We learned how to make a lot of carboxylic acid derivatives from acids in Ch. 20, but now we'll learn what reactions we can do with those derivatives. As a reminder, here are the relative stability rankings:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid chloride</td>
<td>Least stable</td>
</tr>
<tr>
<td>Anhydride</td>
<td>Most stable</td>
</tr>
<tr>
<td>Aldehyde</td>
<td></td>
</tr>
<tr>
<td>Ketone</td>
<td></td>
</tr>
<tr>
<td>Carboxylic acid</td>
<td></td>
</tr>
<tr>
<td>Ester</td>
<td></td>
</tr>
<tr>
<td>Amide</td>
<td></td>
</tr>
<tr>
<td>Nitrile</td>
<td></td>
</tr>
</tbody>
</table>

**Nomenclature**

Cyclic esters and amides are called lactones and lactams respectively. These groups do just the same chemistry as a normal ester or amide, though rings smaller than five or larger than six are often too unstable to form easily.

- **Lactones**
- **Lactams**

Esters are named similarly to carboxylate salts. The alkyl group attached to the oxygen is named first, then the carboxylate name. If the groups have their own substituents, these are listed as usual under IUPAC.

- **Methyl propanoate**
- **Ethyl ethanoate**
- **Ethyl benzoate**
- **Ethyl 2-bromobenzoate**

Acid halides are named by replacing “ic acid” from the parent name with “yl chloride”.

Anhydrides are named by replacing “ic acid” with “ic anhydride”.

- **Propanoyl chloride**
- **Benzoyl chloride**
- **Acetic anhydride**

Amides are named by replacing “oic acid” from the parent name with “amide”. If there are any R groups on the nitrogen, these are named but their location is given as “N”.

- **Propanamide**
- **N-Cyclohexylbenzamide**
- **N,N-dimethylformamide**
  (DMF, a solvent)

Imides are a subset of amines with two acyl groups attached to the same nitrogen. These are mostly named after the diacids they're usually made from.

- **Phthalimide**
- **Phthalic acid**
**Loudon Chapter 21 Review: Carboxylic Acid Derivatives**

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**Hydrolysis of derivatives**

Any of the derivatives of carboxylic acids can be converted back into the acid by using water. If it’s a more stable derivative, you also need either acid or base as a catalyst. The more stable the derivative is, the more powerful conditions you need to make it break up – higher temperatures and more concentrated acid/base.

The mechanism varies slightly depending on which derivative you’re hydrolyzing and whether you’re in acid or base. Kind of like in Ch. 19, if you’re in acid you’ll protonate the carbonyl first to make it more attackable. You’ll also protonate the leaving group, to make it drop off more easily. The mechanism is identical for esters and amides.

![Acid-catalyzed ester hydrolysis](image1)

In base, you just go ahead and attack with OH⁻, because you can’t protonate the carbonyl first. Since the product is a carboxylic acid, it immediately gets deprotonated by the base. Another name for base-catalyzed ester hydrolysis is saponification, since that’s how soap is made. There is a difference here between ester and amide mechanisms: OR is a much better leaving group than NR₂⁻ (the pKas are ~16 and ~35, respectively).

![Base-catalyzed ester hydrolysis](image2)

If you’re hydrolyzing a nitrile, the mechanism is longer. It breaks down into three sections: adding water to make an imidic acid, rearranging to an amide, and hydrolyzing the amide.

The first part looks a lot like addition to a carbonyl, just you’re attacking a triple bond to N instead of a double bond to O. In acid, you have to protonate the nitrogen first.

![Acid-catalyzed nitrile hydrolysis](image3)

Both of these reactions finish up by hydrolyzing the amide, via the mechanism shown above (either in acid or base).
Note that the rearrangement steps going from the imidic acid to the amide look a lot like the keto-enol tautomerization.

The two reactive derivatives, acid chlorides and anhydrides, don’t need a catalyst. They react with water on their own, within minutes. This is not something you’d do on purpose, it’s just something that happens if you don’t keep them away from water or humidity.

Starting from here, I won’t show any mechanisms if they follow the same general pattern shown above. You can figure out the exact details based on conditions.

Reactions with acid chlorides

Being the most reactive derivative, acid chlorides will easily convert to pretty much any other derivative if you combine it with the right reagents. To make an amide, combine it with an amine.

\[
\text{RCOCl} + \text{HNR}_2 \rightarrow \text{RCONR}_2 + \text{HCl (reacts with another molecule of HNR}_2)\]

The problem is that in these reactions, you generate a molecule of HCl. This is not a problem in most cases, but if you’re using amines then HCl will add to it, and make that amine incapable of doing the reaction. If you use equal amounts of acid chloride and amine, the reaction will only go halfway because half the amine gets acidified. There are two ways around this: either use twice as much amine, or throw in one equivalent of some sacrificial amine, usually pyridine or triethylamine, that can soak up HCl but won’t make an amide itself. The overall balanced reactions that give you decent yield are:

\[
\text{RCOCl} + 2\text{HNR}_2 \rightarrow \text{RCO-NR}_2 + \text{HCl} \]

