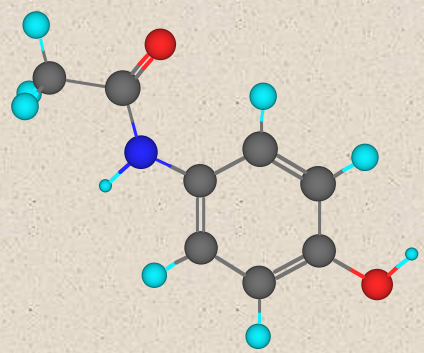
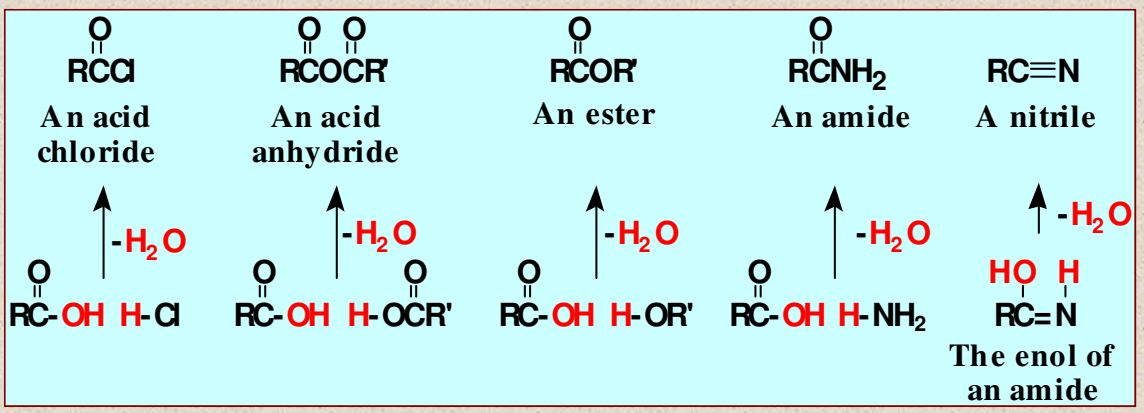
Functional Derivatives of Carboxylic Acids



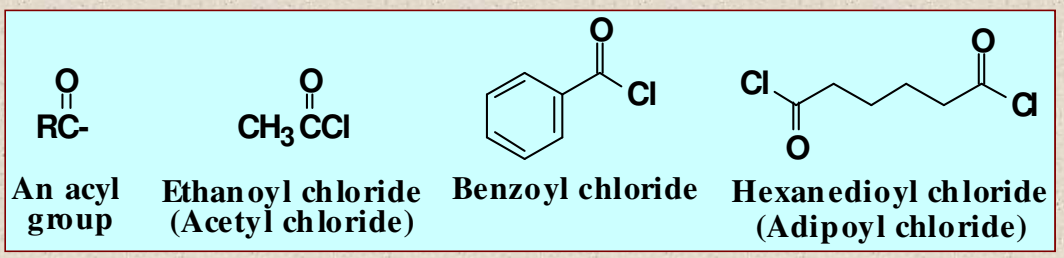
Organic acid derivatives

- There are five classes of organic acid derivatives
- Each arises from a dehydration reaction, usually a **condensation**
- Therefore, each derivative can also be hydrolyzed



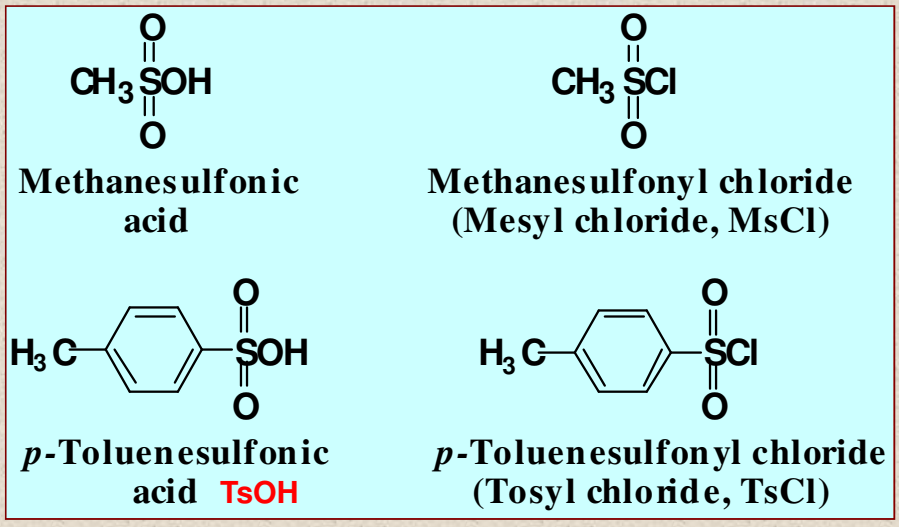
Acid halides

- The functional group of an acid halide is an acyl group bonded to a halogen
  - the most common are the acid chlorides
  - to name, change the suffix -ic acid to -yl halide



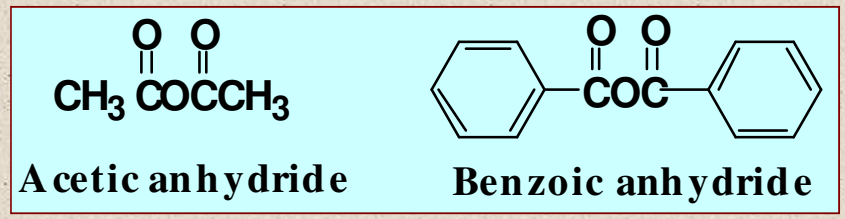
Sulfonyl Chlorides

- replacement of -OH in a sulfonic acid by -Cl gives a **sulfonyl chloride**



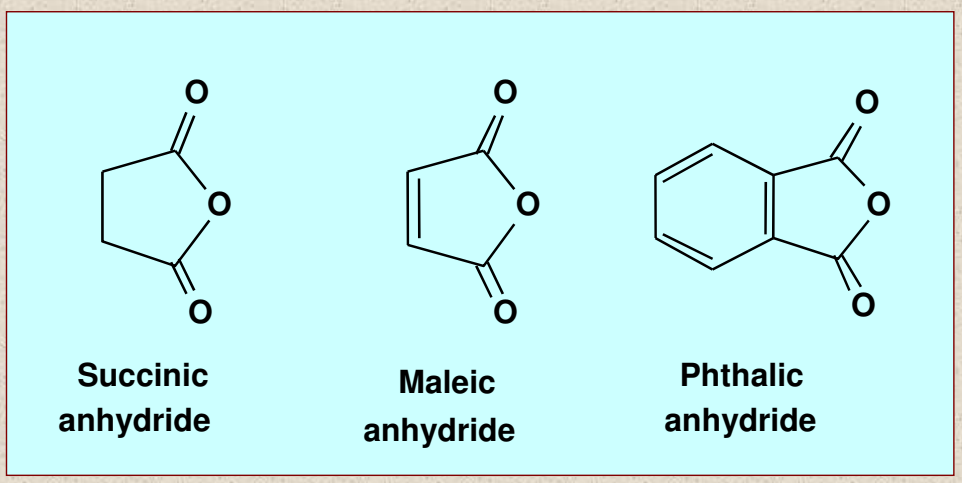
Acid Anhydrides

- The functional group of an acid anhydride is two acyl groups bonded to an oxygen atom
  - the anhydride may be symmetrical (two identical acyl groups) or mixed (two different acyl groups)
  - to name, replace acid of the parent acid by anhydride



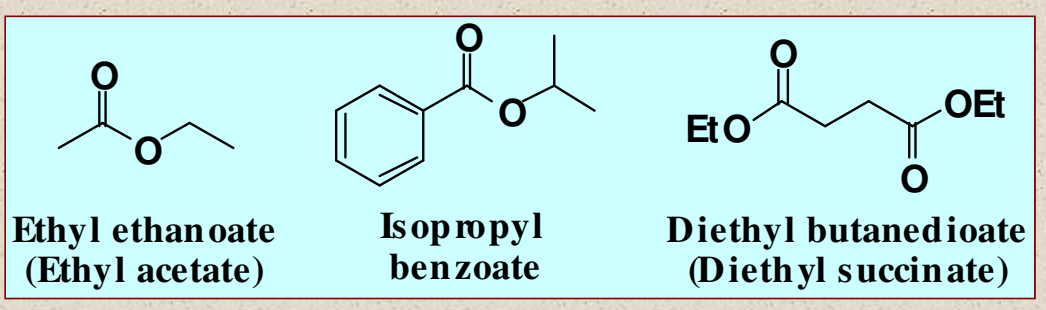
Acid Anhydrides

- Cyclic anhydrides are named from the dicarboxylic acids from which they are derived



Esters

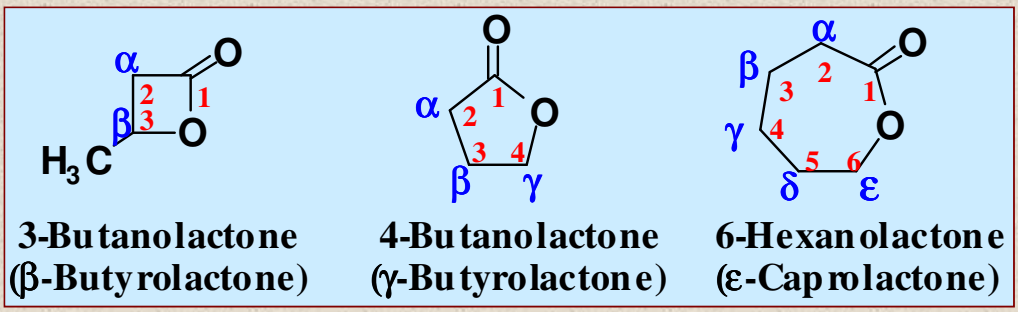
- The functional group of an ester is an acyl group bonded to -OR or -OAr
  - name the alkyl or aryl group bonded to oxygen followed by the name of the **acid**
  - change the suffix -ic acid to -ate



Ethyl ethanoate (Ethyl acetate) | Isopropyl benzoate | Diethyl butanedioate (Diethyl succinate)

Esters

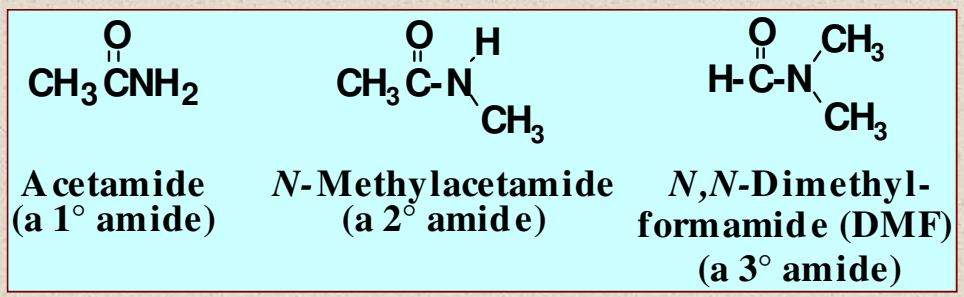
- Cyclic esters are called **lactones**
  - name the parent carboxylic acid, drop the suffix -ic acid and add -olactone



3-Butanolactone (β-Butyrolactone) | 4-Butanolactone (γ-Butyrolactone) | 6-Hexanolactone (ε-Caprolactone)

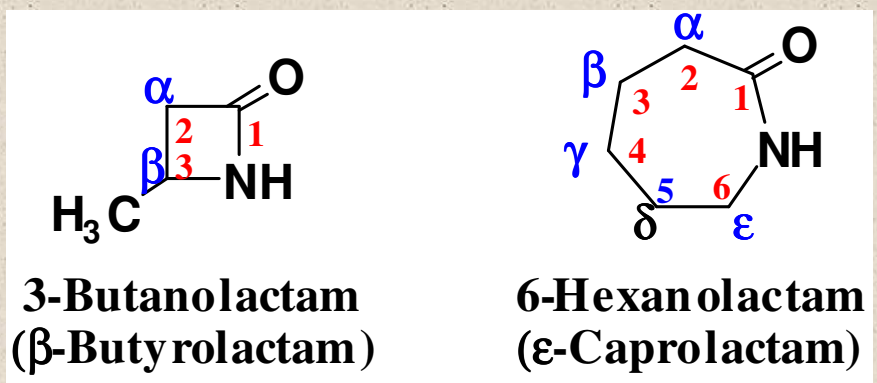
Amides

- The functional group of an amide is an acyl group bonded to a nitrogen atom
  - IUPAC: drop -oic acid from the name of the parent acid and add -amide
  - if the amide nitrogen is bonded to an alkyl or aryl group, name the group and show its location on nitrogen by *N*-



Amides

- Cyclic amides are called **lactams**
  - name the parent carboxylic acid, drop the suffix -ic acid and add -lactam

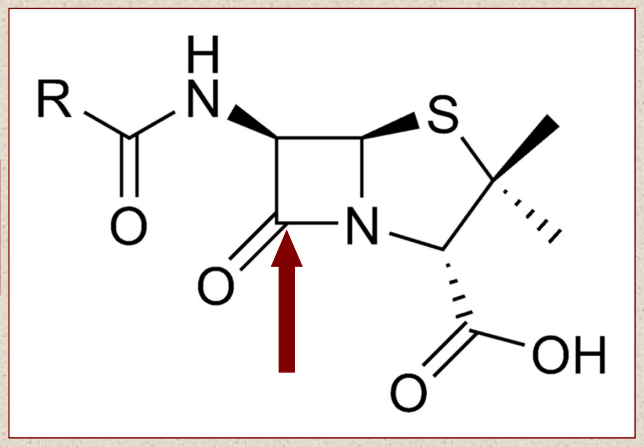


penam –old term for β-lactam

Penicillins

the penicillins are a family of β-lactam antibiotics

The compound is an exceptional "acylating" agent because of the ring strain of the lactam.

