Objectives

- Synthesize phenacetin by the formation of an ether functional group
- Identify the product of the ether synthesis by various methods

Background

Williamson Ether Synthesis

The formation of an ether by reacting an alkyl halide with the conjugate base of an alcohol or phenol is called a Williamson ether synthesis. The Williamson ether synthesis is a popular and robust method to prepare ethers. The general reaction involves placement of the alcohol reactant in a basic solution to form the deprotonated conjugate base, which then functions as a nucleophile in the subsequent reaction with the alkyl halide to yield the ether. The overall mechanism is shown in Figure 1.

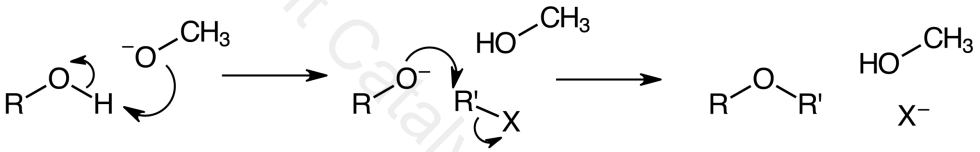

Figure 1 General mechanism for a Williamson ether synthesis

The base in the Williamson ether synthesis needs to be carefully selected and used. The base must be strong enough to deprotonate the alcohol but must be added appropriately to avoid competing reactions. Alkoxide bases like methoxide are often used but needs to be measured carefully. The number of moles of alkoxide ions must be the same number of moles of alcohol so that the conjugate base ion is completely formed. A phenol is often more successful in this first step because phenols are better acids than other alcohols. If the number of moles of alkoxide ion is in excess, then there will be competition for the second step in the reaction, with the alkoxide base acting as a nucleophile.

The second step in the reaction is an S_N2 nucleophilic addition reaction. The S_N2 reaction occurs in one step as the nucleophile is added while the leaving group leaves. The rate-determining step in the concerted reaction is the degree of crowding at the reaction site on the alkyl halide; primary halides are preferred over secondary halides and tertiary halides will generally not undergo S_N2 reactions.

Synthesis of Phenacetin

Phenacetin is a medicinal compound featuring an ether functional group. Phenacetin was once used as an anti-inflammatory and fever reducing drug along with aspirin and caffeine. The use of phenacetin for this purpose has stopped due to the long-term use studies suggesting that it may be a carcinogen.

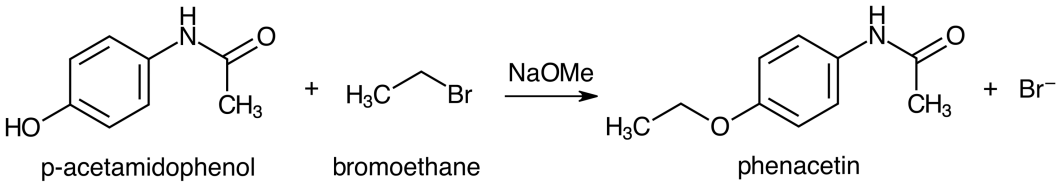

Figure 2 Overall reaction to produce phenacetin using Williamson ether synthesis

Phenacetin, p-ethoxyacetanilide, contains an ether group and an amide group para to each other on a benzene ring. Either of those groups can be added last in the synthesis of phenacetin. For the preparation in this experiment, the amide will already be in place and the ether will be added via a Williamson ether synthesis with sodium methoxide and bromoethane, as shown in Figure 2.

Materials

- 25% sodium methoxide in methanol
- 100% ethanol
- 95% ethanol
- p-Acetamidophenol
- Bromoethane
- Microscale glassware kit
- Pasteur pipette
- Boiling chips
- Sand bath
- Ice bath
- Vacuum filtration set-up
- Melting point apparatus
- FTIR instrument
- NMR instrument
- $CDCl_3$ and NMR tube

Safety goggles are required!

All work should be performed in the fume hood.

Acetanilide is a toxic irritant. Acetone and ethanol are flammable irritants; wash thoroughly if skin contact is made. Activated carbon added to hot solvent can cause the solution to boil over.

