HYDROLYSIS REACTIONS

HYDROLYSIS REACTIONS

HYDROLYSIS means fragmentation by water.

(Bond rupture by using water)

Organic molecules that can be fragment by water:

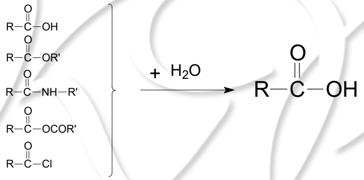
Carboxylic Acid Derivates (Amides, Acid chlorides, Esters, Acid Anhydrides, Nitriles)

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 catalyser in aqueous medium.)

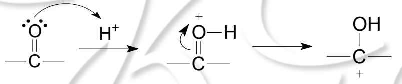
The task of the catalysers is to facilitate electron transfer by activating the bond electrons.

HYDROLYSIS OF CARBOXYLIC ACID DERIVATIVES

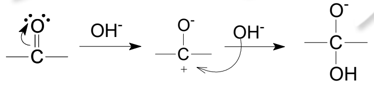


HYDROLYSIS OF CARBOXYLIC ACID DERIVATIVES

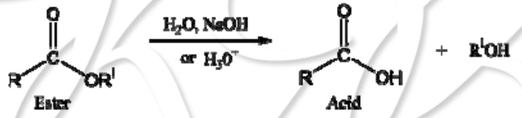
- **HYDROLYSIS in H^+ medium**



- **HYDROLYSIS in OH^- medium**



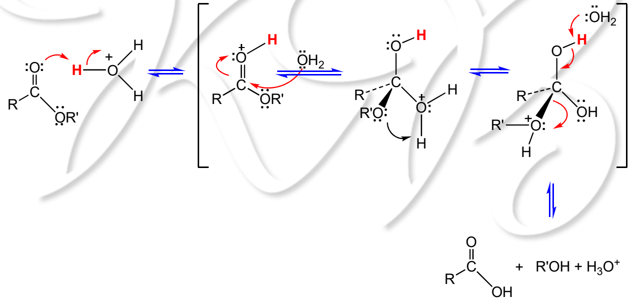
HYDROLYSIS OF ESTERS



Mechanisms of Hydrolysis Reactions of Esters

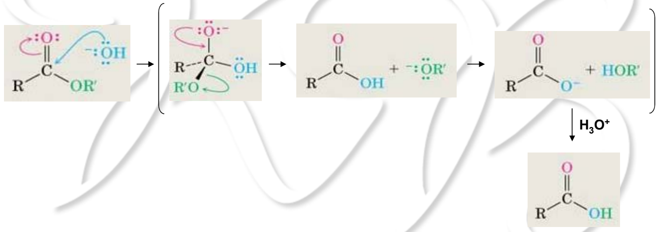
Acid Catalysis

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.



Mechanisms of Hydrolysis Reactions of Esters

Base Catalysis



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 asid-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.

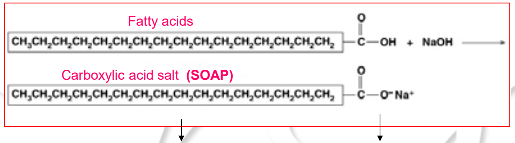
SAPONIFICATION

Alkaline hydrolysis → SAPONIFICATION

↓

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

SAPONIFICATION



Fatty acids

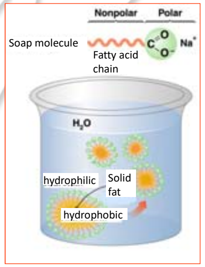
$$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-\overset{O}{\overset{\|}{C}}-OH + NaOH \longrightarrow$$

Carboxylic acid salt **(SOAP)**

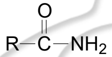
$$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-\overset{O}{\overset{\|}{C}}-O^-Na^+$$

Nonpolar tail (hydrophobic)

Polar head (hydrophilic)



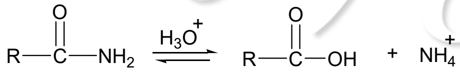
HYDROLYSIS OF AMIDE DERIVATIVES



$$R-\overset{O}{\overset{\|}{C}}-NH_2$$

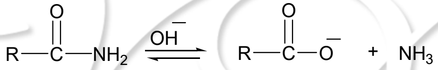
Amides → are found in the structure of proteins.
are more resistant than acids.

