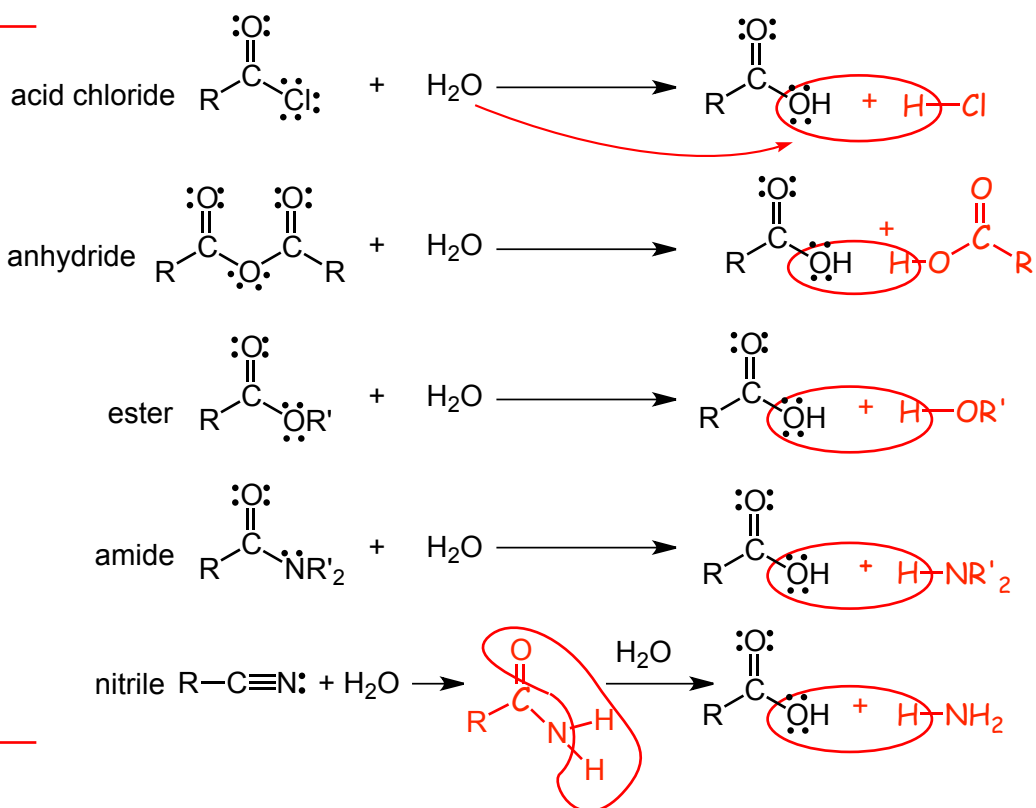


Definition: A carboxylic acid derivative undergoes hydrolysis (bond breaking with water) to form a carboxylic acid:

all
addition/elimination
mechanisms



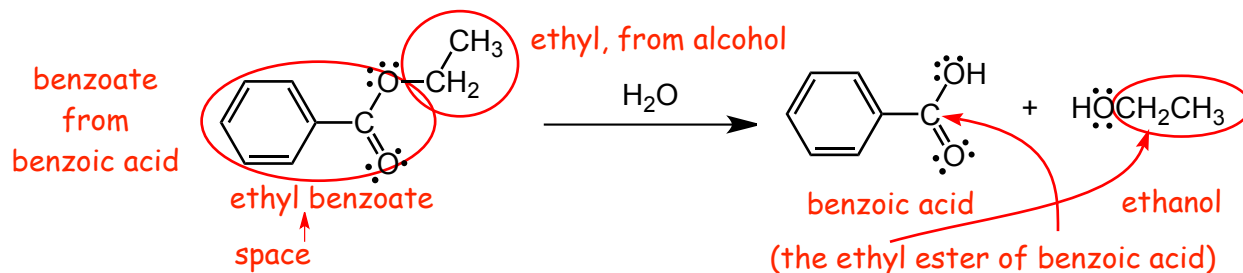
1 Nomenclature

IUPAC priority: acid > **anhydride** > **ester** > **acid halide** > **amide** > **nitrile** > aldehyde > ketone > alcohol > amine > alkene > alkyne > halide

- Priority increases with increasing oxidation state, acids are always the highest priority functional group because they are the most oxidized.
- As we approach the end of the course we don't want to torture you with the nomenclature of **five new** functional groups, and so we will **only** cover the **nomenclature of esters and amides**, because they connect to the acids they are derived from and their hydrolysis reactions that you need to know anyway.

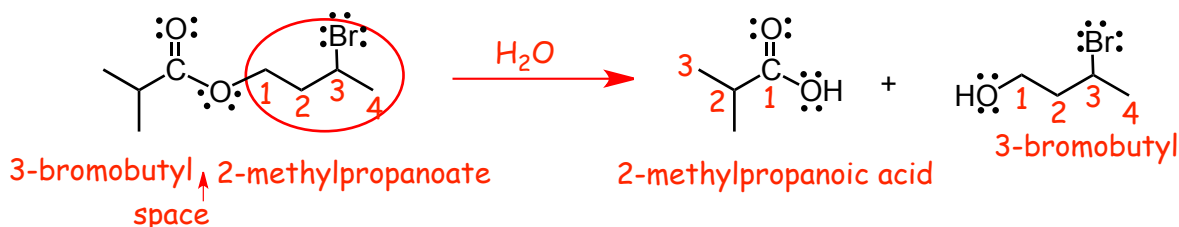
1.1 Ester Nomenclature

- Esters are named from the acids and alcohols that are obtained upon ester hydrolysis.
- Esters have an "**-oate**" suffix.



- Hydrolysis of the ester forms benzoic acid and ethanol.
- The ester is therefore the ethyl ester of benzoic acid, it is called ethyl (from the alcohol) benzoate (from benzoic acid), ethyl benzoate.
- Note the **space** in the name, one of the very few times we have a space in a IUPAC name.

- Hydrolysis of the ester below (stereochemistry ignored) gives 3-bromobutyl alcohol (3-bromobutan-1-ol) and 2-methylpropanoic acid.
- The ester is the 3-bromobutyl ester of 2-methylpropanoic acid:



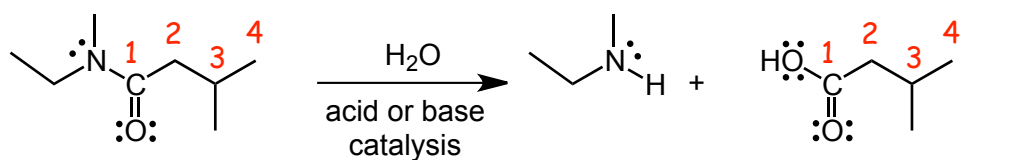
1.2 Amide Nomenclature

- Amides are also named from the acids that are formed upon amide hydrolysis.
- Amides have an "-amide" suffix.
- Hydrolysis of the amide below forms ethanoic acid, the amide is an ethanamide.
- The parts of the molecule attached to the nitrogen are included in the name as substituents attached to nitrogen, and so we have **something new: N-substituents**:



