Organic Reaction Mechanisms-III

Nucleophilic substitution reaction (S_N) :

Replacement (displacement) of an atom or group by an other atom or group in a molecule is known as substitution reaction. If substitution reaction is brought about by a nucleophile then it is known as nucleophilic substitution reaction. Generally substitution takes place at sp^3 carbon.

$R–\ell g + Nu^- \longrightarrow R–Nu + \ell g^-$

Types of nucleophilic substitution reaction :

(I) S_N1 (II) S_N2 (III) S_Ni

Section (A) : Unimolecular nucleophilic substitution reaction (S_N1)

Nucleophilic substitution which involves two step process

(a) **First step :** Slow step which involves ionisation (to form carbocation)

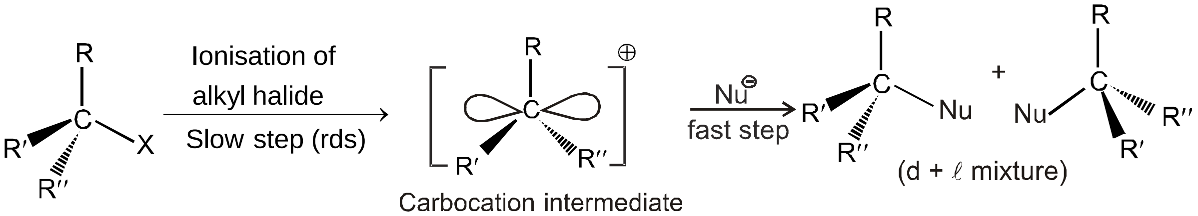
$R–\ell g \longrightarrow R^+ + \ell g^-$

(b) **Second step :** Fast attack of nucleophile on carbocation results into product.

$R^+ + Nu^- \longrightarrow R–Nu$

(1) S_N1 Reaction of Alkyl halide

Mechanism :



Characteristics of S_N1 reactions :

1. It is unimolecular, two step process.
2. Carbocation intermediate is formed, so rearrangement is possible in S_N1 reaction.
3. It is first order reaction.

4. Kinetics of the reaction Rate ∝ [Alkyl halide]

Rate of S_N1 reaction is independent of concentration and reactivity of nucleophile.

5. Energetics of the S_N1 reaction :

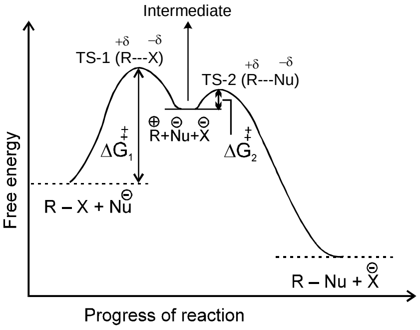


Figure : Free energy diagram for the S_N1 reaction.

6. Factors affecting the rate of S_N1 reaction :

(i) The structure of the substrate : The rds of the S_N1 reaction is ionization step, a carbocation is formed in this step. This ionisation is strongly endothermic process, rate of S_N1 reaction depends strongly on carbocation stability because carbocation is the intermediate of S_N1 reaction which determines the energy of activation of the reaction.

Reactivity of S_N1 ∝ stability of carbocation.

S_N1 reactivity : 3° > 2° > 1° > CH_3–X

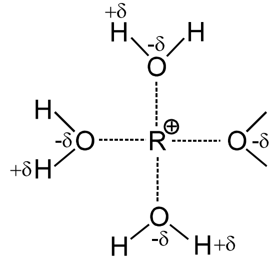
(ii) Concentration and reactivity of the nucleophile : The rate of S_N1 reaction is unaffected by the concentration and nature of the nucleophile.
Weak and neutral nucleophile favours S_N1 reaction.
Mostly solvents (protic) itself functions as nucleophiles in S_N1 reaction, so S_N1 reaction is termed as solvolysis reaction.

water → hydrolysis ; C_2H_5OH → ethanolysis
CH_3COOH → acetolysis ; NH_3 → ammonolysis

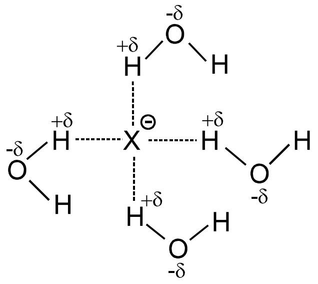
(iii) Effect of the solvent : (Ionising ability of the solvent)
The use of a polar protic solvent will greatly increase the rate of ionisation of an alkyl halide in any S_N1 reaction because it solvate cations and anions so effectively and stabilises the transition state leading to the intermediate carbocation and halide ion, thus the energy of activation is lower.

$$R - X \rightleftarrows \overset{\oplus}{R} + \overset{\ominus}{X} \quad \text{(Solvolysis)}$$

