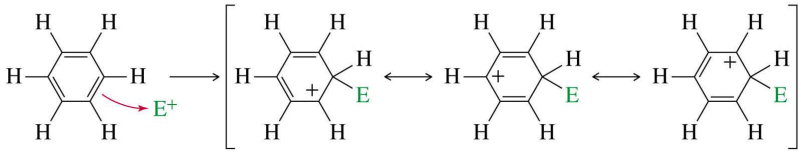
NITRATION OF AROMATIC COMPOUNDS

Res.Asst. Mehmet Murat KIŞLA
Pharmaceutical Chemistry Practice II

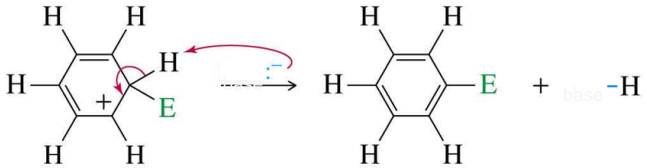
1

Electrophilic Aromatic Substitution

Arenium ion formation as a result of attack on the electrophile (E^+)



In the first step, benzene reacts with an electrophile, forming a carbocation intermediate. (slow)
In the second step, a base in the reaction mixture pulls off a proton from the carbocation intermediate, and the electrons that held the proton move into the ring to re-establish its aromaticity. (fast)



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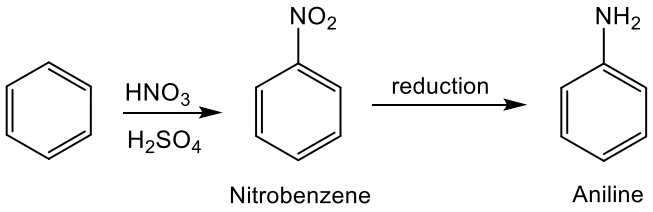
Nitro group (-NO_2) is used in syntheses because it can be converted into other functional groups also it can found in the structure of various active pharmaceutical ingredients.



Nitrobenzene Aniline

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Synthesis of aromatic nitro compounds

- Direct Nitration
- Oxidation of amines
- Conversion of diazonium salts into nitro group

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Direct Nitration(S_E)

Electrophilic nitration mechanism of an aromatic ring:

(A step-by-step examination of how the product is formed from the starting compound is called the **reaction mechanism**.)

- When benzene is treated with a mixture of nitric acid and sulfuric acid, a nitration reaction occurs in which nitrobenzene is formed. **This reaction proceeds via an electrophilic aromatic substitution in which a nitronium ion (NO_2^+) is believed to be the electrophile.** This strong electrophile is formed from the acid-base reaction that takes place between concentrated HNO_3 and H_2SO_4.

$O{=}\overset{+}{N}{=}O$

nitronium ion

NO_2^+ can also be obtained from acetyl nitrate (CH_3COONO_2) and nitronium perchlorate $NO_2^+ClO_4^-$.

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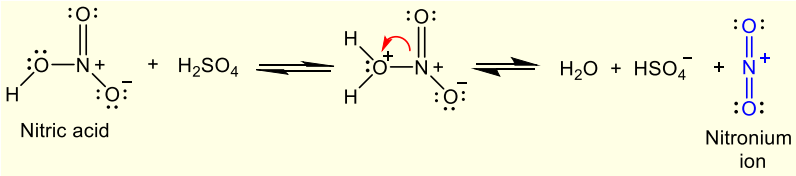

Nitric acid functions as a base to accept a proton from sulfuric acid, followed by loss of water to produce a nitronium ion. It might seem strange that nitric acid functions as a base rather than an acid, but remember that acidity is relative. Sulfuric acid is a much stronger acid than nitric acid. The resulting nitronium ion then serves as an electrophile in an electrophilic aromatic substitution reaction.

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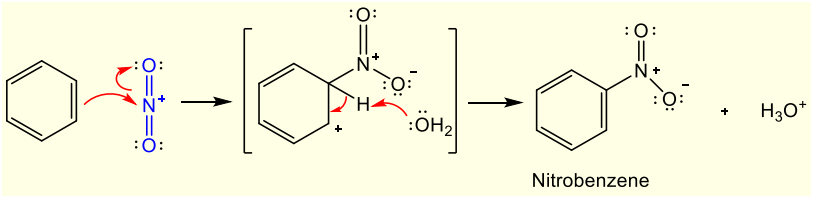
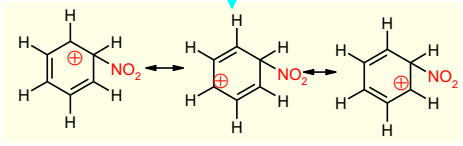
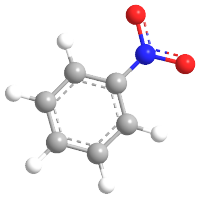
As we mentioned before, the aromatic ring reacts with **NO_2^+** (electrophile), forming a carbocation intermediate.

A base in the reaction mixture pulls off a proton from the carbocation intermediate to give the neutral nitro compound.







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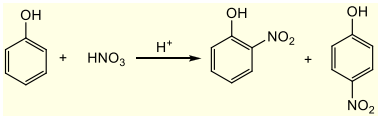
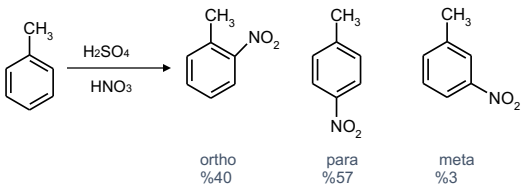
When a mono-substituted aromatic ring undergoes an nitration, nitration is carried out according to the orientation of present substituent.