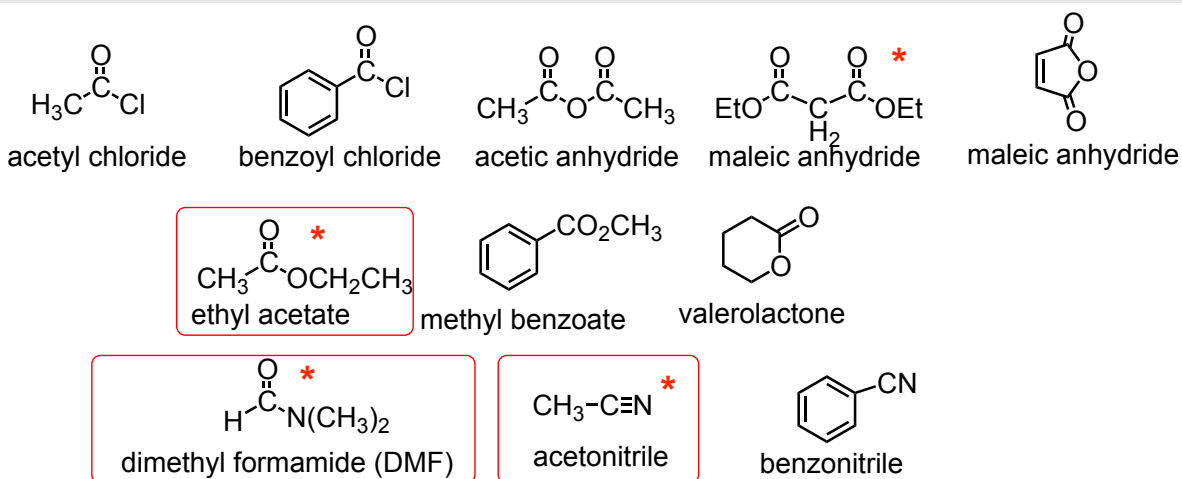
N,N-dimethylethanamide

- The N,N dimethyl says that we have two methyl substituents in the nitrogen.



N-ethyl-N,3-dimethylbutanamide

1.3 Some Common Names for Acid Derivatives

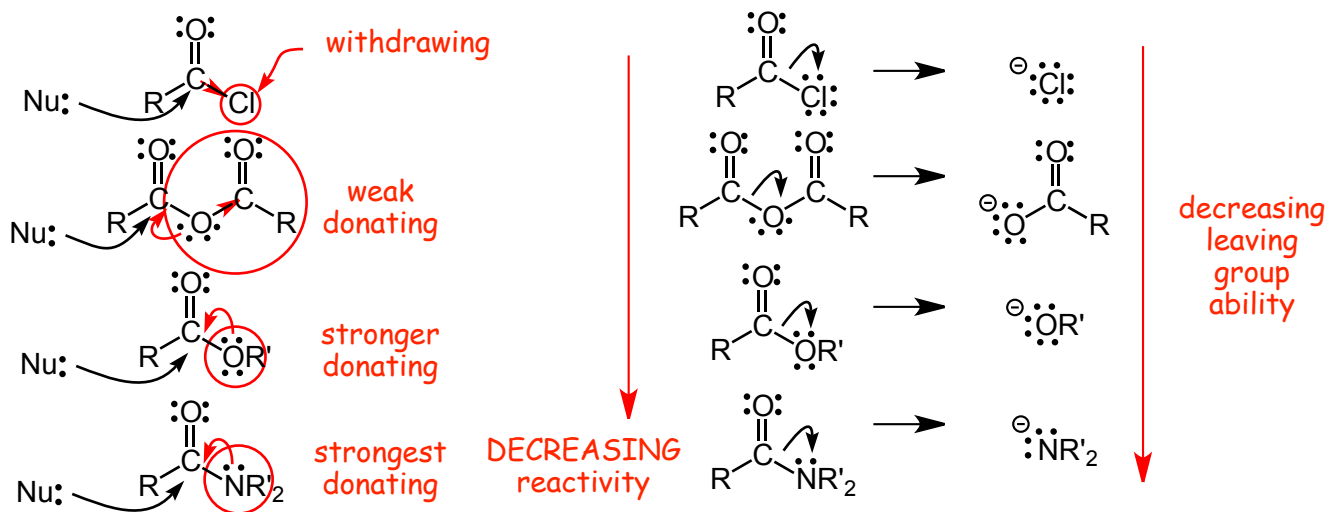


- * Some of these are polar aprotic solvents you have come across previously.

2 The Reactivity Order for Acid Derivatives

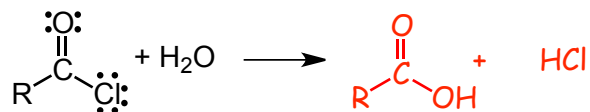
Trends in reactivity order determined by:

- Increasing donating strength of the group attached to the C=O, stabilizes the carbonyl carbon towards nucleophilic attack, decreases reactivity.
- Decreasing leaving group ability results in decreasing reactivity:

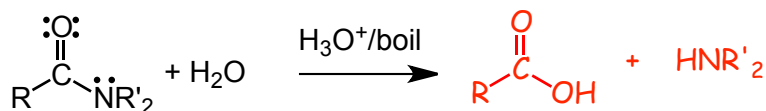


Example of reactivity differences...

- Acid halides spontaneously hydrolyze in water alone, the reaction requires no acid or base catalyst:

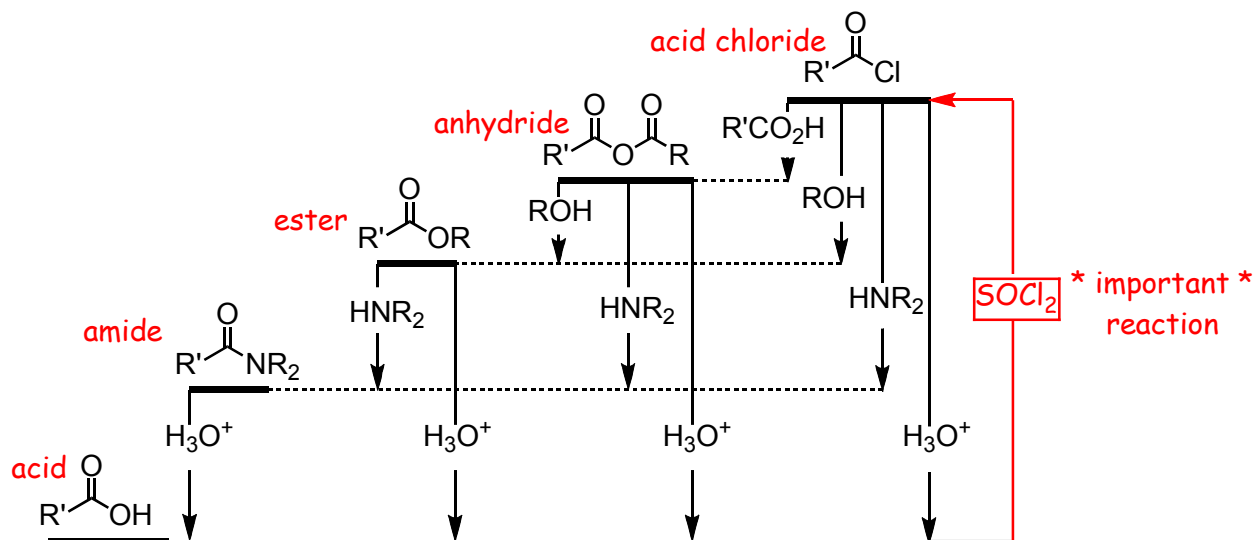


- Amides require boiling H_2O and strong acid (or base) catalysis:



- The same reactivity order is found for acid derivatives in all reactions.

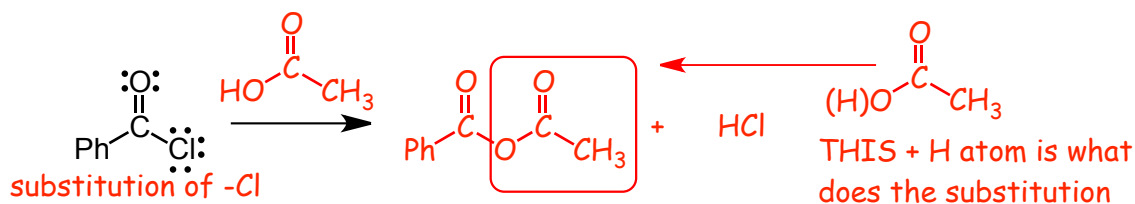
3 Interconversion of Acid Derivatives : Nucleophilic Acyl Substitution



- We can convert a *more* reactive derivative into a *less* reactive derivative, but **not** the other way around!

