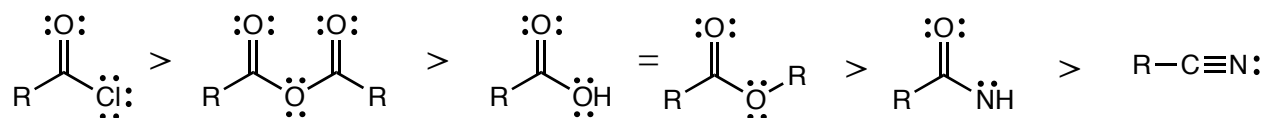


Learning Guide for Chapter 24 - Carboxylic Acid derivatives

- I. Introduction to carboxylic acid derivatives - p 1
- II. Physical properties - p 4
- III. Nomenclature - p 5
- IV. Spectroscopy - p 7
- V. Hydrolysis - p 9
- VI. Interconversion - p 11
- VII. Reduction - p 14
- VIII. Reaction with organolithium reagents - p 16
- IX. Summary of the rxns of each of the carboxylic acid derivatives - p 17

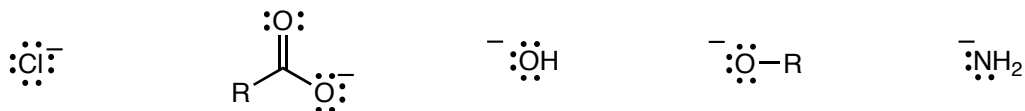
I. Introduction to carboxylic acid derivatives

Acid chlorides, anhydrides, esters, amides, and nitriles are all considered carboxylic acid derivatives because they all are converted to carboxylic acids by a hydrolysis reaction. It is easiest to remember them in the order of their reactivity.

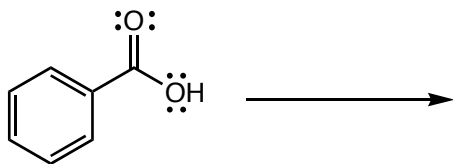


Since the C=O bond is quite polar, compounds with more electronegative substituents attached will be higher in energy and therefore more reactive - the more electronegative elements pull electron density away from the already partially positive carbon.

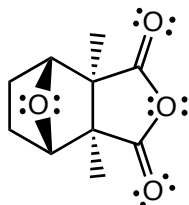
Another way to look at carboxylic acid derivative stability is to consider the stability of the substituents as independent ions - the most stable compounds have the least basic and nucleophilic groups attached to them.



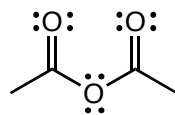
Acid chlorides react rapidly with water, and are therefore not found in nature. They are usually intermediates in a synthesis rather than the end product. Acid chlorides are formed by reaction of carboxylic acids with thionyl chloride or oxalyl chloride.



Anhydrides are less reactive than acid chlorides and are occasionally found in nature. An example is cantharidin, the biological defense mechanism of a blister beetle. It causes blisters on the skin, and can be fatal to horses if they eat hay containing the beetles. Acetic anhydride is used in large quantities in industry for the synthesis of plastics, fibers, and drugs.

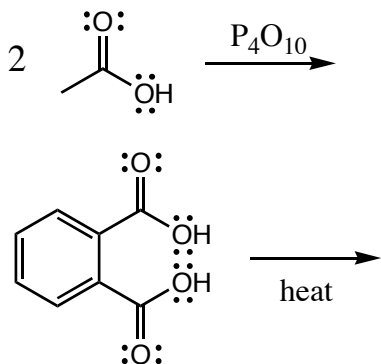


cantharidin

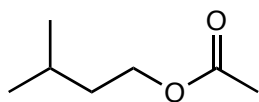


acetic anhydride

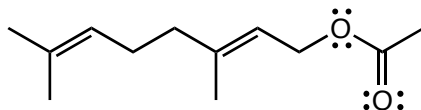
Anhydrides are formed from carboxylic acids by using a strong dehydrating agent such as P_4O_{10} , or by heating diacids which form 5- or 6-membered cyclic anhydrides. They can also be made from acid chlorides, as we shall see.



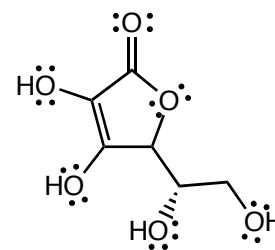
Esters are very common in nature. Many pleasant odors and flavors come from esters, such as isopentyl acetate (banana oil) and geranyl acetate (found in roses, geraniums, and other flowers). Oil of wintergreen contains methyl salicylate. Several widely used polymers can be made by joining molecules together with ester linkages. Cyclic esters are called lactones - ascorbic acid (vitamin C) is an example.



