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Two Methods for the Synthesis of Phenacetin

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PURPOSE OF THE EXPERIMENT

Synthesize phenacetin by formation of an ether functional group and/or an amide functional group. Compare the products by mixture melting point, IR spectroscopy, and NMR spectroscopy.

EXPERIMENTAL OPTIONS

BACKGROUND REQUIRED

You should be familiar with recrystallization, reflux, melting point and mixture melting point measurements, IR spectroscopy, and NMR spectroscopy.

BACKGROUND INFORMATION

Phenacetin is an active constituent of APC tablets, along with aspirin and caffeine. These tablets were used for years as an analgesic to relieve pain and as an antipyretic to reduce fever. They were removed from the market after long-term studies suggested phenacetin is carcinogenic when ingested over long time periods.

Aspirin and phenacetin are synthesized chemically. Caffeine is obtained as a by-product from the production of caffeine-free coffee. These constituents are mixed with binders and inert ingredients to create the tablets.

As shown in Figure 1 on page 2, each organic compound contains more than one functional group. Therefore, more than one method can be used to synthesize each compound.

Phenacetin, *p*-ethoxyacetanilide, contains both an ether group and an amide group substituted *para* on a benzene ring. Either of these functional groups might be produced as the final step in a synthesis of phenacetin.

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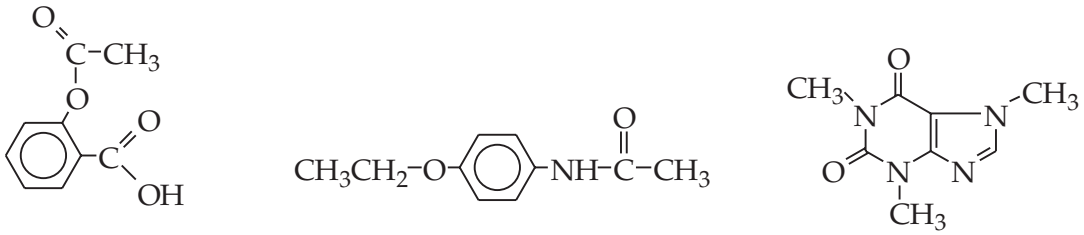
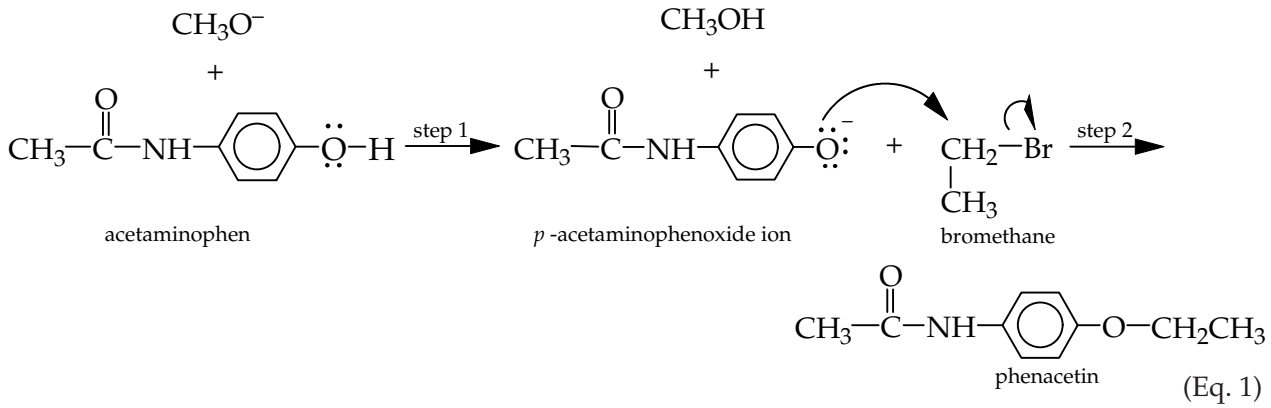


Figure 1 Active constituents in APC analgesic tablets

Williamson Ether Synthesis Equation 1 shows the formation of the ether functional group in phenacetin. The formation of an ether by reaction of an alkyl halide with the conjugate base of an alcohol or phenol is called a **Williamson ether synthesis**. The reactant, acetaminophen (*p*-acetamidophenol), is the active ingredient in Tylenol®.



(Eq. 1)

When *p*-acetamidophenol is placed in a basic solution, a proton is removed from the phenol group, as shown in step 1 of Equation 1. In step 2, the conjugate base of *p*-acetamidophenol, *p*-acetamidophenoxide ion, functions as a nucleophile in its subsequent reaction with bromoethane to yield phenacetin.