3.1 Formation of Anhydrides

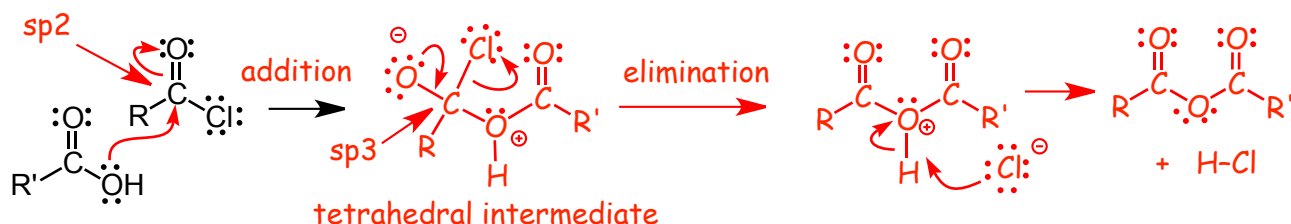
- From an acid chloride using an acid via **substitution**.
- The chloride anion is a **good leaving group**, however, the carbon atom we are substituting is sp² hybridized, **can't do SN1 or SN2**.



- You **don't have to memorize** that the reaction uses a **carboxylic acid** to do the substitution, you **work it out** by looking at the molecular fragment that does the substituting, and then add a hydrogen atom.
- The reaction is **substitution** of -Cl by -CCOCH₃, we need to break the C-Cl bond and make the C-O bond.
- Breaking the C-Cl bond is difficult because the C is sp² hybridized, Cl⁻ is a good leaving group from an sp³ hybridized carbon atom, hence the **addition/elimination** mechanism.

The Mechanism: Return to addition/elimination....

must convert to sp³ before substituting

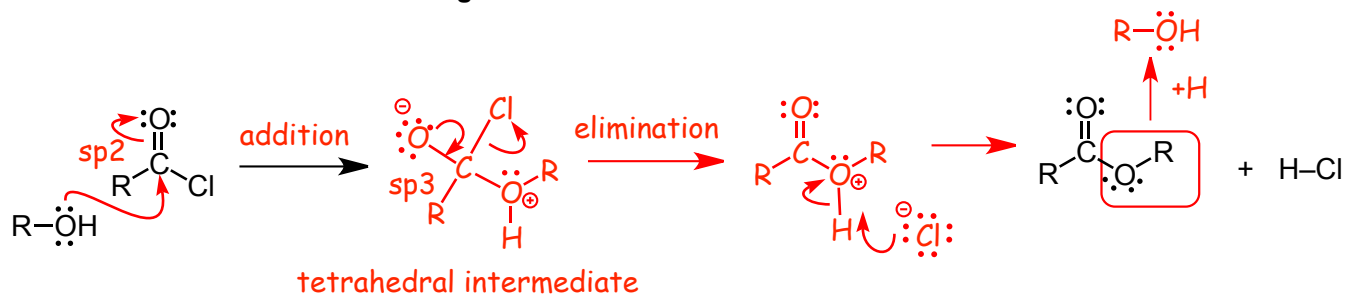


- It is easier to break the C-Cl bond when the carbon is SP³ hybridized, the Cl⁻ anion is a good leaving group from an sp³ hybridized carbon atom, not from an sp² hybridized carbon.

3.2 Formation of Esters

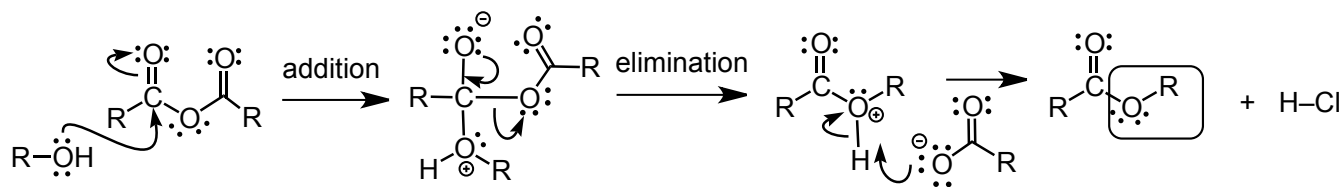
- An ester can be formed from either the more reactive acid chloride or from the more reactive anhydride using an alcohol.

The Mechanism of formation starting with an acid chloride: addition/elimination as above!!



- You **don't have to memorize** that the reaction uses **an alcohol** to do the substitution, you **work it out** by looking at the molecular fragment that does the substituting, and then add a hydrogen atom.
- Again, this reaction is substitution, but we can't break the C-Cl bond when the carbon is sp² hybridized, the bond is too strong. But it is easier to break the bond when the carbon is sp³ hybridized.
- The best leaving group is eliminated from the sp³ hybridized tetrahedral intermediate, in this case Cl⁻.

The Mechanism of formation starting with an anhydride: addition/elimination again:

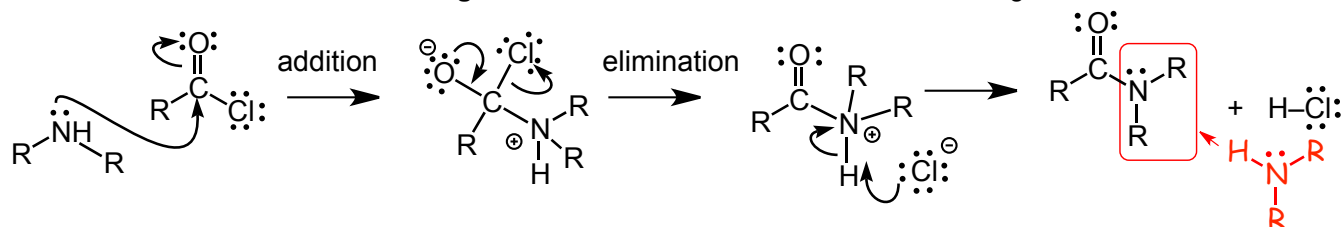


- The mechanism is **identical** to the **addition/elimination** mechanism to the one above.
- Again, this reaction is substitution, but we can't break the C-O bond when the carbon is sp² hybridized, the bond is too strong. But it is easier to break the bond when the carbon is sp³ hybridized.
- The best leaving group is eliminated from the sp³ tetrahedral intermediate, in this case a carboxylate anion.

3.3 Formation of Amides

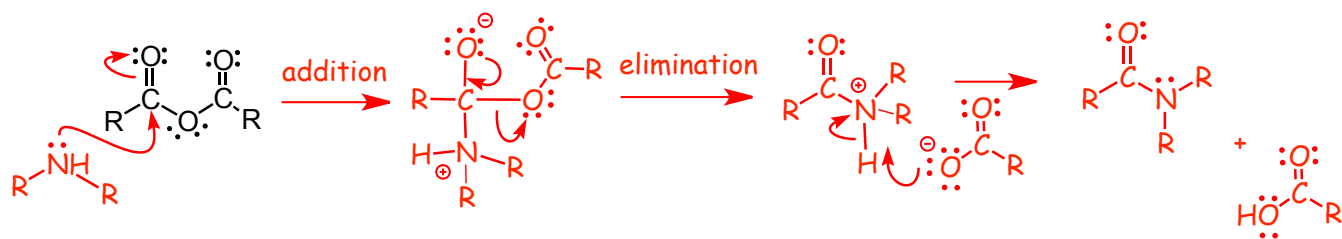
- Amides can be formed from an acid chloride or anhydride using an amine.
- In principle an amide could also be formed from an ester, but nobody does this, the acid chlorides and anhydride routes are much more important because they are much more reactive.

