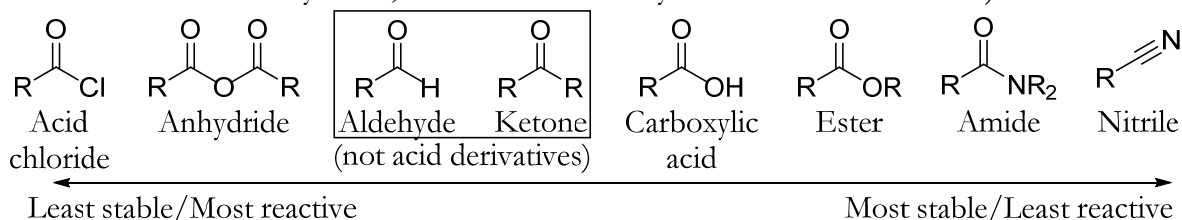# Loudon Chapter 20 Review: Carboxylic Acids
**Jacquie Richardson, CU Boulder – Last updated 11/3/2021**

Ch. 20 & 21 cover compounds which are all at the "three bonds to more electronegative atoms" oxidation state. They're called carboxylic acid derivatives, because they all have a carboxylic acid as the parent compound. If you want to make any of them, you often have to go through the acid form first, although there are cases where you can go directly from one derivative to another.

You can rank them by stability based on the size of the partial positive charge at the carbon. Acyl chlorides have the biggest delta positive and nitriles have the smallest. Aldehydes and ketones are included for comparison – they're less reactive than acid chlorides and anhydrides, but more than everything else. This means that the diols you used to make acetal protecting groups from Ch. 19 will add to aldehydes/ketones but not acids. (They'll also react with acids and anhydrides, but in a different way – we'll see this in Ch. 21.)

Acid chloride	Anhydride	Aldehyde Ketone (not acid derivatives)	Carboxylic acid	Ester	Amide	Nitrile

Least stable/Most reactive   Most stable/Least reactive

Similar to the last chapter, the size of the partial positive charge is dictated by how much stabilization the carbonyl carbon is receiving from the other atoms attached to it. Chlorine is electronegative enough that it's electron-withdrawing overall, and increases the size of the positive charge. Oxygen is electron-donating overall, unless it's sharing with two carboxylic acid groups, like in an anhydride. Nitrogen is even more electron-donating.
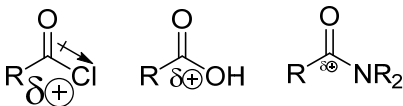

Nomenclature
Acid nomenclature is very similar to aldehydes: they're named by taking the parent chain name (based on the total number of carbons, including the one in the acid group), dropping the "e" and adding "oic acid". The acid carbon is at position one, and other substituents can be named as necessary. If there is an acid group at each end, the "e" is kept and "dioic acid" is added.
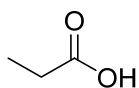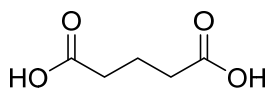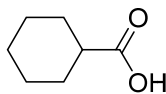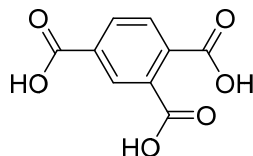
   Propanoic acid   Pentanedioic acid

If there's no way to include the acid as part of the parent chain, it may still be possible to have a COOH group attached to the parent. In this case, add "carboxylic acid" to the end of the parent name.
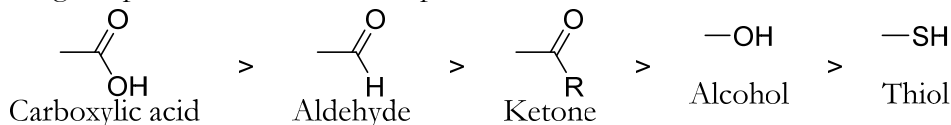
   Cyclohexanecarboxylic acid   1,2,4-Benzenetricarboxylic acid
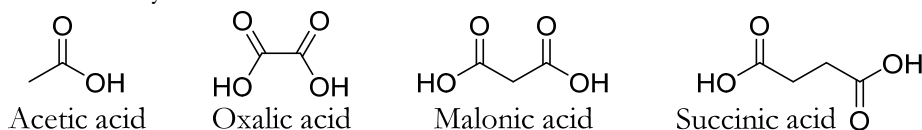
For choosing the parent chain in the first place, acids outrank all the other FGs we've seen.

