Notice that the principles you’ve studied in Chapter 9 for the substitutions and eliminations of alkyl halides are valid for other functional groups—in this case, alcohols.

A. Sulfonate Ester Derivatives of Alcohols

**Structures of Sulfonate Esters** An important method of activating alcohols toward nucleophilic substitution and $\beta$-elimination reactions is to convert them into *sulfonate esters*. Sulfonate esters are derivatives of *sulfonic acids*, which are compounds of the form $R-\text{SO}_3\text{H}$. Some typical sulfonic acids are the following:

- Methanesulfonic acid
- Benzenesulfonic acid
- P-toluenesulfonic acid

(The $p$ in the name of the last compound stands for *para*, which indicates the relative positions of the two groups on the benzene ring. This type of nomenclature is discussed in Chapter 16.) A **sulfonate ester** is a compound in which the acidic hydrogen of a sulfonic acid is replaced by an alkyl or aryl group. Thus, in ethyl benzenesulfonate, the acidic hydrogen of benzenesulfonic acid is replaced by an ethyl group.

[Diagram showing the conversion of an alkyl halide to a sulfonate ester]
Sulfur has more than the octet of electrons in these Lewis structures. Such “octet expansion” is common for atoms in the third and higher periods of the periodic table. Bonding in sulfonic acids and their derivatives is discussed further in Sec. 10.9.

Organic chemists often use abbreviated structures and names for certain sulfonate esters. Esters of methanesulfonic acid are called mesylates (abbreviated R—OMs), and esters of p-toluenesulfonic acid are called tosylates (abbreviated R—OTs).

\[
\begin{align*}
C_2H_5—O=S—CH_3 & \quad \text{is the same as} \quad C_2H_5—OMs \\
\text{ethyl mesylate} & \\
C_3H_7(CH_2)\_9—O=S—CH_3 & \quad \text{is the same as} \quad C_3H_7(CH_2)\_9—OTs \\
\text{sec-butyl p-toluenesulfonate} & \\
& \quad \text{sec-butyl tosylate}
\end{align*}
\]

**PROBLEM 10.11** Draw both the complete structure and the abbreviated structure, and give another name for each of the following compounds.

(a) isopropyl methanesulfonate
(b) methyl p-toluenesulfonate
(c) phenyl tosylate
(d) cyclohexyl mesylate

**Preparation of Sulfonate Esters** Sulfonate esters are prepared from alcohols and other sulfonic acid derivatives called sulfonyl chlorides. For example, p-toluenesulfonyl chloride, often known as tosyl chloride and abbreviated TsCl, is the sulfonyl chloride used to prepare tosylate esters.

\[
\begin{align*}
\text{CH}_3(\text{CH}_2)\_9\text{OH} + \text{Cl—S—CH}_3 & \quad \rightarrow \\
\text{1-decanol} & \\
\text{p-toluenesulfonyl chloride} & \quad \text{(tosyl chloride; a sulfonyle chloride)}
\end{align*}
\]

This is a nucleophilic substitution reaction in which the oxygen of the alcohol displaces chloride ion from the tosyl chloride. The pyridine used as the solvent is a base. Besides catalyzing the reaction, it also neutralizes the HCl that would otherwise form in the reaction (color in Eq. 10.15).
Reactivity of Sulfonate Esters  Sulfonate esters, such as tosylates and mesylates, are useful because they have approximately the same reactivities as the corresponding alkyl bromides in substitution and elimination reactions. (In other words, you can think of a tosylate or mesylate ester group as a “fat” bromo group.) The reason for this similarity is that sulfonate anions, like bromide ions, are good leaving groups. Recall that, among the halides, the weakest bases, bromide and iodide, are the best leaving groups (Sec. 9.4F). In general, good leaving groups are weak bases. Sulfonate anions are weak bases; they are the conjugate bases of sulfonic acids, which are strong acids.

Thus, sulfonate esters prepared from primary and secondary alcohols, like primary and secondary alkyl halides, undergo $S_N2$ reactions in which a sulfonate ion serves as the leaving group.

Similarly, secondary and tertiary sulfonate esters, like the corresponding alkyl halides, undergo E2 reactions with strong bases, and they undergo $S_N1$–E1 solvolysis reactions in polar protic solvents.

Occasionally we’ll need a sulfonate ester that is much more reactive than a tosylate or mesylate. In such a case a trifluoromethanesulfonate ester is used. The trifluoromethanesulfonate group is nicknamed the triflate group and it is abbreviated $\text{OTf}$.