The Mechanism of formation starting with an acid chloride: addition/elimination again

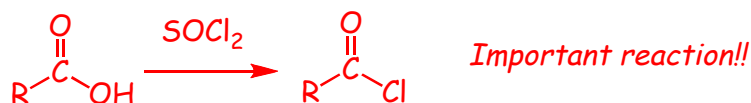


- **Again**, you **don't have to memorize** that the reaction uses **an amine** to do the substitution, you **work it out** by looking at the molecular fragment that does the substituting, and then add a hydrogen atom.

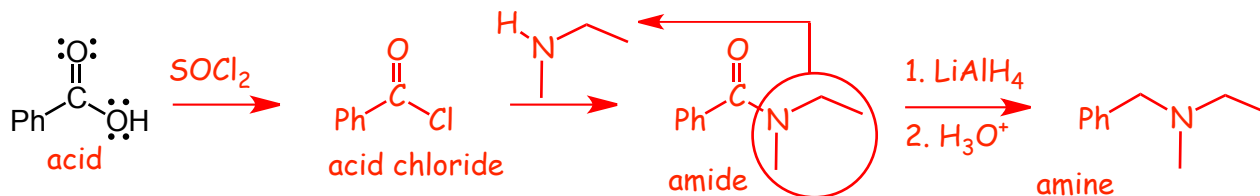
The Mechanism of formation starting with an anhydride: Addition/elimination again:



- As discussed above, we can make all of the derivatives from an acid chloride, therefore:



Example

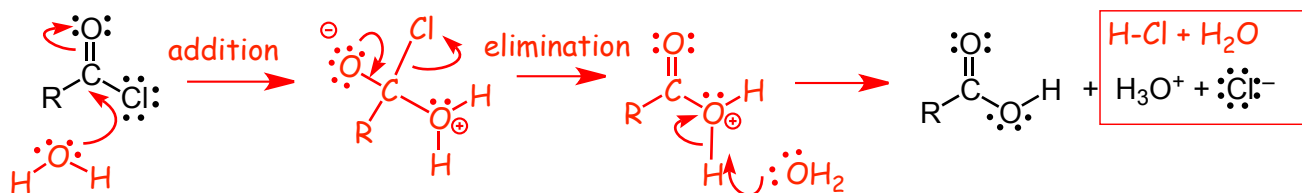


- Recognizing that an amine that is required to react with the acid chloride is easy, it is the nitrogen of the amide and everything attached to it **plus** a hydrogen atom.
- The example above shows how what we are learning now links the chemistry of carboxylic acids through to amines, where we are going next.

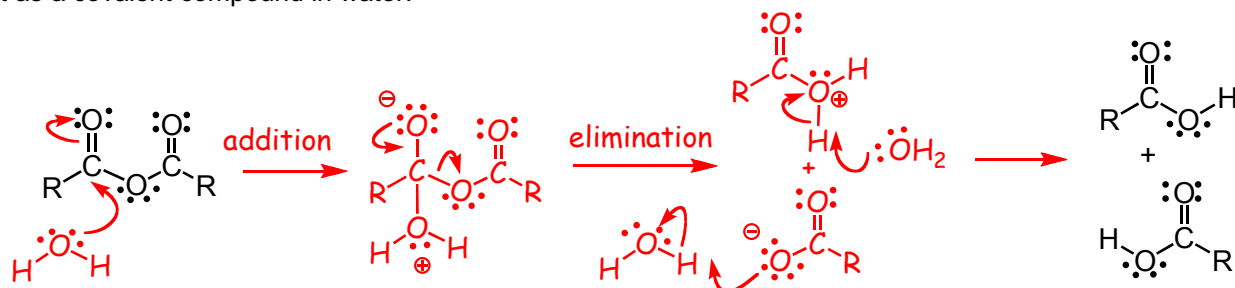
4 Hydrolysis Reactions of Acid Derivatives

4.1 Acid Chlorides and Anhydrides

- Hydrolysis: using water to break bonds.
- Hydrolysis is spontaneous in water for acid chlorides and anhydrides, which means that no catalyst required, they just react directly with water alone.
- No catalyst is required because both acid chlorides and anhydrides have good leaving groups:



- Note that the deprotonation occurs to **water** (not the chloride anion leaving group) due to its overwhelming concentration, not the chloride anion, and that hydronium and chloride are formed overall, since HCl does not exist as a covalent compound in water.

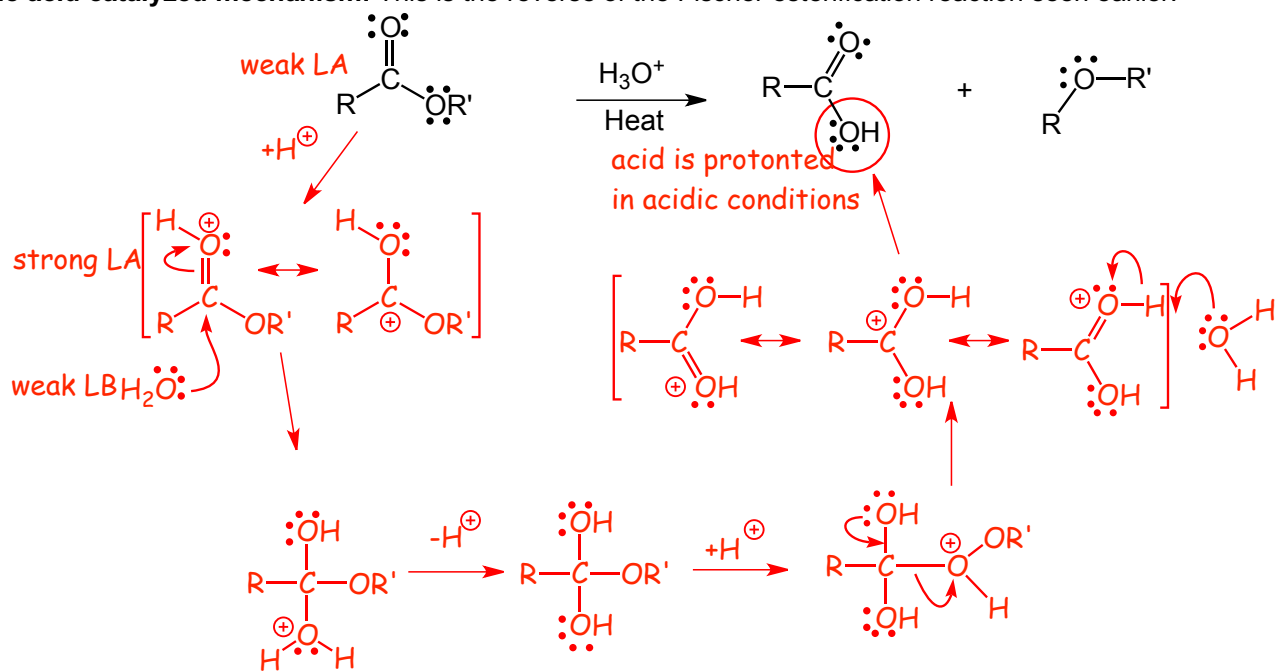


- The products for anhydride hydrolysis are two carboxylic acids, the extent to which they are deprotonated in water will depend upon their specific structures.
- Note that the deprotonation and protonation processes at the end involve water because it is present in by far the highest concentration, hydronium and hydroxide are formed that will then equilibrate with water as usual.

4.2 Esters Require Acid or Base Catalysis

- The ⁻OR leaving group involved in ester hydrolysis is not as good a leaving group, ester hydrolysis thus requires either acid catalysis or the use of hydroxide base.