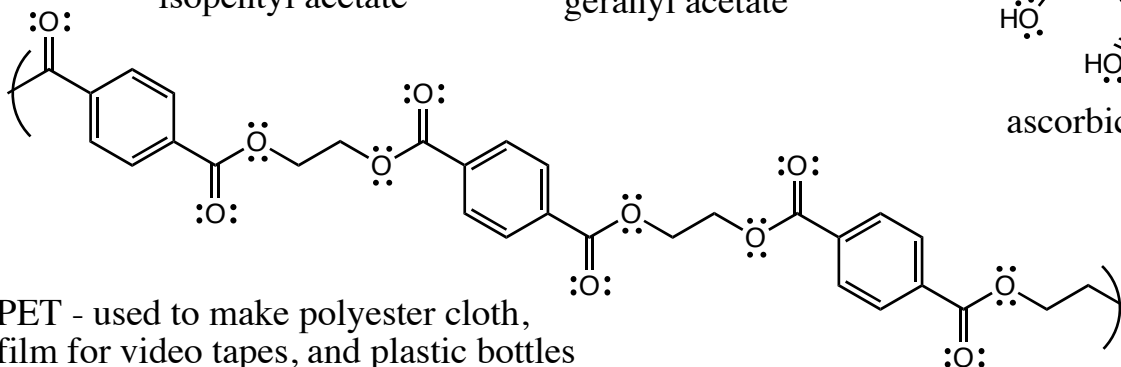
isopentyl acetate



geranyl acetate

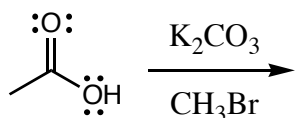
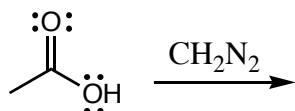
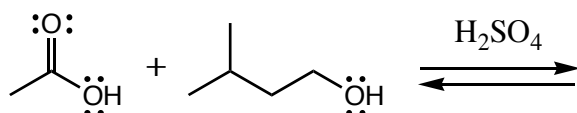


ascorbic acid

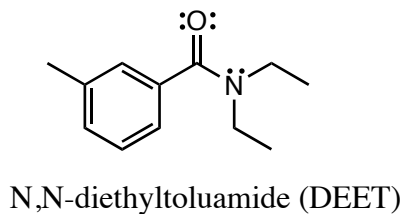


PET - used to make polyester cloth, film for video tapes, and plastic bottles

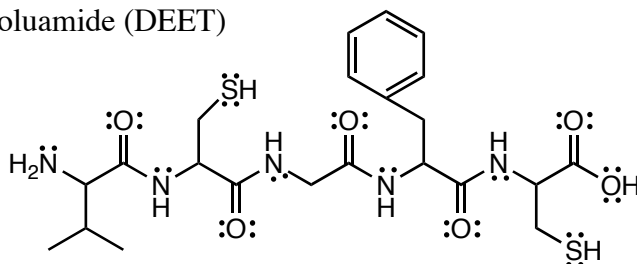
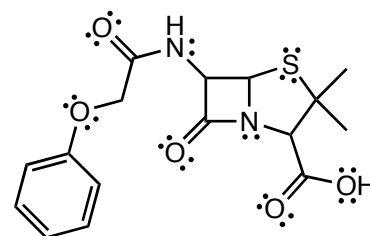
Esters can be formed from carboxylic acids and alcohols by Fischer esterification, by reaction with diazomethane, or by deprotonation followed by a reactive alkyl halide. They can also be formed from acid chlorides and anhydrides, as we shall see.



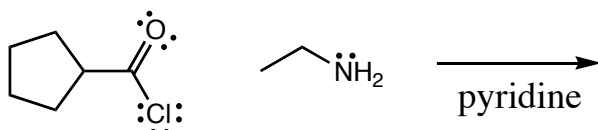
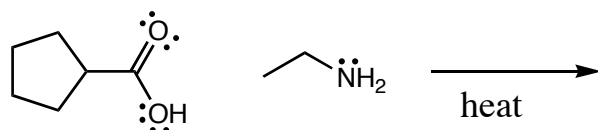
Amides are among the most stable of the carboxylic acid derivatives. They are referred to a primary, secondary, and tertiary in the same way that amines are. An example of a tertiary amide is DEET, an effective insect repellent. Cyclic amides are called lactams, and are found in a number of biological molecules such as penicillin G. Amides can also be made into polymers, both artificial and natural. Proteins are the most important examples of natural amide polymers.



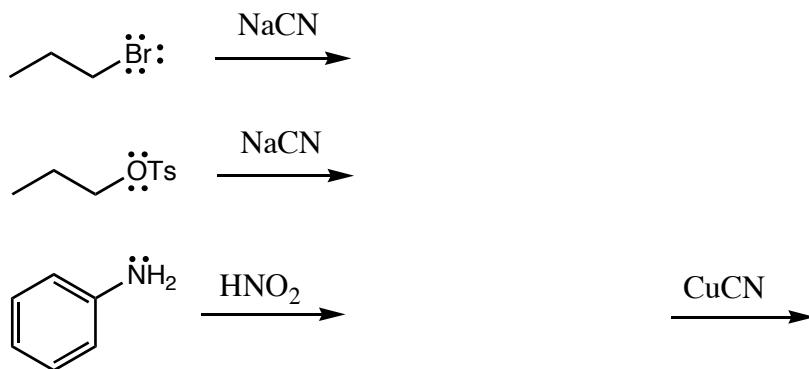
penicillin G



Amides may be formed from carboxylic acids by heating the acid and amine together to drive off water. This reaction is commonly used in industry. In the laboratory, amides are more often formed from amines and acid chlorides, as we saw in Ch 19. Amides can also be made from anhydrides and esters, as we shall see.

