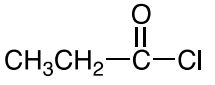
Chapter 20
Carboxylic Acid Derivatives
Nucleophilic Acyl Substitution

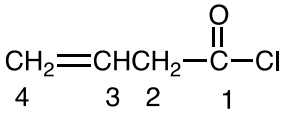
Nomenclature:

In carboxylic acid chlorides, anhydrides, esters and amides, the parent is the carboxylic acid. In each case be sure to include the carbonyl carbon when numbering the chain. This always gets the lowest number.

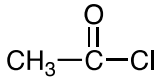
Carboxylic acid chloride (usually abbreviated to acid chloride) acyl chloride: Name acyl group by replacing the parent carboxylic acid ending "-ic acid" with "-yl chloride" (or other halide).

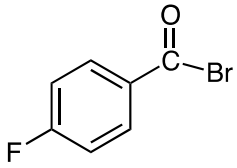

parent carboxylic acid: propanoic acid

propanoyl chloride



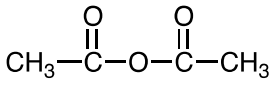
3-butenoyl chloride

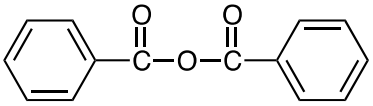

acetyl chloride

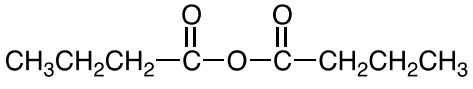


p-fluorobenzoyl bromide

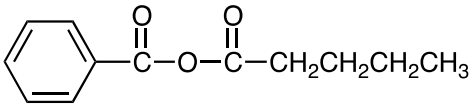
Carboxylic acid anhydride: replace "acid" with "anhydride".


acetic anhydride

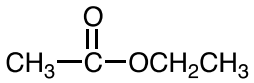

benzoic anhydride


propanoic anhydride

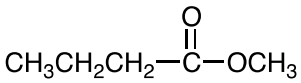
When the two acyl groups are different, list them in alphabetical order.


benzoic pentanoic anhydride

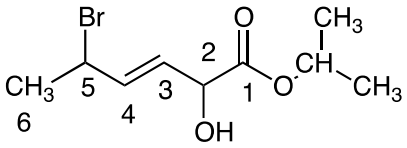
Esters:
Name the alkyl portion first and then name the acyl portion by substituting "-ic acid" of the parent carboxylic acid with "-ate".



ethyl acetate



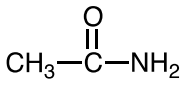
methyl butanoate



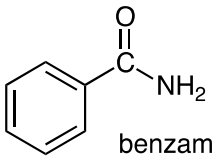
isopropyl 5-bromo-2-hydroxy-3-hexenoate

Amides:

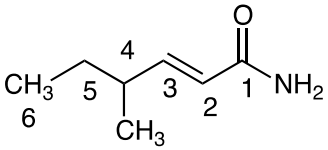
Unsubstituted: Change "-oic acid" of the parent carboxylic acid to "-amide".



acetamide

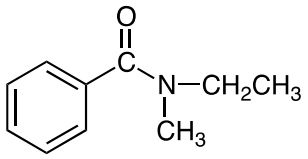


benzamide

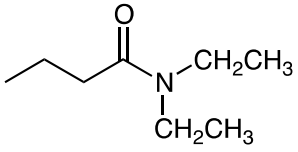


3-methyl-2-hexenamide

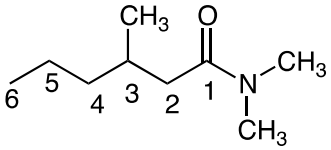
Substituted amides: Name as N-alkyl and N,N-dialkyl derivatives of a parent amide. List the N-alkyl substituents in alphabetical order. If the same N-alkyl substituent reappears as a substituent on the parent chain, the substituent is combined with the N-alkyl substituent as a di-, tri-, etc and its position on the parent indicated by number.



N-ethyl-N-methylbenzamide

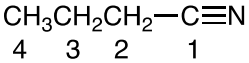


N,N-diethylbutanamide

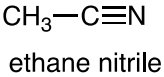


N,N-3-trimethylhexanamide

Nitriles: Add the suffix "-nitrile" to the name of the parent hydrocarbon chain that includes the carbon of the nitrile group itself. Nitriles can also be named by replacing the "-ic acid" or "-oic acid" with "-onitrile".

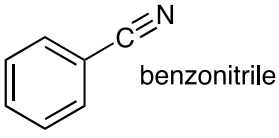


butanenitrile or butanonitrile

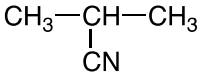


ethane nitrile

acetonitrile



benzonitrile

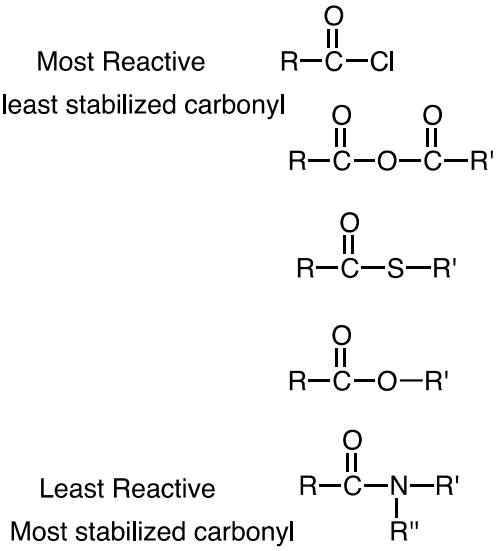


2-methylpropanenitrile (or common name; isopropyl cyanide)

Reactivity Order:

The order of reactivity for the carboxylic acid derivatives is extremely important in organizing the large amount of information and the large number of reactions in this chapter. The reactivity order is as follows:

Acid chloride > anhydride > thioester > ester > amide
Most reactive least reactive



General Rule:

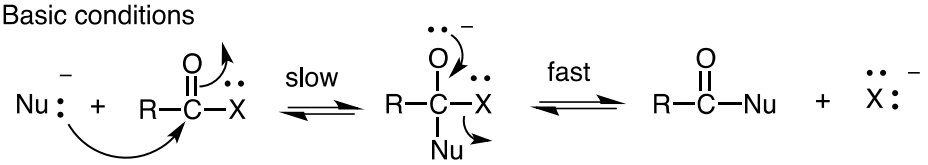
Conversion of one class of compound to another is feasible only in the direction that goes from a more reactive carbonyl (higher in the reactivity order) to a less reactive carbonyl (lower in the reactivity order) or in the driection that converts a less stabilized carbonyl to a more stabilized one.

So, a carboxylic acid chloride can be used to synthesize anhydrides, thioesters, ester and amides but amides can not be used to synthesize any other derivatives.

There is a very large range of reactivity between the most reactive (acid chlorides) and the least reactive (amides). In general, acid chlorides react about 10^{13} times faster in nucleophilic acyl substitution reactions than amides.

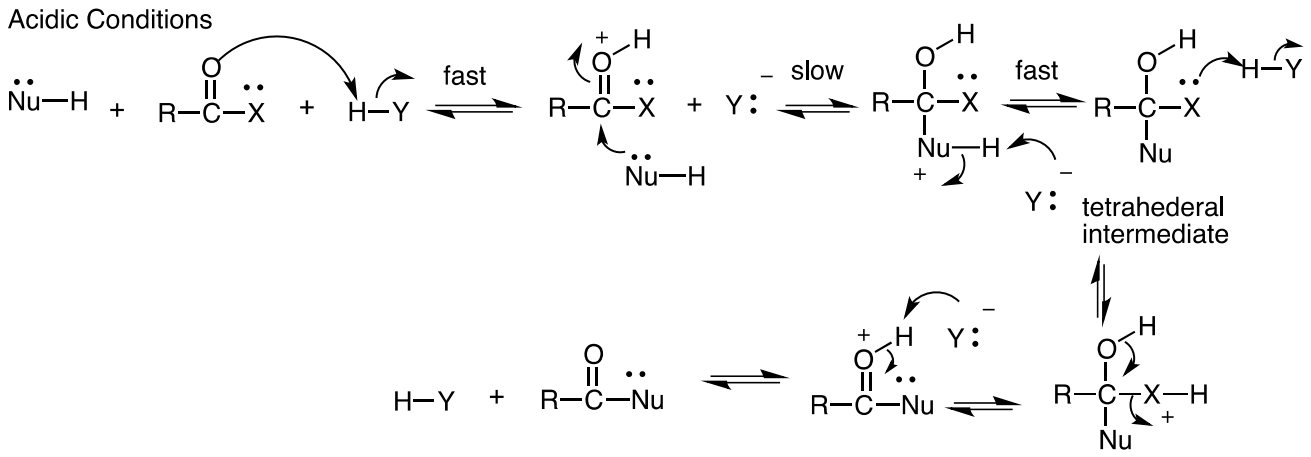
In order to understand the reactivity order, we need to look at the general reaction – nucleophilic acyl substitution - that all of these derivatives undergo. It is shown below for basic conditions in which the nucleophile is an anion. The slow step is the initial attack of the nucleophile on the carbonyl carbon to form the tetrahedral intermediate. Loss of the leaving group - with its electrons – is fast.

Basic conditions



tetrahedral intermediate

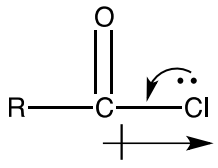
A generalized mechanism in acidic conditions is given below. In acidic conditions there are additional proton transfer steps but these are very fast. All species are already hydrogen-bonded to protons and the proton transfer steps are essentially instantaneous. The slow step is still the attack of the nucleophile on the carbonyl. As we will see, there are minor variations depending on the individual reaction and in writing mechanisms it is common practice to combine the proton transfer steps so as to save writing.



