INSTRUCTOR'S INFORMATION

Two Methods for the Synthesis of Phenacetin

EQUIPMENT

General (Williamson Ether Synthesis)

apparatus, melting point
aspirators, with traps
balance, 0.001-g
chips, boiling
oven, drying
paper, filter, to fit Büchner or Hirsch funnel
pipets, Pasteur, with latex bulbs
press, pellet, IR
spectrometer, nuclear magnetic resonance
spectrophotometer, infrared
tubes, capillary, melting point
tubes, sample, NMR

Individual

Semi-Microscale

2 beakers, 100-mL
beaker, 250-mL
2 clamps, utility
cylinder, graduated, 10-mL
funnel, Büchner, with adapter
flask, filter, 125-mL, with vacuum tubing
glassware, standard taper
  condenser, with tubing
  flask, round-bottom, 25-mL
    *or electric flask heater, with regulator
hot plate*
spatula
stand, support
test tube, 16 × 150-mm

Microscale

apparatus, reflux, conical vial*
  condenser, with tubing
  spin vane, magnetic
  thermometer, –10 to 260 °C
  vial, conical, 5.0-mL
apparatus, reflux, elastomeric connector*
  condenser, with tubing
  connector, elastomeric
  stir bar, magnetic
  flask, round-bottom, 5.0-mL
bath, sand†
  *use available reflux apparatus
  †stirring hot plate with crystallizing dish filled with sand or magnetic stirrer and electric flask heater filled with sand
beaker, 25-mL
beaker, 100-mL
2 clamps, utility
flask, filter, 25-mL, with vacuum tubing
funnel, Hirsch, with adapter
hot plate
microspatula
pipet, graduated, or syringe
stand, support
2 test tubes, 13 × 100-mm

General (Amide Synthesis)

apparatus, melting point
aspirators, with traps
balance, 0.001-g
chips, boiling
oven, drying
paper, filter, to fit Büchner or Hirsch funnel
paper, filter, to fit general-purpose funnel
pipets, Pasteur, with latex bulbs
press, pellet, IR
spectrometer, nuclear magnetic resonance
spectrophotometer, infrared
tubes, capillary, melting point
tubes, sample, NMR

Individual

Semi-Microscale

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

Microscale

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

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

REAGENTS

(Required for 10 students. Reagent amounts include 30% spillage allowance.)

Williamson Ether Synthesis

	Semi-Microscale	*Microscale*
p-acetamidophenol	20 g	2.0 g
bromoethane	22 g	2.2 g
deutero-chloroform	13 mL	13 mL
ethanol, 100%	52 mL	13 mL
ethanol, 95%	78 mL	17 mL
potassium bromide*	1.3 g	1.3 g
25% sodium methoxide in methanol	33 g	3.3 g

Amide Synthesis

	Semi-Microscale	*Microscale*
acetic anhydride	16 mL	3.3 mL
activated carbon	5.2 g	1.3 g
deutero-chloroform	13 mL	13 mL
ethanol, 95%	78 mL	13 mL
hydrochloric acid, conc.	13 mL	2.6 mL
p-phenetidine	17 mL	3.3 mL
potassium bromide*	1.3 g	1.3 g
sodium acetate	26 g	5.5 g

*spectroscopic grade, kept in an oven at 100 °C

PREPARATIONS

none

CHEMICAL HANDLING

Note: The information presented under **CHEMICAL HANDLING** may not conform to the latest Federal and state regulations because the regulations may have changed. Consult the appropriate agency for current information.

Specific information listed here concerning each of the chemicals used in this experiment should be compared to the contents of the corresponding MSDS.

Spillage Cleanup (for ***small*** amounts of liquids and solids in the stockroom)

1. *p*-Acetamidophenol: Sweep up and package for transfer to a chemical landfill.

Or, dispose of by method recommended by local regulations.

2. Acetic anhydride: Dilute with water, transfer to drain, diluting with a large amount of running water.

Or, dispose of by method recommended by local regulations.

3. Activated carbon: Sweep up and transfer to the appropriate collection container.

4. Bromoethane: Mop up and prepare for incineration.

Or, use a spill kit to absorb the compound and dispose of by method recommended by local regulations.

5. *deutero*-Chloroform: See **4.** Bromoethane.

