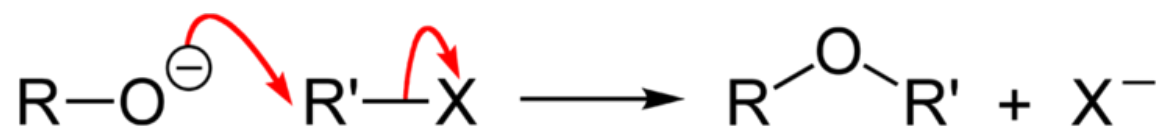


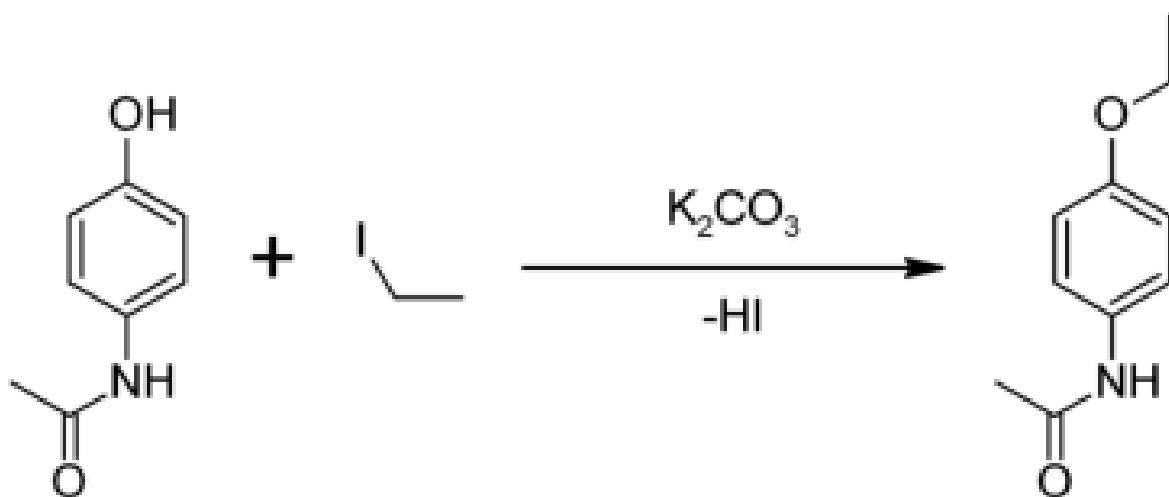
The Williamson ether synthesis

The Williamson ether synthesis is an organic reaction, forming an **ether** from an **alkyl halide** and an **alcohol**. This reaction was developed by Alexander Williamson in 1850. It involves the reaction of an **alkoxide ion** with a primary alkyl **halide** via an **S_N2 reaction**.



The Williamson reaction is widely used in both laboratory and industrial synthesis, and remains the simplest and most popular method of preparing ethers. Both symmetrical and asymmetrical ethers are easily prepared.

The reaction for this week: an example of a Williamson ether synthesis



acetaminophen ethyl iodide

phenacetin

starting material

reagent

product

Phenacetin may be synthesized as an example of the **Williamson ether synthesis**

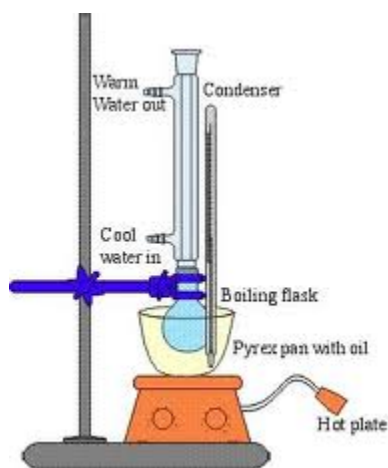
The first synthesis of phenacetin was reported in 1878 by Harmon Morse.

Procedure

1. Weigh an Extra-Strength Tylenol tablet. Pulverize the tablet with mortar and pestle. Weigh out 0.22 g and place it in a dry 15-ml round-bottom flask along with 0.28 g of finely pulverized K_2CO_3 (mortar and pestle) and 3.0 mL of butanone. Carefully add 0.28 mL of ethyl iodide with a syringe.



