PART 5

Project-Based Experiments

56 **EXPERIMENT 56**

Preparation of a C-4 or C-5 Acetate Ester

Esterification

Separatory funnel

Simple distillation

Microwave-assisted chemistry

In this experiment, we prepare an ester from acetic acid and a C-4 or a C-5 alcohol. This experiment is similar to the preparation of isopentyl acetate, which is described in Experiment 12. However, for this experiment, either your instructor will assign, or you will pick, one of the following C-4 or C-5 alcohols for reaction with acetic acid:

1-butanol (*n*-butyl alcohol)	1-pentanol (*n*-pentyl alcohol)
2-butanol (*sec*-butyl alcohol)	2-pentanol
2-methyl-1-propanol (isobutyl alcohol)	3-pentanol
3-methyl-1-butanol (isopentyl alcohol)	cyclopentanol

If an NMR spectrometer is available, your instructor may wish to give you one of these alcohols as an unknown, leaving it to you to determine which alcohol was issued. For this purpose, you could use the infrared and NMR spectra as well as the boiling points of the alcohol and its ester.

As an option, if your classroom is equipped with a microwave reaction system, you may use that equipment to prepare esters of any of the alcohols listed here.

REQUIRED READING

Sign in at www.cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: Techniques *12, 13, and *14

Experiment 12

Essay Esters—Flavors and Fragrances

Technique 7, Section 7.2 (optional)

SPECIAL INSTRUCTIONS

Be careful when dispensing sulfuric and acetic acids. They are very corrosive and will attack your skin upon contact. If you happen to contact one of these acids on your skin, wash the affected area with copious amounts of running water for 10–15 minutes.

If you select 2-butanol as your starting material, reduce the amount of concentrated sulfuric acid to 0.5 mL. Also reduce the heating time to 60 minutes or less. Secondary alcohols have a tendency to give a significant percentage of elimination in strongly acidic solutions. Some of the alcohols may undergo elimination, leading to the formation of some low-boiling material (alkenes). In addition, cyclopentanol forms some dicyclopentyl ether, a solid.

NOTES TO THE INSTRUCTOR

An option that has been included in this experiment involves the use of a microwave reaction system. For those laboratories where such a device is available, we recommend that the instructor load and run the student samples or provide instruction to the students on the use of that particular system. We have not included specific instrument commands in this procedure.

SUGGESTED WASTE DISPOSAL

Any aqueous solutions should be placed in the container designated for dilute aqueous waste. Place any excess ester in the nonhalogenated waste container. Note that your instructor may establish a different method of collecting wastes for this experiment.

PROCEDURE

Apparatus. Assemble a reflux apparatus using a 25-mL round-bottom flask and a water-cooled condenser (see Technique 7, Figure 7.6). In order to control vapors, place a drying tube packed with calcium chloride on top of the condenser. Use a heating mantle to heat the reaction.

Reaction Mixture. Weigh (tare) an empty 10-mL graduated cylinder and record its weight. Place approximately 5.0 mL of your chosen alcohol in the graduated cylinder and reweigh it to determine the weight of alcohol. Disconnect the round-bottom flask from the reflux apparatus, and transfer the alcohol into it. Do not clean or wash the graduated cylinder. Using the same graduated cylinder, measure approximately 7.0 mL of glacial acetic acid (MW = 60.1, d = 1.06 g/mL), and add it to the alcohol already in the flask. Using a calibrated Pasteur pipet, add 1 mL of concentrated sulfuric acid (0.5 mL if you have chosen 2-butanol), mixing immediately (swirl), to the reaction mixture contained in the flask. Add a corundum boiling stone and reconnect the flask. Do not use a calcium carbonate (marble) boiling stone, because it will dissolve in the acidic medium.

Reflux. Start water circulation in the condenser and bring the mixture to a boil. Continue heating under reflux for 60–75 minutes. Then disconnect or remove the heating source, and allow the mixture to cool to room temperature.

Extractions. Disassemble the apparatus, and transfer the reaction mixture to a separatory funnel (125-mL) placed in a ring attached to a ring stand. Be sure that the stopcock is closed and, using a funnel, pour the mixture into the top of the separatory funnel. Also be careful to avoid transferring the boiling stone, or you will need to remove it after the transfer. Add 10 mL of water, stopper the funnel, and mix the phases by careful shaking and venting (see Technique 12, Section 12.4, and Figure 12.6). Allow the phases to separate, and then unstopper the funnel and drain the lower aqueous layer through the stopcock into a beaker or other suitable container. Next, extract the organic layer with 5 mL of 5% aqueous sodium bicarbonate just as you did previously with water. Extract the organic layer once again, this time with 5 mL of saturated aqueous sodium chloride.

Drying. Transfer the crude ester to a clean, dry 25-mL Erlenmeyer flask, and add approximately 1.0 g of granular anhydrous sodium sulfate. Cork the mixture and allow it to stand for 10–15 minutes while you prepare the apparatus for distillation. If the mixture does not appear dry (the drying agent clumps and does not "flow," the solution is cloudy, or drops of water are obvious), transfer the ester to a new clean, dry 25-mL Erlenmeyer flask, and add a new 0.5-g portion of granular anhydrous sodium sulfate to complete the drying.

Distillation. Assemble a distillation apparatus using your smallest round-bottom flask to distill (see Technique 14, Figure 14.1). As an alternative, your instructor may ask you to assemble a "short path" distillation apparatus (see Technique 14, Figure 14.5). Use a heating mantle to heat. Preweigh (tare) and use a 50-mL round-bottom flask or a small Erlenmeyer flask to collect the product. As the distillation begins, collect the initial 2 or 3 drops of liquid in a separate container. This will be the "forerun" material, which will be a mixture of water, unreacted alcohol, and ester. Discard this material. Connect the pre-weighed round-bottom flask and continue the distillation. Immerse the collection flask in a beaker of ice to ensure condensation and to reduce odors. If your alcohol is not an unknown, you can look up its boiling point in a handbook; otherwise, you can expect your ester to have a boiling point between 95°C and 150°C. Continue distillation until only 1 or 2 drops of liquid remain in the distilling flask. Record the observed boiling point *range* in your notebook. Be sure to discard the "forerun" into a designated waste container.

Yield Determination. Weigh the product, and calculate the percentage yield of the ester. At the option of your instructor, determine the boiling point using one of the methods described in Technique 13, Sections 13.2 and 13.3.

Spectroscopy. At your instructor's option, obtain an infrared spectrum using salt plates (see Technique 25, Section 25.2). Compare the spectrum with the one reproduced in Experiment 12. The spectrum of your ester should have similar features to the one shown. Interpret the spectrum and include it in your report to the instructor. You may also be required to determine and interpret the proton and carbon-13 NMR spectra (see Technique 26, Sections 26.1 and 26.2, and Technique 27, Section 27.1). Submit your sample in a properly labeled vial with your report.

Optional Exercise: Gas Chromatography. At your instructor's option, perform a gas chromatographic analysis of your ester. Either your instructor will provide a gas chromatogram of your starting alcohol, or you will be asked to determine one at the same time that you do the analysis of your ester. Using both chromatograms, identify the alcohol and ester peaks, and calculate the percentage of unreacted alcohol (if any) still remaining in your sample. Is there any evidence of a product from a competing elimination reaction? Attach the chromatograms to your notebook or your final report, and be sure to include a discussion of the results in your report.

Optional Procedure: Microwave-Assisted Esterification. Add 1.4 ml of your chosen alcohol, a glass bead, 2 ml glacial acetic acid, and 6 drops of concentrated sulfuric acid to a microwave reaction tube. Place a magnetic stirring bar in the microwave tube, and close the tube with its cap. Submit your prepared reaction tube to your instructor, who will load it into the microwave reaction system or will provide you with operating instructions for your specific system. Allow the samples to react for 15 minutes at 130°C.

When the reaction has been completed, transfer the reaction mixture from the microwave tube into a 15-mL glass centrifuge tube. Add 2 mL 10% sodium bicarbonate, cap the centrifuge tube, and shake it vigorously. Allow the two layers to separate, and remove the bottom aqueous layer using a Pasteur pipet. Repeat the sodium bicarbonate extraction a second time, and remove the bottom aqueous layer. Add 2 mL saturated sodium chloride to the organic layer in the centrifuge tube, and shake the tube vigorously. Using a Pasteur pipet, remove the top organic layer and place it into an Erlenmeyer flask. Dry the organic liquid over anhydrous sodium sulfate for approximately 10 minutes. Transfer the crude ester into a 10-mL round-bottom flask. Place a magnetic stirring bar in the flask, and set up the distillation apparatus as described in Technique 14, Figure 14.1. Proceed with distillation, using the method outlined in the "Distillation" section.

QUESTIONS

1. One method of favoring the formation of an ester is to add excess acetic acid. Suggest another method, involving the right-hand side of the equation, that will favor the formation of the ester.
2. Why is the mixture extracted with sodium bicarbonate? Give an equation and explain its relevance.
3. Why are gas bubbles observed?
4. Using your alcohol, determine which starting material is the limiting reagent in this procedure. Which reagent is used in excess? How great is the molar excess (how many times greater)?
5. Outline a separation scheme for isolating your pure ester from the reaction mixture.
6. Interpret the principal absorption bands in the infrared spectrum of your ester, or if you did not determine the infrared spectrum of your ester, do this for the spectrum of isopentyl acetate shown in Experiment 12. (Technique 25 may be of some help.)
7. Write a mechanism for the acid-catalyzed esterification that uses your alcohol and acetic acid. You may need to consult the chapter on carboxylic acids in your lecture textbook.
8. Tertiary alcohols do not work well in the procedure outlined for this experiment; they give a different product than you might expect. Explain this and draw the expected product from *t*-butyl alcohol (2-methyl-2-propanol).
9. Why is glacial acetic acid designated as "glacial"? (Hint: Consult a handbook of physical properties.)

57 **EXPERIMENT 57**

Isolation of Essential Oils from Allspice, Caraway, Cinnamon, Cloves, Cumin, Fennel, or Star Anise

Steam distillation

Extraction

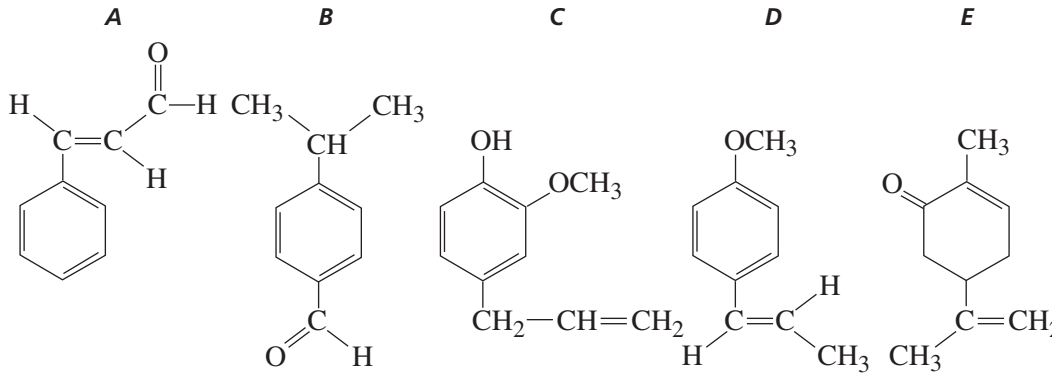
High-performance liquid chromatography

Infrared spectroscopy

Gas chromatography–mass spectrometry

Mini-research project

In Experiment 57A, you will steam distill the essential oil from a spice. Either you will choose, or the instructor will assign you, a spice from the following list: allspice, caraway, cinnamon, cloves, cumin, fennel, or star anise. Each spice produces a relatively pure essential oil. The structures for the major essential-oil components of the spices are shown here. Your spice will yield one of these compounds. You are to determine which structure represents the essential oil that was distilled from your spice.



In trying to determine your structure, be sure to look for the following features (stretching frequencies) in the infrared spectrum: C═O (ketone or aldehyde), C — H (aldehyde), O — H (phenol), C— O (ether), benzene ring, and C═C (alkene). Also be sure to look for the aromatic-ring, out-of-plane bending frequencies, which may help you determine the substitution patterns of the benzene rings (see Technique 25, Section 25.14 C). The out-of-plane bending region may also be of help in determining the degree of substitution on the alkene double bond where it exists (see Technique 25, Section 25.14 B). There are enough differences in the infrared spectra of the five possible compounds that you should be able to identify your essential oil.

If NMR spectroscopy is available, it will provide a nice confirmation of your conclusions. Carbon-13 NMR would be even more informative than proton magnetic resonance. However, neither of these techniques is required for a solution. Your sample of essential oil can also be analyzed by high-performance liquid chromatography.

In Experiment 57B, you will identify the constituents of the essential oil by gas chromatography–mass spectrometry. In Experiment 57C, the techniques described in Experiments 57A and 57B are used in a mini-research project. Your instructor will assign you a particular spice or herb to analyze, or you will choose your own plant material. In this project, you will not have advance information about the components of the plant material that you investigate.

REQUIRED READING

Sign in at www.cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review:	*Technique 12	Extractions, Separations, and Drying Agents
New:	*Technique 18	Steam Distillation
	Technique 21	High-Performance Liquid Chromatography (HPLC)
	Technique 22	Gas Chromatography, Section 22.13
	Technique 28	Mass Spectrometry
	Essay	Terpenes and Phenylpropanoids

SPECIAL INSTRUCTIONS

Foaming can be a serious problem if you use finely ground spices. It is recommended that you use clove buds, whole allspice, whole star anise, or cinnamon sticks in place of the ground spices. However, be sure to cut or break up the large pieces or crush them with a mortar and pestle.

If your instructor assigns the HPLC option, you will have to determine the best operating conditions for your particular instrument and conditions. Your instructor should test this experiment in advance so you can have a good idea of which column to use and which flow rate of solvent works best. Your instructor will provide specific instruction in the operation of the particular HPLC instrument being used in your laboratory. The instructions that follow outline the general procedure.

For experiment 57B, similar instructions should also pertain. Your instructor will provide instruction for preparation of the sample and the operation of the specific GC-MS instrument used in your laboratory. Your instructor should also tell you which column to use and which operating conditions work best. The instructions that follow outline the general procedure.

Your instructor may also assign Experiment 57C, which extends the basic techniques developed in Experiments 57A and 57B to a large list of plant materials. For this assignment, either your instructor will assign you a particular spice or herb to analyze, or you will choose your own plant material to analyze.

SUGGESTED WASTE DISPOSAL

Any aqueous solutions should be placed in the container designated for aqueous wastes. Be sure to place any solid spice residues in the garbage can, because they will plug the sink drain. Mixed organic–aqueous solutions should be disposed of in the container designated for aqueous wastes. Note that your instructor may establish a different method of collecting wastes for this experiment.

NOTES TO THE INSTRUCTOR

If ground spices are used (not recommended), you may want to have the students insert a Claisen head between the round-bottom flask and the distillation head to allow extra volume in case the mixture foams. Problems with foaming can be greatly ameliorated by applying an aspirator vacuum to the spice–water mixture before the steam distillation is begun.

For the HPLC option in Experiment 57A, you must determine the best operating conditions in advance of the experiment. You will also need to prepare instructions for operating your particular instrument. You must test Experiments 57B and 57C in advance, in a similar way to your GC-MS instrument, and prepare operating instructions.

57A **EXPERIMENT 57A**

Isolation of Essential Oils by Steam Distillation

PROCEDURE

Apparatus. Using a 100-mL round-bottom flask to distill and a 50-mL round-bottom flask to collect, assemble a distillation apparatus similar to that shown in Technique 14, Figure 14.1. Use a heating mantle to heat. The collection flask may be immersed in ice to ensure condensation of the distillate.

Preparing the Spice. Weigh approximately 3.0 g of your spice onto a weighing paper, and record the exact weight. If your spice is already ground, you may proceed without grinding it; otherwise, break up the seeds using a mortar and pestle, or cut larger pieces into smaller ones using scissors. Mix the spice with 35–40 mL of water in the 100-mL round-bottom flask, add a boiling stone, and reattach it to your distillation apparatus. Allow the spice to soak in the water for about 15 minutes before beginning the heating. Be sure that all the spice gets thoroughly wetted. Swirl the flask gently, if necessary.

Steam Distillation. Turn on the cooling water in the condenser, and begin heating the mixture to provide a steady rate of distillation. If you approach the boiling point too quickly, you may have difficulty with frothing or bump-over. You will need to find the amount of heat that provides a steady rate of distillation but avoids frothing and/or bumping. A good rate of distillation would be to have 1 drop of liquid collected every 2–5 seconds. Continue distillation until at least 15 mL of distillate has been collected.