Solvated ions



Solvolysis



Solvated ions

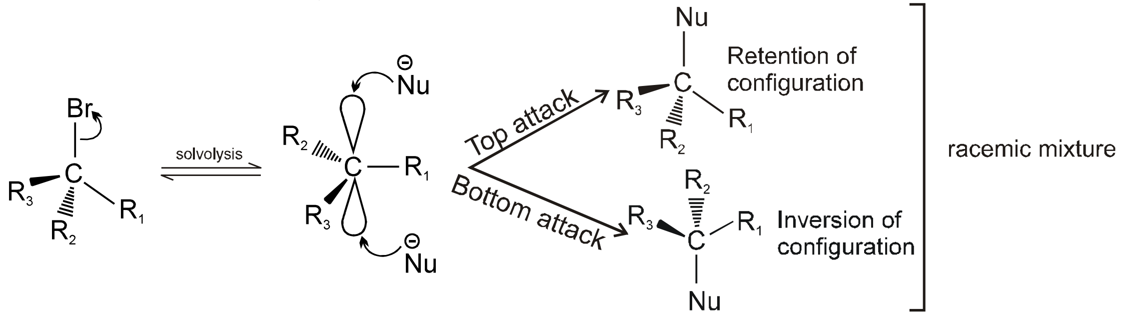
Table : Dielectric constants (∈) and ionisation rate of t-Butylchloride in few common solvents

Solvent	∈	**Relative rate**
H_2O	80	8000
CH_3OH	33	1000
C_2H_5OH	24	200
$(CH_3)_2CO$	21	1
CH_3CO_2H	6	–

(iv) The nature of the leaving group : In the S_N1 reaction the leaving group begins to acquire a negative charge as the transition state is reached` stabilisation of this developing negative charge at the leaving group stabilises the transition state and this lowers the free energy of activation and there by increases the rate of reaction. Leaving ability of halogen is $F^- < Cl^- < Br^- < I^-$

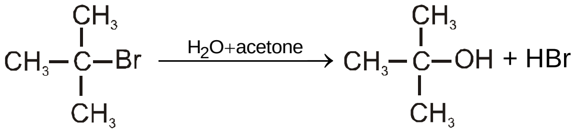
7. Stereochemistry of S_N1 reactions : In the S_N1 mechanism, the carbocation intermediate is sp^2 hybridized and planar, A nucleophile can attack on the carbocation from either face, if reactant is chiral then attack of nucleophile from both faces gives enantiomers as the product, which is called racemisation.

Mechanism of racemisation (S_N1) :



Reagents for alkyl halide are : H_2O , RCOOH , ROH & RSH

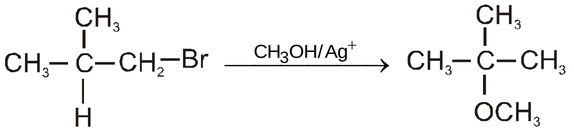
Ex-1.



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-Br \xrightarrow{H_2O+acetone} CH_3-\underset{CH_3}{\overset{CH_3}{C}}-OH + HBr$$

(3° alkyl halide hence no S_N2 reaction)

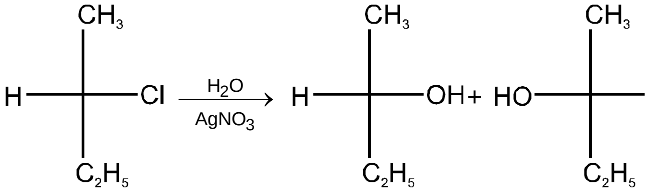
Ex-2.



$$CH_3-\underset{H}{\overset{CH_3}{C}}-CH_2-Br \xrightarrow{CH_3OH/Ag^+} CH_3-\underset{OCH_3}{\overset{CH_3}{C}}-CH_3$$

(carbocation rearrangement)

Ex-3.



(Racemic product)

(2) S_N1 Reaction of Alcohols

(i) Reaction with hydrogen halides

A common method is to treat the alcohol with a hydrohalic acid, usually HI or HBr. These acids are used to convert alcohols into the corresponding alkyl halides.

(i) In acidic solution, an alcohol is in equilibrium with its protonated form. Protonation converts the hydroxy group from a poor leaving group $(OH)^{\ominus}$ into a good leaving group (H_2O). If the alcohol is protonated all the usual substitution and elimination reactions are feasible, depending on the structure (1°, 2°, 3°) of the alcohol.

(ii) Halides are anions of strong acids, so they are weak bases. Solutions of HBr and HI contain nucleophilic $Br^{\ominus}$ and $I^{\ominus}$ ions.

(iii) Concentrated hydrobromic acid rapidly converts t-Butyl alcohol to t-Butyl bromide. The strong acid protonates the hydroxyl group, converting it into a good leaving group. The hindered tertiary carbon atom cannot undergo S_N2 displacement, but it can ionise to a tertiary carbocation. Attack by bromide ion gives the alkyl bromide. The mechanism is similar to S_N1 mechanism.

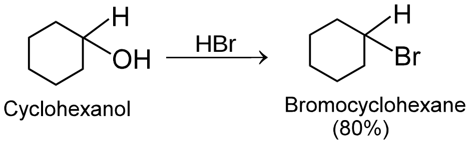
(iv) 1-Butanol reacts with sodium bromide in concentrated sulfuric acid to give 1-Bromobutane by an S_N2 displacement.

$$\underset{1-\text{butanol}}{CH_3(CH_2)_2-CH_2OH} \xrightarrow{NaBr,\ H_2SO_4} \underset{\substack{1-\text{bromobutane}\\(90\%)}}{CH_3(CH_2)_2-CH_2Br}$$

Protonation converts the hydroxy group to a good leaving group, but ionization to a primary carbocation is unfavourable. The protonated unbranched primary alcohol is well suited for the S_N2 displacement.

(v) Secondary alcohols also react with HBr to form alkyl bromides usually by the S_N1 mechanism.

e.g.



(vi) HCl (Hydrochloric acid) reacts with alcohols in much the same way that as the hydrobromic acid.

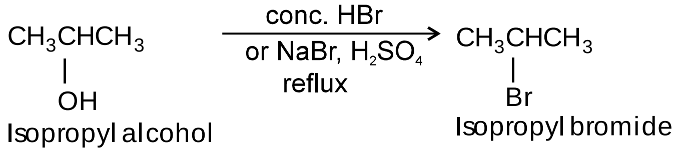
(vii) Chloride ion is a weaker nucleophlile than bromide ion because it is smaller and less polarizable. Lewis acid, such as $ZnCl_2$, is sometimes necessary to promote the reaction of HCl with primary and secondary alcohols.

Mechanism : $R{-}OH \overset{H^{\oplus}}{\rightleftharpoons} R-\overset{\oplus}{O}H_2 \xrightarrow[-H_2O]{RDS} \overset{\oplus}{R} \xrightarrow{X^{\ominus},\ Fast} R-X$

Reactivity of HX : **HI > HBr > HCl**

Reactivity of ROH : **3° > 2° > 1°**

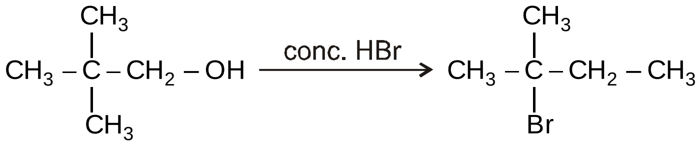
e.g.



$$CH_3CH(OH)CH_3 \xrightarrow[\text{reflux}]{\text{conc. HBr or NaBr, } H_2SO_4} CH_3CH(Br)CH_3$$

Isopropyl alcohol — Isopropyl bromide

e.g.



$$CH_3-C(CH_3)_2-CH_2-OH \xrightarrow{\text{conc. HBr}} CH_3-C(CH_3)(Br)-CH_2-CH_3$$

Lucas Reagent

(i) A mixture of concentrated hydrochloric acid and anhydrous zinc chloride is called the Lucas reagent.

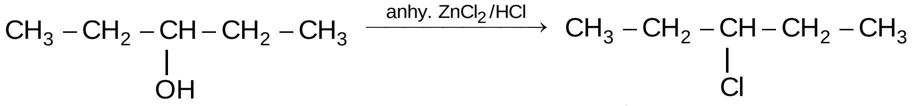
(ii) Whether an alcohol is primary, secondary or tertiary is identified by the Lucas test, which is based upon the difference in reactivity of the three classes of alcohol towards hydrogen halides.

(iii) Alcohol (of not more than six carbons in their molecule) are soluble in the Lucas reagent. The corresponding alkyl chlorides are insoluble.

(iv) Formation of a chloride from an alcohol is indicated by the cloudiness that appears when the chloride separates from the solution hence, the time required for cloudiness to appear is a measure of the reactivity of the alcohol.

(v) A tertiary alcohol reacts immediately with the Lucas reagent, a secondary alcohol reacts within five minutes and a primary alcohol does not react appreciably at room temperature.

e.g.



$$CH_3-CH_2-CH(OH)-CH_2-CH_3 \xrightarrow{\text{anhy. } ZnCl_2/HCl} CH_3-CH_2-CH(Cl)-CH_2-CH_3$$

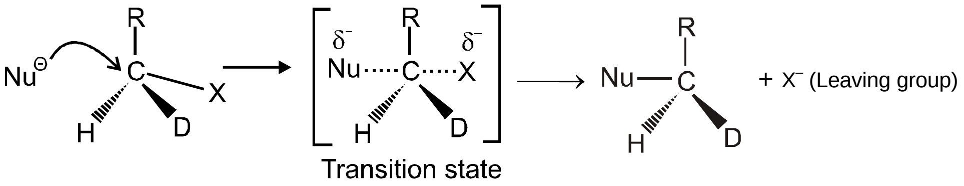
3 – Chloropentane

Section (B) : Bimolecular nucleophilic substitution reaction (S_N2)

Nucleophilic substitution in which incoming group replaces leaving group in one step only.

(1) S_N2 Reaction of Alkyl halide :

Mechanism :



Characteristic of S_N2

1. It is bimolecular, one step concerted process

2. It is second order reaction because in the rds both species are involved

3. Kinetics of the reaction : rate ∝ [alkyl halide] [nucleophile]

rate = k[alkyl halide] [nucleophile]

If the concentration of alkyl halide in the reaction mixture is doubled, the rate of the nucleophilic substitution reaction is double. If the concentration of nucleophile is doubled the rate of reaction is also double. If the concentration of both are doubled then the rate of the reaction quadriples.

4. Energetics of the reaction :

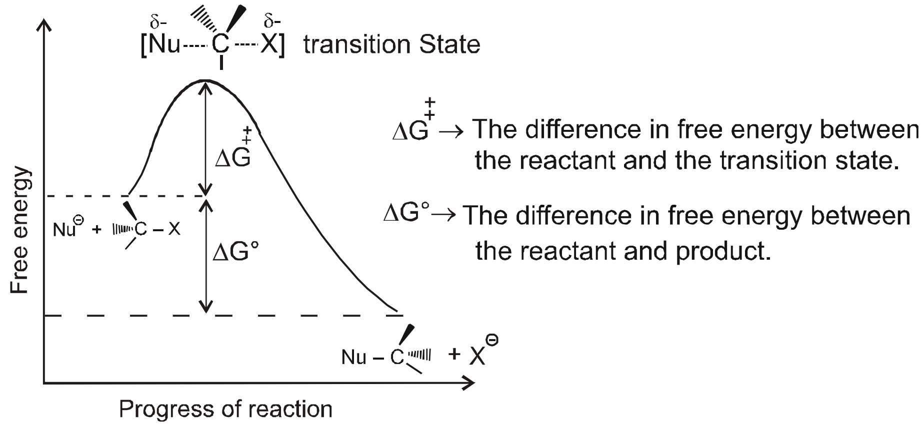
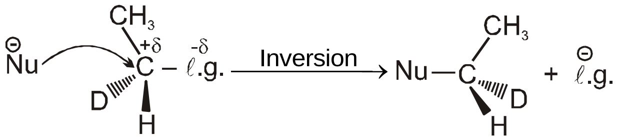


Figure : A free energy diagrams for S_N2 reaction

5. No intermediates are formed in the S_N2 reaction, the reaction proceed through the formation of an unstable arrangment of atoms or groups called transition state.

6. The stereochemistry of S_N2 reaction : As we seen earlier, in an S_N2 mechanism the nucleophile attacks from the back side, that is from the side directly opposite to the leaving group. This mode of attack causes an inversion of configuration at the carbon atom that is the target of nucleophilic attack. This inversion is also known as **Walden inversion**.



7. Factor's affecting the rate of S_N2 reaction : Number of factors affect the relative rate of S_N2 reaction, the most important factors are

(i) Effect of the structure of the substrate :

S_N2 reactivity CH_3 > 1° > 2° >> 3° (unreactive)

The important reason behind this order of reactivity is a steric effect. Very large and bulky groups can often hinder the formation of the required transition state and crowding raises the energy of the transition state and slow down the rate of reaction.

Table : Relative rate of reaction of alkyl halides by S_N2 mechanism.

Substituent	**Compound**	**Relative rate**
Methyl	CH_3X	30
1°	CH_3CH_2X	1
2°	$(CH_3)_2CHX$	0.02
Neopentyl	$(CH_3)_3CCH_2X$	0.00001
3°	$(CH_3)_3CX$	~ 0

(ii) Concentration and reactivity of the nucleophile :

– As nucleophilicity of nucleophile increases rate of S_N2 increases.

– Anionic nucleophiles mostly give S_N2 reaction

– A stronger nucleophile attacks upon α-carbon with faster rate than the rate of departing of leaving group.

(iii) The effect of the solvent : Polar aprotic solvent have crowded positive centre, so they do not solvate the anion appreciably therefore the rate of S_N2 reactions increased when they are carried out in polar aprotic solvent.

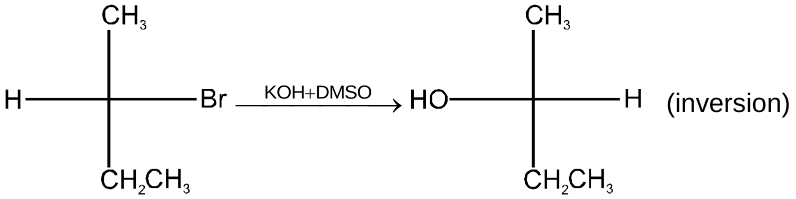
(iv) The nature of the leaving group : Weaker bases are good leaving groups. A good leaving group always stabilise the transition state and lowers its free energy of activation and there by increases the rate of the reaction. Order of leaving ability of halide ion $F^- < Cl^- < Br^- < I^-$

Reagents for alkyl halide are : OH^- , SH^- , I^- ,CN^-, NH_3 .... (**strong anionic nucleophiles)**

Ex-1. $CH_3-Cl \xrightarrow[(:OH^-)\text{strong nucleophile}]{\text{aq.KOH}} CH_3-OH + Cl^-$

Ex-2. $CH_3-CH_2-CH_2-Br \xrightarrow{\text{NaOH+DMF}} CH_3-CH_2-CH_2-OH + Br^-$

Ex-3.



(2) S_N2 Reaction of Alcohol :

(i) Reaction with HX : The protonated β unbranched primary alcohol is well suited for the S_N2 reaction.

Mechanism : $R-OH \overset{H^\oplus}{\rightleftharpoons} R-\overset{\oplus}{O}H_2 \xrightarrow{X^\ominus} R-X + H_2O$

(ii) Reaction with phosphorus trihalides

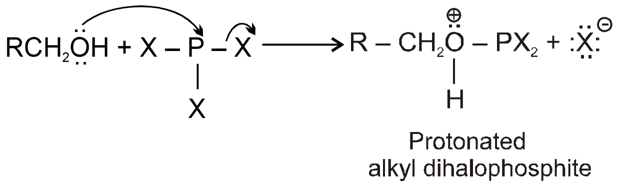
Several phosphorus halides are useful for converting alcohols to alkyl halides. PBr_3, PCl_3, & PCl_5 work well and are commercially available.

Phosphorus halides produce good yields of most primary and secondary alkyl halides, but none works well with tertiary alcohols. The two phosphorus halides used most often are PBr_3 and the P_4/I_2 combination.

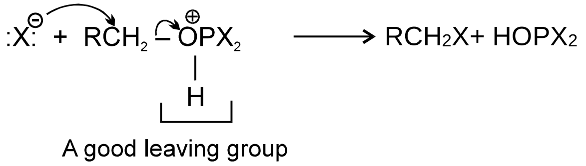
$$3R-OH + PX_3 \xrightarrow{(PX_3 = PCl_3,\ PBr_3,\ PI_3)} 3R-X + H_3PO_3$$

Mechanism :

Step-1 :



Step-2 :



Remarks

The mechanism for the reaction involves attack of the alcohol group on the phosphorus atom, displacing a halide ion and forming a protonated alkyl dihalophosphite

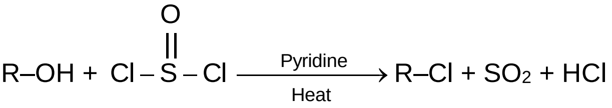
In second step a halide ion acts as nucleophile to displace $HOPX_2$, a good leaving group due to the electronegative atoms bonded to the phosphorus.

(iii) Reaction with PCl_5

$R-OH + PCl_5 \xrightarrow{S_N2} R-Cl + HCl + POCl_3$

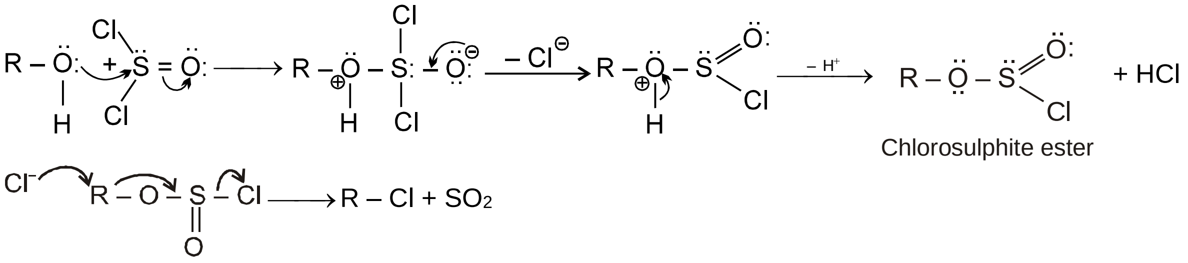
(iv) Reaction with thionyl chloride in presence of pyridine

Thionyl chloride ($SOCl_2$) is often the best reagent for converting an alcohol to an alkyl chloride. The by products (gaseous SO_2 and HCl) leave the reaction mixture and ensure that there can be no reverse reaction.



$$R-OH + Cl-\overset{\overset{O}{||}}{S}-Cl \xrightarrow[\text{Heat}]{\text{Pyridine}} R-Cl + SO_2 + HCl$$

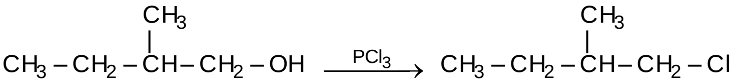
Mechanism :



In the first step, the nonbonding electrons of the hydroxy oxygen atom attack the electrophilic sulphur atom of thionyl chloride. A chloride ion is expelled a proton and gives test of chloro sulphite ester. Second step is an S_N2 mechanism.

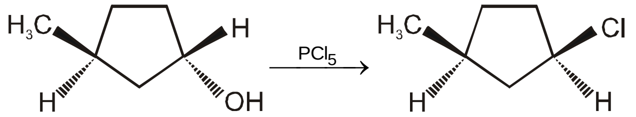
Ex-1. $\underset{\text{n – Pentyl alcohol}}{CH_3CH_2CH_2CH_2CH_2OH} \xrightarrow{HCl\ /\ ZnCl_2} \underset{\text{n – Pentyl chloride}}{CH_3CH_2CH_2CH_2CH_2Cl}$

Ex-2.

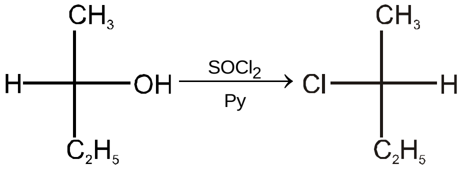


$CH_3-CH_2-\overset{\overset{\displaystyle CH_3}{|}}{C}H-CH_2-OH \xrightarrow{PCl_3} CH_3-CH_2-\overset{\overset{\displaystyle CH_3}{|}}{C}H-CH_2-Cl$

Ex-3.



