

## 7.6: Extra Topics on Nucleophilic Substitution Reaction

Our discussions so far focus on the fundamental concepts about  $S_N1$  and  $S_N2$  mechanism, and the reactions we learned about proceed in the regular way. There are some other conditions can be “added” to the basic nucleophilic substitution reactions, to make the reaction look different, or more challenge. However, understanding the basic concepts well is very helpful for us to deal with various situations. The reaction may look different, but essentially it is still the same.

### 7.6.1 $S_N1$ Reaction with Carbocation Rearrangement

Let's take a look at a  $S_N1$  reaction.

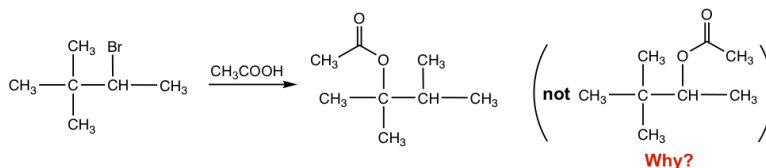


Figure 7.6a Reaction with Carbocation Rearrangement

With the secondary substrate and neutral nucleophile ( $\text{CH}_3\text{COOH}$ ), this is a  $S_N1$  reaction, and solvolysis that  $\text{CH}_3\text{COOH}$  acts as both solvent and nucleophile. It is supposed to give the acetate as product, with the acetate replace the Br. However, as shown in the reaction equation that the acetate was **not** introduced on the carbon with leaving group Br, but was connected on the next carbon instead. What is the reason for the unexpected structure of the product?

For reactions involve carbocation intermediate, it is a common phenomena that the carbocation *might* rearrange, if such rearrangement leads to a **more stable** carbocation, and this is called **carbocation rearrangement**. Because of the carbocation rearrangement, the product of the above reaction is different than expected. This can be explained with the step-by-step mechanism below.

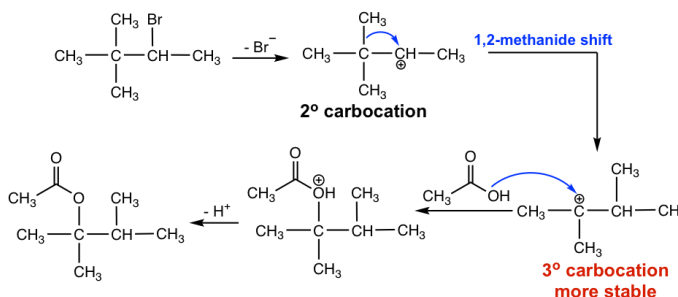


Figure 7.6b Step by step carbocation rearrangement

When  $\text{Br}^-$  leaves, the initial carbocation formed is a **secondary** one. The  $\text{CH}_3$  group on the next carbon then shift with its bonding electrons to the positively charged carbon, and creating a new more stable **tertiary carbocation**. The *tertiary* carbocation then reacts with nucleophile  $\text{CH}_3\text{COOH}$  to give the final acetate product. The  $\text{CH}_3$  group shift with the electron pair, and such move is called 1,2-methanideshift. “1,2-” here refer to the movement occur between two adjacent carbons, not necessarily means C1 and C2.

Other than  $\text{CH}_3$  group, the H atom in other reactions could shift as well with the electron pair, if such shift can lead to a more stable carbocation. The shift of hydrogen is called 1,2-hydride shift. A couple of notes about the carbocation rearrangement:

- Any reaction that involves carbocation intermediate might have rearrangement.
- Not all carbocations rearrange. Carbocations **only** rearrange if they become more stable as a result of the rearrangement.
- The shift is usually 1,2-shift, that means it occur between two adjacent carbons.

### 7.6.2 Intramolecular Nucleophilic Substitution Reaction

For the reactions we learned before, the substrate with leaving group and the nucleophile are always two separate compounds. It is actually possible for one compound containing both leaving group and nucleophile, and the reaction occurs within the same molecule. Such reaction is called the intramolecular (*intra*, Latin for “within”) reaction. Cyclic product is obtained from intramolecular reaction.