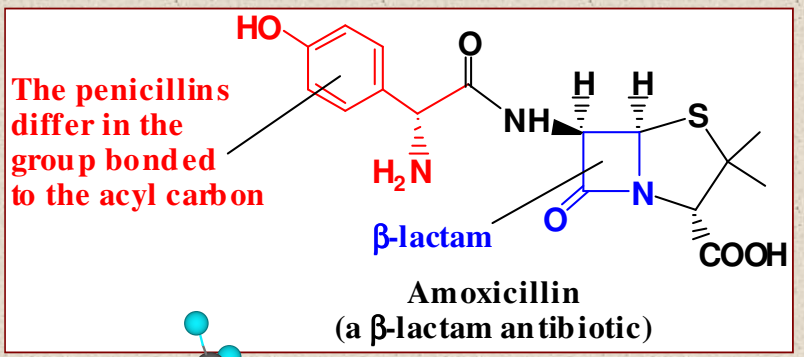


Inhibit cell wall synthesis by acylating and de-activating the required enzymes.

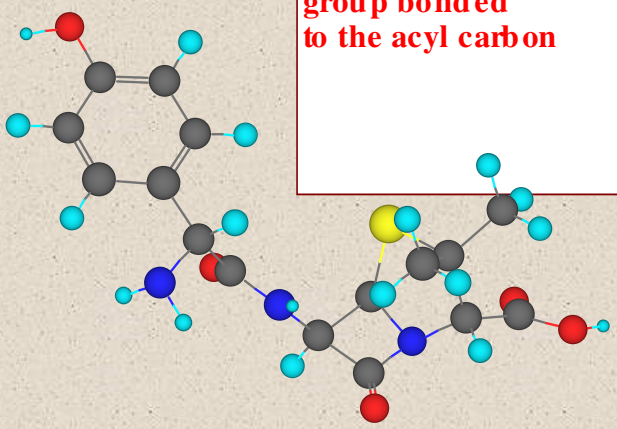
Penicillins

the penicillins are a family of β-lactam antibiotics

The penicillins differ in the group bonded to the acyl carbon

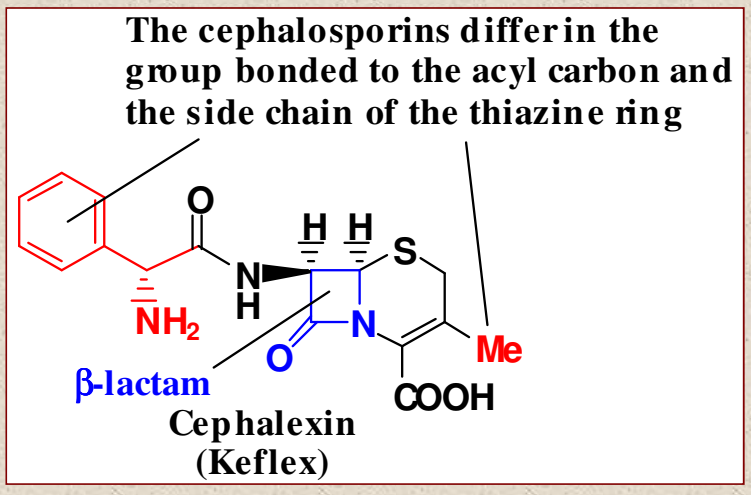


Amoxicillin
(a β-lactam antibiotic)



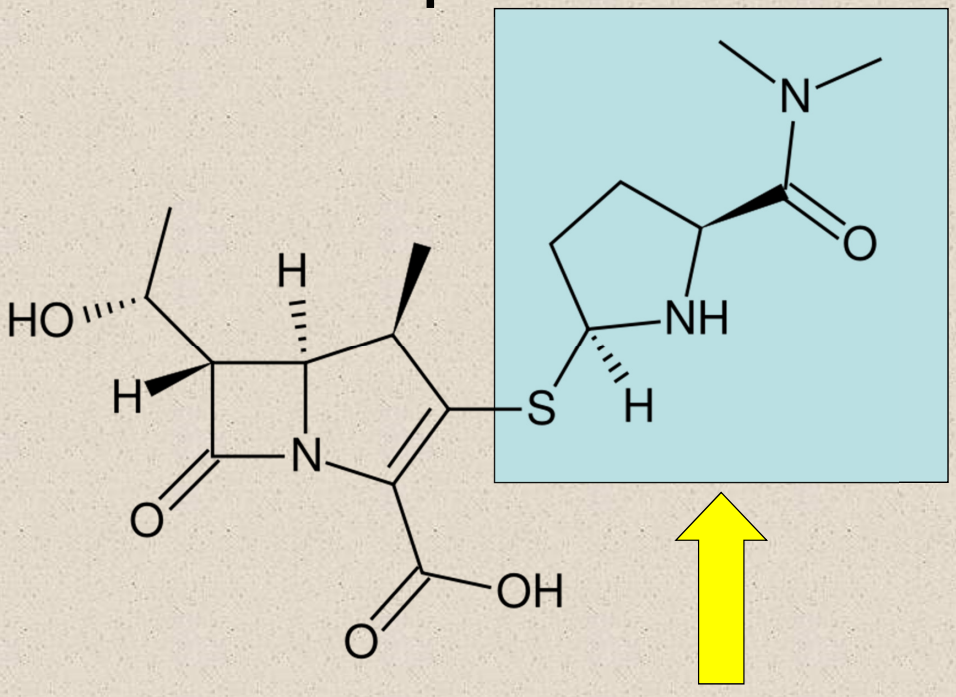
Cephalosporins

the cephalosporins are also **β-lactam antibiotics**



Bacteria develop resistance by producing **β-lactamases-**enzymes, which can hydrolyze the lactam before it can inhibit cell wall synthesis.

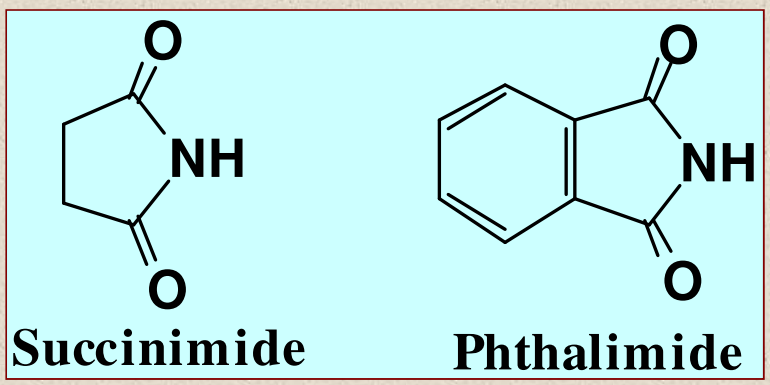
Meropenem



Highly resistant to degradation by beta-lactamases or cephalosporinases.

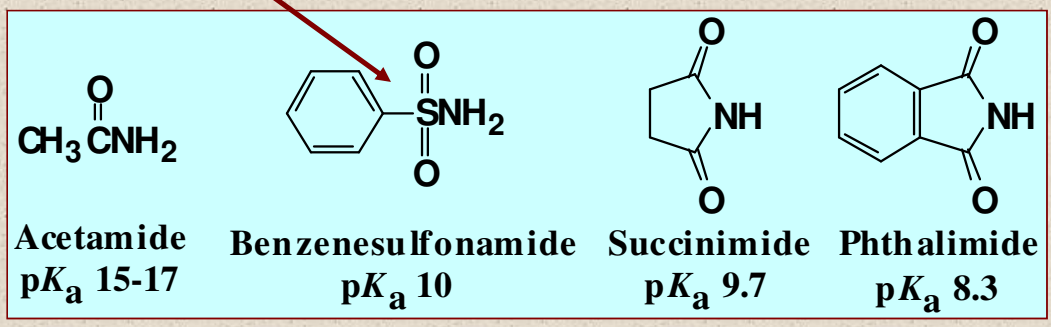
Imides

- The functional group of an **imide** is two acyl groups bonded to nitrogen
  - both succinimide and phthalimide are cyclic imides



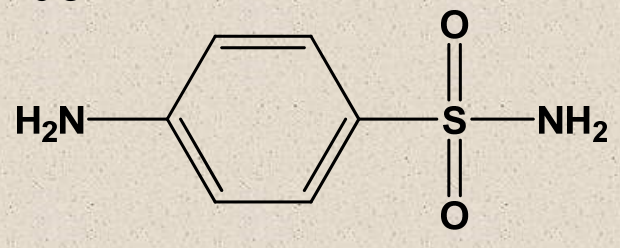
Acidity of N-H bonds

- **Amides** are comparable in acidity to alcohols
  - water-insoluble amides do not react with NaOH or other alkali metal hydroxides to form water-soluble salts
- Sulfonamides and imides are more acidic than amides



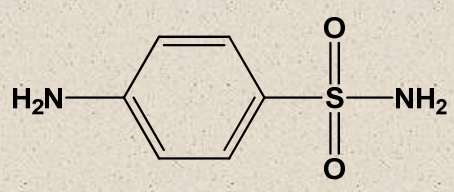
Sulfonamides are the class of "sulfa antibiotics"

Sulfanilamide



As an antibiotic, it functions by competitively inhibiting (i.e. by acting as a substrate analogue) enzymatic reactions involving para-aminobenzoic acid (PABA). PABA is needed in enzymatic reactions that produce folic acid which acts as a coenzyme in the synthesis of purine, pyrimidine and other amino acids.

Sulfanilamide tragedy of 1937:

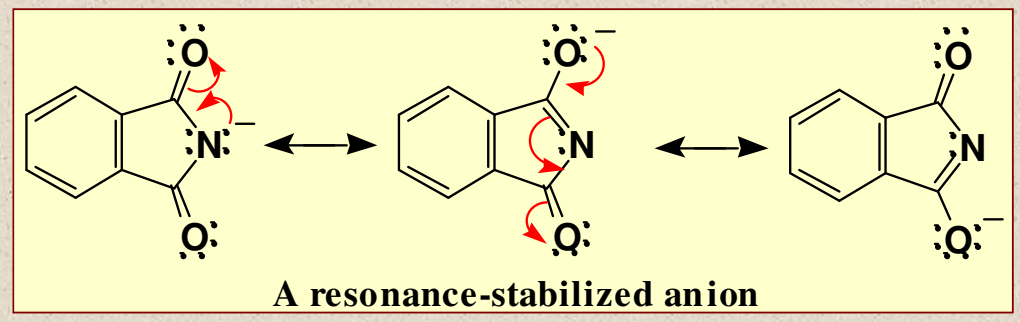


Elixir sulfanilamide was an improperly prepared sulfanilamide medicine that caused mass poisoning in the United States in 1937.
The preparation used **diethylene glycol** as the solvent and caused the deaths of more than 100 people.
The public outcry caused by this incident and other similar disasters led to the passing of the 1938 Federal Food, Drug, and Cosmetic Act.

Acidity of N-H bonds

Imides are more acidic than amides because:

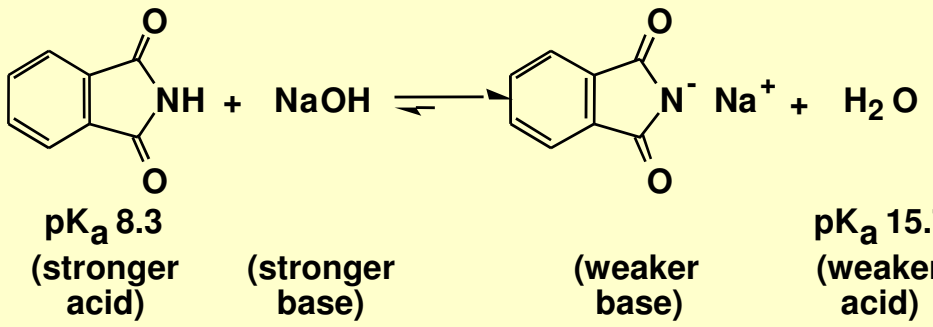
1. the electron-withdrawing inductive of the two adjacent C=O groups weakens the N-H bond, and
2. the imide anion is stabilized by resonance delocalization of the negative charge



A resonance-stabilized anion

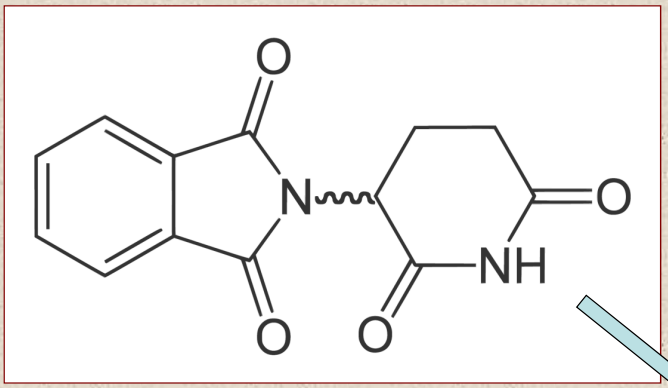
Acidity of N-H bonds

– imides such as phthalimide readily dissolve in aqueous NaOH as water-soluble salts



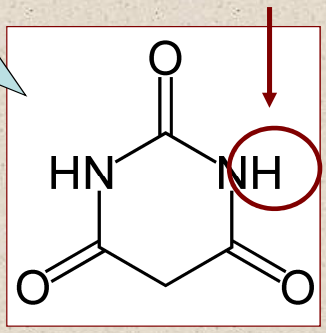
This property is used to render pharmaceutical agents water soluble:

