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

\[
\ce{RCOX + HNR_2 \rightarrow RCONHR_2 + HX}
\]

The ease of formation of amides by the reaction of Equation 24-1 depends a lot on the nature of the leaving group \(\ce{HX}\). The characteristics of a good leaving group were discussed in Sections 8-7C and 8-7D in connection with \(\ce{S_N}\) 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 \(\ce{RCOX}\) compounds and the pK\(_a\) values of \(\ce{HX}\). As a reasonable rule of thumb, the stronger \(\ce{HX}\) is as an acid, the better \(\ce{X}\) is as a leaving group.

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

<table>
<thead>
<tr>
<th>(\ce{RCOX})</th>
<th>(\ce{HX})</th>
<th>pK(_a) of (\ce{HX})</th>
<th>Reactivity in amide formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\ce{OH})</td>
<td>(\ce{H_2O})</td>
<td>16</td>
<td>low*</td>
</tr>
<tr>
<td>(\ce{Cl})</td>
<td>(\ce{HCl})</td>
<td>–6</td>
<td>good</td>
</tr>
<tr>
<td>(\ce{N_3})</td>
<td>(\ce{HN_3})</td>
<td>2</td>
<td>good</td>
</tr>
<tr>
<td>(\ce{OCH_3})</td>
<td>(\ce{HOC_3_CH_3})</td>
<td>16</td>
<td>low</td>
</tr>
<tr>
<td>(\ce{C_6H_5})</td>
<td>(\ce{HOC_6_H_5})</td>
<td>9.99</td>
<td>moderate</td>
</tr>
<tr>
<td>(\ce{C_6H_5NO_2})</td>
<td>(\ce{HOC_6_H_5NO_2})</td>
<td>7.15</td>
<td>good*</td>
</tr>
<tr>
<td>(\ce{C_6_H_5-CH_3})</td>
<td>(\ce{HOC_6_H_5-CH_3})</td>
<td>4.75</td>
<td>moderate</td>
</tr>
<tr>
<td>(\ce{C_6_H_5-O R^*})</td>
<td>–</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.

\[
\ce{CO_2 + OR^* \rightarrow CO_2 + OR^*}
\]
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:

For the preparation of amides of the type \(\ce{R_3CNHCOR}\), 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 \(\ce{RCN}\) (Equation 24-3), and then addition of water (Equation 24-4). We use here the preparation of an \(\ce{N-}\)tert-butylalkanamide as an example; \(\ce{RC \equiv N}\) can be an alkyl cyanide such as ethanenitrile or hydrogen cyanide itself:
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:

\[
\begin{align*}
\text{CH}_3\text{C} & \text{CH}_3
\begin{array}{c}
\text{O} \\
\text{H}_2\text{O} \\
\text{H}^- \text{ or } \text{OH}^-
\end{array}
\xrightarrow{\text{(reflux)}}
\text{CH}_3\text{C} & \text{CH}_3
\begin{array}{c}
\text{O} \\
\text{H}_2\text{O} \\
\text{H}^- \text{ or } \text{OH}^-
\end{array}
\end{align*}
\]

\[\text{CH}_3\text{C} \equiv \text{NH} \quad \text{or} \quad \text{CH}_3\text{C} \equiv \text{NH} + \text{H}_2\text{O} \quad \text{reacting group}
\]

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, \(\text{C}=\text{NR}\) (Section 16-4C). When the \(\text{RNH}_2\) compound is azanol (hydroxylamine), \(\text{HO-NH}_2\), the product is called a ketoxime, or oxime:

\[
\begin{align*}
\text{oxime of cyclohexanone}
\end{align*}
\]

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

\[
\begin{align*}
\text{CH}_3 \quad \text{OH} \\
\text{C} = \text{N} \\
\text{CH}_3
\end{align*}
\xrightarrow{\text{H}_2\text{SO}_4}
\begin{align*}
\text{CH}_3 \quad \text{O} \\
\text{C} \equiv \text{N} \\
\text{CH}_3
\end{align*}
\]

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:

\[
\begin{align*}
\text{R}^' \quad \text{OH} \\
\text{C} = \text{N} \\
\text{R}
\end{align*}
\xrightarrow{\text{H}_2\text{SO}_4}
\begin{align*}
\text{R}^' \quad \text{OH}_2 \quad \text{R}^' \\
\text{C} = \text{N} \\
\text{R}
\end{align*}
\]

\[
\begin{align*}
\text{R} \quad \text{OH} \\
\text{C} = \text{N} \\
\text{R}
\end{align*}
\xrightarrow{\text{C}_6\text{H}_5\text{SO}_2\text{Cl}}
\begin{align*}
\text{R} \quad \text{O-SO}_2\text{C}_6\text{H}_5 \\
\text{C} = \text{N} \\
\text{R}
\end{align*}
\]

Thereafter, a rearrangement occurs resembling the reactions of carbocations (Sections 8-9B and 15-5E). When the cleavage of the \(\text{N-O}\) 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 \(\text{E}\) and \(\text{Z}\) isomers (Section 19-7) and you will notice in Equation 24-5 that the group that migrates is the one that is trans to the leaving group. To some extent the Beckmann rearrangement is an internal \(\text{SN}_2\) 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 (\(\text{\varepsilon}-\text{caprolactam}\)) 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"\(^2\)):

\(^2\)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