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



$$R-\overset{O}{\overset{\|}{C}}-NH_2 \xrightleftharpoons{H_3O^+} R-\overset{O}{\overset{\|}{C}}-OH + NH_4^+$$

HYDROLYSIS OF AMIDE DERIVATIVES



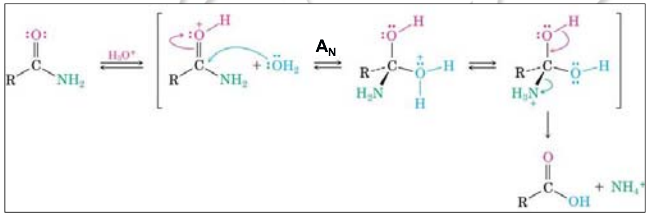
$$R-\overset{O}{\overset{\|}{C}}-NH_2 \underset{}{\overset{\overline{OH}}{\rightleftharpoons}} R-\overset{O}{\overset{\|}{C}}-\overline{O} + NH_3$$

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

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

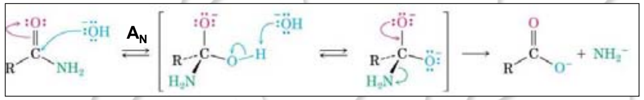
Mechanisms of Hydrolysis Reactions of Amides

ACID CATALYSIS



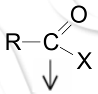
Mechanisms of Hydrolysis Reactions of Amides

BASE CATALYSIS



HYDROLYSIS OF ACID HALIDES

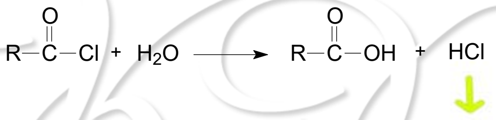
- Since acyl halides and acid anhydrides are active molecules, they hydrolyze under neutral conditions.



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, the used solvents and reagents should be dry.

HYDROLYSIS OF ACID HALIDES

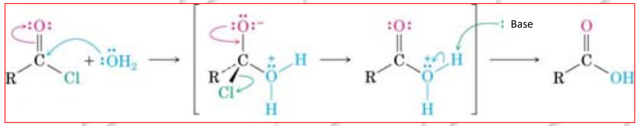


$R-\overset{O}{\overset{\|}{C}}-Cl + H_2O \longrightarrow R-\overset{O}{\overset{\|}{C}}-OH + HCl$

pyridine/ NaOH (to remove)

HYDROLYSIS OF ACID HALIDES

The hydrolysis reaction of acyl chlorides is nucleophilic acyl substitution.

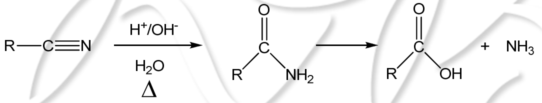


HYDROLYSIS OF NITRILES

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

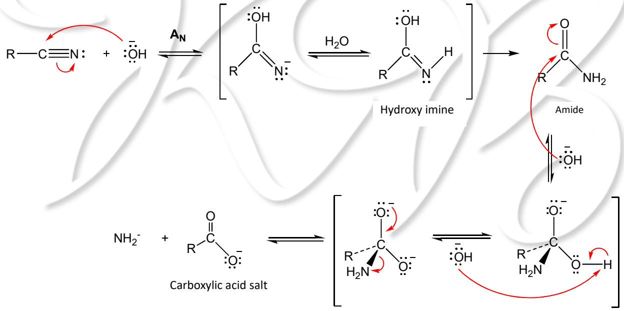
to amid derivatives in moderate conditions,

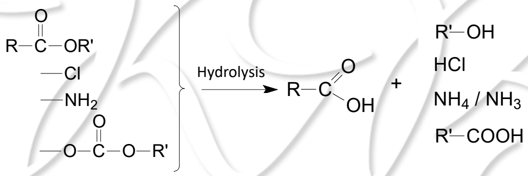
to carboxylic acids on more severe conditions by hydrolysis.

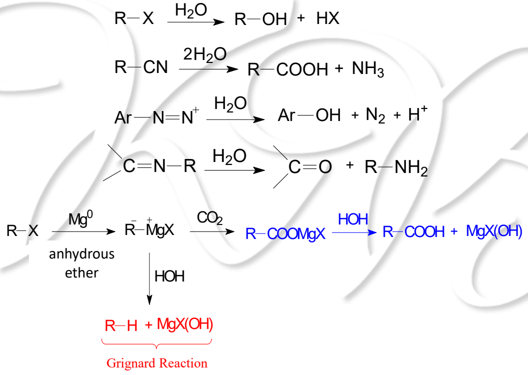


HYDROLYSIS OF NITRILES

BASE CATALYSIS







$R{-}X \xrightarrow{H_2O} R{-}OH + HX$

$R{-}CN \xrightarrow{2H_2O} R{-}COOH + NH_3$

$Ar{-}N{=}N^+ \xrightarrow{H_2O} Ar{-}OH + N_2 + H^+$

$>C{=}N{-}R \xrightarrow{H_2O} >C{=}O + R{-}NH_2$

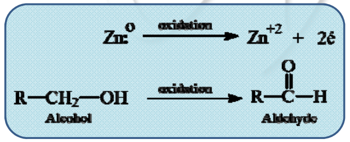
$R{-}X \xrightarrow[\text{anhydrous ether}]{Mg^0} \overset{-}{R}{-}\overset{+}{Mg}X \xrightarrow{CO_2} R{-}COOMgX \xrightarrow{HOH} R{-}COOH + MgX(OH)$

$\overset{-}{R}{-}\overset{+}{Mg}X \xrightarrow{HOH} \underbrace{R{-}H + MgX(OH)}_{\text{Grignard Reaction}}$

Oxidation and Reduction Reactions

Oxidation Reactions

- The oxidation of an organic molecule can be defined as increase in the amount of oxygen or decrease in the amount of hydrogen.
- A decrease in the amount of electrons of atom or ion; or an increase in the value of a functional group is an oxidation reactions.
- Oxidation and reduction refer to the loss or gain of electron of atoms or ions in inorganic (anorganic) chemistry respectively.



