Organic Reaction Mechanisms-III
(Substitution reactions of Haloalkanes, Alcohols, Ethers & Haloarenes)

Introduction :

(a) Alkyl halides :

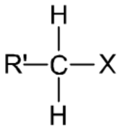
There are three major classes of organohalogen compounds ; the alkyl halides, the vinyl halides, and the aryl halides.

An alkyl halide simply has a halogen atom bonded to one of the sp_3 hybrid carbon atoms of an alkyl group. A vinyl halide or Aryl halide has a halogen atom bonded to one of the sp_2 hybrid carbon atoms. They are different from alkyl halides because their bonding and hybridization are different.

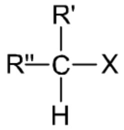
Classification of halides :

(1) Alkyl halides or haloalkanes (R–X) containing sp_3 C–X bond :

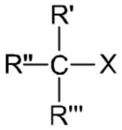
They are classified as primary, secondary or tertiary according to the nature of carbon to which halogen is attached.



Primary (1°)



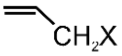
Secondary (2°)

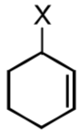


Tertiary (3°)

(2) Allylic halides :

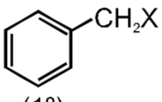
These are the compounds in which the halogen atom is bonded to an sp_3–hybridised carbon atom next to carbon-carbon double bond (C=C) i.e. to an allylic carbon.



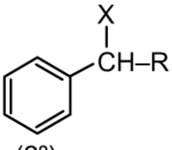


(3) Benzylic halides :

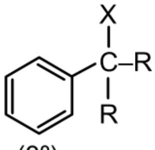
These are the compounds in which the halogen atom is bonded to an sp_3–hybridised carbon atom next to an aromatic ring.



(1°)

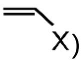
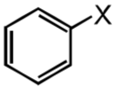


(2°)

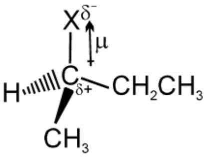


(3°)

(4) Compounds Containing sp_2 C–X Bond :

Vinylic halides (), Aryl halides 

Structure of alkyl halide :

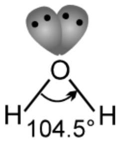


The carbon-halogen bond in an alkyl halide is **polar** because halogen atoms are more electronegative than carbon atom. Most reactions of alkyl halides result from breaking this polarized bond. The carbon atom has a partial positive charge, making it some what **electrophilic**.

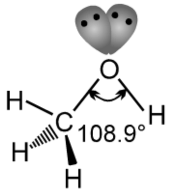
(b) Alcohols :

Alcohols have sp_3 hybridized oxygen atoms, but the C–O–H bond angle in methanol (108.9°) is considerably larger than the H–O–H bond angle in water (104.5°) because the methyl group is much larger than a hydrogen atom.

The bulky methyl group counteracts the bond angle compression caused by oxygen's nonbonding pairs of electrons. The O–H bond lengths are about the same in water and methanol (0.96 Å), but the C–O bond is considerably longer (1.4 Å), reflecting the larger covalent radius of carbon compared to hydrogen.



water

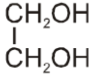


methyl alcohol

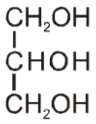
Classification of alcohols:

(1) Monohydric : Contains one –OH group (C_2H_5OH ; $CH_3–CH_2–CH_2–OH$)

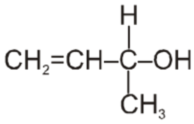
(2) Dihydric : Contains two –OH group

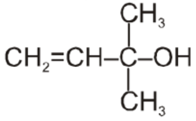

$CH_2OH–CH_2OH$ (Glycol)

(3) Trihydric (Polyhydric): Contains three (or more than three) –OH groups


$CH_2OH–CHOH–CH_2OH$ (Glycerol)

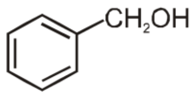
(4) Allylic alcohols : $CH_2=CH–CH_2–OH$;


$CH_2=CH–C(H)(CH_3)–OH$;

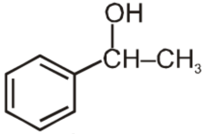

$CH_2=CH–C(CH_3)_2–OH$

(5) Vinylic Alcohol: $CH_2=CH–OH$ (unstable at room temperature)

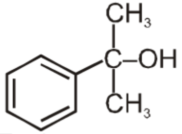
(6) Benzylic alcohols:



Primary



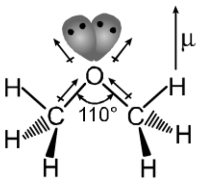
Secondary



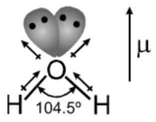
Tertiary

(c) Ethers :

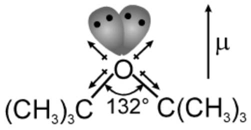
Like water, ethers have a bent structure, with an sp_3 hybrid oxygen atom giving a nearly tetrahedral bond angle.



Dimethyl ether



Water



Di-ter.butyl ether

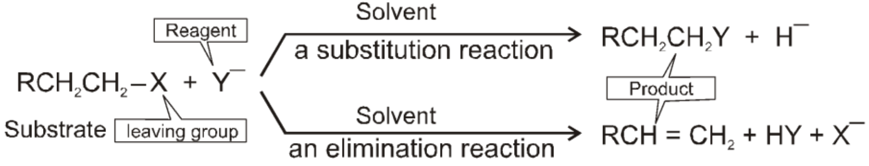
Bonding in ethers is readily understood by comparing ethers with water and alcohol. Van der Waals strain involving alkyl groups causes the bond angle at oxygen to the larger in ethers than in alcohol, and larger in alcohols than in water. An extreme example is di-tert-butyl ether, where steric hindrance between the tert-butyl groups is responsible for a dramatic increase in the C–O–C bond angle.

Classificiation of ethers :

(1) Simple or symmetrical : If the alkyl or aryl groups attached to the oxygen atom are the same.
CH_3OCH_3, $C_2H_5OC_2H_5$

(2) Mixed or unsymmetrical : If the two groups attached to the oxygen atom are different.
$C_2H_5OCH_3$, $C_2H_5OC_6H_5$.

(d) General reactions of alkyl halides, alcohols & ethers :



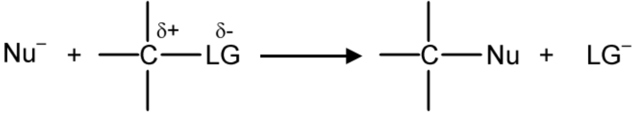
Section (A & B) : Nucleophilic substitution reactions of alkyl halides

What does the term "nucleophilic substitution" imply ?

A nucleophile is an the electron rich species that will react with an electron poor species. A substitution implies that one group replaces another.

Nucleophilic substitution reactions occur when an electron rich species (the nucleophile) reacts at an electrophilic saturated C atom attached to an electronegative group (the leaving group) that can be displaced as shown by the general scheme:

Nucleophilic substitution at sp_3 C-atom.



For alcohols, the rate of substitution reactions increased by using the tosylates(R-OTs), an alternative method of converting the –OH to a better leaving group.

Overview of Nucleophilic substitution at sp_3 C-atom :

There are two fundamental events in a nucleophilic substitution reaction :

Formation of the new σ bond to the nucleophile.

Breaking of the σ bond to the leaving group.

Depending on the relative timing of these events, two different mechanisms are possible:

Bond breaking to form a carbocation preceeds the formation of the new bond : S_N1 reaction

Simultaneous bond formation and bond breaking : S_N2 reaction

A third possibility, where the nucleophile adds then the leaving group departs can't occur because it would require that the electrophilic C become pentavalent.

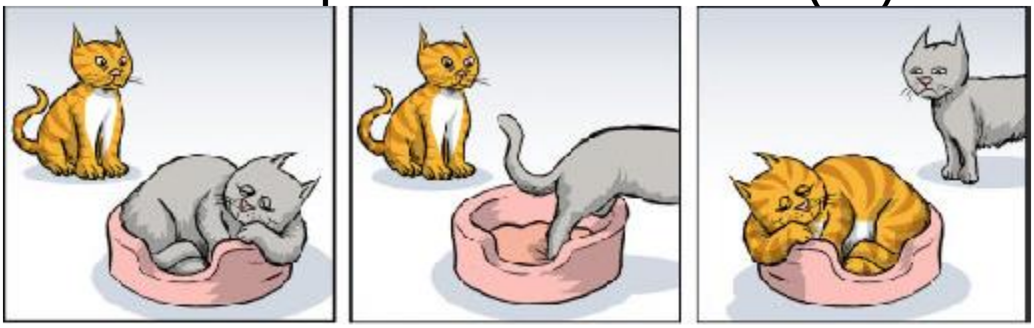
However, it is also useful to appreciate that the overall outcome of the transformation (i.e. the substitution) is often the same regardless of whether it is S_N1 or S_N2, though there may be differences in regiochemistry and stereochemistry (which can provide some evidence as to which mechanistic path is occuring).

Important :

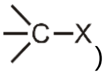
In general terms, the C bearing the LG needs to the sp_3 hybridised in order for these reactions to occur. This is important since students often want to make use of nucleophilic substitution reactions of vinyl (C=C-LG) or aryl (Ar-LG) systems which are not generally effective.

The reasons for this are that the adjacent π bonds are electron rich and will repel the Nu_- or that the vinyl and phenyl carbocations are not very favourable.

(A) Unimolecular nucleophilic substitution reaction (S_N1) :



Cat-1 wait for Cat-2 to leave and then sit in the comfy chair.

