Organic Reaction Mechanisms-I

Section (A): Electrophile, Nucleophile, Nucleophilicity, Leaving group ability & Solvent

An organic reaction can be represented as

Reactant (substrate) + Reagent $\xrightarrow{\text{solvent}}$ Product

Types of bond dissociation :

All reactions are initiated with bond dissociation. There are two types of bond dissociation.

(a) **Homolytic bond dissociation :** A bond dissociation in which a bond pair electron is equally distributed to the bonding atoms.

e.g., $A–B \longrightarrow A^{\bullet} + B^{\bullet}$

A homolytic bond dissociation generates radicals.

(b) **Hetrolytic bond dissociation :** A bond dissociation in which a bond pair electron is shifted to one atom only.

e.g., $A–B \longrightarrow A^{\oplus} + B^{\ominus}$

A hetrolytic bond dissociation always generate a cation and an anion.

Types of reagents :

A reagent generates three type of attacking species. Which are :

(a) Electrophiles (b) Nucleophiles (c) Radicals

(a) **Electrophiles :** Electrophiles are electron deficient species. Which can accept a pair of electron.

e.g. $\overset{\oplus}{H}$, $\overset{\oplus}{Cl}$, $\overset{\oplus}{Br}$, $\overset{\oplus}{NO_2}$, $\overset{\oplus}{CH_3}$ (positively charged species), PCl_5, SO_2, SO_3 BH_3(species with vacant orbital at central atom) carbenes etc.

(b) **Nucleophiles :** Nucleophiles are electron rich species having atleast one unshared pair of electron. It can be neutral or negativetely charged. It is always a lewis base.

e.g. CN^-, OH^-, Br^- , I^- , $\ddot{N}H_3$, $H_2\underset{\cdot\cdot}{\ddot{O}}$ etc.

(c) **Radicals :** It is an electron deficient species with odd electron around an atom.

e.g. $\dot{C}H_3$, $C_2H_5^{\bullet}$, $C_2H_5O^{\bullet}$, $CH_3COO^{\bullet}$, $X^{\bullet}$ etc.

Nucleophilicity :

The tendency to give e^- pair to an electron deficient carbon atom is defined as nucleophilicity.

(i) **Criteria for Nucleophilicity :**

1. The factors which increases e^- density at donor atom increases nucleophilicity.
2. The more polarisable donor atom is the better nucleophile. Therefore size of donor atom increases nucleophilicity also increases.

(ii) **Periodicity :**

Nucleophilicity decreases from left to right in a period.

$:CH_3^{\ominus} > :NH_2^{\ominus} > :OH^{\ominus} > :F^{\ominus}$

∴ In a group, nucleophilicity increases from top to bottom because size of donor atom increases but basicity decreases from top to bottom.

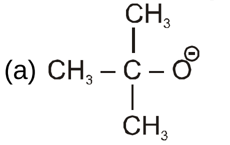
Acidic strength : $HI > HBr > HCl > HF$

Basic strength : $F^- > Cl^- > Br^- > I^-$

Nucleophilicity : $F^- < Cl^- < Br^- < I^-$

(iii) **Nucleophilicity of halogenes in polar aprotic solvents :** $F^- > Cl^- > Br^- > I^-$

(iv) Steric effects on nucleophilicity

(a) 

$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-O^{\ominus}$

t-butoxide ion

(b) $CH_3-CH_2-\overset{\ominus}{O}$

ethoxide ion

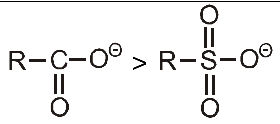
Note : Because (a) can not approach to carbon atom easily.
So, nucleophilicity order is : (b) > (a) and basicity order is : (a) > (b)

Ambident nucleophile :

The species which have more than one nucleophilic site for reaction are called ambident nucleophiles.

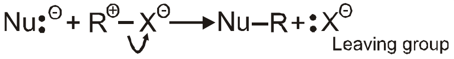
Example : $\overset{\ominus}{C}N$, $NO_2^{\ominus}$, $\overset{\ominus}{O}-CH=S$

Comparision between Nucleophilicity & Basicity :

	Nucleophilicity	**Basicity**	**Remarks**
1	$CH_3^- > NH_2^- > OH^- > F^-$	$CH_3^- > NH_2^- > OH^- > F^-$	If donor atoms belong to same period, then nucleophilicity and basicity order is same
2	$SiH_3^- > PH_2^- > SH^- > Cl^-$	$SiH_3^- > PH_2^- > SH^- > Cl^-$	" " "
3	$F^- < Cl^- < Br^- < I^-$	$F^- > Cl^- > Br^- > I^-$	Down the group nucleophilicity increases while basicity decreases.
4	$OH^- < SH^-$	$OH^- > SH^-$	" " "" " "
5	$RO^- < RS^-$	$RO^- > RS^-$	" " "
6	$RO^- > HO^-$	Same	If donor atom is same, then generally nucleophilicity and basicity order is also same.
7	$RCOO^- < PhO^- < HO^- < RO^-$	Same	" " "
8	 $R-\underset{O}{\overset{\|}{C}}-O^{\ominus} > R-\overset{O}{\underset{O}{S}}-O^{\ominus}$ Tetrahedral (more extensive resonance) [dπ–pπ bonds]	Same	" " "
9	$HO^- > H_2O$	Same	
10	$NH_2^- > NH_3$	Same	
11	$CF_3SO_3^- < PhCOO^- < PhO^- < RO^-$	Same	

Leaving group ability/Nucleofugality :

Weaker bases are always good leaving groups / nucleofuse. A good leaving group always stabilize the transition state and lowers its energy of activation hence increases the rate of the reaction.



$Nu:^{\ominus} + R^{\oplus}-X^{\ominus} \longrightarrow Nu-R + :X^{\ominus}$

Leaving group

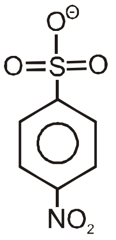
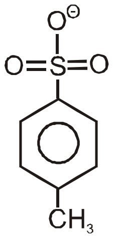
(a) Order of leaving group ability.

1. $\overset{\ominus}{I} > \overset{\ominus}{Br} > \overset{\ominus}{Cl} > \overset{\ominus}{F}$

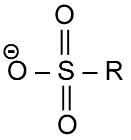
2. $CH_3^- < NH_2^- < OH^- < F^-$

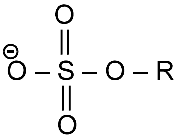
3. $R-COO^- > PhO^- > HO^- > RO^-$

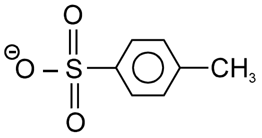
4. $SH^- > OH^-$

5.  > 

6. Other good leaving groups are

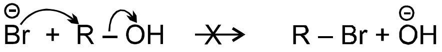

Alkanesulphonate ion

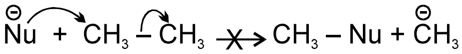

Alkyl sulphate ion


Tosylate ion ($\overset{\ominus}{OTs}$)

$CF_3SO_3^{\ominus}$
Triflate ion
(a super leaving group)

Note : (i) Strong bases rarely act as leaving group →

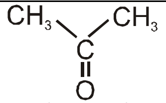
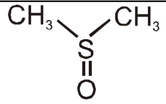
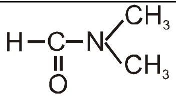
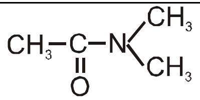
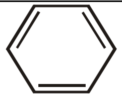
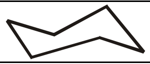

$\overset{\ominus}{Br} + R-OH \not\rightarrow R-Br + \overset{\ominus}{O}H$ (Strong base / poor leaving group)


$\overset{\ominus}{Nu} + CH_3-CH_3 \not\rightarrow CH_3-Nu + \overset{\ominus}{C}H_3$ (It is not a leaving group)

(ii) The leaving group should have lower bond energy with carbon.
(iii) Negative charge should be more stable either by dispersal or declocalization.

Types of solvents :

(a) Non polar solvents
(b) Polar solvents (i) polar protic (ii) polar aprotic
(i) Polar protic : A polar solvent which has acidic hydrogen.
(ii) Polar aprotic : A polar solvent which does not have acidic hydrogen.

	Solvents	**Polar**	**Protic**	**Aprotic**	**Remarks**
1.	H_2O	✓	✓	–	Polar protic solvent
2.	CH_3OH	✓	✓	–	Polar protic solvent
3.	CH_3CH_2OH	✓	✓	–	Polar protic solvent
4.	H–COOH	✓	✓	–	Polar protic solvent
5.	CH_3–COOH	✓	✓	–	Polar protic solvent
6.	NH_3	✓	✓	–	Polar protic solvent
7.	 (acetone)	✓	×	✓	Polar aprotic solvent
8.	 Dimethyl sulphoxide	✓	×	✓	Polar aprotic solvent
9.	 Dimethyl formamide	✓	×	✓	Polar aprotic solvent
10.	 Dimethyl acetamide	✓	×	✓	Polar aprotic solvent
11.		×	×	✓	Non-polar solvent
12.		×	×	✓	Non-polar solvent
13.	$CH_3–CH_2–CH_2–CH_2–CH_3$	×	×	✓	Non-polar solvent

Section (B) : Types of organic reactions and reactions of acidic hydrogen

Compounds having reactive or acidic hydrogen gives acid base reaction.

(i) Reaction with metals : $CH_3COOH + Na \longrightarrow CH_3COONa + ½ H_2$

(ii) Reaction with alkalies : $CH_3COOH + NaOH \longrightarrow CH_3COONa + H_2O$

(iii) Reaction with bicarbonates : $CH_3COOH + NaHCO_3 \longrightarrow CH_3COONa + CO_2\uparrow + H_2O$

(iv) Reaction with NaH : $CH_3COOH + NaH \longrightarrow CH_3COONa + H_2$

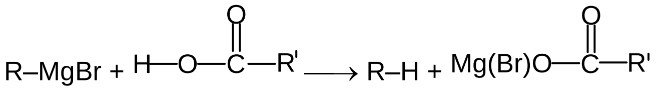
(v) Reaction with Grignard reagent :

$R\text{–}MgBr + Z\text{–}H \longrightarrow R\text{–}H + Mg(Br)Z$

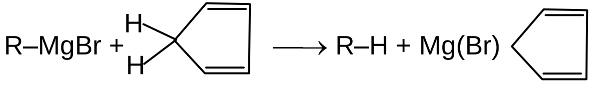
$R\text{–}MgBr + H\text{–}OH \longrightarrow R\text{–}H + Mg(Br)OH$

$R\text{–}MgBr + H\text{–}NHR' \longrightarrow R\text{–}H + Mg(Br)NHR'$

$R\text{–}MgBr + H\text{–}C\equiv C\text{–}R' \longrightarrow R\text{–}H + Mg(Br)C\equiv C\text{–}R'$



$R\text{–}MgBr + H\text{—}O\text{—}\overset{O}{\overset{\|}{C}}\text{—}R' \longrightarrow R\text{–}H + Mg(Br)O\text{—}\overset{O}{\overset{\|}{C}}\text{—}R'$

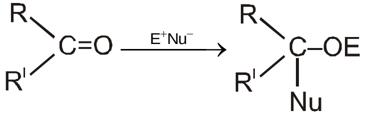


Section (C) : Nucleophilic addition reactions of carbonyl compounds

It is a characteristic reaction of carbonyl compounds (aldehydes and ketones).

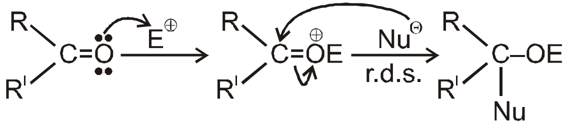
This reaction involves addition of a nuceophile and a electrophile across the (C=O) double bond.

The general nucleophilic addition reaction can be represented as followed :

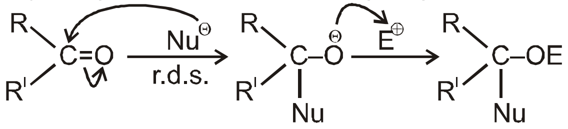


The mechanism can be carried out in following two manners.

