


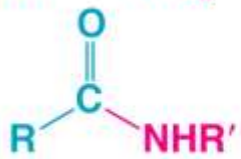





**CARBOXYLIC ACIDS AND THEIR DERIVATIVES:
NUCLEOPHILIC ADDITION-ELIMINATION AT THE ACYL
CARBON**

**RED ANT WAS SOURCE OF
FORMIC ACID (RCOOH)**

○ Introduction

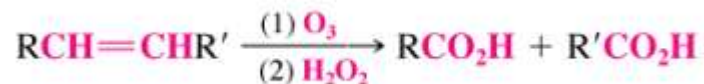
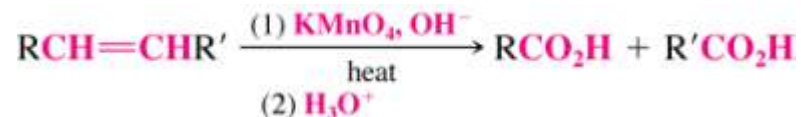
- The carboxyl group ($-\text{CO}_2\text{H}$) is the parent group of a family of compounds called *acyl compounds* or *carboxylic acid derivatives*

Structure	Name	Structure	Name
	Acyl (or acid) chloride		Amide
	Acid anhydride		
	Ester		
	Nitrile		

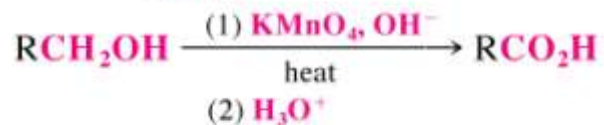
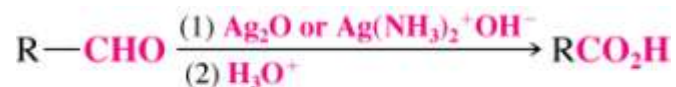


○ Preparation of Carboxylic Acids

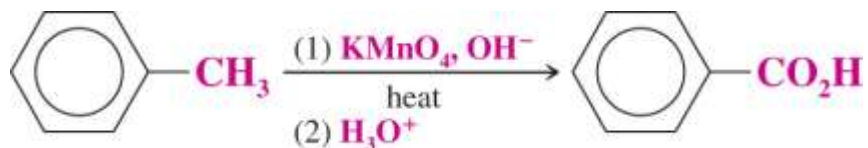
- By Oxidation of Alkanes



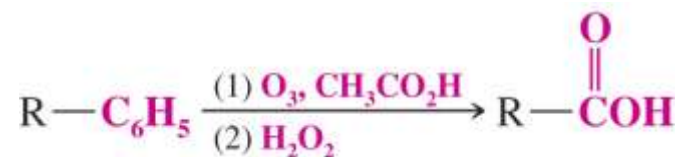
- By Oxidation of Aldehydes and Primary Alcohols



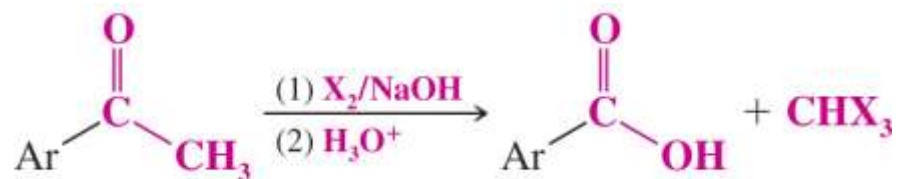
- By Oxidation of Alkylbenzenes



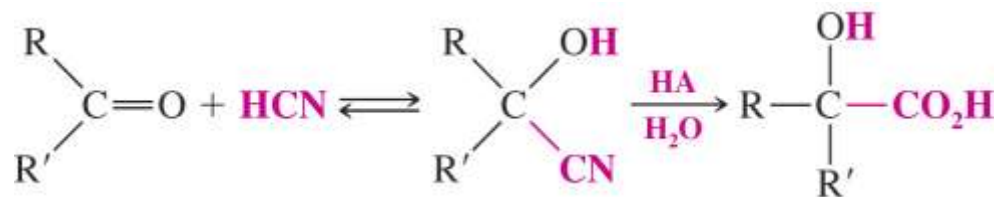
- By Oxidation of the Benzene Ring



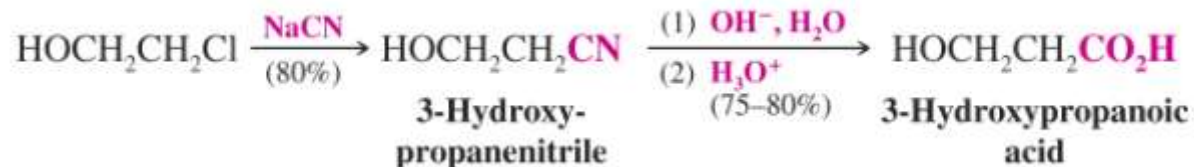
- By Oxidation of Methyl Ketones (The Haloform Reaction)



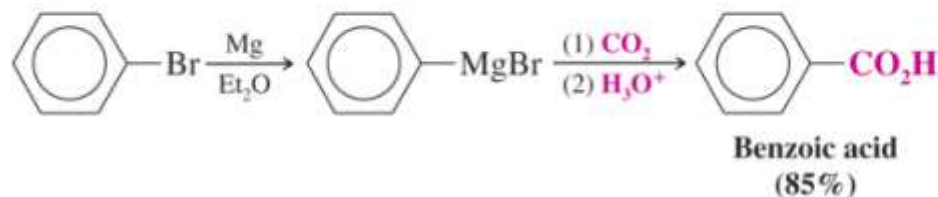
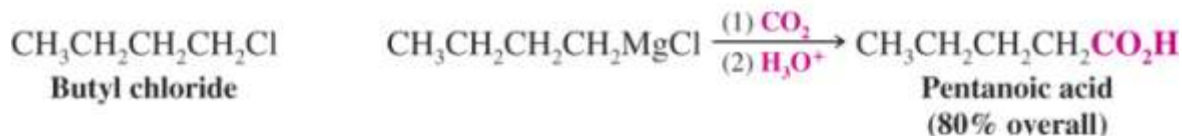
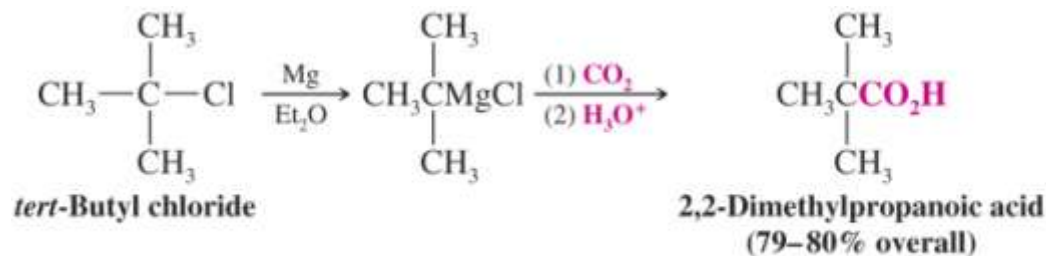
- By Hydrolysis of Cyanohydrins and Other Nitriles
 - Hydrolysis of a cyanohydrin yields an α -hydroxy acid



- Primary alkyl halides can react with cyanide to form nitriles and these can be hydrolyzed to carboxylic acids

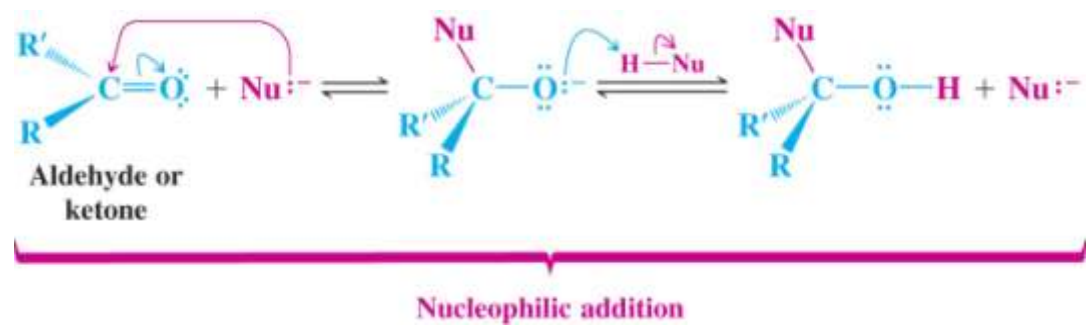


- By Carbonation of Grignard Reagents

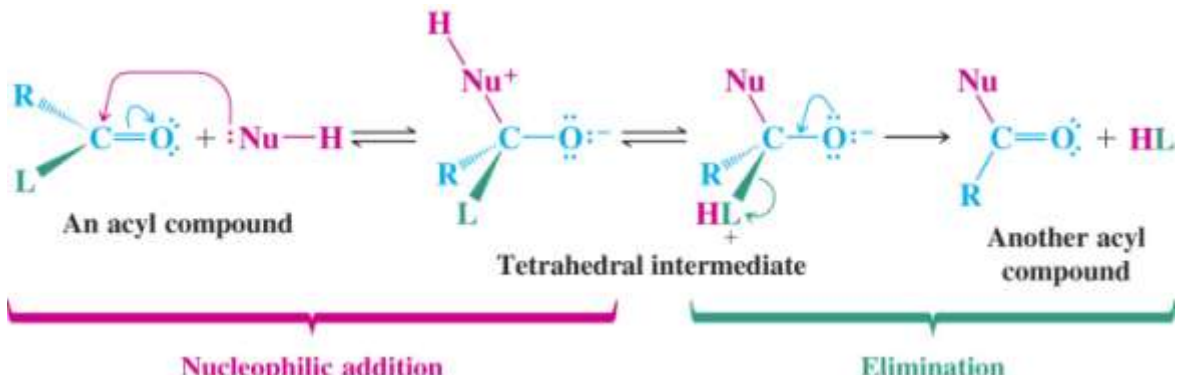


Nucleophilic Addition-Elimination at the Acyl Carbon

- Recall that aldehydes and ketones undergo nucleophilic addition to the carbon-oxygen double bond

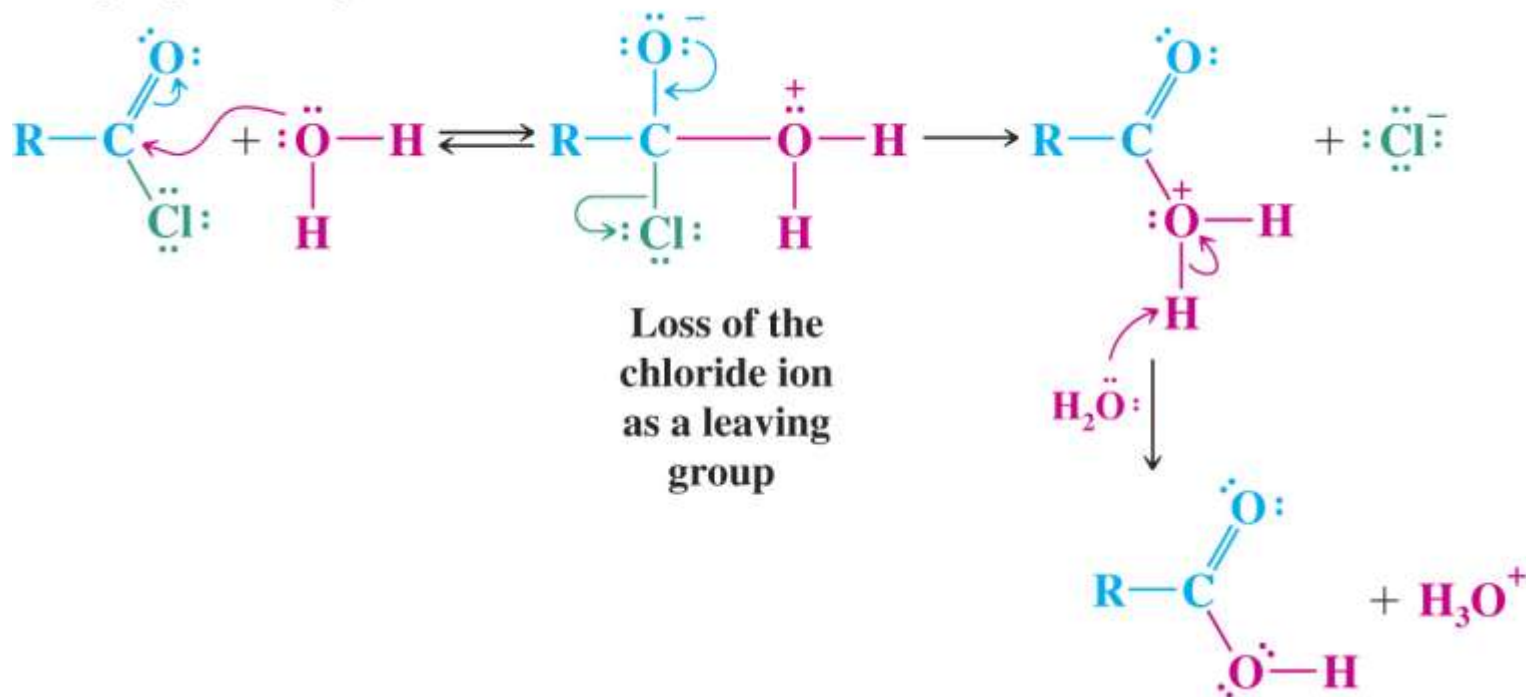


- The carbonyl group of carboxylic acids and their derivatives undergo nucleophilic addition-elimination
 - The nucleophile reacts at the carbonyl group to form a tetrahedral intermediate
 - The tetrahedral intermediate eliminates a leaving group (L)
 - The carbonyl group is regenerated; the net effect is an acyl substitution

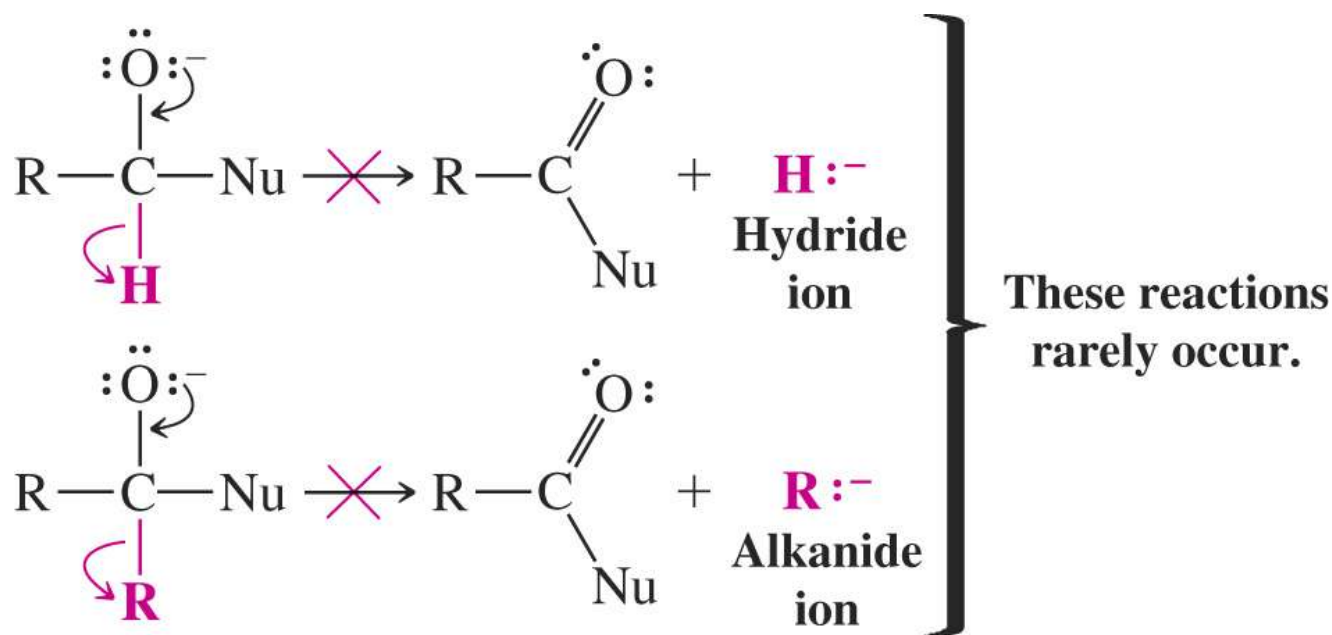


- To undergo nucleophilic addition-elimination the acyl compound must have a good leaving group or a group that can be converted into a good leaving group
 - Acid chlorides react with loss of chloride ion
 - Anhydrides react with loss of a carboxylate ion

Specific Example

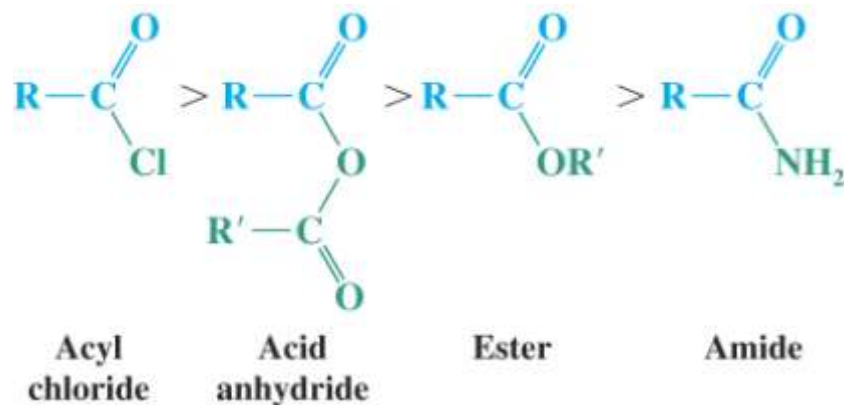


- Esters, carboxylic acids and amides generally react with loss of the leaving groups alcohol, water and amine, respectively
 - These leaving groups are generated by protonation of the acyl compound
- Aldehydes and ketones cannot react by this mechanism because they lack a good leaving group



- Relative Reactivity of Acyl Compounds

- The relative reactivity of carboxylic acids and their derivatives is as follows:

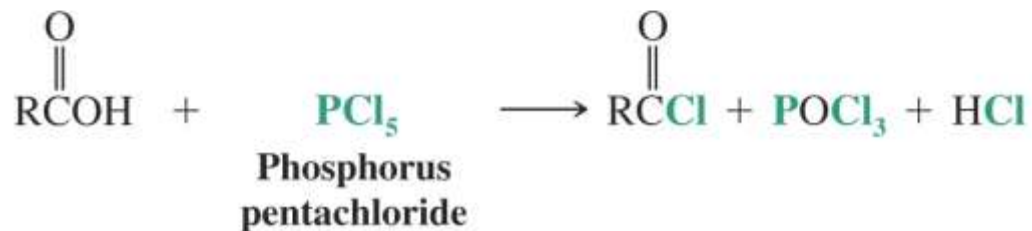
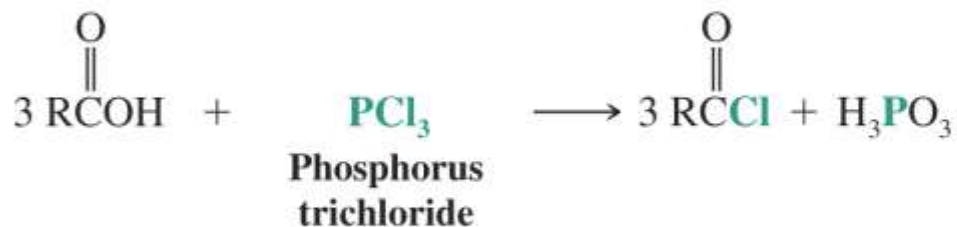
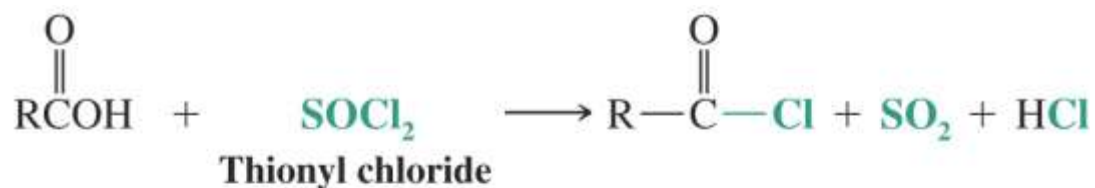


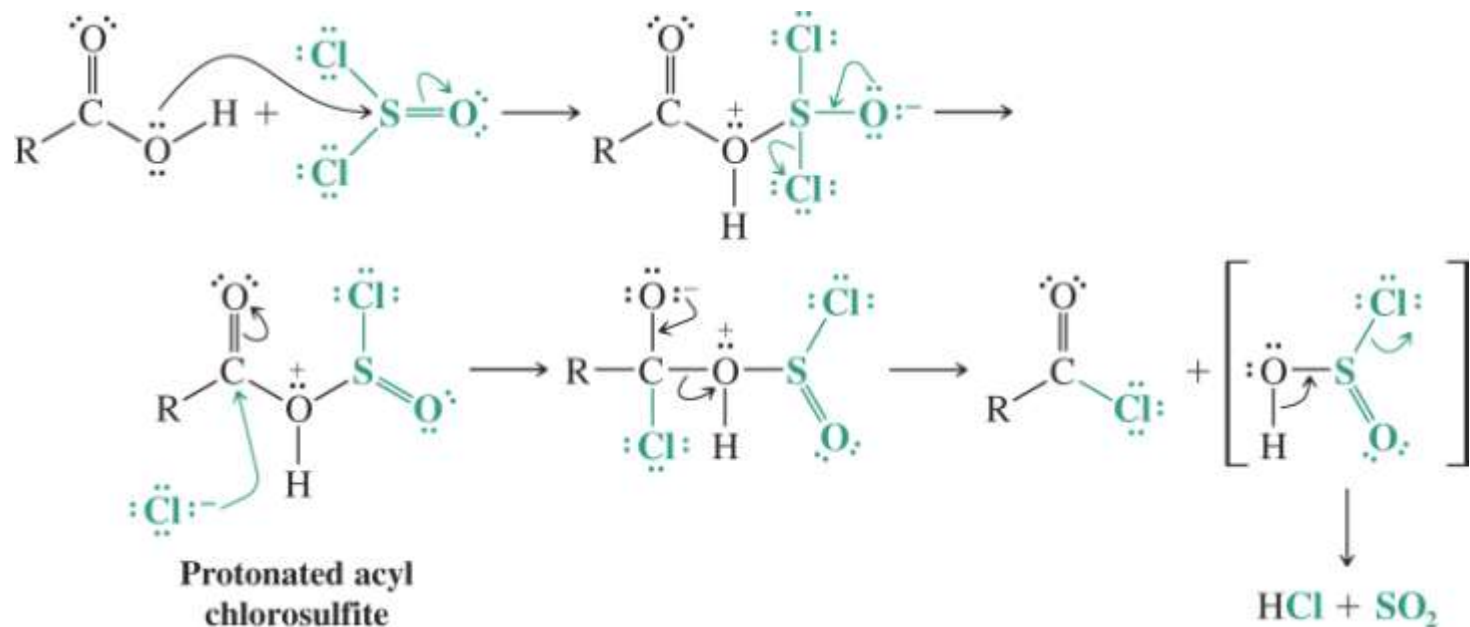
- In general, reactivity can be related to the ability of the leaving group (L) to depart
 - Leaving group ability is inversely related to basicity
 - Chloride is the weakest base and the best leaving group
 - Amines are the strongest bases and the worst leaving groups
- As a general rule, less reactive acyl compounds can be synthesized from more reactive ones
 - Synthesis of more reactive acyl derivatives from less reactive ones is difficult and requires special reagents (if at all possible)

○ Acid Chlorides

• Synthesis of Acid Chlorides

- Acid chlorides are made from carboxylic acids by reaction with thionyl chloride, phosphorus trichloride or phosphorus pentachloride
- These reagents work because they turn the hydroxyl group of the carboxylic acid into an excellent leaving group

