Williamson Ether Synthesis

Overall Reaction

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\begin{align*}
\text{OH} & \quad \text{Br} & \quad \text{Ph} \\
\text{O} & \quad \text{H} & \quad \text{K}_2\text{CO}_3 & \quad \text{DMF} \\
\text{Ph} & \quad \text{O} & \quad \text{H}
\end{align*}
\]

Purpose

This experiment has the following goals:
1. demonstrate an example of an S\(_{N2}\) reaction, the Williamson Ether Synthesis
2. introduce COSY NMR techniques and the idea of spin systems

Background

The S\(_{N2}\) reaction is one of the first reactions taught to students in their first semester of organic chemistry. The reaction is conceptually simple (one-step, nucleophile-electrophile) and serves as a stepping stone for more complex reactions. All the other Big 4 reactions (S\(_{N1}\), E1, E2) are more complicated mechanistically than the S\(_{N2}\).

The S\(_{N2}\) reaction requires three qualities: a strong nucleophile, a good, unhindered leaving group, and a polar, aprotic solvent. For our reaction, we have all three bases covered. The nucleophile is an alkoxide, a deprotonated alcohol. Technically, because our alcohol is a phenol, the conjugate base is called a phenoxide. Phenol itself has a pK\(_{a}\) of about 10, but our alcohol has more resonance opportunities, so the pK\(_{a}\) is down around 8. This is sufficiently acidic for use of weak base like K\(_2\)CO\(_3\) for deprotonation (Scheme 1). The acidic of the aldehyde also helps in purifying the crude product. Our conditions call for excess aldehyde, which we will wash away with base in the work-up. Aside from a good nucleophile, we also have a good, unhindered leaving group in the bromine atom in cinnamyl bromide. Note that not only is this reagent a primary halide, but it also has no β-hydrogens (so no E2 is possible). Finally, our reaction solvent is DMF (N,N-dimethylformamide), a classic solvent for S\(_{N2}\) reactions. With all the conditions in favor of this reaction, it should be no surprise that this reaction works very well.

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\begin{align*}
\text{OH} & \quad \text{K}_2\text{CO}_3 \\
\text{O} & \quad \text{H} \\
\text{O} & \quad \text{H}
\end{align*}
\]

Scheme 1. Resonance explanation for acidity of salicylaldehyde (pK\(_{a}\) 8.0)

Despite the ease of our reaction, a few comments are in order. Our alkyl halide, cinnamyl bromide, is extremely reactive. As an electrophile, it is activated by something called the phenacyl effect (Reeve J. Am. Chem. Soc. 1954, 76, 2280-2281). The phenacyl effect applies to halides that are adjacent to a π-bond, such as a simple double bond, an aromatic ring, or a carbonyl. The neighboring π-bond stabilizes both S\(_{N2}\) substitution and S\(_{N1}\) ionization (Figure 1).
With this type of halide, the choice of solvent is extremely important. Despite being protic, alcohols can often be used as a solvent in many $S_N2$ reactions. Unfortunately, ethanol reacts quickly with cinnamyl bromide under basic conditions to give a substitution product either by an $S_N2$ (more likely) or $S_N1$ pathway (Scheme 2). DMSO (dimethyl sulfoxide) is also a traditional $S_N2$ solvent. However, DMSO is sufficiently nucleophilic at oxygen to attack cinnamyl bromide. Ultimately, the halide is oxidized to an aldehyde in a process called the Kornblum reaction (Kornblum J. Am. Chem. Soc. 1957, 79, 6562). That leaves solvents such as DMF or acetonitrile for our reaction.

Scheme 2. Reaction of cinnamyl bromide with ethanol and DMSO

Our product is an ideal candidate for a COSY spectrum. COSY is an abbreviation of correlated spectrum, a two-dimensional form of NMR. While there are various forms of COSY spectra, the term COSY alone normally refers to $^1H-^1H$ correlated spectra. COSY spectra plot the same $^1H$ spectrum on the x- and y-axes. The diagonal of the plot corresponds to the peaks in the spectra. Any signals not on the diagonal of the plot signify $J$-coupling between nuclei. We will talk more about this in class. It is a very powerful technique for determining a structure and assigning signals.

**Experiment**

In a 20 mL scintillation vial dissolve salicylaldehyde (13 mmol) in DMF (10 mL) with stirring. Add $K_2CO_3$ (15 mmol). In a separate vial dissolve cinnamyl bromide (10 mmol) in DMF (2 mL). Add the halide solution dropwise by Pasteur pipet. Heat the reaction to 60-70° in a shallow sand bath. After 30 minutes, check the reaction by TLC (10% EtOAc/90% Hex) against the bromide starting material. If the reaction is complete, continue on to the work-up. Otherwise, allow the reaction to heat for another 30 minutes. Once complete, pour the reaction
into a 250 mL separatory funnel containing EtOAc (100 mL). Use a small amount of EtOAc to rinse out the reaction vial as necessary. Wash the EtOAc layer with 10% NaOH (2×25 mL) and H₂O (4×25 mL). Dry the EtOAc layer with Na₂SO₄, filter the solution, and concentrate the reaction in a tared, 250 mL round-bottom flask. Determine your percent yield and gather the following data: ¹H NMR and COSY spectra, Rₖ value (10% EtOAc/90% Hex).

**Lab Report**

Aside from the standard lab report items, your report should include the following items in the Discussion Section.

- Fully assign the ¹H NMR spectrum of the crude product through the COSY spectrum. Each peak (or cluster of peaks in case of overlapping signals) should be identified. Include the full assignment on a sheet in your attached spectra with a rationale of the assignments.