24-3A From Carboxylic Acids

Formation of amides from carboxylic acid derivatives already has been discussed in some detail (Section 23-9A):

\[
\begin{align*}
\text{R-C} & \quad + \text{HN}R_2 \rightarrow \text{R-C} \quad \text{N}R_2 \\
& \quad + \text{HX}
\end{align*}
\]

\[\text{(24-1)}\]

The ease of formation of amides by the reaction of Equation 24-1 depends a lot on the nature of the leaving group \(\text{HX}\). The characteristics of a good leaving group were discussed in Sections 8-7C and 8-7D in connection with \(S_N\) reactions, and similar considerations apply here. Some idea of the range of acid derivatives used in amide synthesis can be obtained from Table 24-1, which lists various \(\text{RCOX}\) compounds and the p(K_a) values of \(\text{HX}\). As a reasonable rule of thumb, the stronger \(\text{HX}\) is as an acid, the better \(\text{X}\) is as a leaving group.

**Table 24-1: Derivatives and Reactivity of Carboxylic Acids Commonly Used in Amide Formation**

<table>
<thead>
<tr>
<th>X</th>
<th>HX</th>
<th>p(K_a) of HX</th>
<th>Reactivity in amide formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-OH</td>
<td>H(_2)O</td>
<td>16</td>
<td>low*</td>
</tr>
<tr>
<td>-Cl</td>
<td>HCl</td>
<td>-6</td>
<td>good</td>
</tr>
<tr>
<td>-N(_2)H</td>
<td>H(_2)N</td>
<td>3</td>
<td>good</td>
</tr>
<tr>
<td>-OCH(_2)CH(_3)</td>
<td>H(_2)OCH(_2)CH(_3)</td>
<td>16</td>
<td>low</td>
</tr>
<tr>
<td><img src="image1" alt="苯胺" /></td>
<td><img src="image2" alt="苯胺" /></td>
<td>9.69</td>
<td>moderate</td>
</tr>
<tr>
<td><img src="image3" alt="硝基苯胺" /></td>
<td><img src="image4" alt="硝基苯胺" /></td>
<td>7.15</td>
<td>good*</td>
</tr>
<tr>
<td><img src="image5" alt="苯甲酸" /></td>
<td><img src="image6" alt="苯甲酸" /></td>
<td>4.75</td>
<td>moderate</td>
</tr>
<tr>
<td><img src="image7" alt="其它" /></td>
<td><img src="image8" alt="其它" /></td>
<td>-</td>
<td>good*</td>
</tr>
</tbody>
</table>

*At ordinary temperatures, requires activation through a coupling agent (Section 23-9A), but on strong heating can give amide directly.

*Good leaving group because of stabilization of the type.

*Good leaving group; possibly because of associated decomposition to more stable products.

\[\text{R-C} \quad \text{OR} \rightarrow \text{CO}_2 + \text{R-C} \quad \text{OR}\]
Amides generally are formed from acid chlorides, acid azides, acid anhydrides, and esters. It is not practical to prepare them directly from an amine and a carboxylic acid without strong heating or unless the reaction is coupled to a second reaction that "activates" the acid. Notice that esters of phenols are more reactive toward amines than esters of alcohols because phenols are stronger acids than alcohols.

24-3B From Nitriles

The hydrolysis of nitriles is a satisfactory method for preparation of unsubstituted amides and is particularly convenient when hydrolysis is induced under mildly basic conditions by hydrogen peroxide:

\[
\begin{align*}
R\text{-}C\equiv\text{N} & \xrightarrow{\text{strong acid or strong base}} R\text{-}C\equiv\text{O} \\
 & \xrightarrow{\text{dilute base}} R\text{-}C\equiv\text{N} + \text{H}_2\text{O} \quad \text{or} \\
 & \xrightarrow{\text{dilute base}} R\text{-}C\equiv\text{N} + \text{H}_2\text{O}_2
\end{align*}
\]

For the preparation of amides of the type \(\text{RCOR}_{3}\), which have a tertiary alkyl group bonded to nitrogen, the Ritter reaction of an alcohol or alkene with a nitrile or hydrogen cyanide is highly advantageous. This reaction involves formation of a carbocation by action of strong sulfuric acid on an alkene or an alcohol (Equation 24-2), combination of the carbocation with the unshared electrons on nitrogen of \(\text{RCN}\) (Equation 24-3), and then addition of water (Equation 24-4). We use here the preparation of an \(\text{N-}\text{tert}-\text{butylalkanamide}\) as an example; \(\text{RC\equiv N}\) can be an alkyl cyanide such as ethanenitrile or hydrogen cyanide itself:

\[
\begin{align*}
\text{CH}_3\text{-C\equiv O} & \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_3\text{-C\equiv O} \\
& \xrightarrow{\text{H}_2\text{O}_2} \text{CH}_3\text{-C\equiv O} \\
& \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{-C\equiv O} \\
& \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{-C\equiv O} + \text{H}_2\text{O} \quad \text{a nitrilium ion}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{-C\equiv O} + \text{N\equiv CR} & \xrightarrow{\text{C\equiv N\equiv CR}} \text{CH}_3\text{-C\equiv N\equiv CR} \\
& \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{-C\equiv N\equiv CR} + \text{H}_2\text{O} \\
& \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{-C\equiv N\equiv CR} + \text{H}_2\text{O} \\
& \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{-C\equiv N\equiv CR} + \text{H}_2\text{O}
\end{align*}
\]
This reaction also is useful for the preparation of primary amines by hydrolysis of the amide. It is one of the relatively few practical methods for synthesizing amines with a tertiary alkyl group on the nitrogen:

\[
\begin{align*}
\text{CH}_3\text{C}^\text{\equiv}\text{N}-\text{C}^-\text{R} + \text{H}_2\text{O} & \xrightarrow{\text{H}^+ \text{ or } \text{OH}^- \text{ (reflux)}} \text{CH}_3\text{NH}_2 + \text{HO}^-\text{C}^-\text{R} \\
\end{align*}
\]

### 24-3C The Beckmann Rearrangement of Oximes

You may recall that ketones react with \(\text{RNH}_2\) compounds to give products with a double bond to nitrogen, \(\text{-C=NR}\) (Section 16-4C). When the \(\text{RNH}_2\) compound is azanol (hydroxylamine), \(\text{HO-NH}_2\), the product is called a **ketoxime**, or oxime:

![Oxime of cyclohexanone](image)

Oximes rearrange when heated with a strong acid, and this reaction provides a useful synthesis of amides:

\[
\begin{align*}
\text{CH}_3\text{C}^\text{\equiv}\text{N}-\text{OH} + \text{H}_2\text{O} & \xrightarrow{\text{H}^+} \text{CH}_3\text{C}^\text{\equiv}\text{N}\text{CH}_3 \\
\end{align*}
\]

Oximes rearrange when heated with a strong acid, and this reaction provides a useful synthesis of amides:

\[
\begin{align*}
\text{CH}_3\text{C}^\text{\equiv}\text{N}-\text{OH} & \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_3\text{C}^\text{\equiv}\text{N}\text{CH}_3 \\
\end{align*}
\]

This intriguing reaction is known as the **Beckmann rearrangement**. It has been the subject of a number of mechanistic studies that have shown the acid or acid halide (\(\text{PCl}_3\), \(\text{C}_6\text{H}_5\text{SO}_2\text{Cl}\)) makes the hydroxyl group on nitrogen into a better leaving group by forming \(\text{-OH}_2^+\) or ester intermediates:

\[
\begin{align*}
\text{R}^'\text{C}^\text{\equiv}\text{N}\text{OH} & \xrightarrow{\text{H}_2\text{SO}_4} \text{R}^'\text{C}^\text{\equiv}\text{N} \quad \text{or} \\
\text{R}^'\text{C}^\text{\equiv}\text{N}\text{OH} & \xrightarrow{\text{C}_6\text{H}_5\text{SO}_2\text{Cl}} \text{R}^'\text{C}^\text{\equiv}\text{N} \\
\end{align*}
\]

Thereafter, a rearrangement occurs resembling the reactions of carbocations (Sections 8-9B and 15-5E). When the cleavage of the \(\text{-OH}_2^+\) bond occurs, the nitrogen atom would be left with only six valence electrons. However, as the bond breaks, a substituent \(\text{R}\) on the neighboring carbon moves with its bonding electron pair to the developing positive nitrogen (Equation 24-5):
Oximes with \(\ce{R}\) and \(\ce{R'}\) as different groups exist as \(E\) and \(Z\) isomers (Section 19-7) and you will notice in Equation 24-5 that the group that migrates is the one that is \textit{trans} to the leaving group. To some extent the Beckmann rearrangement is an internal \(S_\text{N}2\) reaction with inversion at the nitrogen. Section 21-10F gives a theoretical treatment of this kind of reaction. The rearrangement product is a nitrilium ion, as in the Ritter reaction (Section 24-3B), which adds water to form the amide.

The synthesis of aza-2-cycloheptanone (\(\varepsilon\)-caprolactam) by the Beckmann rearrangement of the oxime of cyclohexanone is of commercial importance because the lactam is an intermediate in the synthesis of a type of nylon (a polyamide called "nylon-6"\(^2\)):

The number 6 specifies the number of carbons in each monomer unit comprising the polyamide structure. By this code, nylon-6,6 is \(\ce{(-NH(CH_2)_6NHCO(CH_2)_4CO-)}_n\).

**Contributors**