Ex-4.

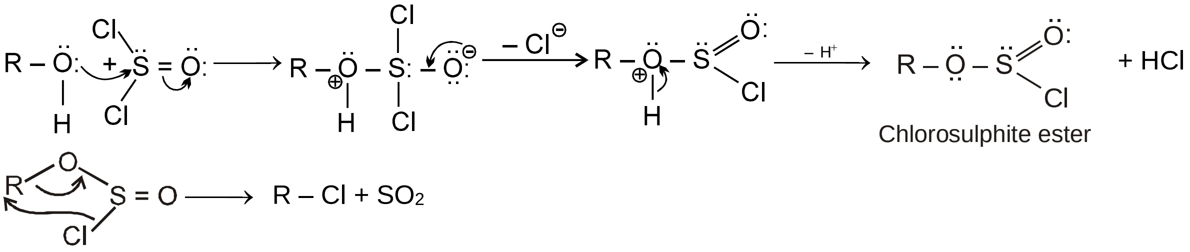


(3) S_Ni Reaction :

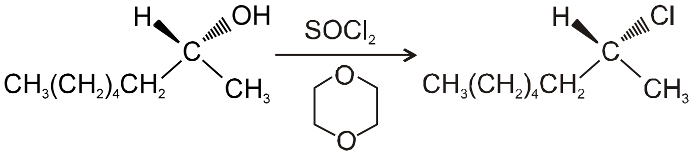
In S_Ni mechanism an internal nucleophile attacks from the same side of leaving group, means retension of configuration. It is an S_Ni mechanism, where i means internal

$$ROH + SOCl_2 \longrightarrow RCl + SO_2\uparrow + HCl\uparrow$$

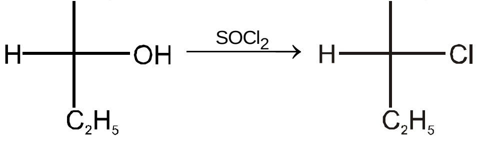
Mechanism :



Ex-1.

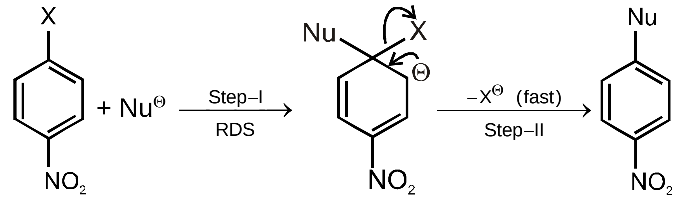


Ex-2.

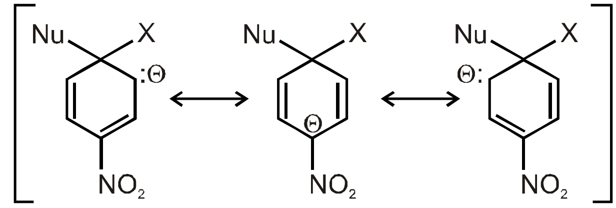


Section (C) : Bimolecular aromatic nucleophilic substitution reaction (S_N2 Ar)

This is the characteristic reaction of arylhalides with ortho or para electron withdrawing substituent. The reaction mechanism can be visualised as :

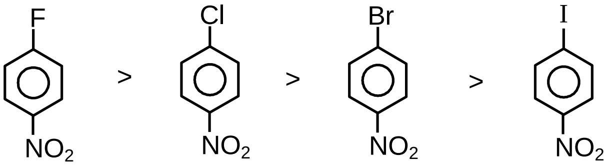


Intermediate ion is stabilized by resonance.

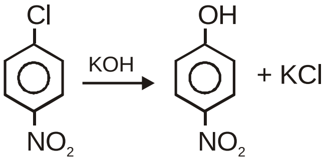


EWG ↑ ⇒ Rate of reaction ↑

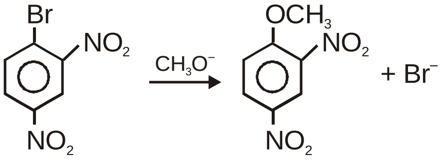
Reactivity order towards S_N2Ar :



Ex-1.



Ex-2.



Section (D) : Nucleophilic substitution reaction of Ethers & Epoxides

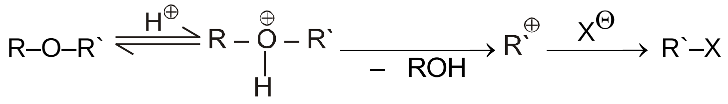
(1) S_N1 Reaction of Ethers

(i) Reaction with HX :

Ethers are unreactive towards most bases, but they can react under acidic conditions. A protonated ether can undergo substitution or elimination with the expulsion of an alcohol. Ethers react with conc. HBr and HI because these reagents are sufficiently acidic to protonate the ether, while bromide iodide are good nucleophiles for the substitution.

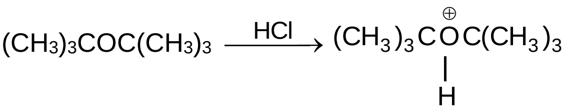
If R or R' is 3° then mechanism will be S_N1 otherwise S_N2.

