

Date:

29 / 12 / 2023



لمجان الشفقات



## تفريغ عضويه 1

Alcohols Phenols ethers

( 11 )

Gufraan Khaseeb

موضوع المحاضرة:

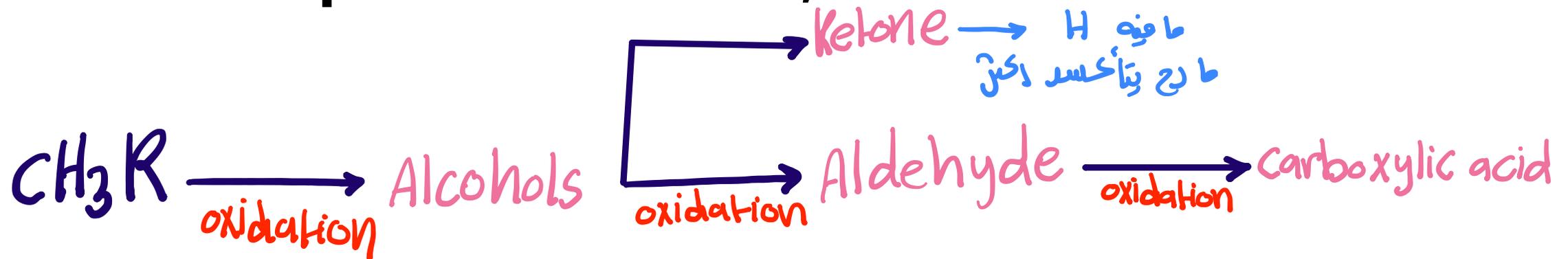
رقم المحاضرة:

إعداد الصيدلانيه:



# Pharmaceutical Organic Chemistry-1

## Chapter-4: Alcohols, Phenols and Ethers



# Alcohols, Phenols and Ethers

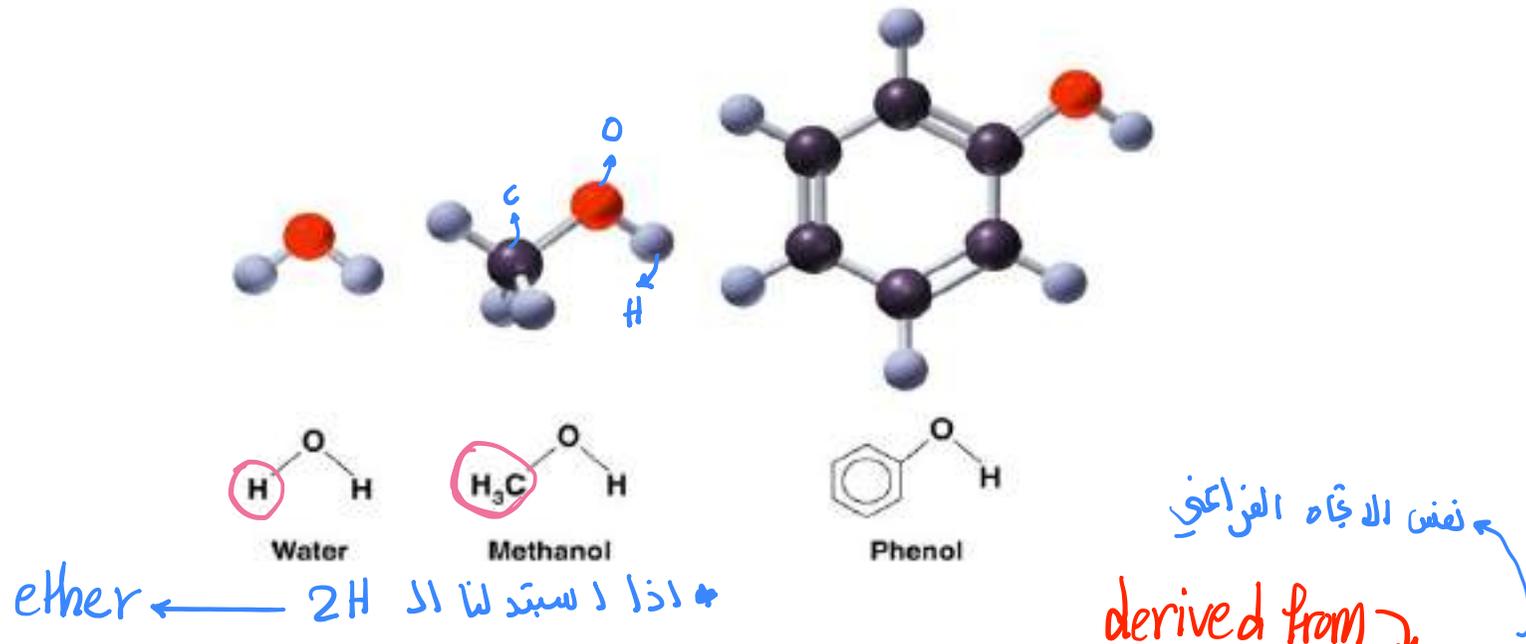
- Alcohols, ethers and phenols have a common functional group, the **hydroxyl group**, -OH.

<b>Ph-O-H</b> Phenol	<b>R-O-R</b> Ethers	<b>R-OH</b> Alcohol	<b>H-O-H</b> Water
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- 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

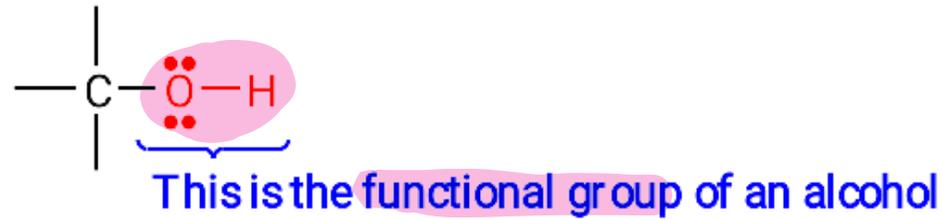
Alcohols and phenols may be viewed as organic derivatives of water.



Alcohols have the general formula R-OH, and structurally similar to water, but with one of the hydrogens replaced by an alkyl group.

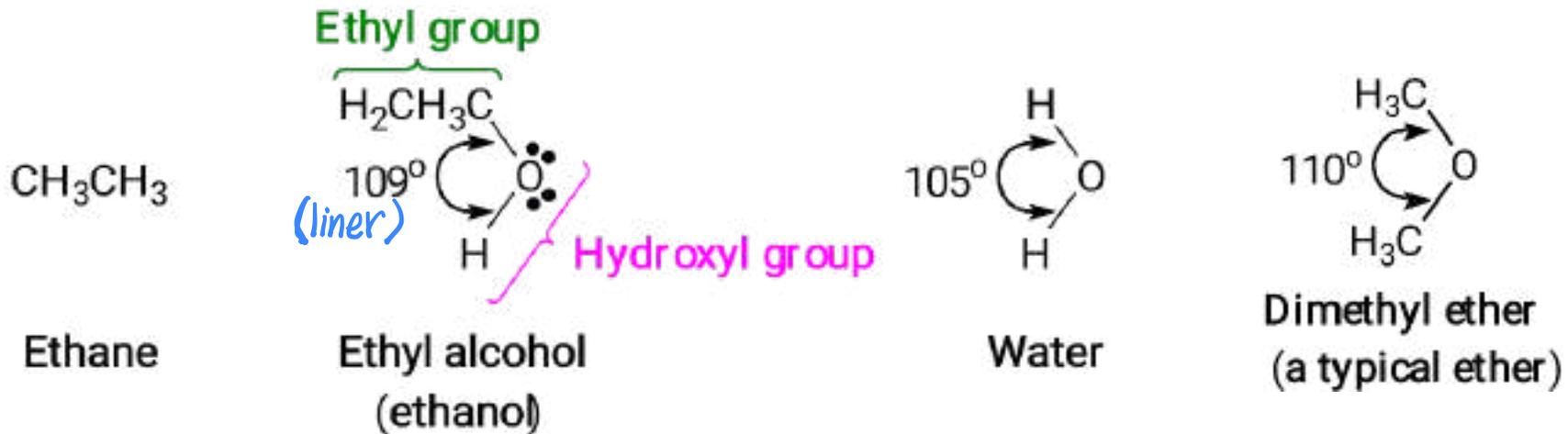
Phenols have a hydroxyl group attached directly to an aromatic ring.

