Williamson Ether Synthesis of an Expectorant – Guaifenesin – and its Isolation from Guai-aid Cough Tablets

In this experiment, Guaifenesin will be simultaneously synthesized in the laboratory and isolated from a Guai-aid cough tablet. The properties of the synthetic and isolated substances will be compared.
Guaifenesin Synthesis:
- Work in partners
- Start the synthesis first
- Get about 80 mL of hexane cooling in an ice bath early on so that it is cold when you need it later!

Guaifenesin Isolation from Tablets:
- Work in partners
- Begin this once the reflux is underway
Williamson Ether Synthesis in its Simplest Form

R\text{OH} \underset{\text{Base}}{\longrightarrow} R\text{O}^- \quad \text{alkoxide}

R' \text{L} \quad \text{R' is primary}

Just an S_N2 reaction!

React Guaiacol with NaOH

0.90-0.95 g of guaiacol
5 mL 2.0 M NaOH

guaiacol

weak nucleophile

strong nucleophile
React phenoxide anion with (±)-3-Chloro-1,2-propanediol

Dissolve 1.00-1.05 g of 3-chloro-1,2-propanediol in 1 ml Water
Add this solution to the solution of deprotonated Guaiacol
Heat at reflux for 30 minutes

(during this time perform the isolation of guaifenesin from a cough tablet)
Isolation of Guaifenesin from a Cough Tablet

Open a single Guai-Aid capsule and add contents to a 50 mL flask

Add ~6 mL of dichloromethane and swirl for 10 minutes

Gravity filter to remove insoluble material

Add 10 mL of hexane in 2 mL portions to the filtrate, with swirling

Cool the solution in an ice bath, then collect the white precipitate by vacuum filtration ⇒ isolated Guaifenesin
Guaifenesin Synthesis: Liquid-liquid extraction

Cool the reaction solution for several minutes in an ice water bath

Neutralize the crude reaction mixture with 2.5 M HCl (optional)

Extract this aqueous solution with dichloromethane

Dry the dichloromethane extract over Na$_2$SO$_4$

Micro-filter the solution (through a pipette with glass wool) into a 50 ml Erlenmeyer flask
Guaifenesin Synthesis: Precipitate the synthesized Guaifenesin

Add hexane (up to 15 mL) with occasional swirling to the residue in the distillation flask

During the addition, occasionally scrape the bottom of the flask to induce precipitation

Once precipitation begins, cool in ice/water bath for 10 minutes

Collect the white precipitate by vacuum filtration $\Rightarrow$ synthesized Guaifenesin
Completing the Experiment

1. Record the mass of synthesized and extracted Guaifenesin

2. Record three melting points (simultaneously)

3. Treat all chemicals used in this experiment as toxic - perform all lab work under the fume hood

4. Hand in a report of results for this experiment, prepare for a quiz on this experiment (and exp. 2) next week