Thalidomide-sedative, hypnotic



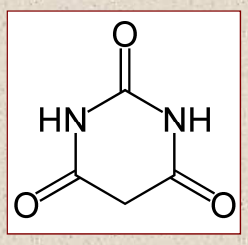
Barbituric Acid

Acidity of this H is used to Make the derivatives soluble

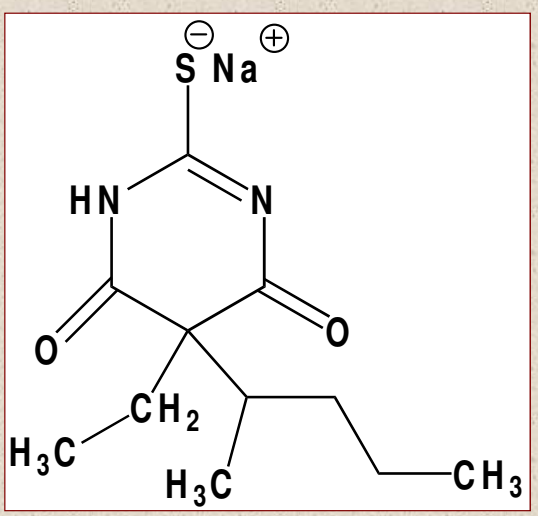


1. **Sedative was used in pregnant women from 1956~1962 in Europe/Africa**
1. **Never approved in US**
2. **Caused birth defects (teratogen)**
3. **Later found use in leprosy treatment**

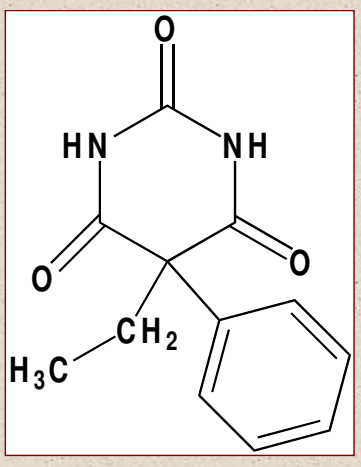
Barbituric Acid



Sodium Pentothal® -Sodium thiopental



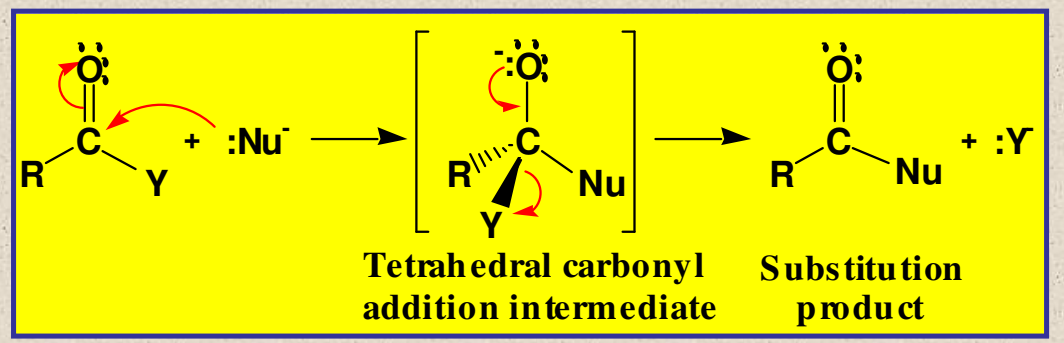
Phenobarbital



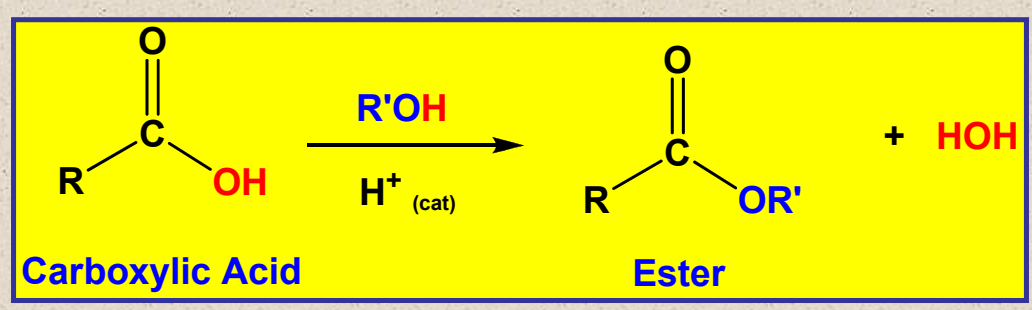
Anticonvulsant, hypnotic, anxiolytic

Characteristic Reactions

- **Nucleophilic acyl substitution:** an addition-elimination sequence resulting in substitution of one nucleophile for another

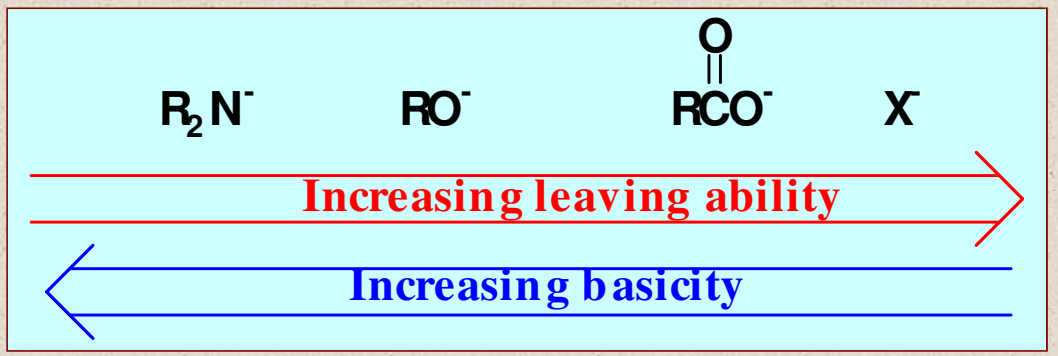


Fischer Esterifications



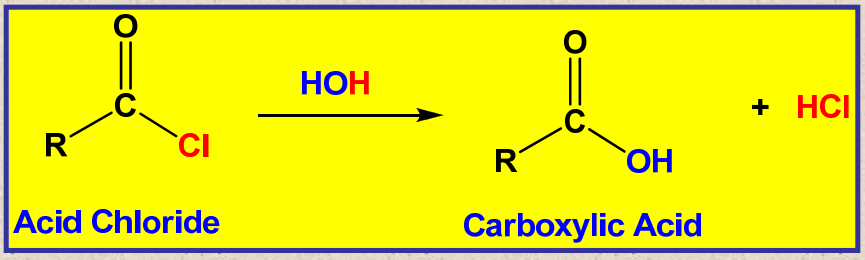
Characteristic Reactions

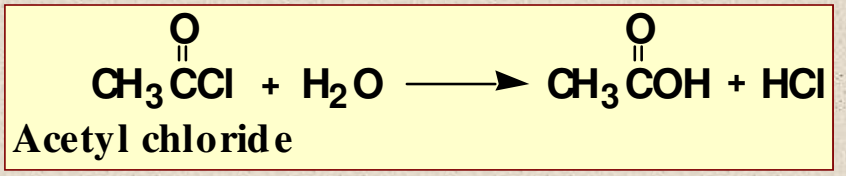
- in the general reaction, the leaving group, as an anion, illustrates an important point:
- the weaker the base, the better the leaving group



Reaction with H_2O - Acid Chlorides

- low-molecular-weight acid chlorides react rapidly with water
- higher molecular-weight acid chlorides are less soluble in water and react less readily

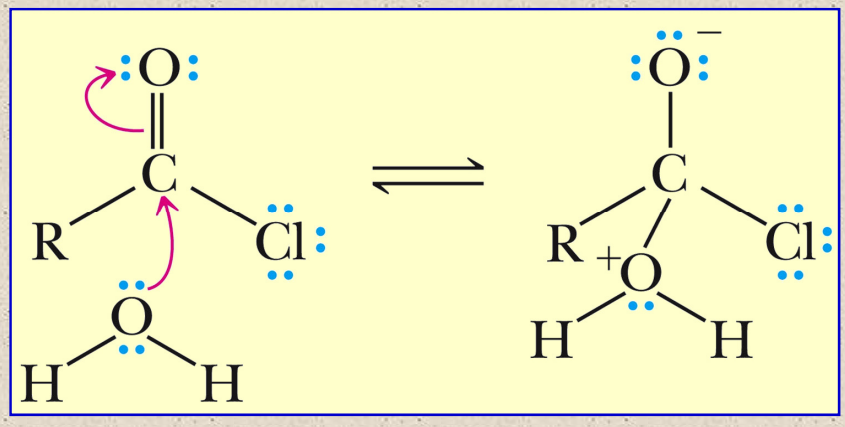




These are hydrolysis reactions- "breaking of bonds with water"

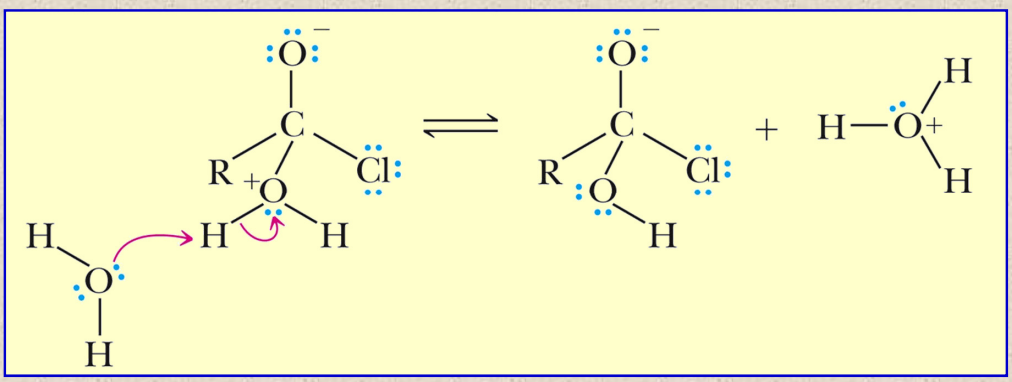
Reaction with H_2O - Acid Chlorides

- **Step 1: Make a new bond between a nucleophile and an electrophile.** Water attacks the carbonyl carbon directly to give a tetrahedral carbonyl addition intermediate.



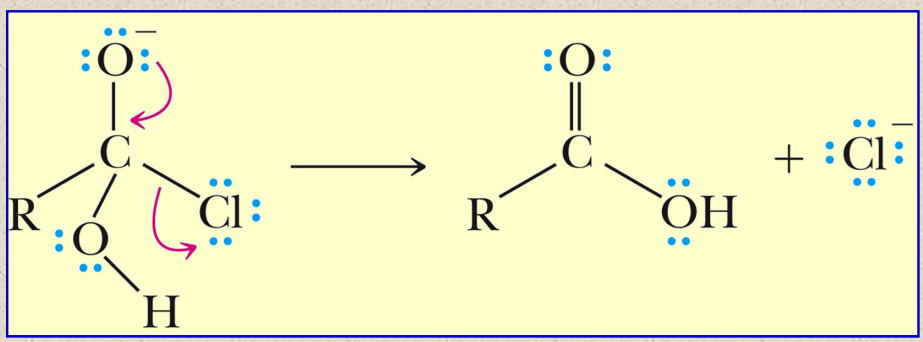
Reaction with H_2O - Acid Chlorides

- **Step 2: Take a proton away.** Proton transfer is rapid and reversible.



Reaction with H_2O - Acid Chlorides

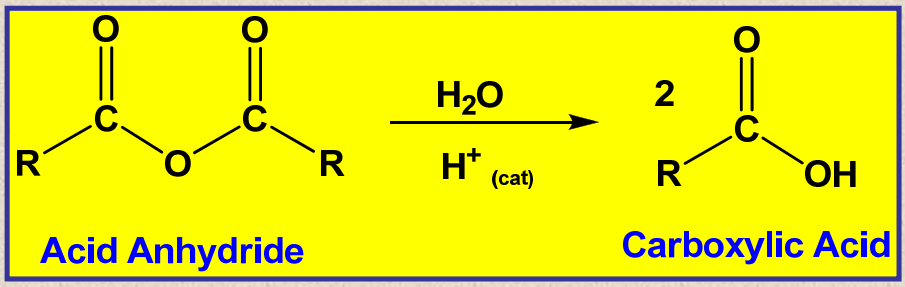
- **Step 3: Break a bond to give stable molecules or ions.** Collapse of the tetrahedral intermediate and expulsion of chloride ion gives the carboxylic acid.

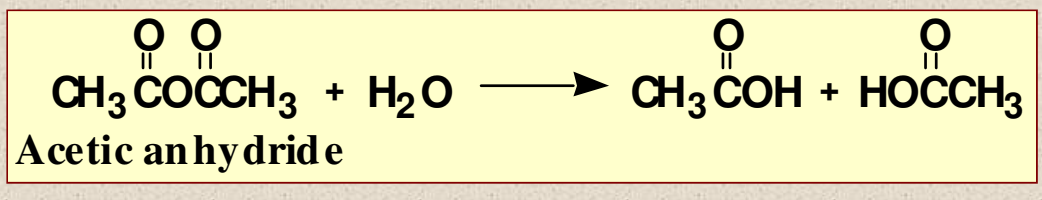


Reaction with H_2O - Anhydrides

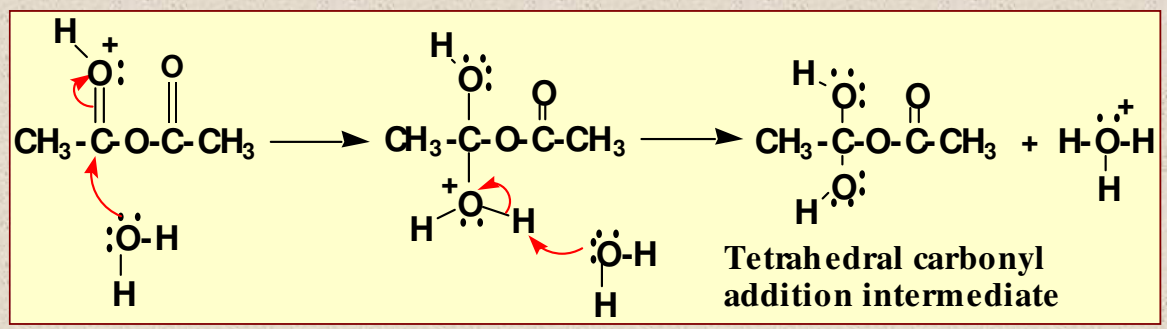
– low-molecular-weight acid anhydrides react readily with water to give two molecules of carboxylic acid

– higher-molecular-weight acid anhydrides also react with water, but less readily