The triflate anion is a particularly weak base. (See Problem 10.46 on p. 478.) Hence, the triflate group is a particularly good leaving group, and triflate esters are highly reactive. For example, consider again the $S_N2$ reaction used to prepare FDG, an imaging agent used in
positron emission tomography (PET). (See Eq. 9.30a on p. 397.) This reaction is far too slow to be useful with a tosylate leaving group. However, the triflate leaving group has considerably greater reactivity and is an ideal leaving group for this reaction, which must be carried out quickly.

Triflate esters are prepared in the same manner as tosylate esters (Eq. 10.15), except that triflic anhydride is used instead of tosyl chloride.

\[
\text{CH}_3(CH_2)_4OH + F_3C-SO_2-CF_3 + \text{pyridine} \rightarrow \text{CH}_3(CH_2)_4OTf + \text{1-pentyl triflate} \ 
\begin{array}{c}
(90\% \text{ yield}) \\
\text{1-pentanol}
\end{array}
\]

The use of sulfonate esters in $S_{N2}$ reactions is illustrated in Study Problem 10.1.

**Study Problem 10.1**

Outline a sequence of reactions for the conversion of 3-pentanol into 3-bromopentane.

**Solution** Before doing anything else, write the problem in terms of structures.

\[
\begin{align*}
\text{CH}_3CH(CH_2)_2CH_3 & \quad \text{ OH} \quad \text{ Br} \\
\text{CH}_3CH(CH_2)_2CH(CH_3) & \quad \rightarrow \\
\text{CH}_3CH(CH_2)_2CH_3 & \quad \text{OH} \quad \text{ OTs} \\
\text{CH}_3CH(CH_2)_2CH(CH_3) & \quad \text{TsCl} \text{ pyridine} \quad \rightarrow \\
\text{CH}_3CH(CH_2)_2CHCH_2CH_3 & \quad \text{CH}_3CH(CH_2)_2CHCH_2CH_3
\end{align*}
\]

Alcohols can be converted into alkyl bromides using HBr and heat (Sec. 10.2). However, because secondary alcohols are prone to carbocation rearrangements, the HBr method is likely to give by-products. However, if conditions can be chosen so that the reaction will occur by the $S_{N2}$ mechanism, carbocation rearrangements will not be an issue. To accomplish this objective, first convert the alcohol into a tosylate or mesylate.

\[
\begin{align*}
\text{CH}_3CH(CH_2)_2CH(CH_3) & \quad + \text{Na}^+ \quad \text{Br}^- \\
\text{CH}_3CH(CH_2)_2CHCH_2CH_3 & \quad \rightarrow \\
\text{CH}_3CH(CH_2)_2CHCH_2CH_3 & \quad + \text{Na}^+ \quad \text{ OTs}
\end{align*}
\]

Next, displace the tosylate group with bromide ion in a polar aprotic solvent such as DMSO (Table 8.2, p. 341).

Because secondary alkyl tosylates, like secondary alkyl halides, are not as reactive as primary ones in the $S_{N2}$ reaction, use of a polar aprotic solvent ensures a reasonable rate of reaction (Sec. 9.4E). This type of solvent also suppresses carbocation formation, which would be more likely to occur in a protic solvent. (The transformation in Eq. 10.18b takes place in 85% yield.)
The E2 reactions of sulfonate esters, like the analogous reactions of alkyl halides, can be used to prepare alkenes:

\[
\text{OTs} + \text{K}^+ (\text{CH}_3)_2\text{CO}^- \xrightarrow{20-25^\circ\text{C}, 30\text{ min}} \xrightarrow{\text{DMSO}} \text{K}^+ \text{OTs} + (\text{CH}_3)_2\text{COH} \quad (10.19)
\]

This reaction is especially useful when the acidic conditions of alcohol dehydration lead to rearrangements or other side reactions, or for primary alcohols in which dehydration is not an option.

To summarize: An alcohol can be made to undergo substitution and elimination reactions typical of the corresponding alkyl halides by converting it into a good leaving group such as a sulfonate ester.

