



Converting Benzaldehyde to Benzilic Acid: A Multistep Synthesis

prepared by Carl T. Wigal, Lebanon Valley College, and
Jerry Manion, University of Central Arkansas

PURPOSE OF THE EXPERIMENT Conduct a multistep synthesis converting benzaldehyde to benzoin, benzoin to benzil, and benzil to benzilic acid.

EXPERIMENTAL OPTIONS Semi-Microscale Synthesis 4
Microscale Synthesis 12

BACKGROUND REQUIRED You should be familiar with vacuum filtration, recrystallization, melting-point measurement, infrared spectroscopy, thin-layer chromatography, and reflux.

BACKGROUND INFORMATION
Benzoin Condensation In 1958, Breslow discovered that in basic solutions, thiazolium salts are effective catalysts for the benzoin condensation. What was of broader significance to Breslow's work was the recognition that several biological cofactors contain a thiazole ring.

Enzymes often require additional small molecules called **coenzymes** as cocatalysts. Much of the bond breaking and bond making in biochemical reactions involve coenzymes. Thiamine pyrophosphate (TPP) is a coenzyme derived from vitamin B₁, also known as thiamine. Thiamine catalyzes the benzoin condensation *in vitro* in the absence of an enzyme.

The mechanism of the thiamine-catalyzed benzoin condensation of benzaldehyde is shown in Figure 1 on the next page.

A carbanion forms when a hydroxide ion deprotonates the thiamine thiazole ring. Carbanion A, being a good nucleophile, undergoes a reversible addition to the benzaldehyde carbonyl, forming an alkylated thiazole derivative, B. The resonance effects of the thiazole ring increase the acidity of the α -hydrogen atom on the carbon atom adjacent to the benzene ring. Increased acidity facilitates proton transfer from the α -carbon to the oxygen, forming carbanion C. Carbanion C then adds to another molecule of benzaldehyde, forming oxyanion D. Oxyanion D is in equilibrium with oxyanion E, which, in turn, eliminates the catalyst and forms benzoin.

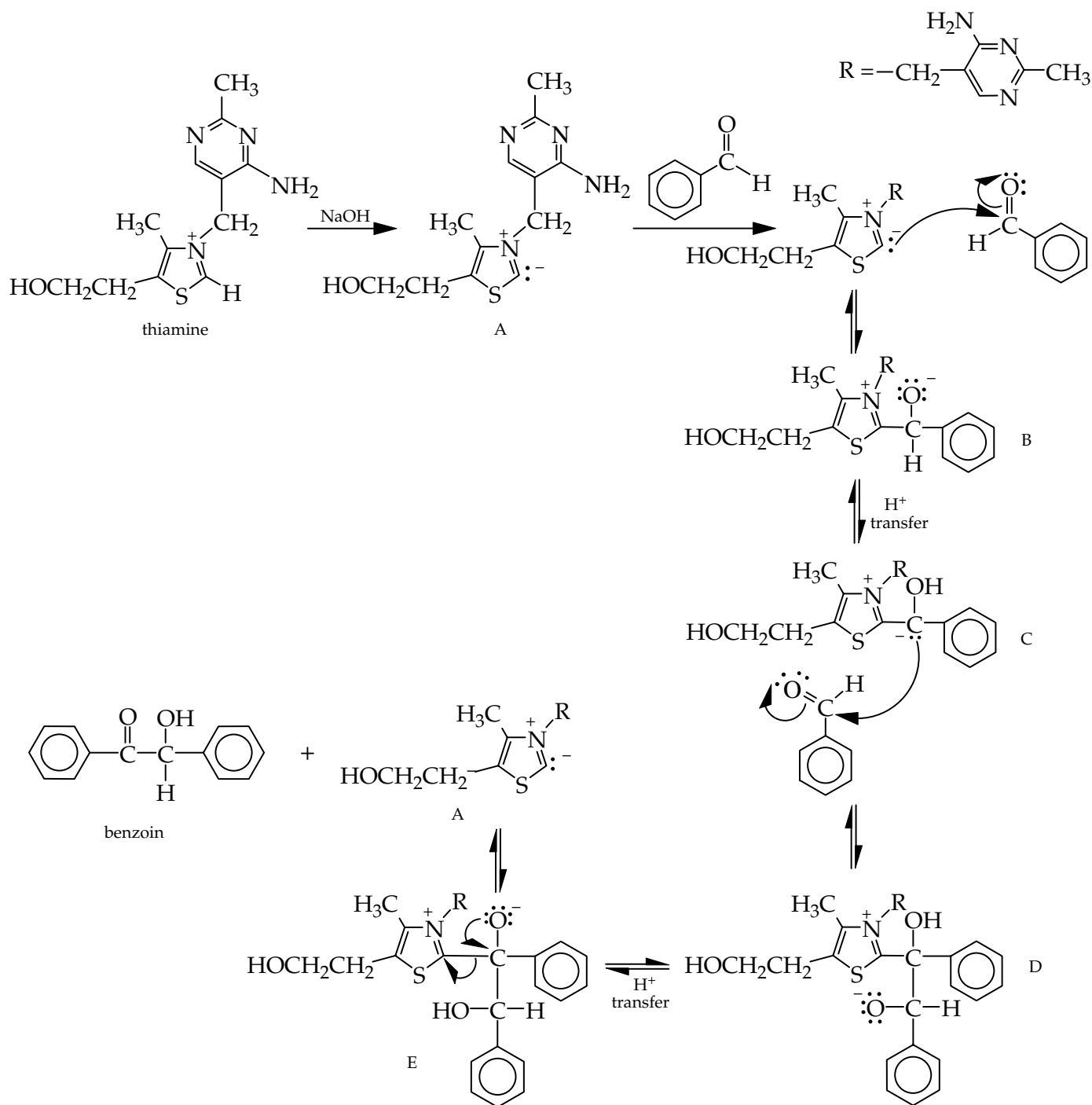
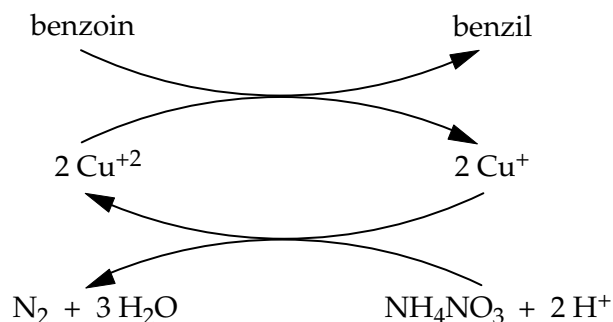


Figure 1 Thiamine-catalyzed benzoin condensation

Benzoin Oxidation Benzoin can be oxidized to the diketone benzil using a Cu^{2+} salt and ammonium nitrate. Only catalytic amounts of copper(II) acetate are necessary because the Cu^{2+} is continuously recycled. The Cu^+ ions are reoxidized to Cu^{2+} by ammonium nitrate, which is present in excess. The pattern is shown in Figure 2.