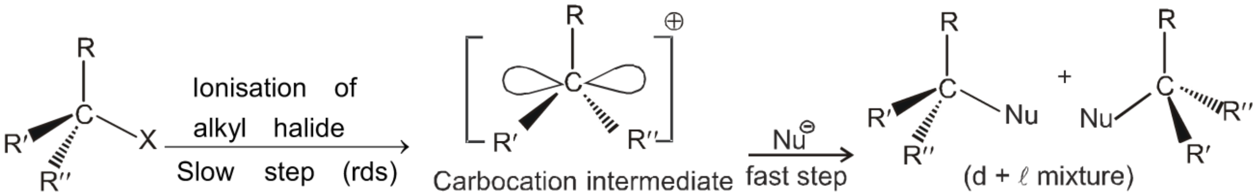
- It is a two step process.
- First step is the heterolytic cleavage of carbon halogen bond () to give carbocation intermediate.

$$R-X \longrightarrow \underset{T.S_1}{[R\cdots X]} \xrightarrow{-X^{\ominus}} R^{\oplus} \qquad (I_{st}\ \text{step is r.d.s.})$$

- In the second step nucleophile attacks from either side of carbocation to generate product (racemic mixture if carbon becomes chiral).

$$R^{\oplus} + Nu_{-} \longrightarrow \underset{T.S_2}{\left[\overset{\delta+}{R}\cdots\cdots\overset{\delta-}{Nu}\right]} \xrightarrow{-X^{\ominus}} R\text{–}Nu \qquad (II_{nd}\ \text{is fast step})$$

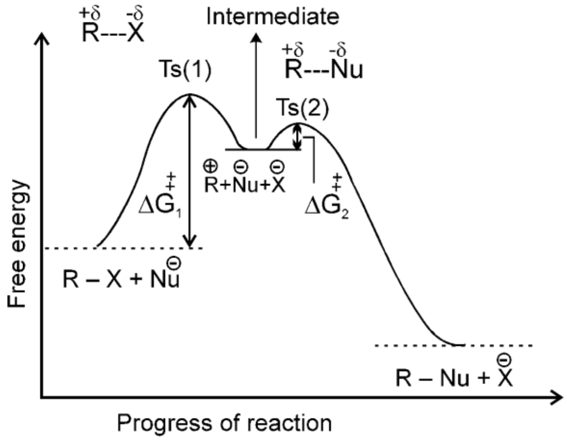
Mechanism :



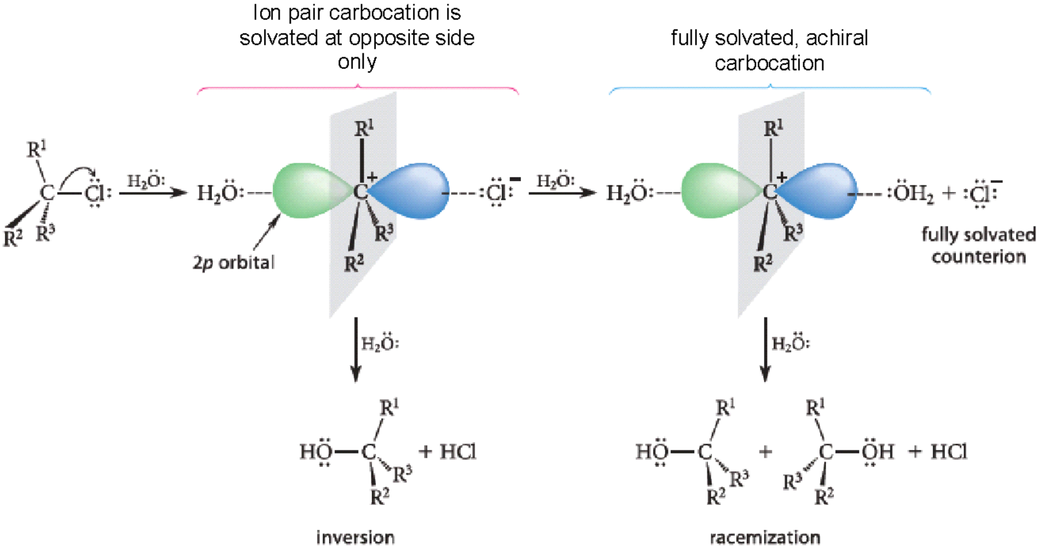
- Carbocation intermediate is formed, so rearrangement is possible in S_N1 reaction.

No. of Steps : 2 step process
Kinetics : Rate ∝ [Alkyl halide]
Molecularity : 1
Order of reaction : 1_{st} order reaction
Intermediate : Carbocation
Rearrangement : Possible

Energetics :



Stereochemistry :



Factors affecting rate of S_N1 reaction :

(1) 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. **S_N1 reactivity : 3° > 2° > 1° > CH_3 – X**

Reactivity of alkyl halides : R–I > R–Br > R–Cl > R–F

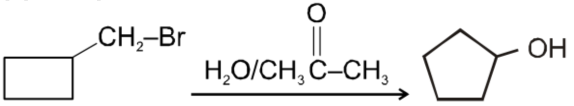
(2) Nucleophile/base : The rate of S_N1 reaction is unaffected by the concentration and nature of the nucleophile. (Weak & Neutral nucleophile favours)

(3) Leaving Group : Good leaving groups favours rate of S_N1 reaction (I^- > Br^- > Cl^->F^-)

(4) Solvent : Polar protic solvents favours rate of S_N1 reaction
Catalyst used is Ag^+.
More polar protic solvent is more favourable for S_N1.
$H_2O > ROH > NH_3$ (order of polar protic solvent).
In S_N1 reaction carbocation is formed along with anion and to solvate these ions, polar protic solvent is used.

(5) Temperature : Favours rate of S_N1 reaction

Ex.



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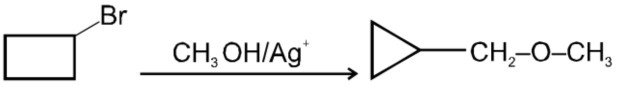

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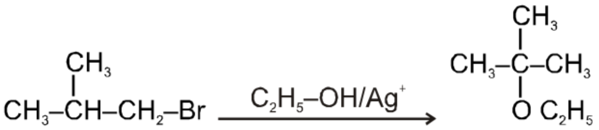

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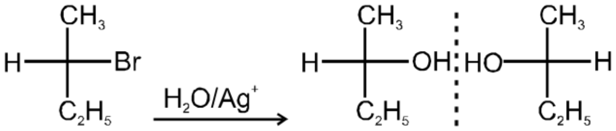

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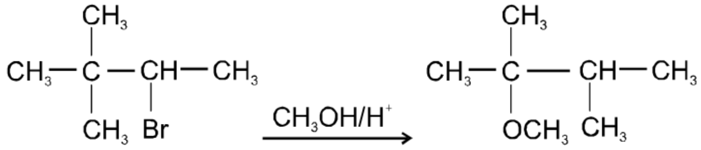


- **Swart's reaction :** Flourine exchange reaction

$R - X + Ag{-}F \xrightarrow{S_N1} R^+ \xrightarrow{F^-} R - F + AgX\downarrow$ ppt + ($R - OH$ + $R{-}OC_2H_5$ minor products)

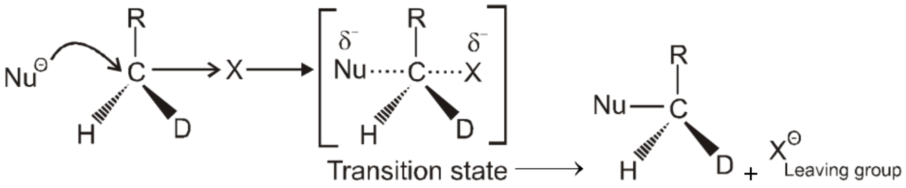
Note : Only AgF is soluble in water among all silver halides.
Other flourination reagent in Swart reaction are Hg_2F_2, CoF_2 & SbF_3.

(B) Bimolecular nucleophilic substitution reaction (S_N2) :

Cat-1 kick the Cat-2 out of his comfy chair.

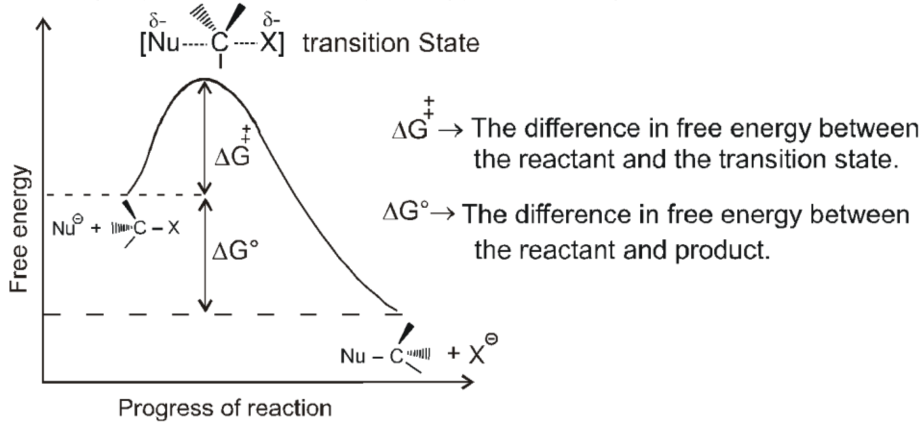
It is a single step reaction as the rate of reaction depends upon concentration of substrate as well as nucleophile.

- In this reaction nucleophile attack from back side on the carbon atom bearing leaving group. it is a concerted reaction where bond breaking and bond formation takes place simultaneously to achieve a transition state (trigonal bipyramidal shape) where half bond has been formed and half bond has been broken.

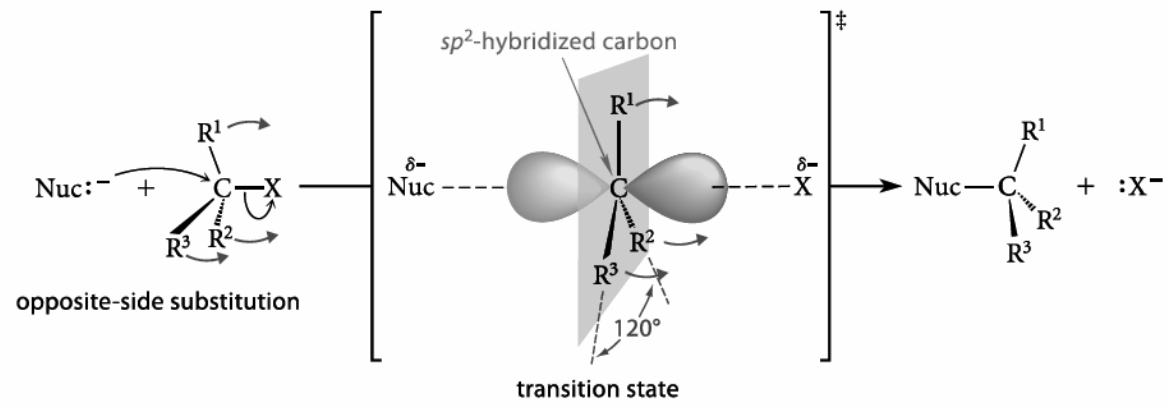


Mechanism :
No. of Steps : 1 step concerted process
Kinetics : rate ∝ [alkyl halide] [nucleophile]
Molecularity : 2
Order of reaction : 2nd order reaction
Intermediate : No intermediate
Rearrangement : Not possible

C-atom is pentavalent sp_2-hybridised and triangular bipyramidal shape in transition state.