$Zn^0 \xrightarrow{\text{oxidation}} Zn^{+2} + 2\acute{e}$

$R{-}CH_2{-}OH \xrightarrow{\text{oxidation}} R{-}\overset{O}{\overset{\|}{C}}{-}H$

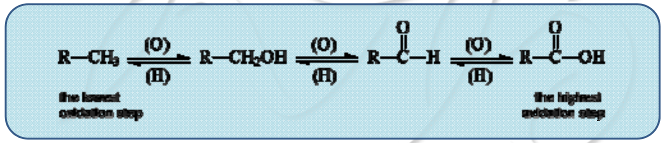
Oxidation Number (Ox. State)

Ox. step	Primary		Secondary	Tertiary	Quaternary
-4	CH_4				
-3		RCH_3			
-2	CH_3OH		R_2CH_2		
-1		RCH_2OH		R_3CH	
0	CH_2O		R_2CHOH		R_4C
+1		RCHO		R_3COH	
+2	HCOOH		R_2CO		
+3		RCOOH			
+4	CO_2				

The oxidation number of a free element is always 0. If an element loses the *n* number of electrons, it is considered to be oxidized by +n value, and if it gains, it is considered to be reduced by -n value. In organic molecules, the oxidation numbers of the "C" atoms can be calculated by considering each "H", -1; each "C", 0; each heteroatoms, +1 values for the 4 bonds of the "C" atoms.

Oxidation and Reduction

When an organic compound undergoes reduction, the reduction reactive oxidazes. When an organic compound undergoes oxidation, the oxydation reactive undergoes reduction. Oxidation and reduction reaction take place at the same time.



$$R-CH_3 \underset{(H)}{\overset{(O)}{\rightleftharpoons}} R-CH_2OH \underset{(H)}{\overset{(O)}{\rightleftharpoons}} R-\overset{\overset{O}{\|}}{C}-H \underset{(H)}{\overset{(O)}{\rightleftharpoons}} R-\overset{\overset{O}{\|}}{C}-OH$$

Applied in industrial and laboratory Oxidation Methods

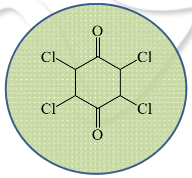
- Oxidation in air or with pure oxygen. (These reactions can be accomplished by biologically catalyzing homogeneous or heterogeneous catalysers.)
- Catalytic dehydrogenation at high temperature. (Vanadium oxides)
- Oxidation with some inorganic substances outside oxygen. (The most commonly used reagents: Sodium dichromate + H_2SO_4 (sulfochromic mixture), in neutral, basic or acidic medium $KMnO_4$, concentrated nitric acid, hydrogen peroxide, ozone, some metallic oxide and peroxides, some oxygenated salts.)
- Oxidation with some organic substances or peroxides and peracides.

Oxidation Reagents

O_2	HNO_3	SO_3	Cl_2	Ag_2O	MnO_2
O_3	RO-NO	$(CH_3)_2S^+-O^-$	Br_2	HgO	MnO_4^-
H_2O_2	Ø-N_2	SeO_2	I_2	$Hg(OAc)_2$	CrO_3
t-BuO-OH	H_2NCl		NBS	$Pb(OAc)_4$	CrO_2Cl_2
R-COO-OH	$H_3N^+-OSO_3^-$		t-BuOCl	$FeCl_3$	OsO_4
	$R_3N^+-O^-$			$Fe(CN)_6^{-3}$	IO_4^-

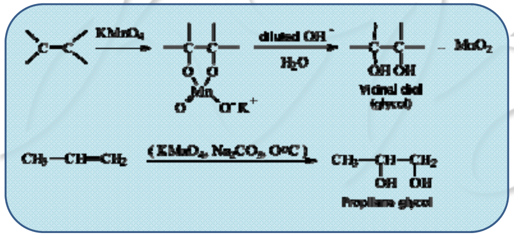
Dehydrogenation (-2H):

- Heat with Pt, Pd, S or Se
- Substituted quinones (**e.g. Chloranil**)



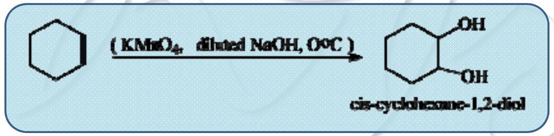
Oxidation of Ethylenic Double Bond and Aromatic Side Chain with $KMnO_4$

In dilute basic medium and in the cold (0-5ºC), $KMnO_4$ acts to dihydroxylate the double bond and glycols (1,2-diols) are formed.