The oxidation mechanism is shown in Figure 3. In the first redox cycle, benzoin donates an electron to Cu^{2+} , forming Cu^+ and benzoin radical cation F. The benzoin radical cation loses a proton to acetate ion

Figure 2 Recycling of copper in the benzoin oxidation



(AcO⁻), forming acetic acid (AcOH) and a resonance-stabilized radical, depicted by structures G and H. Another redox cycle between Cu²⁺ and the radical takes place, forming a second Cu⁺ ion and cation I. Cation I loses a proton to another acetate ion, forming benzil.

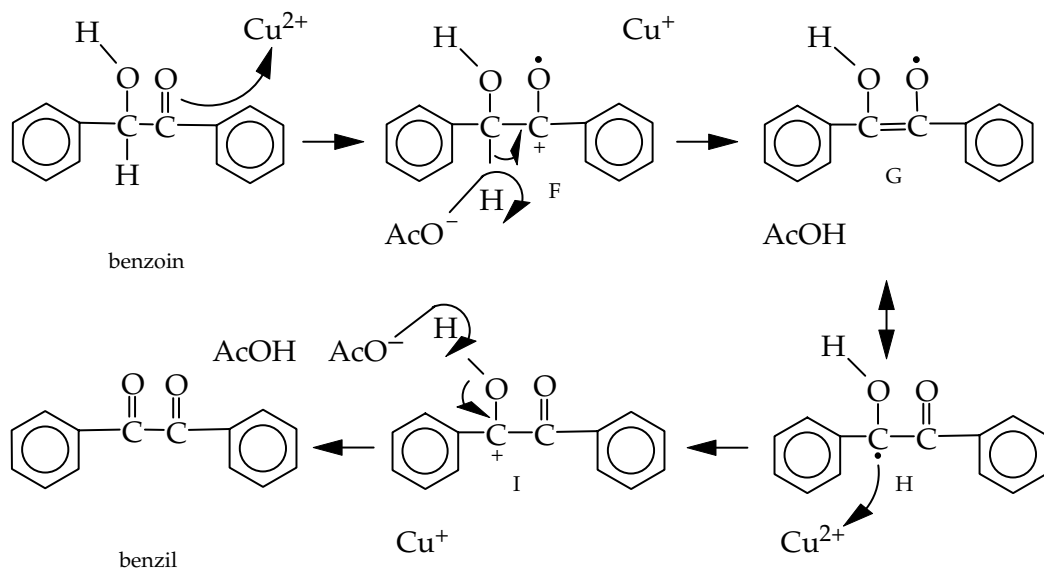


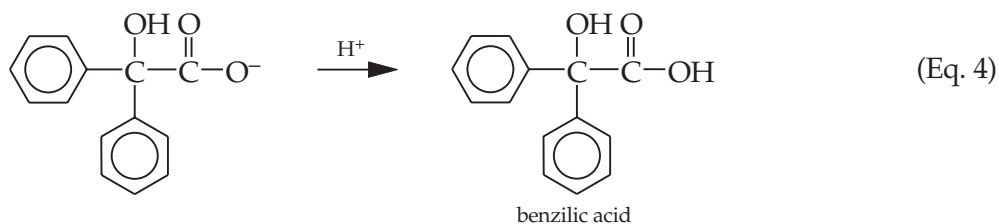
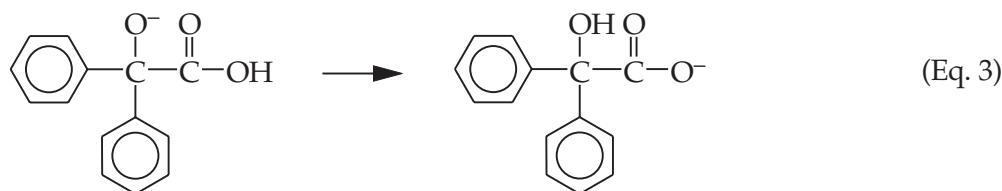
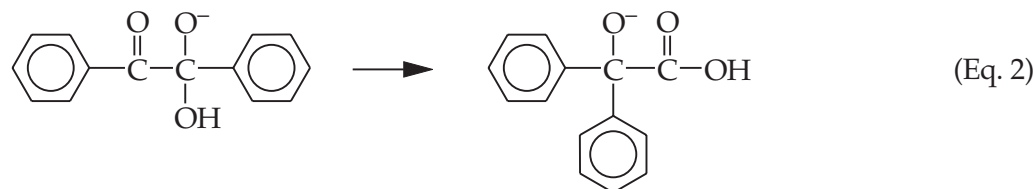
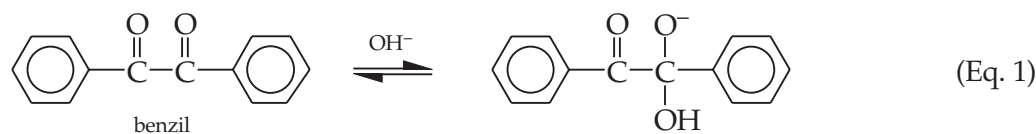
Figure 3 Mechanism for the copper-catalyzed oxidation of benzoin

Benzilic Acid Rearrangement

The benzilic acid rearrangement reaction results when benzil is treated with hydroxide ion, as shown in Equations 1–4 on the next page.

In the first step, shown in Equation 1, hydroxide ion adds to benzil in a rapid, reversible equilibrium reaction. In the second step, the actual rearrangement occurs. A phenyl group migrates, as shown in Equation 2. The third step involves a very rapid proton transfer, as shown in Equation 3. In the final step, shown in Equation 4, the benzilate anion is converted to benzilic acid when the reaction mixture is neutralized by addition of acid.

In this experiment you will first synthesize benzoin from benzaldehyde. You will characterize the product using melting point and IR spectroscopy. In the second synthesis, you will oxidize benzoin to benzil using copper-catalyzed oxidation. You will monitor the reaction using TLC. You will characterize the product using melting point and IR spectroscopy. In the third synthesis, you will conduct the benzilic acid rearrangement by refluxing benzil under alkaline conditions. You will characterize the product using melting point and IR spectroscopy.