The substituent already attached to the aromatic ring determines the location of the new substituent. A substituent will direct an incoming substituent either to the ortho and para positions, or it will direct an incoming substituent to the meta position.

- All activating substituents **(-OH, -NH_2, -NHCOR, alkyl groups)** and the weakly deactivating halogens are ortho *(-o ()* para-*p)* directors.
- All substituents that are more deactivating than the halogens **(-NO_2, -SO_3H, -CHO, -COOH, -COOR etc.)** are meta *(-m)* directors.





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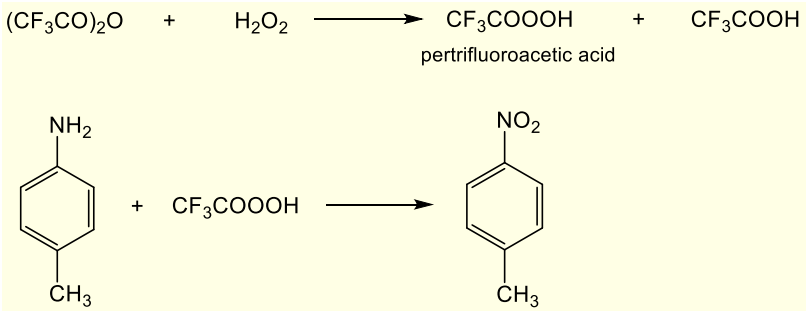
Oxidation of amines

$KMnO_4$ and peroxyacids are used for this purpose.



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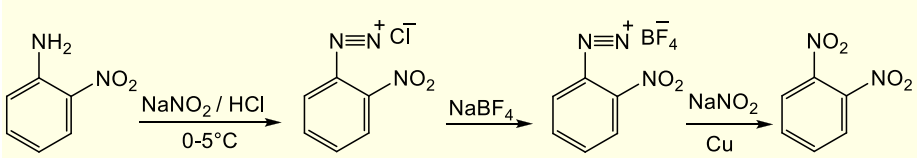
Converting the diazonium salts to the nitro group

It occurs as a result of decomposition of aryl diazonium salt.



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ESTERIFICATION REACTION

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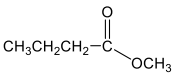
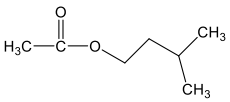
Most natural compounds have ester structure (**RCOOR'**)

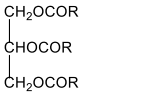
The structures, that give fragrance and aroma to various fruits and flowers, are simple ester structures.



Methyl butanoate
(in pineapple oil)



isopentyl acetate
(in banana oil)



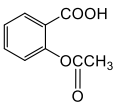
glycerol esters of fatty acids
($R=C_{11-17}$)

The ester derivatives are used for variety purposes both pharmaceutical and chemical industry.

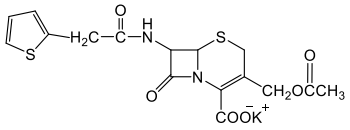
Ethyl acetate ($CH_3COOCH_2CH_3$): solvent

Aspirin : analgesic, antipyretic, anti-inflammatory

Cephalotin: antibiotic



Acetylsalicylic acid



Cephalotin

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Most commonly methods in synthesis of carboxylic acid esters

Ester molecules are generally obtained by the reaction of the alcohol nucleophile with the carbonyl carbon of carboxylic acid with the mechanism of addition.

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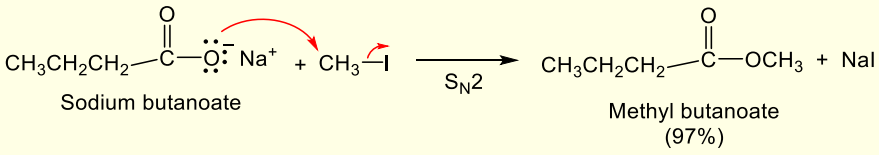
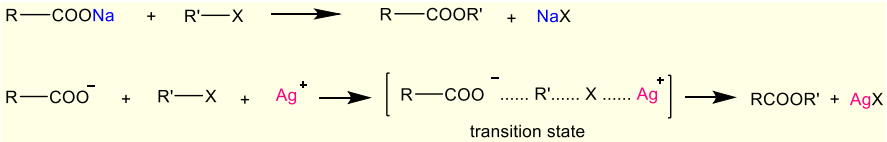
By the reaction of the alkali metal salts of the carboxylic acids with the alkyl halides with the mechanism of S_N2



If the silver salt of the carboxylic acid is selected, the ester yield is higher. Because, in the transition state of the reaction, the interest of the halogen to the Ag^+ ion facilitates the substitution between the carboxylate ion and the halide ion.



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By the reaction of carboxylic acids with alcohols in acidic medium

(Fischer esterification;
acid-catalyzed nucleophilic acyl substitution)

Esterification is a S_N reaction that occur with proton transitions.

After the addition of alcohol on the concentrated solution of the carboxylic acid, the ester is formed if the mixture is heated in the presence of a small amount of 96% H_2SO_4.