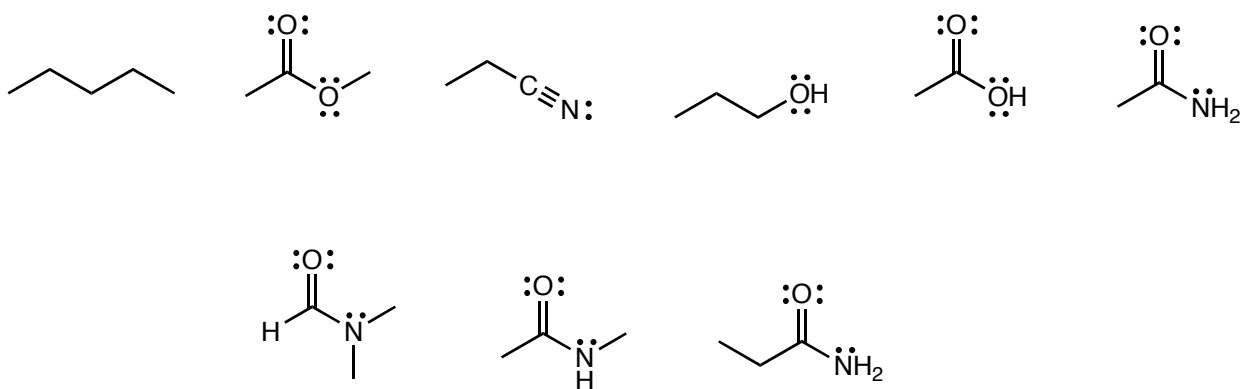


Nitriles are formed from the reaction of cyanides with primary alkyl halides or tosylates or from diazonium ions reacting with cuprous cyanide.

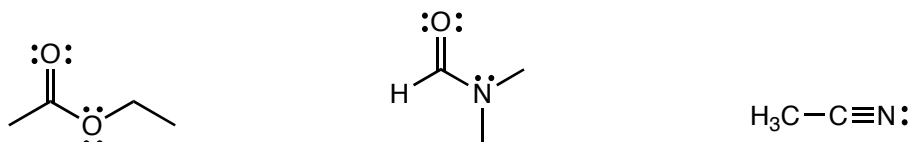


II. Physical properties of carboxylic acid derivatives

Esters have low boiling points, about the same as hydrocarbons of the same molecular weight. Nitriles are similar to alcohols - the strength of the dipole attractions is similar to the hydrogen bonding attractions of alcohols. Amides, however, are higher boiling than carboxylic acids. Primary amides are higher than secondary amides, which are higher again than tertiary amides because of the decreasing possibility for hydrogen bonding.



All carboxylic acid derivatives are soluble in organic solvents such as alcohols, ethers, chlorinated hydrocarbons, and aromatic hydrocarbons. Acid chlorides and anhydrides cannot be dissolved in water because they will react with it. Some small amides, esters, and nitriles are soluble in water. Ethyl acetate, N,N-dimethylformamide, and acetonitrile are often used as reaction solvents.



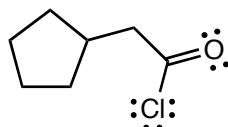
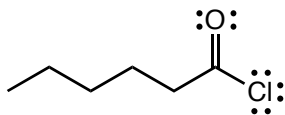
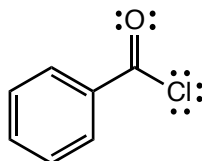
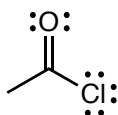
III. Nomenclature of carboxylic acid derivatives

The names of the carboxylic acid derivatives are based on the name of the parent carboxylic acid. The common names of formic acid and acetic acid are always used in for one and two carbon chains.

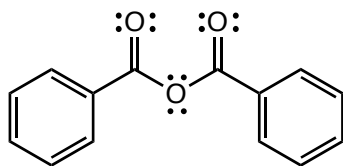
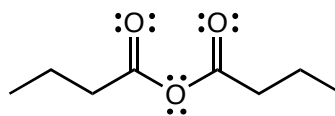
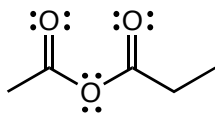
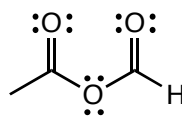
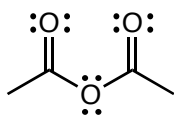
All carboxylic acid derivatives are principle groups. They have less priority than carboxylic acids, but more than aldehydes. Acid chlorides and anhydrides rarely occur in the same compound with other functional groups, so you don't have to worry about them in the ranking. Esters and amides can be named as substituents, but it's quite complicated, and you won't be responsible to do so.