Carboxylic acid	>	Aldehyde	>	Ketone	>	Alcohol	>	Thiol

There are a few nonsystematic names to be aware of here.

Acetic acid   Oxalic acid   Malonic acid   Succinic acid

(Oxalic, malonic and succinic are the first three unsaturated linear dicarboxylic acids. You can remember them with the mnemonic "Oh My, Such Good Apple Pie, Sweet As Sugar!")

Acidity of Carboxylic Groups

Carboxylic acids are acidic because they can easily use resonance to stabilize the negative charge after they lose a proton. Another factor that contributes is the large partial positive charge on the carbonyl carbon, which stabilizes the anion.
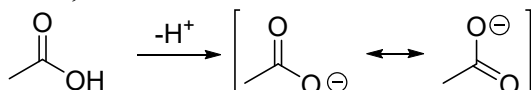
Most carboxylic acids have pKas in the 4-5 range, though they can be higher or lower if there is a group elsewhere in the molecule that stabilizes or destabilizes the charge.

pKa = 4.76   pKa = 0.23   pKa = 10.33
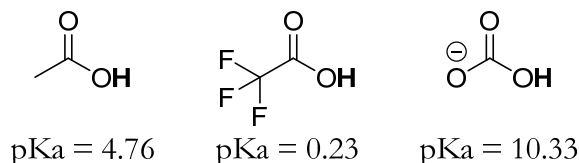
Sulfonic acids are even more acidic because they have three possible resonance forms, and also a bigger partial positive charge on sulfur. They usually have pKas around -3. These are compounds that we saw how to make by sulfonation reactions in Ch. 16.
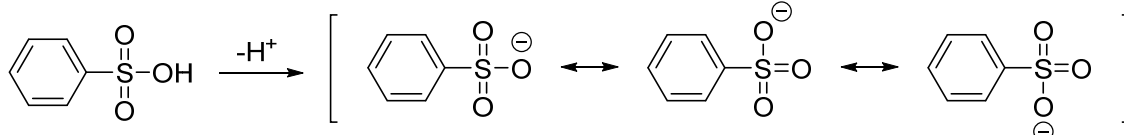
Deprotonated carboxylic acids are called carboxylates. These are commonly used as soaps, especially if they have long alkyl chains, because the polar "head" is soluble in water and the nonpolar "tail" is soluble in grease. This allows them to break the grease into micelles, which can be carried away by water more easily.

Sodium decanoate   Grease droplet   Micelle
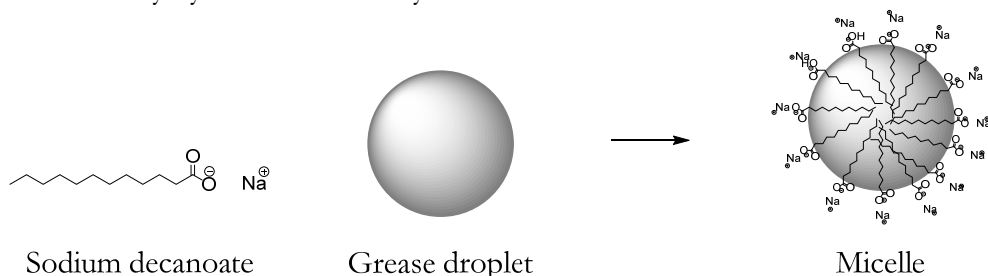
Making carboxylic acids
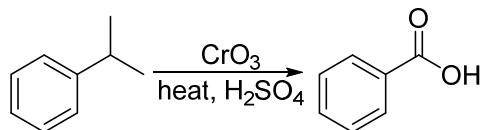
1) Oxidation of primary alcohols and aldehydes: This normally uses something like Jones conditions. We've seen this in Ch. 10 and 19.
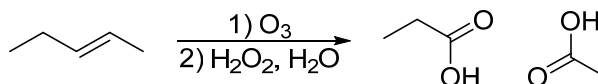
2) Oxidation at the benzylic position: This uses an oxidizer like CrO_3, but in vigorous conditions (usually acid and heat.) This was in Ch. 17.