Normally, in a steam distillation the distillate will be somewhat cloudy due to separation of the essential oil as the vapors cool. However, you may not notice this but still obtain satisfactory results.

Extraction of the Essential Oil. Transfer the distillate to a separatory funnel, and add 5.0 mL of methylene chloride (dichloromethane) to extract the distillate. Shake the funnel vigorously, venting frequently. Allow the layers to separate.

The mixture may be spun in a centrifuge if the layers do not separate well. Stirring gently with a spatula sometimes helps to resolve an emulsion. Adding about 1 mL of a saturated sodium chloride solution will also help. For the following directions, however, be aware that the saturated salt solution is quite dense, and the aqueous layer may change places with the methylene chloride layer, which is normally on the bottom.

Transfer the lower methylene chloride layer to a clean, dry Erlenmeyer flask. Repeat this extraction procedure with a fresh 5.0-mL portion of methylene chloride, and place it in the same Erlenmeyer flask in which you placed the first extraction. If there are visible drops of water, you need to transfer the methylene chloride solution carefully to a clean, dry flask, leaving the drops of water behind.

Drying. Dry the methylene chloride solution by adding granular anhydrous sodium sulfate to the Erlenmeyer flask (see Technique 12, Section 12.9). Let the solution stand for 10–15 minutes, and swirl it occasionally.

Evaporation. While the organic solution is being dried, obtain a clean, dry, medium-sized test tube and weigh (tare) it accurately. Decant a portion (about one-third) of the dried organic layer to this tared test tube, leaving the drying agent behind. Add a boiling stone and, working in a hood, evaporate the methylene chloride from the solution by using a gentle stream of air or nitrogen and heating to about 40°C with a water bath (see Technique 7, Section 7.10). When the first portion is reduced to a small volume of liquid, add a second portion of the methylene chloride solution and evaporate as before. When you add the final portion, use small amounts of clean methylene chloride to rinse the drying agent, enabling you to transfer all of the remaining solution into the tared test tube. Be careful to keep any of the sodium sulfate from being transferred.

CAUTION

The stream of air or nitrogen must be very gentle, or you will blast your solution out of the test tube. In addition, do not overheat the sample, or it may "bump" out of the tube. Do not continue the evaporation beyond the point where all the methylene chloride has evaporated. Your product is a volatile oil (that is, liquid). If you continue to heat and evaporate, you will lose it. It would be better to leave some methylene chloride than to lose your sample.

Yield Determination. When the solvent has been removed, reweigh the test tube. Calculate the weight percentage recovery of the oil from the original amount of spice used.

SPECTROSCOPY

Infrared. Obtain the infrared spectrum of the oil as a pure liquid sample (see Technique 25, Section 25.2). A Pasteur pipet with a narrow tip may be necessary to transfer a sufficient amount of oil to the salt plates. If even this fails, you may add 1 or 2 drops of carbon tetrachloride (tetrachloromethane) to aid in the transfer. This solvent will not interfere with the infrared spectrum. Include the infrared spectrum in your laboratory report, along with an interpretation of the principal peaks.

Nuclear Magnetic Resonance. At the instructor's option, determine the nuclear magnetic resonance spectrum of the oil (see Technique 26, Section 26.1).

REPORT

From the infrared spectrum (and any other data you have used), you should determine the structure (A–E) that best matches the essential oil you isolated from your spice. Label the major peaks in the infrared spectrum, and give an argument that supports your choice of structure. Also be sure to include your weight percentage recovery calculation.

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (OPTIONAL EXERCISE)

Following your instructor's directions, form a small group of students to perform this experiment. Each small group will be assigned the same spice to analyze, and the results obtained will be shared among all students in the group.

Dissolve your sample of essential oil in methanol. A reasonable concentration can be obtained by dissolving 25 mg of your sample in 10 mL of methanol. To remove all traces of dissolved gases and solid impurities, set up a filtering flask with a Büchner funnel and connect it to a vacuum line. Place a 4-μm filter in the Büchner funnel. (*Note:* Be sure to use a piece of filter paper, not one of the colored spacers that are placed between the pieces of filter paper. The spacers are normally blue.) Filter the essential-oil solution by vacuum filtration through the 4-μm filter and place the filtered sample in a *clean* 4-dram snap-cap vial.

Before using the HPLC instrument, be certain you have obtained specific instructions for operating the instrument in your laboratory. Alternatively, your instructor may have someone operate the instrument for you. Before your sample is analyzed on the HPLC instrument, the sample should be filtered one more time, this time through a 0.2-μm filter. The recommended sample size for analysis is 10 μL. The solvent system used for this analysis is a mixture of 80% methanol and 20% water. The instrument will be operated in an isochratic mode.

When you have completed your experiment, report your results by preparing a table showing the retention times of each substance identified in the analysis. Determine the relative percentage of each component, and record these values in your table along with the name of each substance identified.

REFERENCE

McKone, H. T. High Performance Liquid Chromatography of Essential Oils. *J. Chem. Educ.* **1979,** *56,* 698.

57B EXPERIMENT 57B

Identification of the Constituents of Essential Oils by Gas Chromatography–Mass Spectrometry

PROCEDURE

Sample Preparation. Obtain a sample of essential oil by steam distillation of the spice, according to the method shown in Experiment 57A.

Analysis by GC-MS. Your instructor will provide you with specific instructions on how to prepare the sample for the GC-MS analysis. The instructions given here should work with many GC-MS instruments.

For the GC-MS analysis, a very dilute solution (about 500 ppm) is recommended. To prepare this solution, dip an end of a length of capillary tube (ca. 1.8-mm inner diameter, open at both ends) into the sample of the essential oil. Transfer the contents of the capillary tube into a clean, calibrated 15-mL centrifuge tube by flushing methylene chloride through the capillary tube. Note that to avoid getting solvent on your fingers, you will have to hold the capillary tube with a pair of forceps. Add additional methylene chloride to the centrifuge tube to obtain a total volume of 6 mL. Add 1 or 2 microspatulas of granular anhydrous sodium sulfate to the centrifuge tube, place a piece of aluminum foil over the top, and screw the cap over the aluminum foil.

Before injecting the solution onto the GC-MS column, you must filter the solution. Draw a portion of the solution into a clean hypodermic syringe (without needle). Attach a 0.45-μm filter cartridge to the tip of the syringe, and force the solution through the filter cartridge into a clean sample vial. Cover the sample vial with aluminum foil until the solution is used.

Inject the solution onto the column of the GC-MS instrument. As each component in the solution appears on the graph, use the built-in computer library to identify each component. Use the "quality" or "confidence" indicators on the printed lists to determine whether or not the compounds suggested are plausible. In your laboratory report, identify each component of the essential oil by providing its name and structural formula.

57C **EXPERIMENT 57C**

Investigation of the Essential Oils of Herbs and Spices—A Mini-Research Project

PROCEDURE

Obtain a sample of essential oil by steam distillation of the spice or herb, according to the method shown in Experiment 57A. Prepare the sample for analysis by gas chromatography–mass spectrometry by the method described in Experiment 57B. The procedure in Experiment 60 provides some additional guidelines that may be helpful in identifying the compounds.

Using the results of your GC-MS analysis, prepare a brief report describing your experimental method and presenting the results of your analysis. In your report, be sure to identify each important component of the essential oil you analyzed, draw its complete structural formula, and indicate the relative percentage of that substance in the essential-oil mixture.

QUESTIONS (EXPERIMENT 57A)

1. Use a sheet of paper to build a matrix by drawing each of the five possible essential-oil compounds given previously down the left side of the sheet and by listing each of the possible infrared spectral features given previously along the top of the sheet. Draw lines to form boxes. Inside the boxes opposite each compound, note the expected infrared observation. Is the peak expected to be present or absent? If present, give the expected number of peaks and the probable frequencies. A good set of correlation charts and tables will help you with this.
2. Why does the newly condensed steam distillate appear cloudy?
3. After the drying step, what observations will help you to determine if the extracted solution is "dry" (that is, free of water)?

58 **EXPERIMENT 58**

Competing Nucleophiles in S_N1 and S_N2 Reactions: Investigations Using 2-Pentanol and 3-Pentanol

Nucleophilic substitution

Heating under reflux

Extraction

Gas chromatography

NMR spectroscopy

This experiment is based on the procedure outlined in Experiment 20. The purpose of this experiment is to examine the products formed when competing nucleophiles, equimolar concentrations of chloride ions and bromide ions, are allowed to react with either 2-pentanol or 3-pentanol. Based on the products formed in each reaction, students can advance a variety of hypotheses that account for the number and proportions of products formed.

Because the starting alcohols are secondary alcohols, one might expect that the substitution reactions will take place by a combination of S_N1 and S_N2 pathways. You will analyze the products of the three reactions in this experiment by a variety of techniques to determine the relative amounts of alkyl chloride and alkyl bromide formed in each reaction and identify all of the products that are observed.

REQUIRED READING

Sign in at www.cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Experiment 21	Nucleophilic Substitution Reactions: Competing Nucleophiles
*Technique 7	Reaction Methods, Sections 7.2, 7.4, 7.5, and 7.7
*Technique 12	Extractions, Separations, and Drying Agents, Sections 12.5, 12.9, and 12.11
Technique 22	Gas Chromatography
Technique 26	Nuclear Magnetic Resonance Spectroscopy

Before beginning this experiment, review the appropriate chapters on nucleophilic substitution in your lecture textbook.

SPECIAL INSTRUCTIONS

Your instructor will also assign you either 2-pentanol or 3-pentanol. By sharing your results with other students, you will be able to collect data for both alcohols. To analyze the results of both experiments, your instructor will assign specific analysis procedures that the class will accomplish.

The solvent–nucleophile medium contains a high concentration of sulfuric acid. Sulfuric acid is corrosive; be careful when handling it.

During the extractions, the longer your product remains in contact with water or aqueous sodium bicarbonate, the greater the risk that your product will decompose, leading to errors in your analytical results. Be prepared before coming to class, so that you know exactly what you are supposed to do during the purification stage of the experiment.

SUGGESTED WASTE DISPOSAL

When you have completed the two experiments and all the analyses have been completed, discard any remaining alkyl halide mixture in the organic waste container marked for the disposal of halogenated substances. All aqueous solutions produced in this experiment should be disposed of in the container for aqueous waste.

NOTES TO THE INSTRUCTOR

The solvent–nucleophile medium must be prepared in advance for the entire class. Use the following procedure to prepare the medium. This procedure will provide enough solvent–nucleophile medium for about 10 students (assuming no spillage or other types of waste). Place 100 g of ice in a 500-mL Erlenmeyer flask, and carefully add 76 mL concentrated sulfuric acid. Carefully weigh 19.0 g ammonium chloride and 35.0 g ammonium bromide into a beaker. Crush any lumps of the reagents to powder and then, using a powder funnel, transfer the halides to an Erlenmeyer flask. Carefully add the sulfuric acid mixture to the ammonium salts a little at a time. Swirl the mixture vigorously to dissolve the salts. It will probably be necessary to heat the mixture on a steam bath or hot plate to achieve total solution. Keep a thermometer in the mixture, and make sure that the temperature does not exceed 45°C. If necessary, you may add as much as 10 mL of water at this stage. Do not worry if a few small granules do not dissolve. When solution has been achieved, pour the solution into a container that can be kept warm until all students have taken their portions. The temperature of the mixture must be maintained at about 45°C to prevent precipitation of the salts. Be Careful that the solution temperature does not exceed 45°C, however. Place a 20-mL calibrated pipet fitted with a pipet helper in the mixture. The pipet is always left in the mixture to keep it warm.

The gas chromatograph should be prepared as follows: Agilent (J & W) DB5 capillary column (30 m, 0.32 mm ID, 0.25 μm). Set injector temperature at 260°C. FID detector temperature is 280°C. The column oven conditions are as follows: start at 40°C (hold 2 min), increase to 140°C at 20°C/min. (5 min). The helium flow rate is 1.0 mL/min. The hydrogen FID gas makeup flow is 35 mL/min.

PROCEDURE

CAUTION

The solvent–nucleophile medium contains a high concentration of sulfuric acid. This liquid will cause severe burns if it SPILLS your skin.

Apparatus. Assemble an apparatus for reflux using a 20-mL round-bottom flask, a reflux condenser, and a drying tube, as shown in the figure in Experiment 20. Loosely insert dry glass wool into the drying tube, and then add water dropwise onto the glass wool until it is partially moistened. The moistened glass wool will trap the hydrogen chloride and hydrogen bromide gases produced during the reaction. As an alternative, you can use an external gas trap as described in Technique 7, Section 7.8, part B. Do not place the round-bottom flask into the heating mantle until the reaction mixture has been added to the flask. Six Pasteur pipets, two 3-mL conical vials with Teflon cap liners, and a 5-mL conical vial with a Teflon liner should also be assembled for use. All pipets and vials should be clean and dry.

Preparation of Reagents. If a calibrated pipet fitted with a pipet helper is provided, you may adjust the pipet to 10 mL and deliver the solvent–nucleophile medium directly into your 20-mL round-bottom flask (temporarily placed in a beaker for stability). Alternatively, you may use a warm 10-mL graduated cylinder to obtain 10.0 mL of the solvent–nucleophile medium. The graduated cylinder must be warm in order to prevent precipitation of the salts. Heat it by running hot water over the outside of the cylinder or by putting it in the oven for a few minutes. Immediately pour the mixture into the round-bottom flask. With either method, a small portion of the salts in the flask may precipitate as the solution cools. Do not worry about this; the salts will redissolve during the reaction.

Reflux. Assemble the apparatus shown in the figure "Apparatus for Reflux" in Experiment 20. Using the following procedure, add 0.75 mL of either 2-pentanol or 3-pentanol, depending on which alcohol you were assigned, to the solvent nucleophile mixture contained in the reflux apparatus. Dispense the alcohol from the automatic pipet or dispensing pump into a 10 mL beaker. Remove the drying tube and, with a 9-inch Pasteur pipet, dispense the alcohol directly into the round-bottom flask by inserting the Pasteur pipet into the opening of the condenser. Also add an inert boiling stone.[1] Replace the drying tube and start circulating the cooling water. Lower the reflux apparatus so that the round-bottom flask is in the heating mantle. Adjust the heat so that this mixture maintains a *gentle* boiling action. The aluminum block temperature should be about 140 ^{o}C. Be careful to adjust the reflux ring, if one is visible, so that it remains in the lower fourth of the condenser. Violent boiling will cause loss of product. Heat the mixture for 45 minutes.

Purification. When the period of reflux has been completed, discontinue heating, lift the apparatus out of the heating mantle, and allow the reaction mixture to cool. Do not remove the condenser until the flask is cool. Be careful not to shake the hot solution as you lift it from the heating mantle, otherwise a violent boiling and bubbling action will result; this could allow material to be lost out the top of the condenser. After the mixture has cooled for about 5 minutes, immerse the round-bottom flask (with condenser attached) in a beaker of cold tap water (no ice), and wait for this mixture to cool down to room temperature.

An organic layer should be present at the top of the reaction mixture. Add 0.75 mL of pentane to the mixture and *gently* swirl the flask. The purpose of the pentane is to increase the volume of the organic layer so that the following operations are easier to accomplish. Using a Pasteur pipet, transfer most (about 7 mL) of the bottom (aqueous) layer to another container. Be careful that the entire top organic layer remains in the boiling flask. Transfer the remaining aqueous layer and the organic layer to a 3-mL conical vial, taking care to leave behind any solids that may have precipitated. Allow the phases to separate, and remove the bottom (aqueous) layer using a Pasteur pipet.

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[1] Do not use calcium carbonate–based stones or Boileezers, because they will partially dissolve in the highly acidic reaction mixture.

NOTE: For the following sequence of steps, be certain to be well prepared in advance. If you find that you are taking longer than 5 minutes to complete the entire extraction sequence, you probably have affected your results adversely!

Add 1.0 mL of water to the vial and *gently* shake this mixture. Allow the layers to separate and remove the aqueous layer, which is still at the bottom. Extract the organic layer with 1–2 mL of saturated sodium bicarbonate solution, and remove the bottom aqueous layer.