Energetics :
Steriochemistry :
Only one product is formed where inversion of configuration takes place.



- **Factors affecting rate of S_N2 reaction :**

  (1) Substrate : S_N2 reactivity $CH_3 > 1° > 2° >> 3°$

  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 reaction.

  Electron withdrawing group in substrate increases the rate of S_N2 reaction.
  (e.g. $O{=}CH–CH_2–Br > CH_3–O–CH_2–Br > H–CH_2–Br > CH_3–CH_2–Br$)

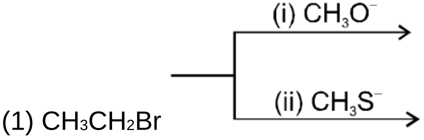
  (2) Nucleophile/base : As nucleophilicity of nucleophile increases rate of S_N2 increases.
  – Mostly Anionic nucleophiles give S_N2 reaction.
  – A stronger nucleophile attacks upon α-carbon with faster rate than the rate of departing of leaving group.

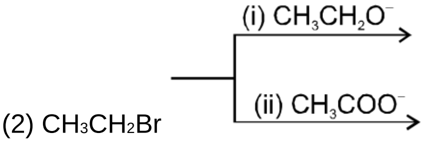
  (3) Leaving Group : Good leaving groups favours rate of S_N2 reaction. ($F^- < Cl^- < Br^- < I^-$)

(4) 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.

(5) Temperature : Favours rate of S_N2 reaction.

Ex. Which one in the given reaction is favourable towards S_N2 reaction?





Ans. (1) In case of (i) rate is slower than (ii) because nucleophilicity increases down the group.

(2) In case of (i) rate of reaction is faster than (ii) becuase (i) ion is more nucleophilic than (ii) it is known that for the same donor atom nucleophilicity and basicity have same order. Acetic acid is stronger acid than ethyl alcohol hence ethoxide ion is stronger base and better nucleophile than acetate ion.

Comparision between S_N1 and S_N2 reaction :

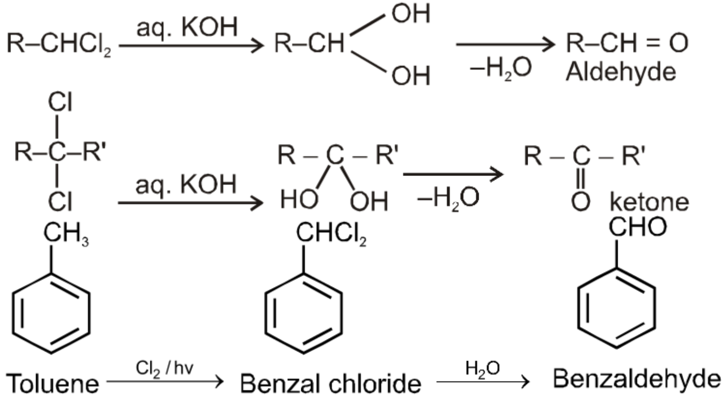
Characteristics	S_N2	S_N1
1. Kinetics	$r \propto [RX][Nu:]$	$r \propto [RX]$
2. Stereochemistry	inversion	racemisation
3. Rearrangement	not possible	possible
4. Nature of R – X	$CH_3–X > RCH_2X > R_2CHX > R_3CX$	$R_3CX > R_2CHX > RCH_2X > CH_3X$
5. Nucleophile	strong anionic	weak neutral
	$R^- > NH_2^- > OR^- > OH^-$	
$H_2O > MeOH > EtOH > NH_3$		
6. Leaving group	$I^- > Br^- > Cl^- > F^-$	(same)
7. Solvent	**polar aprotic**	**polar protic**

(a) Reaction with aqueous KOH & NaOH (Mechanism S_N2) :

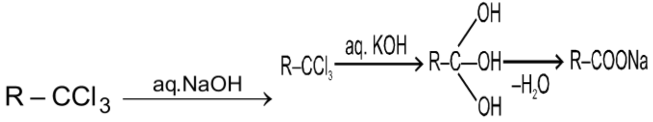
(1) $R – X + NaOH (aq.) \longrightarrow R – OH + NaX$

(2) On aqueous alkali hydrolysis of gem-dihalides :

Terminal gemdihalides will give aldehyde while non-terminal will give ketone as follows



(3) On aqueous alkali hydrolysis of gem-trihalides :



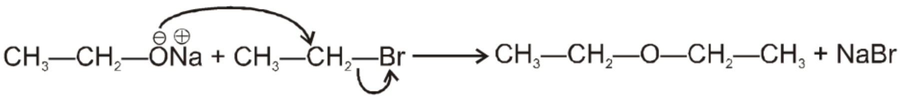
(b) Williamson's synthesis of ethers :

- It is used for the preparation of symmetrical as well as unsymmetrical ether.

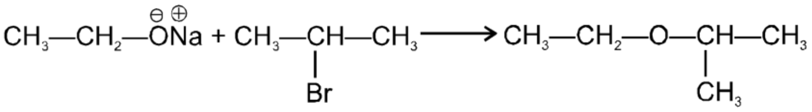
$R—Br + NaOEt \longrightarrow R—OEt + NaBr$

- Williamson's synthesis involve attack of an alkoxide on alkyl halide to give ethers. In place of alkoxide, phenoxide can also be used.
- This is an S_N2 reaction because alkoxide is a strong nucleophile.
- On using 2° & 3° alkylhalide we get alkene not ether as a product.

Ex.

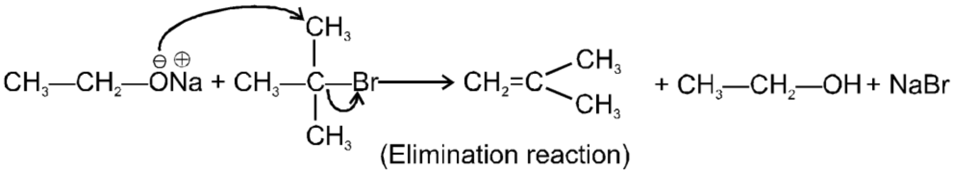


Ex.

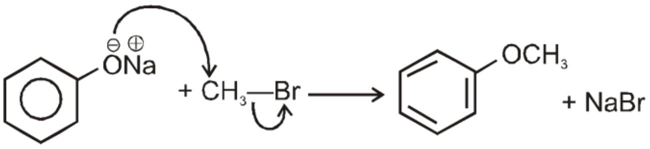


+ CH_3–CH=CH_2

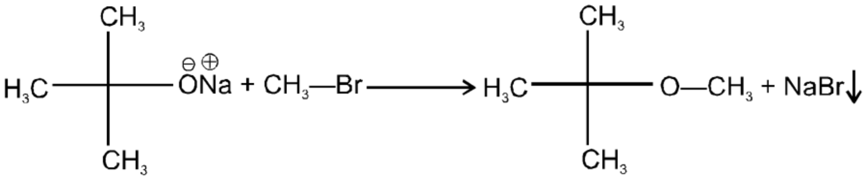
Ex.



Ex.

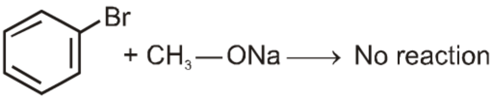


Ex.



Note : ***Vinyl or Aryl halide should not be used because they don't give S_N2 reaction generally.***

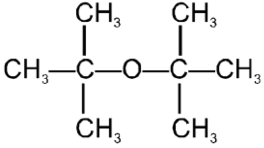
Ex.



Ex. Which of the following ethers cannot prepared by Williamson's synthesis reaction :

(1) CH_3—CH_2—O—CH_3

(2)



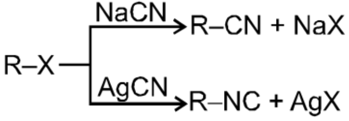
$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-O-\underset{CH_3}{\overset{CH_3}{C}}-CH_3$$

(3) Ph–O–Ph

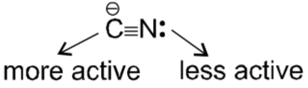
(4) Ph–O–CH_3

Ans. **2 & 3**

(c) Reaction with AgCN and NaCN :



- NaCN is a more ionic hence ionized to give free $\overset{\ominus}{C}N$ (an ambident nucleophile) where carbon side is more active than nitrogen side. That is why with NaCN, RCN is formed.