Let's talk about the reaction mechanism that rationalize the structure and stereochemistry of the product for following reaction.

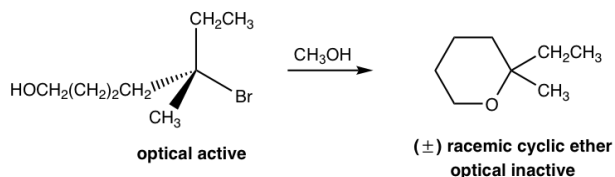


Figure 7.6c Intramolecular Nucleophilic Substitution Reaction

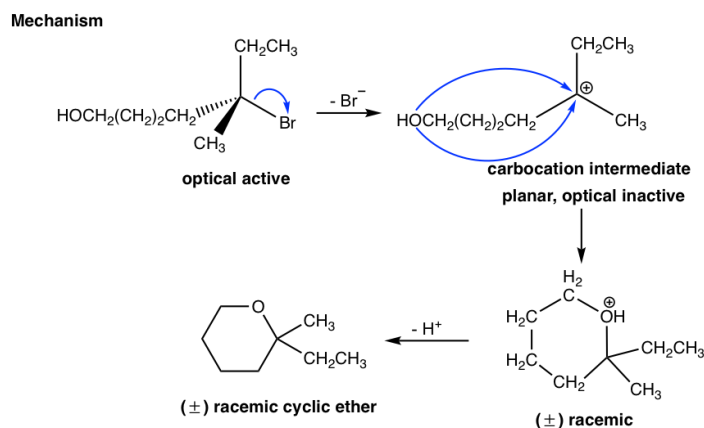


Figure 7.6d Intramolecular Mechanism

In the above reaction, the reactant has two functional groups, bromide ( $\text{Br}$ ) and alcohol ( $\text{OH}$ ). A compound with two functional groups is called **bifunctional molecule**. In this reactant,  $\text{Br}$  is connected on a tertiary carbon that is a good substrate for  $\text{S}_{\text{N}}1$  reaction, and  $\text{OH}$  is a good nucleophile for  $\text{S}_{\text{N}}1$  as well, so the substitution reaction could occur within the same molecule via  $\text{S}_{\text{N}}1$  mechanism. So the reaction occurs between one end of the molecule,  $\text{Br}$ , that acts as the leaving group, and the other part of the molecule,  $\text{OH}$ , which acts as the nucleophile. As a result, a six-membered cyclic ether is formed as the product.

Since the reaction occurs with  $\text{S}_{\text{N}}1$  mechanism, the carbocation intermediate is in trigonal planar shape, and the nucleophile can attack from either side of the carbocation to give both enantiomers. Therefore, the product is the racemic mixture that is optical inactive. This is consistent with the stereochemistry feature of  $\text{S}_{\text{N}}1$  reaction we learned before.

Usually if the intramolecular reaction could produce five- or six-membered ring as the product, the reaction will be highly favored because of the special stability of five- or six-membered ring.

### 7.6.3 Converting Poor Leaving Group to Good Leaving Group

In early discussions about leaving groups (section 7.3), we have mentioned the importance of a good leaving group for both  $\text{S}_{\text{N}}1$  and  $\text{S}_{\text{N}}2$  reactions, that the substitution reaction will not occur is a poor leaving group present. For some situations however, the poor leaving group could be converted to a good leaving group to make the reaction feasible. We will see a couple of strategies for such purpose.