The acid–base equilibrium of step 1 proceeds essentially to completion because phenols ($pK_a \sim 10$), such as *p*-acetamidophenol, are much stronger acids than alcohols ($pK_a \sim 16$), such as the methanol produced in this reaction.

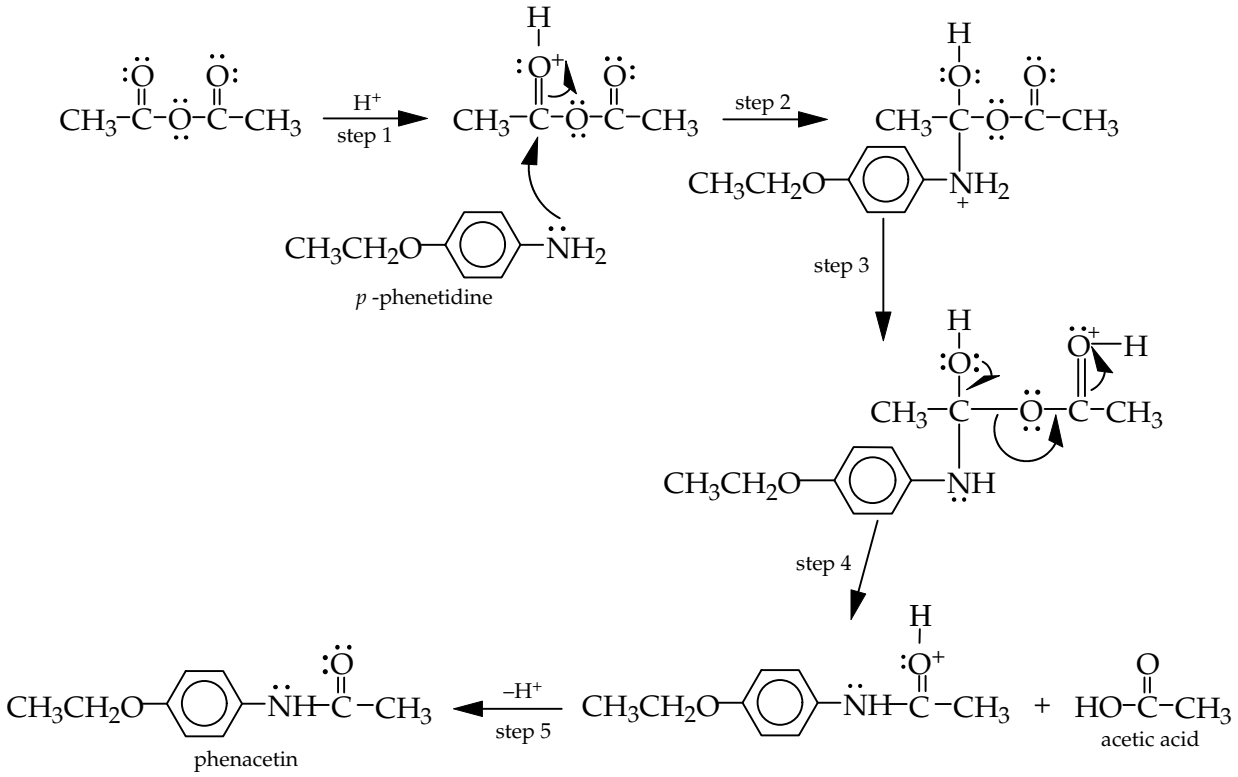
The number of moles of methoxide ion that are added to the reaction flask must exactly equal the number of moles of *p*-acetamidophenol. If insufficient methoxide ion is used, some of the *p*-acetamidophenol will not be converted to its conjugate base and will not be reactive toward the bromoethane. If excess methoxide ion is used, methoxide ion will compete as a nucleophile with the *p*-acetamidophenoxide ion, also reducing the yield of phenacetin.

The second step in the overall process is an S_N2 nucleophilic substitution reaction. S_N2 reactions occur in one step with the leaving group departing simultaneously. An important factor in determining the rate of S_N2 reactions is the degree of crowding at the reaction site in the alkyl halide. For this reason, the reaction proceeds best when relatively uncrowded primary alkyl halides are used.

In practice, this reaction works equally well with most primary halides and might be used to produce a series of phenacetin analogs with

different alkoxy groups. Synthesizing compounds that are related in structure to known beneficial agents is a common method used to search for more effective drugs.