Drying. Using a clean dry Pasteur pipet, transfer the remaining organic layer into a small test tube (10 × 75 mm) containing 3 to 4 microspatulafuls (using the V-grooved end) of anhydrous granular sodium sulfate. Stir the mixture with a microstipatula, put a stopper on the tube, and set it aside for 10–15 minutes or until the solution is clear. If the mixture does not turn clear, add more anhydrous sodium sulfate. Transfer the halide solution with a clean, dry Pasteur pipet to a small vial with a leak-proof cap. GE-MS vials are ideal for this purpose. If possible, analyze your sample the same day. If not, cover the cap with Parafilm and store at room temperature. It is helpful to cover the stopper and cap with Parafilm (on the outside of the stopper and cap). Alternatively, you may use a screw-cap vial with a Teflon liner. *Be sure the cap is screwed on tightly.* Again, it is a good idea to cover the cap with Parafilm. Do not store the liquid in a container with a cork or a rubber stopper, because these will absorb the halides. If it is necessary to store the sample overnight, store it in a refrigerator. This sample can now be analyzed by as many of the methods as your instructor indicates.

Analysis

PROCEDURE

The ratio of secondary pentyl chlorides and bromides must be determined. At your instructor's option, you may do this by gas chromatography, NMR spectroscopy, or both methods.

GAS CHROMATOGRAPHY[2]

The instructor or a laboratory assistant may either make the sample injections or allow you to make them. In the latter case, your instructor will give you adequate instruction beforehand. A reasonable sample size is 2.5 μL. Inject the sample into the gas chromatograph, and record the gas chromatogram. The alkyl chlorides, because of their greatest volatility, have a shorter retention time than the alkyl bromides.

Once the gas chromatogram has been obtained, determine the relative areas of the peaks (see Technique 22, Section 22.12) If the gas chromatograph has an integrator, it will report the areas. Triangulation is the preferred method for determining areas if an integrator is not available. Record the percentages of all alkyl chloride and alkyl bromide products in the reaction mixture.

[2] *Note to the Instructor*: To obtain reasonable results for the gas chromatographic analysis of the pentyl halides, it may be necessary to supply the students with response-factor corrections (see Technique 22, Section 22.13). If pure samples of each product are available, check if the gas chromatograph responds equally to each substance, which is assumed here. Response factors (relative sensitivities) are easily determined by injecting an equimolar mixture of products and comparing peak areas.

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

The instructor or a laboratory assistant will record the NMR spectrum of the reaction mixture.[3] Submit a sample vial containing the mixture for this spectroscopic determination. The spectrum will also contain integration of the important peaks (see Technique 26, "Nuclear Magnetic Resonance Spectroscopy"). Compare the integrals of the *downfield* peaks of the alkyl halide multiplets. The relative heights of these integrals correspond to the relative amounts of each halide in the mixture.

REPORT

Record the percentages of all the alkyl chloride and alkyl bromide products in the reaction mixture for each of the isomeric pentanol substrates. You will need to share your data with results obtained by someone in the class who used the other starting alcohol. Your laboratory report must include the percentages of each alkyl halide, determined by each method used in this experiment, for the two alcohols that were studied. On the basis of the products identified and their relative percentages, develop an argument for a mechanism that will account for all the results obtained. All gas chromatograms and spectra should be attached to the report.

59 EXPERIMENT 59

Friedel–Crafts Acylation

Aromatic substitution

Directive groups

Vacuum distillation

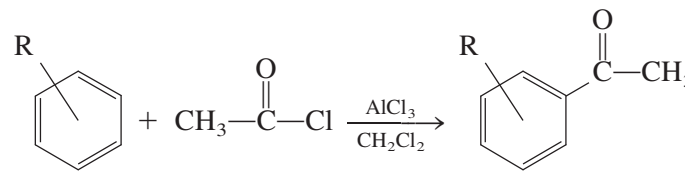
Infrared spectroscopy

NMR spectroscopy (proton/carbon-13)

Structure proof

Gas chromatography (optional)

In this experiment, a Friedel–Crafts acylation of an aromatic compound is undertaken using acetyl chloride.



Aromatic substrate **Acetyl chloride** **An acetophenone derivative**

[3] It is difficult to determine the ratio of pentyl chlorides and pentyl bromides using nuclear magnetic resonance. This method requires at least a 90-MHz instrument. At 300 MHz, the peaks are completely resolved.

If benzene (R = H) were used as the substrate, the product would be a ketone, acetophenone. Instead of using benzene, however, you will perform the acylation on one of the following compounds:

Toluene	Anisole (methoxybenzene)
Ethylbenzene	1,2-Dimethoxybenzene
o-Xylene (1,2-dimethylbenzene)	1,3-Dimethoxybenzene
m-Xylene (1,3-dimethylbenzene)	1,4-Dimethoxybenzene
p-Xylene (1,4-dimethylbenzene)	Mesitylene (1,3,5-trimethylbenzene)
Pseudocumene (1,2,4-trimethylbenzene)	Hemellitol(1,2,3-trimethylbenzene, gives two products)

Except for the last one listed, each of these substrates will give a single product, a *substituted* acetophenone. You are to isolate this product by vacuum distillation and determine its structure by infrared and NMR spectroscopy. That is, you are to determine at which position of the original compound the new acetyl group becomes attached.

This experiment is much the same kind that professional chemists perform every day. A standard procedure, Friedel–Crafts acylation, is applied to a new compound for which the results are not known (at least not to you). A chemist who knows reaction theory well should be able to predict the result in each case. However, once the reaction is completed, the chemist must prove that the expected product has actually been obtained. If it has not, and sometimes surprises do occur, then the structure of the unexpected product must be determined.

To determine the position of substitution, several features of the product's spectra should be examined closely. These include the following.

INFRARED SPECTRUM

- **The C—H out-of-plane bending modes found between 900 and 690 cm^{-1}.** The C—H out-of-plane absorptions (see Technique 25, Figure 25.19A) often allow us to determine the type of ring substitution by their numbers, intensities, and positions.
- **The weak combination and overtone absorptions that occur between 2000 and 1667 cm^{-1}.** This set of combination bands (see Figure 25.19B) may not be as useful as the first set given here because the spectral sample must be very concentrated for them to be visible. But they are often weak. In addition, a broad carbonyl absorption may overlap and obscure this region, rendering it useless.

PROTON-NMR SPECTRUM

- **The integral ratio of the downfield peaks in the aromatic ring resonances found between 6 ppm and 8 ppm.** The acetyl group has a significant anisotropic effect, and those protons found *ortho* to this group on an aromatic ring usually have a greater chemical shift than the other ring protons (see Technique 26, Section 26.8 and Section 26.13).
- **A splitting analysis of the patterns found in the 6–8 ppm region of the NMR spectrum.** The coupling constants for protons in an aromatic ring differ according to their positional relations:

ortho J = 6–10 Hz
meta J = 1–4 Hz
para J = 0–2 Hz

If complex second-order splitting interaction does not occur, a simple splitting diagram will often suffice to determine the positions of substitution for the protons on the ring. For several of these products, however, such an analysis will be difficult. In other cases, one of the easily interpretable patterns like those described in Section 26.13 will be found.

CARBON-13 NMR SPECTRUM

- In *proton-decoupled* carbon-13 spectra, the number of resonances for the aromatic ring carbons (at about 120–130 ppm) will be of help in deciding the substitution patterns of the ring. Ring carbons that are equivalent by symmetry will give rise to a single peak, thereby causing the number of aromatic carbon peaks to fall below the maximum of six. A *p*-disubstituted ring, for instance, will show only four resonances. Carbons that bear a hydrogen usually will have a larger intensity than "quaternary" carbons. (see Technique 27, Section 27.6.)
- In *proton-coupled* carbon-13 spectra, the ring carbons that bear hydrogen atoms will be split into doublets, allowing them to be easily recognized.[1]

As a final note, you should not eschew using the library. Technique 29 outlines how to find several important types of information. Once you think you know the identity of your compound, you might well try to find whether it has been reported previously in the literature and, if so, whether or not the reported data match your own findings. You may also wish to consult some spectroscopy books, such as Pavia, Lampman, Kriz, and Vyryan *Introduction to Spectroscopy*, or one of the other textbooks listed at the end of either Technique 25 or Technique 26, for additional help in interpreting your spectra.

REQUIRED READING

Sign in at www.cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review:	Techniques 5, 6, *12, 25, 26, and 27	
	*Technique 7	Reaction Methods, Sections 7.5 and 7.8
	Technique 13	Physical Constants of Liquids: The Boiling Point and Density
New:	*Technique 16	Vacuum Distillation, Manometers, Sections 16.1, 16.2, and 16.8
Optional:	Technique 22	Gas chromatography

Before you begin this experiment, you should review the chapters in your lecture textbook that deal with electrophilic aromatic substitution. Pay special attention to Friedel–Crafts acylation and to the explanations of directing groups. You should also review what you have learned about infrared and NMR spectra of aromatic compounds.

[1] Note to the instructor: For those not equipped to perform carbon-13 NMR spectroscopy, carbon-13 NMR spectra can be found reproduced in the Instructor's Manual.

SPECIAL INSTRUCTIONS

Both acetyl chloride and aluminum chloride are corrosive reagents. You should not allow them to come into contact with your skin, nor should you breathe them, because they generate HCl on hydrolysis. They may even react explosively on contact with water. When working with aluminum chloride, be especially careful to watch out for the powdered dust. Weighing and dispensing operations should be carried out in a hood. The workup procedure wherein excess aluminum chloride is decomposed with ice water should also be performed in the hood.

Your instructor will either assign you a compound or have you choose one for yourself from the list given at the beginning of this experiment. Although you will acetylate only one of these compounds, you should learn much more from this experiment by comparing your results with those of other students.

Notice that the details of vacuum distillation are left for you to figure out on your own. However, here are two hints. First, all of the products boil between 100°C and 150°C at 20-mm pressure. Second, if your chosen substrate is anisole, the product will be a *solid* with a low melting point and will solidify soon after vacuum distillation is completed. The solid can be distilled, but you should not run any cooling water through the condenser. It will also be worthwhile to preweigh the receiving flask, because it will be difficult to transfer the entire solidified product to another container to determine a yield.

SUGGESTED WASTE DISPOSAL

All aqueous solutions should be collected in a container specially marked for aqueous wastes. Place organic liquids in the container designated for nonhalogenated organic waste unless they contain methylene chloride. Waste materials that contain methylene chloride should be placed in the container designated for halogenated organic wastes. Note that your instructor may establish a different method of collecting wastes for this experiment.

NOTES TO THE INSTRUCTOR

It is suggested that you consider characterizing the Friedel-Crafts products by adding gas chromatography/mass spectrometry to the other spectroscopic techniques described in this experiment. Since most of the products show molecular ions, confirmation can be made of the molecular weight of the acylated product. The gas chromatography component will also help confirm that only a single acylated product was obtained. If the National Institute of Standards and Technology (NIST) database is available, confirmation of structure can be achieved.

You may want to consider omitting the vacuum distillation from this experiment. In almost all cases, a single product is formed, and the vacuum distillation does not materially improve the quality of the product. You may, however, observe unreacted starting material in NMR spectrum and in the gas chromatographic analysis.

A four-step synthesis may be considered by linking together the Friedel-Crafts reaction with the synthesis of a chalcone (Experiment 63) and then preparing an epoxide (Experiment 64) from the chalcone and/or a cyclopropanated chalcone (Experiment 65). It is likely that the Friedel-Crafts reaction should produce enough

acylated product for the reactions that follow. If you choose to link together the chalcone synthesis followed by epoxidation and cyclopropanation, it is suggested that you choose to prepare the acetyl derivatives of toluene, *p*-xylene, mesitylene, or anisole and use one of the recommended aldehydes shown in the following table to make the chalcone in Experiment 63.

Substrate	Aldehyde (Exp 63)
Toluene	4-methylbenzaldehyde 4-nitrobenzaldehyde 4-methoxybenzaldehyde piperonal
p-xylene	4-chlorobenzaldehyde 4-fluorobenzaldehyde 4-methoxybenzaldehyde
mesisylene	4-chlorobenzaldehyde 4-methoxybenzaldehyde
anisole	4-chlorobenzaldehyde 4-fluorobenzaldehyde 4-methylbenzaldehyde piperonal

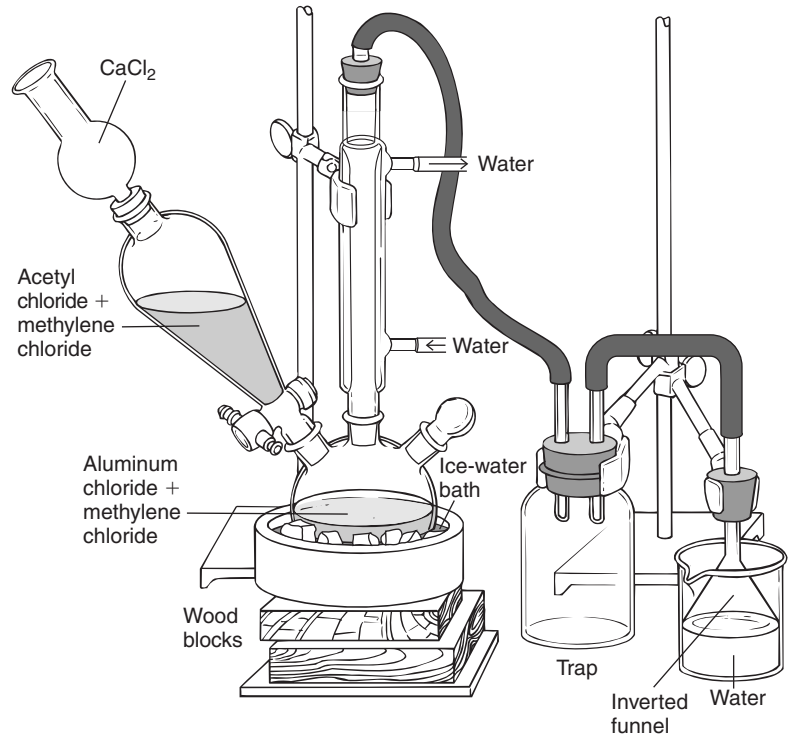
PROCEDURE

Apparatus. Assemble the reaction apparatus as shown in the figure. All the glassware must be *dry*, because both aluminum chloride and acetyl chloride react with water. Using a 500-mL round-bottom flask, attach a reflux condenser to the central neck, a separatory funnel to one side neck, and a stopper to the unused third neck. Place a filled calcium chloride drying tube on top of the addition (separatory) funnel. The entire apparatus, excluding the traps, should be assembled on a single-ring stand so that it can be shaken from time to time. Connect a gas trap to the top of the reflux condenser by attaching a length of flexible rubber tubing from its exit to your aspirator trap. Connect the other side of the aspirator trap to a funnel that is inverted and placed about 2 mm above the surface of a quantity of water in a 250-mL beaker. The inverted funnel, which is a trap for acidic gases, may be supported by placing a one-hole rubber stopper on its stem to allow it to be clamped to a ring stand.

CAUTION

Both aluminum chloride and acetyl chloride are corrosive and noxious. Avoid contact and conduct all weighings in a hood. On contact with water, either compound may react violently.

Starting the Reaction. Measure 25 mL of dichloromethane (methylene chloride) in a graduated cylinder and have it at hand. Working quickly in a hood to avoid reaction of the aluminum chloride with moisture in the air, weigh 14.0 g of anhydrous aluminum chloride into a 125-mL beaker. Using a powder funnel and a large spatula, transfer the aluminum chloride into the three-necked flask via the unused opening.



Apparatus for Friedel–Crafts acylation.

Use the dichloromethane to transfer any last traces of powder into the flask and to rinse the neck of the flask. After adding all of the dichloromethane, replace the stopper and start the cooling water in the condenser. Place an ice-water bath under the three-necked flask, and support it with wooden blocks. Mix and cool the suspension of aluminum chloride in the reaction flask by carefully rotating the entire ring stand to induce the contents of the flask to swirl gently.

Again working in a hood, use a pipet to transfer 8.0 g of acetyl chloride into a 125-mL Erlenmeyer flask. Using a graduated cylinder, add 15 mL of dichloromethane to this flask, and then transfer the mixture to the addition funnel attached to the reaction apparatus. Taking a total of about 15 minutes, slowly add the acetyl chloride solution to the suspension of aluminum chloride in the lower flask. (This should not be done hastily because the reaction is very exothermic; the mixture may boil quite vigorously.) During this addition period, frequently rotate the ring stand to mix and cool the contents of the flask, which should still be immersed in the ice-water bath.

After this addition is complete, dissolve 0.075 mole of your chosen aromatic compound in 10 mL of dichloromethane. Place this solution in the addition funnel, and slowly add it to the cooled acylation mixture over about 30 minutes. Swirl the mixture occasionally, as you watch out for excessive bubbling from the liberation of hydrogen chloride gas.

After this second addition is complete, remove the ice-water bath and allow the mixture to stand at room temperature for an additional 30 minutes. Swirl the reaction mixture frequently during this period.

