By now it should be apparent that hydroxyl groups are very reactive to many reagents. This is both an advantage and a disadvantage in synthesis. To avoid interference by hydroxyl groups, it often is necessary to protect (or mask) them by conversion to less reactive functions. The general principles of how functional groups are protected were outlined and illustrated in Section 13-9. In the case of alcohols the hydroxyl group may be protected by formation of an ether, an ester, or an acetal.

15-9A Ether Formation

A good protecting group is one that does everything you want it to do when you want it to. It must be easily put into place, stable to the reagents from which protection is required, and easily removed when desired. For this reason simple ethers such as methyl or ethyl ethers usually are not suitable protecting groups because they cannot be removed except under rather drastic conditions (Section 15-10).

More suitable ethers are phenylmethyl and trimethylsilyl ethers:

\[
\begin{align*}
R-O-CH_2-\text{phenyl} & \quad R-O-Si(CH_3)_3 \\
\text{alkyl phenylmethyl ether} & \quad \text{alkyl trimethylsilyl ether}
\end{align*}
\]

Both of these ethers are prepared easily by nucleophilic displacements (Equations 15-7 and 15-8) and can be converted back to the parent alcohol under mild conditions, by catalytic hydrogenation for phenylmethyl ethers (Equation 15-9), or by mild acid hydrolysis for trimethylsilyl ethers (Equation 15-10):

\[
\begin{align*}
\text{ROH} + \text{BrCH}_2-\text{phenyl} & \xrightarrow{\text{AgO}} \text{ROCH}_2-\text{phenyl} \\
\text{ROH} + \text{Cl-Si(CH}_3)_3 & \xrightarrow{\text{pyridine as base}} \text{ROSi(CH}_3)_3 \\
\text{RO-CH}_2-\text{phenyl} & \xrightarrow{\text{H}_2, \text{Pd}} \text{ROH} + \text{CH}_2-\text{phenyl} \\
\text{RO-Si(CH}_3)_3 & \xrightarrow{\text{H}_2O, \text{H}^+} \text{ROH} + \text{HOSi(CH}_3)_3
\end{align*}
\]

15-9B Ester Formation

Esters are formed from the alcohol and acyl halide, anhydride, or acid (Section 15-4D). The alcohol can be regenerated easily by either acid or base hydrolysis of the ester:

\[
\begin{align*}
\text{ROH} + \text{Cl-C=CH}_3 & \xrightarrow{\text{HCl}} \text{RO-C=CH}_3 \\
\text{RO-C=CH}_3 & \xrightarrow{\text{H}_2O, \text{H}^+} \text{ROH} + \text{HOC=CH}_3 \\
\text{ROH} + \text{O-C=CH}_3 & \xrightarrow{\text{OH}, \text{H}_2O}
\end{align*}
\]
15-9C Acetal Formation

We have seen that alcohols can be converted reversibly to acetals under acidic conditions (Section 15-4E). The acetal function is a very suitable protecting group for alcohols under basic conditions, but is not useful under acidic conditions because acetals are not stable to acids:

\[
2 \text{ROH} + \text{CH}_2\text{CHO} \xrightleftharpoons[H^+]{} \text{CH}_3\text{C} = \text{O} + \text{H}_2\text{O}
\]

An excellent reagent to form acetals is the unsaturated cyclic ether, \(16\). This ether adds alcohols in the presence of an acid catalyst to give the acetal \(17\):

\[
\text{ROH} + \begin{array}{c}
\text{H}
\end{array} \text{16} \xrightleftharpoons[H^+]{} \begin{array}{c}
\text{H}
\end{array} \text{17}
\]

The 3-oxacyclohexene (dihydropyran) protecting group can be removed readily by treating the acetal, \(17\), with aqueous acid:

\[
\begin{array}{c}
\text{HO}
\end{array} \text{17} \xrightarrow[H_2\text{O}, H^+]{} \begin{array}{c}
\text{H}
\end{array} \begin{array}{c}
\text{H}
\end{array} + \text{ROH}
\]

An example of the use of \(16\) to protect an \(\text{OH}\) function is given in Section 13-10.

Contributors and Attributions