- On the other hand AgCN is more covalent so it is not ionized therefore only nitrogen side is free to act as a nucleophile and give isocyanide (R—NC)

Similarly KNO_2 and $AgNO_2$ gives nitrite an ambident nucleophile with two different points of linkage $[\overset{\ominus}{O} - \ddot{N} = \ddot{O}:]$. The linkage through oxygen results in alkyl nitrites while through nitrogen atom, it leads to nitroalkanes.

$$R - X \xrightarrow{KNO_2} R - O - N = O \text{ (alkyl nitrite)}$$

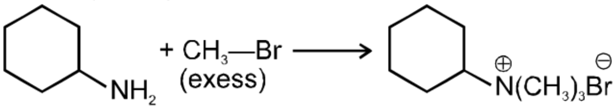
$$R - X \xrightarrow{AgNO_2} RNO_2 \text{ (nitroalkane)}$$

(d) Reaction with NH_3 :

$$\underset{\text{(exess)}}{R—X + NH_3} \longrightarrow \underset{1^\circ \text{ amine}}{R—NH_2} \xrightarrow{R–X} \underset{2^\circ \text{ amine}}{R_2NH} \xrightarrow{R–X} \underset{3^\circ \text{ amine}}{R_3N} \xrightarrow{R–X} \underset{\text{(Tetra alkylammoniumhalide)}}{R_4\overset{\oplus\ominus}{NX}}$$

$$R—X + \underset{\text{(exess)}}{NH_3} \longrightarrow R—NH_2 + HX$$

$$CH_3—CH_2—Br + \underset{\text{(exess)}}{NH_3} \longrightarrow (CH_3—CH_2)_4\overset{\oplus\ominus}{NX}$$



(e) Wurtz Reaction :

This method is used for preparation of higher alkanes from 1° or 2° alkyl halides. In this method two moles of alkyl halides are treated with 'Na' metal in dry ether.

$$\underset{(1^\circ \text{ or } 2^\circ)}{R–X + 2Na + R–X} \xrightarrow[\text{ether (dry)}]{Na} R–R + 2Na–X.$$

Steps involved in wurtz reaction.

$$R–X + 2Na \longrightarrow R–Na + NaX \qquad \text{..........(i)}$$

$$R–X + R–Na \longrightarrow R–R + NaX \qquad \text{.........(ii)}$$

Mechanism

(1) Ionic mechanism

$$2Na \longrightarrow 2Na^{\oplus} + 2e^{\ominus};$$

$$\underset{(1^\circ, 2^\circ)}{R - X} + 2e^- \longrightarrow \overset{\ominus}{R} + \overset{\ominus}{X}$$

$$\overset{\ominus}{R} + \underset{(1^\circ \text{ or } 2^\circ)}{R - X} \xrightarrow{S_N2} R–R$$

$$\overset{\oplus}{Na} + \overset{\ominus}{X} \longrightarrow NaX$$

(2) Free Radical Mechanism

$$Na \longrightarrow Na^+ + e^-$$

$$R–X \longrightarrow R^+ + X^-$$

$$R^+ + e^- \longrightarrow R^\cdot$$

$$R^\cdot + R^\cdot \longrightarrow R–R$$

Remarks :

(1) With 3° R-X S_N2 and free radical coupling is not possible due to steric hinderence so in that case elimination or disproportionation takes place.

(2) In the ionic mechanism alkyl sodium $(\overset{\ominus}{R}\ \overset{\oplus}{Na})$ is strong base as well as nucleophile which gives S_N2 with R–X.

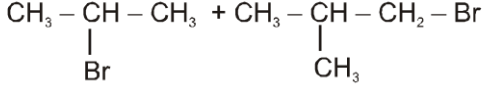
(3) Ether should be dry if moisture is present then ROH is produced instead of R – R with water .

(4) This method is not used for preparation of CH_4.

(5) To get pure alkanes having even number of carbon atoms both alkyl halides must be of same type.
(5) On using two type of alkyl halide we get a mixture of three alkanes because two type of alkyl halides will give us two types of alkyl free radical. Which may combine to each other as well as itself.

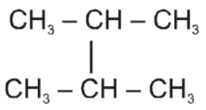
$$R{-}X + R'{-}X \xrightarrow[\text{ether (dry)}]{\text{Na}} R{-}R' + R'{-}R' + R{-}R + NaX$$

Ex. Write the structure of products when structure Ist and IInd undergo Wurtz reaction

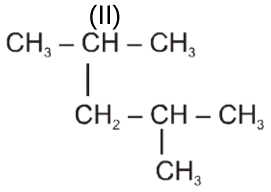


$CH_3-\underset{\displaystyle Br}{\underset{|}{CH}}-CH_3 + CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-Br$

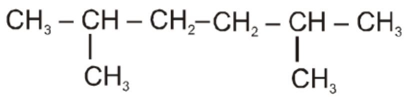
(I) (II)

Ans. (a) 

$CH_3-\underset{\displaystyle CH_3-CH-CH_3}{\underset{|}{CH}}-CH_3$

(b) 

$CH_3-\underset{\displaystyle CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3}{\underset{|}{CH}}-CH_3$

(c) 

$CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3$

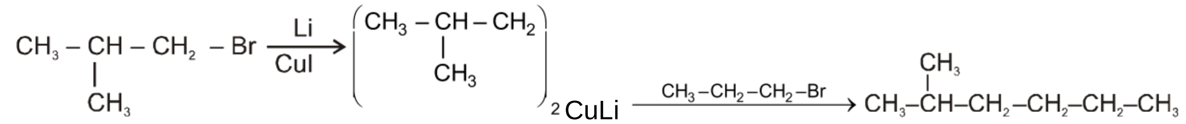
(f) Frankland reaction :

$$R-X + Zn + R{-}X \xrightarrow{\text{Ether}} R-R + ZnX_2$$

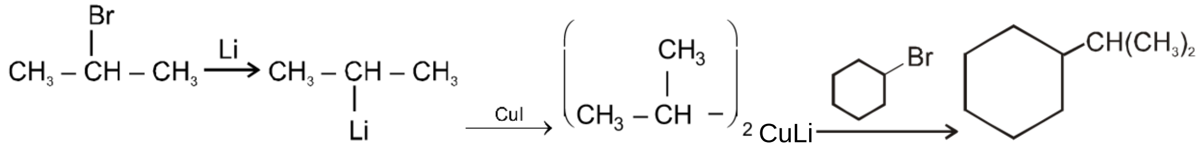
(g) Corey House alkane synthesis :

It is used for the preparation of pure alkane having odd number of carbon atom.

$$\underset{(1°,\,2°,\,3°)}{R-X} \xrightarrow{2Li} \overset{\ominus\ \oplus}{R\,Li} + LiX \xrightarrow{CuX} \underset{\text{(Gilman's reagent)}}{\overset{R_2CuLi}{\text{Lithiumdialkyl cuprate}}} \xrightarrow[S_N2]{R'-X\ (1°>2°)} R-R'$$

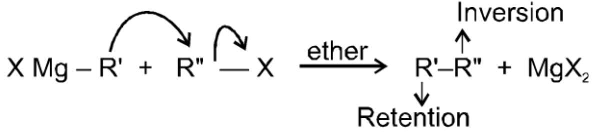
Ex. 

$CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-Br \xrightarrow[CuI]{Li} \left(CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2\right)_2CuLi \xrightarrow{CH_3-CH_2-CH_2-Br} CH_3-\overset{\displaystyle CH_3}{\overset{|}{CH}}-CH_2-CH_2-CH_2-CH_3$

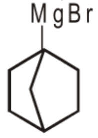
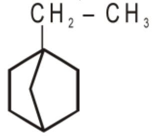


(h) Reaction with Grignard reagent :

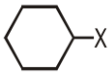
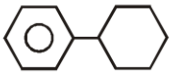
Coupling between a Grignard reagent and alkyl halide containing a reactive halogen atom can be effected directly; this reaction is probably S_N2.

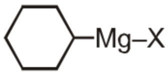


The yield is very good if R" is allyl, benzyl.

Ex.  + $CH_3-CH_2-Br \longrightarrow$ 

Ex.  + $CH_3-CH_2-Mg-Br \longrightarrow$ No reaction

Ex. Ph – MgX +  $\longrightarrow$ 

Ex. Ph–X +  $\longrightarrow$ No reaction

(i) Reaction with chloramine :

$CH_3{-}MgX + Cl-NH_2 \longrightarrow CH_3{-}NH_2 + MgXCl$

(j) Synthesis of higher alkynes :

(1) With Na : When acetylene or 1-alkyne react with Na in presence of liq. NH_3 then an intermediate compound sodium acetylide or sodium alkynide is formed which gives higher alkyne with alkyl halide.

$$2\,H-C\equiv C-H+2\,Na\xrightarrow[-H_2]{liq.\ NH_3}2H-C\equiv \overset{\ominus\ \oplus}{C}Na\xrightarrow[S_N2]{X-R}H-C\equiv C-R$$

$$2R-C\equiv C-H+2Na\xrightarrow[-H_2]{liq.\ NH_3}2R-C\equiv \overset{\ominus\ \oplus}{C}Na\xrightarrow{X-R'}R-C\equiv C-R'$$

(2) With GR : When acetylene or 1–alkyne react with GR then alkane and unsaturated GR is formed which further react with alkyl halide and form higher alkyne.

$$H-C\equiv CH+R-Mg-X\xrightarrow[-RH]{}H-C\equiv C-MgX\xrightarrow[-MgX_2]{XR}H-C\equiv C-R$$

$$R-C\equiv C-H+R-Mg-X\xrightarrow[-RH]{}R-C\equiv C-Mg-X\xrightarrow{R'-X}R-C\equiv C-R'$$

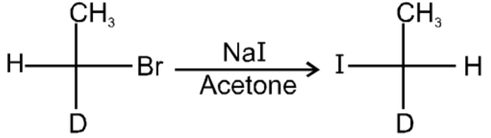
(k) Finkelstein reaction :

$R-OH + HI \longrightarrow R-I \xrightarrow{HI} R-H + I_2$ (reduced) [Final product is Alkane (R-H) not R-I]

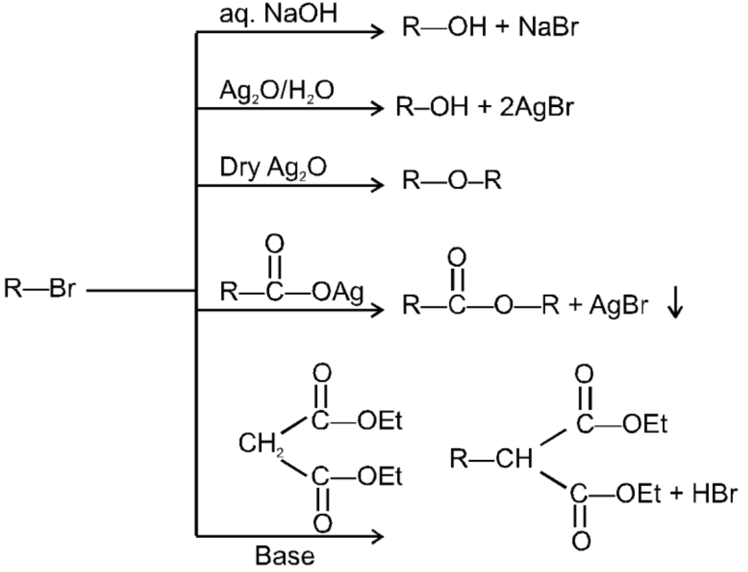
This is a problems that is why iodides are best prepared through halogen exchange reaction. It is also known as Finkelstein reaction. In this reaction R—Cl and R—Br is treated with sodium iodide in acetone.

$$Ph-CH_2-Br\xrightarrow[Acetone]{NaI}\underset{(Soluble)}{Ph-CH_2-I}+NaBr\downarrow\quad ;\quad R-Br\xrightarrow[Acetone]{NaI}R-I+NaBr\downarrow$$

- NaI is soluble in acetone. In this reaction acetone is used because sodium iodide is soluble in acetone but NaBr and NaCl are insoluble so precipitated out. This eliminates any possibility of reverse reaction.
- It is an S_N2 reaction therefore only 1ºRX and 2ºRX is used.



