Carboxylic Acid Derivatives
2 - Synthesis and Interconversions

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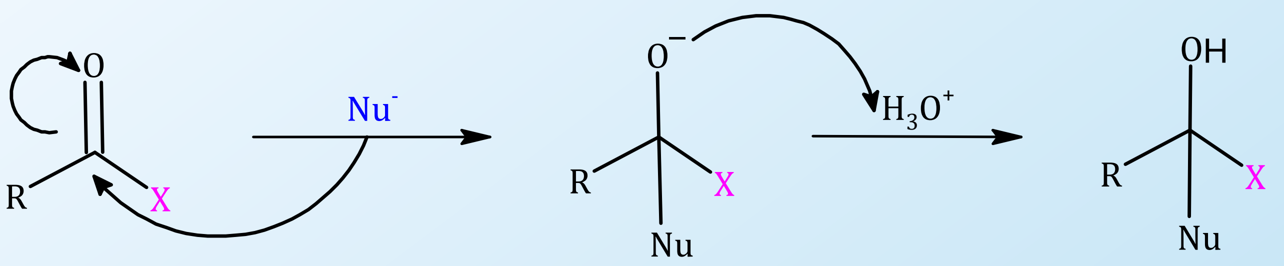
Reactivity of the Derivatives: Nu Addition

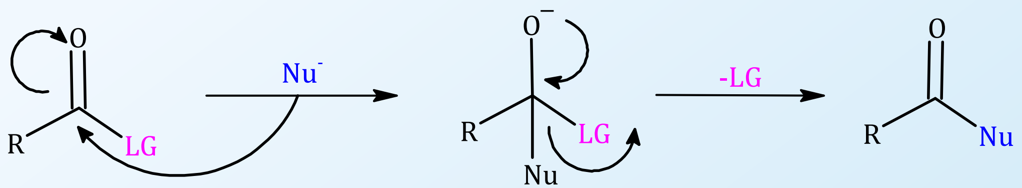
There are two kinds of reactions that occur for acid derivatives – nucleophilic addition and nucleophilic substitution.

In Nucleophilic addition the carbonyl carbon is the electrophile a strong nucleophile is needed to carry out the reaction. The sp^2 hybridized carbonyl C changes to a sp^3 tetrahedral carbon. A chiral center can be generated in these reactions.

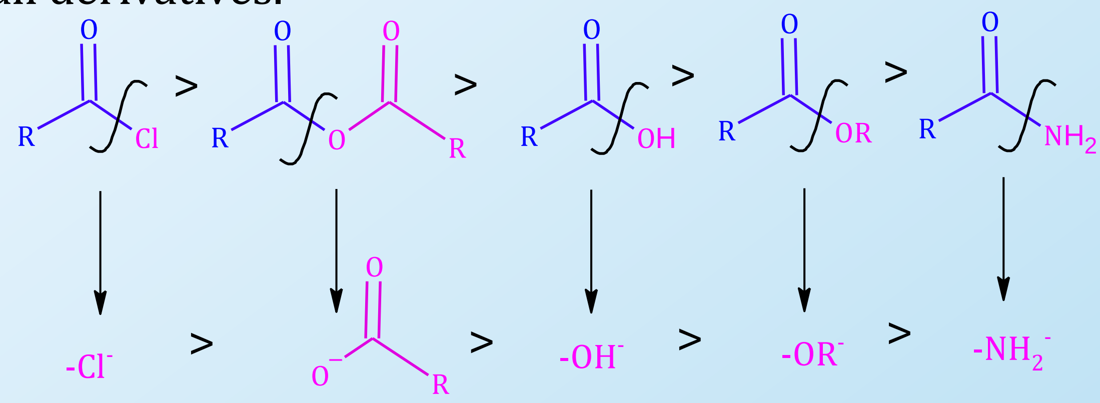


Reactivity of the Derivatives: Nu Substitution

In Nucleophilic substitution the nucleophile may or may not be strong. The functional group is the leaving group, and the carbonyl is restored. The reactivity of the acyl group derivatives depends on the leaving group ability. This type of reaction is good for interconversion of all carboxylic acid derivatives.



Given below are all the derivatives showing the leaving groups (LG) they have and their ability to leave i.e., from weak bases to strongest, making acyl chlorides the most reactive of all derivatives.



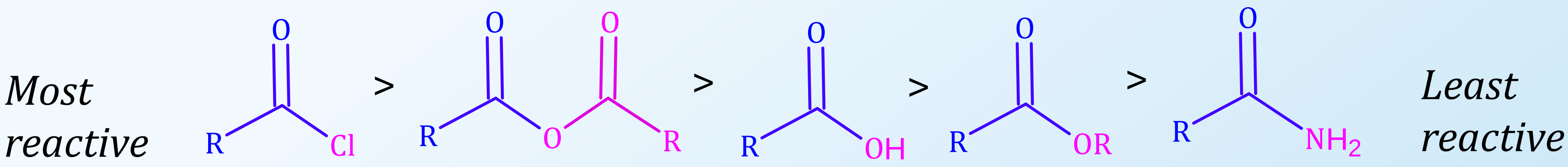
-OCOR-

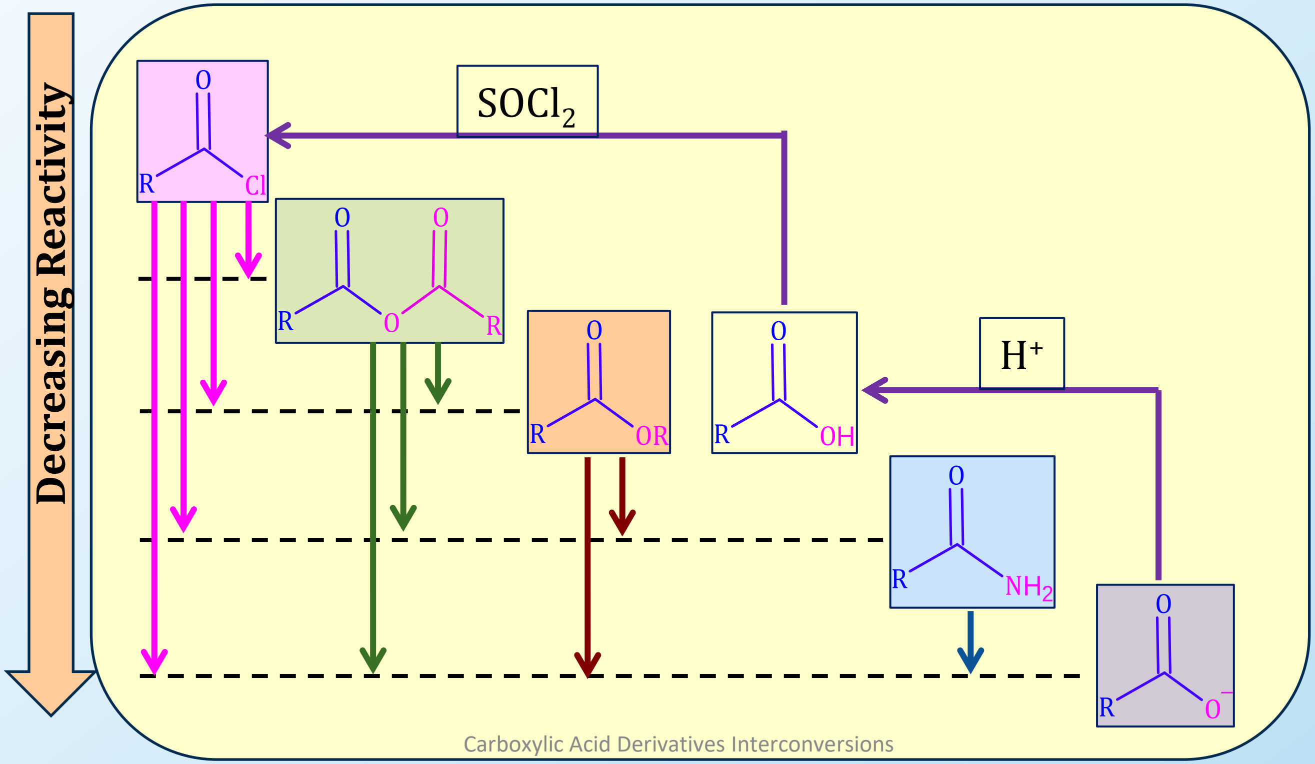
Weakest base/good LG

Strongest base/bad LG

Interconversions of Acid Derivatives

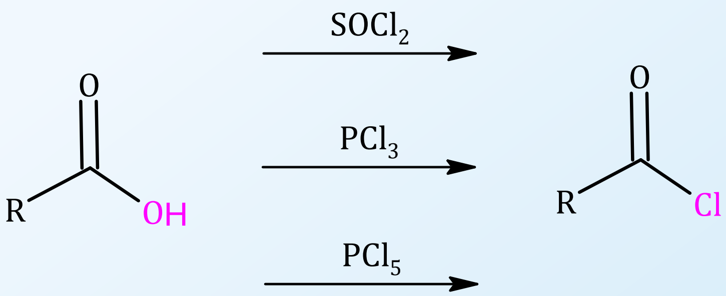
Below is a chart of interconversions possible for each acid derivative. It shows that acyl chloride can be converted to all derivatives, but amides cannot be converted to any derivative. All derivatives will react with water to carboxylic acids.