6. Ethanol: [***Caution:*** Flammable.] Mop up and transfer to drain, diluting with a large amount of running water.

7. Hydrochloric acid, conc.: Cover with powdered sodium hydrogen carbonate ($NaHCO_3$) until no more reaction occurs. Sweep up. Place in glass container and carefully add water. Dissolve the material completely. Pour into drain with a large amount of running water. Pour a solution of 5% $NaHCO_3$ over the original spill site. Mop up with paper towels. Dispose of in trash.

Or, dispose of by method recommended by local regulations.

8. *p*-Phenetidine: See **4.** Bromoethane.

9. Sodium acetate: Dissolve in water. Mop up, transfer to drain, diluting with a large amount of running water.

Or, dispose of by method recommended by local regulations.

10. Sodium methoxide in methanol, 25%: Dilute with water and carefully neutralize with 1*M* HCl. Transfer to drain, diluting with a large amount of running water.

Or, dispose of by method recommended by local regulations.

Collection Containers (for each work station servicing 10 students)

You will need the following appropriately labeled collection containers.

"Recovered Activated Carbon"*
"Recovered deutero-Chloroform"
"Recovered Ethanol–Water"
"Recovered KBr Pellets"
"Recovered Phenacetin"
"Recovered Vacuum Filtrate"
"Used Pasteur Pipets and Capillary Tubes"

*amide synthesis

Disposal

Note: Because of the wide variety of local and state regulations governing the types of mixtures generated in this experiment, consult local authorities for current regulations. Wear appropriate OSHA approved respirator, chemical-resistant gloves, rubber boots, and other protective clothing.

1. Recovered activated carbon: Package for disposal in a chemical landfill.

2. Recovered *deutero*-chloroform: Package for disposal in a chemical incinerator.

3. Recovered ethanol–water: Pour down the drain, diluting with a large amount of running water.

4. Recovered KBr pellets: See **1.** Recovered activated carbon.

5. Recovered phenacetin: See **1.** Recovered activated carbon.

6. Recovered vacuum filtrate: Neutralize and transfer to the drain, diluting with a large amount of running water.

7. Used Pasteur pipets and capillary tubes: Dispose of in a container for broken glass.
Or, package for transfer to a landfill.

Hazard Alert

1. *p*-Acetamidophenol: [*Registry of Toxic Effects of Chemical Substances* (***RTECS***)**:** 8 vols., U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, U.S. Government Printing Office: Washington, D.C., 1987, #AK4200000] Toxic and irritant. Prevent eye, skin, and clothing contact. Avoid inhaling dust and ingesting the compound.

2. Acetic anhydride: (***RTECS#*** AK1925000) Corrosive and lachrymator. Prevent eye, skin, and clothing contact. Avoid inhaling vapors and ingesting the compound.

3. Activated carbon (***RTECS#*** FF5250100): Irritant. Prevent eye, skin, and clothing contact. Avoid inhaling dust and ingesting the compound.

4. Bromoethane (***RTECS#*** KH6475000): Flammable and irritant. Fire hazard. Prevent eye, skin, and clothing contact. Avoid inhaling vapors and ingesting the compound.

5. *deutero*-Chloroform (***RTECS#*** FS9100000): Toxic and suspected carcinogen. Prevent eye, skin, and clothing contact. Avoid inhaling vapors and ingesting the compound.

6. Ethanol (***RTECS#*** KQ6300000): Flammable and irritant. Fire hazard. Prevent eye, skin, and clothing contact. Avoid inhaling vapors and ingesting the compound.

7. Hydrochloric acid, concentrated (***RTECS#*** MW4025000): Toxic, corrosive, and moisture-sensitive. Prevent eye, skin, and clothing contact. Avoid inhaling vapors and ingesting the compound.

8. Phenacetin (*p*-acetophenetidide) (***RTECS#*** AM4375000): Suspected carcinogen. Prevent eye, skin, and clothing contact. Avoid inhaling dust and ingesting the compound.

9. *p*-Phenetidine (***RTECS#*** SI6465500): Irritant and light-sensitive. Prevent eye, skin, and clothing contact. Avoid inhaling vapors and ingesting the compound.

10. Potassium bromide (***RTECS#*** TS7650000): Irritant and hygroscopic. Prevent eye, skin, and clothing contact. Avoid inhaling dust and ingesting the compound.

11. Sodium acetate (***RTECS#*** AJ4300010): Hygroscopic. Prevent eye, skin, and clothing contact. Avoid inhaling dust and ingesting the compound.