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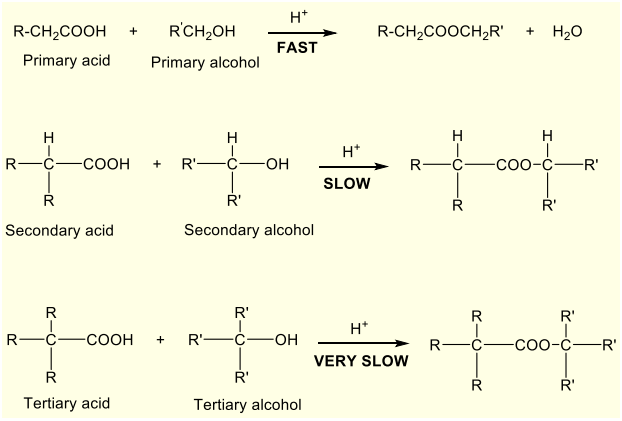
The rate of esterification depends on the type of carboxylic acids or alcohols.

- The ester forming rates of the primary, secondary and tertiary alcohols decrease from the primer to the tertiary.
- Similar to alcohols, carboxyl group, which is bounded the primary carbon, is rapidly esterified. The rate decreases from the primer to the tertiary.



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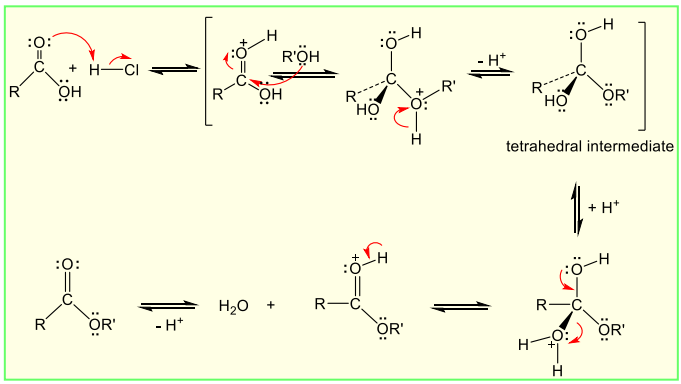
Mechanism of Fischer esterification:

The electrophilic strength of the carbonyl group of the carboxylic acid is not sufficient to interact with the oxygen of alcohol.

- The acid catalyst protonates the carbonyl oxygen of the carboxylic acid. Thus, the carbonyl carbon becomes open for the attack of weak nucleophiles.
- The nucleophilic addition product to the carbonyl carbon of the alcohol (tetrahedral intermediate) is unstable and ester formation occurs by the separation of H_2O .



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Factors affecting the esterification rate:

Inductive Effect

If there is an electronegative atom in the carboxylic acid molecule, this atom increases the electrophile strength of the carboxyl group carbonyl carbon with the inductive effect and it is easier to bind the alcohol. Therefore, the reaction rate increases

The closer the electronegative atom in the molecule is to the carboxyl group, the greater the inductive effect.

For example; chloroacetic acid can be more easily esterified than acetic acid.

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Mesomeric Effect

Benzoic acid gives a slower esterification reaction than acetic acid.

Because the positive charge in the carboxylic acid group carbonyl carbon of the carboxylic acid group is reduced by the electrophilic strength due to the mesomeric effect of the aromatic ring in the conjugated system, the reaction of the alcohol molecule with the alkoxy group will be more difficult and thus the esterification reaction will be slower.

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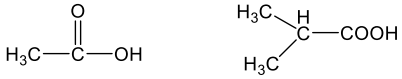
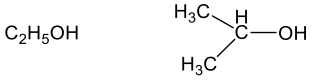
Steric Hindrance

Due to steric hindrance in branched structures, the rate of esterification is reduced.

If there are large groups bounded to the carboxyl group of the carboxylic acid, or if the alcohol molecule is branched, binding to the cationic center is inhibited and the esterification rate decreases.



Isobutyric acid



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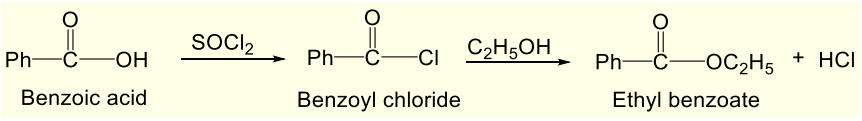
By reaction of acyl chlorides with alcohols

There are two steps in this method.

1. Preparation of acid chlorides. (acyl chlorides)
2. Esterification with the alcohol



The fact that halogens are a well-separated group allows acid chlorides to easily facilitate ester formation by nucleophilic acyl substitution based on the addition-elimination mechanism with alcohols.

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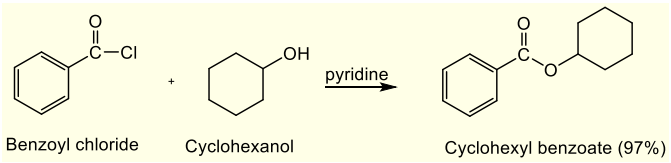
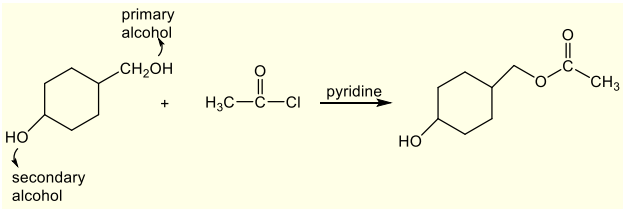
A base such as dimethylaniline, pyridine, triethylamine is used to remove the formed HCl.