Procedure

Williamson Ether Synthesis

1. Place 0.25 mL of 25 % sodium methoxide in methanol, 1.0 mL of 100 % ethanol, and 0.151 g of p-acetamidophenol in a long neck 5 mL round bottom flask.
2. Add a boiling chip to the reaction mixture.
3. Place the round bottom flask in the sand bath and wrap the neck with a wet paper towel.
4. Add 0.12 mL of bromoethane to the reaction mixture flask
5. Adjust the controller for the sand bath to medium to start heating the contents of the flask.
6. Reflux for 45 minutes. Do not boil too vigorously as you want the contents to condense on the sides of the neck of the flask.
7. While refluxing, prepare an ice bath in a 100 mL beaker.
8. Remove the reaction mixture flask from the sand bath and, dropwise, slowly add 1.00 mL of deionized water to the flask.
9. Allow the flask and contents to cool to room temperature.
10. Pour the contents of the flask into a 25 mL beaker.
11. Rinse the flask with 0.5 mL of water and add the rinse to the beaker.
12. Cool the 25 mL beaker with the reaction mixture in the ice bath to crystallize the product.
13. Collect the crystals using vacuum filtration and a Hirsch funnel.
14. Move the impure phenacetin crystals from the Hirsch funnel to a test tube.

15. Heat 1.0 mL of 95 % ethanol in a second test tube to a boil using the sand bath. Do not boil the ethanol away.
16. Using a Pasteur pipet, add hot ethanol dropwise to the phenacetin just until all the crystals dissolve.
17. Place the mixture in the sand bath to bring it back to the boiling point.
18. While the tube is still in the sand bath, use another Pasteur pipet to add deionized water dropwise to the test tube until the solution becomes cloudy.
19. Add ethanol dropwise again until the solution clears up.
20. Set the solution aside to allow it to cool slowly.
21. If the solution becomes milky or an oil appears, add more ethanol, reheat, and allow to cool again.
22. Separate the crystals by vacuum filtration using the Hirsch funnel.
23. Allow the vacuum filtration system to run for a few minutes to dry the crystallizes on the filter paper.
24. Measure and record the mass of the product crystals on the data sheet.
25. Measure and record the melting point of the product crystals on the data sheet.
26. Obtain an IR spectrum of the product crystals.
27. Dissolve a small amount of the crystals in $CDCl_3$, place the solution in an NMR tube, and obtain an NMR spectrum.
28. All solvents are to go into the non-halogenated waste container. Crystals can be dissolved in ethanol and go into the container as well. Wash glassware with soap and water.

Pre-Lab Questions

Prepare for lab by completing and understanding the answers to these questions. Refer to the Background or another resource, such as your textbook, if necessary.

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

2. Calculate the theoretical yield for the Williamson ether synthesis from 0.151 g of p-acetamidophenol and 0.12 mL of bromoethane, which has a density of 1.47 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 the Williamson synthesis of phenacetin?

4. If phenacetin oils out of solution during recrystallization, what steps should be taken to remedy the problem?

5. What will happen to your results if phenacetin is not dried properly when filtered the final time?

Williamson Ether Synthesis Report Sheet

Name _____ Section _____

Date _____ Instructor _____

Williamson Ether Synthesis

Amount of reactant used (grams) _____

Amount of reactant used (moles) _____

Space for calculations:

Product obtained (grams) _____

Product obtained (moles) _____

Space for calculations:

Product theoretical yield _____

Space for calculations:

Product percent yield _____

Space for calculations:

Product melting point _____

Write the equation for the reaction.

Major IR peaks in cm^{-1}

Major NMR peaks in ppm

Post-Lab Questions

1. Is your percent yield within reason of what you would expect? Explain your answer.

2. Does the melting point obtained for your product indicate that your sample is indeed phenacetin? What additional evidence do you have that your product is phenacetin?

3. If there were multiple products, comment on finding the mixture melting point of the products. Does your sample appear to be a mixture or pure?