Mechanism :

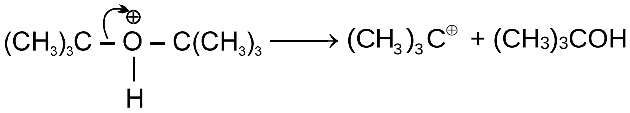


$$R{-}O{-}R' \overset{H^{\oplus}}{\rightleftharpoons} R-\underset{H}{\overset{\oplus}{O}}-R' \xrightarrow[-\ ROH]{} R'^{\oplus} \xrightarrow{X^{\ominus}} R'{-}X$$

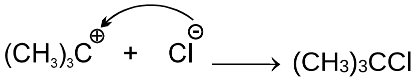
Ex.



$$(CH_3)_3COC(CH_3)_3 \xrightarrow{HCl} (CH_3)_3C\underset{H}{\overset{\oplus}{O}}C(CH_3)_3$$

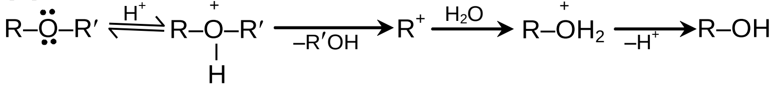


$$(CH_3)_3C-\underset{H}{\overset{\oplus}{O}}-C(CH_3)_3 \longrightarrow (CH_3)_3C^{\oplus} + (CH_3)_3COH$$



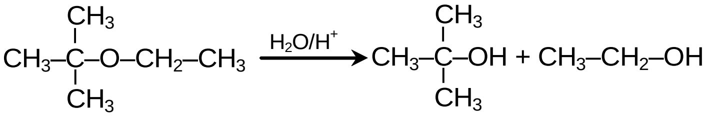
$$(CH_3)_3C^{\oplus} + Cl^{\ominus} \longrightarrow (CH_3)_3CCl$$

(ii) Reaction with H_2O/H^+ :



$$R\text{–}\ddot{\underset{\cdot\cdot}{O}}\text{–}R' \overset{H^+}{\rightleftharpoons} R\text{–}\overset{+}{\underset{H}{O}}\text{–}R' \xrightarrow[-R'OH]{} R^+ \xrightarrow{H_2O} R\text{–}\overset{+}{O}H_2 \xrightarrow[-H^+]{} R\text{–}OH$$

Ex.



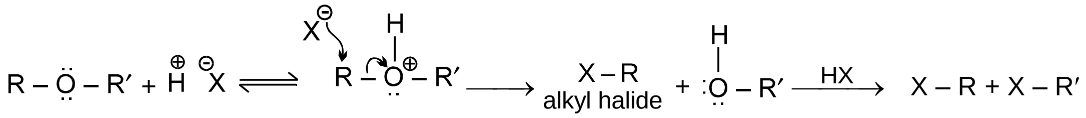
$$CH_3\text{–}\underset{CH_3}{\overset{CH_3}{C}}\text{–}O\text{–}CH_2\text{–}CH_3 \xrightarrow{H_2O/H^+} CH_3\text{–}\underset{CH_3}{\overset{CH_3}{C}}\text{–}OH + CH_3\text{–}CH_2\text{–}OH$$

(2) S_N2 Reaction of Ethers

(i) Reaction with HX :

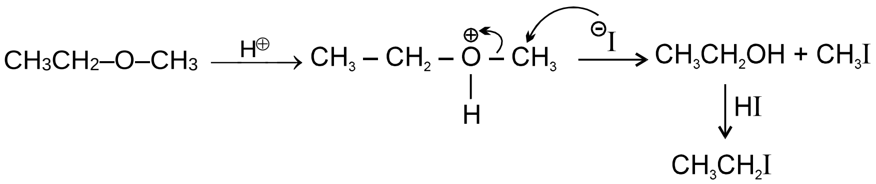
A protonated ether can undergo substitution reaction. Ether react with conc. HBr and HI because these reagents are sufficiently acidic to protonate the ether. If R or R' is 3° then mechanism will be S_N1 otherwise S_N2.

Mechanism :



$$R-\ddot{O}-R' + \overset{\oplus}{H}\ \overset{\ominus}{X} \rightleftharpoons R-\overset{H}{\overset{|}{O^{\oplus}}}-R' \longrightarrow \underset{\text{alkyl halide}}{X-R} + :\overset{H}{\overset{|}{O}}-R' \xrightarrow{HX} X-R + X-R'$$

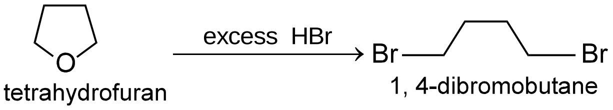
Ex.



