Experiment: **Williamson Ether Synthesis of Ethoxybenzene**

**Background**

Ethers represent an important class of compounds which are exceptionally useful as solvents. Ether functionality also appears in the structures of insecticides and medicines. Codeine, for example, is the methyl ether of morphine. One very important route to synthesizing ethers was discovered by British chemist, Alexander Williamson. In this reaction, an alkoxide ion ($RO^-$) reacts with an alkyl halide or tosylate via an $S_N2$ mechanism. This route allows the formation of asymmetric ethers, which are ethers with two different R groups. It does, however, have all of the limitations associated with $S_N2$ reactions. Therefore, the substrate reacting with the alkoxide must be relatively unhindered to prevent elimination. As a result, primary or methyl substrates are best suited for this reaction.

In this experiment, you will be using the Williamson reaction to make ethoxybenzene (ethyl phenyl ether).

\[
\begin{align*}
\text{sodium phenoxide} & \quad + \quad \text{CH}_3\text{CH}_2\text{I} & \quad \rightarrow \quad \text{ethoxybenzene} \\
\end{align*}
\]

The first step of the reaction is an acid-base reaction, where the acidic proton of phenol is removed with a strong base, sodium hydroxide. As you know, sodium hydroxide is not sufficiently strong to remove the hydrogen from alcohols; however, phenols are a different story. The protons of phenol are nearly one million times more acidic than alcohols, due to the resonance stabilization of the phenoxide anion. The extra stability of the phenoxide ion compared to an alkoxide ion makes reaction of phenol with NaOH favorable. In fact, you will notice the reaction is exothermic when you add the sodium hydroxide to the phenol.

Once the sodium phenoxide has been formed, the ethyl iodide is added and the reaction is refluxed for 45 minutes. Refluxing is a term used to describe boiling the reaction for a period of time with a condenser on top of the round bottom to capture the vapor by cooling and then allow the condensed solvent to drop back into the flask. This allows the reaction mixture to heat at a
constant temperature (equal to the boiling point of the solvent), thus allowing the reaction to proceed with heat added but without the loss of solvent over time.

Initially the methanol is a sufficiently good solvent to maintain a homogeneous mixture. By the end of the reflux time, however, you will probably notice a second phase forming on the top, which will contain your product. After the reflux is complete, you will be extracting into ether and washing a few times. Finally, the ether is evaporated and your product is ready for purification by simple distillation.

You will notice that the phenol bottle is labeled “liquefied phenol.” Pure phenol is a low melting solid, which makes it difficult to handle. It tends to form a solid mass which requires chipping, like you would chip large block of ice, to obtain small enough pieces to weigh. To avoid this, we will be using a solution which is ~90% phenol and ~10% water (by mass), a stable liquid which is easy to weigh.

**Pre-lab Preparation**

Before coming to lab, write the following assignment in your lab notebook.

1. In tabular form write the relevant physical constants for phenol, ethyl iodide and ethoxybenzene (boiling point, density, solubility in water and ether). (You will find ethoxybenzene in the Handbook of Chemistry and Physics under “benzene, -ethoxy” or in some other reference sources under its common name, “phenetole”.)

2. Write a complete mechanism for the reaction of phenol with sodium hydroxide, followed by a mechanism for the reaction of the sodium phenoxide with ethyl iodide.

3. What effect will methanol have on the rate of reaction of sodium phenoxide with ethyl iodide? Is this a good solvent for this type of mechanism? Why do you think this solvent was used?

4. Why does ethyl iodide react well with phenoxide ion?

5. Answer the following questions about the procedure.
   a. At the end of the reflux period, water and diethyl ether are added to the reaction mixture, forming two layers. What materials should be found in the ether layer and which in the water layer? Consider reactants, products and byproducts.
   b. What is the purpose of washing the ether layer with dilute aqueous sodium hydroxide?

6. What temperature range will you collect in the last step of the procedure to obtain reasonably pure product?
Experimental Procedure

Safety Considerations

Phenol and ethyl iodide are toxic. Use gloves (phenol is readily absorbed through the skin) and minimize inhalation by working near a portable hood.

Methanol is an extremely toxic compound which can cause blindness or death if drunk in small quantities or absorbed in large quantities through the skin. If you spill small amounts on the skin, rinse it off immediately with water. If you spill a larger quantity on your clothing or skin, notify your instructor promptly.

Sodium hydroxide is a strong base. If you spill any on yourself, rinse it immediately with water.

You will be working with diethyl ether in this experiment. Ether is very volatile and flammable. All extraction and drying involving the ether solutions must be done in a fume hood. No glassware that has contained ether will be removed from the hood until the odor of ether has disappeared. The only time that you may remove ether from the hood is for the final distillation. Then, stopper the flask with a greased, ground glass stopper before carrying it back to your desk.

Dispose of all organic waste in the containers provided.