The reaction rate varies according to the structure of alcohol.(primary > secondary > tertiary)



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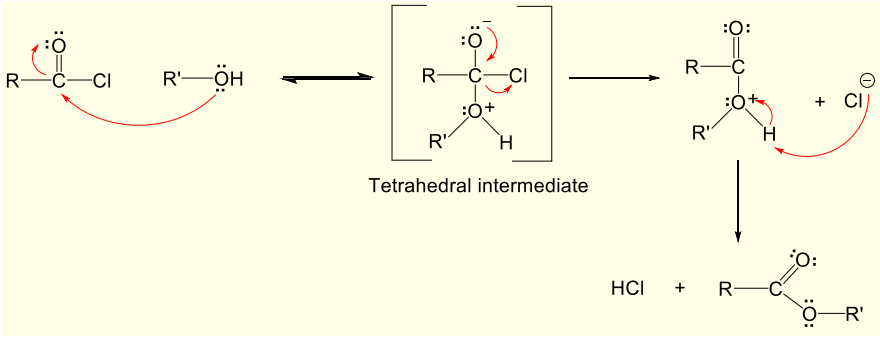
Reaction Mechanism(S_N2) :

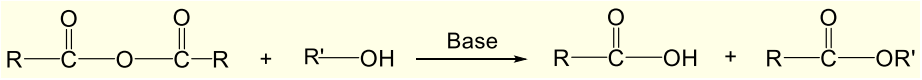
When the alcohol attacks the electrophilic carbonyl group, a tetrahedral intermediate is formed. Formation of esters occur by removing of chloride and then deprotonation.

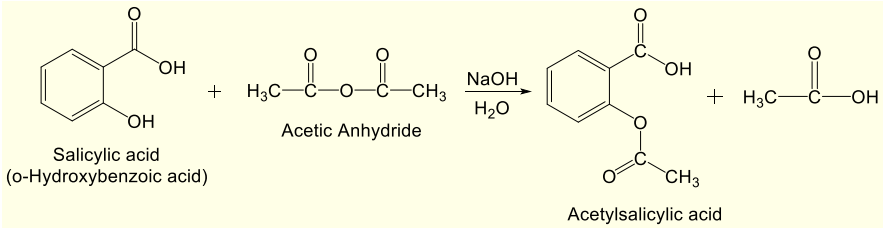


23

By the reaction of acid anhydrides with alcohols

As a result of the reaction of the acid anhydrides with alcohols, one mole of the carboxylic acid is occured with one mole of ester.





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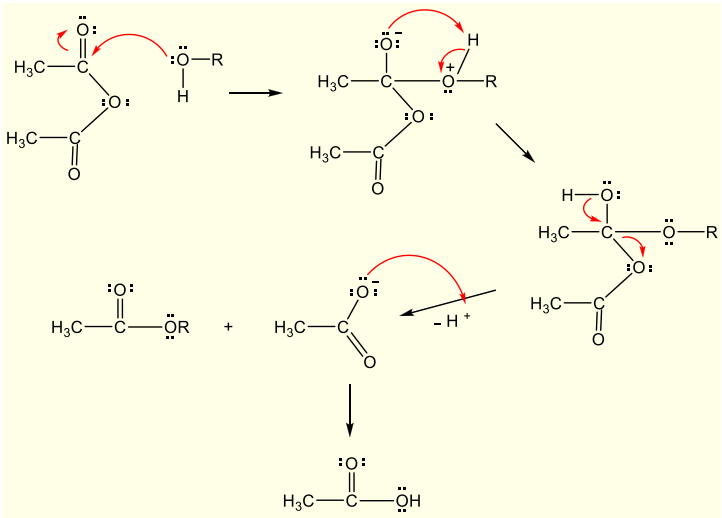
The mechanism of reaction of acid anhydrides with alcohols is similar with those made with acyl chlorides.

With acid anhydrides, the carboxylate anion (-COO^-) is replaced by the halide ion (X^-).



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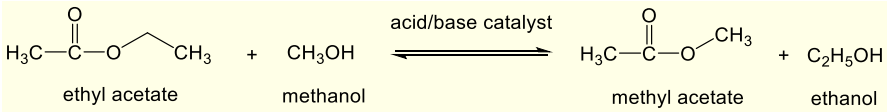
Transesterification

Transesterification is the reaction of an ester and an alcohol to obtain a new ester. Besides the new ester, the alcohol that forms the first ester is occured.



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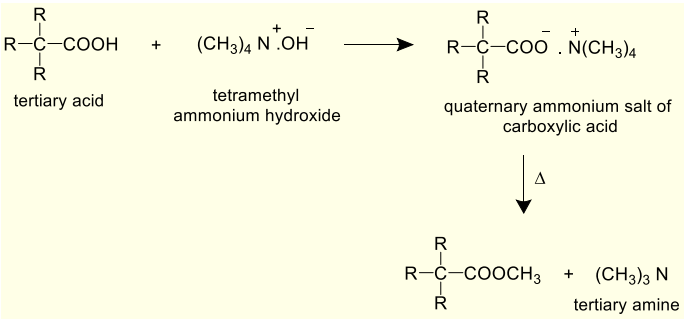
By using quaternary ammonium hydroxides

When the carboxyl group bounds to a tertiary carbon, esterification of some carboxylic acids is inhibited.

In this case, the salt of acid formed by the quaternary ammonium hydroxide is decomposed by heat and the ester is formed.