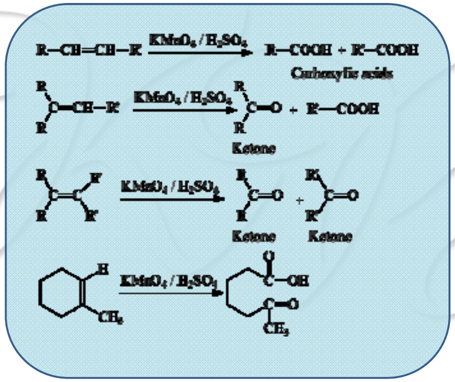


Oxidation of Ethylenic Double Bond and Aromatic Side Chain with $KMnO_4$

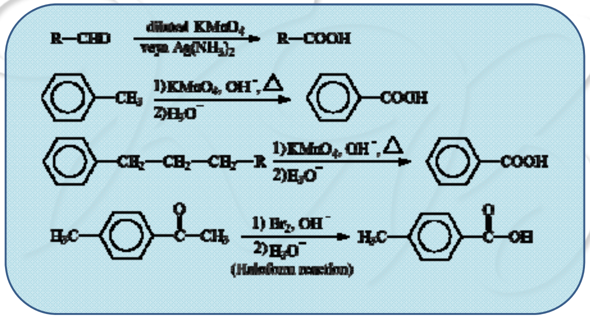
This reaction takes place as cis-addition in stereochemistry.
For example; cis-cyclohexane-1,2-diol is formed from cyclohexene.



The acidic permanganate solution leads to ketone or carboxylic acid formation breaking the double bond according to the environment of the double bond carbon...

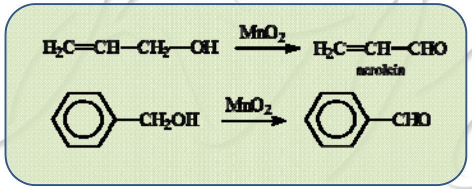


Oxidation in the side chain takes place in the benzylic carbone. Even if there are alkyl groups including multiple "C" atoms, it is always fragmented to benzoic acid...



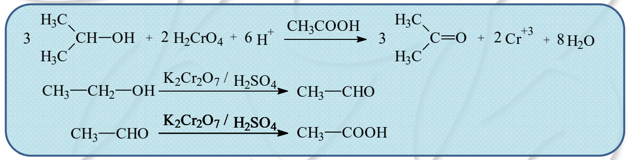
Moderate Oxidation with MnO_2

- Freshly prepared MnO_2 is used in one step oxidation of allylic and benzylic alcohols.
- MnO_2 → Mn^{++} is reduced and there is no oxidation to further steps.



Oxidation of the secondary alcohols with chromic acid (Obtaining of Acetone)

- Acetone is obtained by the addition Chromic acid (H_2CrO_4), CrO_3 or $Na_2Cr_2O_7$ to H_2SO_4. While Cr is reduced from **+6** to **+3**, related compound is oxidized.



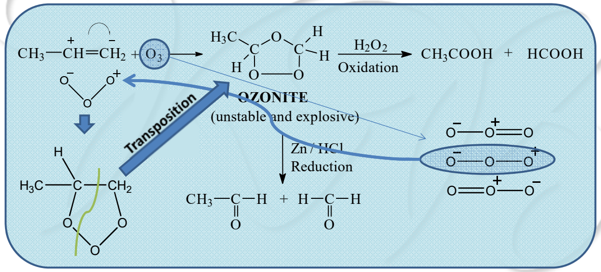
$$CH_3—CH_2—OH \xrightarrow{K_2Cr_2O_7 / H_2SO_4} CH_3—CHO$$

$$CH_3—CHO \xrightarrow{K_2Cr_2O_7 / H_2SO_4} CH_3—COOH$$

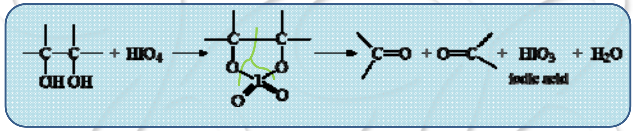
- **Other oxidation reagents including Cr (VI)**

  $Na_2Cr_2O_7$ (sodium bichromate), Na_2CrO_4 (sodium chromate), H_2CrO_4 (chromic acid), CrO_3 (chromic oxide), CrO_2Cl_2 (chromyl chloride)

Oxidation of ethylenic compounds with O_3
(Ozonolysis)

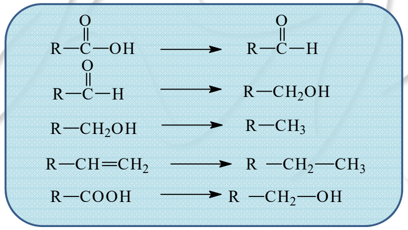


Oxidation with HIO_4 (Periodic Acid) in Vicinal Diols



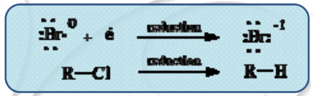
Reduction Reactions

- The reduction of an organic molecule can be defined as increase in the amount of hydrogen or decrease in the amount of oxygen. For example, the conversation of a carboxylic acid to aldehyde is the reduction. Because the amount of oxygen decreases.