To make an ester from an acid chloride, you just need to react it with an alcohol. Only one equivalent is required, but you still need to add some weak base like pyridine to neutralize the HCl.

\[
\text{RCOCl} + \text{ROH} \rightarrow \text{RCO-OR} + \text{HCl}\]

To make an anhydride from an acid chloride, you need to react it with the deprotonated carboxylic acid, known as the carboxylate (usually with a sodium counterion). The acid itself is not strong enough to attack the chloride, but the carboxylate is. This gives NaCl as a byproduct, rather than HCl, so no base is required.

\[
\text{RCOCl} + \text{R'O}^- + \text{Na}^+ \rightarrow \text{RCO-OR} + \text{NaCl}\]

This is a pretty useful reaction for making asymmetric anhydrides, with two different R groups on them. The methods we saw before only give us symmetric anhydrides.

Reactions with anhydrides
Again, as a reactive derivative it’s easy to turn this into other, more stable derivatives. You don’t even need a base like you did with acid chlorides, since you’re not producing HCl as a byproduct.

Reactions with esters
This is more difficult because esters are pretty stable. You can still convert them to other compounds though. If you react an ester with an amine, you can get an amide. If you react an ester with a different alcohol, you get a different ester – this is called transesterification.

Making amides from acids
This is not a reaction we can do easily, because if you combine an acid and an amine they’re much more likely to do acid-base chemistry first.

You can sort of fix this by heating them up to several hundred degrees, but there are better ways of making amides. Usually, you make them from acid chlorides instead.

Reductions
We saw in Ch. 20 that acids can be reduced with LiAlH₄, and we can do the same with esters. LAH will break up the ester group entirely, so you end up with two alcohol molecules, one from each half of the ester.

Amides are the odd one out in this category. Rather than reducing to an alcohol, they actually choose to drop the carbonyl oxygen entirely and keep the nitrogen – this is because oxygen is a better leaving group than nitrogen, since it’s more electronegative.

The OH⁻ is necessary because otherwise you would end up with a protonated version of the product instead. You can also reduce nitriles to primary amines. Again, you need to finish up with OH⁻ so the amine is neutral.

Another exception to this general pattern is reduction of acid chlorides. In this case, we can stop at the “two bonds to more electronegative atoms” oxidation state. You have to use an acid chloride and hydrogenate it with a poisoned catalyst (similar to the Lindlar catalyst we used for alkynes), consisting of Pd/C, quinoline, and sulfur. This is called Rosenmund
reduction. Alternatively, you can use LiAlH(OtBu)_3, otherwise known as lithium tri(tert-butoxy)aluminum hydride. This is a weaker version of LiAlH_4.

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2 \quad \text{Pd/C} \quad \text{O} \\
\text{O} & \quad \text{Pd/C} \quad \text{O} \\
\text{H} & \quad \text{1)} \text{LiAlH(OtBu)}_3 \\
\text{Cl} & \quad \text{2)} \text{H}_3\text{O}^+ \\
\end{align*}
\]

The reason you can get away with both these reactions is because unlike most of the reductions above, acid chlorides are more reactive than the aldehydes they make. A sufficiently weak reducing agent can react with the acid chloride but it can’t react on the aldehyde that gets produced.

**Reactions with Organometallics**

There are two useful reactions that you can do with organometallics: esters plus Grignards/organolithiums, or acid chlorides plus cuprates. Esters will react twice with organometallics. The first time looks just like a Grignard attacking an aldehyde that we saw in Ch. 19, but the biggest difference is that you can kick out a leaving group after this happens. This gives you a ketone which can react with a second equivalent of organometallic.

\[
\begin{align*}
\text{O} & \quad \text{OR} \quad \text{R} \\
\text{R-MgBr} & \quad \text{O} \quad \text{OR} \\
\text{R-MgBr} & \quad \text{H}_2\text{O}^+ \quad \text{R} \quad \text{OR} \\
\end{align*}
\]

Just as we saw in the reductions section, acid chlorides are more reactive than aldehydes or ketones. This means that if we use a weak enough organometallic like a cuprate, we can add just once without risking a second addition.

**Ch. 21 Synthesis Practice**

Here’s a practice problem.

\[
\begin{align*}
\text{CH}_3\text{OH} & \quad \rightarrow \quad \text{CH}_3\text{N} \\
\end{align*}
\]

At some point we’ll need to make a carbon-nitrogen bond. This can best be done by making an amide, but we need to get the carboxylic acid first. Then we can convert to the acid chloride, then the amide.

\[
\begin{align*}
\text{OH} & \quad \text{Jones} \quad \text{O} \\
\text{CO} & \quad \text{SOCl}_2 \\
\text{Cl} & \quad \text{HNMe}_2, \text{pyridine} \\
\text{N} & \quad \text{Cl} \\
\end{align*}
\]

Now we need to get rid of the carbonyl, which can be done with LAH.

\[
\begin{align*}
\text{N} & \quad \text{1)} \text{LiAlH}_4 \\
\text{OH} & \quad \text{2)} \text{H}_3\text{O}^+ \\
\text{OH} & \quad \text{3)} \text{OH}^- \\
\end{align*}
\]