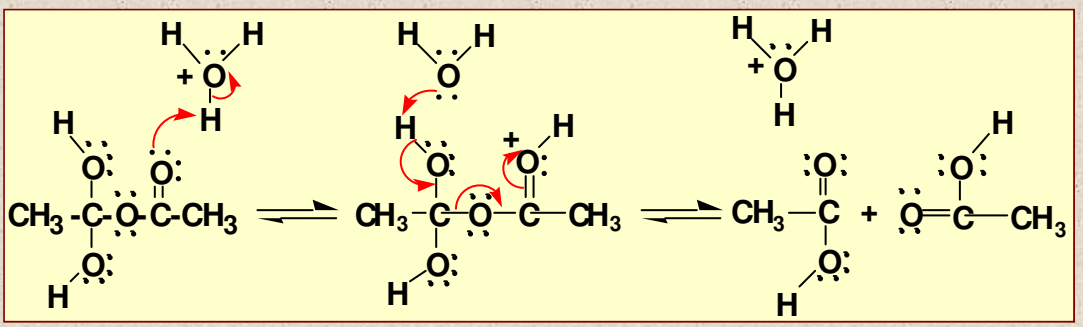




–Step 1: addition of H_2O to give a TCAI



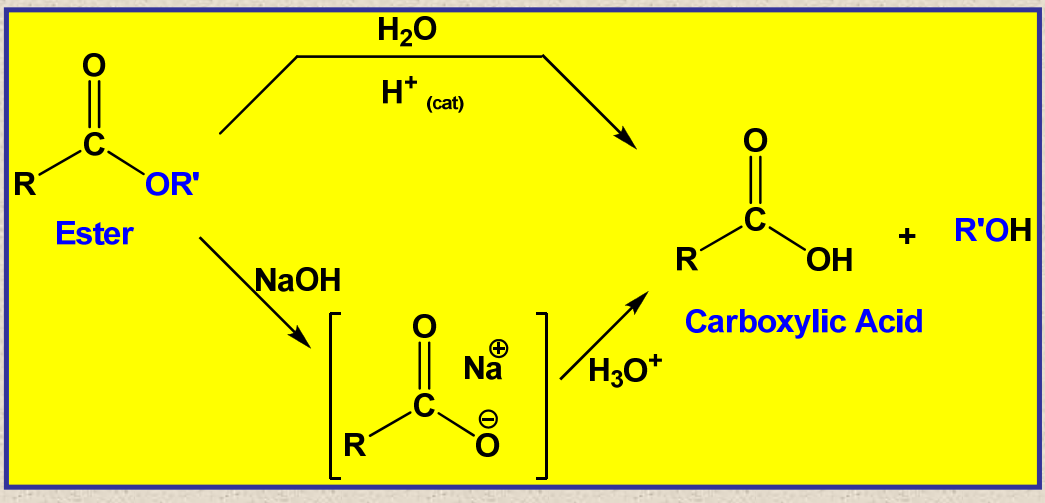
–Step 2: protonation followed collapse of the TCAI



Reaction with H_2O - Esters

- Esters are hydrolyzed only slowly, even in boiling water
  - hydrolysis becomes more rapid if they are heated with either aqueous acid or base
- Hydrolysis in aqueous acid is the reverse of Fischer esterification
  - the role of the acid catalyst is to protonate the carbonyl oxygen and increase its electrophilic character toward attack by water (a weak nucleophile) to form a tetrahedral carbonyl addition intermediate
  - collapse of this intermediate gives the carboxylic acid and alcohol

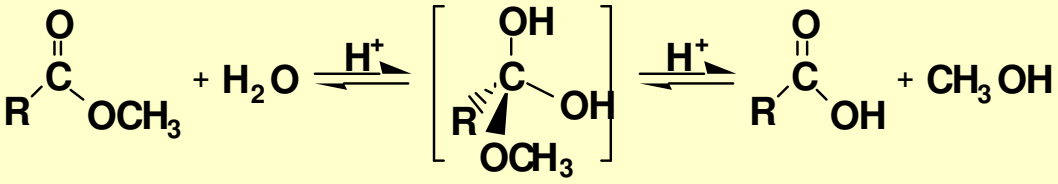
hydrolysis reactions-



(Go to worksheet)

Reaction with H_2O - Esters

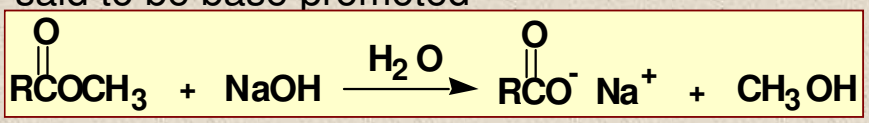
- **Acid-catalyzed ester hydrolysis**



Tetrahedral carbonyl addition intermediate

Reaction with H_2O - Esters

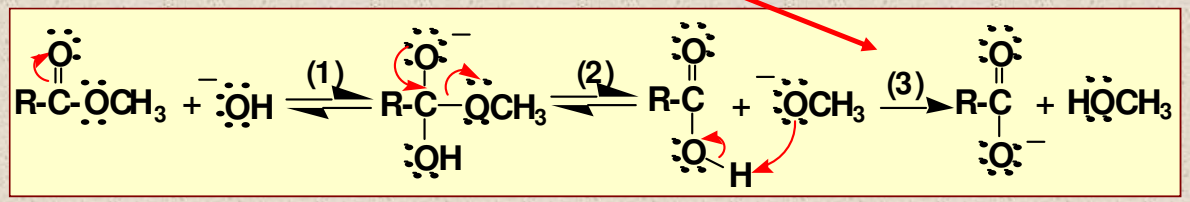
- Hydrolysis of an esters in aqueous base is often called **saponification**
  - each mole of ester hydrolyzed requires 1 mole of base
  - for this reason, ester hydrolysis in aqueous base is said to be base promoted



  - hydrolysis of an ester in aqueous base involves formation of a tetrahedral carbonyl addition intermediate followed by its collapse and proton transfer

Reaction with H_2O - Esters

- Step 1: attack of hydroxide ion (a nucleophile) on the carbonyl carbon (an electrophile)
- Step 2: collapse of the TCAI
- Step 3: proton transfer to the alkoxide ion; **this step is irreversible** and drives saponification to completion

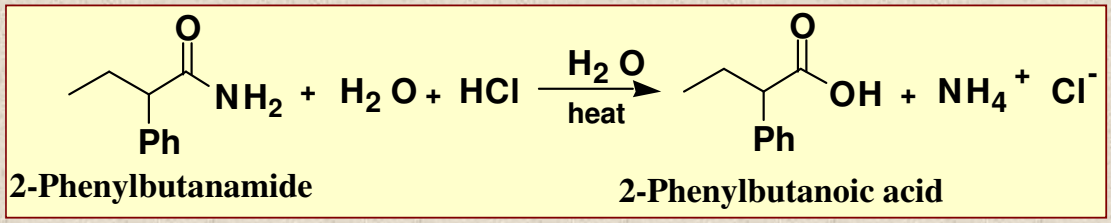


Reaction with H_2O - Amides

Hydrolysis of an amide in aqueous acid

requires 1 mole of acid per mole of amide

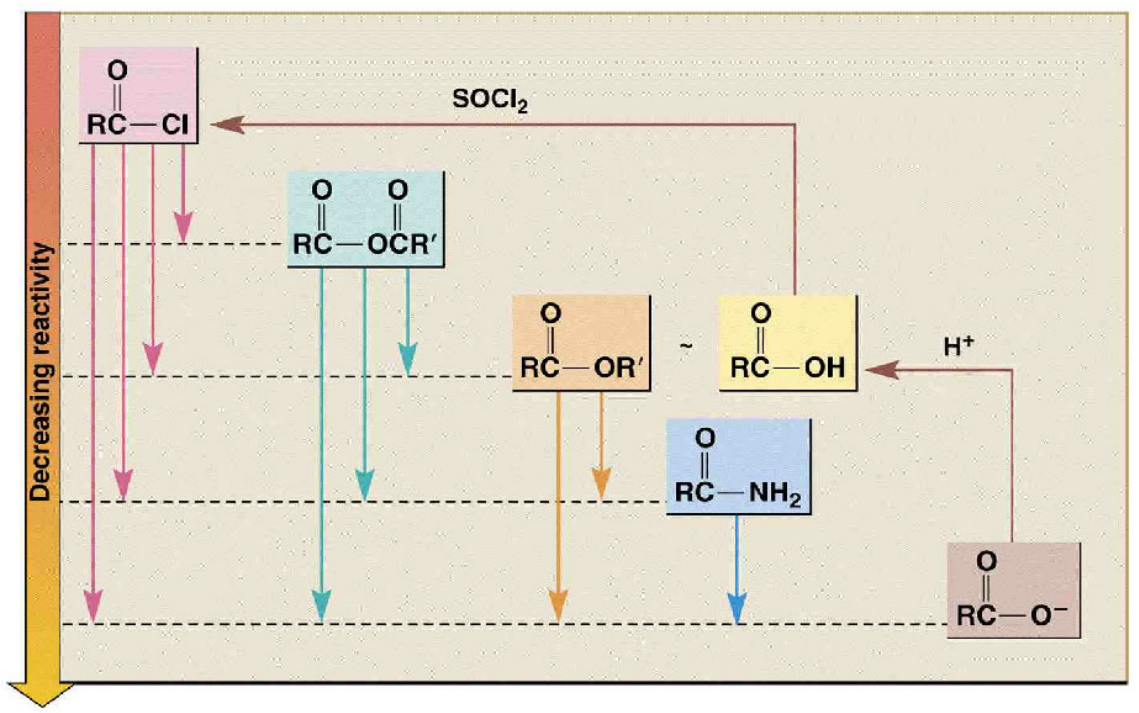
- reaction is driven to completion by the acid-base reaction between the amine or ammonia and the acid



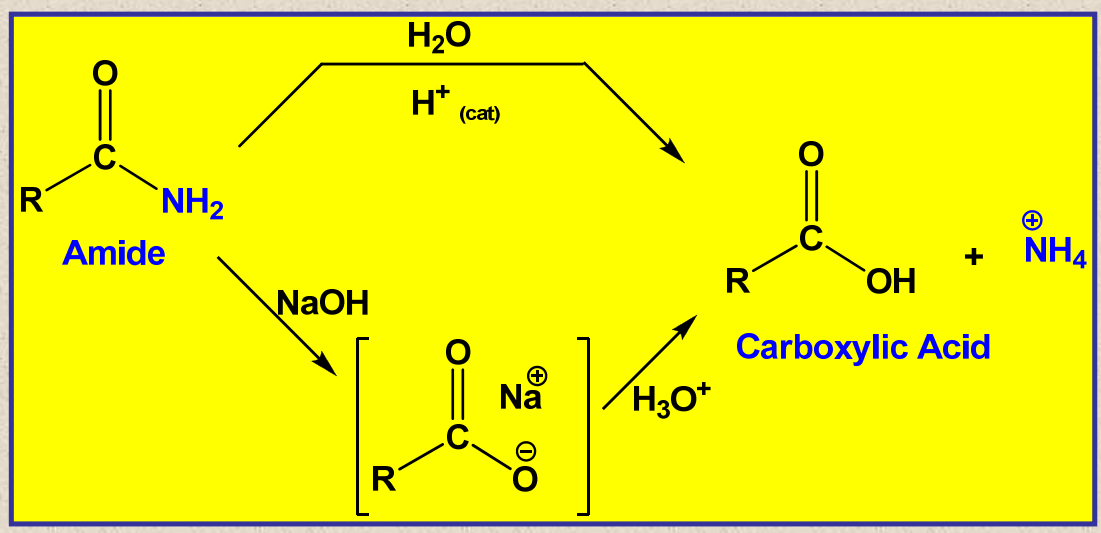
2-Phenylbutanamide

2-Phenylbutanoic acid

The "big picture"

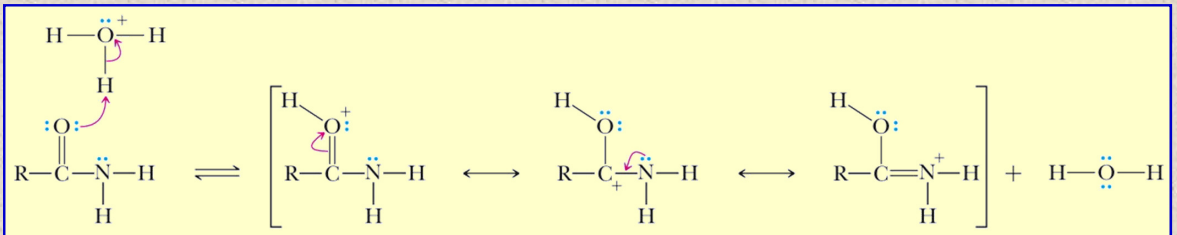


hydrolysis reactions-



Reaction with H_2O – Amides in Acid

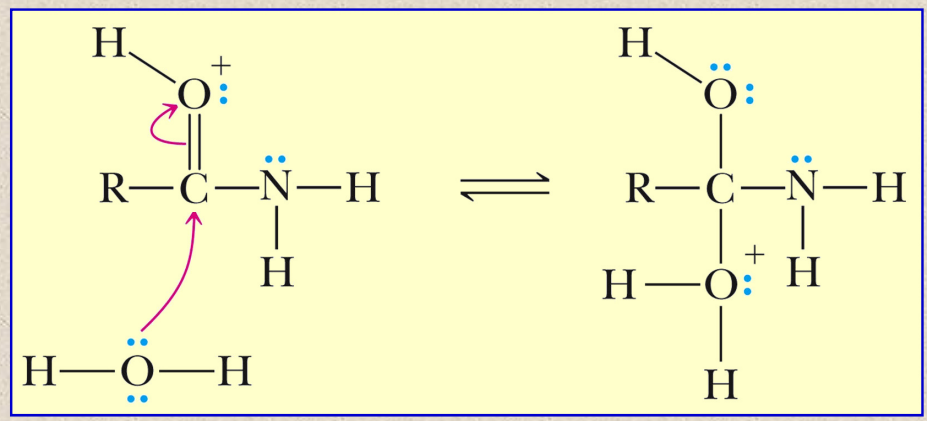
– **Step1: Add a proton.** Protonation of the carbonyl oxygen gives a resonance-stabilized cation intermediate and increases the electrophilic character of the carbonyl carbon.