Semi-Microscale Synthesis

Benzoin Condensation

Equipment

Laboratory Period One

10-mL graduated cylinder
magnetic stir bar
magnetic stirrer
microspatula

Pasteur pipet, with latex bulb
25-mL round-bottom flask, with stopper

Laboratory Period Two

250-mL beaker*
50-mL Erlenmeyer flask
25-mL filter flask, with vacuum tubing
filter paper, to fit Hirsch funnel
glass stirring rod
10-mL graduated cylinder

Hirsch funnel, with adapter
hot plate
melting point capillary tubes
microspatula
Pasteur pipet, with latex bulb
16 × 150-mm test tube
watch glass

*for ice-water bath

Reagents and Properties

substance	quantity	molar mass (g/mol)	mp (°C)	d (g/mL)
benzaldehyde	4.0 mL	106.12		1.044
benzoin*		212.25	135–137	
95% ethanol	40 mL			

potassium bromide [†]	0.100 g		
2.0M sodium hydroxide	3.0 mL		
thiamine hydrochloride	1.0 g	337.27	260
*product	[†] for IR		

Preview

Laboratory Period One

- Place thiamine hydrochloride, distilled water, and 2.0M NaOH into a flask
- Add benzaldehyde and stopper the flask
- Store for 2–7 days

Laboratory Period Two

- Cool the reaction mixture in an ice-water bath
- Use vacuum filtration to collect the crude product
- Weigh the crude product
- Recrystallize the crude product from 95% ethanol
- Use vacuum filtration to collect the purified product
- Dry and weigh the purified product
- Characterize the product using melting point and IR spectroscopy

PROCEDURE The Procedure for this experiment requires time from four consecutive laboratory periods. The first synthesis requires one laboratory period plus a small portion of the immediately preceding laboratory period.

Caution: Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

Always use caution in the laboratory. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Avoid ingesting any of the reagents.

Laboratory Period One

1. Conducting the Benzoin Condensation

Caution: 95% Ethanol is flammable and irritating. Keep away from flames. 2.0M NaOH is corrosive. Benzaldehyde (almond extract) is a suspected carcinogen and mutagen. [NOTE 1] Wear gloves when handling these compounds.

NOTE 1: Benzaldehyde, a suspected carcinogen, is also a certified food flavoring (almond extract). Food substances undergo a much higher scrutiny than do most other chemicals.

Place 1.00 g of thiamine hydrochloride into a 25-mL round-bottom flask. Add 2.0 mL of distilled or deionized water. Mix to dissolve.

Add 8.0 mL of 95% ethanol. Add a magnetic stir bar. Using a magnetic stirrer, stir the solution until it is homogeneous.

Use a Pasteur pipet to add 3.0 mL of 2.0M NaOH dropwise to the stirring solution over a 2-min period. Note that the solution initially turns a bright yellow color that then fades to pale yellow.

When the solution is pale yellow, add 4.0 mL of benzaldehyde. Stir until the mixture is homogeneous.

Stopper the flask. Allow the reaction mixture to stand for 2–7 days.

Laboratory Period Two

2. **Isolating and Purifying the Product** Prepare an ice-water bath using a 250-mL beaker. Pour 10 mL of distilled water into a test tube. Chill the water in the ice-water bath for later use.

Place the reaction flask in the ice-water bath to crystallize the product. If necessary, scratch the bottom of the flask with a glass rod to induce crystallization. Once crystallization has started, allow the flask to remain in the ice-water bath for 5 min.

Collect the crystals by vacuum filtration. Rinse the crystals with 2 mL of the chilled water. Allow the product to air dry in the filter funnel for 5 min. Weigh the product and record its mass.

For recrystallization, place the crude product in a 50-mL Erlenmeyer flask. Add 8.0 mL of 95% ethanol *for every gram* of crude product placed in the flask. Use a hot plate to heat the mixture gently until the ethanol boils. If the product does not completely dissolve, add more ethanol dropwise until all of the solid has dissolved in the boiling solvent.

Allow the solution to cool to room temperature. If necessary, scratch the bottom of the flask to induce crystallization. Then cool the solution in the ice-water bath for 5 min.

Filter the crystals using vacuum filtration. Allow the product to air dry in the filter funnel for 10 min.

Transfer the product from the filter paper to a watch glass to finish drying. Weigh the product and record the mass.

3. **Characterizing the Product** Measure the melting point of your dry product.

Caution: Potassium bromide (KBr) is irritating and hygroscopic.

Prepare a KBr pellet of your product. Record the IR spectrum as directed by your laboratory instructor. Compare your spectrum to a reference spectrum of benzoin.

4. **Cleaning Up** Use the labeled collection containers provided by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands thoroughly with soap or detergent before leaving the laboratory.

Semi-Microscale Synthesis

Benzoin Oxidation

Equipment**Laboratory Period Three**

100-mL beaker	filter paper
250-mL beaker*	forceps
250-mL beaker, with aluminum foil or plastic wrap cover [†]	glass stirring rod
Büchner funnel, with adapter	10-mL graduated cylinder
Bunsen burner	50-mL graduated cylinder
50-mL Erlenmeyer flask	magnetic stir bar
125-mL filter flask, with vacuum tubing	4–5 melting point capillary tubes
	microspatula
	3 open-ended capillary tubes

Pasteur pipet, with latex bulb	support stand
pencil	thermometer, -10 to 260 °C
reflux assembly	3 TLC plates, silica gel,
condenser, with tubing	2.5 × 7.5-cm, with fluorescent
25-mL round-bottom flask	indicator
ruler	2.0-mL transfer pipet
sand bath [†]	2 utility clamps
stirring hot plate [§]	watch glass

*for ice-water bath

[†]or 4-oz screw-cap jar with lid for TLC developing chamber

[‡]crystallizing dish or electric flask heater filled with sand

[§]or electric flask heater and magnetic stirrer

Reagents and Properties

<i>substance</i>	<i>quantity</i>	<i>molar mass</i> (g/mol)	<i>bp</i> (°C)	<i>mp</i> (°C)	<i>d</i> (g/mL)
acetic acid, glacial	6.0 mL	60.05	118		1.049
ammonium nitrate	1.0 g	80.04			
benzil*		210.23		94–95	
benzoin	2.0 g	212.25		135–137	
copper(II) acetate solution	1.5 mL				
dichloromethane	6 mL		40		
ethanol, 95%	< 16 mL				
potassium bromide	0.100 g				

*product

Preview

Laboratory Period Three

- Assemble the reflux apparatus
- Add the benzoin, ammonium nitrate, acetic acid, and copper(II) acetate solution
- Reflux the reaction mixture for up to 60 min
- Monitor the reaction using TLC
- Allow the reaction mixture to cool to room temperature
- Pour the reaction mixture into ice-water solution
- Use vacuum filtration to isolate the crude product
- Recrystallize the product
- Use vacuum filtration to isolate the purified product
- Dry and weigh the product
- Characterize the product using melting point and IR spectroscopy

PROCEDURE **Caution:** Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

Always use caution in the laboratory. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Avoid ingesting any of the reagents.

Laboratory Period Three

5. **Setting Up the Apparatus** Depending upon your glassware, assemble a reflux apparatus similar to that shown in Figure 4.

Caution: Glacial acetic acid is corrosive. Use a *fume hood*. Ammonium nitrate (NH_4NO_3) is oxidizing and irritating. Copper(II) acetate [$\text{Cu}(\text{OAc})_2$] solution is corrosive and irritating.

Remove the 25-mL round-bottom flask from the apparatus. Place a magnetic stir bar in the round-bottom flask.

