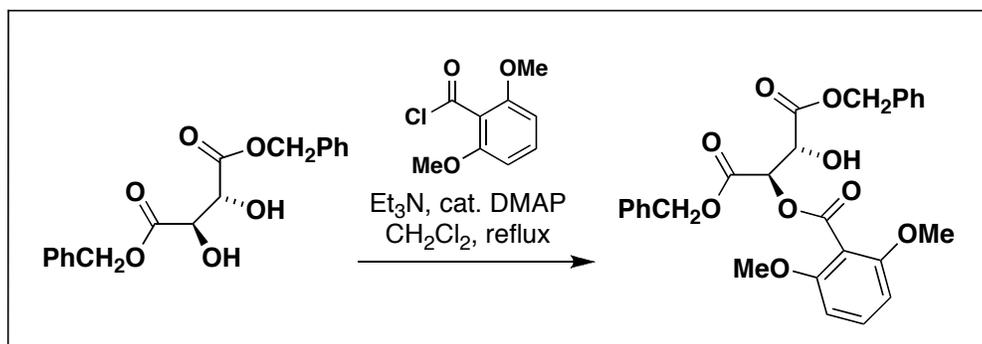


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Days 1-4 Monoesterification of Dibenzyl Tartrate with 2,6-Dimethoxybenzoyl Chloride



Day 1: Purification of Reactants for the Esterification Reaction

Digital Techniques Manual: TLC-The Basics and TLC-Advanced, Distillation I, Recrystallization, Filtration, Melting Point Determination

Mohrig, Hammond, & Schatz: Chapter 6 (Heating and Cooling Methods), Chapter 11 (Boiling Points and Distillation), Chapter 15 (Thin-Layer Chromatography), Chapter 5 (Measuring Mass and Volume), Chapter 9 (Recrystallization), and Chapter 10 (Melting Points and Melting Ranges).

Equipment: Glass-backed silica TLC plates, glass capillary TLC spotters, three TLC chambers with filter paper, TLC developing stock solutions (ceric ammonium molybdenate, phosphomolybdic acid, and p-anisaldehyde), small vials, disposable glass pipettes and pipette bulbs. For distillation: short path distillation head, distillation cow, three 10-mL round-bottomed flasks, 25-mL round-bottomed flask, glass stoppers. For trituration: 250-mL Erlenmeyer flask, spatula, glass rod, Buchner funnel, 500-mL Erlenmeyer filter flask, 100-mL graduated cylinder. For recrystallization: 250-mL Erlenmeyer flask, 50-mL round bottomed flask, 500-mL beaker, vials, filter funnel. Chemicals: diethyl ether, ethyl acetate, hexanes, triethylamine, and calcium hydride.

For optimal results it is necessary to purify the triethylamine that is used as an HCl scavenger in the esterification reaction. In particular, if any water is present in the triethylamine, then it can hydrolyze the acyl chloride faster than your alcohol reacts, and thus reduce the yield of the desired ester product. Triethylamine can be dried by stirring it over calcium hydride and then distilling it into a dry flask at atmospheric pressure under nitrogen.

Transfer 10-15 mL of triethylamine into a 25-mL round-bottomed flask by dispo pipette. Add a magnetic stirbar and ca. 0.5 g of calcium hydride. Attach a short-path distillation head equipped with a thermometer to the distillation flask and equip the still head with an oven-dried cow attached to your nitrogen line via a T connector. Be sure to connect the condenser of the still head to your water line. The third branch of the T connector should be linked to an oil bubbler via Tygon tubing.

The cow should be equipped with three oven-dried, 10-mL, round-bottomed flasks. Stir the triethylamine over calcium hydride for at least 1.5 h. Distill the triethylamine at atmospheric pressure by heating the flask in a sand bath; the boiling point of triethylamine is 89 °C. Collect at least 5 mL of dry triethylamine. Seal the flask containing the distilled triethylamine with a glass stopper. Any other triethylamine that you distill over can be returned to the original bottle. The calcium hydride remaining in the distillation flask should be quenched according to the procedure described in Part VI.

Photo of distillation setup here

The following purification of dibenzyl tartrate should be started while the triethylamine is stirring over calcium hydride. The sample of dibenzyl tartrate you will be given is the crude product from a reaction of benzyl alcohol and tartaric acid that was run by the teaching assistants. The sample of diester is impure and contains a small amount of unreacted benzyl alcohol. Separation of the benzyl alcohol impurity from the diester by chromatography would be difficult, and can be accomplished more easily on a large scale by trituration followed by recrystallization according to the procedure described below.

First, check the purity of your sample of dibenzyl tartrate by TLC analysis on silica gel using the techniques introduced in Module 6. A sample of benzyl alcohol can be obtained for reference from your teaching assistant. For eluant, begin by trying 25% ethyl acetate-hexane, but you may wish to examine other solvent systems. Visualization should be carried out by UV and PMA.

The first step in the purification of the crude dibenzyl tartrate is trituration. Trituration is the process in which a solid is treated with a solvent in which it is not soluble but which does dissolve some of the impurities present. You will be given ca. 10 g of crude dibenzyl tartrate in a 250-mL Erlenmeyer flask. Trituration of your dibenzyl tartrate (the crude material is a gummy solid) is carried out by adding 200 mL of hexane and 10 mL of diethyl ether to the diester in the 250-mL Erlenmeyer. Rub and grind the solid material with a glass rod and metal spatula for 5-10 min to break up clumps and to thoroughly mix the solid with the solvent. Next, add a magnetic stirbar to the flask and stir the mixture for 10 min. Filter the resulting mixture through a filter paper disk on a Buchner funnel into a 500-mL Erlenmeyer filter flask, washing the solid that you collect with three 15-mL portions of

20:1 hexane-ether. Transfer the solid to a tared 250-mL Erlenmeyer flask and record the weight of dibenzyl tartrate (you should have at least 9 g at this stage of the purification).

Recrystallize your dibenzyl tartrate from a mixture of hexane and ethyl acetate according to the following procedure. First, add the *minimum* amount of ethyl acetate to the solid required to dissolve it. Add ethyl acetate in small portions and thoroughly stir the mixture before adding the next portion. A total of approximately 30 mL of ethyl acetate will be needed. Next, add hexane in small portions (ca. 5-10 mL at a time) until the solution just begins to become cloudy. Approximately 50 mL of hexane will be required. Finally, add ethyl acetate again dropwise until the mixture just again becomes clear. At this point, cool the Erlenmeyer flask in an ice-water bath. Dibenzyl tartrate will crystallize and cooling should be continued until no further solid appears (ca. 20 min). Collect the solid by filtration through a filter paper disk on a Buchner funnel into a 500-mL Erlenmeyer filter flask, washing the solid that you collect with three 10-mL portions of cold hexane. Transfer the solid to a tared 500-mL beaker and record the weight of pure dibenzyl tartrate (you should have 8-9 g). Carry out TLC analysis of the product to confirm that no benzyl alcohol is present. Next, dry the solid by spreading it out on the bottom of the beaker, covering the top of the beaker with a Kimwipe secured with a rubber band (to keep out dust), and allowing it to stand exposed to air until your next laboratory period.

Day 2: Setting Up the Esterification Reaction

Digital Techniques Manual: Refluxing a Reaction

Mohrig, Hammond, & Schatz: Chapter 5 (Measuring Mass and Volume), and Chapter 7 (Assembly of Reaction Apparatus and Planning a Chemical Reaction)

Equipment: Disposable glass pipettes and pipette bulbs, sand bath, 250-mL three-necked round-bottomed flask, reflux condenser, three-way stopcock with inlet adapter, magnetic stirbar, oil bubbler, 2 glass stoppers, 100-mL graduated cylinder, 5-mL syringe, heating mantle, dichloromethane, 4-dimethylaminopyridine.

Measure the melting point of your dried dibenzyl tartrate (the mp of pure diester is 49-50 °C). You will need 6.1 g for the esterification reaction that you will set up on this day of Module 7.

The esterification will be carried out in an oven-dried, 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirbar. The center neck of the flask should be fitted with a reflux condenser topped with a inlet adapter connected to a three-way stopcock. One branch of the stopcock is connected by tygon tubing to the nitrogen source, and the other branch to an oil bubbler to allow for the monitoring of the nitrogen flow rate. The two side necks of the reaction flask are capped with glass stoppers. A photograph of the reaction setup is shown in Figure 1 below.