Since the slow step is the attack of the nucleophiles on the carbonyl carbon, what determines the rate of this reaction is the degree of electron deficiency at the carbonyl carbon. As we know, the carbonyl carbon has a partial positive charge so we can also say, that the greater the positive charge on the carbonyl carbon, the more reactive it will be to nucleophiles, which by definition, has to have a partial negative charge and a lone pair.

As we will see, there are two opposing trends: the X-group in each of our carboxylic acid derivatives has a lone pair that can donate electrons to the carbonyl carbon and make the carbonyl carbon LESS electron rich and all of the X-groups have an atom that is MORE electronegative than the carbonyl carbon and so there is an opposing inductive effect that works to decrease the electron density at the carbonyl carbon, making it more positive, and more reactive.

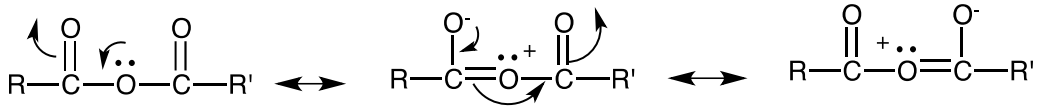
For acid chlorides: The chlorine is a relatively strong electron withdrawing group and the carbonyl carbon – chlorine bond is relatively long because chlorine is in the second row of the periodic table and larger than carbon. This makes the chlorine lone pair 3p orbital too far away to overlap effectively with the π-orbital of the carbonyl and so the net effect is that the carbonyl carbon of acid chlorides is relatively electron deficient and therefore very reactive.



In acid chlorides, the inductive effect of electron withdrawal is stronger than the resonance effect of electron donation.

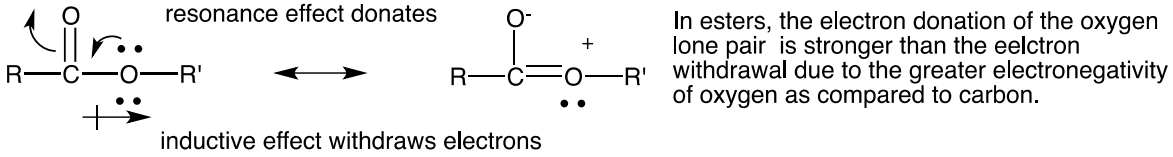
For Acid Anhydrides: oxygen is more electronegative than chlorine (3.44 v. 3.16) and so withdraws electrons from the carbonyl carbon inductively (i.e. through the bond) but oxygen is a first row element and the C-O bond is considerably shorter than the C-Cl bond. Consequently there is much better overlap of the oxygen lone pair with the π-orbital of the

carbonyl. But since there are two carbonyl carbons competing for the oxygen lone pair, the lone pair donation (resonance effect) is diluted.

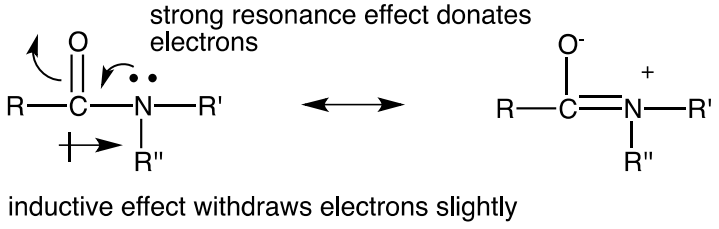


For thioesters: Sulfur is a third row element, like chlorine, and so it is considerably larger than oxygen. The C-S bond is relatively long and this makes for poor overlap of the lone pair 3p orbital and the π-orbital of the carbonyl. But thioesters are less reactive than acid chlorides and anhydrides due to the fact that the sulfur is considerably less electronegative than oxygen and chlorine. The inductive electron withdrawing effect of the sulfur is less than that of oxygen or chlorine due to the decreased electronegativity of sulfur versus oxygen (2.58 v. 3.44).

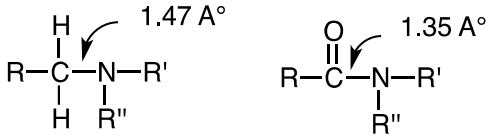
For esters: The oxygen substituent of esters is an overall electron-donating group. There is the electron withdrawing effect due to the greater electronegativity of oxygen as compared to carbon but this is outweighed by the electron donating effect of the oxygen lone pair due to resonance.



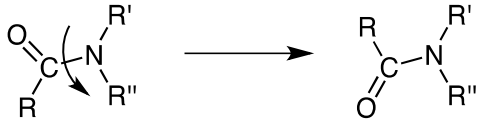
For amides: Nitrogen is less electronegative than oxygen (3.04 v. 3.44) but is still more electronegative than carbon (2.55) so in amides there is still an electron withdrawing inductive effect through the C-N bond but there is a much larger electron donating effect due to resonance donation of the nitrogen lone pair into the carbonyl π-orbital.



The strong resonance donation gives the carbon-nitrogen bond in amides lots of double bond character. The C-N bond in amides is much shorter than a normal C-N bond.

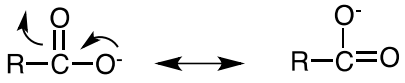


There is a considerable barrier to rotation around the C-N bond since there is a lot of sp^2 character for the amide nitrogen. All of the three bonds of the amide lie in the same plane.



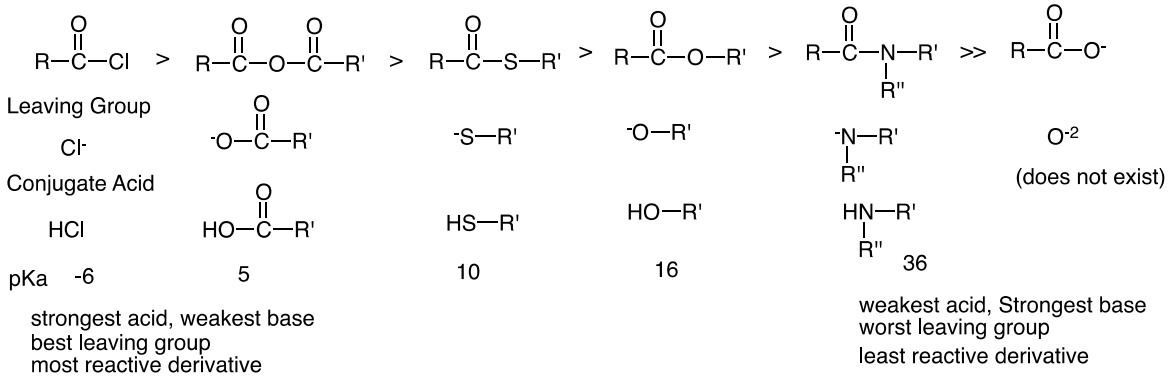
E_{act} = 75 - 85 Kj/mol (18-20 Kcal/mol)

Carboxylate anion: This is also stabilized by resonance. The negatively charged oxygen is a powerful electron donor and so a Carboxylate anion behaves very differently from the other carboxylic acid derivatives under discussion. The carbonyl carbon is not electrophilic and is not attacked by nucleophiles.



Again, to convert one carboxylic acid derivative into another one, the reaction is feasible only if the new derivative lies BELOW it in reactivity or, in other words, only if the conversion is from a less stable carbonyl to a more stable one.

A very useful way to remember the reactivity order is to consider the leaving group ability of the X group. As we discussed above, the slow step (rate determining step) of the reaction is the attack on the carbonyl and loss of the leaving group is fast but the leaving group ability of X does correlate with the overall rate of the reaction. And so we can remember the reactivity order by considering which is the better leaving group. As we know, the more stable the anion – i.e. the weaker the base – the better the leaving group.

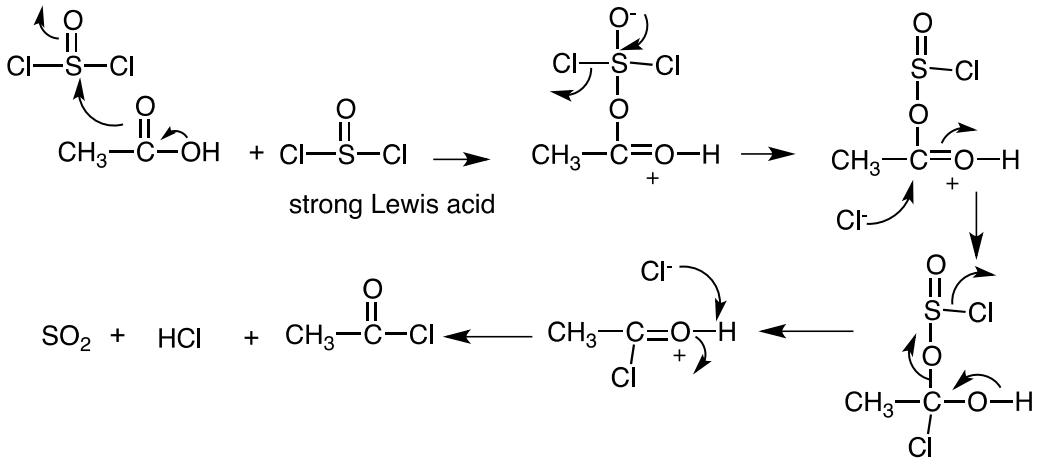


This is simply a mnemonic, a useful way to remember the reactivity order but you can see that there is good correlation between the reactivity and leaving group ability.