COOH > esters / amides > nitriles > aldehydes > ketones > alcohols > amines

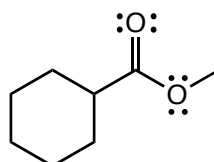
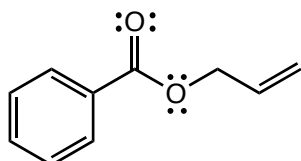
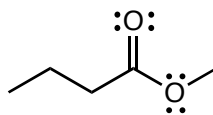
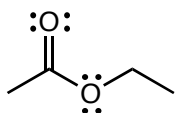
Acid chlorides - drop "ic acid" from the name of the parent carboxylic acid, and add "yl chloride."



Acid anhydrides - change the word "acid" in the parent name to "anhydride." With mixed anhydrides, use the names of both parent acids.



Esters - name the group attached to the O as a substituent, then drop "ic acid" from the name of the parent acid and add "ate."



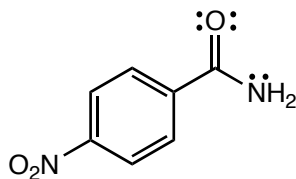
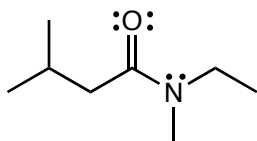
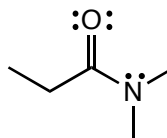
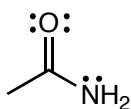
phenyl 2-methylpropanoate

butyl p-chlorobenzoate

isopropyl formate

2-hydroxypropyl decanoate

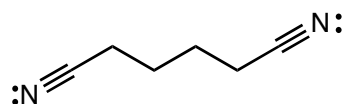
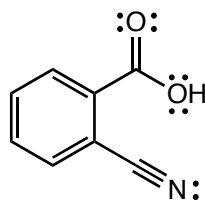
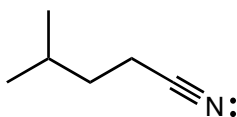
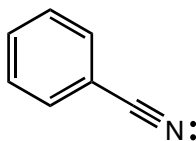
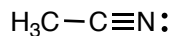
Amides - drop "ic acid" or "oic acid" and add "amide" to the parent name. Groups on the nitrogen are treated as N-substituents.



3-chloro-N-methylpentanamide

N-benzylformamide

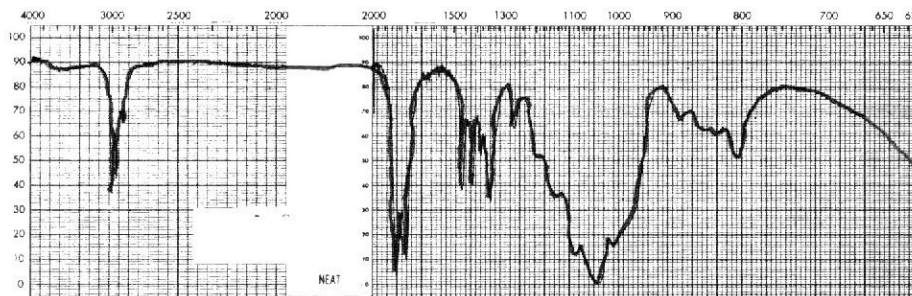
Nitriles - drop "ic acid" from common names of acids and add "onitrile." With regular acid names, go back to the full alkane name and add "nitrile." When a higher priority group is present, name as a cyano substituent.



IV. Spectroscopy of carboxylic acid derivatives

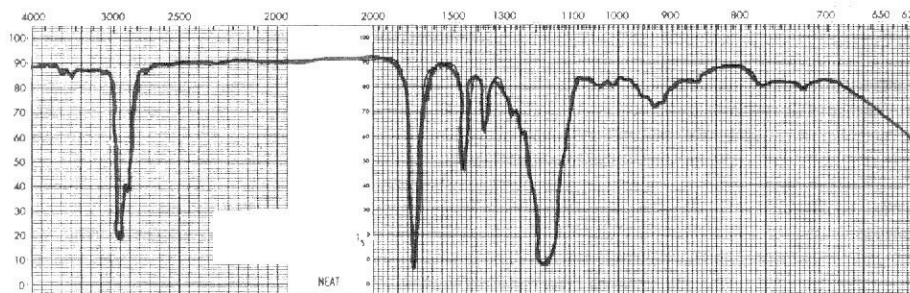
IR - All of the carboxylic acid derivatives have a C=O band, each at a characteristic frequency. When conjugated to a benzene ring or C=C, the frequency is always shifted to a lower wavenumber.

Anhydride - two C=O absorptions at 1760, 1820 cm^{-1} .