#### By Acid Catalyst $\text{H}^+$

**Example:** Propose the mechanism to rationalize the reaction.

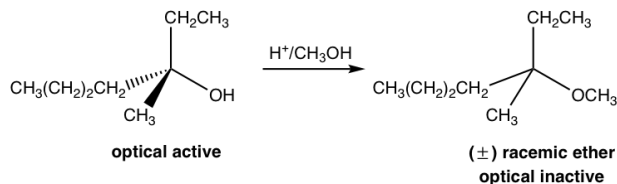
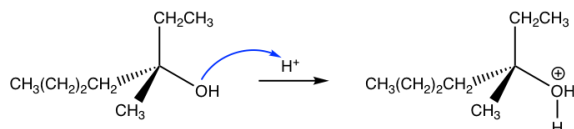


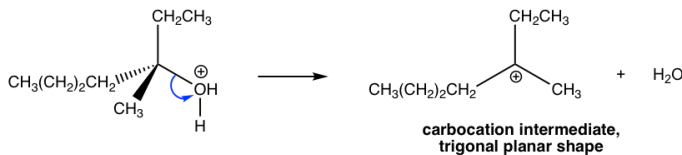
Figure 7.6e Reaction

### Mechanism:

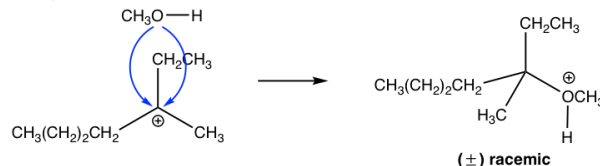
#### Step 1: protonation of OH



#### Step 2: H<sub>2</sub>O departs as leaving group



#### Step 3: CH<sub>3</sub>OH attacks carbocation



#### Step 4: Deprotonation to give neutral product

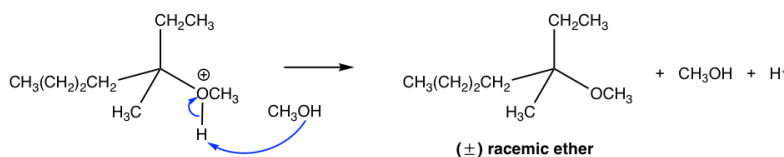


Figure 7.6f Mechanism

The last three steps in the above mechanism are the standard steps of S<sub>N</sub>1 mechanism. However, the reaction won't proceed without the first step. In the first step, which is an acid-base reaction, a proton is rapidly transferred to the OH group, and get the alcohol protonated. By protonation, the OH group is converted to H<sub>2</sub>O, that is a much weaker base therefore a good leaving group. In step 2, water molecule departs with the electron pair and leave behind a carbocation intermediate. The following steps are just S<sub>N</sub>1, that explains why the product is the racemic mixture. The acid H<sup>+</sup> was regenerated in step 4 and can be reused for further reactions, therefore only catalytical amount of H<sup>+</sup> is necessary to start the process.

### By Sulfonyl Chloride

Another commonly applied method for converting OH group to a better leaving group is by introducing a sulfonate ester. When alcohol reacts with sulfonyl chloride, with the presence of weak base, the sulfonate ester is formed.

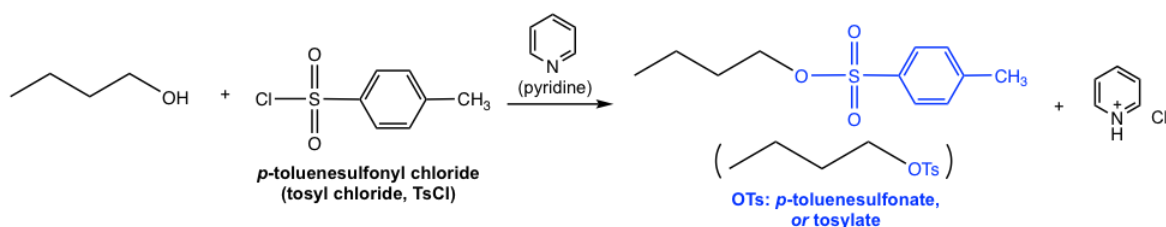


Figure 7.6g Alcohol reacting with tosyl chloride to produce tosylate

As the example shown above, when *p*-toluenesulfonyl chloride (tosyl chloride, TsCl) is used, the resulting ester is *p*-toluenesulfonate (tosylate, OTs). Does tosyl group look familiar to you? Yes, we learned about with this species in **section 3.2**. As the conjugate base of strong acid *p*-toluenesulfonic acid (TsOH), OTs is the very weak base and therefore an excellent leaving group. Pyridine here acts as the weak base to neutralize the side product HCl and facilitate the reaction to completion. The detailed mechanism for this reaction is not required in this course.