Adjust the reagents to match the amount of benzoin you made. For every 2.0 g of benzoin you produced, add 6.0 mL of glacial acetic acid and 1.0 g of NH_4NO_3 . Add your benzoin. For every 2.0 g of benzoin you produced, add 1.5 mL of the $\text{Cu}(\text{OAc})_2$ solution. [NOTE 2]

NOTE 2: The solid materials are not soluble in acetic acid at room temperature. The solids dissolve as the pot is heated for refluxing.

6. **Refluxing the Reaction Mixture**

Reattach the flask to the reflux apparatus. Start the flow of water through the condenser. Heat the reaction mixture to boiling and reflux, while stirring, for up to 60 min.

7. **Setting Up the Chromatography System**

Caution: Do not use a Bunsen burner near flammable 95% ethanol.

Using open-ended capillary tubing and a Bunsen burner, prepare 3–5 micropipets for TLC spotting.

Obtain three 2.5×7.5 -cm silica gel TLC plates. At the top, label the three plates “30 min”, “45 min”, and “60 min”, respectively.

Using a ruler as a straightedge, draw a *very faint* pencil line across each plate 1 cm from the bottom. Do not cut through the silica gel with your marks. Make three small vertical lines that intersect the horizontal line at 6, 12, and 18 mm from the left side of the plate.

Using a pencil, label the plate from left to right below the vertical lines with “Bzo”, “Rxn”, and “Bzl”.

Caution: Benzil is irritating.

Obtain standard samples of benzoin and benzil from your laboratory instructor. Using a micropipet, spot benzoin at the position labeled Bzo on each plate. Discard the micropipet.

Using a new micropipet, spot benzil at the position marked Bzl on each plate. Discard the micropipet.

Caution: Dichloromethane is toxic and irritating.

Prepare a developing chamber by adding 6 mL of dichloromethane to a 250-mL beaker. Add filter paper to the chamber to act as a wick. Cover the chamber with aluminum foil or plastic wrap and set it aside in a *fume hood*.

8. **Monitoring the Reaction** After 30 min, remove the heat from the flask. Allow the reaction mixture to cool for 2 min.

Work quickly to minimize the time the reflux is interrupted. Remove the condenser from the reflux apparatus. Use a micropipet to spot the reaction mixture on the 30 min TLC plate at the position marked Rxn.

Replace the condenser and restart the reflux. Wait to continue timing the reaction until the reaction mixture is boiling.

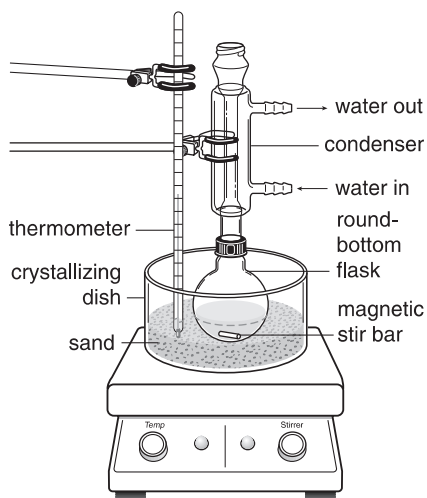


Figure 4 Reflux apparatus with round-bottom flask

In the meantime, place the TLC plate in the developing chamber. Cover the chamber with the foil or plastic wrap. Develop the plate until the eluent is within 1 cm of the top of the plate.

Remove the plate from the chamber. Immediately mark the eluent front with a pencil. Keep the plate in the *fume hood* for 1 min to allow the dichloromethane to evaporate.

Caution: Ultraviolet radiation can cause severe damage to the eyes. Wear UV protective goggles. Do not look directly into the UV lamp.

View the plate under UV light to visualize the spots. Use a pencil to circle each spot. Note the relative amounts of benzoin and benzil from the reaction spot.

After 45 min of reaction time, obtain a second sample for TLC analysis. Analyze as before, using the 45 min plate.

If the reaction is complete, as indicated by the absence of benzoin in the sample, stop the reflux. Cool the reaction for 10 min. Go to Part 9.

If benzoin remains in the reaction mixture, continue the reflux. After 60 min of reaction time, stop the reaction. Obtain a third sample for TLC analysis. Analyze as before, using the 60 min plate. Note whether or not the reaction is complete. In either case, go to Part 9.

9. Collecting, Washing, and Drying the Crystals

Place 40 mL of an ice-water mixture in a 100-mL beaker.

Use forceps to remove the stir bar. Pour the reaction mixture into the 100-mL beaker containing the ice-water mixture. Stir the mixture vigorously with a glass stirring rod to induce crystallization and to break up any lumps of solid material that may form.

Collect the crystals by vacuum filtration. Wash the crystals with 20 mL of distilled water.

Allow the crystals to dry in the Büchner funnel by pulling air through the funnel for 10 min. Weigh your dried product and record its mass.

10. Recrystallizing Benzil

Caution: 95% Ethanol is flammable and toxic. Do not use near an open flame.

Place your crude product in a 50-mL Erlenmeyer flask. Add 8.0 mL of 95% ethanol *for every gram* of crude product placed in the flask.

Use the hot plate to heat the mixture gently until the ethanol boils. If the product does not completely dissolve, gradually add more ethanol dropwise until all of the solid dissolves in the boiling solvent.

Allow the solution to cool to room temperature. If necessary, scratch the bottom of the flask to induce crystallization. [NOTE 3]

Prepare an ice-water bath using a 250-mL beaker. Place the flask containing the solution in the ice-water bath for 5 min to complete the crystallization.

Filter the crystals using vacuum filtration. Allow your product to air dry in the filter funnel for 10 min.

Transfer the product from the filter paper to a watch glass to finish drying. Weigh the product and record the mass.

NOTE 3: Crystallize benzil slowly so that large crystals form. Rapid crystallization of the supersaturated solution forms very fine crystals that are difficult to dry.

11. Characterizing the Product

Measure the melting point of your dry product.

Caution: Potassium bromide (KBr) is irritating and hygroscopic.

Prepare a KBr pellet of your product. Obtain the IR spectrum as directed by your laboratory instructor.

12. **Cleaning Up** Use the labeled collection containers provided by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands thoroughly with soap or detergent before leaving the laboratory.

