY AND ANSWER Either enantiomer of the ketone can transfer an α proton to the $^-$OD ion to form an achiral enolate which can accept a deuteron to form a racemic mixture of the deuterium-labeled product.





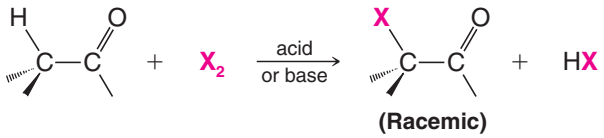
Racemic

Review Problem 18.3

Write a mechanism using sodium ethoxide in ethanol for the epimerization of *cis*-decalone to *trans*-decalone. Draw chair conformational structures that show why *trans*-decalone is more stable than *cis*-decalone. You may find it helpful to also examine handheld molecular models of *cis*- and *trans*-decalone.

18.3B Halogenation at the α Carbon

- Carbonyl compounds bearing an α hydrogen can undergo halogen substitution at the α carbon in the presence of acid or base.

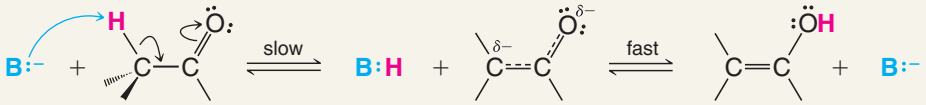


Base-Promoted Halogenation In the presence of bases, halogenation takes place through the slow formation of an enolate anion or an enol followed by a rapid reaction of the enolate or enol with halogen.

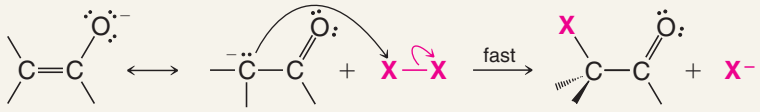
A MECHANISM FOR THE REACTION

Base-Promoted Halogenation of Aldehydes and Ketones

Step 1



Step 2



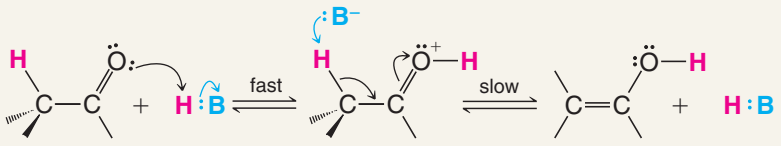
As we shall see in Section 18.3C, multiple halogenations can occur.

Acid-Catalyzed Halogenation In the presence of acids, halogenation takes place through the slow formation of an enol followed by rapid reaction of the enol with the halogen.

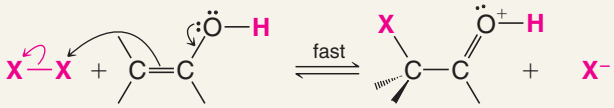
A MECHANISM FOR THE REACTION

Acid-Catalyzed Halogenation of Aldehydes and Ketones

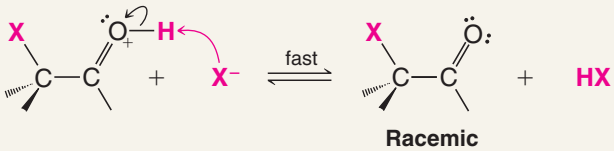
Step 1



Step 2



Step 3



Openmirrors.com

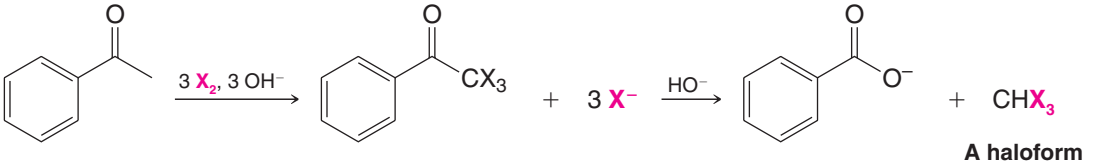
Part of the evidence that supports these mechanisms comes from studies of reaction kinetics. Both base-promoted and acid-catalyzed halogenations of ketones *show initial rates that are independent of the halogen concentration*. The mechanisms that we have written are in accord with this observation: In both instances the slow step of the mechanism occurs before the intervention of the halogen. (The initial rates are also independent of the nature of the halogen; see Review Problem 18.5.)

Review Problem 18.4 Why do we say that the halogenation of ketones in a base is "base promoted" rather than "base catalyzed"?

Review Problem 18.5 Additional evidence for the halogenation mechanisms that we just presented comes from the following facts: **(a)** Optically active 2-methyl-l-phenylbutan-1-one undergoes acid-catalyzed racemization at a rate exactly equivalent to the rate at which it undergoes acid-catalyzed halogenation. **(b)** 2-Methyl-1-phenylbutan-1-one undergoes acid-catalyzed iodination at the same rate that it undergoes acid-catalyzed bromination. **(c)** 2-Methyl-1-phenylbutan-1-one undergoes base-catalyzed hydrogen–deuterium exchange at the same rate that it undergoes base-promoted halogenation. Explain how each of these observations supports the mechanisms that we have presented.

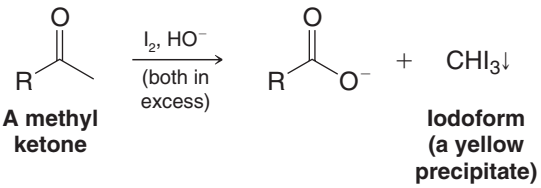
18.3C The Haloform Reaction

When methyl ketones react with halogens in the presence of excess base, multiple halogenations always occur at the carbon of the methyl group. Multiple halogenations occur because introduction of the first halogen (owing to its electronegativity) makes the remaining α hydrogens on the methyl carbon more acidic. The resulting CX_3 group bonded to the carbonyl can be a leaving group, however. Thus, when hydroxide is the base, an acyl substitution reaction follows, leading to a carboxylate salt and a haloform (CHX_3, e.g., chloroform, bromoform, or iodoform). The following is an example.



The haloform reaction is one of the rare instances in which a carbanion acts as a leaving group. This occurs because the trihalomethyl anion is unusually stable; its negative charge is dispersed by the three electronegative halogen atoms (when X = Cl, the conjugate acid, $CHCl_3$, has $pK_a = 13.6$). In the last step, a proton transfer takes place between the carboxylic acid and the trihalomethyl anion.

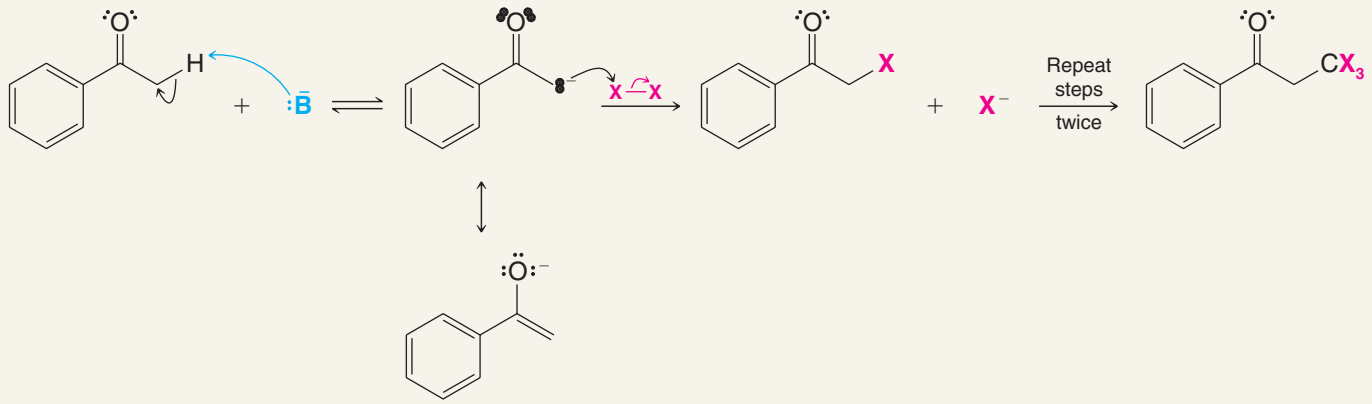
The **haloform reaction** is synthetically useful as a means of converting methyl ketones to carboxylic acids. When the haloform reaction is used in synthesis, chlorine and bromine are most commonly used as the halogen component. Chloroform ($CHCl_3$) and bromoform ($CHBr_3$) are both liquids which are immiscible with water and are easily separated from the aqueous solution containing the carboxylate anion. When iodine is the halogen component, the bright yellow solid iodoform (CHI_3) results. This version is the basis of the iodoform classification test for methyl ketones and methyl secondary alcohols (which are oxidized to methyl ketones first under the reaction conditions):



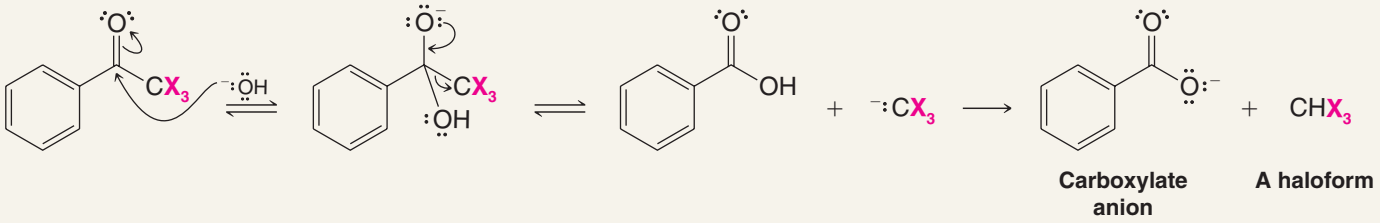
A MECHANISM FOR THE REACTION

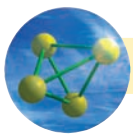
The Haloform Reaction

Halogenation Step



Acyl substitution step





THE CHEMISTRY OF . . .

Chloroform in Drinking Water

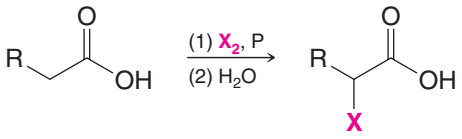
When water is chlorinated to purify it for public consumption, chloroform is produced from organic impurities in the water via the haloform reaction. (Many of these organic impurities are naturally occurring, such as humic substances.) The presence of chloroform in public water is of concern for water treatment plants and environmental officers, because chloroform is carcinogenic. Thus, the technology that solves one problem creates another. It is worth recalling, however, that before chlorination of water was introduced, thousands of people died in epidemics of diseases such as cholera and dysentery.

18.3D α-Halo Carboxylic Acids: The Hell–Volhard–Zelinski Reaction

Carboxylic acids bearing α hydrogen atoms react with bromine or chlorine in the presence of phosphorus (or a phosphorus halide) to give α-halo carboxylic acids through a reaction known as the Hell–Volhard–Zelinski (or HVZ) reaction.

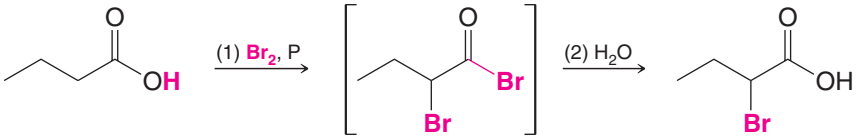
Openmirrors.com

General Reaction



α-Halo acid

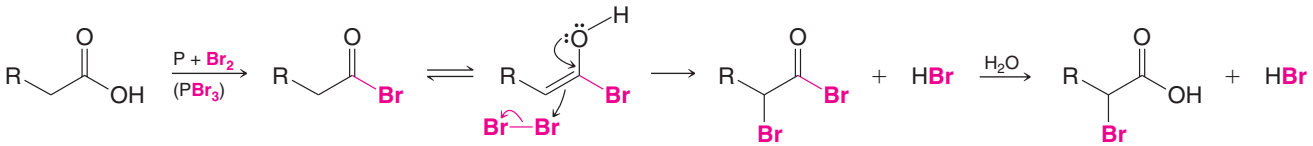
Specific Example



Butanoic acid **2-Bromobutanoic acid (77%)**

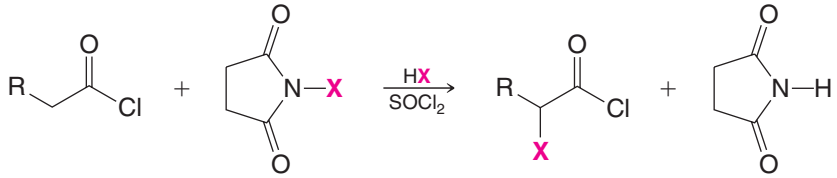
If more than one molar equivalent of bromine or chlorine is used in the reaction, the products obtained are α,α-dihalo acids or α,α,α-trihalo acids.

Important steps in the reaction are formation of an acyl halide and the enol derived from the acyl halide. The acyl halide is key because carboxylic acids do not form enols readily since the carboxylic acid proton is removed before the α hydrogen. Acyl halides lack the carboxylic acid hydrogen.



Acyl bromide **Enol form**

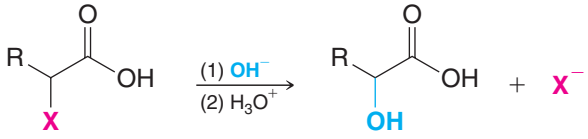
An alternative method for α-halogenation has been developed by D. N. Harpp (McGill University). Acyl chlorides, formed *in situ* by the reaction of the carboxylic acid with $SOCl_2$, are treated with the appropriate *N*-halosuccinimide and a trace of HX to produce α-chloro and α-bromo acyl chlorides.



α-Iodo acyl chlorides can be obtained by using molecular iodine in a similar reaction.

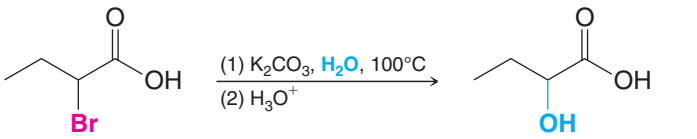
α-Halo acids are important synthetic intermediates because they are capable of reacting with a variety of nucleophiles:

Conversion to α-Hydroxy Acids



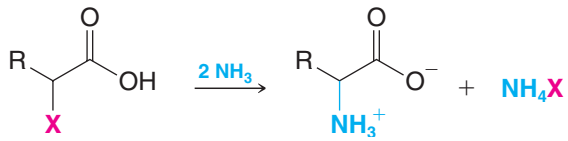
α-Halo acid **α-Hydroxy acid**

Specific Example



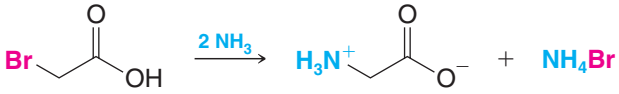
2-Hydroxybutanoic acid (69%)

Conversion to α-Amino Acids



α-Halo acid **α-Amino acid**

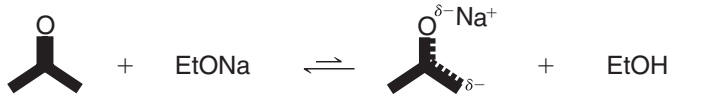
Specific Example



Aminoacetic acid (glycine) (60-64%)

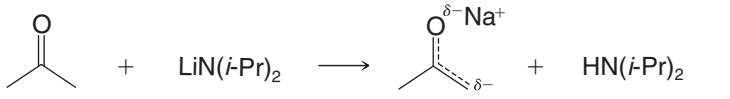
18.4 *Lithium Enolates*

The position of the equilibrium by which an enolate forms depends on the strength of the base used. If the base employed is a weaker base than the enolate, then the equilibrium lies to the left. This is the case, for example, when a ketone is treated with sodium ethoxide in ethanol.



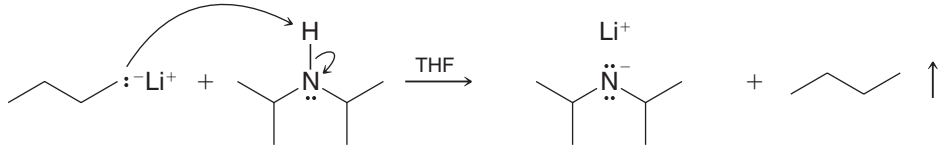
Weaker acid (pK_a = 19) **Weaker base** **Stronger base** **Stronger acid (pK_a = 16)**

On the other hand, if a very strong base is employed, the equilibrium lies far to the right. One very useful strong base for converting carbonyl compounds to enolates is **lithium diisopropylamide (LDA)** or LiN(i-Pr)2:



Ketone (stronger acid) (pK_a = 19) **LDA (stronger base)** **Enolate (weaker base)** **Diisopropylamine (weaker acid) (pK_a = 38)**

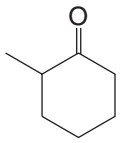
- Lithium diisopropylamide (LDA) can be prepared by dissolving diisopropylamine in a solvent such as diethyl ether or THF and treating it with an alkyllithium:



Butyllithium (BuLi) **Diisopropylamine (pK_a = 38)** **Lithium diisopropylamide [LDA or $LiN(i\text{-}Pr)_2$]** **Butane (pK_a = 50)**

Openmirrors.com

18.4A Regioselective Formation of Enolates



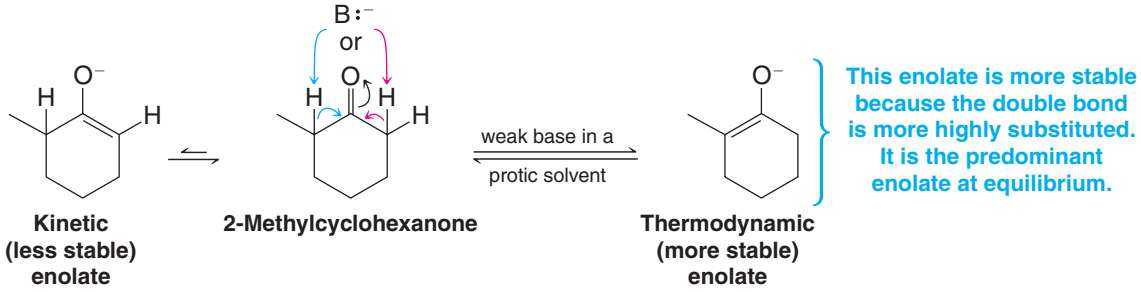
2-Methylcyclohexanone

An unsymmetrical ketone such as 2-methylcyclohexanone can form two possible enolates, arising by removal of an α hydrogen from one side or the other of the carbonyl group. Which enolate predominates in the reaction depends on whether the enolate is formed under conditions that favor an acid–base equilibrium.

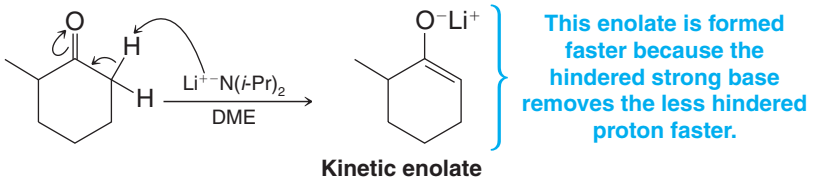
- The **thermodynamic enolate** is that which is most stable among the possible enolates. Enolate stability is evaluated in the same way as for alkenes, meaning that the more highly substituted enolate is the more stable one.
- The **thermodynamic enolate** predominates under conditions where a deprotonation–protonation equilibrium allows interconversion among the possible enolates, such that eventually the more stable enolate exists in higher concentration. This is the case when the pK_a of the conjugate acid of the base is similar to the pK_a of the α hydrogen of the carbonyl compound. Use of hydroxide or an alkoxide in a protic solvent favors formation of the thermodynamic enolate.
- The **kinetic enolate** is that which is formed fastest. It is usually formed by removal of the least sterically hindered α hydrogen.
- The **kinetic enolate** predominates under conditions that do not favor equilibrium among the possible enolates. Use of a very strong and sterically hindered base in an aprotic solvent, such as LDA in tetrahydrofuran (THF) or dimethoxyethane (DME) favors formation of the kinetic enolate.

Conditions favoring formation of the thermodynamic and kinetic enolates from 2-methylcyclohexanone are illustrated below.

Formation of a Thermodynamic Enolate



Formation of a Kinetic Enolate

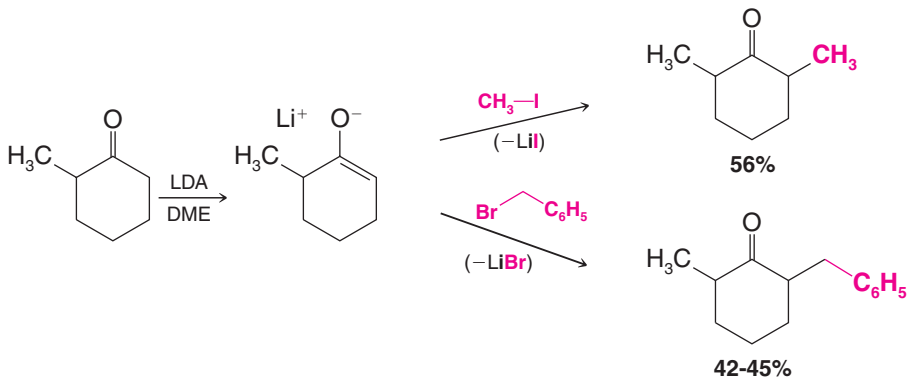


18.4B Direct Alkylation of Ketones via Lithium Enolates

Helpful Hint

Alkylation of lithium enolates is a useful method for synthesis.

The formation of lithium enolates using lithium diisopropylamide furnishes a useful way of alkylating ketones in a regioselective way. For example, the lithium enolate formed from 2-methylcyclohexanone can be methylated or benzylated at the less hindered α carbon by allowing it to react with LDA followed by methyl iodide or benzyl bromide, respectively:



Alkylation reactions like these have an important limitation, however, because the reactions are S_N2 reactions, and also because enolates are strong bases.

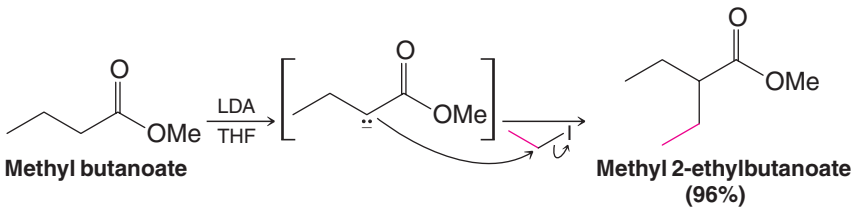
- Successful alkylations occur only when primary alkyl, primary benzylic, and primary allylic halides are used. With secondary and tertiary halides, elimination becomes the main course of the reaction.

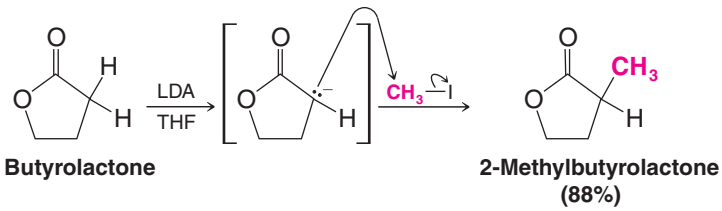
Helpful Hint

Proper choice of the alkylating agent is key to successful lithium enolate alkylation.

18.4C Direct Alkylation of Esters

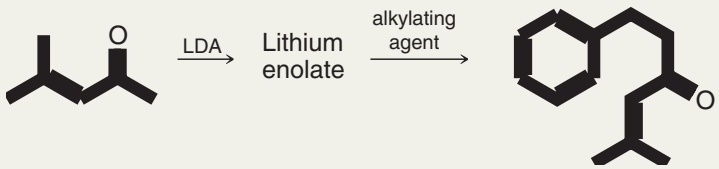
Examples of the **direct alkylation** of esters are shown below. In the second example the ester is a lactone (Section 17.7C):



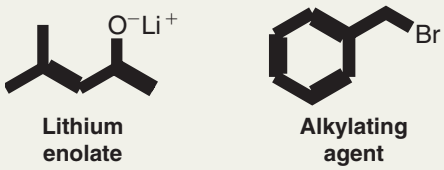


Solved Problem 18.3

The following synthesis illustrates the alkylation of a ketone via a lithium enolate. Give the structures of the enolate and the alkylating agent.



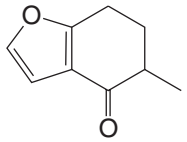
ANSWER



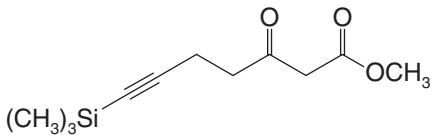
Openmirrors.com

Review Problem 18.6

(a) Write a reaction involving a lithium enolate for introduction of the methyl group in the following compound (an intermediate in a synthesis by E. J. Corey of cafestol, an anti-inflammatory agent found in coffee beans):

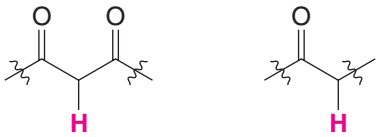


(b) Dienolates can be formed from β-keto esters using two equivalents of LDA. The dienolate can then be alkylated selectively at the more basic of the two enolate carbons. Write a reaction for synthesis of the following compound using a dienolate and the appropriate alkyl halide:

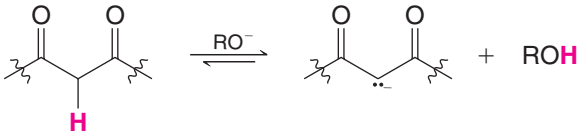


18.5 Enolates of β-Dicarbonyl Compounds

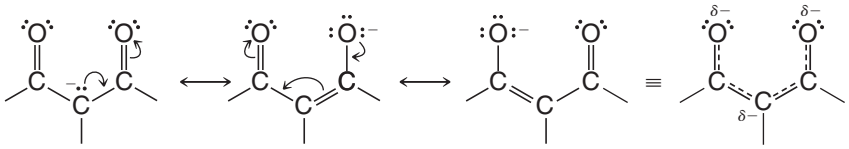
- Hydrogen atoms that are between two carbonyl groups, as in a **β-dicarbonyl compound**, have pK_a values in the range of 9–11. Such α-hydrogen atoms are much more acidic than α hydrogens adjacent to only one carbonyl group, which have pK_a values of 18–20.



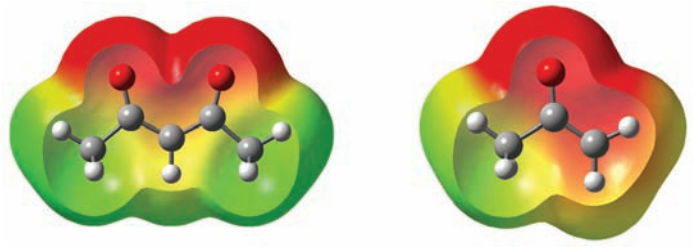
- A much weaker base than LDA, such as an alkoxide, can be used to form an enolate from a β-dicarbonyl compound.



We can account for the greater acidity of β-dicarbonyl systems, as compared to single carbonyl systems, by delocalization of the negative charge to two oxygen atoms instead of one. We can represent this delocalization by drawing contributing resonance structures for a β-dicarbonyl enolate and its resonance hybrid:

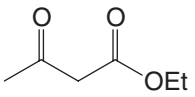


We can visualize the enhanced charge delocalization of a β-dicarbonyl enolate by examining maps of electrostatic potential for enolates derived from pentane-2,4-dione and acetone. Here we see that the negative charge of the enolate from pentane-2,4-dione is associated substantially with the two oxygen atoms, as compared with the enolate from acetone, where significant negative charge in the enolate remains at the α-carbon atom:

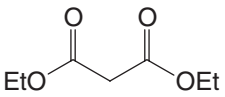


Pentane-2,4-dione enolate Acetone enolate

Two specific β-dicarbonyl compounds have had broad use in organic synthesis. These are acetoacetic ester (ethyl acetoacetate, ethyl 3-oxobutanoate), which can be used to make substituted acetone derivatives, and diethyl malonate (diethyl 1,3-propanedicarboxylic acid), which can be used to make substituted acetic acid derivatives. We shall consider syntheses involving ethyl acetoacetate and diethyl malonate in the upcoming sections of this chapter.



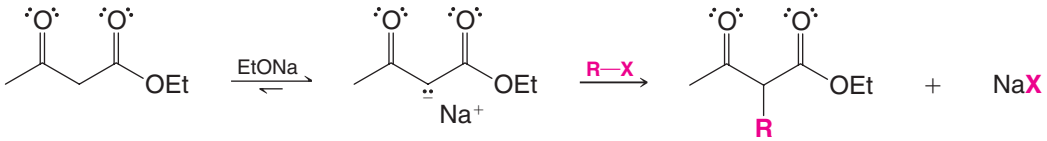
Acetoacetic ester (ethyl acetoacetate; ethyl 3-oxobutanoate)



Diethyl malonate (diethyl 1,3-propanedicarboxylic acid)

18.6 *Synthesis of Methyl Ketones: The Acetoacetic Ester Synthesis*

Acetoacetic ester, because it is a β-dicarbonyl compound, can easily be converted to an enolate using sodium ethoxide. We can then alkylate the resulting enolate (called sodioacetoacetic ester) with an alkyl halide. This process is called an **acetoacetic ester synthesis**.

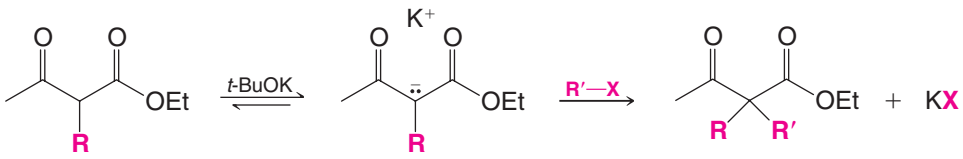


Acetoacetic ester **Sodioacetoacetic ester** **Monoalkylacetoacetic ester**

- Since the alkylation in the reaction above is an S_N2 reaction, the best yields are obtained from the use of primary alkyl halides (including primary allylic and benzylic halides) or methyl halides. Secondary halides give lower yields, and tertiary halides give only elimination.

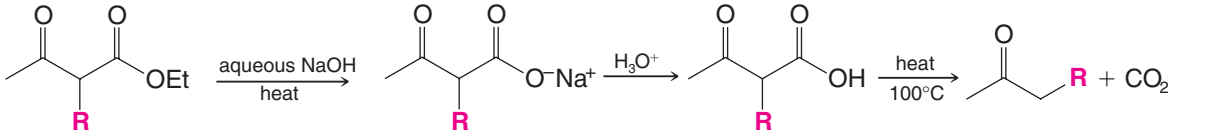
Dialkylation The monoalkylacetoacetic ester shown above still has one appreciably acidic hydrogen, and, if we desire, we can carry out a second alkylation. Because a monoalkylacetoacetic ester is somewhat less acidic than acetoacetic ester itself due to the electron-donating effect of the added alkyl group, it is usually helpful to use a stronger base than ethoxide ion for the second alkylation. Use of potassium *tert*-butoxide is common because it is a stronger base than sodium ethoxide. Potassium *tert*-butoxide, because of its steric bulk, is also not likely to cause transesterification.

Openmirrors.com



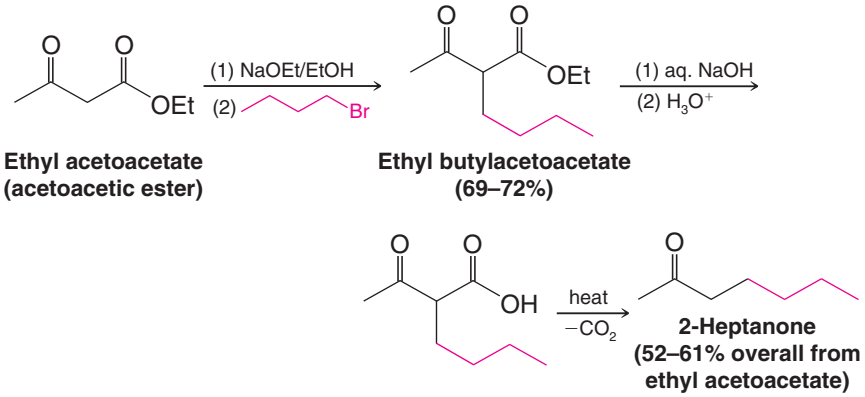
Monoalkylacetoacetic ester **Dialkylacetoacetic ester**

Substituted Methyl Ketones To synthesize a monosubstituted methyl ketone (monosubstituted acetone), we carry out only one alkylation. Then we hydrolyze the monoalkylacetoacetic ester using aqueous sodium or potassium hydroxide. Subsequent acidification of the mixture gives an alkyl-acetoacetic acid, and heating this β-keto acid to 100°C brings about decarboxylation (Section 17.10):



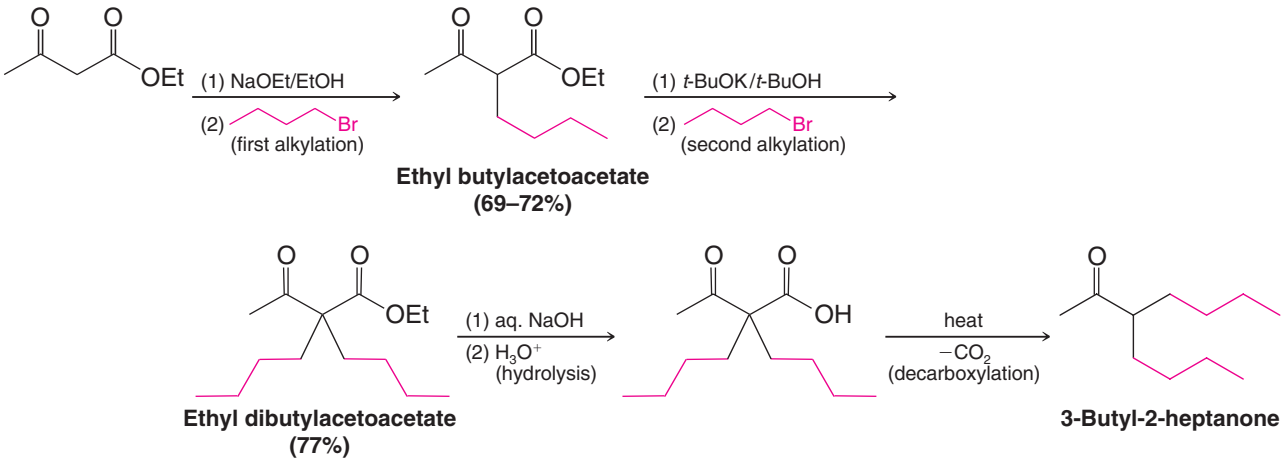
Basic hydrolysis of the ester group **Acidification** **Decarboxylation of the β-keto acid**

A specific example is the following synthesis of 2-heptanone:



Ethyl acetoacetate (acetoacetic ester) **Ethyl butylacetoacetate (69–72%)** **2-Heptanone (52–61% overall from ethyl acetoacetate)**

If our goal is the preparation of a disubstituted acetone, we carry out two successive alkylations, we hydrolyze the dialkylacetoacetic ester that is produced, and then we decarboxylate the dialkylacetoacetic acid. An example of this procedure is the synthesis of 3-butyl-2-heptanone.

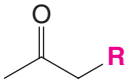


Ethyl butylacetoacetate (69–72%)

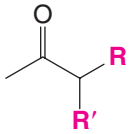
Ethyl dibutylacetoacetate (77%) **3-Butyl-2-heptanone**

Although both alkylations in the example just given were carried out with the same alkyl halide, we could have used different alkyl halides if our synthesis had required it.

- As we have seen, ethyl acetoacetate is a useful reagent for the preparation of substituted acetones (methyl ketones) of the types shown below.



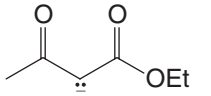
A monosubstituted acetone



A disubstituted acetone

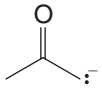
- Ethyl acetoacetate therefore serves as the synthetic equivalent of the enolate from acetone shown below.

A **synthetic equivalent** is a reagent whose structure, when incorporated into a product, gives the appearance of having come from one type of precursor when as a reactant it actually had a different structural origin. Although it is possible to form the enolate of acetone, use of ethyl acetoacetate as a synthetic equivalent is often more convenient because its α hydrogens are so much more acidic (pK_a = 9–11) than those of acetone itself (pK_a = 19–20). If we had wanted to use the acetone enolate directly, we would have had to use a much stronger base and other special conditions (see Section 18.4).



Ethyl acetoacetate ion

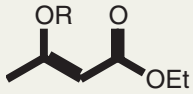
is the synthetic equivalent of



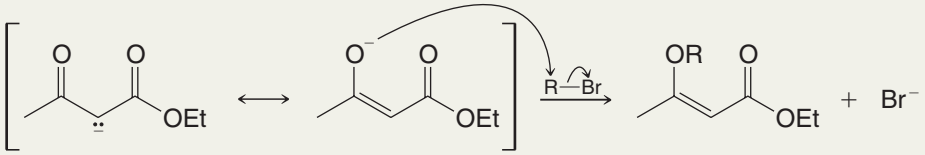
Acetone enolate

Solved Problem 18.4

Explain how compounds with the following general structure are formed as occasional side products of sodioacetoacetic ester alkylations.



STRATEGY AND ANSWER The partially negative oxygen atom of the sodioacetoacetic ester enolate acts as a nucleophile.

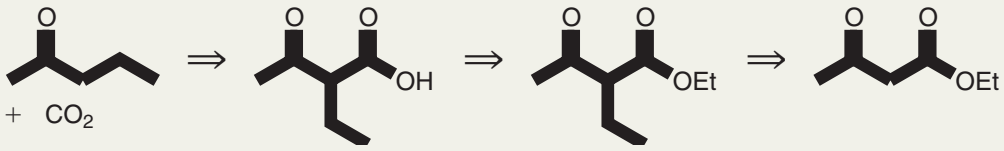


Solved Problem 18.5

Show how you would use the acetoacetic ester synthesis to prepare 2-pentanone.

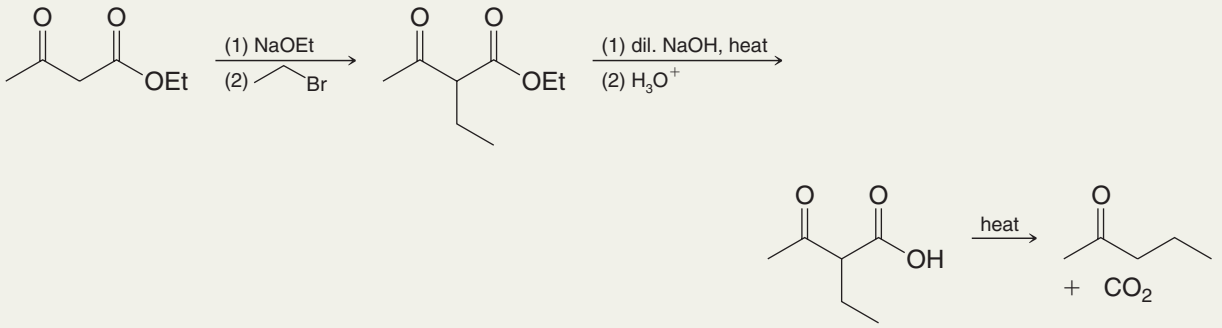
STRATEGY AND ANSWER

Retrosynthetic Analysis



Openmirrors.com

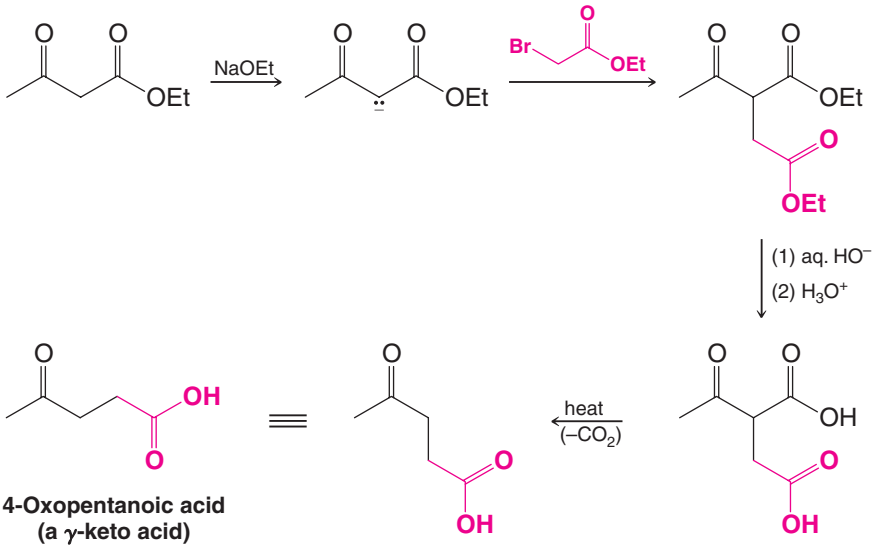
Synthesis



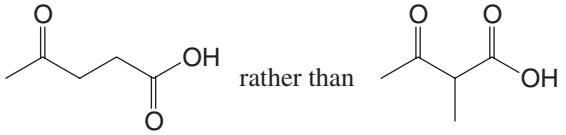
Review Problem 18.7 Show how you would use the acetoacetic ester synthesis to prepare (**a**) 3-propyl-2-hexanone and (**b**) 4-phenyl-2-butanone.

Review Problem 18.8 The acetoacetic ester synthesis generally gives best yields when primary halides are used in the alkylation step. Secondary halides give low yields, and tertiary halides give practically no alkylation product at all. (**a**) Explain. (**b**) What products would you expect from the reaction of sodioacetoacetic ester and *tert*-butyl bromide? (**c**) Bromobenzene cannot be used as an arylating agent in an acetoacetic ester synthesis in the manner we have just described. Why not?

The acetoacetic ester synthesis can also be carried out using halo esters and halo ketones. The use of an α-halo ester provides a convenient synthesis of γ-keto acids:

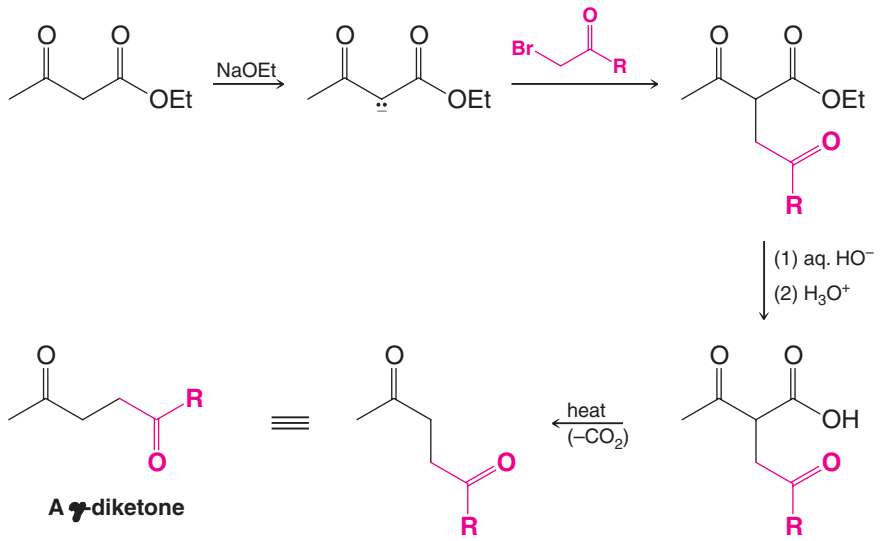


Review Problem 18.9 In the synthesis of the keto acid just given, the dicarboxylic acid decarboxylates in a specific way; it gives



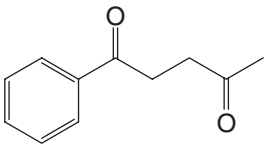
Explain.

The use of an α-halo ketone in an acetoacetic ester synthesis provides a general method for preparing γ-diketones:



How would you use the acetoacetic ester synthesis to prepare the following?

Review Problem 18.10

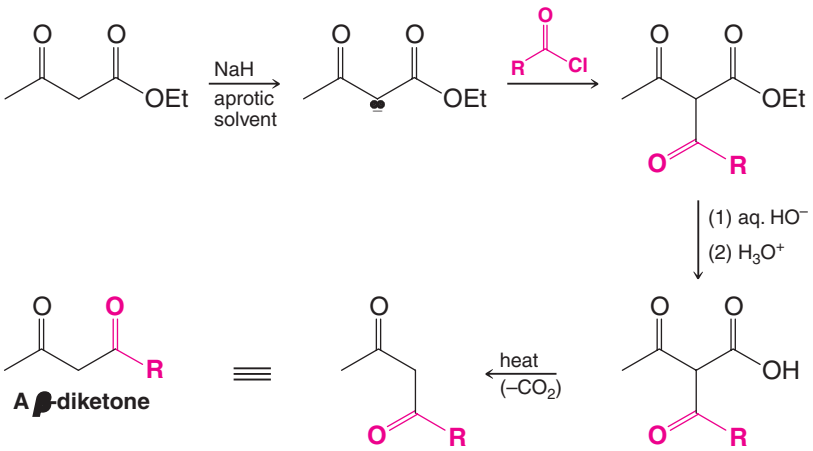


18.6A Acylation

Anions obtained from acetoacetic esters undergo acylation when they are treated with acyl chlorides or acid anhydrides. Because both of these acylating agents react with alcohols, acylation reactions cannot be carried out in ethanol and must be carried out in aprotic solvents such as DMF or DMSO (Section 6.13C). (If the reaction were to be carried out in ethanol, using sodium ethoxide, for example, then the acyl chloride would be rapidly converted to an ethyl ester and the ethoxide ion would be neutralized.) Sodium hydride can be used to generate the enolate ion in an aprotic solvent:

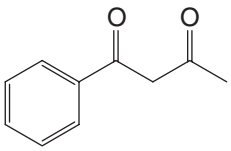
Helpful Hint

A method for synthesizing β-dicarbonyl compounds



How would you use the acetoacetic ester synthesis to prepare the following?

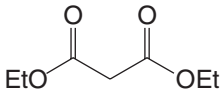
Review Problem 18.11



Openmirrors.com

18.7 Synthesis of Substituted Acetic Acids: The Malonic Ester Synthesis

A useful counterpart of the acetoacetic ester synthesis—one that allows the synthesis of *mono-* and *disubstituted acetic acids*—is called the **malonic ester synthesis.** The starting compound is the diester of a β-dicarboxylic acid, called a malonic ester. The most commonly used malonic ester is diethyl malonate.



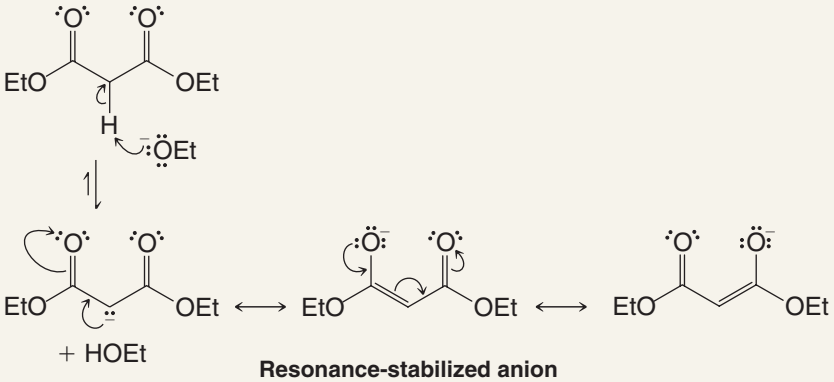
Diethyl malonate (a β-dicarboxylic acid ester)

We shall see by examining the following mechanism that the malonic ester synthesis resembles the acetoacetic ester synthesis in several respects.

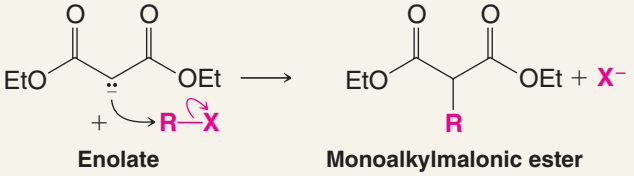
A MECHANISM FOR THE REACTION

The Malonic Ester Synthesis of Substituted Acetic Acids

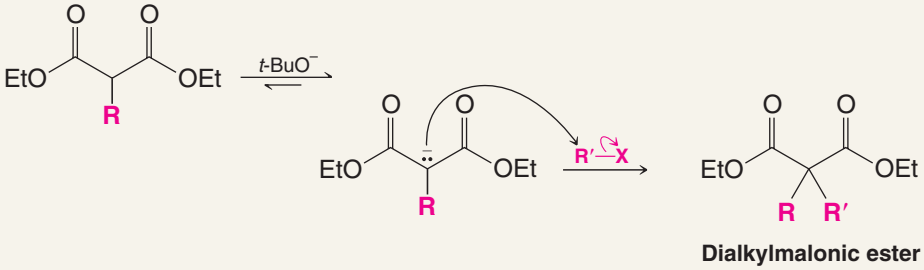
Step 1 *Diethyl malonate, the starting compound, forms a relatively stable enolate:*



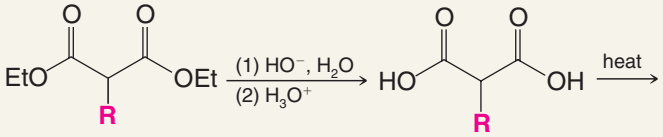
Step 2 *This enolate can be alkylated in an S_N2 reaction,*



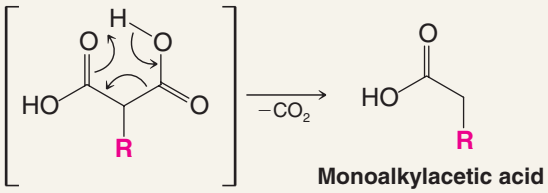
and the product can be alkylated again if our synthesis requires it:



Step 3 *The mono- or dialkylmalonic ester can then be hydrolyzed to a mono- or dialkylmalonic acid, and substituted malonic acids decarboxylate readily. Decarboxylation gives a mono- or disubstituted acetic acid:*

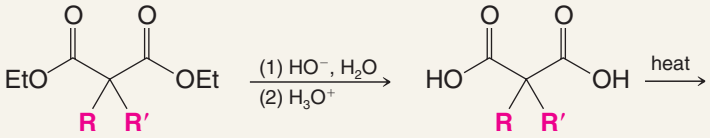


Monoalkylmalonic ester

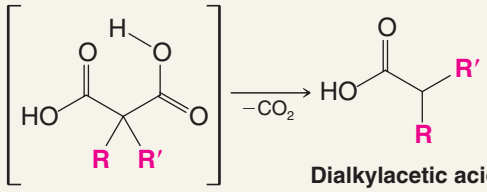


Monoalkylacetic acid

or after dialkylation,



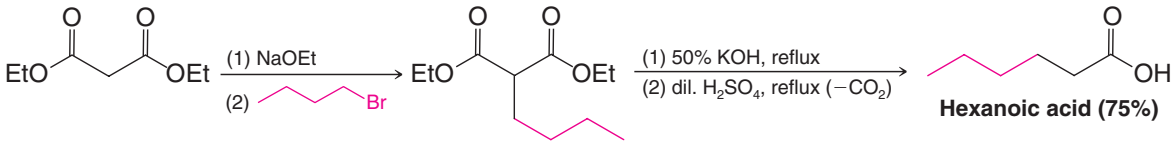
Dialkylmalonic ester



Dialkylacetic acid

Two specific examples of the malonic ester synthesis are the syntheses of hexanoic acid and 2-ethylpentanoic acid that follow.

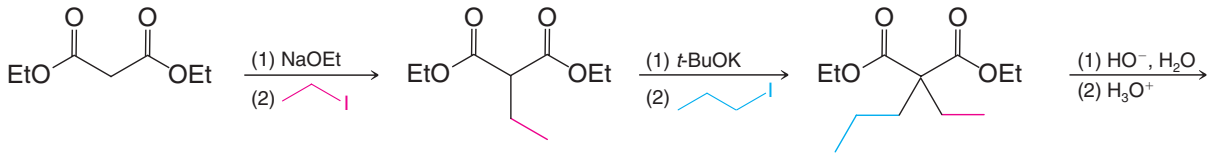
A Malonic Ester Synthesis of Hexanoic Acid



Hexanoic acid (75%)

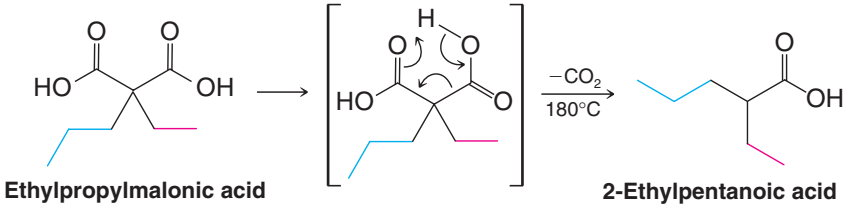
Diethyl butylmalonate (80–90%)

A Malonic Ester Synthesis of 2-Ethylpentanoic Acid



Diethyl ethylmalonate

Diethyl ethylpropylmalonate



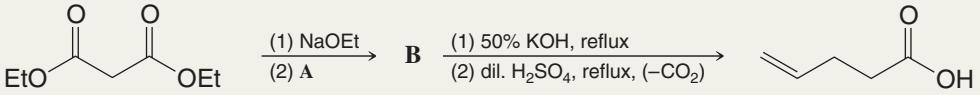
Ethylpropylmalonic acid

2-Ethylpentanoic acid

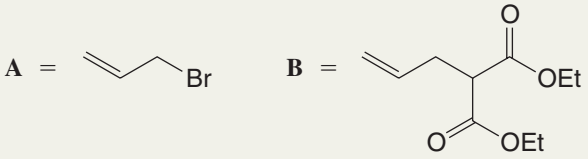
Openmirrors.com

Solved Problem 18.6

Provide structures for compounds **A** and **B** in the following synthesis.



