Experiment 5: Nucleophilic Substitution
Synthesis of Propyl $p$-tolyl ether

Prelab Reading: Solubility and Extraction

\[ \text{S}_2\text{N}2: \quad \text{LG} + \text{Nuc} \rightarrow \text{LG} - \text{Nuc} \]

\( \text{LG} = \text{Leaving Group} \)
\( \text{Nuc} = \text{Nucleophile} \)

Introduction

Nucleophilic substitution reactions provide a way to bring about many different useful functional group interconversions on organic compounds. By appropriate choice of reactants and conditions, very high yield substitutions can be carried out by way of an $S_N1$ or $S_N2$ reaction. In this experiment we will carry out an $S_N2$ reaction to synthesize propyl $p$-tolyl ether using the so called Williamson ether synthesis.

$S_N2$ Reaction: Synthesis of Propyl $p$-tolyl ether

Procedure

In a 10 mL round bottom flask equipped with a magnetic stir bar, $p$-Cresol ((0.80 mL, 0.83 g, 7.6 mmol) is combined with 1.3 mL of 25% aqueous NaOH. (Caution! Wear protective gloves when dispensing $p$-Cresol. Avoid contact with skin. See Note 1 below.) The solution is stirred to mix thoroughly, and 90 mg of tetrabutylammonium bromide is added followed by 0.70 mL (0.95 g, 7.7 mmol) of 1-bromopropane. The round bottom flask is fitted with a water-cooled reflux condensor and heated at reflux for one hour (see Figure 7.1, page 70). The reaction mixture is allowed to cool to room temperature, and 5mL of diethyl ether is added. The organic and aqueous layers are transferred to a 60 mL separatory funnel. The aqueous layer is removed (Note 2), and the organic layer is washed with 2 mL of 5% NaOH, followed by washing with 2 mL of water. The organic layer is then dried with anhydrous MgSO$_4$ (Note 3), filtered to remove the drying agent (Note 4), and transferred to a tared 50 mL beaker containing a boiling chip. The diethyl ether is evaporated in a fume hood using a hot plate on low heat setting. When the boiling ceases, Propyl $p$-tolyl ether remains as a colorless liquid. The percent yield is determined and the product is analyzed by $^1$H NMR (in CDCl$_3$ solvent).

(See Notes on back side of page)
Notes

1. **p-Cresol is toxic and can be absorbed through the skin. Wear protective gloves while dispensing, and then immediately dispose of the gloves to prevent reuse.**

2. Make sure you know which phase is organic and which phase is aqueous.

3. The amount of anhydrous magnesium sulfate needed to dry the organic phase will vary from sample to sample. To determine the correct amount, add the amount of solid that fits on the tip of a spatula to the organic phase. Swirl the flask and observe the appearance of the magnesium sulfate. If the solid sticks to itself and the sides of the flask, the solution was damp and more anhydrous magnesium sulfate is needed. If the organic phase was damp, add another small amount of drying agent and swirl the flask. The organic phase is dry when the magnesium sulfate remains powdery and does not stick together.

4. Use gravity filtration with fluted filter paper to remove the drying agent.