Other than introducing OTs, other commonly applied sulfonyl chlorides include MsCl and TfCl, and the sulfonate ester OMs (mesylate) and OTf (triflate) are formed respectively.

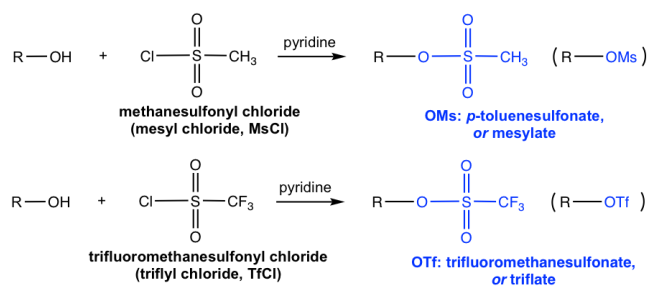


Figure 7.6h Conversion of Alcohol to Mesylate or Triflate

Once the primary alcohol has been converted to OTs (or OMs, OTf), it is then the good substrate for  $\text{S}_{\text{N}}2$  reaction. With the appropriate nucleophile added in a separate step, for example  $\text{CH}_3\text{O}^-$ , the  $\text{S}_{\text{N}}2$  reaction takes place readily to give ether as the final product, as shown below.

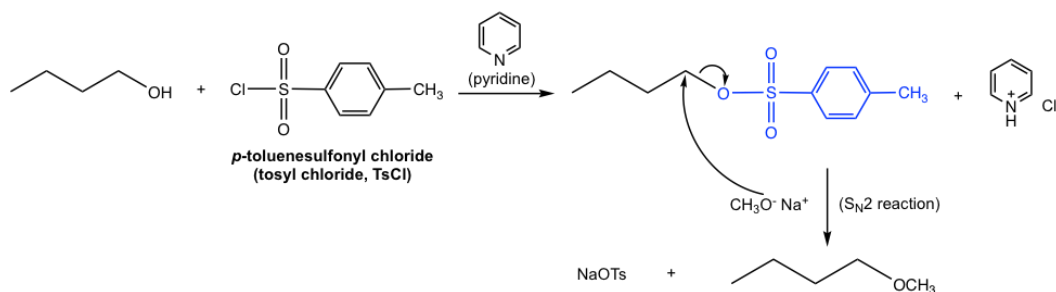


Figure 7.6i Step by step synthesis scheme of butyl methyl ether from 1-butanol (with structures of intermediates shown)

The overall synthesis of butyl methyl ether from 1-butanol involves two separate steps: the conversion of OH to OTs, and then the replacement of OTs by  $\text{CH}_3\text{O}$  through  $\text{S}_{\text{N}}2$  reaction. The two steps have to be carried out one after the other, however the whole synthesis scheme can also be shown as below:

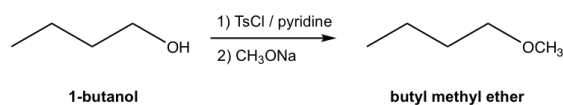


Figure 7.6j Synthesis scheme of butyl methyl ether from 1-butanol (structures of intermediates are NOT shown)

Note:

- Figure 7.6j represents the common and conventional way to show the multiple-step synthesis in organic chemistry. The reaction conditions (reagent, catalyst, solvent, temperature etc.) for each step are shown on top and bottom of the equation arrow. Only the structures of starting material and final product(s) are shown, and the structures of the intermediate products for each step are not included.
- The individual steps need to be labelled as 1), 2) etc. for the proper order, they can not be mixed together.

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