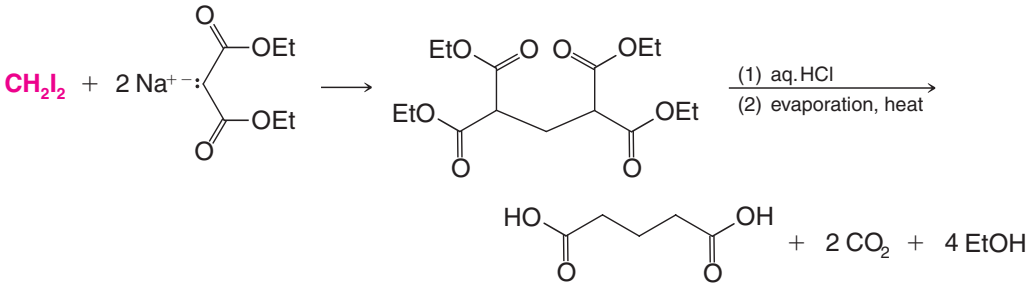
ANSWER



Review Problem 18.12

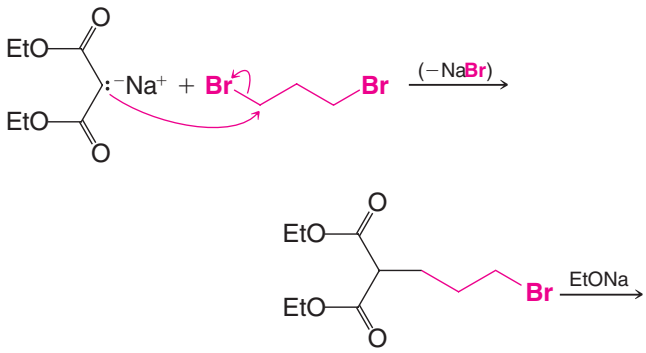
Outline all steps in a malonic ester synthesis of each of the following: **(a)** pentanoic acid, **(b)** 2-methylpentanoic acid, and **(c)** 4-methylpentanoic acid.

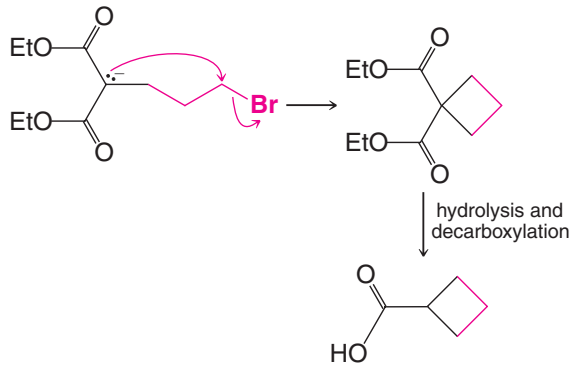
Two variations of the malonic ester synthesis make use of dihaloalkanes. In the first of these, two molar equivalents of sodiomalonic ester are allowed to react with a dihaloalkane. Two consecutive alkylations occur, giving a tetraester; hydrolysis and decarboxylation of the tetraester yield a dicarboxylic acid. An example is the synthesis of glutaric acid:



Glutaric acid
(80% from tetraester)

In a second variation, one molar equivalent of sodiomalonic ester is allowed to react with one molar equivalent of a dihaloalkane. This reaction gives a haloalkylmalonic ester, which, when treated with sodium ethoxide, undergoes an internal alkylation reaction. This method has been used to prepare three-, four-, five-, and six-membered rings. An example is the synthesis of cyclobutanecarboxylic acid:



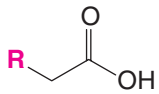


Cyclobutanecarboxylic acid

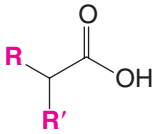
- As we have seen, the malonic ester synthesis is a useful method for preparing mono- and dialkylacetic acids:

Helpful Hint

The malonic ester synthesis is a tool for synthesizing substituted acetic acids.

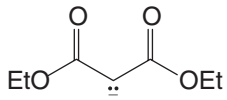


A monoalkylacetic acid



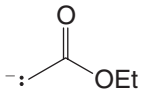
A dialkylacetic acid

- Thus, the malonic ester synthesis provides us with a synthetic equivalent of an ester enolate of acetic acid or acetic acid dianion.

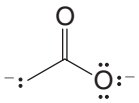


Diethyl malonate anion

is the synthetic equivalent of



and

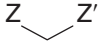


Direct formation of such anions is possible (Section 18.4), but it is often more convenient to use diethyl malonate as a synthetic equivalent because its α hydrogens are more easily removed.

In Special Topic E we shall see biosynthetic equivalents of these anions.

18.8 Further Reactions of Active Hydrogen Compounds

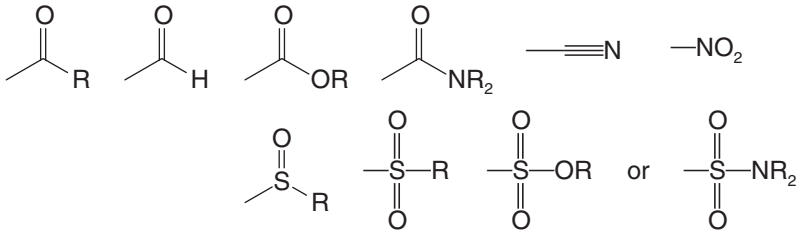
Because of the acidity of their methylene hydrogens malonic esters, acetoacetic esters, and similar compounds are often called **active hydrogen compounds** or **active methylene compounds**. Generally speaking, active hydrogen compounds have two electron-withdrawing groups attached to the same carbon atom:



Active hydrogen compound
(Z and Z′ are electron-withdrawing groups.)

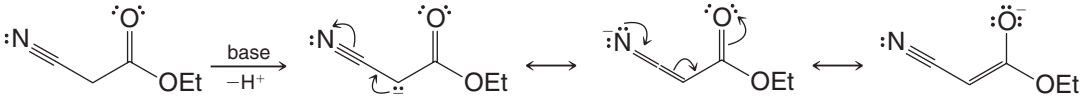
Openmirrors.com

The electron-withdrawing groups can be a variety of substituents, including



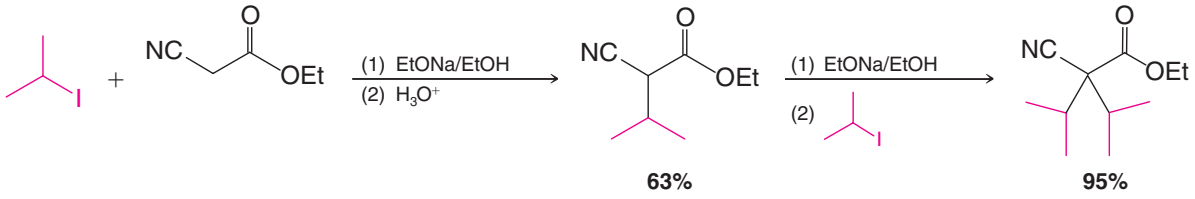
The range of pK_a values for such active methylene compounds is 3–13.

Ethyl cyanoacetate, for example, reacts with a base to yield a resonance-stabilized anion:



Ethyl cyanoacetate **Resonance structures for ethyl cyanoacetate anion**

Ethyl cyanoacetate anions also undergo alkylations. They can be dialkylated with isopropyl iodide, for example:



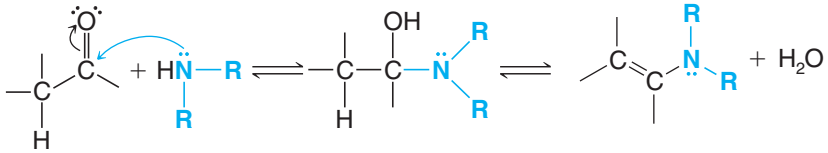
63% **95%**

Review Problem 18.13

The antiepileptic drug valproic acid is 2-propylpentanoic acid (administered as the sodium salt). One commercial synthesis of valproic acid begins with ethyl cyanoacetate. The penultimate step of this synthesis involves a decarboxylation, and the last step involves hydrolysis of a nitrile. Outline this synthesis.

18.9 *Synthesis of Enamines: Stork Enamine Reactions*

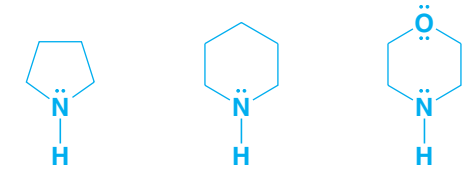
Aldehydes and ketones react with secondary amines to form compounds called **enamines.** The general reaction for enamine formation can be written as follows:



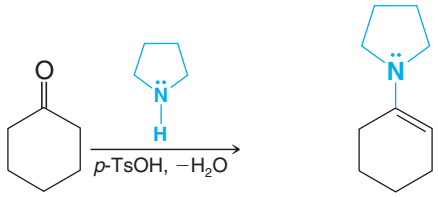
Aldehyde or ketone **2° Amine** **Enamine**

See Section 16.8C for the mechanism of enamine formation.

Since enamine formation requires the loss of a molecule of water, enamine preparations are usually carried out in a way that allows water to be removed as an azeotrope or by a drying agent. This removal of water drives the reversible reaction to completion. Enamine formation is also catalyzed by the presence of a trace of an acid. The secondary amines most commonly used to prepare enamines are cyclic amines such as pyrrolidine, piperidine, and morpholine:

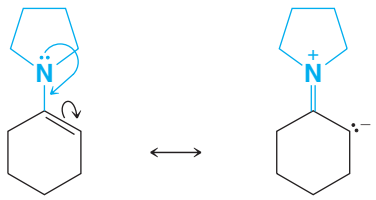


Cyclohexanone, for example, reacts with pyrrolidine in the following way:



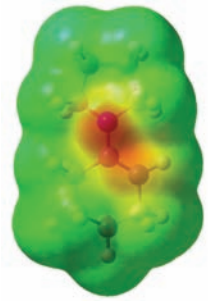
***N*-(1-Cyclohexenyl)pyrrolidine (an enamine)**

Enamines are good nucleophiles. Examination of the resonance structures that follow show that we should expect enamines to have both a nucleophilic nitrogen and a *nucleophilic carbon*. A map of electrostatic potential highlights the nucleophilic region of an enamine.



Contribution to the hybrid made by this structure confers nucleophilicity on nitrogen.

Contribution to the hybrid made by this structure confers nucleophilicity on carbon and decreases the nucleophilicity of nitrogen.



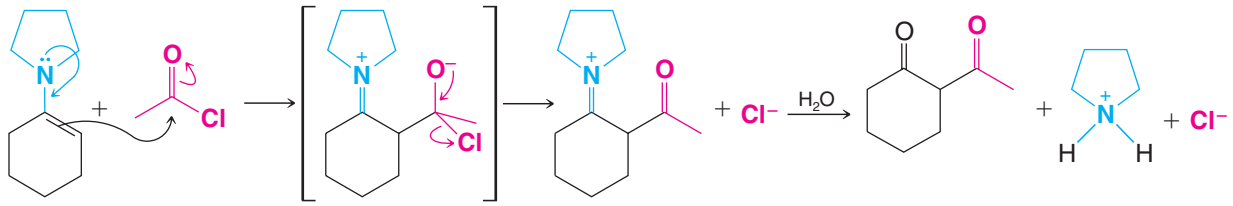
A map of electrostatic potential for *N*-(1-cyclohexenyl)pyrrolidine shows the distribution of negative charge and the nucleophilic region of an enamine.

The nucleophilicity of the carbon of enamines makes them particularly useful reagents in organic synthesis because they can be **acylated, alkylated,** and used in **Michael additions** (see Section 19.7A). Enamines can be used as synthetic equivalents of aldehyde or ketone enolates because the alkene carbon of an enamine reacts the same way as does the α carbon of an aldehyde or ketone enolate and, after hydrolysis, the products are the same. Development of these techniques originated with the work of Gilbert Stork of Columbia University, and in his honor they have come to be known as **Stork enamine reactions.**

Helpful Hint

Enamines are the synthetic equivalents of aldehyde and ketone enolates.

When an enamine reacts with an acyl halide or an acid anhydride, the product is the *C*-acylated compound. The iminium ion that forms hydrolyzes when water is added, and the overall reaction provides a synthesis of β-diketones:

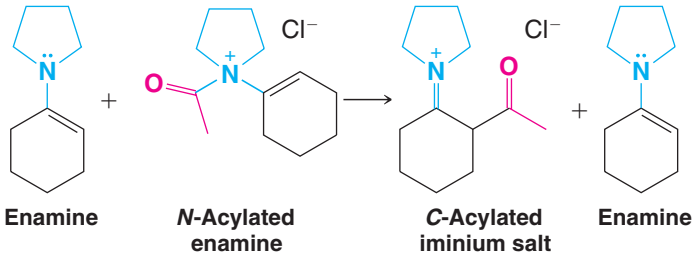


Iminium salt

2-Acetylcyclohexanone (a β-diketone)

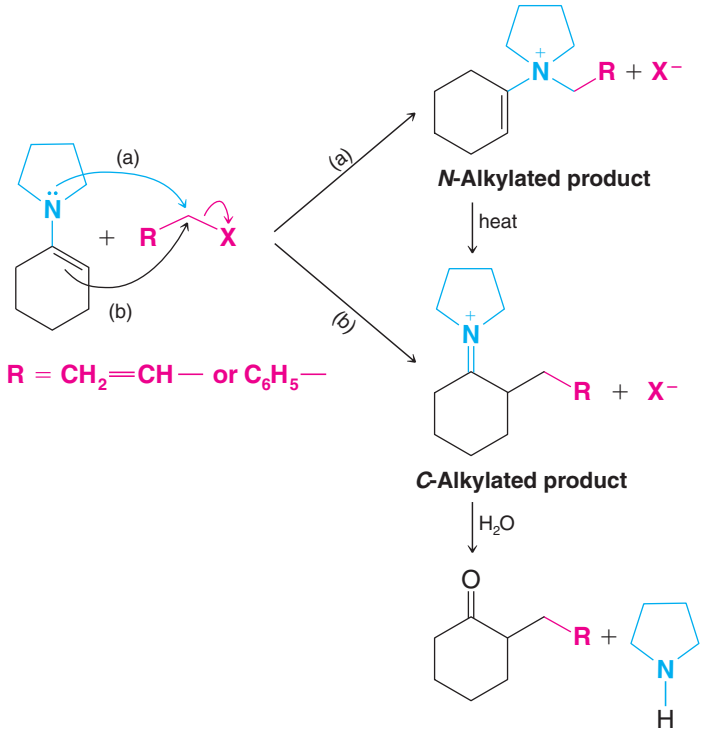
Openmirrors.com

Although *N*-acylation may occur in this synthesis, the *N*-acyl product is unstable and can act as an acylating agent itself:

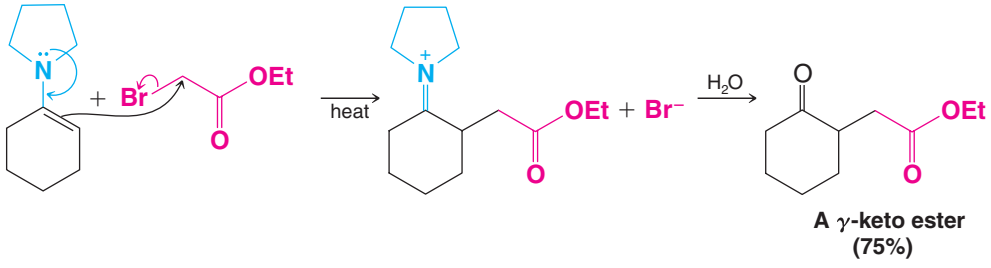


As a consequence, the yields of *C*-acylated products are generally high.

Enamines can be alkylated as well as acylated. Although alkylation may lead to the formation of a considerable amount of *N*-alkylated product, heating the *N*-alkylated product often converts it to a *C*-alkyl compound. This rearrangement is particularly favored when the alkyl halide is an allylic halide, benzylic halide, or α-haloacetic ester:

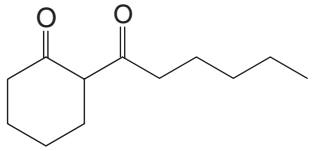


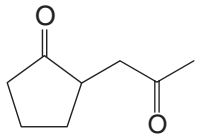
Enamine alkylations are S_N2 reactions; therefore, when we choose our alkylating agents, we are usually restricted to the use of methyl, primary, allylic, and benzylic halides. α-Halo esters can also be used as the alkylating agents, and this reaction provides a convenient synthesis of γ-keto esters:

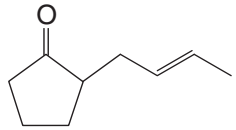


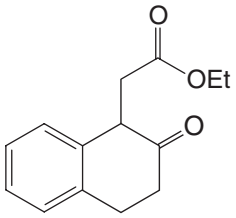
Review Problem 18.14

Show how you could employ enamines in syntheses of the following compounds:

(a) 

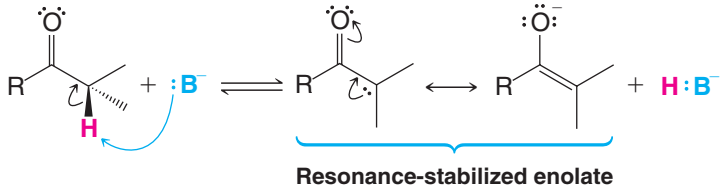
(c) 

(b) 

(d) 

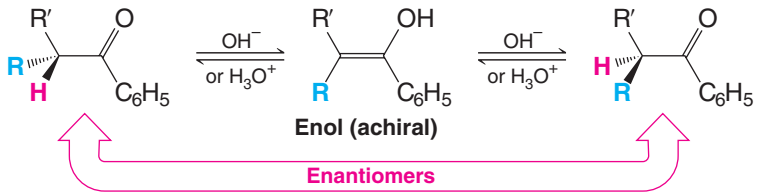
18.10 Summary of Enolate Chemistry

1. ***Formation of an Enolate*** **(Section 18.1)**



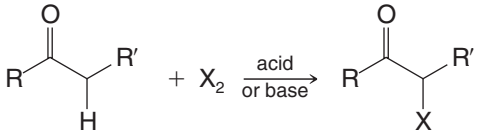
:B⁻ = :ÖH, :ÖR, or :N(*i*-Pr)$_2$ **(Section 18.4)**

2. ***Racemization*** **(Section 18.3A)**

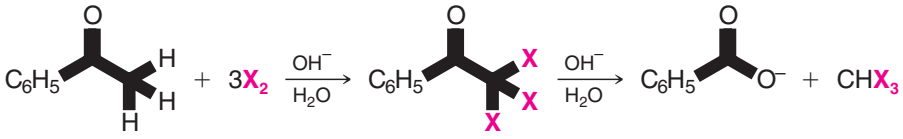


3. ***Halogenation of Aldehydes and Ketones*** **(Sections 18.3B and 18.3C)**

General Reaction

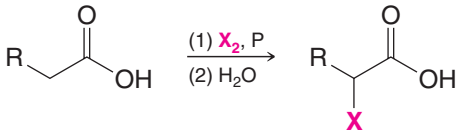


Specific Example—Haloform Reaction



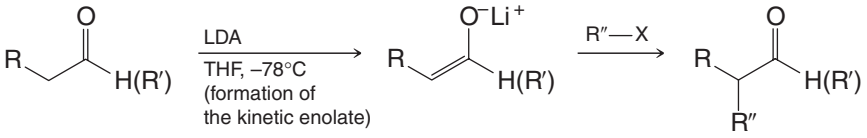
Openmirrors.com

4. ***Halogenation of Carboxylic Acids: The HVZ Reaction*** **(Section 18.3D)**

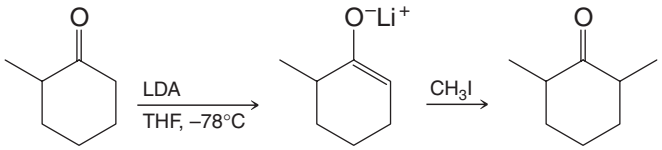


5. ***Direct Alkylation via Lithium Enolates*** **(Section 18.4)**

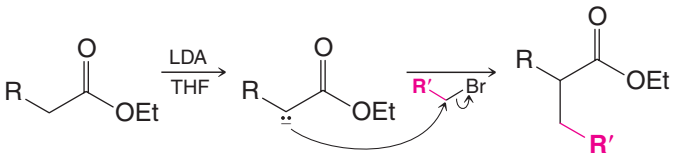
General Reaction



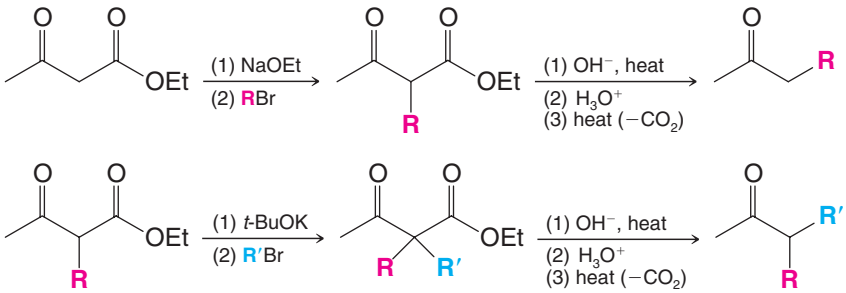
Specific Example



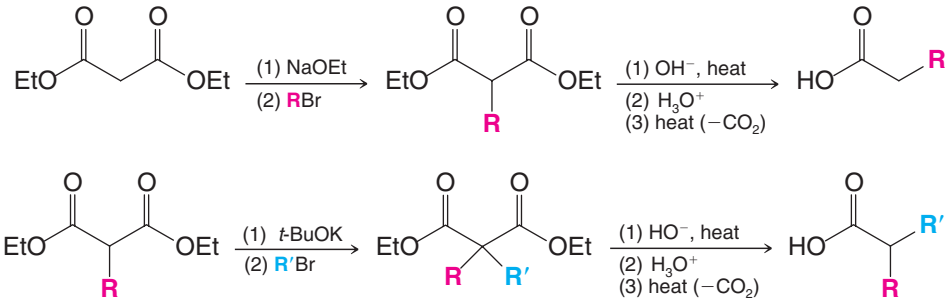
6. ***Direct Alkylation of Esters*** **(Section 18.4C)**



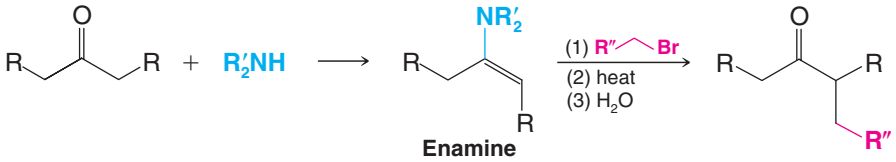
7. ***Acetoacetic Ester Synthesis*** **(Section 18.6)**



8. ***Malonic Ester Synthesis*** **(Section 18.7)**



9. ***Stork Enamine Reaction*** **(Section 18.9)**



Enamine

Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com)

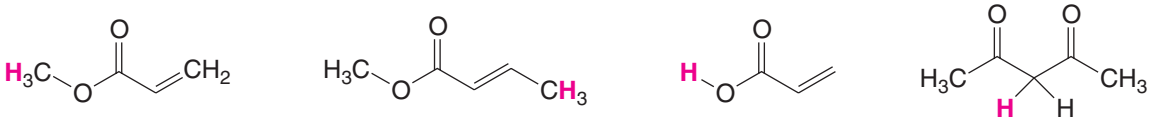
Problems

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

ENOLATES, ENOLS, AND CARBONYL α-CARBON REACTIVITY

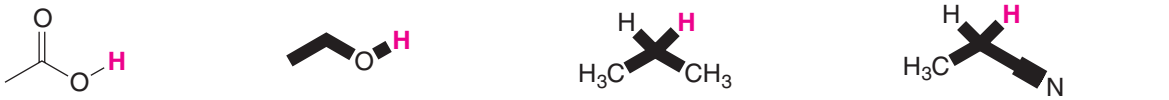
18.15 Rank the following in order of increasing acidity for the indicated hydrogen atoms (bold) (1 = least acidic; 4 = most acidic).

(a)

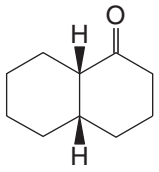


(b)

(c)



18.16 Treating a solution of *cis*-1-decalone with base causes an isomerization to take place. When the system reaches equilibrium, the solution is found to contain about 95% *trans*-1-decalone and about 5% *cis*-1-decalone. Explain this isomerization.



***cis*-1-Decalone**

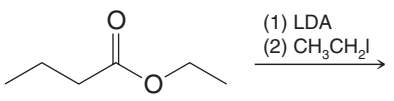
18.17 Explain the variation in enol content that is observed for solutions of acetylacetone (pentane-2,4-dione) in the several solvents indicated:

Solvent	% Enol
H_2O	15
CH_3CN	58
C_6H_{14}	92
Gas phase	92

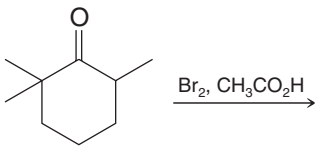
Openmirrors.com

18.18 Provide a structural formula for the product from each of the following reactions.

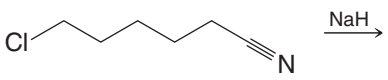
(a)



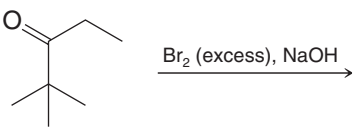
(b)



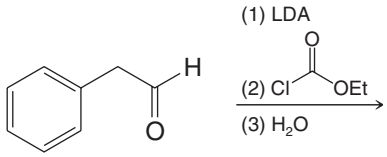
(c)



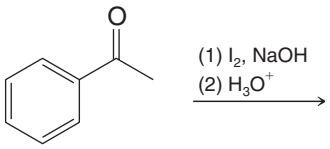
(d)



(e)

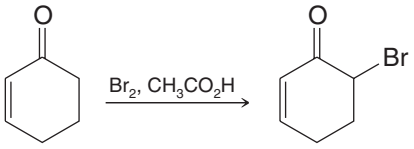


(f)

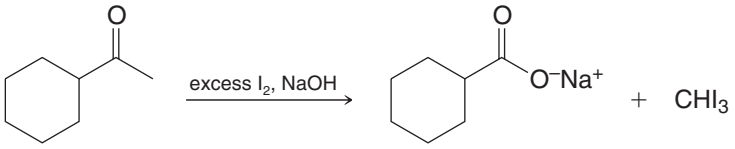


18.19 Write a stepwise mechanism for each of the following reactions.

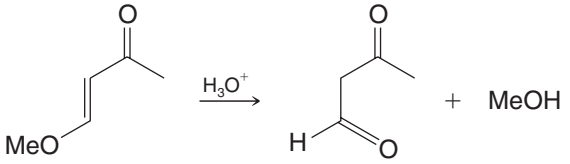
(a)



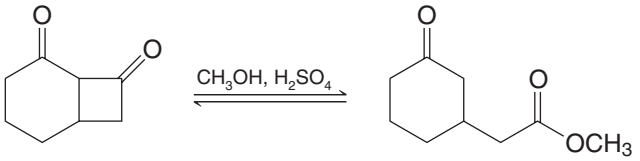
(b)



(c)

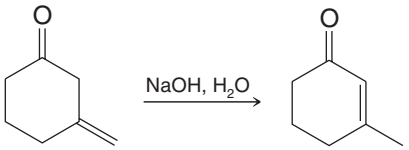


(d)

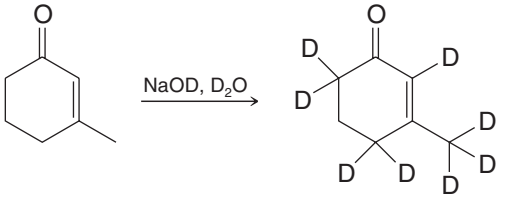


18.20 Write a stepwise mechanism for each of the following reactions.

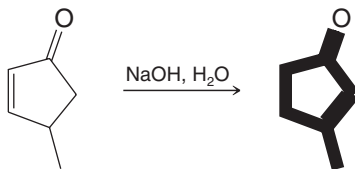
(a)



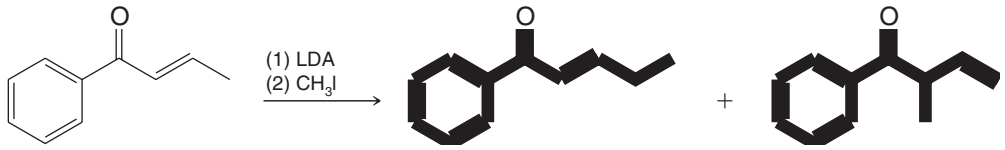
(b)



(c)



(d)



ACETOACETIC ESTER AND MALONIC ESTER SYNTHESES

18.21 Outline syntheses of each of the following from acetoacetic ester and any other required reagents:

(a) *tert*-Butyl methyl ketone

(b) 2-Hexanone

(c) 2,5-Hexanedione

(d) 4-Hydroxypentanoic acid

(e) 2-Ethyl-1,3-butanediol

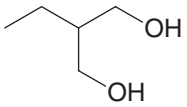
(f) 1-Phenyl-1,3-butanediol

18.22 Outline syntheses of each of the following from diethyl malonate and any other required reagents:

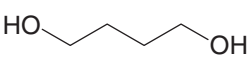
(a) 2-Methylbutanoic acid

(b) 4-Methyl-1-pentanol

(c)

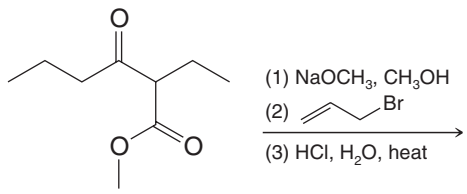


(d)

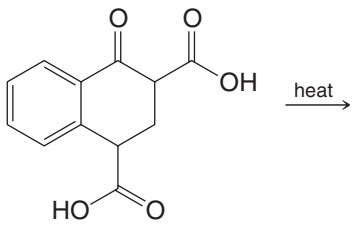


18.23 Provide a structural formula for the product from each of the following reactions.

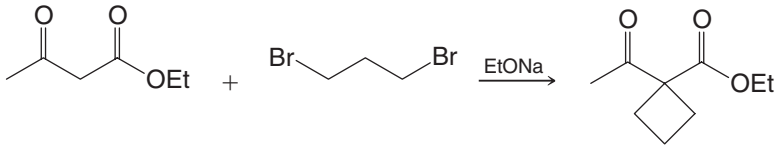
(a)



(b)



18.24 The synthesis of cyclobutanecarboxylic acid given in Section 18.7 was first carried out by William Perkin, Jr., in 1883, and it represented one of the first syntheses of an organic compound with a ring smaller than six carbon atoms. (There was a general feeling at the time that such compounds would be too unstable to exist.) Earlier in 1883, Perkin reported what he mistakenly believed to be a cyclobutane derivative obtained from the reaction of acetoacetic ester and 1,3-dibromopropane. The reaction that Perkin had expected to take place was the following:

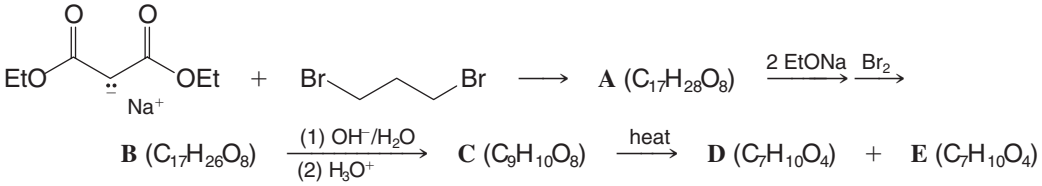


The molecular formula for his product agreed with the formulation given in the preceding reaction, and alkaline hydrolysis and acidification gave a nicely crystalline acid (also having the expected molecular formula). The acid, however, was quite stable to heat and resisted decarboxylation. Perkin later found that both the ester and the acid contained six-membered rings (five carbon atoms and one oxygen atom). Recall the charge distribution in the enolate ion obtained from acetoacetic ester and propose structures for Perkin's ester and acid.

Openmirrors.com

18.25 **(a)** In 1884 Perkin achieved a successful synthesis of cyclopropanecarboxylic acid from sodiomalonic ester and 1,2-dibromoethane. Outline the reactions involved in this synthesis.

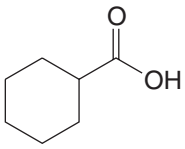
(b) In 1885 Perkin synthesized five-membered carbocyclic compounds **D** and **E** in the following way:

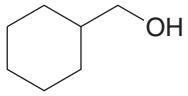


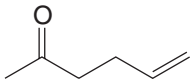
where **D** and **E** are diastereomers; **D** can be resolved into enantiomeric forms while **E** cannot. What are the structures of **A**–**E**?

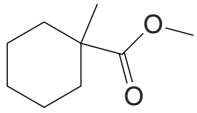
(c) Ten years later Perkin was able to synthesize 1,4-dibromobutane; he later used this compound and diethyl malonate to prepare cyclopentanecarboxylic acid. Show the reactions involved.

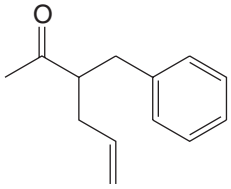
18.26 Synthesize each of the following compounds from diethyl malonate or ethyl acetoacetate and any other organic and inorganic reagents.

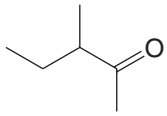
(a)


(b)


(c)


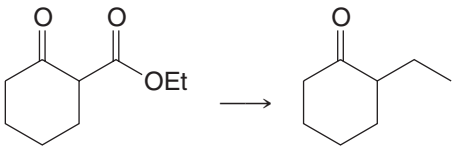
(d)


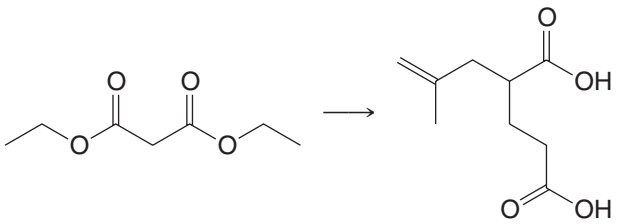
(e)


(f)


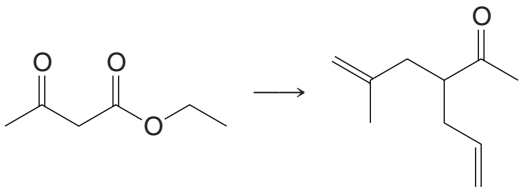
GENERAL PROBLEMS

18.27 Outline a reaction sequence for synthesis of each of the following compounds from the indicated starting material and any other organic or inorganic reagents needed.

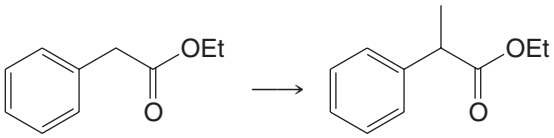
(a)


(b)


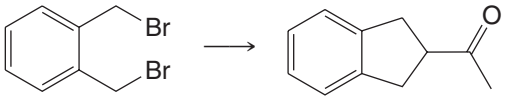
(c)



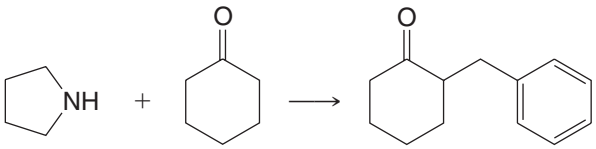
(d)



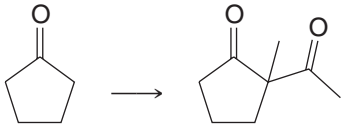
(e)



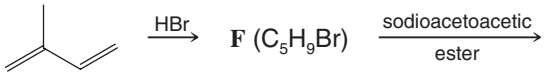
(f)

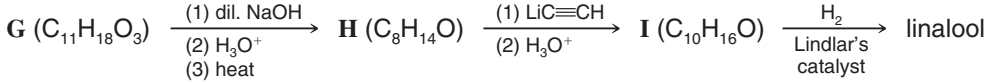


(g)



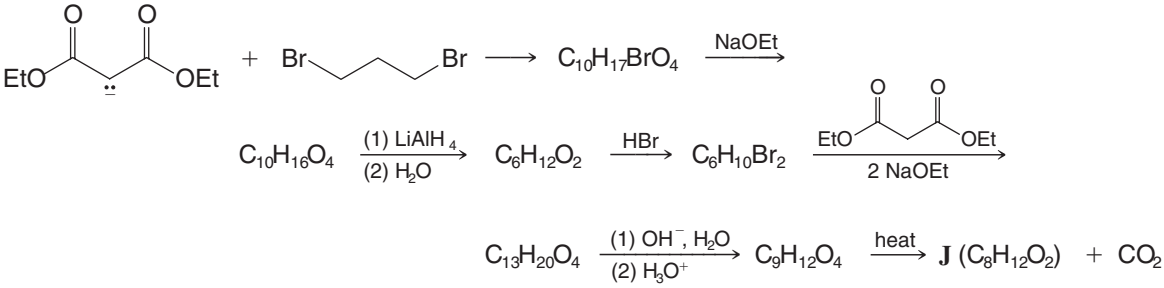
18.28 Linalool, a fragrant compound that can be isolated from a variety of plants, is 3,7-dimethyl-1,6-octadien-3-ol. Linalool is used in making perfumes, and it can be synthesized in the following way:





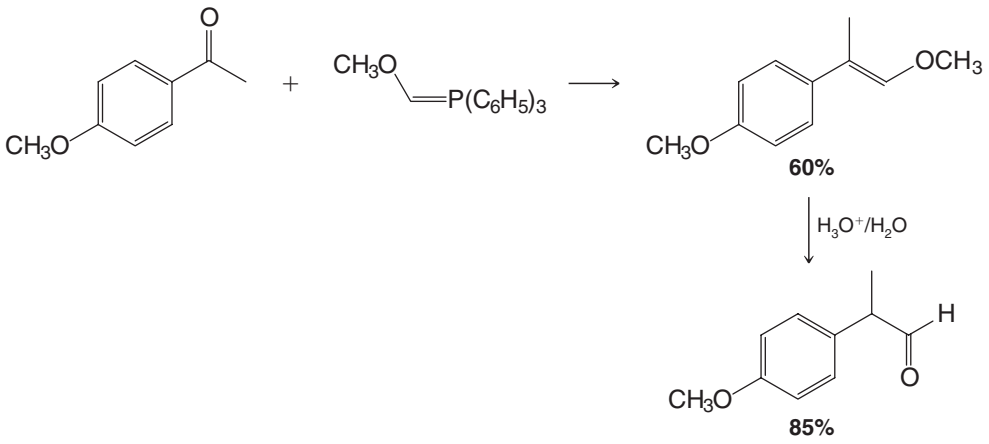
Outline the reactions involved. [*Hint*: Compound **F** is the more stable isomer capable of being produced in the first step.]

18.29 Compound **J**, a compound with two four-membered rings, has been synthesized by the following route. Outline the steps that are involved.



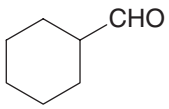
Openmirrors.com

18.30 The Wittig reaction (Section 16.10) can be used in the synthesis of aldehydes, for example,



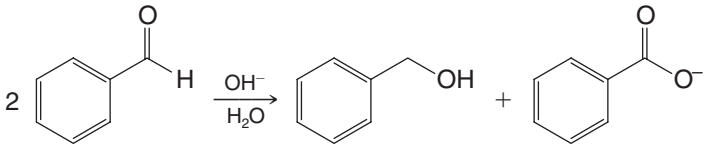
(a) How would you prepare $CH_3OCH{=}P(C_6H_5)_3$?

(b) Show with a mechanism how the second reaction produces an aldehyde.

(c) How would you use this method to prepare 

from cyclohexanone?

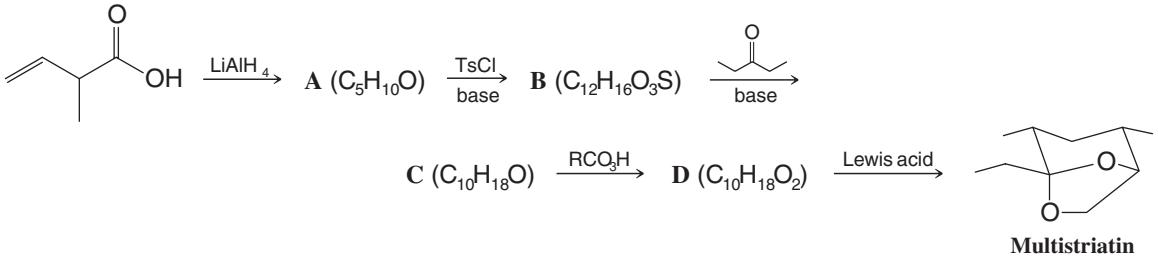
18.31 Aldehydes that have no a hydrogen undergo an intermolecular oxidation–reduction called the **Cannizzaro reaction** when they are treated with concentrated base. An example is the following reaction of benzaldehyde:



(a) When the reaction is carried out in D_2O, the benzyl alcohol that is isolated contains no deuterium bound to carbon. It is $C_6H_5CH_2OD$. What does this suggest about the mechanism for the reaction?

(b) When $(CH_3)_2CHCHO$ and $Ba(OH)_2/H_2O$ are heated in a sealed tube, the reaction produces only $(CH_3)_2CHCH_2OH$ and $[(CH_3)_2CHCO_2]_2Ba$. Provide an explanation for the formation of these products.

18.32 Shown below is a synthesis of the elm bark beetle pheromone, multistriatin (see Problem 16.44). Give structures for compounds **A, B, C**, and **D**.



Multistriatin

SPECTROSCOPY

18.33 **(a)** A compound **U** ($C_9H_{10}O$) gives a negative iodoform test. The IR spectrum of **U** shows a strong absorption peak at 1690 cm^{-1}. The ^1H NMR spectrum of **U** gives the following:

Triplet	δ 1.2 (3H)
Quartet	δ 3.0 (2H)
Multiplet	δ 7.7 (5H)

What is the structure of **U**?

(b) A compound **V** is an isomer of **U**. Compound **V** gives a positive iodoform test; its IR spectrum shows a strong peak at 1705 cm^{-1}. The ^1H NMR spectrum of **V** gives the following:

Singlet	δ 2.0 (3H)
Singlet	δ 3.5 (2H)
Multiplet	δ 7.1 (5H)

What is the structure of **V**?

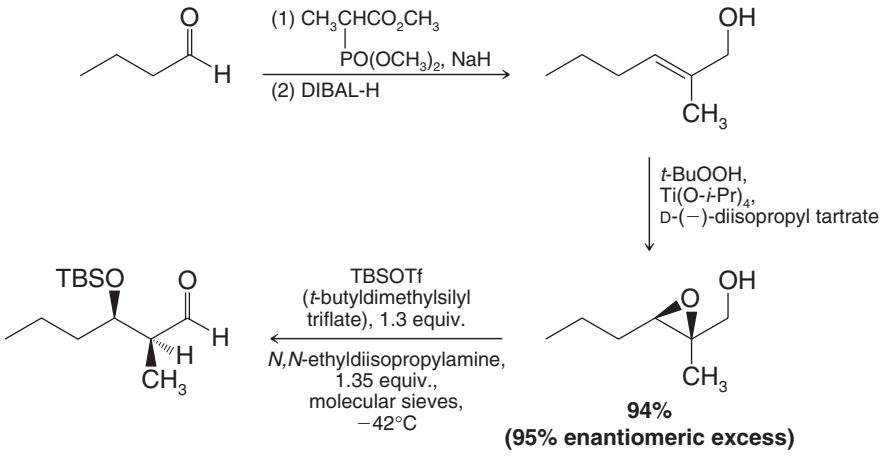
18.34 Compound **A** has the molecular formula $C_6H_{12}O_3$ and shows a strong IR absorption peak at 1710 cm^{-1}. When treated with iodine in aqueous sodium hydroxide, **A** gives a yellow precipitate. When **A** is treated with Tollens' reagent (a test for an aldehyde or a group that can be hydrolyzed to an aldehyde), no reaction occurs; however, if **A** is treated first with water containing a drop of sulfuric acid and then with Tollens' reagent, a silver mirror (positive Tollens' test) forms in the test tube. Compound **A** shows the following ^1H NMR spectrum:

Singlet	δ 2.1
Doublet	δ 2.6
Singlet	δ 3.2 (6H)
Triplet	δ 4.7

Write a structure for **A**.

Challenge Problem

18.35 The following is an example of a reaction sequence developed by Derin C. D'Amico and Michael E. Jung (UCLA) that results in enantiospecific formation of two new chirality centers and a carbon—carbon bond. The sequence includes a Horner–Wadsworth–Emmons reaction (Section 16.10B), a Sharpless asymmetric epoxidation (Section 11.13), and a novel rearrangement that ultimately leads to the product. Propose a mechanism for rearrangement of the epoxy alcohol under the conditions shown to form the aldol product. [*Hint*: The rearrangement can also be accomplished by preparing a trialkylsilyl ether from the epoxy alcohol in a separate reaction first and then treating the resulting silyl ether with a Lewis acid catalyst (e.g., BF_3).]



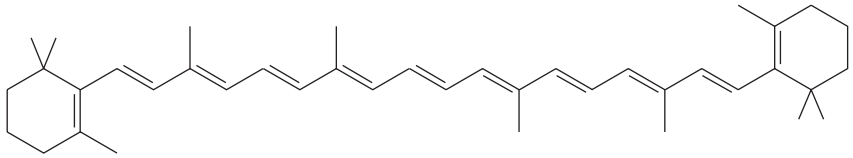
Learning Group Problems

β-CAROTENE, DEHYDROABEITIC ACID

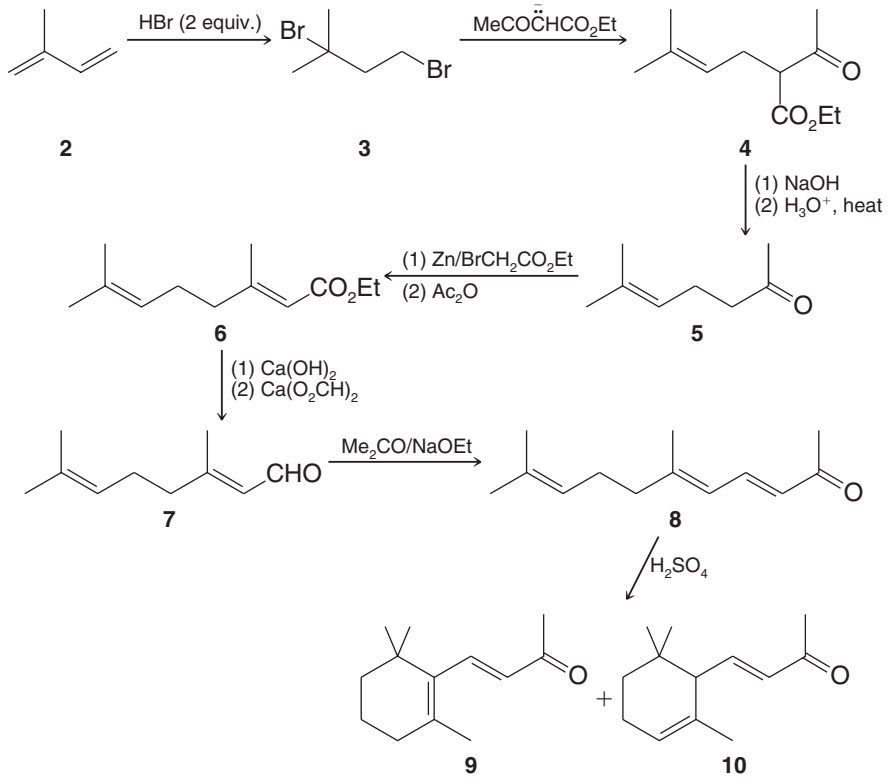
1. β-Carotene is a highly conjugated hydrocarbon with an orange-red color. Its biosynthesis occurs via the isoprene pathway (Special Topic E), and it is found in, among other sources, pumpkins. One of the chemical syntheses of β-carotene was accomplished near the turn of the twentieth century by W. Ipatiew (*Ber.* **1901**, *34*, 594–596). The

Openmirrors.com

first few steps of this synthesis involve chemistry that should be familiar to you. Write mechanisms for all of the reactions from compounds **2** to **5**, and from **8** to **9** and **10**.



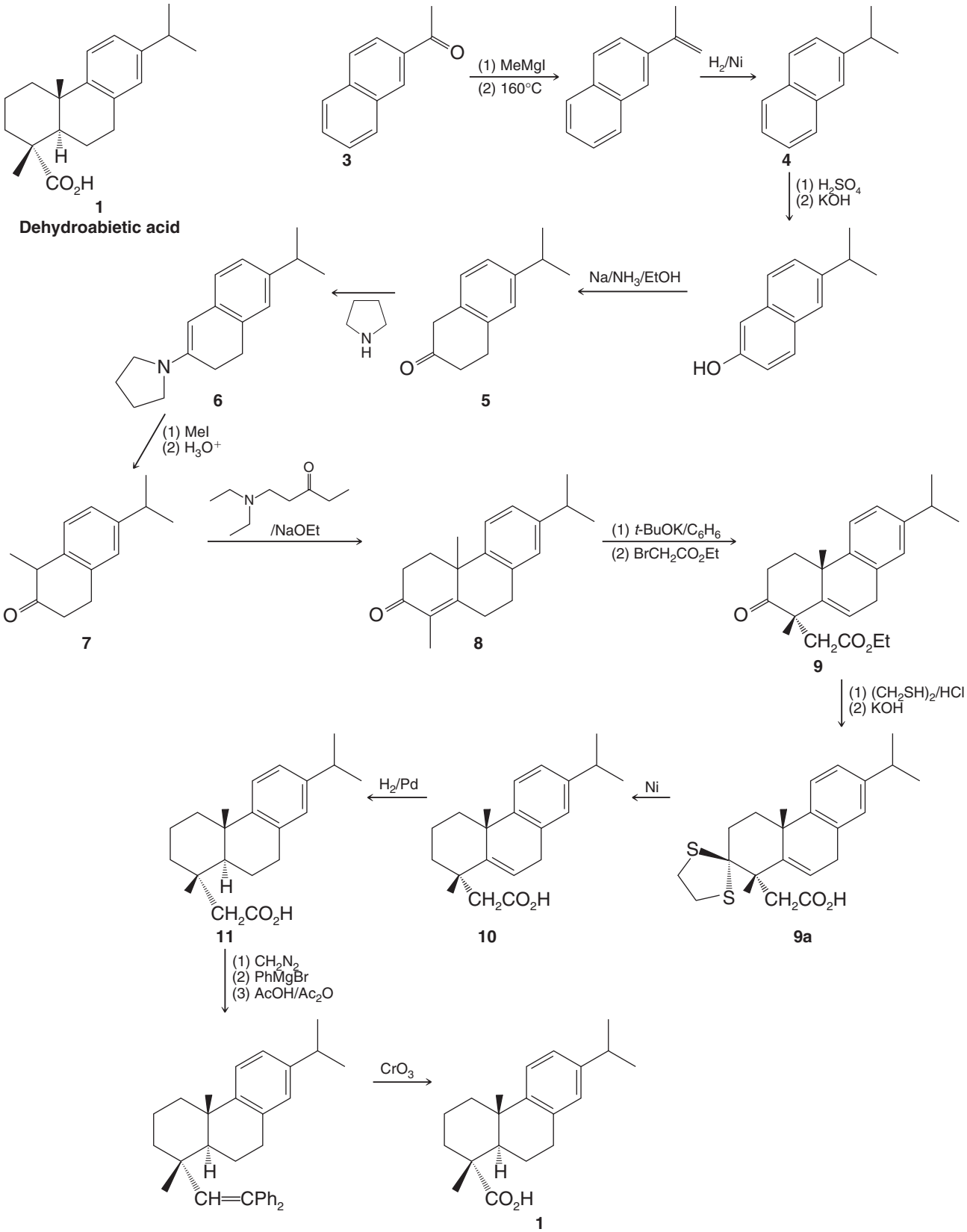
***β*-Carotene**



2. Dehydroabietic acid is a natural product isolated from *Pinus palustris*. It is structurally related to abietic acid, which comes from rosin. The synthesis of dehydroabietic acid (*J. Am. Chem. Soc*. **1962**, *84*, 284–292) was accomplished by Gilbert Stork. In the course of this synthesis, Stork discovered his famous enamine reaction.

(a) Write detailed mechanisms for the reactions from **5** to **7** below.

(b) Write detailed mechanisms for all of the reactions from **8** to **9a** in Stork's synthesis of dehydroabietic acid. Note that **9a** contains a dithioacetal, which forms similarly to acetals you have already studied (Chapter 16).



(Structures from Fleming, I., *Selected Organic Synthesis*, p. 76. Copyright John Wiley & Sons, Limited. Reproduced with permission.)