Cation stabilized by resonance delocalization

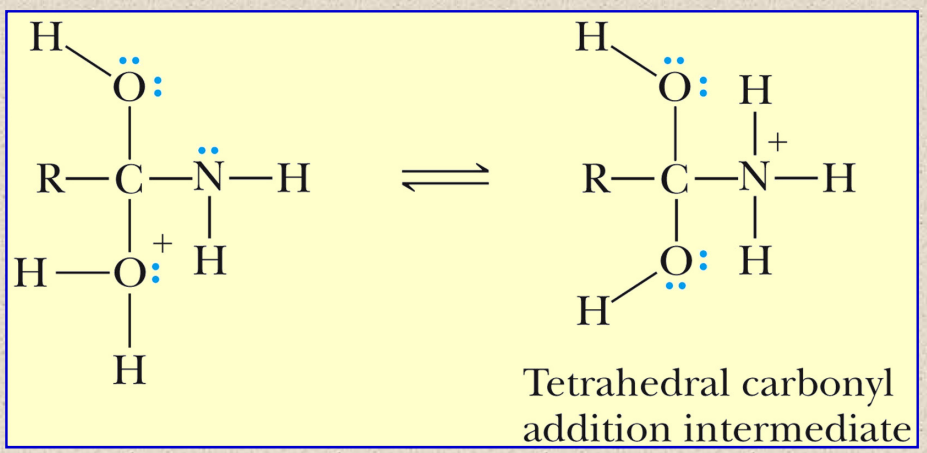
Reaction with H_2O – Amides in Acid

– **Step 2: Make a new bond between a nucleophile and an electrophile.** Addition of water to the carbonyl carbon.



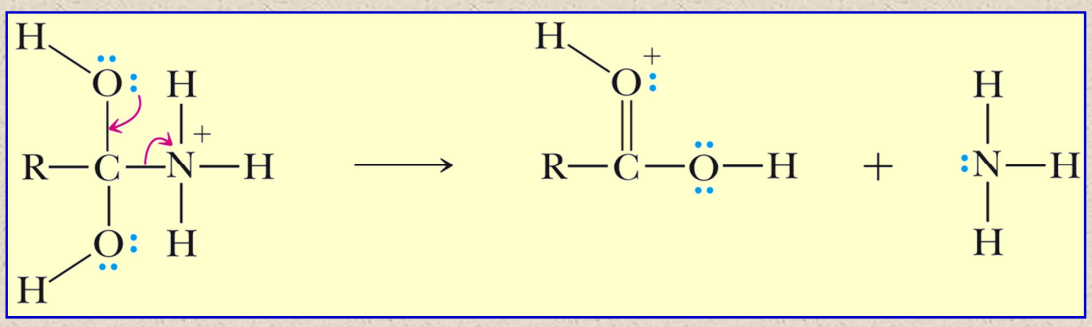
Reaction with H_2O – Amides in Acid

- **Step 3: Take a proton away/add a proton.** Proton transfer between O and N gives a tetrahedral carbonyl addition intermediate.



Reaction with H_2O – Amides in Acid

- **Step 4: Break a bond to make stable molecules or ions.** Note that the leaving group is a neutral amine (a weaker base), a far better leaving group.

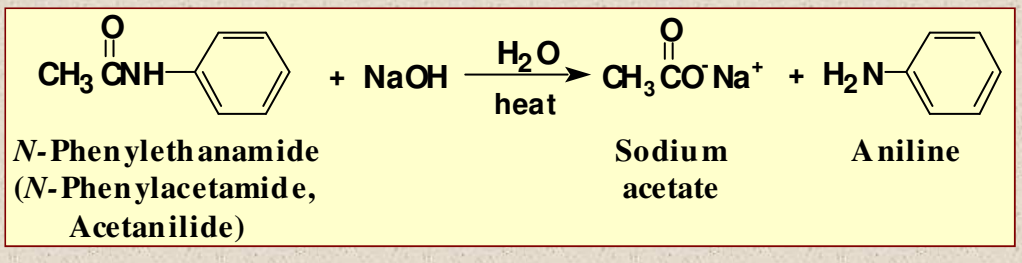


Reaction with H_2O - Amides

Hydrolysis of an amide in aqueous base

requires 1 mole of base per mole of amide

– reaction is driven to completion by the irreversible formation of the carboxylate sale



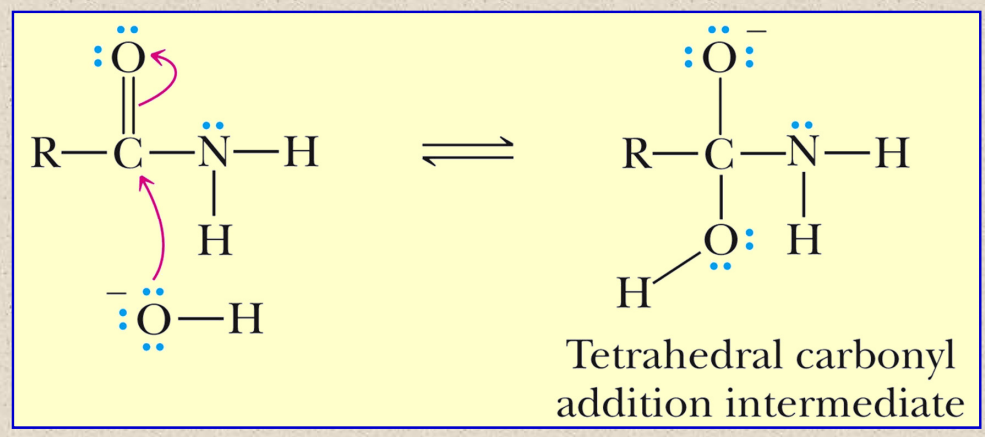
N-Phenylethanamide (*N*-Phenylacetamide, Acetanilide)

Sodium acetate

Aniline

Reaction with H_2O – Amides in Base

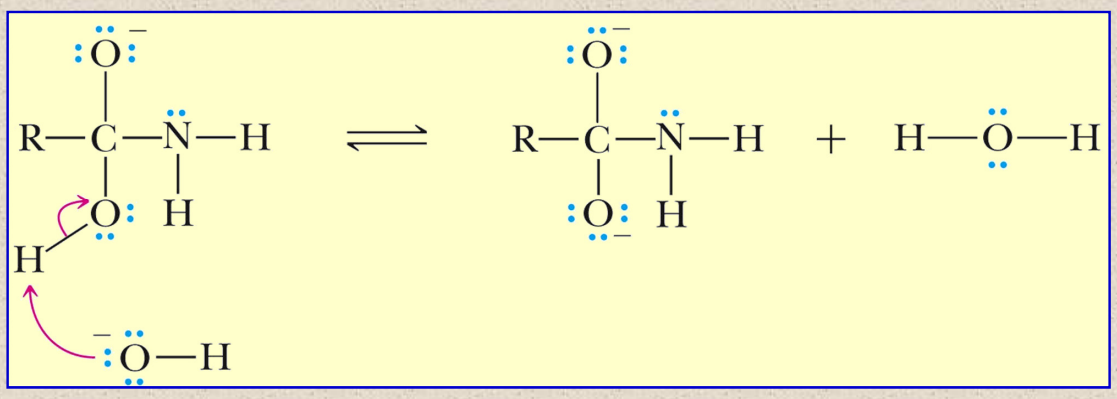
- **Step 1: Make a bond between a nucleophile and an electrophile.** Addition of hydroxide ion to the carbonyl carbon gives a tetrahedral carbonyl addition intermediate.



Tetrahedral carbonyl addition intermediate

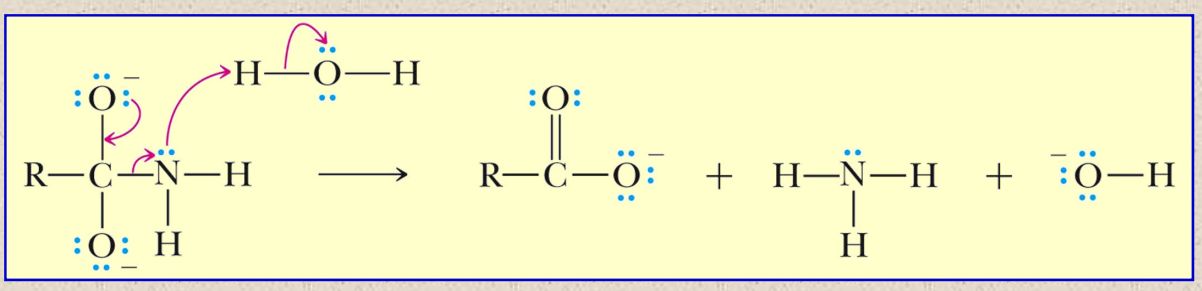
Reaction with H_2O – Amides in Base

- **Step 2: Take proton away**. This step creates a **dianionic** intermediate, which has enough negative charge to expel the amide anion.

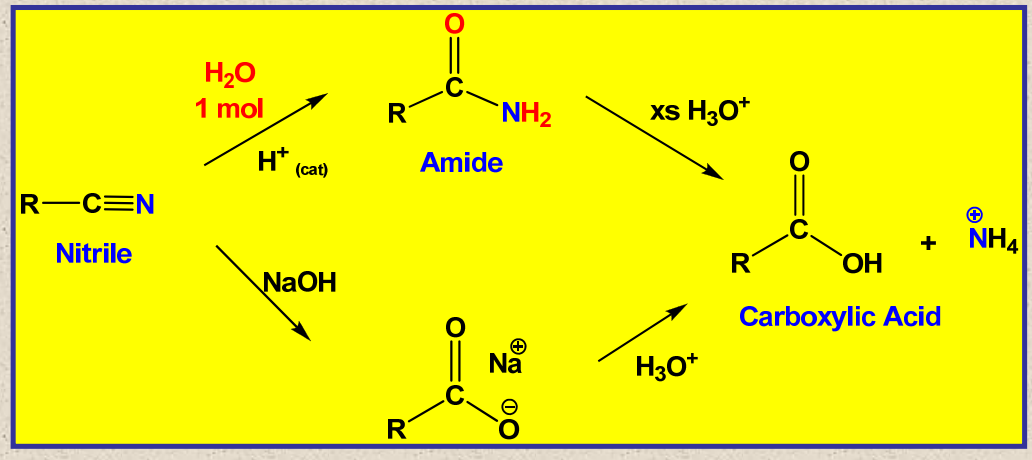


Reaction with H_2O – Amides in Base

- **Step 3: Break a bond to give stable molecules or ions/add a proton.** The amide anion has so little lifetime in water because it is so basic; therefore, it will be instantly protonated by water.



hydrolysis reactions-



Reaction with H_2O - Nitriles

- The cyano group is hydrolyzed in aqueous acid to a carboxyl group and ammonium ion

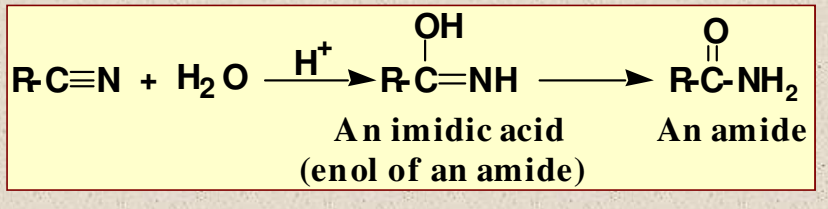
$$\underset{\text{Phenylacetonitrile}}{Ph{-}CH_2C{\equiv}N} + 2H_2O + H_2SO_4 \xrightarrow[\text{heat}]{H_2O} \underset{\text{Phenylacetic acid}}{Ph{-}CH_2COH} + \underset{\text{Ammonium hydrogen sulfate}}{NH_4^+HSO_4^-}$$

  - protonation of the cyano nitrogen gives a cation that reacts with water to give an imidic acid
  - keto-enol tautomerism gives the amide

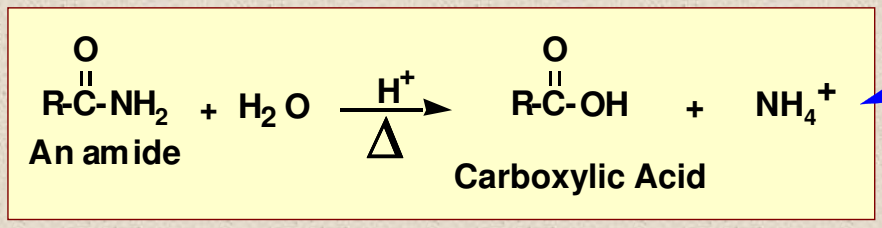
$$R{-}C{\equiv}N + H_2O \xrightarrow{H^+} \underset{\text{An imidic acid (enol of an amide)}}{R{-}C(OH){=}NH} \longrightarrow \underset{\text{An amide}}{R{-}C(=O){-}NH_2}$$

Can stop at the amide if: 1 mol H_2O and cat H_2SO_4 is used.

Reaction with H_2O - Nitriles

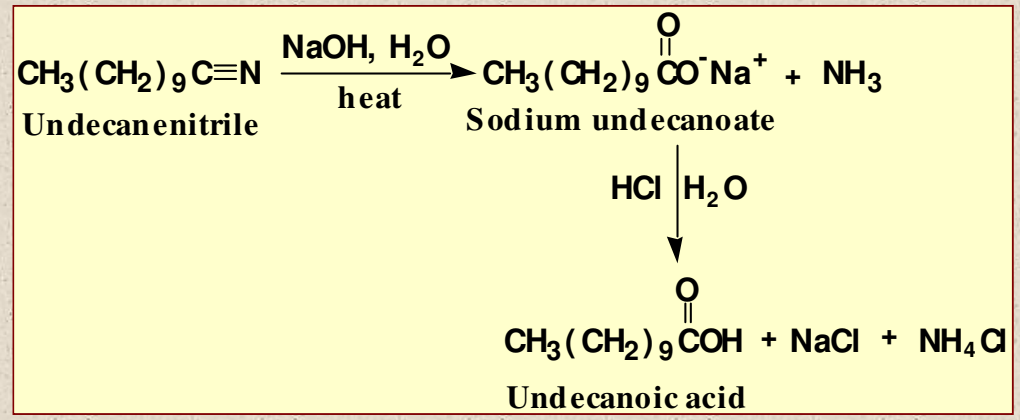


Note: ***In excess aqueous acid-*** the amide continues to undergo hydrolysis to give the carboxylic acid:



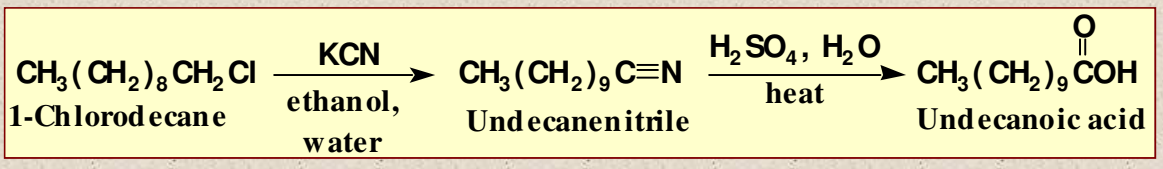
Reaction with H_2O - Nitriles

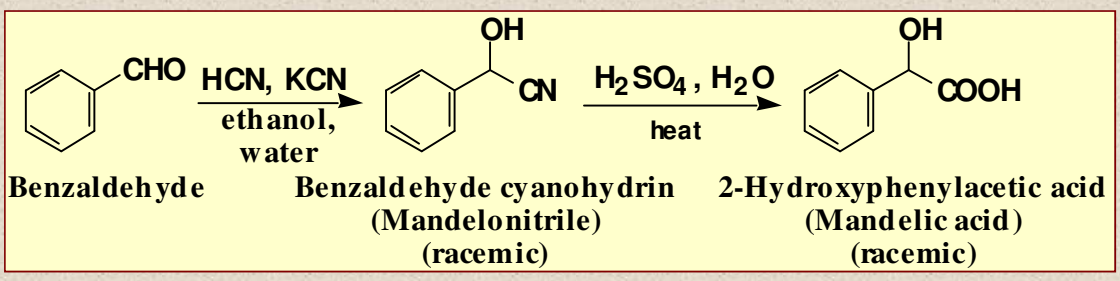
– hydrolysis of a cyano group in aqueous base gives a carboxylic anion and ammonia; acidification converts the carboxylic anion to the carboxylic acid



Reaction with H_2O - Nitriles

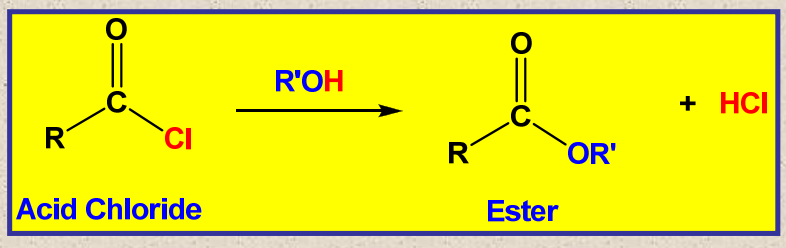
- hydrolysis of nitriles is a valuable route to carboxylic acids
- Molar excess of aqueous acid MUST be used:

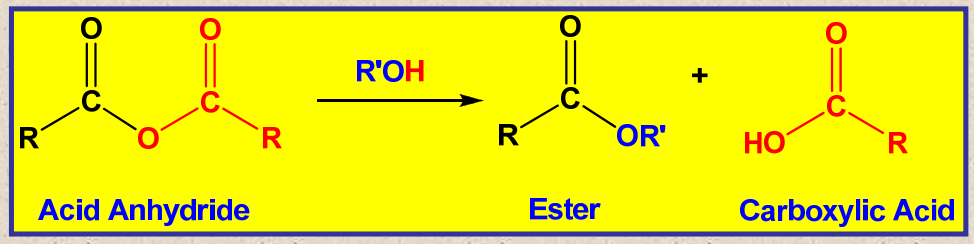


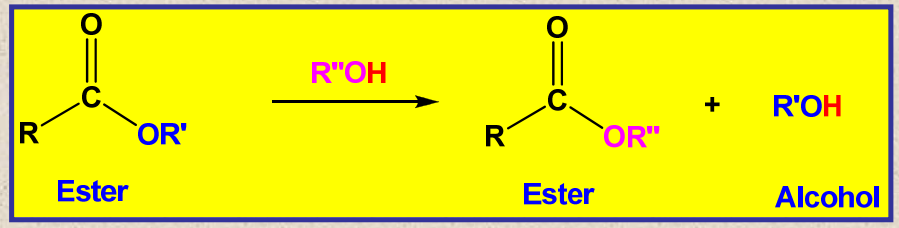


See worksheet

Acylation Reactions to form Esters:

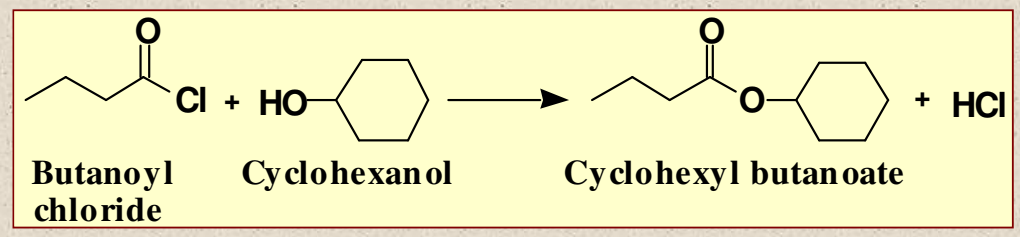






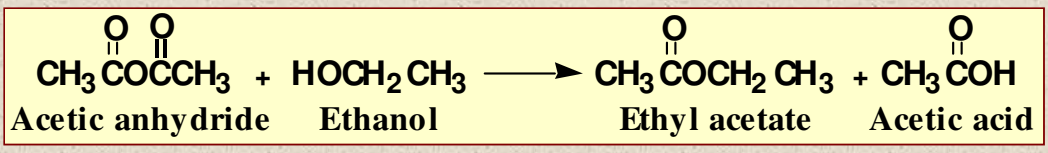
Reaction with Alcohols

- Acid halides react with alcohols to give esters
  - acid halides are so reactive toward even weak nucleophiles such as alcohols that no catalyst is necessary
  - where the alcohol or resulting ester is sensitive to HCl, reaction is carried out in the presence of a 3° amine to neutralize the acid

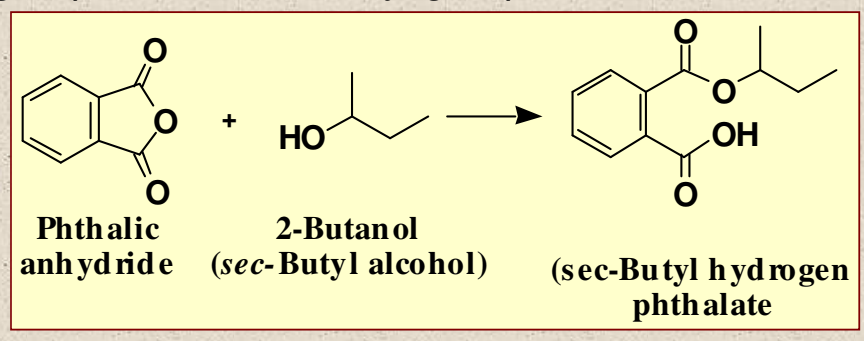


Reaction with Alcohols

- Acid anhydrides react with alcohols to give one mole of ester and one mole of carboxylic acid

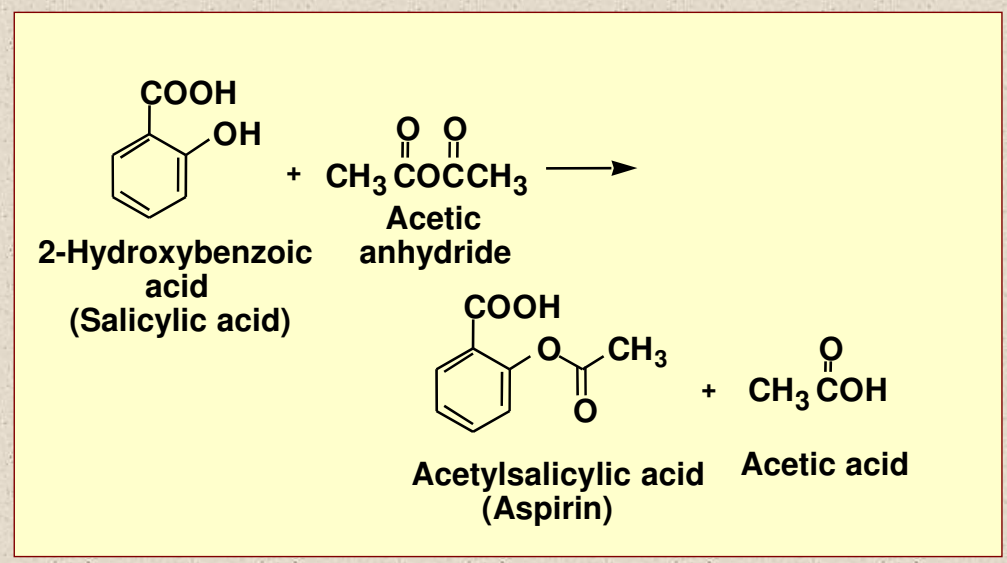


  - cyclic anhydrides react with alcohols to give one ester group and one carboxyl group



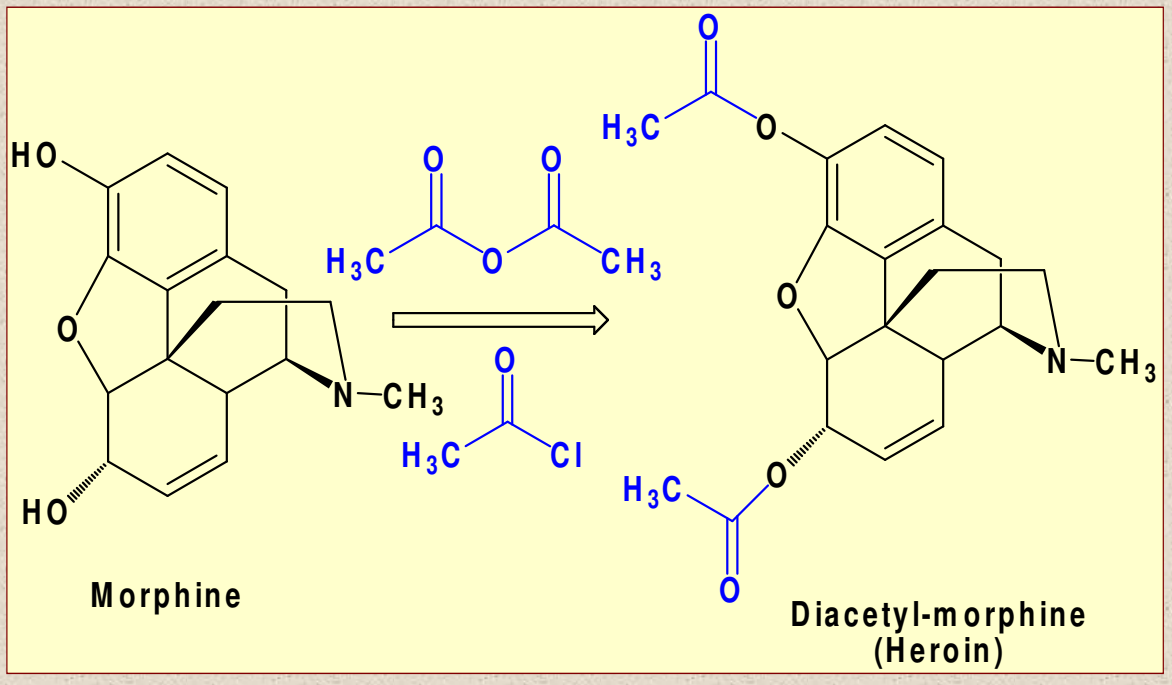
Use in Practice

– aspirin is synthesized by treating salicylic acid with acetic anhydride



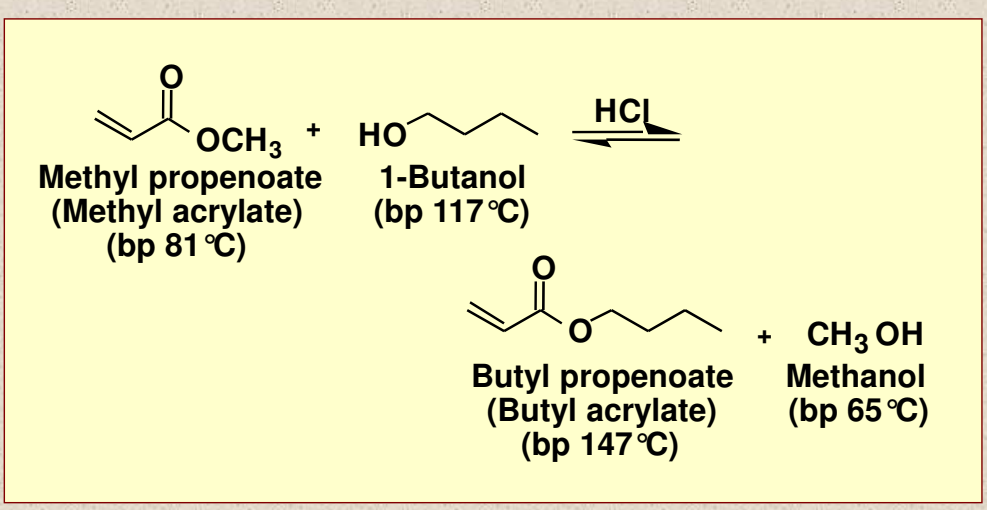
Use in Practice

Both Acid anhydrides or acid chlorides can be used as acylating agents:

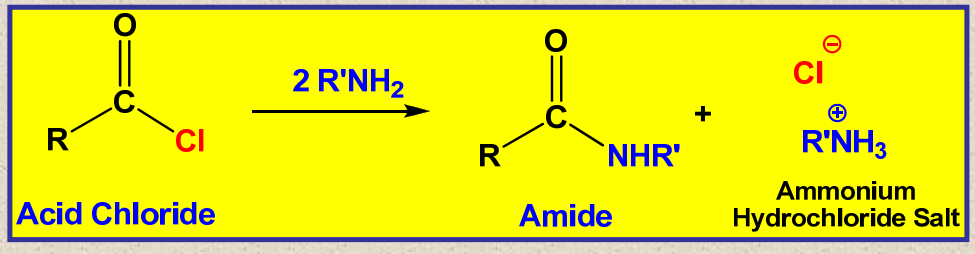


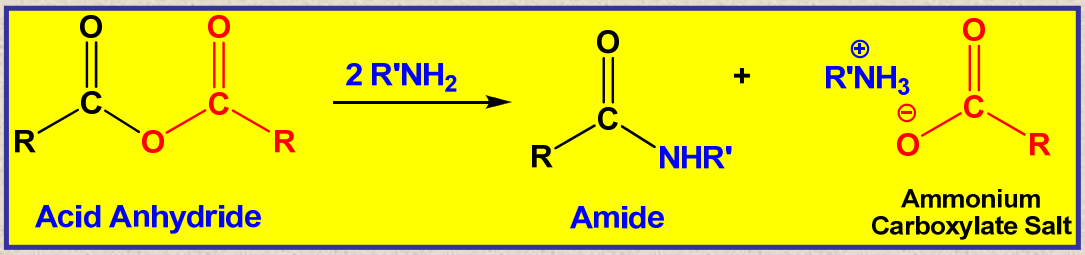
Reaction with Alcohols

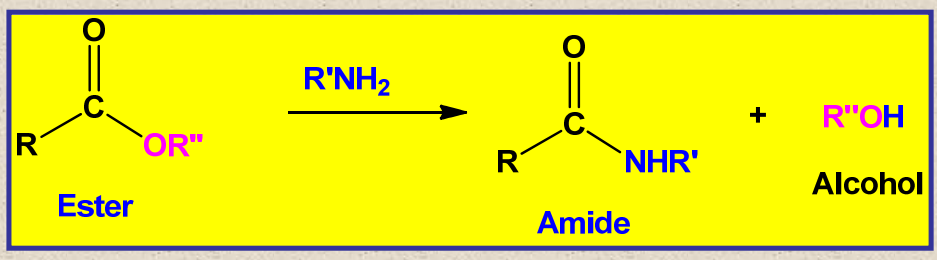
- Esters react with alcohols in the presence of an acid catalyst in an equilibrium reaction called **transesterification**



Acylation Reactions to form Amides:



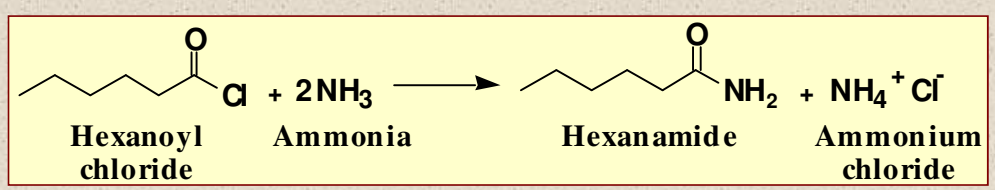




Reaction with Ammonia

Acid halides react with ammonia, 1° amines, and 2° amines to form amides

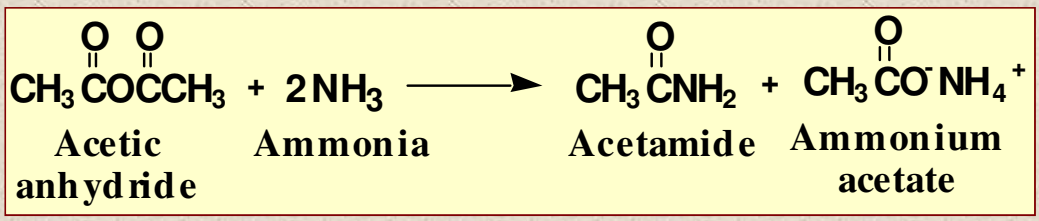
- 2 moles of the amine are required per mole of acid chloride



Reaction with Ammonia

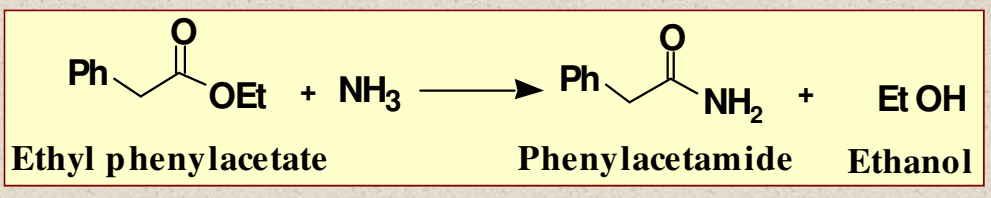
Acid anhydrides react with ammonia, and 1° and 2° amines to form amides

- 2 moles of ammonia or amine are required



Reaction with Ammonia

- Esters react with ammonia, and 1° and 2° amines to form amides
  - esters are less reactive than either acid halides or acid anhydrides

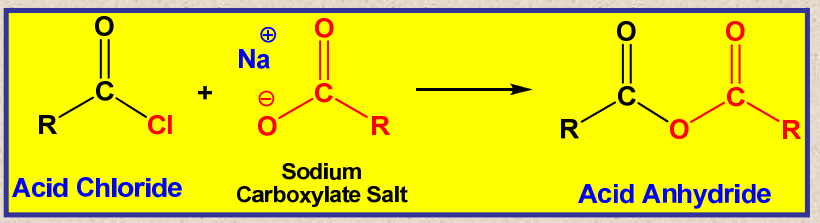


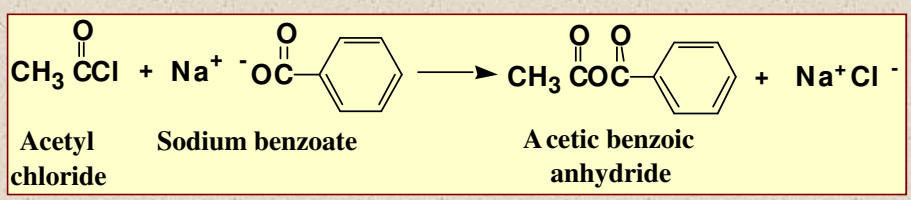
- Amides do not react with ammonia, or 1° or 2° amines

Acid Chlorides with Salts

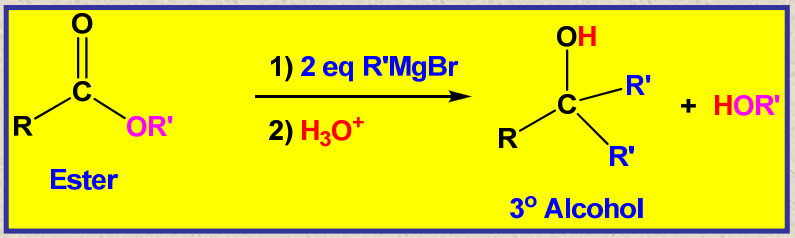
Acid chlorides react with salts of carboxylic acids to give anhydrides

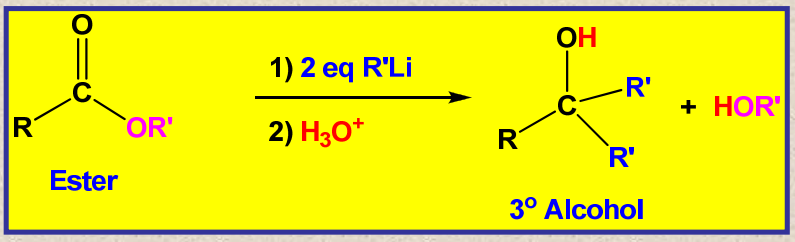
- most commonly used are sodium or potassium salts

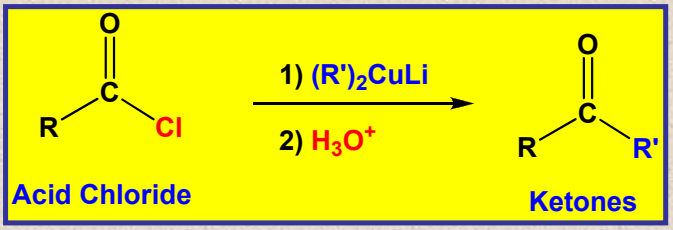




Reactions with Organometallic Reagents:

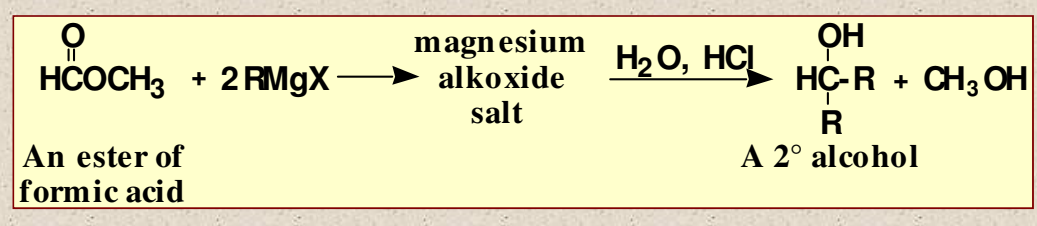






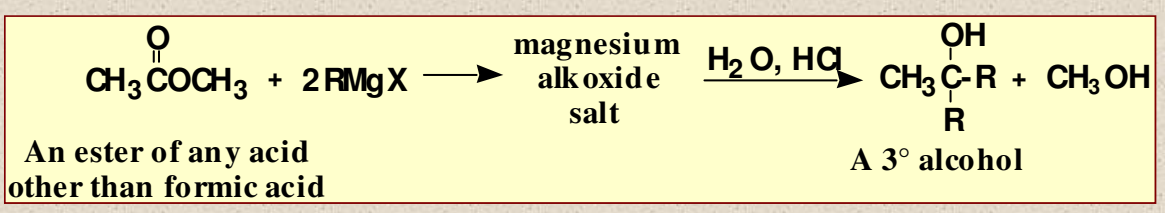
Reactions with Grignard Reagents

–treating a formic ester with 2 moles of Grignard reagent followed by hydrolysis in aqueous acid gives a 2° alcohol



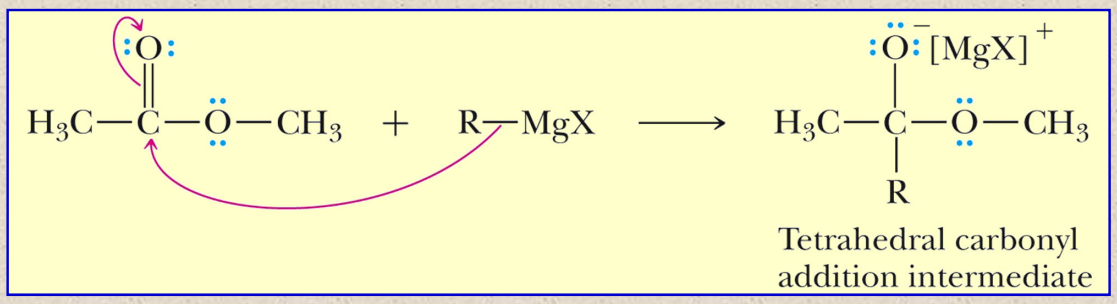
Reactions with Grignard Reagents

– treating other esters with a Grignard reagent followed by hydrolysis in aqueous acid gives a 3° alcohol



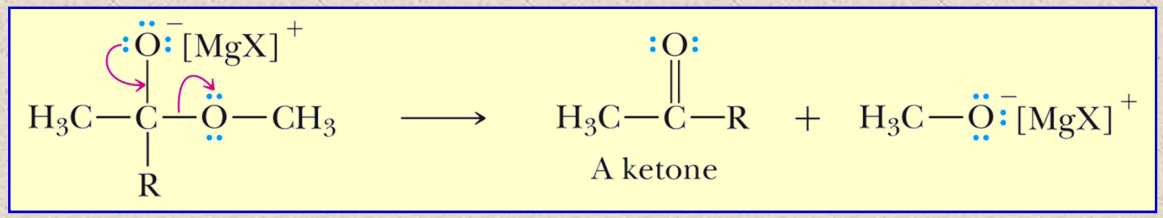
Reactions with Grignard Reagents

– **Step 1: Make a new bond between a nucleophile and an electrophile.** Reaction of the ester with one mole of Grignard reagent forms a tetrahedral carbonyl addition intermediate.



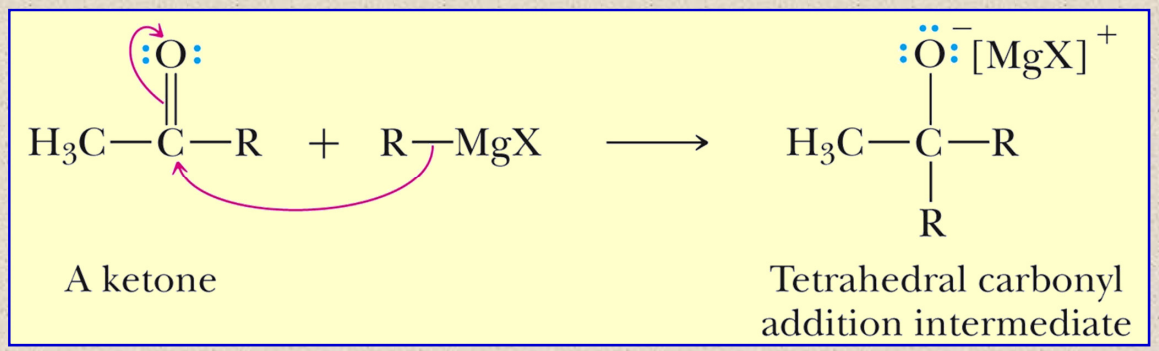
Reactions with Grignard Reagents

- **Step 2: Break a bond to give stable molecules or ions.** Collapse of the intermediate and expulsion of alkoxide ion gives a ketone and a magnesium alkoxide.



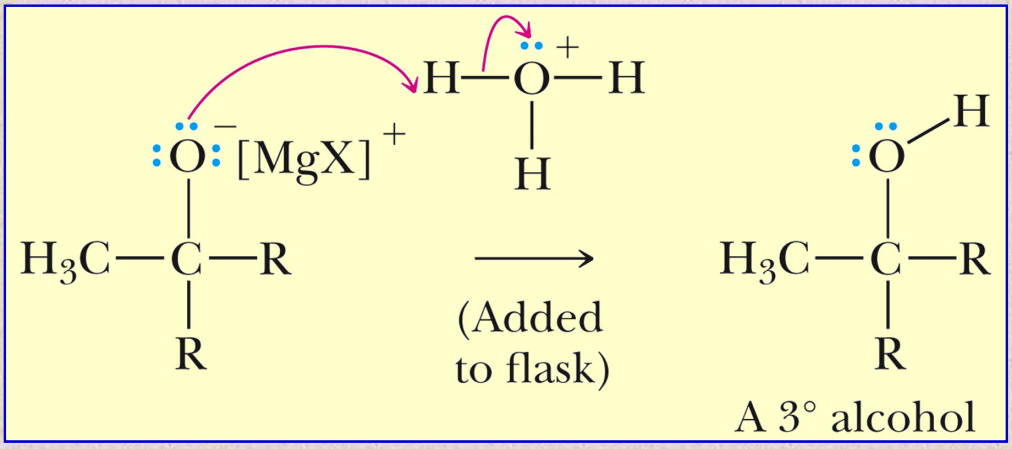
Reactions with Grignard Reagents

- **Step 3: Make a new bond between a nucleophile and an electrophile.** The ketone reacts with a second mole of Grignard reagent to give a second tetrahedral carbonyl addition intermediate.



Reactions with Grignard Reagents

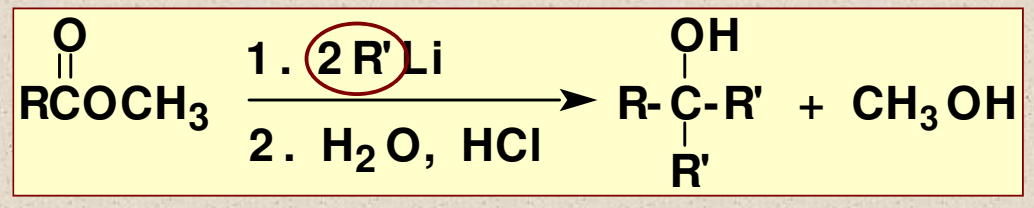
- **Step 4: Add a proton.** The resulting hydrolysis gives a tertiary alcohol.



Reactions with Organolithium

Organolithium compounds are even more powerful nucleophiles than Grignard reagents

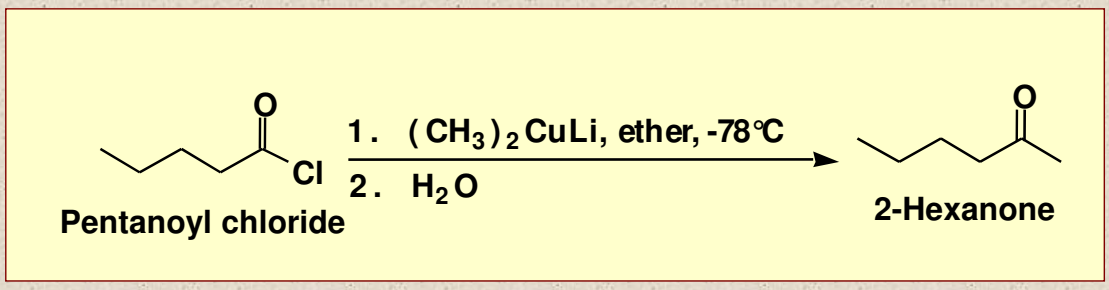
- they react with esters to give the same types of 2° and 3° alcohols as do Grignard reagents
- and often in higher yields



Reactions with Organocuprate Reagents

Acid chlorides at -78°C react with Gilman reagents to give ketones

– under these conditions, the TCAI is stable, and it is not until acid hydrolysis that the ketone is liberated

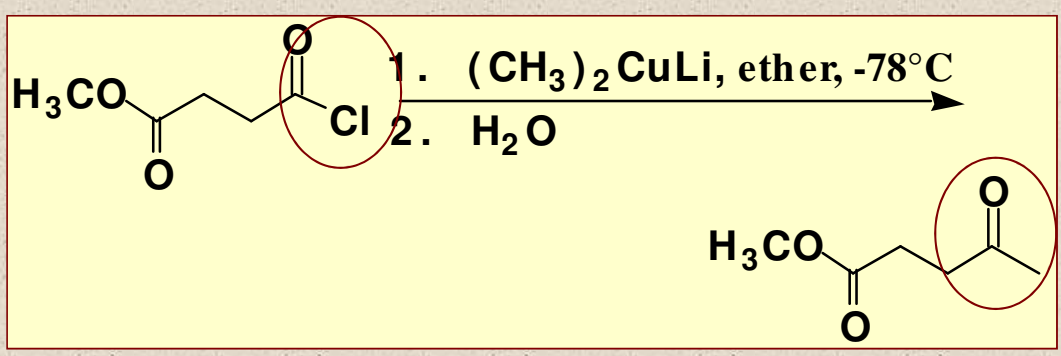


Pentanoyl chloride — 2-Hexanone

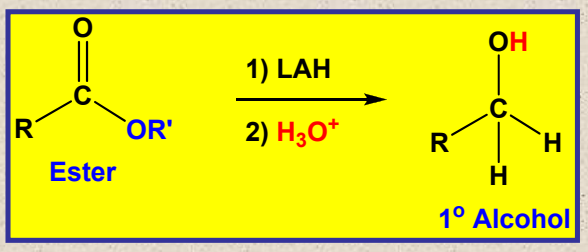
This is analogous to Gilman coupling with alkyl halides.

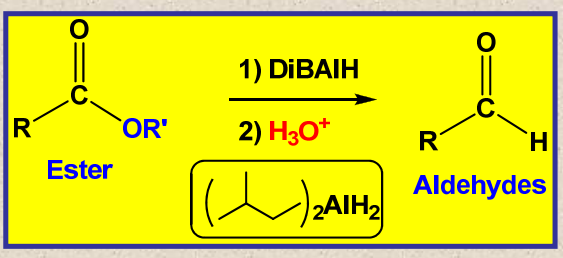
Reactions with Organocuprate Reagents

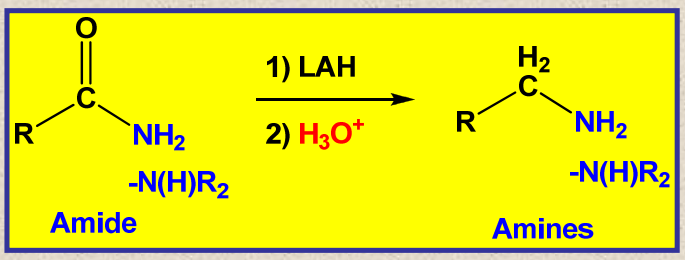
Gilman reagents react only with acid chlorides they do not react with acid anhydrides, esters, amides, or nitriles under the conditions described

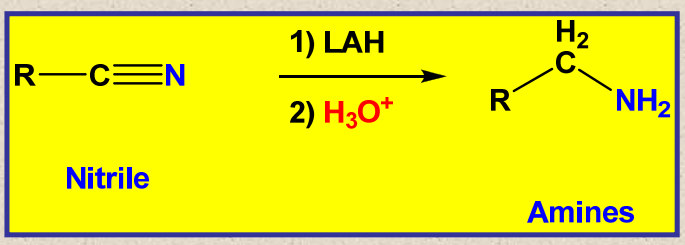


Reductions:





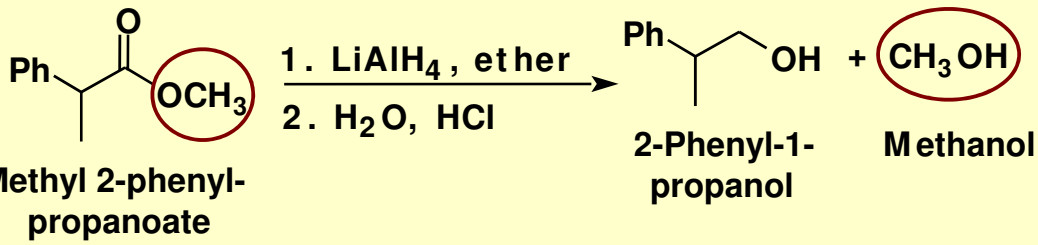




Reduction - Esters by $LiAlH_4$

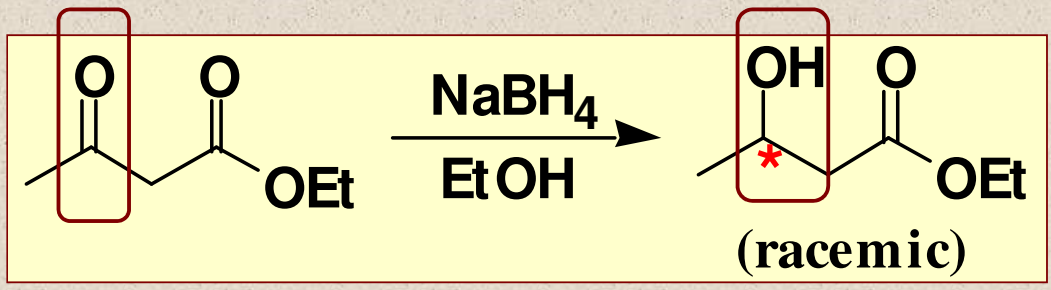
Most reductions of carbonyl compounds now use hydride reducing agents

- esters are reduced by $LiAlH_4$ to two alcohols
- the alcohol derived from the carbonyl group is primary



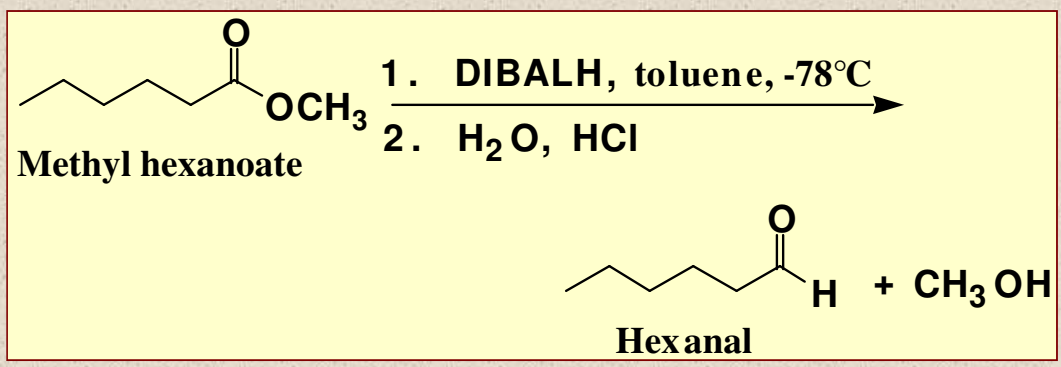
Reduction - Esters & $NaBH_4$

- **$NaBH_4$ does not normally reduce esters,** but it does reduce aldehydes and ketones
- Selective reduction is often possible by the proper choice of reducing agents and experimental conditions



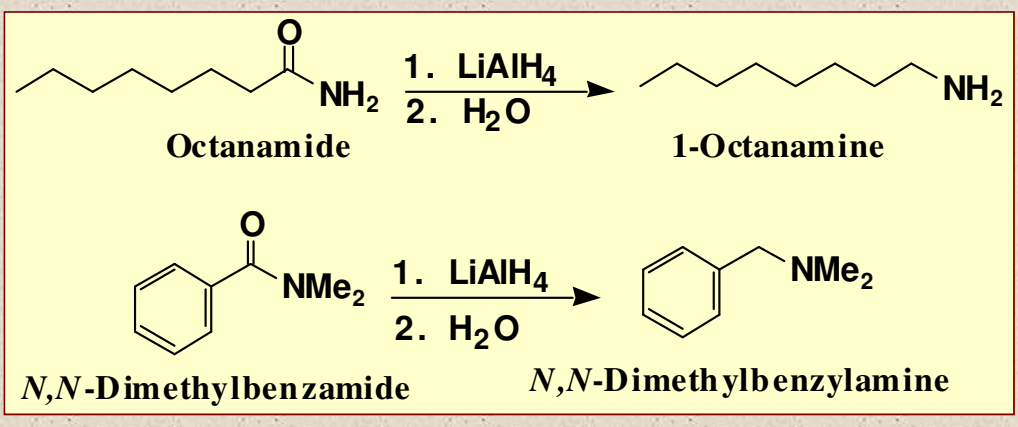
Reduction - Esters by DIBAlH

- Diisobutylaluminum hydride (**DIBAlH**) at -78°C selectively reduces an ester to an aldehyde
  - at -78°C, the TCAI does not collapse and it is not until hydrolysis in aqueous acid that the carbonyl group of the aldehyde is liberated



Reduction - Amides by $LiAlH_4$

- $LiAlH_4$ reduction of an amide gives a 1°, 2°, or 3° amine, depending on the degree of substitution of the amide



Reduction - Nitriles by $LiAlH_4$

- The cyano group of a nitrile is reduced by $LiAlH_4$ to a 1° amine