Amide Synthesis Equation 2 shows the synthesis of phenacetin by formation of an amide functional group. In step 1, acetic anhydride is protonated to increase its reactivity. In step 2, *p*-phenetidine (*p*-ethoxyaniline) acts as a nucleophile and attacks the carbonyl carbon of acetic anhydride to form a tetrahedral intermediate.



(Eq. 2)

In step 3, a proton shift occurs. In step 4, acetic acid leaves to form protonated phenacetin. Finally, in step 5, the proton is removed.

Control of the solution acidity is important in maximizing the product yield. Protonation activates the acetic anhydride toward nucleophilic attack; however, if the pH of the solution is too low, *p*-phenetidine is converted to its conjugate acid and is unavailable for the reaction. A buffer solution consisting of acetic acid and its conjugate base sodium acetate is used to control the pH.

A fundamental principle in chemistry is that the properties of a substance do not depend upon its source. Consequently, samples of phenacetin synthesized by either of the methods described above should be identical.

In this experiment, you will prepare phenacetin by the Williamson ether synthesis and by the amide synthesis. You will compare the products by melting point measurement, infrared spectroscopy, and/or nuclear magnetic resonance spectroscopy.

Williamson Ether Synthesis of Phenacetin

Semi-Microscale Synthesis

Equipment

2 beakers, 100-mL
250-mL beaker
boiling chip
Büchner funnel, with adapter
125-mL filter flask, with vacuum tubing
filter paper
10-mL graduated cylinder
hot plate*
melting point capillary tubes
2 Pasteur pipets, with latex bulb
spatula
standard taper glassware
condenser, with tubing
25-mL round-bottom flask
support stand
16 × 150-mm test tube
2 utility clamps

*or electric flask heater, with regulator

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	*mp (°C)*	*bp (°C)*
p-acetamidophenol	1.51 g	151.17	169–172	
bromoethane	1.64 g	108.97		37–40
deutero-chloroform*	1 mL	120		61
ethanol, 100%	4 mL	46.07		78
ethanol, 95%	6 mL			
phenacetin†		179	134–136	
potassium bromide‡	100 mg			
25% sodium methoxide in methanol	2.5 mL			

*for NMR
†product
‡for IR

Preview

- Place sodium methoxide solution, 100% ethanol, and *p*-acetamidophenol in a reaction flask
- Assemble the reflux apparatus
- Add bromoethane
- Reflux the mixture for 45 min
- Add water to the hot reaction mixture and cool it in ice to crystallize the product
- Isolate the crude product by vacuum filtration
- Purify the product by recrystallization from an ethanol–water mixture
- Isolate the purified phenacetin by vacuum filtration; dry and weigh the crystals
- Characterize the product by melting point and infrared and/or NMR 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.

1. Refluxing the Reaction Mixture

Caution: *p*-Acetamidophenol is toxic and irritating. Ethanol is flammable and irritating. 25% Sodium methoxide in methanol is flammable, toxic, and corrosive. Keep away from flames or other heat sources.

Place 2.5 mL of 25% sodium methoxide in methanol, 4 mL of 100% ethanol, and 1.51 g of *p*-acetamidophenol in a 25-mL round-bottom flask. Add a boiling chip.

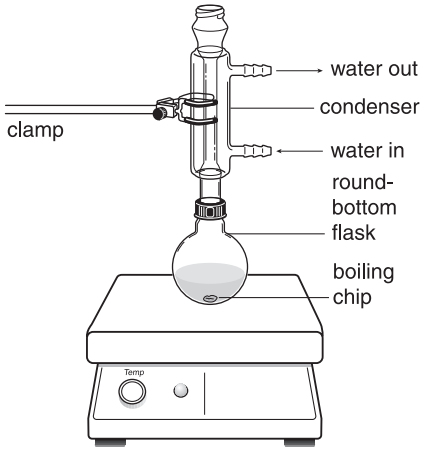


Figure 2 Semi-microscale reflux apparatus

Caution: Bromoethane is flammable and irritating. Keep away from flames or other heat sources.

Use this flask to set up the reflux apparatus shown in Figure 2. Immediately before joining the flask to the condenser, add 1.64 g (1.12 mL) of bromoethane to the flask. Turn on the water to the condenser. Adjust the flask heater to produce moderate boiling. Reflux the mixture for 45 min.

Prepare an ice bath in a 250-mL beaker.

When the reflux time is completed, remove the heater. While the reaction mixture is still hot, slowly add 12 mL of distilled or deionized water through the top of the condenser. Allow the reaction mixture to cool to room temperature.