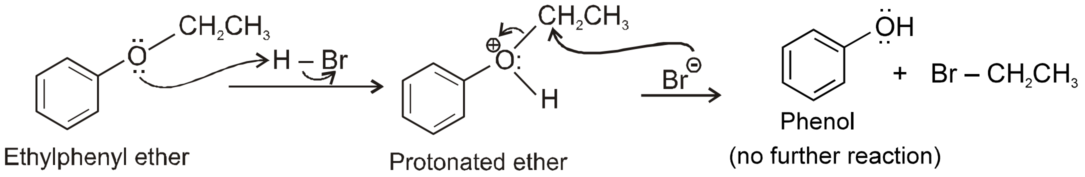
$$CH_3CH_2\text{–}O\text{–}CH_3 \xrightarrow{H^{\oplus}} CH_3-CH_2-\underset{H}{\overset{\oplus}{O}}-CH_3 \xrightarrow{\ominus I} CH_3CH_2OH + CH_3I$$

$$CH_3CH_2OH \xrightarrow{HI} CH_3CH_2I$$

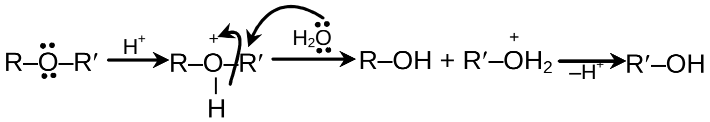
Ex.



Ex.



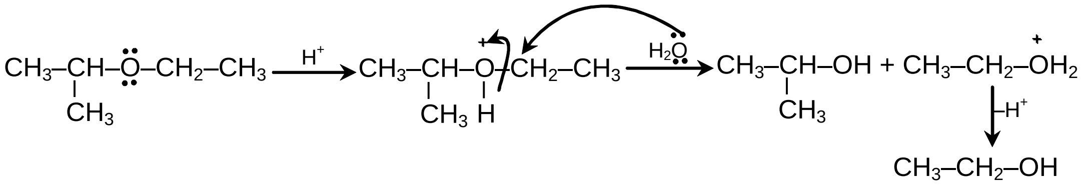
(ii) Reaction with H_2O/H^+ :



$$R\text{–}\ddot{O}\text{–}R' \xrightarrow{H^+} R\text{–}\underset{H}{\overset{+}{O}}\text{–}R' \xrightarrow{H_2\ddot{O}} R\text{–}OH + R'\text{–}\overset{+}{O}H_2 \xrightarrow[-H^+]{} R'\text{–}OH$$

(Steric crowding R > R′)

Ex.



$$CH_3\text{–}\underset{CH_3}{CH}\text{–}\ddot{O}\text{–}CH_2\text{–}CH_3 \xrightarrow{H^+} CH_3\text{–}\underset{CH_3}{CH}\text{–}\underset{H}{\overset{+}{O}}\text{–}CH_2\text{–}CH_3 \xrightarrow{H_2\ddot{O}} CH_3\text{–}\underset{CH_3}{CH}\text{–}OH + CH_3\text{–}CH_2\text{–}\overset{+}{O}H_2$$

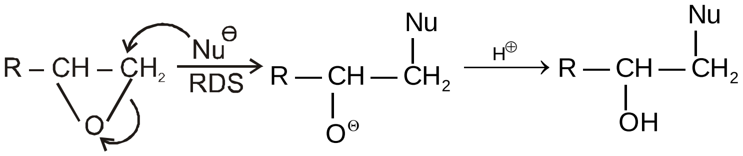
$$CH_3\text{–}CH_2\text{–}\overset{+}{O}H_2 \xrightarrow{-H^+} CH_3\text{–}CH_2\text{–}OH$$

(3) Nucleophilic substitution reaction of Epoxide :

Epoxides are much more reactive than ether because of angle strain in three membered ring therefore epoxide readily undergo nucleophilic substitution reaction.

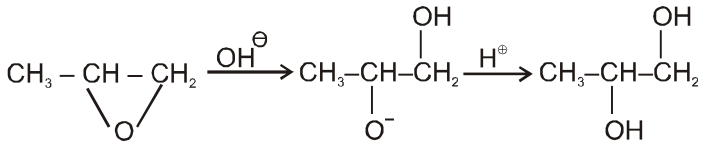
In basic medium mechanism is S_N2. Nucleophile atacks on less hindered carbon.

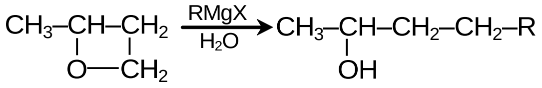
Mechanism :



$$R-\underset{O^{\ominus}}{CH}-\overset{Nu}{CH_2} \xrightarrow{H^{\oplus}} R-\underset{OH}{CH}-\overset{Nu}{CH_2}$$

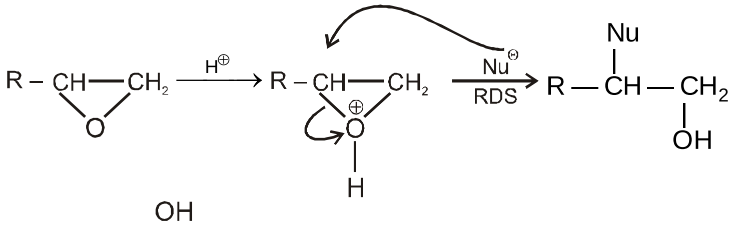
Ex.





In acidic medium mechanism is S_N1 type. Nucleophile attacks on more substituted carbon.

Mechanism :



Ex.