Acid chlorides

Preparation

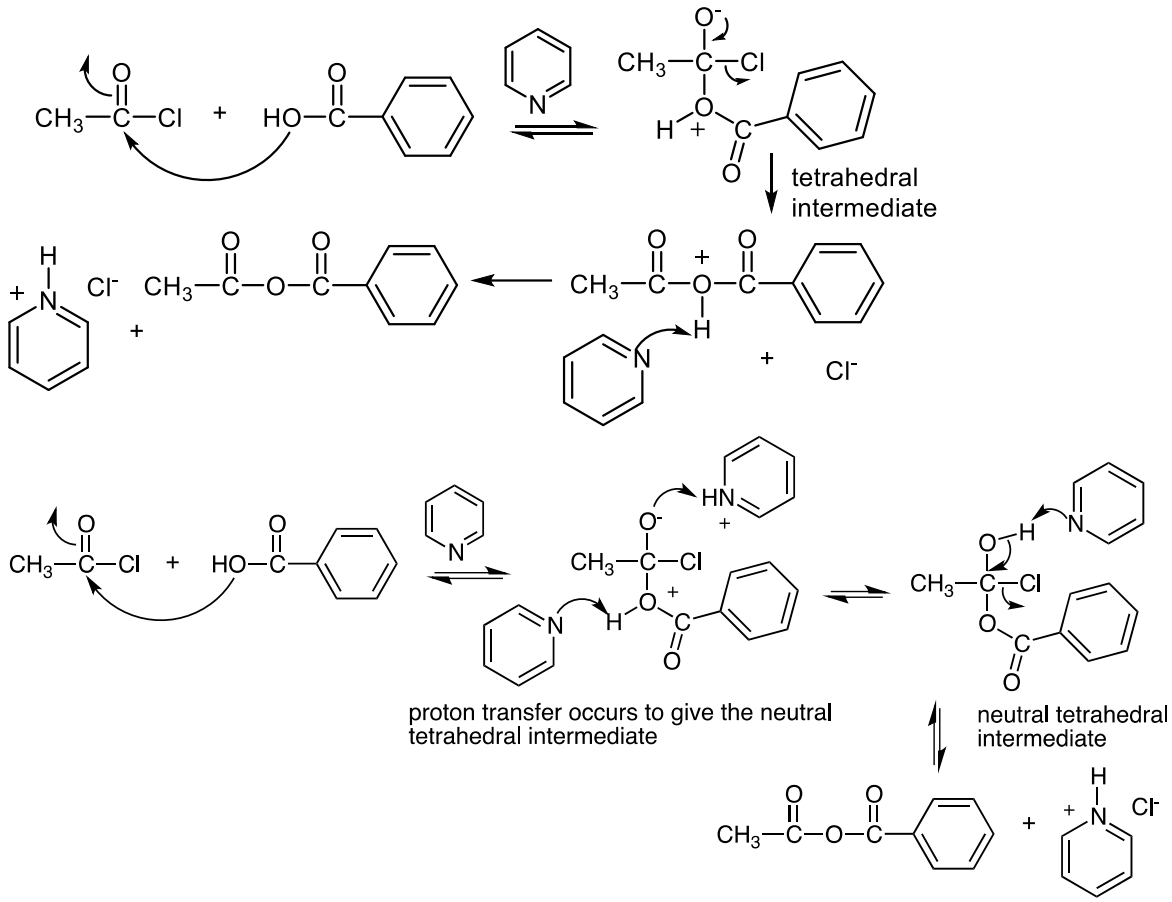
Acid chlorides are extremely reactive and are generally prepared *in situ* from carboxylic acids by heating in a solution of thionyl chloride. The thionyl chloride is generally used in excess as the solvent and when the reaction is finished the excess is removed by distillation, leaving behind the moisture sensitive and highly reactive acid chloride. Aqueous workups are to be avoided since the acid chlorides react rapidly with water to reform the carboxylic acid.



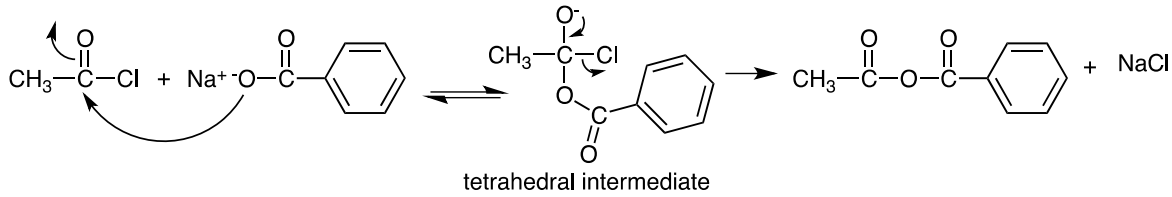
Reactions of Acid chlorides

Acid chlorides are the most reactive of the carboxylic acid derivatives and can therefore be used to prepare all of the other derivatives: (1) anhydrides (2) thioesters (3) esters (4) amides (5) carboxylic acids.

(1) Anhydride preparation:



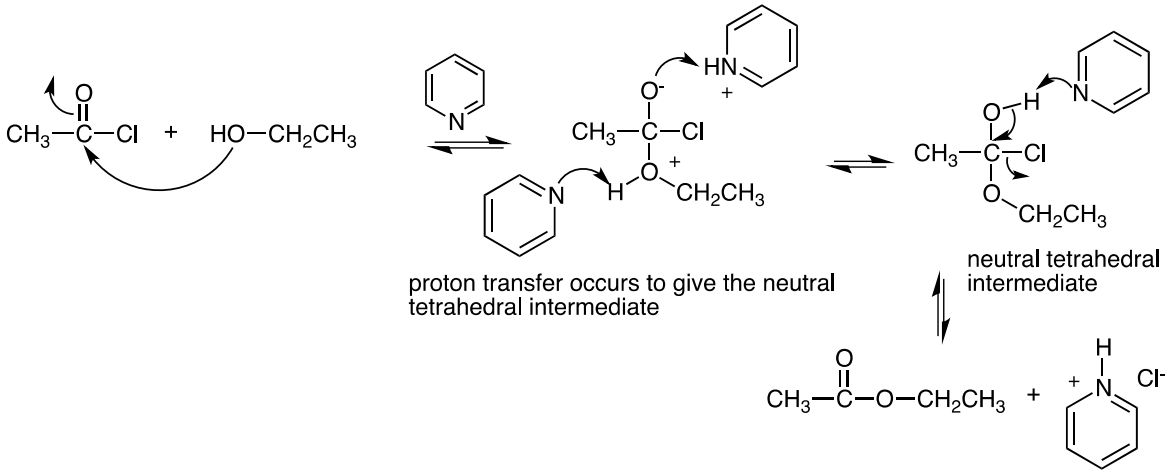
(b) We can also use the carboxylate salt in which case we do not need to add pyridine. The by-product is NaCl, rather than HCl.



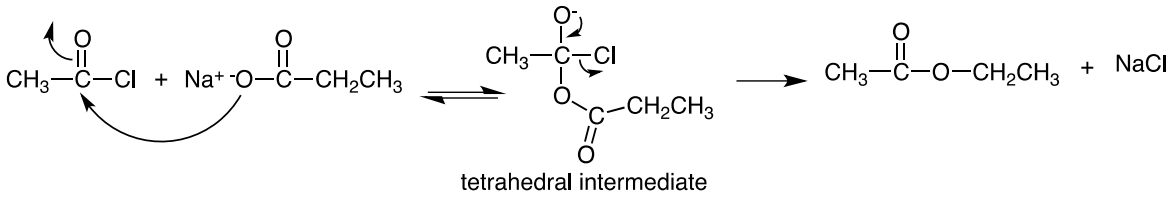
(2) Ester Preparation

As with the preparation of anhydrides, we can use neutral conditions (alcohol with a mild base) or basic conditions (alkoxides).

(a) From neutral alcohols with pyridine as the base:

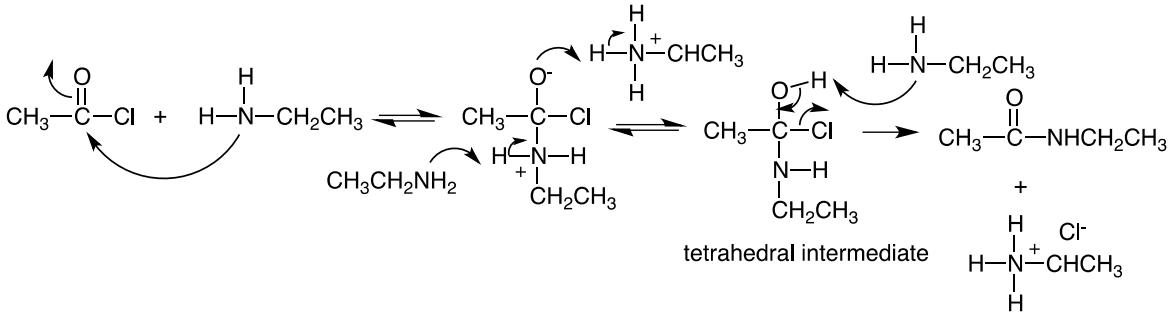


(b) From basic alkoxides: No pyridine is needed.



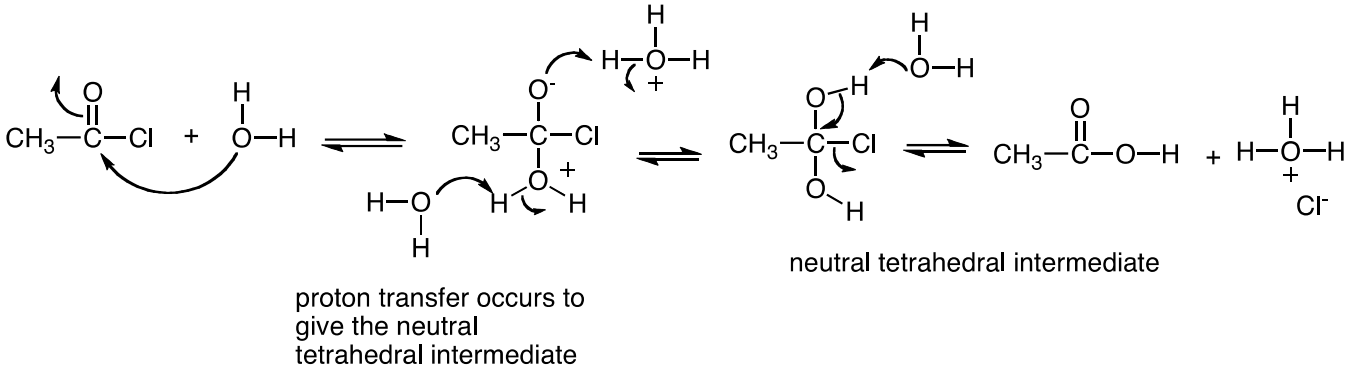
(3) Preparation of amides

We prepare amides from ammonia and primary and secondary amines. Tertiary amines give unstable products that cannot be isolated. Since amines are fairly strong bases and good nucleophiles we (1) don not need to add a second base such as pyridine and we simply use an excess of the amine to neutralize the HCl that is produced (provided that our amine is relatively inexpensive). And (2) we do not need to use an amine anion since the neutral amine is an excellent nucleophile.