Turn off the water and remove the reflux condenser.

Pour the reaction mixture into a 100-mL beaker. Rinse the round-bottom flask with 3 mL of water and add the rinse to the beaker.

Cool the beaker in the ice bath to crystallize the product. Collect the product by vacuum filtration using a Büchner funnel.

NOTE 1: Food and drug substances undergo a much higher scrutiny than do most other chemicals. Use normal precautions when working with phenacetin.

2. Recrystallizing the Crude Phenacetin

Caution: Phenacetin is a suspected carcinogen. [NOTE 1]

Purify the product by recrystallization from an ethanol–water mixture as follows: [NOTE 2] Place the impure phenacetin in a 100-mL beaker. Put 6 mL of 95% ethanol into a test tube and heat to boiling. Maintain the temperature of the ethanol close to the boiling point, but do not allow the ethanol to boil away.

Add hot ethanol to the phenacetin until the solid just dissolves. Once the solid has dissolved, use a Pasteur pipet to add water dropwise to decrease the solubility of the phenacetin *while maintaining the solution at a temperature close to its boiling point*. Once the solution becomes cloudy, add hot ethanol dropwise to bring the product back into solution. Then set it aside to cool slowly. If the solution appears milky or if an oil appears, add more ethanol and heat to redissolve. Then cool the solution again.

Isolate the purified phenacetin by vacuum filtration using a Büchner funnel. Pull air through the funnel for 5 min to dry the product. Alternatively, dry the product in a 110 °C drying oven. Weigh the product and record its mass.

NOTE 2: Phenacetin is very soluble in ethanol and quite insoluble in water. Because ethanol and water are miscible liquids, a mixture of the two solvents can be used for recrystallization. *Take great care with the recrystallization or low product yields will result.*

3. Characterizing the Product Measure the melting point of your product. If product is available from the amide synthesis, conduct a mixture melting point. Thoroughly mix equal amounts of phenacetin from each procedure. Take the melting point of the mixture.

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

Obtain an infrared spectrum of your product by preparing a KBr pellet or as indicated by your laboratory instructor.

Caution: *deutero*-Chloroform is toxic and a suspected carcinogen. Dispense in a ***fume hood*** or glove box. Wear protective gloves.

Dissolve a small amount of the product in *deutero*-chloroform. Place the solution in a NMR sample tube. Obtain a NMR spectrum as directed by your laboratory instructor.

4. Cleaning Up Place your recovered materials in the appropriate labeled collection containers as directed by your laboratory instructor. Clean your glassware with soap or detergent.

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

Williamson Ether Synthesis of Phenacetin

Microscale Synthesis

Equipment

25-mL beaker
100-mL beaker
conical vial reflux apparatus*
  condenser, with tubing
  5.0-mL conical vial
  magnetic spin vane
  thermometer, –10 to 260 °C
elastomeric connector
  reflux apparatus*
    condenser, with tubing
    elastomeric connector
    magnetic stir bar
    5.0-mL round-bottom flask
25-mL filter flask,
  with vacuum tubing
filter paper
graduated pipet or syringe
Hirsch funnel, with adapter
hot plate
melting point capillary tubes
microspatula
2 Pasteur pipets, with latex bulb
sand bath†
support stand
2 test tubes, 13 × 100-mm
2 utility clamps

*use reflux apparatus indicated by your laboratory instructor

†stirring hot plate with crystallizing dish filled with sand or magnetic stirrer and electric flask heater filled with sand

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	*mp (°C)*	*bp (°C)*
p-acetamidophenol	0.151 g	151.17	169–172	
bromoethane	0.17 g	108.97		37–40
deutero-chloroform*	1 mL	120		61
ethanol, 100%	1.0 mL	46.07		78
ethanol, 95%	1.5 mL			
phenacetin†		179	134–136	
potassium bromide‡	100 mg			
25% sodium methoxide in methanol	0.25 mL			

*for NMR

†product

‡for IR

Preview

- Place sodium methoxide solution, ethanol, and *p*-acetamidophenol in a reaction flask or vial
- Assemble the reflux apparatus
- Add bromoethane through the condenser
- Reflux the mixture for 45 min
- Add water to the hot reaction mixture and cool it in ice to crystallize the product
- Isolate the crude product by vacuum filtration
- Purify the product by recrystallization from an ethanol–water mixture

- Isolate the purified phenacetin by vacuum filtration; dry and weigh the crystals
- Characterize the product by melting point and infrared and/or NMR 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.