3) Ozonolysis: This is less useful because you have to break carbon-carbon bonds to do it. This is from Ch. 5.

4) Grignards attacking CO_2: This is a new one in Ch. 20, but it's similar to something we saw before. Ch. 19 shows how to use a Grignard to attack a carbonyl. We can do the same thing by attacking carbon dioxide, which is kind of like a "double carbonyl". Then, we just finish it off the same way, with an acid workup.
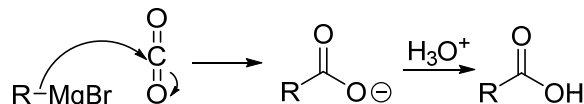

Note that whatever R was, we've just added one carbon to it overall. This is a useful way of extending chains one carbon at a time. The only limitation is that R has to be compatible with Grignards – no alcohols or unprotected carbonyls, etc.

5) S_N2 with a cyano group, followed by hydrolysis: This one doesn't show up until Ch. 22, but it's a useful complement to the Grignard/CO_2 reactions shown above, and worth mentioning here. In this case, we can make a particular acid derivative by using S_N2 to replace a leaving group with a ^-CN. Then, we can convert the nitrile to the parent acid compound by hydrolysis, which we'll see the mechanism for in the next chapter.
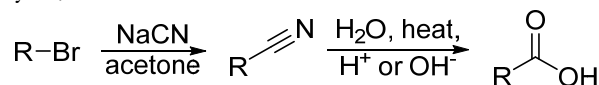
Like the Grignard reaction above, this ends up extending the chain length by one carbon. The only requirement is that R has to be S_N2-capable, so primary is best, and the molecule can't have any other groups sensitive to hydrolysis.

6) Conversion from any other acid derivative: Again, this is Ch. 21 chemistry, but you can take any of the compounds shown at the beginning of this packet and convert them to the acid by hydrolysis. We'll see the mechanism later. If it's something more reactive than acid (like anhydrides and acid chlorides), you only need water. If it's less reactive, you need water, heat, and either acid or base.
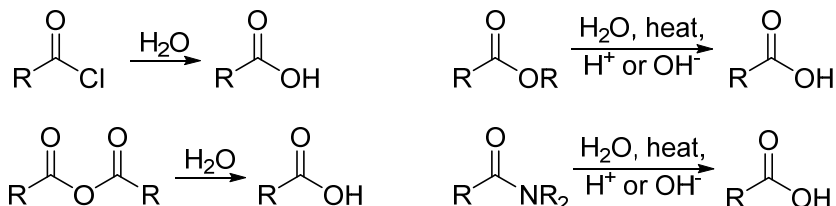

General idea of mechanisms

Most of the reactions in Ch. 20 and 21 involve swapping out the group beside the carbonyl. Unlike S_N2, you can't just attack and kick out the leaving group at the same time. You attack first and break up the carbon-oxygen double bond. This gets you to a point where the

central carbon has four total groups attached – the tetrahedral intermediate. Then the oxygen's lone pair comes back down and kicks out the leaving group. The general idea looks like this.
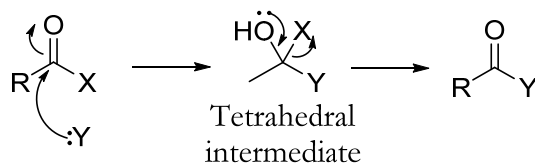

Depending on what you're doing and whether it's in acidic or basic conditions, there might be a few extra steps somewhere in there to account for protonation or deprotonation. But the general pattern is still the same for most of the reactions in these chapters.