Semi-Microscale Synthesis

Benzilic Acid Rearrangement

Equipment

Laboratory Period Four

3 beakers, 250-mL	hot plate
boiling chip	melting point capillary tube
Büchner funnel, with adapter	microspatula
condenser	pH paper
250-mL filter flask, with vacuum tubing	1.0-mL pipet*
filter paper	25 mL round-bottom flask
funnel, general purpose	support stand
glass stirring rod	thermometer, -10 to 260 °C
10-mL graduated cylinder	utility clamp
100-mL graduated cylinder	watch glass

*or adjustable micropipet, 100–1000 µL

Reagents and Properties

<i>substance</i>	<i>quantity</i>	<i>molar mass</i> (g/mol)	<i>bp</i> (°C)	<i>mp</i> (°C)
benzil	1.0 g	210		94–5
benzoic acid*		228		150–3
carbon, decolorizing	1.0 g			
Celite filtering aid	0.5 g			
ethanol	3.0 mL	46	78	
hydrochloric acid, 12M	15 mL			
ice				
potassium bromide [†]	0.5 g			
potassium hydroxide, 30%	2.5 mL			

*product †for KBr pellets

Preview

Laboratory Period Four

- Prepare a boiling-water bath
- Mix ethanol, KOH solution, and benzil
- Reflux the mixture for 15 min
- Dissolve potassium benzoate in distilled or deionized water, decolorize, and remove impurities by filtration

- Acidify the filtrate to precipitate benzilic acid
- Isolate the product by filtration
- Recrystallize the product from distilled or deionized water
- Dry and weigh the product
- Characterize product by melting point and IR spectroscopy

PROCEDURE **Caution:** Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

Always use caution in the laboratory. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Avoid ingesting any of the reagents.

Laboratory Period Four

13. Preparing the Boiling-Water Bath

To prepare a boiling-water bath, add 150 mL of tap water to a 250-mL beaker. Heat the water to boiling.

14. Conducting the Reaction

Caution: Ethanol is flammable and toxic. Keep away from flames or other heat sources. 30% Potassium hydroxide (KOH) is corrosive and toxic. Benzil is irritating.

Adjust the reagents to match the amount of benzil you made. For every 1.0 g of benzil you produced, place 3.0 mL of ethanol and 2.5 mL of 30% aqueous KOH into a 25-mL round-bottom flask. Mix by swirling. Then add your benzil and a small boiling chip.

Use the round-bottom flask to assemble a reflux apparatus. Clamp the neck of the round-bottom flask to a support stand and place the flask in the boiling water bath. Heat the reaction mixture to boiling and allow it to reflux for 15 min. [NOTE 4]

NOTE 4: As the benzil dissolves, the mixture may turn blue. The mixture turns brown during the reflux period.

After the reflux period is complete, pour the hot reaction mixture into 100 mL of distilled or deionized water in a 250-mL beaker. Allow this mixture to stand for 5 min. Then warm the mixture to 50 °C to dissolve the sodium benzilate. [NOTE 5]

NOTE 5: Unreacted benzil and some reaction by-products such as diphenylmethanol will remain undissolved at this point.

Caution: Decolorizing carbon is an irritant.

While maintaining the mixture at about 50 °C, add 1.0 g of decolorizing carbon and 0.5 g of Celite filtering aid. Swirl the mixture for 1 min. Filter the mixture through a folded or fluted filter paper to remove the carbon and Celite.

15. Recovering the Benzilic Acid

Caution: 12M Hydrochloric acid (HCl) is toxic and corrosive. Use a *fume hood*.

Place about 50 g of ice in a 250-mL beaker. Add 10–20 mL of the potassium benzilate solution. Working in a *fume hood*, add 15 mL of 12M HCl with stirring. Scratch the sides of the beaker to induce crystallization of the benzilic acid produced.

Add the remaining potassium benzilate solution with stirring. Once the addition is complete, test the resulting mixture with pH paper. If necessary, add additional hydrochloric acid until the pH is 3 or lower.

Cool the mixture in an ice-water bath. Isolate the crude benzilic acid by vacuum filtration. Wash the solid in the funnel with a small amount of cold distilled or deionized water.

Recrystallize the benzilic acid by dissolving it in a minimum amount of boiling distilled water and then allowing the solution to cool slowly to room temperature, scratching the sides of the beaker as necessary to induce crystal formation. Cool the mixture in an ice-water bath and isolate the crystals by vacuum filtration.

Transfer the solid to a watch glass and allow it to air dry for at least 24 hr. Alternatively, dry the solid in a drying oven for 20–30 min.

Weigh the dry benzilic acid and record its mass.

16. **Characterizing the Product** Measure the melting point of your dry product.

Caution: Potassium bromide (KBr) is irritating and hygroscopic.

Prepare a KBr pellet of your product. Obtain the IR spectrum as directed by your laboratory instructor.

17. **Cleaning Up** Use the labeled collection containers provided by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands thoroughly with soap or detergent before leaving the laboratory.

Microscale Synthesis

Benzoin Condensation

Equipment

Laboratory Period One

magnetic stir bar or spin vane	Pasteur pipet, with latex bulb
magnetic stirrer	1.00- or 2.00-mL transfer pipet
micropipet, 100 to 1000- μ L	5-mL vial, with cap
microspatula	

Laboratory Period Two

250-mL beaker*	hot plate
25-mL filter flask, with vacuum tubing	melting point capillary tubes
filter paper, to fit Hirsch funnel	microspatula
glass stirring rod	13 \times 100-mm test tube
10-mL graduated cylinder	1-mL transfer pipet
Hirsch funnel, with adapter	5-mL vial
	watch glass

*for ice-water bath

Reagents and Properties

<i>substance</i>	<i>quantity</i>	<i>molar mass</i> (g/mol)	<i>mp</i> ($^{\circ}$ C)	<i>d</i> (g/mL)
benzaldehyde	1.00 mL	106.12		1.044
benzoin*		212.25	135–137	
95% ethanol	11 mL			
potassium bromide [†]	0.100 g			
2.0M sodium hydroxide	0.5 mL			
thiamine hydrochloride	0.170 g	337.27	260	

*product [†]for IR

Preview

Laboratory Period One

- Place thiamine hydrochloride, water, and 2.0M NaOH into a 5-mL vial
- Add benzaldehyde and cap the vial
- Store for 2–7 days

Laboratory Period Two

- Cool the reaction mixture in an ice-water bath
- Use vacuum filtration to collect the crude product
- Weigh the crude product
- Recrystallize the crude product from 95% ethanol
- Use vacuum filtration to collect the purified product
- Dry and weigh the purified product
- Characterize the product using melting point and IR spectroscopy

PROCEDURE The Procedure for this experiment requires time from four consecutive laboratory periods. The first synthesis requires one laboratory period plus a small portion of the immediately preceding laboratory period.

Caution: Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

Always use caution in the laboratory. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Avoid ingesting any of the reagents.

Laboratory Period One

1. Conducting the Benzoin Condensation

Caution: 95% Ethanol is flammable and irritating. Keep away from flames. 2.0M NaOH is corrosive. Benzaldehyde (almond extract) is a suspected carcinogen and mutagen. [NOTE 1] Wear gloves when handling these compounds.

Place 0.170 g (170 mg) of thiamine hydrochloride into a 5-mL vial. Add 350 μ L of distilled or deionized water. Mix to dissolve.

Add 2.00 mL of 95% ethanol. Add a magnetic spin vane or stir bar. Using a magnetic stirrer, stir the solution until it is homogeneous.