(4) Hydrolysis of Acid Chlorides

Acid chlorides are easily hydrolyzed by water to give the carboxylic acid. This is not a useful reaction synthetically since acid chlorides are produced from carboxylic acids but it is a reaction that we must be aware of and usually try to avoid.



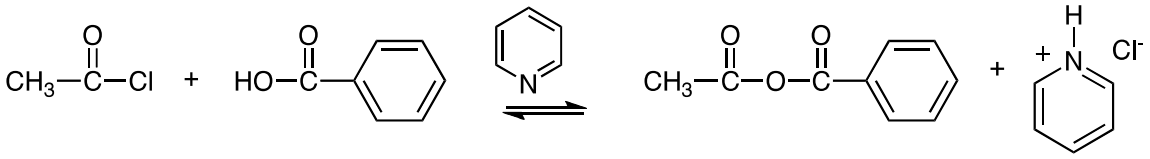
Anhydrides

After acid chlorides, the next most reactive derivatives are the anhydrides. They can be used to form the esters and amides and are also subject to hydrolysis.

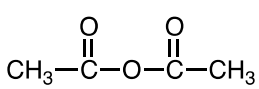
It is best to think of acid chlorides and anhydrides as reagents used for the preparation of the more stable end products, the esters and the amides.

Preparation

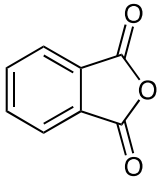
In the laboratory anhydrides are usually prepared from acid chlorides, as we have just seen.



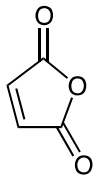
Other common derivatives are prepared by special methods on an industrial scale. These include



acetic anhydride



phthalic anhydride



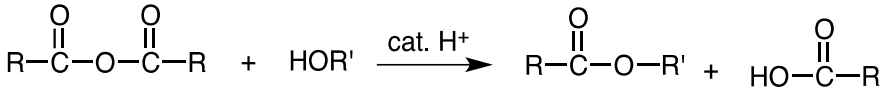
maleic anhydride

Reactions of Anhydrides

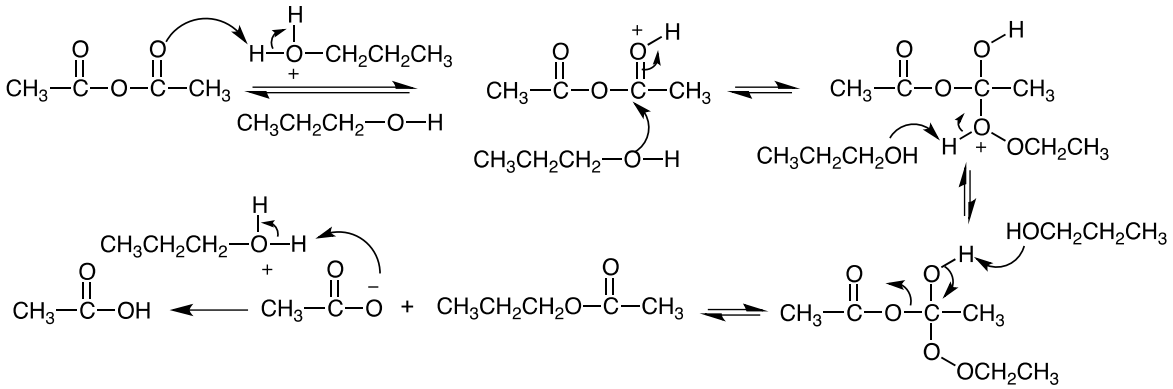
Since a nucleophile can attack either carbonyl, symmetrical anhydrides are usually used so as to give one product.

(1) Preparation of Esters

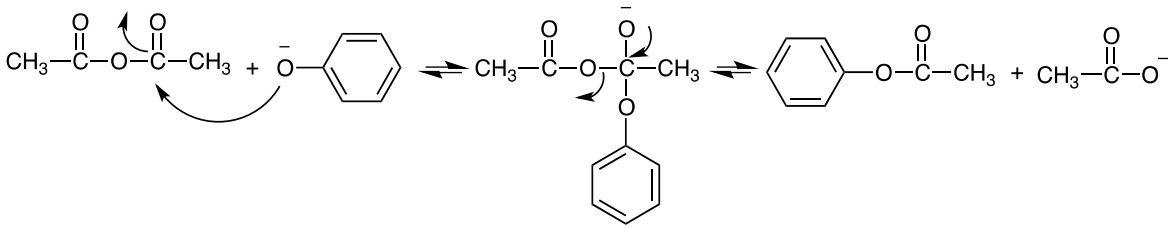
(a) We can use neutral alcohols. With the neutral alcohols we usually use acid catalysis to activate the carbonyl carbon of the anhydride to nucleophilic attack since the neutral alcohol is a relatively weak nucleophile. Acid catalysis increases the rate of formation of the tetrahedral intermediate.



For example:

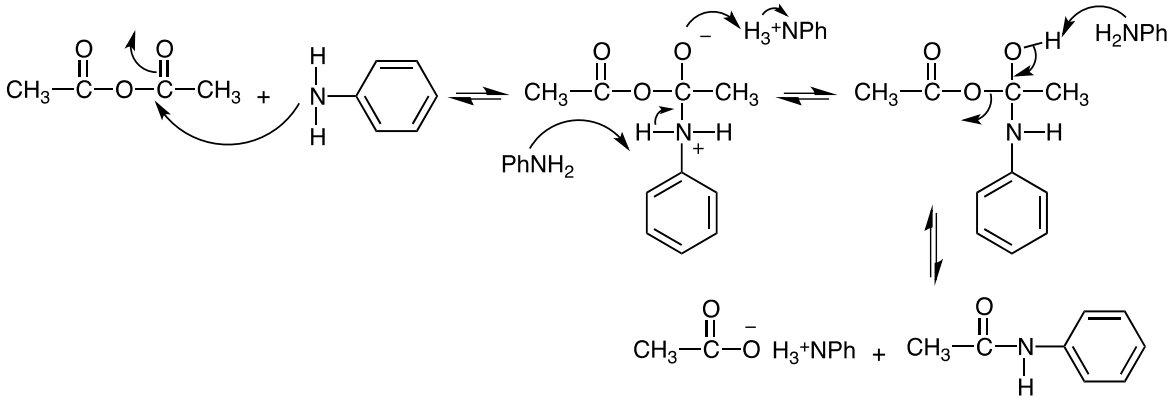


(b) Esters can also be formed from anhydrides in basic conditions using alkoxides.



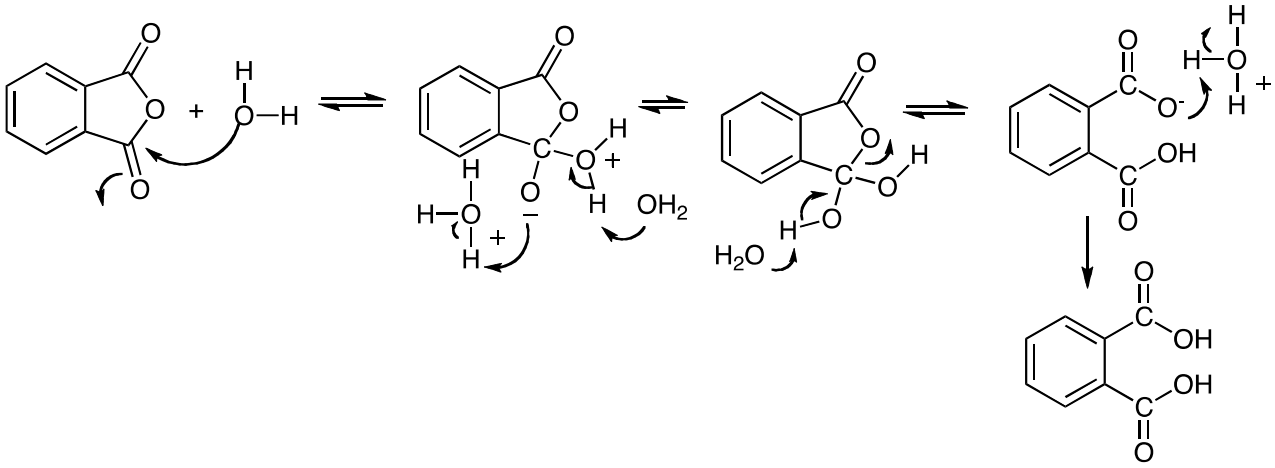
(2) Amide formation from anhydrides

Primary and secondary amines react with anhydrides to give amides. No catalysis is needed, since amines are basic and good nucleophiles. Use of acid would protonate the amine rather than the carbonyl carbon, making the amine non-nucleophilic.



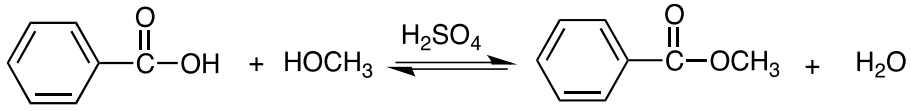
(3) Hydrolysis

Anhydrides are not stable in water and are converted back to the parent carboxylic acids. The reaction is generally slow at room temperature and is accelerated by heat.