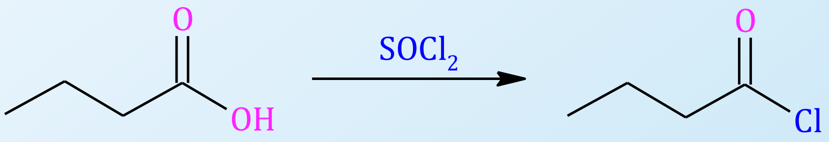


Acyl Chlorides: Synthesis

Acyl chlorides can be synthesized by treating a carboxylic acid with thionyl chloride, phosphorous pentachloride or phosphorous trichloride.



For example: butanoic acid to give butanoyl chloride using thionyl chloride.



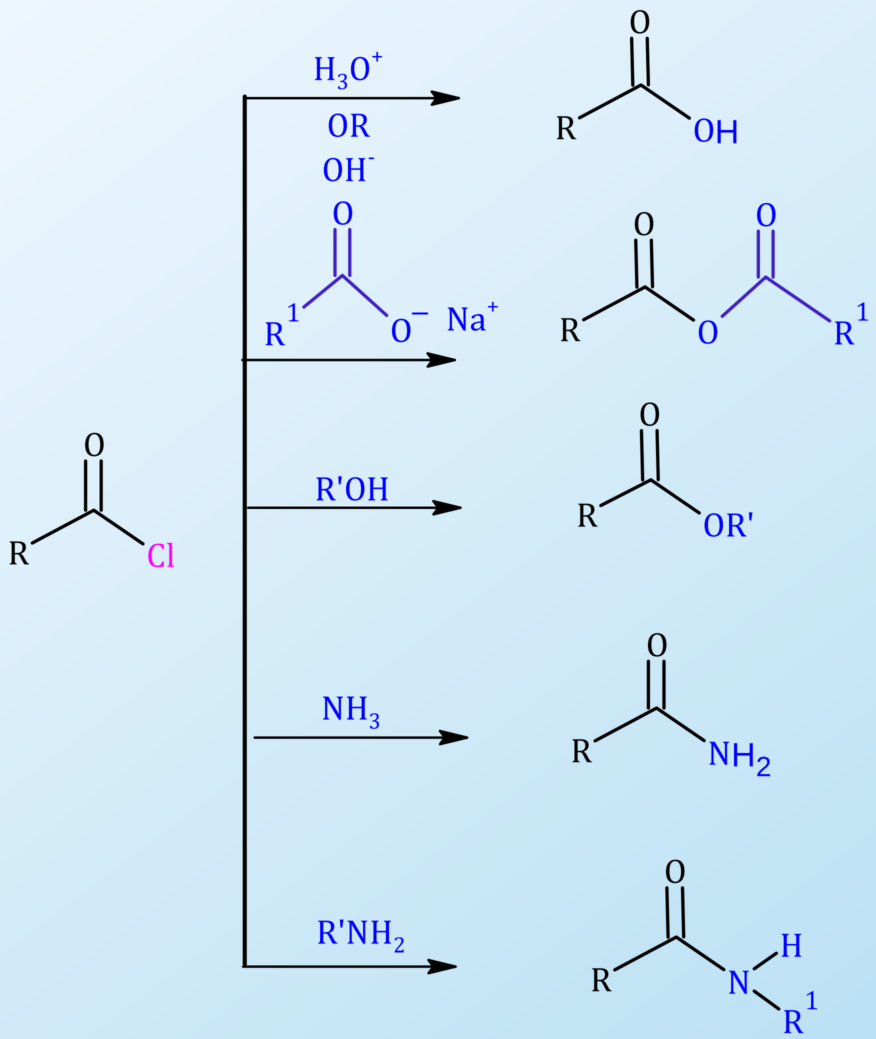
Acyl Chlorides: Reactions

Acyl chlorides are the most reactive acyl compounds and can be used to make any of the other derivatives.

Since it is easy to make acyl chloride from carboxylic acids, they can be used to synthesize any acyl derivative from a carboxylic acid.

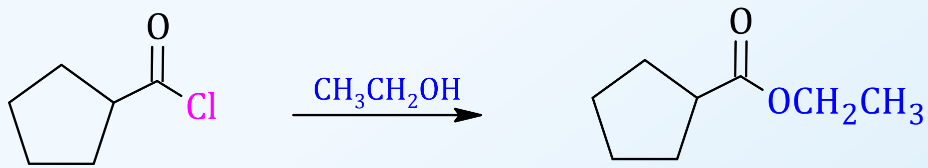
Acyl chlorides react readily with water to form carboxylic acids, but this is not a synthetically useful reaction.

Examples of some these reactions are given on the next slide.

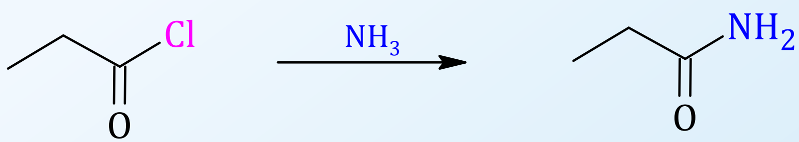


Acyl Chlorides: Reactions Examples

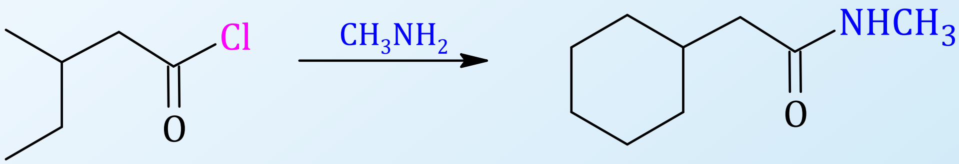
Below are examples of acyl chlorides giving the different derivatives.



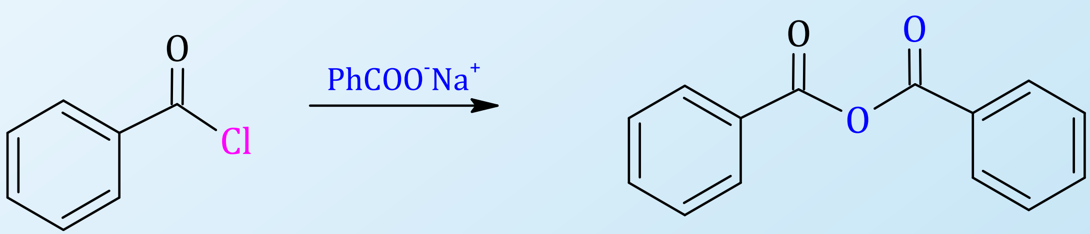
Carboxylic ester



Amide



Substituted amide

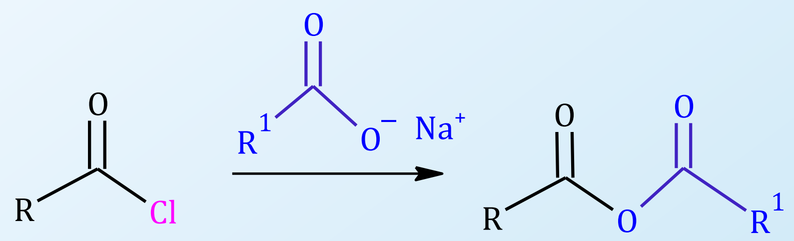


Carboxylic anhydride

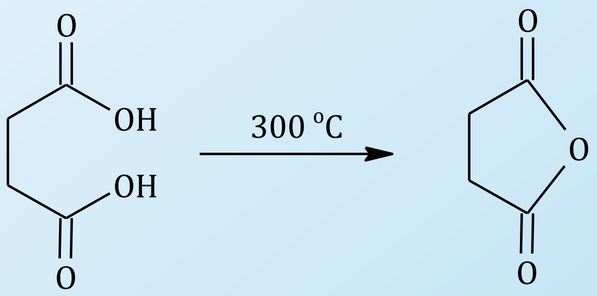
Anhydrides: Synthesis

Anhydrides can be made from carboxylic acids and acyl chlorides. Anhydrides can be symmetric or asymmetric. Acyl chlorides are a good way to make asymmetric anhydrides. Anhydrides are internal groups hence can be also be cyclic and diacids are usually used to make them.