While stirring, use a Pasteur pipet to add 0.5 mL of 2.0M NaOH dropwise to the solution over a 2-min period. Note that the solution initially turns a bright yellow color that then fades to pale yellow.

When the solution is pale yellow, add 1.00 mL of benzaldehyde. Stir until the mixture is homogeneous.

Cap the vial. Allow it to stand for 2–7 days.

NOTE 1: Benzaldehyde, a suspected carcinogen, is also a certified food flavoring (almond extract). Food substances undergo a much higher scrutiny than do most other chemicals.

Laboratory Period Two

2. Isolating and Purifying the Product

Prepare an ice-water bath using a 250-mL beaker. Place 2 mL of distilled water into a test tube. Chill the water in the ice-water bath for later use.

Place the reaction vial in the ice-water bath to crystallize the product. If necessary, scratch the bottom and sides of the vial with a glass rod to induce crystallization. Once crystallization has started, allow the flask to remain in the ice-water bath for 5 min.

Collect the crystals using vacuum filtration. Rinse the crystals with 2 mL of the chilled water. Allow the product to air dry in the filter funnel for 5 min. Weigh the product and record its mass.

For recrystallization, place the crude product into a 5-mL vial. Add 8.0 mL of 95% ethanol *for every gram* of crude product placed in the flask. Use a hot plate to heat the mixture gently until the ethanol boils. If the product does not completely dissolve, add more ethanol dropwise until all of the solid has dissolved in the boiling solvent.

Allow the solution to cool to room temperature. If necessary, scratch the bottom of the vial to induce crystallization. Then cool the solution in the ice-water bath for 5 min.

Filter the crystals using vacuum filtration. Allow the product to air dry in the filter funnel for 10 min.

Transfer the product from the filter paper to a watch glass to finish drying. Weigh the product and record its mass.

3. **Characterizing the Product** Measure the melting point of your dry product.

Caution: Potassium bromide (KBr) is irritating and hygroscopic.

Prepare a KBr pellet of your product. Record the IR spectrum as directed by your laboratory instructor. Compare your spectrum to a reference spectrum of benzoin.

4. **Cleaning Up** Use the labeled collection containers provided by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands thoroughly with soap or detergent before leaving the laboratory.

Microscale Synthesis

Benzoin Oxidation

Equipment

Laboratory Period Three

50-mL beaker	filter paper
100-mL beaker*	forceps
250-mL beaker, with aluminum foil or plastic wrap cover [†]	glass stirring rod
Bunsen burner	10-mL graduated cylinder
conical vial reflux assembly [‡]	Hirsch funnel, with adapter
condenser, with tubing	magnetic spin vane or stir bar
5.0-mL conical vial	4–5 melting point capillary tubes
elastomeric connector	microspatula
reflux assembly [‡]	3 open-ended capillary tubes
condenser, with tubing	2 Pasteur pipets, with latex bulb
elastomeric connector	pencil
5.0-mL round-bottom flask	ruler
10-mL Erlenmeyer flask [§]	sand bath**
25-mL filter flask, with vacuum tubing	stirring hot plate ^{††}
	support stand
	thermometer, –10 to 260 °C

3 TLC plates, silica gel, 2.0-mL transfer pipet
 2.5 × 7.5-cm, with fluorescent indicator 2 utility clamps
 1.0-mL transfer pipet^{‡‡} watch glass

*for ice-water bath

[†]or 4-oz screw-cap jar with lid for TLC developing chamber

[‡]use the reflux assembly indicated by your laboratory instructor

[§]or 13 × 100-mm test tube

**crystallizing dish or electric flask heater filled with sand

^{††}or electric flask heater and magnetic stirrer

^{‡‡}or 1.000-mL micropipet

Reagents and Properties

substance	quantity	molar mass (g/mol)	bp (°C)	mp (°C)	d (g/mL)
acetic acid, glacial	1.5 mL	60.05	118		1.049
ammonium nitrate	0.250 g	80.04			
benzil*		210.23		94–95	
benzoin	0.500 g	212.25		135–137	
copper(II) acetate solution	0.5 mL				
dichloromethane	6 mL		40		
ethanol, 95%	< 4.0 mL				
potassium bromide	0.100 g				

*product

Preview

Laboratory Period Three

- Assemble the reflux apparatus
- Add the benzoin, ammonium nitrate, acetic acid, and copper(II) acetate solution
- Reflux the reaction mixture for up to 60 min
- Monitor the reaction using TLC
- Allow the reaction mixture to cool to room temperature
- Pour the reaction mixture into ice-water solution
- Use vacuum filtration to isolate the crude product
- Recrystallize the product
- Use vacuum filtration to isolate the purified product
- Dry and weigh the product
- Characterize the product using melting point and IR spectroscopy

PROCEDURE **Caution:** Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

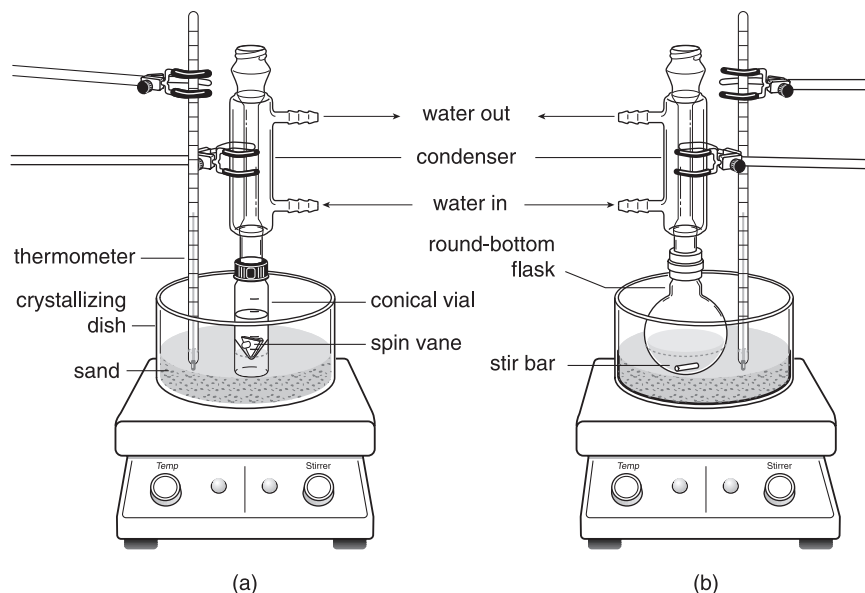
Always use caution in the laboratory. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Avoid ingesting any of the reagents.

Laboratory Period Three

5. Setting Up the Apparatus

Depending upon your glassware, assemble a reflux apparatus similar to that shown in Figure 5(a) or 5(b).

Figure 5 Microscale reflux apparatus with (a) conical vial or (b) round-bottom flask and elastomeric connectors



Caution: Glacial acetic acid is corrosive. Use a *fume hood*. Ammonium nitrate (NH_4NO_3) is oxidizing and irritating. Copper(II) acetate [$\text{Cu}(\text{OAc})_2$] solution is corrosive and irritating.