Esters - C=O at 1735 cm^{-1}

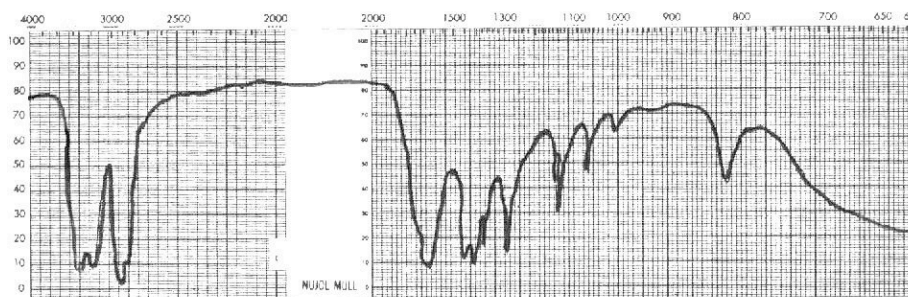
C-O at $1000\text{-}1300\text{ cm}^{-1}$



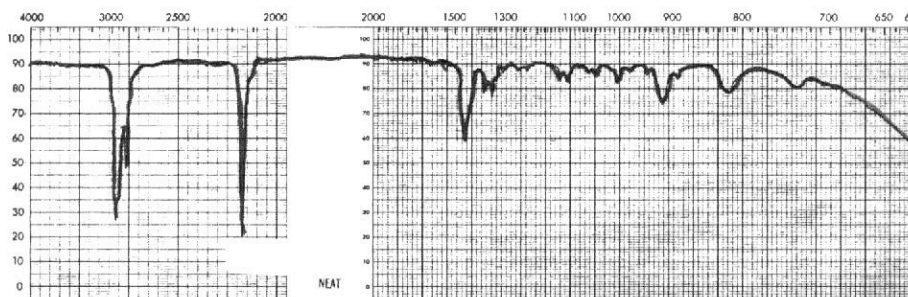
Amides - C=O at 1650 cm^{-1}

N-H $3200\text{-}3400\text{ cm}^{-1}$ (2 for primary, 1 for secondary, none for tertiary)

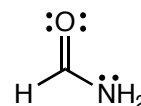
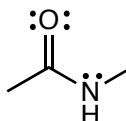
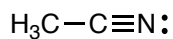
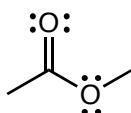
NH₂ scissor sometimes overlaps C=O



Nitriles - triple bond at $2260\text{-}2200\text{ cm}^{-1}$



NMR - protons on C's next to C=O's are around $2.0\text{-}2.5\text{ ppm}$ for all functional groups
 protons on C's next to O's are between $3\text{-}4\text{ ppm}$ in alcohols, ethers, and esters
 protons on C's next to N's are between $2.5\text{ and }3.0$ for amines and amides
 amide H's are variable, but usually appear between $5\text{-}8\text{ ppm}$ and exchange w/D₂O
 H's on C=O's are about $9\text{-}11\text{ ppm}$ for aldehydes, 8 ppm for formic acid derivatives

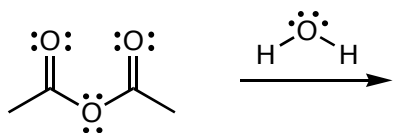
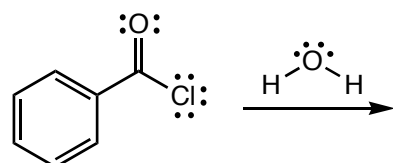


V. Hydrolysis of carboxylic acid derivatives

All carboxylic acid derivatives can be hydrolyzed to form carboxylic acids. The word "hydrolysis" comes from "hydro" meaning water and "lysis" meaning to cut, implying that these compounds are cut with water.

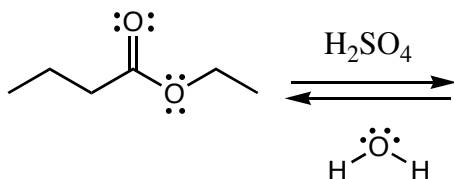
Acid chlorides, anhydrides - react easily with water. Reactions involving these functional groups must be kept dry in order to avoid this side reaction. During the work-up the reaction is quenched with water and the acid chloride or anhydride undergoes hydrolysis.

The mechanism for both of these reactions follows the typical pattern for carboxylic acid derivatives. The nucleophile attacks and the C=O electrons are pushed up; then the electrons come back down and push off a chloride or carboxylate ion. A water molecule or carboxylate ion then comes back and deprotonates the OH.

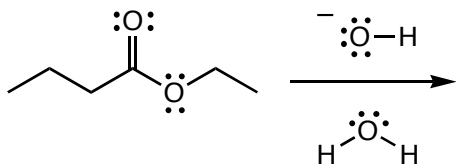


Esters, amides and nitriles do not simply react with water - they must be activated by acid in the presence of water or attacked by hydroxide in order to be hydrolyzed, and either reaction must be heated. Esters are the easiest to hydrolyze; amides require much stronger acid or base, and nitriles likewise require strenuous conditions.