1) **Acid chlorides and carboxylic acids** are used to form mixed or symmetrical anhydrides. It is necessary to use a base such as pyridine.

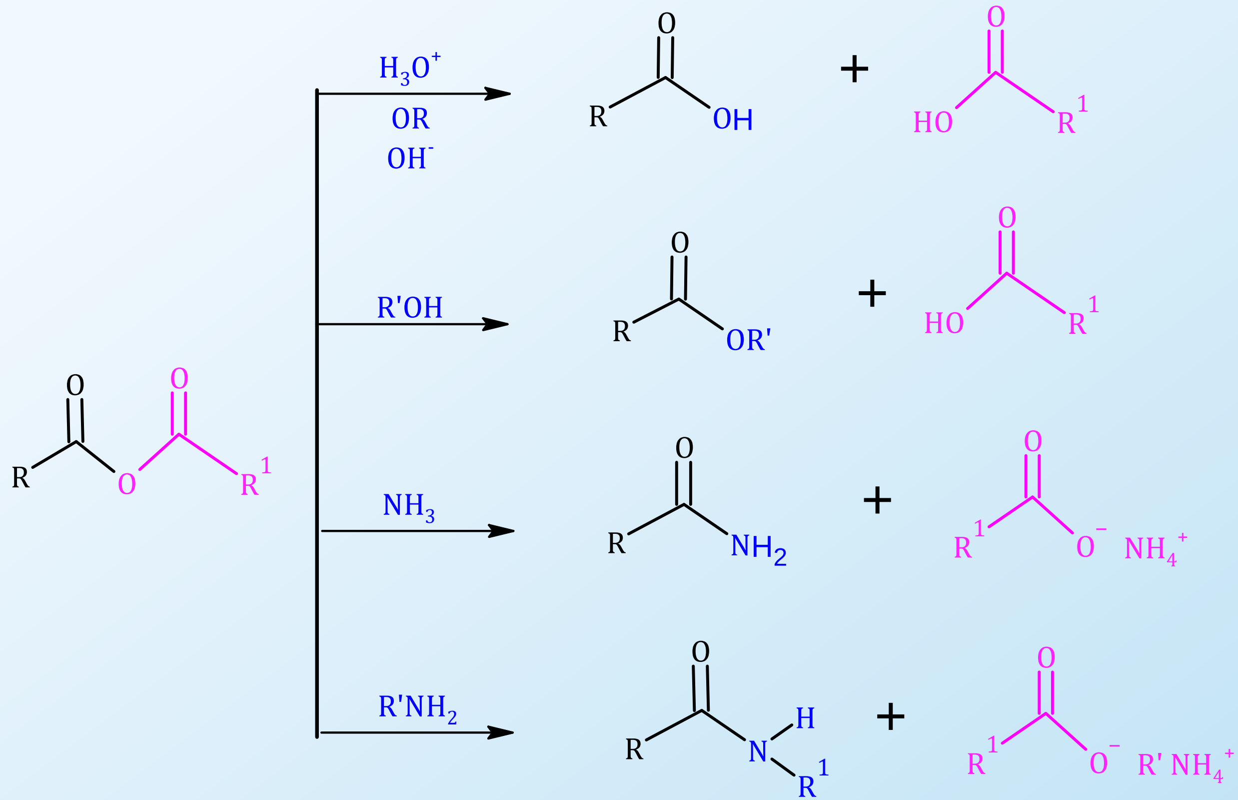


2) **Carboxylic acid dehydration:** This is a great way to make cyclic anhydrides with 5- and 6-membered rings can be synthesized by heating the appropriate diacid.



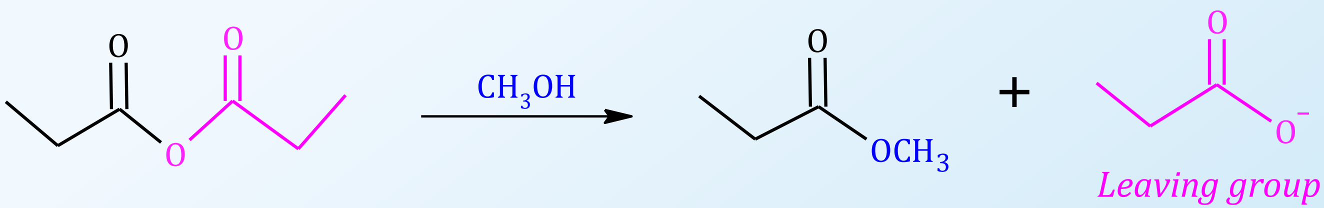
Anhydrides: Reactions

Anhydride reactions are less than acyl chlorides as they are less reactive than acyl chlorides. They can still react with water to form acids. Below are the generic reactions and as usual, examples of these reactions are on the next slide.

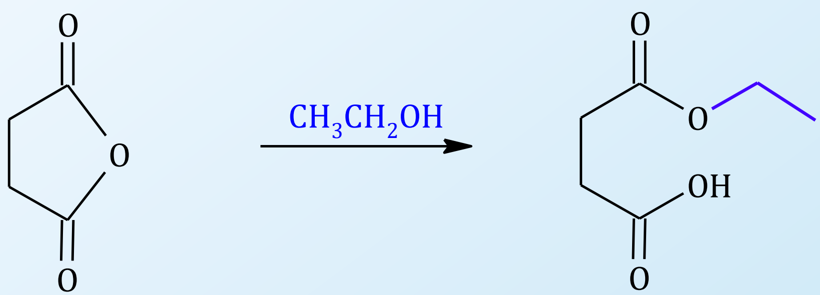


Anhydrides: Reactions Examples

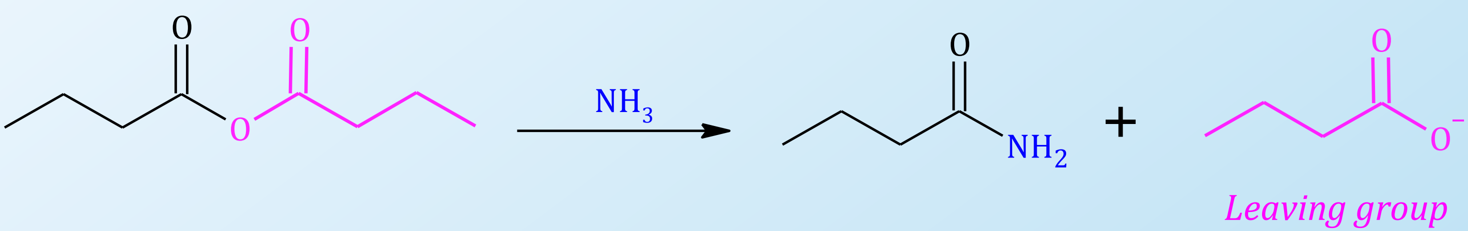
Below are examples of anhydrides to make different derivatives. Anhydrides will seem like they are fragmenting, but the leaving group that is also an organic fragment. Note that in cyclic anhydrides the leaving group stays on the original molecule.



Carboxylic ester



Carboxylic ester

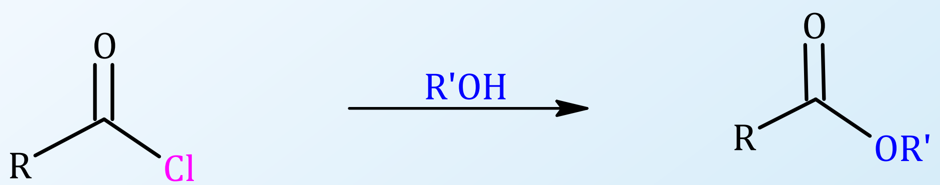


Amide

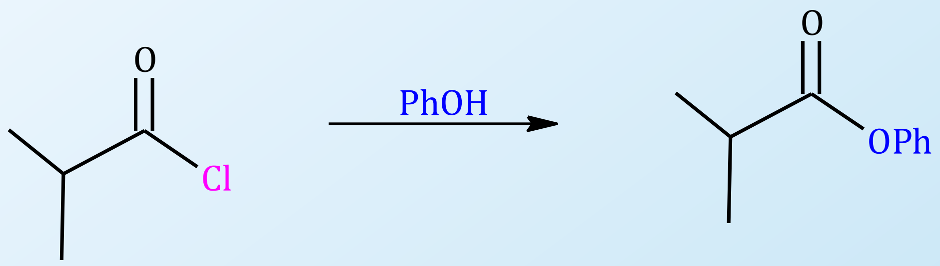
Esters: Synthesis from Acyl Chlorides

Esters are the more stable of the carboxylic derivatives. They can be synthesized from acyl chlorides, anhydrides and acids as shown below. All esters will need an alcohol for the synthesis. Esters are internal groups and can thus form cyclic structures called lactones.