(a) Acid catalysed (first attack is of electrophile)



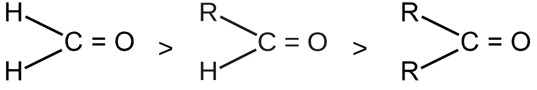
(b) Base catalysed (first attack is of nucleophile)



Acid catalysed nucleophilic addition is generally faster than base catalysed.

The reactivity of the carbonyl group arises from the electronegativity of the oxygen atom and the resulting polarization of the carbon-oxygen double bond. The electrophilic carbonyl carbon atom is sp^2 hybridized and flat, hence it is relatively unhindered and open to attack from either face of the double bond.

Reactivity : Aldehydes are more reactive than ketones in nucleophilic addition reactions.



There are two factors which influence the reactivity of ketone and aldehyde.

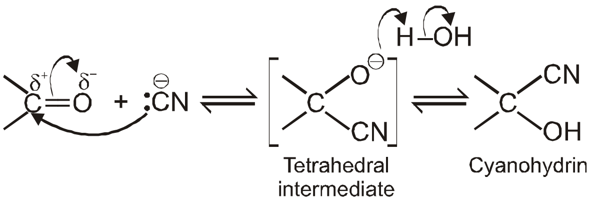
(i) Inductive effect (ii) steric factor

(i) + I effect of alkyl group decrease the amount of charge on C^+ ($C^+\text{–}O^-$) in ketones.

(ii) Steric effect also causes the less reactivity of carbonyl group.

(i) Addition of hydrogen cyanide (HCN)

$HCN + OH^- \longleftrightarrow :\overset{-}{C}N + H_2O$



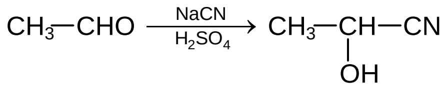
Note : (i) Addition of HCN over aldehyde and ketones gives cyanohydrin.

(ii) Cyanohydrin on acid hydrolysis gives α-hydroxy acid.

(iii) Cyanohydrin on treating with $NH_3(l)$ followed by acid hydrolysis gives α-amino acid.

(iv) In case of ketone cyanohydrin formation is reversible due to bulky groups of ketone which hinder the formation.

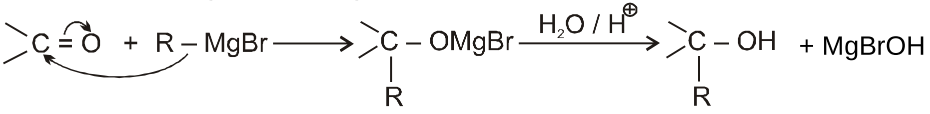
e.g.



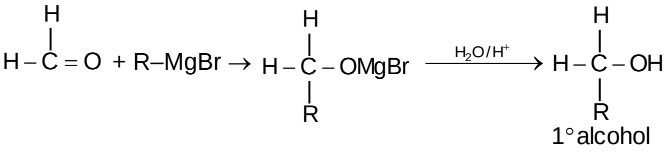
$$CH_3-CHO \xrightarrow[H_2SO_4]{NaCN} CH_3-\underset{\displaystyle OH}{\underset{|}{C}H}-CN$$

Acetaldehyde Cyanohydrin

(ii) Addition of Grignard reagent :



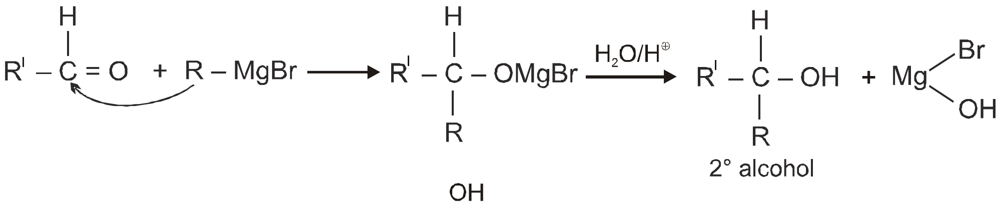
(a) When formaldehyde is treated with Grignard reagent followed by acid hydrolysis primary alcohol is obtained.