**PROBLEMS**

**10.13** Design a preparation of each of the following compounds from an alcohol using sulfonate ester methodology.

(a)  
(b)  

**10.14** Give the product that results from each of the following sequences of reactions.

(a)  
(b)  

**B. Alkylating Agents**

As you’ve learned, alkyl halides, alkyl tosylates, and other sulfonate esters are reactive in nucleophilic substitution reactions. In a nucleophilic substitution, an alkyl group is transferred from the leaving group to the nucleophile.

\[
\text{a nucleophile} \quad \xrightarrow{\text{a leaving group such as a halide or sulfonate ester}} \quad \text{Nuc}^- \xrightarrow{\text{X}} \quad \text{Nuc} \xrightarrow{\text{R}} \xrightarrow{\text{an alkyl group (R) is transferred from X to Nuc}} \text{R} + \text{X}^- \quad (10.20)
\]

The nucleophile is said to be alkylated by the alkyl halide or the sulfonate ester in the same sense that a Brønsted base is protonated by a strong acid. For this reason, alkyl halides, sulfonate esters, and related compounds are sometimes referred to as alkylating agents. To say that a compound is a good alkylating agent means that it reacts rapidly with nucleophiles in S_N2 or S_N1 reactions to transfer an alkyl group.
C. Ester Derivatives of Strong Inorganic Acids

The esters of strong inorganic acids exemplify another type of alkylating agent (Sec. 10.3B). Like tosylates and mesylates, these compounds are derived conceptually by replacing the acidic hydrogen of a strong acid (in this case an inorganic acid) with an alkyl group. For example, dimethyl sulfate is an ester in which the acidic hydrogens of sulfuric acid are replaced by methyl groups.

\[
\text{sulfuric acid} \quad \text{dimethyl sulfate}
\]

Alkyl esters of strong inorganic acids are typically very potent alkylating agents because they contain leaving groups that are very weak bases. For example, dimethyl sulfate is a very effective methylating agent, as shown in the following example.

\[
\begin{align*}
\text{(CH}_3\text{)}_2\text{CH}^- \quad & \quad \text{H}_3\text{C} \quad \text{O} \quad \text{S} \quad \text{O} \quad \text{H} \\
\text{isopropoxide anion} & \quad \rightarrow \\
\text{dimethyl sulfate} \quad & \quad \text{(CH}_3\text{)}_2\text{CH}^- \quad \text{O} \quad \text{S} \quad \text{O} \quad \text{CH}_3
\end{align*}
\]

Dimethyl sulfate and diethyl sulfate are available commercially. These reagents, like other reactive alkylating agents, are toxic because they react with nucleophilic functional groups on proteins and nucleic acids (Sec. 25.5C).

Certain alkyl esters of phosphoric acid are utilized in nature as alkylating agents (Sec. 17.6). DNA and RNA themselves are polymerized dialkyl esters of phosphoric acid (Sec. 25.5B).

Along the same line, alkyl halides can even be thought of as alkyl esters of the halogen acids. Methyl iodide, for example, is conceptually derived by replacing the acidic hydrogen of HI with a methyl group. As you have learned, this “ester” is also an effective alkylating agent.

PROBLEMS

10.15 Phosphoric acid, $H_3PO_4$, has the following structure.

![](image)

(a) Draw the structure of trimethyl phosphate.
(b) Draw the structure of the monoethyl ester of phosphoric acid.

10.16 Predict the products in the reaction of dimethyl sulfate with each of the following nucleophiles.

(a) $\text{CH}_3\text{NH}_2$  (b) water  (c) sodium ethoxide  (d) sodium 1-propanethiolate methylamine
D. Reactions of Alcohols with Thionyl Chloride and Phosphorus Tribromide

In most cases, the preparation of primary alkyl chlorides from alcohols with HCl is not as satisfactory as the preparation of the analogous alkyl bromides with HBr (Sec. 10.2). A better method for the preparation of primary alkyl chlorides is the reaction of alcohols with thionyl chloride:

\[
\text{CH}_3(CH_2)_6CH_2OH + \text{SOCl}_2 \xrightarrow{\text{pyridine}} \text{CH}_3(CH_2)_6CH_2Cl + SO_2 \uparrow + \text{HCl}
\] (10.22)

\(1\)-octanol \hspace{1cm} \text{thionyl chloride} \hspace{1cm} \text{1-chlorooctane} \hspace{1cm} (80\% \text{ yield})

Thionyl chloride is a dense, fuming liquid (bp 75–76°C). One advantage of using thionyl chloride for the preparation of alkyl chlorides is that the by-products of the reaction are HCl, which reacts with the base pyridine, and sulfur dioxide (SO\(_2\)), a gas. Consequently, there are no separation problems in the purification of the product alkyl chlorides.