1) Acyl chlorides

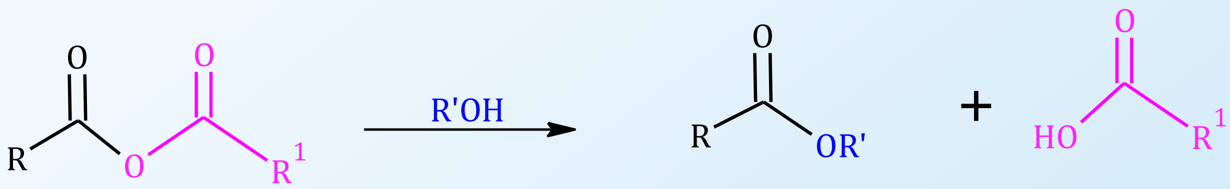


Example:

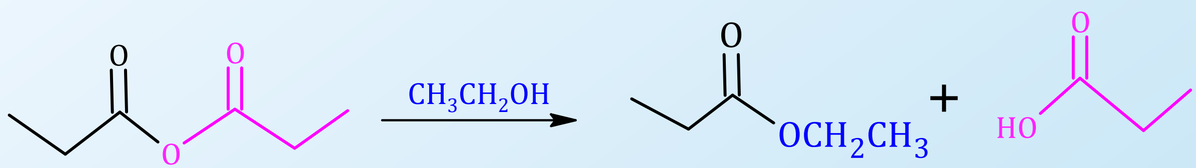


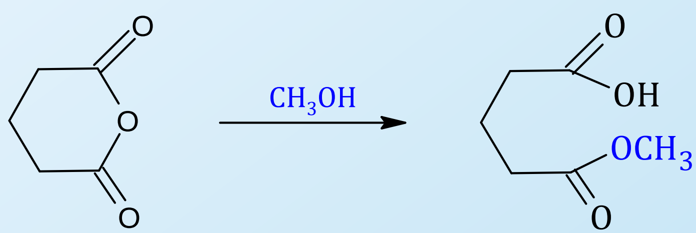
Esters: Synthesis from Anhydrides

2) From anhydrides: Anhydrides are little less reactive than acyl chlorides, but they still give esters in good yield. Note that in cyclic anhydride the leaving group stays on the parent molecule.



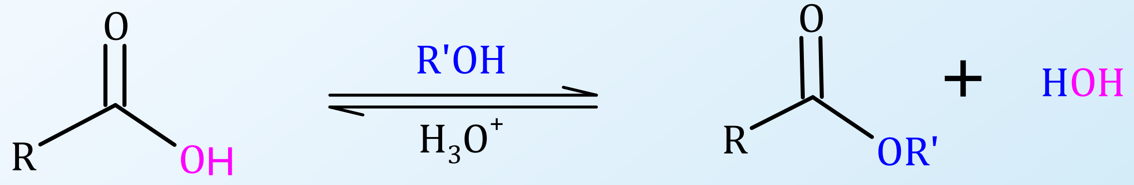
Example:



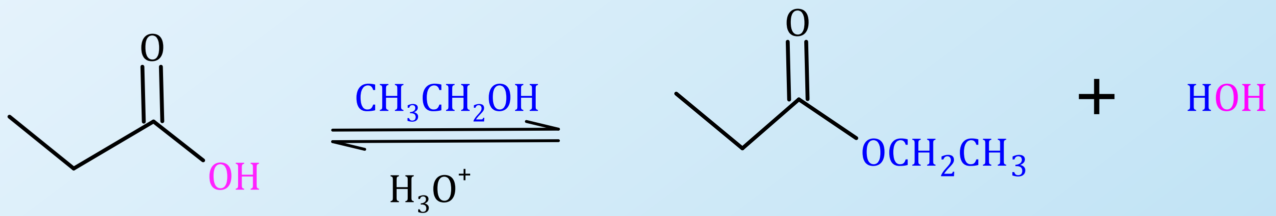


Esters: Synthesis from Carboxylic Acids

3) From Acids Carboxylic acids can form esters in presence of an acid or base. Fischer esterification is carried out in presence of acid catalyst. The reaction is in equilibrium and can be shifted to the products by removing water (product) or shifted backwards by adding water. We will be covering only the acid catalyzed mechanism here.

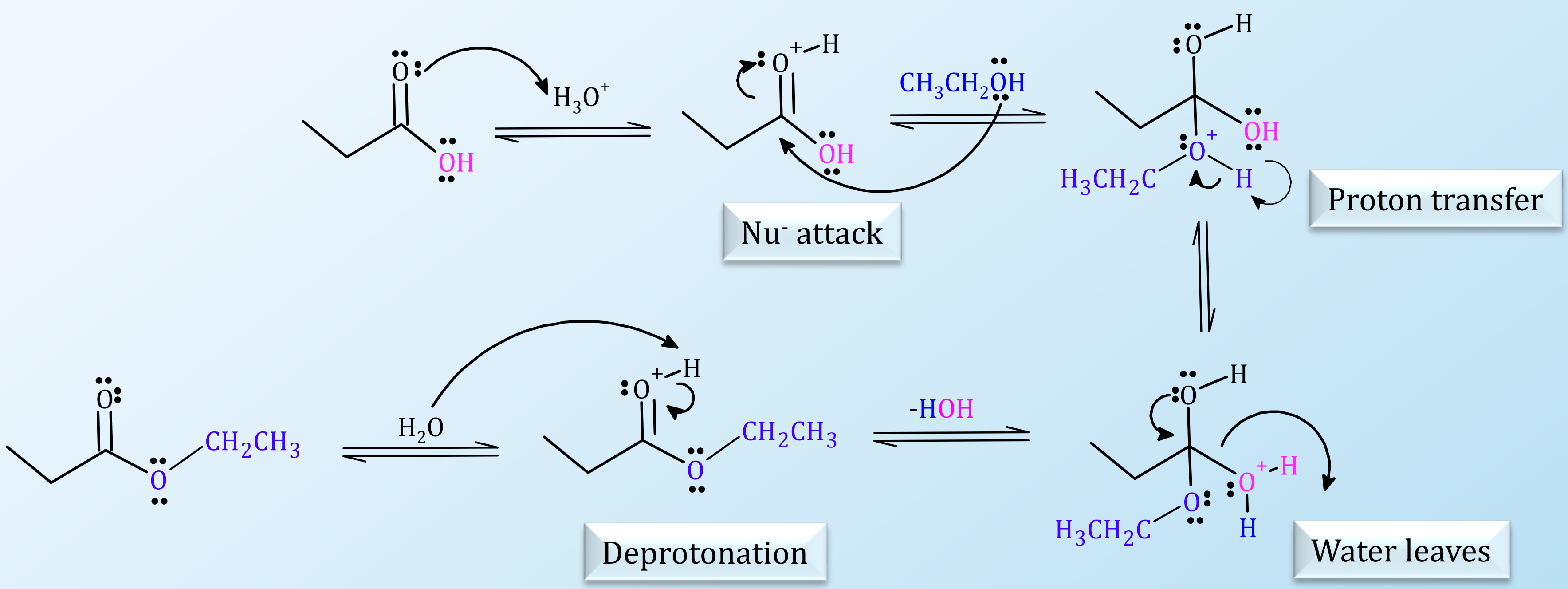


Fisher esterification shows that the OH of acid is part of the leaving group in the water molecule lost. The OH of alcohol is not part of the water. This has been verified by extensive research and thus the mechanism of esterification can be written out as shown on the next slide.