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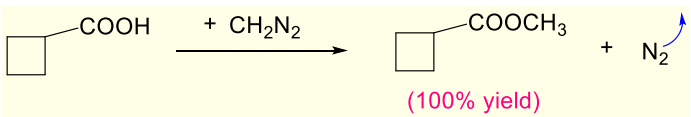
By using of diazomethane

Because of occuring nitrogen gas (N_2), which is the perfect leaving group, at the end of the reaction; diazomethane (CH_2N_2), turns into a very active methylating reagent when it finds the proton source.

Methyl esters of carboxylic acids can be obtained by treating acids with diazomethane solution with ether.

Advantages; quantitative reaction, easy for purification
Disadvantages; diazomethane is toxic and explosive

It is applied in the synthesis of sensitive carboxylic acid esters.



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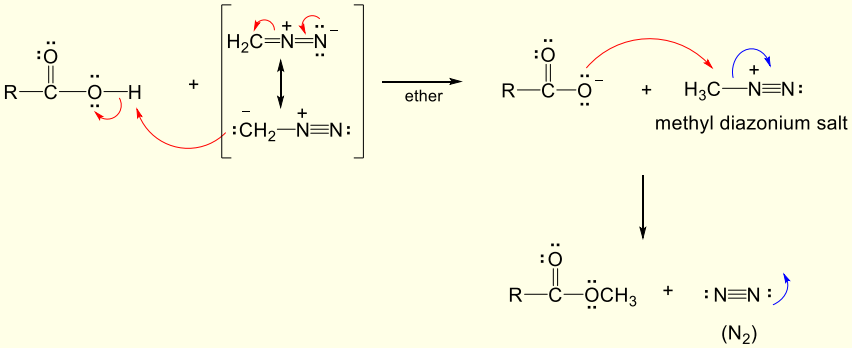
Mechanism



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AMIDIFICATION REACTIONS

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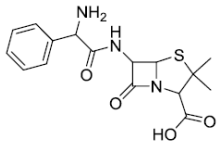
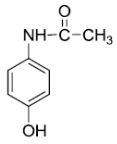
Amide formation reactions

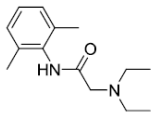
An amide functional group is widely found in living organisms as well as many drug active substance (penicillins, cephalosporins etc.)



ampicillin



paracetamol



lidocaine

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- Amides are obtained from acyl chlorides, acyl anhydrides, esters, carboxylic acids and carboxylic acid salts.
- In all methods, the acyl is formed by reacting ammonia or amine with nucleophilic addition-separation mechanism.

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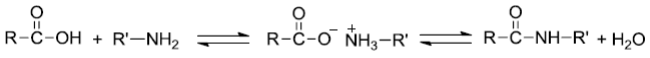
•Reaction of carboxylic acids with amines

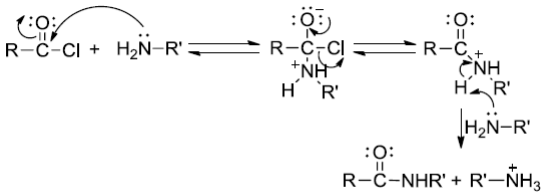
Reaction of carboxylic acid with amines forms ammonium salts. Then amide derivatives are obtained by leaving of H_2O.

This method is not very preferred in the production of amide because of the low activity of carboxylic acids.



•Reaction of acyl chlorides with amines

In this method at the end of the reaction HCl occurs. For neutralize that the starting chemical amine is used to 2 times the mol of chloride, or the alkaline materials such as triethylamine and pyridine are used.



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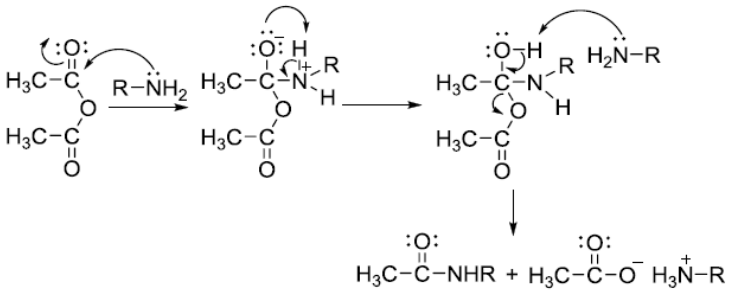
Reaction of acid anhydrides with amines

Reaction of acid anhydrides with amines forms one mol of amide and one mol of amine salt of carboxylic acid. This method is commonly used for synthesis of acetamide derivatives.



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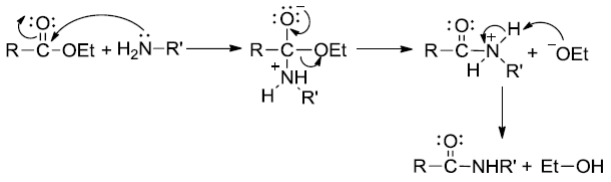
Reaction of esters with amines

Although it is slower than acyl chlorides and acid anhydrides with amines; this method is preferred.