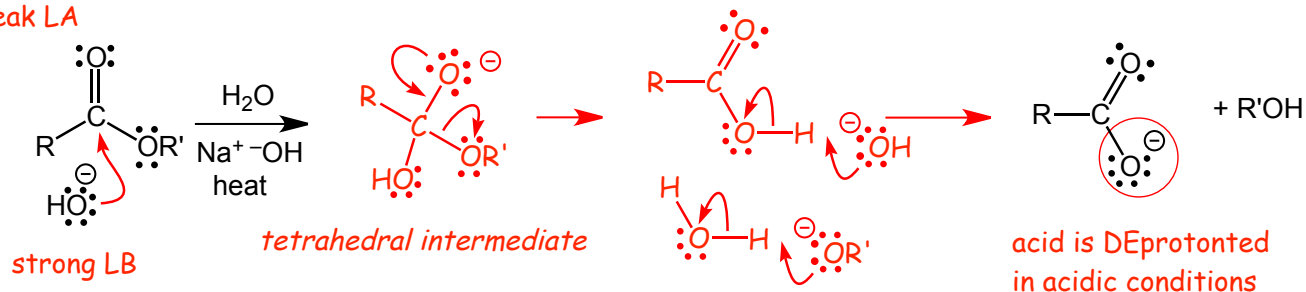
The acid catalyzed mechanism: This is the reverse of the Fischer esterification reaction seen earlier:



Ester Hydrolysis using Base

- There is no acid in this case, thus, protonation **cannot be** the first step.
- However, the C=O does not need to be protonated because now we have a **strong LB/Nucleophile** in the form of OH^- to react with the C=O bond:

weak LA



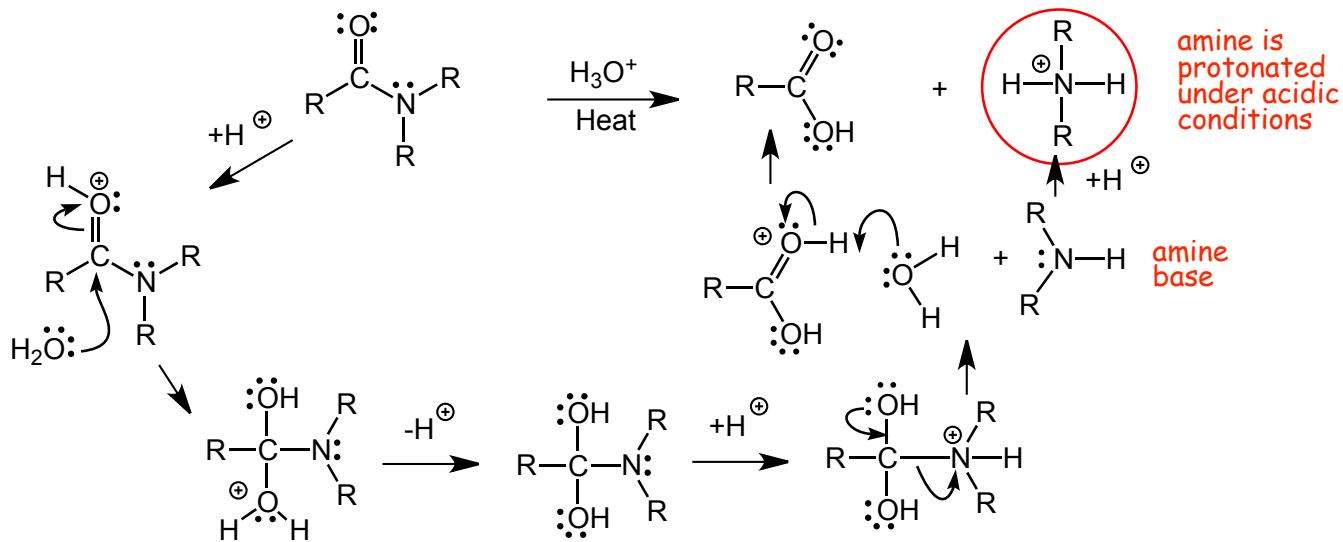
- Normally oxygen anions are **poor** leaving groups, however, $-\text{OR}'$ can be a leaving group from the tetrahedral intermediate because we are starting with an anion (the hydroxide base), i.e. we start with high energy high chemical potential energy electrons.
- The reaction makes a carboxylate anion in the end because the carboxylic acid deprotonates to the base catalyst.
- Because the carboxylate anion is formed, the base is not technically a catalyst in this case.
- **Ester hydrolysis with a base is called a saponification reaction** (soap-making reaction), because the carboxylates of fatty acids are soaps.
- In general, do **not** have any positively charged species in a mechanism under base catalyzed conditions!

4.3 Amides Require Forcing Conditions

- Amide bonds are difficult to hydrolyze, which is good since they form the peptide linkage in proteins!
- The problem is that a nitrogen anion is a **very poor** leaving group.
- Forcing conditions usually means boiling water, or extended reaction times or high concentrations of acid or base.

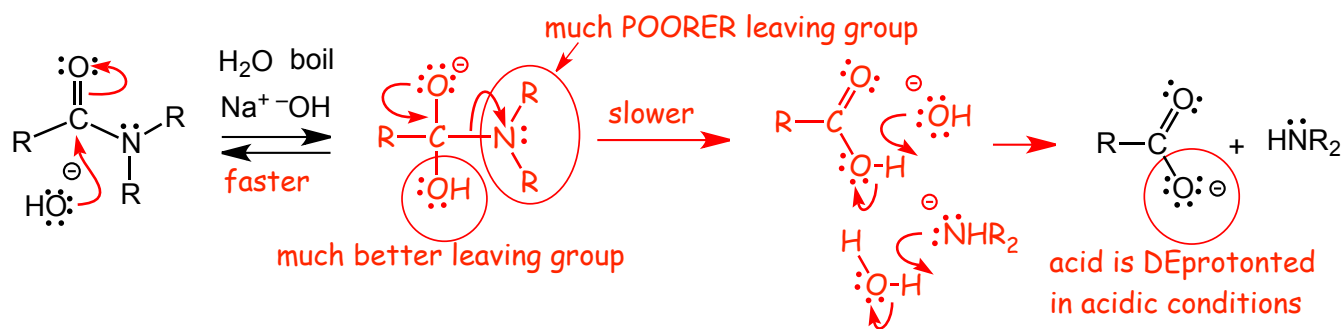
Acid catalyzed mechanism

- The mechanism is summarized below, it was covered previously in the carboxylic acids notes in the section acid synthesis by hydrolysis of nitriles.
- Nitrile hydrolysis proceeds via an amide which is further hydrolyzed under acidic conditions to a carboxylic acid
- It is identical to the ester acid catalyzed mechanism (except that the resonance contributors are not shown in the mechanism below).
- An amine is generated as a leaving group, amines are bases and will be protonated under the acidic reaction conditions.