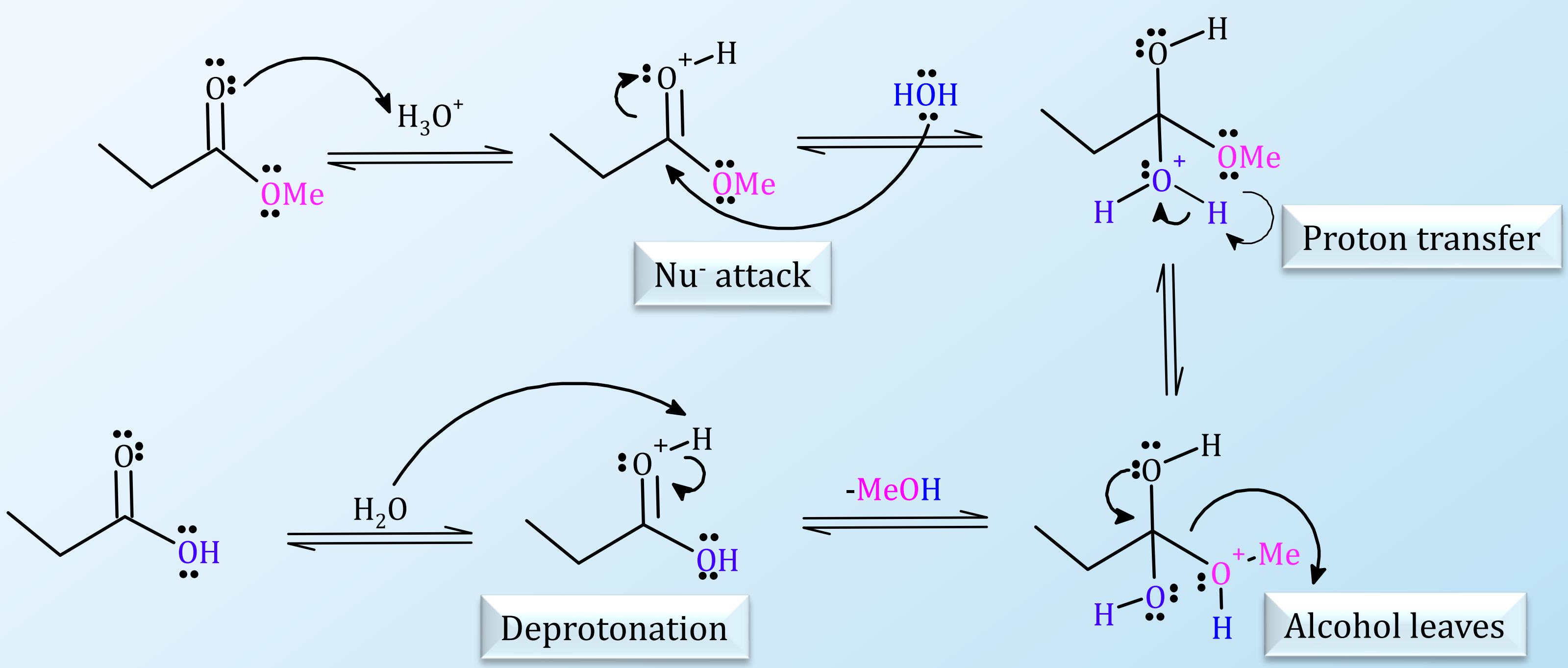
Mechanism of Esterification

In acidic mechanism the acid is the carbonyl oxygen is the nucleophile and it initiates the reaction by getting protonated from the acid. The electrophilic carbonyl carbon, with the oxonium ion, now gets attacked by the nucleophilic oxygen of alcohol. The next step is proton transfer from alcohol to the OH of the acid to become a good leaving group (water). Finally, the water leaves to eventually give the ester. We can see how the OH group of the acid is the LG.



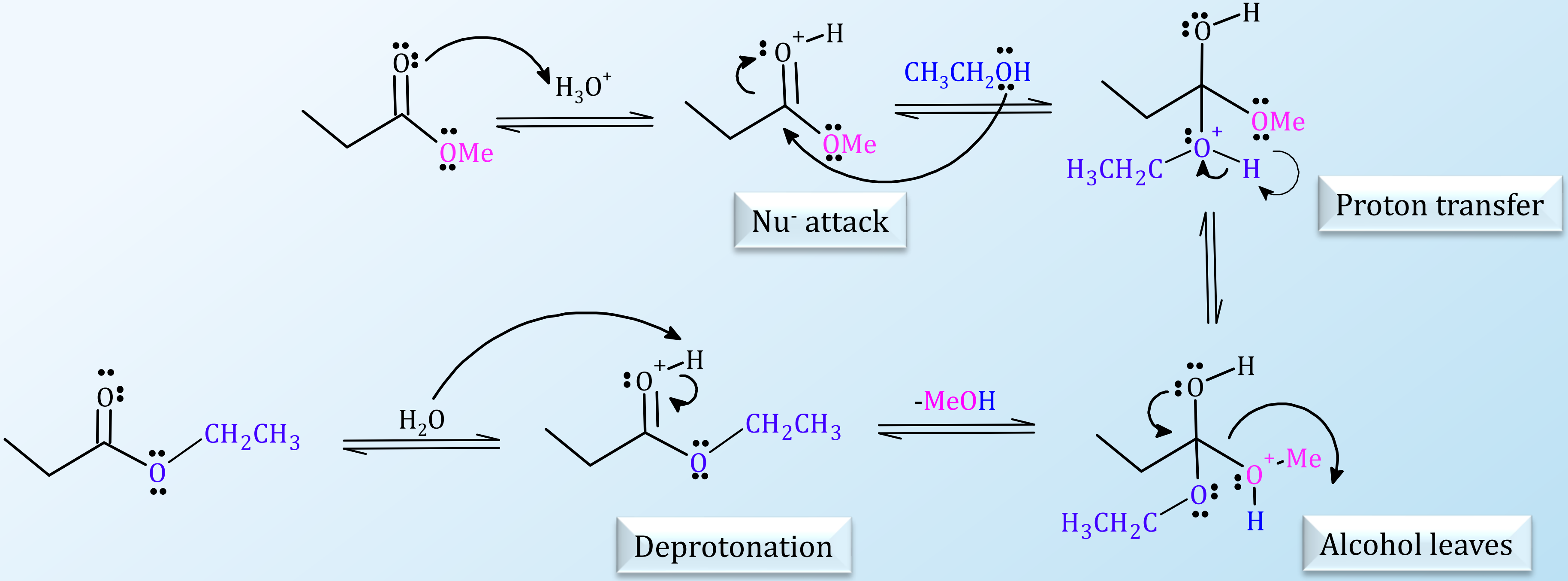
Mechanism of Hydrolysis

This reaction is the reaction of esters, but we will cover it here as we have just learned the mechanism of esterification. Acidic hydrolysis of an ester follows the same process as esterification but now the nucleophile is water instead of alcohol. The alcohol is the leaving group. Note that since esterification is in equilibrium, the reaction is carried out with careful monitoring of water as it can shift the reaction forward or backward.



Mechanism of Trans Esterification

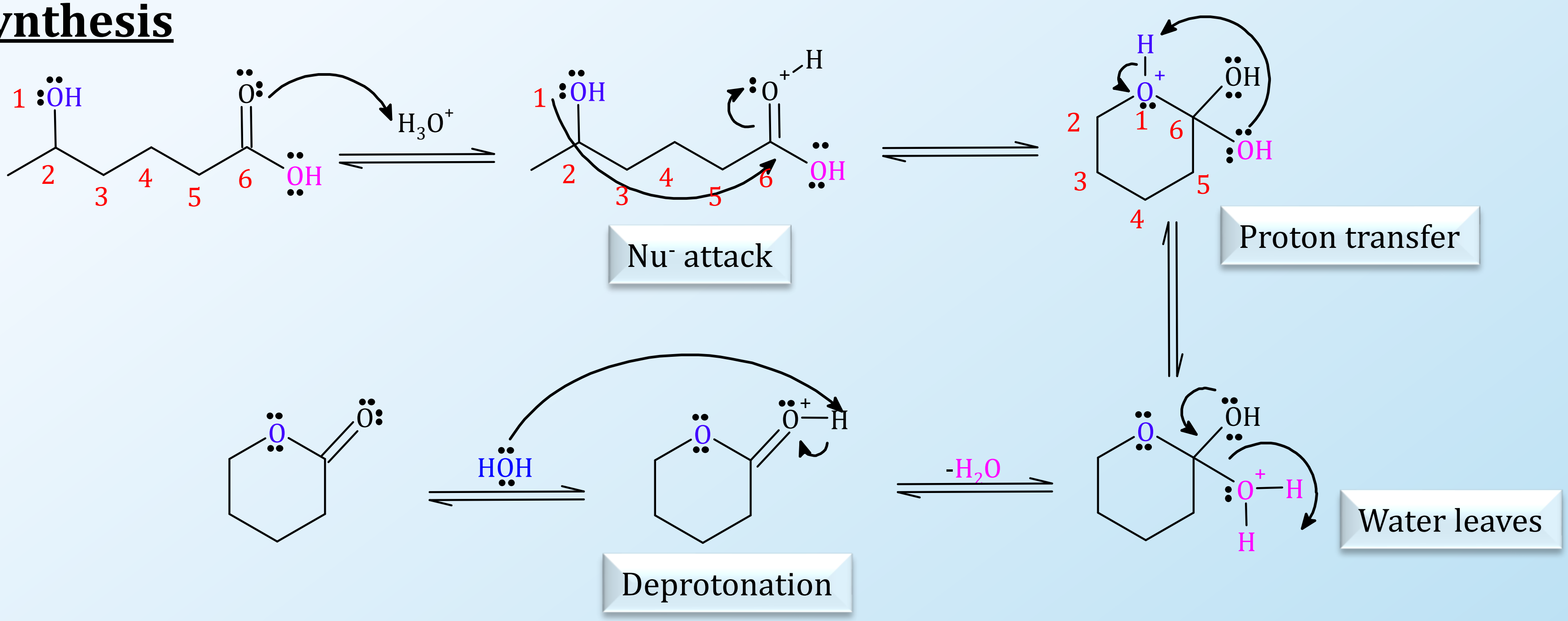
Esterification reaction is so versatile that in presence of an acid the alcohol component of the ester can be switched if needed. This process is called transesterification, and its mechanism is the same as esterification except it is done in presence of another alcohol.