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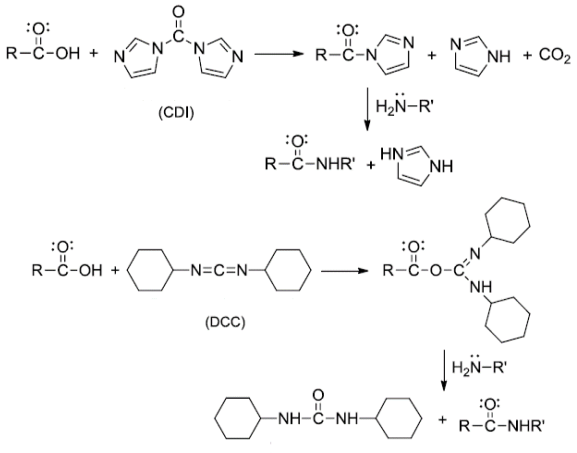
Some reagents used in amide synthesis

Some of the reagents frequently used in amide synthesis are carbonyldiimidazole (CDI) and dicyclohexylcarbodiimide (DCC).
Amides are obtained by reacting the carboxylic acids with amines through an active intermediate with these reagents.



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HYDROLYSIS REACTIONS

Res.Asst. Mehmet Murat KIŞLA
Pharmaceutical Chemistry Practice II

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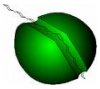
HYDROLYSIS REACTIONS

HYDROLYSIS means fragmentation by water.

(Bond rupture by using water)

Organic molecules that can be fragmented by water:

Carboxylic Acid Derivates (Amides, Acid chlorides, Esters, Acid Anhydrides, Nitriles)



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HYDROLYSIS REACTIONS

Hydrolysis occurs slowly when it is made only with water, but the reaction rate increases if the reaction is in the presence of acid or base. (Hydrolysis is carried out using an acid or base catalyst in aqueous medium.)

The task of the catalysts is to facilitate electron transfer by activating the bond electrons.

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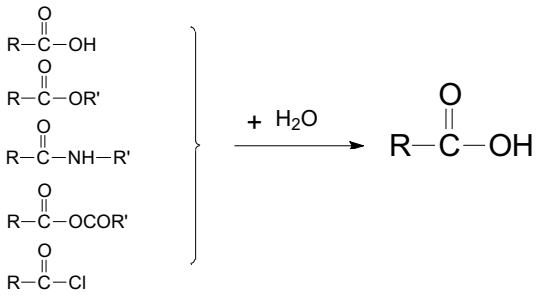
HYDROLYSIS OF CARBOXYLIC ACID DERIVATIVES



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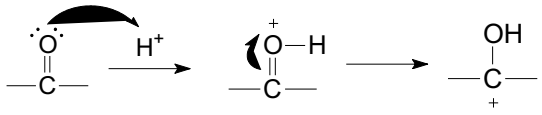
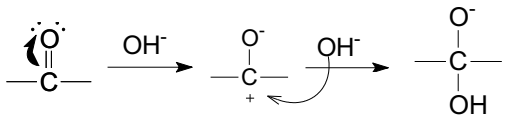
HYDROLYSIS OF CARBOXYLIC ACID DERIVATIVES

- **HYDROLYSIS in H^+ medium**



- **HYDROLYSIS in OH^- medium**



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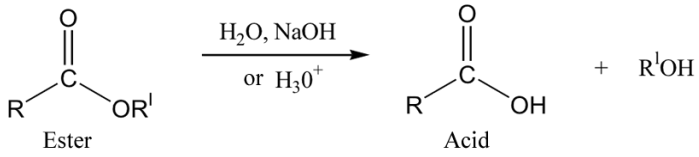
HYDROLYSIS OF ESTERS



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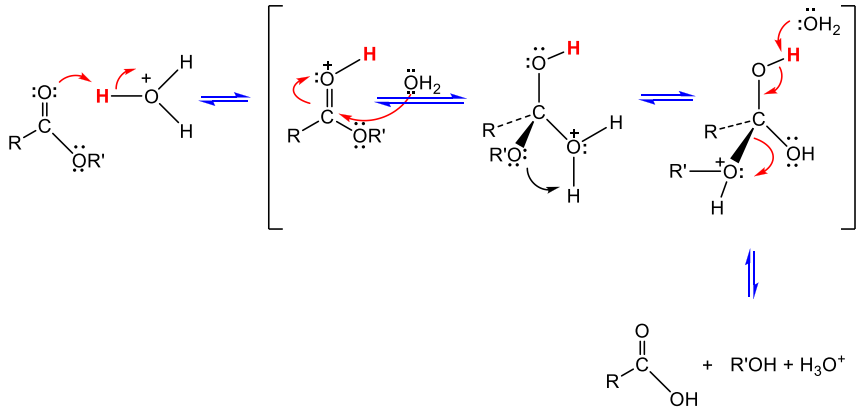
Mechanisms of Hydrolysis Reactions of Esters

Acid Catalysis

Hydrolysis of the esters in the acidic medium is the conversion of the equilibrium in the Fischer ester synthesis method to carboxylic acid and alcohol by addition of water to the medium.