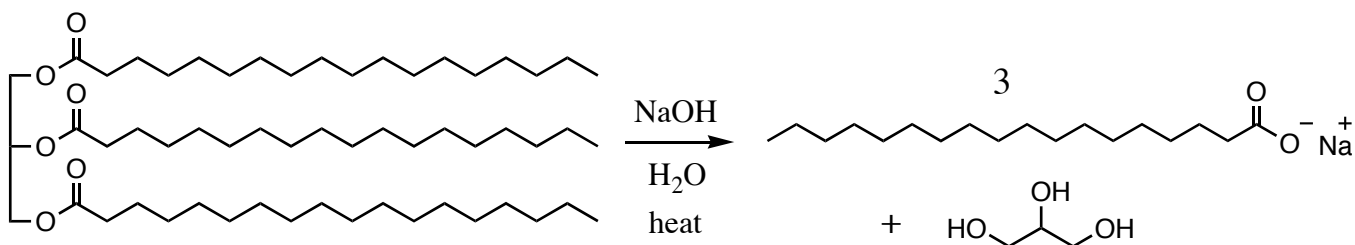
Esters - acid-catalyzed hydrolysis is the opposite of the Fischer esterification. It has an equilibrium constant near 1 and must be driven forward by using water as the solvent or removal of the resulting alcohol.



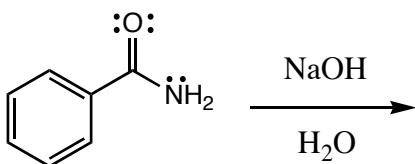
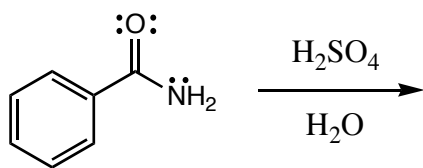
Base-catalyzed hydrolysis of esters is called saponification. It is not reversible because of the last acid-base reaction at the end.



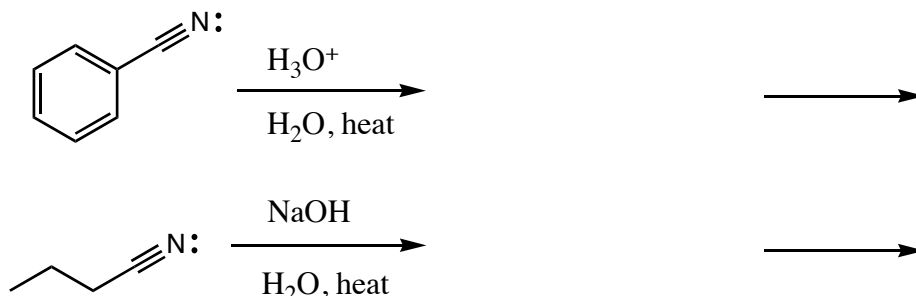
The term saponification comes from the original use of this reaction in making soap. Recall that saturated fats are triesters of long chain fatty acids and glycerol. Saponification yields the carboxylate anions of these fatty acids, which arrange themselves as micelles and are good for dissolving dirt and grease. Base was obtained from water soaked in wood ashes.



Amides - require strongly acidic or basic conditions such as 6M HCl or 40% NaOH. The mechanisms are analogous to the ester mechanisms. Note that in both cases, the equilibrium is driven forward by a final acid-base reaction.



Nitriles can be hydrolyzed to amides using mild acid or base. Under more strenuous conditions, the amide is then hydrolyzed to the carboxylic acid. You will not need to know these mechanisms - they are similar to the ones we've discussed, with a few extra twists.

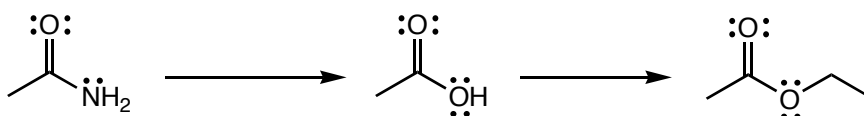


VI. Interconversion of carboxylic acid derivatives

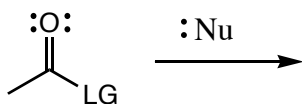
As a general rule, carboxylic acid derivatives can be converted into any other derivative that is less reactive than the original. Esters can also be made into other esters by a transesterification reaction.

carboxylic acid acid chloride anhydride ester amide

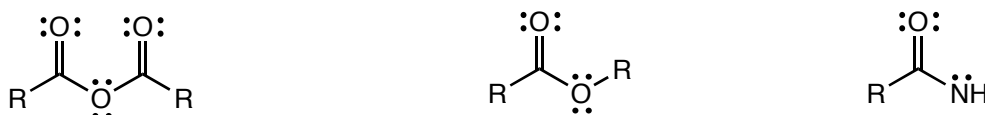
The only way to go from a more reactive to a less reactive derivative is to first hydrolyze to the carboxylic acid.