# Alcohols



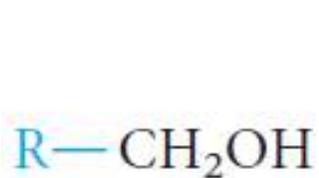
Alcohols can be viewed in two ways structurally:

- (1) as **hydroxyl derivatives** of alkanes  $\rightarrow$  alkane + remove H and replaced it with OH  
 and (2) as **alkyl derivatives** of water  $\rightarrow$  water molecule + remove H and replaced it with R

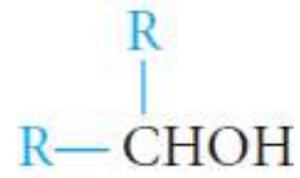


# Classification of Alcohols

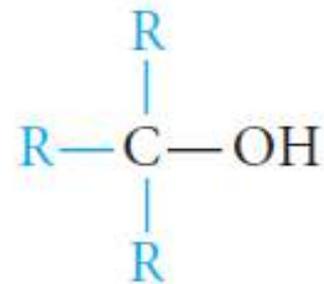
- 0 **Alcohols** are classified as **primary** ( $1^\circ$ ), **secondary** ( $2^\circ$ ), or **tertiary** ( $3^\circ$ ), depending on whether one, two, or three organic groups are connected to the hydroxyl-bearing carbon atom.



primary ( $1^\circ$ )

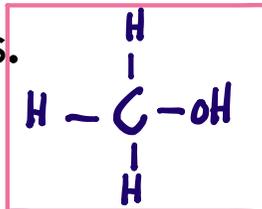


secondary ( $2^\circ$ )



tertiary ( $3^\circ$ )

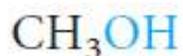
- 0 **Methyl alcohol**, which is not strictly covered by this classification, is usually grouped with the **primary** alcohols.



# Nomenclature of Alcohols

- 0 The **common names** for the simplest alcohols consist of **alkyl group** attached to the hydroxyl function followed by the word alcohol: *Alkyl alcohol*.
- 0 In the **IUPAC system**, alcohols are named according to the following rules.
  1. Select the **longest continuous carbon chain that contains the -OH group**.

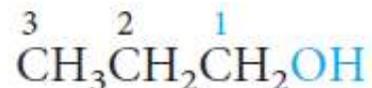
Drop the **-e** ending of the parent alkane and replace it by the suffix **-ol**: *Alkanol*
  2. When **isomers are possible**, the chain is numbered so as to give the **functional group (-OH) the lowest possible number**.



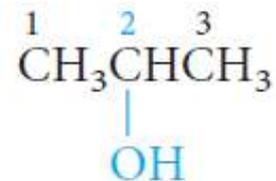
methanol  
(methyl alcohol)



ethanol  
(ethyl alcohol)

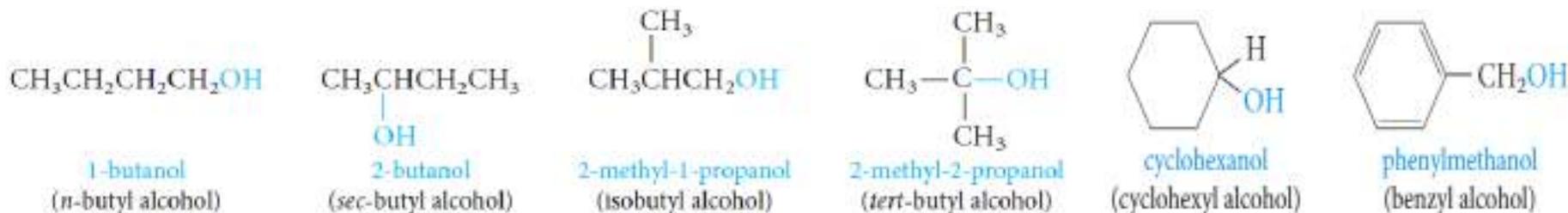


1-propanol  
(*n*-propyl alcohol)



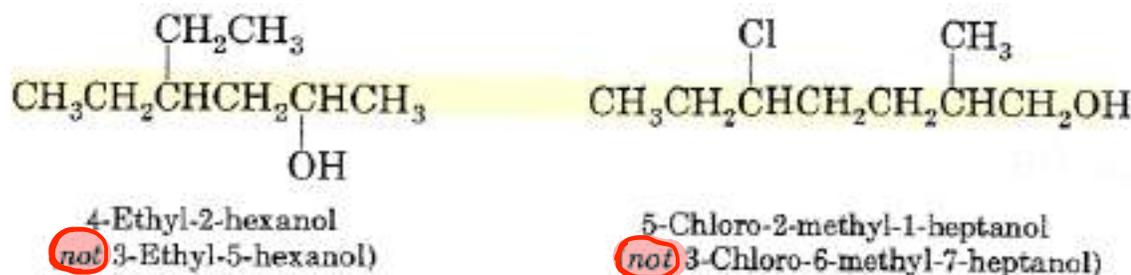
2-propanol  
(isopropyl alcohol)

# Nomenclature of Alcohols



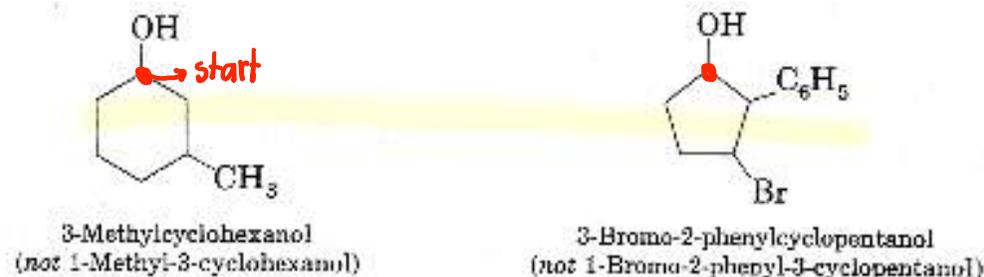
**3. When alkyl side chains or other groups are present,** they are named alphabetically and their positions are indicated by a number.

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



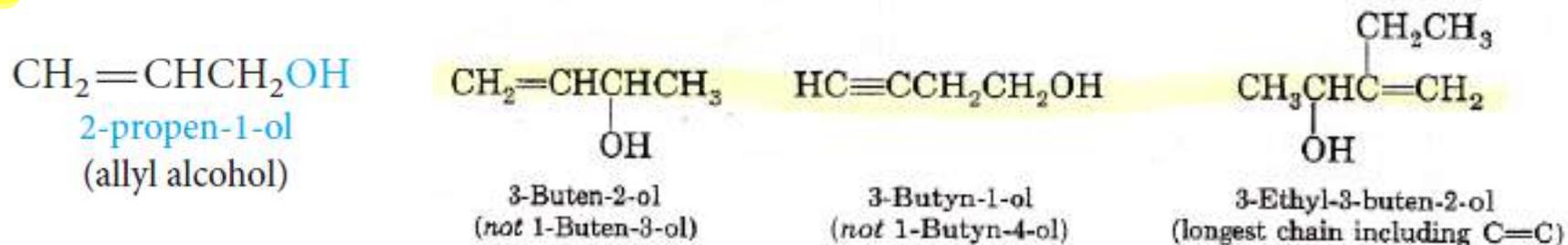
# Nomenclature of Alcohols

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



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.**

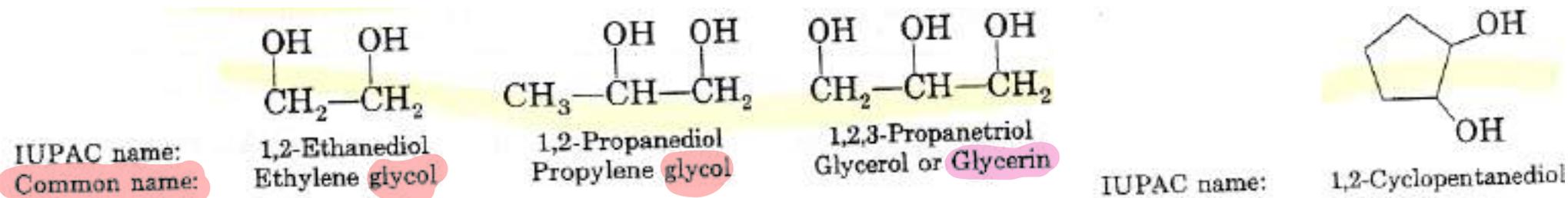


## Alcohols with More Than One Hydroxyl Group

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.

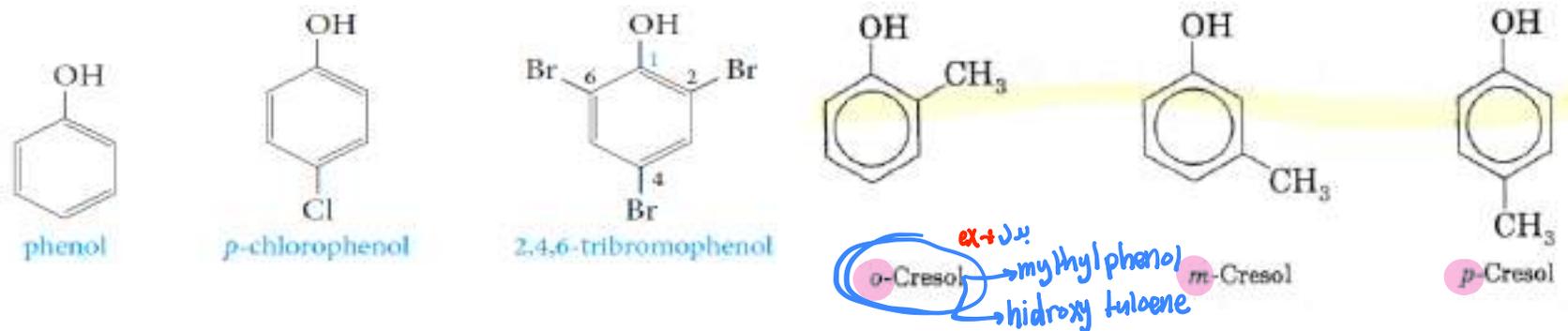


- Ethylene glycol is used as the “permanent” antifreeze in automobile radiators and as a raw material in the manufacture of Dacron. (in cars) → clothes
- Ethylene glycol is completely miscible with water.
- Glycerol is a syrupy, colorless, water-soluble, high-boiling liquid with a distinctly sweet taste.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

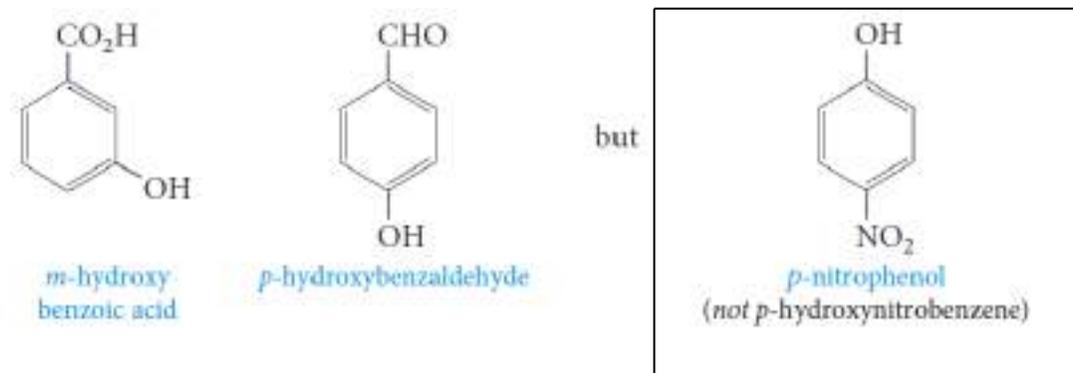
سایه

# Nomenclature of Phenols

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



○ 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**.



# 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

$\approx (1-8)(C)$

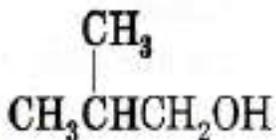
- The **lower alcohols** are completely **miscible with water**.  $\rightarrow$  because (the OH = H bond with water)
- As the number of **carbons in the alcohol increases**, the **solubility in water decreases**.

## 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**.



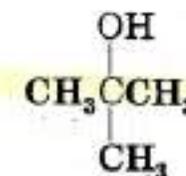
1-Butanol  
(mol wt = 74; bp = 118°C)



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

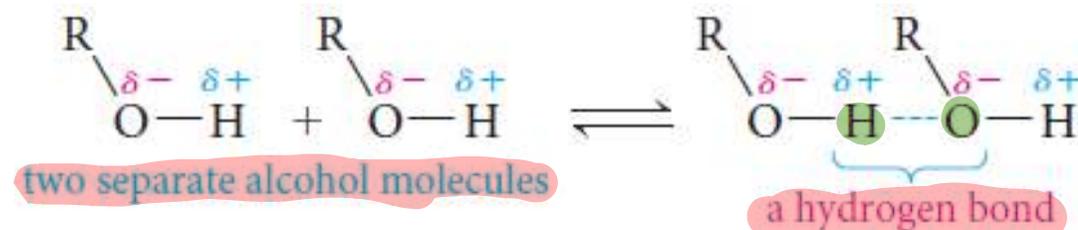
- The **boiling points** (bp's) of alcohols are much higher than those of **ethers** or **hydrocarbons** with similar molecular weights.

↑ bp need ↑ energy  
(ليتبخر الكحول (يتطاير))

	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>3</sub> OCH <sub>3</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>3</sub>
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 Alcohols

- Consequently, alcohols have relatively **high boiling points because they must supply enough heat to break the hydrogen bonds** before each molecule. *the H bond عادة بتكون خفيفة*
- Hydrogen bonds are weaker than ordinary covalent bonds. *لكن لما يزيد عددها بتسوي روابط قوية*
- **Water**, of course, is also a hydrogen-bonded liquid. *↳ it need more energy to break it to make the bp for the molecules*
- 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 <sub>2</sub> O g/100 g at 20°C
methanol	CH <sub>3</sub> OH	65	completely miscible
ethanol	CH <sub>3</sub> CH <sub>2</sub> OH	78.5	completely miscible
1-propanol	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> OH	97	completely miscible
1-butanol	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	117.7	7.9
1-pentanol	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	137.9	2.7
1-hexanol	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	155.8	0.59

# Physical Properties of Phenols

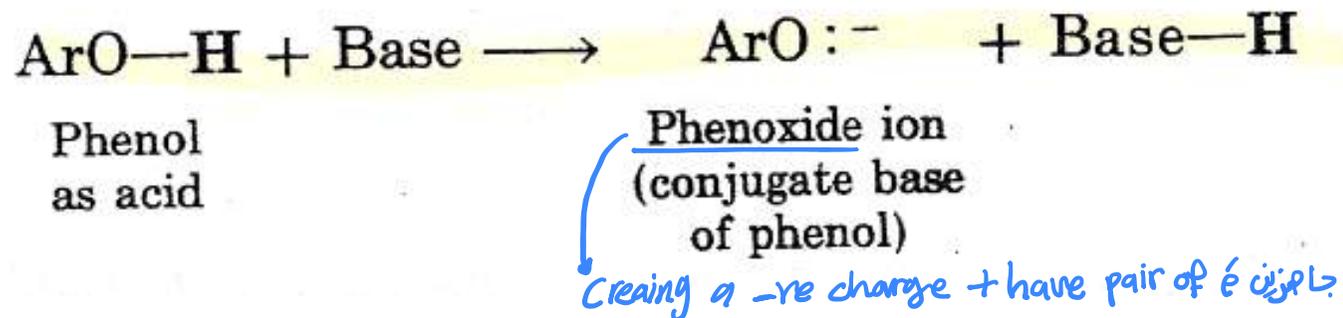
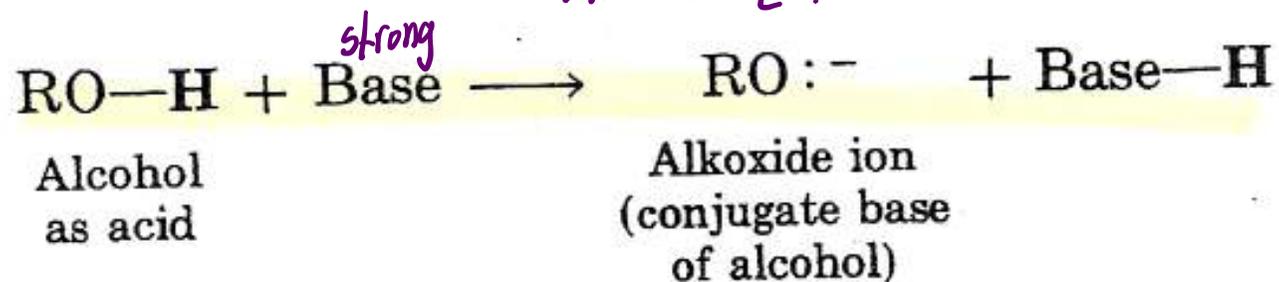
- **Phenol** is a colorless, crystalline, low-melting solid, with a high boiling point, that is **moderately** soluble in water.
- Most other phenols also **are solids**, with **slight solubility** in water and high boiling points.
- The most significant physical property that **distinguishes alcohols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

(acidic compounds)  
The proton انزل بقدر

# The Acidity of Alcohols and Phenols

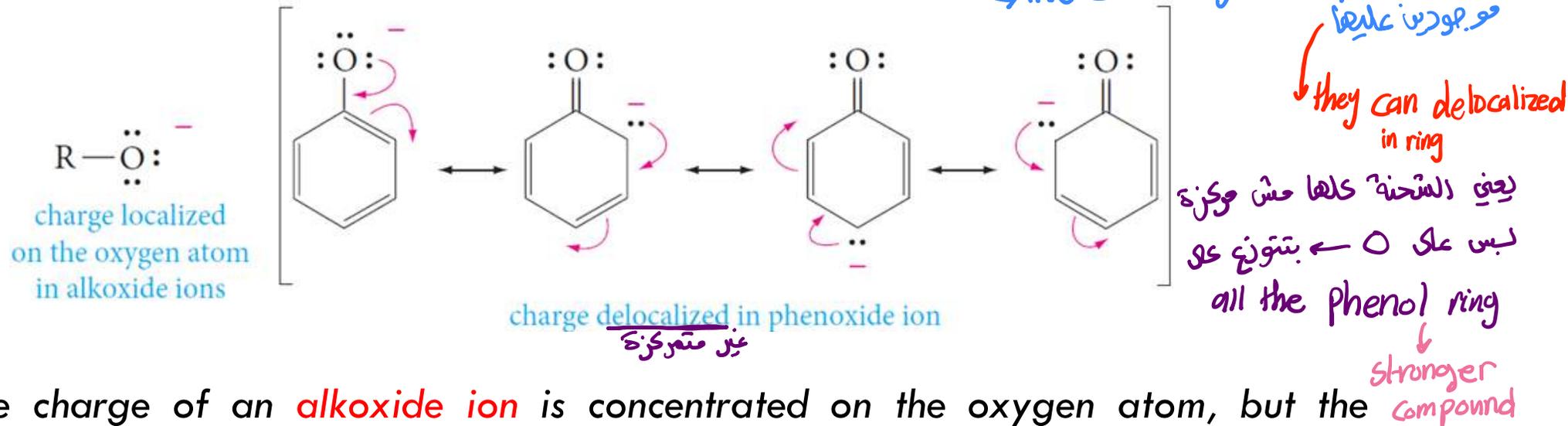
## 0 Like water, alcohols and phenols are weak acids.