Isolation of Product. Disconnect the gas trap, the condenser, and the separatory funnel, and take the three-necked flask to a hood. Pour the entire reaction mixture into a mixture of 50 g of ice and 25 mL of concentrated hydrochloric acid placed in a 400-mL beaker. Stir this mixture thoroughly for 10–15 minutes. Using a separatory funnel, separate the organic layer and save it. Extract the aqueous layer with 30 mL of dichloromethane, and add the

extract to the organic layer saved earlier. Wash the combined organic layers with 50 mL of saturated sodium bicarbonate solution. If a significant amount of acid is present, violent foaming will occur at this stage due to evolution of CO_2. Continue mixing and venting until the carbon dioxide emission ceases. Extract with a second portion of sodium bicarbonate if necessary. Separate the organic layer and dry it over granular anhydrous sodium sulfate for 10–15 minutes. Decant or filter to remove the drying agent from the solution. You may stop here and store your solution in a tightly stoppered flask.

Removal of Dichloromethane. Assemble an apparatus for simple distillation (see Technique 14, Figure 14.1). Add a boiling stone, and remove the dichloromethane by distillation. Dichloromethane boils at a fairly low temperature (bp 40°C). Place the recovered dichloromethane in a container designated for this purpose. Allow the dichloromethane to be driven off completely, otherwise it will cause foaming during the vacuum distillation. Monitor the evaporation by periodically checking the level in the flask and the amount of boiling action. Methylene chloride is removed, when the volume becomes constant.

NOTE: Review Technique 16, Sections 16.1 and 16.2, before proceeding.

Vacuum Distillation. Assemble an apparatus for vacuum distillation using an aspirator as shown in Technique 16, Figure 16.1. A manometer should be attached as shown in Technique 16, Figure 16.12. Using the manometer, check if the apparatus is vacuum tight and will achieve a good vacuum (less than 30–40 mmHg) before you proceed. If you do not have sufficient vacuum, recheck all joints and tubing connections until you locate the difficulty. Once all problems are solved, you may distill your product mixture at reduced pressure to yield the aromatic ketone that is your final product.

Determination of Yield. Transfer the product to a preweighed storage container, and determine its weight. Calculate the percentage yield. Determine the boiling point of your product using the macroscale method (see Technique 13, Section 13.2).

Spectroscopy. Determine both the infrared and the NMR spectra (proton and carbon-13). The infrared spectra may be determined neat, using salt plates (see Technique 25, Section 25.2), except for the product from anisole, which is a solid. For this product, one of the solution spectrum techniques (see Technique 25, Section 25.6) should be used. The proton NMR spectra can be determined as described in Technique 26, Section 26.1. The carbon-13 spectra can be run as described in Technique 27, Section 27.1.

The Report. In the usual fashion, you should report the boiling point (or melting point) of your product, calculate the percentage yield, and construct a separation scheme diagram. You should also give the actual structure of your product. Include the infrared and NMR spectra, and discuss carefully what you learned from each spectrum. If they did not help you determine the structure, explain the reason. As many peaks as possible should be assigned on each spectrum and all important features explained, including the NMR splitting patterns, if possible. Consult a handbook for the boiling point (or melting point) of the possible products. Discuss any literature you consulted, and compare the reported results with your own.

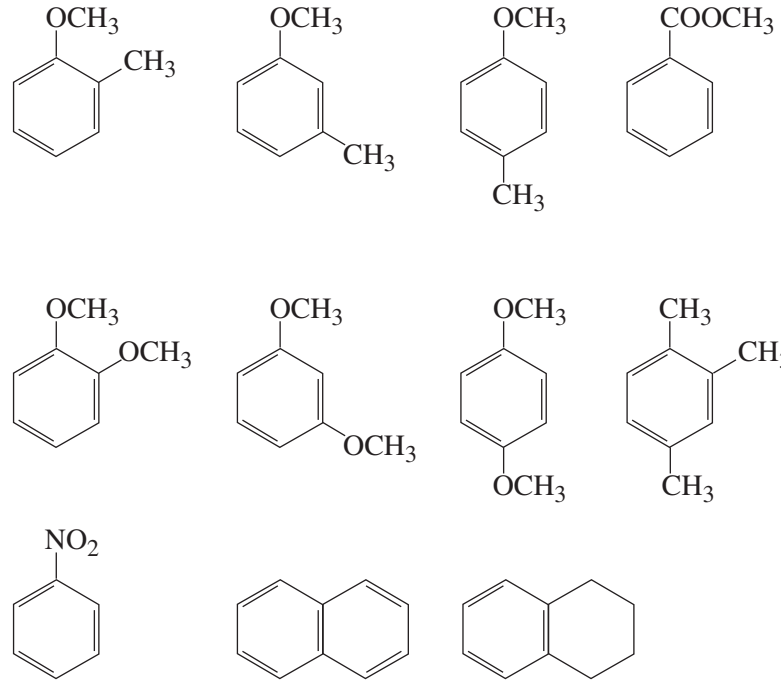
You should explain in terms of aromatic substitution theory why the substitution occurred at the position observed and why a single substitution product was obtained. Could you have predicted the result in advance?

REFERENCE

Schatz, Paul F. Friedel-Crafts Acylation. *J.Chem. Educ.* **1979,** *56,* 480.

QUESTIONS

1. The following are all relatively inexpensive aromatic compounds that could have been used as substrates in this reaction. Predict the product or products, if any, that would be obtained on acylation of each of them using acetyl chloride.



2. Why is it that only monosubstitution products are obtained in the acylation of the substrate compounds chosen for this experiment?

3. Draw a full mechanism for the acylation of the compound you chose for this experiment. Include attention to any relevant directive effects.

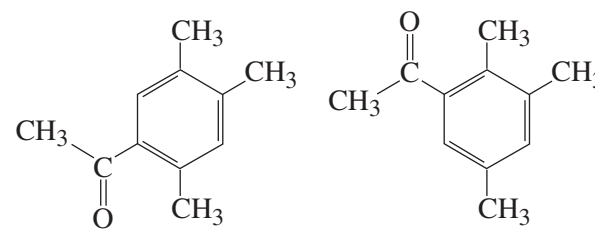
4. Why do none of the substrates given as choices for this experiment include any with meta-directing groups?

5. Acylation of n-propylbenzene gives an unexpected (?) side product. Explain this occurrence and give a mechanism.

6. Write equations for what happens when aluminum chloride is hydrolyzed in water. Do the same for acetyl chloride.

7. Explain carefully, with a drawing, why the proton-substituted *ortho* to an acetyl group normally have a greater chemical shift than the other protons on the ring.

8. The compounds shown are possible acylation products from 1,2,4-trimethylbenzene (pseudocumene). Explain the only way you could distinguish these two products by NMR spectroscopy.



60 **EXPERIMENT 60**

The Analysis of Antihistamine Drugs by Gas Chromatography–Mass Spectrometry

Gas chromatography–mass spectrometry

Critical thinking application

The use of **gas chromatography–mass spectrometry (GC-MS)** as an analytical technique is growing in importance. GC-MS is a very powerful technique in which a gas chromatograph is coupled to a mass spectrometer that functions as the detector. If a sample is sufficiently volatile to be injected into a gas chromatograph, the mass spectrometer can detect each component in the sample and display its mass spectrum. The user can identify the substance by comparing its mass spectrum with the mass spectrum of a known substance. The instrument can also make this comparison internally, by comparing the spectrum with spectra stored in its computer memory.

Antihistamines are a class of pharmaceutical agents commonly used to combat symptoms of allergies and colds. They reduce physiological effects of histamine production. Histamine, a protein, is normally released in the bloodstream as part of the body's reaction to intrusions by pollen, dust, molds, pet hair, and other **allergens** (substances that cause an allergic reaction). Even certain foods can cause an allergic response in some people. Excessive amounts of histamine can cause various disorders, including asthma, hay fever, sneezing, nasal secretions, skin irritations and swelling, hives, digestive disorders, and watering eyes. People take antihistamines to reduce these symptoms. Unfortunately, antihistamines also have some side effects, the most important of which is drowsiness. In fact, certain antihistamines are also sold as sleep aids.

In this experiment, you will prepare solutions of common over-the-counter antihistamine and cold-remedy tablets. The samples, once prepared, will be analyzed using a GC-MS instrument, and you will use the results to identify the significant antihistamine substances that compose the original tablet.

REQUIRED READING

New:	Technique 22	Gas Chromatography, Section 22.13
	Technique 28	Mass Spectrometry
	Technique 29	Guide to the Chemical Literature

SPECIAL INSTRUCTIONS

This experiment requires the use of a GC-MS instrument. Before using this instrument, be certain to obtain instructions on its operation. Your instructor may choose to perform the injections instead.

SUGGESTED WASTE DISPOSAL

Dispose of all solutions by discarding them in the container specified for nonhalogenated organic solvents. If your antihistamine contains either brompheniramine or chlorpheniramine, discard the solutions in the container specified for halogenated organic wastes.

PROCEDURE

Before beginning this experiment, you will need to rinse two 50-mL beakers, a syringe, and a snap-cap sample vial with HPLC-grade or spectrograde ethanol. The glassware should be clean and dry before rinsing. Two rinsings of each item of glassware are recommended.

If your tablet has a colored coating, remove it by chipping it away with a microspatula. Grind the tablet to a fine powder using a mortar and pestle. Weigh approximately 0.100 g of the powdered tablet into a 50-mL beaker that has been pre-rinsed with ethanol. Add 10 mL of HPLC-grade ethanol to the beaker, and let this solution stand, covered, for several minutes. Filter this solution by gravity through a fluted filter into a second, pre-rinsed 50-mL beaker.

Draw the filtered solution into a pre-rinsed 5-mL syringe (without a needle), attach a 0.45-μm filter cartridge to the syringe, and expel the solution through the filter cartridge into a pre-rinsed sample vial. Repeat this process with a second syringe filled with solution. Cover the top of the sample vial with a square of aluminum foil and attach the snap-cap to the vial, over the top of the foil. Label the vial and store it in the refrigerator.

Analyze the sample by gas chromatography–mass spectrometry. Your instructor or laboratory assistant may either make the sample injections or allow you to make them. In the latter case, your instructor will give you adequate instructions beforehand. A reasonable sample size is 2 μL. Inject the sample into the gas chromatograph, and obtain the printout of the total ion chromatogram, along with the mass spectrum of each component. You should also obtain the results of a library search for each component.

The library search will give you a list of components detected in your sample and the retention time and relative area for each component. The results will also list possible substances that the computer has tried to match against the mass spectrum of each component. This list—often called a "hit list"—will include the name of each possible compound, its Chemical Abstracts Registry number (CAS number), and a "quality" ("confidence") measure, expressed as a percentage. The "quality" parameter estimates how closely the mass spectrum of the substance on the "hit list" fits the observed spectrum of that component in the gas chromatogram.

In your report, you should identify each significant component in the sample and provide its name and structural formula. You may have to use the CAS number as a key to look up the complete name and structure of the compound (see Technique 29, Section 29.11). You may need to search a computerized database to get the necessary information, or you may be able to find it in the *Aldrich Handbook of Fine Chemicals,* issued by the Aldrich Chemical Company. Current issues of this catalog include listings of substances by CAS number. In your report, you should also record the relative percentage of the substance in the tablet extract. Finally, your instructor may also ask you to include the "quality" parameter from the "hit list." If possible, determine which components have antihistamine activity and which ones are present for another purpose. *The Merck Index* may provide this information.

61 **EXPERIMENT 61**

Carbonation of an Unknown Aromatic Halide

Grignard reaction

Crystallization and melting point

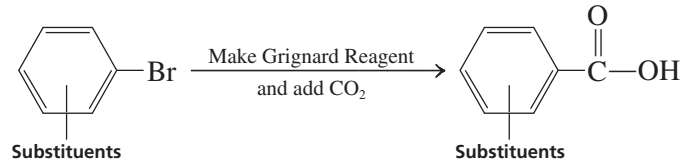
Student-designed project

Identification of an unknown

Carbon-13 and proton NMR (optional)

In this experiment, you will be issued an unknown aromatic halide. Your project is to convert it to a carboxylic acid using the Grignard reaction.

Convert the unknown halide to a carboxylic acid, purify the crude acid by crystallization, determine its melting point, and identify the starting compound based on the melting point of its acid derivative. At the option of your instructor, you might be asked to use NMR spectroscopy on either your product or your starting material.



You will be assigned one of the unknown starting materials shown in the following two lists. The compounds in List A can be identified by using the melting point of the carboxylic acid you obtain and not by any other data. If you have NMR available (especially carbon-13 NMR), your instructor may wish to expand the list of possible unknowns to include List B.

List A[1]		**List B**[1,2]	
Bromo compound	**Mp of acid**	**Bromo compound**	**Mp of acid**
2-bromoanisole	98–100	1-bromo-4-butylbenzene	100–113
3-bromoanisole	106–108	2-bromotoluene	103–105
1-bromo-2,4-dimethylbenzene	124–126	3-bromotoluene	108–110
1-bromo-2,5-dimethylbenzene	132–134	1-bromo-2,6-dimethylbenzene	114–116
1-bromo-4-propylbenzene	142–144	1-bromo-2,3-dimethylbenzene	145–147
1-bromo-2,4,6-trimethylbenzene	154–155	4-bromotoluene	180–182
1-bromo-4-*t*-butylbenzene	165–167		
1-bromo-3,5-dimethylbenzene	172–174		
4-bromoanisole	182–185		

[1]Except for the anisole- and toluene-based halides, the compounds in both lists are consistently named so that the bromo group is given the same priority as the carboxyl group that will replace it. In several cases, therefore, the name given is not necessarily the correct IUPAC name.

[2]These compounds can be used only if NMR is available. They cannot be distinguished from those in column A by melting point alone.

REQUIRED READING

Sign in at www.cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review:

*Technique 11	Crystallization: Purification of Solids
Technique 25	Infrared Spectroscopy, Sections 25.4, 25.5, and 25.14
Technique 26	Nuclear Magnetic Resonance Spectroscopy, Sections 26.1, 26.2, and 26.13
Technique 27	Carbon-13 Nuclear Magnetic Resonance Spectroscopy, Sections 27.1 and 27.7

SPECIAL INSTRUCTIONS

If you are unable to identify your product based on its melting point, you may be required to use NMR spectroscopy.

NOTES TO THE INSTRUCTOR

This experiment will require you to provide a great deal of assistance to each student. As a result, it may be very difficult to use this experiment with a large class. It is a good idea to have the students prepare and present their procedures for approval before they are allowed to begin the experimental work. This experiment could require three to four periods.

Be sure that any halides you use have at least 90% purity. Avoid technical-grade chemicals, otherwise it will be difficult for the students to achieve a good melting point. These compounds have a very strange type of naming in the Aldrich catalog (such as 3-bromo-*o*-xylene). Be sure you see the Instructor's Manual for correct ordering instructions.

PROCEDURE

You are asked to devise the entire experimental procedure together with reagent quantities. You should also prepare a separation scheme. Your plan should be presented to your instructor for approval before you begin work. It may be helpful to consult Experiment 33B, which is closely related to this one.

You may assume that your unknown has a molecular weight of about 200 mass units, and you should use about 3 g of your starting halide. Be sure, however, that you check the stoichiometry and use a reasonable amount of magnesium. In order to determine an accurate melting point, be sure that the compound is both pure and dry. It may be necessary to crystallize your product more than one time. Most carboxylic acids can be crystallized from water or an ethanol–water mixed solvent. It is recommended that you consult *The Merck Index,* the *Handbook of Chemistry and Physics,* or another handbook to determine the best solvent for your final crystallizations.

SPECTROSCOPY

Infrared Spectrum. An infrared spectrum should be determined to verify that the product is a carboxylic acid. The products are all solids, and the best method to determine the infrared spectrum would be through the use of a KBr pellet (see Technique 25, Section 25.5) or by the dry-film method (see Technique 25, Section 25.4).

NMR Spectrum. If your instructor asks you to determine NMR spectra for your product, you should check its solubility in $CHCl_3$. If it dissolves in $CHCl_3$, it will probably dissolve in $CDCl_3$, the usual NMR solvent. However, many acids do not dissolve in $CDCl_3$. The commercial solvent called Unisol[1] (a mixture of $CDCl_3$ and DMSO-d_6) will dissolve most, but not all, carboxylic acids. If your product does not dissolve in Unisol, a D_2O-NaOD solution (see Technique 26, Section 26.2) may be used. If possible, you should determine the carbon-13 NMR as well as the proton spectrum.