12. Sodium methoxide in methanol, 25% (***RTECS#*** PC3570000): Flammable, toxic, and corrosive. Fire hazard. Prevent eye, skin, and clothing contact. Avoid inhaling vapors and ingesting the compound.

COMMENTS ON THE EXPERIMENT

Estimated bench time is 2.5–3 hr for each synthesis.

1. You may wish to have half the class prepare phenacetin by the Williamson ether synthesis and half by the amide synthesis. They can exchange products for the mixture melting point.

2. Emphasize to students that great care must be taken in recrystallizing phenacetin or a significant reduction in yield will occur, especially with the microscale procedures.

3. You may need to remind students that a mixture melting point will be the same as either "unmixed" product if the two products are the same, whereas a depression of melting point is common when two products are different, even if they have the same initial melting point.

4. For the Williamson synthesis, some "bumping" may occur during the reflux period due to superheating of the reaction mixture because of the formation of a NaBr precipitate.

5. For the Williamson synthesis, methyl iodide, 1-bromopropane, and 1-bromobutane may be substituted for bromoethane with no significant decrease in yield. However, the comparison with the amide synthesis will be lost.

6. You may choose to photocopy the attached data sheet for student use.

REPRESENTATIVE STUDENT DATA

Student yields are typically 50% for both the Williamson synthesis and the amide synthesis. Yields will be much lower for microscale preparations if students are not meticulous with the recrystallization step. Student mixture melting point measurements show both products to be the same. Both IR and NMR product spectra compare well with commercial phenacetin.

ANSWERS TO POST-LABORATORY QUESTIONS

1. Percent yields will vary, but should be 40 to 60%.

2. The melting point of 134–136 °C matches that reported for phenacetin. The IR spectrum and the NMR spectrum match that of phenacetin.

3. The mixture melting point of the two products is identical to each melting point taken individually, indicating that the two products are the same substance. If they were different substances, the melting point would have been lowered.

4.

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

5. Each proton is adjacent to the other proton. The coupling between them causes the splitting of each signal into a doublet. When the difference in chemical shifts of the two signals is not significantly larger than the coupling constant, the inside peak of the doublet is larger than the outside peak.

ANSWERS TO PRE-LABORATORY ASSIGNMENT

1. While phenacetin is a suspected carcinogen, that evaluation is based on ingestion of phenacetin as a drug. Drugs undergo a higher level of scrutiny than do most laboratory chemicals. Normal precautions of avoiding contact with eyes, skin, and clothing and not inhaling or ingesting phenacetin should be followed.

2. AP = *p*-acetamidophenol; P = phenacetin; Ptd = *p*-phenetidine

Semi-Microscale

$$(1.51\ \text{g AP})\left(\frac{1\ \text{mol AP}}{151\ \text{g}}\right)\left(\frac{179\ \text{g}}{1\ \text{mol P}}\right) = 1.79\ \text{g P}$$

$$(1.38\ \text{g Ptd})\left(\frac{1\ \text{mol Ptd}}{137\ \text{g}}\right)\left(\frac{179\ \text{g}}{1\ \text{mol P}}\right) = 1.80\ \text{g P}$$

Microscale

$$(0.151\ \text{g AP})\left(\frac{1\ \text{mol AP}}{151\ \text{g}}\right)\left(\frac{179\ \text{g}}{1\ \text{mol P}}\right) = 0.179\ \text{g P}$$

$$(0.266\ \text{g Ptd})\left(\frac{1\ \text{mol Ptd}}{137\ \text{g}}\right)\left(\frac{179\ \text{g}}{1\ \text{mol P}}\right) = 0.348\ \text{g P}$$

3. 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, it will compete as a nucleophile with the *p*-acetamidophenol, also reducing the yield of phenacetin.

4. If the solution should appear milky or if an oil appears, add more ethanol and heat to redissolve; then cool the solution again.

5. The sodium acetate produces an acid–base buffer that maintains the pH of the reaction mixture at a value that provides the optimum reaction rate.

name section date

Data Sheet

Phenacetin Synthesis

	Williamson Synthesis	*amide synthesis*
amount of aromatic reactant used, g	_____	_____
mol	_____	_____
product obtained, g	_____	_____
mol	_____	_____
product theoretical yield, g	_____	_____
mol	_____	_____
product yield, %	_____	_____

Write the equation for reaction.

Product Characterization

	Williamson synthesis	*amide synthesis*
melting point, °C	————————	————————
mixture melting point, °C	————————	
major IR bands, cm^{-1}		
NMR bands, ppm		