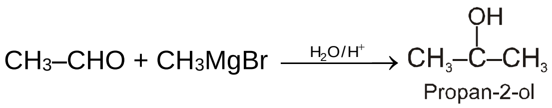
e.g. $HCHO + CH_3MgBr \xrightarrow{H_2O/H^+} CH_3-CH_2-OH$

Ethanol

(b) When aldehyde except formaldehyde is treated with Grignard reagent followed by hydrolysis 2° alcohol is obtained.



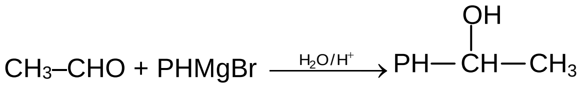
e.g.



$$CH_3\text{–}CHO + CH_3MgBr \xrightarrow{H_2O/H^+} CH_3\text{–}\overset{\displaystyle OH}{\overset{|}{C}}\text{–}CH_3$$

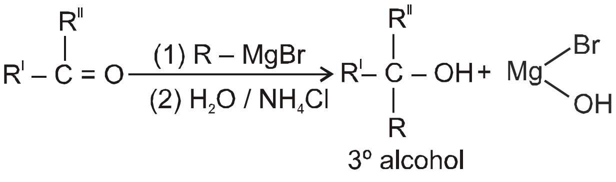
Propan-2-ol

e.g.

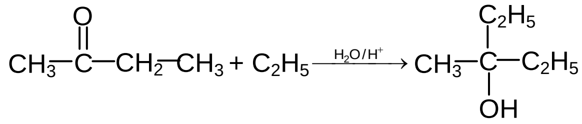


$$CH_3\text{–}CHO + PHMgBr \xrightarrow{H_2O/H^+} PH-\overset{\displaystyle OH}{\overset{|}{C}H}-CH_3$$

(c) When ketone is treated with Grignard reagent followed by acid hydrolysis 3° alcohol is obtained.



e.g.

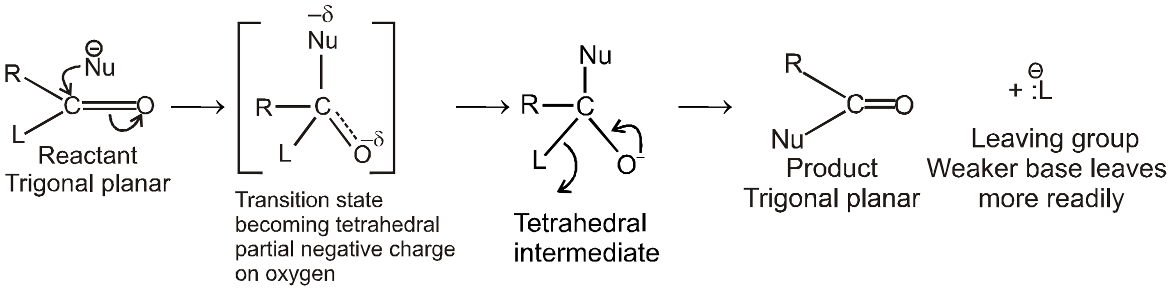


$$CH_3-\overset{O}{\overset{||}{C}}-CH_2-CH_3 + C_2H_5 \xrightarrow{H_2O/H^+} CH_3-\underset{OH}{\overset{C_2H_5}{C}}-C_2H_5$$

3-Methylpentan-3-ol

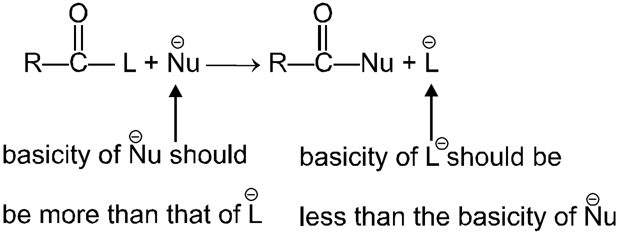
Section (D) : Bimolecular nucleophilic substitution reaction with tetrahedral intermediate (S_N2Th)

Characteristic reaction of acid and it's derivatives (acid halide, anhydride, ester and amide) is S_N2Th. Nucleophilic acyl substitution usually takes place by an **addition-elimination** mechanism.The incoming nucleophile adds to the carbonyl to form a tetrasubstituted intermediate with a tetrahedral carbon.