REPORT

The report should include a balanced equation for the preparation of your acid. You should calculate both the theoretical and percentage yields. Write out your complete procedure as you actually performed it. Include the actual results of your melting-point determination(s), and compare it (them) to the expected result.

Include an infrared spectrum of your product, and interpret the major absorption peaks. Attempt to use the overtone and out-of-plane absorption bands to explain the substitution pattern of your ring. If you determined NMR spectra, you should include them along with an interpretation of the peaks and splitting patterns. See if you can work out a complete tree diagram for the aromatic ring.

62 **EXPERIMENT 62**

The Aldehyde Enigma

Aldehyde chemistry

Extraction

Crystallization

Spectroscopy

Devising a procedure

Critical-thinking application

The reaction mixture in this experiment contains 4-chlorobenzaldehyde, methanol, and aqueous potassium hydroxide. A reaction occurs that produces two organic compounds, compound 1 and compound 2. Both are solids at room temperature. Your task is to isolate, purify, and identify both compounds. A specific procedure is given for preparing the compounds, but you will need to work out the procedures for most other parts of this experiment.

[1] Unisol is a mixture of chloroform-d and DMSO-d_6 available from Norell, Inc., 120 Marlin Lane, Mays Landing, NJ 08330.

SPECIAL INSTRUCTIONS

If the work on this experiment is done in pairs, work closely together as a team, dividing up the work equitably. A logical division of labor is for one student to work on compound 1 and the other to work on compound 2. Whether you work in pairs or not, you will need to plan your work carefully before coming to the laboratory to make efficient use of class time.

SUGGESTED WASTE DISPOSAL

Dispose of all filtrates into the container designated for halogenated organic wastes.

PROCEDURE

This procedure should produce enough of each compound to complete the experiment; however, in some cases, it may be necessary to run the reaction a second time. Although this experiment can be done individually, it works especially well for two students to work together.

CAUTION

Be sure there is no acetone present on any of the glassware. Acetone will interfere with the desired reaction.

Running the Reaction. Add 1.50 g of 4-chlorobenzaldehyde and 4.0 mL of methanol to a 25-mL round-bottom flask. With gentle swirling, add 4.0 mL of an aqueous potassium hydroxide solution with a Pasteur pipet.[1] *Avoid getting potassium hydroxide solution on the ground-glass joint!* Add a stir bar to the flask and attach a water-cooled condenser. Using a hot-water bath, heat the reaction mixture at about 65°C with stirring for 1 hour. Cool the mixture to room temperature, and add 10 mL of water to the flask. Pour the mixture into a beaker, and use another 10 mL of water to aid the transfer into the beaker.

Using a separatory funnel, extract the reaction mixture with 10 mL of methylene chloride. Drain the organic layer (bottom) into another container. Extract the aqueous layer with another 10-mL portion of methylene chloride. Combine the organic layers. The organic layer contains compound 1, and the aqueous layer contains compound 2.

Organic Layer. Wash the organic layer 2 times with 10-mL portions of 5% aqueous sodium bicarbonate solution. Then wash the organic layer with an equal volume of water. If an emulsion forms, use a little saturated sodium chloride solution to break it. Dry the organic layer over granular anhydrous sodium sulfate for 10 –15 minutes. After the dried solution is removed from the drying agent, the organic layer should contain only compound 1 and methylene chloride. Isolate compound 1 by removing the methylene chloride.

Purify compound 1 by crystallization. See "Testing Solvents for Crystallization," Technique 11, Section 11.6, for instructions on how to determine an appropriate solvent. You should try 95% ethanol and xylene. After determining the best solvent, crystallize

[1]Dissolve 61.7 g of potassium hydroxide in 100 mL of water.

the compound using a hot-water bath at about 70°C, to avoid melting the solid. Identify compound 1 using some or all of the techniques given in the next section, "Identification of Compounds."

Aqueous layer. To precipitate compound 2, add 10 mL of cold water and acidify with 6 M HCl. As acid is added, stir the mixture. Do not overacidify the solution; pH 3 or 4 is fine. If no precipitate is formed on acidification, add saturated NaCl to aid the process. This is called "salting out."

Isolate compound 2, and dry it in an oven at about 110°C. Purify it by crystallization (see Technique 11, Section 11.6). You should try using methanol and 95% ethanol. After determining the best solvent, purify the compound by crystallization, and identify the purified solid using some or all of the techniques given in the next section, "Identification of Compounds."

IDENTIFICATION OF COMPOUNDS

Identify compound 1 and compound 2 using any of the following techniques:

1. *Melting point:* Consult a handbook for literature values.
2. *Infrared spectroscopy:* KBr pellet is preferred.
3. *Proton and/or carbon NMR:* Compound 1 dissolves easily in $CDCl_3$; use deuterated DMSO or Unisol to dissolve compound 2.[2]
4. *"Wet" chemical tests:* Some of the tests listed in Experiment 55 may be helpful, such as solubility tests, Beilstein test for halide, and others you may think appropriate.
5. *Physical properties:* Color and shape of crystals may also be helpful.

REPORT

Write out a complete procedure by which you synthesized and isolated compounds 1 and 2. Describe the results of your experiments to determine a good crystallization solvent for both compounds. Draw the structures of compounds 1 and 2. Give all melting-point data and results of other tests used to identify the two compounds. Identify significant peaks in the infrared spectrum and proton/carbon NMR spectra. Show clearly how all of these results confirm the identity of the two compounds. Write a balanced equation for the synthesis of compounds 1 and 2. What type of reaction is this? Propose a mechanism for the reaction. Determine the percentage yield of each of the compounds.

[2] Unisol is a mixture of chloroform-d and DMSO-d_6 available from Norell, Inc., 120 Marlin Lane, Mays Landing, NJ 08330.

63 **EXPERIMENT 63**

Synthesis of Substituted Chalcones: A Guided-Inquiry Experience

Crystallization

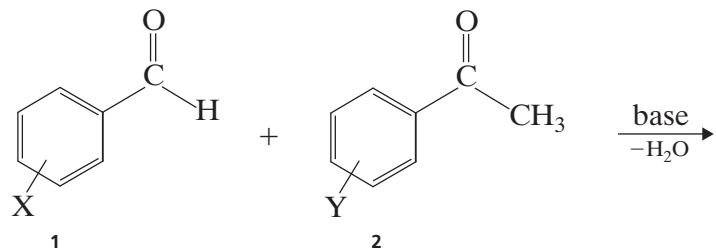
Aldol condensation

Use of the chemical literature

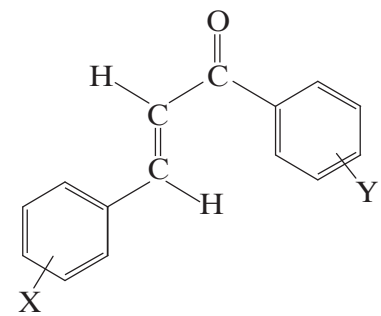
Project-based experiment

In Experiment 37, you were introduced to the **aldol condensation reaction**, which you used to prepare a variety of **benzalacetophenones** or **chalcones**. In this experiment, you will again prepare chalcones, but you will do so in a guided-inquiry experiment that simulates some of the methodology that you are likely to use in research.

You will select from a variety of substituted benzaldehydes (1) and substituted acetophenones (2) to prepare benzalacetophenones (chalcones) (3) that bear a combination of substituents in each of the aromatic rings (see figure).



1 2



3

Once you have selected your starting materials, you will determine the complete structure of the condensation product that you expect to be formed in your reaction. You will also determine the molecular formula. With this information, you will be able to conduct an online literature search of *Chemical Abstracts* using **STN Easy** or SciFinder Scholar. From the literature search, you will be able to obtain the complete name of your target chalcone, its CAS Registry Number, and literature citations from the primary chemical literature. These literature citations should be able to afford you characterization information about your target chalcone, including melting points, infrared spectra, and NMR spectra.

After you have conducted the literature search, the final step will be to prepare your chalcone and compare its properties with those that you were able to find in the literature.

The purpose of this experiment is to introduce you to many of the activities that you are likely to encounter in research. These include an examination of the target molecule, selection of appropriate starting materials, a thorough search of the primary chemical literature, laboratory synthesis of the desired compound, and characterization (including a comparison of the physical properties of the product with published values found in journal articles or other tables of data).

REQUIRED READING

Sign in at www.cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review:	*Technique 8	Filtration, Section 8.3
	*Technique 11	Crystallization: Purification of Solids, Section 11.3
	Experiment 2	Crystallization
New:	Technique 29	Guide to the Chemical Literature

SPECIAL INSTRUCTIONS

Before beginning this experiment, you should select a substituted benzaldehyde and a substituted acetophenone. Your instructor will determine the method of assigning these reactants. You should also sign up for an STN Easy or SciFinder Scholar computer session. Your instructor will provide you with instructions on how to conduct an online computer search. Before coming to the computer session, you should work out the structure of your target compound and determine its molecular formula.

Note that sodium hydroxide solutions are caustic. Be careful when handling the substituted benzaldehydes and acetophenones. Wear personal protective equipment and work in a well-ventilated area.

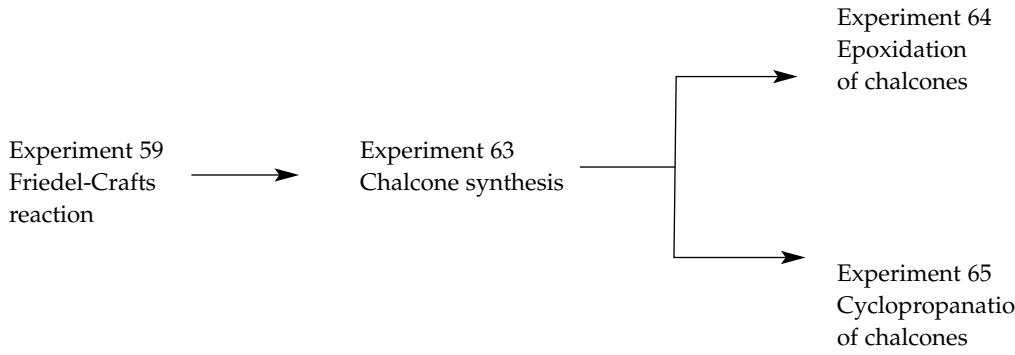
SUGGESTED WASTE DISPOSAL

All filtrates should be poured into a waste container designated for nonhalogenated organic waste. Note that your instructor may establish a different method of collecting wastes for this experiment.

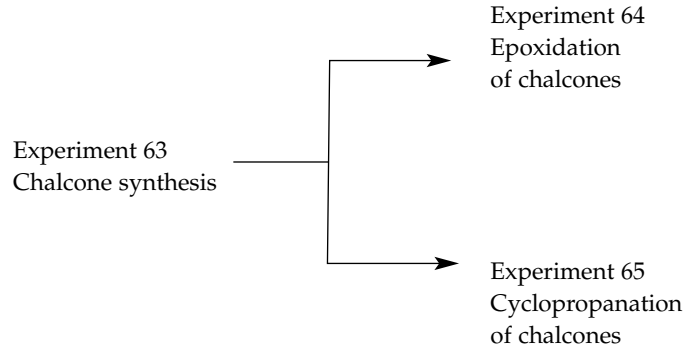
NOTES TO THE INSTRUCTOR

It is best to introduce this project two to three weeks before the date of the actual chalcone synthesis to allow time for searching the literature. You will have to develop a method of assigning a target compound to each student. You will also have to schedule computer time for the online searching of *Chemical Abstracts.* We recommend that you prepare a handout that describes how to search *Chemical Abstracts* using STN Easy or SciFinder Scholar. The handout should guide the students through the process of finding the registry number for the target compound and for finding pertinent references, with particular attention to references describing the preparation of the compound. Finally, you will have to determine whether to require a formal laboratory report and what the expected format should be.

You may choose to create a multistep synthesis by linking this experiment to the Friedel-Crafts acylation reaction (Experiment 59) for the preparation of the substituted acetophenone. Experiment 59 contains suggestions for Friedel-Crafts acetophenones that work well when converted to chalcones. Following the synthesis of the chalcone in the current experiment, you can then carry out the cyclopropanation reaction (Experiment 65) and/or the epoxidation of the chalcone (Experiment 64). If the multistep scheme is to be followed, you should ask the class to scale up the chalcone preparation in order to have enough material to complete Experiment 64 and 65.



Another multistep synthesis, shown below, involves linking the synthesis of a chalcone in Experiment 63 with the epoxidation of the chalcone (Experiment 64) and/or the cyclopropanation of the chalcone (Experiment 65). If you plan for creating a multistep synthesis as described here, it may be a good idea to make a larger quantity of chalcone by scaling up the amounts of substituted acetophenone and substituted benzaldehyde used to prepare the chalcone.



PROCEDURE

Before beginning the synthesis of your chalcone, determine its structure and molecular formula and perform the online search of *Chemical Abstracts,* following the instructions that your instructor provides.

Running the Reaction. Place 0.005 moles of your substituted benzaldehyde into a *tared* 50-mL Erlenmeyer flask, and reweigh the flask to determine the weight of material transferred.

Add 0.005 moles of the substituted acetophenone and 4.0 mL of 95% ethanol to the flask that contains the substituted benzaldehyde. Add a magnetic stirring bar to the flask. Swirl the flask to mix the reagents, and dissolve any solids present. It may be necessary to

warm the mixture on a steam bath or hot plate to dissolve the solids. If this is necessary, the solution should be cooled to room temperature before proceeding to the next step.

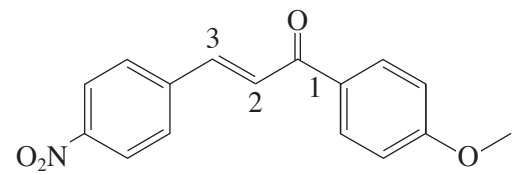
Add 0.5 mL of sodium hydroxide solution to the benzaldehyde/acetophenone mixture.[1] Add a magnetic stir bar and stir the mixture. Before the mixture solidifies, you may observe some cloudiness. *Wait until the cloudiness has been replaced with an obvious precipitate settling out to the bottom of the flask before proceeding to the next paragraph.* Continue stirring until solid forms (approximately 3 to 5 minutes).[2] Scratching the inside of the flask with your microspatula or glass stirring rod may help to crystallize the chalcone.[3]

Isolation of the Crude Product. Add 10 mL of ice water to the flask *after a solid has formed as indicated in the previous paragraph*. Stir the solid in the mixture with a spatula to break up the solid mass. Transfer the mixture to a small beaker with 5 mL of ice water. Stir the precipitate to break it up, and then collect the solid, under vacuum, on a Hirsch or Büchner funnel. Wash the product with cold water. Allow the solid to air dry for about 30 minutes. Weigh the solid.

Crystallization. Crystallize your entire sample from hot 95% ethanol. You will have to use the crystallization techniques introduced in Experiment 2 to crystallize the chalcone. Once the crystals have been allowed to dry thoroughly, weigh the solid, determine the percentage yield, and determine the melting point.

Spectroscopy. Determine the infrared spectrum of your product. Dissolve some of your chalcone in $CDCl_3$ (in some cases DMSO-d_6 may be required for sparingly soluble compounds) for ^1H NMR analysis. The chalcone spectrum will show a pair of doublets ($^3J \approx 16$ Hz appearing near 7.7 and 7.3 ppm) for the two vinyl protons in the starting chalcone. These vinyl protons in the chalcone appear in the same region as the aromatic protons on the benzene rings. However, the doublets for the protons in the benzene ring are more narrowly spaced ($^3J = 7$ Hz) than the doublets for the vinyl protons. Often you will see a singlet at 7.25 ppm for $CHCl_3$ present in the $CDCl_3$ solvent. In addition, a water peak may appear near 1.5 ppm. If deuterated DMSO had been used as solvent, you may see a pattern at about 2.6 ppm for non-deuterated DMSO. At the option of your instructor, determine the ^{13}C spectrum.

Laboratory Report. At the option of your instructor, you may be required to write a formal laboratory report. If this is the case, use the format that your instructor provides, or base your report on the style found in the *Journal of Organic Chemistry* (see Technique 29). If a literature search is required, use *SciFinder Scholar* to search for the melting point of your chalcone for comparison with the value you obtain. It should be noted here that when searching the chemical literature with *SciFinder Scholar*, you will find that *Chemical Abstracts* often does not use the name "chalcone" as the name of your compound. As an example, notice the name that is assigned to the following structure.



(E)-1-(4-methoxphenyl)-3-(4-nitrophenyl)-2-propen-1-one

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[1] This reagent should be prepared in advance by the instructor in the ratio of 6.0 g of sodium hydroxide to 10 mL of water.

