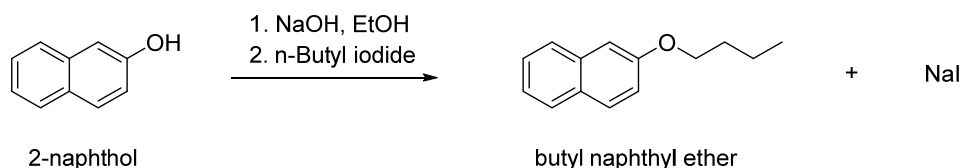


## Nucleophilic displacement - Formation of an ether by an S<sub>N</sub>2 reaction – The Williamson-Ether Synthesis

Bond formation by use of an S<sub>N</sub>2 reaction is very important for organic and biological synthesis. Many new bonds formed make use of this versatile reaction pathway. In this reaction, one partner is the nucleophile and the other partner is the electrophile. The electrophile will have a leaving group that will be lost in the reaction.

In the S<sub>N</sub>2 reaction that you will be performing, the nucleophile will displace the iodide to form butyl naphthyl ether and sodium iodide. Can you think of any possible undesired side reactions?

**Equation 1.** The S<sub>N</sub>2 reaction that will be performed in this experiment.



### Pre-lab questions:

In addition to the standard pre-lab write-up in your notebook, provide answers to the following questions:

1. What is the active nucleophile in this reaction (draw the structure)?
2. What is the electrophile?
3. What is the leaving group?
4. Draw a mechanism for the reaction using electron pushing arrows showing all intermediates and formal charges.
5. You will be using TLC in this experiment. Which compound do you expect to have the higher R<sub>f</sub> value, 2-naphthol or butyl naphthyl ether? Why?

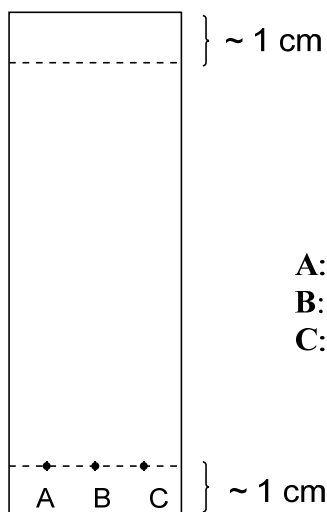
### The Procedure: Butyl naphthyl ether via an S<sub>N</sub>2 reaction.

1. Add 0.064 g (64 mg) of sodium hydroxide, 0.200 g of 2-naphthol and a few boiling stones to your 10 mL round-bottomed flask (RBF). Add 3 mL absolute ethanol and attach the air-condenser. Turn on your sand bath to 30% (no higher).
2. Lower your assembly so the flask is just hovering above the sand. You can adjust height as needed later. Air is used to condense the vapor inside the column, so it is important that the solution boils gently. Reflux (vapor condensing on the inside wall of the column and draining back into the reaction) the mixture until all solids have dissolved and a further 25 minutes.
3. After the 25 min reflux, raise your assembly and cool the solution for **3 minutes**.

- Through the top of the air-condenser, add 0.200 mL of n-butyl iodide. Lower the assembly so the flask is just hovering above the sand, adjusting height as needed, and gently reflux for 1 hour. If the solution begins to vigorously boil simply move some sand away with a micro-spatula. You will have to find a good balance with the sand. Cool about 25 mL of water in an ice bath about 10 minutes before the reaction is complete.
- Carefully pour the reaction mixture directly over about 10 g of ice in a beaker. *Do not weigh 10 g of ice.* A 50 mL beaker filled to about the 30 mL mark is fine.
- Using your reserved cold water, rinse the RBF with 2 x 1 mL portions and transfer to your ice/reaction mixture in the beaker.
- Stir beaker contents with your glass rod until most (95%) of the ice melts and collect the product via suction filtration (this filtration will be slow due to the viscosity of ice-cold water and the porosity of the filter paper).
- Rinse the product with the ice-cold water and allow to dry under suction for 25 minutes.
- Using a small amount of your product, analyze your reaction via TLC, and place the rest of your product in your lab drawer to air dry. Obtain a melting point<sup>1</sup> during morning hours.
- Determine the percent yield.
- If you come to obtain a melting point and you find your product has melted, that is ok. Comment on this in the results and discussion section of your formal report.

### TLC Analysis

- Dissolve your saved product from above in a small amount of ethyl acetate. Do the same with 2-naphthol.
- Prepare a TLC plate with 3 lanes, as shown below.



<sup>1</sup> The melting point of butyl naphthyl ether is 33 – 35 °C

3. You will use two different solvent systems for your TLC analysis, one by you and one by your hood partner. Your available solvents are ethyl acetate (EtOAc) and hexanes. You will need to mix your own solvent composition (a solvent system) and run a TLC. A common mixture is 95:5, but you will need to determine which is best and which component dominates the solvent mixture. For example, 95:5 EtOAc:hexanes or 95:5 hexanes:EtOAc.
4. Record which composition you *first* used, save this TLC plate, and run a TLC in your hood mate's first chosen solvent system. Save this TLC plate as well.
5. Continue exploring solvent systems between you and your hood mate until you see decent separation between SM and product. A good solvent system is one that moves both compounds off the baseline, but you can still see separation between the spots. Save the TLC plate of the best solvent system found (either yours or your hood partners).
6. Tape all three TLC plates side by side in your lab notebook. Take a picture and include this picture in your results and discussion section of your formal report.

**Typed Formal Report:**

1. Provide a heading, purpose and a reaction scheme for the reaction.
  - a. See the handout "The Typed, Formal Report" on the course website.
2. Write out a complete experimental procedure for this S<sub>N</sub>2 reaction using the example in the aforementioned handout as a template.
3. A results and discussion section that includes how you knew your product was pure (melting point and TLC spot comparison), your yield and a discussion of why (if) your yield was low. Again, refer to the handout mentioned in 1 and 2.
4. Be sure to include all aspects of the formal report (see handout).

In addition to the formal report, provide answers to the questions below. Your answers to these questions may be hand-written or typed and placed at the page of your formal report.

**Post-lab questions:**

1. Can you predict an undesirable side reaction that might occur involving the deprotonated ethanol (sodium ethoxide)?
2. Why is it important to mix the naphthol with sodium hydroxide before adding the n-butyl iodide? What happens during this time?
3. Why does naphthol react with sodium hydroxide? Why does ethanol not react to the extent that naphthol does with sodium hydroxide?
4. What is the better nucleophile, sodium naphthoxide or naphthol? Why?

5. Why is it important to fully cool the product in an ice bath prior to isolation by suction filtration? Why do you need to rinse your product with ice water instead of room temperature water?

### Health and Safety Notes

- As always, safety glasses or goggles must be worn at all times in the laboratory.
- Handle all reagents and solvents with care.
- Be sure to dispose of all waste in their appropriate containers.

### Study Guide

- Be able to write the mechanism for an  $S_N2$  reaction using electron pushing arrows.
- Be able to predict the products of  $S_N2$  substitution reactions between a nucleophile and an electrophile.
- Know why it is important in this lab to add the sodium hydroxide before adding the *n*-butyl iodide.
- Be able to answer the post- and pre-lab questions.

**Practice Problems** (Your TA will not collect these; they are for your own benefit).Predict the products of the following  $S_N2$  substitution reactions: