# Pharmaceutical Organic Chemistry-1

## Chapter-4: Alcohols, Phenols and Ethers

# Alcohols, Phenols and Ethers

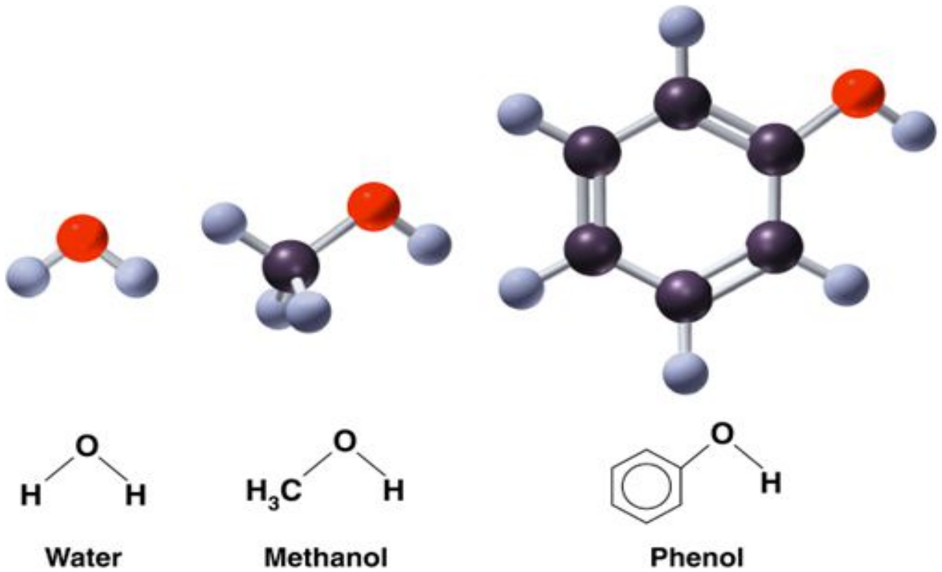
- Alcohols, ethers and phenols have a common functional group, the hydroxyl group, -OH.

| Ph-O-H | R-O-R | R-OH | H-O-H |
|---|---|---|---|
| Phenol | Ethers | Alcohol | Water |

- Alcohols are compounds whose molecules have a hydroxyl group attached to a *saturated* carbon atom.
- Phenols are compounds that have a hydroxyl group attached directly to a *benzene ring* .
- Ethers are compounds whose molecules have an oxygen atom bonded to two carbon atom.

# Alcohols and Phenols

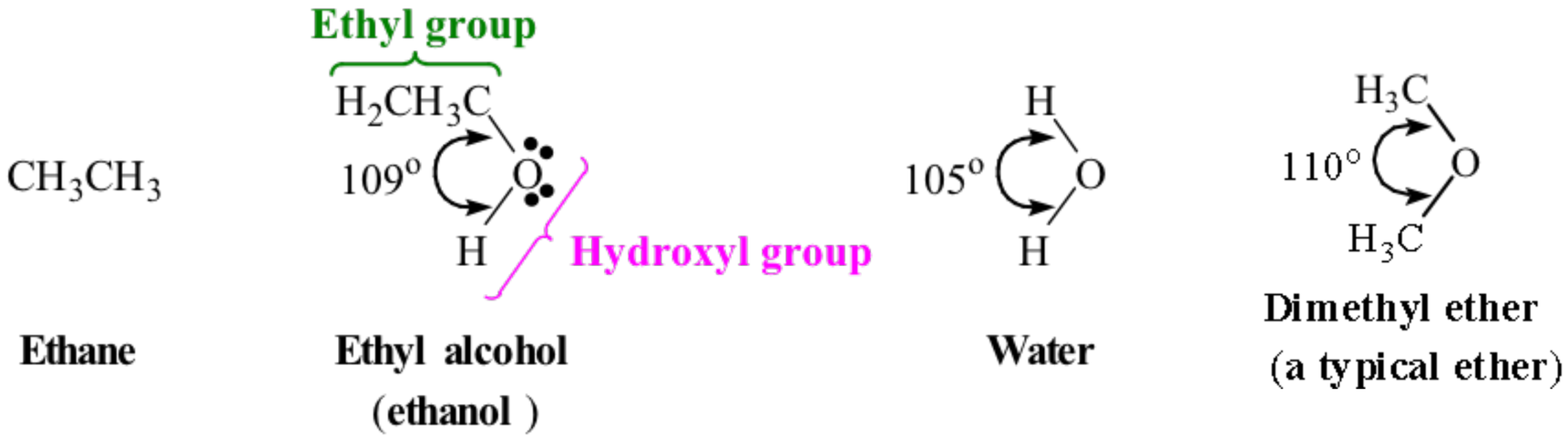
- **Alcohols and phenols** may be viewed as organic *derivatives of water*.




- **Alcohols** have the general formula R-OH, and structurally similar to water, but with one of the hydrogens replaced by an alkyl group.
- **Phenols** have a hydroxyl group attached directly to an aromatic ring.

# Alcohols

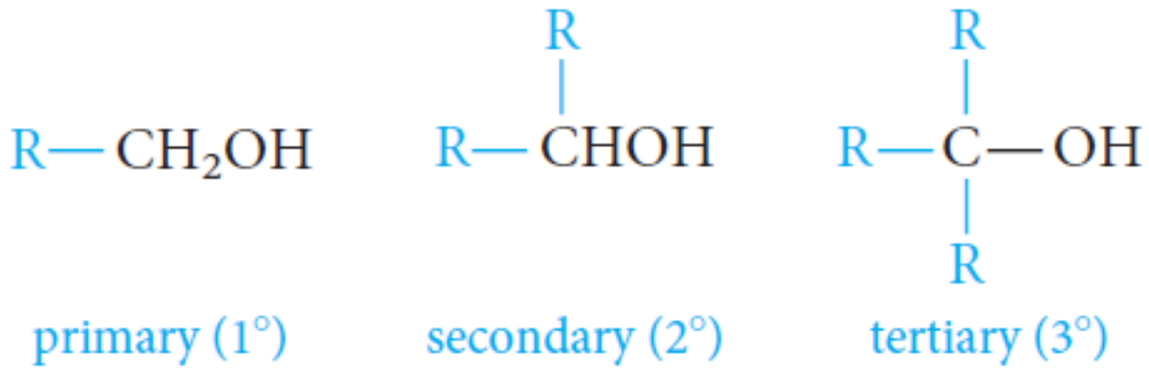

- Alcohols can be viewed in two ways structurally:
  ((1))as **hydroxyl derivatives** of alkanes
  and (2) as **alkyl derivatives** of water.




**Ethane** | **Ethyl alcohol (ethanol )** | **Water** | **Dimethyl ether (a typical ether)**

# Classification of Alcohols

- **Alcohols** are classified as primary (1°), secondary (2°), or tertiary (3°), depending on whether one, two, or three organic groups are connected to the hydroxyl-bearing carbon atom.

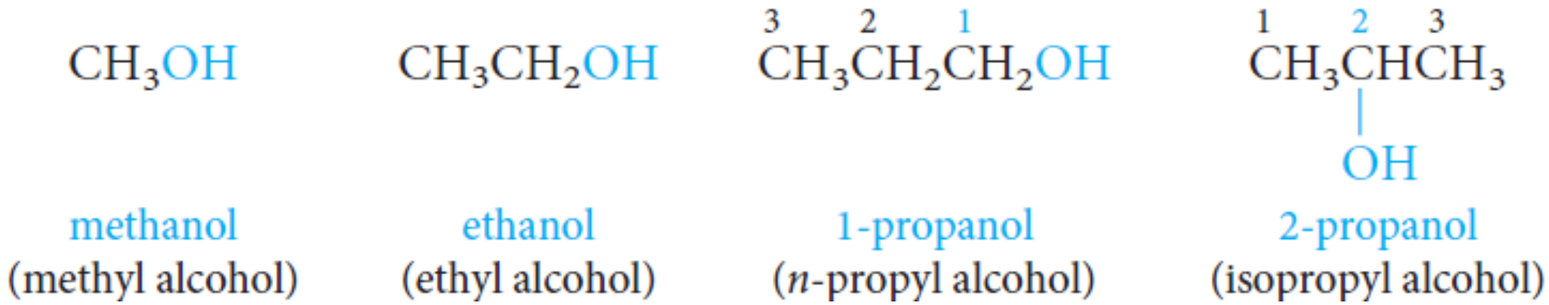



- **Methyl alcohol**, which is not strictly covered by this classification, is usually grouped with the primary alcohols.

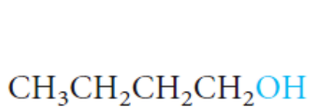
# Nomenclature of Alcohols

- The **common names** for the simplest alcohols consist of alkyl group attached to the hydroxyl function followed by the word alcohol: Alkyl *alcohol* .
- In the **IUPAC system,** alcohols are named according to the following rules.

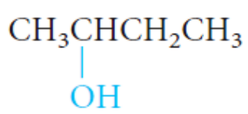
1. Select the longest continuous carbon chain that *contains the* -OH *group*.
   Drop the – *e* ending of the parent alkane and replace it by the suffix *-ol:* *Alkanol*
2. When isomers are possible, the chain is numbered so as to give the functional group (-OH) the *lowest possible number*.



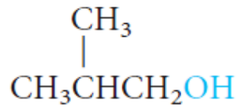
# Nomenclature of Alcohols



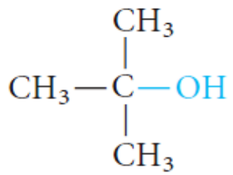
1-butanol
(*n*-butyl alcohol)



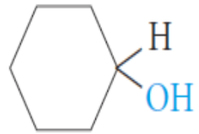
2-butanol
(*sec*-butyl alcohol)



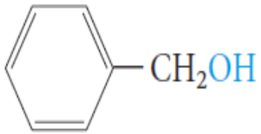
2-methyl-1-propanol
(isobutyl alcohol)



2-methyl-2-propanol
(*tert*-butyl alcohol)



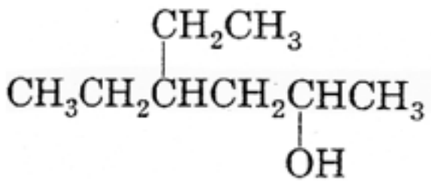
cyclohexanol
(cyclohexyl alcohol)



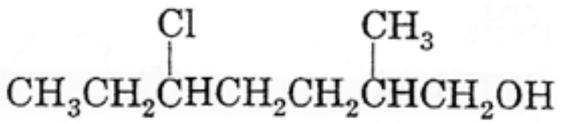
phenylmethanol
(benzyl alcohol)

**3. When alkyl side chains or other groups are present,** they are named alphabetically and their positions are indicated by a number.

*The position of the functional group (-OH) is always given the lowest possible number at the end of the name.*



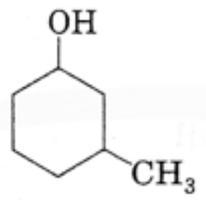
4-Ethyl-2-hexanol
(*not* 3-Ethyl-5-hexanol)



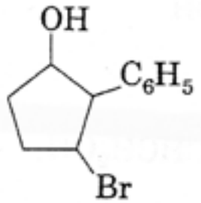
5-Chloro-2-methyl-1-heptanol
(*not* 3-Chloro-6-methyl-7-heptanol)

# Nomenclature of Alcohols

**For cyclic alcohols**, numbering always starts from the carbon bearing the -OH group.



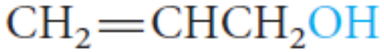

3-Methylcyclohexanol
(*not* 1-Methyl-3-cyclohexanol)



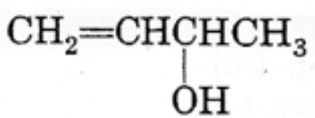

3-Bromo-2-phenylcyclopentanol
(*not* 1-Bromo-2-phenyl-3-cyclopentanol)

**4. With Unsaturated Alcohols; If a molecule contains both an -OH group and a C=C or C-C triple bond,** the -OH group takes preference before the double or triple bonds in getting the lower number.

*The name should include (if possible) both the hydroxyl and the unsaturated groups, even if this does not make the longest chain the parent hydrocarbon.*

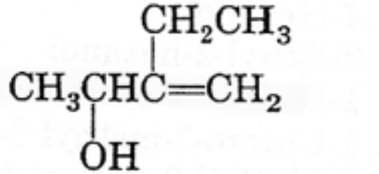



2-propen-1-ol
(allyl alcohol)




3-Buten-2-ol
(*not* 1-Buten-3-ol)


3-Butyn-1-ol
(*not* 1-Butyn-4-ol)

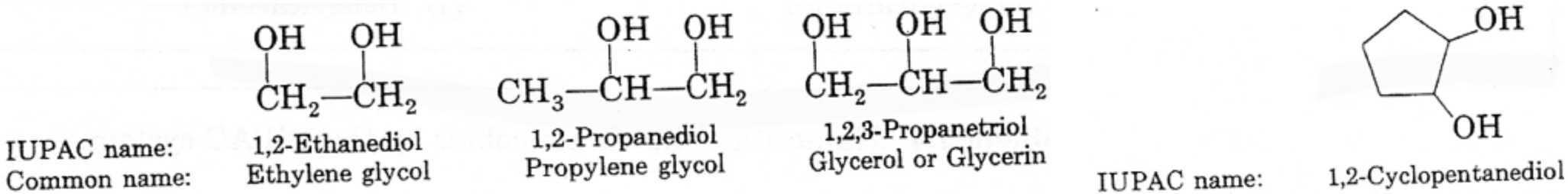



3-Ethyl-3-buten-2-ol
(longest chain including C=C)

# Nomenclature of Alcohols

## Alcohols with More Than One Hydroxyl Group

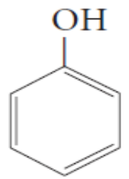
- Compounds with two adjacent alcohol groups are called *glycols*.
  *The most important example is ethylene glycol.*
- Compounds with more than two hydroxyl groups are also known, and several, such as glycerol and sorbitol, are important commercial chemicals.



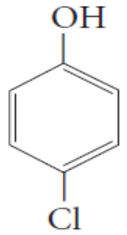

- *Ethylene glycol is used as the "permanent" antifreeze in automobile radiators and as a raw material in the manufacture of Dacron.*
- *Ethylene glycol is completely miscible with water.*
- *Glycerol is a syrupy, colorless, water-soluble, high-boiling liquid with a distinctly sweet taste. Its soothing qualities make it useful in shaving and toilet soaps and in cough drops and syrups.*

# Nomenclature of Phenols

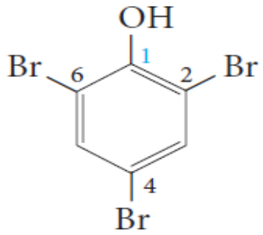
- **Phenols** are usually named as derivatives of the parent compounds.



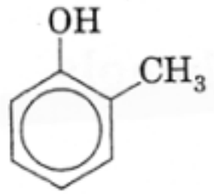
phenol



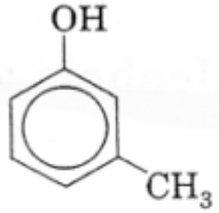
*p*-chlorophenol



2,4,6-tribromophenol



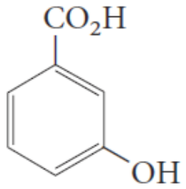
*o*-Cresol



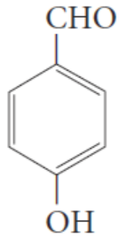
*m*-Cresol

*p*-Cresol

- The hydroxyl group is named as a substituent when it occurs in the same molecule with carboxylic acid, aldehyde, or ketone functionalities, which have **priority in naming**.

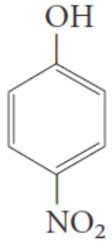


*m*-hydroxy benzoic acid



*p*-hydroxybenzaldehyde

but



*p*-nitrophenol
(*not* *p*-hydroxynitrobenzene)

# Physical Properties of Alcohols

## Physical State

*The simplest alcohol, methanol, is a liquid at room temperature.*

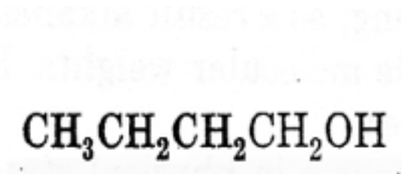
*In contrast, alkanes from methane to butane (C1-C4)are gases.*

## Solubility

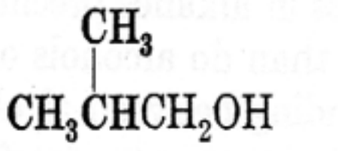
- *The lower alcohols are completely miscible with water.*
- *As the number of carbons in the alcohol increases, the solubility in water*

## Boiling Points

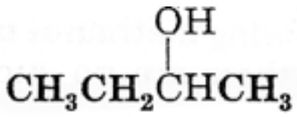
- *Series of normal alcohols; The boiling points increase with increase in molecular weights.*
- *A comparison of boiling points among isomeric alcohols; The boiling points decrease as the number of alkyl branches from the carbinol group increases.*



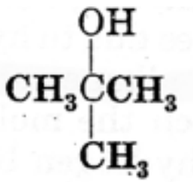

1-Butanol
(mol wt = 74; bp = 118°C)




2-Methyl-1-propanol
(mol wt = 74; bp = 108°C)




2-Butanol
(mol wt = 74; bp = 99.5°C)




2-Methyl-2-propanol
(mol wt = 74; bp = 83°C)

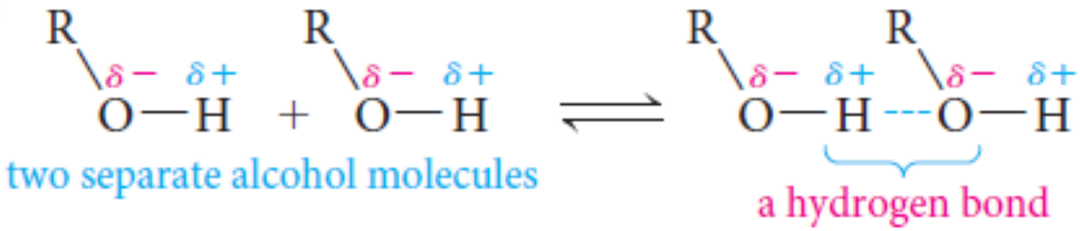
# Hydrogen Bonding in Alcohols

- The **boiling points** (bp's) of alcohols are much higher than those of ethers or hydrocarbons with similar molecular weights.

| | $CH_3CH_2OH$ | $CH_3OCH_3$ | $CH_3CH_2CH_3$ |
|---|---|---|---|
| mol wt | 46 | 46 | 44 |
| bp | +78.5°C | −24°C | −42°C |

*Why?* Because alcohols form *hydrogen bonds* with one another.

*The O-H bond is polarized by the high electronegativity of the oxygen atom and places a partial positive charge on the hydrogen atom and a partial negative charge on the oxygen atom*




*Two or more alcohol molecules thus become loosely bonded to one another through hydrogen bonds.*

# Hydrogen Bonding in Alcohol

- Consequently, alcohols have relatively high boiling points because they must supply enough heat to break the hydrogen bonds before each molecule.
- Hydrogen bonds are weaker than ordinary covalent bonds.
- Water, of course, is also a hydrogen-bonded liquid.
- The lower molecular-weight alcohols can readily replace water molecules in the hydrogen bonded network.
- This accounts for the complete miscibility of the lower alcohols with water.
- However, as the organic chain lengthens and the alcohol becomes relatively more hydrocarbon like, its water solubility decreases.

**Table 7.1 Boiling Point and Water Solubility of Some Alcohols**

| Name | Formula | bp, °C | Solubility in $H_2O$ g/100 g at 20°C |
|---|---|---|---|
| methanol | $CH_3OH$ | 65 | completely miscible |
| ethanol | $CH_3CH_2OH$ | 78.5 | completely miscible |
| 1-propanol | $CH_3CH_2CH_2OH$ | 97 | completely miscible |
| 1-butanol | $CH_3CH_2CH_2CH_2OH$ | 117.7 | 7.9 |
| 1-pentanol | $CH_3CH_2CH_2CH_2CH_2OH$ | 137.9 | 2.7 |
| 1-hexanol | $CH_3CH_2CH_2CH_2CH_2CH_2OH$ | 155.8 | 0.59 |

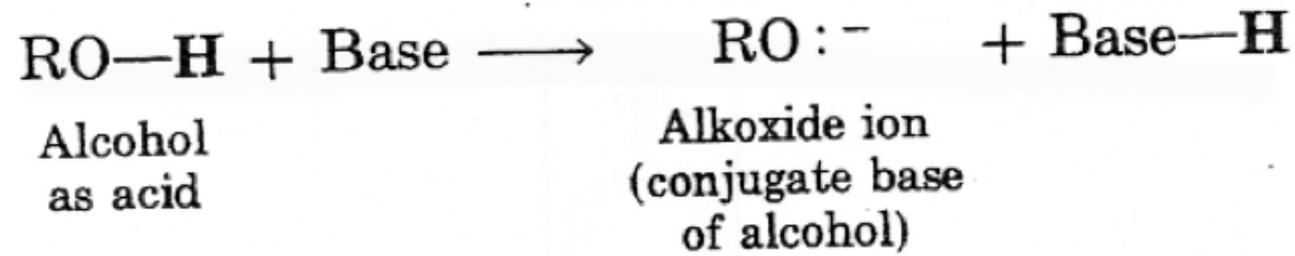
# Physical Properties of Phenols

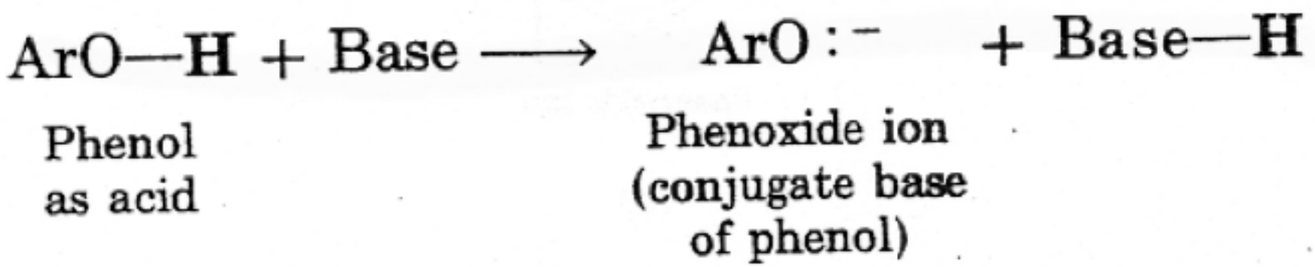
- **Phenol** is a colorless, crystalline, low-melting solid, with a high boiling point, that is moderately soluble in water.
- Most other phenols also are solids, with slight solubility in water and high boiling points.
- The most significant physical property that distinguishes alcohols from phenols is the acidity of phenols.

# The Acidity of Alcohols and Phenols

- **Like water, alcohols and phenols are weak acids.**

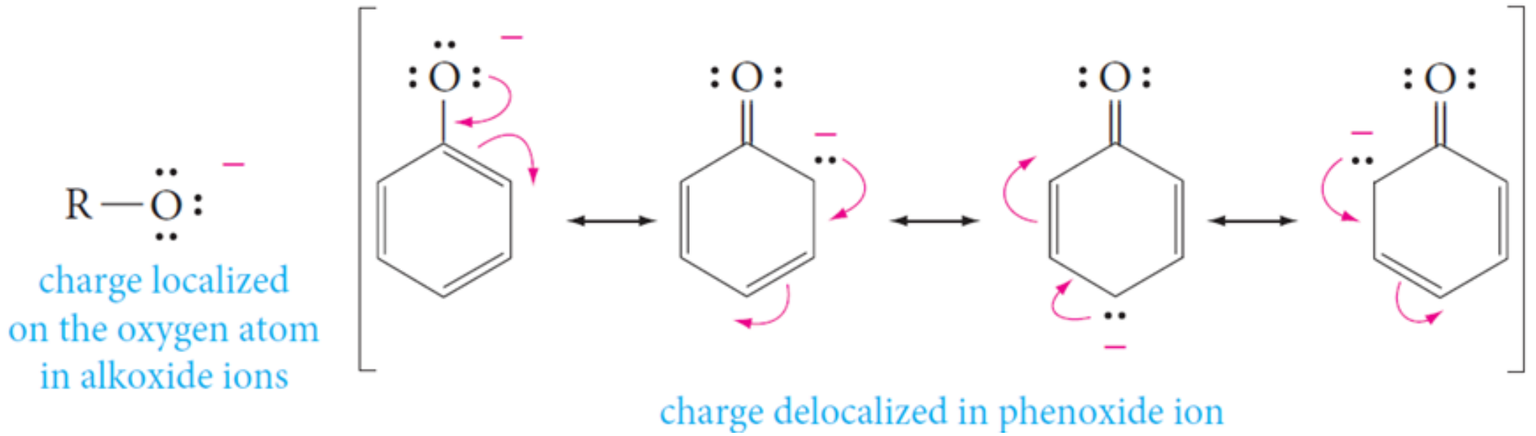
  *The hydroxyl group can act as a proton donor, and dissociation occurs in a manner similar to that for water*



# The Acidity of Alcohols and Phenol

- **Phenols are stronger acids than alcohols** mainly because the corresponding phenoxide ions are stabilized by resonance.

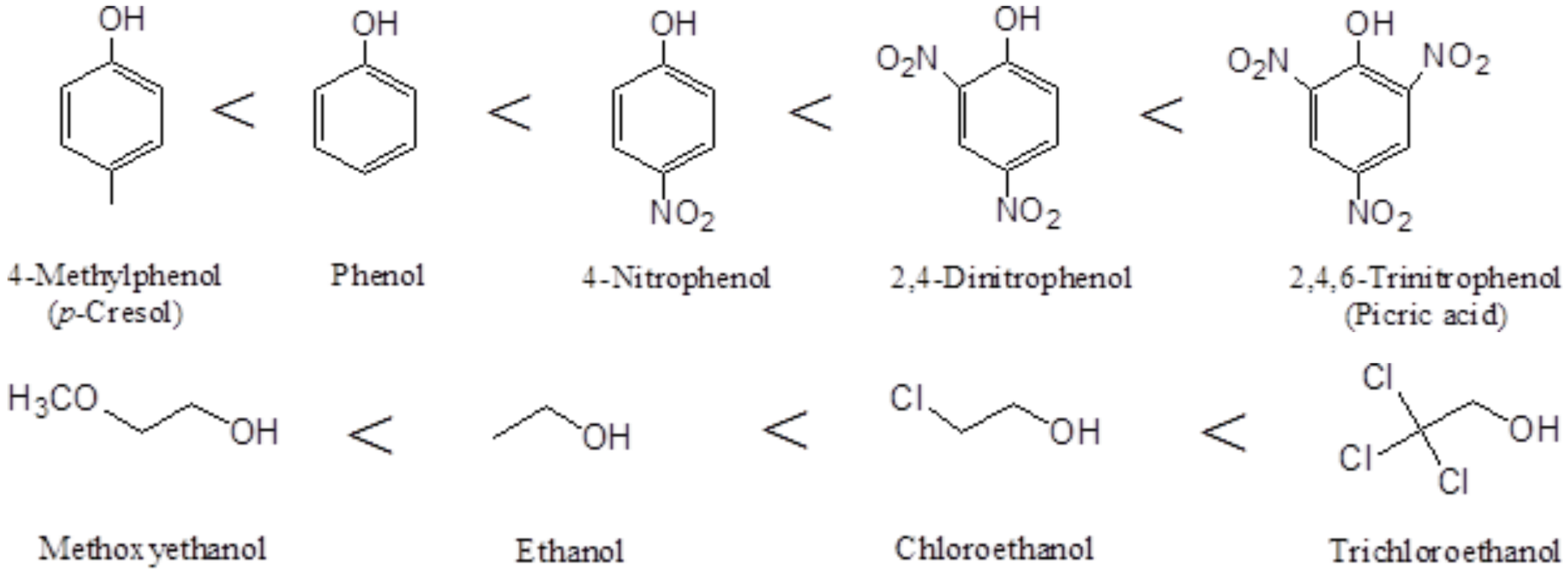



*The negative charge of an alkoxide ion is concentrated on the oxygen atom, but the negative charge on a phenoxide ion can be delocalized to the ortho and para ring positions through resonance.*

*Because phenoxide ions are stabilized in this way, the equilibrium for their formation is more favorable than that for alkoxide ions*

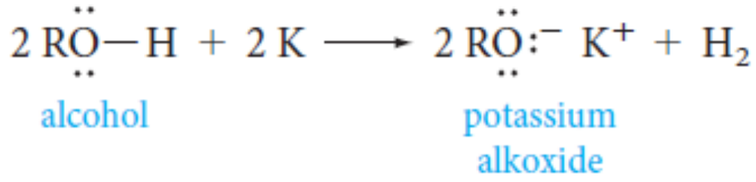
# The Acidity of Alcohols and Phenol

- All **electron-withdrawing groups increase acidity** by stabilizing the conjugate base. **Electron-donating groups decrease acidity** because they destabilize the conjugate base.



# The Acidity of Alcohols and Phenol

- **Alkoxides**, the conjugate bases of alcohols, can be prepared by the reaction of an alcohol with sodium or potassium metal.

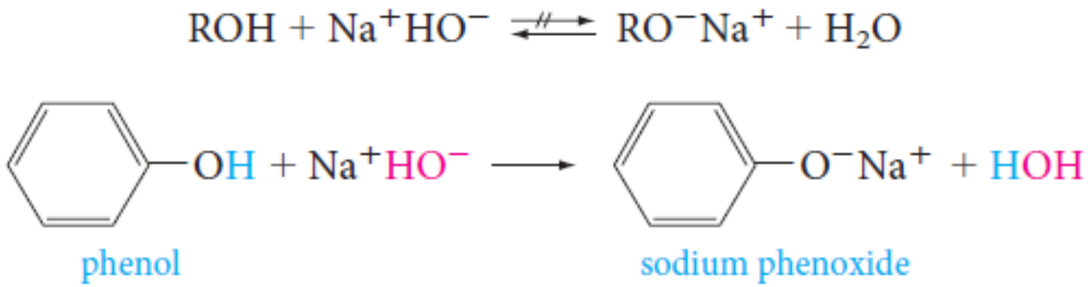



- Treatment of alcohols with sodium hydroxide does not convert them to their alkoxides.

*This is because alkoxides are stronger bases than hydroxide ion, so the reaction goes in the reverse direction.*

*Since alcohols are weaker acids than water, it is not possible to form the salt of an alcohol in aqueous alkaline solutions.*

- Treatment of phenols with sodium hydroxide converts them to phenoxide ions.



# Preparation of Alcohols

- ***F r o m***

## A. Hydration of Alkenes

1. **Addition of water to a double bond in the presence of an *acid catalyst, H+***
2. **The addition follows *Markovnikov's rule*.**
3. ***It is not possible to prepare primary alcohols*** **except Ethanol.**

$$RCH{=}CHR + H{-}OH \overset{H^+}{\rightleftharpoons} RCH(H)CH(OH)R$$

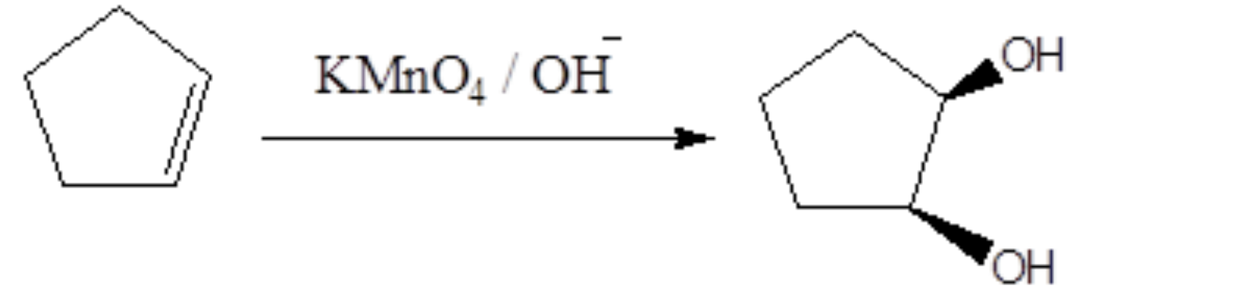
$$CH_3CH{=}CH_2 + H{-}OH \overset{H^+}{\rightleftharpoons} CH_3CH(OH)CH_3$$

Propene — 2-Propanol (major product)

- ***From Alkenes***

## B. Oxidation of Cycloalkenes

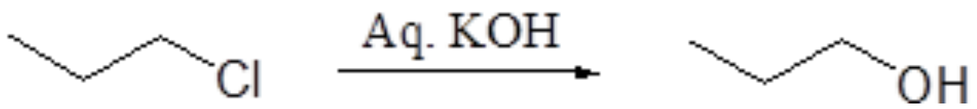
**Alkenes react with alkaline potassium permanganate to form glycols (compounds with two adjacent hydroxyl groups).**




Cyclopentene *cis*-Cyclopentane-1,2-diol

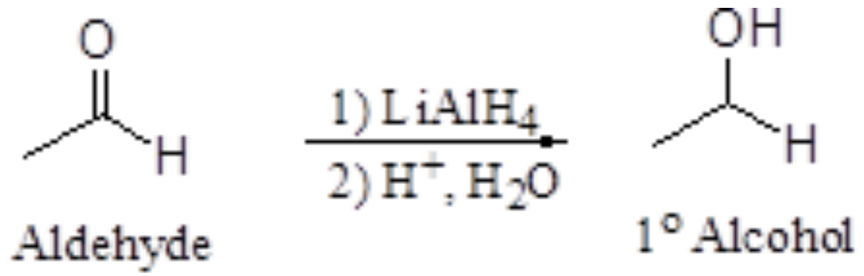
# Preparation of Alcohols

- ***Nucleophilic Substitution of Alkyl Halide***



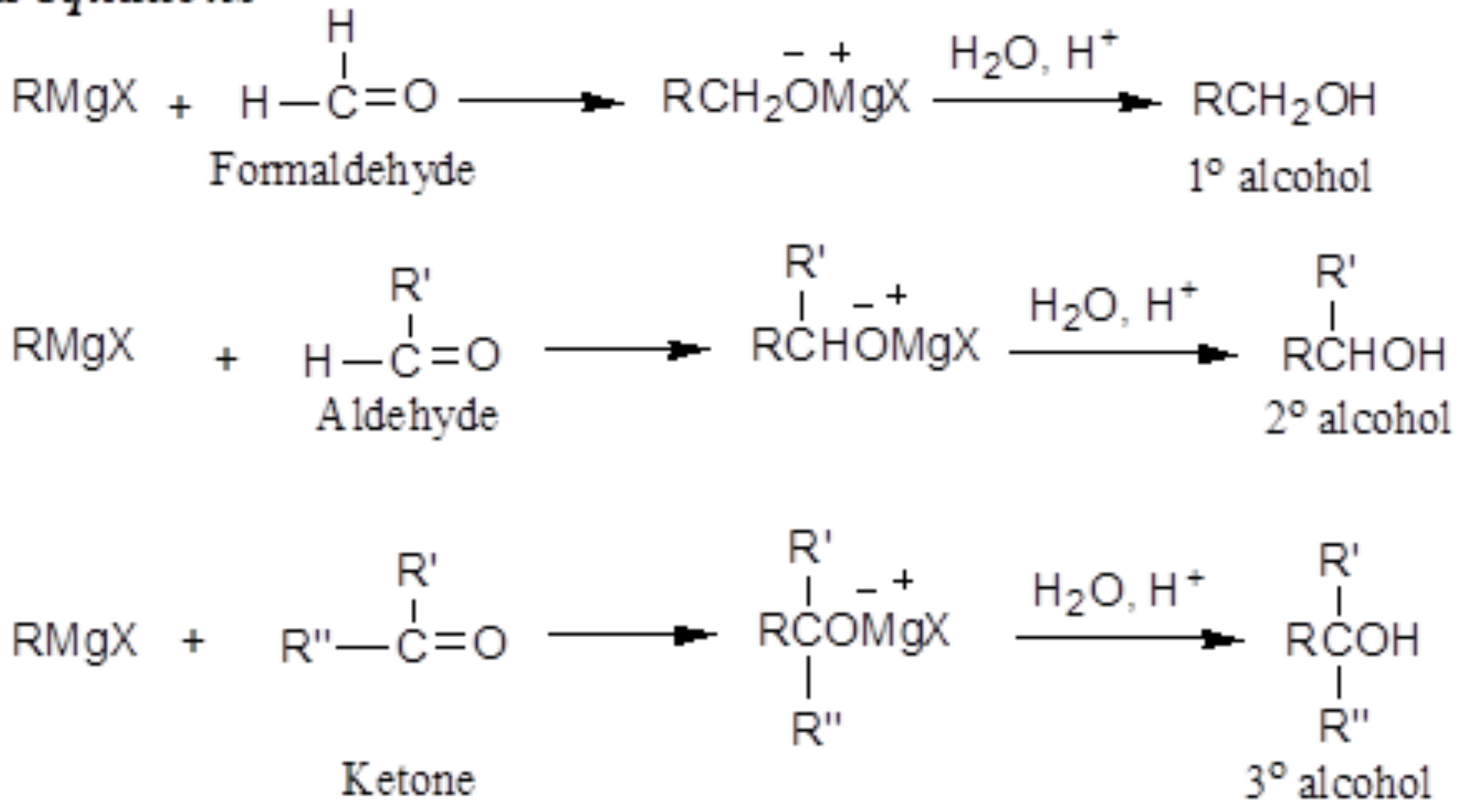

- ***Reduction of Ketones, and Aldehydes***

*Aldehydes and ketones are easily reduced to primary and secondary alcohols, respectively.*



## ○ *Addition of Grignard's Reagent to Aldehydes and Ketones*

***General equations***



# Reactions of Alcohols and Phenols

- **Alcohols** undergo two kinds of reactions:
  - **Those that involve the breaking of the oxygen-hydrogen bond (C-O-H).**
  - **Those that involve the rupture of the carbon-oxygen bond (C-OH).**
- **Phenols** do not participate in reactions where the C-OH bond is broken.

# Reactions of Alcohols

## A) Those that involve the breaking of the oxygen-hydrogen bond (CO-H).

### 1) Reactions of Alcohols and Phenols as Acids: Salt Formation.

$$R{-}OH + Na^+\,OH^- \longrightarrow \text{No reaction}$$

$$2\,CH_3O{-}H + 2\,Na \longrightarrow 2\,CH_3O{:}^-\,Na^+ + H_2\uparrow$$

Methanol — Sodium methoxide


Phenol (as an acid) — Sodium hydroxide (a base) — Sodium phenoxide (a salt)

## B) Those that involve the rupture of the carbon-oxygen bond (C–OH)

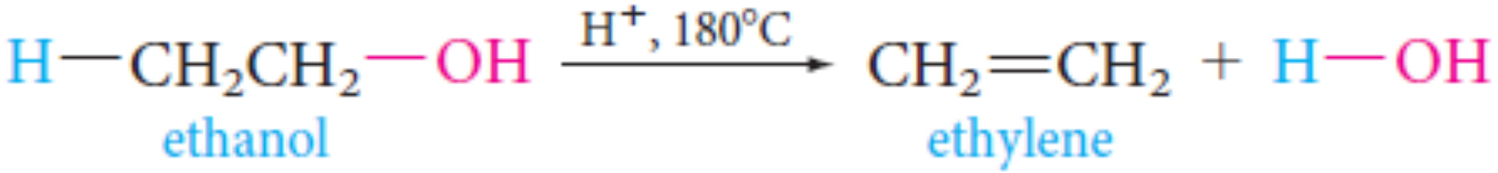
### 1) The Reaction of Alcohols with Hydrogen Halides: Alkyl Halides

*Alcohols react with hydrogen halides (HCl, HBr and HI) to give alkyl halides.*


### 2) Dehydration of Alcohols: Formation of Alkenes

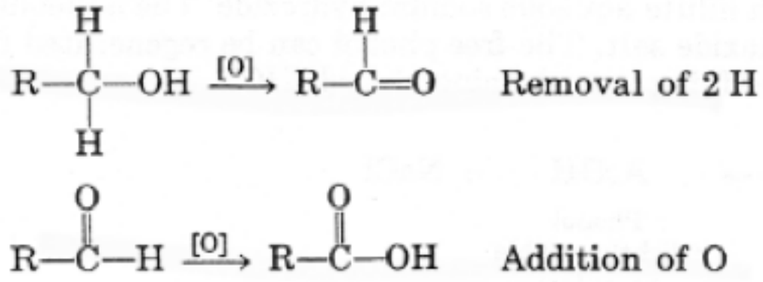
*Alcohols can be dehydrated by heating them with strong*

$3^0 > 2^0 > 1^0$



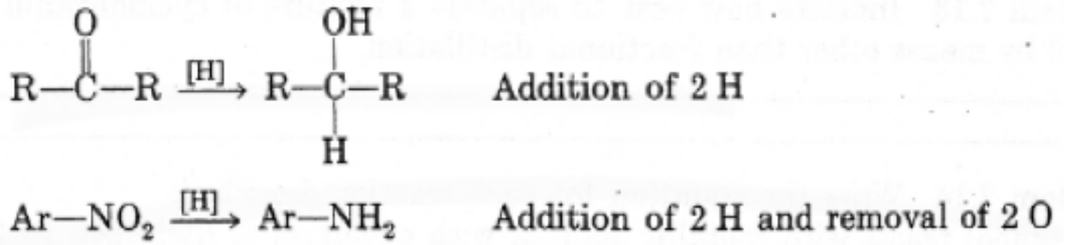
## C) Oxidation Reactions

- **Oxidation** is the removal of H from a compound and/or the addition of O to a compound.




*An oxidizing agent is the chemical reagent that does the oxidation.*

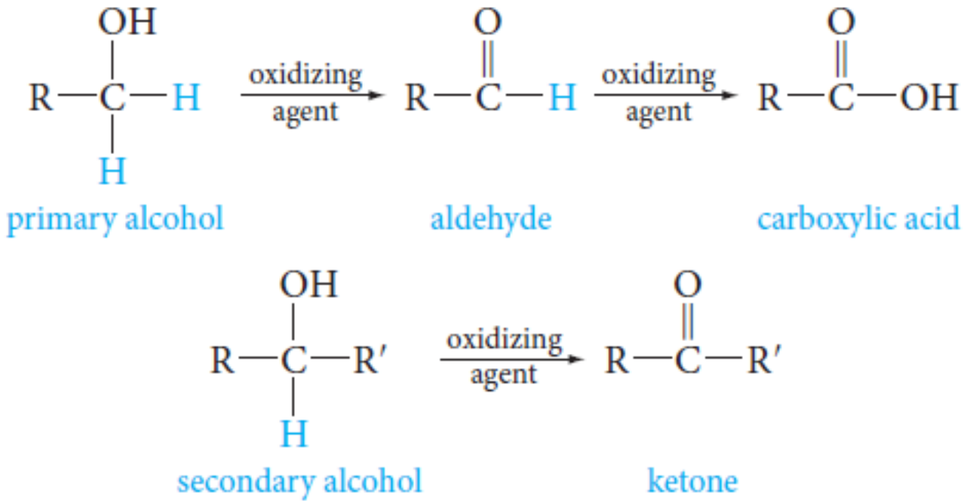
- **Reduction** is the addition of H to a compound and/or the removal of O from a compound.




*A reducing agent is a substance that does the reduction.*

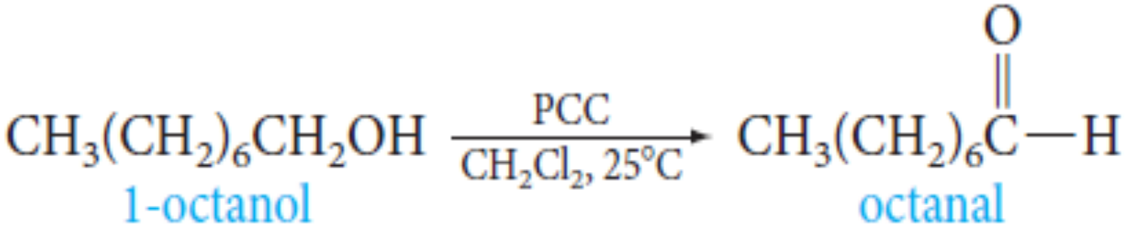
# C) Oxidation Reactions

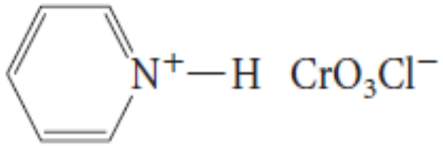
- **Alcohols with at least one hydrogen attached to the hydroxyl-bearing carbon can be oxidized to carbonyl compounds.**
  - **Primary alcohols** give aldehydes, which may be further oxidized to carboxylic acids.
  - **Secondary alcohols** give ketones.
  - **Tertiary alcohols**, having no hydrogen atom on hydroxyl-bearing carbon, *do not undergo oxidation*.



## C) Oxidation Reactions

- **Primary alcohols**, oxidation can be stopped at aldehyde stage by special reagents, such as "pyridinium chlorochromate (PCC)".

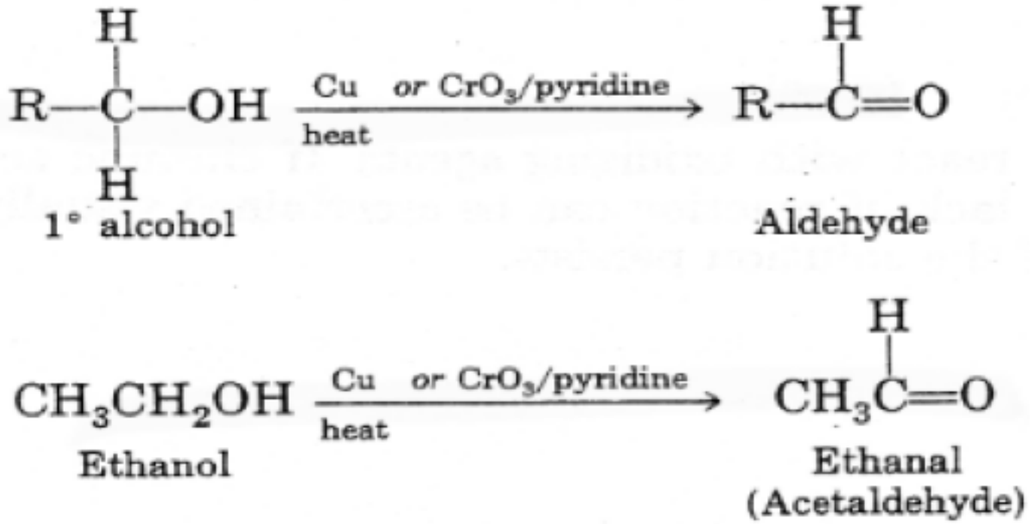



pyridinium chlorochromate
(PCC)

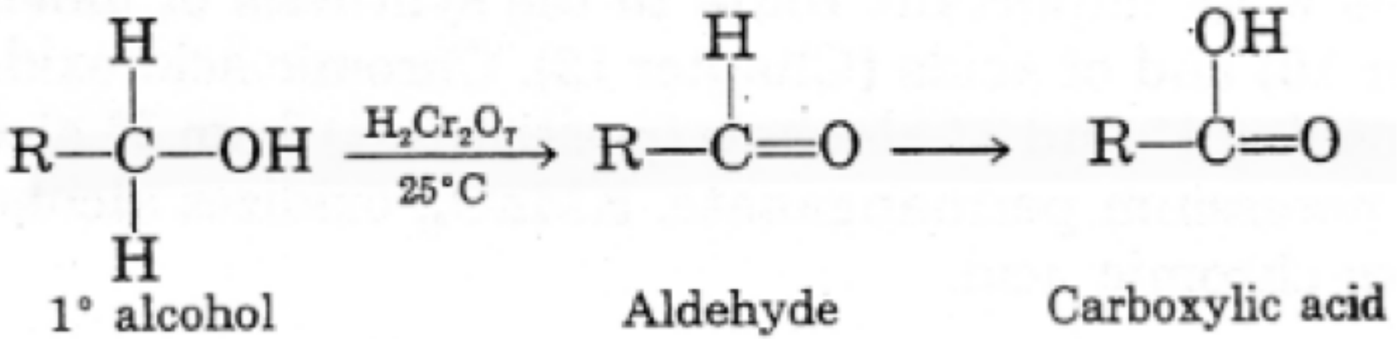
## C) Oxidation Reactions

- **Primary alcohols** yield aldehydes when treated with *mild* oxidizing agents such as hot metallic copper or $CrO_3$ in pyridine.



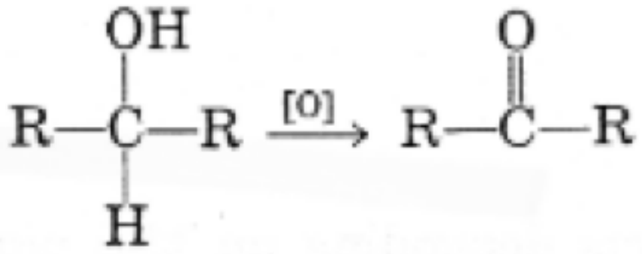
## C) Oxidation Reactions

- **Primary alcohols** yield aldehydes when treated with *stronger oxidizing agents*, such as chromic acid, $H_2Cr_2O_7$, or neutral potassium permanganate, $KMnO_4$, the intermediate aldehydes formed initially are oxidized further to carboxylic acids.

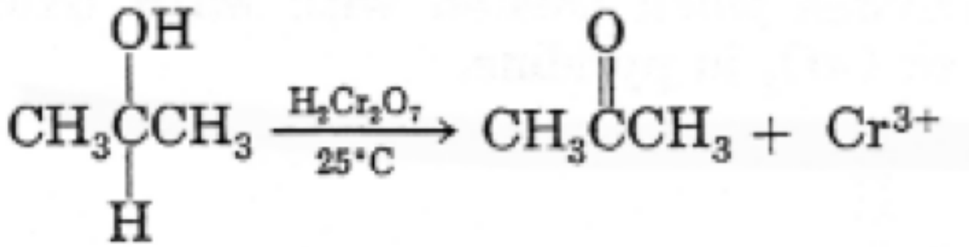


## C) Oxidation Reactions

- **Secondary alcohols**, when treated with *any* of the oxidizing agents mentioned previously, yield ketones.




2° alcohol Ketone




2-Propanol (orange) Acetone (green)

# Preparation of Phenols

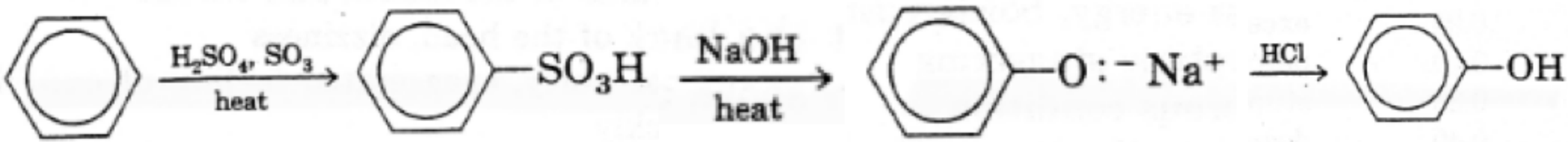
- ***The Alkali Fusion of Sulfonates***

**The alkali fusion of sulfonates involves the following steps:**

1. **Sulfonation** of an aromatic ring.

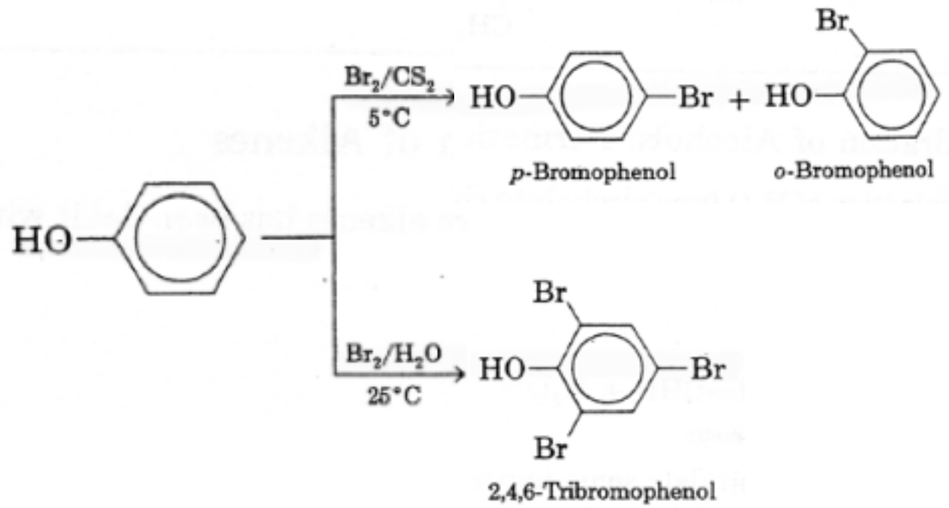
2. **Melting** (**fusion**) of the aromatic sulfonic acid with sodium hydroxide to give a phenoxide salt.

3. **Acidification** of the phenoxide with HCl to produce the phenol.



# Reactions of Phenols

- **Halogenation takes place *without catalyst.***




- **The products depend on the solvent used.**
  - In *aprotic solvents (*solvents that do not release protons) ($CCl_4$, $CS_2$)-bromination gives a mixture of *o*- and *p*-bromophenol.
  - In *protic solvents (solvents that can release protons)* ($H_2O$)-halogenation gives a trisubstituted phenol is produced.

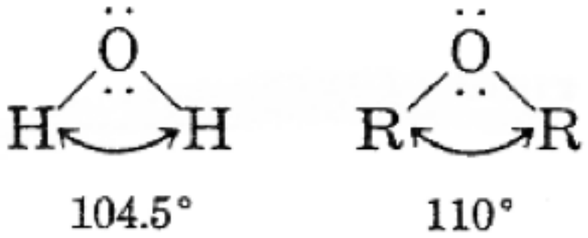
# Ethers

# Structure of Ethers

- All **ethers** are compounds in which two organic groups are connected to a single oxygen atom.
- The **general formula for an ether** is R-O-R', where R and R' may be identical or different, and they may be alkyl or aryl groups

**R—O—R, Ar—O—R, or Ar—O—Ar**

- The geometry of simple ethers is similar to that of water.



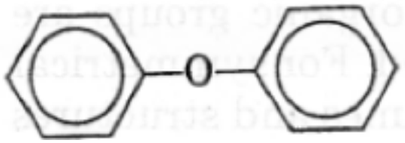
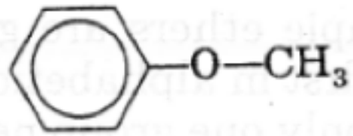
# Structure of Ethers

- **The ether is classified as**
  - **Symmetrical ethers;**
    When the organic groups attached to the oxygen are identical.
  - **Unsymmetrical ethers (mixed ethers);**
    When the organic groups attached to the oxygen are different.

# Nomenclature of Ethers

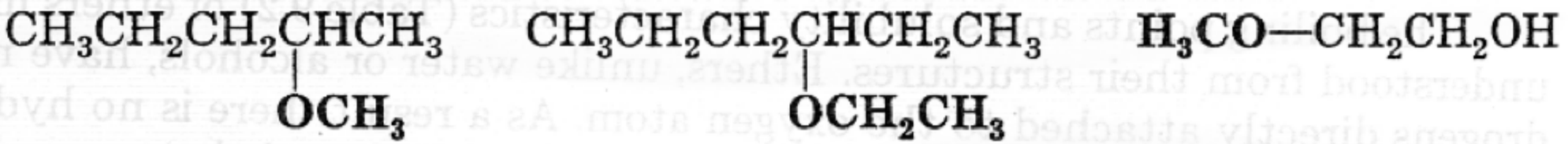
## Common Names

Ethers are usually named by giving the name of each alkyl or aryl group, in alphabetical order, followed by the word *ether.*

| | |
|---|---|
| Methyl ether | $CH_3—O—CH_3$ |
| Ethyl ether | $CH_3CH_2—O—CH_2CH_3$ |
| Vinyl ether | $CH_2=CH—O—CH=CH_2$ |
| Phenyl ether |  |
| Ethyl methyl ether | $CH_3—O—CH_2CH_3$ |
| Ethyl-*n*-propyl ether | $CH_3CH_2—O—CH_2CH_2CH_3$ |
| *t*-Butyl methyl ether | $(CH_3)_3C—O—CH_3$ |
| Methyl phenyl ether (anisole) |  |

## IUPAC System

For ethers with more complex structures, it may be necessary to name the -OR group as an alkoxy group. In the IUPAC system, the smaller alkoxy group is named as a substituent.



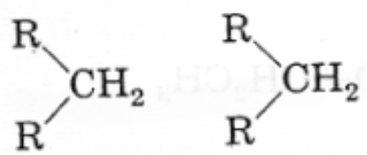
# Physical Properties of Ethers

## Physical State

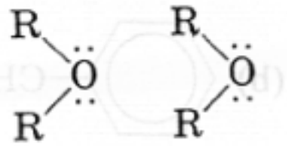
Ethers are colorless compounds with characteristic, relatively pleasant odors.

## Boiling Points

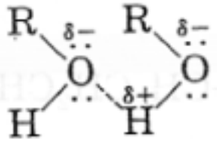
- *They have lower boiling points (bp,s) than alcohols with an equal number of carbon atoms.*
- In fact, an ether has nearly the same bp as the corresponding hydrocarbon in which a -$CH_2$- group replaces the ether's oxygen.
- *Because of their structures (no O-H bonds), ether molecules cannot form hydrogen bonds with one another.*



*Alkanes:* No hydrogen bonding between molecules; low boiling points



*Ethers:* No hydrogen bonding between molecules; low boiling points



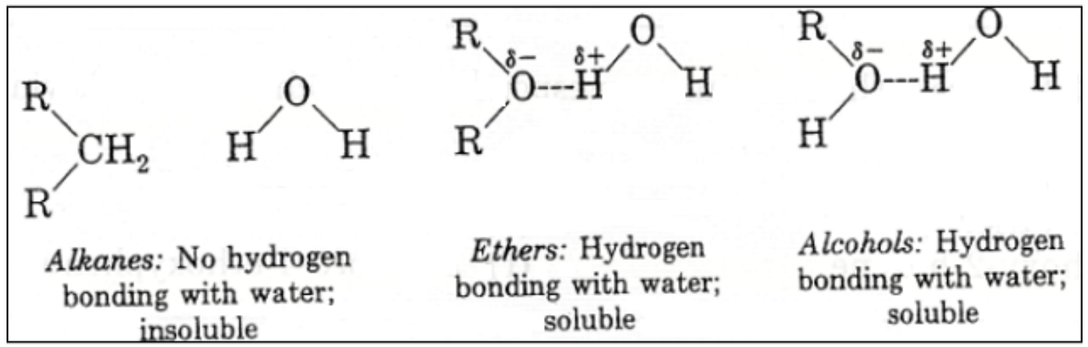
*Alcohols:* Hydrogen bonding between molecules; high boiling points

| Compound | Formula | bp | mol wt | Water solubility (g/100 mL, 20°C) |
|---|---|---|---|---|
| 1-butanol | $CH_3CH_2CH_2CH_2OH$ | 118°C | 74 | 7.9 |
| diethyl ether | $CH_3CH_2—O—CH_2CH_3$ | 35°C | 74 | 7.5 |
| pentane | $CH_3CH_2—CH_2—CH_2CH_3$ | 36°C | 72 | 0.03 |

# Physical Properties of Ether

## Solubility

- Low-molecular-weight ethers, such as dimethyl ether, are quite soluble in water.
- *Ether molecules can form hydrogen bonds to water.*




*Alkanes:* No hydrogen bonding with water; insoluble

*Ethers:* Hydrogen bonding with water; soluble

*Alcohols:* Hydrogen bonding with water; soluble

| Structure | Name | Mol.wt. | Bp (°C) | Solubility in $H_2O$ At 20 °C |
|---|---|---|---|---|
| $CH_3CH_2CH_3$ | propane | 44 | −42 | insoluble |
| $CH_3OCH_3$ | methyl ether | 46 | −24 | soluble |
| $CH_3CH_2OH$ | ethanol | 46 | 78 | soluble |
| $CH_3CH_2CH_2CH_3$ | *n*-butane | 58 | −0.5 | insoluble |
| $CH_3CH_2OCH_3$ | ethyl methyl ether | 60 | 8 | soluble |
| $CH_3CH_2CH_2OH$ | 1-propanol | 60 | 97 | soluble |
| $CH_3(CH_2)_3CH_3$ | *n*-pentane | 72 | 35 | insoluble |
| $CH_3CH_2OCH_2CH_3$ | ethyl ether | 74 | 36 | 7.5 g/100 g |
| $CH_3(CH_2)_2CH_2OH$ | 1-butanol | 74 | 118 | 7.9 g/100 g |
| $CH_3(CH_2)_5CH_3$ | *n*-heptane | 100 | 98 | insoluble |
| $CH_3(CH_2)_2O(CH_2)_2CH_3$ | *n*-propyl ether | 102 | 91 | 0.2 g/100 g |
| $CH_3(CH_2)_4CH_2OH$ | 1-hexanol | 102 | 157 | 0.6 g/100 g |

# Preparation of Ethers

- **There are *two general methods* for synthesizing ethers.**

**1) Dehydration of alcohols**

It is used commercially and in the laboratory to make certain symmetrical ethers.

**2) Williamson synthesis**

General laboratory method used to prepare all kinds of ethers, symmetrical and unsymmetrical.

## 1) Dehydration of Alcohols

It takes place in the presence of acid catalysts ($H_2SO_4$, $H_3PO_4$) (intermolecular reaction)

$$R{-}OH + H{-}OR \xrightarrow[\text{heat}]{H^+} R{-}O{-}R + H_2O$$

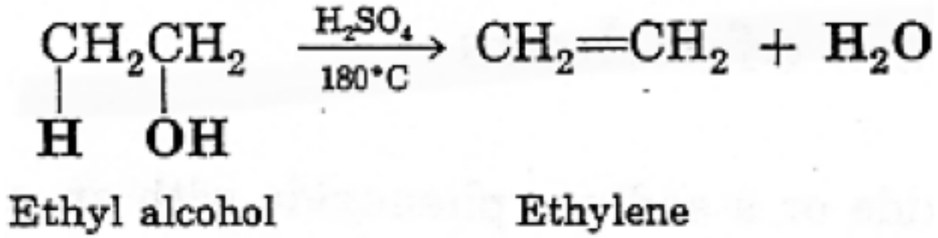
**Example;**

The most important commercial ether is diethyl ether. It is prepared from ethanol and sulfuric acid.

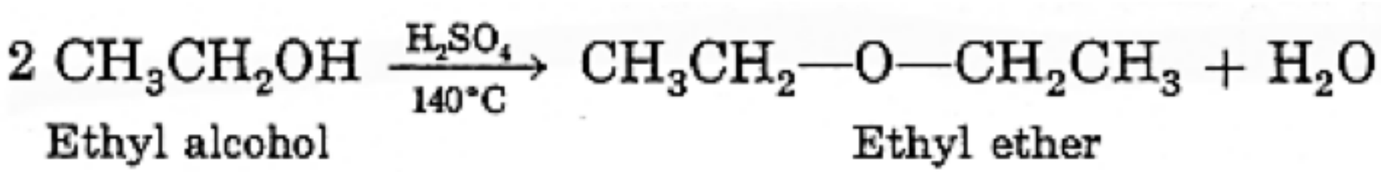
$$\underset{\text{ethanol}}{CH_3CH_2OH} + HOCH_2CH_3 \xrightarrow[140^\circ C]{H_2SO_4} \underset{\text{diethyl ether}}{CH_3CH_2OCH_2CH_3} + H_2O$$

## Scope and Limitations

- When ethyl alcohol is dehydrated by sulfuric acid at 180° C, the dominant product is ethylene.




- **To prepare ethyl ether**
  - Dissolve ethyl alcohol in sulfuric acid at ambient temperature.
  - Heat the solution to 140°C while adding more alcohol.



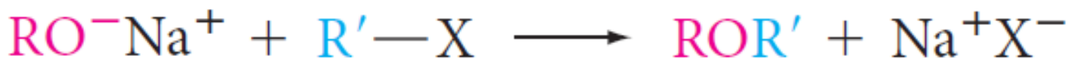
## 2) Williamson Synthesis

- This method has two steps;

1) An alcohol is converted to its alkoxide by treatment with a reactive metal (sodium or potassium).

$$2\,ROH + 2\,Na \longrightarrow 2\,RO^{-}Na^{+} + H_2$$

2) Displacement is carried out between the alkoxide and an alkyl halide.

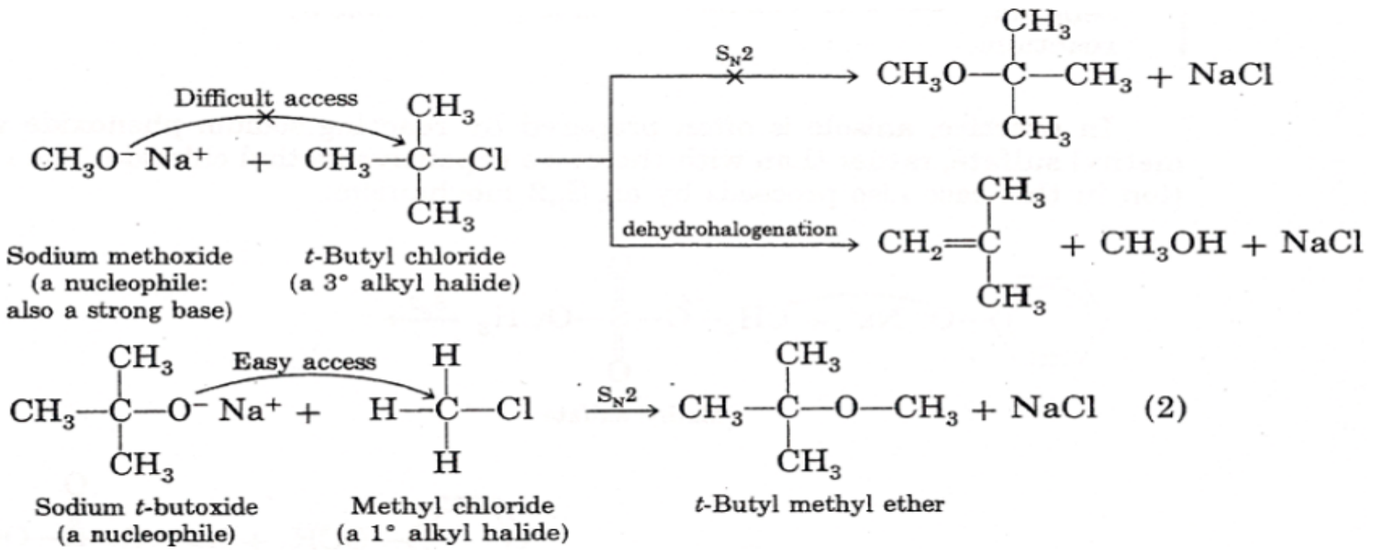


$$RO^{-}Na^{+} + R'—X \longrightarrow ROR' + Na^{+}X^{-}$$

- To obtain the best yields of mixed dialkyl ethers, we select a 1° rather than a 2°or 3°alkyl halide and react it with a sodium alkoxide
- To prepare an alkyl aryl ether, we must be careful not to pick a combination in which one of the reagents has a halogen directly attached to an aromatic ring.

## 2) Williamson Synthesis

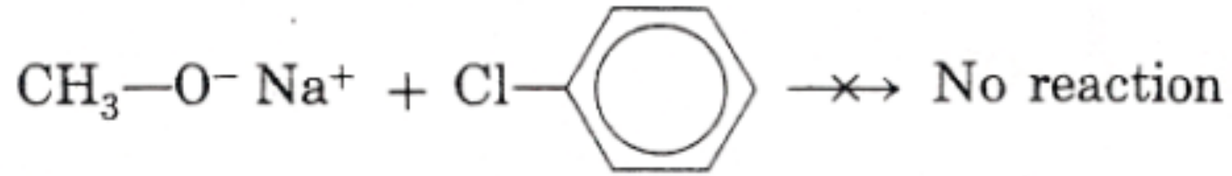
- **Example 1; Preparation of *t*-butyl methyl ether, $(CH_3)_3C$-O-$CH_3$**
  - **In theory, this could be done by either of two reactions.**
    1. You could react sodium methoxide, $CH_3O$-$Na^+$, with *t*-butyl chloride, $(CH_3)_3C$-Cl. *This combination leads to dehydrohalogenation to an alkene, an elimination reaction.*
    2. You could react sodium *t*-butoxide, $(CH_3)_3C$-O-$Na^+$, with methyl chloride, $CH_3$-Cl. *This route gives the desired ether by substitution.*



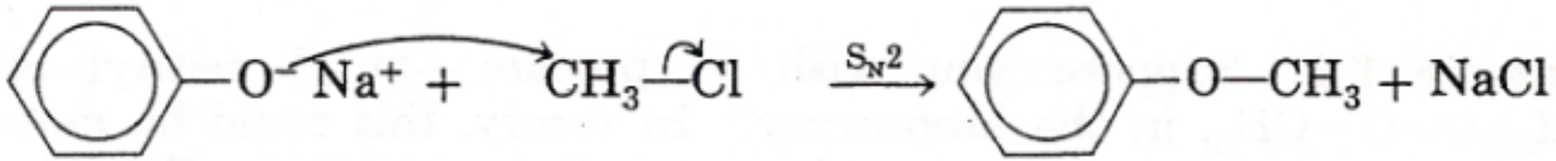
## 2) Williamson Synthesis

**Example 2; Assume you need to synthesize methyl phenyl ether (anisole), $CH_3$-O-$C_6H_5$, by the Williamson method.**

- *In theory, you could obtain anisole in either of two ways.*




Sodium methoxide (a nucleophile) Chlorobenzene (an aryl halide)




Sodium phenoxide (a nucleophile) Methyl chloride (a 1° alkyl halide) Anisole

# Reactions of Ethers

- **Ethers** are quite stable compounds.
- The **ether** linkage does not react with bases, reducing agents, oxidizing agents, or active metals.
- ***Ethers*** *react only under strongly acidic conditions.*

## Cleavage of Ethers by Hot Concentrated Acids

- When **ethers** are heated in concentrated acid solutions, the ether linkage is broken.

$$CH_3CH_2\ddot{\underset{\ddot{}}{O}}CH_2CH_3 + \underset{(conc)}{HI} \xrightarrow{heat} CH_3CH_2OH + CH_3CH_2I$$

- The acids most often used in this reaction are HI, HBr, and HCl.
- If an *excess of acid* is present, the alcohol initially produced is converted into an alkyl halide by the reaction.

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

For example,

$$CH_3CH_2{-}O{-}CH_2CH_3 + \underset{(conc)}{2\,HBr} \xrightarrow{heat} 2\,CH_3CH_2Br + H_2O$$