Making esters from acids
Fischer esterification is the simplest way of making esters. You can react the carboxylic acid with the alcohol and some catalytic H_2SO_4.
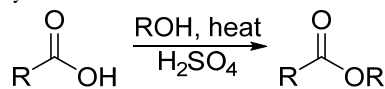

The mechanism is pretty much the same as the general pattern, but you protonate the carbonyl first since you're in acid. You also need to protonate the OH before it will leave.
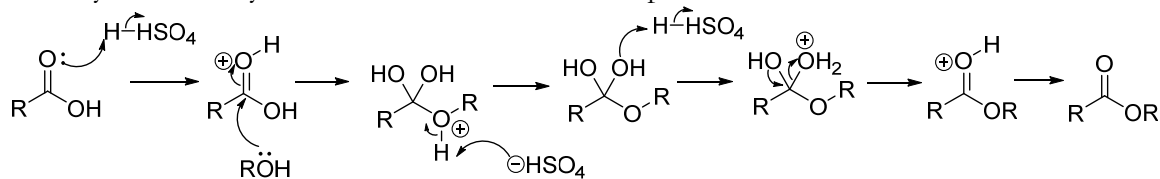
Note that in the middle you have the neutral tetrahedral intermediate. Another option we have is different from that general reaction pattern shown above. Instead, we keep both the oxygens that started out in the acid, and just stick an R group onto one of them. This is called alkylation, and you need a good leaving group on R to do it. One way is with diazomethane, CH_2N_2. The leaving group here is spectacularly good, since it's nitrogen gas which leaves. Diazomethane also acts as its own base first, to deprotonated the acid.
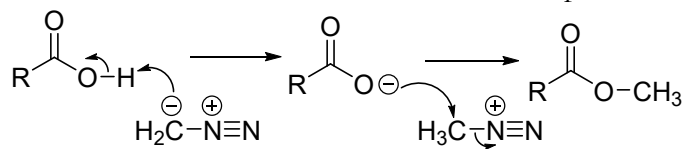
Note that the oxygens stay on the molecule the entire time, just one of them gets alkylated. The other option uses a slightly less good leaving group, and you need a different mild base to deprotonated the acid in the first step.
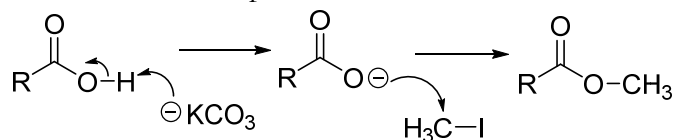

Overall, these are written as:

You can sometimes use different R groups instead of just CH_3, but they have to be very good at doing S_N2. Benzylic positions are an okay choice. Usually, though, these reactions are considered the best way to make methyl esters (with an OCH_3 group) and not much else.

**Making anhydrides and chlorides from acids**

For chlorides, we can use the same special reagent we used to turn alcohols into alkyl chlorides: $SOCl_2$ or a similar molecule, PCl_5. We still don't cover the mechanism.
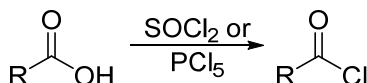
To make the anhydride, we have a couple of options. The name 'anhydride' means it's had a molecule of water removed. If you take two carboxylic acid molecules, stick them together, and remove a water, you get an anhydride. You can do this by using a very powerful dehydrating reagent, P_2O_5. This takes two copies of the same acid and converts them to the anhydride.
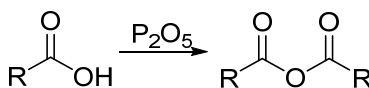

There's another option that only works to make five- or six-membered cyclic anhydrides. If you mix it with an acyclic anhydride, they'll swap which one is the acid and which is the anhydride.
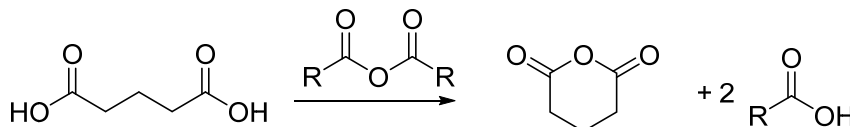