Remove the 5.0-mL conical vial (round-bottom flask) from the apparatus. Place a magnetic spin vane (stir bar) in the vial (flask).

Adjust the reagents to match the amount of benzoin you made. For every 0.500 g of benzoin you produced, transfer 1.5 mL of glacial acetic acid and 0.250 g of NH_4NO_3 to the vial (flask). Add your benzoin. For every 0.500 g of benzoin you produced, add 0.5 mL of the $\text{Cu}(\text{OAc})_2$ solution. [NOTE 2]

NOTE 2: The solid materials are not soluble in acetic acid at room temperature. The solids dissolve as the pot is heated for refluxing.

6. Refluxing the Reaction Mixture

Reattach the conical vial (flask) to the reflux apparatus. Start the flow of water through the condenser. Heat the reaction mixture to boiling and reflux, while stirring, for 60 min.

7. Setting Up the Chromatography System

Caution: Do not use a Bunsen burner near flammable 95% ethanol.

Using open-ended capillary tubing and a Bunsen burner, prepare 3–5 micropipets for TLC spotting.

Obtain three 2.5 × 7.5-cm silica gel TLC plates. At the top, label the three plates “30 min”, “45 min”, and “60 min”, respectively.

Using a ruler as a straightedge, draw a *very faint* pencil line across each plate 1 cm from the bottom. Do not cut through the silica gel with your marks. Make three small vertical lines that intersect the horizontal line at 6, 12, and 18 mm from the left side of the plate.

Using a pencil, label the plate from left to right below the vertical lines with “Bzo”, “Rxn”, and “Bzl”.

Caution: Benzil is irritating.

Obtain standard samples of benzoin and benzil from your laboratory instructor. Using a micropipet, spot benzoin at the position labeled Bzo on each plate. Discard the micropipet.

Using a new micropipet, spot benzil at the position marked Bzl on each plate. Discard the micropipet.

Caution: Dichloromethane is toxic and irritating.

Prepare a developing chamber by adding 6 mL of dichloromethane to a 250-mL beaker. Add filter paper to the chamber to act as a wick. Cover the chamber with aluminum foil or plastic wrap and set it aside in a *fume hood*.

8. Monitoring the Reaction

After 30 min, remove the heat from the vial (flask). Allow the reaction mixture to cool for 2 min.

Work quickly to minimize the time the reflux is interrupted. Remove the condenser from the reflux apparatus. Use a micropipet to spot the reaction mixture on the 30 min TLC plate at the position marked Rxn.

Replace the condenser and restart the reflux. Wait to continue timing the reaction until the reaction mixture is boiling.

In the meantime, place the TLC plate in the developing chamber. Cover the chamber with the foil or plastic wrap. Develop the plate until the eluent is within 1 cm of the top of the plate.

Remove the plate from the chamber. Immediately mark the eluent front with a pencil. Keep the plate in the *fume hood* for 1 min to allow the dichloromethane to evaporate.

Caution: Ultraviolet radiation can cause severe damage to the eyes.

Wear UV protective goggles. Do not look directly into the UV lamp.

View the plate under UV light to visualize the spots. Use a pencil to circle each spot. Note the relative amounts of benzoin and benzil from the reaction spot.

After 45 min of reaction time, obtain a second sample for TLC analysis. Analyze as before, using the 45 min plate.

If the reaction is complete, as indicated by the absence of benzoin in the sample, stop the reflux. Cool the reaction for 10 min. Go to Part 9.

If benzoin remains in the reaction mixture, continue the reflux. After 60 min of reaction time, stop the reaction. Obtain a third sample for TLC analysis. Analyze as before, using the 60 min plate. Note whether or not the reaction is complete. In either case, go to Part 9.

9. Collecting, Washing, and Drying the Crystals

Place 10 mL of an ice-water mixture in a 50-mL beaker.

Use forceps to remove the stir bar from the reaction vial (flask). Pour the reaction mixture into the 50-mL beaker containing the ice-water mixture. Stir the mixture vigorously with a glass stirring rod to induce crystallization and to break up any lumps of solid material that may form.

Collect the crystals using vacuum filtration. Wash the crystals with 5 mL of distilled water.

Allow the crystals to dry in the Hirsch funnel by pulling air through the funnel for 10 min. Weigh your dried product and record its mass.

10. Recrystallizing Benzil

Caution: 95% Ethanol is flammable and toxic. Do not use near an open flame.

Place your crude product in a 10-mL Erlenmeyer flask or a 13 × 100-mm test tube. Add 0.8 mL of 95% ethanol *for every 0.100 g* of crude product placed in the flask.

Use a hot plate to heat the mixture gently until the ethanol boils. If the product does not completely dissolve, gradually add more ethanol dropwise until all of the solid dissolves in the boiling solvent.

Allow the solution to cool to room temperature. If necessary, scratch the bottom of the flask (tube) to induce crystallization. [NOTE 3]

NOTE 3: Crystallize benzil slowly so that large crystals form. Rapid crystallization of the supersaturated solution forms very fine crystals that are difficult to dry.

Prepare an ice-water bath using a 100-mL beaker. Place the flask (tube) containing the solution in the ice-water bath for 5 min to complete the crystallization.

Filter the crystals using vacuum filtration. Allow your product to air dry in the filter funnel for 10 min.

Transfer the product from the filter paper to a watch glass to finish drying. Weigh the product and record its mass.

11. **Characterizing the Product** Measure the melting point of your dry product.

Caution: Potassium bromide (KBr) is irritating and hygroscopic.

Prepare a KBr pellet of your product. Obtain the IR spectrum as directed by your laboratory instructor.

12. **Cleaning Up** Use the labeled collection containers provided by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands thoroughly with soap or detergent before leaving the laboratory.

Microscale Synthesis

Benzilic Acid Rearrangement

Equipment

Laboratory Period Four

2 beakers, 50-mL	Hirsch funnel, with adapter
2 beakers, 100-mL*	hot plate
boiling chip	melting point capillary tube
25-mL filter flask, with vacuum tubing	microspatula
filter funnel	1.0-mL pipet [†]
filter paper	support stand
glass stirring rod	2 test tubes, 13 × 100-mm
10-mL graduated cylinder	utility clamp
100-mL graduated cylinder	watch glass

*for boiling-water and ice-water baths

[†]or adjustable micropipet, 100–1000 μL

Reagents and Properties

substance	quantity	molar mass (g/mol)	bp (°C)	mp (°C)
benzil	0.100 g	210		94–5
benzilic acid*		228		150–3
carbon, decolorizing	0.050 g			

ethanol	0.5 mL	46	78
hydrochloric acid, 1M	3.0 mL		
ice			
potassium bromide [†]	0.5 g		
potassium hydroxide, 30%	0.25 mL		
*product	[†] for KBr pellets		

Preview

Laboratory Period Four

- Prepare a boiling-water bath
- Mix ethanol, KOH solution, and benzil in a test tube
- Reflux the mixture for 10 min
- Acidify the reaction mixture, decolorize, and remove impurities by filtration
- Acidify the filtrate to precipitate benzilic acid
- Isolate the product by filtration
- Dry and weigh the product
- Characterize the product using melting point and IR spectroscopy

PROCEDURE **Caution:** Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

Always use caution in the laboratory. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Avoid ingesting any of the reagents.

