Last time: reaction of amides

The acid protonates the carbonyl oxygen.

The nucleophile attacks the carbonyl carbon.

Tetrahedral intermediate I:

Either NH$_2$ or OH can be protonated.

Tetrahedral intermediate II:

The weaker base is expelled.

Tetrahedral intermediate III:
Application to amine synthesis:

\[ \text{RCH}_2\text{Br} \xrightarrow{\text{Gabriel synthesis}} \text{RCH}_2\text{NH}_2 \]

**alkyl halide**

**primary amine**

**phthalamide**

**an \( N \)-substituted phthalamide**

\[ \text{HCl, H}_2\text{O} \xrightarrow{\Delta} \]

**phthalic acid**

**primary alkyl ammonium ion**
Dehydration reaction of a primary amide produce a nitrile:

$$\text{CH}_3\text{CH}_2\text{C}==\text{N}$$
1. A nitrile can be prepared from an $S_{N2}$ reaction
2. A nitrile can be converted to a carboxylic acid with $\text{H}_2\text{O}$ and $\text{H}^+$. 

\[ \text{CH}_3\text{CH}_2\text{Br} \overset{\text{C} \equiv \text{N}}{\underset{\text{DMF}}{\xrightarrow{\text{an } S_{N2} \text{ reaction}}}} \text{CH}_3\text{CH}_2\text{C} \equiv \text{N} \overset{\text{HCl, H}_2\text{O}}{\underset{\Delta}{\xrightarrow{\text{a caboxylic acid}}}} \text{CH}_3\text{CH}_2\text{CO}_2\text{H} \]
Mechanism for the hydrolysis of a nitrile

\[ R-C\equiv N: + H_2O \rightarrow R-C\equiv NH + H_2O: \]

- Oxygen loses a proton
- Nitrogen gains a proton
- Resonance contributors for a protonated amide
- A carboxylic acid

(several steps)
• A nitrile can easily be converted to an amine via hydrogenation reaction

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C}≡\text{N} \xrightarrow{\text{H}_2/\text{Pt/C}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2
\]

pentanenitrile \hspace{1cm} pentylamine
Reactions of carboxylic acids:

\[
\text{CH}_3\text{C}(-\text{OH})\text{CH}_3 + \text{CH}_3\text{CH}_2\text{NH}_2 \rightarrow \text{CH}_3\text{C}(-\text{O}^-\text{H}_3\text{NCH}_2\text{CH}_3)\text{CH}_3
\]

an ammonium carboxylate salt

\[
\text{CH}_3\text{CH}_2\text{C}(-\text{OH})\text{CH}_3 + \text{NH}_3 \rightarrow \text{CH}_3\text{CH}_2\text{C}(-\text{O}^-\text{NH}_4)\text{CH}_3
\]

relative reactivities toward nucleophilic acyl substitution

most reactive: \( R\text{C}(-\text{OH})\text{R} \rangle \text{R}\text{C}(-\text{NH}_2)\text{R} \rangle \text{R}\text{C}(-\text{O}^-)\text{R} \) least reactive
Nucleophilic acyl substitutions of carboxylic acids:
Preparation of cyclic esters:

\[
\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COH} \xrightarrow{\text{HCl}} \text{cyclic ester with four intervening carbon atoms}
\]

\[
\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COH} \xrightarrow{\text{HCl}} \text{cyclic ester with three intervening carbon atoms}
\]
Converting carboxylic acids to carbonyl halides

$$\text{CH}_3\text{C} = \text{OH} + \text{SOCl}_2 \overset{\Delta}{\rightarrow} \text{CH}_3\text{C}l + \text{SO}_2 + \text{HCl}$$

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{C} = \text{OH} + \text{PCl}_3 \overset{\Delta}{\rightarrow} \text{CH}_3\text{CH}_2\text{CH}_2\text{C}l + \text{H}_3\text{PO}_3$$

$$\text{C} = \text{OH} + \text{PBr}_3 \overset{\Delta}{\rightarrow} \text{C} = \text{Br} + \text{H}_3\text{PO}_3$$
good leaving groups

a better leaving group than a chloride ion
Expression for a multi-step reaction:

