## Purpose

To synthesize phenacetin through the Williamson ether synthesis method.

### Learning Objectives

Explain the mechanism of the reaction.

Relate the mechanism to the laboratory procedure.

Interpret instructions to determine quantities of reagents needed for reaction.

Carry out and interpret thin-layer chromatography to monitor the progress of the reaction.

Purify a product using extraction and recrystallization.

Identify a product from IR spectrometry.

Identify the product of a reaction from $^{1}H$ NMR spectroscopy.

### Equipment

- 5-mL conical vial
- drying tube
- cotton
- air condenser
- hot plate
- water bath
- 1-mL syringe
- small beakers
- electronic balance
- ice
- Büchner funnel
- filter paper
- filter flask
- vacuum tubing
- Infrared spectrometer
- IR Sample Prep materials (KCl salt plates, KBr pellet, ATR, etc.)
- NMR spectrometer
- NMR tube

### Chemicals

- DI water
- methyl ethyl ketone
- acetominophen
- potassium carbonate
- ethyl iodide
- anhydrous calcium chloride
- methylene choride
- 1 M NaOH(aq)
- $CDCl_3$(for NMR)

## Theory and Background

The Williamson ether synthesis involves the synthesis of an ether using an alkyl halide and an alkoxide usually in an alcohol solvent. You will use this process of displacing a halide (R–X where X = Cl, Br, I) by an alkoxide anion (R–O–) to form an ether. Discovered in 1850, the Williamson ether synthesis is still today one of the most reliable ways to synthesize an ether. However, elimination reactions (E2) predominate when tertiary and sometimes secondary alkyl halides are used in the presence of alkoxides, which are also strong bases.

The principal starting material of this reaction is N-(4-hydroxyphenyl)-acetamide, a compound also known as acetaminophen. Acetominophen is an analgesic (a medication that reduces or eliminates pain) and antipyretic (a medication that reduces fever) and is found in many over-the-counter drugs. For example, it is the active ingredient of many Tylenol products. The principal product phenacetin was once the active ingredient of several analgesic and antipyretic Excedrin medications but has been banned in the U.S. since 1931 due to serious health concerns.

The phenol of acetaminophen is a relatively poor nucleophile. However, the presence of the base (potassium carbonate) causes the generation of the conjugate base of acetaminophen. This new species is called a phenoxide anion, and it serves as a more potent nucleophile than the starting alcohol. The phenoxide anion then displaces iodide via nucleophilic attack with inversion in a one-step process. The rate of the reaction depends on the concentration of both the phenoxide anion and the iodoethane; so the reaction is described as $S_N2$ (substitution nucleophilic bimolecular). The Williamson ether synthesis of phenacetin is shown in Figure 6A.1

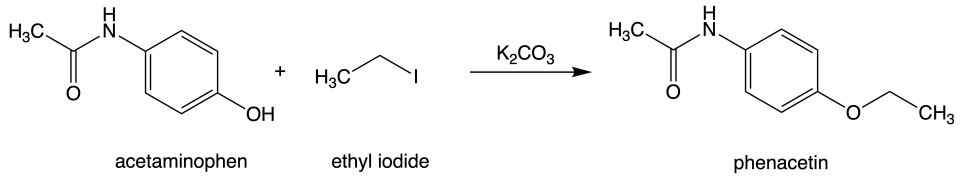


**Figure 6A.1:** Williamson ether synthesis of phenacetin

## Prelab

Draw and upload the curved arrow mechanism for the synthesis of phenacetin using the Williamson ether synthesis.

Fill in the physical constants and data in Table 6A.1. Read through the procedure below to determine how much of each reagent you will add. You only need to include the physical constants and data that have bearing on your experiment. For example, the boiling point of your solvent is important, but not the mmols of solvent used.

**Table 6A.1:** Reagent Quantities and Physical Properties

| **Reagent** | **Formula** | **MW (g/mol)** | **Equiv** | **Density** | **Volume (mL)** | **Mass (g)** | **mmol** | **mp (°C)** | **bp (°C)** |
|---|---|---|---|---|---|---|---|---|---|
| Acetominophen | _____ | _____ | _____ | – | – | _____ | _____ | – | – |
| Potassium Carbonate | _____ | _____ | _____ | – | – | _____ | _____ | – | – |
| Methyl Ethyl Ketone | _____ | _____ | _____ | _____ | _____ | _____ | – | – | _____ |
| Ethyl Iodide | _____ | _____ | _____ | _____ | _____ | _____ | _____ | _____ | _____ |
| Phenacetin (product) | _____ | _____ | _____ | – | – | _____ | _____ | _____ | – |

# Procedure

## Safety Precautions

Ethyl iodide is very corrosive and should only be handled in the hood.