Openmirrors.com

Summary of Mechanisms

Enolates: α-Substitution

General Reaction

Some groups that increase α-hydrogen acidity

(and in general, other groups that can stabilize an α-carbanion)

Typical bases (⁻:A) and solvents for enolate formation

I. HO^- in H_2O or ROH; or RO^- in ROH;
Useful for reactions involving thermodynamically favored enolates and equilibrium product control

II. LDA (lithium diisopropylamide) in THF or DME;
Useful, in general, for forming enolates in aprotic solvents (especially kinetically favored enolates and direct alkylation)

Possible electrophiles (E–A)

H—A
Deprotonation–protonation
(may lead to racemization or epimerization)

:X—X:
Halogenation

R′—X:
Alkylation

Product(s)

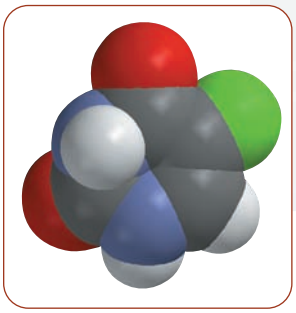
Substitution of enolate α hydrogen by H, X, or R

WILEY PLUS See *Special Topic C* in *WileyPLUS*

19

Condensation and Conjugate Addition Reactions of Carbonyl Compounds

More Chemistry of Enolates



5-Fluorouracil, an enzyme inhibitor that has anticancer activity by masquerading as a natural substrate.

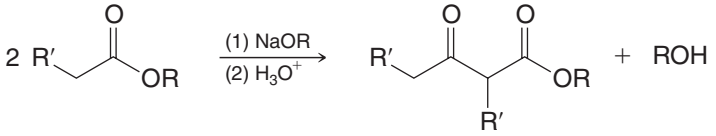
In this chapter we shall consider two additional reaction types of carbonyl compounds: condensation reactions and conjugate addition reactions. Both of these types of reactions involve enolates or enols. Carbonyl condensation and conjugate addition reactions are very useful in synthesis, and also have important biological significance, as we shall see in due course. One biomedical example relates to the cancer-fighting mechanism of 5-fluorouracil (see molecular model), which masquerades as the natural metabolite uracil in a conjugate addition reaction. In doing so, 5-fluorouracil irreversibly halts biosynthesis of a key DNA building block, thus taking its anticancer effect. Many drugs used in medicine take their effect by acting as imposters for natural compounds. We shall see how 5-fluorouracil works in "The Chemistry of. . . A Suicide Enzyme Substrate" later in this chapter.

Openmirrors.com

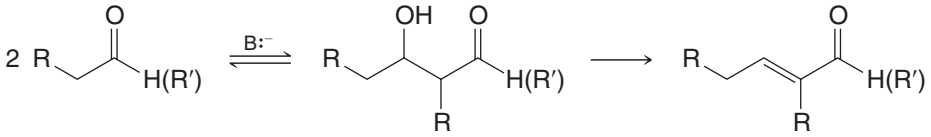
19.1 Introduction

In carbonyl **condensation reactions** the enolate or enol of one carbonyl compound reacts with the carbonyl group of another to join the two reactants. As part of the process, a new molecule that is derived from them "condenses" (forms). Often this molecule is that of an alcohol or water. The main types of condensation reactions we shall study are the **Claisen condensation** and the **aldol condensation**. Aldol condensations are preceded mechanistically by aldol additions, which we shall also study. The name **aldol** derives from the fact that **al**dehyde and alcoh**ol** functional groups are present in the products of many aldol reactions.

An Example of a Claisen Condensation



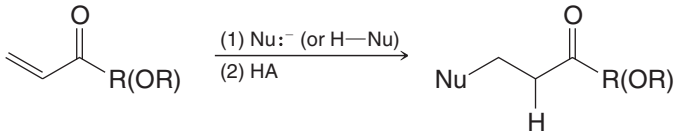
An Example of an Aldol Addition and Condensation



Aldol addition product **Aldol condensation product**

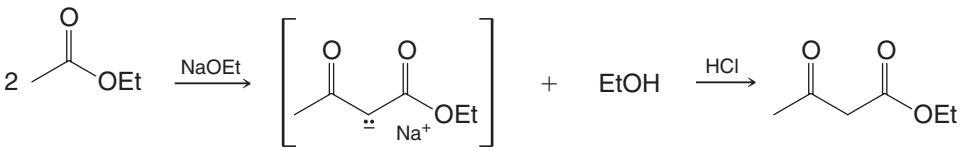
Conjugate addition reactions involve a nucleophile, which is often an enolate, adding to the β position of an α,β-unsaturated carbonyl compound. One of the most common conjugate addition reactions is the Michael addition. As we shall see, the aldol condensation provides a way to synthesize α,β-unsaturated carbonyl compounds that we can then use for subsequent conjugate addition reactions.

An Example of Conjugate Addition



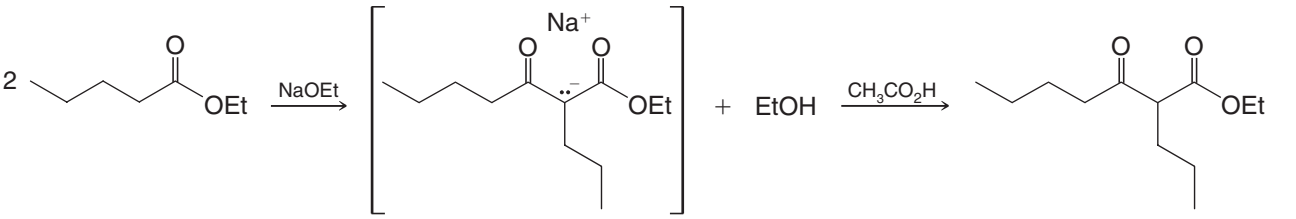
19.2 The Claisen Condensation: A Synthesis of β-Keto Esters

The Claisen condensation is a carbon–carbon bond-forming reaction that is useful for synthesizing β-keto esters. In Chapter 18 we saw how β-keto esters are useful in synthesis. In a Claisen condensation, the enolate of one ester molecule adds to the carbonyl group of another, resulting in an acyl substitution reaction that forms a β-keto ester and an alcohol molecule. The alcohol molecule that is formed derives from the alkoxyl group of the ester. A classic example is the Claisen condensation by which ethyl acetoacetate (acetoacetic ester) can be synthesized.



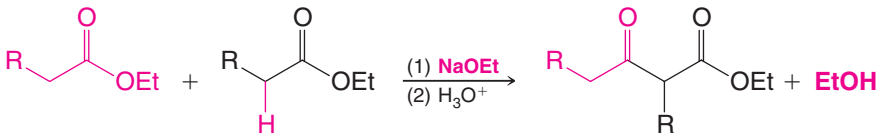
Sodioacetoacetic ester **(removed by distillation)** **Ethyl acetoacetate (acetoacetic ester) (76%)**

Another example is the Claisen condensation of two molecules of ethyl pentanoate, leading to ethyl 3-oxo-2-propylheptanoate.



Ethyl pentanoate **Ethyl 3-oxo-2-propylheptanoate (77%)**

If we look closely at these examples, we can see that, overall, both reactions involve a condensation in which one ester loses an α hydrogen and the other loses an ethoxide ion:



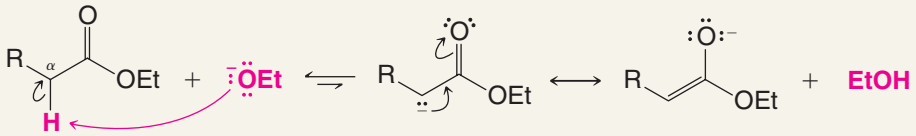
(R may also be H) **A β-keto ester**

We can understand how this happens if we examine the reaction mechanism in detail. In doing so, we shall see that the Claisen condensation mechanism is a classic example of acyl substitution (nucleophilic addition–elimination at a carbonyl group).

A MECHANISM FOR THE REACTION

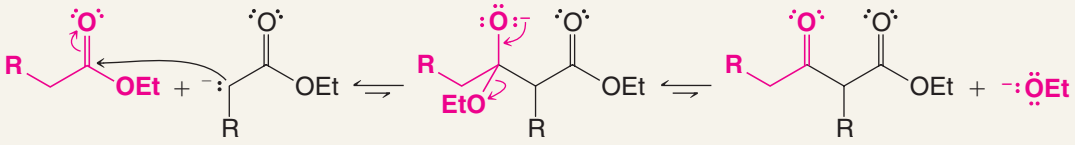
The Claisen Condensation

Step 1



An alkoxide base removes an α proton from the ester, generating a nucleophilic enolate ion. (The alkoxide base used to form the enolate should have the same alkyl group as the ester, e.g., ethoxide for an ethyl ester; otherwise transesterification may occur.) Although the α protons of an ester are not as acidic as those of aldehydes and ketones, the resulting enolate is stabilized by resonance in a similar way.

Step 2

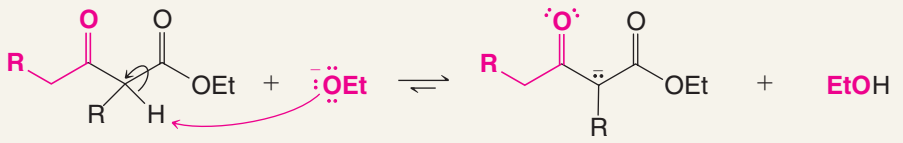


Nucleophilic addition **Tetrahedral intermediate and elimination**

The enolate attacks the carbonyl carbon of another ester molecule, forming a tetrahedral intermediate. The tetrahedral intermediate expels an alkoxide ion, resulting in substitution of the alkoxide by the group derived from the enolate. The net result is nucleophilic addition–elimination at the ester carbonyl group. *The overall equilibrium for the process is unfavorable thus far, however*, but it is drawn toward the final product by removal of the acidic α hydrogen from the new β-dicarbonyl system.

Openmirrors.com

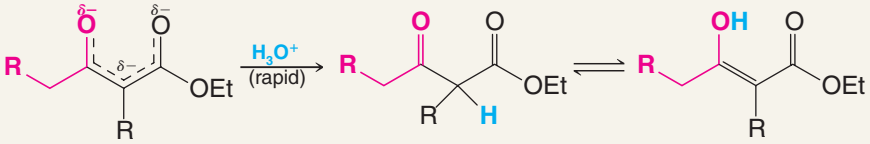
Step 3



β-Keto ester (pK_a ~9; stronger acid) **Ethoxide ion (stronger base)** **β-Keto ester anion (weaker base)** **Ethanol (pK_a 16; weaker acid)**

An alkoxide ion removes an α proton from the newly formed condensation product, resulting in a resonance stabilized β-keto ester ion. This step is highly favorable and draws the overall equilibrium toward product formation. The alcohol by-product (ethanol in this case) can be distilled from the reaction mixture as it forms, thereby further drawing the equilibrium toward the desired product.

Step 4



Keto form **Enol form**

Addition of acid quenches the reaction by neutralizing the base and protonating the Claisen condensation product. The β-keto ester product exists as an equilibrium mixture of its keto and enol tautomers.

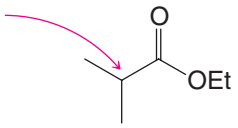
- When planning a reaction with an ester and an alkoxide ion it is important to use an alkoxide that has the same alkyl group as the alkoxyl group of the ester.

The alkoxyl group of the ester and the alkoxide must be the same so as to avoid transesterification (which occurs with alkoxides by the same mechanism as base-promoted ester hydrolysis; Section 17.7B). Ethyl esters and methyl esters, as it turns out, are the most common ester reactants in these types of syntheses. Therefore, we use sodium ethoxide when ethyl esters are involved and sodium methoxide when methyl esters are involved. (There are some occasions when we shall choose to use other bases, but we shall discuss these later.)

- Esters that have only one α hydrogen do not undergo the usual Claisen condensation.

An example of an ester that does not react in a normal Claisen condensation, because it has only one α hydrogen, is ethyl 2-methylpropanoate:

The α carbon has only one hydrogen.



This ester does not undergo a Claisen condensation.

Ethyl 2-methylpropanoate

- Inspection of the mechanism just given will make clear why this is so: an ester with only one α hydrogen will not have an acidic hydrogen when step 3 is reached, and step 3 provides the favorable equilibrium that ensures the success of the reaction.

In Section 19.2B we shall see how esters with only one α hydrogen can be converted to a β-keto ester by a method that uses a strong base.

Review Problem 19.1

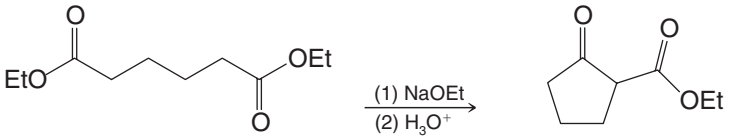
(a) Write a mechanism for all steps of the Claisen condensation that take place when ethyl propanoate reacts with ethoxide ion. **(b)** What products form when the reaction mixture is acidified?

Review Problem 19.2

Since the products obtained from Claisen condensations are β-keto esters, subsequent hydrolysis and decarboxylation of these products give a general method for the synthesis of ketones. Show how you would employ this technique in a synthesis of 4-heptanone.

19.2A Intramolecular Claisen Condensations: The Dieckmann Condensation

An intramolecular Claisen condensation is called a **Dieckmann condensation**. For example, when diethyl hexanedioate is heated with sodium ethoxide, subsequent acidification of the reaction mixture gives ethyl 2-oxocyclopentanecarboxylate:



Diethyl hexanedioate (diethyl adipate)

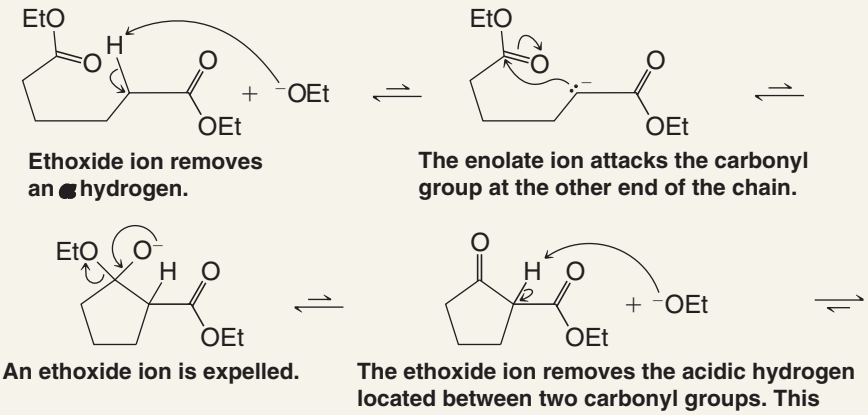
Ethyl 2-oxocyclopentanecarboxylate (74–81%)

- In general, the Dieckmann condensation is useful only for the preparation of five- and six-membered rings.

Rings smaller than five are disfavored due to angle strain. Rings larger than seven are entropically less favorable due to the greater number of conformations available to a longer chain precursor, in which case intermolecular condensation begins to compete strongly.

A MECHANISM FOR THE REACTION

The Dieckmann Condensation



Ethoxide ion removes an α hydrogen.

The enolate ion attacks the carbonyl group at the other end of the chain.

An ethoxide ion is expelled.

The ethoxide ion removes the acidic hydrogen located between two carbonyl groups. This favorable equilibrium drives the reaction.

Addition of aqueous acid rapidly protonates the anion, giving the final product.

Review Problem 19.3

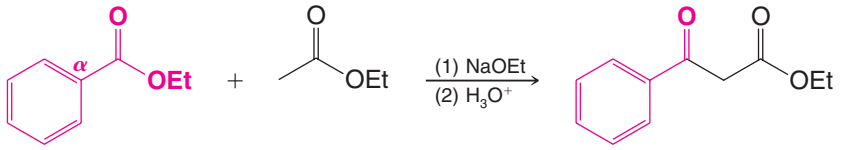
(a) What product would you expect from a Dieckmann condensation of diethyl heptanedioate? **(b)** Can you account for the fact that diethyl pentanedioate (diethyl glutarate) does not undergo a Dieckmann condensation?

Openmirrors.com

19.2B Crossed Claisen Condensations

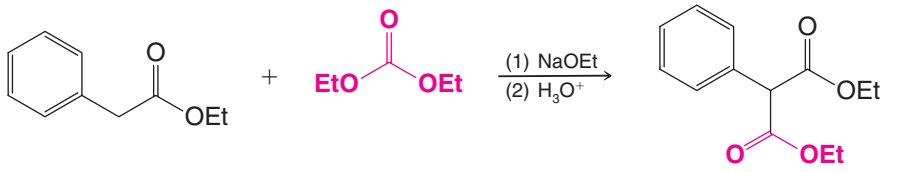
- Crossed Claisen condensations are possible **when one ester component has no α hydrogens** and, therefore, is unable to form an enolate ion and undergo self-condensation.

Ethyl benzoate, for example, condenses with ethyl acetate to give ethyl benzoylacetate:



Ethyl benzoate (no α hydrogen) — **Ethyl benzoylacetate (60%)**

Ethyl phenylacetate condenses with diethyl carbonate to give diethyl phenylmalonate:



Ethyl phenylacetate — **Diethyl carbonate (no α carbon)** — **Diethyl phenylmalonate (65%)**

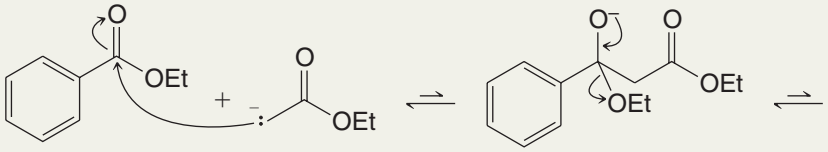
Solved Problem 19.1

Write a mechanism for all of the steps in the Claisen condensation above between ethyl benzoate and ethyl acetate.

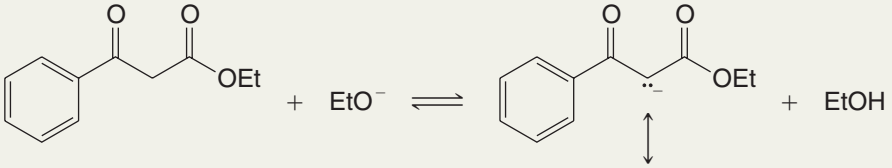
ANSWER

Step 1

Step 2

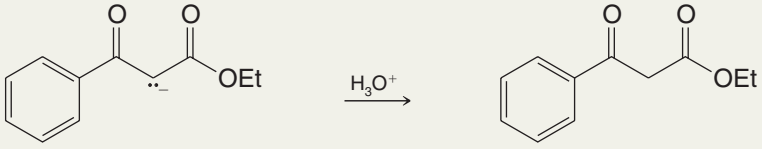


Step 3



other resonance structures

Step 4



Write mechanisms that account for the products that are formed in the crossed Claisen condensation just illustrated of ethyl phenylacetate with diethyl carbonate.

Review Problem 19.4

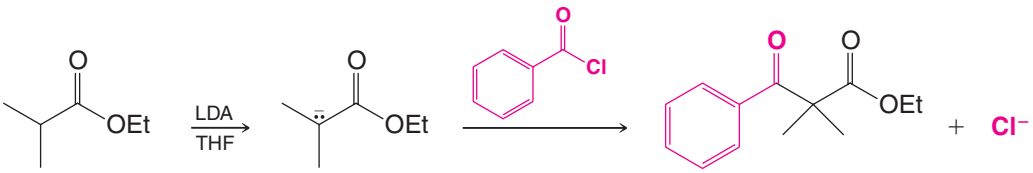
What products would you expect to obtain from each of the following crossed Claisen condensations?

(a) Ethyl propanoate + diethyl oxalate $\xrightarrow[(2)\ H_3O^+]{(1)\ NaOEt}$

(b) Ethyl acetate + ethyl formate $\xrightarrow[(2)\ H_3O^+]{(1)\ NaOEt}$

Review Problem 19.5

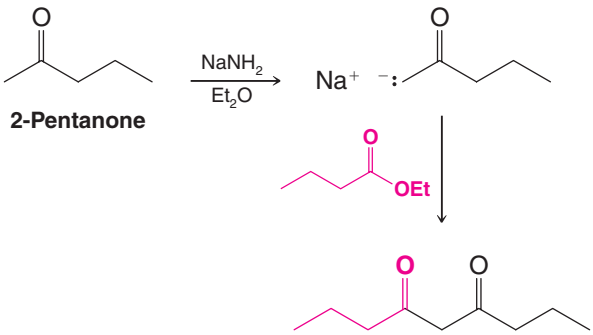
As we learned earlier in this section, esters that have only one α hydrogen cannot be converted to β-keto esters by sodium ethoxide. However, they can be converted to β-keto esters by reactions that use very strong bases such as lithium diisopropylamide (LDA) (Section 18.4). The strong base converts the ester to its enolate ion in nearly quantitative yield. This allows us to *acylate* the enolate ion by treating it with an acyl chloride or an ester. An example of this technique using LDA is shown here:



Ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate

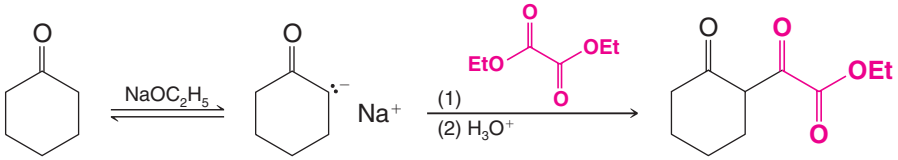
19.3 β-Dicarbonyl Compounds by Acylation of Ketone Enolates

Enolate ions derived from ketones also react with esters in nucleophilic substitution reactions that resemble Claisen condensations. In the following first example, although two anions are possible from the reaction of the ketone with sodium amide, the major product is derived from the primary carbanion. This is because (a) the primary α hydrogens are slightly more acidic than the secondary α hydrogens and (b) in the presence of the strong base ($NaNH_2$) in an aprotic solvent (Et_2O), the kinetic enolate is formed (see Section 18.4). LDA could be used similarly as the base.



2-Pentanone

4,6-Nonanedione (76%)

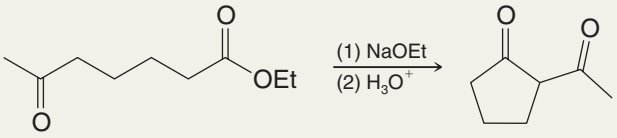


67%

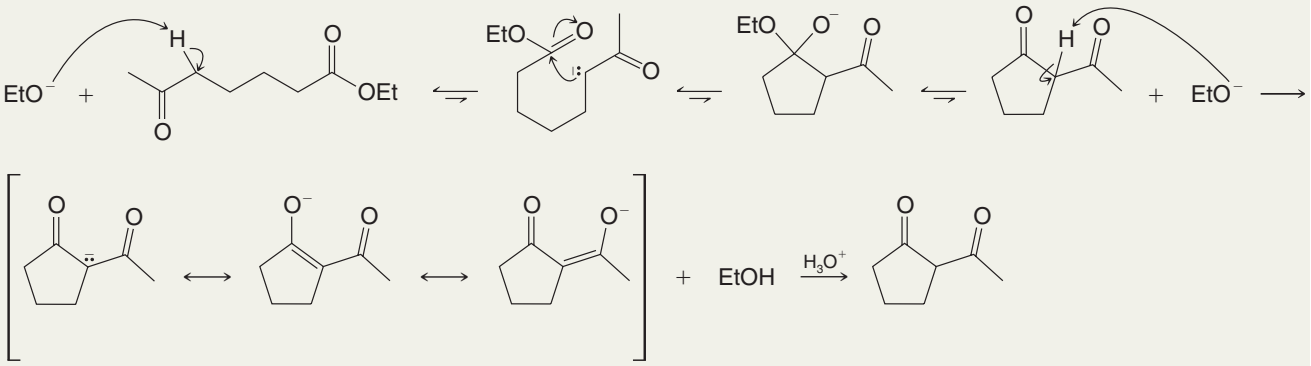
Openmirrors.com

Solved Problem 19.2

Keto esters are capable of undergoing cyclization reactions similar to the Dieckmann condensation. Write a mechanism for the following reaction.

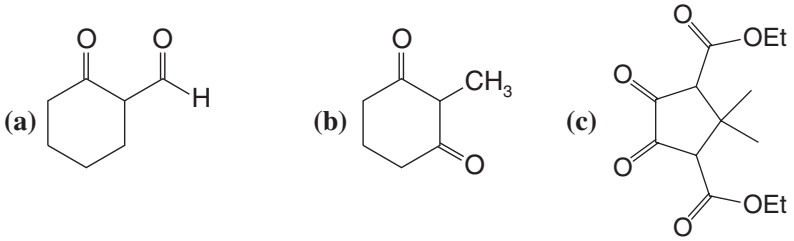


ANSWER



Review Problem 19.6

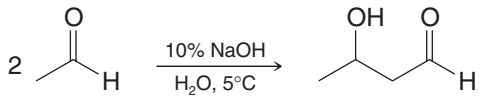
Show how you might synthesize each of the following compounds using, as your starting materials, esters, ketones, acyl halides, and so on:



19.4 *Aldol Reactions: Addition of Enolates and Enols to Aldehydes and Ketones*

- Aldol additions and aldol condensations together represent an important class of carbon–carbon bond-forming reaction.

An aldol reaction begins with addition of an enolate or enol to the carbonyl group of an aldehyde or ketone, leading to a β-hydroxy aldehyde or ketone as the initial product. A simple example is shown below, whereby two molecules of acetaldehyde (ethanal) react to form 3-hydroxybutanal. 3-Hydroxybutanal is an "aldol" because it contains both an **ald**ehyde and an alcoh**ol** functional group. Reactions of this general type are known as **aldol additions**.



3-Hydroxybutanal (50%)

As we shall see, the initial aldol addition product often dehydrates to form an α,β-unsaturated aldehyde or ketone. When this is the result, the overall reaction is an **aldol condensation**. First let us consider the mechanism of an aldol addition.

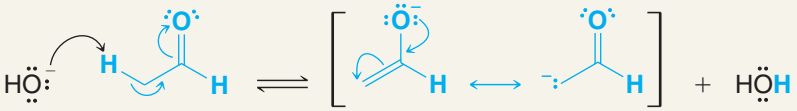
19.4A Aldol Addition Reactions

An aldol addition is an equilibrium reaction when it is conducted in a protic solvent with a base such as hydroxide or an alkoxide. The mechanism for an aldol addition involving an aldehyde is shown below.

A MECHANISM FOR THE REACTION

The Aldol Addition

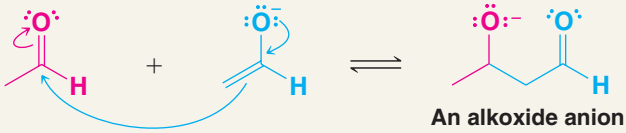
Step 1 ***Enolate formation***



Enolate anion

In this step the base (a hydroxide ion) removes a proton from the carbon of one molecule of acetaldehyde to give a resonance-stabilized enolate.

Step 2 ***Addition of the enolate***



An alkoxide anion

The enolate then acts as a nucleophile and attacks the carbonyl carbon of a second molecule of acetaldehyde, producing an alkoxide anion.

Step 3 ***Protonation of the alkoxide***

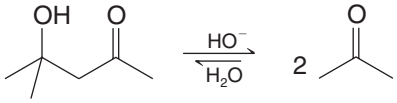
Stronger base — The aldol product — Weaker base

The alkoxide anion now removes a proton from a molecule of water to form the aldol.

With ketones, the addition step leading to the aldol is unfavorable due to steric hindrance, and the equilibrium favors the aldol precursors rather than the addition product (Section 19.4B). However, as we shall see in Section 19.4C, dehydration of the aldol addition product can draw the equilibrium toward completion, whether the reactant is an aldehyde or a ketone. Enolate additions to both aldehydes and ketones are also feasible when a stronger base (such as LDA) is used in an aprotic solvent (Section 19.5B).

19.4B The Retro-Aldol Reaction

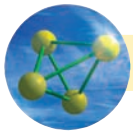
Because the steps in an aldol addition mechanism are readily reversible, a **retro-aldol reaction** can occur that converts a β-hydroxy aldehyde or ketone back to the precursors of an aldol addition. For example, when 4-hydroxy-4-methyl-2-pentanone is heated with hydroxide in water, the final equilibrium mixture consists primarily of acetone, the retro-aldol product.



Helpful Hint

See "The Chemistry of... A Retro-Aldol Reaction in Glycolysis: Dividing Assets to Double the ATP Yield" for an important biochemical application that increases the energy yield from glucose.

Openmirrors.com

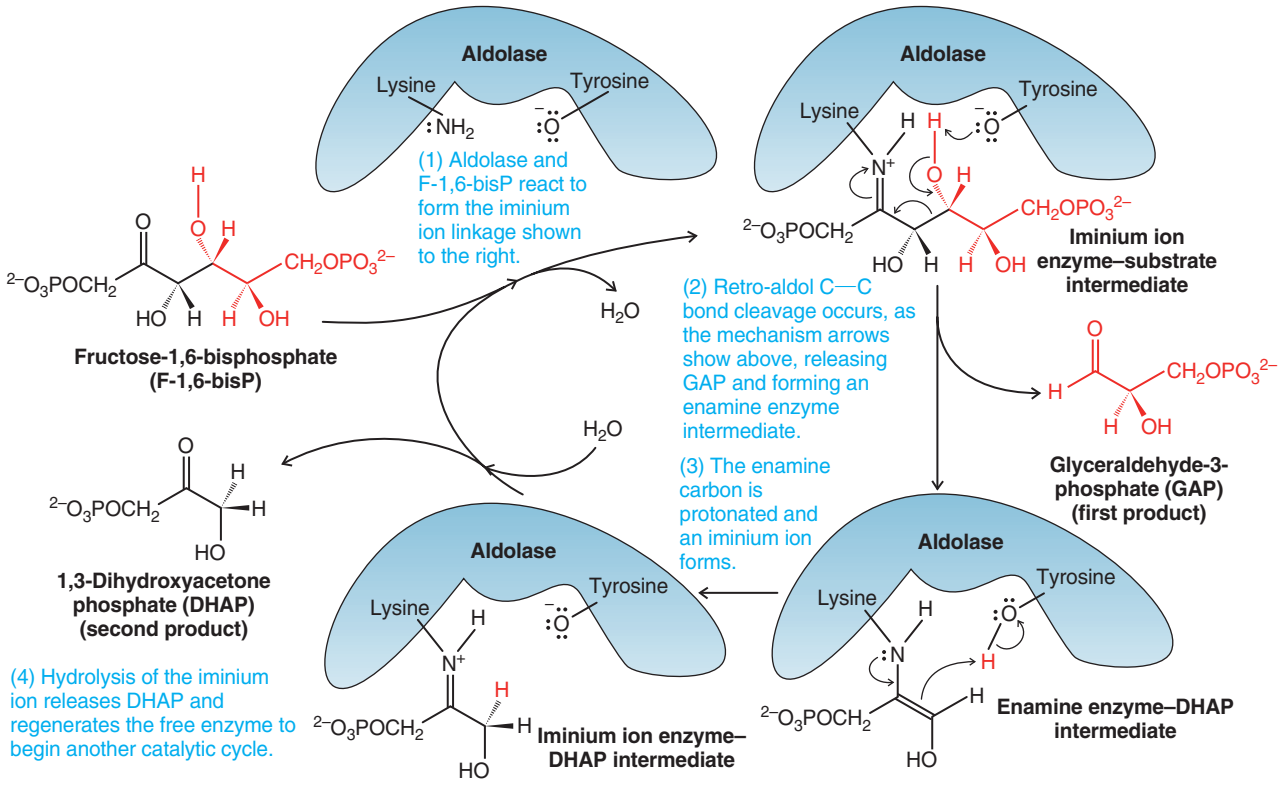


THE CHEMISTRY OF . . .

A Retro-Aldol Reaction in Glycolysis—Dividing Assets to Double the ATP Yield

Glycolysis is a fundamental pathway for production of ATP in living systems. The pathway begins with glucose and ends with two molecules of pyruvate and a net yield of two ATP molecules. Aldolase, an enzyme in glycolysis, plays a key role by dividing the six-carbon compound fructose-1,6-bisphosphate (derived from glucose) into two compounds that each have three carbons, glyceraldehyde-3-phosphate (GAP) and 1,3-dihydroxyacetone phosphate (DHAP). This process is essential because it provides two three-carbon units for the final stage of glycolysis, wherein the net yield of two ATP molecules per glucose is realized. (Two ATP molecules are consumed to form fructose-1,6-bisphosphate, and only two are generated per pyruvate. Thus, two passages through the second stage of glycolysis are necessary to obtain a net yield of two ATP molecules per glucose.)

The cleavage reaction catalyzed by aldolase is a net retro-aldol reaction. Details of the mechanism are shown here, beginning at the left with fructose-1,6-bisphosphate.



Two key intermediates in the aldolase mechanism involve functional groups that we have studied (Chapter 16)—an imine (protonated in the form of an iminium cation) and an enamine. In the mechanism of aldolase, an iminium cation acts as a sink for electron density during C—C bond cleavage (step 2), much like a carbonyl group does in a typical retro-aldol reaction. In this step the iminium cation is converted to an enamine, corresponding to the enolate or enol that is formed when a carbonyl group accepts electron density during C—C bond cleavage in an ordinary retro-aldol reaction. The enamine intermediate is then a source of an electron pair used to bond with a proton taken from the tyrosine hydroxyl at the aldolase active site (step 3). Lastly, the resulting iminium group undergoes hydrolysis (step 4), freeing aldolase for another catalytic cycle and releasing DHAP, the second product of the retro-aldol reaction. Then, by the process described in "The Chemistry of . . . TIM (Triose Phosphate Isomerase and Carbon Recycling via Enol" (Chapter 18), DHAP undergoes isomerization to GAP for processing to pyruvate and synthesis of two more ATP molecules.

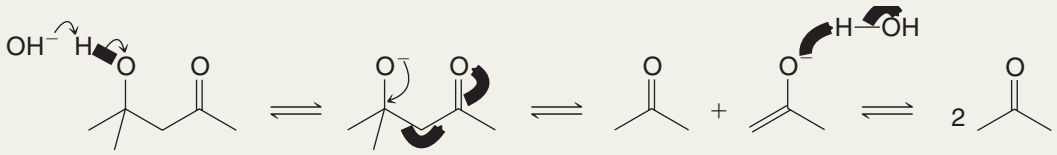
As we have seen with aldolase, imine and enamine functional groups have widespread roles in biological chemistry. Yet the functions of imines and enamines in biology are just as we would predict based on their native chemical reactivity.

This result is not surprising, because we know that the equilibrium for an aldol addition (the reverse of the reaction above) is not favorable when the enolate adds to a ketone. But, as mentioned earlier, dehydration of an aldol addition product can draw the equilibrium forward. We shall discuss the dehydration of aldols next (Section 19.4C).

Solved Problem 19.3

The carbon–carbon bond cleavage step in a retro-aldol reaction involves, under basic conditions, a leaving group that is an enolate, or under acidic conditions, an enol. Write a mechanism for the retro-aldol reaction of 4-hydroxy-4-methyl-2-pentanone under basic conditions (shown above).

STRATEGY AND ANSWER Base removes the proton from the β-hydroxyl group, setting the stage for reversal of the aldol addition. As the alkoxide reverts to the carbonyl group, a carbon–carbon bond breaks with expulsion of the enolate as a leaving group. This liberates one of the original carbonyl molecules. Protonation of the enolate forms the other.

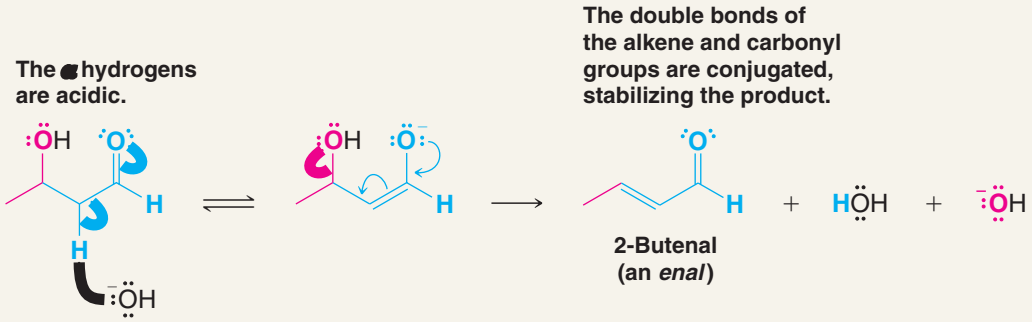


19.4C Aldol Condensation Reactions: Dehydration of the Aldol Addition Product

Dehydration of an aldol addition product leads to a conjugated α,β-unsaturated carbonyl system. The overall process is called an **aldol condensation,** and the product can be called an enal (alk*ene* *al*dehyde) or enone (alk*ene* ket*one*), depending on the carbonyl group in the product. The stability of the conjugated enal or enone system means that the dehydration equilibrium is essentially irreversible. For example, the aldol addition reaction that leads to 3-hydroxybutanal, shown in Section 19.4, dehydrates on heating to form 2-butenal. A mechanism for the dehydration is shown here.

A MECHANISM FOR THE REACTION

Dehydration of the Aldol Addition Product



Even though hydroxide is a leaving group in this reaction, the fact that each dehydrated molecule forms irreversibly, due to the stability from conjugation, draws the reaction forward.

Openmirrors.com

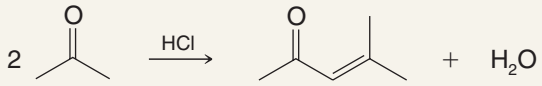
19.4D Acid-Catalyzed Aldol Condensations

Aldol reactions can occur under acid catalysis, in which case the reaction generally leads to the α,β-unsaturated product by direct dehydration of the β-hydroxy aldol intermediate. This is one way by which ketones can successfully be utilized in an aldol reaction. The following is an example, in which acetone forms its aldol condensation product, 4-methylpent-3-en-2-one, on treatment with hydrogen chloride.

A MECHANISM FOR THE REACTION

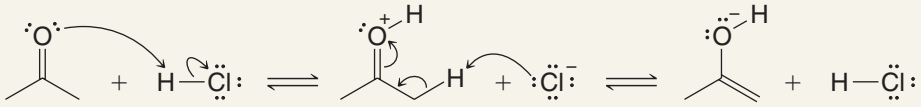
The Acid-Catalyzed Aldol Reaction

REACTION

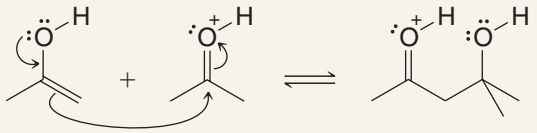


4-Methylpent-3-en-2-one

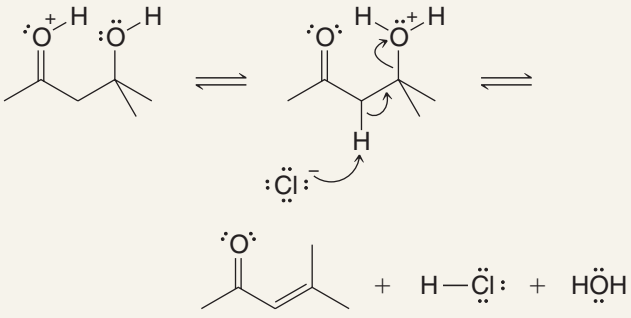
MECHANISM



The mechanism begins with the acid-catalyzed formation of the enol.



Then the enol adds to the protonated carbonyl group of another molecule of acetone.



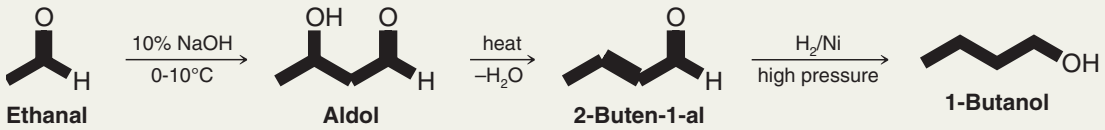
Finally, proton transfers and dehydration lead to the product.

Acid catalysis can promote further reactions after the aldol condensation. An example is given in Review Problem 19.8. Generally, it is more common in synthesis for an aldol reaction to be conducted under basic rather than acidic conditions.

Solved Problem 19.4

One industrial process for the synthesis of 1-butanol begins with ethanal. Show how this synthesis might be carried out.

STRATEGY AND ANSWER Ethanal can be converted to an aldol via an aldol addition. Then, dehydration would produce 2-buten-1-al, which can be hydrogenated to furnish 1-butanol.



The acid-catalyzed aldol condensation of acetone (just shown) also produces some 2,6-dimethylhepta-2,5-dien-4-one. Give a mechanism that explains the formation of this product.

Review Problem 19.7

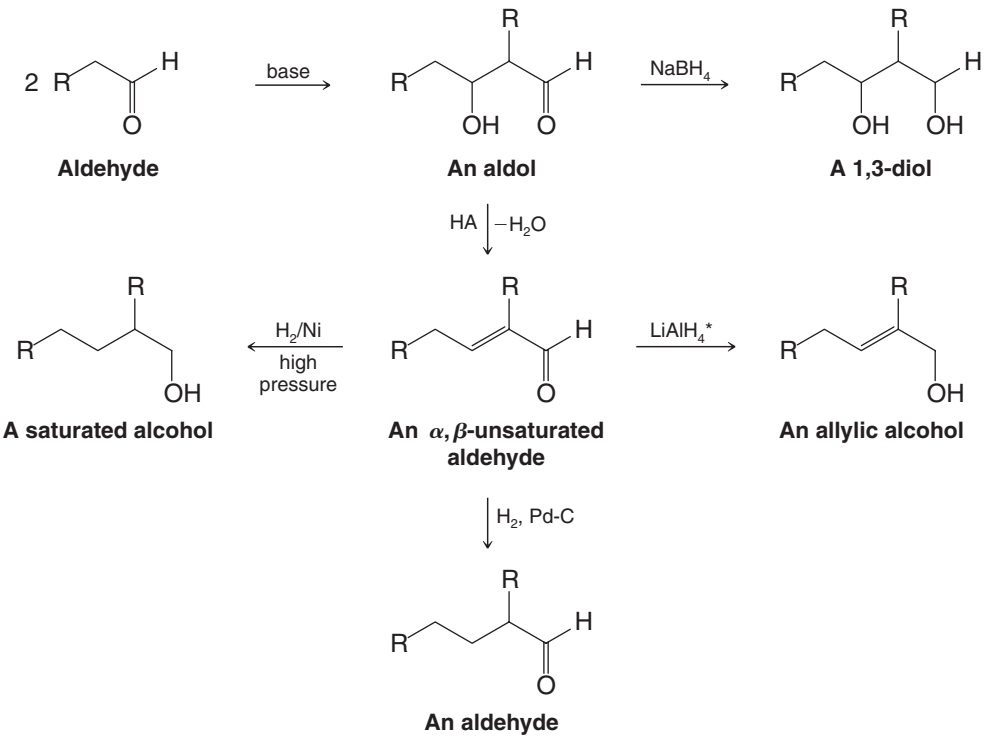
Heating acetone with sulfuric acid leads to the formation of mesitylene (1,3,5-trimethylbenzene). Propose a mechanism for this reaction.

Review Problem 19.8

19.4E Synthetic Applications of Aldol Reactions

As we are beginning to see, aldol additions and aldol condensations are important methods for carbon–carbon bond formation. They also result in β-hydroxy and α,β-unsaturated carbonyl compounds that are themselves useful for further synthetic transformations. Some representative reactions are shown below.

The Aldol Reaction in Synthesis



*$LiAlH_4$ reduces the carbonyl group of α,β-unsaturated aldehydes and ketones cleanly. $NaBH_4$ often reduces the carbon–carbon double bond as well.

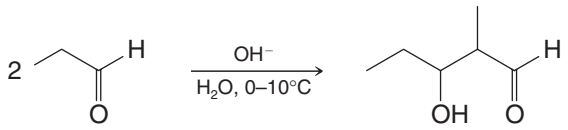
Helpful Hint

The aldol reaction: a tool for synthesis. See also the Synthetic Connections review at the end of the chapter.

Openmirrors.com

Review Problem 19.9

(a) Provide a mechanism for the aldol addition of propanal shown here.



Propanal **3-Hydroxy-2-methylpentanal (55–60%)**

(b) How can you account for the fact that the product of the aldol addition is 3-hydroxy-2-methylpentanal and not 4-hydroxyhexanal?

(c) What products would be formed if the reaction mixture were heated?

Review Problem 19.10

Show how each of the following products could be synthesized from butanal:

(a) 2-Ethyl-3-hydroxyhexanal

(b) 2-Ethylhex-2-en-1-ol

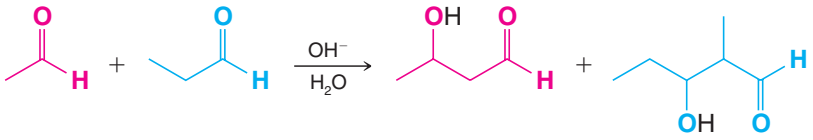
(c) 2-Ethylhexan-1-ol

(d) 2-Ethylhexane-1,3-diol (the insect repellent "6–12")

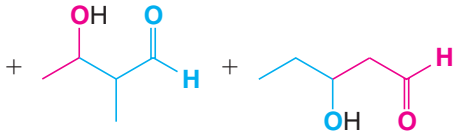
Thus far we have only considered examples of aldol reactions where the reactant forms a product by dimerization. In the coming sections we shall discuss the use of aldol reactions to more generally prepare β-hydroxy and α,β-unsaturated carbonyl compounds. We shall then study reactions called conjugate addition reactions (Section 19.7), by which we can further build on the α,β-unsaturated carbonyl systems that result from aldol condensations.

19.5 Crossed Aldol Condensations

An aldol reaction that starts with two different carbonyl compounds is called a **crossed aldol reaction**. Unless specific conditions are involved, a crossed aldol reaction can lead to a mixture of products from various pairings of the carbonyl reactants, as the following example illustrates with ethanal and propanal.



Ethanal **Propanal** **3-Hydroxybutanal (from two molecules of ethanal)** **3-Hydroxy-2-methylpentanal (from two molecules of propanal)**



3-Hydroxy-2-methylbutanal (from one molecule of ethanal and one molecule of propanal) **3-Hydroxypentanal**

We shall therefore consider crossed aldol condensations by two general approaches that allow control over the distribution of products. The first approach hinges on structural factors of the carbonyl reactants and the role that favorable or unfavorable aldol addition equilibria play in determining the product distribution. In this approach relatively weak bases such as hydroxide or an alkoxide are used in a protic solvent such as water or an alcohol. The second

approach, called a directed aldol reaction, involves use of a strong base such as LDA in an aprotic solvent. With a strong base, one reactant can be converted essentially completely to its enolate, which can then be allowed to react with the other carbonyl reactant.

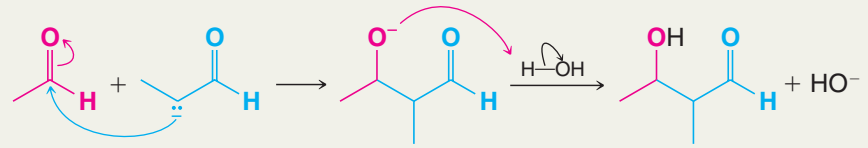
Solved Problem 19.5

Show how each of the four products shown at the beginning of this section is formed in the crossed aldol addition between ethanal and propanal.

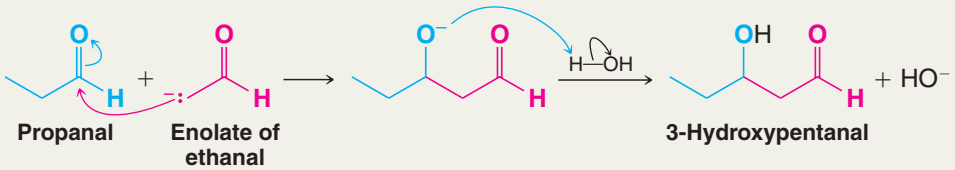
ANSWER In the basic aqueous solution, four organic entities will initially be present: molecules of ethanal, molecules of propanal, enolate anions derived from ethanal, and enolate anions derived from propanal.

We have already seen (Section 19.4) how a molecule of ethanal can react with its enolate to form 3-hydroxybutanal (aldol). We have also seen (Review Problem 19.9) how propanal can react with its enolate anion to form 3-hydroxy-2-methylpentanal. The other two products are formed as follows.

3-Hydroxy-2-methylbutanal results when the enolate of propanal reacts with ethanal.



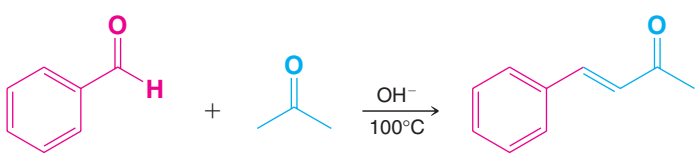
And finally, 3-hydroxypentanal results when the enolate of ethanal reacts with propanal.



19.5A Crossed Aldol Condensations Using Weak Bases

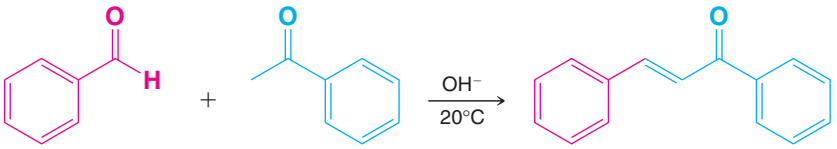
Crossed aldol reactions are possible with weak bases such as hydroxide or an alkoxide when one carbonyl reactant does not have an α hydrogen. A reactant without α hydrogens cannot self-condense because it cannot form an enolate. We avoid self-condensation of the other reactant, that which has an α hydrogen, by adding it slowly to a solution of the first reactant and the base. Under these conditions the concentration of the reactant with an α hydrogen is always low, and it is present mostly in its enolate form. The main reaction that takes place is between this enolate and the carbonyl compound that has no α hydrogens. The reactions shown in Table 19.1 on the bottom of the next page illustrate results from this approach.

The crossed aldol examples shown in Table 19.1 involve aldehydes as both reactants. A ketone can be used as one reactant, however, because ketones do not self-condense appreciably due to steric hindrance in the aldol addition stage. The following are examples of crossed aldol condensations where one reactant is a ketone. Reactions such as these are sometimes called Claisen–Schmidt condensations. Schmidt discovered and Claisen developed this type of aldol reaction in the late 1800s.



4-Phenylbut-3-en-2-one (benzalacetone) (70%)

Openmirrors.com



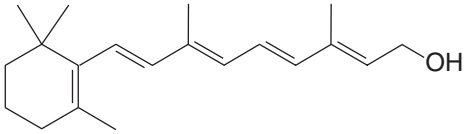
1,3-Diphenylprop-2-en-1-one (benzalacetophenone) (85%)

In these reactions, dehydration occurs readily because the double bond that forms is conjugated both with the carbonyl group and with the benzene ring. In general, dehydration of the aldol is especially favorable when it leads to extended conjugation.

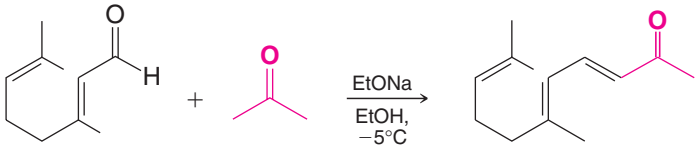
As a further example, an important step in a commercial synthesis of vitamin A makes use of a crossed aldol condensation between geranial and acetone:

Helpful Hint

See "The Chemistry of... Antibody-catalyzed Aldol Condensations" in Wiley Plus for a method that uses the selectivity of antibodies to catalyze aldol reactions.

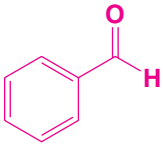
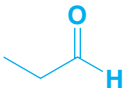
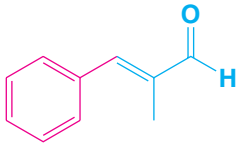
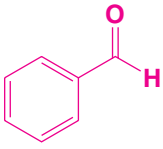
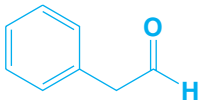
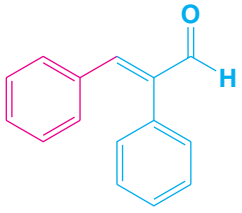
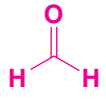
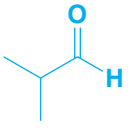
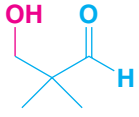


Vitamin A



Geranial **Pseudoionone (49%)**

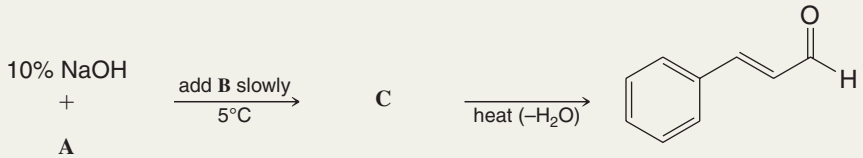
TABLE 19.1 Crossed Aldol Reactions

This Reactant with No α Hydrogen Is Placed in Base	This Reactant with an α Hydrogen Is Added Slowly	Product
		
Benzaldehyde	Propanal	2-Methyl-3-phenyl-2-propenal (α-methylcinnamaldehyde) (68%)
		
Benzaldehyde	Phenylacetaldehyde	2,3-Diphenyl-2-propenal
		
Formaldehyde	2-Methylpropanal	3-Hydroxy-2,2-dimethylpropanal (>64%)

Geranial is a naturally occurring aldehyde that can be obtained from lemongrass oil. Its α hydrogen is *vinylic* and, therefore, not appreciably acidic. Notice, in this reaction, too, dehydration occurs readily because dehydration extends the conjugated system.

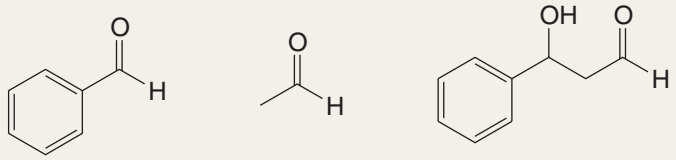
Solved Problem 19.6

Outlined below is a practical crossed aldol reaction that can be used for the synthesis of cinnamaldehyde (the essence of cinnamon, used in cooking). Provide the missing ingredients for this recipe.