The tetrahedral intermediate formed, when a nucleophile attacks the carbonyl carbon of a carboxylic acid derivative, is not stable and can not be isolated.

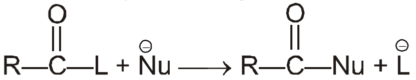
A pair of nonbonding electrons on the oxygen reforms the π bond, and either $L^\ominus$ or $Nu^\ominus$ is eliminated with its bonding electrons. Whether $L^\ominus$ or $Nu^\ominus$ is eliminated depends on their relative basicities. The weaker base is preferentially eliminated because the weaker base is the better leaving group.



$$R-\overset{O}{\overset{||}{C}}-L + \overset{\ominus}{Nu} \longrightarrow R-\overset{O}{\overset{||}{C}}-Nu + \overset{\ominus}{L}$$

Thus carboxylic acid derivatives will undergo a nucleophilic acyl substitution reaction provided that the incoming nucleophile is a stronger base than the group that is to be replaced. If the incoming nucleophile and the group attached to acyl group in the starting material have similar basicities, the tetrahedral intermediate can expect either group with similar ease. A mixture of starting material and substitution product will result.

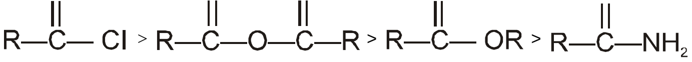
Conditions for acyl nucleophilic substitution reactions :



$$R-\overset{O}{\overset{||}{C}}-L + \overset{\ominus}{Nu} \longrightarrow R-\overset{O}{\overset{||}{C}}-Nu + \overset{\ominus}{L}$$

(i) $L^\ominus$ must be better leaving group than $Nu^\ominus$, i.e., basicity of $Nu^\ominus$ should be more than that of $L^\ominus$.
(ii) $Nu^\ominus$ must be a strong enough nucleophilic to attack RCOL.
(iii) Carbonyl carbon must be enough electrophilic to react with $Nu^\ominus$.

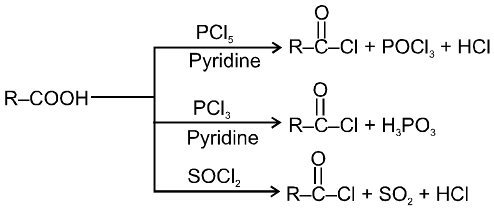
Reactivity order :



$$R-\overset{O}{\overset{||}{C}}-Cl > R-\overset{O}{\overset{||}{C}}-O-\overset{O}{\overset{||}{C}}-R > R-\overset{O}{\overset{||}{C}}-OR > R-\overset{O}{\overset{||}{C}}-NH_2$$

(a) S_N2Th Reaction of carboxylic acid :

(i) Formation of acid chlorides :



$$\mathrm{R{-}COOH} \xrightarrow[\text{Pyridine}]{PCl_5} \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}Cl} + POCl_3 + HCl$$

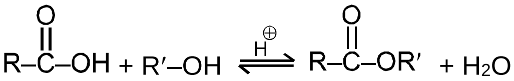
$$\mathrm{R{-}COOH} \xrightarrow[\text{Pyridine}]{PCl_3} \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}Cl} + H_3PO_3$$

$$\mathrm{R{-}COOH} \xrightarrow{SOCl_2} \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}Cl} + SO_2 + HCl$$

(ii) Fisher's Esterification :

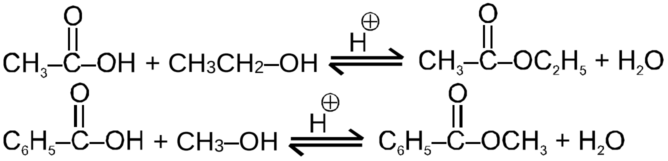
Carboxylic acids reacts with alcohol to form esters through a condensation reaction known as esterification.