(l) Other examples of S_N2 reaction of alkyl halides :



Examples of Nucleophilic Substitution of Alkyl Halides (R–X) :

$R–X + Nu^- \longrightarrow R–Nu + X$ (Here X = halogen & R,R′R″R‴ = Alkyl group).

S.No.	Reagent	Nucleophile (Nu^-)	Substitution product R–Nu	Class of main product	Main Mechanism
1	aq. NaOH (KOH)	HO^-	ROH	Alcohol	S_N2
2	H_2O	H_2O	ROH	Alcohol	S_N1
3	ROH	RO^-	ROR	Ether	S_N1
4	H_2S	HS^-	RSH	Thiol	S_N1
5	RSH	RS^-	RSR	Thioether or Sulphide	S_N1
6	NaSH or KSH	HS^-	RSH	Thiol	S_N2
7	RCOOH	$RCOO^-$	RCOOR	Ester	S_N1
8	RSK or RSNa	RS^-	RSR	Thioether or Sulphide	S_N2
9	NaN_3	N_3^-	RN_3	Alkyl azide	S_N2
10	aq. AgF, Hg_2F_2, CoF_2 & SbF_3 (Swart reaction)	F^-	RF	Alkyl fluoride	S_N1
11	Aq. $AgNO_3$, aq. $SbCl_5$	HO^-	ROH	Alcohol	S_N1
12	aq. Acetone	HO^-	ROH	Alcohol	S_N1
13	$AgNO_3$	NO_3^-	RNO_3	Nitrate	S_N2
14	NaOR′	$R'O^-$	ROR′	Ether	S_N2
15	NaI + Acetone (Finkelstein reaction)	I^-	R–I	Alkyl iodide	S_N2
16	NH_3	NH_3	RNH_2	Primary amine	S_N2
17	$R'NH_2$	$R'NH_2$	RNHR′	Sec. amine	S_N2
18	R′R″NH	R′R″NH	RNR′R″	Tert. amine	S_N2
19	R′R″R‴N	R′R″R‴N	$R'R''R'''N^+R\ X^-$	Alkyl ammonium salt	S_N2
20	KCN	$^-C{\equiv}N:$	RCN	Nitrile (cyanide)	S_N2
21	AgCN	–NC	RNC (isocyanide)	Isonitrile	S_N2
22	KNO_2	$O{=}N{-}O^-$	R–O–N=O	Alkyl nitrite	S_N2
23	$AgNO_2$	$-NO_2$	$R-NO_2$	Nitroalkane	S_N2
24	R′COOAg	$R'COO^-$	R′COOR	Ester	S_N2
25	$LiAlH_4$	H^-	RH	Hydrocarbon	S_N2
26	R'^-M^+	R'^-	RR′	Alkane	S_N2

Section (C) : Nucleophilic substitution (S_N) reaction of alcohols

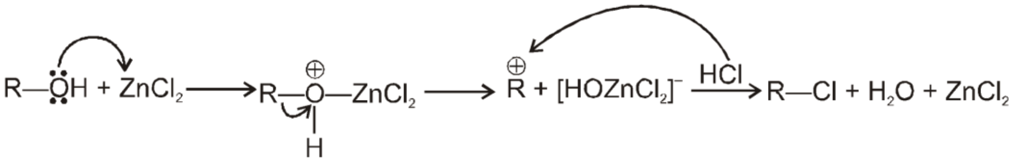
S_N1 reaction of alcohols :

(i) Reaction with H–X : β-branched 1ºalcohol, 2º alcohol and 3º alcohol give S_N1 reaction.

(ii) Lucas reagent : The 1 : 1 mixture of anhydrous $ZnCl_2$: HCl (conc.) is called Lucas reagent which is used to distinguish between 1º, 2º and 3º alcohols.

$$R{-}CH_2{-}OH \xrightarrow[ZnCl_2]{HCl} R{-}CH_2{-}Cl$$

Mechanism :

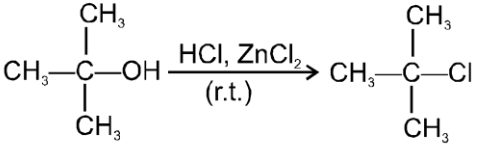


ZnCl

$ZnCl_2$ increases the rate of reaction by making –OH group into a much better leaving group just through complexation.

Reactivity of alcohols is 3ºROH > 2ºROH > 1ºROH

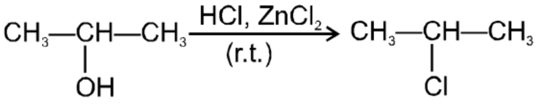
Ex.



$$CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}OH \xrightarrow[(r.t.)]{HCl,\ ZnCl_2} CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}Cl$$

(Turbidity appears quickly)

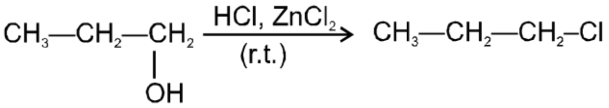
Ex.



$$CH_3{-}\underset{OH}{CH}{-}CH_3 \xrightarrow[(r.t.)]{HCl,\ ZnCl_2} CH_3{-}\underset{Cl}{CH}{-}CH_3$$

(Turbidity appears within 5 to 10 min.)

Ex.



$$CH_3{-}CH_2{-}\underset{OH}{CH_2} \xrightarrow[(r.t.)]{HCl,\ ZnCl_2} CH_3{-}CH_2{-}CH_2{-}Cl$$

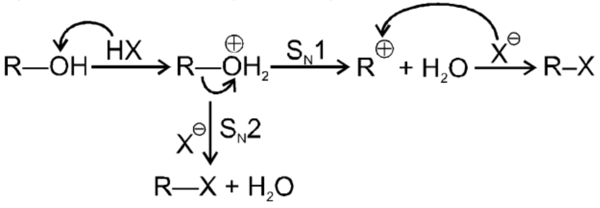
(Turbidity appears 30 to 60 min.)

S_N2 reaction of alcohols :

(a) In presence of HX :

$R{-}OH + HX \longrightarrow RX + H_2O$

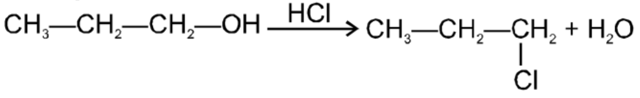
This is a nucleophilic substitution (S_N1/S_N2)



Mechanism :

Note : ***Mainly β-unsubstituted 1º alcohol give S_N2 reaction with HX.***

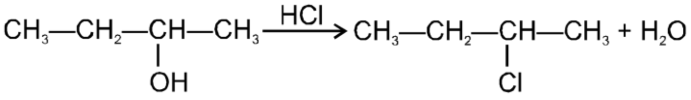
Ex.



$$CH_3{-}CH_2{-}CH_2{-}OH \xrightarrow{HCl} CH_3{-}CH_2{-}\underset{Cl}{CH_2} + H_2O$$

; (S_N2)

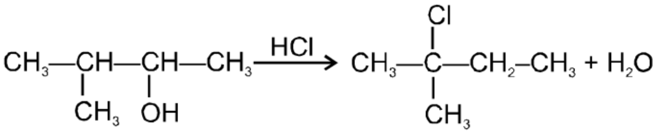
Ex.



$$CH_3{-}CH_2{-}\underset{OH}{CH}{-}CH_3 \xrightarrow{HCl} CH_3{-}CH_2{-}\underset{Cl}{CH}{-}CH_3 + H_2O$$

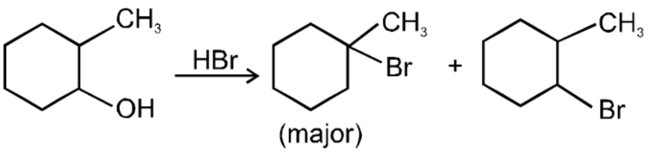
; (S_N1)

Ex.



$$CH_3{-}\underset{CH_3}{CH}{-}\underset{OH}{CH}{-}CH_3 \xrightarrow{HCl} CH_3{-}\overset{Cl}{\underset{CH_3}{C}}{-}CH_2{-}CH_3 + H_2O$$

; (S_N1)

Ex. 

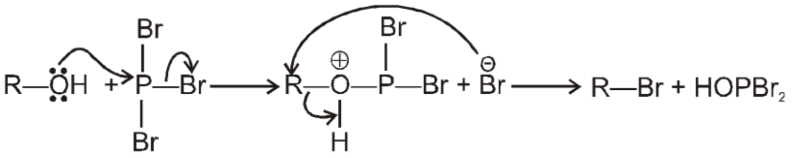
; (S_N1)

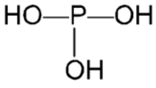
- Reactivity of HX is HI > HBr > HCl > HF.

(b) In presence of PX_3 ($P_4 + I_2$) :

$$R\text{–}OH \xrightarrow{PBr_3} R\text{–}Br$$

Mechanism :

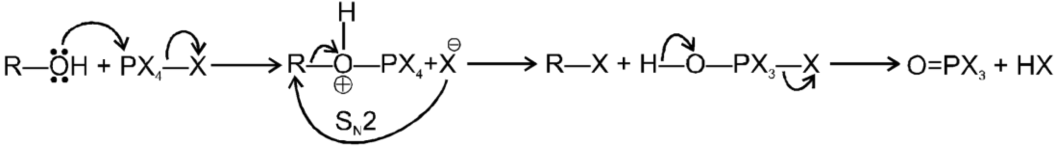


2R—OH + $HOPBr_2$ ——→ 2R–Br + 

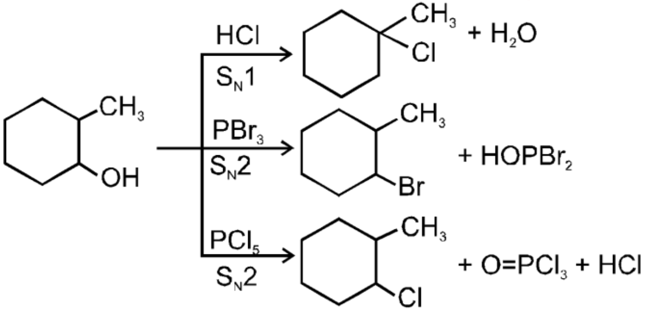
$$2R\text{—}OH + HOPBr_2 \longrightarrow 2R\text{–}Br + \underset{\displaystyle OH}{\underset{|}{HO\text{—}P\text{—}OH}}$$

Note : Phosphorus tribromide and triiodide are usually generated in situation (produced in the reaction mixture) by the reaction of red phosphorus with bromine and iodine respectively.

(c) In presence of PX_5 :



Both the PX_3 & PX_5 proceeds via S_N2 pathways, No.rearrangement occurs.
Only 1ºR—OH and 2ºR—OH undergo this type of reaction. 3º R—OH undergoes elimination reaction.

Ex. 

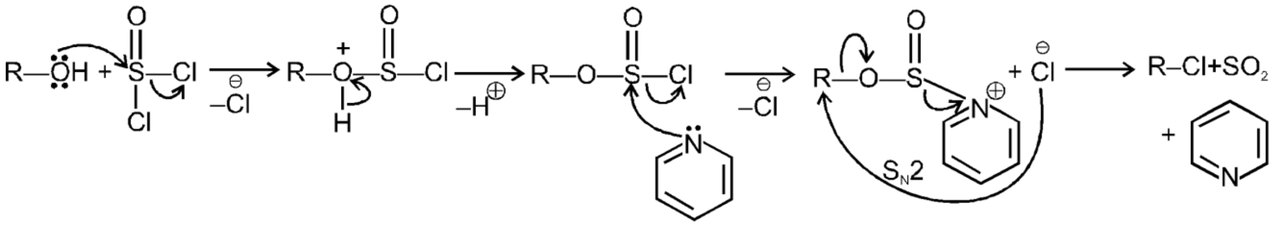
(d) In persence of $SOCl_2$ (Thionyl chloride) with pyridine

(Industrial method of preparation of Alkylchloride) :

Thionyl chloride is preferred because the other two products are escapable gases. Hence the reaction gives pure alkyl halides. It is known as **Darzen process.**

$$R\text{—}OH \xrightarrow[\text{pyridine}]{SOCl_2} R\text{—}Cl + SO_2\ (S_N2)$$

Mechanism :

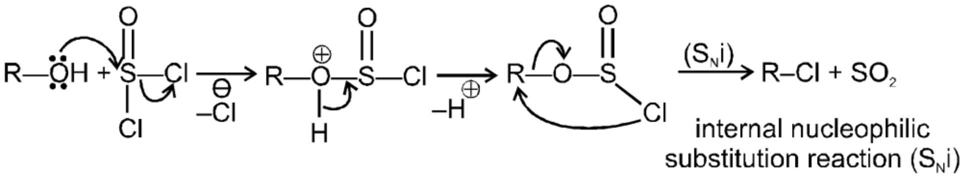


- $SOCl_2$ with pyridine undergo S_N2 reaction so inversion of configuration is obtained in product.

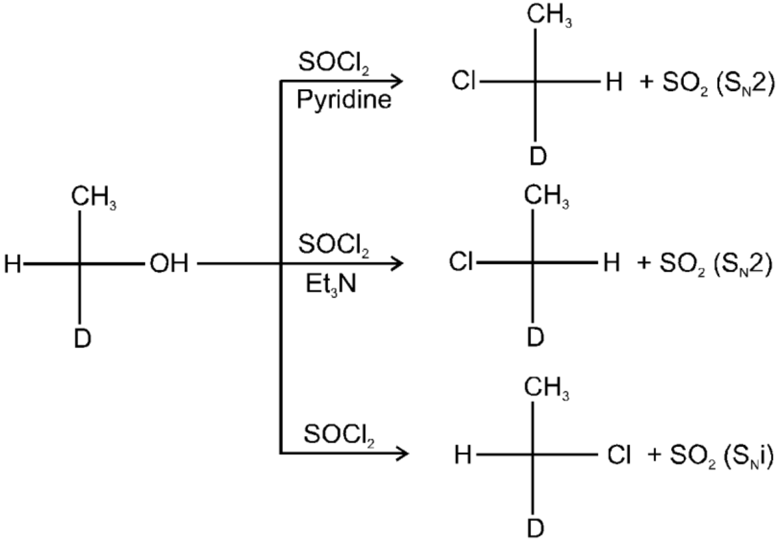
(e) In persence of $SOCl_2$ without pyridine : [S_Ni reaction of alcohol]

$R—OH \xrightarrow{SOCl_2} R—Cl + SO_2\ (S_Ni)$

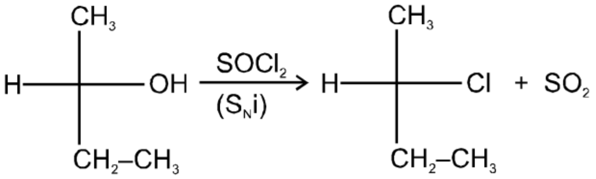
Mechanism :



$SOCl_2$ without pyridine or base undergo S_Ni reaction, so **retention of configuration** is obtained in product.



Ex.



Ex.

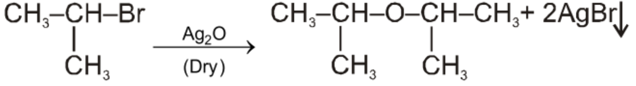
Section (D): Preparation and chemical reactions of ethers

(a) Preparation of ether :

(i) From Wiliamsons synthesis method :

$R–X + R'\overset{-}{O}\overset{+}{Na} \longrightarrow R–O–R' + NaX$

(ii) By using dry Ag₂O : $R–X \xrightarrow[(Dry)]{Ag_2O} R–O–R + 2\ AgX$



$CH_3-\underset{CH_3}{\underset{|}{C}H}-Br \xrightarrow[(Dry)]{Ag_2O} CH_3-\underset{CH_3}{\underset{|}{C}H}-O-\underset{CH_3}{\underset{|}{C}H}-CH_3 + 2AgBr\downarrow$

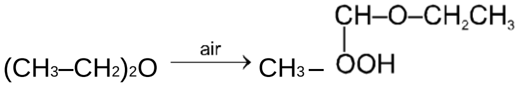
Ex.

(iii) From alcohols :

$R–O–H + H_2SO_4 \xrightarrow{140^\circ C} R–O–R + H_2O$
(1^o alcohol)

(b) Purification of ethers :

On standing in contact with air they form unstable peroxide ($R_2O \rightarrow O$) which is explosive in nature. Peroxide is formed at the carbon atom next to the etherial oxygen.

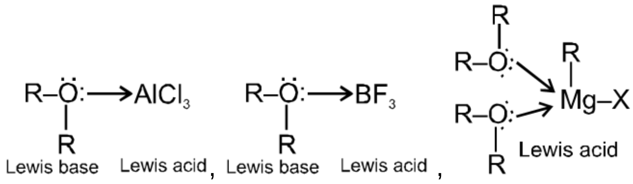


$(CH_3–CH_2)_2O \xrightarrow{air} CH_3-\overset{\overset{CH-O-CH_2CH_3}{|}}{OOH}$

- The presence of peroxide in ether can be identified on shaking it with freshly prepared ferrous sulphate solution followed by addition of potassium thiocyanate. This result into red colour of ferric thiocyanate. During the reaction peroxide oxidises Fe^{2+} to Fe^{3+} which reacts with thiocyanate ion to give red colour of ferric thiocyanate.

$$Fe^{2+} \xrightarrow{\text{peroxide}} Fe^{3+} \xrightarrow{CNS^{\ominus}} \underset{\text{(Red colour)}}{Fe(CNS)_3}$$

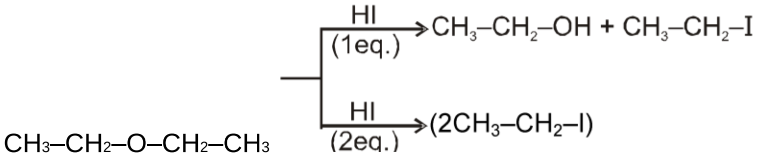
- Ethers are purified from peroxide before use. The peroxide from ether can be removed by treating ether with KI solution where peroxide is reduced to ether and iodide ion is oxidised to I_2 molecule.
- Peroxide formation can be checked by adding few ammount of Cu_2O in ether.
- Ether is lewis base hence forms co-ordinate bond with lewis acid.



(c) Chemical properties of ethers :

(i) Reaction with HI :

$$R{-}O{-}R' \xrightarrow[\text{(1 eq.)}]{HI} R{-}OH + R'\,I$$



Ex. $CH_3{-}CH_2{-}O{-}CH_2{-}CH_3$

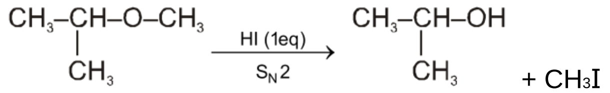
$$CH_3{-}CH_2{-}O{-}CH_2{-}CH_3 \xrightarrow[\text{(1eq.)}]{HI} CH_3{-}CH_2{-}OH + CH_3{-}CH_2{-}I$$

$$CH_3{-}CH_2{-}O{-}CH_2{-}CH_3 \xrightarrow[\text{(2eq.)}]{HI} (2CH_3{-}CH_2{-}I)$$

- Those protic acids whose conjugate base is a good nucleophile leads to cleavage of ethers. HI is such a very prominent acid of this kind.
- In most cases of unsymmetrical ethers 1 eq. of HI leads to give a mixture of four products in which it is not easy to predict the major product. However if 2 eq. of HI is used then two iodides are obtained.

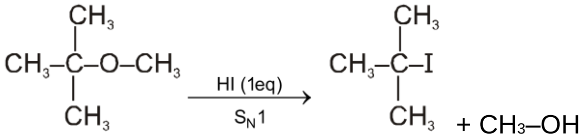
Ex. $$CH_3{-}CH_2{-}O{-}CH_3 \xrightarrow[S_N2]{HI\ (1eq)} CH_3{-}I + CH_3{-}CH_2{-}OH.$$

Ex.



$$CH_3{-}\underset{\substack{|\\CH_3}}{CH}{-}O{-}CH_3 \xrightarrow[S_N2]{HI\ (1eq)} CH_3{-}\underset{\substack{|\\CH_3}}{CH}{-}OH + CH_3I$$

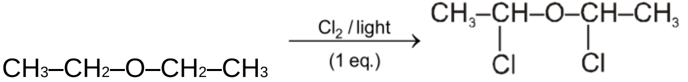
Ex.



$$CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\substack{|\\CH_3}}{C}}{-}O{-}CH_3 \xrightarrow[S_N1]{HI\ (1eq)} CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\substack{|\\CH_3}}{C}}{-}I + CH_3{-}OH$$

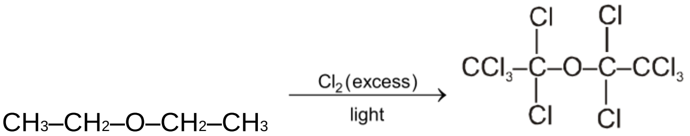
(ii) Other Reactions of Ethers :

Ex.



$$CH_3{-}CH_2{-}O{-}CH_2{-}CH_3 \xrightarrow[\text{(1 eq.)}]{Cl_2\,/\,light} CH_3{-}\underset{\substack{|\\Cl}}{CH}{-}O{-}\underset{\substack{|\\Cl}}{CH}{-}CH_3$$

Ex.



$$CH_3{-}CH_2{-}O{-}CH_2{-}CH_3 \xrightarrow[light]{Cl_2\,(excess)} CCl_3{-}\overset{\substack{Cl\\|}}{\underset{\substack{|\\Cl}}{C}}{-}O{-}\overset{\substack{Cl\\|}}{\underset{\substack{|\\Cl}}{C}}{-}CCl_3$$

Ex. $$CH_3{-}CH_2{-}O{-}CH_2{-}CH_3 \xrightarrow{dil.\ H_2SO_4} CH_3{-}CH_2{-}OH + CH_3{-}CH_2{-}OSO_3H \xrightarrow{H_2O} CH_3{-}CH_2{-}OH$$

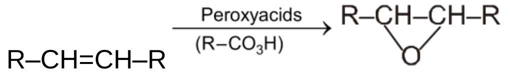
Ex. $$CH_3{-}CH_2{-}O{-}CH_2{-}CH_3 \xrightarrow{Conc.\ H_2SO_4} CH_3{-}CH_2{-}OH + CH_3{-}CH_2{-}OSO_3H \xrightarrow{\Delta} CH_2 = CH_2$$

Ex. $$CH_3{-}CH_2{-}O{-}CH_2{-}CH_3 \xrightarrow[(2)\ AlCl_3]{(1)\ CH_3COCl} CH_3{-}CH_2{-}Cl + CH_3{-}COOCH_2{-}CH_3$$

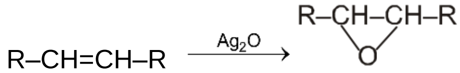
Ex. $$CH_3{-}CH_2{-}O{-}CH_2{-}CH_3 \xrightarrow[(2)\ AlCl_3]{(1)\ (CH_3CO)_2O} 2CH_3{-}COOCH_2{-}CH_3$$

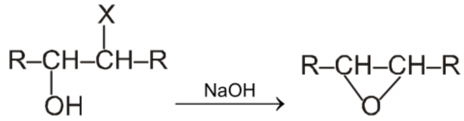
(d) Epoxides

(i) Preparation of epoxides : Epoxides are strained ethers and are more reactive than normal ethers. These may be prepared by following methods

(a)


(syn addition)

(b)


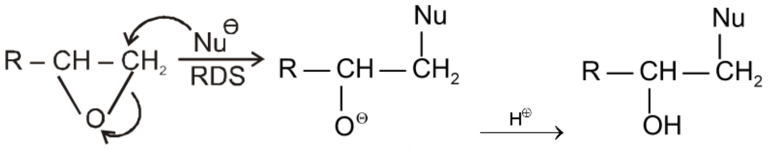
(c)


(ii) S_N Reaction of epoxides :

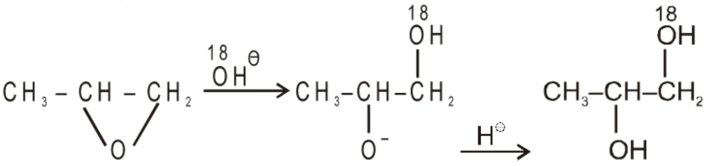
Epoxides are much more reactive than other ethers because of angle strain therefore epoxide readily undergo nucleophilic substitution reaction.

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

Mechanism :

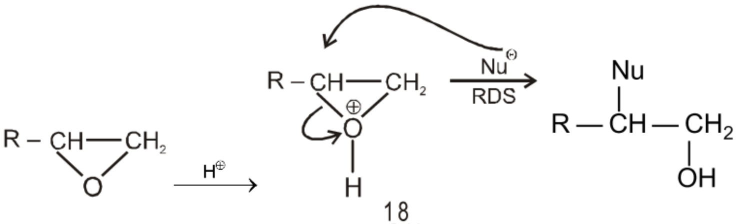


Ex.



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

Mechanism :



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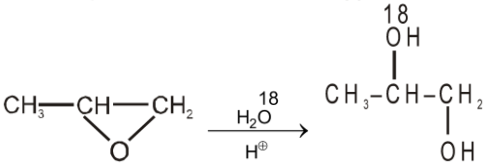
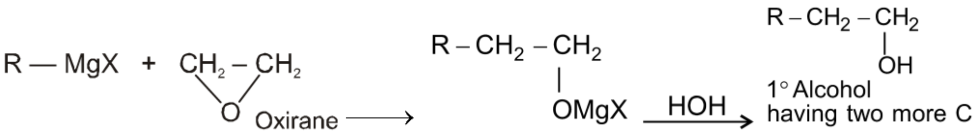
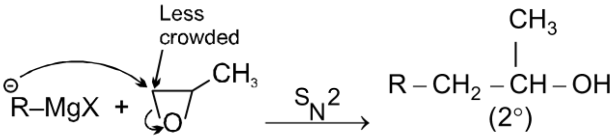


(3) Reaction with Grignard Reagent : [Mechanism S_N2]

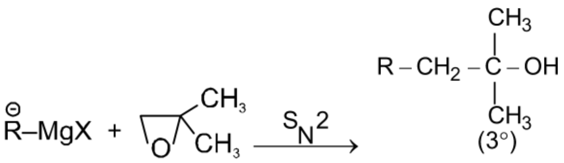
Ex.



Ex.



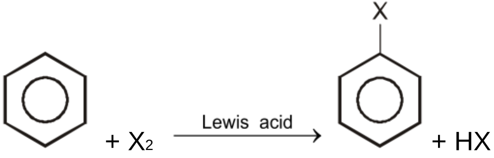
Ex.



Section (E): Preparation and nucleophilic substitution of Haloarenes

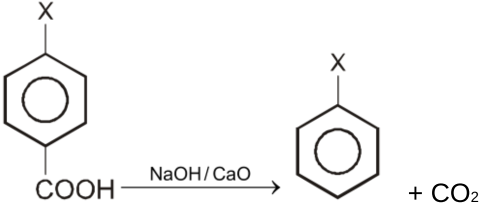
(a) Preparation of aryl halides (haloarenes)

1. By halogenation of benzene :



$X_2 = Cl_2, Br_2$; Lewis acid = $FeCl_3$, $AlCl_3$, $ZnCl_2$, etc.

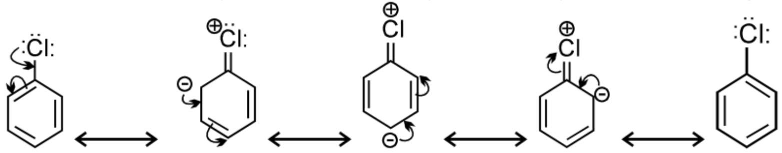
2. By Decarboxylation :



(b) Nucleophilic substitution reaction of aryl halides :

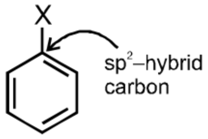
Aryl halides are extremely less reactive towards nucleophilic substitution reactions due to the following reasons :

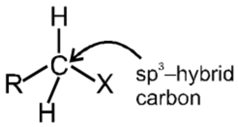
(i) Resonance effect : In haloarenes, the electron pairs on halogen atom are in conjugation with π-electrons of the ring and the following resonating structures are possible.



C—Cl bond acquires a partial double bond character due to resonance. As a result, the bond cleavage in haloarene is difficult than haloalkane and therefore, they are less reactive towards nucleophilic substitution reaction.

(ii) Difference in hybridisation of carbon atom in C—X bond: In haloalkane, the carbon atom attached to halogen is sp^3 hybridised while in case of haloarene, the carbon atom attached to halogen is sp^2-hybridised.





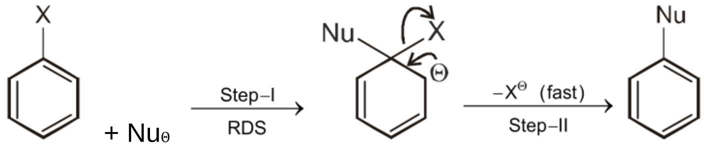
The sp^2 hybridised carbon with a greater s-character is more electronegative and can hold the electron pair of C—X bond more tightly than sp^3-hybridised carbon in haloalkane with less s-chararcter. Thus, C—Cl bond length in haloalkane is 177pm while in haloarene is 169 pm. Since it is difficult to break a shorter bond than a longer bond, therefore, haloarenes are less reactive than haloalkanes towards nucleophilic substitution reaction.

(iii) Instability of phenyl cation: In case of haloarenes, the phenyl cation formed as a result of self-ionisation will not be stabilised by resonance and therefore, S_N1 mechanism is ruled out.

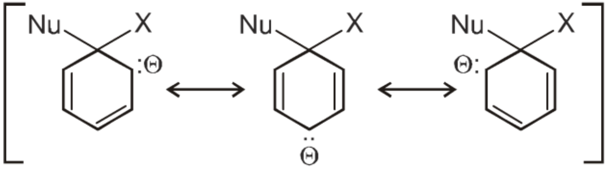
(iv) Because of repulsion between the electron rich nucleophile and electron rich arenes.

Mechanism: Bimolecular nucleophilic substitution S_N2 Ar

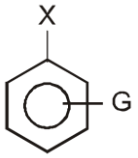
An electron withdrawing group at ortho or para positions with respect to a good leaving groups are necessary conditions for S_N2 Ar.



Intermediate ion is stabilized by resonance, and stable salts are called Meisenheimer salts.



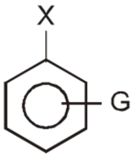
- A group that withdraws electrons tends to neutralize the negative charge of the ring and this dispersal of the charge stabilizes the carbanion.



G withdraws electrons : stabilizes carbanion, activates the Ar-S_N2 reaction.

($-\overset{+}{N}(CH_3)_3$, $-NO_2$, –CN, $-SO_3H$, –COOH, –CHO, –COR, –X)

- A group that releases electrons tends to intensify the negative charge, destabilizes the carbanion, and thus slows down reaction.



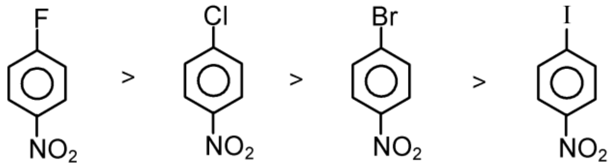
G ($-NH_2$, –OH, –OR, –R) releases electrons : destabilizes carbanion, deactivates the Ar-S_N2 reaction.

Element effect :

The fact that fluoro is the most reactive among the halogens in most ArS_N2 but in S_N1 & S_N2 mechanism where fluoro is the poorest leaving group and least reactive among halogens.

EWG ↑ Rate of reaction ↑

Reactivity order towards (S_N2Ar)



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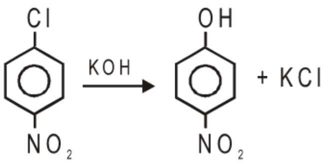

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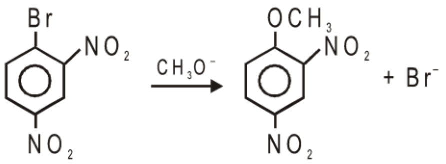
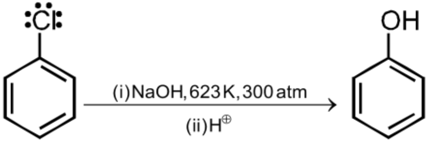
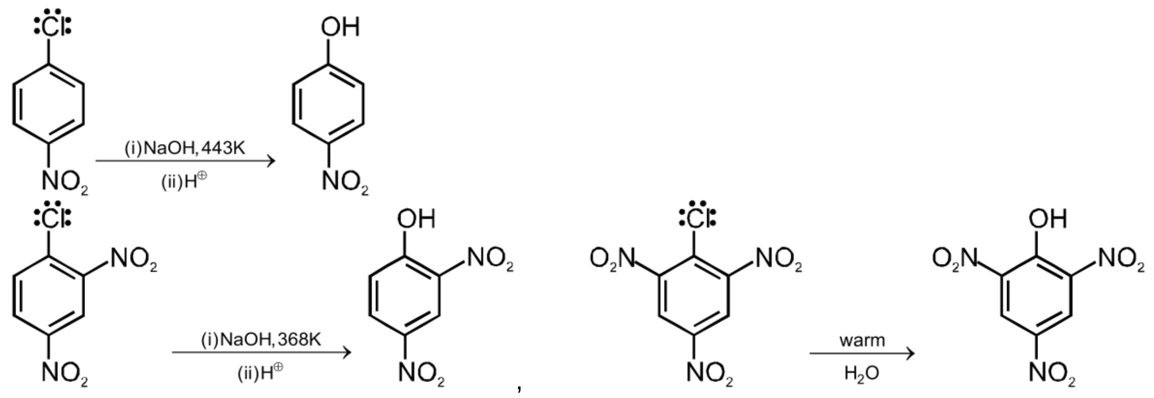


Replacement by hydroxyl group:

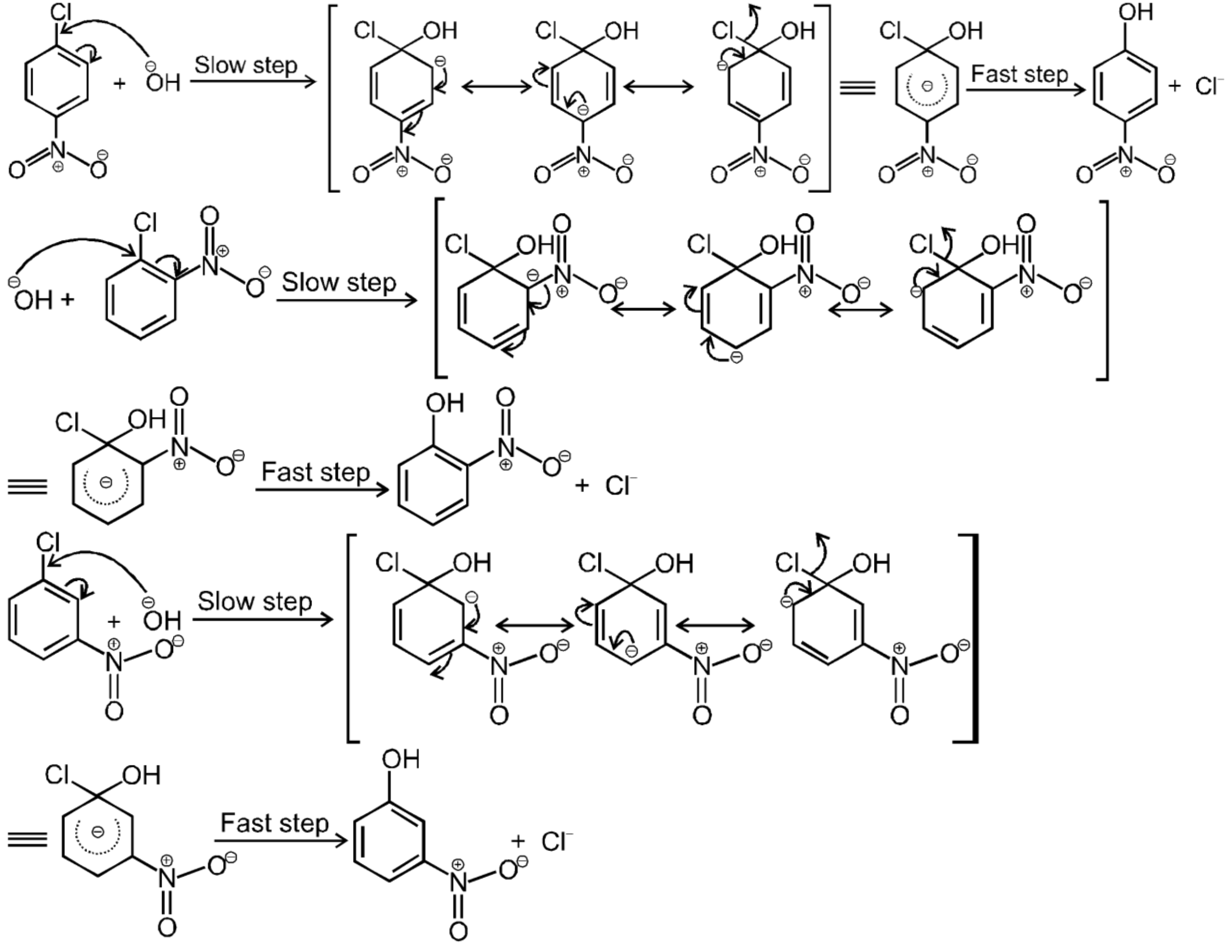
Chlorobenzene can be converted into phenol by heating in aqueous sodium hydroxide solution at a temperature of 623 K and a pressure of 300 atmosphere.



The presence of an electron withdrawing group ($-NO_2$) at ortho and para positions increases the reactivity of haloarenes.



The effect is pronounced when (–NO_2) group is introduced at ortho and para positions. However, no effect on reactivity of haloarenes is observed by the presence of electron withdrawing group at meta-position. Mechanism of the reaction is as depicted :



Can you think why does NO_2 group show its effect only at ortho- and para- positions and not at meta-position?

As shown, the presence of nitro group at ortho- and para-positions withdraws the electron density from the benzene ring and thus facilitates the attack of the nucleophile on haloarene. The carbanion thus formed is stabilised through resonance. The negative charge appeared at ortho- and para- positions with respect to the halogen substituent is stabilised by –NO_2 group while in case of meta-nitrobenzene, none of the resonating structures bear the negative charge on carbon atom bearing the –NO_2 group. Therefore, the presence of nitro group at meta- position does not stabilise the negative charge and no significant effect on reactivity is observed by the presence of –NO_2 group at meta-position.