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 Phenols

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



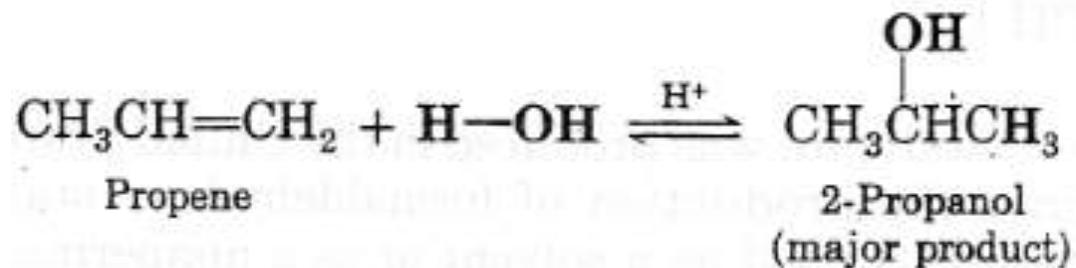
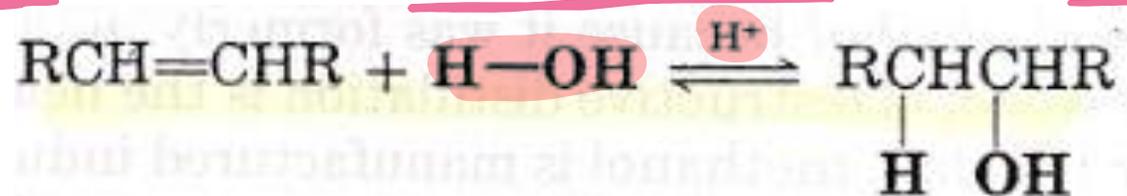


# Preparation of Alcohols

## 0 From Alkenes

### A. Hydration of Alkenes

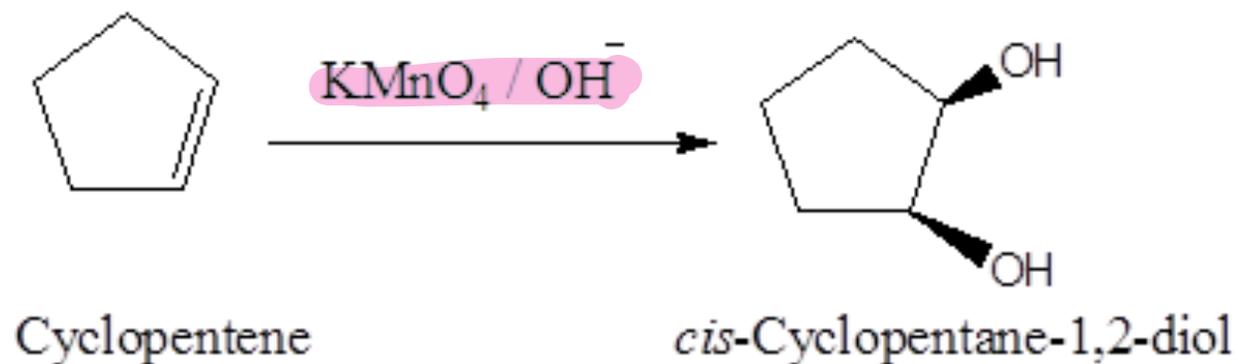
1. Addition of water to a double bond in the presence of an acid catalyst,  $H^+$ .
2. The addition follows Markovnikov's rule  $\rightarrow H^+$  يذهب الى ابي عليا اكثر
3. It is not possible to prepare primary alcohols except Ethanol.



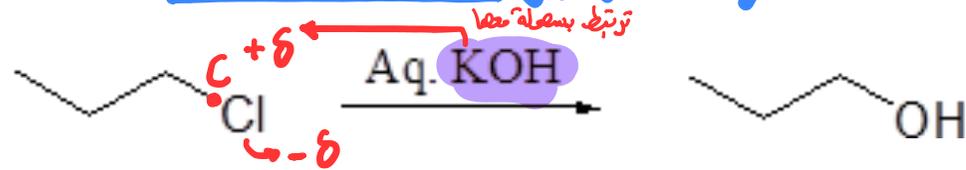
## O From Alkenes

### B. Oxidation of Cycloalkenes

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

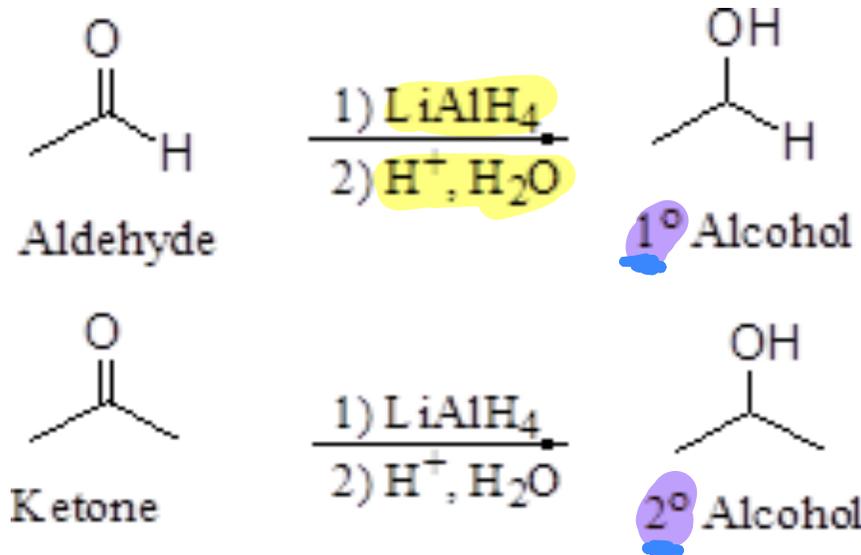


## ○ Nucleophilic Substitution of Alkyl Halide ( $R-X$ )



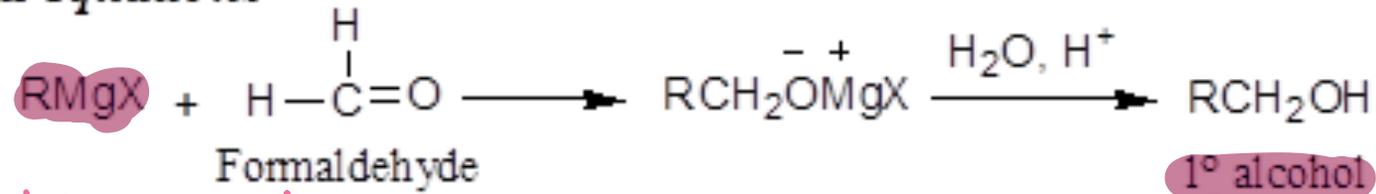
## ○ Reduction of Ketones, and Aldehydes

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

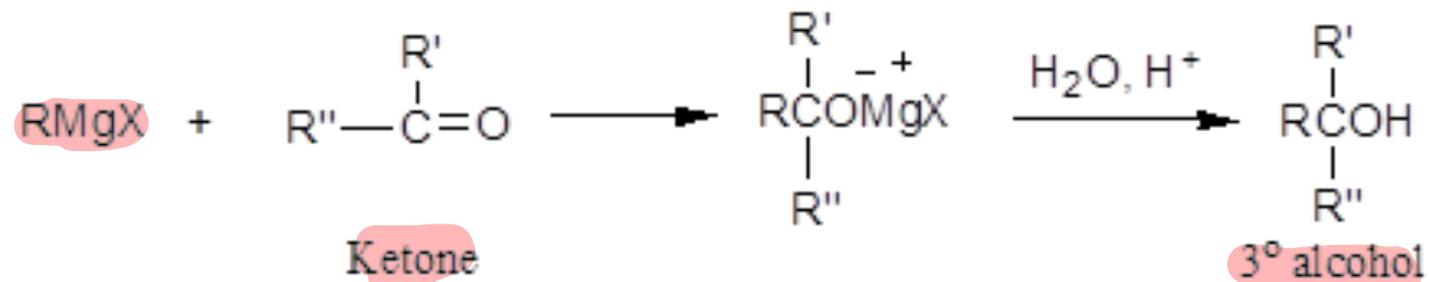
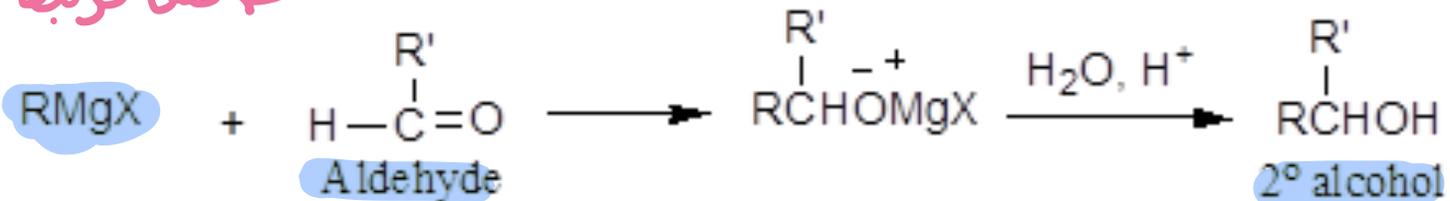


## 0 Addition of Grignard's Reagent to Aldehydes and Ketones (التفاعل بزيادتي)

General equations



لأنه صحت مرتبط مع R group



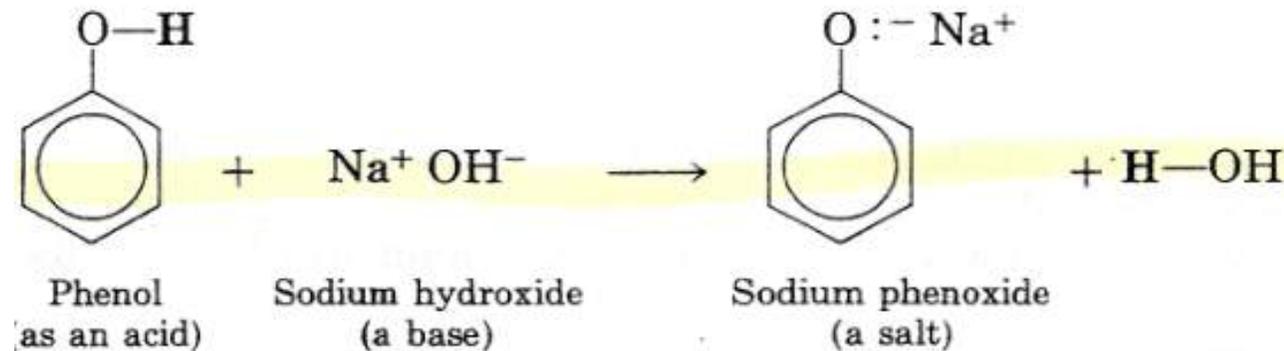
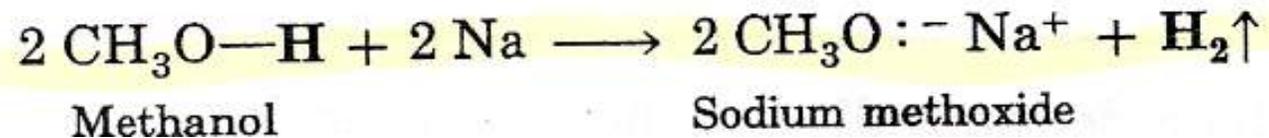
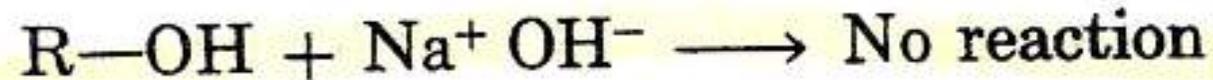
# Reactions of Alcohols and Phenols

- **Alcohols** undergo two kinds of reactions:
  - Those that involve the **breaking of the oxygen-hydrogen** bond (CO-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.



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

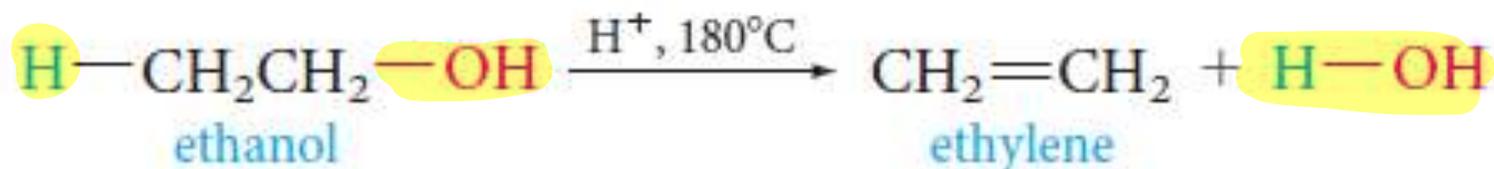
1) The Reaction of Alcohols with Hydrogen Halides: Alkyl Halides

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



2) Dehydration of Alcohols: Formation of Alkenes

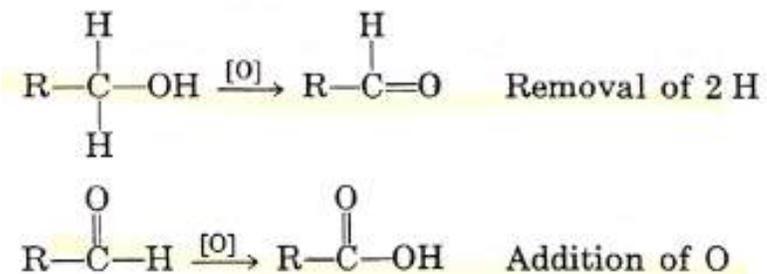
Alcohols can be dehydrated by heating them with strong acid.  $3^\circ > 2^\circ > 1^\circ$



## C) Oxidation Reactions

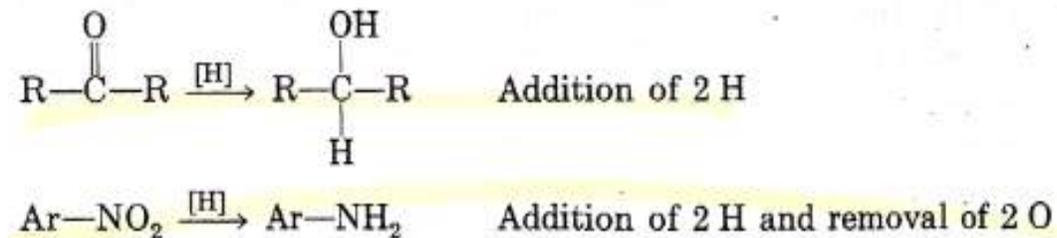
□ **Oxidation** is the **removal of H** from a compound and/or the **addition of O** to a compound.

the alcohol  
Ketone or  
aldehyde  
بيحول الـ



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.

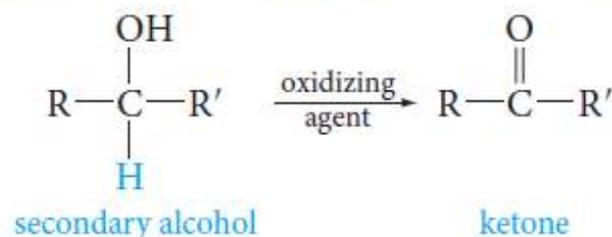
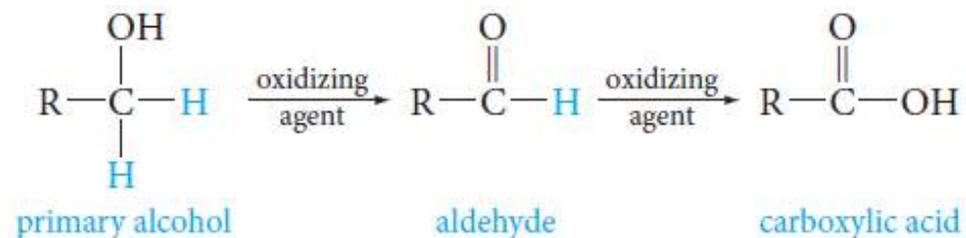
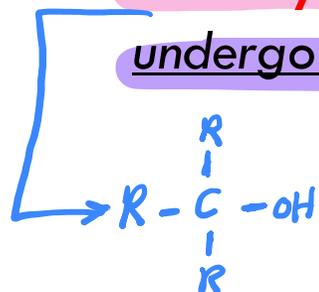
## C) Oxidation Reactions

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.

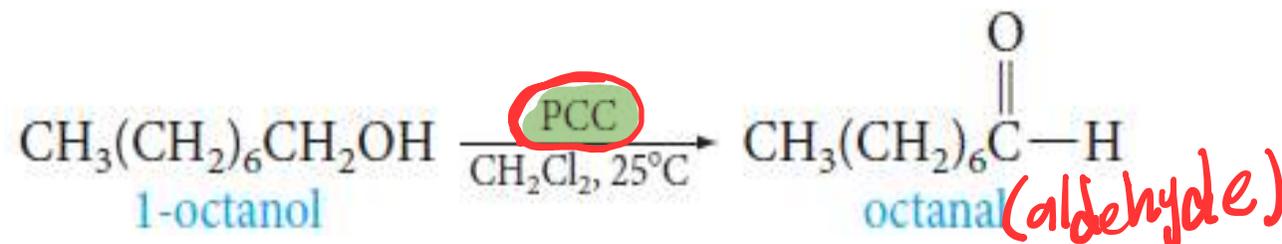
Secondary alcohols give ketones.  $\rightarrow$  Q (justify) *لانه اذا في H التفاعل بعمل اذا ما في reaction it be stop*

Tertiary alcohols, having no hydrogen atom on hydroxyl-bearing carbon, do not undergo oxidation.



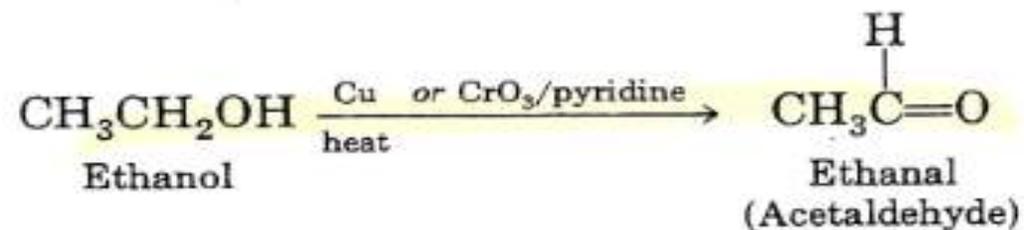
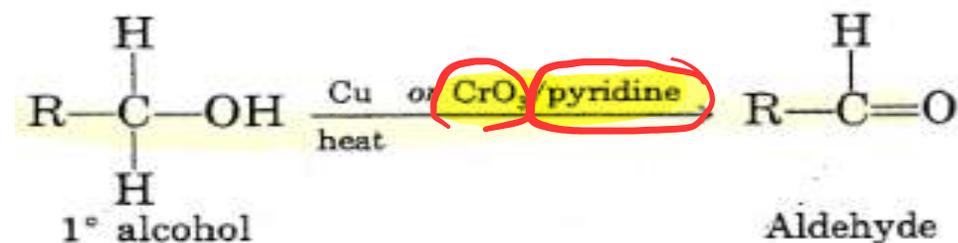
## C) Oxidation Reactions

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



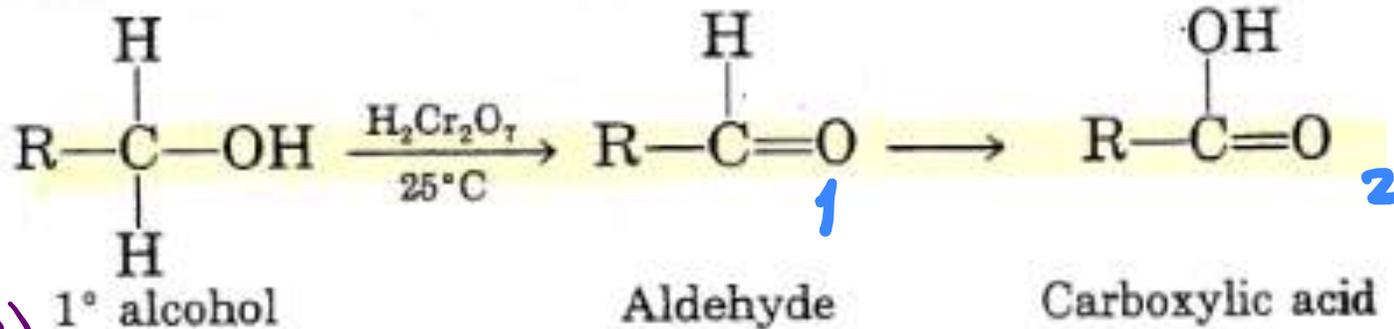
## C) Oxidation Reactions

- **Primary alcohols** yield **aldehydes** when treated with **mild oxidizing agents** such as hot metallic copper or **CrO<sub>3</sub> in pyridine**.



## C) Oxidation Reactions

**O 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**.



(كيف السؤال في الامتحان)

بليست alcohol و انتخبه

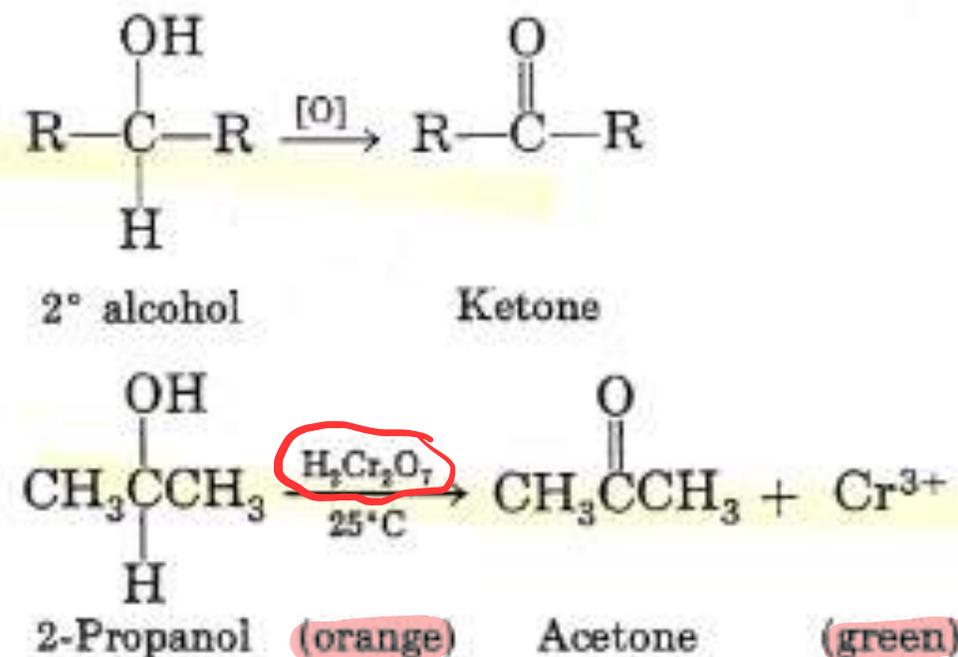
Carboxylic acid

الجواب (استخدمت strong oxidizing agents)

بليست alcohol و وقفه  
aldehyde (استخدمت  $CrO_3$ )

## C) Oxidation Reactions

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

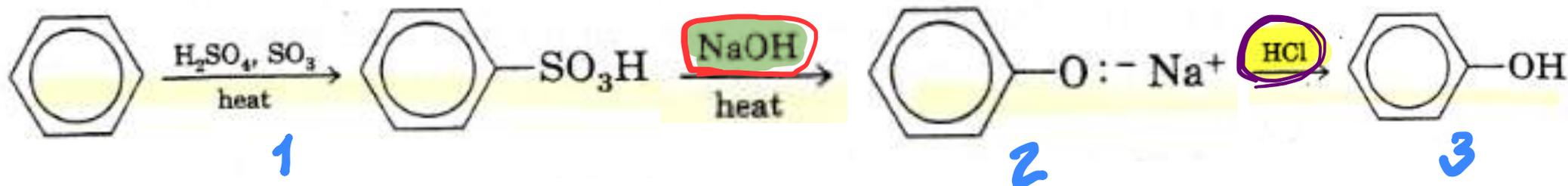


# Preparation of Phenols

## O The Alkali Fusion of Sulfonates

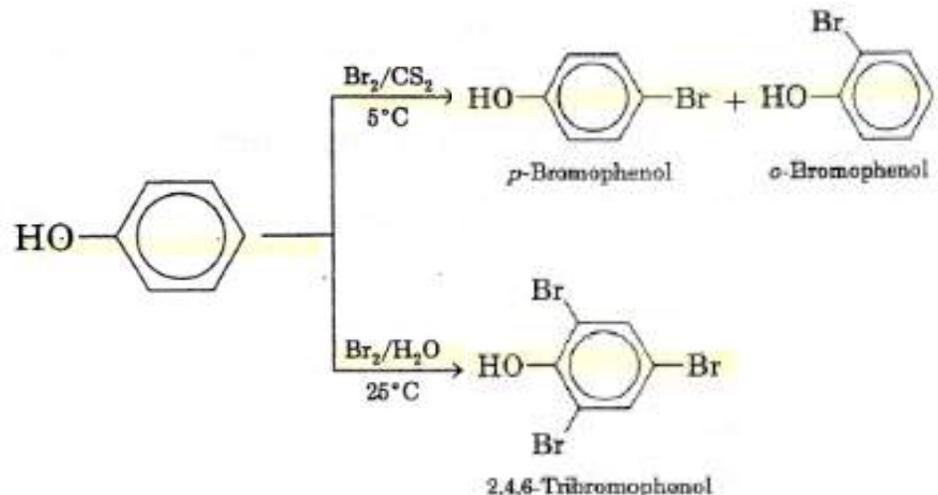
The alkali fusion of sulfonates involves the following steps;

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) ( $\text{CCl}_4$ ,  $\text{CS}_2$ )-bromination gives a mixture of *o*- and *p*-bromophenol.
- In **protic solvents** (solvents that can release protons) ( $\text{H}_2\text{O}$ )-halogenation gives a trisubstituted phenol is produced.

# Ethers

# Structure of Ethers

- 0 All **ethers** are compounds in which **two organic groups** are **connected** to a **single oxygen atom**.
- 0 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**



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



## O The ether is classified as

### □ Symmetrical ethers;

When the organic groups attached to the oxygen are **identical**.

### □ Unsymmetrical ethers (mixed ethers);

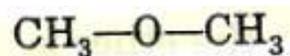
When the organic groups attached to the oxygen are **different**.

# Nomenclature of Ethers

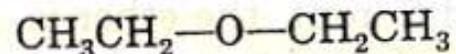
## Common Names

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

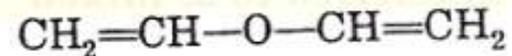
✿ Methyl ether



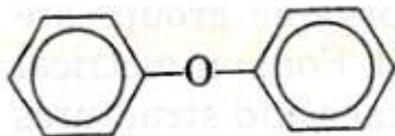
✿ Ethyl ether



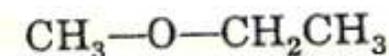
✿ Vinyl ether



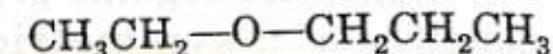
✿ Phenyl ether



Ethyl methyl ether



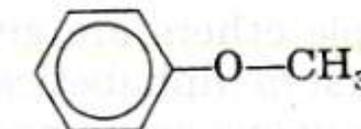
Ethyl-*n*-propyl ether



*t*-Butyl methyl ether

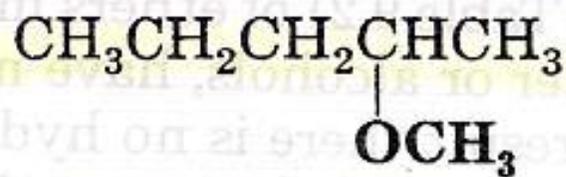


Methyl phenyl ether  
(anisole)

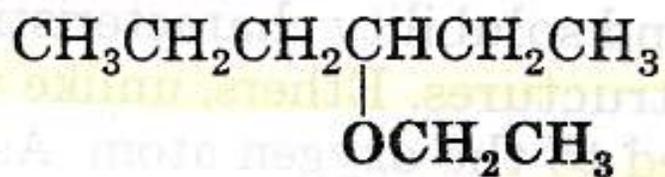


## IUPAC System

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.



2-Methoxypentane



3-Ethoxyhexane



2-Methoxyethanol

alcohol  
+ ether  
(الكحوليات والأكسول)

بأى طريقة التسمية؟

→ the IUPAC naming

# Physical Properties of Ethers

Q: table → ترتيب حسب  
the pb property

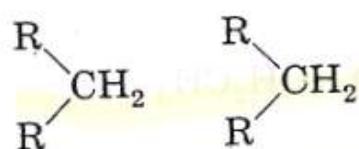
A: Alcohol higher than  
Ether higher than  
hydrocarbon

## Physical State

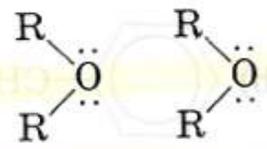
Ethers are colorless compounds with characteristic, relatively pleasant odors.

## Boiling Points

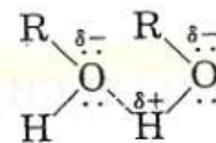
- They have lower boiling points (bp,s) than alcohols with an equal number of carbon atoms.
- In fact, an ether has nearly the same bp as the corresponding hydrocarbon in which a -CH<sub>2</sub>- group replaces the ether's oxygen.  
*the same molecular weight*
- Because of their structures (no O-H bonds), 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

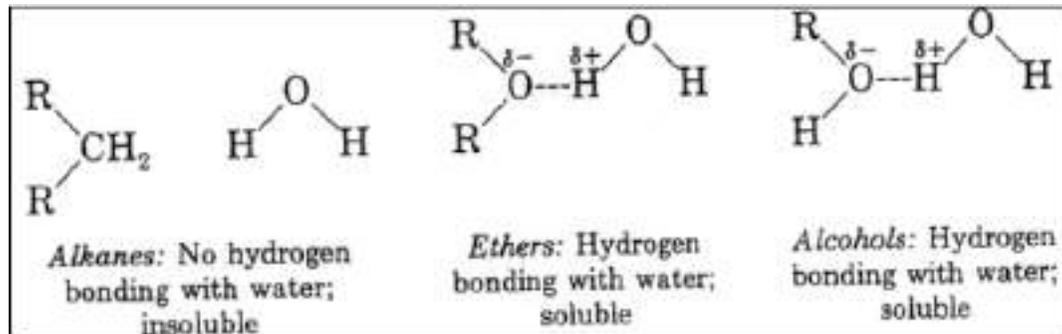


Alcohols: Hydrogen bonding between molecules; high boiling points

Compound	Formula	bp	mol wt	Water solubility (g/100 mL, 20°C)
1-butanol	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	118°C	74	7.9
diethyl ether	CH <sub>3</sub> CH <sub>2</sub> -O-CH <sub>2</sub> CH <sub>3</sub>	35°C	74	7.5
pentane	CH <sub>3</sub> CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> CH <sub>3</sub>	36°C	72	0.03

## Solubility

- Low-molecular-weight ethers, such as dimethyl ether, are quite soluble in water.
- Ether molecules can form hydrogen bonds to water. *(only one)* *(أقل من الكحول)*



• إذا وصلت عدد C إلى 8 وأكثر يعني الجزء اللطيفيليك part will be heavier

Structure	Name	Mol.wt.	Bp (°C)	Solubility in H <sub>2</sub> O At 20 °C
CH <sub>3</sub> CH <sub>2</sub> CH <sub>3</sub>	propane	44	-42	insoluble
CH <sub>3</sub> OCH <sub>3</sub>	methyl ether	46	-24	soluble
CH <sub>3</sub> CH <sub>2</sub> OH	ethanol	46	78	soluble
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	n-butane	58	-0.5	insoluble
CH <sub>3</sub> CH <sub>2</sub> OCH <sub>3</sub>	ethyl methyl ether	60	8	soluble
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> OH	1-propanol	60	97	soluble
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	n-pentane	72	35	insoluble
CH <sub>3</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub>	ethyl ether	74	36	7.5 g/100 g
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> OH	1-butanol	74	118	7.9 g/100 g
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	n-heptane	100	98	insoluble
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	n-propyl ether	102	91	0.2 g/100 g
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub> OH	1-hexanol	102	157	0.6 g/100 g

# Preparation of Ethers

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

## 1) Dehydration of alcohols

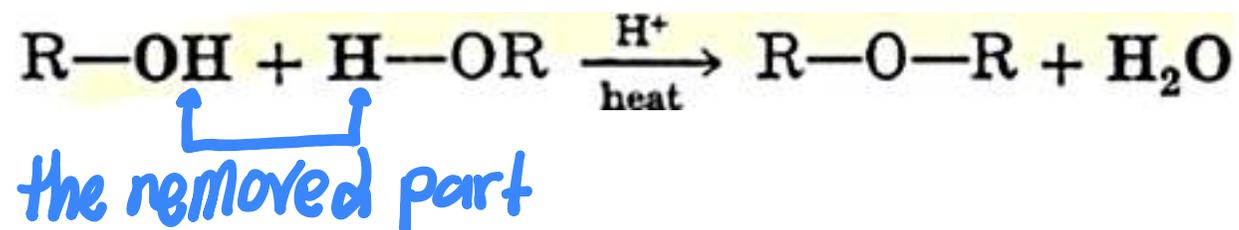
It is used **commercially** and in the **laboratory** to make certain **symmetrical ethers**.

## 2) Williamson synthesis

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

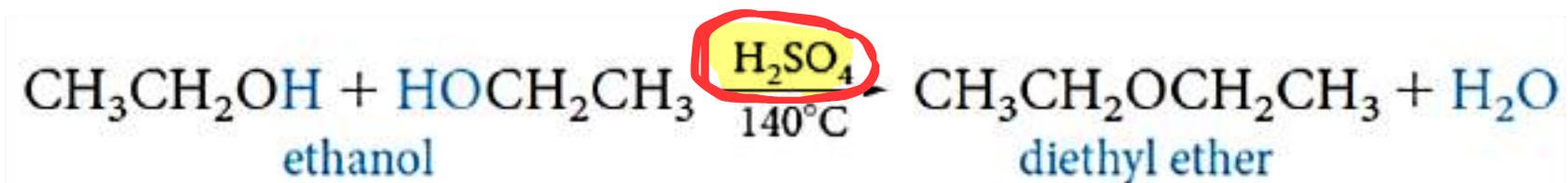
## 1) Dehydration of Alcohols

It takes place in the presence of acid catalysts ( $\text{H}_2\text{SO}_4$ ,  $\text{H}_3\text{PO}_4$ ) (intermolecular reaction)  
*sometimes the same molecule loose both (OH and H) → ether in alkenes 2<sup>th</sup> (byproduct)*



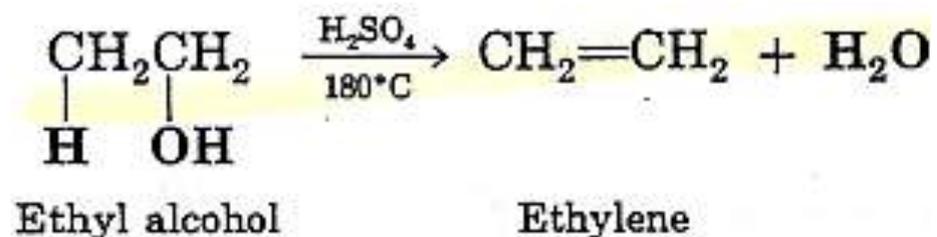
### Example;

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



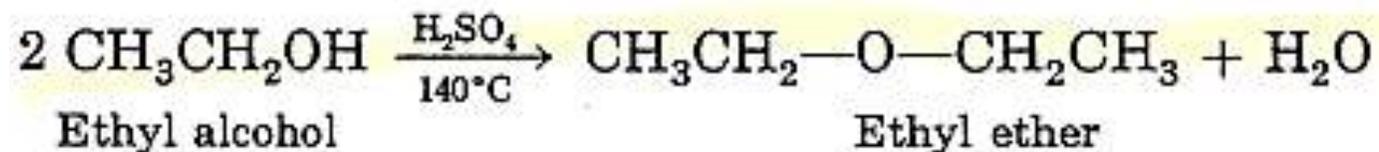
## Scope and Limitations

- 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

# Preparation of Ethers

(طرفين التفاعل)

$R_1 \rightarrow$  from alcohol

$R_2 \rightarrow$  from alkyl halide

(قبل هذه الخطوة لازم نجبر  $R_2, R_1$ )

اعفروض الناتج  
ether

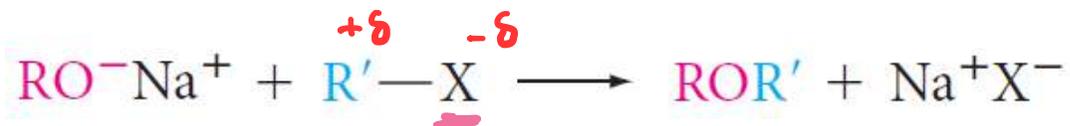
- This method has two steps;

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



$\rightarrow$  nucleophile (any atom rich in  $e^-$ )

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



- To obtain the best yields of mixed dialkyl ethers, we select a  $1^\circ$  rather than a  $2^\circ$  or  $3^\circ$  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, $(\text{CH}_3)_3\text{C-O-CH}_3$ .

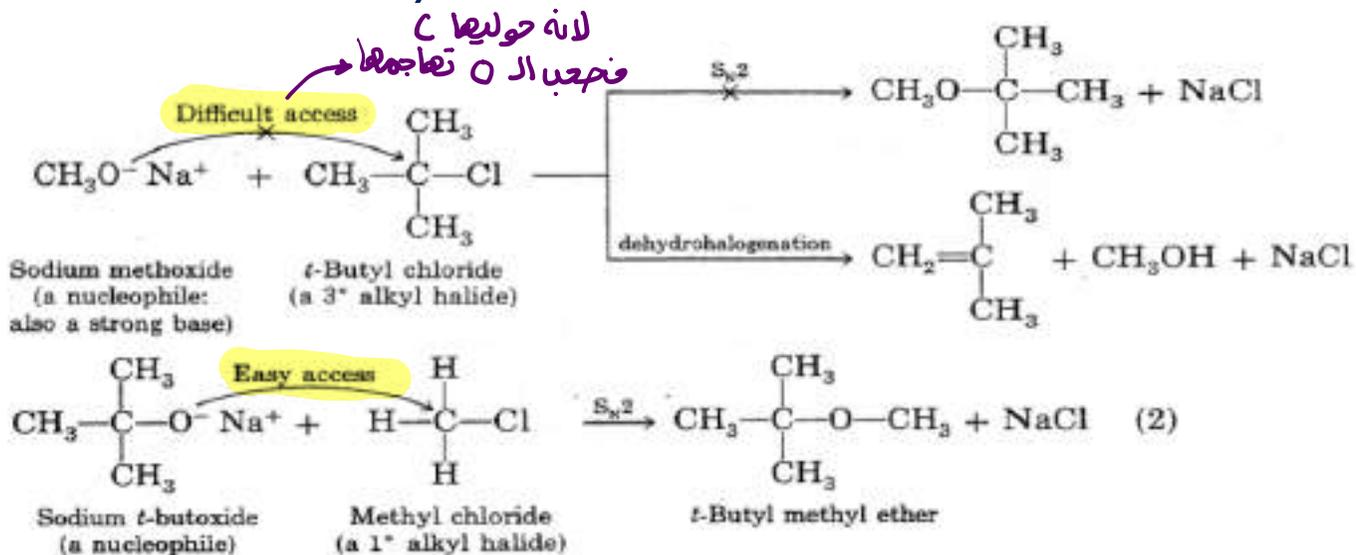
□ In theory, this could be done by either of two reactions.

1. You could react sodium methoxide,  $\text{CH}_3\text{O}^-\text{Na}^+$ , with *t*-butyl chloride,  $(\text{CH}_3)_3\text{C-Cl}$ .

*This combination leads to dehydrohalogenation to an alkene, an elimination reaction.*

2. You could react sodium *t*-butoxide,  $(\text{CH}_3)_3\text{C-O}^-\text{Na}^+$ , with methyl chloride,  $\text{CH}_3\text{Cl}$ .

*This route gives the desired ether by substitution.*

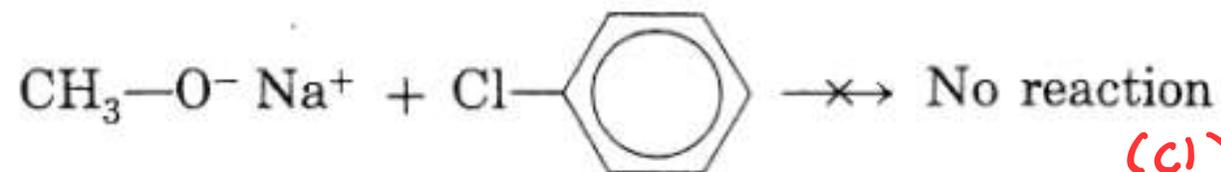


(the starting point) *نقطة***2) Williamson Synthesis**

**Example 2;** Assume you need to synthesize **methyl phenyl ether (anisole),  $\text{CH}_3\text{-O-C}_6\text{H}_5$** , by the Williamson method.

مركب نهائي

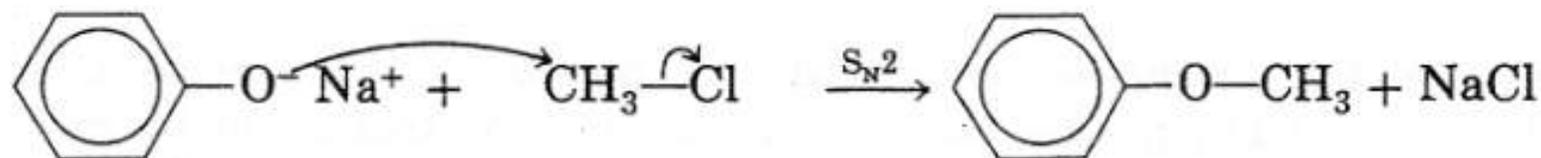
□ In theory, you could obtain anisole in either of two ways.



Sodium methoxide  
(a nucleophile)

Chlorobenzene  
(an aryl halide)

لانه صعب جدا  
(O) محل محل ال (Cl)



Sodium phenoxide  
(a nucleophile)

Methyl chloride  
(a 1° alkyl halide)

Anisole

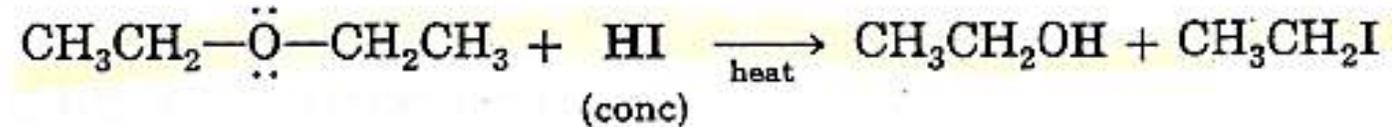
# Reactions of Ethers

- **Ethers** are quite stable compounds. (alkane أثير)
- 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.



to  
 ↓ alcohol ↓ alkyl  
 halide

- 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.



For example,

