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

\[
\ce{R-CO + HNR_2 -> R-CONR_2 + HX}
\]

The ease of formation of amides by the reaction of Equation 24-1 depends a lot on the nature of the leaving group \(\text{HX}\). The characteristics of a good leaving group were discussed in Sections 8-7C and 8-7D in connection with \(S_{\text{N}}\) 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>(-\text{OH})</td>
<td>HCH</td>
<td>16</td>
<td>low*</td>
</tr>
<tr>
<td>(-\text{Cl})</td>
<td>HCl</td>
<td>-6</td>
<td>good</td>
</tr>
<tr>
<td>(-\text{N}_3)</td>
<td>HN_3</td>
<td>3</td>
<td>good</td>
</tr>
<tr>
<td>(-\text{OCH}_3\text{CH}_3)</td>
<td>HOC_3_CH_3</td>
<td>16</td>
<td>low</td>
</tr>
<tr>
<td>(-\text{O-C-N})</td>
<td>(\text{HO-C-N})</td>
<td>9.69</td>
<td>moderate</td>
</tr>
<tr>
<td>(-\text{O-C-NOO})</td>
<td>(\text{HO-C-NOO})</td>
<td>7.15</td>
<td>good*</td>
</tr>
<tr>
<td>(-\text{O-C-CH}_3)</td>
<td>(\text{HO-C-CH}_3)</td>
<td>4.75</td>
<td>moderate</td>
</tr>
<tr>
<td>(-\text{O-C-OR}^*)</td>
<td>–</td>
<td>–</td>
<td>good*</td>
</tr>
</tbody>
</table>

*At ordinary temperatures, requires activation through a coupling agent (Section 23-5A), but on strong heating can give amide directly.

*Good leaving group because of stabilization of the type

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N}
\end{align*}
\]

etc.

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

\[
\text{O} \quad \text{CO}_2 + \text{OR}
\]

*Good leaving group.
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:

\[
\begin{align*}
\text{R} & \text{C} = \text{N} \\
\text{H}_2\text{O} & \begin{cases}
\text{strong acid or} \\
\text{strong base}
\end{cases} \\
\text{H}_2\text{O}, \text{H}_2\text{O}_2 & \begin{cases}
\text{dilute base}
\end{cases}
\end{align*}
\]

For the preparation of amides of the type \(\text{R}_3\text{CNHCOR}\), 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 \(\text{N}\) -tert-butylalkanamide as an example; \(\text{RC \equiv N}\) 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:

![Chemical reaction diagram]

24-3C The Beckmann Rearrangement of Oximes

You may recall that ketones react with \(\ce{RNH_2}\) compounds to give products with a double bond to nitrogen, \(\ce{-C=NR}\) (Section 16-4C). When the \(\ce{RNH_2}\) compound is azanol (hydroxylamine), \(\ce{HO-NH_2}\), the product is called a ketoxime, or oxime:

![Oxime reaction diagram]

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

![Amide synthesis diagram]

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 (\(\ce{PCl_3}\), \(\ce{C_6H_5SO_2Cl}\)) makes the hydroxyl group on nitrogen into a better leaving group by forming \(\ce{-OH^+}\) or ester intermediates:

![Beckmann rearrangement diagram]

Thereafter, a rearrangement occurs resembling the reactions of carbocations (Sections 8-9B and 15-5E). When the cleavage of the \(\ce{-N-O}\) bond occurs, the nitrogen atom would be left with only six valence electrons. However, as the bond breaks, a substituent \(\ce{R}\) on the neighboring carbon moves with its bonding electron pair to the developing positive nitrogen (Equation 24-5):
Oximes with \(\text{R}\) and \(\text{R'}\) 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"\(^2\)):

\(^2\)The number 6 specifies the number of carbons in each monomer unit comprising the polyamide structure. By this code, nylon-6,6 is \(\text{(-NH(CH}_2\text{)}_6\text{NHCO(CH}_2\text{)}_4\text{CO-)}_n\).

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**Contributors**