General Reaction :



$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OH} + \mathrm{R'{-}OH} \overset{\overset{\oplus}{H}}{\rightleftharpoons} \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OR'} + H_2O$$

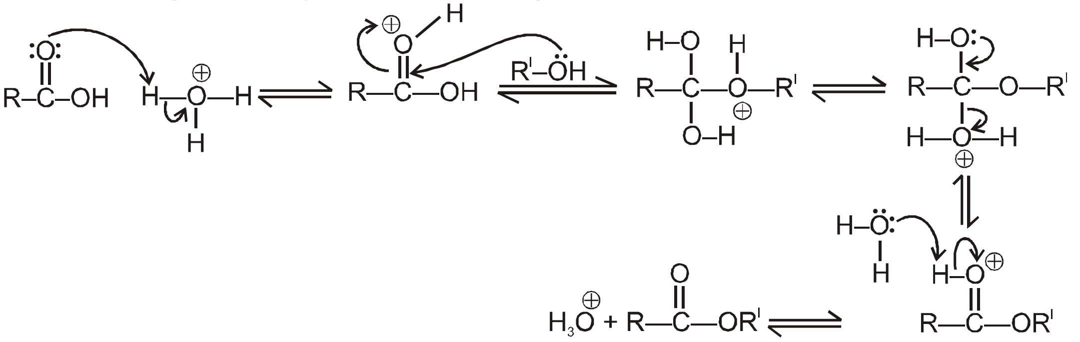
Specific Examples:



$$\mathrm{CH_3{-}\overset{O}{\overset{\|}{C}}{-}OH} + \mathrm{CH_3CH_2{-}OH} \overset{\overset{\oplus}{H}}{\rightleftharpoons} \mathrm{CH_3{-}\overset{O}{\overset{\|}{C}}{-}OC_2H_5} + H_2O$$

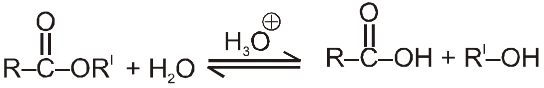
$$\mathrm{C_6H_5{-}\overset{O}{\overset{\|}{C}}{-}OH} + \mathrm{CH_3{-}OH} \overset{\overset{\oplus}{H}}{\rightleftharpoons} \mathrm{C_6H_5{-}\overset{O}{\overset{\|}{C}}{-}OCH_3} + H_2O$$

Mechanism : (Acid catalysed esterification)



If we follow the forward reactions in this mechanism, we have the mechanism for the acid catalysed esterification of an acid. If however, we follow the reverse reactions, we have the mechanism for the acid catalysed hydrolysis of an ester.

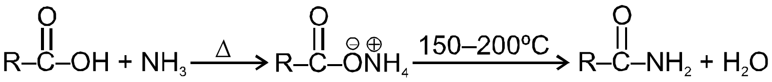
Acid catalysed ester hydrolysis.



$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OR'} + H_2O \overset{H_3\overset{\oplus}{O}}{\rightleftharpoons} \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OH} + \mathrm{R'{-}OH}$$

Which result we obtain will depend on the conditions we choose. If we want to esterify an acid, we use an excess of the alcohol and, if possible remove the water as it is formed. If we want to hydrolyse an ester, we use a large excess of water that is we reflux the ester with dilute aqueous HCl or dilute aqueous H_2SO_4.

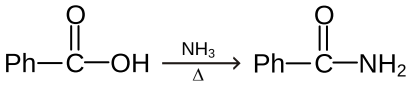
(iii) Formation of amides :



$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OH} + NH_3 \xrightarrow{\Delta} \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\overset{\ominus}{O}\overset{\oplus}{N}H_4} \xrightarrow{150\text{–}200^{\circ}C} \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}NH_2} + H_2O$$

In fact amides can not be prepared from carboxylic acids and amines unless the ammonium salt is heated strongly to dehydrate it. This is not usually a good method of preparing amides.