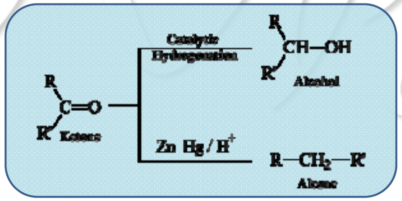


Reduction Reactions

- An increase in the amount of electrons of atom or ion; or a decrease in the value of a functional group is a reduction reactions.



- There are many reduction reagent depending on the substance to be reduced and the degree of reduction.



Applied in industrial and laboratory Reduction Reactions

- Hydrogen (H_2) can reduce = and ≡ bonds in the alcenes and alkynes in company with metallic catalyser as Pt, Pd or Ni, unsaturated bonds of carbonyl groups (C=O) and -NO_2 group.
- Nucleophilic hydride donors such as $LiAlH_4$, $NaBH_4$ etc. are more carbonyl derivatives reducing compounds without affecting ethylenic unsaturated bonds.
- The solutions of tin, iron, zinc metals with HCl are usually used for reduction of -NO_2 group to -NH_2 group.
- Reductions can also be made with ethanol / Na and 2-propanol / Al mixtures

Reduction Reagents

- **Catalytic hydrogenation:** H_2 + Pt, Pd or Ni
- **Hydrides:** $LiAlH_4$, AlH_3, $NaBH_4$, BH_3, R_2BH
- **Metals:** Li, Na, K, Zn, Mg
- **Others:** NH_2NH_2, R_3P:, SO_3^{-2}, $SnCl_2$, $FeCl_2$

Reduction of Alkyl Halides, Carboxylic acid and Derivatives with $LiAlH_4$

$LiAlH_4$ is a strong reduction reagent. It is used to reduce many functional groups except isolated carbon-carbon double and triple bonds. It is a hydride (H^-) source.

$LiAlH_4$ combines with all kinds of acidic proton and causes H_2 ↑ out. Dry ethers or tetrahydrofuran (THF) are used as solvants as they also cause H_2 ↑ out with water proton.

- **Preparation of hydrocarbons from halogenated derivatives:**

$$4\,H_2C{=}CH{-}CH_2Cl \xrightarrow{LiAlH_4} 4\,H_2C{=}CH{-}CH_3 \;+\; LiCl \;+\; AlCl_3$$

Preparation of Primary Amines by Action from Amides ve Nitriles

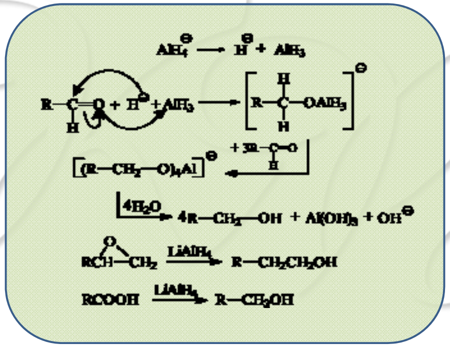
$$R{-}C{\equiv}N \xrightarrow{LiAlH_4} R{-}CH_2{-}NH_2$$

$$R{-}CONH_2 \xrightarrow{LiAlH_4} R{-}CH_2{-}NH_2$$

- $LiAlH_4$ is converted to alcohols by reducing R-CHO, R_2C=O, R-COOH, $RCH{-}CH_2$ (with O bridging), RCOOR, RCOCl molecules.

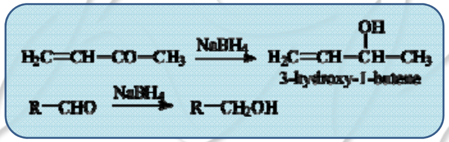
$$R{-}CHO \xrightarrow{LiAlH_4} R{-}CH_2OH$$

Reaction Mechanism of $LiAlH_4$



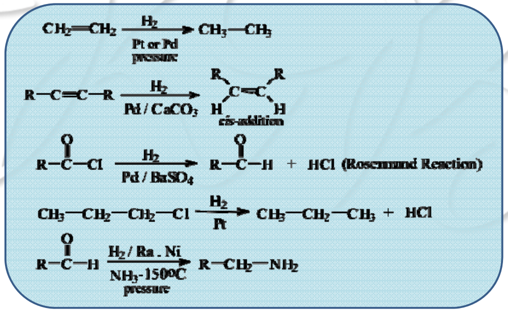
Reduction of Carbonyl Derivatives with $NaBH_4$

$NaBH_4$ is a weaker reduction agent than $LiAlH_4$. It is used to reduce aldehydes and ketones majorly. The reduction process with $NaBH_4$ can be carried out in an aqueous medium or alcohol.



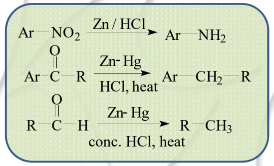
Catalytic Reduction (Hydrogenolysis)

Hydrogenolysis is called that is opened by hydrogen and a metal catalyser the bond in the ethylenic and acetylenic unsaturated structures and the bond between carbon and heteroatom. These metals are platinum (Pt), rutenium (Ru), palladium (Pd) and nickel (Ni).