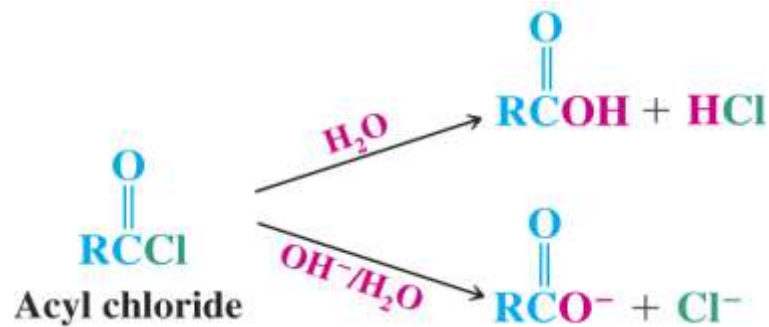
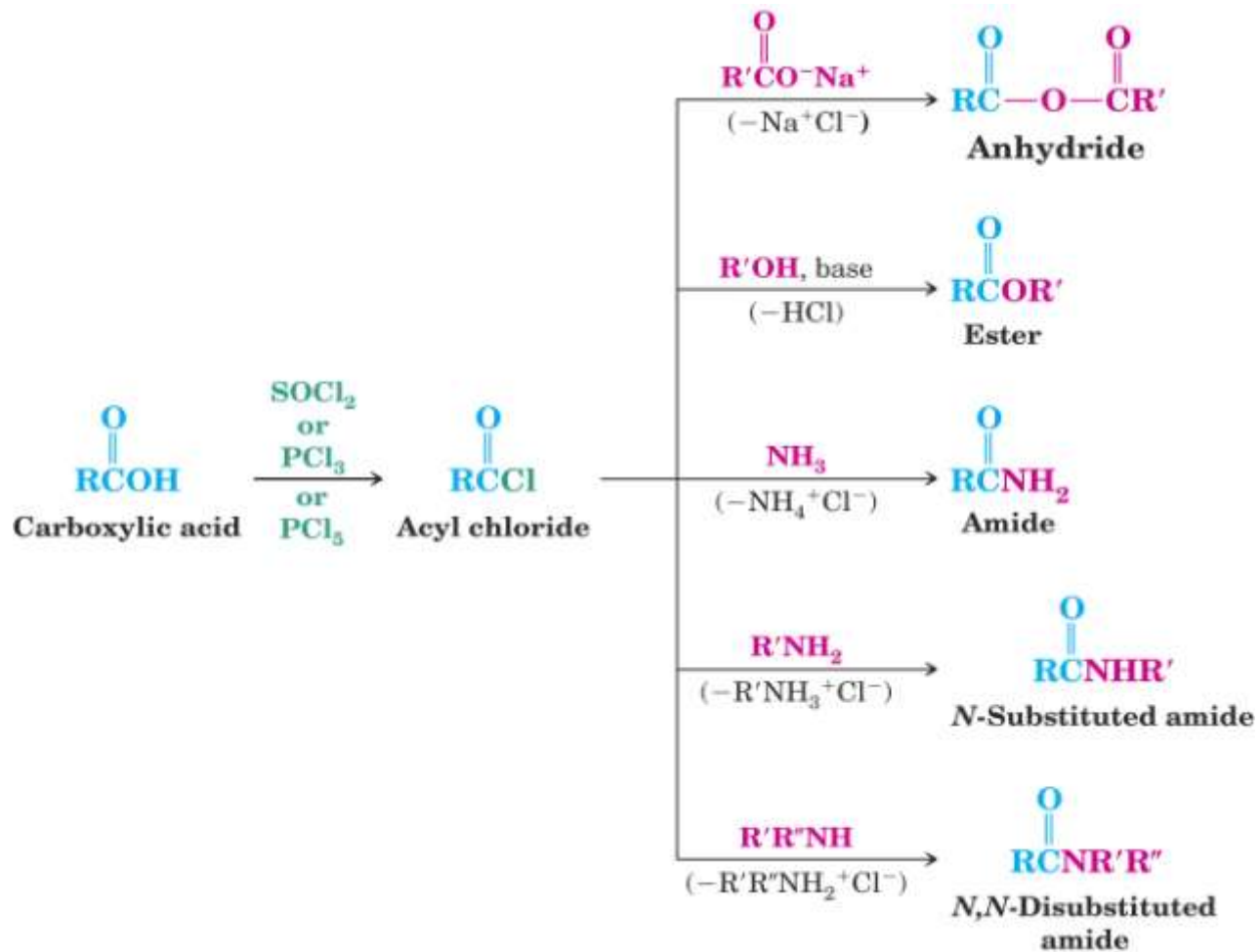




- **Reactions of Acyl Chlorides**

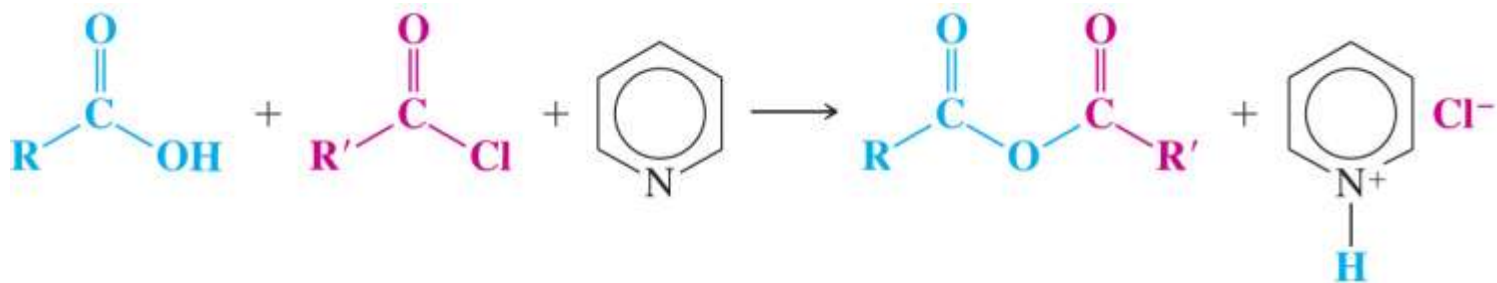
- Acyl chlorides are the most reactive acyl compounds and can be used to make any of the other derivatives
- Since acyl chlorides are easily made from carboxylic acids they provide a way to synthesize any acyl compound from a carboxylic acid
- Acyl chlorides react readily with water, but this is not a synthetically useful reaction



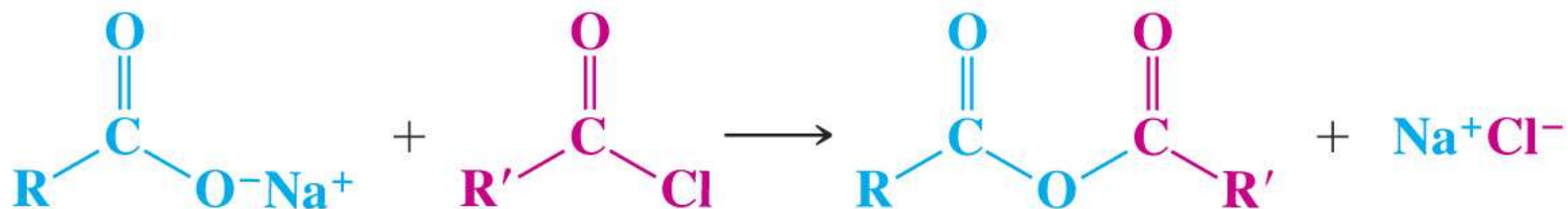


Carboxylic Acid Anhydrides

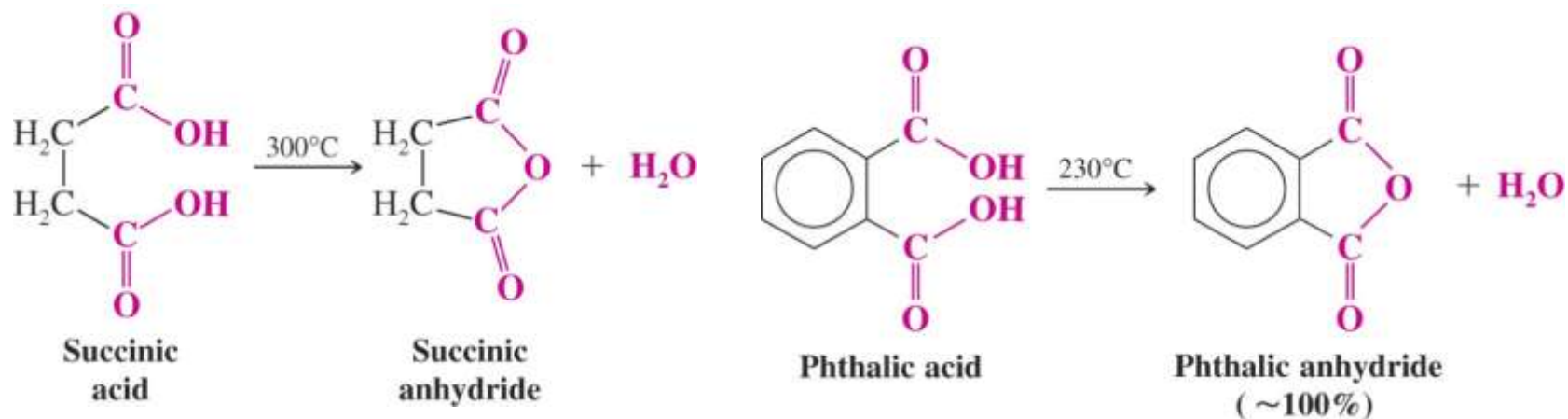
- Synthesis of Carboxylic Acid Anhydrides
 - Acid chlorides react with carboxylic acids to form mixed or symmetrical anhydrides
 - It is necessary to use a base such as pyridine



- Sodium carboxylates react readily with acid chlorides to form anhydrides



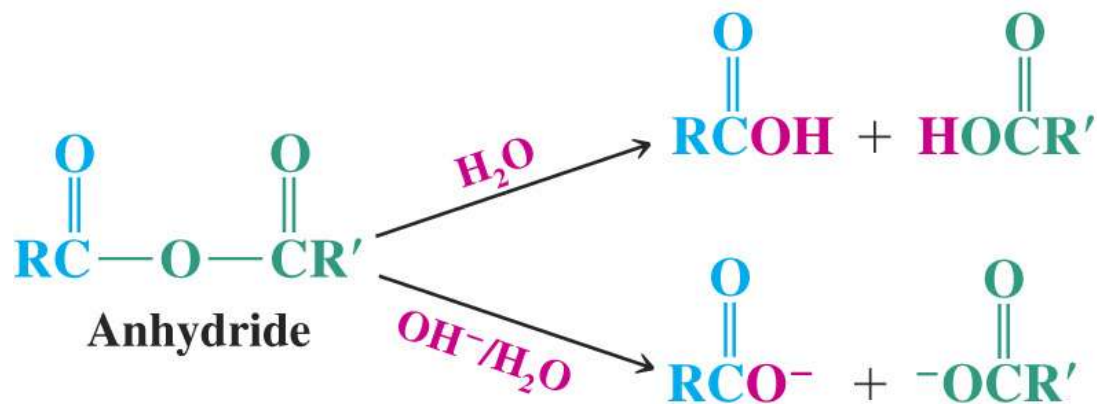
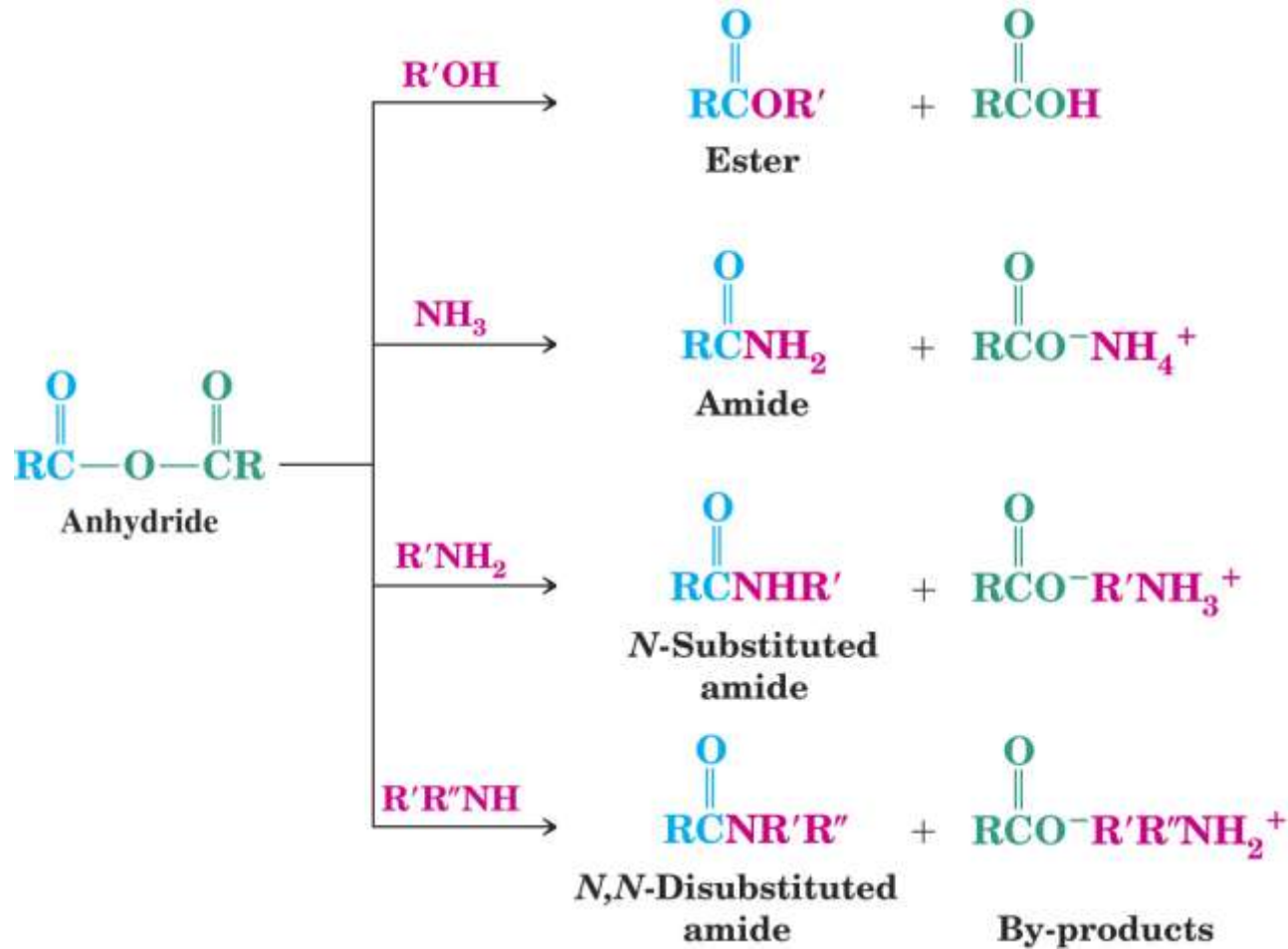
- Cyclic anhydrides with 5- and 6-membered rings can be synthesized by heating the appropriate diacid



- Reactions of Carboxylic Acid Anhydrides

- Carboxylic acid anhydrides are very reactive and can be used to synthesize esters and amides
 - Hydrolysis of an anhydride yields the corresponding carboxylic acids

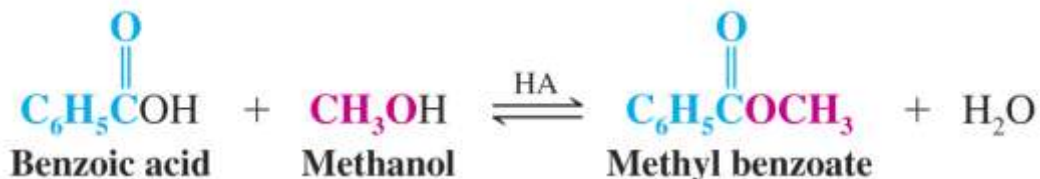
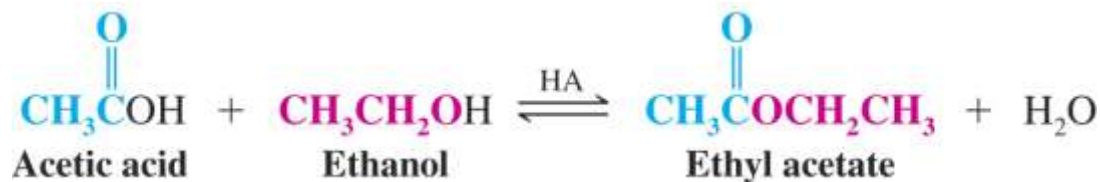
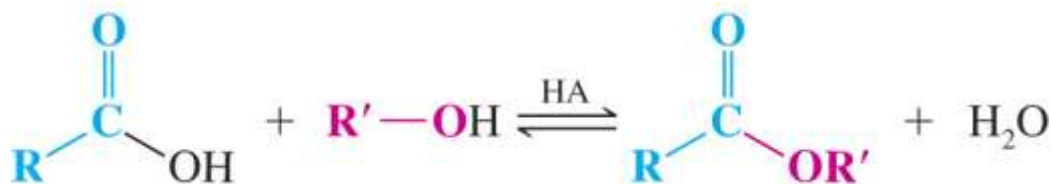




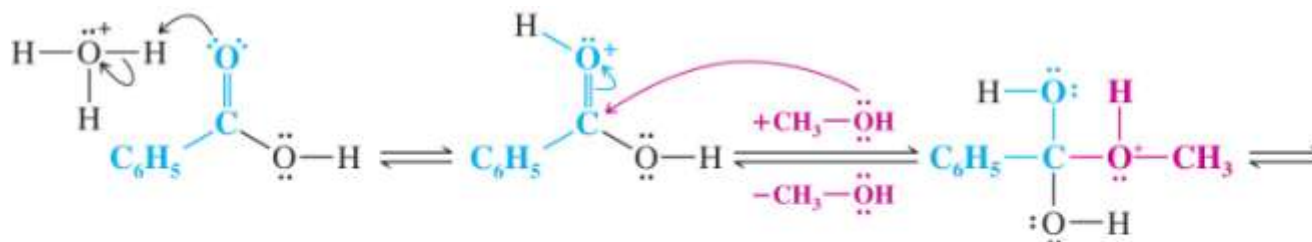
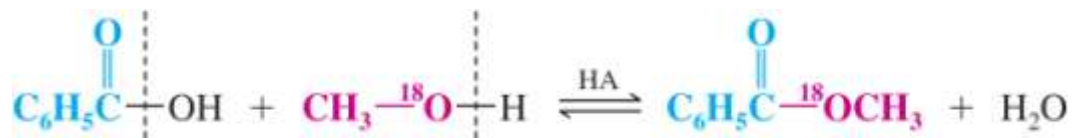
○ Esters

• Synthesis of Esters: Esterification

- Acid catalyzed reaction of alcohols and carboxylic acids to form esters is called Fischer esterification
- Fischer esterification is an equilibrium process
 - Ester formation is favored by use of a large excess of either the alcohol or carboxylic acid
 - Ester formation is also favored by removal of water



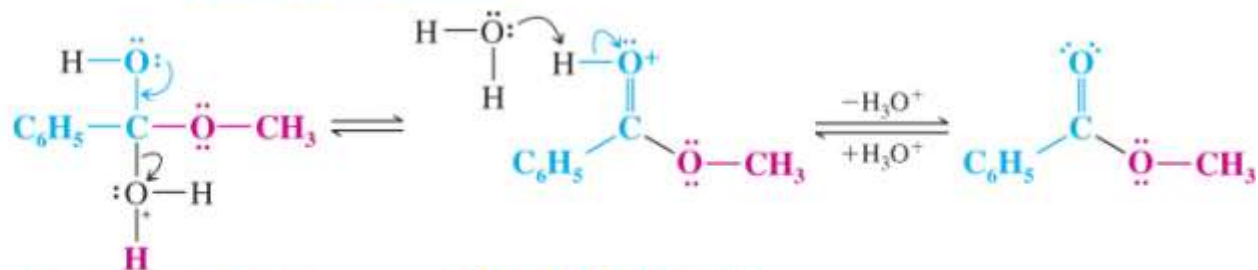
- Esterification with labeled methanol gives a product labeled only at the oxygen atom bonded to the methyl group
 - A mechanism consistent with this observation is shown below



The carboxylic acid accepts a proton from the strong acid catalyst.

The alcohol attacks the protonated carbonyl group to give a tetrahedral intermediate.

A proton is lost at one oxygen atom and gained at another.

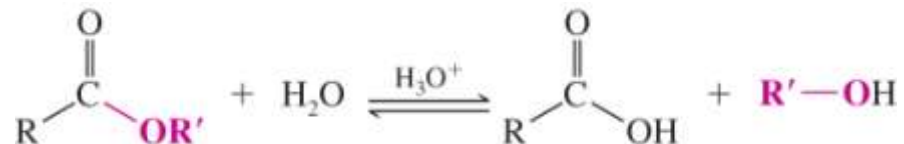


Loss of a molecule of water gives a protonated ester.

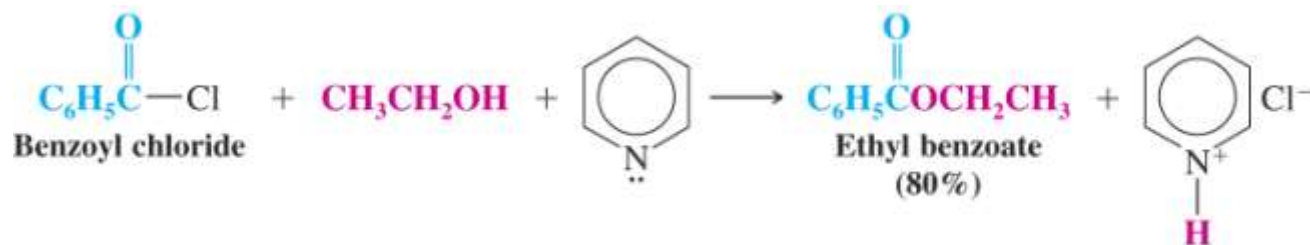
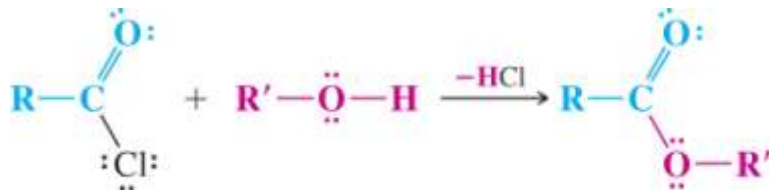
Transfer of a proton to a base leads to the ester.



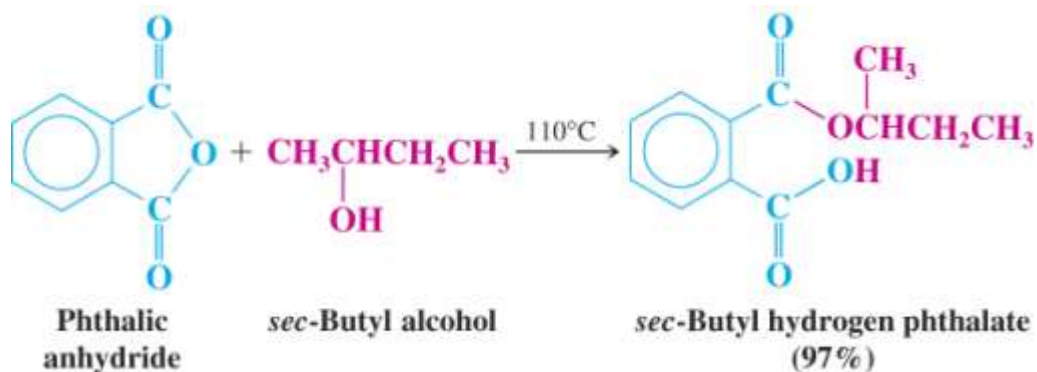
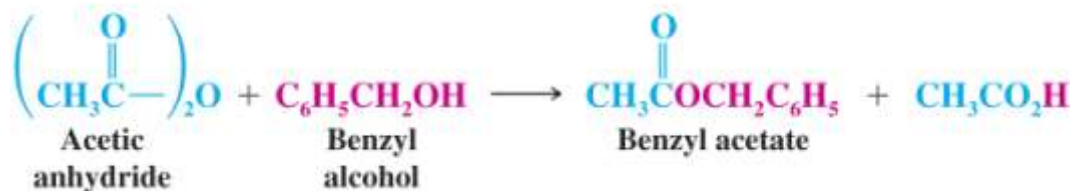
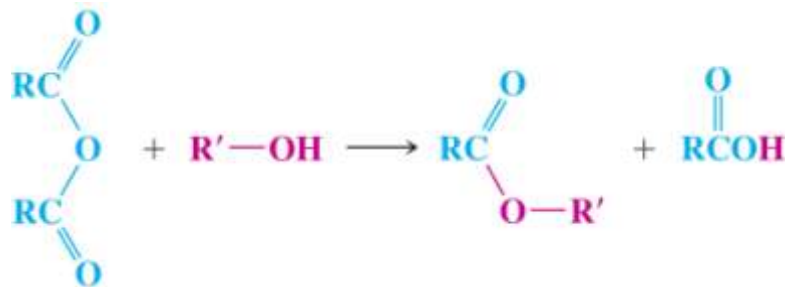
- The reverse reaction is acid-catalyzed ester hydrolysis
 - Ester hydrolysis is favored by use of dilute aqueous acid



- Esters from Acid Chlorides
 - Acid chlorides react readily with alcohols in the presence of a base (e.g. pyridine) to form esters

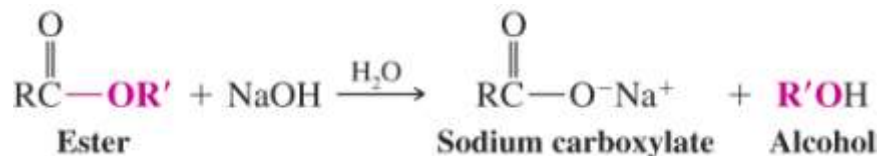


- Esters from Carboxylic Acid Anhydrides
 - Alcohols react readily with anhydrides to form esters

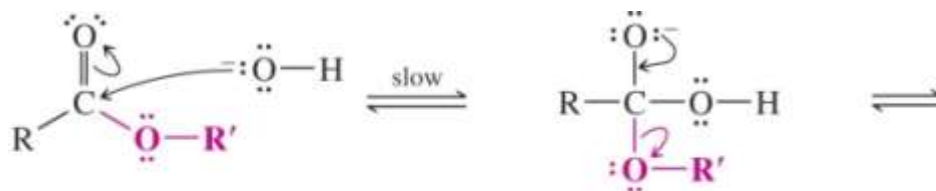


- Base-Promoted Hydrolysis of Esters: Saponification

- Reaction of an ester with sodium hydroxide results in the formation of a sodium carboxylate and an alcohol

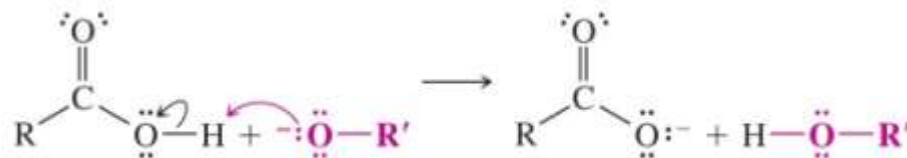


- The mechanism is reversible until the alcohol product is formed
- Protonation of the alkoxide by the initially formed carboxylic acid is irreversible
 - This step draws the overall equilibrium toward completion of the hydrolysis



A hydroxide ion attacks the carbonyl carbon atom.

The tetrahedral intermediate expels an alkoxide ion.

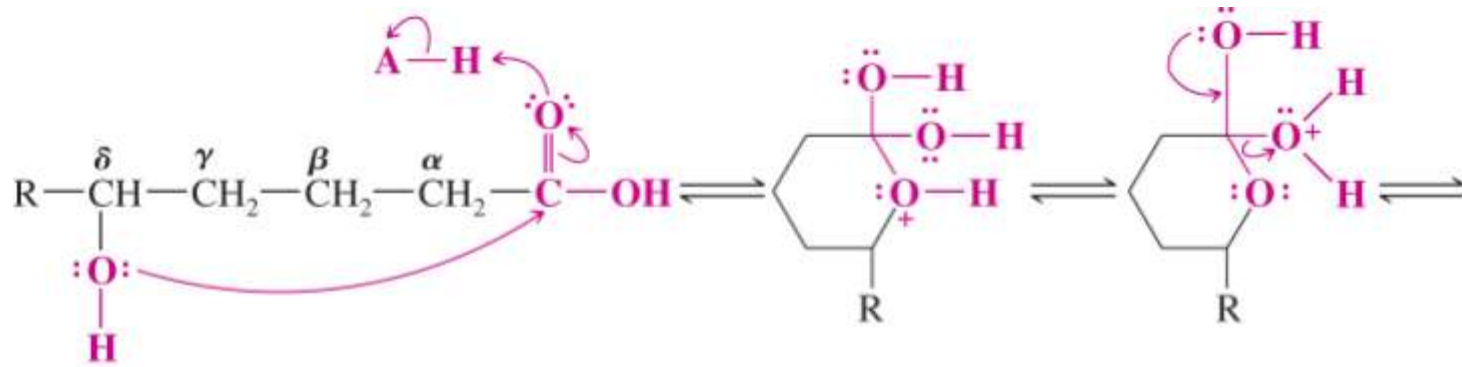


Transfer of a proton leads to the products of the reaction.

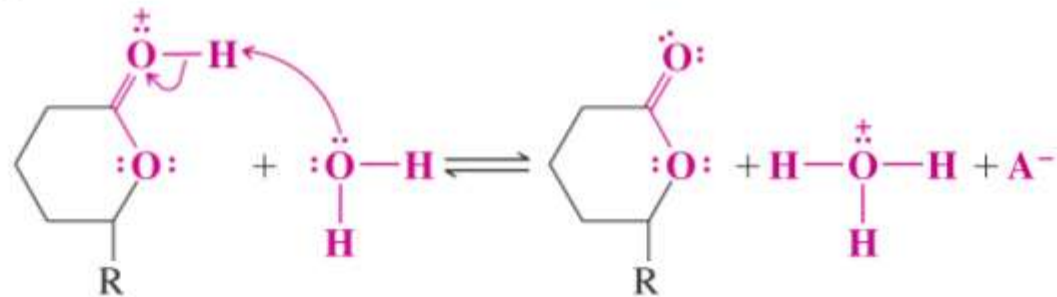


- Lactones

- γ - or δ -Hydroxyacids undergo acid catalyzed reaction to give cyclic esters known as γ - or δ -lactones, respectively



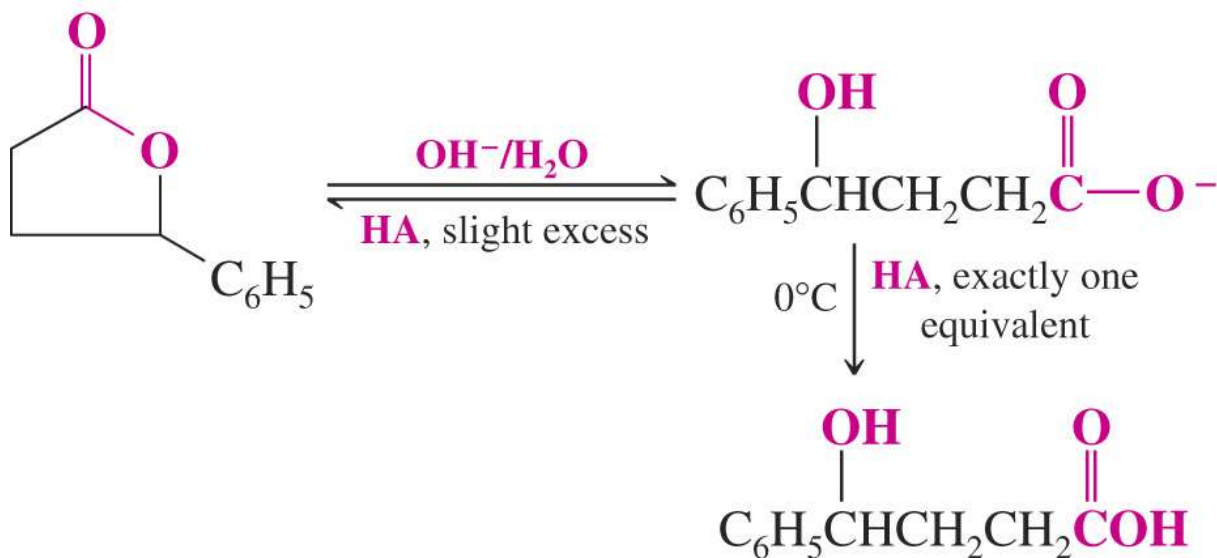
A δ -hydroxy acid



A δ -lactone



- Lactones can be hydrolyzed with aqueous base
- Acidification of the carboxylate product can lead back to the original lactone if too much acid is added



○ Amides

• Synthesis of Amides

○ Amides From Acyl Chlorides

- Ammonia, primary or secondary amines react with acid chlorides to form amides
- An excess of amine is added to neutralize the HCl formed in the reaction
- Carboxylic acids can be converted to amides via the corresponding acid chloride



Reactant

Ammonia; R', R'' = H
 1° Amine; R' = H, R'' = alkyl, aryl
 2° Amine; R', R'' = alkyl, aryl

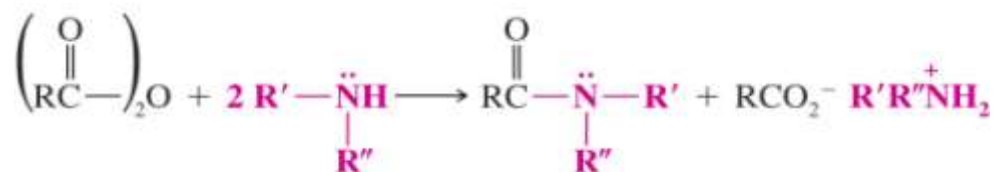
Product

Unsubstituted amide; R', R'' = H
 N-Substituted amide; R' = H, R'' = alkyl, aryl
 N,N-Disubstituted amide; R', R'' = alkyl, aryl



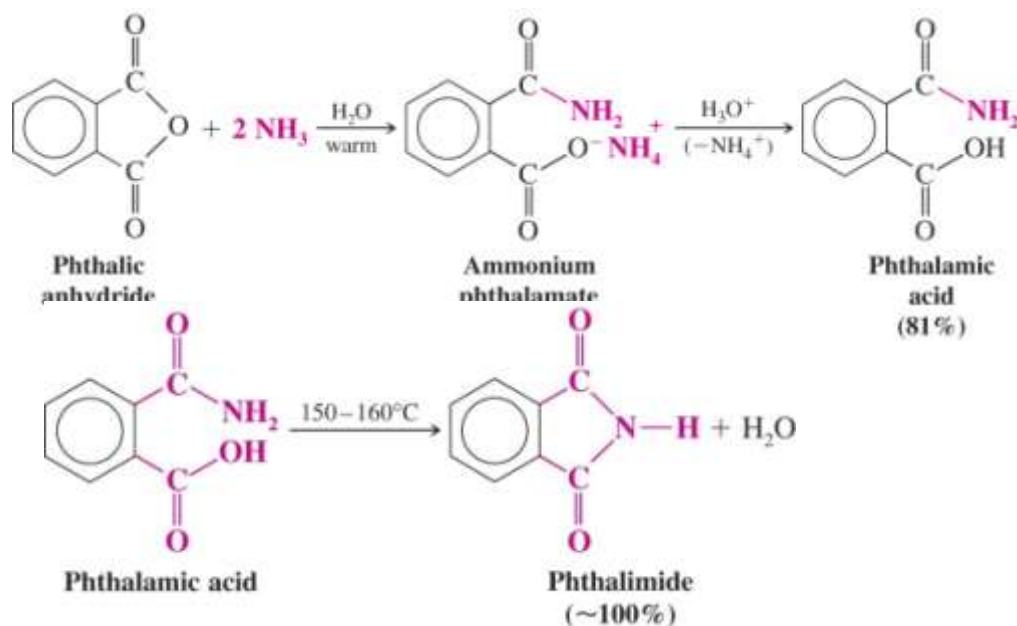
- Amides from Carboxylic Anhydrides

- Anhydrides react with 2 equivalents of amine to produce an amide and an ammonium carboxylate

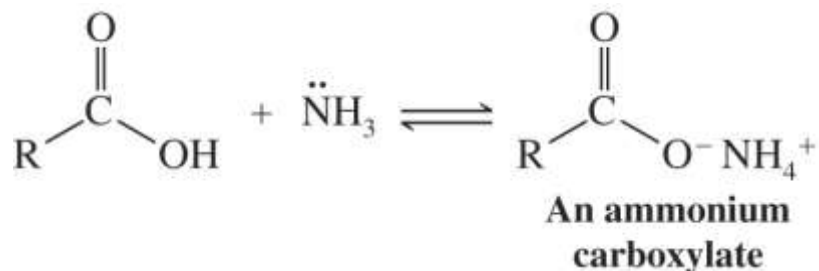


R', R'' can be H, alkyl or aryl

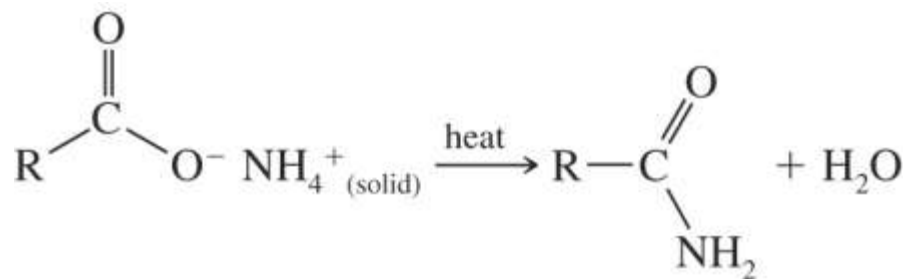
- Reaction of a cyclic anhydride with an amine, followed by acidification yields a product containing both amide and carboxylic acid functional groups
- Heating this product results in the formation of a cyclic imide



- Amides from Carboxylic Acids and Ammonium Carboxylates
- Direct reaction of carboxylic acids and ammonia yields ammonium salts



- Some ammonium salts of carboxylic acids can be dehydrated to the amide at high temperatures
- This is generally a poor method of amide synthesis

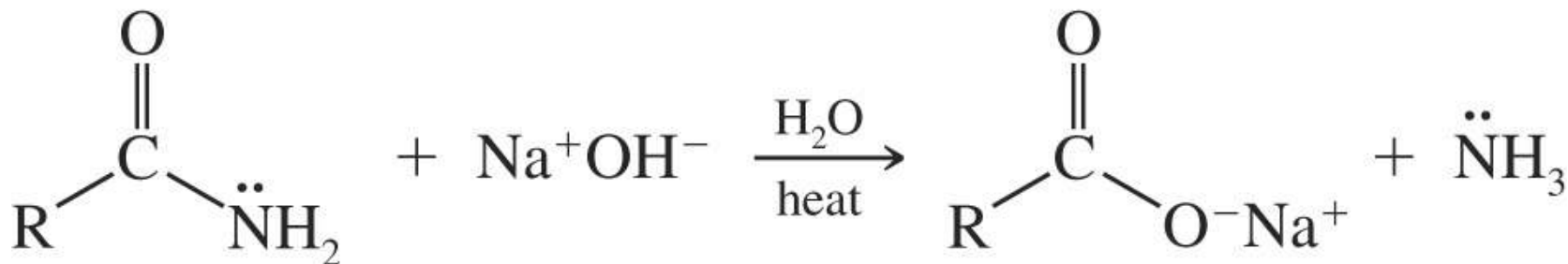
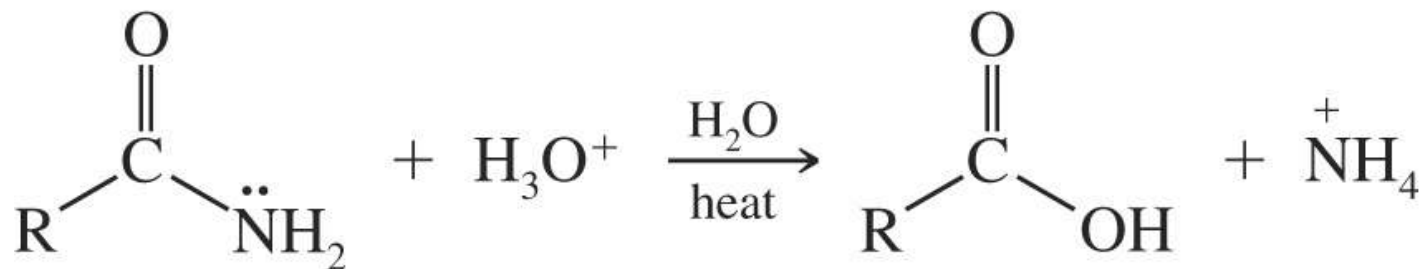


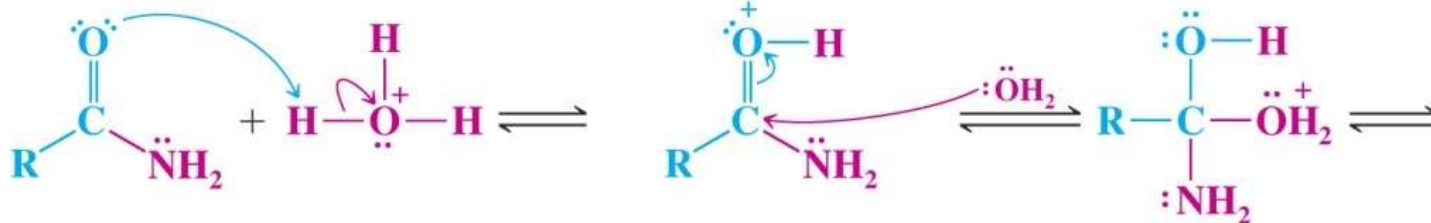
- A good way to synthesize an amide is to convert a carboxylic acid to an acid chloride and to then to react the acid chloride with ammonia or an amine

- Hydrolysis of Amides

- Heating an amide in concentrated aqueous acid or base causes hydrolysis

- Hydrolysis of an amide is slower than hydrolysis of an ester

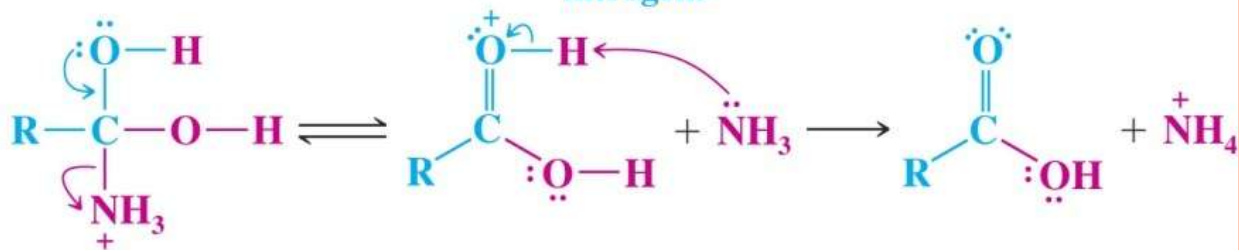




The amide carbonyl accepts a proton from the aqueous acid.

A water molecule attacks the protonated carbonyl to give a tetrahedral intermediate.

A proton is lost at one oxygen and gained at the nitrogen.



Loss of a molecule of ammonia gives a protonated carboxylic acid.

Transfer of a proton to ammonia leads to the carboxylic acid and an ammonium ion.





A hydroxide ion attacks the acyl carbon of the amide.

A hydroxide ion removes a proton to give a dianion.

The dianion loses a molecule of ammonia (or an amine); this step is synchronized with a proton transfer from water due to the basicity of NH_2^- .