Cinnamaldehyde

STRATEGY AND ANSWER Compound **A** is benzaldehyde, **B** is ethanal (acetaldehyde), and the intermediate **C** is shown below.



A **B** **C**

Review Problem 19.11

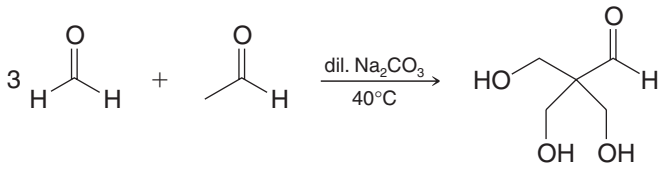
Outlined below is a synthesis of a compound used in perfumes, called lily aldehyde. Provide all of the missing structures.

p-tert-Butylbenzyl alcohol $\xrightarrow[CH_2Cl_2]{PCC}$ $C_{11}H_{14}O$ $\xrightarrow[OH^-]{propanal}$

$C_{14}H_{18}O$ $\xrightarrow{H_2,\ Pd–C}$ lily aldehyde ($C_{14}H_{20}O$)

Review Problem 19.12

When excess formaldehyde in basic solution is treated with ethanal, the following reaction takes place:

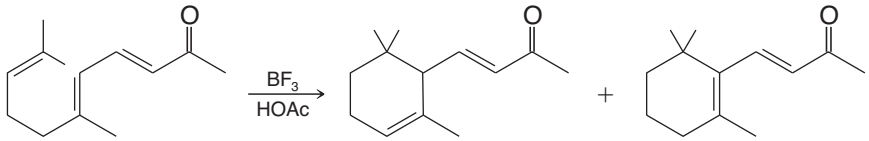


82%

Write a mechanism that accounts for the formation of the product.

Review Problem 19.13

When pseudoionone is treated with BF_3 in acetic acid, ring closure takes place and α- and β-ionone are produced. This is the next step in the vitamin A synthesis.



Pseudoionone **α-Ionone** **β-Ionone**

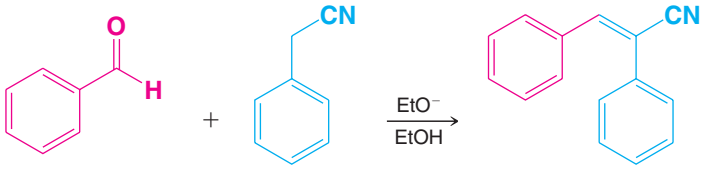
(a) Write mechanisms that explain the formation of α- and β-ionone.

(b) β-Ionone is the major product. How can you explain this?

(c) Which ionone would you expect to absorb at longer wavelengths in the UV–visible region? Why?

Openmirrors.com

Nitriles with α hydrogens are also weakly acidic ($pK_a \cong 25$) and consequently these nitriles undergo condensations of the aldol type. An example is the condensation of benzaldehyde with phenylacetonitrile:



Review Problem 19.14

(a) Write resonance structures for the anion of acetonitrile that account for its being much more acidic than ethane. **(b)** Give a step-by-step mechanism for the condensation of benzaldehyde with acetonitrile.

19.5B Crossed Aldol Condensations Using Strong Bases: Lithium Enolates and Directed Aldol Reactions

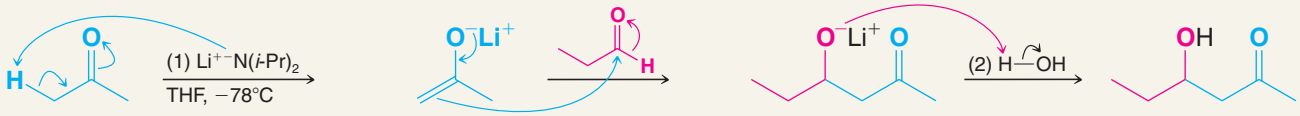
Helpful Hint

Lithium enolates are useful for crossed aldol syntheses.

One of the most effective and versatile ways to bring about a crossed aldol reaction is to use a lithium enolate obtained from a ketone as one component and an aldehyde or ketone as the other. An example of this approach, called a **directed aldol reaction**, is shown by the following mechanism.

A MECHANISM FOR THE REACTION

A Directed Aldol Synthesis Using a Lithium Enolate



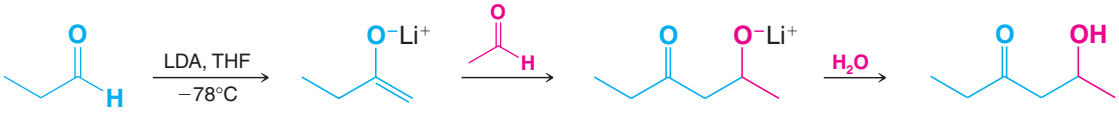
The ketone is added to $LiN(i\text{-}Pr)_2$ (LDA), a strong base, which removes an α hydrogen from the ketone to produce an enolate.

The aldehyde is added and the enolate reacts with the aldehyde at its carbonyl carbon.

An acid–base reaction occurs when water is added at the end, protonating the lithium alkoxide.

Regioselectivity can be achieved when unsymmetrical ketones are used in directed aldol reactions by generating the kinetic enolate using lithium diisopropylamide (LDA). This ensures production of the enolate in which the proton has been removed from the less substituted α carbon. The following is an example:

An Aldol Reaction via the Kinetic Enolate (Using LDA)

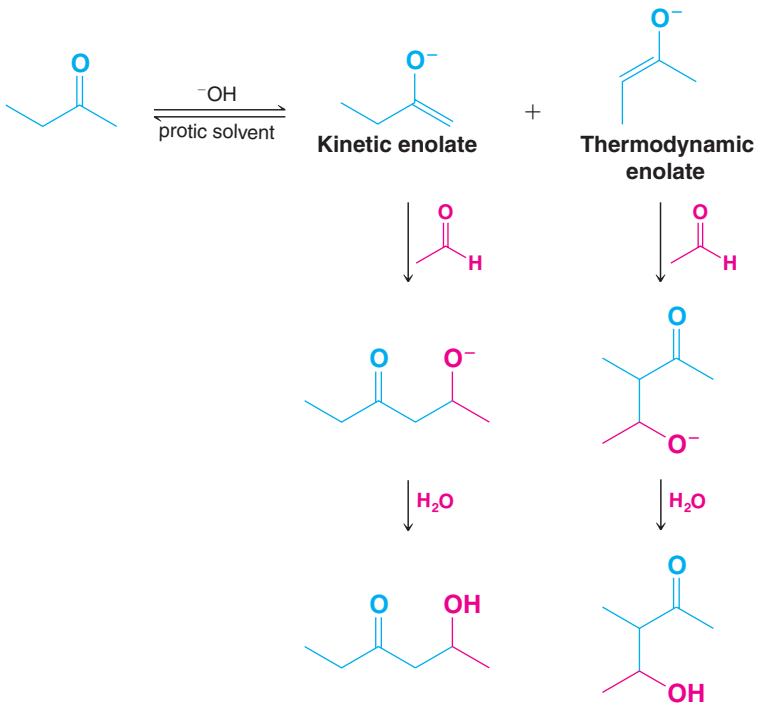


75%

A single crossed aldol product results.

If this aldol reaction had been carried out in the classic way (Section 19.5A) using hydroxide ion as the base, then at least two products would have been formed in significant amounts. Both the kinetic and thermodynamic enolates would have been formed from the ketone, and each of these would have added to the carbonyl carbon of the aldehyde:

An Aldol Reaction That Produces a Mixture via Both Kinetic and Thermodynamic Enolates (Using a Weaker Base under Protic Conditions)



A mixture of crossed aldol products results.

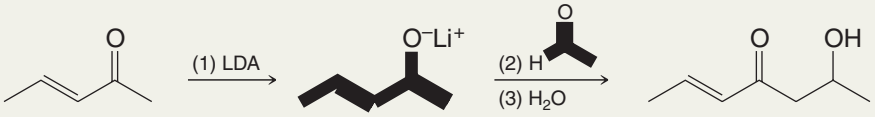
Solved Problem 19.7

Outline a directed aldol synthesis of the following compound.

STRATEGY AND ANSWER

Retrosynthetic Analysis

Synthesis

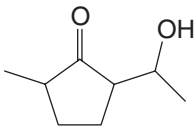


Openmirrors.com

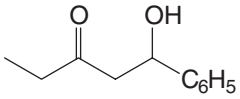
Review Problem 19.15

Starting with ketones and aldehydes of your choice, outline a directed aldol synthesis of each of the following using lithium enolates:

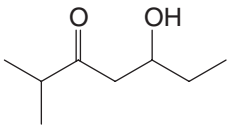
(a)



(b)

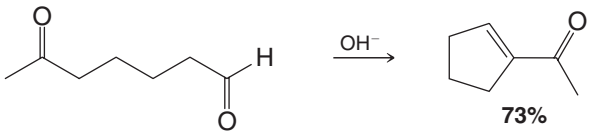


(c)



19.6 Cyclizations via Aldol Condensations

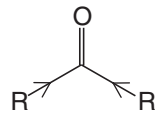
The aldol condensation also offers a convenient way to synthesize molecules with five- and six-membered rings (and sometimes even larger rings). This can be done by an intramolecular aldol condensation using a dialdehyde, a keto aldehyde, or a diketone as the substrate. For example, the following keto aldehyde cyclizes to yield 1-cyclopentenyl methyl ketone:



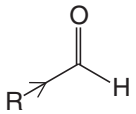
73%

This reaction almost certainly involves the formation of at least three different enolates. However, it is the enolate from the ketone side of the molecule that adds to the aldehyde group leading to the product.

The reason the aldehyde group undergoes addition preferentially may arise from the greater reactivity of aldehydes toward nucleophilic addition generally. The carbonyl carbon atom of a ketone is less positive (and therefore less reactive toward a nucleophile) because it bears two electron-releasing alkyl groups; it is also more sterically hindered:



Ketones are less reactive toward nucleophiles.



Aldehydes are more reactive toward nucleophiles.

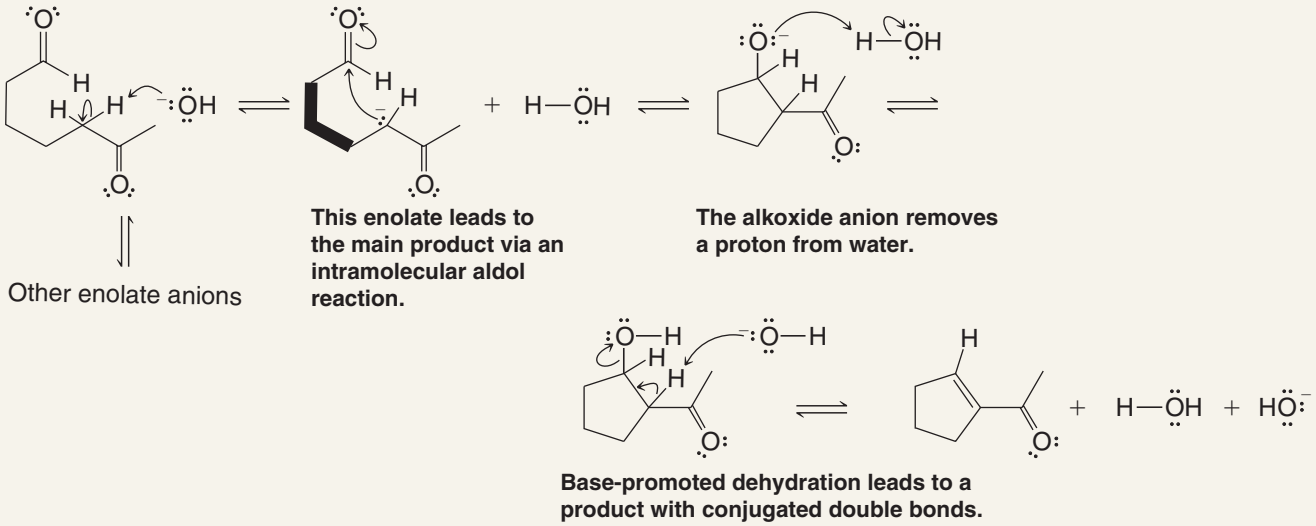
Helpful Hint

Selectivity in aldol cyclizations is influenced by carbonyl type and ring size.

In reactions of this type, five-membered rings form far more readily than seven-membered rings, and six-membered rings are more favorable than four- or eight-membered rings, when possible.

A MECHANISM FOR THE REACTION

The Aldol Cyclization

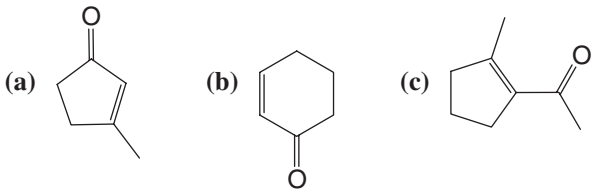


Assuming that dehydration occurs, write the structures of the two other products that might have resulted from the aldol cyclization just given. (One of these products will have a five-membered ring and the other will have a seven-membered ring.)

Review Problem 19.16

What starting compound would you use in an aldol cyclization to prepare each of the following?

Review Problem 19.17



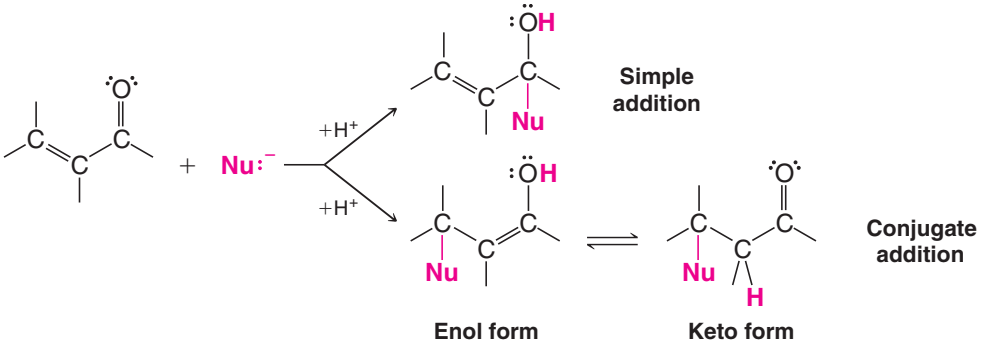
What experimental conditions would favor the cyclization process in an intramolecular aldol reaction over intermolecular condensation?

Review Problem 19.18

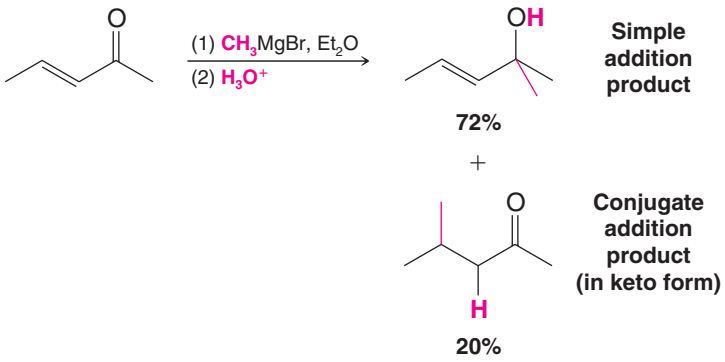
19.7 Additions to α,β-Unsaturated Aldehydes and Ketones

When α,β-unsaturated aldehydes and ketones react with nucleophilic reagents, they may do so in two ways. They may react by a **simple addition,** that is, one in which the nucleophile adds across the double bond of the carbonyl group; or they may react by a **conjugate addition.** These two processes resemble the 1,2- and the 1,4-addition reactions of conjugated dienes (Section 13.10):

Openmirrors.com



In many instances both modes of addition occur in the same mixture. As an example, let us consider the Grignard reaction shown here:

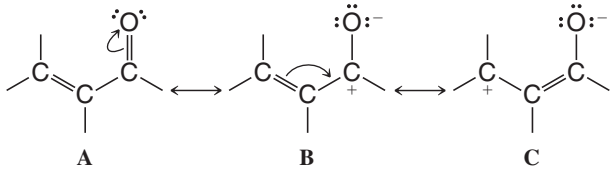


In this example we see that simple addition is favored, and this is generally the case with strong nucleophiles. Conjugate addition is favored when weaker nucleophiles are employed.

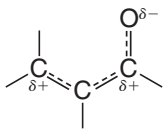
Helpful Hint

Note the influence of nucleophile strength on conjugate versus simple addition.

If we examine the resonance structures that contribute to the overall hybrid for an α,β-unsaturated aldehyde or ketone (see structures **A**–**C**), we shall be in a better position to understand these reactions:

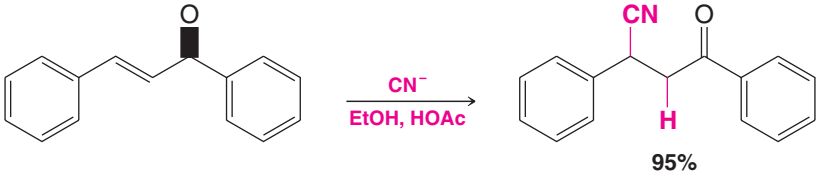


Although structures **B** and **C** involve separated charges, they make a significant contribution to the hybrid because, in each, the negative charge is carried by electronegative oxygen. Structures **B** and **C** also indicate that *both the carbonyl carbon and the β carbon should bear a partial positive charge*. They indicate that we should represent the hybrid in the following way:



This structure tells us that we should expect a nucleophilic reagent to attack either the carbonyl carbon or the β carbon.

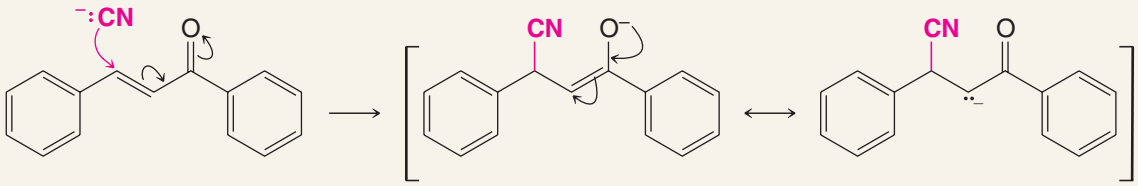
Almost every nucleophilic reagent that adds at the carbonyl carbon of a simple aldehyde or ketone is capable of adding at the β carbon of an α,β-unsaturated carbonyl compound. In many instances when weaker nucleophiles are used, conjugate addition is the major reaction path. Consider the following addition of hydrogen cyanide:



95%

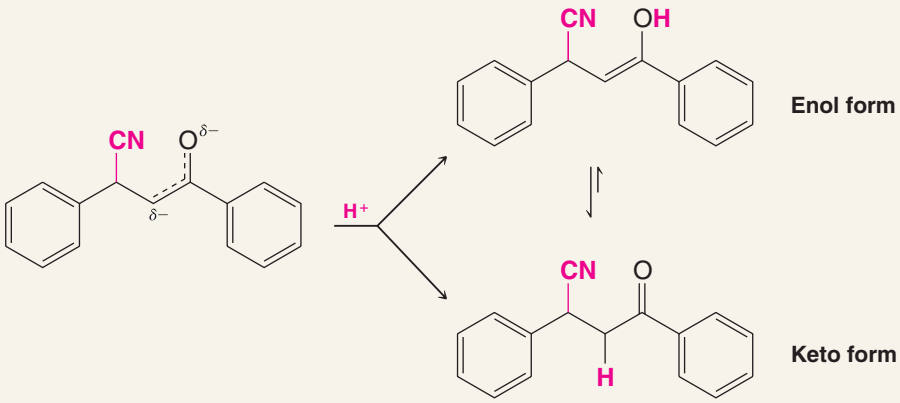
A MECHANISM FOR THE REACTION

The Conjugate Addition of HCN

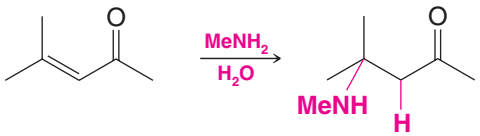


Enolate intermediate

Then, the enolate intermediate accepts a proton in either of two ways:



Another example of this type of addition is the following:



75%

Openmirrors.com

A MECHANISM FOR THE REACTION

The Conjugate Addition of an Amine

The nucleophile attacks the partially positive β carbon.

In two separate steps, a proton is lost from the nitrogen atom and a proton is gained at the oxygen.

Enol form

Keto form

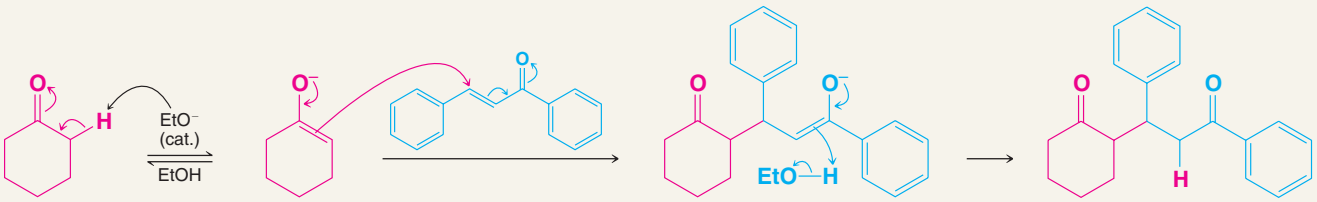
We shall see examples of biochemically relevant conjugate additions in "The Chemistry of . . . Calicheamicin γ_1^I Activation for Cleavage of DNA" (see Section 19.7B) and in "The Chemistry of . . . A Suicide Enzyme Substrate" (Section 19.8).

19.7A Conjugate Additions of Enolates: Michael Additions

Conjugate additions of enolates to α,β-unsaturated carbonyl compounds are known generally as Michael additions (after their discovery, in 1887, by Arthur Michael, of Tufts University and later of Harvard University). The following mechanism box provides an example of a Michael addition.

A MECHANISM FOR THE REACTION

The Michael Addition

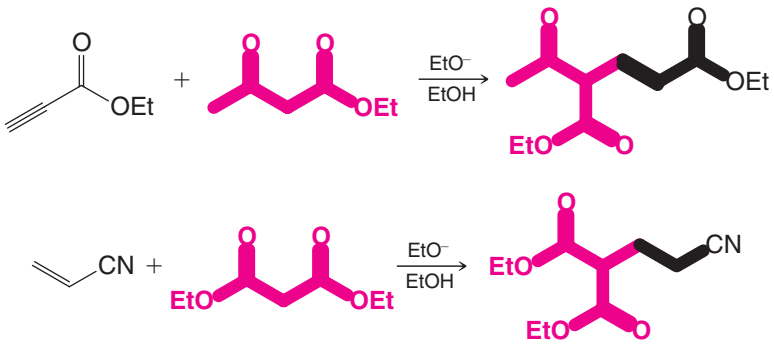


A base removes an α proton to form an enolate from one carbonyl reactant.

This enolate adds to the β carbon of the α,β-unstaturated carbonyl compound, forming a new carbon–carbon bond between them. As this bond is formed, electron density in the α,β-unsaturated compound shifts to its carbonyl oxygen, leading to a new enolate.

Protonation of the resulting enolate leads to the final Michael addition product.

Michael additions take place with a variety of other reagents; these include acetylenic esters and α,β-unsaturated nitriles:

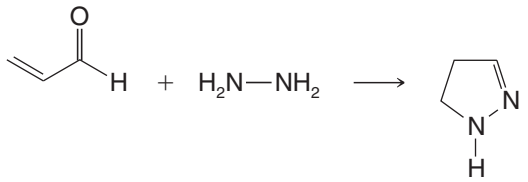


What product would you expect to obtain from the base-catalyzed Michael reaction of **(a)** 1,3-diphenylprop-2-en-1-one (Section 19.5A) and acetophenone and **(b)** 1,3-diphenylprop-2-en-1-one and cyclopentadiene? Show all steps in each mechanism.

Review Problem 19.19

When acrolein (propenal) reacts with hydrazine, the product is a dihydropyrazole:

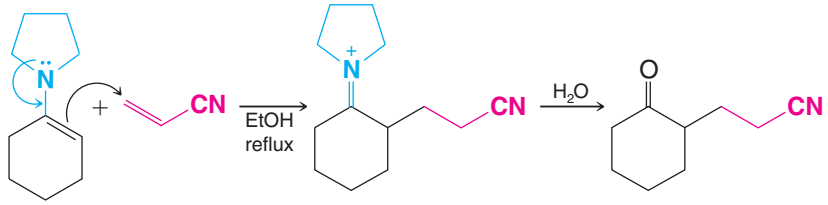
Review Problem 19.20



Acrolein **Hydrazine** **A dihydropyrazole**

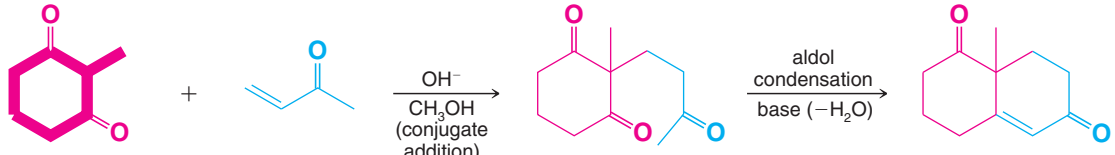
Suggest a mechanism that explains this reaction.

Enamines can also be used in Michael additions. An example is the following:



19.7B The Robinson Annulation

A Michael addition followed by a simple aldol condensation may be used to build one ring onto another. This procedure is known as the *Robinson annulation* (ring-forming) reaction (after the English chemist, Sir Robert Robinson, who won the Nobel Prize in Chemistry in 1947 for his research on naturally occurring compounds):

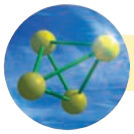


2-Methylcyclohexane-1,3-dione **Methyl vinyl ketone**

(a) Propose step-by-step mechanisms for both transformations of the Robinson annulation sequence just shown. **(b)** Would you expect 2-methylcyclohexane-1,3-dione to be more or less acidic than cyclohexanone? Explain your answer.

Review Problem 19.21

Openmirrors.com

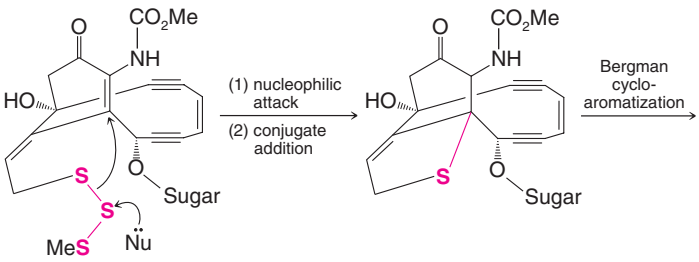


THE CHEMISTRY OF . . .

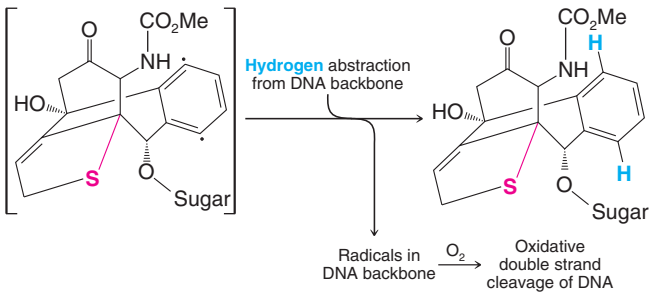
Calicheamicin γ_1^I Activation for Cleavage of DNA

In "The Chemistry of . . . Calicheamicin γ_1^I" in Chapter 10, we described a potent antitumor antibiotic called calicheamicin γ_1^I. Now that we have considered conjugate addition reactions, it is time to revisit this fascinating molecule. The molecular machinery of calicheamicin γ_1^I for destroying DNA is unleashed by attack of a nucleophile on the trisulfide linkage shown in the accompanying scheme. The sulfur anion that initially was a leaving group from the trisulfide immediately becomes a nucleophile that attacks the bridgehead alkene carbon. This alkene carbon is electrophilic because it is conjugated with the adjoining carbonyl group. Attack by the sulfur nucleophile on the alkene carbon is a *conjugate addition*.

Now that the bridgehead carbon is tetrahedral, the geometry of the bicyclic structure favors conversion of the enediyne to a 1,4-benzenoid diradical by a reaction called the Bergman cycloaromatization (after R. G. Bergman of the University of California, Berkeley). Once the calicheamicin diradical is formed it can pluck two hydrogen atoms from the DNA backbone, converting the DNA to a reactive diradical and ultimately resulting in DNA cleavage and the death of the cell.



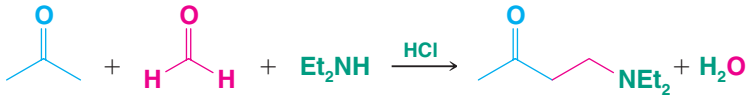
Calicheamicin γ_1^I



Reprinted from CURRENT BIOLOGY, *Vol 1*, Nicolaou, "Chemistry and biology of the calicheamicins," copyright 1994 with permission of Elsevier.

19.8 *The Mannich Reaction*

Compounds capable of forming an enol react with imines from formaldehyde and a primary or secondary amine to yield β-aminoalkyl carbonyl compounds called Mannich bases. The following reaction of acetone, formaldehyde, and diethylamine is an example:



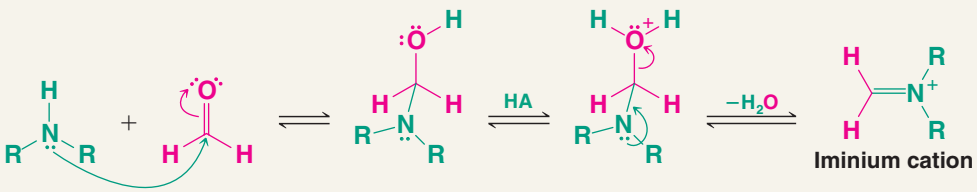
A Mannich base

The **Mannich reaction** apparently proceeds through a variety of mechanisms depending on the reactants and the conditions that are employed. The mechanism below appears to operate in neutral or acidic media. Note the aspects in common with imine formation and with reactions of enols and carbonyl groups.

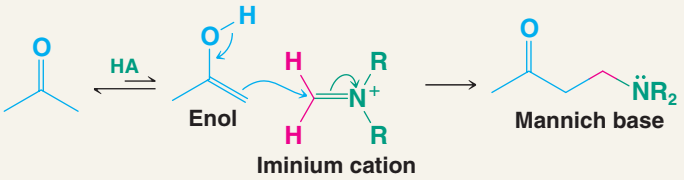
A MECHANISM FOR THE REACTION

The Mannich Reaction

Step 1



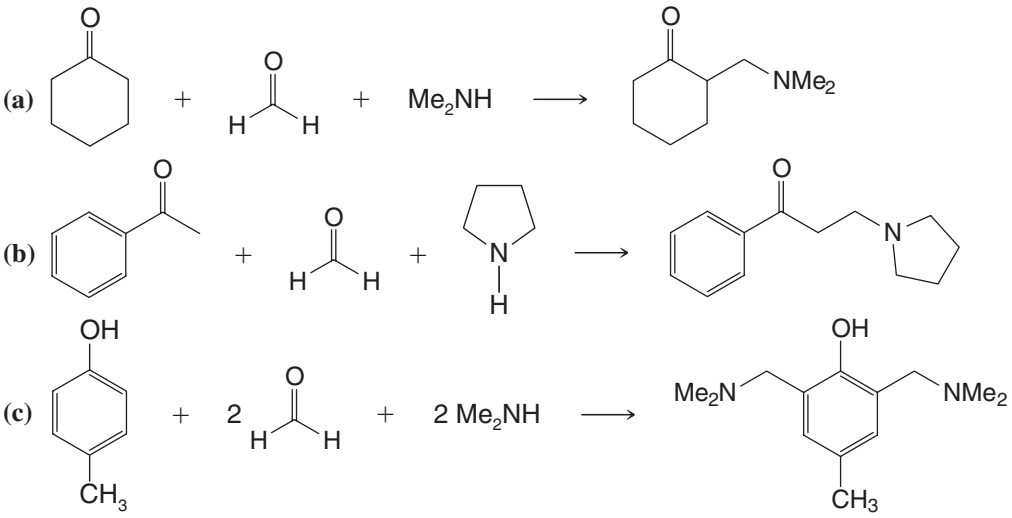
Step 2

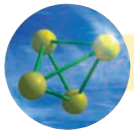


The enol form of the active hydrogen compound reacts with the iminium cation to form a β-aminocarbonyl compound (a Mannich base).

Review Problem 19.22

Outline reasonable mechanisms that account for the products of the following Mannich reactions:





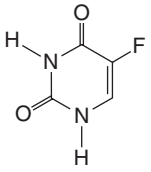
THE CHEMISTRY OF . . .

A Suicide Enzyme Substrate

5-Fluorouracil is a chemical imposter for uracil and a potent clinical anticancer drug. This effect arises because 5-fluorouracil irreversibly destroys the ability of thymidylate synthase (an enzyme) to catalyze a key transformation needed for DNA synthesis. 5-Fluorouracil acts as a mechanism-based inhibitor (or suicide substrate) because it engages thymidylate synthase as though it were the normal substrate but then leads to self-destruction of the enzyme's activity by its

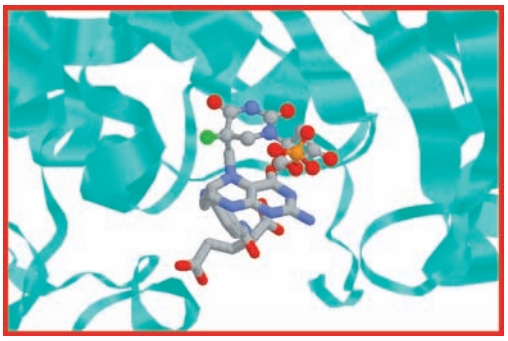
Openmirrors.com

own mechanistic pathway. The initial deception is possible because the fluorine atom in the inhibitor occupies roughly the same amount of space as the hydrogen atom does in the natural substrate. Disruption of the enzyme's mechanism occurs because a fluorine atom cannot be removed by a base in the way that is possible for a hydrogen atom to be removed.

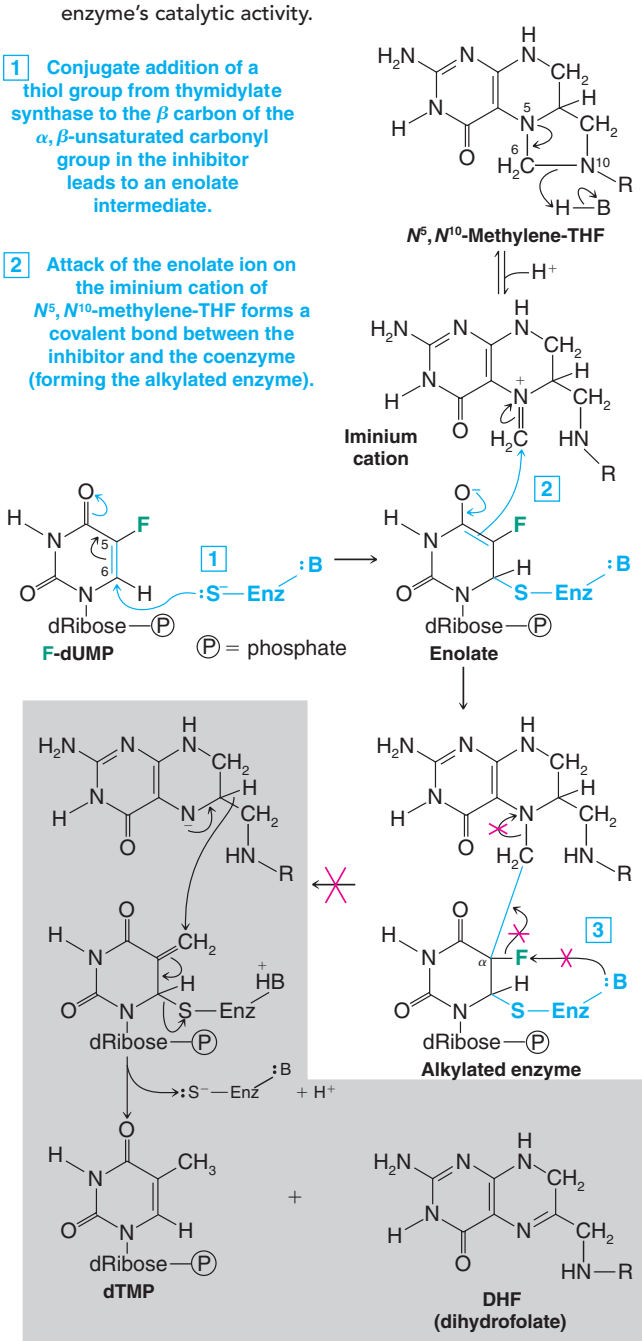


5-Fluorouracil

The mechanism of thymidylate synthase in both its normal mode and when it is about to be blocked by the inhibitor involves attack of an enolate ion on an iminium cation. This process is closely analogous to the Mannich reaction discussed in Section 19.8. The enolate ion in this attack arises by conjugate addition of a thiol group from thymidylate synthase to the α,β-unsaturated carbonyl group of the substrate. This process is analogous to the way an enolate intermediate occurs in a Michael addition. The iminium ion that is attacked in this process derives from the coenzyme N^5,N^{10}-methylenetetrahydrofolate (N^5,N^{10}-methylene-THF). Attack by the enolate in this step forms the bond that covalently links the substrate to the enzyme. It is this bond that cannot be broken when the fluorinated inhibitor is used. The mechanism of inhibition is shown at right.

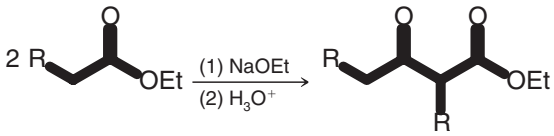


5-Fluorodeoxyuracil monophosphate covalently bound to tetrahydrofolate in thymidylate synthase, blocking the enzyme's catalytic activity.

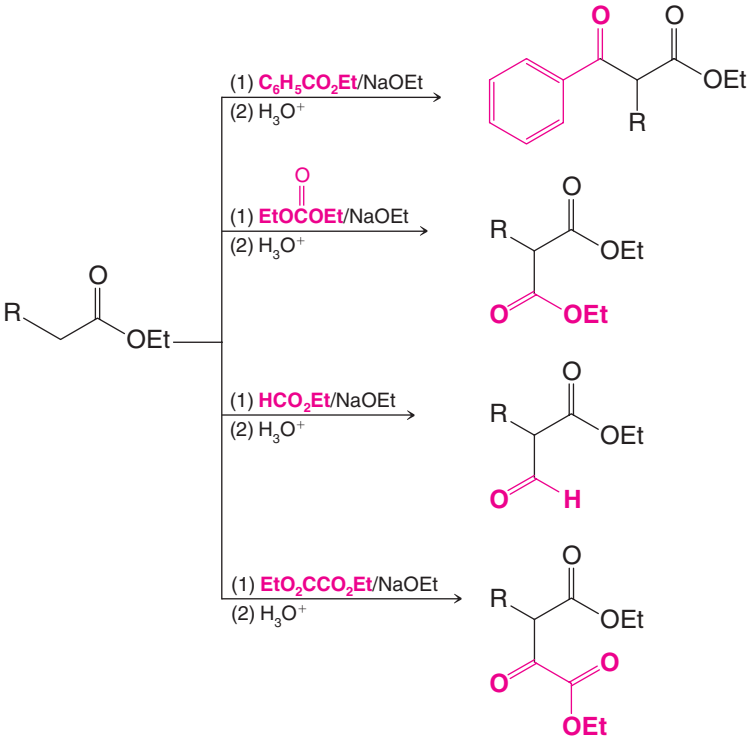


19.9 Summary of Important Reactions

1. Claisen Condensation (Section 19.2):

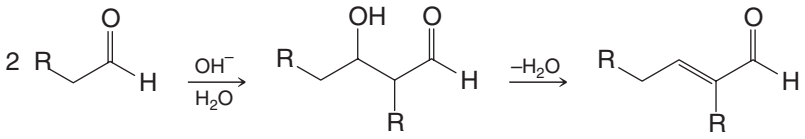


2. Crossed Claisen Condensation (Section 19.2B):

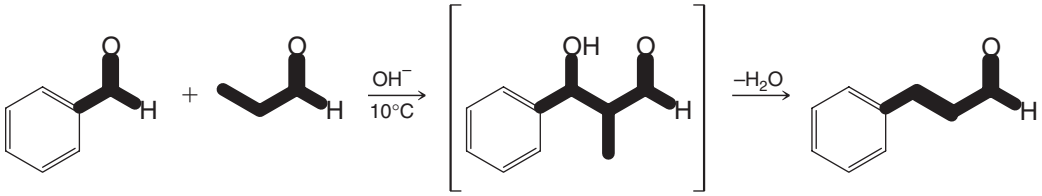


3. Aldol Reaction (Section 19.4)

General Reaction



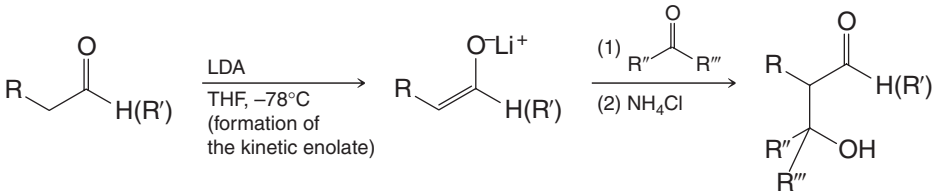
Specific Example



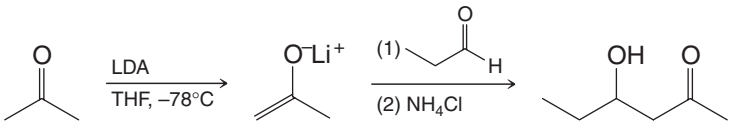
Openmirrors.com

4. Directed Aldol Reactions via Lithium Enolates (Section 19.5B)

General Reaction

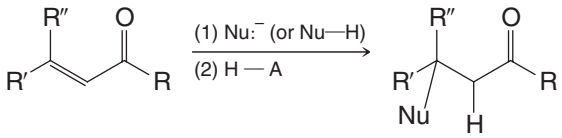


Specific Example



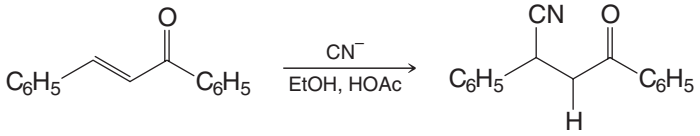
5. Conjugate Addition (Section 19.7)

General Example

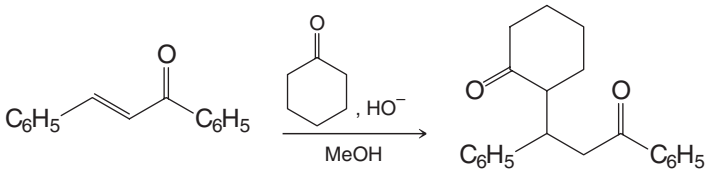


Nu:⁻ = CN^-; an enolate (Michael addition); R‴MgBr
Nu—H = 1° or 2° amines; an enamine

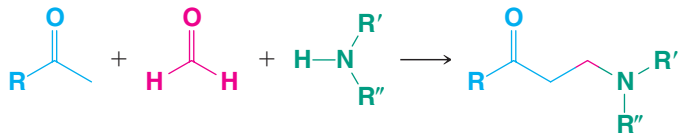
Specific Example



Specific Example (Michael Addition)



6. Mannich Reaction (Section 19.8):



Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com)

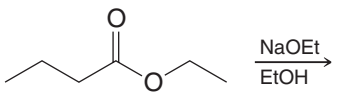
Problems

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

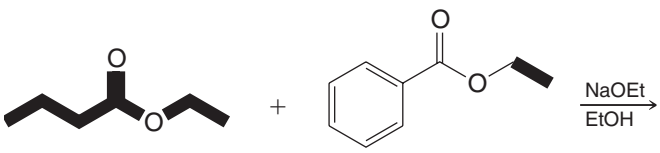
CLAISEN CONDENSATION REACTIONS

19.23 Write a structural formula for the product from each of the following reactions.

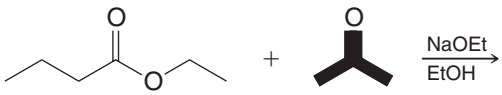
(a)



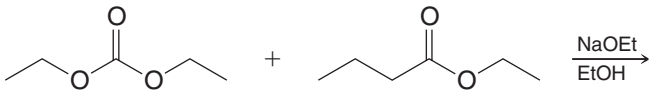
(b)



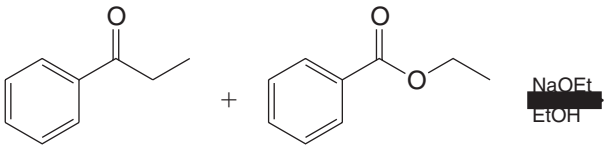
(c)



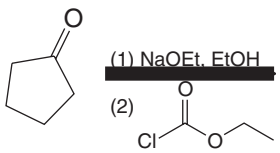
(d)



(e)



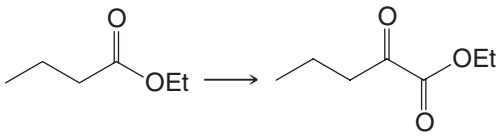
(f)



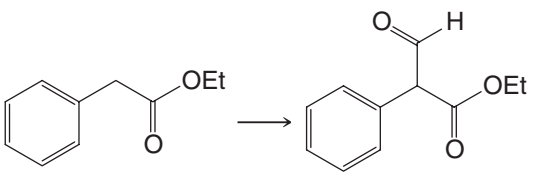
19.24 Show all steps in the following syntheses. You may use any other needed reagents but you should begin with the compound given.

(a)

(b)

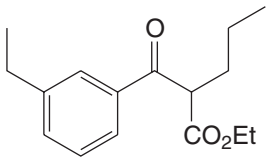


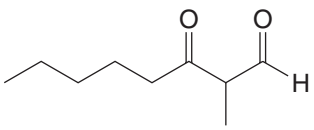
(c)

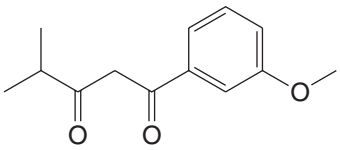


Openmirrors.com

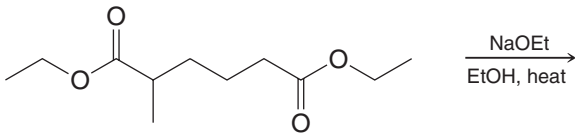
19.25 Provide the starting materials needed to synthesize each compound by acylation of an enolate.

(a) 

(b) 

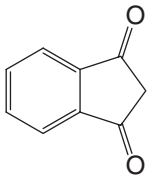
(c) 

19.26 Write structural formulas for both of the possible products from the following Dieckmann condensation, and predict which one would likely predominate.

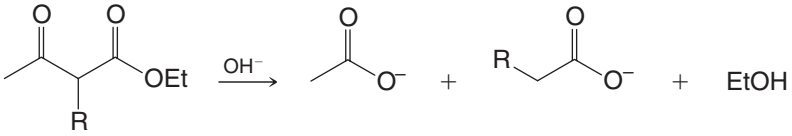


19.27 When a Dieckmann condensation is attempted with diethyl succinate, the product obtained has the molecular formula $C_{12}H_{16}O_6$. What is the structure of this compound?

19.28 Show how this diketone could be prepared by a condensation reaction:

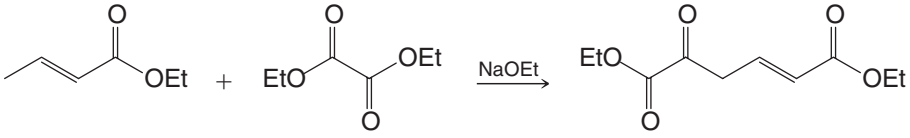


19.29 In contrast to the reaction with dilute alkali (Section 18.6), when concentrated solutions of NaOH are used, acetoacetic esters undergo cleavage as shown below.



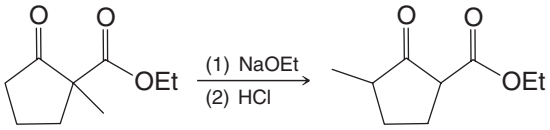
Provide a mechanistic explanation for this outcome.

19.30 Write a detailed mechanism for the following reaction.

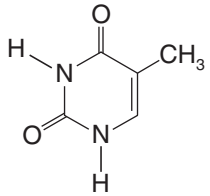


Ethyl crotonate **Diethyl oxalate**

19.31 In the presence of sodium ethoxide the following transformation occurs. Explain.



19.32 Thymine is one of the heterocyclic bases found in DNA. Starting with ethyl propanoate and using any other needed reagents, show how you might synthesize thymine.

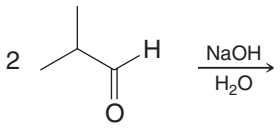


Thymine

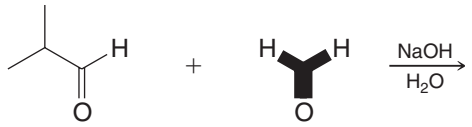
ALDOL REACTIONS

19.33 Predict the products from each of the following crossed aldol reactions.

(a)

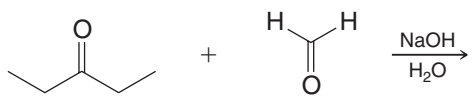


(b)

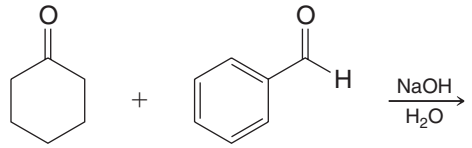


(c)

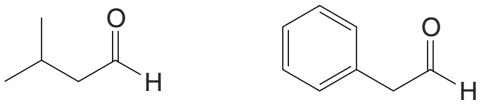
(d)



(e)

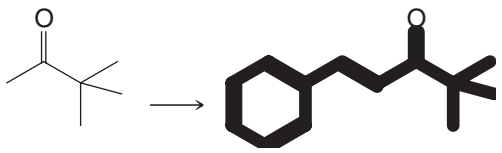


19.34 What four β-hydroxy aldehydes would be formed by a crossed aldol reaction between the following compounds?

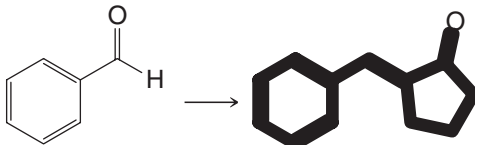


19.35 Show how each of the following transformations could be accomplished. You may use any other required reagents.

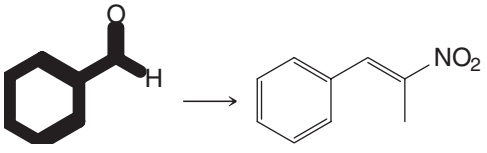
(a)



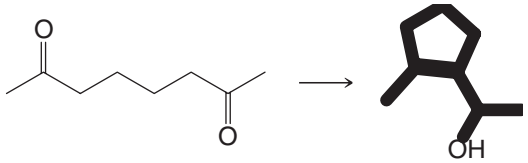
(b)



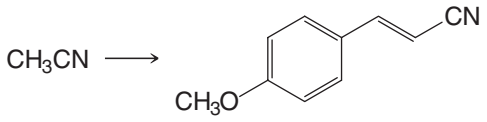
(c)



(d)

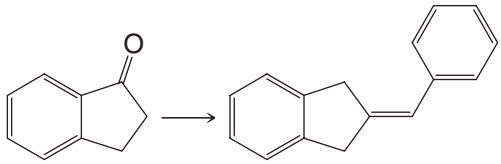


(e)



(f)

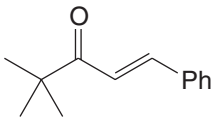
(g)



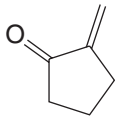
Openmirrors.com

19.36 What starting materials are needed to synthesize each of the following compounds using an aldol reaction?

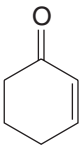
(a)



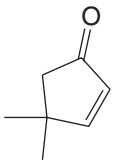
(b)



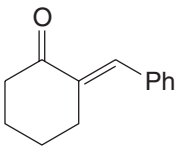
(c)



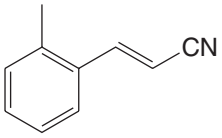
(d)



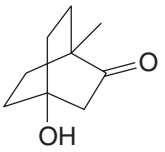
(e)



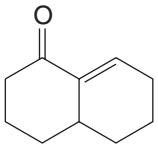
(f)



(g)

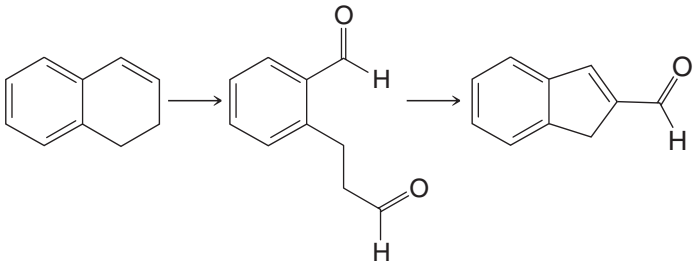


(h)

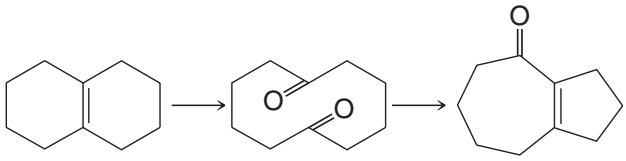


19.37 What reagents would you use to bring about each step of the following syntheses?

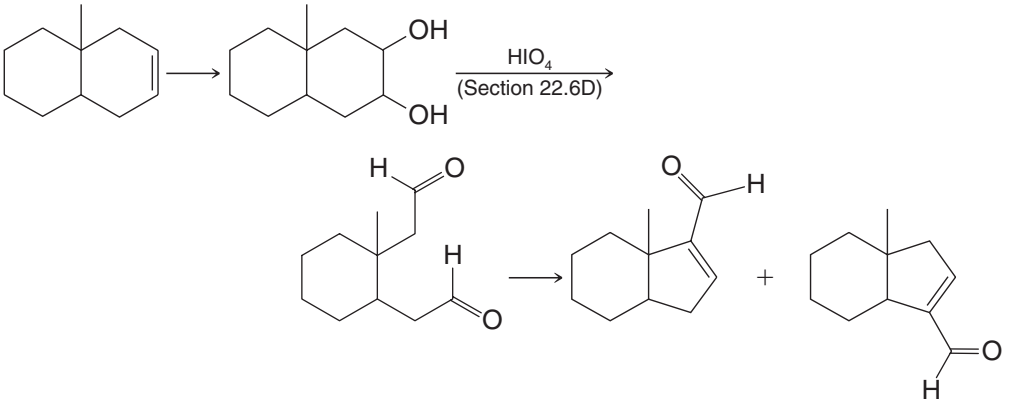
(a)



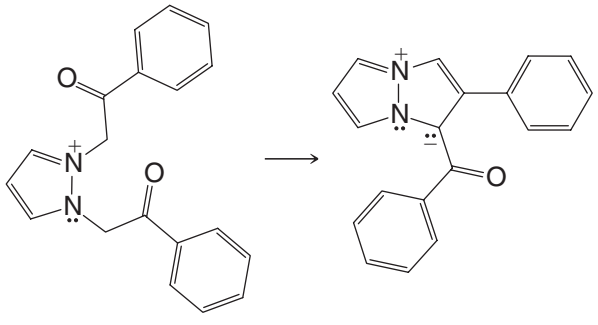
(b)



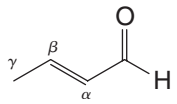
(c)



(d)



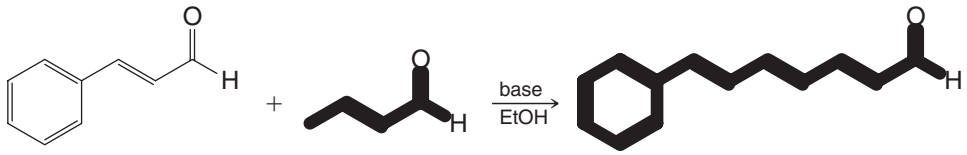
19.38 The hydrogen atoms of the γ carbon of crotonaldehyde are appreciably acidic ($pK_a \cong 20$).