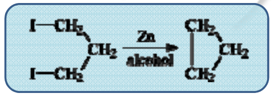


Examples of Reduction using Metal / Acid System

- It is used Zn, Fe, Sn / HCl, H_2SO_4 and $SnCl_2$, $FeSO_4$. When metal is treated with acid, the hydrogen gas is formed on the rise.

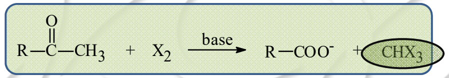


- Zn also reduces in aqueous and alcoholic medium.



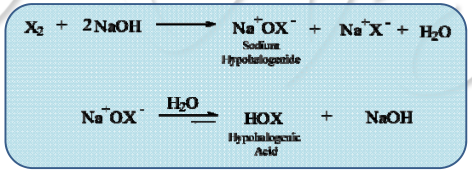
Haloform Reaction

- The halogenation of the α-C atom of many ketone compounds can be carried out in the form of total halogenation in a basic medium. So methyl ketones [CH_3-CO-] contain three halogen atoms in α-C and are formed trihalomethyl ketones.



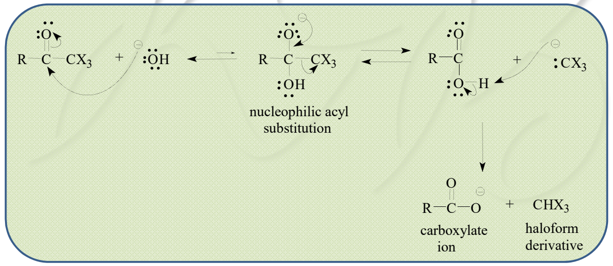
$$R-\overset{\overset{O}{\|}}{C}-CH_3 + X_2 \xrightarrow{\text{base}} R-COO^- + CHX_3$$

- The haloform reaction takes place via the hypohalogenide derivative of halogens in basic medium.



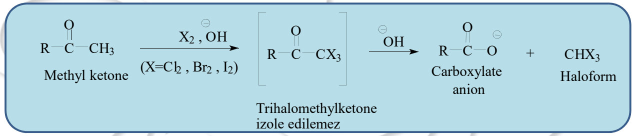
Reaction Mechanism

- The trihalomethyl group of the resulting compound forms a leaving group for the nucleophilic acyl substitution, resulting in the formation of the carboxylated aryl which is displaced by the basic OH⁻ group of the medium. However, the immediate rapid proton exchange completes the formation of the haloform derivative with the carboxylate anion.

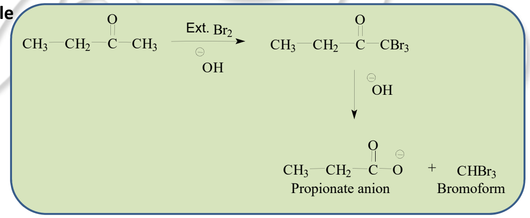


Haloform Reaction

- **General Reaction Equation**

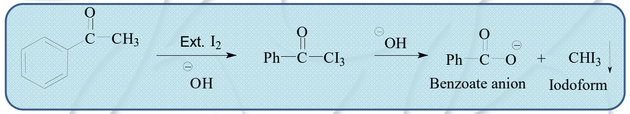


- **Example**

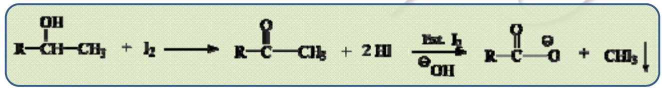


Haloform Reaction

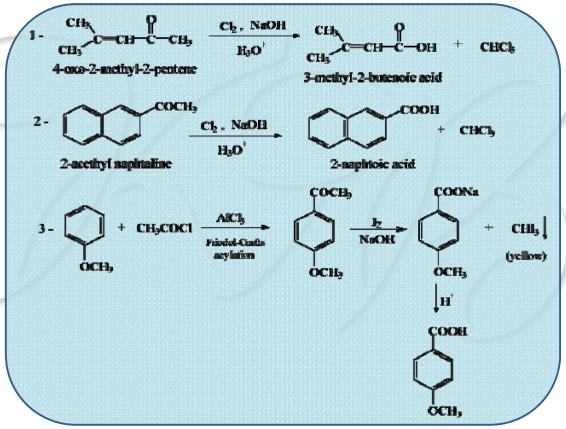
- When halogen is I_2, the haloform derivative (iodoform) is a solid compound which can be isolated in the form of a yellow precipitate. This reaction can also be used as a diagnostic reaction for methyl ketones with the so-called "iodoform test". However bromoform and chloroform are liquid and volatile. They can not be easily isolated from the reaction medium.



- Since I_2 is an oxidant, a positive iodoform test with alcohols is observed. Because first, the alcohol is oxidized to methyl ketone, followed by the haloform reaction.