1. Refluxing the Reaction Mixture

Caution: *p*-Acetamidophenol is toxic and irritating. Ethanol is flammable and irritating. 25% Sodium methoxide in methanol is flammable, toxic, and corrosive. Keep away from flames or other heat sources.

Place exactly 0.25 mL of 25% sodium methoxide in methanol, 1.0 mL of 100% ethanol, and 0.151 g of *p*-acetamidophenol in a 5-mL conical vial or 5-mL round-bottom flask. Add a magnetic spin vane or stir bar. If a magnetic stirrer is not available, add a boiling chip. Use this vial(flask) to set up the reflux apparatus shown in Figure 3.

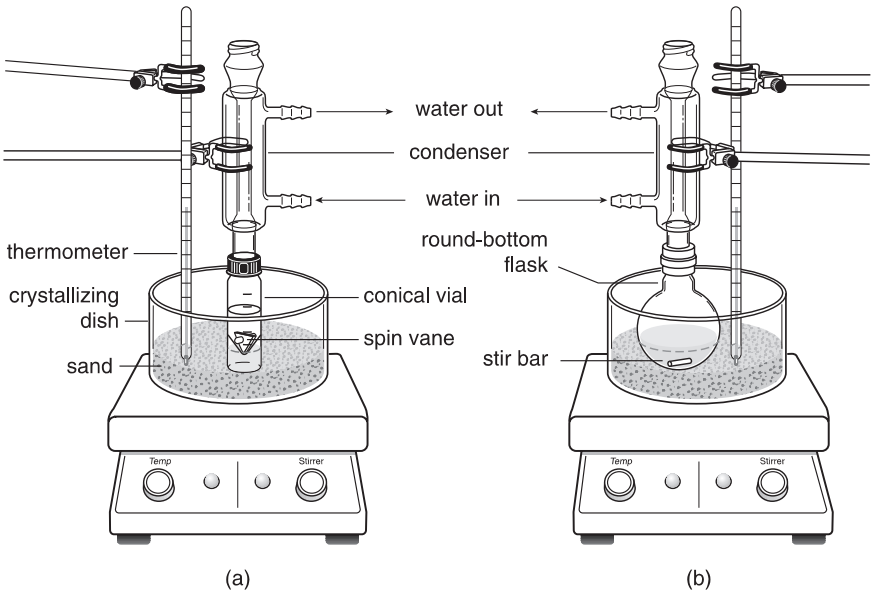


Figure 3 Microscale reflux apparatus with (a) conical vial or (b) round-bottom flask and elastomeric connectors

Carefully add 0.17 g (0.12 mL) of bromoethane through the top of the condenser. Turn on the water to the condenser. Adjust the sand bath to produce moderate boiling. Reflux the mixture for 45 min.

Prepare an ice bath in a 100-mL beaker.

When the reflux time is completed, remove the heater. While the reaction mixture is still hot, slowly add 1.0 mL of distilled or deionized water through the top of the condenser. Allow the reaction mixture to cool to room temperature.

Turn off the water and remove the reflux condenser.

Pour the reaction mixture into a 25-mL beaker. Rinse the vial (flask) with 0.5 mL of water and add the rinse to the beaker.

Cool the beaker in the ice bath to crystallize the product. Collect the product by vacuum filtration using a Hirsch funnel.

2. Recrystallizing the Crude Phenacetin

Caution: Phenacetin is a suspected carcinogen. [NOTE 1]

Purify the product by recrystallization from an ethanol–water mixture as follows: [NOTE 2] Place the impure phenacetin in a 13 × 100-mm test tube. Add 1 mL of 95% ethanol to a second test tube. Use a sand bath to heat the ethanol to boiling. Maintain the temperature of the ethanol close to the boiling point, but do not allow the ethanol to boil away.

Using a Pasteur pipet, add the hot ethanol dropwise to just dissolve the phenacetin. Place this mixture on a sand bath and heat to the boiling point.

Once the solid has dissolved, use a Pasteur pipet to add water dropwise to decrease the solubility of the phenacetin *while maintaining the solution at a temperature close to its boiling point*. Once the solution becomes cloudy, add ethanol dropwise to bring the product back into solution. Then set it aside to cool slowly. If the solution appears milky or if an oil appears, add more ethanol and heat to redissolve, then cool the solution again.

Isolate the purified phenacetin by vacuum filtration using a Hirsch funnel. Pull air through the funnel for 5 min to dry the product. Alternatively, dry the product in a 110 °C drying oven. Weigh the product and record its mass.