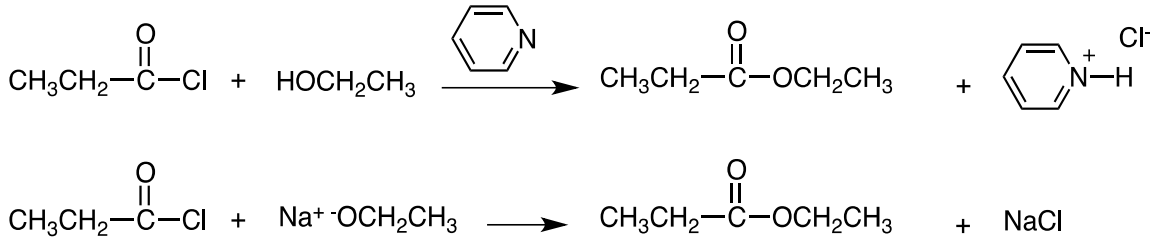


Esters

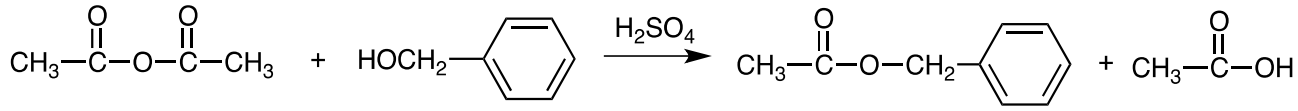
Preparation:
(1) As we saw, esters can be prepared directly from carboxylic acids and alcohols under conditions of acid catalysis.



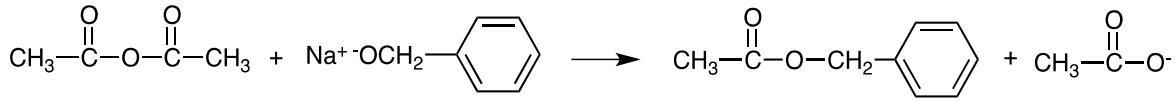
(2) From acid chlorides



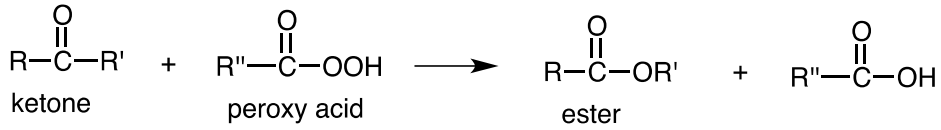
(3) From anhydrides:
Acidic conditions:



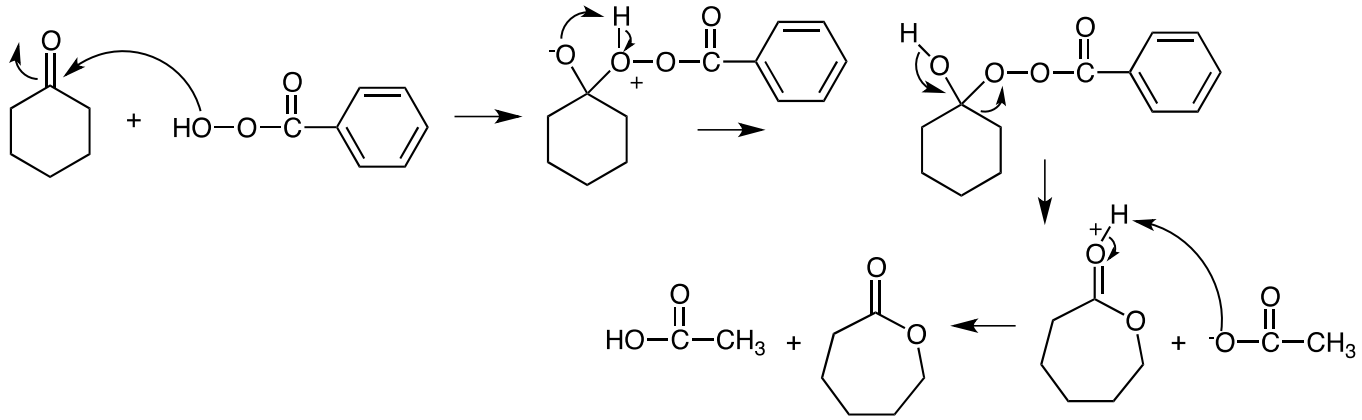
Basic conditions:



(4) Baeyer-Villiger oxidation of ketones with peroxy acids. An alkyl or aryl group migrates from carbon to oxygen.

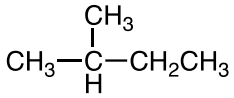


Generally the more electron rich group migrates (3° > 2° > cyclohexyl > benzyl > phenyl > 1° > methyl). This reaction is very useful for cyclic symmetric ketones. The product is a lactone (cyclic ester) that contains one more atom, so it is a ring-expansion reaction. For example:



Physical Properties of Esters

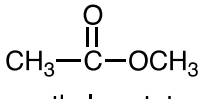
Esters are moderately polar compounds that have higher boiling points than hydrocarbons but lower than alcohols and much lower than carboxylic acids. Esters cannot donate hydrogen-bonds but they can accept them, so they have some solubility in water.



2-methylbutane

b.p. 28°C

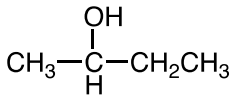
solubility in H_2O



methyl acetate

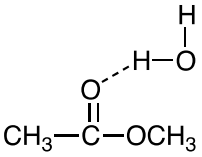
b.p. 57°C

33 g/100mL



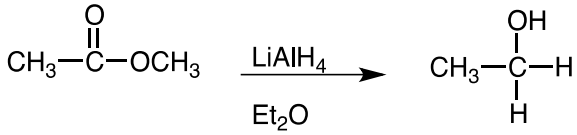
2-butanol

b.p. 99°C

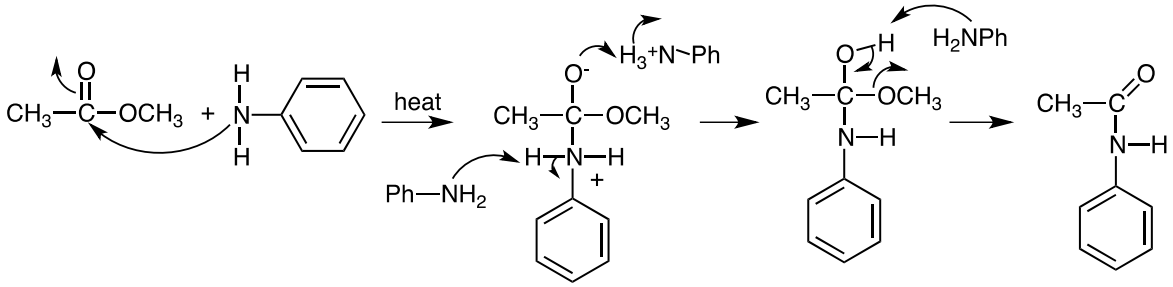


Reactions of Esters

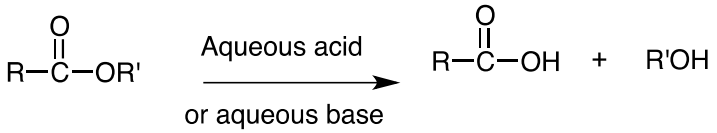
(1) (Review) Reduction with lithium aluminum hydride to a primary alcohol.



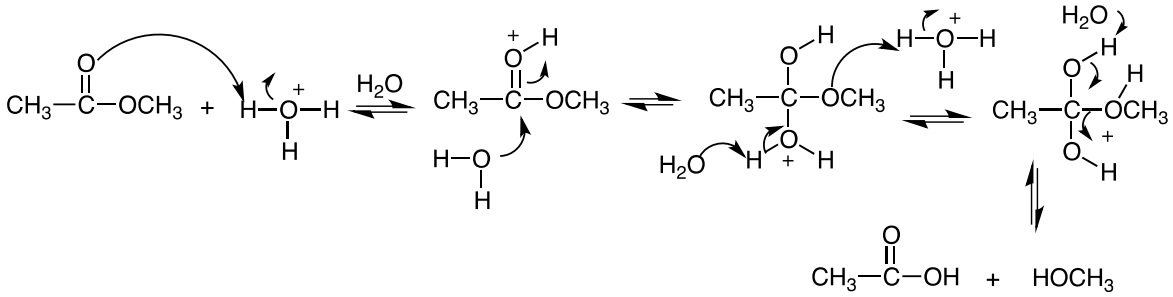
(2) Conversion of esters to amides with primary and secondary amines. Amides are below esters in the reactivity scale and so can be converted to amides.



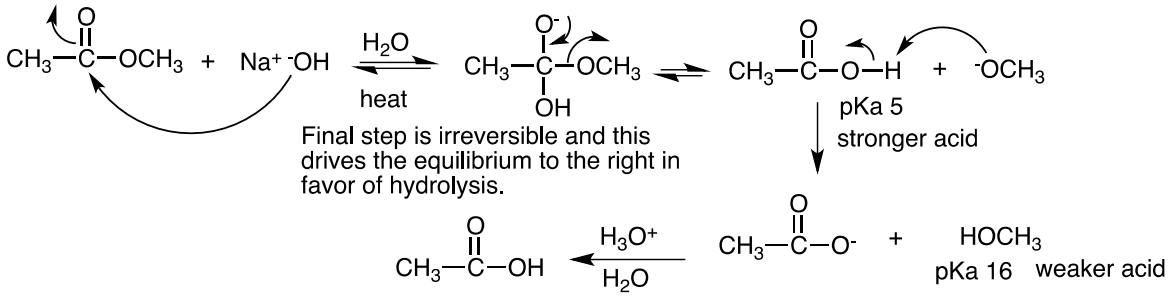
(3) Hydrolysis of esters to carboxylic acids in acidic or basic conditions.



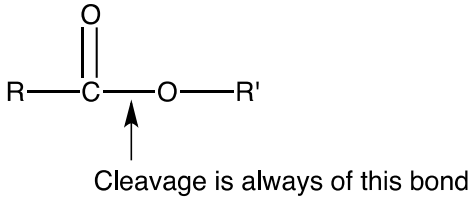
(a) Ester hydrolysis in acidic conditions is fully reversible and is the exact reverse of ester formation. We drive the reaction to the right in favor of hydrolysis by using an excess of water.