1. Add 5.9 mL of 90% phenol (provides 6.0 g of the 90% solution) to a 50-mL round bottom flask. If the liquified phenol has some different concentration, use the amount specified on the reagent bottles placed out in the lab. Add 5 mL of methanol to the flask. Add it in such a way as to wash any phenol from the ground glass neck of the flask. Swirl the flask to mix the two reagents and add a few boiling stones.

2. Prepare an ice-water bath in case it is needed in this next step. Then weigh 4.1 g of 50% NaOH (by mass) into a beaker. Add the sodium hydroxide dropwise to the round bottom flask while swirling. If too much heat is generated, cool the flask using the ice bath to stop the methanol from boiling.

3. Measure out 4.2 mL of ethyl iodide into a graduated cylinder and add it to the reaction mixture. After the addition is complete, swirl the flask to mix the contents.

4. Attach a water cooled reflux condenser directly to the top of the round bottom flask and begin heating the reaction mixture. Once the solvent begins to boil, you should be able to see a line in the reflux condenser where the liquid is condensing and the dropping back into the flask. Once this steady boiling and condensing is underway, you have begun refluxing and can start timing the reflux period. Reflux the reaction mixture for 45 minutes.
5. While the reaction is refluxing, your instructor may want to use part of this time to talk with you about the reaction, the mechanism, or the experimental procedure. Use any other time available to set up your final distillation, a simple distillation with a 25-mL distilling flask. Be sure that the distillation apparatus is dry, greased and tightly connected.

6. At the end of the reflux period, cool the reaction mixture to room temperature using an ice bath and then transfer it to a 50-mL separatory funnel in a fume hood. Rinse the reaction flask with 15 mL of ether and add it to the reaction mixture. Then add 10 mL of water to the reaction mixture.

7. Stopper the separatory funnel, vent it, and then shake the mixture with frequent venting. Allow the layers to separate and draw off the water layer.

8. Pour the ether layer into a beaker and then return the aqueous layer to the separatory funnel. Extract the water layer with one additional 15 mL portion of ether. Drain the water layer and then add the first ether wash to the separatory funnel, combining the first and second washes into one portion of organic material.

9. Wash this ether layer with 15 mL of 6% NaOH. Separate the layers and retain the ether layer. (The layers may be very difficult to see. If so, hold the separatory funnel up to the light in the hood and swirl gently until you can identify the interface.) Drain the aqueous layer.

10. Finally, wash the ether layer with 10 mL of saturated sodium chloride solution. Separate the layers and retain the ether layer. Note: The purpose of washing with saturated sodium chloride is to remove water from the ether later. Because ether has a highly electronegative oxygen atom in the molecule, water can hydrogen bond with it. Consequently, water is slightly soluble in ether and vice versa. A saturated salt solution, because it is so concentrated, will seek to dilute itself by extracting water from the wet ether solution. For this reason, ether extracts are often washed with saturated salt solutions as the last of several washings with aqueous solutions.

11. In a small Erlenmeyer flask, dry the ether solution with anhydrous calcium chloride pellets. Add enough calcium chloride so that the most recently added pellets don’t clump with the ones added earlier in the drying. Stopper the flask and let it sit in the hood for at least ten minutes. Note: The product may still look cloudy after drying but distillation will remove any impurities.

12. Pour the dried solution into a round bottom flask containing two or three boiling stones. Make sure choose a round bottom flask that is large enough. (The distilling flask should never be more than about half-full at the start of a distillation.) Distill off the ether into a round bottom flask.

13. After all of the ether has been distilled off, the collection of liquid will stop as the remaining product is heated to its boiling point. Wrap the distilling flask in foil to help speed the distillation of your product. Continue to collect any first fraction until you are
think it is time to change flasks to collect the product based on your pre-lab analysis. When you have reached a reasonable temperature for your product, remove the first receiving flask with the ether and replace it with a tared round bottom flask to collect your product. Collect your product based on the temperature range expected but remember, it is not safe to distill to dryness. Weigh your product.

14. Check with your instructor to see if further characterization of your product is required. Dispose of all waste in the appropriate container.

### Post-Lab and Report Requirements

For this report, include answers to the following questions.

1. Calculate the moles of all reactants. Remember to take into account the fact that the phenol you weighed was not pure. Determine the mass of the phenol used from the percentage given on the reagent bottle. Use this information to calculate your theoretical yield and percentage yield for this experiment.

2. Give a detailed description of sources of yield loss. Give both chemical reasons (side reactions of the limiting reagent or further reactions of the product) and physical reasons (procedural loss of limiting reagent or product) why you got a lower than 100% yield.

3. Why does the procedure use fewer moles of sodium hydroxide than phenol? (What side reaction(s) might occur if you have excess sodium hydroxide?) At what point in the purification procedure is the excess phenol separated from the product?

4. Do you think the reaction with phenoxide would be faster or slower with each of the following substrates than with the ethyl iodide you used in this experiment? Explain.
   
   a. ethyl chloride
   
   b. methyl iodide