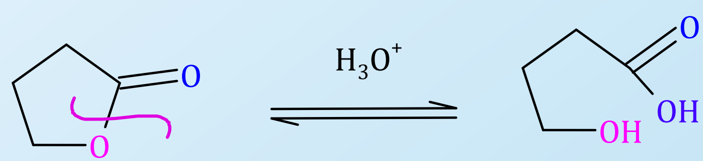
Formation of Cyclic Esters: Lactones

Lactones can be made by the internal cyclization of an acid and alcohol group in the same compound. This cyclization has the same mechanism as acid esterification. Acid hydrolysis of the lactone will open the ring to give back the acid and alcohol.

Synthesis

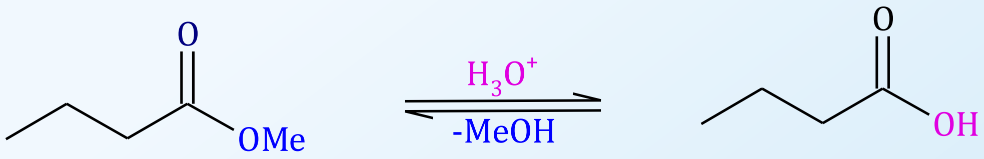


Hydrolysis

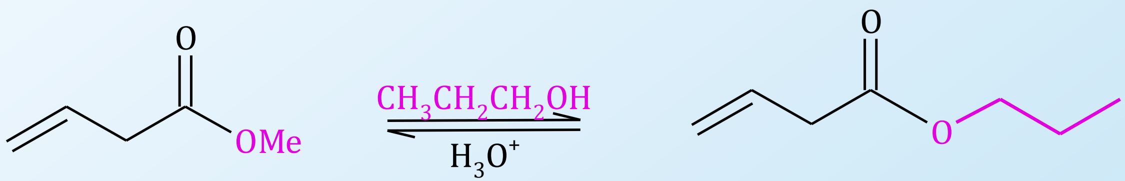


Esters: Reactions

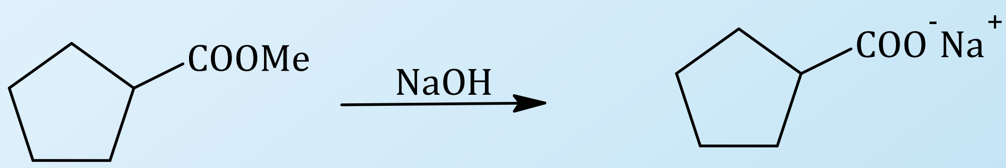
1) **Hydrolysis**: Acids can be acid hydrolyzed to give acid and alcohol. *Mechanism is given the previous slides.*



2) **Transesterifcation**: One ester can be converted to another in presence of an alcohol and a catalyst. *Mechanism is given the previous slides.*

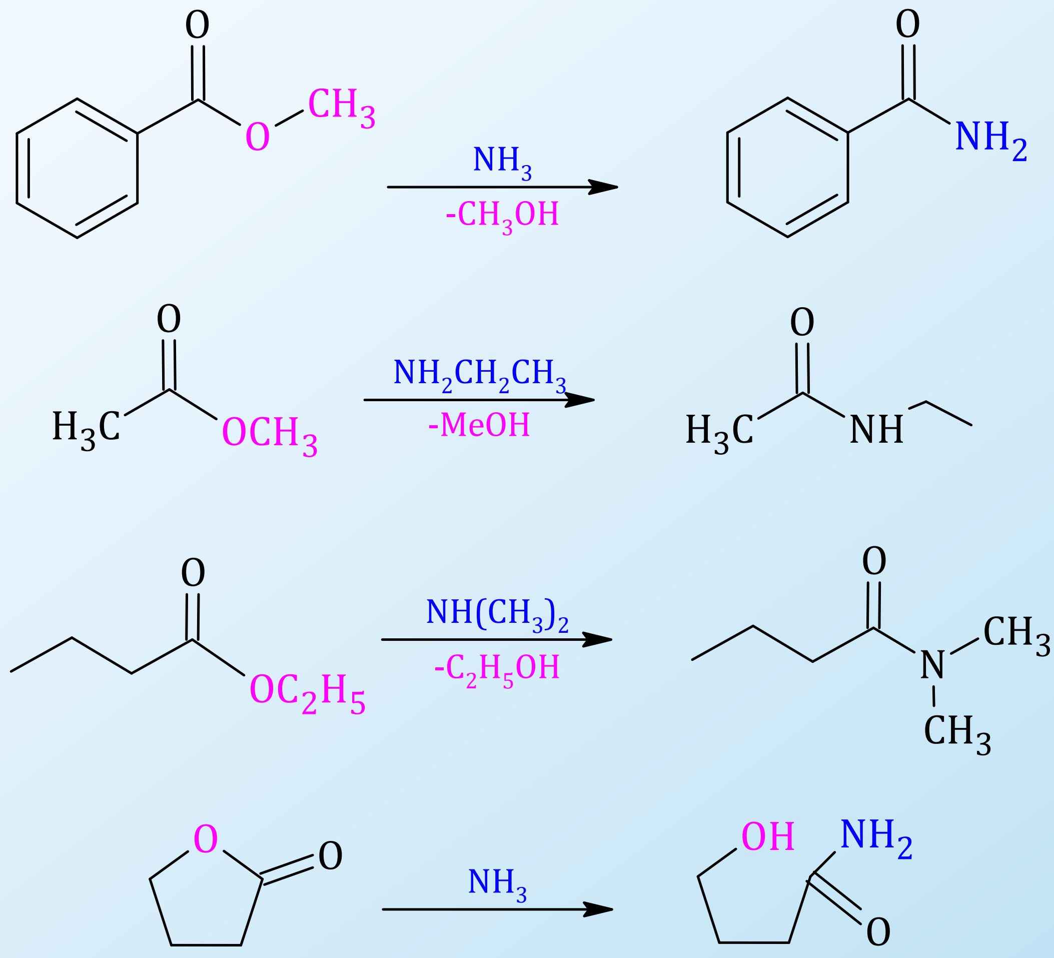


3) **Saponification**: Treatment of ester with strong base gives a carboxylate salt. Used mostly to prepare soaps.



Esters: Reactions

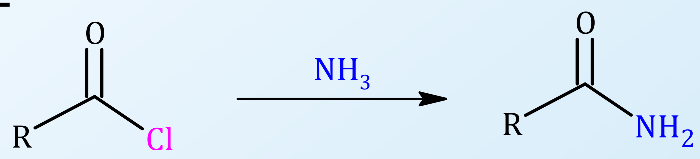
4) Amides: Amides can be formed by treating esters with ammonia or primary and secondary amines as shown below. Note – it is not easy to make amides from esters as esters are quite unreactive.



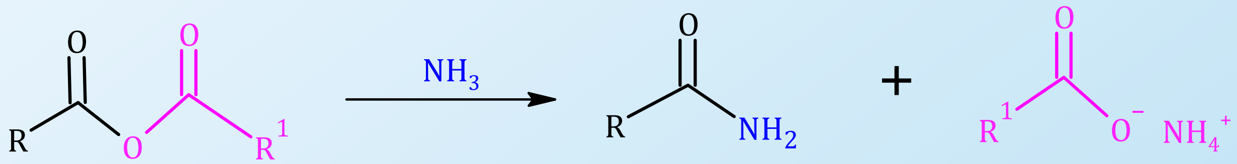
Amides: Synthesis

Amides are the most stable of all the carboxylic derivatives. They can be synthesized from acyl chlorides, anhydrides and acids as shown below. All amides will need ammonia or a primary or secondary amine the synthesis. Amides are internal groups and can thus form cyclic structures called lactams. Next slide has some examples. Note – it is not easy to make amides from esters as esters are quite unreactive.