Crotonaldehyde

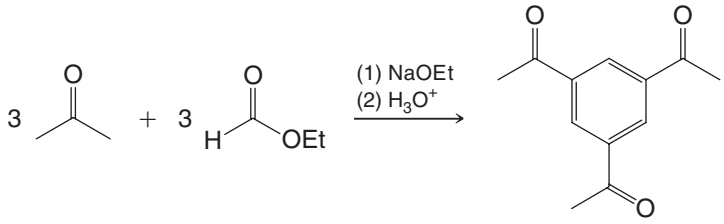
(a) Write resonance structures that will explain this fact.

(b) Write a mechanism that accounts for the following reaction:



87%

19.39 Provide a mechanism for the following reaction.

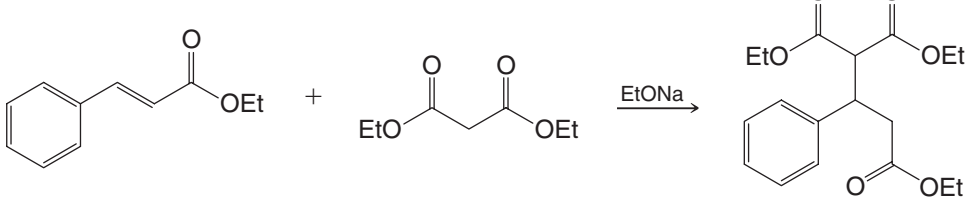


19.40 When the aldol reaction of acetaldehyde is carried out in D_2O, no deuterium is found in the methyl group of unreacted aldehyde. However, in the aldol reaction of acetone, deuterium is incorporated in the methyl group of the unreacted acetone. Explain this difference in behavior.

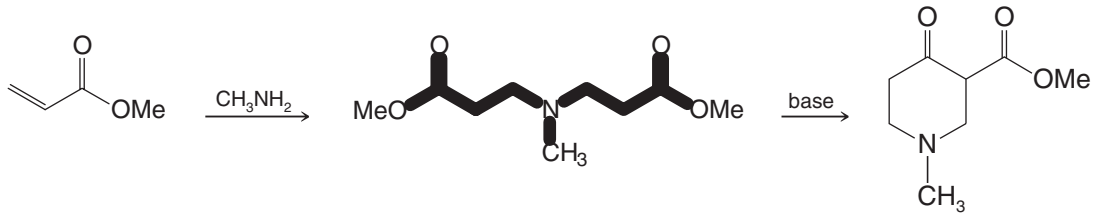
CONJUGATE ADDITION REACTIONS

19.41 Write mechanisms that account for the products of the following reactions:

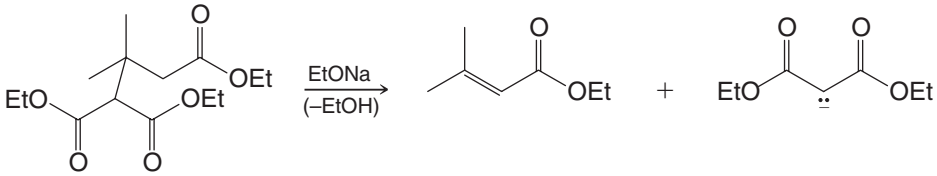
(a)



(b)

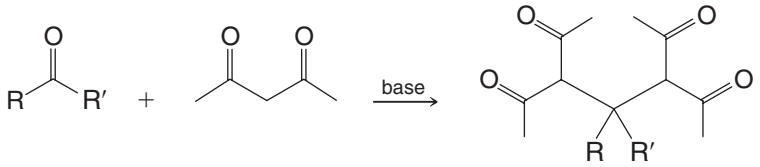


(c)



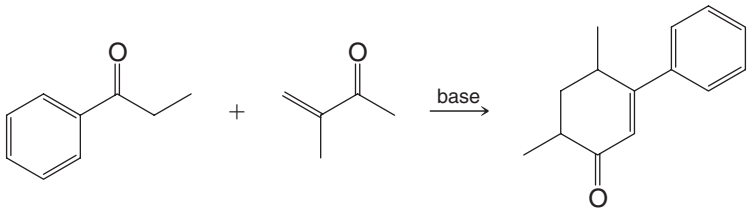
Openmirrors.com

19.42 Condensations in which the active hydrogen compound is a β-keto ester or a β-diketone often yield products that result from one molecule of aldehyde or ketone and two molecules of the active methylene component. For example,

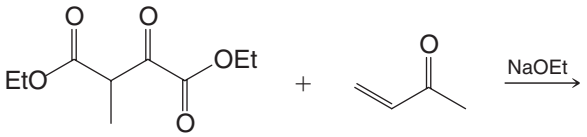


Suggest a reasonable mechanism that accounts for the formation of these products.

19.43 The following reaction illustrates the Robinson annulation reaction (Section 19.7A). Provide a mechanism.



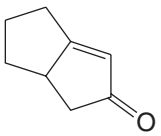
19.44 What is the structure of the *cyclic* compound that forms after the Michael addition of **1** to **2** in the presence of sodium ethoxide?

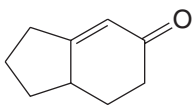


1 **2**

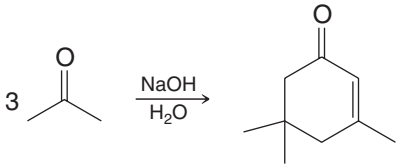
GENERAL PROBLEMS

19.45 Synthesize each compound starting from cyclopentanone.

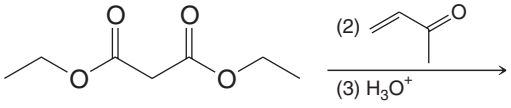
(a) 

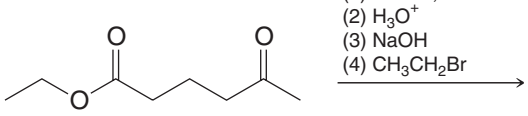
(b) 

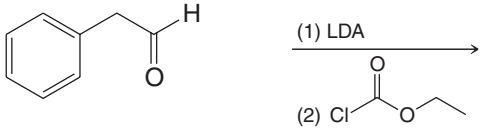
19.46 Provide a mechanism for the following reaction.

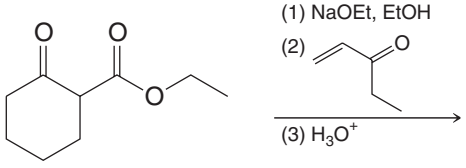


19.47 Predict the products of the following reactions.

(a) 

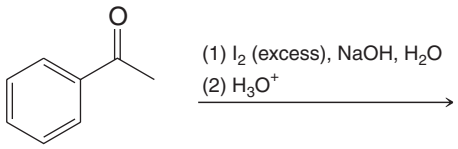
(c) 

(b) 

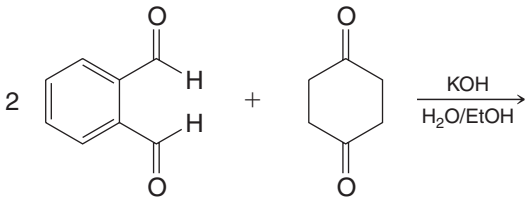
(d) 

19.48 Predict the products from the following reactions.

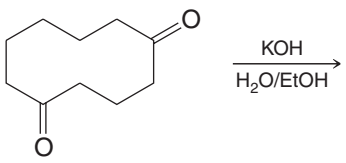
(a)



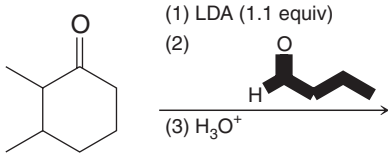
(b)



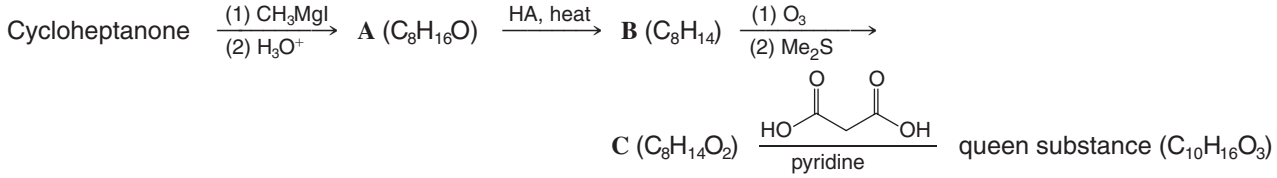
(c)



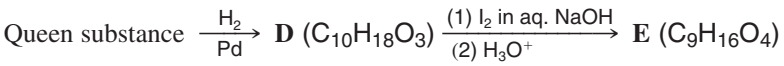
(d)



19.49 The mandibular glands of queen bees secrete a fluid that contains a remarkable compound known as "queen substance." When even an exceedingly small amount of the queen substance is transferred to worker bees, it inhibits the development of their ovaries and prevents the workers from bearing new queens. Queen substance, a monocarboxylic acid with the molecular formula $C_{10}H_{16}O_3$, has been synthesized by the following route:

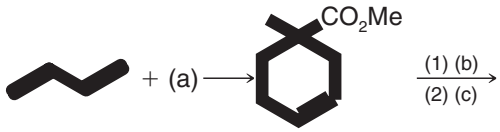


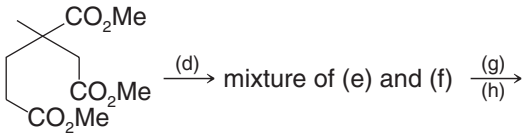
On catalytic hydrogenation, queen substance yields compound **D**, which, on treatment with iodine in sodium hydroxide and subsequent acidification, yields a dicarboxylic acid **E**; that is,

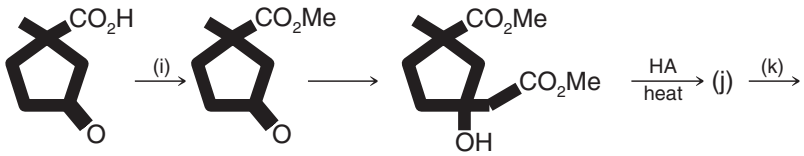


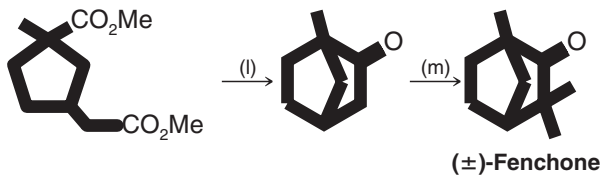
Provide structures for the queen substance and compounds **A–E**.

19.50 (+)-Fenchone is a terpenoid that can be isolated from fennel oil. (±)-Fenchone has been synthesized through the following route. Supply the missing intermediates and reagents.





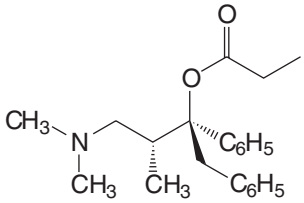




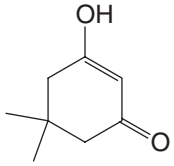
(±)-Fenchone

Openmirrors.com

19.51 Outline a racemic synthesis of the analgesic Darvon (below) starting with ethyl phenyl ketone.



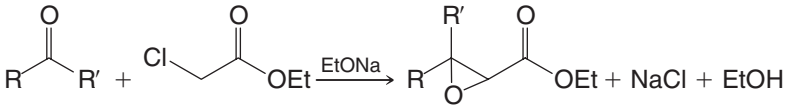
19.52 Show how dimedone can be synthesized from malonic ester and 4-methyl-3-penten-2-one (mesityl oxide) under basic conditions.



Dimedone

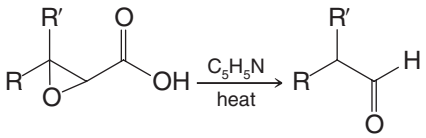
19.53 Write the mechanistic steps in the cyclization of ethyl phenylacetoacetate (ethyl 3-oxo-4-phenylbutanoate) in concentrated sulfuric acid to form naphthoresorcinol (1,3-naphthalenediol).

19.54 When an aldehyde or a ketone is condensed with ethyl α-chloroacetate in the presence of sodium ethoxide, the product is an α,β-epoxy ester called a *glycidic ester*. The synthesis is called the Darzens condensation.

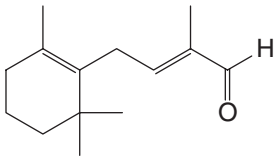


A glycidic ester

(a) Outline a reasonable mechanism for the Darzens condensation. **(b)** Hydrolysis of the epoxy ester leads to an epoxy acid that, on heating with pyridine, furnishes an aldehyde. What is happening here?



(c) Starting with β-ionone (Review Problem 19.13), show how you might synthesize the following aldehyde. (This aldehyde is an intermediate in an industrial synthesis of vitamin A.)

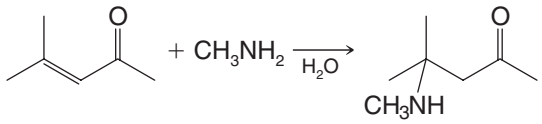


19.55 The *Perkin condensation* is an aldol-type condensation in which an aromatic aldehyde (ArCHO) reacts with a carboxylic acid anhydride, $(RCH_2CO)_2O$, to give an α,β-unsaturated acid ($ArCH{=}CRCO_2H$). The catalyst that is usually employed is the potassium salt of the carboxylic acid (RCH_2CO_2K). **(a)** Outline the Perkin condensation that takes place when benzaldehyde reacts with propanoic anhydride in the presence of potassium propanoate. **(b)** How would you use a Perkin condensation to prepare *p*-chlorocinnamic acid, p-$ClC_6H_4CH{=}CHCO_2H$?

SPECTROSCOPY

19.56 **(a)** Infrared spectroscopy provides an easy method for deciding whether the product obtained from the addition of a Grignard reagent to an α,β-unsaturated ketone is the simple addition product or the conjugate addition product. Explain. (What peak or peaks would you look for?)

(b) How might you follow the rate of the following reaction using UV spectroscopy?



19.57 Allowing acetone to react with 2 molar equivalents of benzaldehyde in the presence of KOH in ethanol leads to the formation of compound **X**. The ^{13}C NMR spectrum of **X** is given in Fig. 19.1. Propose a structure for compound **X**.

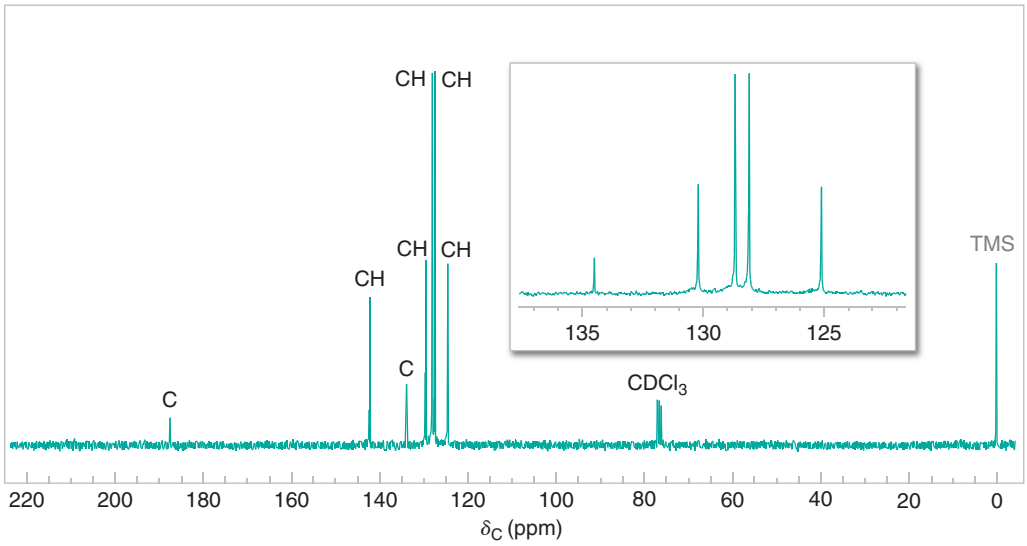
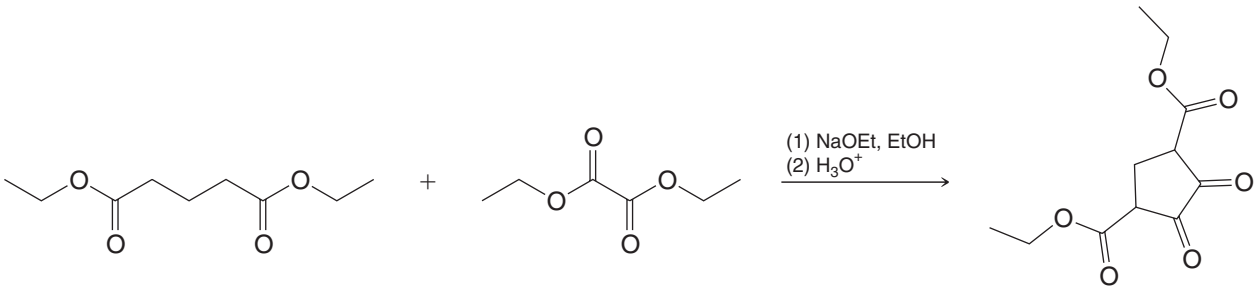


Figure 19.1 The broadband proton-decoupled ^{13}C NMR spectrum of compound **X**, Problem 19.57. Information from the DEPT ^{13}C NMR spectra is given above the peaks.

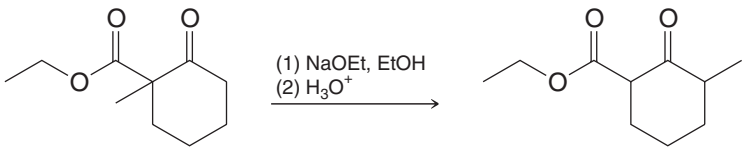
Challenge Problems

19.58 Provide a mechanism for each of the following reactions.

(a)

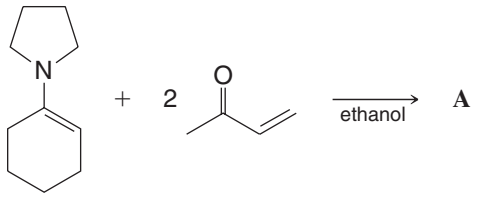


(b)



Openmirrors.com

19.59 **(a)** Deduce the structure of product **A**, which is highly symmetrical:



The following are selected spectral data for **A**:

MS (*m/z*): 220 ($M\cdot^+$)

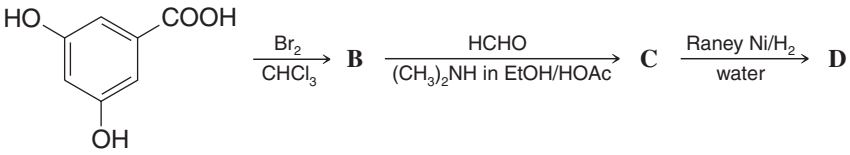
IR (cm^{-1}): 2930, 2860, 1715

^{1}H **NMR** (δ): 1.25 (m), 1.29 (m), 1.76 (m), 1.77 (m), 2.14 (s), and 2.22 (t); (area ratios 2:1:2:1:2:2, respectively)

^{13}C **NMR** (δ): 23 (CH_2), 26 (CH_2), 27 (CH_2), 29 (C), 39 (CH), 41 (CH_2), 46 (CH_2), 208 (C)

(b) Write a mechanism that explains the formation of **A**.

19.60 Write the structures of the three products involved in this reaction sequence:



Spectral data for **B**:

MS (*m/z*): 314, 312, 310 (relative abundance 1:2:1)

^{1}H **NMR** (δ): only 6.80 (s) after treatment with D_2O

Data for **C**:

MS (*m/z*): 371, 369, 367 (relative abundance 1:2:1)

^{1}H **NMR** (δ): 2.48 (s) and 4.99 (s) in area ratio 3:1; broad singlets at 5.5 and 11 disappeared after treatment with D_2O.

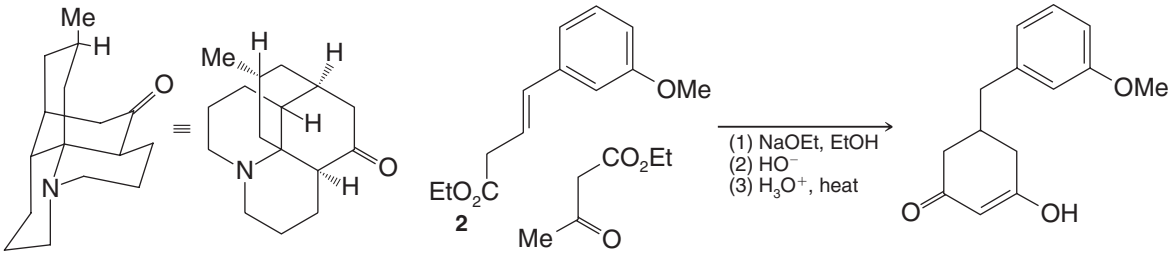
Data for **D**:

MS (*m/z*): 369 ($M\cdot^+ - CH_3$) [when studied as its tris(trimethylsilyl) derivative]

^{1}H **NMR** (δ): 2.16 (s) and 7.18 (s) in area ratio 3:2; broad singlets at 5.4 and 11 disappeared after treatment with D_2O.

Learning Group Problems

1. Lycopodine is a naturally occurring amine. As such, it belongs to the family of natural products called alkaloids. Its synthesis (*J. Am. Chem. Soc*. **1968**, *90*, 1647–1648) was accomplished by one of the great synthetic organic chemists of our time, Gilbert Stork (Columbia University). Write a detailed mechanism for all the steps that occur when **2** reacts with ethyl acetoacetate in the presence of ethoxide ion. Note that a necessary part of the mechanism will be a base-catalyzed isomerization (via a conjugated enolate) of the alkene in **2** to form the corresponding α,β-unsaturated ester.

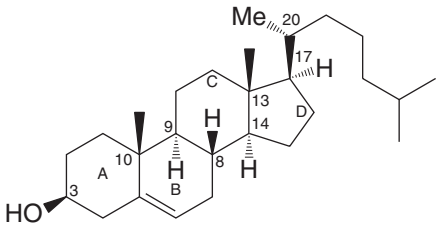


1
Lycopodine

2

3

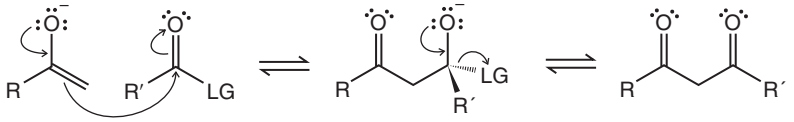
2. Steroids are an extremely important class of natural and pharmaceutical compounds. Synthetic efforts directed toward steroids have been underway for many years and continue to be an area of important research. The synthesis of cholesterol by R. B. Woodward (Harvard University, recipient of the Nobel Prize in Chemistry for 1965) and coworkers represents a paramount accomplishment in steroid synthesis, and it is rich with examples of carbonyl chemistry and other reactions we have studied. Selected reactions from Woodward's cholesterol synthesis and the questions for this Learning Group Problem are shown in the WileyPlus materials for this chapter. Access those materials online to complete this problem.



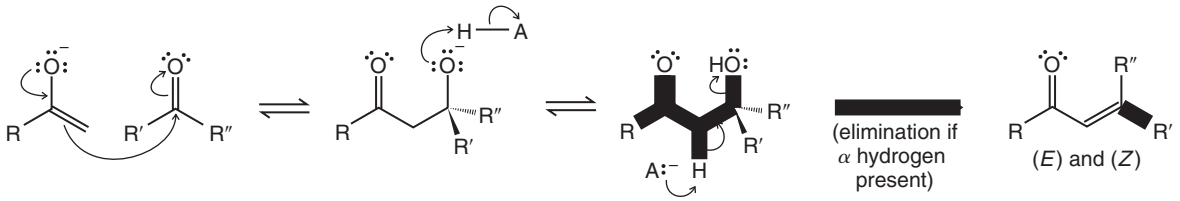
Cholesterol

Summary of Mechanisms

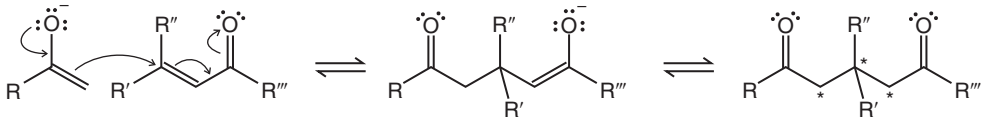
Enolate Reactions with Carbonyl Electrophiles



Acyl substitution (addition–elimination), e.g., Claisen condensation when LG = OR



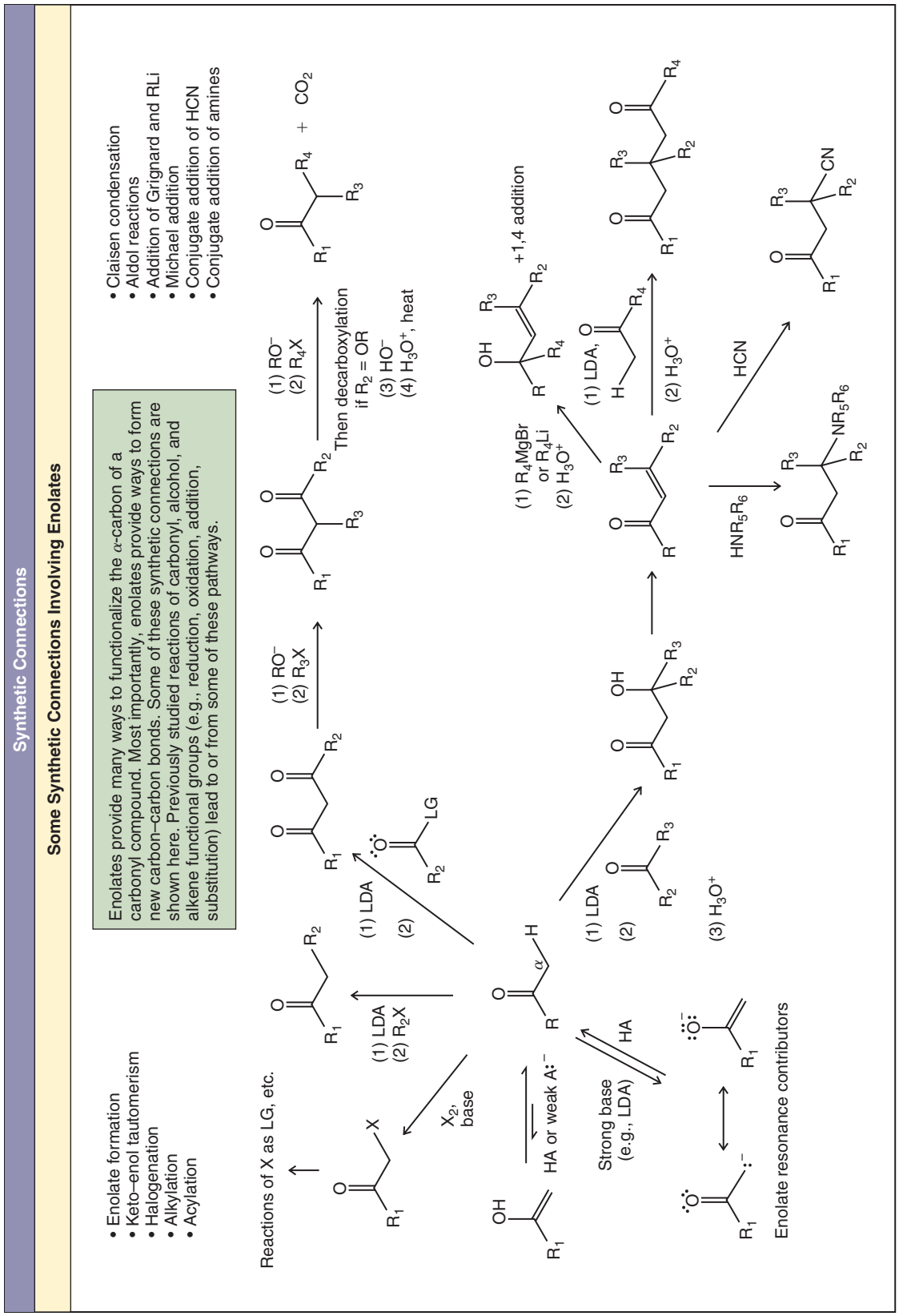
Aldol reactions (addition and condensation)



* may be chirality centers

Michael (conjugate) addition

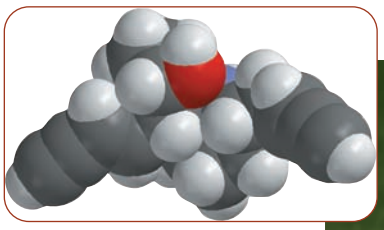
Openmirrors.com



WILEY PLUS See *Special Topics D and E* in *WileyPLUS*

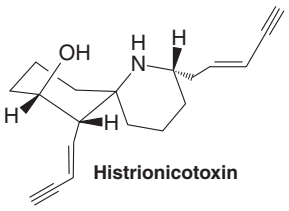
20

Amines

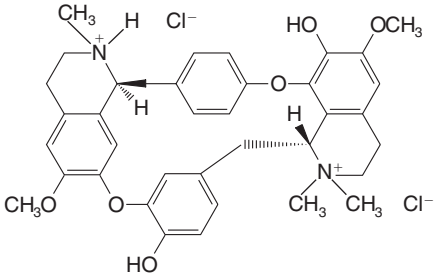


Histrionicotoxin, a paralyzing neurotoxin from certain poison dart frogs.

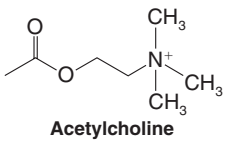
Colombian poison dart frogs are tiny, beautiful, and deadly. They produce a poison called histrionicotoxin, which is an amine that causes paralysis. Death from histrionicotoxin results by suffocation through paralysis of the victim's respiratory muscles. (A molecular model of histrionicotoxin is shown above.) Curare, the Amazonian arrow poison that is a mixture of compounds from a woody vine, contains another paralytic neurotoxin, called *d*-tubocurarine. Histrionicotoxin and *d*-tubocurarine both block the action of acetylcholine, an important neurotransmitter. Amines like these and others have fascinating roles in biological systems, as we shall see in this chapter while studying the properties, reactivity, and synthesis of amines.



Histrionicotoxin



***d*-Tubocurarine chloride**



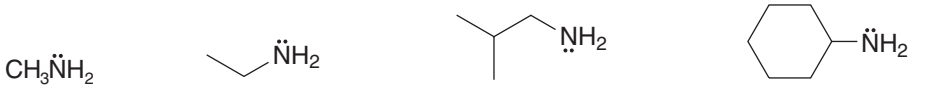
Acetylcholine

Openmirrors.com

20.1 Nomenclature

In common nomenclature most primary amines are named as *alkylamines*. In systematic nomenclature (blue names in parentheses below) they are named by adding the suffix *-amine* to the name of the chain or ring system to which the NH_2 group is attached with replacement of the final *-e*. Amines are classified as being **primary** (**1**°), **secondary** (**2**°), or **tertiary** (**3**°) on the basis of the number of organic groups attached to the nitrogen (Section 2.8).

Primary Amines



Methylamine (methanamine) | **Ethylamine** (ethanamine) | **Isobutylamine** (2-methyl-1-propanamine) | **Cyclohexylamine** (cyclohexanamine)

Most secondary and tertiary amines are named in the same general way. In common nomenclature we either designate the organic groups individually if they are different or use the prefixes di- or tri- if they are the same. In systematic nomenclature we use the locant *N* to designate substituents attached to a nitrogen atom.

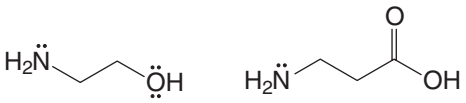
Secondary Amines

Ethylmethylamine (*N*-methylethanamine) | **Diethylamine** (*N*-ethylethanamine)

Tertiary Amines

Triethylamine (*N*,*N*-diethylethanamine) | **Ethylmethylpropylamine** (*N*-ethyl-*N*-methyl-1-propanamine)

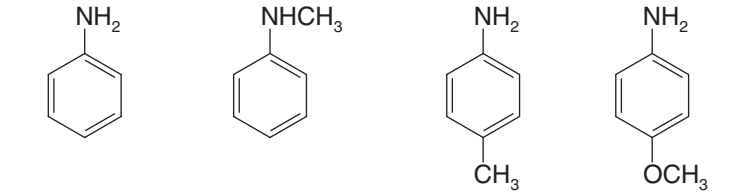
In the IUPAC system, the substituent —NH_2 is called the *amino* group. We often use this system for naming amines containing an OH group or a CO_2H group:



2-Aminoethanol | **3-Aminopropanoic acid**

20.1A Arylamines

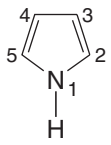
Some common **arylamines** have the following names:



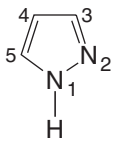
Aniline (benzenamine) | ***N*-Methylaniline** (*N*-methylbenzenamine) | ***p*-Toluidine** (4-methylbenzenamine) | ***p*-Anisidine** (4-methoxybenzenamine)

20.1B Heterocyclic Amines

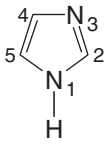
The important **heterocyclic amines** all have common names. In systematic replacement nomenclature the prefixes *aza-*, *diaza-*, and *triaza-* are used to indicate that nitrogen atoms have replaced carbon atoms in the corresponding hydrocarbon. A nitrogen atom in the ring (or the highest atomic weight heteroatom, as in the case of thiazole) is designated position 1 and numbering proceeds to give the lowest overall set of locants to the heteroatoms:



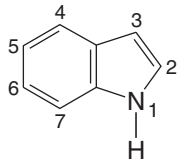
Pyrrole
(1-azacyclopenta-2,4-diene)



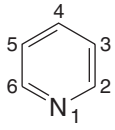
Pyrazole
(1,2-diazacyclopenta-2,4-diene)



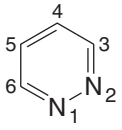
Imidazole
(1,3-diazacyclopenta-2,4-diene)



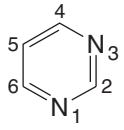
Indole
(1-azaindene)



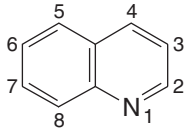
Pyridine
(azabenzene)



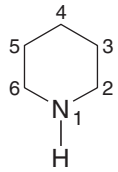
Pyridazine
(1,2-diazabenzene)



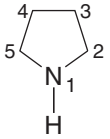
Pyrimidine
(1,3-diazabenzene)



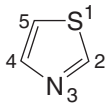
Quinoline
(1-azanaphthalene)



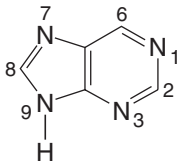
Piperidine
(azacyclohexane)



Pyrrolidine
(azacyclopentane)



Thiazole
(1-thia-3-azacyclopenta-2,4-diene)



Purine

20.2 Physical Properties and Structure of Amines

20.2A Physical Properties

Amines are moderately polar substances; they have boiling points that are higher than those of alkanes but generally lower than those of alcohols of comparable molecular weight. Molecules of primary and secondary amines can form strong hydrogen bonds to each other and to water. Molecules of tertiary amines cannot form hydrogen bonds to each other, but they can form hydrogen bonds to molecules of water or other hydroxylic solvents. As a result, tertiary amines generally boil at lower temperatures than primary and secondary amines of comparable molecular weight, but all low-molecular-weight amines are very water soluble.

Table 20.1 lists the physical properties of some common amines.

20.2B Structure of Amines

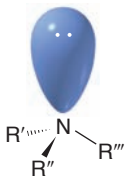
The nitrogen atom of most amines is like that of ammonia; it is approximately sp^3 hybridized. The three alkyl groups (or hydrogen atoms) occupy corners of a tetrahedron; the sp^3 orbital containing the unshared electron pair is directed toward the other corner. We describe the shape of the amine by the location of the atoms as being **trigonal pyramidal** (Section 1.16B). However, if we were to consider the unshared electron pair as being a group we would describe the geometry of the amine as being tetrahedral. The electrostatic potential

Openmirrors.com

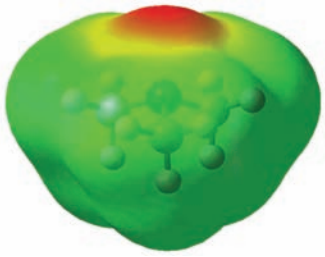
TABLE 20.1 Physical Properties of Amines

Name	Structure	mp (°C)	bp (°C)	Water Solubility (25°C) (g 100 mL^{-1})	pK_a (aminium ion)
Primary Amines					
Methylamine	CH_3NH_2	−94	−6	Very soluble	10.64
Ethylamine	$CH_3CH_2NH_2$	−81	17	Very soluble	10.75
Isopropylamine	$(CH_3)_2CHNH_2$	−101	33	Very soluble	10.73
Cyclohexylamine	Cyclo-$C_6H_{11}NH_2$	−18	134	Slightly soluble	10.64
Benzylamine	$C_6H_5CH_2NH_2$	10	185	Slightly soluble	9.30
Aniline	$C_6H_5NH_2$	−6	184	3.7	4.58
4-Methylaniline	4-$CH_3C_6H_4NH_2$	44	200	Slightly soluble	5.08
4-Nitroaniline	4-$NO_2C_6H_4NH_2$	148	332	Insoluble	1.00
Secondary Amines					
Dimethylamine	$(CH_3)_2NH$	−92	7	Very soluble	10.72
Diethylamine	$(CH_3CH_2)_2NH$	−48	56	Very soluble	10.98
Diphenylamine	$(C_6H_5)_2NH$	53	302	Insoluble	0.80
Tertiary Amines					
Trimethylamine	$(CH_3)_3N$	−117	2.9	Very soluble	9.70
Triethylamine	$(CH_3CH_2)_3N$	−115	90	14	10.76
N,N-Dimethylaniline	$C_6H_5N(CH_3)_2$	3	194	Slightly soluble	5.06

map for the van der Waals surface of trimethylamine indicates localization of negative charge where the nonbonding electrons are found on the nitrogen:



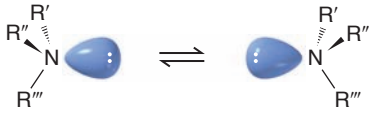
Structure of an amine



A calculated structure for trimethylamine The electrostatic potential map shows charge associated with the nitrogen unshared electron pair.

The bond angles are what one would expect of a tetrahedral structure; they are very close to 109.5°. The bond angles for trimethylamine, for example, are 108°.

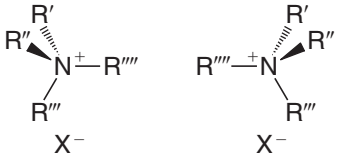
If the alkyl groups of a tertiary amine are all different, the amine will be chiral. There will be two enantiomeric forms of the tertiary amine, and, theoretically, we ought to be able to resolve (separate) these enantiomers. In practice, however, resolution is usually impossible because the enantiomers interconvert rapidly:



Interconversion of amine enantiomers

This interconversion occurs through what is called a **pyramidal** or **nitrogen inversion**. The barrier to the interconversion is about 25 kJ mol^{-1} for most simple amines, low enough to occur readily at room temperature. In the transition state for the inversion, the nitrogen atom becomes sp^2 hybridized with the unshared electron pair occupying a *p* orbital.

Ammonium salts cannot undergo nitrogen inversion because they do not have an unshared pair. Therefore, those quaternary ammonium salts with four different groups are chiral and can be resolved into separate (relatively stable) enantiomers:



Quaternary ammonium salts such as these can be resolved.

20.3 Basicity of Amines: Amine Salts

- Amines are relatively weak bases. Most are stronger bases than water but are far weaker bases than hydroxide ions, alkoxide ions, and alkanide anions.

A convenient way to compare the base strengths of amines is to compare the pK_a values of their conjugate acids, the corresponding alkylaminium ions (Sections 3.6C and 20.3D).

$$RNH_3^+ + H_2O \rightleftharpoons RNH_2 + H_3O^+$$

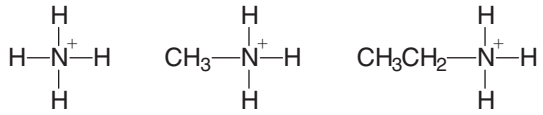
$$K_a = \frac{[RHN_2][\,H_3O^+]}{[RNH_3^+]}$$

$$pK_a = -\log K_a$$

The equilibrium for an amine that is relatively more basic will lie more toward the left in the above chemical equation than for an amine that is less basic.

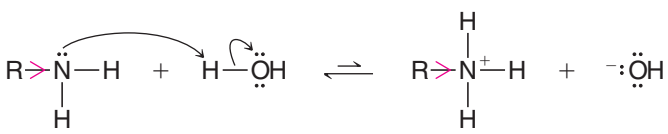
- The aminium ion of a more basic amine will have a larger pK_a than the aminium ion of a less basic amine.

When we compare aminium ion acidities in terms of this equilibrium, we see that most primary alkylaminium ions (RNH_3^+) are less acidic than ammonium ion (NH_4^+). In other words, primary alkylamines (RHN_2) are more basic than ammonia (NH_3):



Aminium ion pK_a	**9.26**	**10.64**	**10.75**

We can account for this on the basis of the electron-releasing ability of an alkyl group. An alkyl group releases electrons, and it *stabilizes* the alkylaminium ion that results from the acid–base reaction *by dispersing its positive charge*. It stabilizes the alkylaminium ion to a greater extent than it stabilizes the amine:



By releasing electrons, R → stabilizes the alkylaminium ion through dispersal of charge.

Openmirrors.com

This explanation is supported by measurements showing that in the *gas phase* the basicities of the following amines increase with increasing methyl substitution:

$$\underset{3^\circ}{(CH_3)_3N} > \underset{2^\circ}{(CH_3)_2NH} > \underset{1^\circ}{CH_3NH_2} > NH_3$$

Gas phase

This is not the order of basicity of these amines in aqueous solution, however. In aqueous solution (Table 20.1) the order is

$$\underset{2^\circ}{(CH_3)_2NH} > \underset{1^\circ}{CH_3NH_2} > \underset{3^\circ}{(CH_3)_3N} > NH_3$$

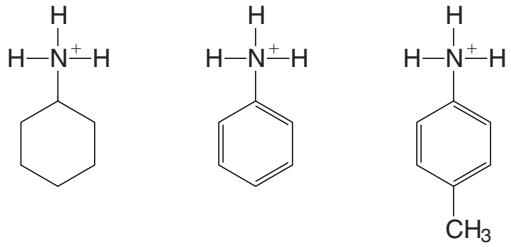
Aqueous solution

The reason for this apparent anomaly is now known. In aqueous solution the aminium ions formed from secondary and primary amines are stabilized by solvation through hydrogen bonding much more effectively than are the aminium ions formed from tertiary amines. The aminium ion formed from a tertiary amine such as $(CH_3)_3NH^+$ has only one hydrogen to use in hydrogen bonding to water molecules, whereas the aminium ions from secondary and primary amines have two and three hydrogens, respectively. Poorer solvation of the aminium ion formed from a tertiary amine more than counteracts the electron-releasing effect of the three methyl groups and makes the tertiary amine less basic than primary and secondary amines in aqueous solution. The electron-releasing effect does, however, make the tertiary amine more basic than ammonia.

20.3A Basicity of Arylamines

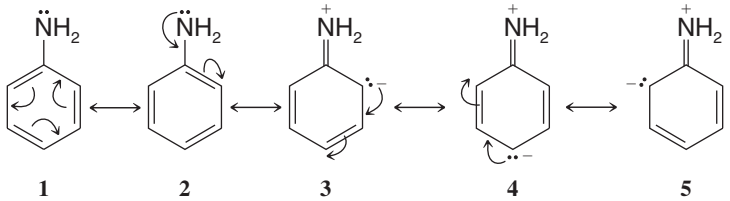
- Aromatic amines are much weaker bases than alkylamines.

Considering amine basicity from the perspective of aminium ion acidity, when we examine the pK_a values of the conjugate acids of aromatic amines (e.g., aniline and 4-methylaniline) in Table 20.1, we see that they are much weaker bases than the nonaromatic amine, cyclohexylamine:



Aminium ion pK_a	**10.64**	**4.58**	**5.08**

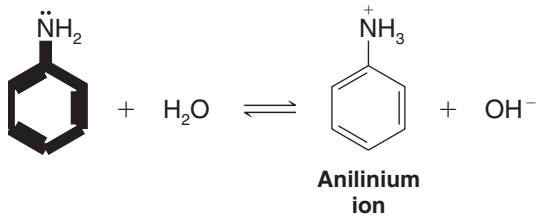
We can account for this effect, in part, on the basis of resonance contributions to the overall hybrid of an arylamine. For aniline, the following contributors are important:



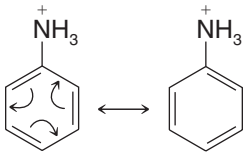
1 **2** **3** **4** **5**

Structures **1** and **2** are the Kekulé structures that contribute to any benzene derivative. Structures **3–5**, however, *delocalize* the unshared electron pair of the nitrogen over the ortho and para positions of the ring. This delocalization of the electron pair makes it less available to a proton, and *delocalization of the electron pair stabilizes aniline*.

When aniline accepts a proton it becomes an anilinium ion:



Once the electron pair of the nitrogen atom accepts the proton, it is no longer available to participate in resonance, and hence we are only able to write *two* resonance structures for the anilinium ion—the two Kekulé structures:



Structures corresponding to **3–5** are not possible for the anilinium ion, and, consequently, although resonance does stabilize the anilinium ion considerably, resonance does not stabilize the anilinium ion to as great an extent as it does aniline itself. This greater stabilization of the reactant (aniline) when compared to that of the product (anilinium ion) means that ΔH° for the reaction

$$\text{Aniline} + H_2O \longrightarrow \text{anilinium ion} + OH^-$$

will be a larger positive quantity than that for the reaction

$$\text{Cyclohexylamine} + H_2O \longrightarrow \text{cyclohexylaminium ion} + OH^-$$

(See Fig. 20.1.) Aniline, as a result, is the weaker base.

Another important effect in explaining the lower basicity of aromatic amines is the **electron-withdrawing effect of a phenyl group**. Because the carbon atoms of a phenyl

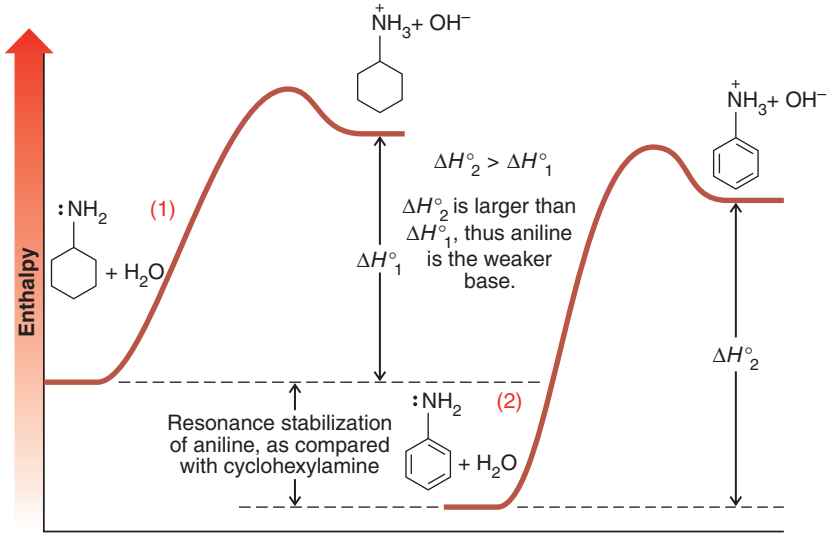


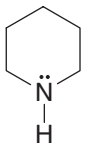
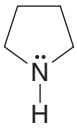
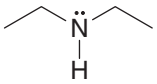
Figure 20.1 Enthalpy diagram for (1) the reaction of cyclohexylamine with H_2O and (2) the reaction of aniline with H_2O. (The curves are aligned for comparison only and are not to scale.) Protonation of aniline has a larger ΔH° than protonation of cyclohexylamine, thus aniline is a weaker base.

Openmirrors.com

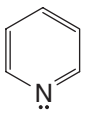
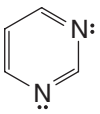
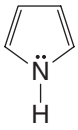
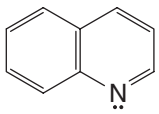
group are sp^2 hybridized, they are more electronegative (and therefore more electron withdrawing) than the sp^3-hybridized carbon atoms of alkyl groups. We shall discuss this effect further in Section 21.5A.

20.3B Basicity of Heterocyclic Amines

Nonaromatic heterocyclic amines have basicities that are approximately the same as those of acyclic amines:

			
pK_a of corresponding aminium ion	**Piperidine 11.20**	**Pyrrolidine 11.11**	**Diethylamine 10.98**

In aqueous solution, aromatic heterocyclic amines such as pyridine, pyrimidine, and pyrrole are much weaker bases than nonaromatic amines or ammonia. (In the gas phase, however, pyridine and pyrrole are more basic than ammonia, indicating that solvation has a very important effect on their relative basicities; see Section 20.3.)

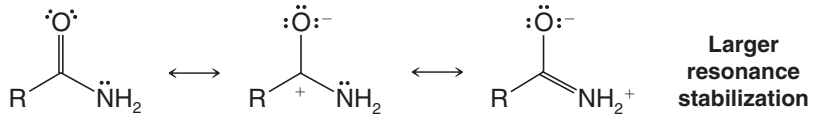
				
pK_a of corresponding aminium ion	**Pyridine 5.23**	**Pyrimidine 2.70**	**Pyrrole 0.40**	**Quinoline 4.5**

20.3C Amines versus Amides

- Amides are far less basic than amines (even less basic than arylamines). The pK_a of the conjugate acid of a typical amide is about zero.

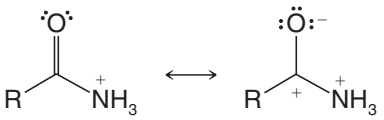
The lower basicity of amides when compared to amines can be understood in terms of resonance and inductive effects. An amide is stabilized by resonance involving the nonbonding pair of electrons on the nitrogen atom. However, an amide protonated on its nitrogen atom lacks this type of resonance stabilization. This is shown in the following resonance structures:

Amide

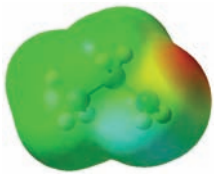


Larger resonance stabilization

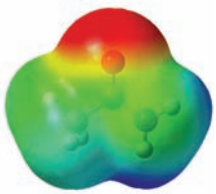
N-Protonated Amide



Smaller resonance stabilization



Ethylamine

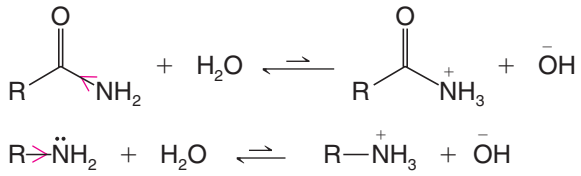


Acetamide

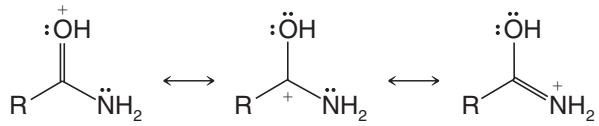
Figure 20.2 Calculated electrostatic potential maps (calibrated to the same charge scale) for ethylamine and acetamide. The map for ethylamine shows localization of negative charge at the unshared electron pair of nitrogen. The map for acetamide shows most of the negative charge at its oxygen atom instead of at nitrogen, due to the electron-withdrawing effect of the carbonyl group.