NOTE 1: Food and drug substances undergo a much higher scrutiny than do most other chemicals. Use normal precautions when working with phenacetin.

NOTE 2: Phenacetin is very soluble in ethanol and quite insoluble in water. Because ethanol and water are miscible liquids, a mixture of the two solvents can be used for recrystallization. *Take great care with the recrystallization or low product yields will result.*

3. Characterizing the Product

Measure the melting point of your product. If product is available from the amide synthesis, conduct a mixture melting point. Thoroughly mix equal amounts of phenacetin from each procedure. Take the melting point of the mixture.

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

Obtain an infrared spectrum of your product by preparing a KBr pellet or as indicated by your laboratory instructor.

Caution: *deutero*-Chloroform is toxic and a suspected carcinogen. Dispense in a ***fume hood*** or glove box. Wear protective gloves.

Dissolve a small amount of the product in *deutero*-chloroform. Place the solution in a NMR sample tube. Obtain a NMR spectrum as directed by your laboratory instructor.

4. Cleaning Up

Place your recovered materials in the appropriate labeled collection containers as directed by your laboratory instructor. Clean your glassware with soap or detergent.

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

Amide Synthesis of Phenacetin

Semi-Microscale Synthesis

Equipment

100-mL beaker
250-mL beaker
400-mL beaker
Büchner funnel, with adapter
25-mL Erlenmeyer flask
125-mL Erlenmeyer flask
125-mL filter flask, with vacuum tubing
filter papers
funnel, general-purpose
glass stirring rod
25-mL graduated cylinder
hot plate
melting point capillary tubes
spatula
support ring or funnel support
support stand
16 × 150-mm test tube
thermometer, –10 to 260 °C

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	*mp (°C)*	*bp (°C)*
acetic anhydride	1.2 mL	102.09		138–140
activated carbon	0.4 g			
deutero-chloroform*	1 mL	120		61
ethanol, 95%	6 mL			
hydrochloric acid, concentrated	1.0 mL			
phenacetin†		179	134–136	
p-phenetidine	1.38 g	137.18	4	250
potassium bromide‡	100 mg			
sodium acetate	2.0 g	82.03		

*for NMR
†product
‡for IR

Preview

- Decolorize the *p*-phenetidine
- Combine the solution of *p*-phenetidine with acetic anhydride and sodium acetate
- Isolate the crude product by vacuum filtration
- Purify the product by recrystallization from an ethanol–water mixture
- Isolate the purified phenacetin by vacuum filtration; dry and weigh the crystals
- Characterize the product by melting point and infrared and/or NMR 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.

1. Conducting the Reaction

Caution: Activated carbon and *p*-phenetidine are irritating.

Concentrated hydrochloric acid (HCl) is toxic and corrosive. It can cause severe burns. Use a ***fume hood*** when using concentrated HCl.

In a 250 mL-beaker, add 1.0 mL of conc. HCl to 25 mL of distilled or deionized water. Dissolve 1.38 g (1.3 mL) of *p*-phenetidine (*p*-ethoxyaniline) in the solution.

Decolorize the solution by stirring it with 0.4 g of activated carbon for 1–2 min. Remove the carbon by gravity filtration.

Place the decolorized *p*-phenetidine solution in a 125-mL Erlenmeyer flask. Warm it on a hot plate to 50 °C.

Using a 25-mL Erlenmeyer flask, dissolve 2 g of sodium acetate in 6 mL of water. Warm it on a hot plate to 50 °C.

Add 1.2 mL of acetic anhydride to the *p*-phenetidine solution and swirl to mix. Add, all at once, the sodium acetate solution to the *p*-phenetidine solution and swirl to mix. Allow the reaction mixture to stand for 15 min, maintaining the temperature at 50 °C.

Prepare an ice bath using a 400-mL beaker. Cool the reaction mixture in the ice bath.

Stir vigorously during the crystallization of the product. Collect the crystals by vacuum filtration using a Büchner funnel.

NOTE 1: Food and drug substances undergo a much higher scrutiny than do most other chemicals. Use normal precautions when working with phenacetin.

2. Recrystallizing the Crude Phenacetin

Caution: Phenacetin is a suspected carcinogen. [NOTE 1] Ethanol is flammable and irritating. Keep away from flames or other heat sources.