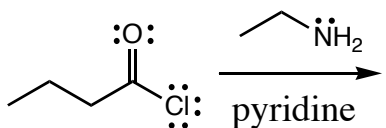
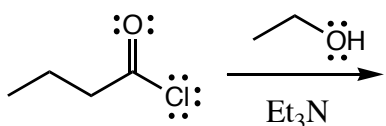
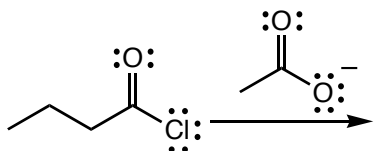
The general mechanism for converting a more reactive derivative into a less reactive one is shown below. If the Nu originally had an H attached, it will be removed in an additional step.



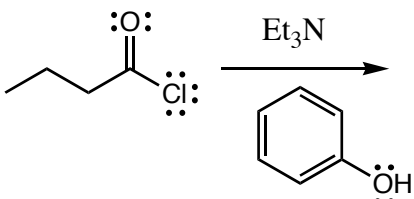
When making anhydrides, the nucleophile is a carboxylate anion. When making esters, the nucleophile may be an alcohol or an alkoxide. When making amides, the nucleophile is ammonia or an amine.



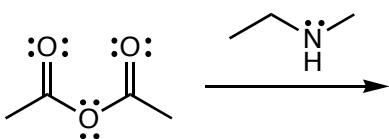
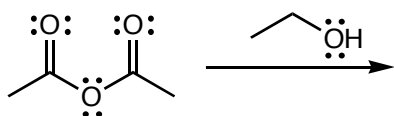
Acid chlorides - can be converted to anhydrides, esters, and amides by reacting them with carboxylate anions, alcohols, or amines. A non-nucleophilic base such as pyridine or triethylamine is used as the base to pull off the H when making esters or amides.



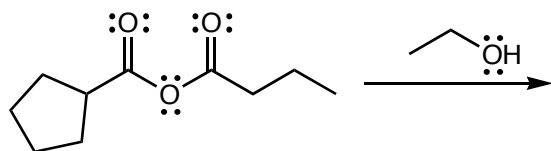
Note that this method allows us to make esters that can't be made directly from carboxylic acids, including tertiary and phenyl esters.



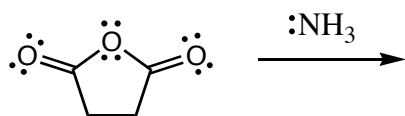
Anhydrides - can be made into esters or amides by reacting with alcohols, ammonia, or amines. The carboxylate ion leaving group serves as the base to pull off the hydrogen at the end, forming a carboxylic acid as an additional product.



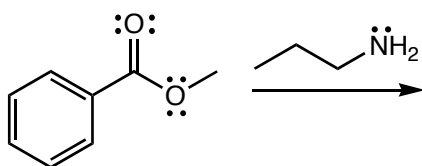
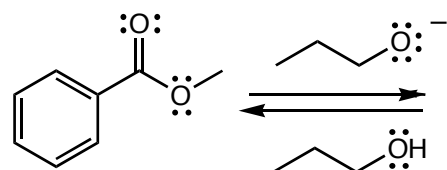
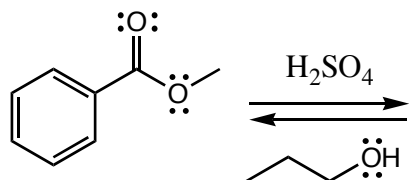
If a mixed anhydride is used, two sets of products are possible, depending on which C=O is attacked.



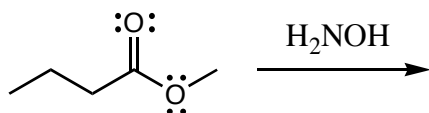
A cyclic anhydride gives a compound with a carboxylic acid and an ester or amide which would otherwise be difficult to synthesize.



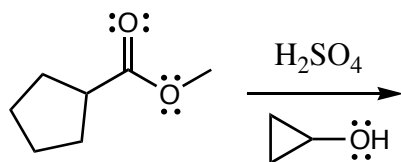
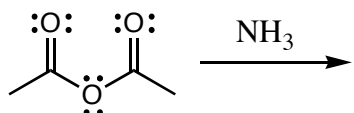
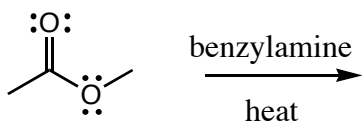
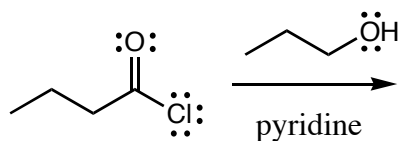
Esters - can be converted to other esters or to amides. Amines are strong enough nucleophiles to attack an ester, but alcohols are not. When converting an ester to another ester (called a transesterification), the ester must be activated by acid or attacked by an alkoxide. The mechanisms have the same steps as the hydrolysis of an ester.