Laboratory Period Four

13. Preparing the Water Baths

To prepare a boiling-water bath, add 50 mL of tap water to a 100-mL beaker. Place the beaker on a hot plate and heat the water to boiling.

To prepare an ice-water bath, fill a second 100-mL beaker three-quarters full with ice. Add tap water to cover the ice.

Pour 2 mL of distilled or deionized water into a test tube. Put the test tube into the ice-water bath to chill the water for later use.

14. Conducting the Reaction

Caution: Ethanol is flammable and toxic. Keep away from flames or other heat sources. 30% Potassium hydroxide (KOH) and 1M hydrochloric acid (HCl) are toxic and corrosive. Benzil is irritating.

Adjust the reagents to match the amount of benzil you made. For every 0.100 g of benzil you produced, place 0.5 mL of ethanol and 0.25 mL of 30% aqueous KOH into a test tube. Add your benzil and a small boiling chip.

Clamp the test tube in the boiling-water bath so that only 5 mm of the test tube is submerged in the water. Heat the reaction mixture to boiling. Reflux the mixture for 15 min. [NOTE 4]

Place 2 mL of distilled or deionized water into a 50-mL beaker. Add *exactly* 1 mL of 1M HCl for every 0.100 g of benzil you produced. Do not add excess HCl or the benzilic acid will precipitate prematurely.

When the reflux time is complete, pour the reaction mixture into the beaker containing the HCl. Note that diphenylmethanol, a by-product of the rearrangement reaction, separates as a brown, sticky precipitate.

Caution: Decolorizing carbon is an irritant.

NOTE 4: As the benzil dissolves, the mixture may turn blue. The mixture turns brown during the reflux period.

20 SYNT 743/Converting Benzaldehyde to Benzilic Acid: A Multistep Synthesis

NOTE 5: The filtrate should be colorless or only faintly yellow at this point.

Add 0.050 g (50 mg) of decolorizing carbon to the reaction mixture. Gravity filter the mixture to remove the carbon and diphenylmethanol.
[NOTE 5]

15. Recovering the Benzilic Acid

Place 2 mL of 1M HCl into a clean 50-mL beaker. Add the filtrate to the HCl to precipitate the benzilic acid. Mix thoroughly.

Isolate the benzilic acid by vacuum filtration using a Hirsch funnel. Rinse the beaker with 2 mL of the chilled distilled water. Then use the rinse to wash the precipitate in the Hirsch funnel.

Transfer the product from the filter paper to a watch glass to finish drying. Weigh the product and record its mass.

16. Characterizing the Product

Measure the melting point of your benzilic acid product.

Caution: Potassium bromide (KBr) is irritating and hygroscopic.

Prepare a KBr pellet of your product. Obtain the IR spectrum as directed by your laboratory instructor.

17. Cleaning Up

Use the labeled collection containers provided by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands thoroughly with soap or detergent before leaving the laboratory.

Post-Laboratory Questions Benzoin Condensation

1. Calculate the percent yield of benzoin after recrystallization, using Equation 5.

$$\text{percent yield, \%} = \left(\frac{\text{actual yield, g}}{\text{theoretical yield, g}} \right) (100\%) \quad (\text{Eq. 5})$$

2. The benzoin molecule contains one chiral center, yet the product produced in this reaction is not optically active. Briefly explain.
3. Clearly label your IR spectrum of benzoin. Assign the appropriate vibrational modes to the following peaks:
 - (a) 3400 cm^{-1}
 - (b) 3052 cm^{-1}
 - (c) 1676 cm^{-1}

Benzoin Oxidation

4. Calculate the percent yield of benzil from benzoin after recrystallization, using Equation 5 in Post-Laboratory Question 1.
5. Calculate the overall percent yield of benzil from benzaldehyde.
6. Use your TLC data to explain whether or not the oxidation reaction went to completion.
7. Describe the major differences and similarities between the IR spectra of benzoin and benzil. Compare your product IR spectrum with spectra for benzoin and benzil.
8. Benzoin can also undergo reduction with reagents like NaBH_4 . Propose a structure for the product obtained from the reduction of benzoin. Discuss the stereochemical aspects of this material.

Benzilic Acid Rearrangement

9. Calculate the percent yield of benzilic acid from benzil, using Equation 5 in Post-Laboratory Question 1.
10. Calculate the overall percent yield of benzilic acid from benzaldehyde.
11. Compare your IR spectrum with the spectrum for benzilic acid provided by your laboratory instructor. Assign the following absorption bands in your infrared spectrum to a functional group in the benzilic acid product molecules.
 - (a) 3400 cm^{-1}
 - (b) $3500 - 2500 \text{ cm}^{-1}$
 - (c) 1750 cm^{-1}
 - (d) 700 cm^{-1}
12. Compare the melting point observed for your product with the accepted melting point for benzilic acid.

NAME

SECTION

DATE

SYNT 743/Converting Benzaldehyde to Benzilic Acid: A Multistep Synthesis

Pre-Laboratory Assignment

Benzoin Condensation

1. What safety precautions must be taken when using sodium hydroxide?
2. Calculate the number of moles of benzaldehyde and thiamine hydrochloride used in the Procedure. Explain why benzaldehyde is used for the theoretical yield calculation even though fewer moles of thiamine hydrochloride are present in the reaction.
3. Calculate the theoretical yield for the benzoin condensation. Show the calculations here and in your laboratory notebook.

Benzoin Oxidation

4. What safety precautions must be taken when using glacial acetic acid?
5. Calculate the theoretical yield for the production of benzil from 2.0 g (0.500 g) benzoin. Show your results here and in your laboratory notebook.

6. Calculate the overall theoretical yield of benzil from 4.0 mL (1.00 mL) of benzaldehyde. Show your results here and in your laboratory notebook.

Benzilic Acid Rearrangement

7. Why should you avoid contact of your skin with 30% KOH solution?
8. Calculate the theoretical yield of benzilic acid from 1.0 g (0.100 g) of benzil. Record your calculations here and in your laboratory notebook.
9. Calculate the overall theoretical yield of benzilic acid from 4.0 mL (1.00 mL) of benzaldehyde. Show your results here and in your laboratory notebook.
10. What by-product is formed along with benzilic acid in this experiment? Draw a structural formula for this substance.
11. The initial step in the accepted mechanism for the benzilic acid rearrangement involves attack of hydroxide ion at a carbonyl carbon in a benzil molecule. Why might this mode of attack be expected?