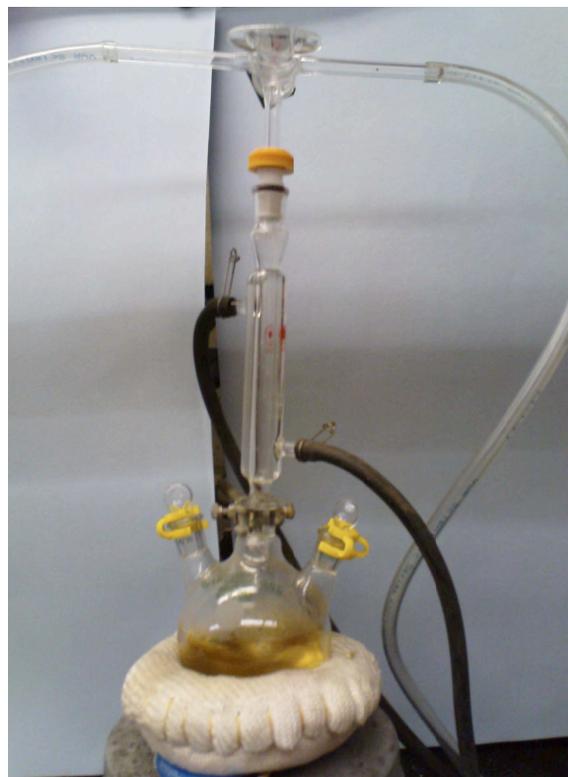
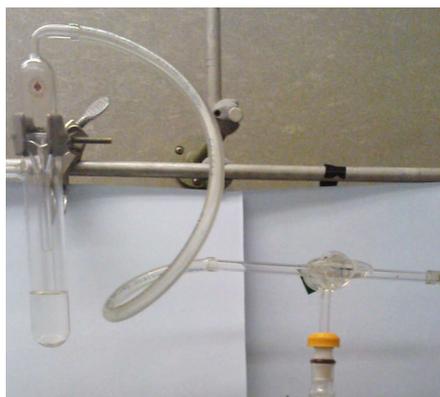


Figure 1. Reaction setup for the esterification reaction.

Remove the flask from the oven and quickly assemble it and begin the flow of nitrogen while it is still hot. The reaction flask is flushed with nitrogen for 5 min by turning the three-way stopcock so as to temporarily cut off flow to the bubbler and to direct nitrogen into the flask while a glass stopper is removed from one of the side necks. With the flow of nitrogen continuing, the flask is then charged via the open side neck with 6.1 g (18.5 mmol, 1.02 equiv) of dibenzyl tartrate (a solid) and then 100 mL of dichloromethane (previously dried over 4A molecular sieves) is added in one portion. Triethylamine (4 mL, 28.8 mmol, 1.58 equiv), previously distilled from calcium hydride, is then added with a 5 mL syringe followed by 4-dimethylaminopyridine (0.050 g, 0.4 mmol, 0.02 equiv). 4-Dimethylaminopyridine is a solid with mp 112-114 °C. The side neck is capped with a glass stopper, the three-way stopcock is adjusted so that it is open to the nitrogen source, flask, and the bubbler, and the reaction mixture is cooled in an ice-water bath. Once the reaction mixture has reached ca. 0 °C, the first portion of 2,6-dimethoxybenzoyl chloride is added by momentarily opening a side neck and adding the acyl chloride. Commercially available 2,6-dimethoxybenzoyl chloride is only 80% pure, so a total of 4.65 g of this material must be used in order to have 18.2 mmol (1.0 equiv) of acyl chloride. Note that 2,6-dimethoxybenzoyl chloride is a solid with mp 64-66 °C. The acyl chloride is added in five portions at ca. 10-min intervals. After the last portion is added, the ice bath is replaced with a heating mantle and the reaction mixture is heated at a gentle reflux (the boiling point of dichloromethane is 40 °C). Place a tag on your flask with your name and indicating the time that reflux was begun. A teaching assistant will shut off the heat 24 h after the time you indicate on the tag and the reaction will be allowed to run at room temperature until your next laboratory period.

Day 3: Workup of the Esterification Reaction

Digital Techniques Manual: Reaction Workup I and II

Mohrig, Hammond, & Schatz: Chapter 8 (Extraction and Drying Organic Liquids).

Equipment: Disposable glass pipettes and pipette bulbs, 100-mL graduated cylinder, 500-mL separatory funnel, 1-L Erlenmeyer, two 500-mL Erlenmeyers, 250-mL round-bottomed flask, 50-mL round-bottomed flask, filter funnel, fluted filter paper, dichloromethane, saturated sodium bicarbonate solution, saturated NaCl solution, anhydrous sodium sulfate.

Confirm that the esterification reaction is complete by performing TLC analysis on a sample of the reaction mixture withdrawn from the flask through a side neck with your TLC spotter. If TLC indicates that substantial starting material remains, consult with your teaching assistant.

The workup outlined below is designed to remove any carboxylic acid impurities; the excess triethylamine (bp 89 °C) will be removed after the workup by rotary evaporation. First, transfer the reaction mixture to a 500-mL separatory funnel, rinsing the flask with a small amount of dichloromethane and water to ensure complete transfer of the contents of the flask. Extract the organic solution with 100 mL of water, and then back-extract the aqueous phase with 50 mL of dichloromethane. Extract the combined organic phases with three 75-mL portions of saturated sodium bicarbonate solution and then 75 mL of water. Transfer the organic solution to a 500-mL Erlenmeyer flask and dry it over anhydrous sodium sulfate. Filter the solution into a 250-mL round-bottomed flask and concentrate it by rotary evaporation at ca. 20 Torr and 40 °C to remove the dichloromethane and triethylamine. Transfer the product to a tared 50-mL round-bottomed flask using a small amount of dichloromethane and again concentrate the solution. Record the weight of your “crude product” and check it by TLC analysis using 3:1:5 hexane-diethyl ether-dichloromethane as eluant. You should obtain ca. 9 g of crude esterification product as a gold or brown-colored viscous liquid.

Day 4: Purification of the Esterification Product

Digital Techniques Manual: Column Chromatography

Mohrig, Hammond, & Schatz: Chapter 17 (Liquid Chromatography) and Chapter 19 pp 269-276 (NMR Instrumentation and Sample Preparation)

Equipment: Chromatography column (67 cm length, 55 mm width) with adapter and tubing for top of column for applying pressure, funnel, 100-mL graduated cylinder, 230-400 mesh silica gel 60, sand, 18 x 150-mm test tubes, test tube racks, round-bottomed flasks (50 and 500 mL), 1-L beaker, NMR tube, hexanes, diethyl ether, dichloromethane, and CDCl₃.

Purify your crude esterification product by flash column chromatography on 200 g of silica gel. Weigh out the silica gel in a 1-L beaker (200 g will come to about the 450-mL mark). Prepare the

column using a 3:1:5 mixture of hexanes-diethyl ether-dichloromethane and then elute with the same solvent system. For general guidance, refer to the Digital Techniques Manual, Chapter 17 of Mohrig et al., and your experience with column chromatography from Module 6. Be sure to save a small sample of the crude reaction product to use as a TLC reference sample; this should be spotted in lane 1 on each plate as you monitor the fractions obtained in your chromatography. Collect 20-mL fractions in test tubes and identify the fractions containing your esterification product by TLC analysis (remember that it is usually not necessary to perform TLC analysis of every fraction). Combine the desired fractions in a 500-mL round-bottomed flask and concentrate by rotary evaporation to remove all of the solvent. Transfer the product to a tared 50-mL round-bottomed flask using dichloromethane and again remove all of the solvent by rotary evaporation. Record the weight of your purified esterification product and record the results of all TLC analyses and the details of your chromatographic purification following the same guidelines described in Module 6. The *Organic Syntheses* procedure reports obtaining 7.1-7.5 g (78-82% yield) of esterification product; you will need at least 3 g to go on to the next step in the synthesis. Be sure that your notebook record of the chromatographic purification is detailed and complete. Record the amount of silica gel used, and for each fraction collected indicate the volume and the eluant. Draw TLC plates (using the format described in Module 6) showing all of the fractions that were monitored by TLC analysis.

Obtain a proton NMR spectrum of a small sample of your purified product in CDCl_3 . Note that if solvent (e.g., ether, hexanes, or dichloromethane) appears in your spectrum, you will have to concentrate your product further by rotary evaporation, record the new (solvent-free) weight of product, and run another NMR spectrum to confirm the purity of your material. If necessary, the NMR spectrum can be run on an "off-day" for your group or at the beginning of Day 5 of the module. NMR data for dibenzyl mono(2,6-dimethoxybenzoyl)tartrate can be found in the *Organic Syntheses* paper by Yamamoto et al.

Submit a copy of the NMR spectrum to your TA who must approve it before you proceed to the next phase of the experiment. Also report the weight of your purified product to your TA.