[2] In some cases, chalcone may not precipitate. If this is the case, stopper the flask and allow it to stand until the next laboratory period. It is sometimes helpful to add an additional portion of base. Usually chalcone will precipitate during that time.

[3] In some cases, the aldol intermediate does not eliminate to form chalcone leading to an OH group in the infrared spectrum. In addition, chalcone may undergo a Michael addition of the enolate of the acetophenone on the chalcone. If either of these reactions occur, the ^1H NMR spectrum will show peaks in the 2.0–4.2 ppm range.

Submit the purified sample of your chalcone in a labeled vial to the instructor unless it is to be used in Experiment 64 and 65.

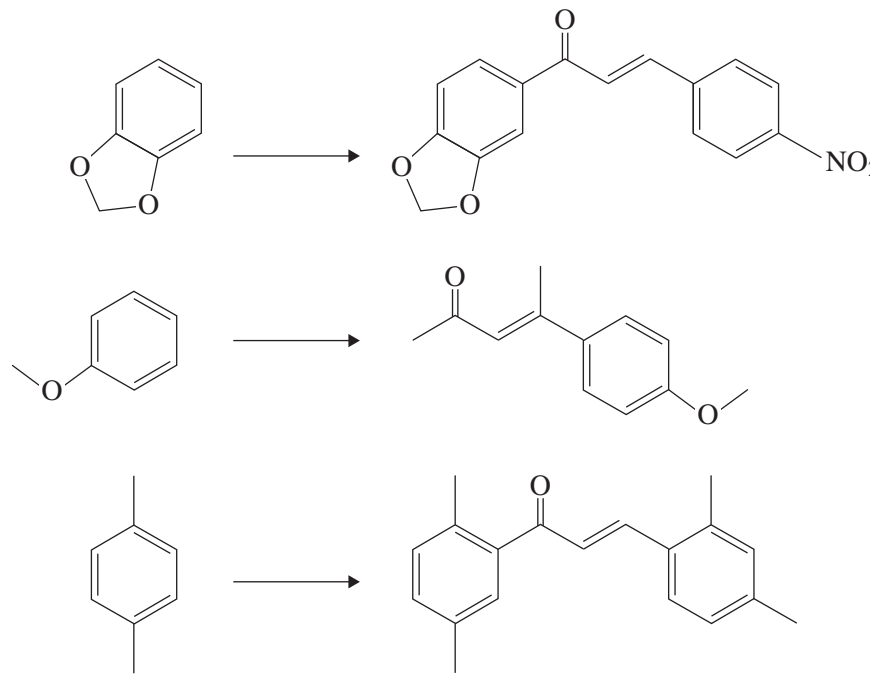
REFERENCES

Vyvyan, J. R.; Pavia, D. L.; Lampman, G. M.; Kriz, G. S. Preparing Students for Research: Synthesis of Substituted Chalcones as a Comprehensive Guided-Inquiry Experience. *J. Chem. Educ.* **2002,** *79*, 1119–1121.

Crouch, R. D.; Richardson, A.; Howard, J. L.; Harker, R. L.; Barker, K. H. The Aldol Addition and Condensation: The Effect of Conditions on Reaction Pathway. *J. Chem. Educ.* **2007,** *84*, 475–476.

QUESTIONS

1. Show how you begin with the indicated starting material and the Friedel-Crafts reaction to prepare the indicated chalcone products. You will require aldehydes and ketones in addition to the indicated starting material.



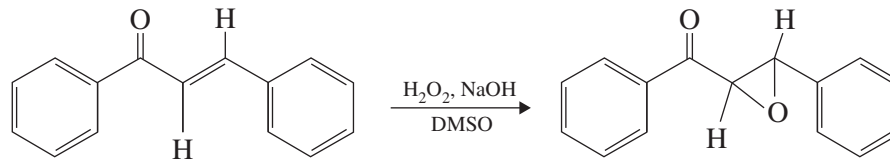
64 **EXPERIMENT 64**

Green Epoxidation of Chalcones

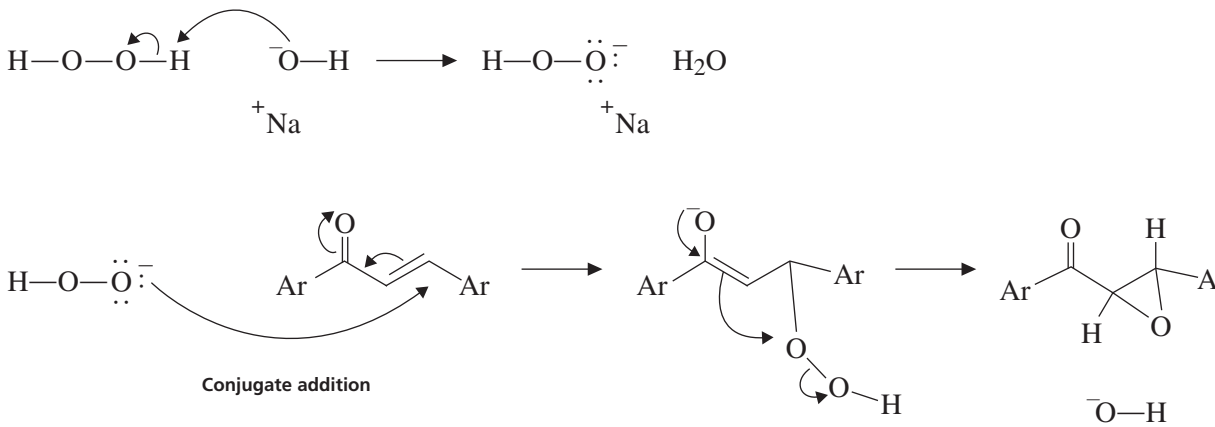
Green chemistry

Reactions of Chalcones

Epoxides are important intermediates widely used in multistep synthesis, and you have seen or will see them being used as intermediates in organic synthesis in your organic chemistry lecture courses. The common epoxidation reagent, *m*-chloroperoxybenzoic acid (*m*-CPBA), that you may have learnt your lecture courses, does not work well on electron-poor conjugated ketones such as the chalcones employed in this experiment. Instead, we will use hydrogen peroxide in aqueous sodium hydroxide to prepare the epoxide. A "green" epoxidation of chalcones using these reagents has been reported in the literature, and this technique will be employed in this experiment.[1] The reaction is conducted in a not-so-green mixture of methanol, water, and dimethylsulfoxide (DMSO). DMSO is required to improve the solubility of the highly polar chalcones. The reaction mixture is stirred in an ice bath at 0°C for 1 hr to yield reasonable yields of epoxides. For example *trans*-chalcone (l,3-diphenyl-2-propen-l-one) produces a 95% yield of the epoxide. Typical yields range from about 60 to 95% with other chalcones. To confirm that you have prepared the epoxide, you will analyze your product with ^{1}H NMR.



The mechanism follows the following pathway:



[1] Fioroni, G.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. Epoxidation of α, β-Unsaturated Ketones in Water. An Environmentally Benign Protocol. *Green Chemistry* **2003,** *5*, 425–428. Experiment developed by Butler, G., and Lampman, G.M., Western Washington University, Bellingham, WA.

REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: Techniques 6, *7, *8, *11, 25, and 26

Read: Preparation of epoxides and reactions of epoxides in your lecture textbook

SUGGESTED WASTE DISPOSAL

Dispose of all aqueous wastes in the container designated for aqueous waste. Place the organic waste in the nonhalogenated organic waste container.

NOTES TO THE INSTRUCTOR

Strong electron-releasing groups such as methoxy and methylenedioxy tend to retard the epoxide formation reaction on chalcones, leading to some residual chalcone remaining in the product. Alkyl groups are also electron-releasing, and they retard the formation of the epoxide. However, electron-withdrawing groups such as nitro and halogens enhance the reactivity of the chalcone. When halogen atoms are present along with methoxy, methylenedioxy, or alkyl groups, most of the chalcone is converted to the epoxide.

Students can determine the percent conversion of the chalcone to the epoxide by integrating one of the vinyl protons remaining in the aromatic region for the chalcone starting material and comparing that integral with the integral value for one of the protons on the epoxide ring. See the Spectroscopy section below for details.

PROCEDURE

Starting the Reaction. Add 0.50 mmole of your selected chalcone from Experiment 63, 3.5 mL of methanol, and a stir bar to a 50-mL round-bottom flask. Stir and gently heat the mixture for a few minutes to see if the chalcone will dissolve in methanol. If the chalcone does dissolve, proceed to the next paragraph. Most chalcones require some dimethylsulfoxide (DMSO) in addition to methanol to dissolve. Gradually add DMSO in 0.5-mL portions using a plastic Pasteur pipet until the chalcone dissolves with slight heating and stirring. It may take as much as 1 to 3 mL of DMSO to completely dissolve the chalcone. Now cool the round-bottom flask to room temperature. Some of the chalcone may precipitate as the temperature is lowered to room temperature, but the majority of the chalcone will remain in solution. You may proceed with the next step even if some solid remains.

Add 0.25 mL of 2 M aqueous sodium hydroxide using a plastic disposable pipet. Now add 65 μL of 30% hydrogen peroxide using an automatic pipet. Support the flask in an ice/water bath with a clamp, but do not stopper the flask. Stir the mixture in an ice bath for 1 hr. Add more ice when necessary to keep the mixture between 0 and 2°C. Some chalcone will precipitate when the flask is cooled in the ice bath, but this should not be of concern because the chalcone will be converted to the epoxide even if some solid remains. Do not add any more DMSO.

Extraction with Diethyl Ether. Following the 1-hr reaction period, discontinue the stirring and add 5 mL of ice-cold water. A solid or possibly an oil should form. To extract the epoxide from the aqueous layer, add 10 mL of diethyl ether to the flask. Swirl the flask to help the epoxide dissolve in diethyl ether. If necessary, add more diethyl ether to help dissolve the

epoxide. The idea is to create two relatively clear layers, one aqueous and one organic layer. The amount of diethyl ether added is not critical.

Carefully transfer the mixture from the round-bottom flask to a separatory funnel. When pouring from the flask, use a funnel and a stir rod to direct the liquid into the funnel so that the liquid ends up in the funnel rather than on the surface of your hood! (It is difficult to pour from a flask with no lip!). Shake the funnel vigorously to extract the mixture, remove the lower aqueous layer, and pour the remaining ether layer from the top of the funnel into an Erlenmeyer flask. Now reintroduce the aqueous layer back into the separatory funnel, and re-extract it with another 10-mL portion of diethyl ether. After shaking, remove the lower aqueous layer, and again pour the ether extract from the top of the separatory funnel into the Erlenmeyer flask containing the first ether extract.

Drying and Removal of Diethyl Ether. Add anhydrous magnesium sulfate to the Erlenmeyer flask to dry the ether extracts. Cork the flask, and occasionally swirl the flask over a 5-min to 10-min period to dry the solution. Gravity filter the solution through a piece of fluted filter paper into a preweighed 50 or 100-mL round-bottom flask (instructor-provided, if necessary). Remove the ether on the rotary evaporator, under vacuum. If a rotary evaporator is not available, your instructor will recommend an alternate method of removing solvent. A solid or an oil will form when the ether is removed. After the ether is removed on the rotary evaporator, use a vacuum pump to remove the remaining solvent.

Isolation of the Epoxide. Reweigh the flask to determine the yield of the epoxide. Ideally, the isolated epoxide should be a solid, but often you will isolate an oily semi-solid (in the case of the oily semi-solid, proceed to the next paragraph). If a good-quality solid is obtained (check with your instructor for advice), add 8 mL of water to the solid to remove the DMSO that may have been extracted into ether. Bend the larger of the two spatulas you have in your drawer, and try to remove as much solid as possible from the sides and bottom of the round-bottom flask. Pour the solution containing the solid into a Hirsch or Büchner funnel attached to a filter flask, under vacuum, to collect the solid epoxide on filter paper. You may use additional cold water to aid the transfer process. Allow the solid to dry in an open container. When dry, weigh the solid and calculate the percentage yield. Also determine the melting point.

If the epoxide is an oily semi-solid, it will not be possible to collect the material on a Hirsch or Büchner funnel. Weigh the material and calculate the percentage yield. Dissolve the sample in $CDCl_3$, and obtain the ^1H NMR spectrum as described in the next section.

Spectroscopy. Determine the infrared spectrum of your product. Dissolve some of your epoxide in $CDCl_3$ for ^1H NMR analysis. Compare the ^1H NMR spectrum of the starting chalcone with the spectrum of the epoxide. The starting chalcone spectrum will show a pair of doublets ($^3J \approx 16$ Hz appearing near 7.7 and 7.3 ppm) for the two vinyl protons in the starting chalcone. These vinyl protons in the chalcone appear in the same region as the aromatic protons on the benzene rings. However, the doublets for the protons in the benzene ring are more narrowly spaced ($^3J = 7$ Hz) than the doublets for the vinyl protons. The vinyl protons in the starting chalcone will be replaced with two peaks (actually a pair of doublets when expanded) near 4.0 to 4.4 ppm. The protons on the epoxide ring look like singlets in the NMR, but they are actually two finely spaced doublets ($^3J = 1.5$ to 2Hz). Remember, that you may see peaks in the spectrum for any remaining DMSO at about 2.6 ppm. In addition, it is common to see a singlet for water appearing at about 1.5 ppm. At the option of your instructor, determine the ^{13}C spectrum.

Determine the percent conversion of the chalcone to the epoxide by integrating one of the vinyl protons that remains in the aromatic region for the chalcone starting material and comparing that integral with the integral value for one of the protons on the epoxide ring.

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Dixon, C. E.; Pyne, S. G. Synthesis of Epoxidated Chalcone Derivatives. *J. Chem. Educ.* **1992,** *69,* 1032–1033.

Fiorini, G.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. Epoxidation of α, β-Unsaturated Ketones in Water: An Environmentally Benign Protocol. *Green Chem.* **2003,** *5,* 425–428.

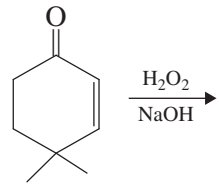
Fraile, J. M.; Garcia, J. I. Mayoral, J. A.; Sebti, S. Tahir, R. Modified Natural Phosphates: Easily Accessible Basic Catalyst for the Epoxidation of Electron-Deficient Alkenes. *Green Chem.* **2001,** *3,* 27–274.

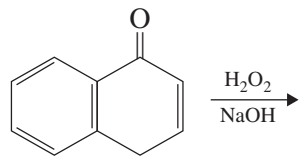
Maloney, G. P. Synthesis of 3-(2′-methoxy, 5′-bromophenyl)-2, 3-epoxyphenyl Propanone, a Novel Epoxidated Chalcone Derivative. *J. Chem. Educ.* **1990,** *67,* 617–618.

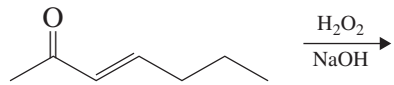
QUESTIONS

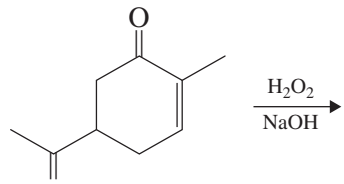
1. Summarize the changes you expected to observe in the IR and ^{1}H NMR spectra of your epoxide product relative to the chalcone starting material.

2. Draw the structures of the products expected in the following reactions.



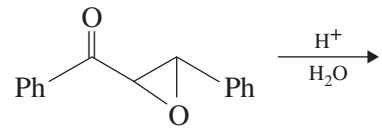






There are two C=C double bonds, but only one reacts. Why?

3. Draw the structure of the product expected in the following reaction.

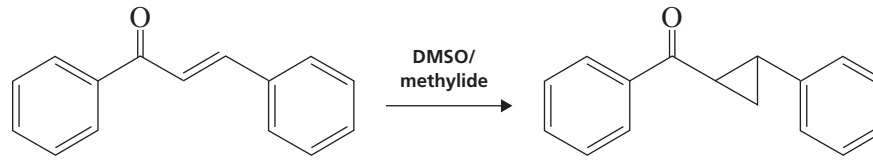


65 **EXPERIMENT 65**

Cyclopropanation of Chalcones

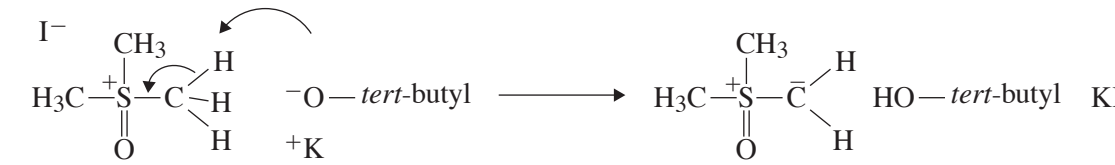
Reaction of chalcones

The Corey–Chaykovsky reaction will be used to cyclopropanate your chalcone from Experiment 63. The reaction involves the reaction of trimethylsulfoxonium iodide and potassium *tert*-butoxide in anhydrous dimethylsulfoxide (DMSO).[1] The reaction is stirred at room temperature for 1 hr. For example, *trans*-chalcone (l,3-diphenyl-2-propen-l-one) produces an 88% yield of the cyclopropanated product. You will analyze your product by ^{1}H NMR and infrared spectroscopy.