However, a more important factor accounting for amides being weaker bases than amines is the powerful electron-withdrawing effect of the carbonyl group of the amide. This effect is illustrated by the electrostatic potential maps for ethylamine and acetamide shown in Fig. 20.2. Significant negative charge is localized at the position of the nonbonding electron pair in ethylamine (as indicated by the red color). In acetamide, however, less negative charge resides near the nitrogen than in ethylamine.

Comparing the following equilibria, the reaction with the amide lies more to the left than the corresponding reaction with an amine. This is consistent with the amine being a stronger base than an amide.

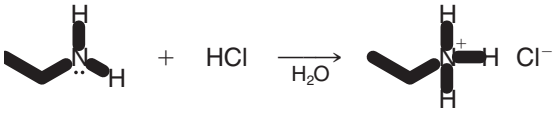


The nitrogen atoms of amides are so weakly basic that when an amide accepts a proton, it does so on its oxygen atom instead (see the mechanism for hydrolysis of an amide, Section 17.8F). Protonation on the oxygen atom occurs even though oxygen atoms (because of their greater electronegativity) are typically less basic than nitrogen atoms. Notice, however, that if an amide accepts a proton on its oxygen atom, resonance stabilization involving the nonbonding electron pair of the nitrogen atom is possible:

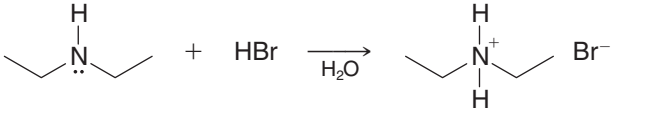


20.3D Aminium Salts and Quaternary Ammonium Salts

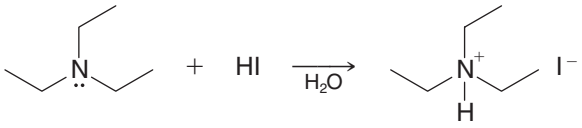
When primary, secondary, and tertiary amines act as bases and react with acids, they form compounds called **aminium salts**. In an aminium salt the positively charged nitrogen atom is attached to at least one hydrogen atom:



Ethylaminium chloride
(an aminium salt)

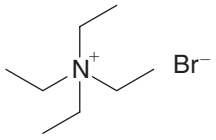


Diethylaminium bromide



Triethylaminium iodide

When the central nitrogen atom of a compound is positively charged *but is not attached to a hydrogen atom*, the compound is called a **quaternary ammonium salt**. For example,



Tetraethylammonium bromide
(a quaternary ammonium salt)

Quaternary ammonium halides—because they do not have an unshared electron pair on the nitrogen atom—cannot act as bases. Quaternary ammonium *hydroxides*, however, are strong bases. As solids, or in solution, they consist *entirely* of quaternary ammonium cations (R_4N^+) and hydroxide ions (OH^-); they are, therefore, strong bases—as strong as sodium

Openmirrors.com

or potassium hydroxide. Quaternary ammonium hydroxides react with acids to form quaternary ammonium salts:

$$(CH_3)_4\overset{+}{N}OH^- + HCl \rightarrow (CH_3)_4\overset{+}{N}Cl^- + H_2O$$

In Section 20.12A we shall see how quaternary ammonium salts can be used to form alkenes by a reaction called the *Hofmann elimination*.

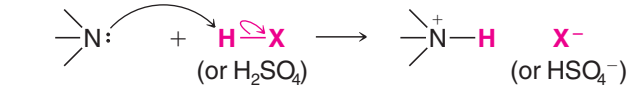
20.3E Solubility of Amines in Aqueous Acids

Helpful Hint

You may make use of the basicity of amines in your organic chemistry laboratory work for the separation of compounds or for the characterization of unknowns.

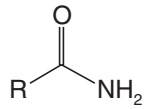
- Almost all alkylaminium chloride, bromide, iodide, and sulfate salts are soluble in water. Thus, primary, secondary, or tertiary amines that are not soluble in water will dissolve in dilute aqueous HCl, HBr, HI, and H_2SO_4.

Solubility in dilute acid provides a convenient chemical method for distinguishing amines from nonbasic compounds that are insoluble in water. Solubility in dilute acid also gives us a useful method for separating amines from nonbasic compounds that are insoluble in water. The amine can be extracted into aqueous acid (dilute HCl) and then recovered by making the aqueous solution basic and extracting the amine into ether or CH_2Cl_2.



Water-insoluble amine — **Water-soluble aminium salt**

Because amides are far less basic than amines, water-insoluble amides *do not dissolve* in dilute aqueous HCl, HBr, HI, or H_2SO_4:



Water-insoluble amide (not soluble in aqueous acids)

Review Problem 20.1

Outline a procedure for separating hexylamine from cyclohexane using dilute HCl, aqueous NaOH, and diethyl ether.

Review Problem 20.2

Outline a procedure for separating a mixture of benzoic acid, 4-methylphenol, aniline, and benzene using acids, bases, and organic solvents.

20.3F Amines as Resolving Agents

- Enantiomerically pure amines are often used to resolve racemic forms of acidic compounds by the formation of diastereomeric salts.

We can illustrate the principles involved in **resolution** by showing how a racemic form of an organic acid might be resolved (separated) into its enantiomers with the single enantiomer of an **amine as a resolving agent** (Fig. 20.3).

Helpful Hint

See "The Chemistry of... HPLC Resolution of Enantiomers" in WileyPLUS for information about another technique for resolving enantiomers.

In this procedure the single enantiomer of an amine, (*R*)-1-phenylethylamine, is added to a solution of the racemic form of an acid. The salts that form are *diastereomers*. The chirality centers of the acid portion of the salts are enantiomerically related to each other, but the chirality centers of the amine portion are not. The diastereomers have different solubilities and can be separated by careful crystallization. The separated salts are then acidified with hydrochloric acid and the enantiomeric acids are obtained from the separate solutions. The amine remains in solution as its hydrochloride salt.

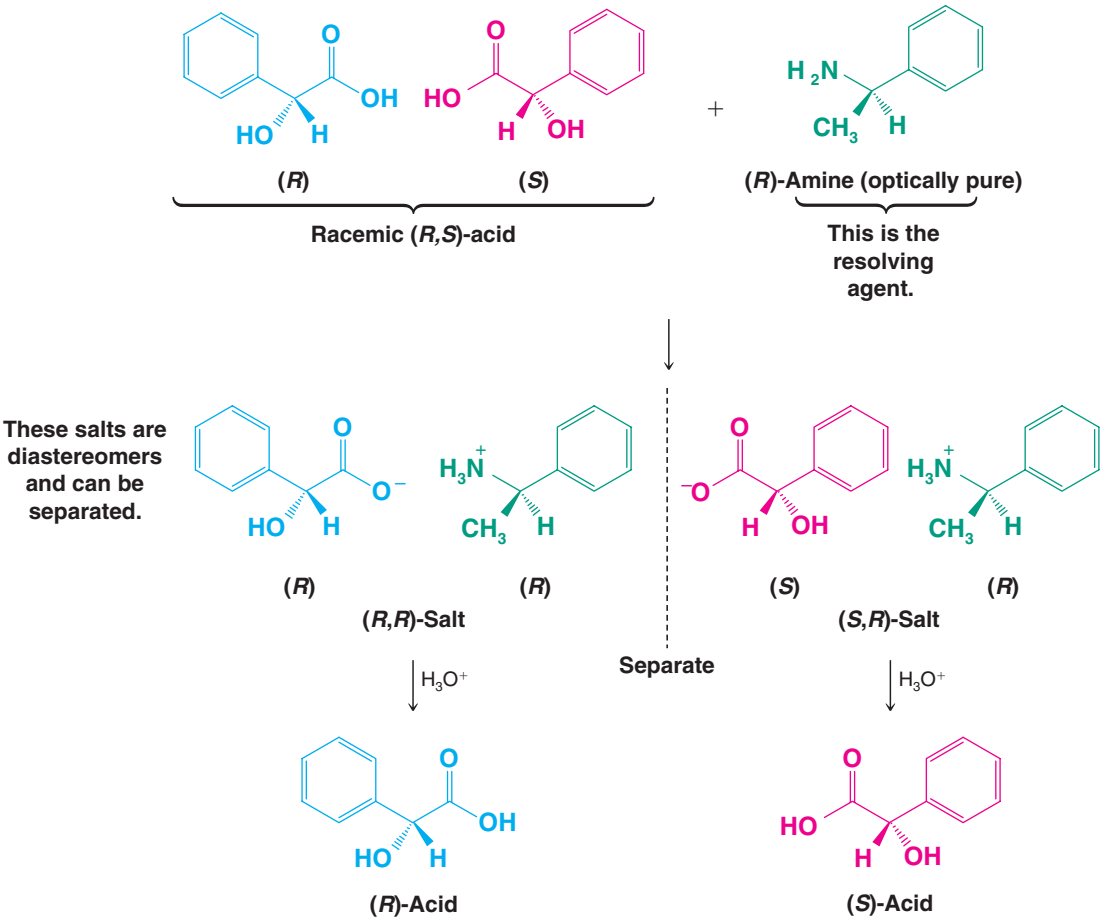
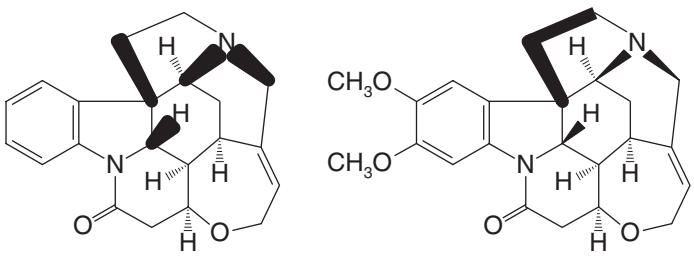
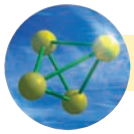


Figure 20.3 Resolution of the racemic form of an organic acid by the use of an optically active amine. Acidification of the separated diastereomeric salts causes the enantiomeric acids to precipitate (assuming they are insoluble in water) and leaves the resolving agent in solution as its conjugate acid.

Single enantiomers that are employed as resolving agents are often readily available from natural sources. Because most of the chiral organic molecules that occur in living organisms are synthesized by enzymatically catalyzed reactions, most of them occur as single enantiomers. Naturally occurring optically active amines such as (−)-quinine (See "The Chemistry of . . . Biologically Important Amines" later in this section), (−)-strychnine, and (−)-brucine are often employed as resolving agents for racemic acids. Acids such as (+)- or (−)-tartaric acid (Section 5.15A) are often used for resolving racemic bases.



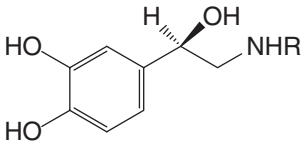
Openmirrors.com



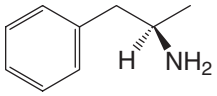
THE CHEMISTRY OF . . .

Biologically Important Amines

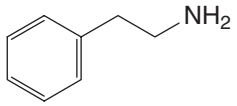
A large number of medically and biologically important compounds are amines. Listed here are some important examples:



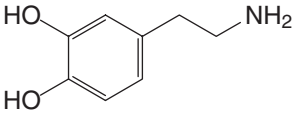
R = CH_3, Adrenaline (epinephrine)
R = H, Noradrenaline (norepinephrine)



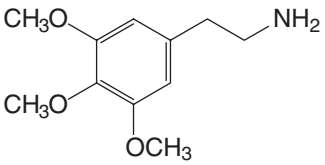
Amphetamine (benzedrine)



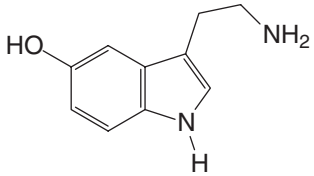
2-Phenylethylamine



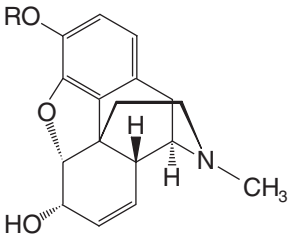
Dopamine



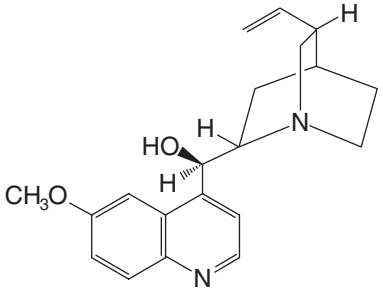
Mescaline



Serotonin



Morphine (R = H)
Codeine (R = CH_3)



(−)-Quinine

2-Phenylethylamines

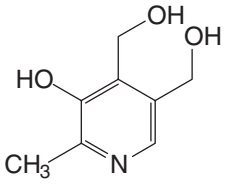
Many phenylethylamine compounds have powerful physiological and psychological effects. Adrenaline and noradrenaline are two hormones secreted in the medulla of the adrenal gland. Released into the bloodstream when an animal senses danger, adrenaline causes an increase in blood pressure, a strengthening of the heart rate, and a widening of the passages of the lungs. All of these effects prepare the animal to fight or to flee. Noradrenaline also causes an increase in blood pressure, and it is involved in the transmission of impulses from the end of one nerve fiber to the next. Dopamine and serotonin are important neurotransmitters in the brain. Abnormalities in the level of dopamine in the brain are associated with many psychiatric disorders, including Parkinson's disease. Dopamine plays a pivotal role in the regulation and control of movement, motivation, and cognition. Serotonin is a compound of particular interest because it appears to be important in maintaining stable mental processes. It has been suggested that the mental disorder schizophrenia may be connected with abnormalities in the metabolism of serotonin.

Amphetamine (a powerful stimulant) and mescaline (a hallucinogen) have structures similar to those of serotonin, adrenaline, and noradrenaline. They are all derivatives of 2-phenylethylamine. (In serotonin the nitrogen is connected to the benzene ring to create a five-membered ring.) The structural similarities of these compounds must be related to their physiological and psychological effects because many other compounds with similar properties are also derivatives of 2-phenylethylamine. Examples (not shown) are *N*-methylamphetamine and LSD (lysergic acid diethylamide). Even morphine and codeine, two powerful analgesics, have a 2-phenylethylamine system as a part of their structures. [Morphine and codeine are examples of compounds called alkaloids (Special Topic F). Try to locate the 2-phenylethylamine system in their structures.]

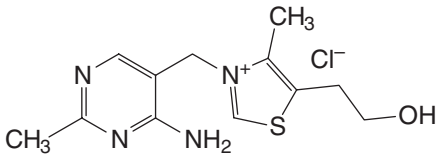
Vitamins and Antihistamines

A number of amines are vitamins. These include nicotinic acid and nicotinamide, pyridoxine (vitamin B_6, see "The Chemistry of . . . Pyridoxal Phosphate" in *WileyPLUS* for Chapter 16), and thiamine chloride (vitamin B_1, see "The

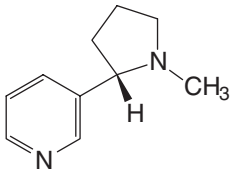
Chemistry of . . . Thiamine," in *WileyPLUS* for Chapter 17). Nicotine is a toxic alkaloid found in tobacco that makes smoking habit forming. Histamine, another toxic amine, is found bound to proteins in nearly all tissues of the body. Release of free histamine causes the symptoms associated with allergic reactions and the common cold. Chlorpheniramine, an "antihistamine," is an ingredient of many over-the-counter cold remedies.



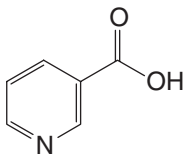
Pyridoxine (vitamin B_6)



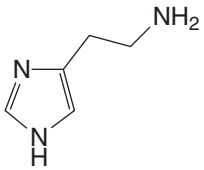
Thiamine chloride (vitamin B_1)



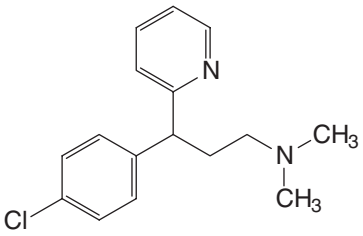
Nicotine



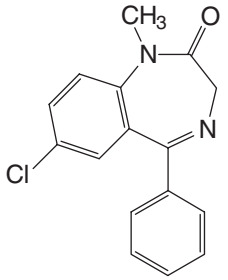
Nicotinic acid (niacin)



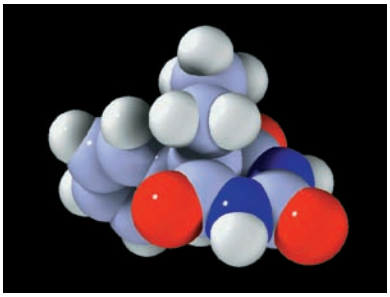
Histamine



Chlorpheniramine



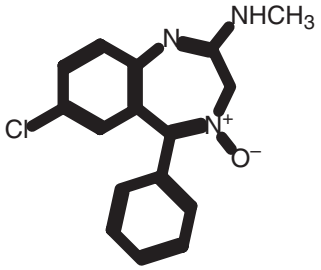
Valium (diazepam)



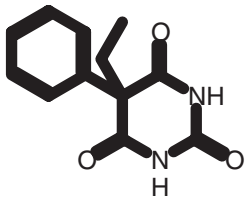
Phenobarbital.

Tranquilizers

Valium (diazepam) is a widely prescribed tranquilizer. Chlordiazepoxide is a closely related compound. Phenobarbital (also see the model) is used to control epileptic seizures and as a sedative for insomnia and relief of anxiety.



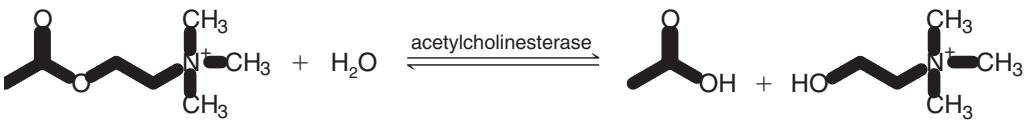
Chlordiazepoxide



Phenobarbital

Neurotransmitters

Nerve cells interact with other nerve cells or with muscles at junctions, or gaps, called synapses. Nerve impulses are carried across the synaptic gap by chemical compounds called *neurotransmitters*. Acetylcholine (see the following reaction) is an important neurotransmitter at neuromuscular synapses called *cholinergic synapses*. Acetylcholine contains a quaternary ammonium group. Being small and ionic, acetylcholine is highly soluble in water and highly diffusible, qualities that suit its role as a neurotransmitter. Acetylcholine molecules are released by the presynaptic membrane in the neuron in packets of about 10^4 molecules. The packet of molecules then diffuses across the synaptic gap.

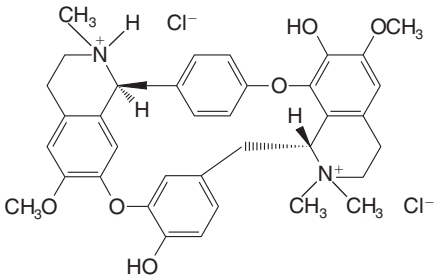


Acetylcholine **Choline**

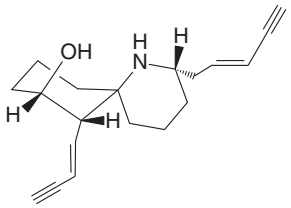
Openmirrors.com

Having carried a nerve impulse across the synapse to the muscle where it triggers an electrical response, the acetylcholine molecules must be hydrolyzed (to choline) within a few milliseconds to allow the arrival of the next impulse. This hydrolysis is catalyzed by an enzyme of almost perfect efficiency called *acetylcholinesterase*.

The acetylcholine receptor on the postsynaptic membrane of muscle is the target for some of the most deadly neurotoxins, including *d*-tubocurarine and histrionicotoxin, shown here.



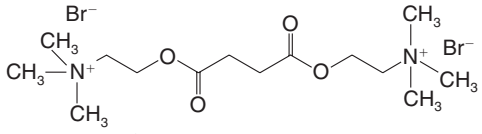
***d*-Tubocurarine chloride**



Histrionicotoxin

When *d*-tubocurarine binds at the acetylcholine receptor site, it prevents opening of the ion channels that depolarize the membrane. This prevents a nerve impulse, and results in paralysis.

Even though *d*-tubocurarine and histrionicotoxin are deadly poisons, both have been useful in research. For example, experiments in respiratory physiology that require absence of normal breathing patterns have involved curare-induced temporary (and voluntary!) respiratory paralysis of a researcher. While the experiment is underway and until the effects of the curare are reversed, the researcher is kept alive by a hospital respirator. In similar fashion, *d*-tubocurarine, as well as succinylcholine bromide, is used as a muscle relaxant during some surgeries.



Succinylcholine bromide

20.4 *Preparation of Amines*

In this section we discuss a variety of ways to synthesize amines. Some of these methods will be new to you, while others are methods you have studied earlier in the context of related functional groups and reactions. Later, in Chapter 24, you will see how some of the methods presented here, as well as some others for asymmetric synthesis, can be used to synthesize α-amino acids, the building blocks of peptides and proteins.

20.4A Through Nucleophilic Substitution Reactions

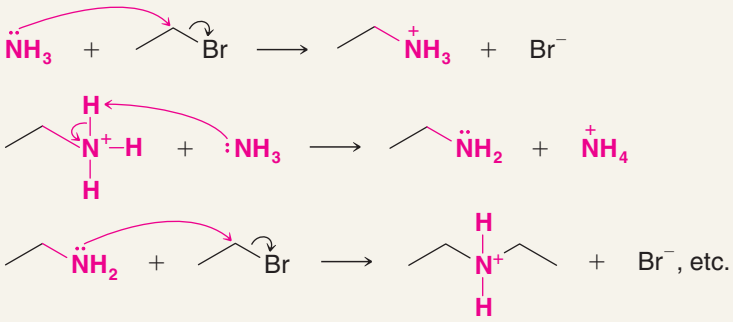
Alkylation of Ammonia Salts of primary amines can be prepared from ammonia and alkyl halides by nucleophilic substitution reactions. Subsequent treatment of the resulting aminium salts with a base gives primary amines:

- This method is of very limited synthetic application because multiple alkylations occur.

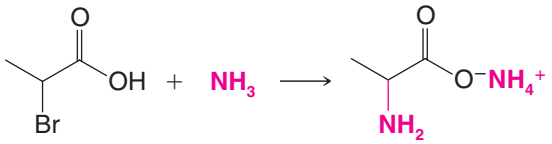
When ethyl bromide reacts with ammonia, for example, the ethylaminium bromide that is produced initially can react with ammonia to liberate ethylamine. Ethylamine can then compete with ammonia and react with ethyl bromide to give diethylaminium bromide. Repetitions of alkylation and proton transfer reactions ultimately produce some tertiary amines and even some quaternary ammonium salts if the alkyl halide is present in excess.

A MECHANISM FOR THE REACTION

Alkylation of NH_3

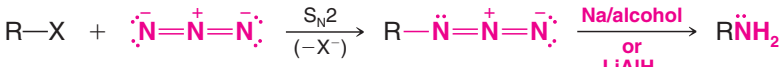


Multiple alkylations can be minimized by using a large excess of ammonia. (Why?) An example of this technique can be seen in the synthesis of alanine from 2-bromopropanoic acid:



(1 mol) **(70 mol)** **Alanine (65–70%)**

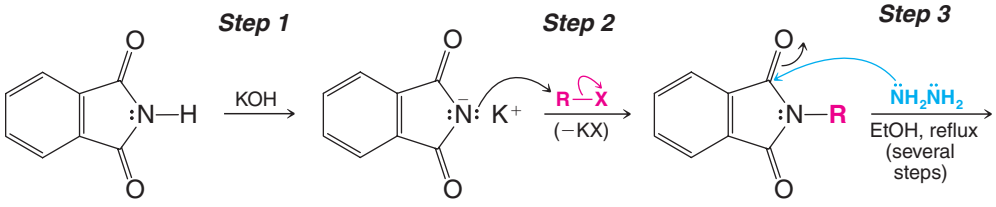
Alkylation of Azide Ion and Reduction A much better method for preparing a primary amine from an alkyl halide is first to convert the alkyl halide to an alkyl azide ($R—N_3$) by a nucleophilic substitution reaction, then reduce the azide to a primary amine with sodium and alcohol or with lithium aluminum hydride.



Azide ion (a good nucleophile) **Alkyl azide**

A word of caution: Alkyl azides are explosive, and low-molecular-weight alkyl azides should not be isolated but should be kept in solution. Sodium azide is used in automotive airbags.

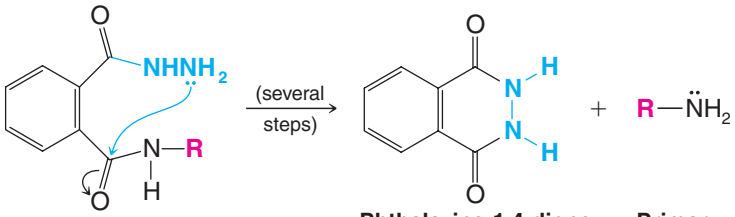
The Gabriel Synthesis Potassium phthalimide (see the following reaction) can also be used to prepare primary amines by a method known as the *Gabriel synthesis*. This synthesis also avoids the complications of multiple alkylations that occur when alkyl halides are treated with ammonia:



Phthalimide ***N*-Alkylphthalimide**

Openmirrors.com

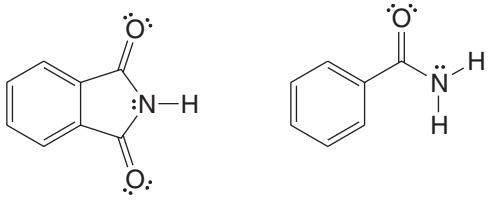
(continued from previous page)



Phthalimide is quite acidic ($pK_a = 9$); it can be converted to potassium phthalimide by potassium hydroxide (step 1). The phthalimide anion is a strong nucleophile and (in step 2) it reacts with an alkyl halide by an S_N2 mechanism to give an *N*-alkylphthalimide. At this point, the *N*-alkylphthalimide can be hydrolyzed with aqueous acid or base, but the hydrolysis is often difficult. It is often more convenient to treat the *N*-alkylphthalimide with hydrazine (NH_2NH_2) in refluxing ethanol (step 3) to give a primary amine and phthalazine-1,4-dione.

Review Problem 20.3

(a) Write resonance structures for the phthalimide anion that account for the acidity of phthalimide. **(b)** Would you expect phthalimide to be more or less acidic than benzamide? Why? **(c)** In step 3 of our reaction several steps have been omitted. Propose reasonable mechanisms for these steps.

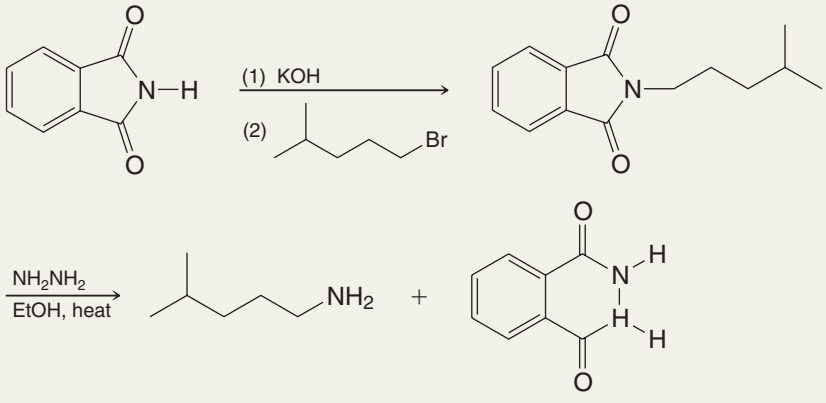


Syntheses of amines using the Gabriel synthesis are, as we might expect, restricted to the use of methyl, primary, and secondary alkyl halides. The use of tertiary halides leads almost exclusively to eliminations.

Solved Problem 20.1

Outline a synthesis of 4-methylpentanamine using the Gabriel synthesis.

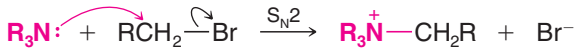
ANSWER



Review Problem 20.4

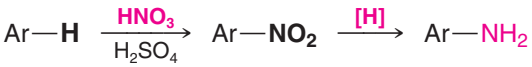
Outline a preparation of benzylamine using the Gabriel synthesis.

Alkylation of Tertiary Amines Multiple alkylations are not a problem when tertiary amines are alkylated with methyl or primary halides. Reactions such as the following take place in good yield:



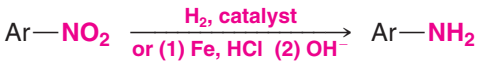
20.4B Preparation of Aromatic Amines through Reduction of Nitro Compounds

The most widely used method for preparing aromatic amines involves nitration of the ring and subsequent reduction of the nitro group to an amino group:

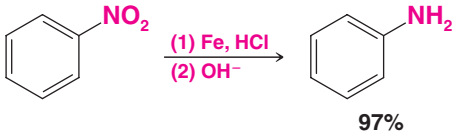


We studied ring nitration in Chapter 15 and saw there that it is applicable to a wide variety of aromatic compounds. Reduction of the nitro group can also be carried out in a number of ways. The most frequently used methods employ catalytic hydrogenation, or treatment of the nitro compound with acid and iron. Zinc, tin, or a metal salt such as $SnCl_2$ can also be used. Overall, this is a $6e^-$ reduction.

General Reaction

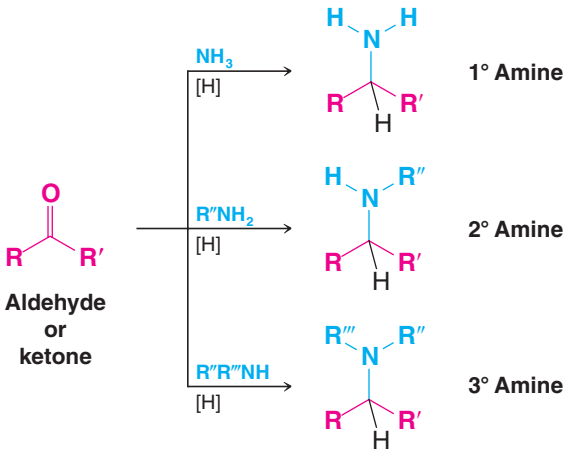


Specific Example



20.4C Preparation of Primary, Secondary, and Tertiary Amines through Reductive Amination

Aldehydes and ketones can be converted to amines through catalytic or chemical reduction in the presence of ammonia or an amine. Primary, secondary, and tertiary amines can be prepared this way:

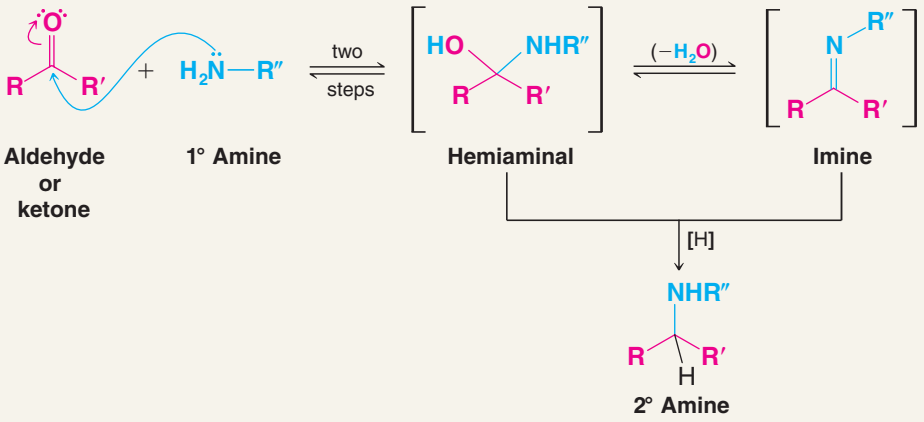


This process, called **reductive amination** of the aldehyde or ketone (or *reductive alkylation* of the amine), appears to proceed through the following general mechanism (illustrated with a 1° amine).

Openmirrors.com

A MECHANISM FOR THE REACTION

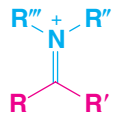
Reductive Amination



Helpful Hint

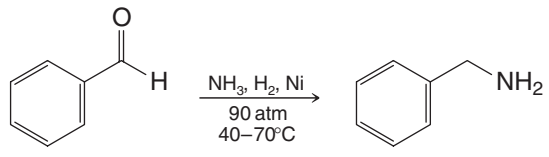
We saw the importance of imines in "The Chemistry of . . . Pyridoxal Phosphate" (vitamin B_6) in *WileyPLUS* for Chapter 16 (Section 16.8).

When ammonia or a primary amine is used, there are two possible pathways to the product: via an amino alcohol that is similar to a hemiacetal and is called a *hemiaminal* or via an imine (Section 16.8A). When secondary amines are used, an imine cannot form, and, therefore, the pathway is through the hemiaminal or through an iminium ion:

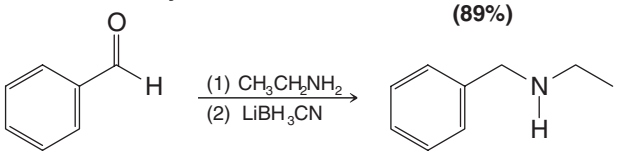


Iminium ion

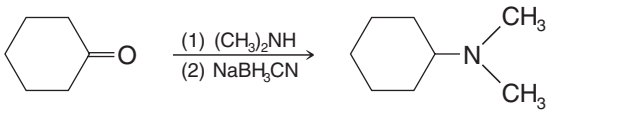
The reducing agents employed include hydrogen and a catalyst (such as nickel) or $NaBH_3CN$ or $LiBH_3CN$ (sodium or lithium cyanoborohydride). The latter two reducing agents are similar to $NaBH_4$ and are especially effective in reductive aminations. Three specific examples of reductive amination follow:



Benzaldehyde → **Benzylamine (89%)**



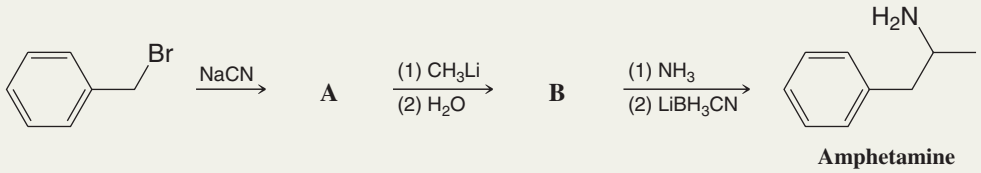
Benzaldehyde → ***N*-Benzylethanamine (89%)**



Cyclohexanone → ***N,N*-Dimethylcyclohexanamine (52–54%)**

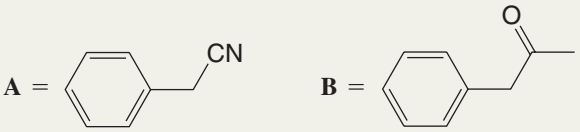
Solved Problem 20.2

Outlined below is a synthesis of the stimulant amphetamine. Provide the intermediates **A** and **B**.



Amphetamine

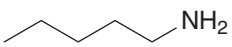
ANSWER



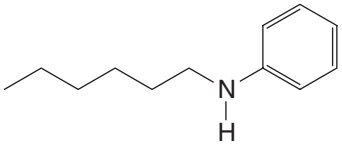
Review Problem 20.5

Show how you might prepare each of the following amines through reductive amination:

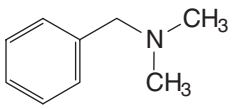
(a)



(b)

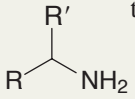


(c)



Solved Problem 20.3

Reductive amination of a ketone is almost always a better method for the synthesis of an amine of the type

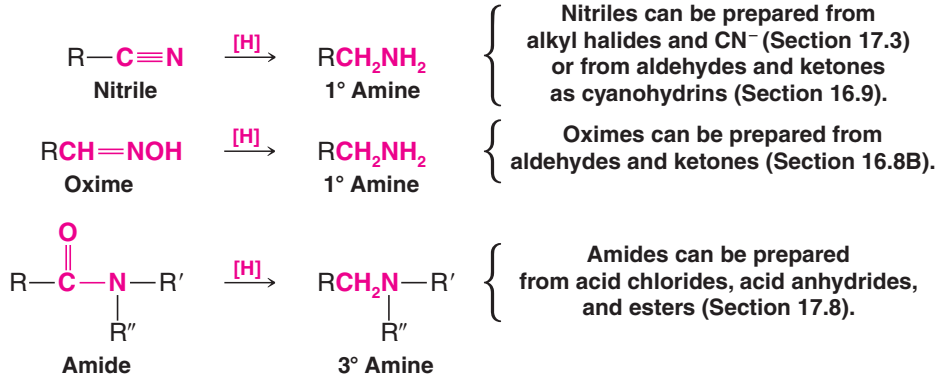


than treatment of an alkyl halide with ammonia. Explain why this is true.

STRATEGY AND ANSWER Consider the structure of the required alkyl halide. Reaction of a secondary halide with ammonia would inevitably be accompanied by considerable elimination, thereby decreasing the yield of the secondary amine. Multiple *N*-alkylations may also occur.

20.4D Preparation of Primary, Secondary, or Tertiary Amines through Reduction of Nitriles, Oximes, and Amides

Nitriles, oximes, and amides can be reduced to amines. Reduction of a nitrile or an oxime yields a primary amine; reduction of an amide can yield a primary, secondary, or tertiary amine:

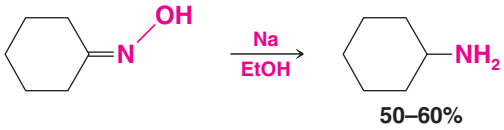


Openmirrors.com

(In the last example, if R′ = H and R″ = H, the product is a 1° amine; if only R′ = H, the product is a 2° amine.)

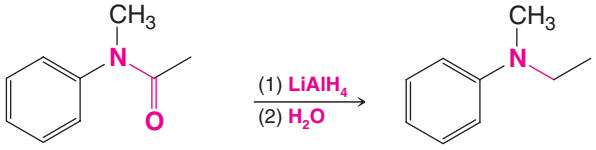
All of these reductions can be carried out with hydrogen and a catalyst or with $LiAlH_4$. Oximes are also conveniently reduced with sodium in ethanol.

Specific examples follow:



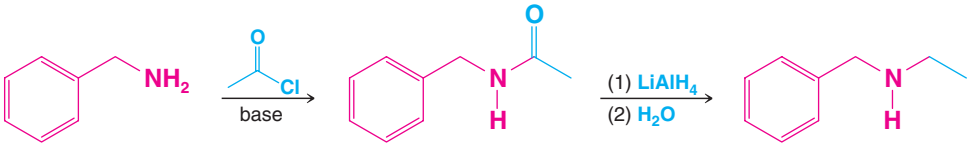
50–60%

2-Phenylethanenitrile (phenylacetonitrile) — **2-Phenylethanamine (71%)**



***N*-Methylacetanilide** — ***N*-Ethyl-*N*-methylaniline**

Reduction of an amide is the last step in a useful procedure for **monoalkylation of an amine**. The process begins with *acylation* of the amine using an acyl chloride or acid anhydride; then the amide is reduced with lithium aluminum hydride. For example,



Benzylamine — **Benzylethylamine**

Solved Problem 20.4

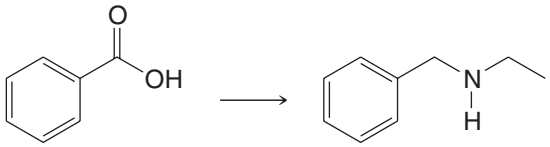
Show how you might synthesize 2-propanamine from a three-carbon starting material that is a ketone, aldehyde, nitrile, or amide.

STRATEGY AND ANSWER We begin by recognizing that 2-propanamine has a primary amine group bonded to a secondary carbon. Neither a three-carbon nitrile nor a three-carbon amide can lead to this structural unit from a C_3 starting material. An oxime can lead to the proper structure, but we must start with a three-carbon ketone rather than an aldehyde. Therefore, we choose propanone as our starting material, convert it to an oxime, and then reduce the oxime to an amine.

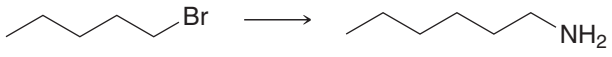
Review Problem 20.6

Show how you might utilize the reduction of an amide, oxime, or nitrile to carry out each of the following transformations:

(a)



(b)

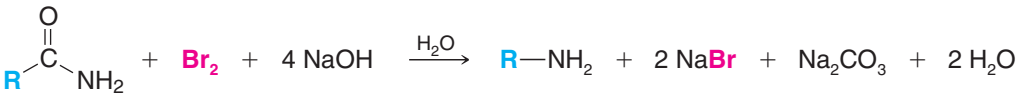


(c) 

(d) 

20.4E Preparation of Primary Amines through the Hofmann and Curtius Rearrangements

Hofmann Rearrangement Amides with no substituent on the nitrogen react with solutions of bromine or chlorine in sodium hydroxide to yield amines through a reaction known as the *Hofmann rearrangement* or *Hofmann degradation*:

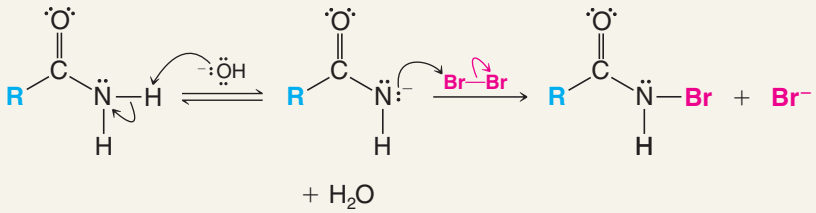


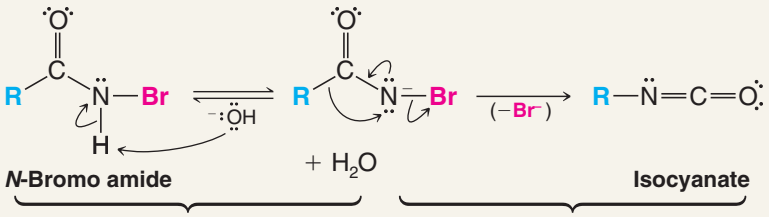
From this equation we can see that the carbonyl carbon atom of the amide is lost (as CO_3^{2-}) and that the R group of the amide becomes attached to the nitrogen of the amine. Primary amines made this way are not contaminated by 2° or 3° amines.

The mechanism for this interesting reaction is shown in the following scheme. In the first two steps the amide undergoes a base-promoted bromination, in a manner analogous to the base-promoted halogenation of a ketone that we studied in Section 18.3B. (The electron-withdrawing acyl group of the amide makes the amido hydrogens much more acidic than those of an amine.) The *N*-bromo amide then reacts with hydroxide ion to produce an anion, which spontaneously rearranges with the loss of a bromide ion to produce an isocyanate (Section 17.9A). In the rearrangement the R— group migrates with its electrons from the acyl carbon to the nitrogen atom at the same time the bromide ion departs. The isocyanate that forms in the mixture is quickly hydrolyzed by the aqueous base to a carbamate ion, which undergoes spontaneous decarboxylation resulting in the formation of the amine.

A MECHANISM FOR THE REACTION

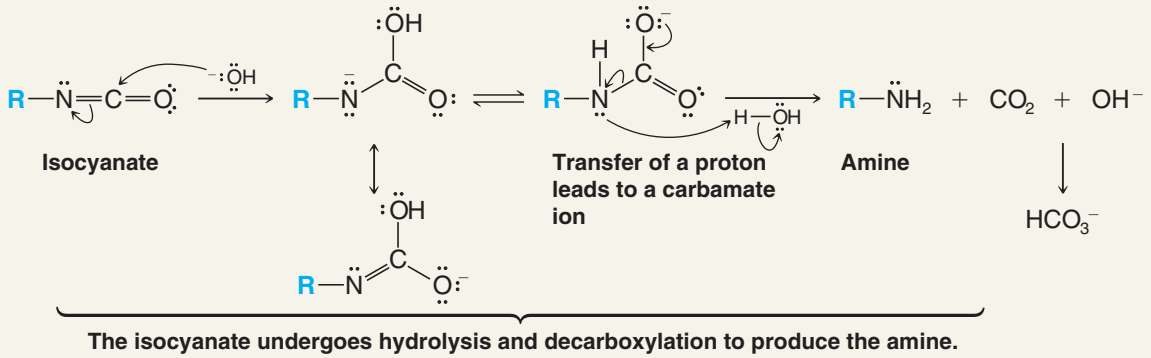
The Hofmann Rearrangement





(continued on the next page)

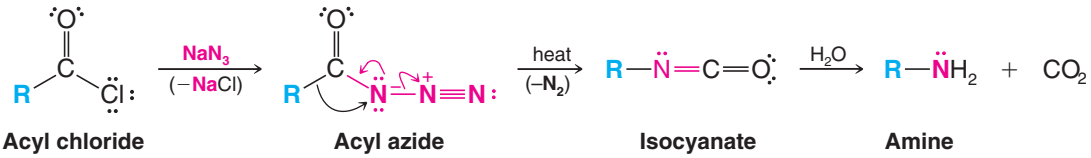
Openmirrors.com



An examination of the first two steps of this mechanism shows that, initially, two hydrogen atoms must be present on the nitrogen of the amide for the reaction to occur. Consequently, the Hofmann rearrangement is limited to amides of the type $RCONH_2$.

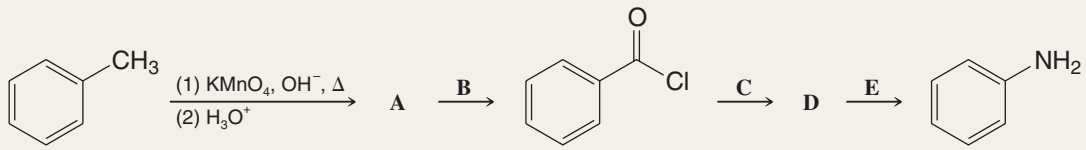
Studies of the Hofmann rearrangement of optically active amides in which the chirality center is directly attached to the carbonyl group have shown that these reactions occur with *retention of configuration*. Thus, the R group migrates to nitrogen with its electrons, *but without inversion*.

Curtius Rearrangement The *Curtius rearrangement* is a rearrangement that occurs with acyl azides. It resembles the Hofmann rearrangement in that an R— group migrates from the acyl carbon to the nitrogen atom as the leaving group departs. In this instance the leaving group is N_2 (the best of all possible leaving groups since it is highly stable, is virtually nonbasic, and being a gas, removes itself from the medium). Acyl azides are easily prepared by allowing acyl chlorides to react with sodium azide. Heating the acyl azide brings about the rearrangement; afterward, adding water causes hydrolysis and decarboxylation of the isocyanate:



Solved Problem 20.5

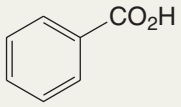
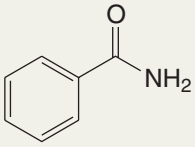
The reaction sequence below shows how a methyl group on a benzene ring can be replaced by an amino group. Supply the missing reagents and intermediates.



STRATEGY AND ANSWER

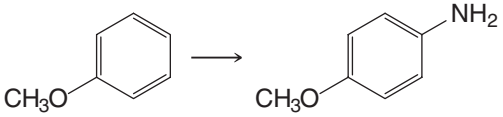
An acid chloride results from treatment of **A** with **B**. Therefore, **A** is likely to be a carboxylic acid, a conclusion that is consistent with the oxidizing conditions that led to formation of **A** from methylbenzene (toluene). **B** must be a reagent that can lead to an acid chloride. Thionyl chloride or PCl_5 would suffice. Overall, **C, D**, and **E** involve introduction of the nitrogen atom and loss of the carbonyl carbon. This sequence is consistent with preparation of an amide followed by a Hofmann rearrangement.

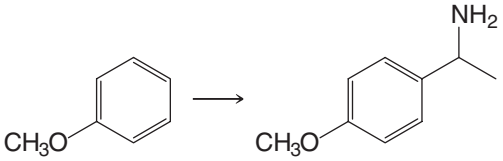
(continued on the next page)

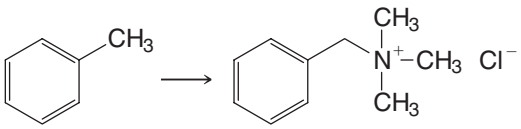
A =  **B** = SO_2Cl **C** = NH_3 **D** =  **E** = Br_2/OH^-

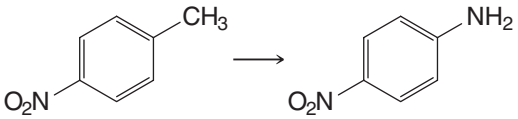
Review Problem 20.7

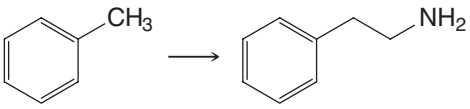
Using a different method for each part, but taking care in each case to select a *good* method, show how each of the following transformations might be accomplished:

(a) 

(b) 

(c) 

(d) 

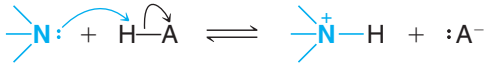
(e) 

20.5 Reactions of Amines

We have encountered a number of important reactions of amines in earlier sections. In Section 20.3 we saw reactions in which primary, secondary, and tertiary amines act *as bases*. In Section 20.4 we saw their reactions as *nucleophiles* in *alkylation reactions*, and in Chapter 17 as *nucleophiles* in *acylation reactions*. In Chapter 15 we saw that an amino group on an aromatic ring acts as a powerful *activating group* and as an *ortho–para director*.

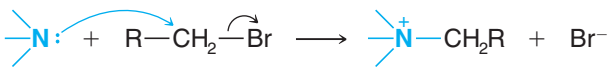
The feature of amines that underlies all of these reactions and that forms a basis for our understanding of most of the chemistry of amines is the ability of nitrogen to share an electron pair:

Acid–Base Reactions



An amine acting as a base

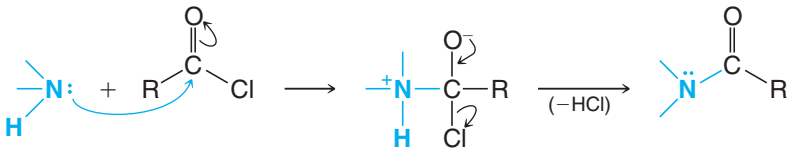
Alkylation



An amine acting as a nucleophile in an alkylation reaction

Openmirrors.com

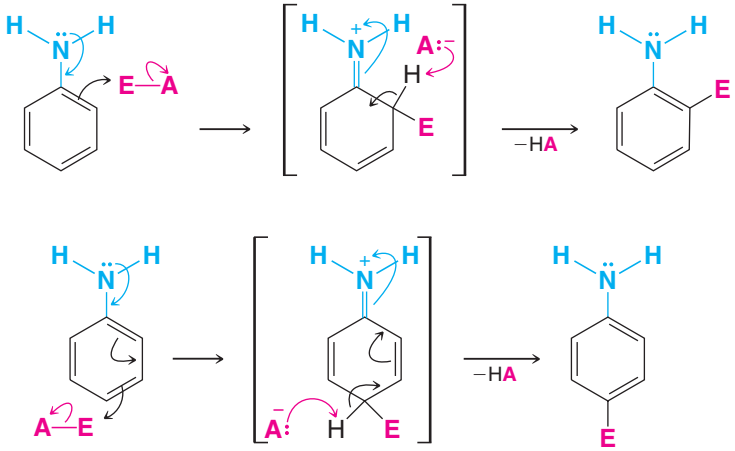
Acylation



An amine acting as a nucleophile in an acylation reaction

In the preceding examples the amine acts as a nucleophile by donating its electron pair to an electrophilic reagent. In the following example, resonance contributions involving the nitrogen electron pair make *carbon* atoms nucleophilic:

Electrophilic Aromatic Substitution



The amino group acting as an activating group and as an ortho–para director in electrophilic aromatic substitution

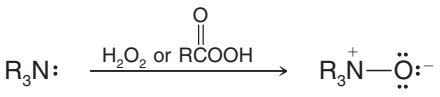
Review Problem 20.8

Review the chemistry of amines given in earlier sections and provide a specific example for each of the previously illustrated reactions.

20.5A Oxidation of Amines

Primary and secondary aliphatic amines are subject to oxidation, although in most instances useful products are not obtained. Complicated side reactions often occur, causing the formation of complex mixtures.

Tertiary amines can be oxidized cleanly to tertiary amine oxides. This transformation can be brought about by using hydrogen peroxide or a peroxy acid:



A tertiary amine oxide

Tertiary amine oxides undergo a useful elimination reaction to be discussed in Section 20.12B.

Arylamines are very easily oxidized by a variety of reagents, including the oxygen in air. Oxidation is not confined to the amino group but also occurs in the ring. (The amino group through its electron-donating ability makes the ring electron rich and hence especially susceptible to oxidation.) The oxidation of other functional groups on an aromatic ring cannot usually be accomplished when an amino group is present on the ring, because oxidation of the ring takes place first.

