

EXPERIMENT 2

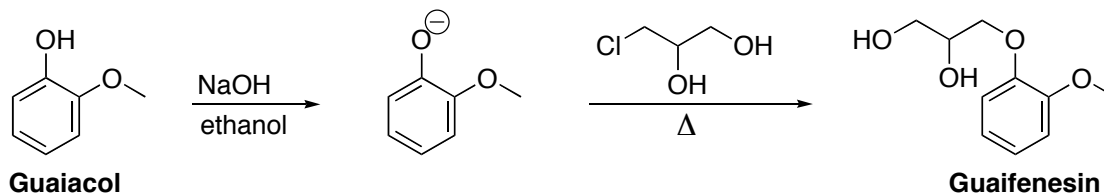
WILLIAMSON ETHER SYNTHESIS OF GUAIFENESIN AND ISOLATION OF AN EXPECTORANT FROM COUGH TABLETS

Reading Assignment: Smith Section 9.6

Pre-lab Questions:

- 1) Draw both enantiomers of guaifenesin, and indicate which is enantiomer is the most potent. Why is guaifenesin administered as a racemic mixture, when the *S*-(+)-enantiomer is actually more potent (*why not just administer the (S)-(+)-enantiomer?*)
- 2) Provide a mechanism for the deprotonation of guaiacol, and its subsequent reaction with (\pm)-3-chloro-1,2-propanediol.
- 3) Considering the mechanism in question 2 above, what are some possible competing reactions that might be expected to lower the yield of your product?
- 4) What is the limiting reagent in this ether synthesis (both steps taken together)?

Guaifenesin is used as an expectorant in many common cold & cough syrups, including Benylin, Robitussin & Novahistex. It loosens and thins bronchial secretions, which leads to more productive cough. It is also available in tablet form both over-the-counter, and in a higher-dose prescription form. The compound is administered in racemic form, although it has been suggested that the (*S*)-(+)-enantiomer is more potent. We will synthesize guaifenesin using a Williamson ether synthesis. In this experiment, (\pm)-3-chloro-1,2-propane-diol will be allowed to react with the conjugate base of Guaiacol (2-methoxyphenol) *via* an S_N2 reaction to provide guaifenesin as a racemic mixture. The same material will also be isolated from over the counter tablets *via* a simple extraction. The product in each case will be compared by IR spectroscopy.



Safety Precautions:

(\pm)-3-chloro-1,2-propane-diol is a highly toxic liquid by skin absorption, ingestion, and particularly inhalation, and can target the central nervous system. It is also a suspected carcinogen. Wear protective gloves, goggles, and a lab coat or apron, and do all work in the hood. Guaiacol is also toxic, and should be handled with caution. Sodium hydroxide is toxic and causes severe burns. Aqueous ethanol, ethyl acetate, and hexanes are all flammable solvents. No special precautions are necessary with the guaifenesin tablets.

Part A: Williamson Ether Synthesis of (±)-Guaifenesin

To 25 mL round-bottom flask containing a magnetic stir bar, dissolve guaiacol (2-methoxyphenol, 0.55 g, 5 mmole) in 3 mL 95% ethanol in a fume hood. To this, add 1 mL of 6.25 M NaOH solution. Reflux for 10 minutes using a hot water bath. Gradually add 1.0 mL of a 50% solution of (±)-3-chloro-1,2-propane-diol in ethanol dropwise to the phenoxide ion solution (through the top of the reflux condenser, over a period of 5-10 minutes). Almost immediately, a white precipitate will form. Continue to reflux the mixture for an additional hour. (*During this time, you can begin part B.*) After one hour, remove the reaction from the heat source, and allow to cool for a few minutes. Remove the ethanol on the rotary evaporator. Add 3 mL water to dissolve precipitated NaCl, then pour mixture into a separatory funnel, and extract the aqueous solution twice with 2 × 10 mL ethyl acetate. Dry the combined organic layers with MgSO₄. Vacuum filter to remove the drying agent, then remove the solvent *via* rotary evaporator to yield a pale yellow oil. Place the flask containing the oil in an ice-water bath, and add 10 mL hexanes. Rapid stirring using a magnetic stir bar will usually cause a white solid (guaifenesin) to precipitate. If guaifenesin precipitates, collect the crude solid by vacuum-filtration. If guaifenesin doesn't precipitate, thoroughly remove the solvent *via* rotary evaporator. Calculate a yield for the purified product and obtain an IR spectrum.

Part B: Isolation of (±)-Guaifenesin from a cold tablet:

During the one-hour reflux period for Part A, crush a single Guai-Aid tablet to a powder, using a mortar and pestle (*or if capsules are available, simply open up the capsule to release the guaifenesin powder*). Add to 5 mL ethyl acetate in a small Erlenmeyer, and stir for 10 minutes. Remove any insoluble material by gravity filtration, using fluted filter paper. Add 10 mL hexanes to the filtrate in 2 mL portions. White crystals of pure guaifenesin will form upon standing for a few minutes. After cooling in an ice bath, collect the precipitate by vacuum filtration, and wash with 5 mL *cold* hexanes. Take an IR of your isolated product.

In your report, compare the two samples of guaifenesin. Are the IR's identical? If not, explain any differences.

Reference:

1. This procedure is adapted from: Stabile, Ryan G.; P. Dicks, Andrew P. *J. Chem Ed.* **2003**, 80(3), 313-315.

Post-lab Questions:

- 1) When the phenoxide anion is allowed to react with (±)-3-chloro-1,2-propane-diol in Part A, why doesn't it deprotonate either of the alcohol groups in (±)-3-chloro-1,2-propane-diol?
- 2) Typical yields in the *J. Chem. Ed.* procedure for synthesis of guaifenesin (*see reference above*) range from 45-60%. Considering the competing reactions

discussed in Prelab question 3, suggest some experimental modifications that are expected to improve the yield? Be specific about the reasons for your changes. It may be helpful for you to know that this procedure was adapted from earlier reported syntheses of guaifenesin involving reaction times of 8 hours.

- 3) Justify the use of NaOH rather than a stronger base to deprotonate guaiacol. What special problems are introduced by using a stronger base than NaOH?