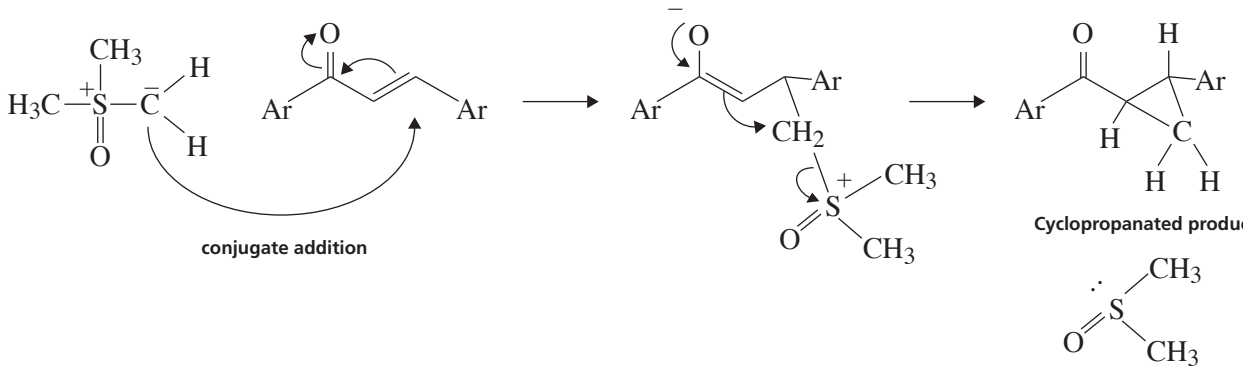


trans-chalcone — Cyclopropanated product

The mechanism follows the pathway below:



trimethylsulfoxonium iodide — ylide (methylide)



[1] Ciaccio, J. A.; Aman, C. E. Instant Methylide Modification of the Corey-Chaykovsky Cyclopropanation Reaction. *Synthetic Communications* **2006,** *36,* 1333–1341. This experiment was developed by Truong, T. and Lampman, G. M., Western Washington University, Bellingham, WA.

REQUIRED READING

Sign in at www.cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: Techniques 5, 6, *7, *8, *12, 20, 25, and 26

SUGGESTED WASTE DISPOSAL

Dispose of all aqueous wastes in the container designated for aqueous waste. Place the organic waste in the nonhalogenated organic waste container. Methylene chloride should be placed in the halogenated waste container.

NOTES TO THE INSTRUCTOR

Chalcones usually react completely in the cyclopropanation reaction, leaving little or no starting chalcone in the product.

PROCEDURE

Starting the Reaction. Dissolve the 0.50 mmole of the chalcone from Experiment 63 in 2.0 mL of *anhydrous* dimethylsulfoxide (DMSO)[2] in a 25-mL round-bottom flask. Allow the solid to dissolve.[3] Add a stir bar. Add to the solution a dry mixture of $Me_3S(O)I$ and KO-*tert*-butoxide (0.20 g, 0.6 mmol)[4] in one batch. Now add a drying tube filled with $CaCl_2$ to the flask. Stir the solution for 1 hour at room temperature.

Extraction with Diethyl Ether. Transfer the mixture to a separatory funnel, and add 25 mL of saturated aqueous sodium chloride solution, using some of the sodium chloride solution to aid in the transfer of the reaction mixture to the funnel. Extract the mixture with a 15-mL portion of diethyl ether. Remove the lower aqueous layer, and pour the ether layer from the top of the separatory funnel into a beaker. Return the aqueous layer to the funnel, and re-extract it with another 15-mL portion of diethyl ether. Combine the two ether layers in the same beaker. Pour the ether extracts back into the separatory funnel, and re-extract the ether layer with two 25-mL portions of water, followed by extraction with 25-mL of saturated sodium chloride, each time draining the lower aqueous layer and saving the ether layer.

Drying and Removal of Diethyl Ether. Pour the diethyl ether layer from the top of the funnel into a dry Erlenmeyer flask, and dry the ether with anhydrous magnesium sulfate. Occasionally swirl the solution with the drying agent over a period of about 10 minutes. Gravity filter the solution through a piece of fluted filter paper into a *preweighed* 50- or 100-mL round-bottom flask (instructor-provided, if necessary). Remove the ether on the rotary evaporator, under vacuum. After the ether is removed on the rotary evaporator, use a vacuum pump to remove

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[2] Alfa Aesar, dimethyl sulfoxide, anhydrous, packaged under argon, Stock #43998, CAS #67-68-5

[3] You may need to add more *anhydrous* DMSO to completely dissolve the chalcone.

[4] The laboratory assistant should prepare the mixture by combining timethylsulfoxonium iodide ($Me_3S(O)I$, 5.90 g; 26.8 mmol) with potassium *tert*-butoxide (KO-*tert*-Bu, 3.00 g; 26.7 mmol). Grind the mixture so that the two compounds are equally distributed and mixed with each other. One gram of this mixture provides 3.0 mmol of methylide/g or 0.6 mmole/0.2 g. Store the mixture in a desiccator.

any remaining ether from the sample. The product is likely to be an oil. Weigh the product, and determine the percentage yield.

Thin layer chromatography (optional). Check the purity of the product by TLC. Dissolve a small amount of the product in methylene chloride, and spot it on the plate. Also spot a dilute solution of the starting chalcone on the plate. Develop the plate in methylene chloride, and use the UV lamp to visualize the spots to see if there are any byproducts or starting chalcone in your cyclopropanated product.

Spectroscopy. Determine the infrared spectrum of your product. Prepare an NMR sample for ^1H analysis in $CDCl_3$. When the proton spectrum is returned to you, look for the disappearance of a pair of doublets ($^3J \approx 15$ Hz appearing near 7.7 and 7.3 ppm) for the vinyl protons in the starting chalcone (the normal expectation is for the chalcone to react completely). These doublets can be distinguished easily from the aromatic protons' doublets, which are more narrowly spaced ($^3J = 7$ Hz). These vinyl protons appear in the same region as the aromatic protons. The vinyl protons in the starting chalcone should be replaced by two cyclopropyl protons appearing at about 1.5 and 1.9 ppm for the diastereotopic protons in the CH_2 group. The two remaining cyclopropyl protons appear at about 2.6 and 2.88 ppm.[5] At the option of your instructor, determine the ^{13}C spectrum.

REFERENCES

Ciaccio, J. A.; Aman, C. E. Instant Methylide Modification of the Corey-Chaykovsky Cyclopropanation Reaction. *Synthetic Comm.* **2006,** *36*, 1333–1341.

Corey, E. J.; Chaykovsky, M. Dimethyloxosulfonium Methylide and Dimethylsulfonium Methylide, Formation and Application to Organic Synthesis. *J. Am. Chem. Soc.* **1965,** *87,* 1353–1364.

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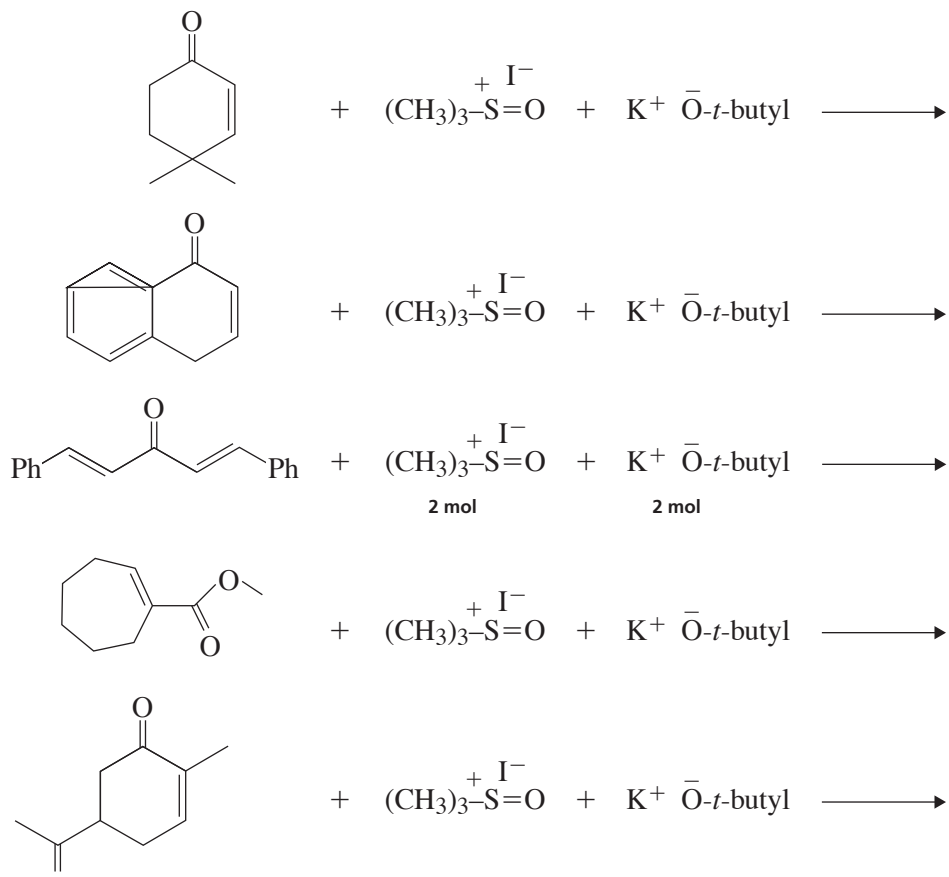
Paxton, R. J.; Taylor, R. J. K. Improved Dimethylsulfoxonium Methylide Cyclopropanation Procedures, including a Tandem Oxidation Variant. *Synlett* **2007,** 633–637.

Yanovskaya, L. A.; Dombrovsky, V. A.; Chizhov, O. S.; Zolotarev, B. M.; Subbotin, O. A.; Kucherov, V. F. Synthesis and Properties of *trans*-1-Aryl-2-Benzoylcyclopropanes and their Vinylogues. *Tetrahedron* **1972,** *28,* 1565–1573.

QUESTIONS

1. Summarize the changes you expect to observe in the IR and ^1H NMR spectra of your cyclopropane product relative to the chalcone starting material.
2. Draw the structures of the products expected in the following reactions.

[5] If instrumentation is available, run a gHSQC NMR experiment to confirm the assignment of the diastereotopic protons. This heteronuclear 2-D NMR experiment plots the carbon spectrum vs. the proton spectrum. The diastereotopic protons will correlate with only one ^{13}C peak at about 19 ppm. The other two cyclopropyl ring protons appear around 29 and 30 ppm in the ^{13}C spectrum.



There are two C═C double bonds, but only one reacts. Why?

66 **EXPERIMENT 66**

Michael and Aldol Condensation Reactions

Aldol condensation

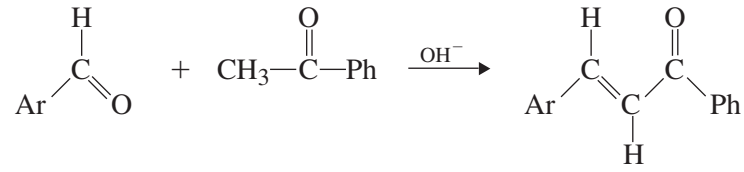
Michael reaction (conjugate addition)

Crystallization

Devising a procedure

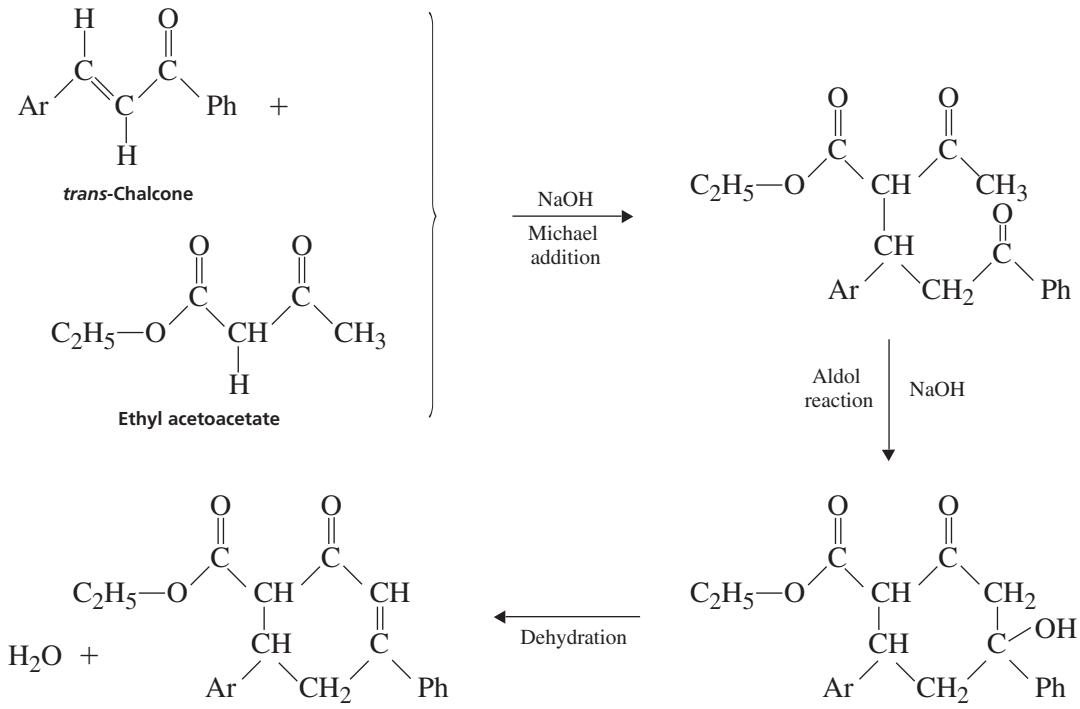
Critical-thinking application

In Experiment 37 ("The Aldol Condensation Reaction: Preparation of Benzalacetophenones"), substituted benzaldehydes are reacted with acetophenone in a crossed aldol condensation to prepare benzalacetophenones (chalcones). This is illustrated in the following reaction, where Ar and Ph are used as abbreviation for a substituted benzene ring and the phenyl group, respectively.



A benzaldehyde **Acetophenone** **A *trans*-chalcone**

Experiment 39 involves the reaction between ethyl acetoacetate and *trans*-chalcone in the presence of base. Under the conditions of this experiment, a sequence of three reactions takes place: a Michael addition followed by an internal aldol reaction and a dehydration.



The purpose of this experiment is to combine the reactions introduced in Experiments 37 and 39 in the form of a project. Starting with one of four possible substituted benzaldehydes, you will synthesize a chalcone using the procedure given in Experiment 37. After performing a melting point to verify that this step has been completed successfully, you will perform a Michael/aldol reaction with the chalcone and ethyl acetoacetate using the procedure given in Experiment 39. The identity of this final product will be confirmed by its melting point and possibly infrared and NMR spectroscopy.

You will be assigned one of the aromatic aldehydes shown in the following list. For each aldehyde, the melting points of the corresponding chalcone and the Michael/aldol product are given.

Aldehyde	Chalcone (mp,°C)	Michael/Aldol Product (mp,°C)
4-Chlorobenzaldehyde	114–115	141–143
4-Methoxybenzaldehyde	73–74	106–108
4-MethylbenzaIdehyde	92–94	139–142
Piperonaldehyde	121–122	146–147

REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: *Technique 11 Crystallization: Purification of Solids

SUGGESTED WASTE DISPOSAL

If your starting compound is 4-chlorobenzaldehyde, all filtrates should be poured into a waste container designated for halogenated organic wastes. If you use one of the other three aldehydes, dispose of all filtrates in the container designated for nonhalogenated organic wastes.

NOTES TO THE INSTRUCTOR

Some students may require individual help for this experiment. As a result, it may be difficult to use this experiment with a large class. It is a good idea to have students prepare and present their procedure for approval before allowing them to begin the experimental work. The chalcones should be finely ground before being used in the second part of the experiment.

You may choose to have students react ethyl acetoacetate with one of the chalcones synthesized in Experiment 63. Because the product of the reaction may yield an unknown Michael/aldol product, students will have the opportunity to conduct original research. A literature search may be incorporated with this exercise to determine if the compound has been synthesized previously.