20.6 Reactions of Amines with Nitrous Acid

Nitrous acid (HONO) is a weak, unstable acid. It is always prepared *in situ*, usually by treating sodium nitrite ($NaNO_2$) with an aqueous solution of a strong acid:

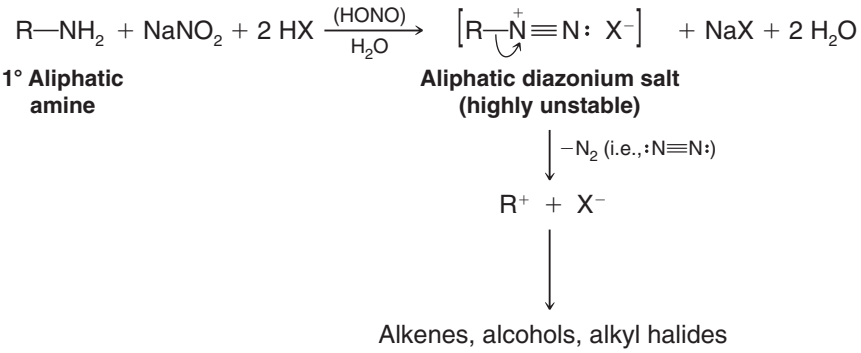
$$HCl_{(aq)} + NaNO_{2(aq)} \longrightarrow HONO_{(aq)} + NaCl_{(aq)}$$
$$H_2SO_4 + 2\ NaNO_{2(aq)} \longrightarrow 2\ HONO_{(aq)} + Na_2SO_{4(aq)}$$

Nitrous acid reacts with all classes of amines. The products that we obtain from these reactions depend on whether the amine is primary, secondary, or tertiary and whether the amine is aliphatic or aromatic.

20.6A Reactions of Primary Aliphatic Amines with Nitrous Acid

Primary aliphatic amines react with nitrous acid through a reaction called *diazotization* to yield highly unstable aliphatic **diazonium salts**. Even at low temperatures, *aliphatic* diazonium salts decompose spontaneously by losing nitrogen to form carbocations. The carbocations go on to produce mixtures of alkenes, alcohols, and alkyl halides by removal of a proton, reaction with H_2O, and reaction with X^-:

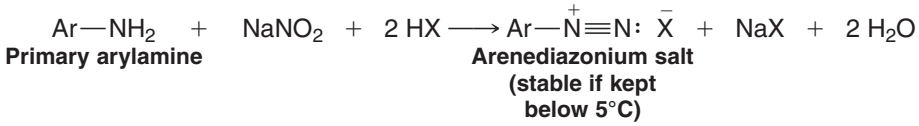
General Reaction



Diazotizations of primary aliphatic amines are of little synthetic importance because they yield such a complex mixture of products. Diazotizations of primary aliphatic amines are used in some analytical procedures, however, because the evolution of nitrogen is quantitative. They can also be used to generate and thus study the behavior of carbocations in water, acetic acid, and other solvents.

20.6B Reactions of Primary Arylamines with Nitrous Acid

The most important reaction of amines with nitrous acid, by far, is the reaction of primary arylamines. We shall see why in Section 20.7. Primary arylamines react with nitrous acid to give arenediazonium salts. Even though arenediazonium salts are unstable, they are still far more stable than aliphatic diazonium salts; they do not decompose at an appreciable rate in solution when the temperature of the reaction mixture is kept below 5°C:



Diazotization of a primary amine takes place through a series of steps. In the presence of strong acid, nitrous acid dissociates to produce ^+NO ions. These ions then react with the nitrogen of the amine to form an unstable *N*-nitrosoaminium ion as an intermediate. This intermediate then loses a proton to form an *N*-nitrosoamine, which, in turn, tautomerizes to a diazohydroxide in a reaction that is similar to keto–enol tautomerization. Then, in the presence of acid, the diazohydroxide loses water to form the diazonium ion.

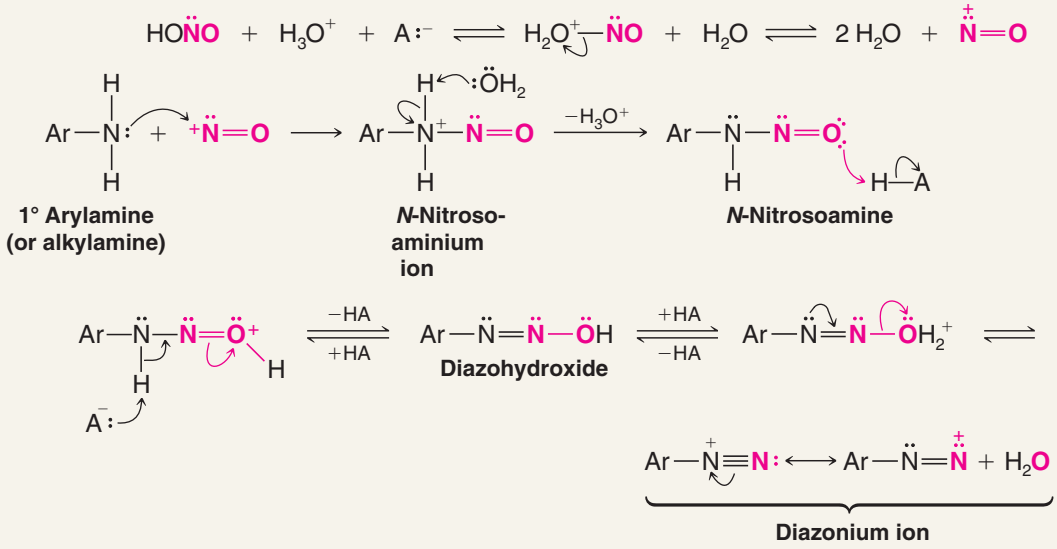
Helpful Hint

Primary arylamines can be converted to aryl halides, nitriles, and phenols via aryl diazonium ions (Section 20.7).

Openmirrors.com

A MECHANISM FOR THE REACTION

Diazotization



Diazotization reactions of primary arylamines are of considerable synthetic importance because the diazonium group, $-\overset{+}{\text{N}}\equiv\text{N}$: can be replaced by a variety of other functional groups. We shall examine these reactions in Section 20.7.

THE CHEMISTRY OF . . .

N-Nitrosoamines

N-Nitrosoamines are very powerful carcinogens which scientists fear may be present in many foods, especially in cooked meats that have been cured with sodium nitrite.

Sodium nitrite is added to many meats (e.g., bacon, ham, frankfurters, sausages, and corned beef) to inhibit the growth of *Clostridium botulinum* (the bacterium that produces botulinus toxin) and to keep red meats from turning brown. (Food poisoning by botulinus toxin is often fatal.) In the presence of acid or under the influence of heat, sodium nitrite reacts with amines always present in the meat to produce *N*-nitrosoamines. Cooked bacon, for example, has been shown to contain *N*-nitrosodimethylamine and *N*-nitrosopyrrolidine.

There is also concern that nitrites from food may produce nitrosoamines when they react with amines in the presence of the acid found in the stomach. In 1976, the FDA reduced the permissible amount of nitrite allowed in cured meats from 200 parts per million (ppm) to 50–125 ppm. Nitrites (and nitrates that can be converted to nitrites by bacteria) also occur naturally in many foods.

Cigarette smoke is known to contain *N*-nitrosodimethylamine. Someone smoking a pack of cigarettes a day inhales about 0.8 μg of *N*-nitrosodimethylamine, and even more has been shown to be present in the sidestream smoke.

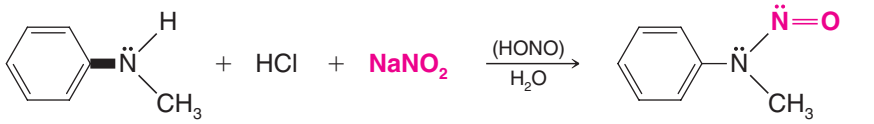
A processed food preserved with sodium nitrite.

20.6C Reactions of Secondary Amines with Nitrous Acid

Secondary amines—both aryl and alkyl—react with nitrous acid to yield *N*-nitrosoamines. ***N*-Nitrosoamines** usually separate from the reaction mixture as oily yellow liquids:

Specific Examples

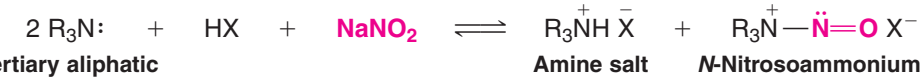
Dimethylamine — ***N*-Nitrosodimethylamine (a yellow oil)**



***N*-Methylaniline** — ***N*-Nitroso-*N*-methylaniline (87–93%) (a yellow oil)**

20.6D Reactions of Tertiary Amines with Nitrous Acid

When a tertiary aliphatic amine is mixed with nitrous acid, an equilibrium is established among the tertiary amine, its salt, and an *N*-nitrosoammonium compound:

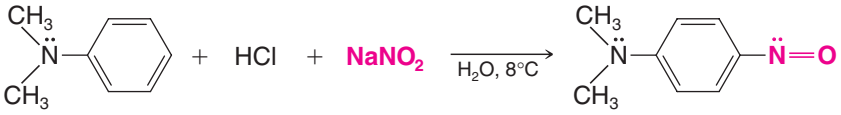


Tertiary aliphatic amine — **Amine salt** — ***N*-Nitrosoammonium compound**

Although *N*-nitrosoammonium compounds are stable at low temperatures, at higher temperatures and in aqueous acid they decompose to produce aldehydes or ketones. These reactions are of little synthetic importance, however.

Tertiary arylamines react with nitrous acid to form *C*-nitroso aromatic compounds. Nitrosation takes place almost exclusively at the para position if it is open and, if not, at the ortho position. The reaction (see Review Problem 20.9) is another example of electrophilic aromatic substitution.

Specific Example



***p*-Nitroso-*N*,*N*-dimethylaniline (80–90%)**

Review Problem 20.9

Para-nitrosation of *N*,*N*-dimethylaniline (*C*-nitrosation) is believed to take place through an electrophilic attack by $\overset{+}{N}O$ ions. **(a)** Show how $\overset{+}{N}O$ ions might be formed in an aqueous solution of $NaNO_2$ and HCl. **(b)** Write a mechanism for *p*-nitrosation of *N*,*N*-dimethylaniline. **(c)** Tertiary aromatic amines and phenols undergo *C*-nitrosation reactions, whereas most other benzene derivatives do not. How can you account for this difference?

20.7 Replacement Reactions of Arenediazonium Salts

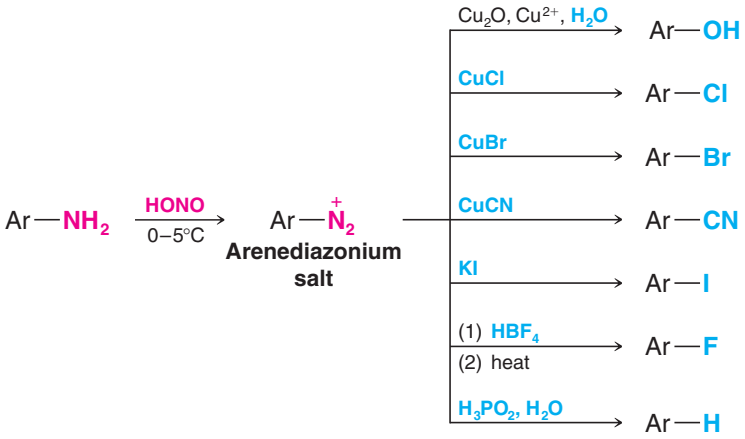
- Arenediazonium salts are highly useful intermediates in the synthesis of aromatic compounds, because the diazonium group can be replaced by any one of a number of other atoms or groups, including —F, —Cl, —Br, —I, —CN, —OH, and —H.

Diazonium salts are almost always prepared by diazotizing primary aromatic amines. Primary arylamines can be synthesized through reduction of nitro compounds that are readily available through direct nitration reactions.

Openmirrors.com

20.7A Syntheses Using Diazonium Salts

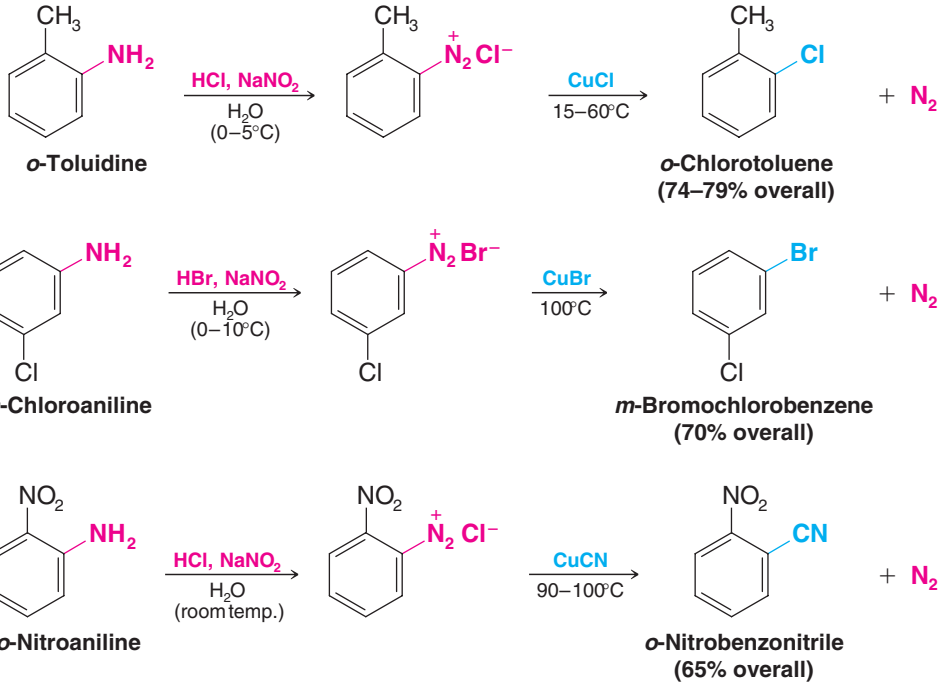
Most arenediazonium salts are unstable at temperatures above 5–10°C, and many explode when dry. Fortunately, however, most of the replacement reactions of diazonium salts do not require their isolation. We simply add another reagent (CuCl, CuBr, KI, etc.) to the mixture, gently warm the solution, and the replacement (accompanied by the evolution of nitrogen) takes place:



Only in the replacement of the diazonium group by —F need we isolate a diazonium salt. We do this by adding HBF_4 to the mixture, causing the sparingly soluble and reasonably stable arenediazonium fluoroborate, $ArN_2^+\ BF_4^-$, to precipitate.

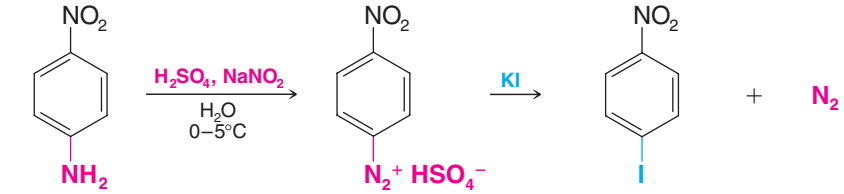
20.7B The Sandmeyer Reaction: Replacement of the Diazonium Group by —Cl, —Br, or —CN

Arenediazonium salts react with cuprous chloride, cuprous bromide, and cuprous cyanide to give products in which the diazonium group has been replaced by —Cl, —Br, and —CN, respectively. These reactions are known generally as *Sandmeyer reactions*. Several specific examples follow. The mechanisms of these replacement reactions are not fully understood; the reactions appear to be radical in nature, not ionic.



20.7C Replacement by —I

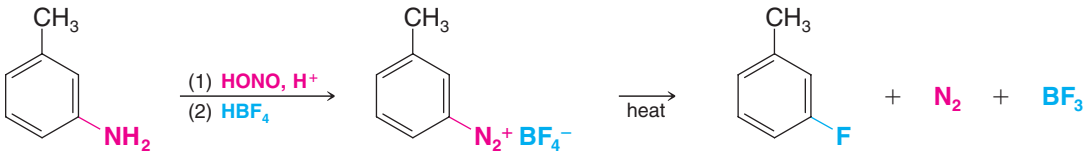
Arenediazonium salts react with potassium iodide to give products in which the diazonium group has been replaced by —I. An example is the synthesis of *p*-iodonitrobenzene:



p-Nitroaniline — *p*-Iodonitrobenzene (81% overall)

20.7D Replacement by —F

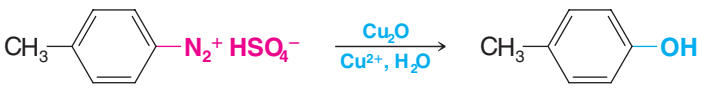
The diazonium group can be replaced by fluorine by treating the diazonium salt with fluoroboric acid (HBF_4). The diazonium fluoroborate that precipitates is isolated, dried, and heated until decomposition occurs. An aryl fluoride is produced:



m-Toluidine — *m*-Toluenediazonium fluoroborate (79%) — *m*-Fluorotoluene (69%)

20.7E Replacement by —OH

The diazonium group can be replaced by a hydroxyl group by adding cuprous oxide to a dilute solution of the diazonium salt containing a large excess of cupric nitrate:



p-Toluenediazonium hydrogen sulfate — *p*-Cresol (93%)

This variation of the Sandmeyer reaction (developed by T. Cohen, University of Pittsburgh) is a much simpler and safer procedure than an older method for phenol preparation, which required heating the diazonium salt with concentrated aqueous acid.

Review Problem 20.10

In the preceding examples of diazonium reactions, we have illustrated syntheses beginning with the compounds (a)–(d) here. Show how you might prepare each of the following compounds from benzene:

(a) *m*-Chloroaniline **(b)** *m*-Bromoaniline **(c)** *o*-Nitroaniline **(d)** *p*-Nitroaniline

20.7F Replacement by Hydrogen: Deamination by Diazotization

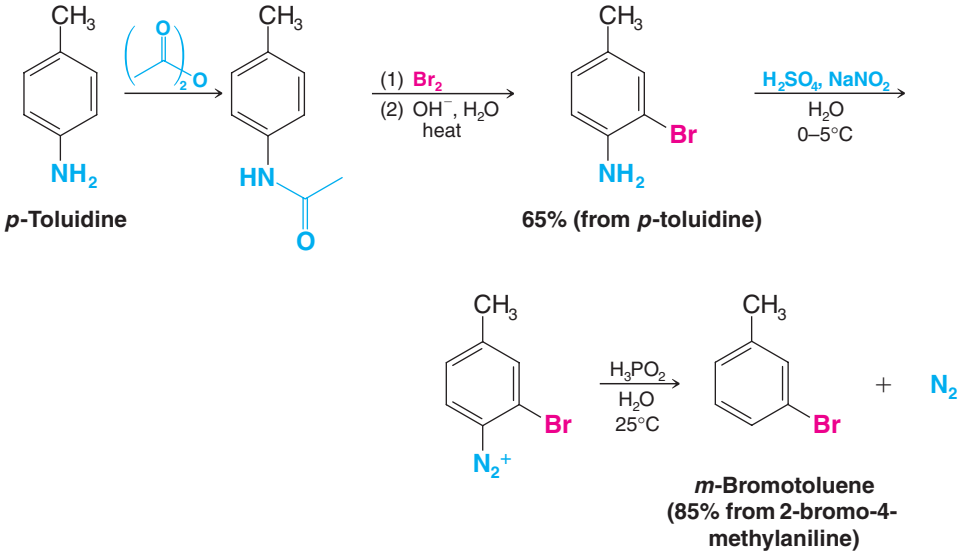
Arenediazonium salts react with hypophosphorous acid (H_3PO_2) to yield products in which the diazonium group has been replaced by —H.

Since we usually begin a synthesis using diazonium salts by nitrating an aromatic compound, that is, replacing —H by $—NO_2$ and then by $—NH_2$, it may seem strange that we would ever want to replace a diazonium group by —H. However, replacement of the diazonium group by —H can be a useful reaction. We can introduce an amino group into an aromatic ring to influence the orientation of a subsequent reaction. Later we can remove

Openmirrors.com

the amino group (i.e., carry out a *deamination*) by diazotizing it and treating the diazonium salt with H_3PO_2.

We can see an example of the usefulness of a deamination reaction in the following synthesis of *m*-bromotoluene.

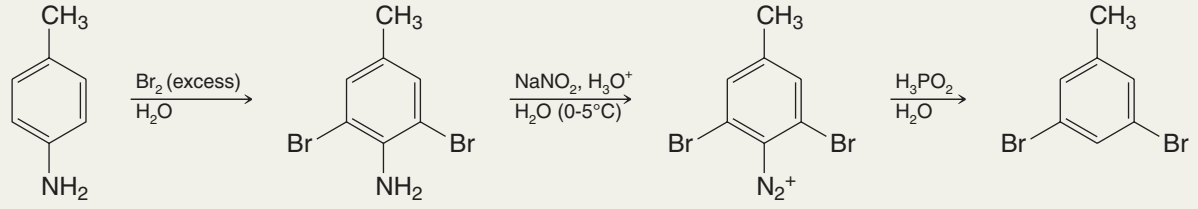


We cannot prepare *m*-bromotoluene by direct bromination of toluene or by a Friedel–Crafts alkylation of bromobenzene because both reactions give *o*- and *p*-bromotoluene. (Both CH_3— and Br— are ortho–para directors.) However, if we begin with *p*-toluidine (prepared by nitrating toluene, separating the para isomer, and reducing the nitro group), we can carry out the sequence of reactions shown and obtain *m*-bromotoluene in good yield. The first step, synthesis of the *N*-acetyl derivative of *p*-toluidine, is done to reduce the activating effect of the amino group. (Otherwise both ortho positions would be brominated.) Later, the acetyl group is removed by hydrolysis.

Solved Problem 20.6

Suggest how you might modify the preceding synthesis in order to prepare 3,5-dibromotoluene.

STRATEGY AND ANSWER An amino group is a stronger activating group than an amido group. If we brominate directly with the amino group present, rather than after converting the amine to an amide, we can brominate both ortho positions. We must also be sure to provide sufficient bromine.



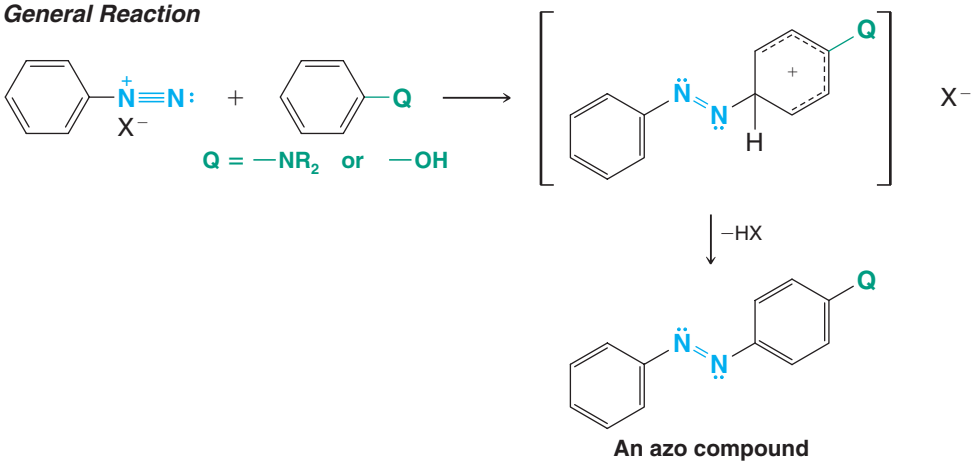
Review Problem 20.11 **(a)** In Section 20.7D we showed a synthesis of *m*-fluorotoluene starting with *m*-toluidine. How would you prepare *m*-toluidine from toluene? **(b)** How would you prepare *m*-chlorotoluene? **(c)** *m*-Bromotoluene? **(d)** *m*-Iodotoluene? **(e)** *m*-Tolunitrile (*m*-$CH_3C_6H_4CN$)? **(f)** *m*-Toluic acid?

Review Problem 20.12 Starting with *p*-nitroaniline [Review Problem 20.10 (d)], show how you might synthesize 1,2,3-tribromobenzene.

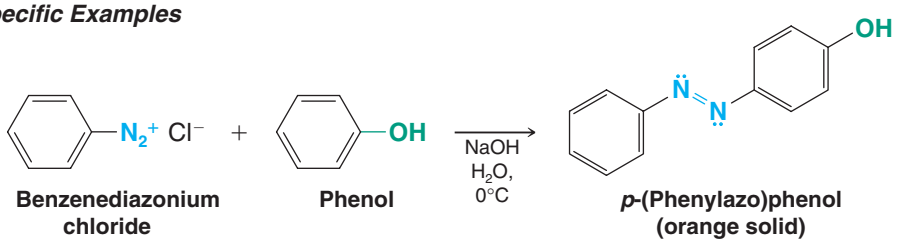
20.8 Coupling Reactions of Arenediazonium Salts

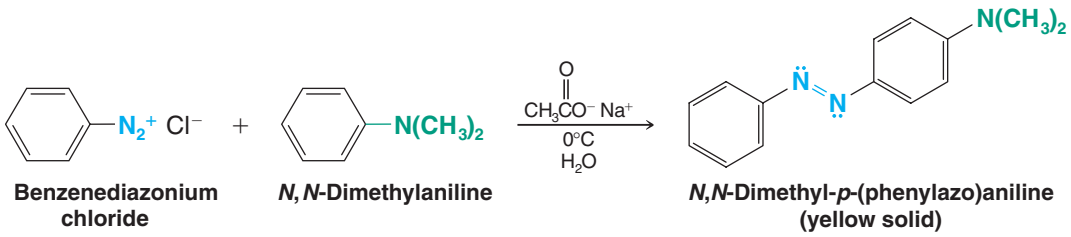
Arenediazonium ions are weak electrophiles; they react with highly reactive aromatic compounds—with phenols and tertiary arylamines—to yield *azo* compounds. This electrophilic aromatic substitution is often called a *diazo coupling reaction*.

General Reaction

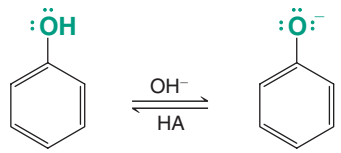


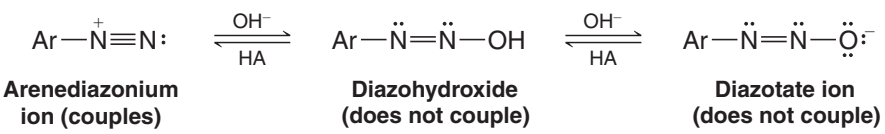
Specific Examples





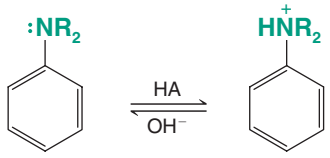
Couplings between arenediazonium cations and phenols take place most rapidly in *slightly* alkaline solution. Under these conditions an appreciable amount of the phenol is present as a phenoxide ion, ArO^-, and phenoxide ions are even more reactive toward electrophilic substitution than are phenols themselves. (Why?) If the solution is too alkaline (pH > 10), however, the arenediazonium salt itself reacts with hydroxide ion to form a relatively unreactive diazohydroxide or diazotate ion:





Openmirrors.com

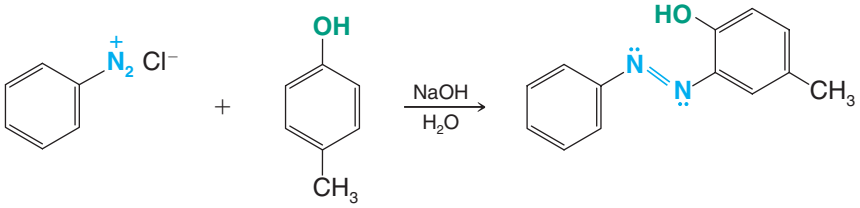
Couplings between arenediazonium cations and amines take place most rapidly in slightly acidic solutions (pH 5–7). Under these conditions the concentration of the arenediazonium cation is at a maximum; at the same time an excessive amount of the amine has not been converted to an unreactive aminium salt:



Amine (couples) **Aminium salt (does not couple)**

If the pH of the solution is lower than 5, the rate of amine coupling is low.

With phenols and aniline derivatives, coupling takes place almost exclusively at the para position if it is open. If it is not, coupling takes place at the ortho position.

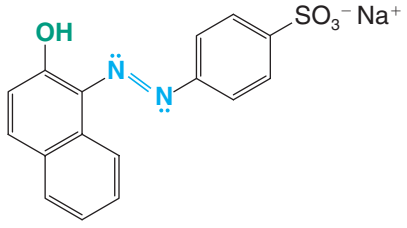


4-Methylphenol (*p*-cresol) **4-Methyl-2-(phenylazo)phenol**

Azo compounds are usually intensely colored because the azo (diazenediyl) linkage, —N═N—, brings the two aromatic rings into conjugation. This gives an extended system of delocalized π electrons and allows absorption of light in the visible region. Azo compounds, because of their intense colors and because they can be synthesized from relatively inexpensive compounds, are used extensively as *dyes*.

Azo dyes almost always contain one or more $—SO_3^-\ Na^+$ groups to confer water solubility on the dye and assist in binding the dye to the surfaces of polar fibers (wool, cotton, or nylon). Many dyes are made by coupling reactions of naphthylamines and naphthols.

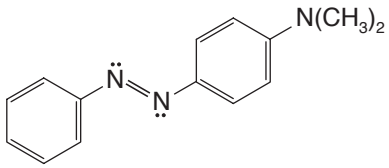
Orange II, a dye introduced in 1876, is made from 2-naphthol:



Orange II

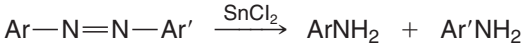
Review Problem 20.13 Outline a synthesis of orange II from 2-naphthol and *p*-aminobenzenesulfonic acid.

Review Problem 20.14 Butter yellow is a dye once used to color margarine. It has since been shown to be carcinogenic, and its use in food is no longer permitted. Outline a synthesis of butter yellow from benzene and *N*,*N*-dimethylaniline.



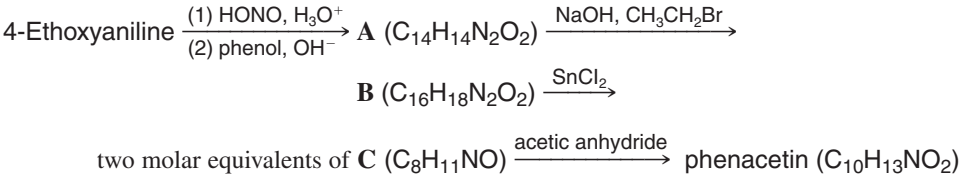
Butter yellow

Azo compounds can be reduced to amines by a variety of reagents including stannous chloride ($SnCl_2$):



$$Ar{-}N{=}N{-}Ar' \xrightarrow{SnCl_2} ArNH_2 + Ar'NH_2$$

This reduction can be useful in synthesis as the following example shows:



$$\text{4-Ethoxyaniline} \xrightarrow[\text{(2) phenol, } OH^-]{\text{(1) HONO, } H_3O^+} \mathbf{A}\ (C_{14}H_{14}N_2O_2) \xrightarrow{NaOH,\ CH_3CH_2Br} \mathbf{B}\ (C_{16}H_{18}N_2O_2) \xrightarrow{SnCl_2}$$

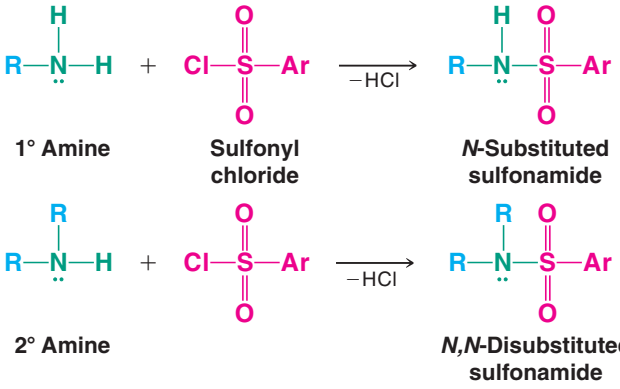
$$\text{two molar equivalents of } \mathbf{C}\ (C_8H_{11}NO) \xrightarrow{\text{acetic anhydride}} \text{phenacetin } (C_{10}H_{13}NO_2)$$

Give a structure for phenacetin and for the intermediates **A, B,** and **C.** (Phenacetin, formerly used as an analgesic, is also the subject of Problem 17.45.)

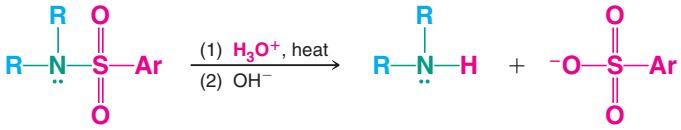
Review Problem 20.15

20.9 Reactions of Amines with Sulfonyl Chlorides

Primary and secondary amines react with sulfonyl chlorides to form **sulfonamides**:



When heated with aqueous acid, sulfonamides are hydrolyzed to amines:



$$R{-}N(R){-}S(=O)_2{-}Ar \xrightarrow[\text{(2) } OH^-]{\text{(1) } H_3O^+,\ \text{heat}} R{-}N(R){-}H + {}^-O{-}S(=O)_2{-}Ar$$

This hydrolysis is much slower, however, than hydrolysis of carboxamides.

20.9A The Hinsberg Test

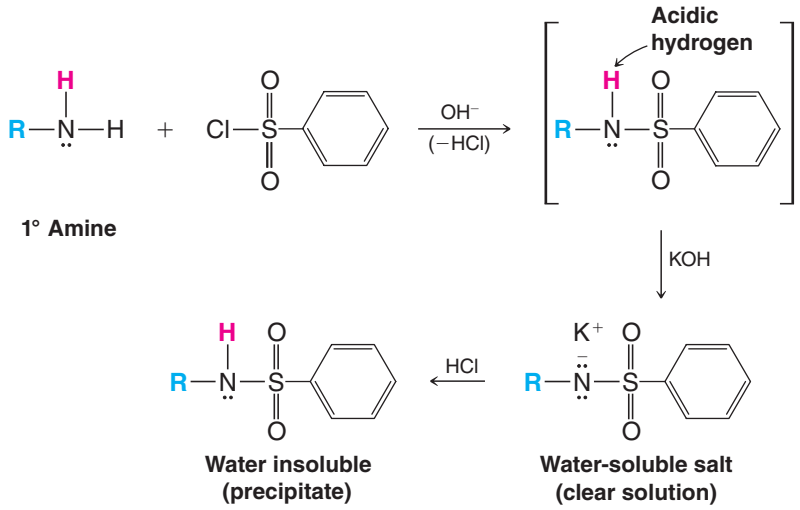
- Sulfonamide formation is the basis for a chemical test, called the Hinsberg test, that can be used to demonstrate whether an amine is primary, secondary, or tertiary.

A Hinsberg test involves two steps. First, a mixture containing a small amount of the amine and benzenesulfonyl chloride is shaken with *excess* potassium hydroxide. Next, after allowing time for a reaction to take place, the mixture is acidified. Each type of amine—primary, secondary, or tertiary—gives a different set of *visible* results after each of these two stages of the test.

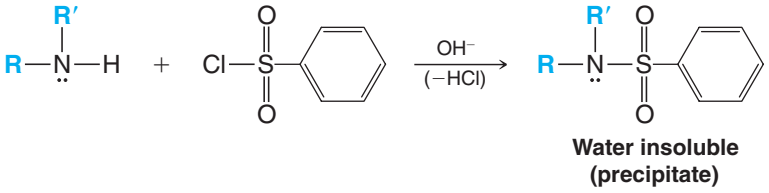
Primary amines react with benzenesulfonyl chloride to form *N*-substituted benzenesulfonamides. These, in turn, undergo acid–base reactions with the excess potassium hydroxide to form water-soluble potassium salts. (These reactions take place because the hydrogen attached to nitrogen is made acidic by the strongly electron-withdrawing $-SO_2-$ group.)

Openmirrors.com

At this stage our test tube contains a clear solution. Acidification of this solution will, in the next stage, cause the water-insoluble *N*-substituted sulfonamide to precipitate:



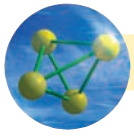
Secondary amines react with benzenesulfonyl chloride in aqueous potassium hydroxide to form insoluble *N*,*N*-disubstituted sulfonamides that precipitate after the first stage. *N*,*N*-Disubstituted sulfonamides do not dissolve in aqueous potassium hydroxide because they do not have an acidic hydrogen. Acidification of the mixture obtained from a secondary amine produces no visible result; the nonbasic *N*,*N*-disubstituted sulfonamide remains as a precipitate and no new precipitate forms:



If the amine is a tertiary amine and if it is water insoluble, no apparent change will take place in the mixture as we shake it with benzenesulfonyl chloride and aqueous KOH. When we acidify the mixture, the tertiary amine dissolves because it forms a water-soluble salt.

Review Problem 20.16 An amine **A** has the molecular formula C_7H_9N. Compound **A** reacts with benzenesulfonyl chloride in aqueous potassium hydroxide to give a clear solution; acidification of the solution gives a precipitate. When **A** is treated with $NaNO_2$ and HCl at 0–5°C, and then with 2-naphthol, an intensely colored compound is formed. Compound **A** gives a single strong IR absorption peak at 815 cm^{-1}. What is the structure of **A**?

Review Problem 20.17 Sulfonamides of primary amines are often used to synthesize *pure* secondary amines. Suggest how this synthesis is carried out.



THE CHEMISTRY OF . . .

Chemotherapy and Sulfa Drugs

Chemotherapy

Chemotherapy is defined as the use of chemical agents selectively to destroy infectious cells without simultaneously destroying the host. Although it may be difficult to believe (in this age of "wonder drugs"), chemotherapy is a relatively modern phenomenon. Before 1900 only three specific chemical remedies were known: mercury (for syphilis—but often with disastrous results), cinchona bark (for malaria), and ipecacuanha (for dysentery).

Paul Ehrlich's work in chemotherapy led to his sharing one-half of the 1908 Nobel Prize in Physiology or Medicine with Ilya Mechnikov.

Modern chemotherapy began with the work of Paul Ehrlich early in the twentieth century—particularly with his discovery in 1907 of the curative properties of a dye called trypan red I when used against experimental trypanosomiasis and with his discovery in 1909 of salvarsan as a remedy for syphilis. Ehrlich was awarded one-half of the Nobel Prize in Physiology or Medicine in 1908. He invented the term "chemotherapy," and in his research he sought what he called "magic bullets," that is, chemicals that would be toxic to infectious microorganisms but harmless to humans.

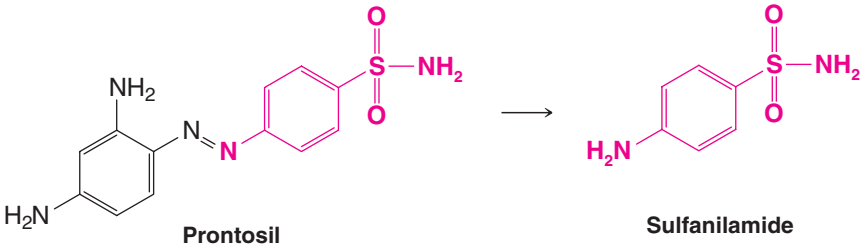
As a medical student, Ehrlich had been impressed with the ability of certain dyes to stain tissues selectively. Working on the idea that "staining" was a result of a chemical reaction between the tissue and the dye, Ehrlich sought dyes with selective affinities for microorganisms. He hoped that in this way he might find a dye that could be modified so as to render it specifically lethal to microorganisms.

Sulfa Drugs

Between 1909 and 1935, tens of thousands of chemicals, including many dyes, were tested by Ehrlich and others in a search for such "magic bullets." Very few compounds, however, were found to have any promising effect. Then, in 1935, an amazing event happened. The daughter of Gerhard Domagk, a doctor employed by a German dye manufacturer, contracted a streptococcal infection from a pin prick. As his daughter neared death, Domagk decided to give her an oral dose of a dye called prontosil. Prontosil had been developed at Domagk's firm (I. G. Farbenindustrie), and tests with mice had shown that prontosil inhibited the growth of streptococci. Within a short time the little girl recovered. Domagk's gamble not only saved his daughter's life, but it also initiated a new and spectacularly productive phase in modern chemotherapy. G. Domagk was awarded the Nobel Prize in Physiology or Medicine in 1939 but was unable to accept it until 1947.

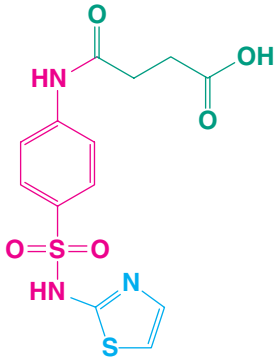
Gerhard Domagk won the 1939 Nobel Prize in Physiology or Medicine for discovering the antibacterial effects of prontosil.

In 1936, Ernest Fourneau of the Pasteur Institute in Paris demonstrated that prontosil breaks down in the human body to produce sulfanilamide, and that sulfanilamide is the actual active agent against streptococci. Prontosil, therefore, is a prodrug because it is converted to the active compound *in vivo*.

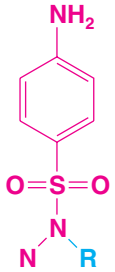


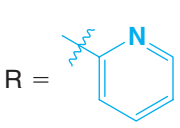
Prontosil **Sulfanilamide**

Fourneau's announcement of this result set in motion a search for other chemicals (related to sulfanilamide) that might have even better chemotherapeutic effects. Literally thousands of chemical variations were played on the sulfanilamide theme; the structure of sulfanilamide was varied in almost every imaginable way. The best therapeutic results were obtained from compounds in which one hydrogen of the $-SO_2NH_2$ group was replaced by some other group, usually a heterocyclic ring (shown in blue in the following structures). Among the most successful variations were the following compounds. Sulfanilamide itself is too toxic for general use.

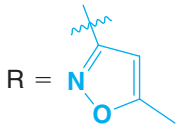


Succinylsulfathiazole

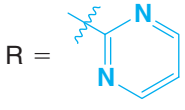




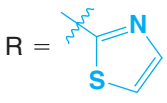
Sulfapyridine



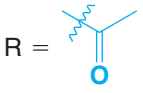
Sulfamethoxazole



Sulfadiazene



Sulfathiazole



Sulfacetamide

Openmirrors.com

Sulfapyridine was shown to be effective against pneumonia in 1938. (Before that time pneumonia epidemics had brought death to tens of thousands.) Sulfacetamide was first used successfully in treating urinary tract infections in 1941. Succinoylsulfathiazole and the related compound phthalylsulfathiazole were used as chemotherapeutic agents against infections of the gastrointestinal tract beginning in 1942. (Both compounds are slowly hydrolyzed internally to sulfathiazole.) Sulfathiazole saved the lives of countless wounded soldiers during World War II.

In 1940 a discovery by D. D. Woods laid the groundwork for our understanding of how the **sulfa drugs** work. Woods observed that the inhibition of growth of certain microorganisms by sulfanilamide is competitively overcome by *p*-aminobenzoic acid. Woods noticed the structural similarity between the two compounds (Fig. 20.4) and reasoned that the two compounds compete with each other in some essential metabolic process.

Essential Nutrients and Antimetabolites

All higher animals and many microorganisms lack the biochemical ability to synthesize certain essential organic compounds. These essential nutrients include vitamins, certain amino acids, unsaturated carboxylic acids, purines, and pyrimidines. The aromatic amine *p*-aminobenzoic acid is an essential nutrient for those bacteria that are sensitive to sulfanilamide therapy. Enzymes within these bacteria use *p*-aminobenzoic acid to synthesize another essential compound called *folic acid*:

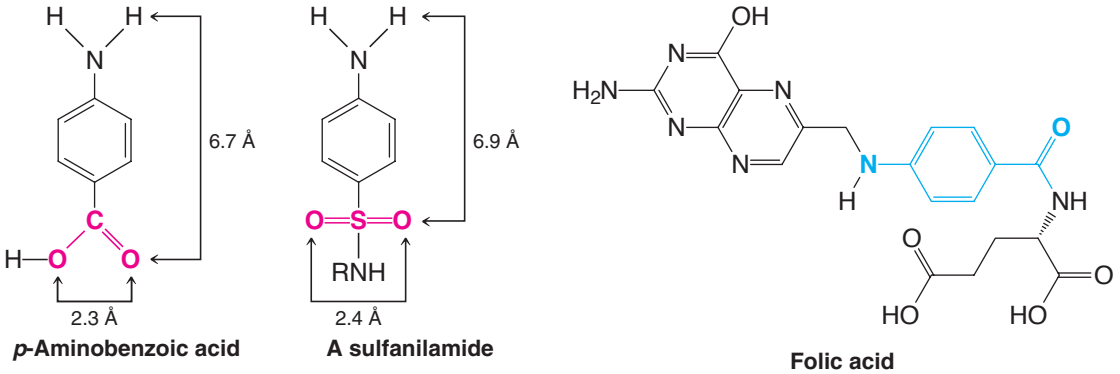
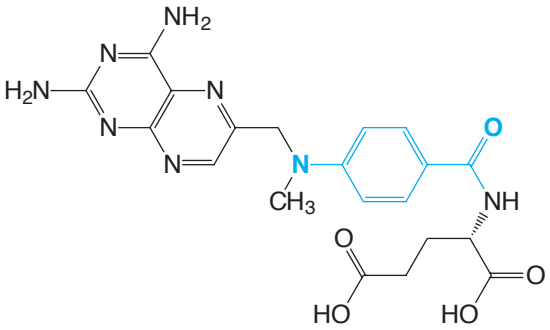


Figure 20.4 The structural similarity of *p*-aminobenzoic acid and a sulfanilamide. (Reprinted with permission of John Wiley and Sons, Inc. from Korolkovas, *Essentials of Molecular Pharmacology*, Copyright 1970.)

Chemicals that inhibit the growth of microbes are called *antimetabolites*. The sulfanilamides are antimetabolites for those bacteria that require *p*-aminobenzoic acid. The sulfanilamides apparently inhibit those enzymatic steps of the bacteria that are involved in the synthesis of folic acid. The bacterial enzymes are apparently unable to distinguish between a molecule of a sulfanilamide and a molecule of *p*-aminobenzoic acid; thus, sulfanilamide inhibits the bacterial enzyme. Because the microorganism is unable to synthesize enough folic acid when sulfanilamide is present, it dies. Humans are unaffected by sulfanilamide therapy because we derive our folic acid from dietary sources (folic acid is a vitamin) and do not synthesize it from *p*-aminobenzoic acid.

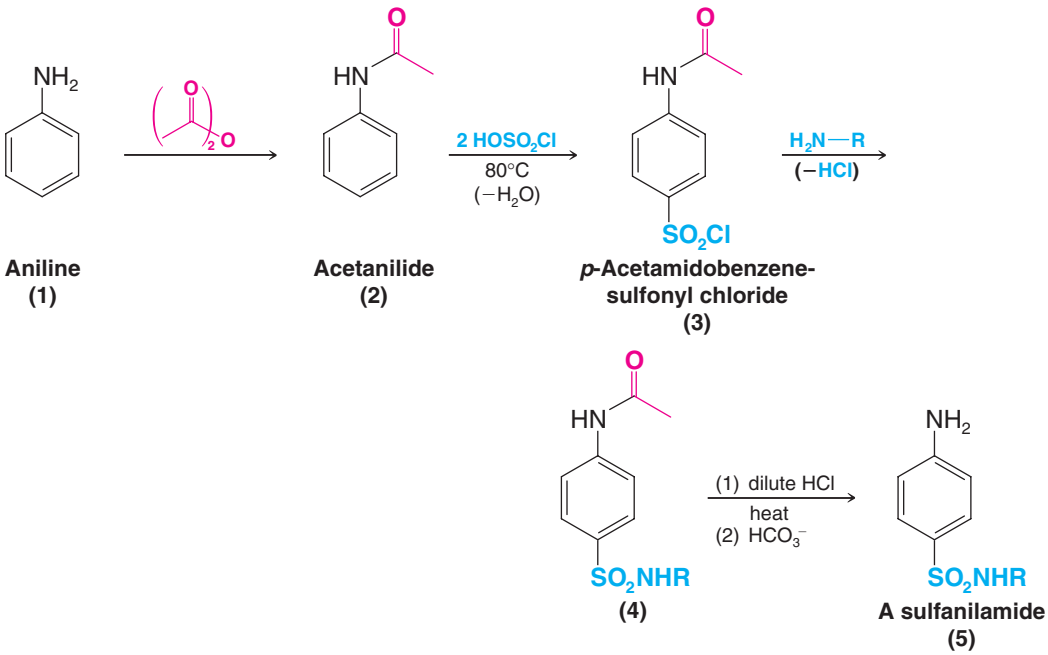
The discovery of the mode of action of the sulfanilamides has led to the development of many new and effective antimetabolites. One example is *methotrexate*, a derivative of folic acid that has been used successfully in treating certain carcinomas as well as rheumatoid arthritis:



Methotrexate, by virtue of its resemblance to folic acid, can enter into some of the same reactions as folic acid, but it cannot serve the same function, particularly in important reactions involved in cell division. Although methotrexate is toxic to all dividing cells, those cells that divide most rapidly—*cancer cells*—are most vulnerable to its effect.

20.10 Synthesis of Sulfa Drugs

Sulfanilamides can be synthesized from aniline through the following sequence of reactions:



Acetylation of aniline produces acetanilide **(2)** and protects the amino group from the reagent to be used next. Treatment of **2** with chlorosulfonic acid brings about an electrophilic aromatic substitution reaction and yields *p*-acetamidobenzenesulfonyl chloride **(3).** Addition of ammonia or a primary amine gives the diamide, **4** (an amide of both a carboxylic acid and a sulfonic acid). Finally, refluxing **4** with dilute hydrochloric acid selectively hydrolyzes the carboxamide linkage and produces a sulfanilamide. (Hydrolysis of carboxamides is much more rapid than that of sulfonamides.)

Review Problem 20.18

(a) Starting with aniline and assuming that you have 2-aminothiazole available, show how you would synthesize sulfathiazole. **(b)** How would you convert sulfathiazole to succinylsulfathiazole?

2-Aminothiazole

20.11 Analysis of Amines

20.11A Chemical Analysis

Amines are characterized by their basicity and, thus, by their ability to dissolve in dilute aqueous acid (Sections 20.3A, 20.3E). Moist pH paper can be used to test for the presence of an amine functional group in an unknown compound. If the compound is an amine, the pH paper shows the presence of a base. The unknown amine can then readily be classified as 1°, 2°, or 3° by IR spectroscopy (see below). Primary, secondary, and tertiary amines can also be distinguished from each other on the basis of the Hinsberg test (Section 20.9A). Primary aromatic amines are often detected through diazonium salt formation and subsequent coupling with 2-naphthol to form a brightly colored azo dye (Section 20.8).

Openmirrors.com

20.11B Spectroscopic Analysis

Infrared Spectra Primary and secondary amines are characterized by IR absorption bands in the 3300–3555-cm^{-1} region that arise from N—H stretching vibrations. Primary amines give two bands in this region (see Fig. 20.5); secondary amines generally give only one. Tertiary amines, because they have no N—H group, do not absorb in this region. Absorption bands arising from C—N stretching vibrations of aliphatic amines occur in the 1020–1220-cm^{-1} region but are usually weak and difficult to identify. Aromatic amines generally give a strong C—N stretching band in the 1250–1360-cm^{-1} region. Figure 20.5 shows an annotated IR spectrum of 4-methylaniline.

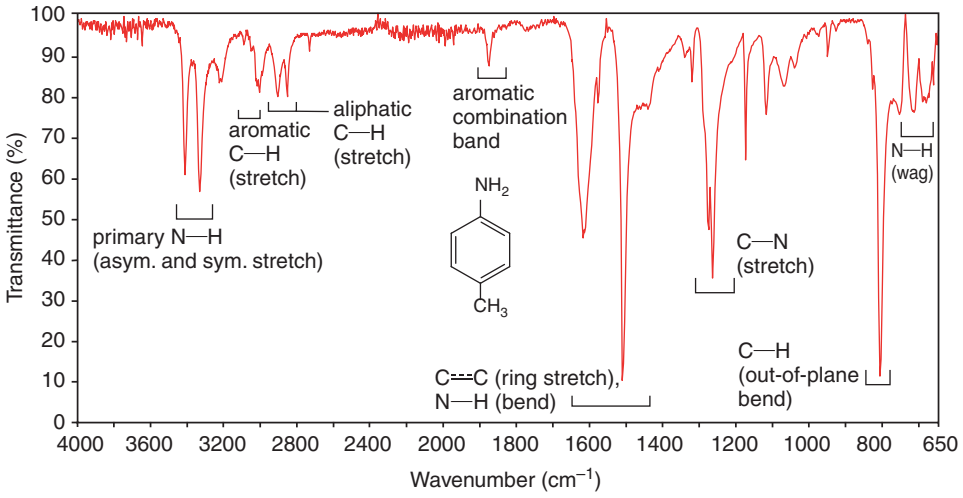


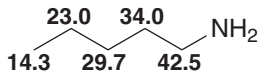
Figure 20.5 Annotated IR spectrum of 4-methylaniline.

^{1}H NMR Spectra Primary and secondary amines show N—H proton signals in the region δ 0.5–5. These signals are usually broad, and their exact position depends on the nature of the solvent, the purity of the sample, the concentration, and the temperature. Because of proton exchange, N—H protons are not usually coupled to protons on adjacent carbons. As such, they are difficult to identify and are best detected by proton counting or by adding a small amount of D_2O to the sample. Exchange of N—D deuterons for the N—H protons takes place, and the N—H signal disappears from the spectrum.