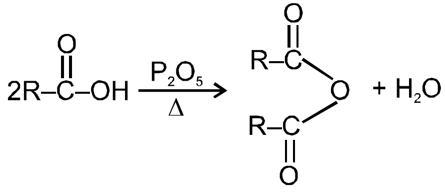
e.g.



$$\mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}OH} \xrightarrow[\Delta]{NH_3} \mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}NH_2}$$

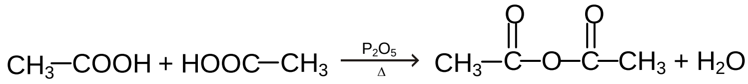
Benzoic acid Benzamide

(iv) Formation of acid anhydride :



$$2R-\overset{\overset{O}{\|}}{C}-OH \xrightarrow[\Delta]{P_2O_5} (R-\overset{\overset{O}{\|}}{C})_2O + H_2O$$

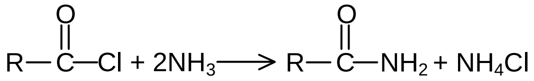
e.g.



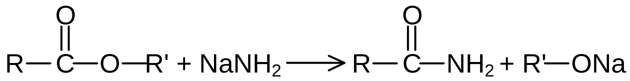
$$CH_3-COOH + HOOC-CH_3 \xrightarrow[\Delta]{P_2O_5} CH_3-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-CH_3 + H_2O$$

(b) S_N2Th Reaction of acid derivatives :

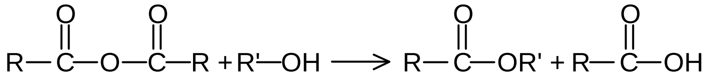
(i) Conversion of acid derivatives to other acid derivatives.



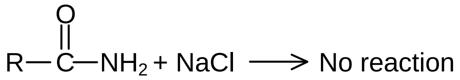
$$R-\overset{\overset{O}{\|}}{C}-Cl + 2NH_3 \longrightarrow R-\overset{\overset{O}{\|}}{C}-NH_2 + NH_4Cl$$



$$R-\overset{\overset{O}{\|}}{C}-O-R' + NaNH_2 \longrightarrow R-\overset{\overset{O}{\|}}{C}-NH_2 + R'-ONa$$



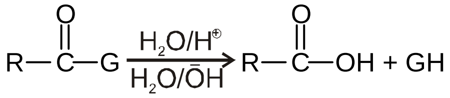
$$R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R + R'-OH \longrightarrow R-\overset{\overset{O}{\|}}{C}-OR' + R-\overset{\overset{O}{\|}}{C}-OH$$



$$R-\overset{\overset{O}{\|}}{C}-NH_2 + NaCl \longrightarrow \text{No reaction}$$

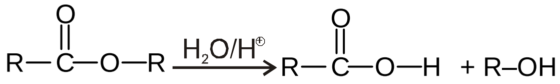
Note: An S_N2Th reaction is feasible when nucleophile is more basic than the leaving group.

(ii) Hydrolysis of acid derivatives :



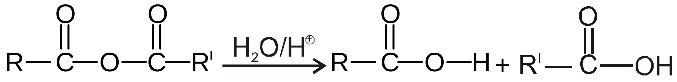
$$R-\overset{\overset{O}{\|}}{C}-G \xrightarrow[H_2O/\overset{-}{O}H]{H_2O/H^{\oplus}} R-\overset{\overset{O}{\|}}{C}-OH + GH$$

e.g.



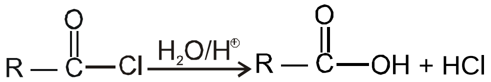
$$R-\overset{\overset{O}{\|}}{C}-O-R \xrightarrow{H_2O/H^{\oplus}} R-\overset{\overset{O}{\|}}{C}-O-H + R-OH$$

e.g.



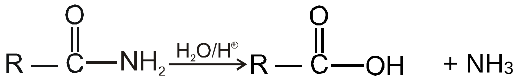
$$R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R' \xrightarrow{H_2O/H^{\oplus}} R-\overset{\overset{O}{\|}}{C}-O-H + R'-\overset{\overset{O}{\|}}{C}-OH$$

e.g.



$$R-\overset{\overset{O}{\|}}{C}-Cl \xrightarrow{H_2O/H^{\oplus}} R-\overset{\overset{O}{\|}}{C}-OH + HCl$$

e.g.



$$R-\overset{\overset{O}{\|}}{C}-NH_2 \xrightarrow{H_2O/H^{\oplus}} R-\overset{\overset{O}{\|}}{C}-OH + NH_3$$

Note: Hydrolysis of amides and esters are not possible in neutral medium.