Purify the product by recrystallization from an ethanol–water mixture as follows: [NOTE 2] Place the impure phenacetin in a 100-mL beaker. Put 6 mL of 95% ethanol into a test tube and heat to boiling. Maintain the temperature of the ethanol close to the boiling point, but do not allow the ethanol to boil away.

Add hot ethanol to the phenacetin until the solid just dissolves. Once the solid has dissolved, use a Pasteur pipet to add water dropwise to decrease the solubility of the phenacetin *while maintaining the solution at a temperature close to its boiling point*. Once the solution becomes cloudy, add hot ethanol dropwise to bring the product back into solution. Then set it aside to cool slowly. If the solution appears milky or if an oil appears, add more ethanol and heat to redissolve. Then cool the solution again.

Isolate the purified phenacetin by vacuum filtration using a Büchner funnel. Pull air through the funnel for 5 min to dry the product. Alternatively, dry the product in a 110 °C drying oven. Weigh the product and record its mass.

NOTE 2: Phenacetin is very soluble in ethanol and quite insoluble in water. Because ethanol and water are miscible liquids, a mixture of the two solvents can be used for recrystallization. *Take great care with the recrystallization or low product yields will result.*

3. Characterizing the Product

Measure the melting point of your product. If product is available from the Williamson ether synthesis, conduct a mixture melting point. Thor-

oughly mix equal amounts of phenacetin from each procedure. Take the melting point of the mixture.

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

Obtain an infrared spectrum of your product by preparing a KBr pellet or as indicated by your laboratory instructor.

Caution: *deutero*-Chloroform is toxic and a suspected carcinogen. Dispense in a ***fume hood*** or glove box. Wear protective gloves.

Dissolve a small amount of the product in *deutero*-chloroform. Place the solution in a NMR sample tube. Obtain a NMR spectrum as directed by your laboratory instructor.

4. Cleaning Up Place your recovered materials in the appropriate labeled collection containers as directed by your laboratory instructor. Clean your glassware with soap or detergent.

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

Amide Synthesis of Phenacetin

Microscale Synthesis

Equipment

50-mL beaker	Hirsch funnel, with adapter
100-mL beaker	hot plate
2 Erlenmeyer flasks, 25-mL	melting point capillary tubes
25-mL filter flask, with vacuum tubing	microspatula
	2 Pasteur pipets, with latex bulb
filter papers	sand bath*
funnel, general-purpose	support ring or funnel support
glass stirring rod	support stand
10-mL graduated cylinder	2 test tubes, 13 × 100-mm
1.0-mL graduated pipet or syringe	thermometer, –10 to 260 °C

* stirring hot plate with crystallizing dish filled with sand or magnetic stirrer and electric flask heater filled with sand

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	*mp (°C)*	*bp (°C)*
acetic anhydride	0.25 mL	102.09		138–140
activated carbon	0.1 g			
deutero-chloroform*	1 mL	120		61
ethanol, 95%	1.5 mL			
hydrochloric acid, concentrated	0.2 mL			
phenacetin†		179	134–136	
p-phenetidine	0.266 g	137.18	4	250
potassium bromide‡	100 mg			
sodium acetate	0.42 g	82.03		

*for NMR
†product
‡for IR

Preview

- Decolorize the *p*-phenetidine
- Combine the solution of *p*-phenetidine with acetic anhydride and sodium acetate
- Isolate the crude product by vacuum filtration
- Purify the product by recrystallization from an ethanol–water mixture
- Isolate the purified phenacetin by vacuum filtration; dry and weigh the crystals
- Characterize the product by melting point and infrared and/or NMR 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.

1. Conducting the Reaction

Caution: Activated carbon and *p*-phenetidine are irritating.

Concentrated hydrochloric acid (HCl) is toxic and corrosive. It can cause severe burns. Use a ***fume hood*** when working with concentrated HCl.

In a 50 mL-beaker, add 0.2 mL of conc. HCl to 5 mL of distilled or deionized water. Dissolve 0.266 g (0.25 mL) of *p*-phenetidine (*p*-ethoxyaniline) in the solution.

Decolorize the solution by stirring it with 0.1 g of activated carbon for 1–2 min. Remove the carbon by gravity filtration.

Place the decolorized *p*-phenetidine solution in a 25-mL Erlenmeyer flask. Warm it on a hot plate to 50 °C.

Using a 25-mL Erlenmeyer flask, dissolve 0.42 g of sodium acetate in 1.5 mL of water. Warm it on a hot plate to 50 °C.