When hydroxylamine is used as the nucleophile, the product forms a colored complex with Fe^{+3} ions - this is the basis of the hydroxamate test for esters.



Practice:



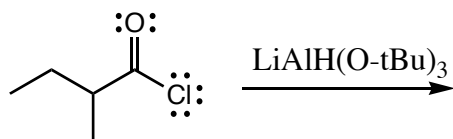
VII. Reduction of carboxylic acid derivatives

Carboxylic acid derivatives can be reduced to form alcohols, aldehydes, or amines. All carboxylic acid derivatives require LiAlH_4 to be completely reduced.

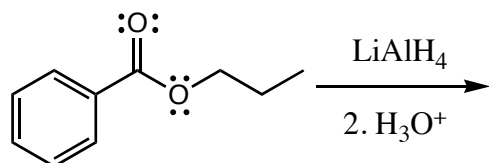
Acid chlorides and anhydrides can be reduced to alcohols by lithium aluminum hydride, but since they are made from carboxylic acids which can also be reduced to alcohols, this is a pretty much a wasted step.



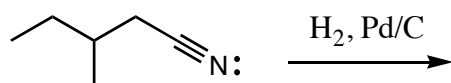
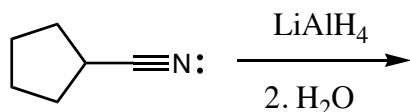
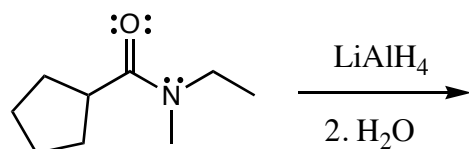
Acid chlorides can be reduced to aldehydes by a less active form of lithium aluminum hydride, as we have seen previously.



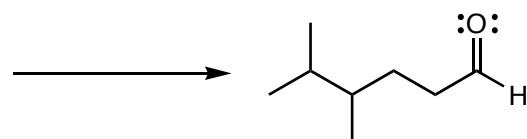
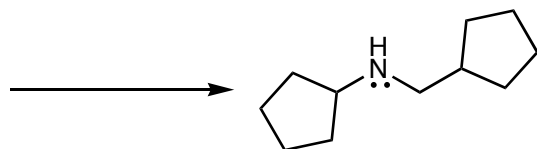
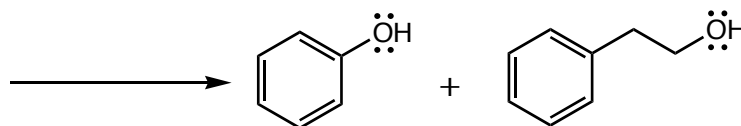
Esters are reduced by lithium aluminum hydride to form two alcohols.



Amides and nitriles are both reduced by lithium aluminum hydride to form amines. Nitriles may also be reduced using catalytic hydrogenation.

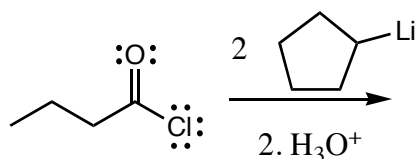
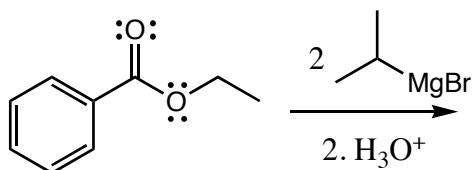


Practice - what compounds could be reduced with what reagents to give the following?

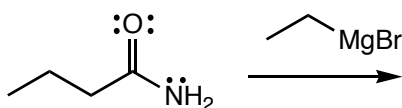


VIII. Addition of organometallic reagents to carboxylic acid derivatives

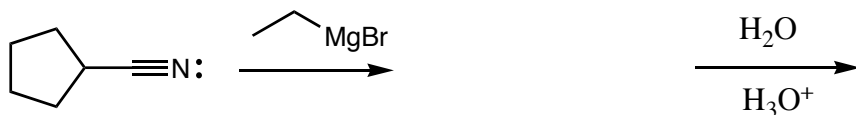
Grignard or organolithium reagents add to acid chlorides or esters to give tertiary alcohols in which the organometallic R group has been substituted twice. In the first step, a ketone is formed which then reacts again.



Primary and secondary amides cannot be attacked by organometallic reagents because they are acidic. The organometallic reagent simply acts as a base to deprotonate the amide.



Nitriles are attacked by organometallic reagents to form the conjugate base of an imine. Upon hydrolysis, a ketone or aldehyde is formed.



IX. Summary of reactions of carboxylic acid derivatives

	<u>acid chloride</u>	<u>anhydride</u>	<u>ester</u>	<u>amide</u>	<u>nitrile</u>
hydrolysis					
reduction					
organo-metallic reagent					
carboxylate					
alcohol					
amine					