2. Add a stir bar; attach a microscale water-cooled condenser to the flask. Heat the mixture under reflux directly on a hot plate at medium setting for 1 hour. In the meantime, obtain the IR of acetaminophen.

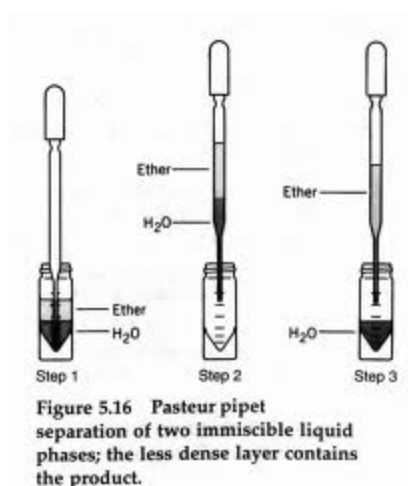


3. Turn off the heat. Allow the mixture to cool down. Add 4 mL of water to the flask and transfer its contents to a 16 x 125 mm test tube with a screw cap. Rinse round-bottom flask 4 times with

1 mL of tert-butyl methyl ether (BME) and add the rinsings to the test tube.



4. Cap the test tube and shake the layers. Vent to release the pressure by unscrew the cap momentarily. With a Pasteur pipet remove the lower (aqueous) layer. Transfer the aqueous layer to another 16 x 125 mm, screw-cap test tube. Keep the organic layer in the original test tube.



5. **Extract** the aqueous layer with 2.5 ml, of BME. Remove the aqueous layer with a Pasteur pipet (save it until the end in a labeled test tube, and then discard it) Transfer the organic layer to the screw-cap test tube with the original organic layer.
6. Add 2.5 ml, of 5% aqueous NaOH to the combined organic layers and shake well. Let the layers settle and remove the lower aqueous layer with a Pasteur

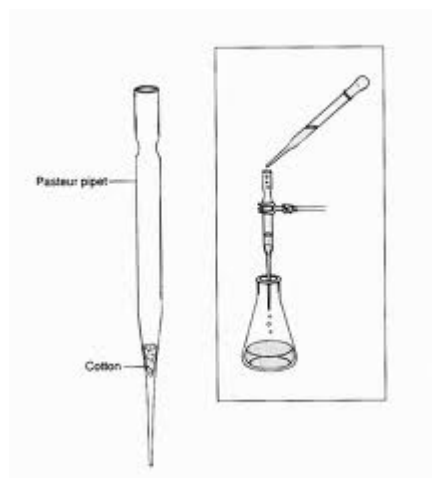
pipet. Repeat the **extraction** with another 2.5-ml portion of 5% NaOH. Save the aqueous layers until the end of the experiment.

7. **Extract** the organic layer with 2.5 ml, of saturated sodium chloride solution. If emulsions form during these extractions, they can be broken by centrifugation (1000-2000 rpm for a



few minutes). Dry the organic layer by adding magnesium sulfate little by little with a microspatula until the solid runs freely in the liquid. Let the system stand for 5 minutes with occasional swirling.

8. **Filter** the mixture using a Pasteur pipet with a cotton plug and receive the



filtrate in a dry, pre-tared, 25-ml round-bottom flask. Evaporate off the solvent using a rota-vap. Weigh the flask with the product. Calculate the crude %

yield. Scrape out the crude phenacetin and determine its **melting point**.

9. Review **recrystallization** from mixed solvents and microscale recrystallization. Using a Craig tube,



recrystallize the product by dissolving it in the minimum amount of hot ethyl acetate. Heat the system in a sand bath, and continuously stir it by rolling a microspatula between your fingers. To the hot solution add hot hexane

dropwise until the solution becomes cloudy. Cool the solution to induce crystallization and collect the crystals by centrifugation. Determine the weight and **melting point**.

10. Obtain the IR spectrum of acetaminophen and phenacetin. Compare the IR of the product with the spectrum shown in Figure 15.2. If possible, obtain the ^1H -NMR of the product in CDCl_3 .