PROCEDURE

Your instructor will assign you one of the substituted benzaldehydes, given in the table above, to use in this experiment. To prepare the chalcone, refer to the procedure in Experiment 37. To convert the chalcone to the Michael/aldol product, refer to the procedure given in Experiment 39. Using these procedures as a guide, devise the entire experimental procedure together with reagent quantities. The chalcone you prepare should be finely ground before using it in the second part of this experiment.

Initially, you should follow the procedures in Experiments 37 and 39 as closely as possible with appropriate adjustments in the scale of the reaction. Another part of the

procedure in Experiment 39 must also be modified (see "Removal of Catalyst" in Experiment 39). The purpose of adding acetone in this step is to dissolve your product, leaving the solid catalyst behind. Depending on which substituted benzaldehyde you started with, different volumes of acetone may be required. Rather than following the instructions to add 7 mL of acetone, you should add a smaller portion and then stir with a spatula to see if most of the solid dissolves. If it does not, continue to add more acetone in small portions while stirring the mixture. When it is clear that most of the solid has dissolved, then you can stop adding acetone. It is likely that you will need to add more than 7 mL of acetone, assuming the same scale as in Experiment 39.

If either procedure in Experiment 37 or 39 does not work, you may need to modify the procedure and run the experiment again. An unsuccessful procedure will most likely be indicated by either the melting point or the spectral data. The problem you would most likely encounter in preparing the chalcone is difficulty in getting the product to solidify from the reaction mixture. The Michael/aldol reaction is more complicated, because there are two intermediate compounds that could be present in a significant amount in the final sample. If this occurs, both the melting point and the infrared spectrum may provide clues about what happened. It is possible you will need to increase the reaction time for this part of the experiment.

You must pay attention to scale so that you prepare enough of the chalcone for use in the next step and so that you finish up with a reasonable amount of the final product, about 0.3–0.6g. It is possible, therefore, that the amounts of reagents given in Experiments 37 and 39 will need to be adjusted. If the scale needs to be changed in either experiment, be sure to adjust the amounts of all reagents proportionately and make any necessary changes in the glassware. In making your initial decision about scale, assume that the percentage yield of the chalcone after crystallization will be about 50%. Likewise, assume that the procedure in Experiment 39 will result in about a 50% yield.

To determine an accurate melting point of the chalcone or final product, the sample must be pure and dry. In most cases, 95% ethanol can be used to crystallize these compounds. If this solvent does not work, you can use the procedure in Technique 11, Section 11.6, to find an appropriate solvent. Other solvents to be tried include methanol or a mixture of ethanol and water. If you are unsuccessful in finding an appropriate solvent, consult your instructor.

It is particularly important that the chalcone be highly pure before going on to the next step. When you determine the amount of hot solvent to add when crystallizing the chalcone, it is best to add more than the minimum amount required to dissolve the solid. Otherwise, the amount of mother liquor may be so small that many of the impurities will not be removed during the vacuum filtration step. If the melting point after crystallization is not within 3–4°C of the melting point given in the table at the beginning of this experiment, you may need to crystallize the material a second time.

SPECTROSCOPY

Infrared Spectrum. You should obtain an infrared spectrum of the chalcone and the final product to verify the identity of each product in the reaction sequence. Obtain the infrared spectrum by the dry-film method (see Technique 25, Section 25.4) or as a KBr pellet (see Technique 25, Section 25.5). For the Michael/aldol product, you should observe absorbances at about 1735 and 1660 cm^{-1} for the ester carbonyl and enone groups, respectively.

NMR Spectrum. Your instructor may also want you to determine the proton and carbon NMR spectra of each product. These may be run in $CDCl_3$ solvent. Some of the expected signals can be determined by referring to the NMR spectrum shown in Figure 2, Experiment 39. Although this spectrum are for a slightly different compound, many of the signals will have similar splitting patterns and similar chemical shifts.

REPORT

The report should include balanced equations for the preparation of the chalcone and the Michael/aldol product. You should calculate both the theoretical and percentage yields for each step. Write out your complete procedure as you actually performed it. Include the actual results of your melting-point determinations, and compare them to the expected results.

Include any infrared spectra obtained, and interpret the major absorption peaks. If you determined NMR spectra, you should include them, along with an interpretation of the peaks and splitting patterns.

REFERENCE

Garcia-Raso, A.; Garcia-Raso, J.; Campaner, B.; Maestres, R; Sinisterra, J. V. An Improved Procedure for the Michael Reaction of Chalcones. *Synthesis* **1982,** 1037.

67 EXPERIMENT 67

Esterification Reactions of Vanillin: The Use of NMR to Determine a Structure

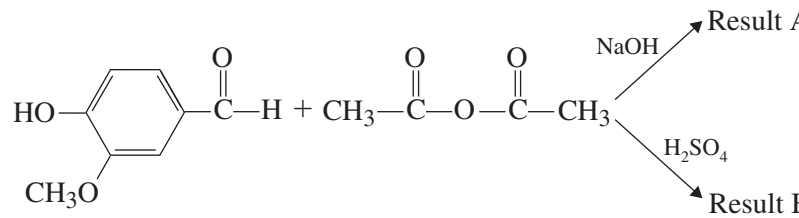
Esterification

Crystallization

Nuclear magnetic resonance

Critical-thinking application

The reaction of vanillin with acetic anhydride in the presence of base is an example of the esterification of a phenol. The product, which is a white solid, can be characterized easily by its infrared and NMR spectra.



Vanillin

When vanillin is esterified with acetic anhydride under acidic conditions, however, the product that is isolated has a different melting point and different spectra. The object of this experiment is to identify the products formed in each of these reactions and to propose mechanisms that will explain why the reaction proceeds differently under basic and acidic conditions.

Experiment 67 is based on a paper presented at the 12th Biennial Conference on Chemical Education, Davis, California, August 2–7, 1992, by Professor Rosemary Fowler, Cottey College, Nevada, Missouri. The authors are grateful to Professor Fowler for her generosity in sharing her ideas.

REQUIRED READING

Sign in at www.cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: Techniques *8, *11, 25, and 26

You should also read the sections in your lecture textbook that deal with the formation of esters and nucleophilic addition reactions of aldehydes.

SPECIAL INSTRUCTIONS

Sulfuric acid is very corrosive. Avoid contact with your skin.

SUGGESTED WASTE DISPOSAL

All filtrates and organic residues should be disposed of into the container designated for nonhalogenated organic wastes. Dispose of solutions used for NMR spectroscopy in the waste container designated for the disposal of halogenated materials.

PROCEDURE

Preparation of 4-Acetoxy-3-Methoxybenzaldehyde (Vanillyl Acetate). Dissolve 1.50 g of vanillin in 25 mL of 10% sodium hydroxide in a 250-mL Erlenmeyer flask. Add 30 g of crushed ice and 4.0 mL of acetic anhydride. Stopper the flask with a clean rubber stopper, and shake it several times over a 20-minute period. On adding acetic anhydride, a cloudy, milky white precipitate forms immediately. Filter the precipitate using a Hirsch funnel or a small Büchner funnel, and wash the solid with three 5-mL portions of ice-cold water.

Recrystallize the solid from 95% ethyl alcohol. Heat the mixture in a hot-water bath at about 60°C to avoid melting the solid. When the crystals are dry, weigh them and calculate the percentage yield. Obtain the melting point (literature value is 77–79°C). Determine the infrared spectrum of the product using the dry-film method. Determine the proton-NMR spectrum of the product in $CDCl_3$ solution. Using the spectral data, confirm that the structure of the product is consistent with the predicted result.

Esterification of Vanillin in the Presence of Acid. Dissolve 1.50 g of vanillin in 10 mL of acetic anhydride in a 125-mL Erlenmeyer flask. Place a magnetic stir bar in the flask, and stir the mixture at room temperature until the solid dissolves. While continuing to stir the mixture, add 10 drops of 1.0 M sulfuric acid to the reaction mixture. Stopper the flask and stir at room temperature for 1 hour. During this period, the solution will turn purple or purple-orange in color.

At the end of the reaction period, cool the flask in an ice-water bath for 4–5 minutes. Add 35 mL of ice-cold water to the mixture in the flask. Tightly stopper the flask with a clean rubber stopper, and while holding your thumb on the stopper, shake the flask vigorously—almost as hard as you can shake! Continue to cool and shake the flask to induce crystallization. Crystallization has occurred when you can see small solid clumps separating from the cloudy liquid and settling to the bottom of the flask. (If crystallization does not occur after

10–15 minutes, it may be necessary to seed the mixture with a small crystal of the product.) Filter the product on a Hirsch or a small Büchner funnel, and wash the solid with three 5-mL portions of ice-cold water.

Recrystallize the crude product from hot 95% ethanol. Allow the crystals to dry. Weigh the dried crystals, calculate the percentage yield, and determine the melting point (literature value is 90–91°C). Determine the infrared spectrum of the product using the dry-film method. Determine the proton NMR spectrum of the product in $CDCl_3$ solution.

REPORT

Compare the two sets of spectra obtained for the base- and acid-promoted reactions. Using the spectra, identify the structures of the compounds formed in each reaction. Record the melting points and compare them to the literature values. Write balanced equations for both reactions and calculate the percentage yields. Outline mechanistic pathways to account for the formation of both products isolated in this experiment.

68 **EXPERIMENT 68**

An Oxidation Puzzle

Oxidation of alcohols

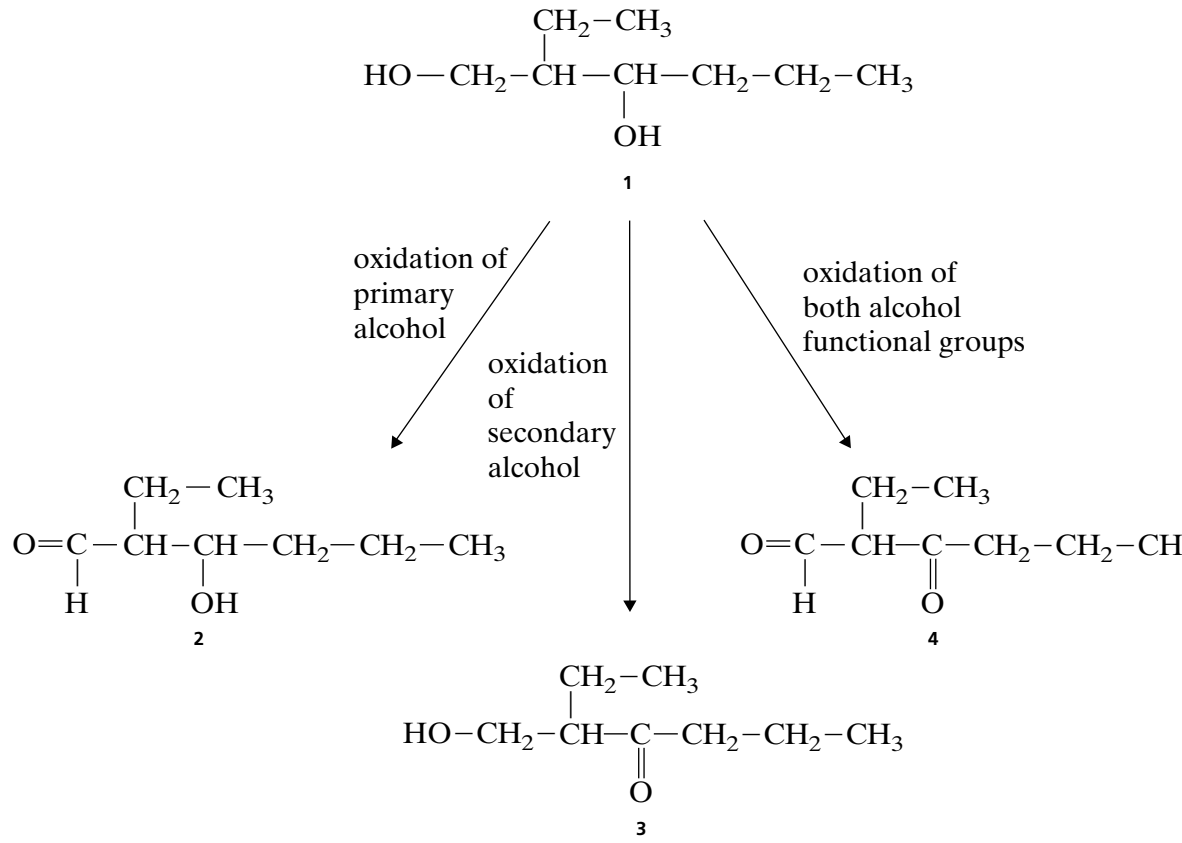
Infrared spectroscopy

Critical-thinking application

Sodium hypochlorite in acetic acid is an oxidizing agent capable of oxidizing alcohols to the corresponding aldehydes or ketones. In this experiment, you will oxidize a diol, 2-ethyl-1,3-hexanediol (1), and then use infrared spectroscopy to determine which of the alcohol functional groups was oxidized.

You will determine whether the oxidation occurred selectively (and which functional group was oxidized) or whether both functional groups were oxidized at the same time. The possible outcomes of the oxidation are shown in the figure. If only the primary alcohol is oxidized, an aldehyde (2) will be formed; if only the secondary alcohol is oxidized, a ketone (3) will be the product. If both alcohol functional groups are oxidized, compound (4) will be observed. Your assignment will be to use infrared spectroscopy to determine the structure of the product and decide which of these three possible outcomes actually takes place.

Experiment 68 is adapted from Pelter, M. W.; Macudzinski, R. M.; Passarelli, M. E. A Microscale Oxidation Puzzle, *Journal of Chemical Education,* 2000, *77,* 1481.



REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: Techniques *12 and 25

SPECIAL INSTRUCTIONS

Glacial acetic acid is corrosive; it can cause burns on the skin and on mucous membranes in the nose and mouth. Its vapors are also hazardous. Dispense it in the hood, and use personal protective equipment. Avoid contact with skin, eyes, and clothing. Sodium hypochlorite emits chlorine gas, which is a respiratory and eye irritant. Dispense it in a fume hood.

SUGGESTED WASTE DISPOSAL

All aqueous solutions should be collected in a container specially marked for aqueous wastes. Place organic liquids in the container designated for nonhalogenated organic waste. Note that your instructor may establish a different method of collecting wastes for this experiment.

PROCEDURE

Dispense 0.5 mL of 2-ethyl-1,3-hexanediol into a *tared* 10-mL Erlenmeyer flask. An automatic pipet is a useful device to dispense this quantity of diol. Reweigh the flask to determine the weight of diol added. Add 3 mL of glacial acetic acid; also add a magnetic stirring bar. Have a thermometer available to monitor the temperature of the reaction.

Place the mixture in an ice bath on a magnetic stirrer. While the mixture is stirring, slowly add 3 mL of a 6% aqueous sodium hypochlorite solution to the mixture.[1] Be careful not to allow the reaction temperature to rise above 30°C by controlling the rate of addition. Allow the solution to stir for 1 hour. In order to determine whether there is excess hypochlorite, test the solution periodically by placing a drop of the reaction mixture on a strip of potassium iodide–starch test paper. A blue-black color indicates that there is an excess of hypochlorite. If there is no color change, add an additional 0.5 mL of sodium hypochlorite solution, stir for several minutes, and repeat the starch-iodide test. Continue this process until the paper turns blue-black.

When the reaction is complete, pour the mixture into 10 –15 mL of an ice–salt mixture. Extract the mixture with three 5-mL portions of diethyl ether. It may be convenient to perform this extraction in a 15-mL centrifuge tube rather than a separatory funnel (see Technique 12, Section 12.7, for a description of this method). Collect the ether extracts, and wash them with two 3-mL portions of saturated aqueous sodium carbonate solution, followed by two 3-mL portions of 5% aqueous sodium hydroxide. The ether layer should appear basic when tested with a moistened piece of red litmus paper. If it does not, wash the ether layer with an additional 3-mL portion of 5% aqueous sodium hydroxide.

Dry the ether layer over magnesium sulfate. Decant or filter the dried solution into a tared 25-mL filter flask, and remove the solvent under reduced pressure (see Technique 7, Section 7.10). Determine the infrared spectrum of the residue as a pure liquid sample (see Technique 25, Section 25.2).

REPORT

Using your infrared spectrum, determine the structure of the oxidation product (see the structures of the possible products at the beginning of this experiment). Is the oxidation selective? Did the hypochlorite oxidize both alcohol functional groups? If the oxidation was selective, which functional group was transformed?

[1] Your instructor will have prepared this solution in advance.

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