Protons on the α carbon of an aliphatic amine are deshielded by the electron-withdrawing effect of the nitrogen and absorb typically in the δ 2.2–2.9 region; protons on the β carbon are not deshielded as much and absorb in the range δ 1.0–1.7.

Figure 20.6 (next page) shows an annotated ^{1}H NMR spectrum of diisopropylamine.

^{13}C NMR Spectra The α carbon of an aliphatic amine experiences deshielding by the electronegative nitrogen, and its absorption is shifted downfield, typically appearing at δ 30–60. The shift is not as great as for the α carbon of an alcohol (typically δ 50–75), however, because nitrogen is less electronegative than oxygen. The downfield shift is even less for the β carbon, and so on down the chain, as the chemical shifts of the carbons of pentylamine show:



^{13}C NMR chemical shifts (δ)

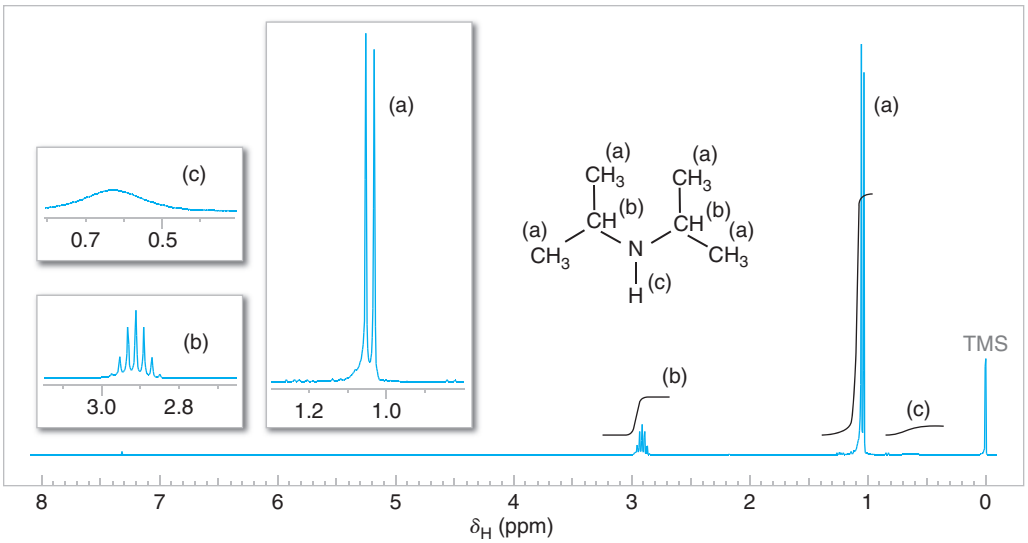


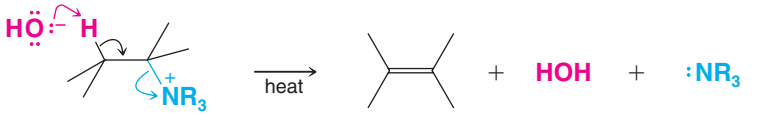
Figure 20.6 The 300-MHz ^{1}H NMR spectrum of diisopropylamine. Note the integral for the broad NH peak at approximately δ 0.7. Vertical expansions are not to scale.

Mass Spectra of Amines The molecular ion in the mass spectrum of an amine has an odd number mass (unless there is an even number of nitrogen atoms in the molecule). The peak for the molecular ion is usually strong for aromatic and cyclic aliphatic amines but weak for acyclic aliphatic amines. Cleavage between the α and β carbons of aliphatic amines is a common mode of fragmentation.

20.12 *Eliminations Involving Ammonium Compounds*

20.12A The Hofmann Elimination

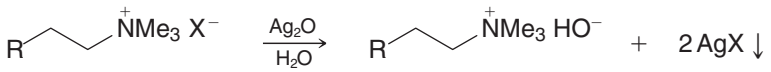
All of the eliminations that we have described so far have involved electrically neutral substrates. However, eliminations are known in which the substrate bears a positive charge. One of the most important of these is the E2-type elimination that takes place when a quaternary ammonium hydroxide is heated. The products are an alkene, water, and a tertiary amine:



A quaternary ammonium hydroxide — **An alkene** — **A tertiary amine**

This reaction was discovered in 1851 by August W. von Hofmann and has since come to bear his name.

Quaternary ammonium hydroxides can be prepared from quaternary ammonium halides in aqueous solution through the use of silver oxide or an ion exchange resin:



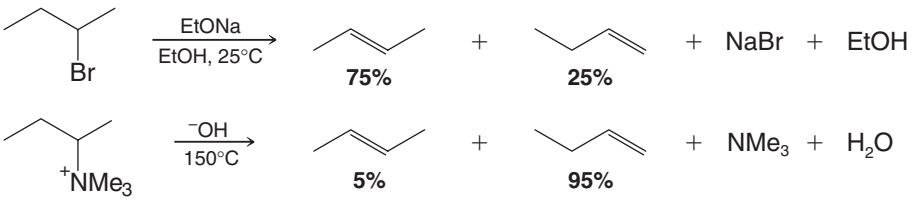
A quaternary ammonium halide — **A quaternary ammonium hydroxide**

Silver halide precipitates from the solution and can be removed by filtration. The quaternary ammonium hydroxide can then be obtained by evaporation of the water.

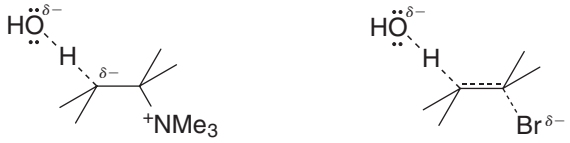
Although most eliminations involving neutral substrates tend to follow the *Zaitsev rule* (Section 7.6B), eliminations with charged substrates tend to follow what is called the

Openmirrors.com

Hofmann rule and *yield mainly the least substituted alkene*. We can see an example of this behavior if we compare the following reactions:



The precise mechanistic reasons for these differences are complex and are not yet fully understood. One possible explanation is that the transition states of elimination reactions with charged substrates have considerable carbanionic character. Therefore, these transition states show little resemblance to the final alkene product and are not stabilized appreciably by a developing double bond:

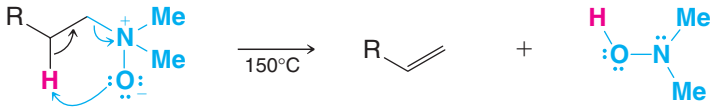


Carbanion-like transition state (gives Hofmann orientation) | **Alkene-like transition state (gives Zaitsev orientation)**

With a charged substrate, the base attacks the most acidic hydrogen instead. A primary hydrogen atom is more acidic because its carbon atom bears only one electron-releasing group.

20.12B The Cope Elimination

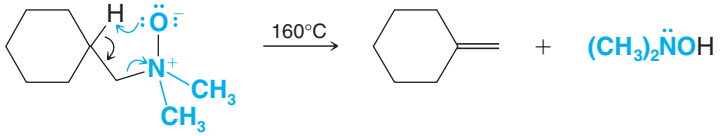
Tertiary amine oxides undergo the elimination of a dialkylhydroxylamine when they are heated. The reaction is called the Cope elimination, it is a syn elimination and proceeds through a cyclic transition state.



A tertiary amine oxide | **An alkene** | ***N,N*-Dimethylhydroxylamine**

Tertiary amine oxides are easily prepared by treating tertiary amines with hydrogen peroxide (Section 20.5A).

The Cope elimination is useful synthetically. Consider the following synthesis of methylenecyclohexane:

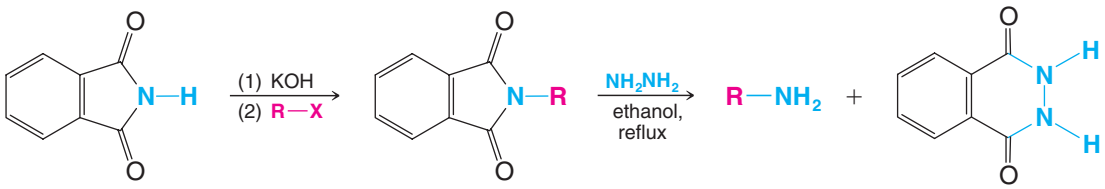


98%

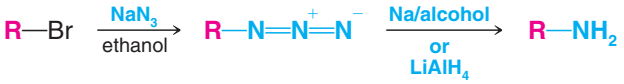
20.13 Summary of Preparations and Reactions of Amines

Preparation of Amines

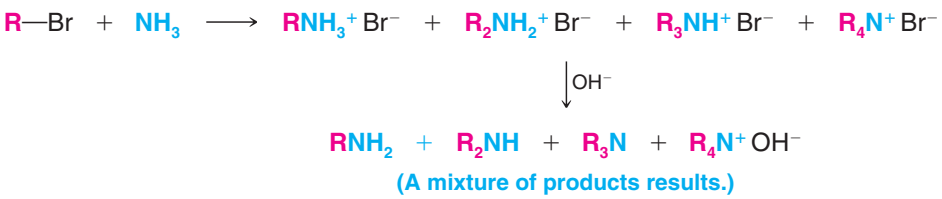
1. Gabriel synthesis (discussed in Section 20.4A):



2. By reduction of alkyl azides (discussed in Section 20.4A):

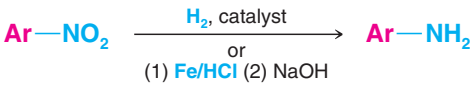


3. By amination of alkyl halides (discussed in Section 20.4A):

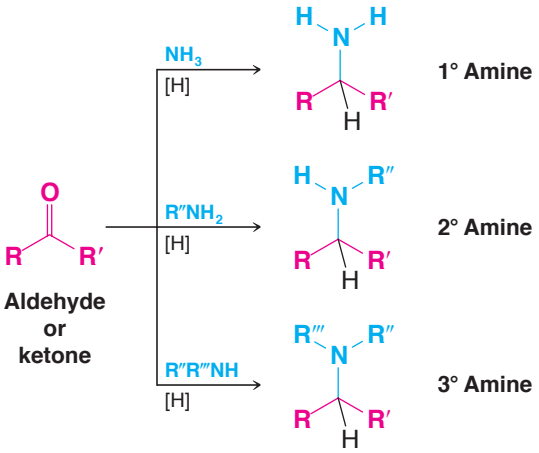


(R = a 1° alkyl group)

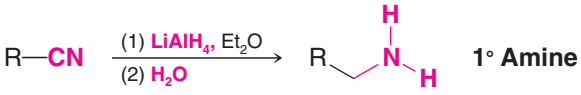
4. By reduction of nitroarenes (discussed in Section 20.4B):

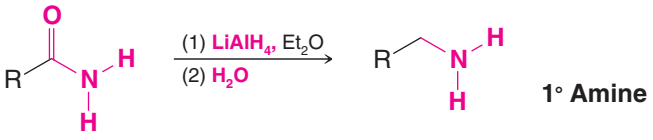


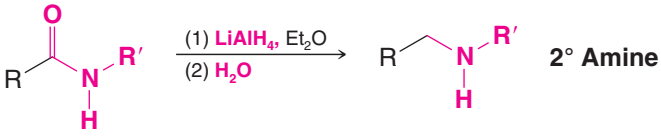
5. By reductive amination (discussed in Section 20.4C):

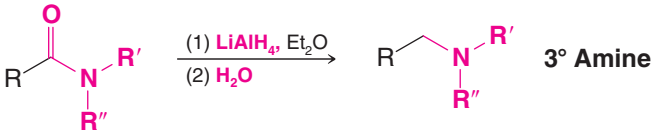


6. By reduction of nitriles, oximes, and amides (discussed in Section 20.4D):





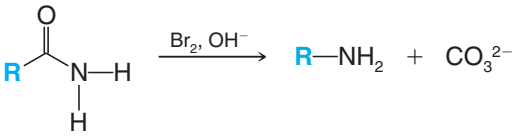




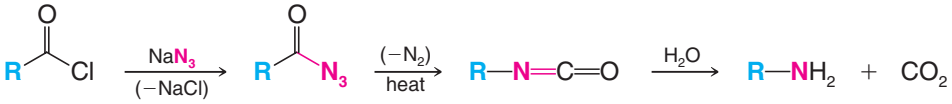
Openmirrors.com

7. Through the Hofmann and Curtius rearrangements (discussed in Section 20.4E):

Hofmann Rearrangement



Curtius Rearrangement

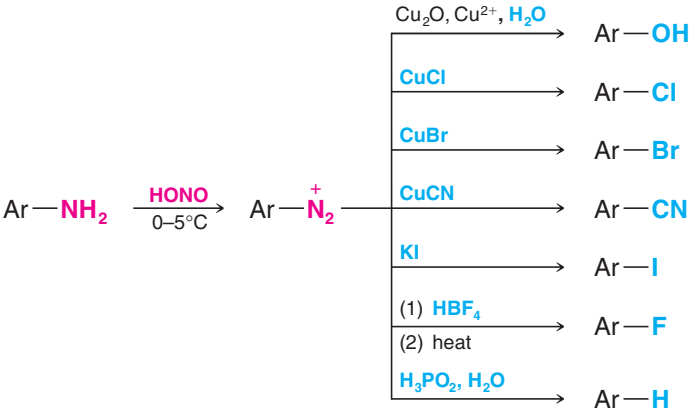


Reactions of Amines

1. As bases (discussed in Section 20.3):

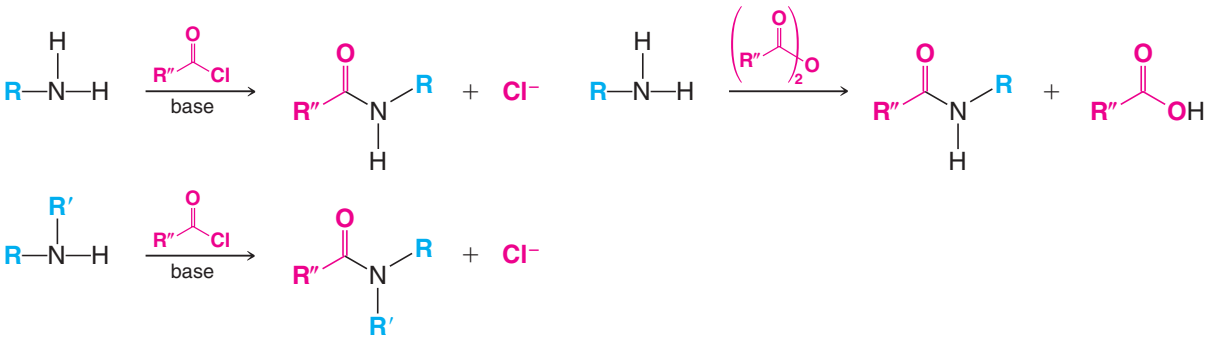
(R, R′, and/or R″ may be alkyl, H, or Ar)

2. Diazotization of 1° arylamines and replacement of, or coupling with, the diazonium group (discussed in Sections 20.7 and 20.8):



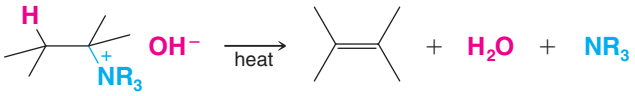
3. Conversion to sulfonamides (discussed in Section 20.9):

4. Conversion to amides (discussed in Section 17.8):

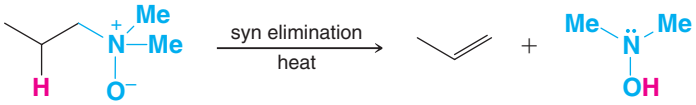


5. Hofmann and Cope eliminations (discussed in Section 20.12):

Hofmann Elimination



Cope Elimination



Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com)

Problems

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

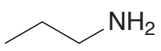
NOMENCLATURE

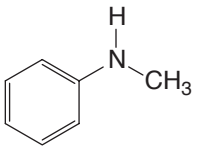
20.19 Write structural formulas for each of the following compounds:

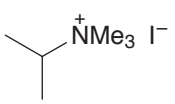
(a) Benzylmethylamine
(b) Triisopropylamine
(c) *N*-Ethyl-*N*-methylaniline
(d) *m*-Toluidine
(e) 2-Methylpyrrole
(f) *N*-Ethylpiperidine
(g) *N*-Ethylpyridinium bromide
(h) 3-Pyridinecarboxylic acid
(i) Indole
(j) Acetanilide
(k) Dimethylaminium chloride
(l) 2-Methylimidazole
(m) 3-Aminopropan-1-ol
(n) Tetrapropylammonium chloride
(o) Pyrrolidine
(p) *N*,*N*-Dimethyl-*p*-toluidine
(q) 4-Methoxyaniline
(r) Tetramethylammonium hydroxide
(s) *p*-Aminobenzoic acid
(t) *N*-Methylaniline

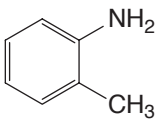
Openmirrors.com

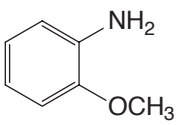
20.20 Give common or systematic names for each of the following compounds:

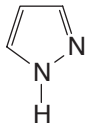
(a) 

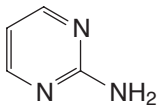
(b) 

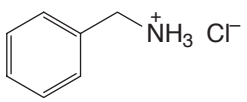
(c) 

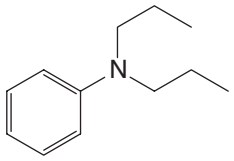
(d) 

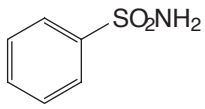
(e) 

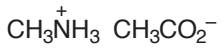
(f) 

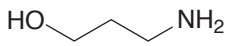
(g) 

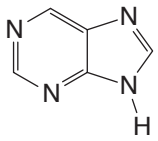
(h) 

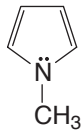
(i) 

(j) 

(k) 

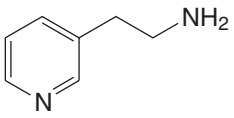
(l) 

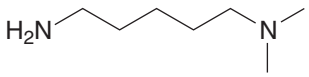
(m) 

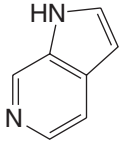
(n) 

AMINE SYNTHESIS AND REACTIVITY

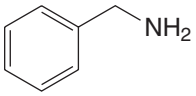
20.21 Which is the most basic nitrogen in each compound. Explain your choices.

(a) 

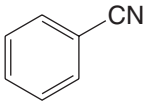
(b) 

(c) 

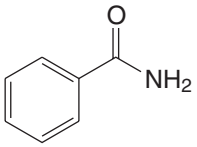
20.22 Show how you might prepare benzylamine from each of the following compounds:



Benzylamine

(a) 

Benzonitrile

(b) 

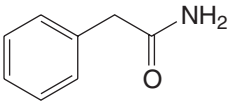
Benzamide

(c) Benzyl bromide (two ways)

(d) Benzyl tosylate

(e) Benzaldehyde

(f) Phenylnitromethane

(g) 

Phenylacetamide

20.23 Show how you might prepare aniline from each of the following compounds:

(a) Benzene **(b)** Bromobenzene **(c)** Benzamide

20.24 Show how you might synthesize each of the following compounds from 1-butanol:

(a) Butylamine (free of 2° and 3° amines)

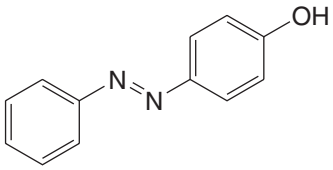
(b) Pentylamine

(c) Propylamine

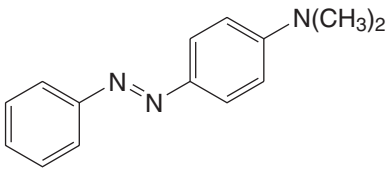
(d) Butylmethylamine

20.25 Show how you might convert aniline into each of the following compounds. (You need not repeat steps carried out in earlier parts of this problem.)

(a) Acetanilide
(b) *N*-Phenylphthalimide
(c) *p*-Nitroaniline
(d) Sulfanilamide
(e) *N*,*N*-Dimethylaniline
(f) Fluorobenzene
(g) Chlorobenzene
(h) Bromobenzene
(i) Iodobenzene
(j) Benzonitrile
(k) Benzoic acid
(l) Phenol
(m) Benzene
(n)

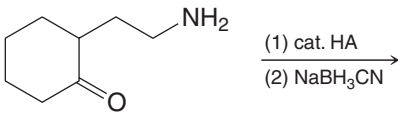


(o)

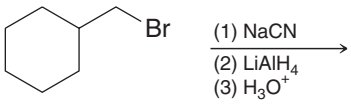


20.26 Provide the major organic product from each of the following reactions.

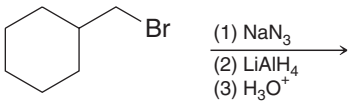
(a)



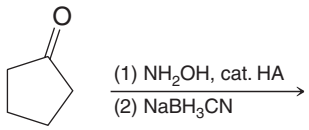
(b)



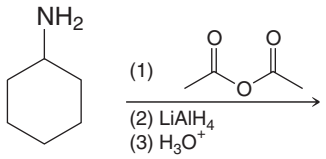
(c)



(d)



(e)



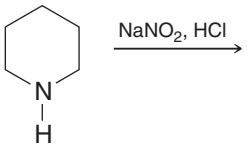
20.27 What products would you expect to be formed when each of the following amines reacts with aqueous sodium nitrite and hydrochloric acid?

(a) Propylamine
(b) Dipropylamine
(c) *N*-Propylaniline
(d) *N*,*N*-Dipropylaniline
(e) *p*-Propylaniline

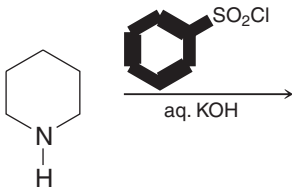
20.28 **(a)** What products would you expect to be formed when each of the amines in the preceding problem reacts with benzenesulfonyl chloride and excess aqueous potassium hydroxide? **(b)** What would you observe in each reaction? **(c)** What would you observe when the resulting solution or mixture is acidified?

20.29 What product would you expect to obtain from each of the following reactions?

(a)



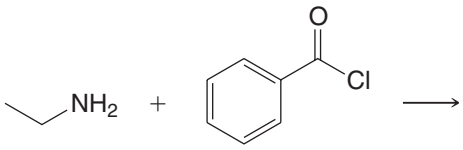
(b)



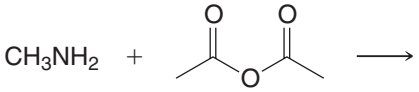
Openmirrors.com

20.30 Give structures for the products of each of the following reactions:

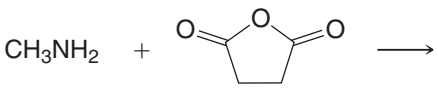
(a)



(b)

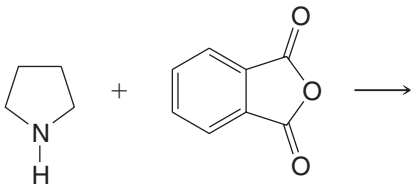


(c)

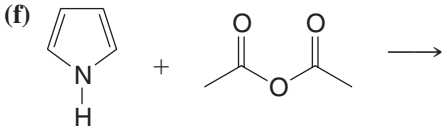


(d) Product of (c) $\xrightarrow{\text{heat}}$

(e)



(f)



(g) Aniline + propanoyl chloride $\longrightarrow$

(h) Tetraethylammonium hydroxide $\xrightarrow{\text{heat}}$

(i) *p*-Toluidine + Br_2 (excess) $\xrightarrow[H_2O]{}$

20.31 Starting with benzene or toluene, outline a synthesis of each of the following compounds using diazonium salts as intermediates. (You need not repeat syntheses carried out in earlier parts of this problem.)

(a) *p*-Fluorotoluene

(b) *o*-Iodotoluene

(c) *p*-Cresol

(d) *m*-Dichlorobenzene

(e) *m*-$C_6H_4(CN)_2$

(f) *m*-Bromobenzonitrile

(g) 1,3-Dibromo-5-nitrobenzene

(h) 3,5-Dibromoaniline

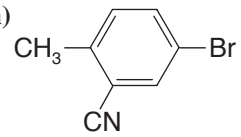
(i) 3,4,5-Tribromophenol

(j) 3,4,5-Tribromobenzonitrile

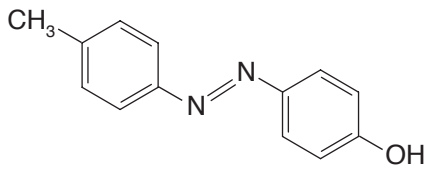
(k) 2,6-Dibromobenzoic acid

(l) 1,3-Dibromo-2-iodobenzene

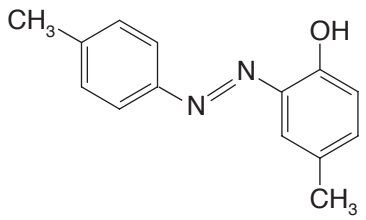
(m)



(n)



(o)



20.32 Write equations for simple chemical tests that would distinguish between

(a) Benzylamine and benzamide

(b) Allylamine and propylamine

(c) *p*-Toluidine and *N*-methylaniline

(d) Cyclohexylamine and piperidine

(e) Pyridine and benzene

(f) Cyclohexylamine and aniline

(g) Triethylamine and diethylamine

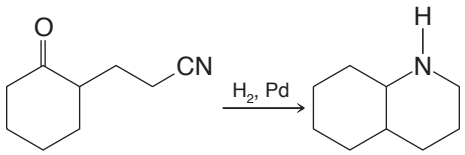
(h) Tripropylaminium chloride and tetrapropylammonium chloride

(i) Tetrapropylammonium chloride and tetrapropylammonium hydroxide

20.33 Describe with equations how you might separate a mixture of aniline, *p*-cresol, benzoic acid, and toluene using ordinary laboratory reagents.

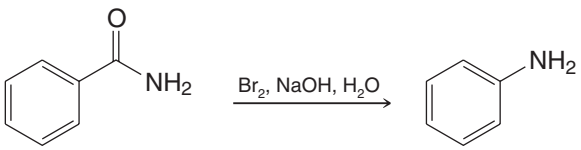
MECHANISMS

20.34 Using reactions that we have studied in this chapter, propose a mechanism that accounts for the following reaction:

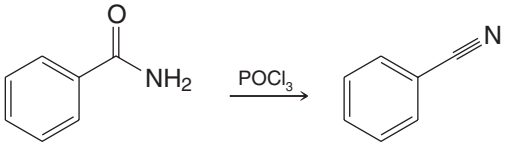


20.35 Provide a detailed mechanism for each of the following reactions.

(a)



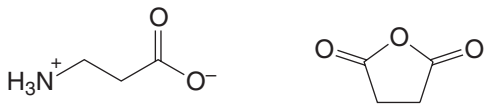
(b)



20.36 Suggest an experiment to test the proposition that the Hofmann reaction is an intramolecular rearrangement, that is, one in which the migrating R group never fully separates from the amide molecule.

GENERAL SYNTHESIS

20.37 Show how you might synthesize β-aminopropionic acid from succinic anhydride. (β-Aminopropionic acid is used in the synthesis of pantothenic acid, a precursor of coenzyme A.)



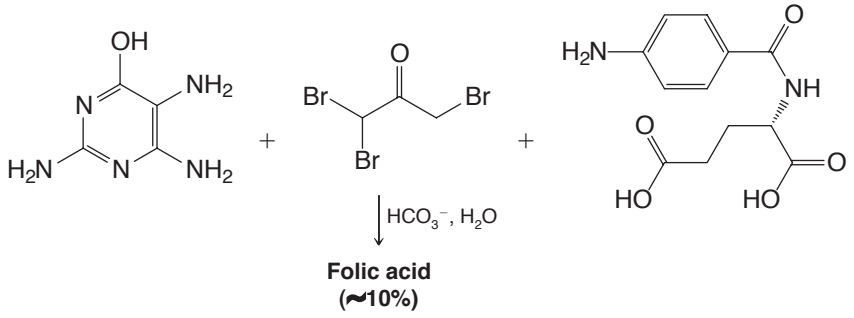
β-Aminopropanoic acid **Succinic anhydride**

20.38 Show how you might synthesize each of the following from the compounds indicated and any other needed reagents:

(a) $Me_3N^+(CH_2)_{10}N^+Me_3\ 2Br^-$ from 1,10-decanediol

(b) Succinylcholine bromide (see "The Chemistry of. . . Biologically Important Amines" in Section 20.3) from succinic acid, 2-bromoethanol, and trimethylamine

20.39 A commercial synthesis of folic acid consists of heating the following three compounds with aqueous sodium bicarbonate. Propose reasonable mechanisms for the reactions that lead to folic acid. Hint: The first step involves formation of an imine between the lower right NH_2 group of the heterocyclic amine and the ketone.



Folic acid (~10%)

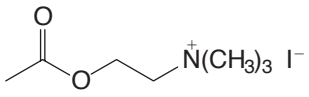
Openmirrors.com

20.40 Give structures for compounds **R–W:**

N-Methylpiperidine $\xrightarrow{CH_3I}$ **R** ($C_7H_{16}NI$) $\xrightarrow[H_2O]{Ag_2O}$ **S** ($C_7H_{17}NO$) $\xrightarrow[\text{heat}]{(-H_2O)}$

T ($C_7H_{15}N$) $\xrightarrow{CH_3I}$ **U** ($C_5H_{18}NI$) $\xrightarrow[H_2O]{Ag_2O}$ **V** ($C_8H_{19}NO$) $\xrightarrow{\text{heat}}$ **W** (C_5H_8) + H_2O + $(CH_3)_3N$

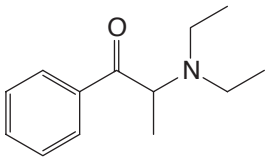
20.41 Outline a synthesis of acetylcholine iodide using dimethylamine, oxirane, iodomethane, and acetyl chloride as starting materials.



Acetylcholine iodide

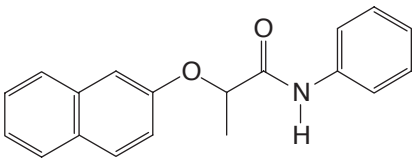
20.42 Ethanolamine, $HOCH_2CH_2NH_2$, and diethanolamine, $(HOCH_2CH_2)_2NH$, are used commercially to form emulsifying agents and to absorb acidic gases. Propose syntheses of these two compounds.

20.43 Diethylpropion (shown here) is a compound used in the treatment of anorexia. Propose a synthesis of diethylpropion starting with benzene and using any other needed reagents.



Diethylpropion

20.44 Using as starting materials 2-chloropropanoic acid, aniline, and 2-naphthol, propose a synthesis of naproanilide, a herbicide used in rice paddies in Asia:



Naproanilide

SPECTROSCOPY

20.45 When compound **W** ($C_{15}H_{17}N$) is treated with benzenesulfonyl chloride and aqueous potassium hydroxide, no apparent change occurs. Acidification of this mixture gives a clear solution. The ^1H NMR spectrum of **W** is shown in Fig. 20.7. Propose a structure for **W.**

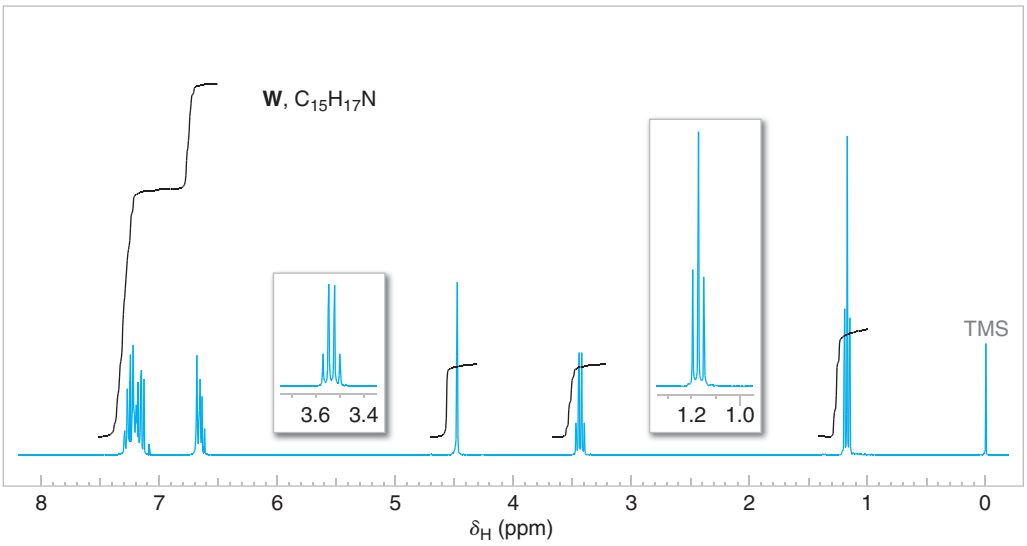


Figure 20.7 The 300-MHz ^1H NMR spectrum of compound **W**, Problem 20.45. Expansions of the signals are shown in the offset plots.

20.46 Propose structures for compounds **X, Y,** and **Z:**

$$\mathbf{X}\ (C_7H_7Br) \xrightarrow{NaCN} \mathbf{Y}\ (C_8H_7N) \xrightarrow{LiAlH_4} \mathbf{Z}\ (C_8H_{11}N)$$

The ^{1}H NMR spectrum of **X** gives two signals, a multiplet at δ 7.3 (5H) and a singlet at δ 4.25 (2H); the 680–840-cm^{-1} region of the IR spectrum of **X** shows peaks at 690 and 770 cm^{-1}. The ^{1}H NMR spectrum of **Y** is similar to that of **X**: multiplet at δ 7.3 (5H), singlet at δ 3.7 (2H). The ^{1}H NMR spectrum of **Z** is shown in Fig. 20.8.

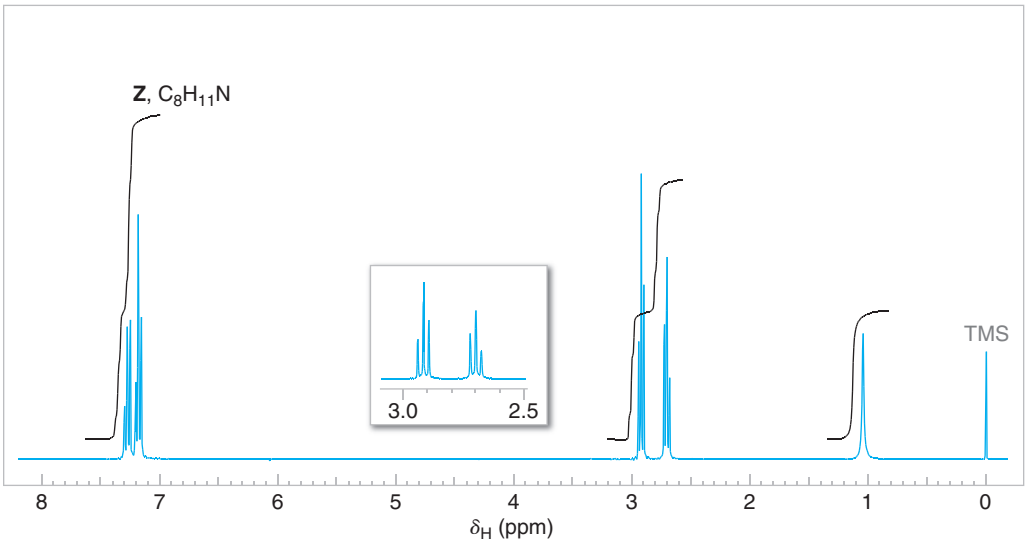


Figure 20.8 The 300-MHz ^{1}H NMR spectrum of compound **Z**, Problem 20.46. Expansion of the signals is shown in the offset plot.

20.47 Compound **A** ($C_{10}H_{15}N$) is soluble in dilute HCl. The IR absorption spectrum shows two bands in the 3300–3500-cm^{-1} region. The broadband proton-decoupled ^{13}C spectrum of **A** is given in Fig. 20.9. Propose a structure for **A.**

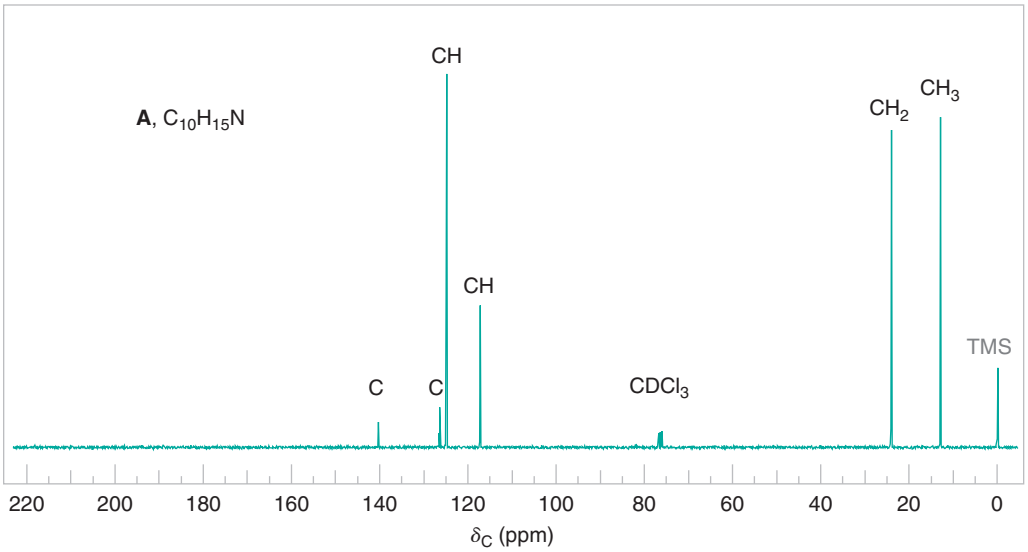


Figure 20.9 The broadband proton-decoupled ^{13}C NMR spectra of compounds **A, B,** and **C**, Problems 20.47–20.49. Information from the DEPT ^{13}C NMR spectra is given above each peak.

Openmirrors.com

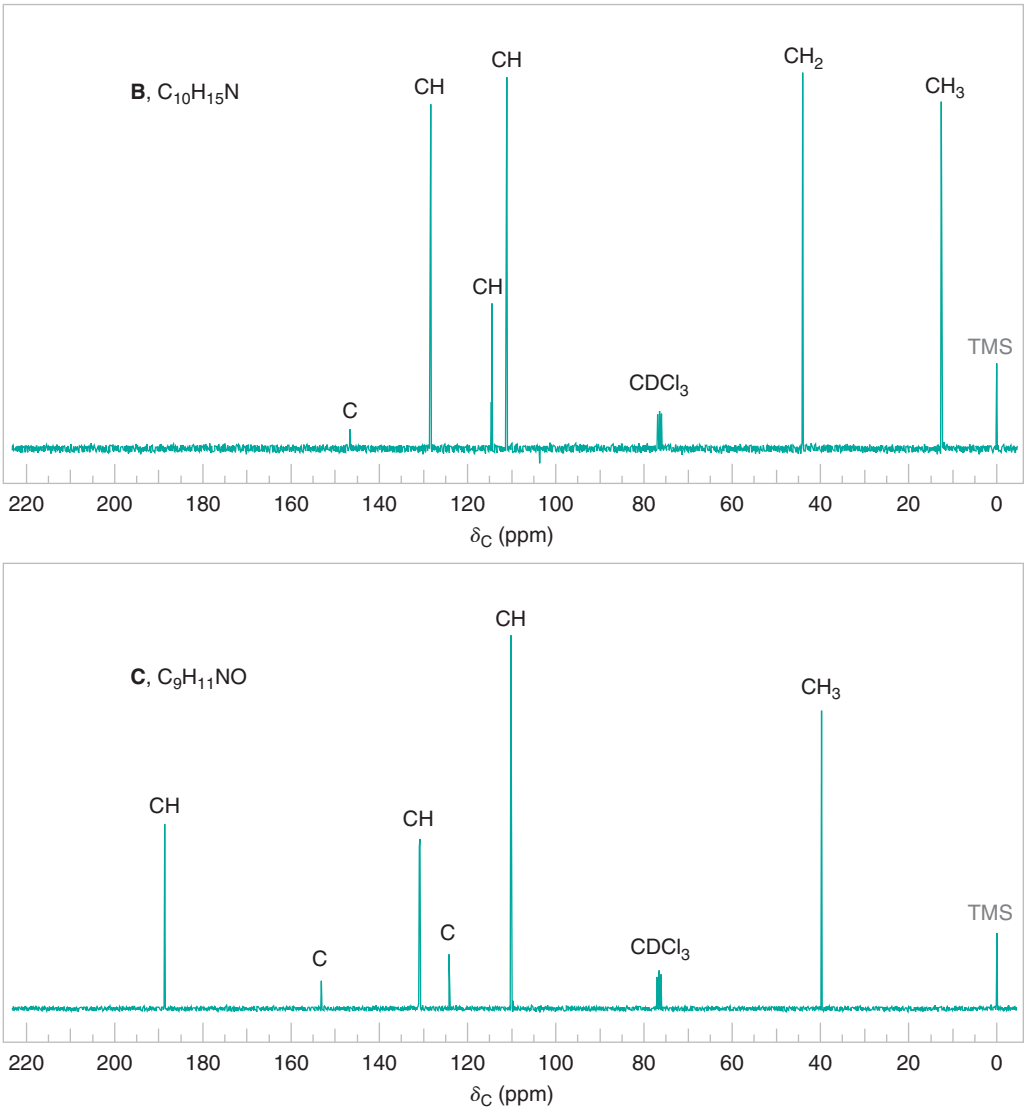


Figure 20.9 *(continued)*

20.48 Compound **B,** an isomer of **A** (Problem 20.47), is also soluble in dilute HCl. The IR spectrum of **B** shows no bands in the 3300–3500-cm^{-1} region. The broadband proton-decoupled ^{13}C spectrum of **B** is given in Fig. 20.9. Propose a structure for **B.**

20.49 Compound **C** ($C_9H_{11}NO$) gives a positive Tollens' test (can be oxidized to a carboxylic acid) and is soluble in dilute HCl. The IR spectrum of **C** shows a strong band near 1695 cm^{-1} but shows no bands in the 3300–3500-cm^{-1} region. The broadband proton-decoupled ^{13}C NMR spectrum of **C** is shown in Fig. 20.9. Propose a structure for **C.**

Challenge Problems

20.50 When phenyl isothiocyanate, $C_6H_5N{=}C{=}S$, is reduced with lithium aluminum hydride, the product formed has these spectral data:

MS (*m/z*): 107, 106

IR (cm^{-1}): 3330 (sharp), 3050, 2815, 760, 700

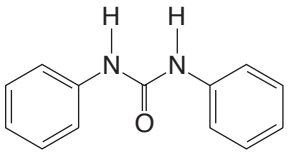
^{1}H NMR (δ): 2.7 (s, 3H), 3.5 (broad, 1H), 6.6 (d, 2H), 6.7 (t, 1H) 7.2 (t, 2H)

^{13}C NMR (δ): 30 (CH_3), 112 (CH), 117 (CH), 129 (CH), 150 (C)

(a) What is the structure of the product?

(b) What is the structure that accounts for the 106 *m/z* peak and how is it formed? (It is an iminium ion.)

20.51 When *N*,*N*′-diphenylurea **(A)** is reacted with tosyl chloride in pyridine, it yields product **B.**



A

The spectral data for **B** include:

MS (*m/z*): 194 ($M^{+\cdot}$)

IR (cm^{-1}): 3060, 2130, 1590, 1490, 760, 700

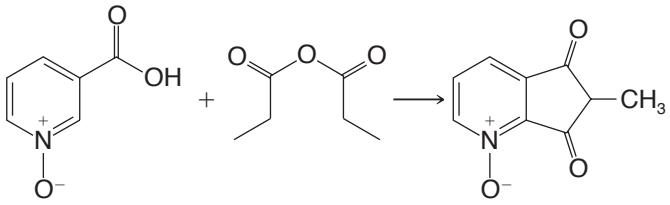
^{1}H NMR (δ): only 6.9–7.4 (m)

^{13}C NMR (δ): 122 (CH), 127 (CH), 130 (CH), 149 (C), and 163 (C)

(a) What is the structure of **B?**

(b) Write a mechanism for the formation of **B.**

20.52 Propose a mechanism that can explain the occurrence of this reaction:



20.53 When acetone is treated with anhydrous ammonia in the presence of anhydrous calcium chloride (a common drying agent), crystalline product **C** is obtained on concentration of the organic liquid phase of the reaction mixture. These are spectral data for product **C**:

MS (*m/z*): 155 ($M^{+\cdot}$), 140

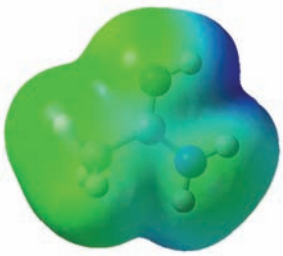
IR (cm^{-1}): 3350 (sharp), 2850–2960, 1705

^{1}H NMR (δ): 2.3 (s, 4H), 1.7 (1H; disappears in D_2O), and 1.2 (s, 12H)

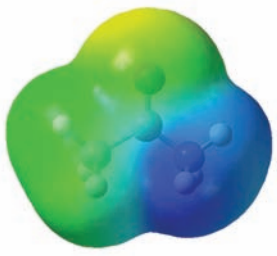
(a) What is the structure of **C?**

(b) Propose a mechanism for the formation of **C.**

20.54 The difference in positive-charge distribution in an amide that accepts a proton on its oxygen or its nitrogen atom can be visualized with electrostatic potential maps. Consider the electrostatic potential maps for acetamide in its O—H and N—H protonated forms shown below. On the basis of the electrostatic potential maps, which protonated form appears to delocalize, and hence stabilize, the formal positive charge more effectively? Discuss your conclusion in terms of resonance contributors for the two possible protonated forms of acetamide.



Acetamide protonated on oxygen

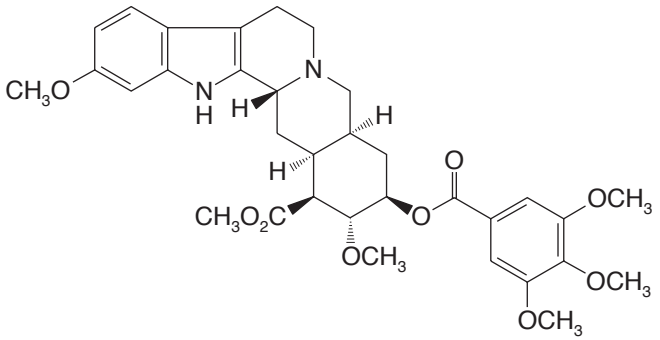


Acetamide protonated on nitrogen

Openmirrors.com

Learning Group Problems

1. Reserpine is a natural product belonging to the family of alkaloids (see Special Topic F). Reserpine was isolated from the Indian snakeroot *Rauwolfia serpentina*. Clinical applications of reserpine include treatment of hypertension and nervous and mental disorders. The synthesis of reserpine, which contains six chirality centers, was a landmark accomplishment reported by R. B. Woodward in 1955. Incorporated in the synthesis are several reactions involving amines and related nitrogen-containing functional groups, as we shall see on the following page.



Reserpine

(a) The goal of the first two steps shown in the scheme on the following page, prior to formation of the amide, is preparation of a secondary amine. Draw the structure of the products labeled **A** and **B** from the first and second reactions, respectively. Write a mechanism for formation of **A.**

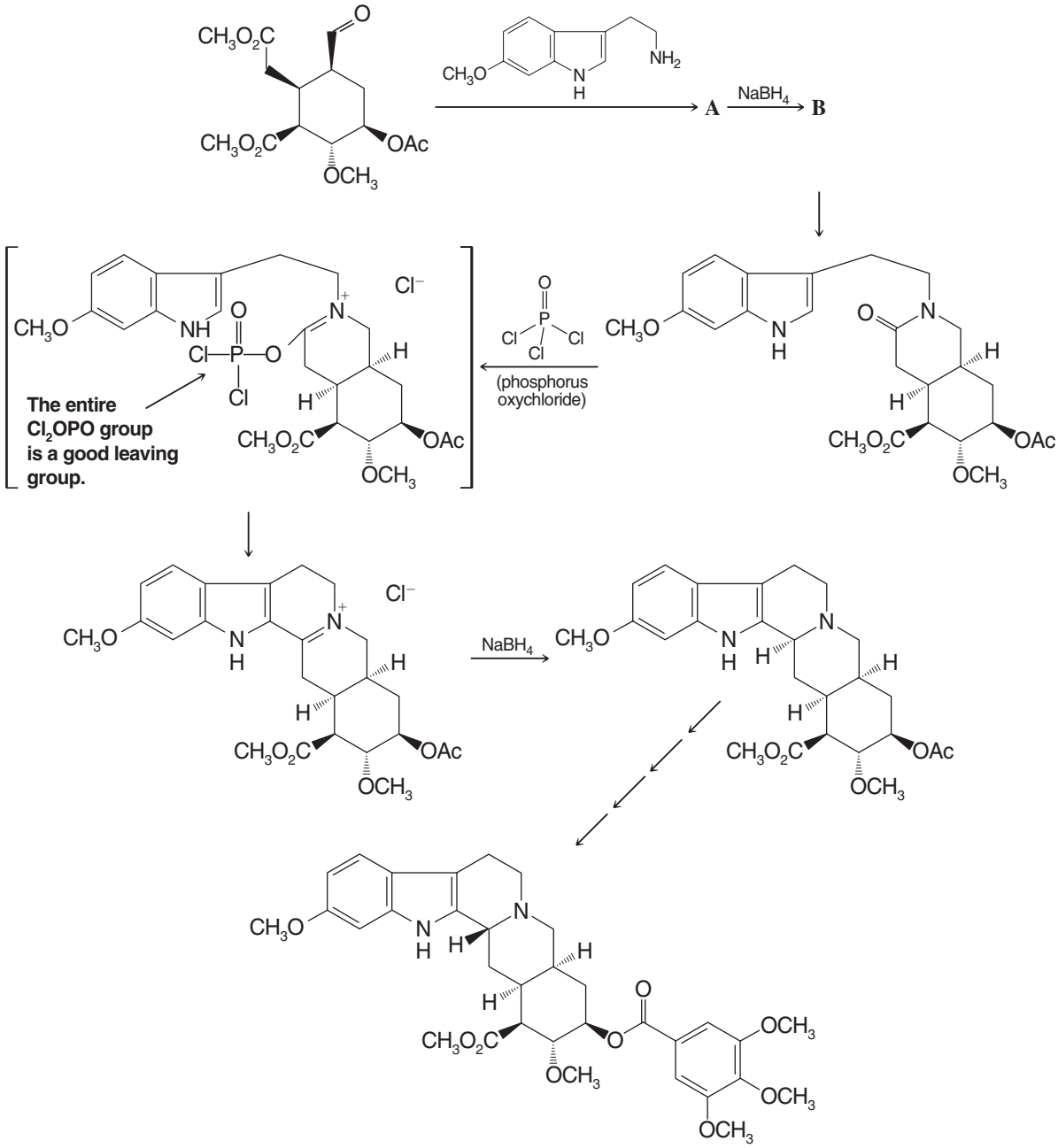
(b) The next sequence of reactions involves formation of a tertiary amine together with closure of a new ring. Write curved arrows to show how the amide functional group reacts with phosphorus oxychloride ($POCl_3$) to place the leaving group on the bracketed intermediate.

(c) The ring closure from the bracketed intermediate involves a type of electrophilic aromatic substitution reaction characteristic of indole rings. Identify the part of the structure that contains the indole ring. Write mechanism arrows to show how the nitrogen in the indole ring, via conjugation, can cause electrons from the adjacent carbon to attack an electrophile. In this case, the attack by the indole ring in the bracketed intermediate is an addition–elimination reaction, somewhat like reactions that occur at carbonyls bearing leaving groups.

2. **(a)** A student was given a mixture of two unknown compounds and asked to separate and identify them. One of the compounds was an amine and the other was a neutral compound (neither appreciably acidic nor basic). Describe how you would go about separating the unknown amine from the neutral compound using extraction techniques involving diethyl ether and solutions of aqueous 5% HCl and 5% $NaHCO_3$. The mixture as a whole was soluble in diethyl ether, but neither component was soluble in water at pH 7. Using R groups on a generic amine, write out the reactions for any acid–base steps you propose and explain why the compound of interest will be in the ether layer or aqueous layer at any given time during the process.

(b) Once the amine was successfully isolated and purified, it was reacted with benzenesulfonyl chloride in the presence of aqueous potassium hydroxide. The reaction led to a solution that on acidification produced a precipitate. The results just described constitute a test (Hinsberg's) for the class of an amine. What class of amine was the unknown compound: primary, secondary, or tertiary? Write the reactions involved for a generic amine of the class you believe this one to be.

(Reactions for Problem 1, previous page)



Reserpine

(Problem 2, continued)

(c) The unknown amine was then analyzed by IR, NMR, and MS. The following data were obtained. On the basis of this information, deduce the structure of the unknown amine. Assign the spectral data to specific aspects of the structure you propose for the amine.

IR (cm^{-1}): 3360, 3280, 3020, 2962, 1604, 1450, 1368, 1021, 855, 763, 700, 538

^{1}H NMR (δ): 1.35 (d, 3H), 1.8 (bs, 2H), 4.1 (q, 1H), 7.3 (m, 5H)

MS (*m/z*): 121, 120, 118, 106 (base peak), 79, 77, 51, 44, 42, 28, 18, 15

WILEY PLUS See *Special Topic F* in *WileyPLUS*

Openmirrors.com