## Williamson Ether Reaction

1. To a 5-mL conical vial, add a spin vane and 2.0 mL of methyl ethyl ketone (MEK, 2-butanone).

2. Add 150 mg of acetaminophen, 315 mg of potassium carbonate, and 0.40 mL of ethyl iodide (all reagents should be added in the fume hood).

   The potassium carbonate will not fully dissolve in MEK.

3. Prepare a drying tube by plugging one end with cotton, filling the tube with anhydrous calcium chloride, and then plugging the other end with cotton.

   The bottle of calcium chloride should remain closed when not in use.

4. Attach an air condenser and the drying tube to the conical vial.

5. Heat the reaction at reflux for one hour. The term reflux means to bring a solution to a boil without decreasing its volume. This is accomplished by adding an air-cooled or water-cooled condensing apparatus so that most of the solvent escaping is condensed and allowed to fall back into the solution.

## Monitor Reaction by TLC

Typically you should be monitoring reactions with a 3-lane TLC where the first lane is the starting material or the limiting reagent, the third lane is the crude reaction at any given time, and the second lane is a co-spot of lanes 1 and 3. It is not a good idea to tape TLC plates in your notebook because the silica gel can dry, flake off, and possibly be inhaled (which is not good; asbestos is a form of silicate). Always draw them in your notebook and then discard them.

6. Monitor the reaction by TLC every 20 minutes. Do this by preparing a TLC plate with three lanes. In the far left lane and in the middle lane, spot a dilute sample of the starting acetaminophen. In the far right lane and

in the middle lane, spot a sample of your reaction mixture. Try ethyl acetate as the developing solvent first.

7. Make sure you draw your developed TLC plate into your notebook.

## Work-up

8. At the end of one hour, or when the reaction has gone to completion (whichever comes first), cool the conical vial in a water bath.

9. While the reaction is cooling, prepare a small pipette filter by taking a 1-mL syringe and plugging it with cotton.

10. Weigh a small beaker (record the weight), place the pipette in a clamp and place the beaker underneath the pipette.

11. Transfer the cooled reaction mixture into the beaker by running through the cotton-plugged pipette.

12. Use 1 mL of methylene chloride to carefully rinse the reaction vessel to ensure all the product is transferred to the new beaker.

13. Add a boiling stone to the beaker containing the filtered reaction mixture and boil off the MEK and methylene chloride. MEK has a high boiling point (80 °C). Due to the high solubility of MEK in water ($K > 10$) it is important to remove it before performing an extraction.

14. Once the solvents are removed, dissolve the remaining solids in 2.0 mL of methylene chloride, and wash this organic phase with 1.0 mL of 1 M aqueous NaOH by adding the 1 M NaOH solution to the beaker, mixing the two layers, and then removing the aqueous phase.

15. Evaporate the methylene chloride on a hot plate.

16. Weigh the beaker and crude product.

## Recrystallization

17. Prepare a beaker with ~10 mL of DI water.

18. Heat this beaker until the water is boiling.

19. Place the beaker containing your crude product on the hot plate and slowly add small amounts of boiling water to this beaker until the solid has dissolved.

> Do not add any more solvent than necessary. You will need to be careful to make sure you add just the minimal amount necessary!

20. Once the solid has dissolved, allow the solution to cool to room temperature and then place in an ice bath to induce further cooling and crystallization.

21. Collect the crystals formed using vacuum filtration, washing the crystals with minimal amounts of cold DI water.

22. Allow the crystals to dry over the vacuum.

23. Obtain the mass of the purified phenacetin.

24. Obtain melting point of the purified phenacetin.

25. Obtain an IR spectrum of the purified phenacetin.

26. Show your results to your TA; if your data indicates that your product is pure, you may obtain a $^{1}$H-NMR spectrum of your sample from the benchtop NMR spectrophotometer in the instrument room. Your TA will instruct you on how to do this.

## Clean Up

27. Clean your glassware and benchtop.

28. Dispose of all aqueous waste in the aqueous waste container.

29. Place organic solvent in appropriate waste containers.

## Among other things in your lab report:

- Discuss how the various conditions of the reaction (temperature, reagents used, etc.) helped to synthesize the product successfully.
- Discuss the mechanism of the reaction and how that relates to the reaction setup.
- Discuss your use (and your results) of TLC and recrystallization.
- Annotate the IR of your product as well as the spectra (both IR and $^{1}$H-NMR).