+ R'OH + H_3O^+

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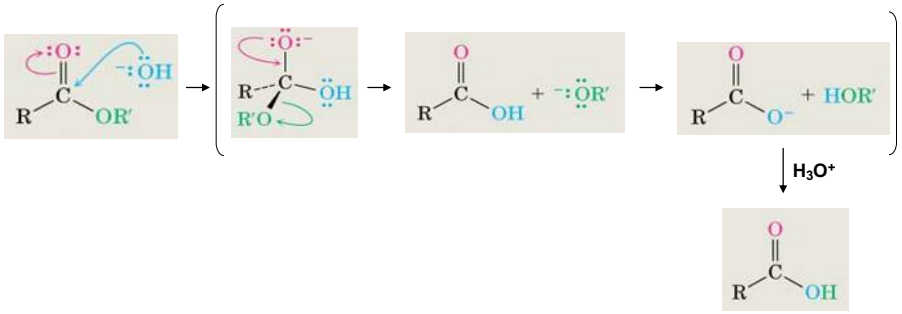
Mechanisms of Hydrolysis Reactions of Esters

Base Catalysis



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Mechanisms of Hydrolysis Reactions of Esters

When hydrolysis is compared with acid and base catalysis, most significant difference can be summarized as follows:

* While water, which is a weak nucleophile in acid-catalyzed hydrolysis, is added to carbonyl group ($C=O^+H$) increasing electrophilic charge by taking proton; OH^-, which is a strong nucleophile in base-catalyzed hydrolysis, is added to the weak electrophilic C=O bond.

* Carboxylic acid salt and alcohol are formed by base-catalyzed hydrolysis.

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SAPONIFICATION

Alkaline hydrolysis → SAPONIFICATION

↓

(Soaps are obtained by alkaline hydrolysis of glycerol esters of high-carbon fatty acids.)

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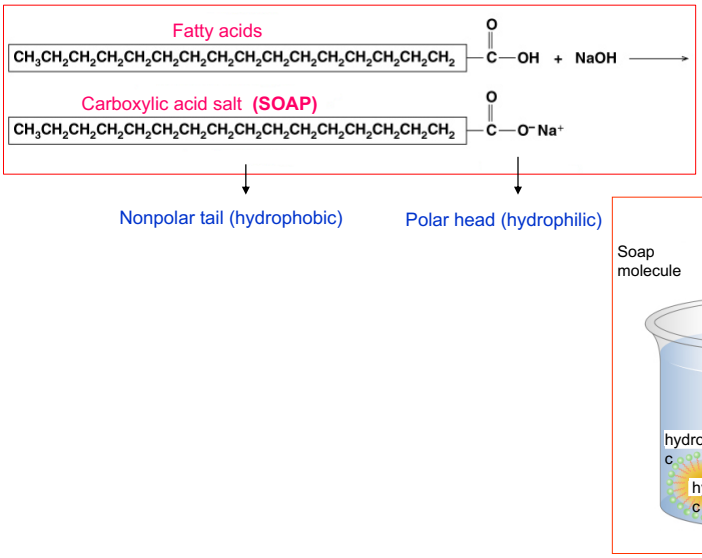
SAPONIFICATION



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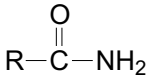
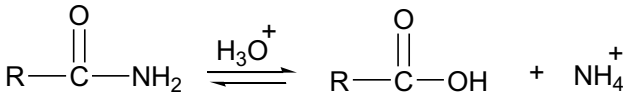
HYDROLYSIS OF AMIDE DERIVATIVES



Amides → are found in the structure of proteins.
are more resistant than acids.

When heated with aqueous acid and alkalines, they are hydrolyzed to the amines and carboxylic acids.



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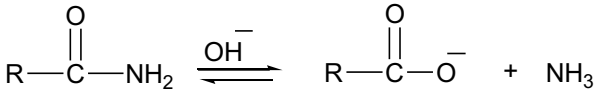
HYDROLYSIS OF AMIDE DERIVATIVES



The appearance of ammonia in the basic environment can be understood from the smell or blue color of the litmus paper.

If the amide used is *N*-substituted amide, primary or secondary amines are formed instead of ammonia.

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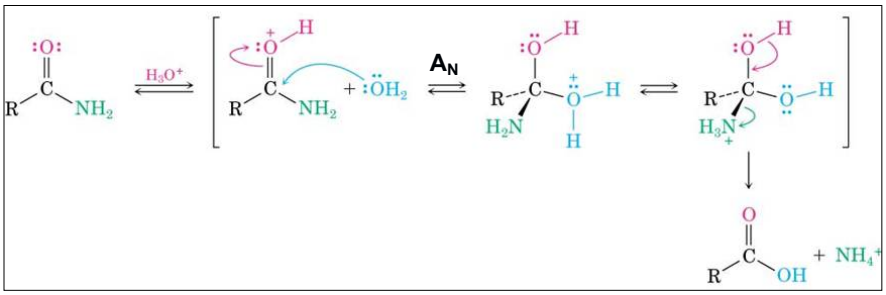
Mechanisms of Hydrolysis Reactions of Amides

ACID CATALYSIS



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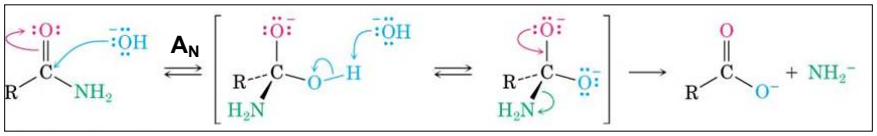
Mechanisms of Hydrolysis Reactions of Amides

BASE CATALYSIS



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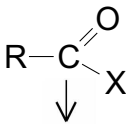
HYDROLYSIS OF ACID HALIDES

- Since acyl halides and acid anhydrides are active molecules, they get hydrolysed under neutral conditions.



Since the electrophilic charge of carbonyl carbon is greater than the alkyl carbon, the substitution of halogen is easier.

- To avoid hydrolysis of these compounds, acyl halides and anhydrides should be stored under dry N_2, and the used solvents and reagents should be dry.

