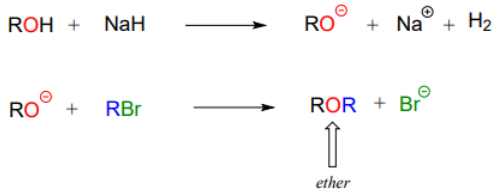
8.9: Nucleophilic substitution in the Lab

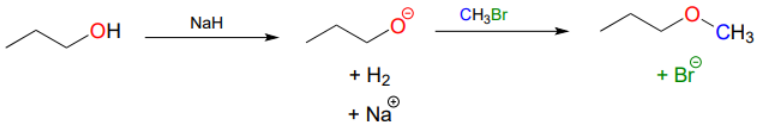
The Williamson ether synthesis

Synthetic organic chemists often make use of a reaction that is conceptually very similar to the SAM-dependent methylation reactions we saw earlier. The 'Williamson ether synthesis' is named for Alexander William Williamson, who developed the reaction in 1850.

In the Williamson ether synthesis, an alcohol is first deprotonated by a strong base, typically sodium hydride. An alkyl halide is then added to the reaction mixture, and the alkoxide ion, a powerful nucleophile, displaces the halide leaving group in an S_N2 reaction.

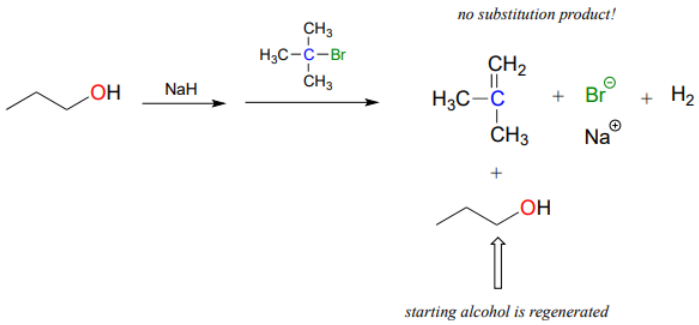


For example, below we see methyl bromide performing the role of methyl group donor, analogous to the role played by SAM in biochemical methylation reactions:



Notice the difference between this non-biological laboratory reaction and the biological, enzyme-catalyzed SAM methylation reaction we saw earlier. Deprotonation of the nucleophile occurs as a separate step, before the nucleophile attacks. Contrast this solution reaction (with two bimolecular steps) to the enzyme-catalyzed S_N2 reaction (SAM methylation) we saw earlier, which involves a single, concerted trimolecular step. Also notice that this non-biological reaction involves a highly basic reagent (sodium hydride) and intermediate (propanoate anion), which would be unreasonable to propose for a reaction taking place under physiological conditions.

The Williamson ether synthesis will only work with methyl or primary alkyl halides. If a secondary or tertiary alkyl halide is used, the result will be formation of an alkene in what is called an 'elimination' reaction:



We will study elimination reactions in chapter 14.

? Exercise 8.9.1

A rookie organic chemist ran the reaction shown above, hoping to synthesize an ether. Instead, he got the alkene shown. What alkyl halide/alcohol combination should he have used instead to get the ether product he was trying for?

Turning a poor leaving group into a good one - tosylates

In section 8.4 it was mentioned how, in metabolic pathways, the relatively poor OH leaving group of an alcohol can be converted into a phosphate or diphosphate, which when stabilized by noncovalent interactions inside an enzyme active site can be a very good leaving group.

In laboratory synthesis, a similar goal can be accomplished by converting an alcohol (a poor leaving group)to an organic tosylate (a good leaving group) using tosyl chloride (the terms 'tosylate' and 'OTs', are abbreviations for para-toluene sulfonate). The alcohol to tosylate reaction is not something we are equipped yet to understand, but if we consider that the pKa of para-toluene sulfonic acid is -2.8, we realize that the para-toluene sulfonate anion is a very weak base and thus an very good leaving group. Conversion of alcohols to organic tosylates is a very common step in organic synthesis schemes.