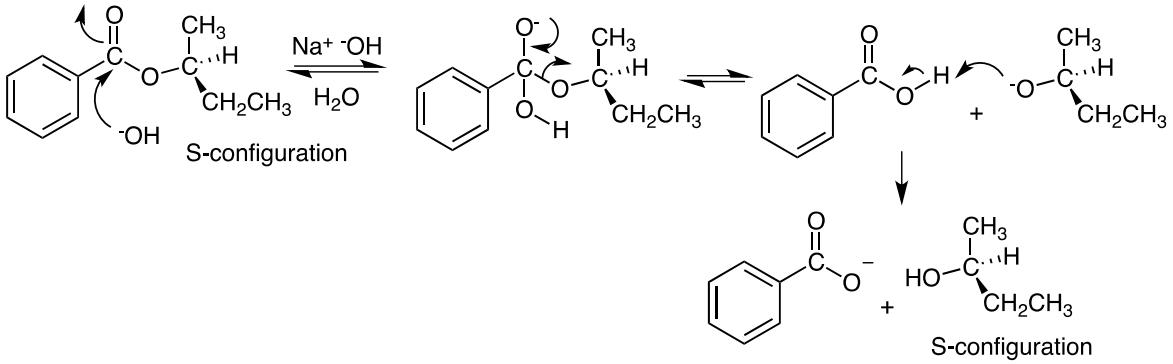
(b) Ester hydrolysis can also take place in basic conditions using aqueous sodium hydroxide. This reaction is called saponification (from the Latin *sapon* for soap because the basic hydrolysis of animal fat was a traditional way of making soap). One advantage of the basic hydrolysis is the reaction is irreversible. The initial carboxylic acid formed is irreversibly deprotonated by the basic hydroxide solution. To isolate the neutral carboxylic a final protonation step is required. The pH is made acidic by the addition of aqueous HCl.



Note that cleavage always occurs between the carbonyl carbon and the oxygen, not between the alcohol carbon and the oxygen.

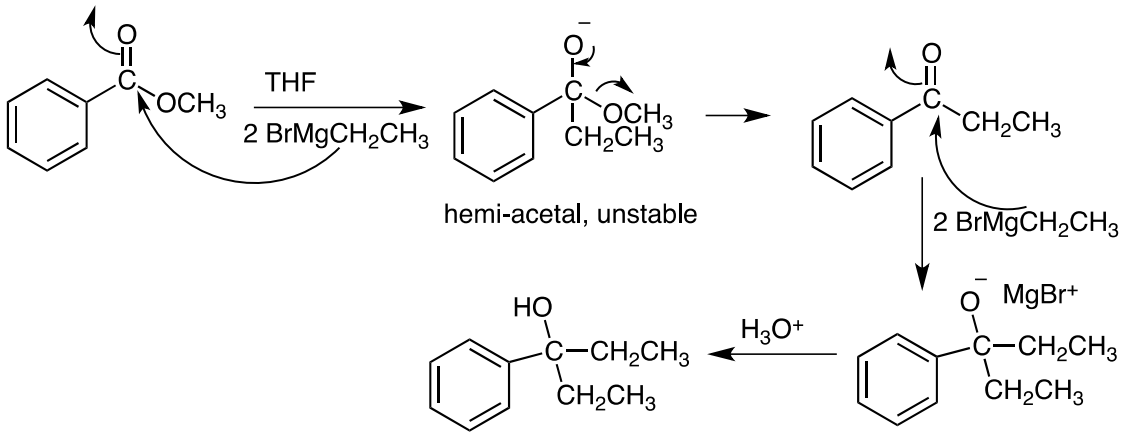


Therefore cleavage of esters with optically active alcohols results in retention of configuration of the alcohol moiety.



(4) Reaction of Esters with Grignard and organolithium reagents.

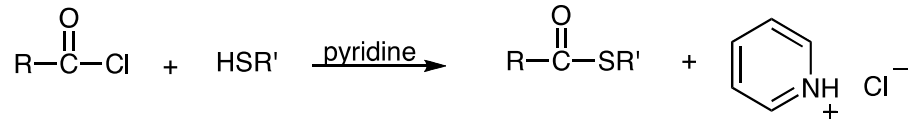
Grignard and organolithium reagents react twice with esters to give tertiary alcohols in which two of the substituents are the same.

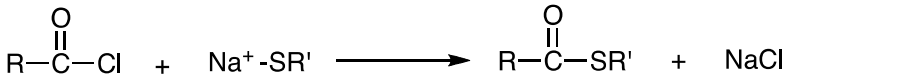


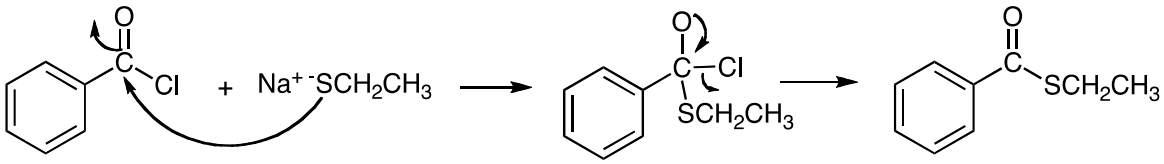
Thioesters

Preparation: Thioesters can be prepared from acid chlorides or anhydrides using the same conditions as discussed above for esters.

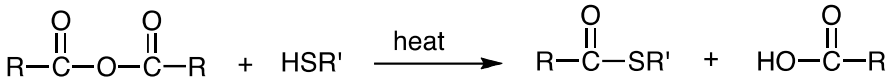
From acid chlorides:





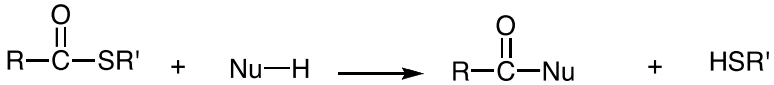


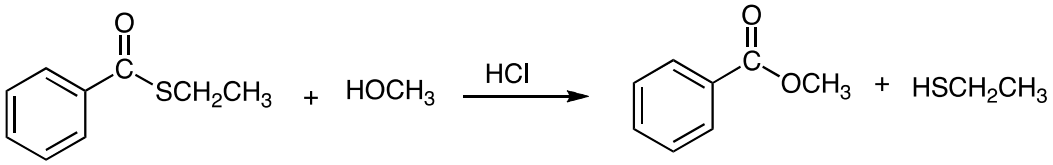
From anhydrides



Reactions

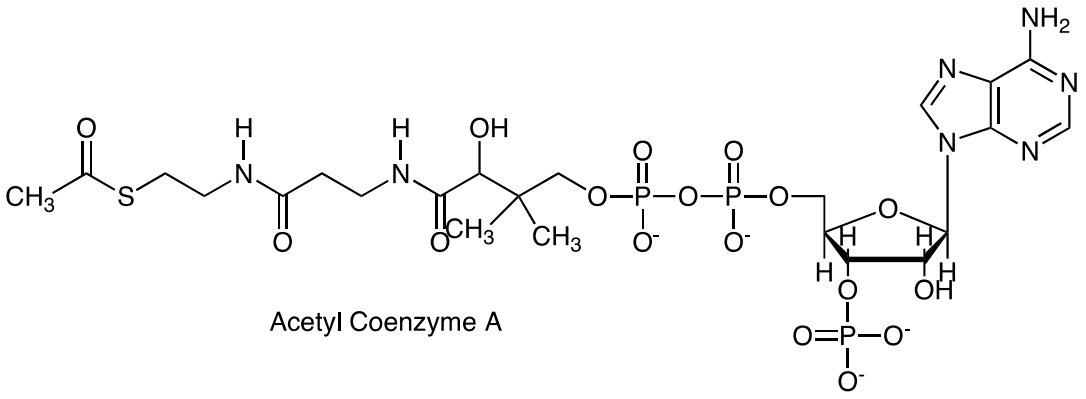
Thioesters will react with alcohols, alkoxides and amides. They see limited use in laboratory synthesis but are very important in biological systems.



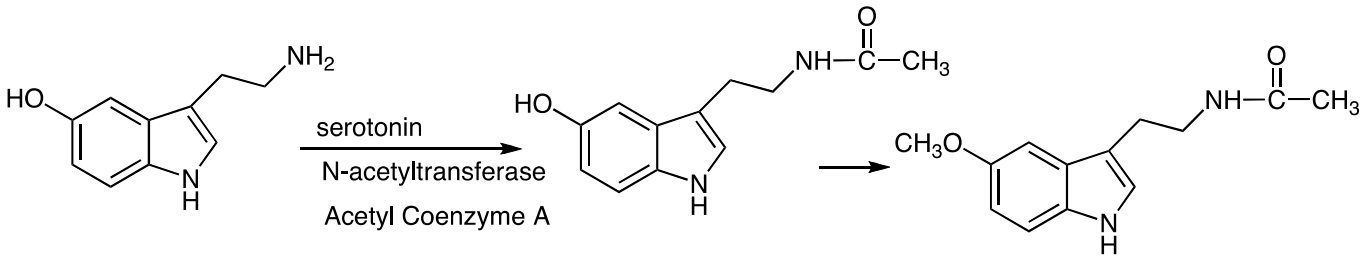


Thioesters are about as reactive as esters even though the ΔG for hydrolysis is more negative. The rates for hydrolysis are about the same as for esters.

But thioesters are much more reactive toward amine nucleophiles than esters. This helps to account for the importance of thioesters in biochemistry. Many biochemical reactions involve acyl transfer. The thioester, acetyl coenzyme A transfers acyl groups to alcohols, amines and other nucleophiles.



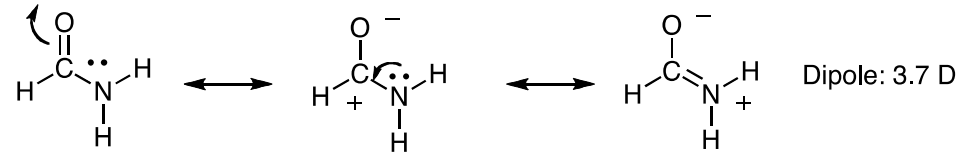
Acetyl coenzyme A has many functions. One of them is in the biosynthesis of melatonin. Melatonin is a hormone secreted by the pineal gland. It regulates circadian rhythms, including the wake-sleep cycle.



Amides

Amides are a very important functional group, especially in biochemistry since the bond in all proteins (the "peptide" bond) is an amide linkage.

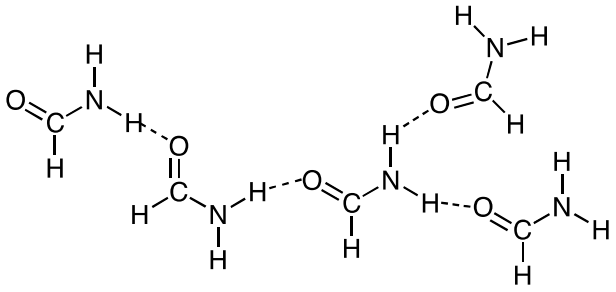
Amides have strong dipole moments due to the considerable electron donation of the nitrogen lone pair. This gives the C-N bond considerable double bond characters, as we have discussed.

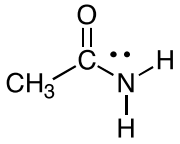


formamide

Delocalization of the nitrogen lone pair decreases the amount of positive charge at the carbonyl carbon, making it less electrophilic toward nucleophilic attack.

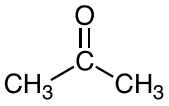
Amides are capable of strong intermolecular hydrogen-bonding, giving very high boiling points, much higher even than carboxylic acids.





acetamide

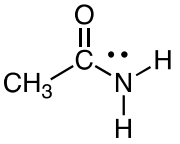
b.p. 221°C



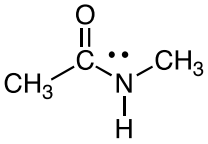
acetone

b.p. 56°C

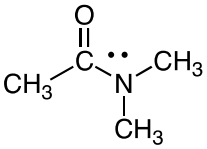
The boiling point decreases as the number of hydrogen-bonds decreases.



b.p. 221°C



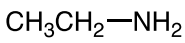
b.p. 206°C



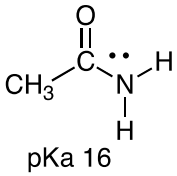
b.p. 165°C

Acidity of Amides

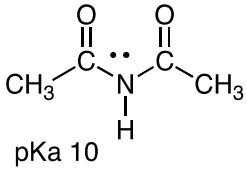
Since nitrogen is less electronegative than oxygen the N-H bond is stronger than the O-H bond or a carboxylic acid and amides are much weaker acids. They are comparable in acidity to alcohols, with pKa's of ~16.



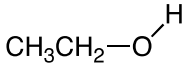
pKa 36



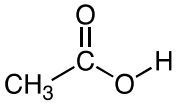
pKa 16



pKa 10



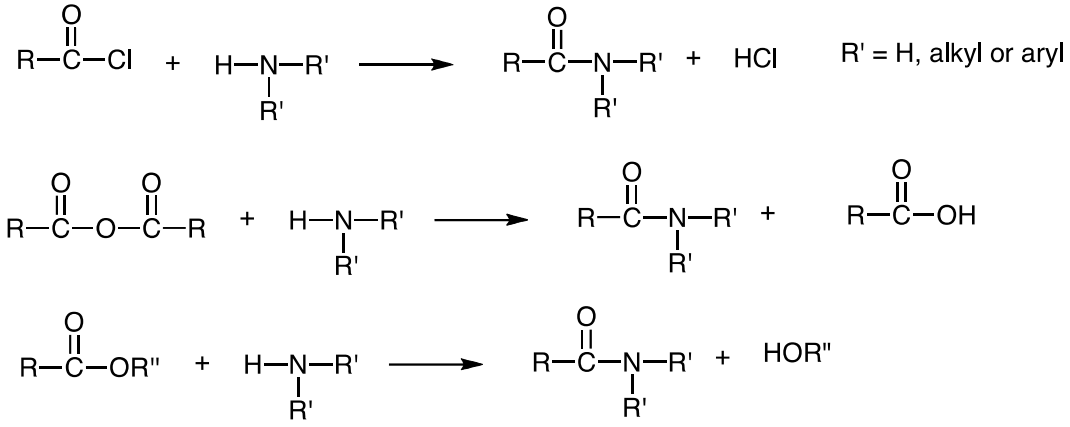
pKa 16



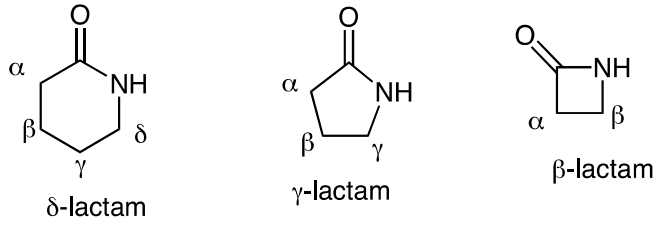
pKa 4.78

Synthesis of Amides

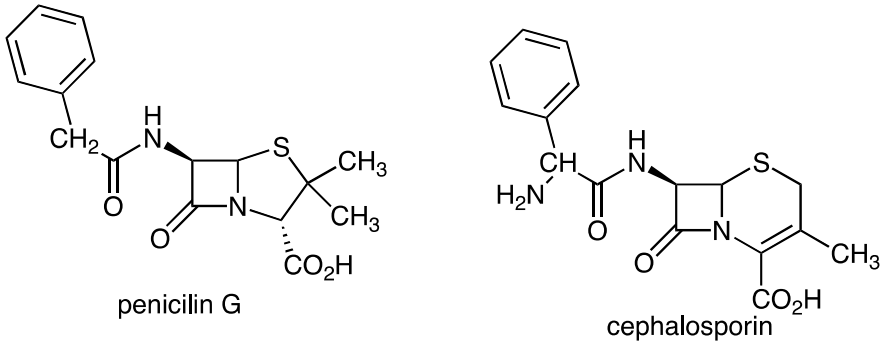
As we have seen, amides are at the bottom of the reactivity scale and can be synthesized by all of the other derivatives we have talked about: from (1) acid chlorides, (2) anhydrides, (3) thioesters, (4) from esters. Since an acid is produced when acid chlorides or anhydrides are used, an extra equivalent of the amine is often added so as to neutralize this acid. If the amine is expensive, another base may be added.



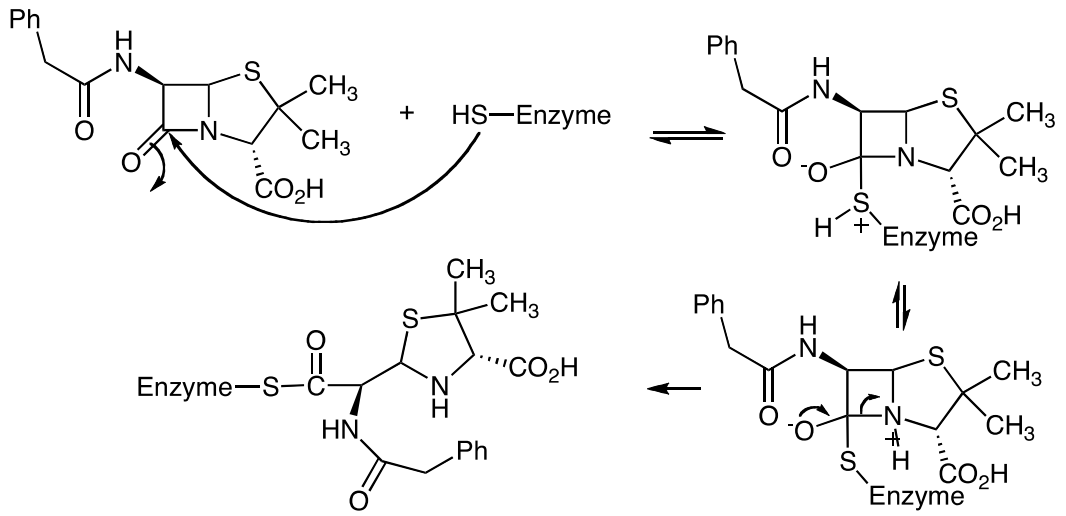
Cyclic amides or lactams can be formed.



The β-lactams are very important in medicinal chemistry since they are the key reactive functional group in the penicillin antibiotics.



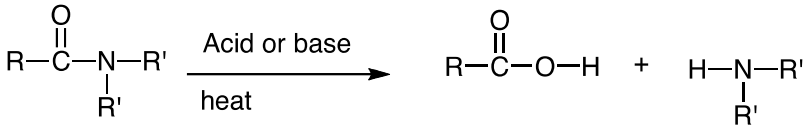
The 4-membered ring lactam is much more reactive than normal lactams due to angle strain. It undergoes a ring opening reaction when attacked by a sulfhydryl group of one of the bacterial enzymes involved in cell wall synthesis. Humans do not have this enzyme and therefore are not harmed by the drug. The penicillin is a "suicide inhibitor" because it forms an irreversible covalent bond with the target bacterial enzyme, shutting down its function and eventually leading to death of the bacterial cell.



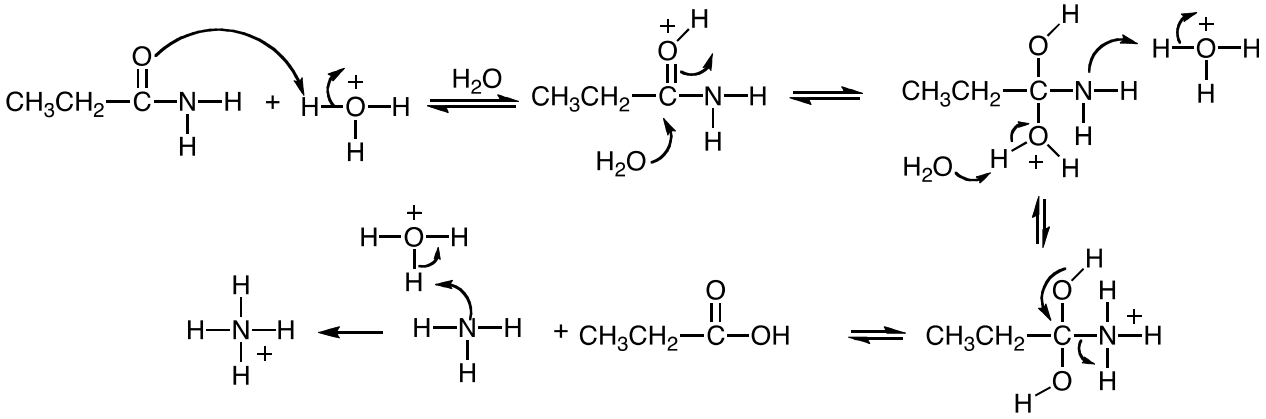
Covalent adduct of enyme and penicilin

Reactions of Amides

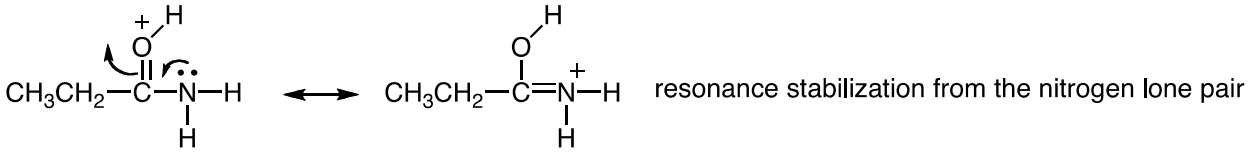
Because amides are the least reactive of the carboxylic acid derivatives, the only significant reactions they undergo are hydrolysis. This occurs under acidic or basic conditions.

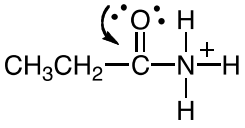


Acidic Conditions



Note that in the first step, protonation of the amide occurs on the carbonyl oxygen, not on the nitrogen. Protonation on the carbonyl allows for resonance stabilization of the resulting cation by the nitrogen lone pair. If protonation were to occur on the nitrogen, no such resonance stabilization by oxygen lone pair would be possible.

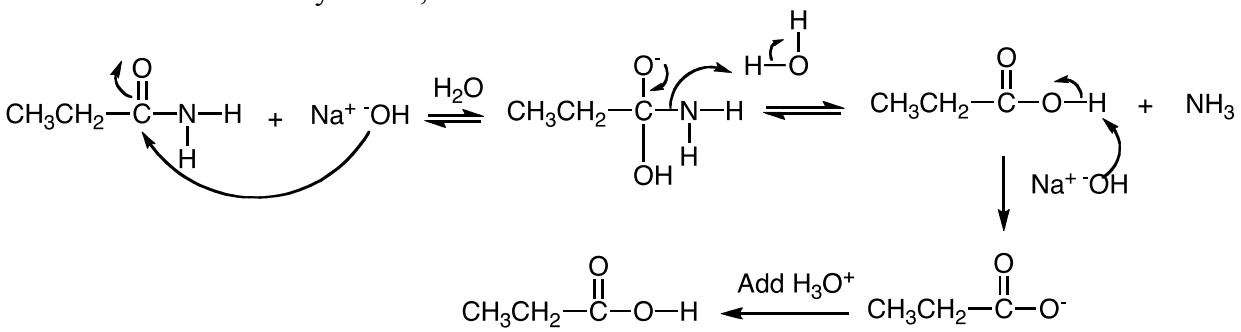




No resonance stabilization possible from the oxygen lone pair since the carbon would then have five bonds.

Basic conditions

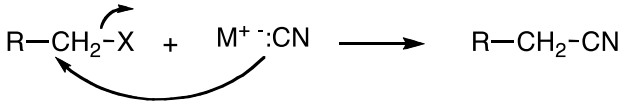
The final step is irreversible deprotonation of the carboxylic acid in the basic conditions. To isolate the neutral carboxylic acid, acid must be added to neutralize the solution.



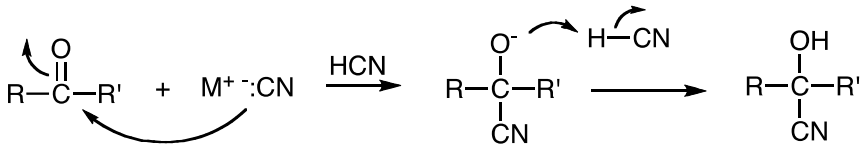
Nitriles

Preparation

(1) Nitriles can be prepared by means of an S_N2 reaction of cyanide anion with alkyl halides.

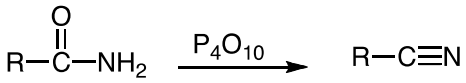


(2) By reaction of cyanide anion with an aldehyde or ketone to form the cyanohydrin.



(3) Dehydration of Amides

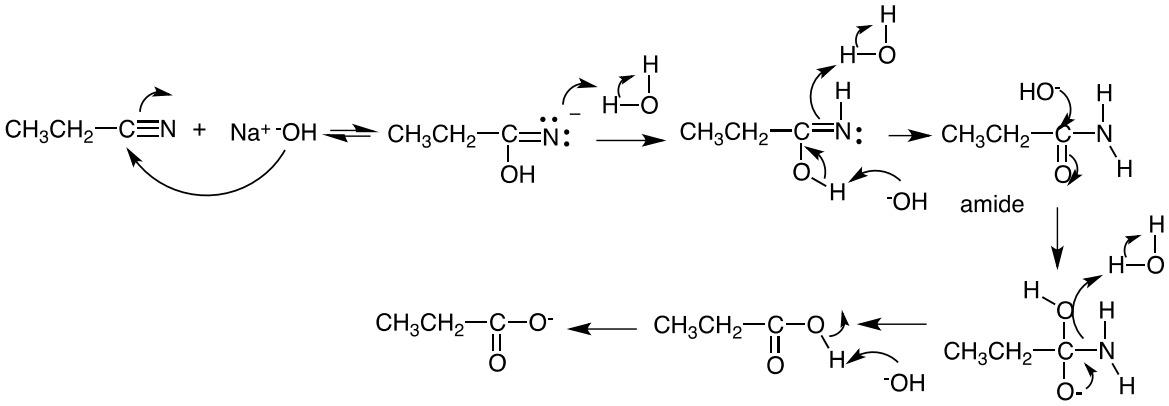
Amides can be dehydrated using a strong dehydrating agent such as phosphorus pentoxide, which is the anhydride of phosphoric acid.



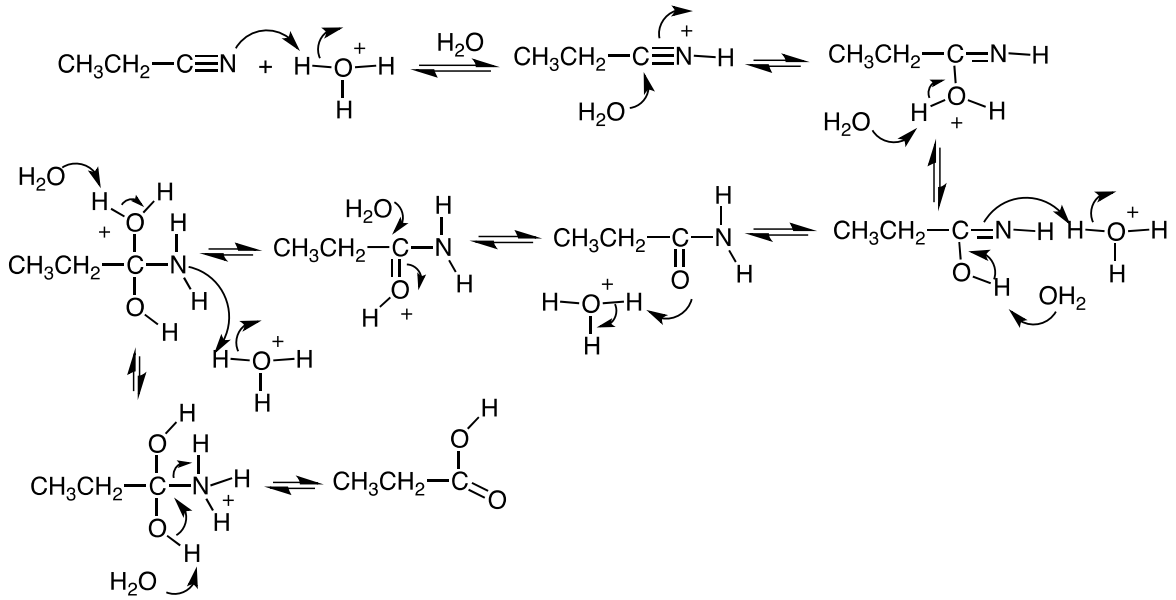
Reactions of Nitriles

(1) Hydrolysis: Nitriles can be hydrolyzed in either acidic or basic conditions. Nitriles are quite stable and need fairly high temperatures for the hydrolysis.

(a) Basic hydrolysis:
Hydroxide attacks the nitrile carbon and the nitrogen gets a negative charge. The nitrogen anion then is protonated by water. This initial intermediate rearranges to the amide. The amide can be isolated but it is usually hydrolyzed to the carboxylic acid.



(2) Acidic Hydrolysis:



(3) Reaction of Nitriles with Grignard and organolithium reagents:

Nitriles are electrophilic and are attacked by Grignards and organolithium reagents to give ketones after the work up. Unlike esters, they react only once since the initial intermediate is an anion that is no longer electrophilic. Hydrolysis of the imine occurs during the acidic workup.