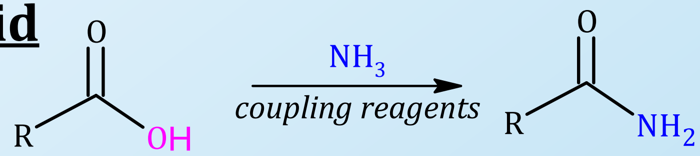
From Acyl Chlorides



From Anhydrides

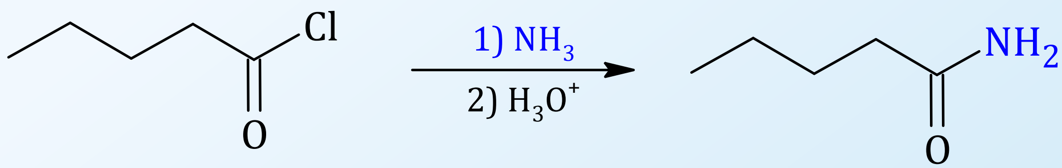


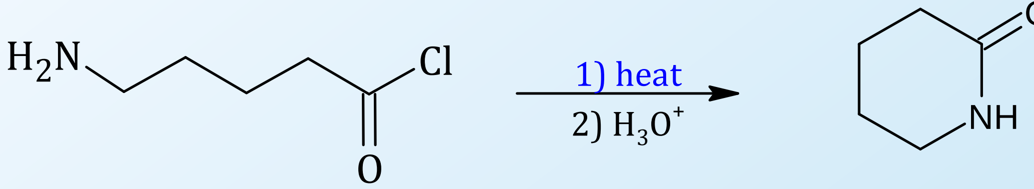
From Carboxylic Acid



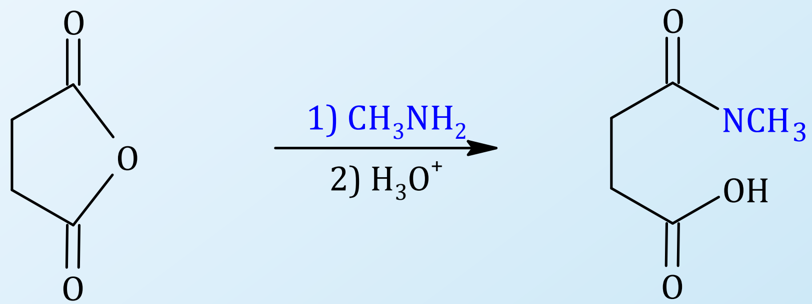
Amides: Synthesis Examples

From Acyl Chlorides

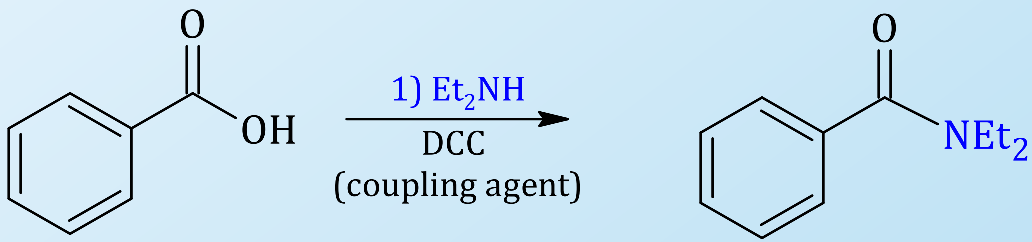




From Anhydrides



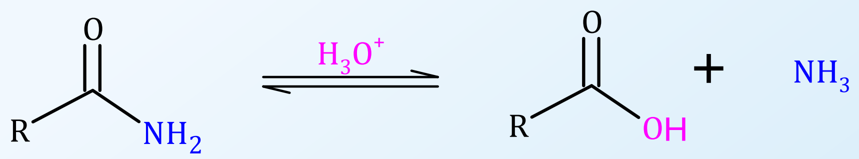
From Carboxylic Acid

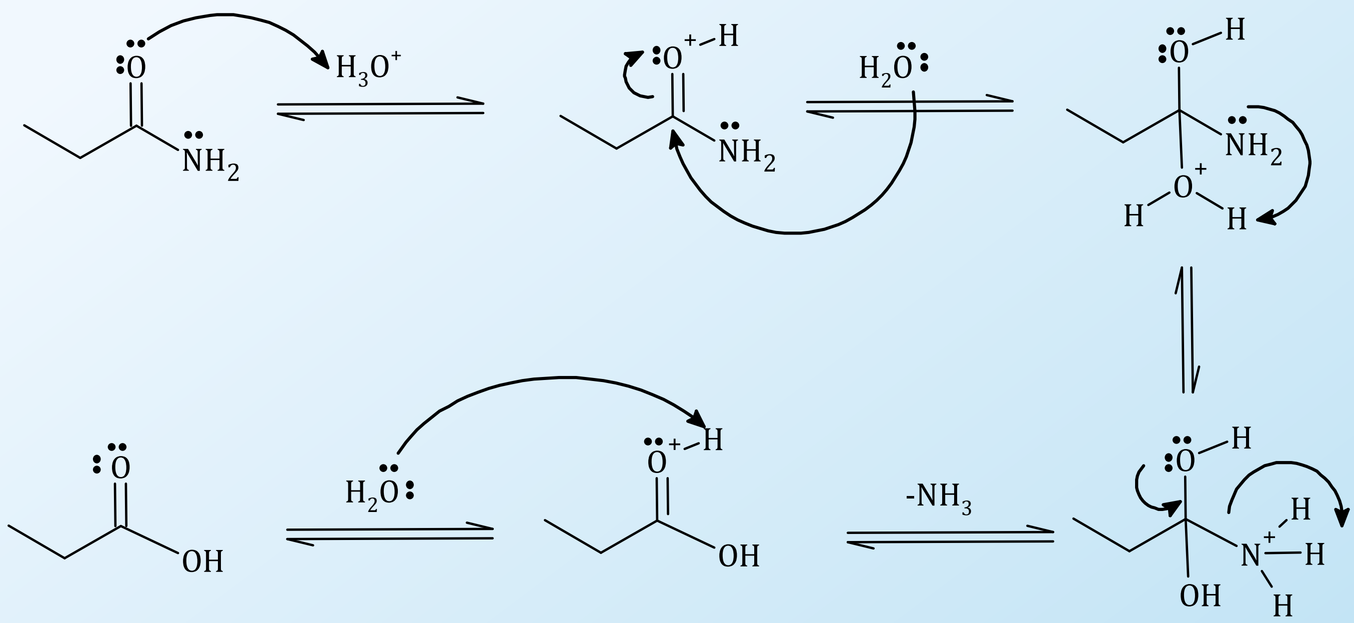


Amides: Reactions (Hydrolysis)

The only reaction for amides (for now) is hydrolysis to give the acid and amine as products.

Hydrolysis

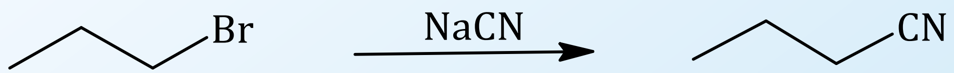




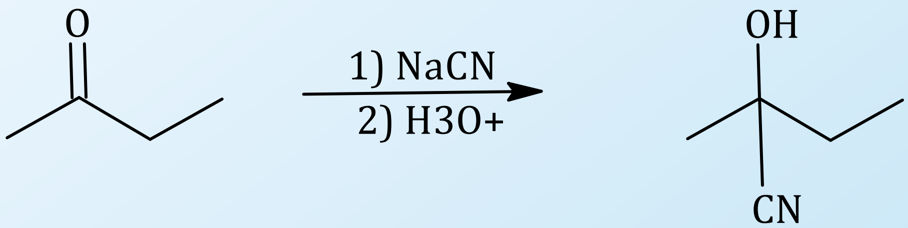
Nitriles: Synthesis

Nitriles are different from the other acid derivatives since they don't have a carbonyl group or any oxygen. Their synthesis and reactions are also quite different, but if you look carefully, you will find some interconversion from other acid derivatives.

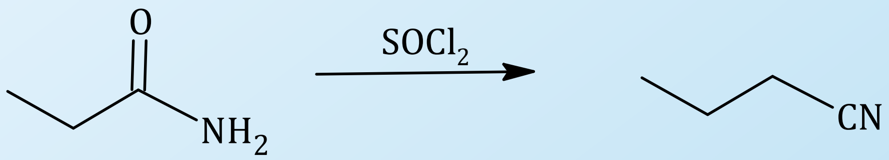
From Alkyl Halides (S_N2 reaction). Note that a C has been added to the substrate.



From Aldehydes and Ketones - Formation of cyanohydrin.

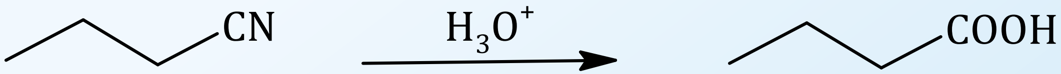


From dehydration of amides - Interconversion from acid derivative.



Reactions: Nitriles (Hydrolysis)

Hydrolysis of nitriles gives carboxylic acid.