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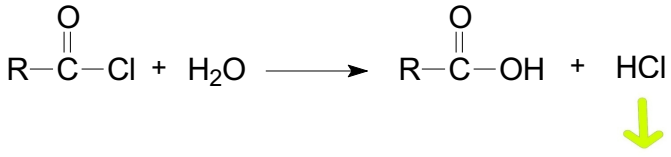
HYDROLYSIS OF ACID HALIDES



pyridine/ NaOH (to remove)

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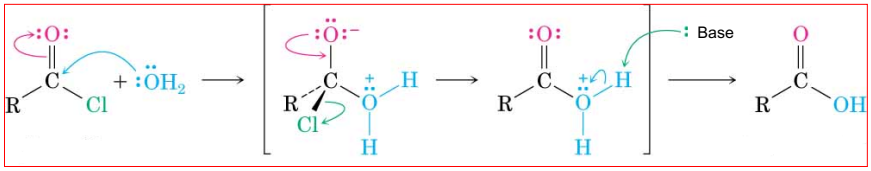
HYDROLYSIS OF ACID HALIDES

The hydrolysis reaction of acyl chlorides is nucleophilic acyl substitution.



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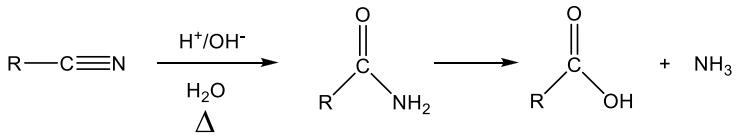
HYDROLYSIS OF NITRILES

When nitriles are heated in aqueous acid or alkaline medium, they get converted ...

into amid derivatives in moderate conditions,

into carboxylic acids on more severe conditions by hydrolysis.



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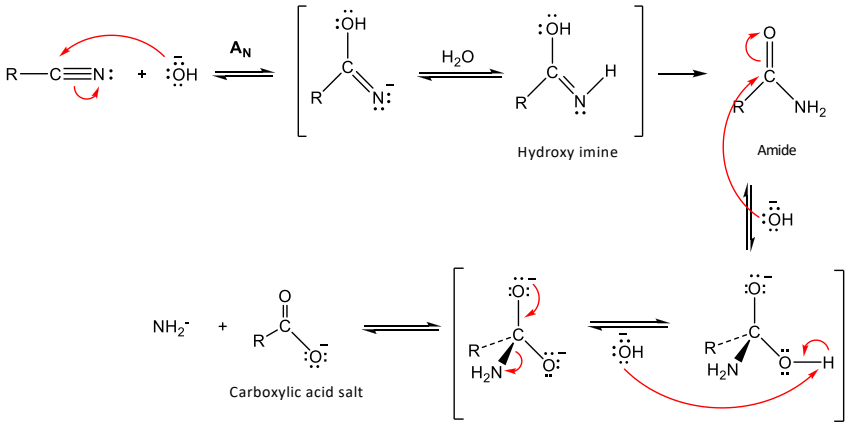
HYDROLYSIS OF NITRILES

BASE CATALYSIS



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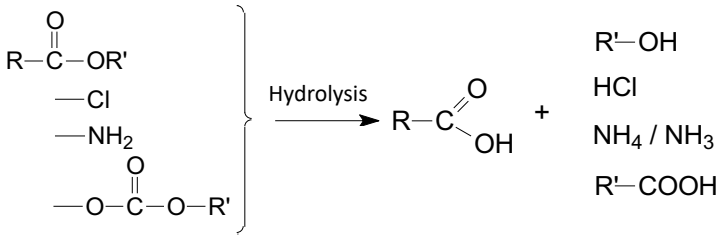
R—C—OR'
—Cl
—NH2
—O—C—O—R'
Hydrolysis
R—C
OH
+
R'—OH
HCl
NH4 / NH3
R'—COOH

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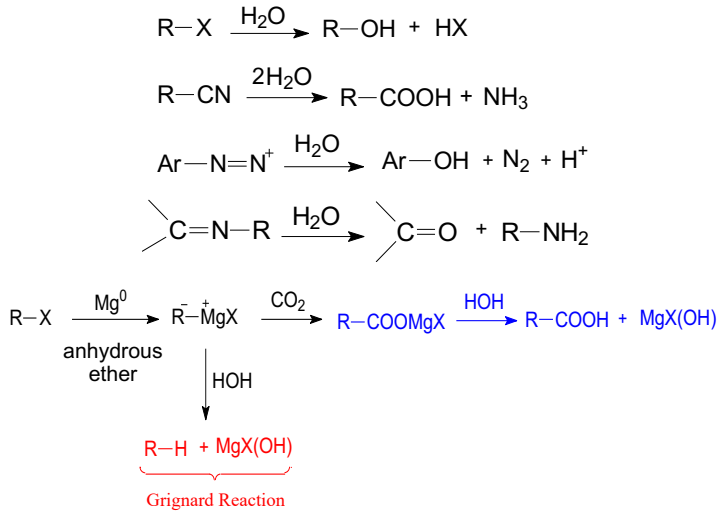
R—X + H2O → R—OH + HX
R—CN + 2H2O → R—COOH + NH3
Ar—N=N+ + H2O → Ar—OH + N2 + H+
C=N—R + H2O → C=O + R—NH2
R—X
Mg0
anhydrous ether
R—MgX
CO2
R—COOMgX
HOH
R—COOH + MgX(OH)
HOH
R—H + MgX(OH)
Grignard Reaction

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