The preparation of an alkyl chloride from an alcohol with thionyl chloride, like the use of a sulfonate ester, involves the conversion of the alcohol \(\text{—OH} \) group into a good leaving group. When an alcohol reacts with thionyl chloride, a \text{chlorosulfite ester} intermediate is formed. (This reaction is analogous to Eq. 10.15.)

\[
\text{RCH}_2\text{OH} + \text{Cl} \rightleftharpoons \text{SO} \rightleftharpoons \text{Cl} + \text{pyridine} \rightarrow \text{RCH}_2\text{OSO} + \text{pyridine} \text{ (solvent)}
\] (10.23)

The chlorosulfite ester reacts readily with nucleophiles because the chlorosulfite group, \(\text{—O—SO—Cl}\), is a very weak base and thus a very good leaving group. The chlorosulfite ester is usually not isolated, but reacts with the chloride ion formed in Eq. 10.23 to give the alkyl chloride. The displaced \(\text{—O—SO—Cl}\) ion is unstable and decomposes to \(\text{SO}_2\) and \(\text{Cl}^-\).

\[
\text{R—CH}_2\left\langle \begin{array}{c}
\text{O} \\
\text{Cl}^- \\
\end{array} \right\rangle \rightleftharpoons \text{Cl} \rightarrow \text{R—CH}_2\left\langle \begin{array}{c}
\text{O} \\
\text{Cl}^- \\
\end{array} \right\rangle \rightarrow \text{O} + \text{Cl}^- \quad \text{(10.24)}
\]

In other words, thionyl chloride provides the conversion into a good leaving group and a source of the displacing halide ion within the same reaction!

Although the thionyl chloride method is most useful with primary alcohols, it can also be used with secondary alcohols, although rearrangements in such cases have been known to occur. Rearrangements are best avoided in the preparation of secondary alkyl halides by using the reaction of a halide ion with a sulfonate ester in a polar aprotic solvent (as in Study Problem 10.1).

A related method for the preparation of alkyl bromides involves the use of phosphorus tribromide (PBr\(_3\)).

\[
3 \text{cyclopentanol} + \text{PBr}_3 \xrightarrow{9^\circ\text{C}} \xrightarrow{3 \text{h}} 3 \text{bromocyclopentane} \text{ (81\% yield)}
\] (10.25)
This reagent is related to thionyl chloride in the sense that it converts the —OH group into a good leaving group and, at the same time, provides a source of halide ion (bromide ion in this case) to effect the substitution reaction.

\[
\text{RCH}_2\text{OH} + \text{PBr}_3 \rightarrow \text{Br}^+ + \text{RCH}_2\text{O}^+ + \text{PBr}_2
\]

\[
\text{RCH}_2\text{OH} + \text{PBr}_3 \rightarrow \text{RCH}_2\text{Br} + \text{HBr} + \text{PBr}_2
\]

(As Eq. 10.25 shows, all three bromines of PBr$_3$ can be used; Eq. 10.26 gives the mechanism of the first substitution only.)

This reaction is considerably more general than the reaction of alcohols with HBr because it can be used with alcohols containing other functional groups that are acid-sensitive and would not survive treatment with HBr. Also, when used with secondary alcohols, the risk of rearrangement, although not totally absent, is less than with HBr.

**PROBLEMS**

10.17 Give three reactions that illustrate the preparation of 1-bromobutane from 1-butanol.

10.18 (a) According to the mechanism of the reaction shown in Eq. 10.24, what would be the absolute configuration of the alkyl chloride obtained from the reaction of thionyl chloride with (S)-CH$_3$CH$_2$CH$_2$CHD—OH? Explain.

(b) According to the mechanism shown in Eq. 10.26, what would be the absolute configuration of 2-bromopentane obtained from the reaction of PBr$_3$ with the R enantiomer of 2-pentanol? Explain.

**10.4 CONVERSION OF ALCOHOLS INTO ALKYL HALIDES: SUMMARY**

You have now studied a variety of reactions that can be used to convert alcohols into alkyl halides. These are

1. reaction with hydrogen halides
2. formation of sulfonate esters followed by $S_N2$ reaction with halide ions
3. reaction with SOCl$_2$ or PBr$_3$.

Which method should be used in a given situation? The method of choice depends on the structure of the alcohol and on the type of alkyl halide (chloride, bromide, iodide) to be prepared.

*Primary Alcohols:* Alkyl bromides are prepared from primary alcohols by the reaction of the alcohol with concentrated HBr or with PBr$_3$. HBr is often chosen for convenience and because the reagent is relatively inexpensive. The reaction with PBr$_3$ is quite general, but it is particularly useful when the alcohol contains another functional group that would be adversely affected by the strongly acidic conditions of the HBr reaction. (You’ll learn about such functional groups in later chapters.) Primary alkyl iodides can be prepared with HI, which is usually supplied by mixing an iodide salt such as KI with a strong acid such as phosphoric acid. Thionyl chloride is the method of choice for the preparation of primary alkyl chlorides.