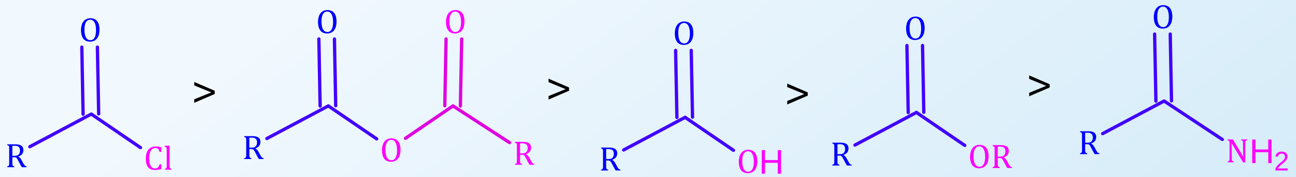


There are other reactions of nitriles, but here we are covering only the interconversions of carboxylic acid derivatives.

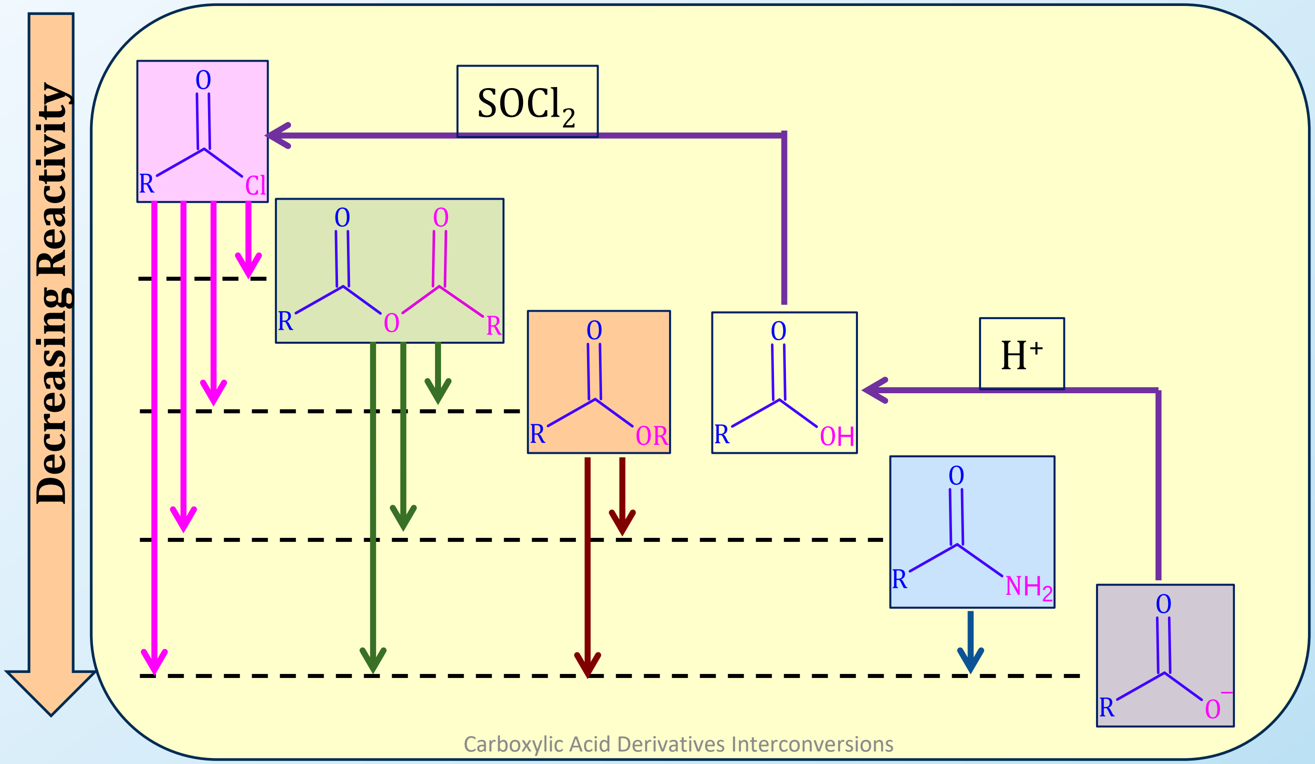
Interconversions of Acid Derivatives

Again, here is the chart of interconversions possible for each acid derivative. All reactions we have covered so far shows how this chart can be used.

Most reactive

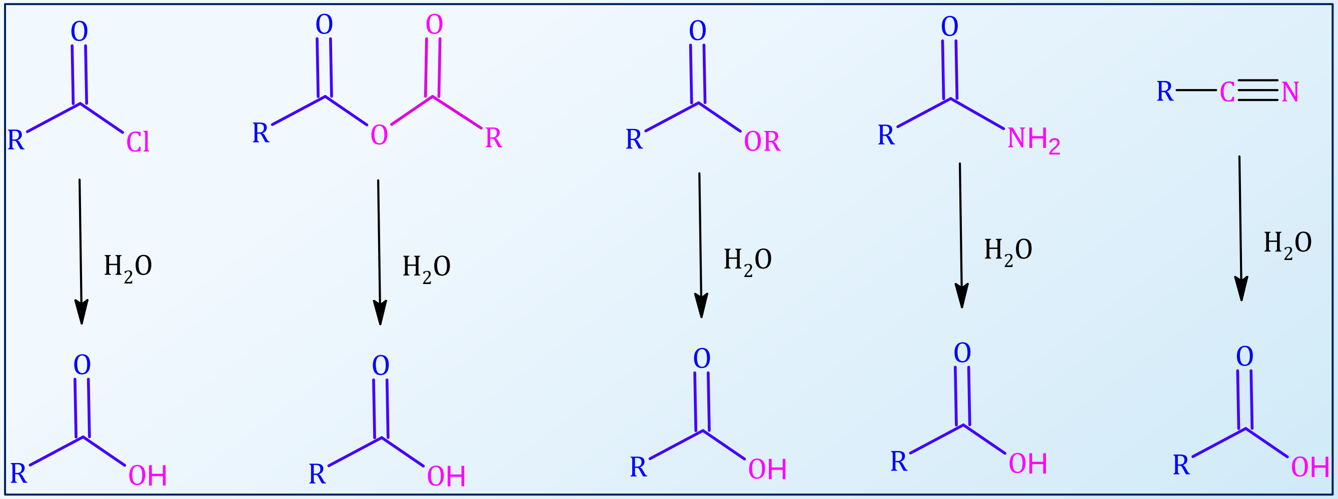


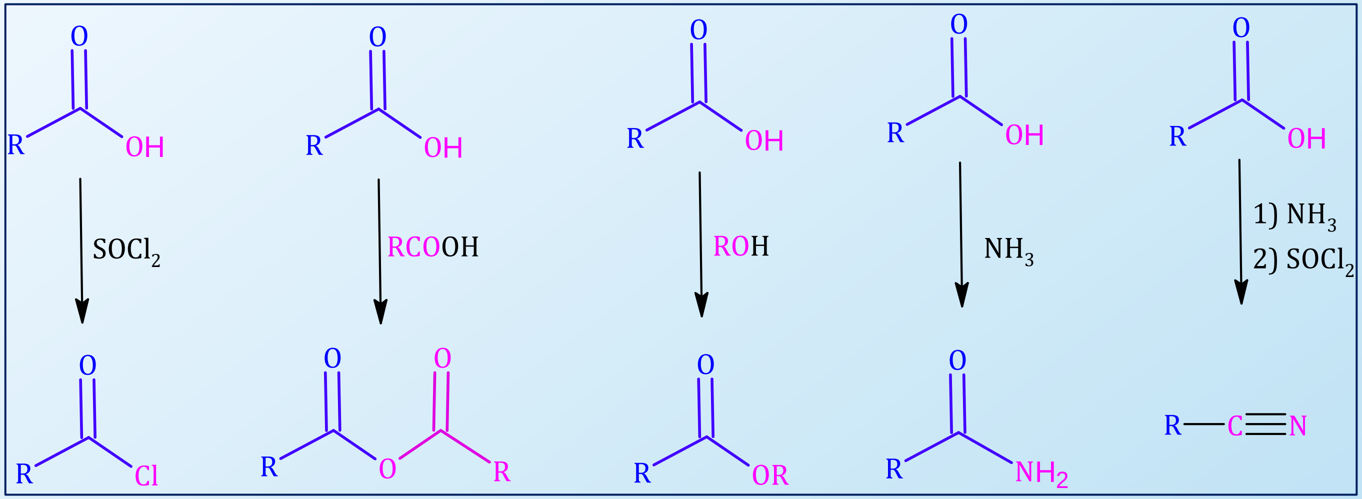
Least reactive



Reactivity of all Derivatives

Here are all derivatives and their conversion to carboxylic acid.





Key Concepts

- Synthesis and Reactions of all derivatives
- Mechanism of esterification