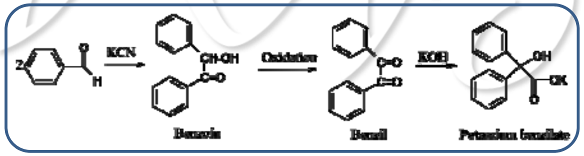


Example Haloform Reactions

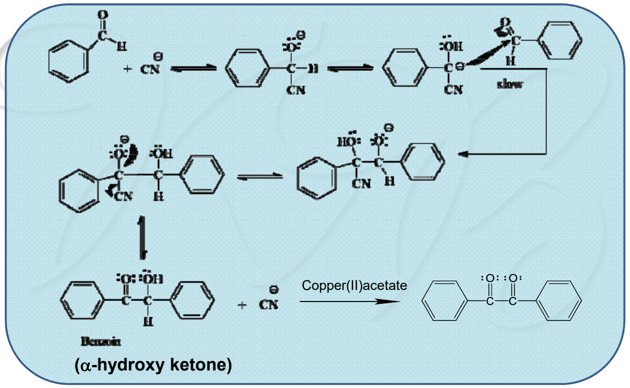


Benzilic Acid Synthesis

- Benzilic acid synthesis can be seen as a method of obtaining α-hydroxy carboxylic acid. The benzilic acid is synthesized by the action of benzaldehyde.
- When the benzaldehyde molecule is boiled with KCN in alcoholic medium, the two molecule benzaldehyde gives the benzoin molecule as a condensed molecule.
- Benzil molecule with α-diketone structure is formed by oxidation of benzoin. The benzilic acid salt is formed by the molecular rearrangement (**conversion reaction**) of this structure in the alkaline solution.

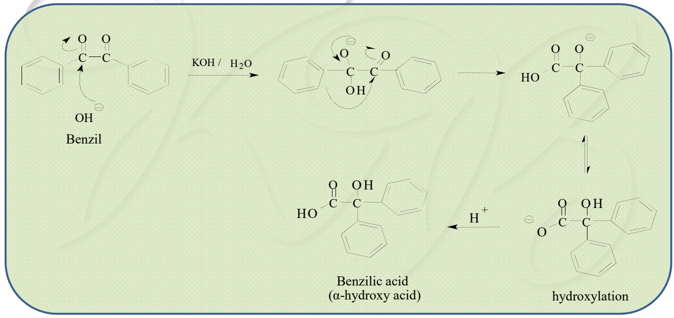


General Reaction Equation



(α-hydroxy ketone)

General Reaction Equation

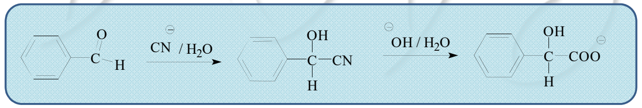


Benzilic acid
(α-hydroxy acid)

Benzilic Acid Synthesis (summary)

As a side product in the formation of benzoin:

- 1- Cannizaro product can be formed.
- 2- Cyanohydrine derivative can be formed. Hydrolysis of this derivative then gives α-hydroxy carboxylic acids.



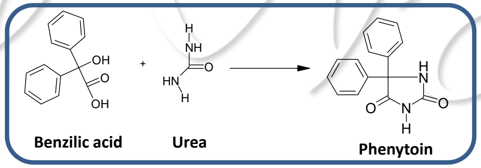
Benzilic Acid Synthesis (summary)

Many condensation reactions are generally catalyzed with bases. However, differently, the benzaldehyde is catalyzed with the cyanide ion using KCN. Benzyl gives benzilic acid, which is α-hydroxyl carboxylic acid, with strong bases. The reaction is carried out in hot and aqueous ethanolic medium with the aid of concentrated sodium or potassium hydroxide. In order for this reaction to occur;

- **Diketone is required.**
- **The yield decreases with the introduction of alkyl groups instead of phenyl.**
- **OH^- attack is toward carbonyl (C=O), which has less electron density.**
- **OH^- is not catalyser.**

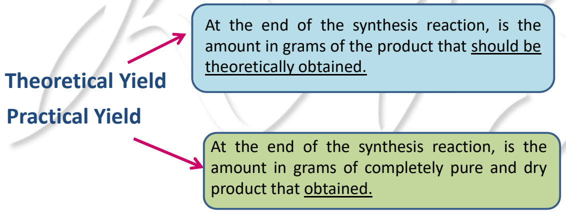
Transposition Conversion Reactions Rearrangement

- Conversion or transposition reactions are formed by a new arrangement in the molecule to form a more stable thermodynamic structure of the result molecule. As a result, when compared to the starting molecule, they are referred as transposition or conversion reactions to be rearrangement or a change in the molecule skeleton.
- The benzylic acid obtained in this way is a pharmaceutically important substance and is used, for example, in the synthesis of anticonvulsant (antiepileptic) drugs. For example; benzilic acid and urea are used in the synthesis of an anticonvulsant compound is called phenytoin.



Calculation of Yield in Synthesis Reactions

The yield of products produced in synthesis reactions of organic compounds is lower than calculated theoretically. For this reason,, **practical yield** must also be calculated besides **theoretical yield**.