Add 0.25 mL of acetic anhydride to the *p*-phenetidine solution and swirl to mix. Add, all at once, the sodium acetate solution to the *p*-phenetidine solution and swirl to mix. Allow the reaction mixture to stand for 15 min, maintaining the temperature at 50 °C.

Prepare an ice bath using a 100-mL beaker. Cool the reaction mixture in the ice bath.

Stir vigorously during the crystallization of the product. Collect the crystals by vacuum filtration using a Hirsch funnel.

NOTE 1: Food and drug substances undergo a much higher scrutiny than do most other chemicals. Use normal precautions when working with phenacetin.

2. Recrystallizing the Crude Phenacetin

Caution: Phenacetin is a suspected carcinogen. [NOTE 1] Ethanol is flammable and irritating. Keep away from flames or other heat sources.

Purify the product by recrystallization from an ethanol–water mixture as follows: [NOTE 2] Place the impure phenacetin in a 13 × 100-mm test tube. Add 1 mL of 95% ethanol to a second test tube. Use a sand bath to heat the ethanol to boiling. Maintain the temperature of the ethanol close to the boiling point, but do not allow the ethanol to boil away.

Using a Pasteur pipet, add the hot ethanol dropwise to just dissolve the phenacetin. Place this mixture on a sand bath and heat to the boiling point.

Once the solid has dissolved, use a Pasteur pipet to add water dropwise to decrease the solubility of the phenacetin *while maintaining the so-*

NOTE 2: Phenacetin is very soluble in ethanol and quite insoluble in water. Because ethanol and water are miscible liquids, a mixture of the two solvents can be used for recrystallization. *Take great care with the recrystallization or low product yields will result.*

lution at a temperature close to its boiling point. Once the solution becomes cloudy, add ethanol dropwise to bring the product back into solution. Then set it aside to cool slowly. If the solution appears milky or if an oil appears, add more ethanol and heat to redissolve, then cool the solution again.

Isolate the purified phenacetin by vacuum filtration using a Hirsch funnel. Pull air through the funnel for 5 min to dry the product. Alternatively, dry the product in a 110 °C drying oven. Weigh the product and record its mass.

3. Characterizing the Product

Measure the melting point of your product. If product is available from the Williamson ether synthesis, conduct a mixture melting point. Thoroughly mix equal amounts of phenacetin from each procedure. Take the melting point of the mixture.

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

Obtain an infrared spectrum of your product by preparing a KBr pellet or as indicated by your laboratory instructor.

Caution: *deutero*-Chloroform is toxic and a suspected carcinogen. Dispense in a ***fume hood*** or glove box. Wear protective gloves.

Dissolve a small amount of the product in *deutero*-chloroform. Place the solution in a NMR sample tube. Obtain a NMR spectrum as directed by your laboratory instructor.

4. Cleaning Up

Place your recovered materials in the appropriate labeled collection containers as directed 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

1. Calculate the percent yield of phenacetin obtained in both the Williamson ether synthesis and the amide synthesis.
2. Does the melting point obtained for your product indicate that the sample is indeed phenacetin? What additional evidence can you cite that your product is phenacetin?
3. Comment on the value of finding the mixture melting point of the products from the two procedures in this module. What does this value indicate about the identities of the two products?
4. The infrared spectrum of phenacetin shows absorption bands at the following positions. Match each absorption band with the structural characteristic indicated by that absorption band.

_____ (a) 3300 cm^{-1}	(1) C – O – C
_____ (b) 1653 cm^{-1}	(2) C = O
_____ (c) 1244 and 1047 cm^{-1}	(3) *para* disubstituted benzene
_____ (d) 837 cm^{-1}	(4) N – H

5. The aromatic region (7–8 ppm) of the proton NMR spectrum of compounds with *para* disubstituted benzene rings such as phenacetin is often referred to as an AB pattern. This pattern has two doublet signals coupled to each other. Explain the origin of this AB pattern.

NAME SECTION DATE

SYNT 726/Two Methods for the Synthesis of Phenacetin

Pre-Laboratory Assignment

1. What precautions should one use when working with phenacetin?

2. Calculate the theoretical yield in grams for the Williamson ether synthesis of phenacetin. Repeat the calculation for the amide synthesis of phenacetin. (The density of *p*-phenetidine is 1.065 g/mL.)

3. Why is it important that the number of moles of methoxide ion be the same as the number of moles of *p*-acetamidophenol used for Williamson synthesis of phenacetin?

4. If phenacetin "oils out" of solution during a recrystallization, what remedial action should be taken?

5. What role does the sodium acetate play in the synthesis of the amide functional group of phenacetin?

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