Step 1:

\[ \text{Step 1: } \text{SOCl}_2 \rightarrow \text{?} \]

Step 2:

\[ \text{Step 2: } \text{CH}_3\text{OH} \rightarrow \text{?} \]
Reaction: carboxylic acids $\rightarrow$ acid anhydride
Activation of carboxylic acids by cells

\[ \text{R-COO}^- + \text{P-O-P-O-P-O-P-Ad} \xrightarrow{\text{enzyme}} \text{R-C-PO}_4^- + \text{P-O-P-O-P-Ad} \]

\[ \text{R-COO}^- + \text{P-O-P-O-P-O-P-Ad} \xrightarrow{\text{enzyme}} \text{R-C-PO}_4^- + \text{P-O-Ad} \]

\[ \text{R-COO}^- + \text{P-O-P-O-P-O-P-Ad} \xrightarrow{\text{enzyme}} \text{R-C-PO}_4^- + \text{P-O-Ad} \]

\[ \text{CH}_3\text{COO}^- + \text{P-O-P-O-P-O-P-Ad} \xrightarrow{\text{enzyme}} \text{CH}_3\text{C-PO}_4^- + \text{P-O-Ad} \]

\[ \text{CH}_3\text{COO}^- + \text{P-O-P-O-P-O-P-Ad} \xrightarrow{\text{CoASH}} \text{CH}_3\text{C-S-CoA} + \text{AMP} \]

acetyl-CoA
Bioactivation of Acetate

The $\text{^\text{-SCoA}}$ leaving group is highly functionalized so that acetyl transfer does not occur randomly.
Thioester is more reactive than ester:

- Electron-delocalization is weaker when Y=S:

- RS\(^{-}\) is a weaker base & better leaving group

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{SH} & \quad \text{pK}_a = 10.5 \\
\text{CH}_3\text{CH}_2\text{OH} & \quad \text{pK}_a = 15.9
\end{align*}
\]
Quiz #1

Show the reaction mechanism for:

\[
\text{acetaminophen (Tylenol)}
\]
Chapter 18
Carbonyl Compounds II

Reactions of Aldehydes and Ketones
More Reactions of Carboxylic Acid Derivatives
Reactions of $\alpha,\beta$-Unsaturated Carbonyl Compounds
Aldehydes and ketones

formaldehyde

an aldehyde

a ketone
Nomenclature of aldehydes

**Note:** important common name - formaldehyde
Nomenclature of aldehydes

systematic name: \textit{trans}-2-methylcyclohexanecarbaldehyde

benzenecarbaldehyde
Nomenclature of ketones

systematic name: propanone  
common name: acetone  
derived name: dimethyl ketone

3-hexanone  
ethyl propyl ketone  
6-methyl-2-heptanone  
isoheptyl methyl ketone

Note: important common name - acetone
Nomenclature of ketones

The carbonyl is assumed to be at the 1-position in cyclic ketones.
Nomenclature of ketones

Systematic name: 1-phenylethanone (acetophenone)  1-phenyl-1-butanone  diphenylmethanone (benzophenone)
If a compound has more than one functional group, the one(s) with the lower priority is indicated by its prefix:

<table>
<thead>
<tr>
<th>Class</th>
<th>Suffix name</th>
<th>Prefix name</th>
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<tbody>
<tr>
<td>Carboxylic acid</td>
<td>-oic acid</td>
<td>Carboxy</td>
</tr>
<tr>
<td>Ester</td>
<td>-oate</td>
<td>Alkoxy/alkoxycarbonyl</td>
</tr>
<tr>
<td>Amide</td>
<td>-amide</td>
<td>Amido</td>
</tr>
<tr>
<td>Nitrile</td>
<td>-nitrile</td>
<td>Cyano</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>-al</td>
<td>Oxo (=O)</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>-al</td>
<td>Formyl (CH=O)</td>
</tr>
<tr>
<td>Ketone</td>
<td>-one</td>
<td>Oxo (=O)</td>
</tr>
<tr>
<td>Alcohol</td>
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<td>Hydroxy</td>
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<tr>
<td>Alkyl halide</td>
<td>—</td>
<td>Halo</td>
</tr>
</tbody>
</table>

Table 18.1 Summary of Functional Group Nomenclature