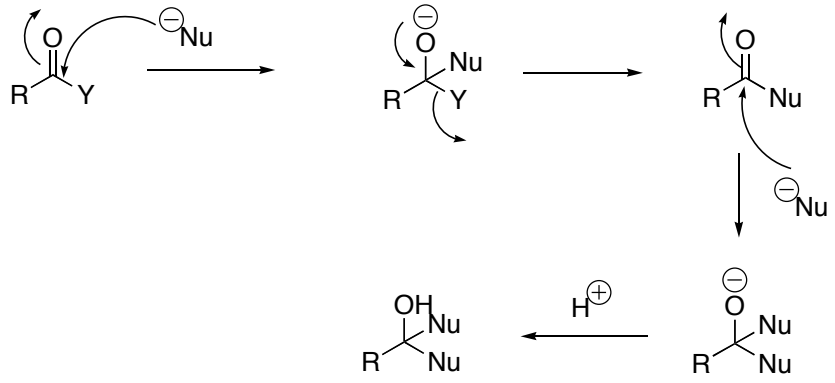
Reactions of Carboxylic Acids and Derivatives: Strong Nucleophiles

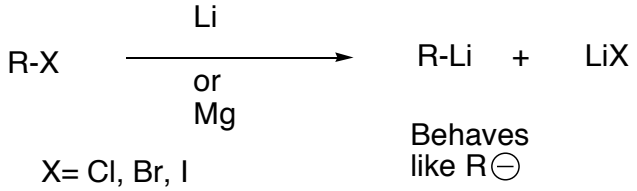
The strong nucleophiles (Nu: $^-$) that we have learned in this course are either hydride anion (H^-) or alkyl anion (R^-). As well, remember that attack by strong nucleophiles is not reversible.

Hydride anion comes from hydride donor such as $LiAlH_4$ or $NaBH_4$ (however, $NaBH_4$ is not strong enough reaction on carboxylic acid derivatives except for acid chlorides). Alkyl anion comes from RM, where R is an alkyl group and M is a metal (these reagents include Grignard reagents (RMgX) and alkyl lithium reagents RLi). Grignard reagents fail with carboxylic acids, but alkyl lithium reagents can be used.

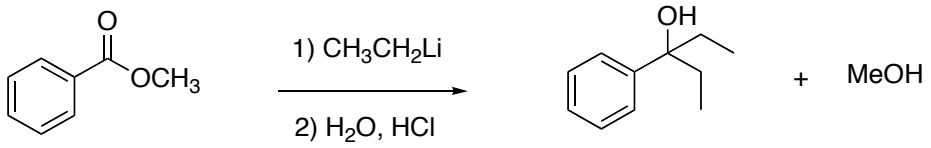
General mechanism:



Alkyl anion as nucleophile

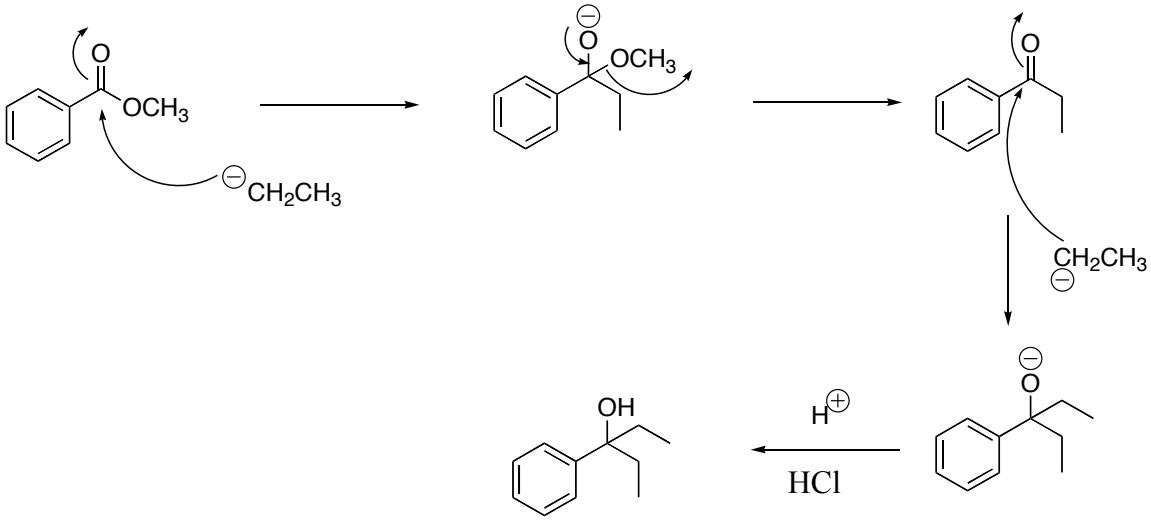


Example:

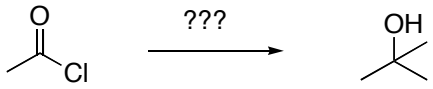


methyl benzoate

mechanism:



Example:



What reagent would you use for this reaction?

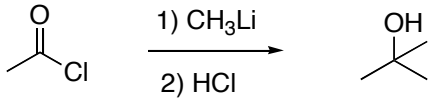
Let's analyze this: *what has changed between the two molecules?*
The Cl group has gone, there are three methyl groups attached to the center carbon, and carbon oxygen double bond is singly bonded. As the mechanism above, methyl anion is used.

Analysis of Problem

Add	Reagent	Remove
H+	HCl	
CH_3^-	CH_3Li	
CH_3^-	CH_3Li	

- Cl

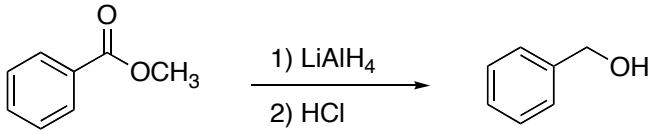
Answer:

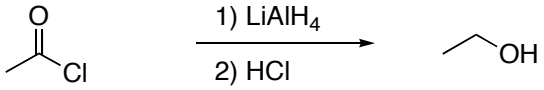


H^- ($LiAlH_4$) as nucleophile:

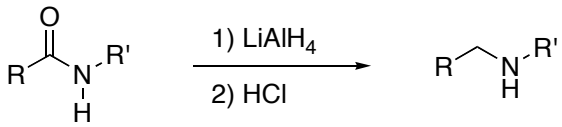
The mechanism of hydride anion attack carboxylic acid derivatives is same as shown above for the alkyl anion attack.

Example:





"Exception" for $LiAlH_4$

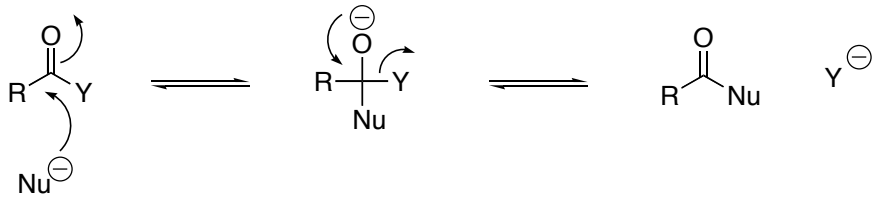


General Reaction of any Carboxylic Acid Derivative with a Weak Nucleophile

The chemistry of carboxylic acid derivatives is dominated by the nucleophilic acyl substitution reaction. Mechanistically, these substitutions take place by addition of a nucleophile to the polar carbonyl group of the acid derivative, followed by expulsion of a leaving group from the tetrahedral intermediate. These reactions takes place in both

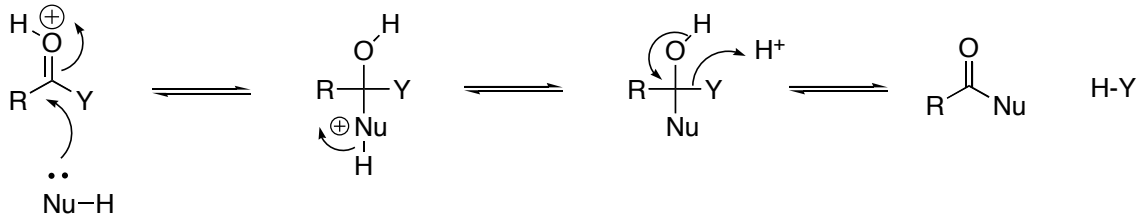
acidic and basic environments and have slight mechanistic differences. These reactions are also reversible with weak nucleophiles.

Under basic conditions, the anionic nucleophile will attack the carbonyl of the carboxylic acid derivative to form the tetrahedral intermediate. This intermediate will then displace the leaving group (shown as Y) to yield the substituted carboxylic acid and the Y anion. If the Y anion is quite basic (e.g. amide anion $R_2N:^-$ or alkoxide/hydroxide anion RO^-) it will leave only as a neutral species after protonation of the nitrogen or oxygen.



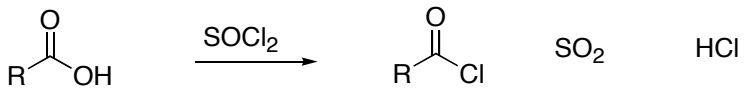
tetrahedral intermediate

Under acidic conditions, a lone pair of electrons from the nucleophile will attack the protonated carbonyl group of the carboxylic acid derivative to form a positively charged tetrahedral intermediate. Loss of a proton then yields the neutral species. The intermediate then displaces the leaving group, which is protonated to yield the substituted carboxylic acid and the protonated leaving group.



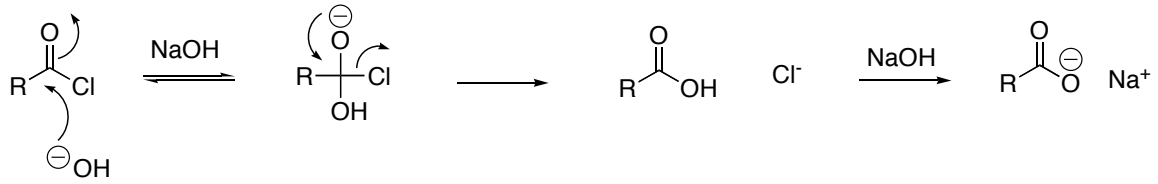
Preparation of Acid Chlorides

Acid chlorides are prepared from carboxylic acids by reaction with thionyl chloride ($SOCl_2$) by a mechanism we will not discuss now.

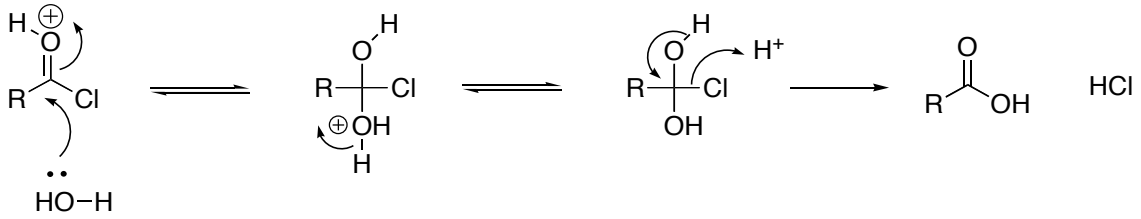


Hydrolysis of Acid Chlorides

Acid chlorides react under acidic or basic conditions to yield carboxylic acids. This hydrolysis reaction is a typical nucleophilic acyl substitution. Acid halides, anhydrides, esters and amides react in a similar fashion under these hydrolysis conditions. Under basic conditions, the hydroxide anion attacks the carbonyl group of the acid chloride to yield a tetrahedral intermediate reversibly, which then displaces the chloride irreversibly to yield the carboxylic acid. Since we are under basic conditions, the base will deprotonate the acid to yield the carboxylate salt. The displacement step of the reaction is irreversible because the chloride is a far better atom to stabilize a negative charge than the oxygen.



Under acidic conditions, the protonated carbonyl group of the acid chloride is attacked by water to yield the tetrahedral intermediate, which is then deprotonated to become a neutral species. The intermediate then displaces the chloride anion to yield the carboxylic acid. Once again the displacement step of the reaction is irreversible due to the reasons given above.

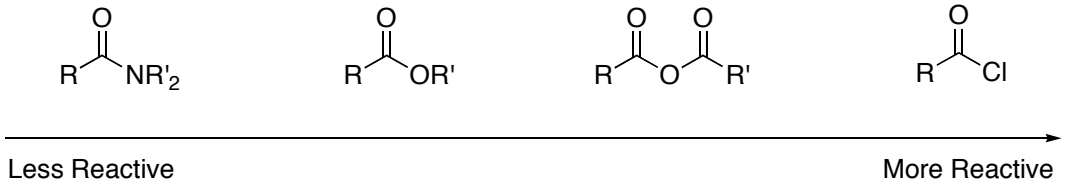


Reactivity of Carboxylic acid Derivatives

Nucleophilic acyl substitution reactions usually take place in two steps: addition of the nucleophile and elimination of a leaving group. Although both steps can affect the overall rate of the reaction, it is generally the first step that is rate-limiting. Therefore any factor that makes the carbonyl group of the carboxylic acid derivative more easily attacked will favor the reaction.

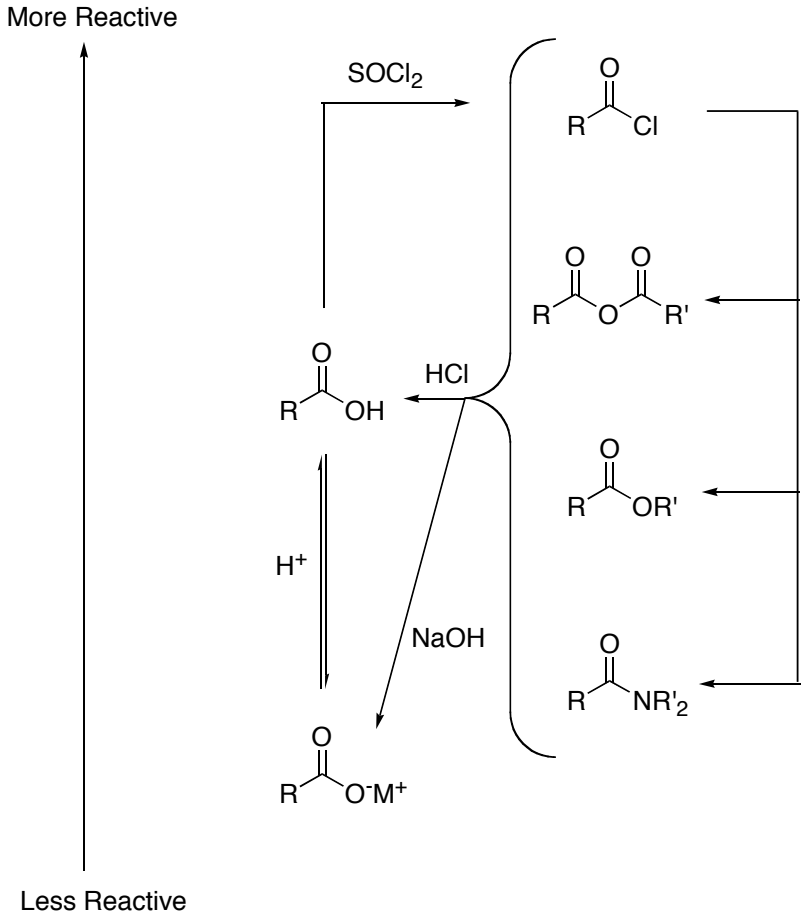
Electronically, polarized acid derivatives are attacked more readily than less polar ones. Thus, acid chlorides are more reactive than anhydrides, which are more reactive than esters, which are more reactive than amides. This is due to the electronegative group,

such as chlorine, polarizing the carbonyl group more strongly than an alkoxy group (ester) or an amino group (amide).

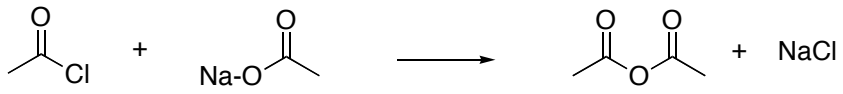


An important factor of the observed reactivity order is that it is possible to transform a more reactive acid derivative into a less reactive one. Acid chlorides for example can be converted into anhydrides, ester and amides but amides cannot readily be converted into esters, anhydrides or acid chlorides directly.

The chart below will help you remember the reactivity order and the possible transformations. The reactivity of a carboxylic acid is approximately between an anhydride and an ester. The carboxylate salt is the least reactive but is easily converted to the carboxylic acid with acidic treatment. Using the chart, the carboxylic acid can easily be converted to the acid chloride by treatment with thionyl chloride ($SOCl_2$). The acid chloride can then be converted to a less reactive derivative such as an anhydride, ester or amide. As seen from the chart, an anhydride can be directly converted to an ester or an amide. An ester can be directly converted to an amide. Each of these derivatives can be converted back to the carboxylic acid or carboxylate salt by either acid or base hydrolysis. Using the chart, an amide cannot be directly converted to an acid chloride. First the amide must be hydrolyzed to the carboxylic acid by acid or base, then reacted with thionyl chloride to yield the acid chloride.

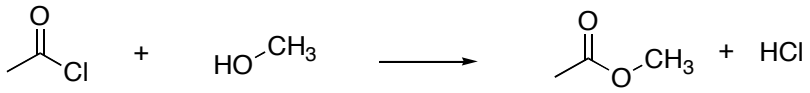

More Reactive
Less Reactive
SOCl2
HCl
H+
NaOH
R
Cl
R'
OH
OR'
NR'2
O-M+

An example is the conversion of acetyl chloride to acetic anhydride. Since an acid chloride is more reactive than an anhydride, treatment of acetyl chloride with carboxylate salt of acetic acid (sodium acetate) will give acetic anhydride and sodium chloride.



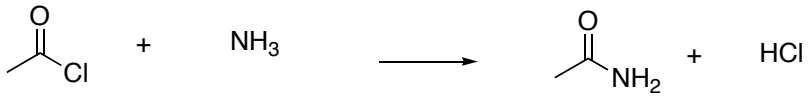
acetyl chloride acetic anhydride

Another example is the conversion of acetyl chloride to methyl acetate. An acid chloride is more reactive than an ester, therefore treatment of acetyl chloride with methanol will yield methyl acetate and HCl.



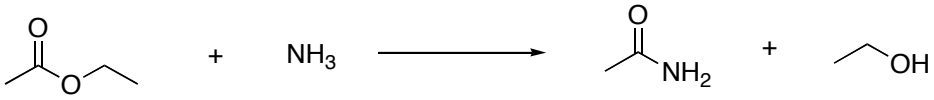
acetyl chloride methanol methyl acetate

Another example is the conversion of acetyl chloride to acetamide. An acid chloride is more reactive than an amide, therefore treatment of acetyl chloride with ammonia will yield acetamide.

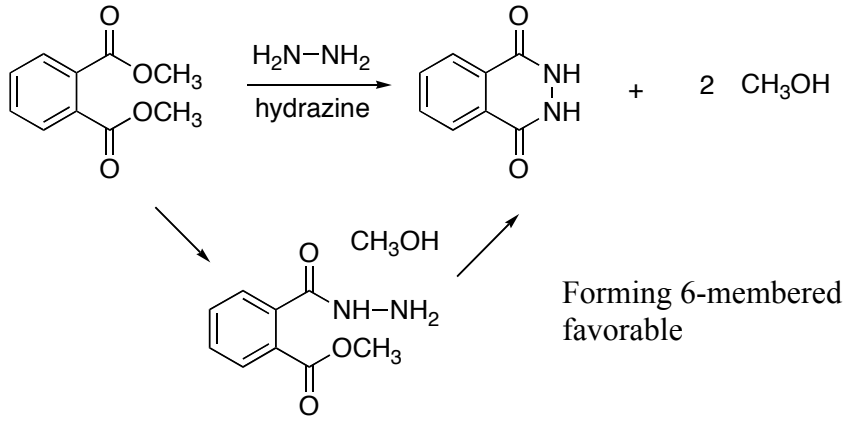


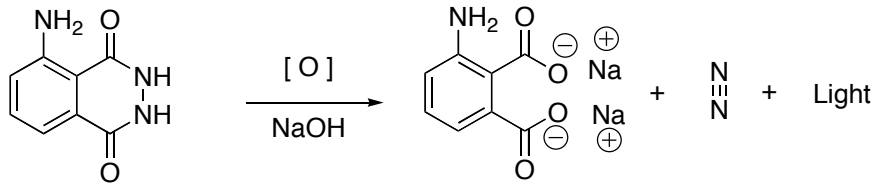
acetyl chloride ammonia acetamide

The above acetamide can be prepared from ester as well, since esters are more reactive than amides.



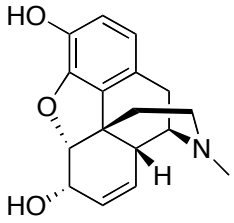
In each of the above examples, the reverse reaction will NOT proceed





Alkaloids

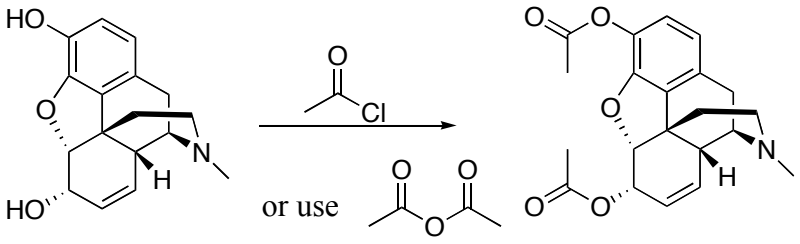
Nitrogen-containing compounds from plant sources are referred to as alkaloids. The study of alkaloids provided much of the growth of organic chemistry in the nineteenth century and still remains a growing area of research. One particular group of alkaloids are the morphine alkaloids.



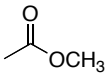
Morphine

Morphine was the first alkaloid isolated in pure form from the poppy. Morphine has addictive properties and is also an analgesic (pain killer). Therefore derivatives of morphine were synthesized to try to separate the addictive properties from the analgesic properties. One of the first such derivatives involved the treatment of morphine with acetyl chloride to yield an acetylated derivative of morphine. This compound was found to be 1000x better of an analgesic and was referred to as the "hero" compound. This

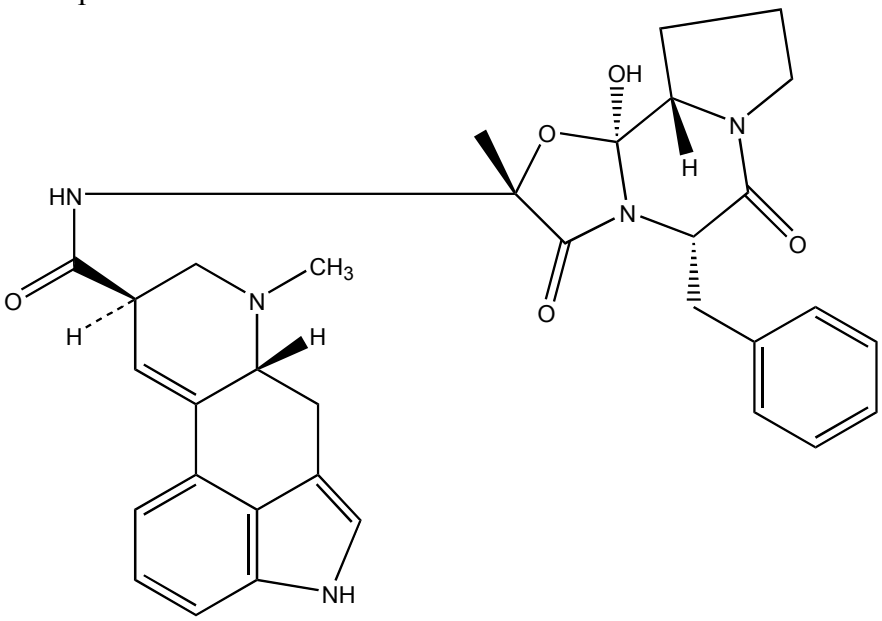
compound was also found to be 1000x more addictive than morphine and is commonly known as heroin.



Morphine Heroin

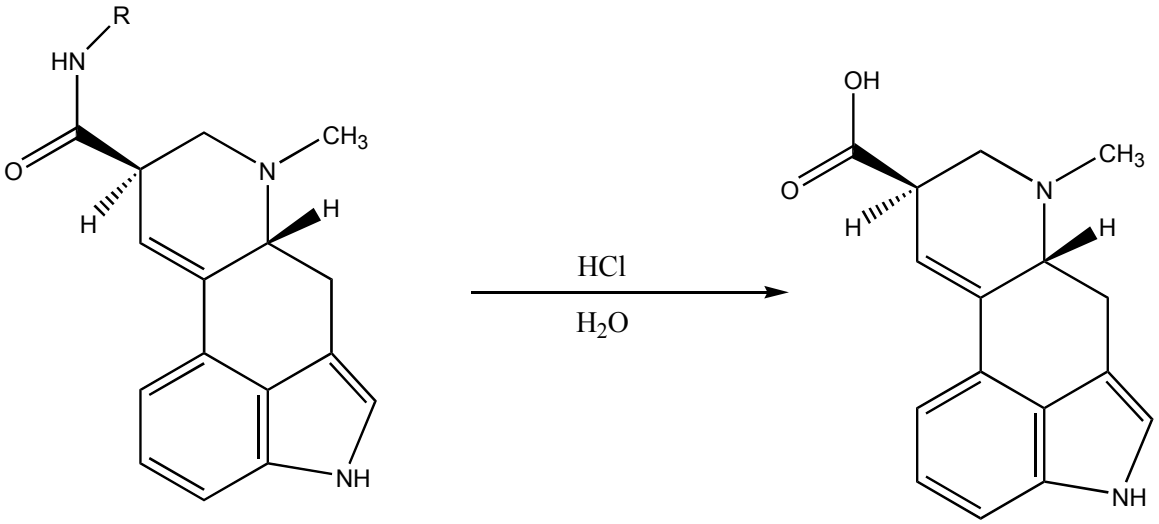
However, the above reaction does not really work(very slow) with   and it does not with 

Example:



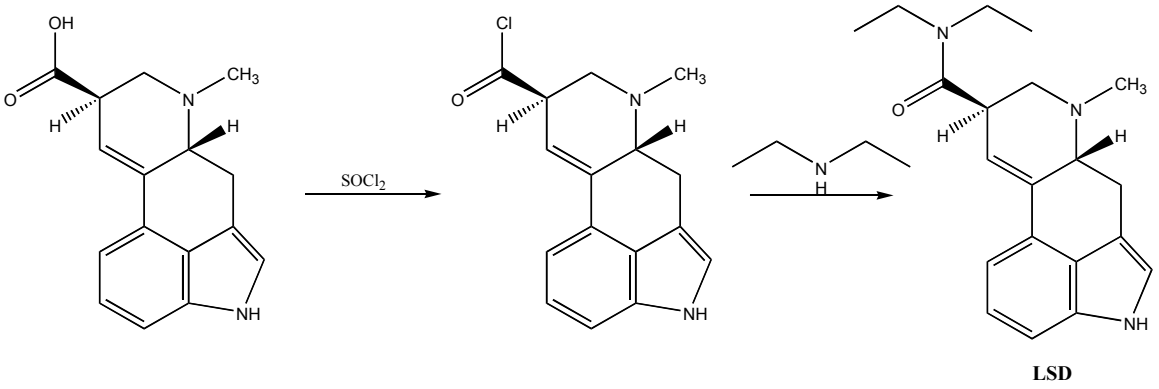
This structurally complicated molecule is called ergotamine. It is a mycotoxin produced by fungi *Claviceps paspalii* and it causes constriction of blood vessels. It is the cause for the disease St. Anthony's Fire in the middle ages through contamination on rye.

When ergotamine is treated with acid/water, what is the bond that will react with the left side of the structure?



At the left hand of the structure, there is amide functionality. When treated with acid in water, the amide is hydrolyzed to carboxylic acid.

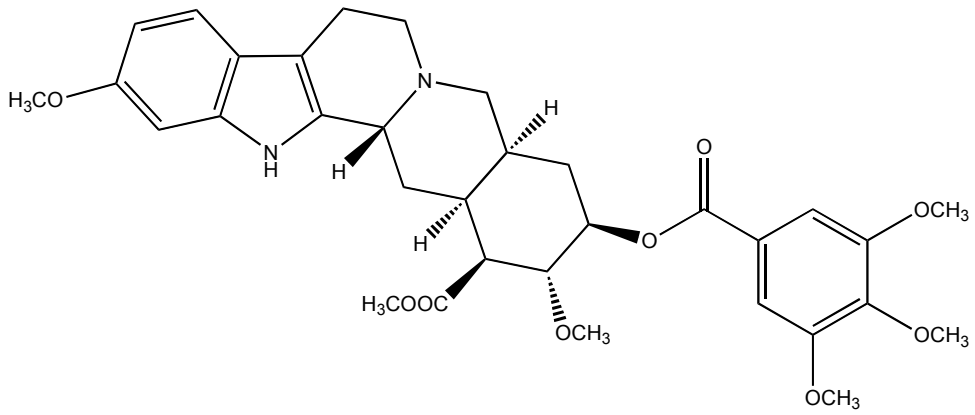
In 1938, Alberta Hoffman, as part of a large research program searching for medically useful ergot alkaloid derivatives, discovered/synthesized LSD.



LSD

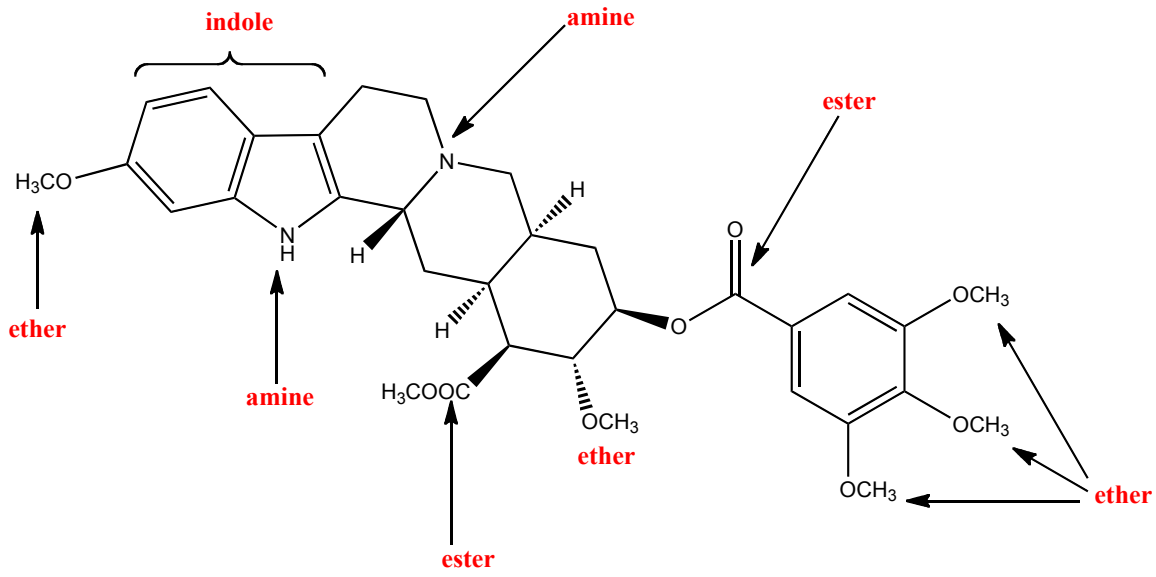
Note that acid cannot go directly to amide. It must go through the acid halide intermediate before being finally converted to amide.

Example:

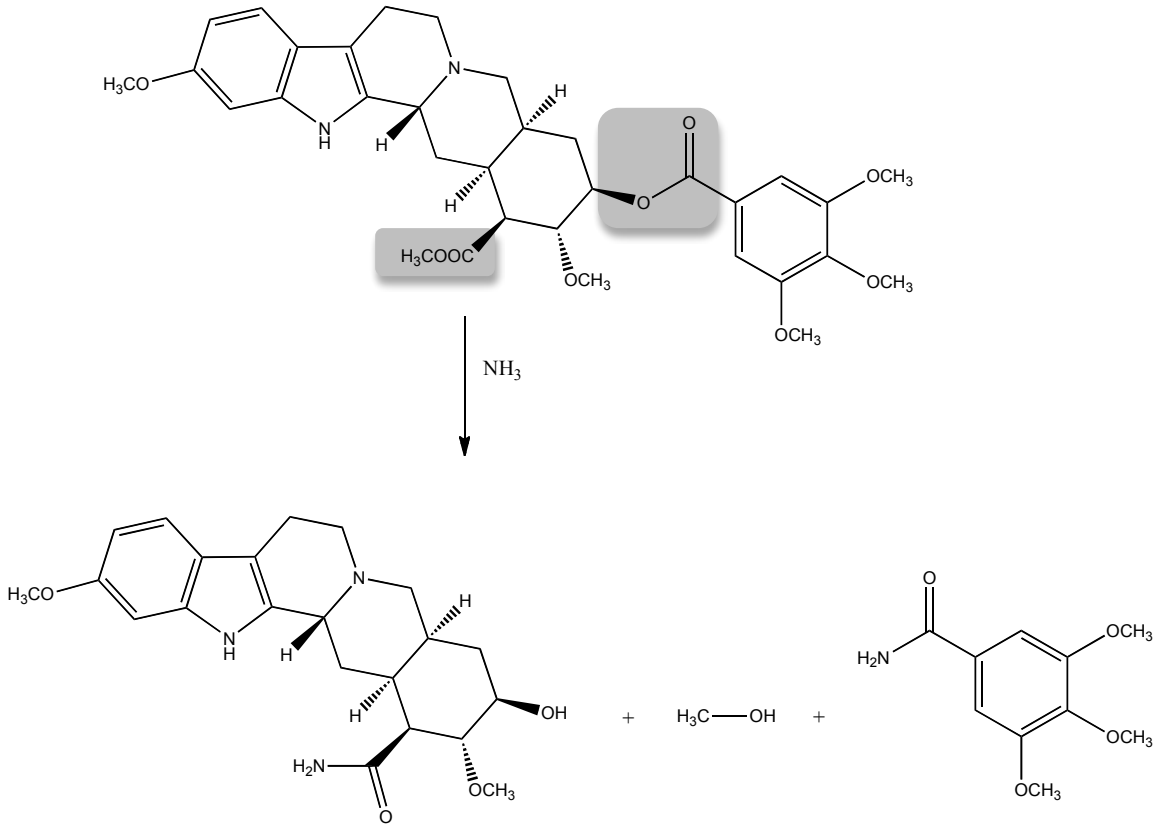


Reserpine

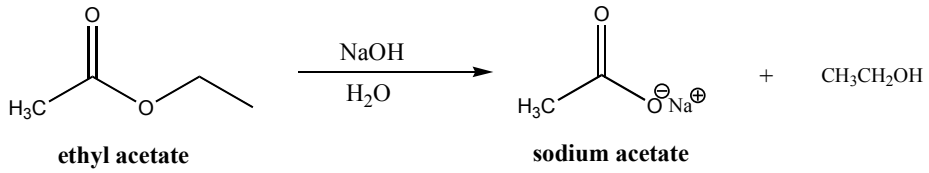
The molecule above is reserpine. It is isolated from Indian snake root (Rauwolfia serpentina) and was found to reduce blood pressure. It is also used to treat schizophrenia. However, it causes depression.
Although it is a big molecule, you should be able to calculate its formula and molecular weight, as well as identify all of its functional groups.



When it is allowed to react with ammonia, the esters are converted to amides. Since there are two ester functional group in this molecule, there would be two amides formed as products. The groups that react are highlighted in the starting material.

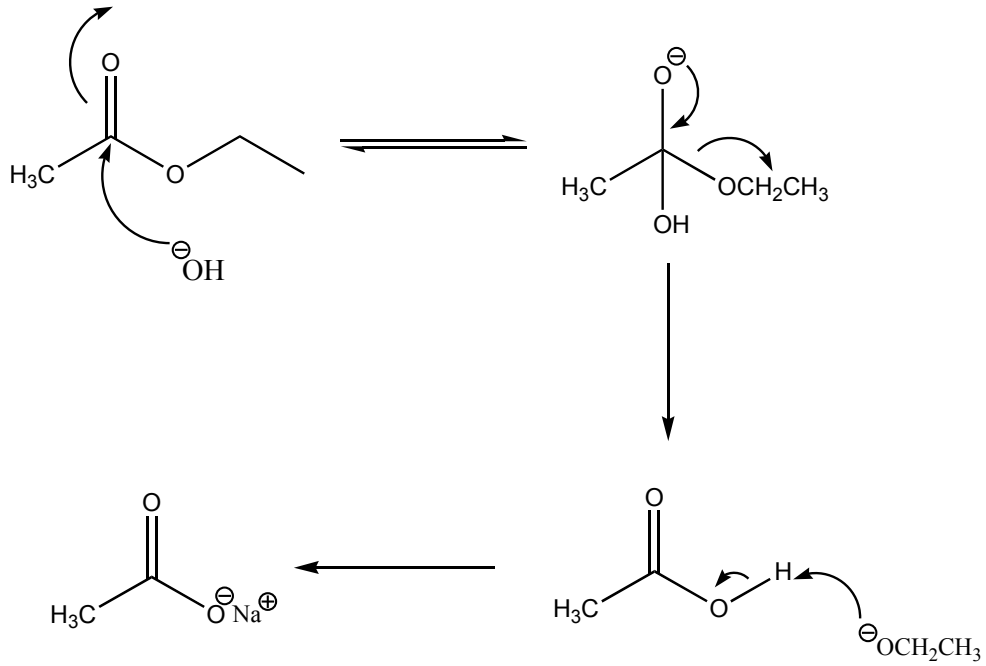


Hydrolysis of Esters



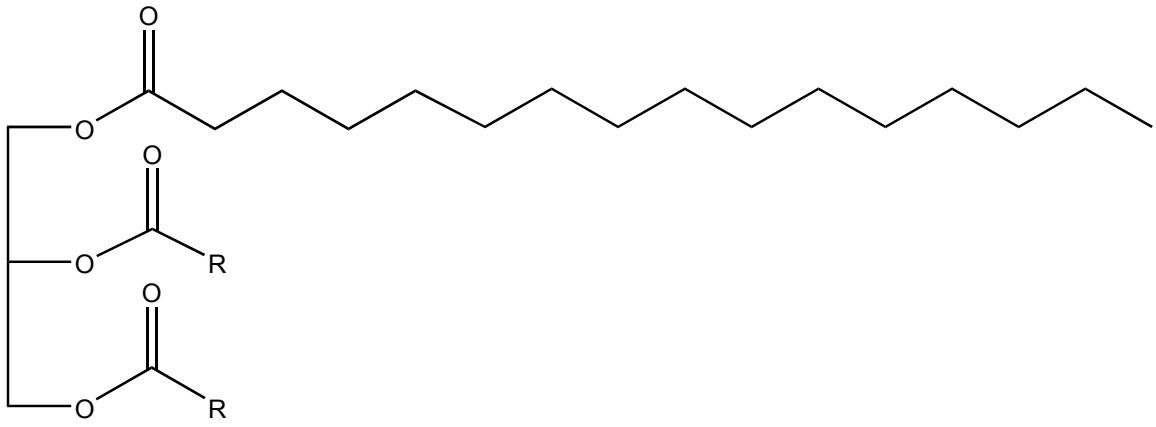
ethyl acetate **sodium acetate**

Mechanism:



The hydroxide anion attacks the carbonyl carbon in the first step, and a tetrahedral intermediate is formed. This process is reversible (so if the negative charge on oxygen comes down and kicks out the OH group instead of ethoxide anion in the second step, we get the starting material again).
In the second step, The ethoxide anion is ejected and carboxylic acid is formed. However, under the basic conditions, the proton on carbonxylic acid is abstracted by the ethoxide anion to form carboxylate anion and ethanol.
The pKa for acetic acid is 4.5, whereas the pKa of ethanol is 17. Ethoxide is a stronger base, therefore it will deprotonate the acetic acid to give acetate.

The process of hydrolyzing esters with base is called **saponification**. Saponification means process of making soap. When you accidentally pour NaOH in your hand, you feel your hand has a soapy feeling. What occurs is that the fat (triglyceride) in your hand is getting hydrolyzed.



glycerol triester = triglyceride