Theoretical Yield

At the end of the synthesis reaction, is the amount in grams of the product that should be theoretically obtained.

Practical Yield

At the end of the synthesis reaction, is the amount in grams of completely pure and dry product that obtained.

Reasons why practical yield is lower than theoretical yield

- Reversibility of reactions.
- Başlangıç maddesinin, ürün yanında başka yan (parazit) reaksiyonlar vererek harcanması. Spending of the starting substance by giving other side (parasite) reactions beside the product.
- The reagents used are volatile and all of the calculated starting substance has not entered the reaction.
- The resulting product has side reactions due to some physical and chemical effects or decrease of the amount by decay up to be taken from the reaction medium.
- The reagents used are not in the desired purity.
- Mechanical losses that may occur during product purification.

Yield Calculation

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

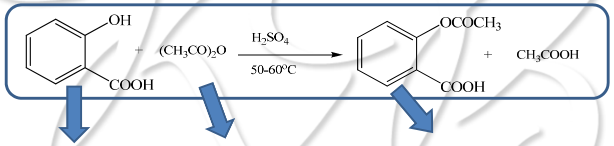
- When the yield calculation is made, it should be determined which of the starting substances is the Basic Substance.

Totally spent (consumed) substance by entering all into the reaction

- After the basic substance is detected, the yield calculation is made on this substance. Because, in order to be able to calculate the yield, the starting substance selected must be completely reacted so that mistakes are prevented.

Example 1 (Calculation of yield over **weight** in aspirin synthesis reaction)

1.3 g salicylic acid and 2 g (1.9 ml) acetic anhydride were reacted to yield 1.6 g aspirin. Calculate the yield of the reaction according to these data.



M.W. = 138.12 g/mole	M.W. = 102.09 g/mole	M.W. = 180.15 g/mole
1.3/138.12=0.0094 mole	2/102.09=0.0195 mole	1.6/180.15=0.0089 mole

Solution

All of 0.0094 mol substance react, so **salicylic acid is** **basic substance**. Yield calculation is made over this substance.

Calculation of theoritical yield:

From 138.12 g salicylic acid — 180.15 g Aspirin is obtained
From 1.3 g salicylic acid — X g Aspirin is obtained

X= 1.3 x 180.15 / 138.12 = 1.69 g =**Theoretical yield**
The amount obtained in practice = 1.6 g =**Practical yield**

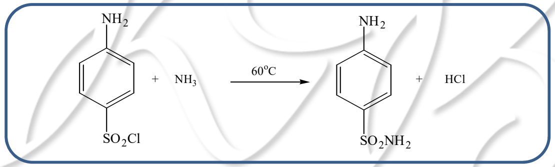
1.69 g product — %100
1.6 g product — % X

X = 1.6 x 100 / 1.69 = %94.6

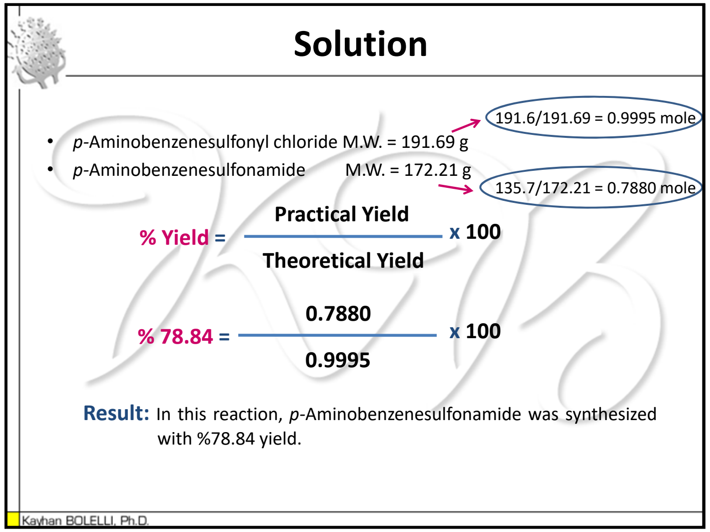
Result : In this reaction, aspirin was synthesized with %94.6 yield.

Example 2 (Calculation of yield over **mole** in *p*-aminobenzenesulfonamide synthesis reaction)

191.6 g *p*-aminobenzenesulfonyl chloride and 500 ml ammonia were reacted to yield 135.7 g *p*-aminobenzenesulfonamide. Calculate the yield of the reaction according to these data.



p-Aminobenzenesulfonyl chloride	*p*-Aminobenzenesulfonamide
M.W. = 191.69 g	**M.W. = 172.21 g**



Solution

- *p*-Aminobenzenesulfonyl chloride M.W. = 191.69 g
- *p*-Aminobenzenesulfonamide M.W. = 172.21 g

191.6/191.69 = 0.9995 mole

135.7/172.21 = 0.7880 mole

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

$$\% \, 78.84 = \frac{0.7880}{0.9995} \times 100$$

Result: In this reaction, *p*-Aminobenzenesulfonamide was synthesized with %78.84 yield.