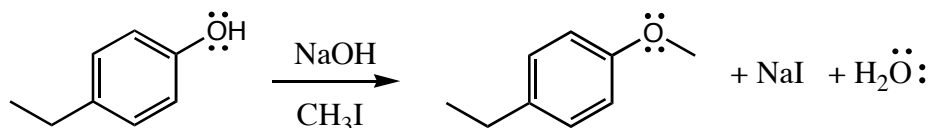


# Williamson Ether Synthesis

## Introduction

In this reaction, an alcohol is deprotonated to form a good nucleophile, which then attacks the electrophile methyl iodide to form an ether. Tetrabutylammonium bromide, a phase transfer catalyst, is used to carry ions back and forth between the organic phase and the aqueous phase.



Before coming to lab, please review the following techniques: "Reluxing a reaction," "Extraction and washing," "Drying an Organic Solvent," "Evaporating an Organic Solvent," "Analyzing a Solution by Thin Layer Chromatography (TLC)," "Separating Mixtures by Column Chromatography," and "Characterizing Compounds by IR." Notice that this lab brings together most of the techniques that we have used this semester. Then complete the following table before coming to class so that you will be prepared to start the reaction when you arrive. Write an introduction in your lab notebook.

reagent	volume	density	mass	MW	mmoles	eq
4-ethylphenol	x	x	150 mg			1.00
25 % NaOH (aq)		1.250 g/ml	soln: NaOH:			1.59
TBAB	x	x				0.045
methyl iodide						2.61
4-ethylanisole	x	x				

## Procedure

Set up the reaction:

- Add 4-ethylphenol, sodium hydroxide, and a spin vane to 5 ml conical vial and heat gently until it turns to a liquid.
- Add tetrabutylammonium bromide, then top with a reflux condenser and add the methyl iodide through the top.

Run the reaction:

- Reflux gently for one hour. The methyl iodide is very volatile, so if you heat it too much, it will escape the reflux condenser and no product will form. However, if the reaction is not refluxed, it will not have enough energy to proceed. Turn the heat up slowly until the reaction is just boiling. Keep watching during the reflux to be sure it is just boiling.

Isolate the product:

- Allow the reaction to cool; when it has reached room temperature, cool it briefly in an ice bath.
- Remove the spin vane and rinse it into the vial with 1-2 ml of ether. Add a little distilled water to make the aqueous layer big enough to handle.
- Remove the aqueous layer with a pipet and put it in a sep funnel. Extract with ether, then drain off the water layer and set it aside.
- Add the original ether layer to the ether extract now in the sep funnel. A white solid may form; don't worry about it, since your product is a liquid. Just don't lose any of the ether layer. Eventually the white solid will dissolve. Wash the combined ether extracts with 5% sodium hydroxide, draining it off after mixing.
- Then wash with distilled water to remove any sodium hydroxide.
- Dry the ether layer over sodium sulfate. What you have now is a solution of the crude product – it means that you have the product in the ether but haven't purified it yet.
- Prepare a TLC plate with three hash marks - one for the starting material, one for the crude product, and one for the final product. Spot the starting material and crude product but don't develop it yet.

Purify the product:

- Purify the product by making a miniature chromatography column from a Pasteur pipet. Place a small wad of cotton in the bottom and fill it up about half way with silica gel.
- Add the solution containing the product to the column and push it through with a pipet to load the column (some of the pure product may come through at this point).
- Then elute the column with 5 ml of dichloromethane. The combined solution should contain the purified product.
- Spot the purified product on your TLC plate. Look at it under UV light - if this final spot is too faint to be seen, spot it multiple times, letting the spot evaporate in between, until it is clearly visible.

- Develop the TLC plate in dichloromethane, remembering to cover it with a watch glass. Analyze the results. Could you tell the starting material from the product? Was the crude product pure? How about the final product?
- Transfer the solution to a tared round bottom flask and evaporate it.

Characterize the product:

- Observe the final product and note its odor, comparing it to a description of pure, authentic 4-ethylanisole: clear, colorless liquid with an odor of anise (licorice).
- Obtain a mass and calculate the % yield.
- Obtain an IR and compare it to the IR of the starting material. What bands appeared and disappeared?
- Write a conclusion which discusses the appearance and odor of the product, mass and % yield, what you learned from the TLC plate, and what your IR told you.

### Questions

- 1) Draw the mechanism for this reaction. What is the nucleophile and what is the electrophile?
- 2) Ordinarily, alcohols are not strong enough acids to react with NaOH. Why is our alcohol different? What is its approximate  $pK_a$ ?
- 3) Washing the product with aqueous base should remove most of the remaining starting material. Why does it do this?
- 4) The miniature chromatography column is designed to remove any of the starting material that still remains in the solution. Why does 4-ethylphenol run more slowly on the column than the product?
- 5) If you weren't told how long to reflux this reaction and wanted to know if it was finished, how you use TLC to determine this?
- 6) The structure of tetrabutylammonium bromide is written on the white board. By looking at this structure, explain how this reagent can carry ions into the organic phase.