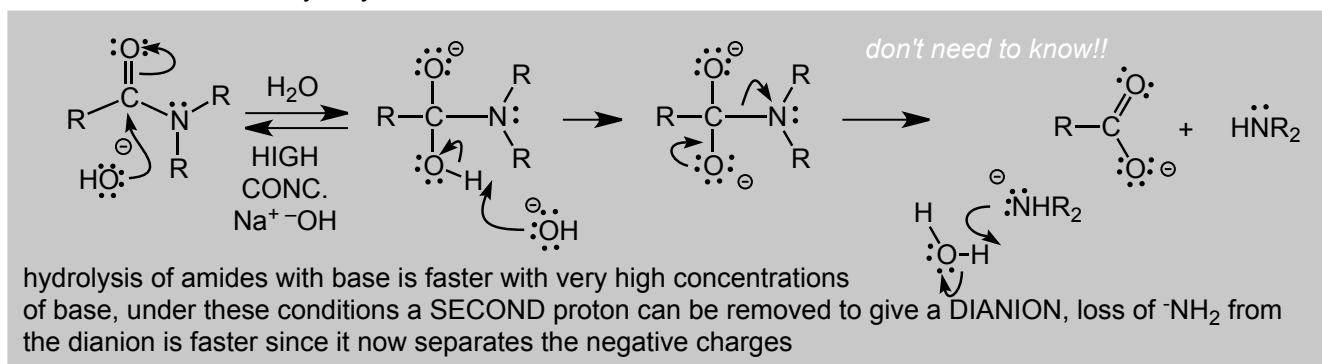


Amide Hydrolysis using Base

- As usual, the mechanism with base is considerably shorter than the acid catalyzed mechanism:



- $-NH_2$ is a **very poor** leaving group, most of the time the tetrahedral intermediate will eliminate **hydroxide** instead, which will regenerate the starting materials, as shown above, **however**, eventually a $-NH_2$ will leave, and when that happens the carboxylic acid will deprotonate which will help to make this overall slow reaction irreversible.
- Because the carboxylate anion is formed, the base is not technically a catalyst in this case.
- One more detail about hydrolysis of amides under basic conditions.....

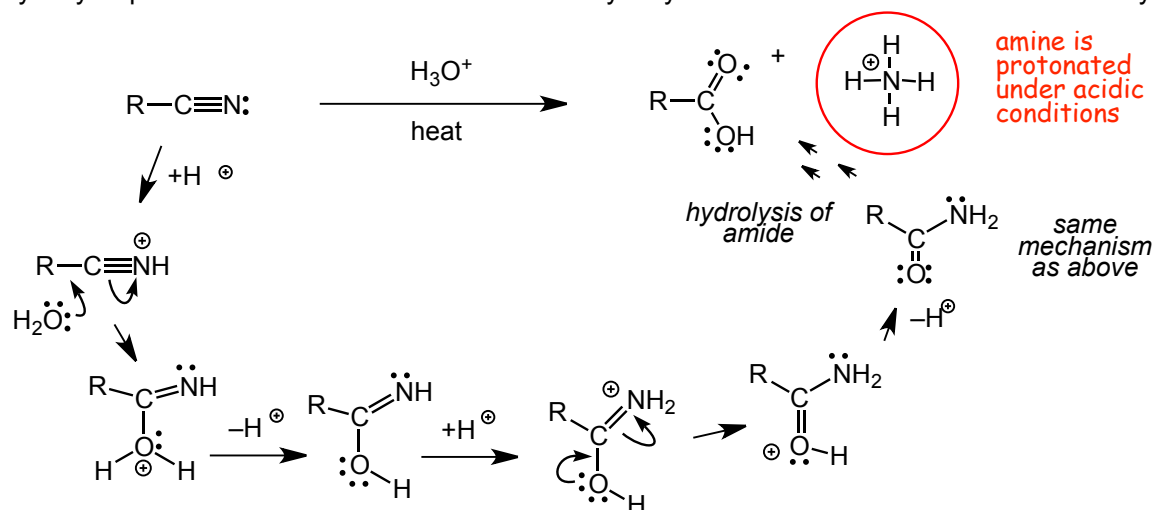


4.4 Nitriles Also Require Forcing Conditions

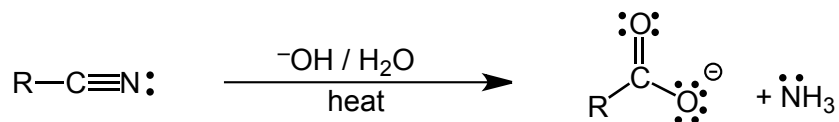
- Complete hydrolysis of a nitrile consists of water addition to form an amide which further hydrolyzes to a carboxylic acid and an amine.
- Forcing conditions are usually required, which means boiling water, and/or extended reaction times.

Acid catalyzed mechanism

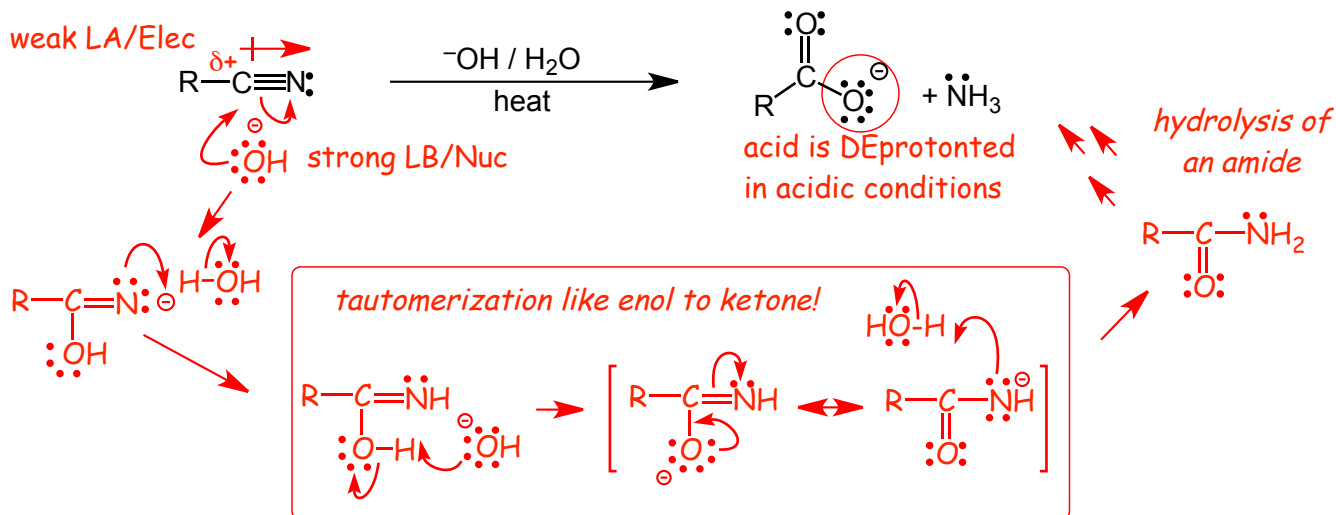
- This mechanism was covered previously in the carboxylic acids notes in the section acid synthesis by hydrolysis of nitriles
- Nitrile hydrolysis proceeds via an amide which is further hydrolyzed under acidic conditions to a carboxylic acid.



Hydrolysis reaction and mechanism under basic conditions



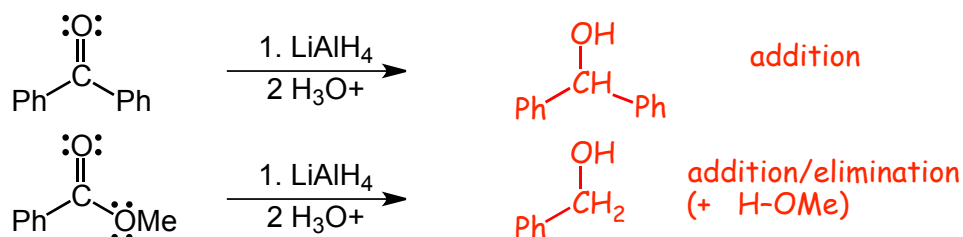
- Under basic conditions the carboxylate conjugate base anion of the acid will be formed.
- The hydrolysis mechanism will also proceed via an amide as an intermediate, once the amide is formed hydrolysis will be as shown above:



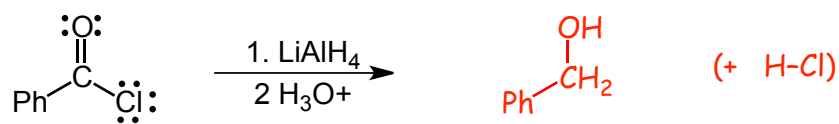
- The first steps in the mechanism are straightforward, the strong LB/Nucleophile hydroxide attacks that carbon of the nitrile that has a partial positive charge, followed by protonation, at this point we have now broken one of the C-N bonds and made a C-O bond, so this is good progress.
- The next steps look a little odd (circled above), we are tempted to have hydroxide attack the C=N carbon again, **but**, remember that the reaction proceeds via an **amide**, and the circled steps form the amide via a mechanism that we have **seen before**.
- This is the **same** as enol to ketone tautomerization with base, this part of the reaction proceeds via the same mechanism and for the same reason!
- A weaker C=N bond is converted into a stronger C=O bond by deprotonation followed by reprotonation.
- So we see that we are starting to see chemistry and principles that we already know again, which is a good thing, although nobody can pretend that it is easy to see the tautomerization reaction in this new context!

5 Reduction of Acid Derivatives Using LiAlH₄

As we have seen previously: Reduction of **esters** using LiAlH₄ - via an addition/elimination again.

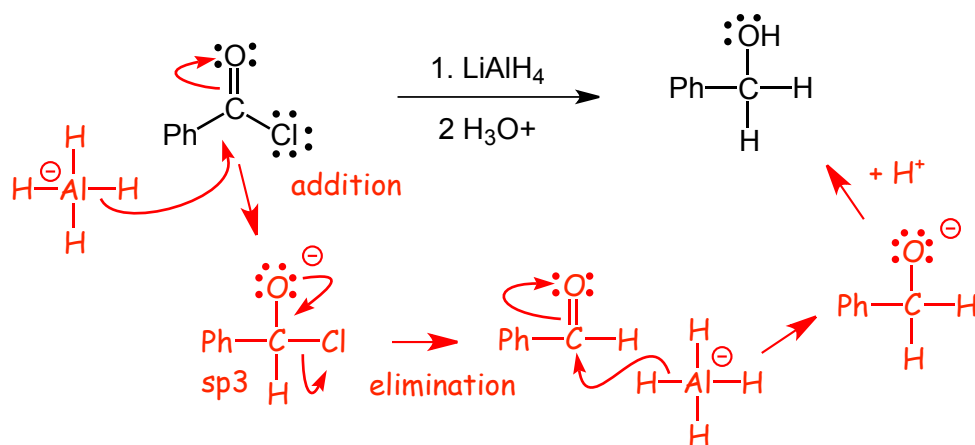


By analogy: Reduction of acid chlorides by addition/elimination:

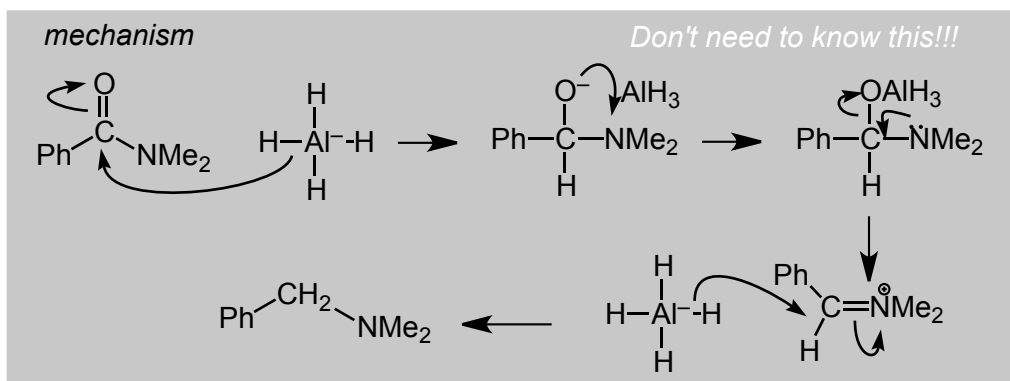


- We have **seen** the **addition/elimination** mechanism when we learned about LiAlH₄ reduction of esters.
- With esters the leaving group is ⁻OR, with acid chlorides the leaving group is ⁻Cl.

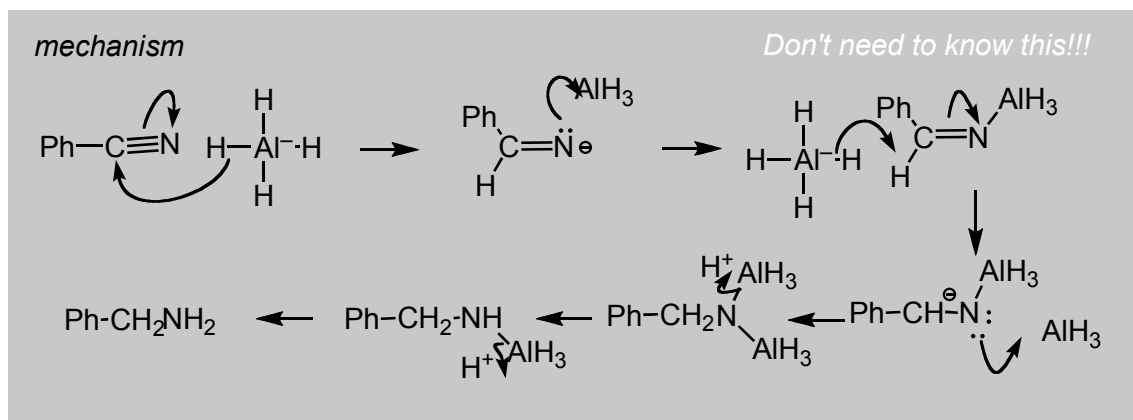
• The mechanism starts with the expected addition/elimination to a carbonyl that has a leaving group, ester and acid halide (recall Grignard reactions with acid halides and esters), via the usual sp³ hybridized tetrahedral intermediate:



Amides are different: Why? because ⁻NH₂ is such a poor leaving group!



Nitriles are also different, Why? because they don't **have** a leaving group!

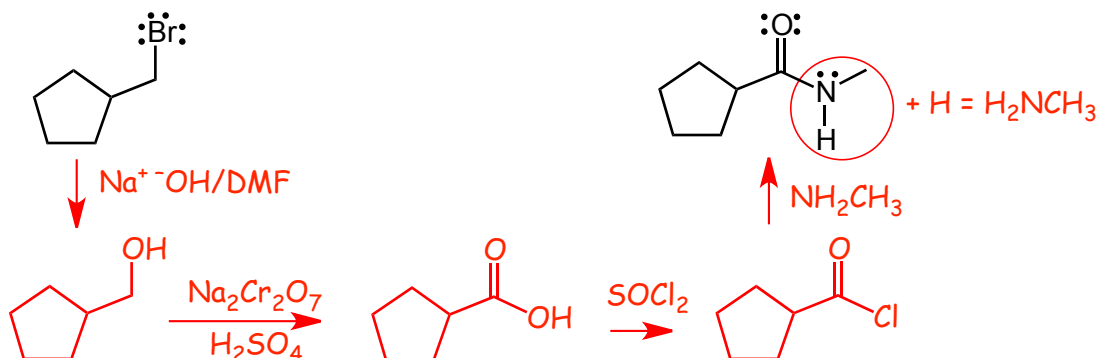


• These examples show how the synthesis of amides and nitriles is connected to the synthesis of amines, which we need to know for the next section of the notes, **and**, therefore, is also connected to the synthesis of carboxylic acids.

6 Synthesis Using Acid Derivatives

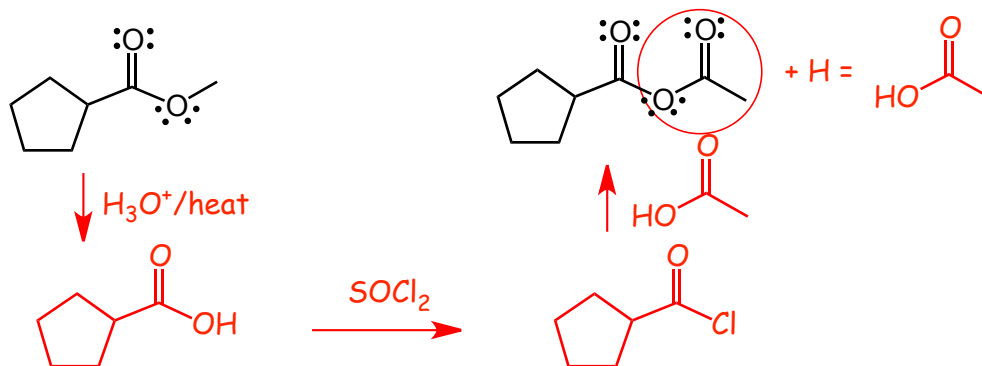
• We will see that the strategy is quite straightforward, the acid derivative will almost always come from the corresponding acid chloride, which comes from a carboxylic acid using SOCl_2 .
 • The problem will usually be one of how to make the carboxylic acid, fortunately we have several ways of doing that.

Example Problem 1



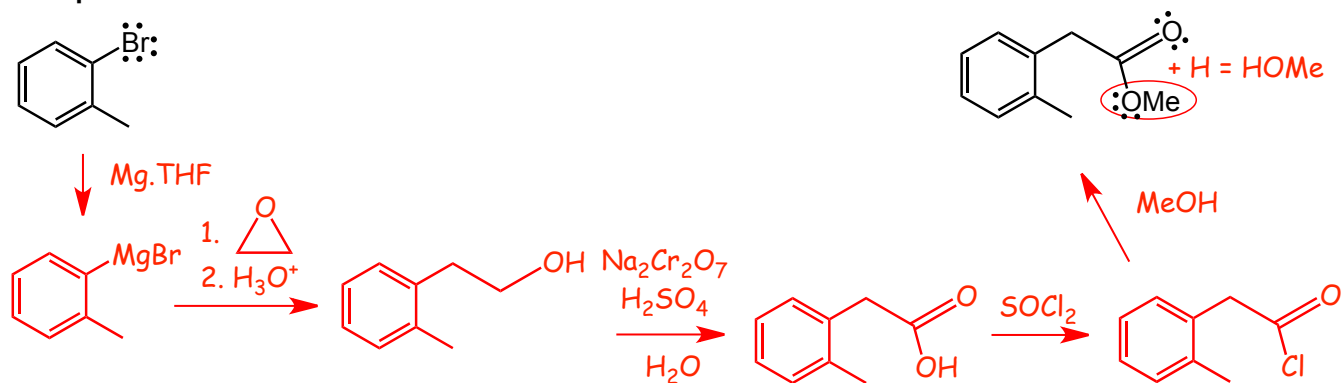
• **The strategy:** make the derivative (an amide in this case) form the acid chloride, make the acid chloride from a carboxylic acid, then the problem simply becomes how to make the carboxylic acid
 • To identify what is required to react with the acid chloride to make the amide, recognize that this is simply the nitrogen and everything that is attached to it **plus** a H atom, no other reagents are required except an amine.
 • No carbon atoms need to be added here, therefore make the carboxylic acid by oxidizing a primary alcohol.
 • Don't get confused by the simple $\text{S}_{\text{N}}2$ reaction in the first step that converts the bromide into the alcohol.

Example Problem 2



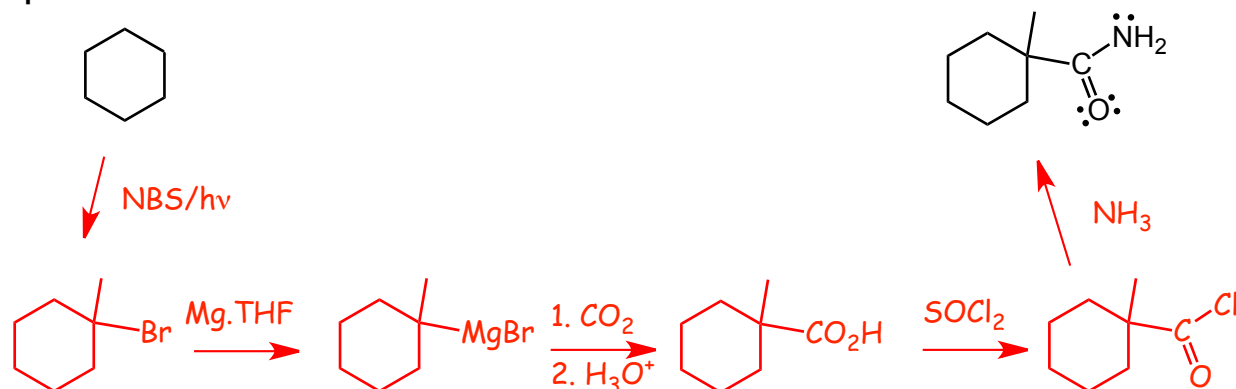
• **The strategy:** Make the derivative (an anhydride in this case) form the acid chloride, make the acid chloride from a carboxylic acid, then the problem simply becomes how to make the carboxylic acid.
 • To identify what is required to react with the acid chloride to make the anhydride, recognize that this is simply the oxygen and everything that is attached to it **plus** a H atom, no other reagents are required.
 • No carbon atoms need to be added here, therefore make the carboxylic acid by hydrolyzing the ester.

Example Problem 3



- **The strategy:** Make the derivative (an ester in this case) from the acid chloride, make the acid chloride from a carboxylic acid, then the problem simply becomes how to make the carboxylic acid.
- To identify what is required to react with the acid chloride to make the anhydride, recognize that this is simply the oxygen and everything that is attached to it **plus** a H atom, no other reagents, just methanol in this case.
- **Two** carbon atoms need to be added here, however, a malonic ester synthesis will not work because we would need to do an $\text{S}_{\text{N}}2$ reaction at an sp^2 hybridized carbon atom.
- For this problem we need to go back to our earlier C-C bond forming reactions, a Grignard with an epoxide works well here.

Example Problem 4



- **The strategy:** Make the derivative (an amide in this case) from the acid chloride, make the acid chloride from a carboxylic acid, then the problem simply becomes how to make the carboxylic acid.
- **One** carbon atom needs to be added in this synthesis, the nitrile method cannot be used to make the carboxylic acid here because it would require doing an $\text{S}_{\text{N}}2$ reaction at a tertiary carbon atom.

7 Summary of Acid Derivative Reactions

Do not start studying by trying to memorize the reactions here!

Work as many problems as you can, with this list of reactions in front of you if necessary, so that you can get through as many problems as you can without getting stuck on the reagents/conditions, and so that you can learn and practice solving reaction problems. Use this list **after** you have worked all of the problems, and just before an exam. By then you will have learned a lot of the reagents/conditions just by using them and you will only have to memorize what you haven't learned yet. Then do the following:

- Cover the entire page of reagents/conditions with a long vertical strip of paper, see if you can write down the reagents/conditions for each reaction, check to see which you get correct, if **completely** correct, circle Y, if incorrect or even slightly incorrect, circle N. In this way you keep track of what you know and what you don't know.
- Keep coming back to this list and do the same thing only for those reactions you circled N, until all are circled Y.

Knowing the reagents/conditions on this page is **insufficient** to do well on an exam since you will **also** need to recognize how to use and solve reaction problems in different contexts, this page **only** helps you to learn the reagents/conditions that you have **not yet** learned by working problems.

You have seen several of these reactions in earlier sections!