Reductions

Like we saw in Ch. 19, you can reduce carbonyl compounds with hydrides. You can do the same with acids, which are reduced from the "three bonds to more electronegative atoms" oxidation state to the "one bond to more electronegative atoms" oxidation state. Since acids are less reactive than aldehydes and ketones, LAH is needed.
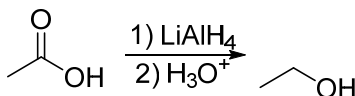
An important thing to point out is that *NaBH₄ does not work for carboxylic acids* – it only works for aldehydes, ketones, acid chlorides and anhydrides. This means we can reduce these groups without reducing acids:
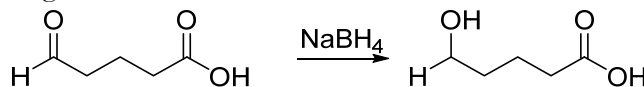
What if we want to reduce only the acid? Since acetal protecting groups only react with aldehydes, we can protect those groups, reduce the acid with LAH, and then deprotect.
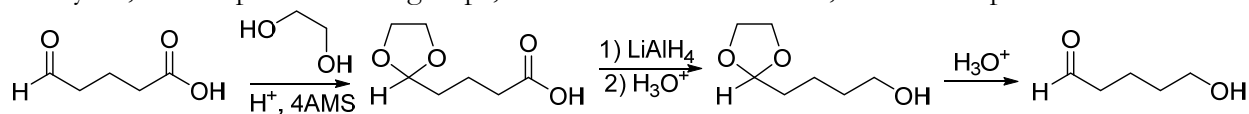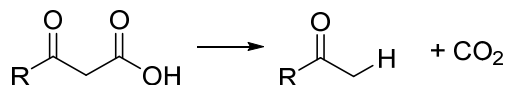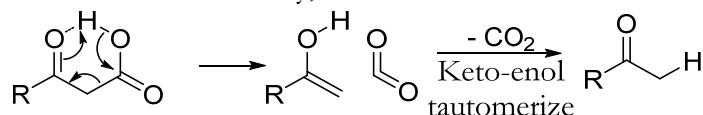

Decarboxylation

If the molecule has a β-ketoacid - a carboxylic acid two carbons away from any type of carbonyl (often a ketone, but can be aldehyde, acid, ester, etc.) - then the entire CO_2 unit can detach. The H that was part of the acid ends up attached where the CO_2 used to be.

The mechanism for this is actually not too different from that for Diels-Alder. It helps to keep in mind that the molecule is capable of hydrogen-bonding to itself, so it normally looks a little different than what's shown up there. There's already a partial bond between the other carbonyl and the H (you can show this as a dotted line). During the mechanism, the carbonyl breaks and formally makes a new OH bond. Everything else clicks around the six-membered ring, like in Diels-Alder. Finally, an acidic keto-enol tautomerization happens.
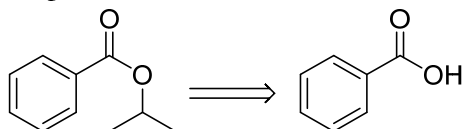

Ch. 20 Synthesis Practice
Let's try doing this:
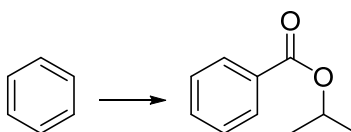
This is an ester, so the easiest option is Fischer esterification from the carboxylic acid.

We don't know any way to add a carboxyl group directly onto benzene, but we do know two different ways to convert a halogen to a carboxyl group: convert to a Grignard and attack CO_2, or do S_N2 with ^-CN and then hydrolyze. Only the first option works here.

 Works okay

 Doesn't work - no S_N2 on aryl halides
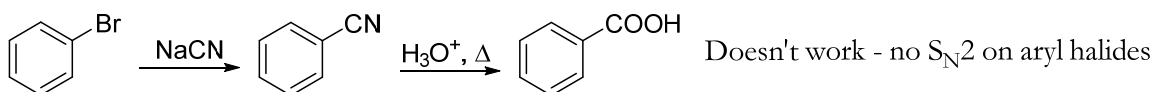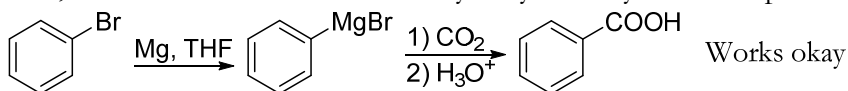
We can get the halogen onto the ring with EAS. Overall, our synthesis looks like: