Alcohols and Phenols

Part B

B. Pharm. Semester-1
Course Code: 0510210; Session: 2022-2023

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Learning Outcomes

At the end of this lesson, students will be able to describe

- **Reactions of Alcohols**
- **Preparation of Phenols**
- **Reaction of Phenols**
- **Spectroscopy of alcohols and Phenols**

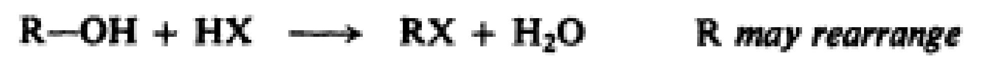
Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the organic chemistry.

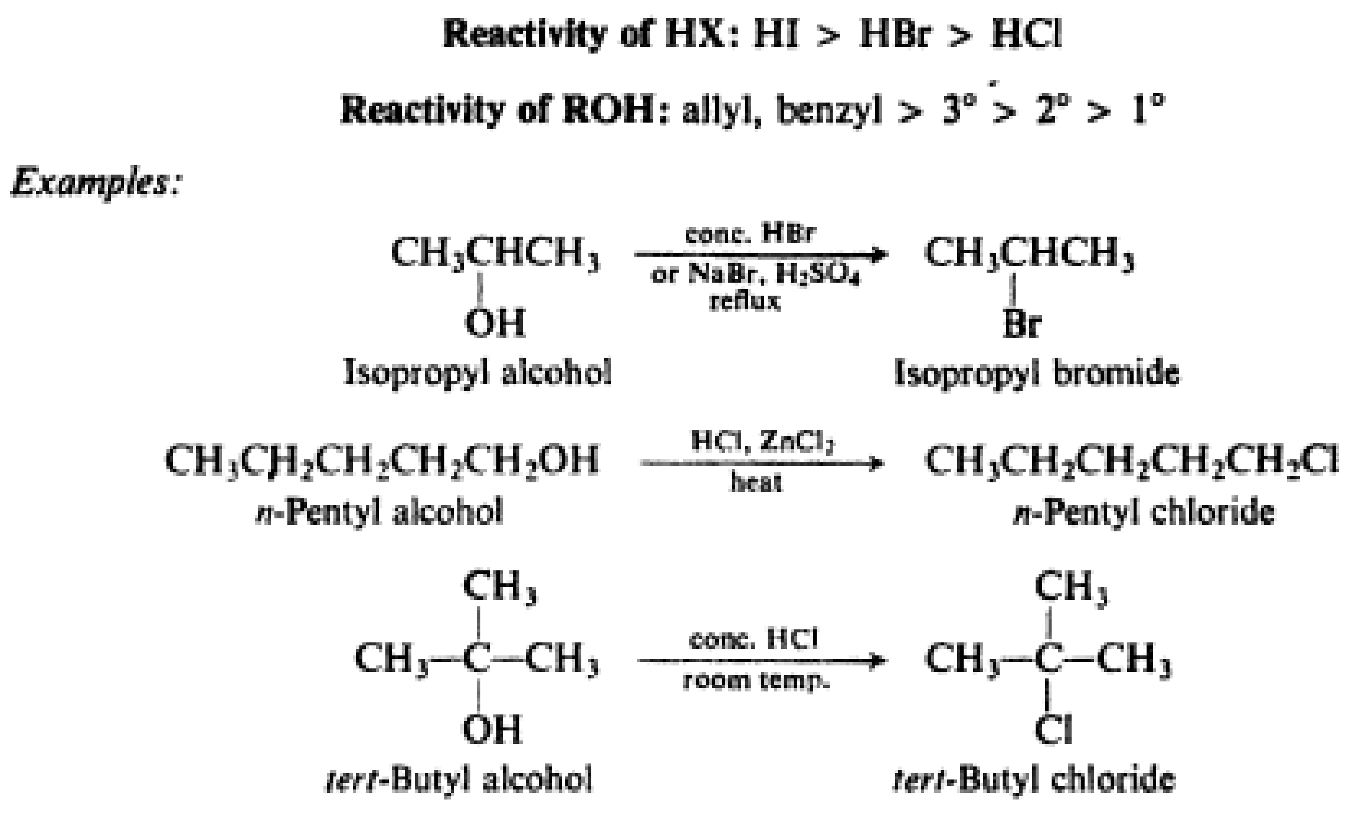
Reactions of Alcohols

1. Reaction with hydrogen halides
2. Reaction with phosphorus trihalides.
3. Reaction with *p*-toluenesulfonylchloride
4. Dehydration.
5. Reaction as acids: reaction with active metals
6. Ester formation.
7. Oxidation.
8. Protection-deprotection

1. Reaction with hydrogen halides



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



Reactivity of HX: HI > HBr > HCl

Reactivity of ROH: allyl, benzyl > 3° > 2° > 1°

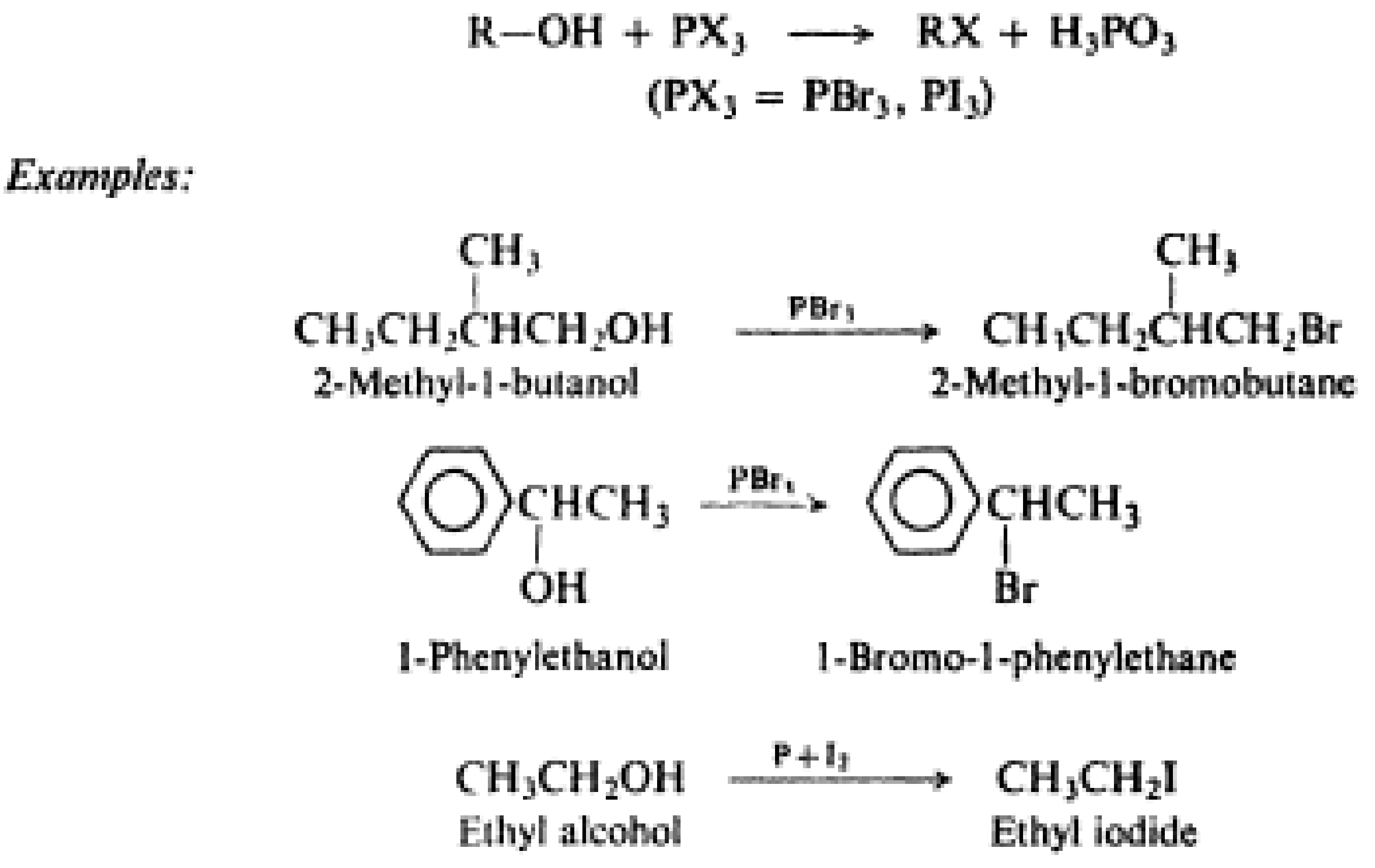
Examples:

$$\underset{\text{Isopropyl alcohol}}{CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_3} \xrightarrow[\text{or NaBr, } H_2SO_4\text{, reflux}]{\text{conc. HBr}} \underset{\text{Isopropyl bromide}}{CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_3}$$

$$\underset{n\text{-Pentyl alcohol}}{CH_3CH_2CH_2CH_2CH_2OH} \xrightarrow[\text{heat}]{HCl,\ ZnCl_2} \underset{n\text{-Pentyl chloride}}{CH_3CH_2CH_2CH_2CH_2Cl}$$

$$\underset{tert\text{-Butyl alcohol}}{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle OH}{\underset{|}{C}}}}{-}CH_3} \xrightarrow[\text{room temp.}]{\text{conc. HCl}} \underset{tert\text{-Butyl chloride}}{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle Cl}{\underset{|}{C}}}}{-}CH_3}$$

2. Reaction with phosphorus trihalides



$$R{-}OH + PX_3 \longrightarrow RX + H_3PO_3$$

$$(PX_3 = PBr_3, PI_3)$$

Examples:

$$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2OH \xrightarrow{PBr_3} CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2Br$$

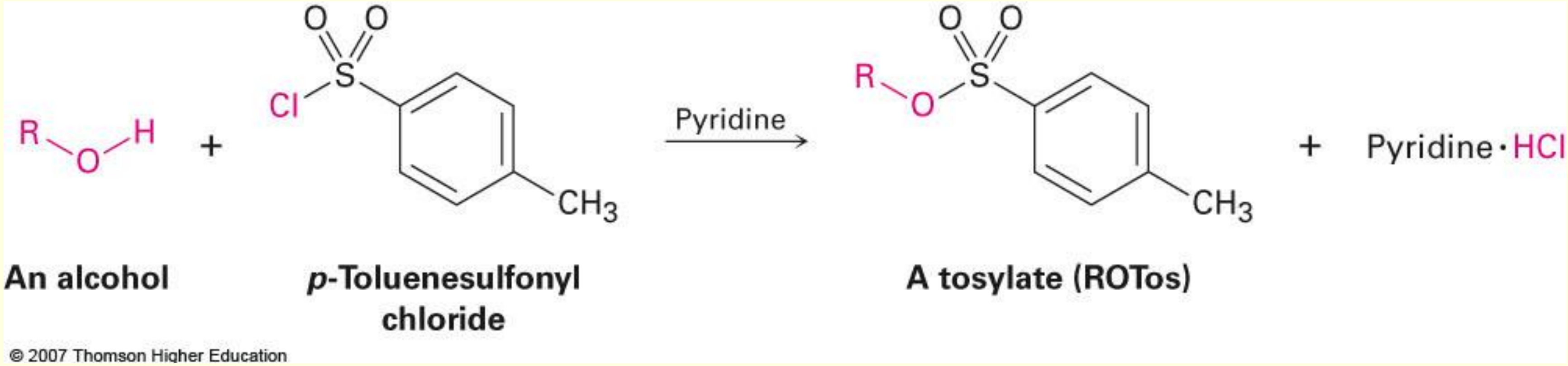
2-Methyl-1-butanol → 2-Methyl-1-bromobutane

1-Phenylethanol → 1-Bromo-1-phenylethane

$$CH_3CH_2OH \xrightarrow{P + I_2} CH_3CH_2I$$

Ethyl alcohol → Ethyl iodide

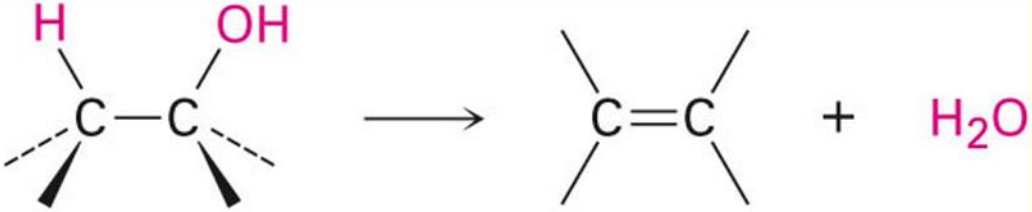
3. Reaction with *p*- toluenesulfonylchloride



- Reaction with *p*-toluenesulfonyl chloride (tosyl chloride, *p*-TosCl) in pyridine yields alkyl tosylates, ROTos.
- Formation of the tosylate does not involve the C–O bond so configuration at a chirality center is maintained.
- Alkyl tosylates react like alkyl halides.

4. Dehydration

A dehydration reaction

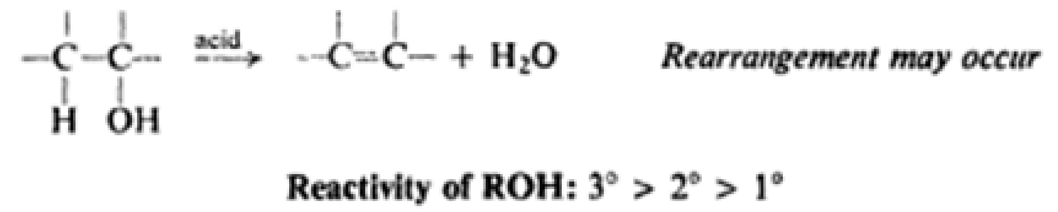


The general reaction: forming an alkene from an alcohol through loss of O-H and H (hence dehydration) of the neighboring C–H to give π-bond, specific reagents are needed.

Dehydration generally requires acid catalysts.

Reactivity of alcohols = tertiary>secondary>primary

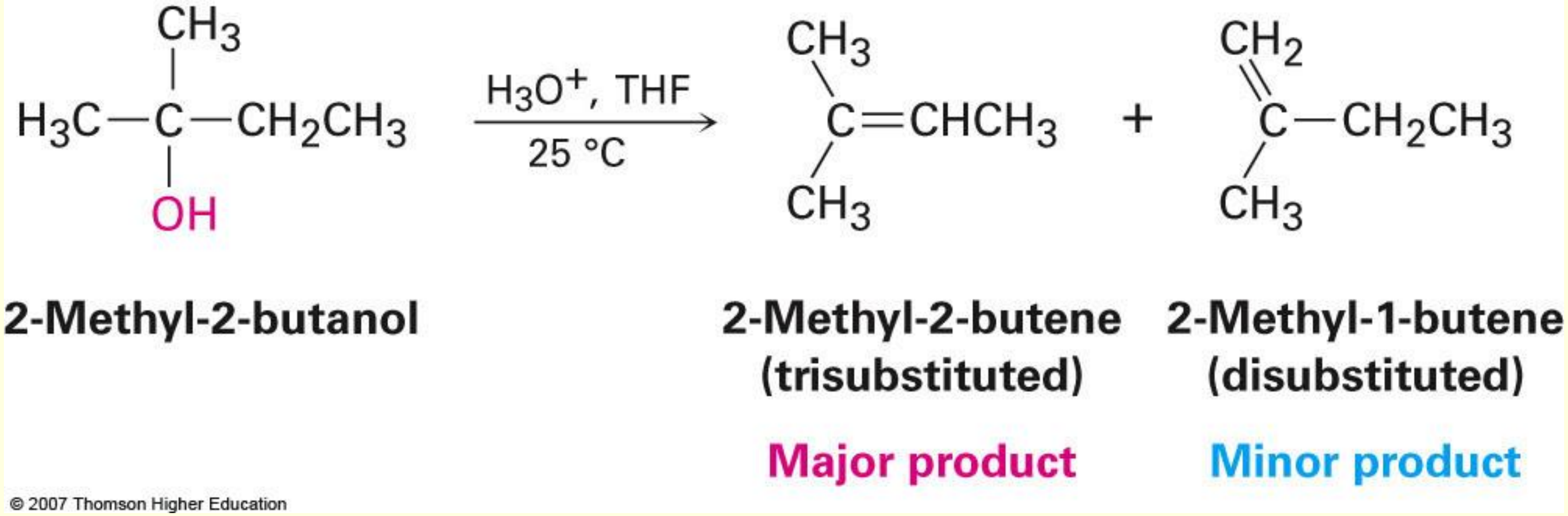
4. Dehydration



$$-\underset{H}{\overset{|}{C}}-\underset{OH}{\overset{|}{C}}- \xrightarrow{acid} -\overset{|}{C}=\overset{|}{C}- + H_2O$$

Rearrangement may occur

Reactivity of ROH: 3° > 2° > 1°



2-Methyl-2-butanol

2-Methyl-2-butene (trisubstituted)

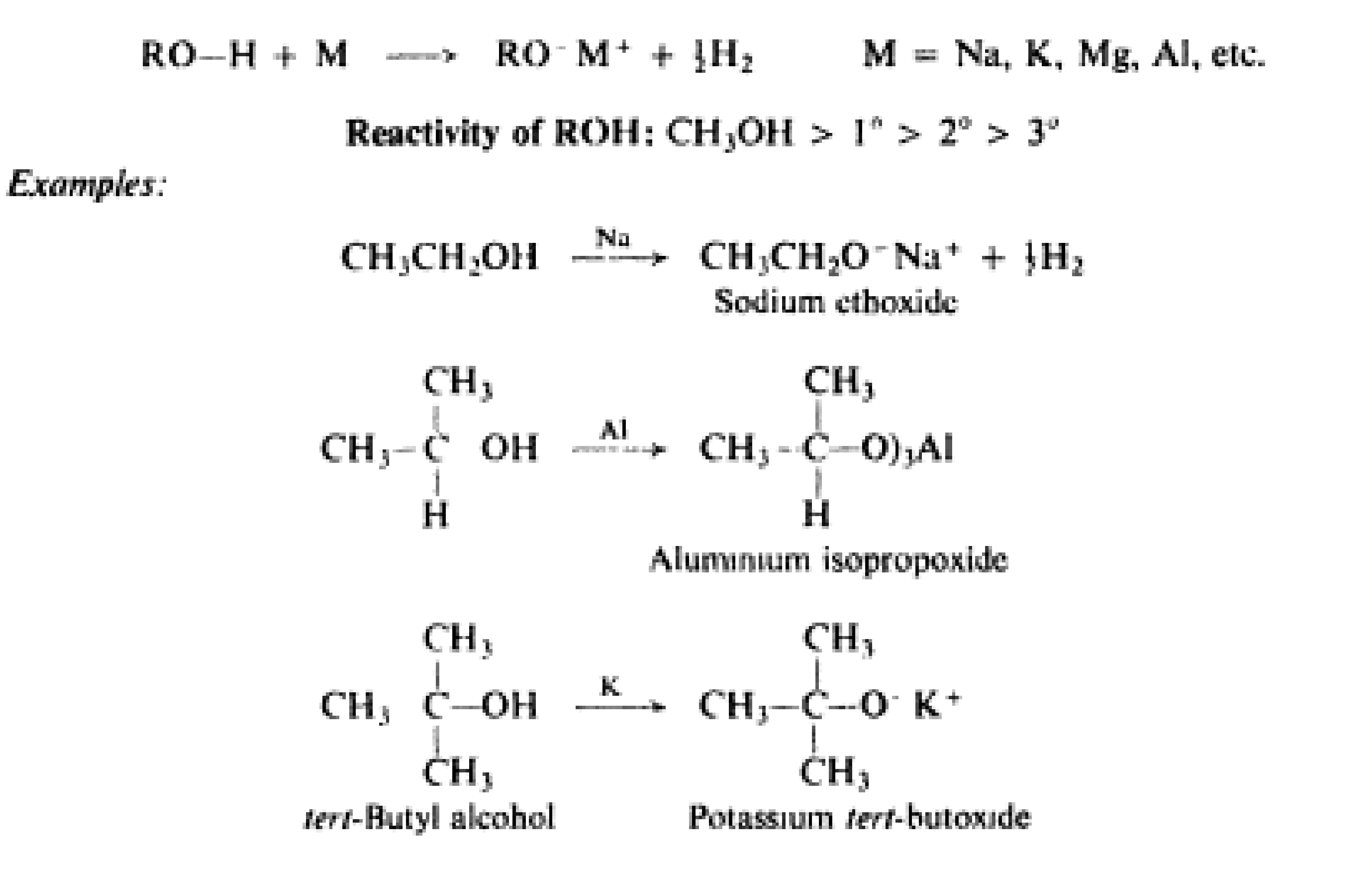
Major product

2-Methyl-1-butene (disubstituted)

Minor product

- Tertiary alcohols are readily dehydrated with acid.
- Secondary alcohols require severe conditions (75% H_2SO_4, 100°C) - sensitive molecules don't survive.
- Primary alcohols require very harsh conditions–impractical.

5. Reaction as acids: reaction with active metals



$$RO{-}H + M \longrightarrow RO^-M^+ + \tfrac{1}{2}H_2 \qquad M = Na, K, Mg, Al, etc.$$

Reactivity of ROH: $CH_3OH > 1° > 2° > 3°$

Examples:

$$CH_3CH_2OH \xrightarrow{Na} CH_3CH_2O^-Na^+ + \tfrac{1}{2}H_2$$

Sodium ethoxide

$$CH_3{-}\underset{H}{\overset{CH_3}{C}}\;OH \xrightarrow{Al} CH_3{-}\underset{H}{\overset{CH_3}{C}}{-}O)_3Al$$

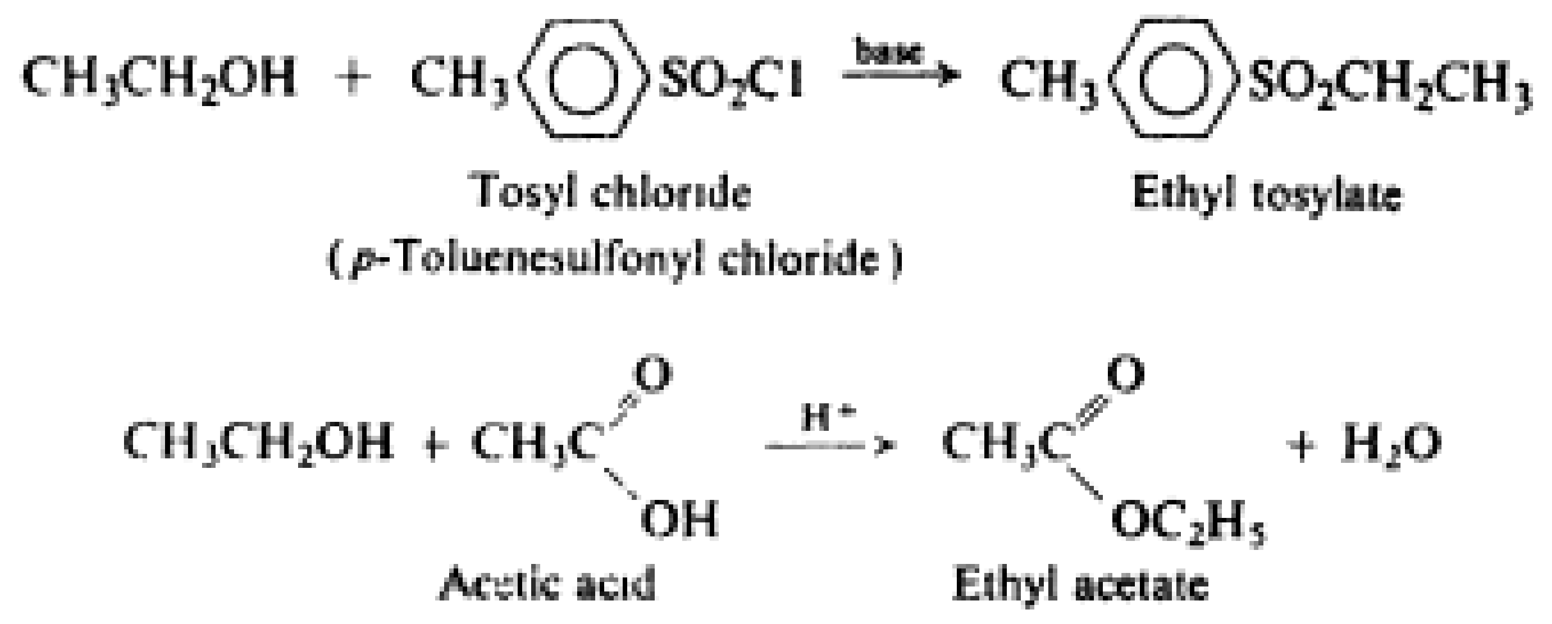
Aluminum isopropoxide

$$CH_3\;\underset{CH_3}{\overset{CH_3}{C}}{-}OH \xrightarrow{K} CH_3{-}\underset{CH_3}{\overset{CH_3}{C}}{-}O^-\,K^+$$

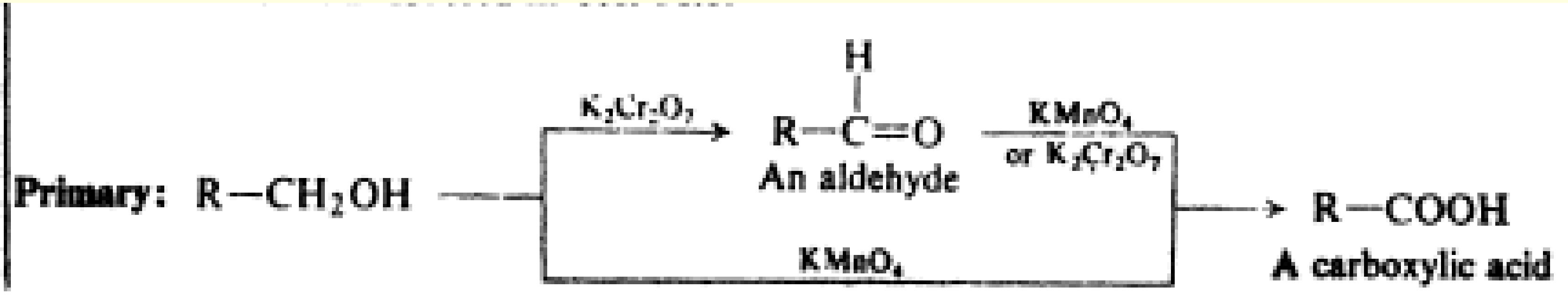
tert-Butyl alcohol

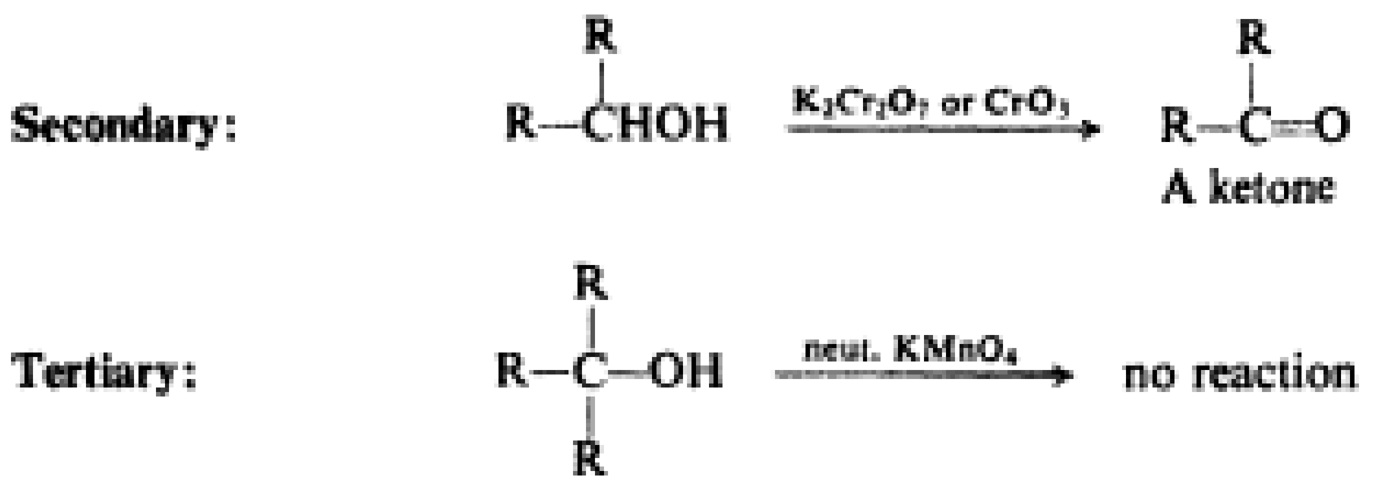
Potassium *tert*-butoxide

6. Ester formation



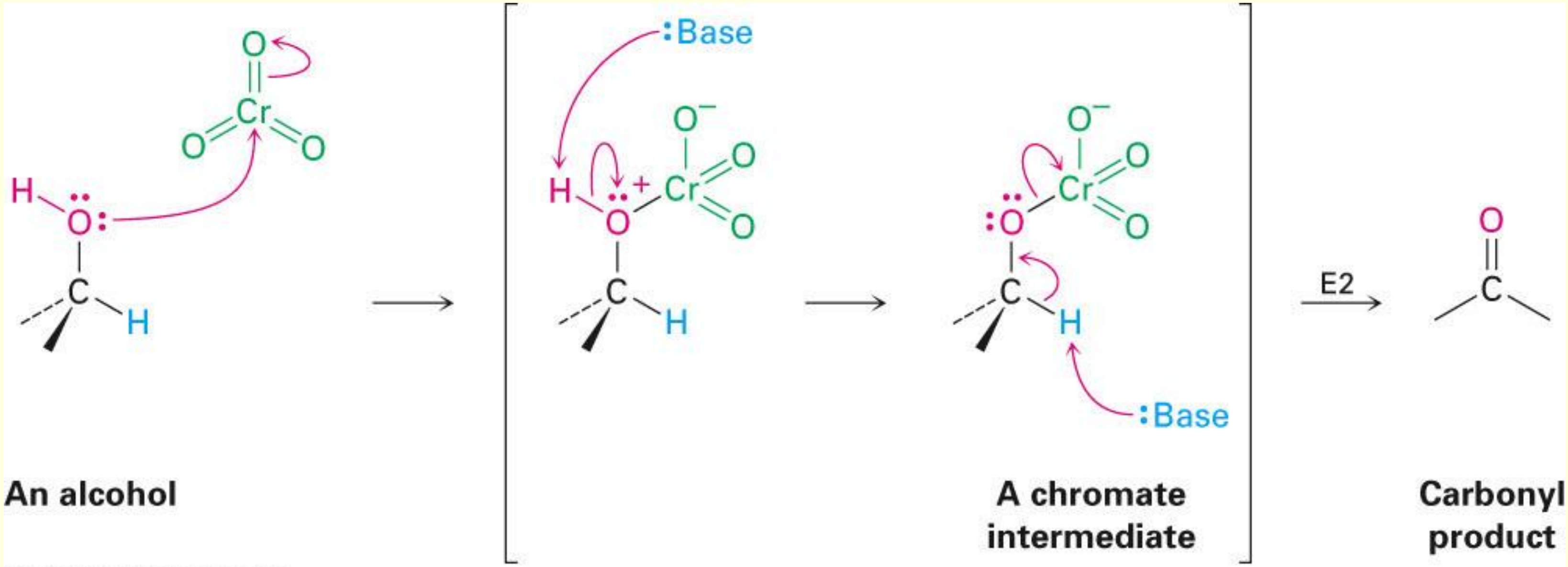
7. Oxidation


Primary:
R—CH₂OH
K₂Cr₂O₇
H
R—C=O
An aldehyde
KMnO₄
or K₂Cr₂O₇
KMnO₄
R—COOH
A carboxylic acid

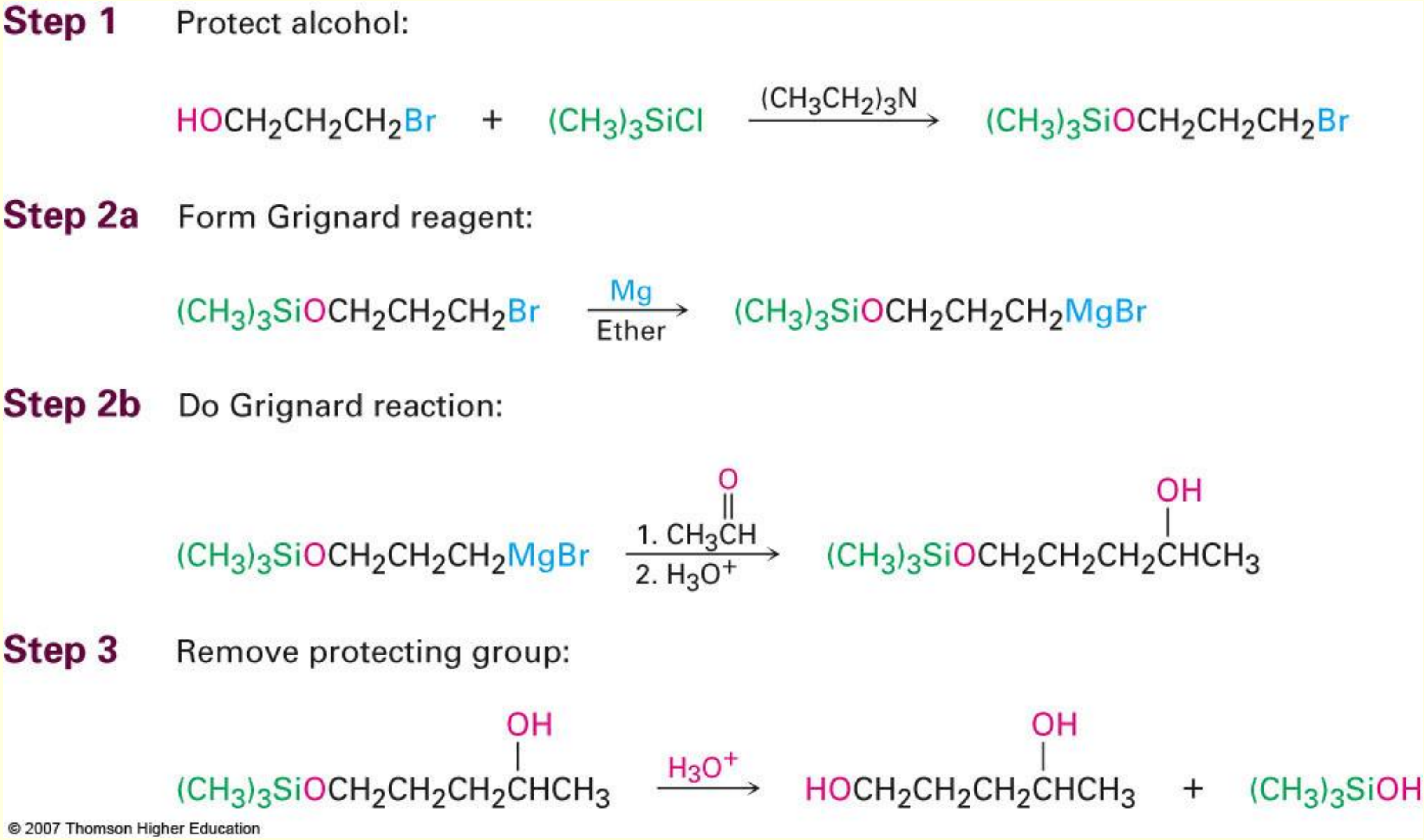

Secondary:
R
R—CHOH
K₂Cr₂O₇ or CrO₃
R
R—C=O
A ketone
Tertiary:
R
R—C—OH
R
neut. KMnO₄
no reaction

Mechanism of Chromic Acid Oxidation

- Alcohol forms a chromate ester followed by elimination with electron transfer to give ketone.
- The mechanism was determined by observing the effects of isotopes.



8. Protection-deprotection



Step 1 Protect alcohol:

$$HOCH_2CH_2CH_2Br + (CH_3)_3SiCl \xrightarrow{(CH_3CH_2)_3N} (CH_3)_3SiOCH_2CH_2CH_2Br$$

Step 2a Form Grignard reagent:

$$(CH_3)_3SiOCH_2CH_2CH_2Br \xrightarrow[\text{Ether}]{\text{Mg}} (CH_3)_3SiOCH_2CH_2CH_2MgBr$$

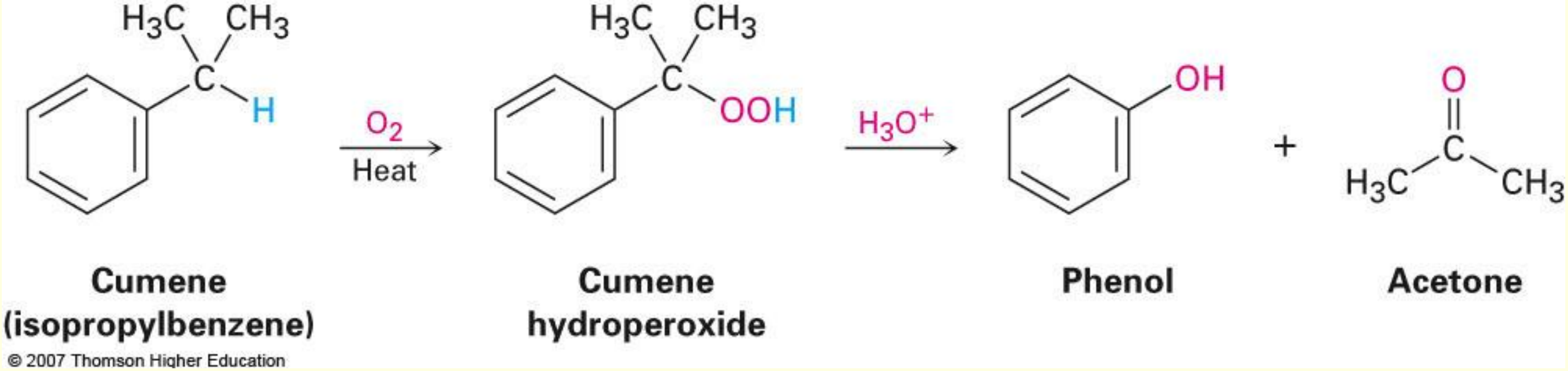
Step 2b Do Grignard reaction:

$$(CH_3)_3SiOCH_2CH_2CH_2MgBr \xrightarrow[\text{2. } H_3O^+]{\text{1. } CH_3\overset{\overset{O}{\|}}{C}H} (CH_3)_3SiOCH_2CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_3$$

Step 3 Remove protecting group:

$$(CH_3)_3SiOCH_2CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_3 \xrightarrow{H_3O^+} HOCH_2CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_3 + (CH_3)_3SiOH$$

Phenol: Preparation



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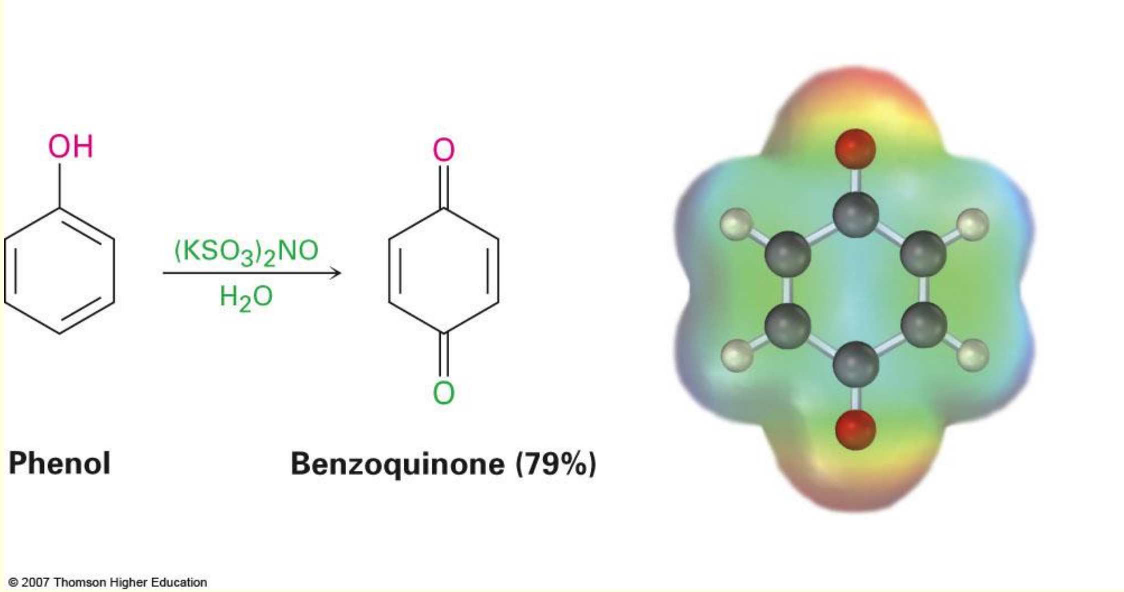
- Industrial process from readily available cumene.
- Forms cumene hydroperoxide with oxygen at high temperature.
- Converted into phenol and acetone by acid.

Phenol: Reactions



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- The hydroxyl group is a strongly activating, making phenols substrates for electrophilic halogenation, nitration, sulfonation, and Friedel–Crafts reactions.
- Reaction of a phenol with strong oxidizing agents yields a quinone. Fremy's salt [$(KSO_3)_2NO$] works under mild conditions through a radical mechanism.

IR Spectroscopy of Alcohols and Phenols

- Characteristic O–H stretching absorption at 3300 to 3600 cm^{-1} in the infrared
- Sharp absorption near 3600 cm^{-1} except if H-bonded: then broad absorption 3300 to 3400 cm^{-1} range
- Strong C–O stretching absorption near 1050 cm^{-1}
- Phenol OH absorbs near 3500 cm^{-1}

IR Spectroscopy of Alcohols and Phenols

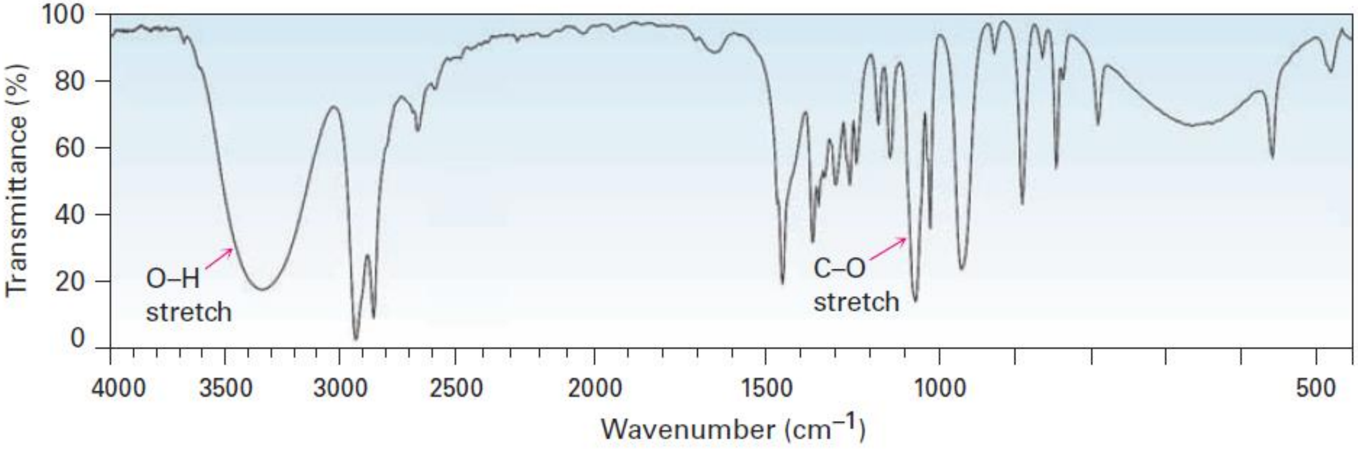


Figure 17.11 Infrared spectrum of cyclohexanol. Characteristic O—H and C—O stretching absorptions are indicated.

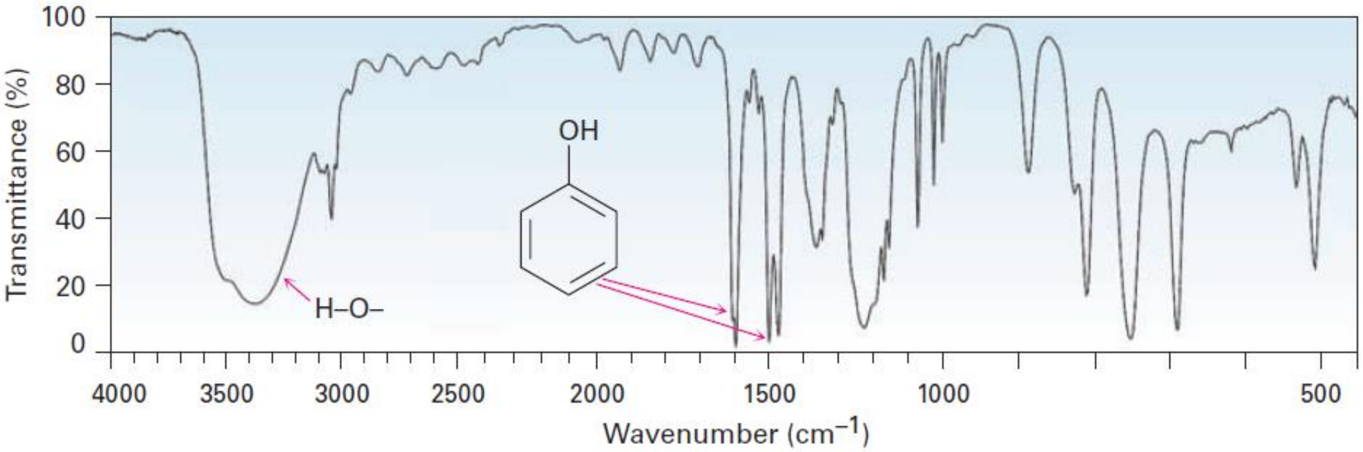


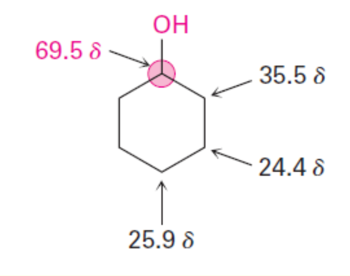
Figure 17.12 Infrared spectrum of phenol.

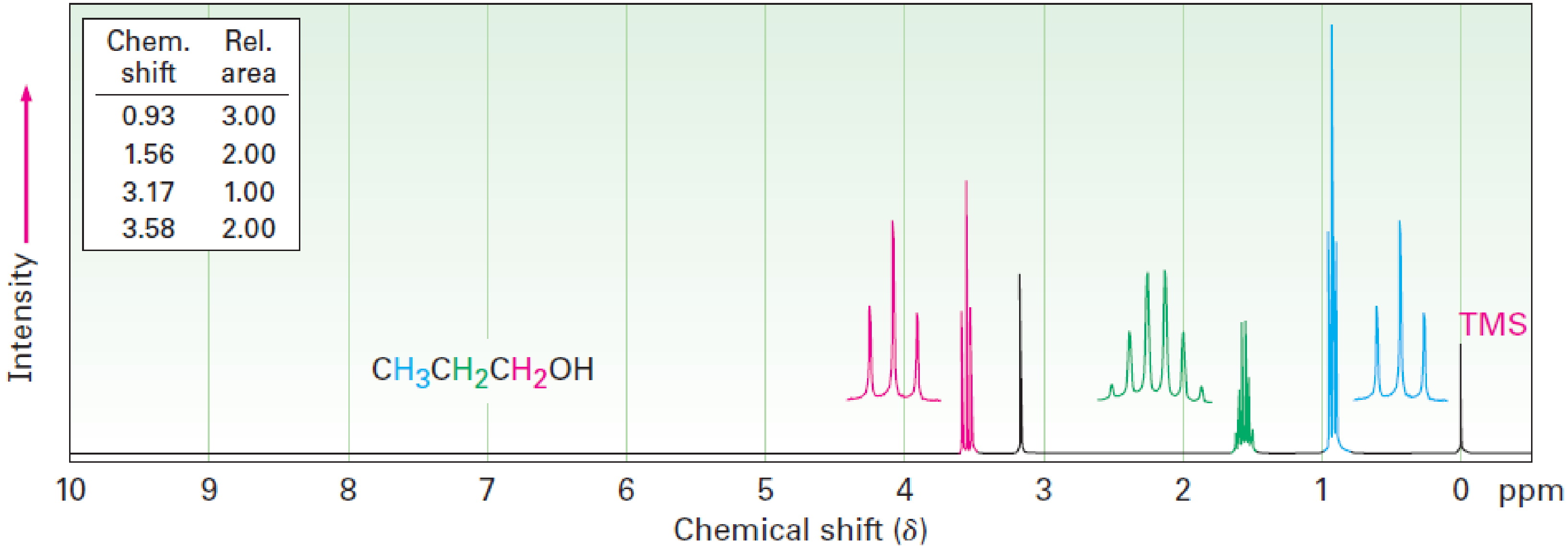
NMR Spectroscopy of Alcohols and Phenols

- ^{13}C NMR: C bonded to -OH absorbs at a lower field, δ 50 to 80 ppm.
- ^{1}H NMR: electron-withdrawing effect of the nearby oxygen, absorbs at δ 3.5 to 4.
  - Usually no spin-spin coupling between O–H proton and neighboring protons on C due to exchange reactions with moisture or acids
  - Spin–spin splitting is observed between protons on the oxygen-bearing carbon and other neighbors
- Phenol O–H protons absorb at δ 3 to 8 ppm.

NMR Spectroscopy of Alcohols and Phenols

CARBON-NMR OF PHENOL



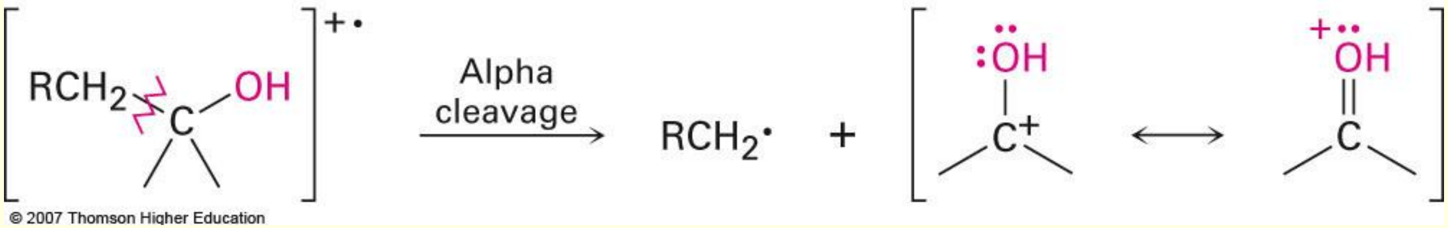


Chem. shift	Rel. area
0.93	3.00
1.56	2.00
3.17	1.00
3.58	2.00

Figure 17.13 ^{1}H NMR spectrum of 1-propanol. The protons on the oxygen-bearing carbon are split into a triplet at 3.58 δ.

MASS Spectrometry of Alcohols and Phenols

- Alcohols undergo α-cleavage, a C–C bond nearest the hydroxyl group is broken, yielding a neutral radical plus a charged oxygen-containing fragment.
- Alcohols undergo dehydration to yield an alkene radical anion.



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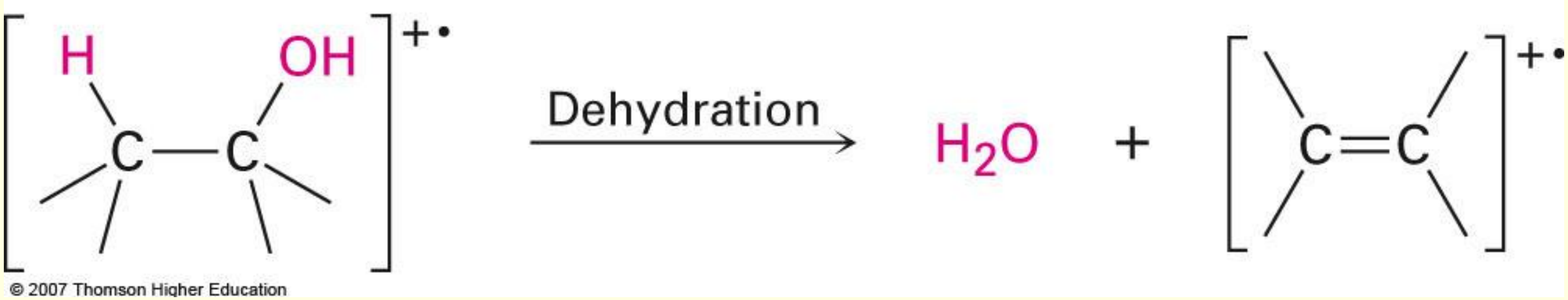

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Mass Spectrum of Butanol

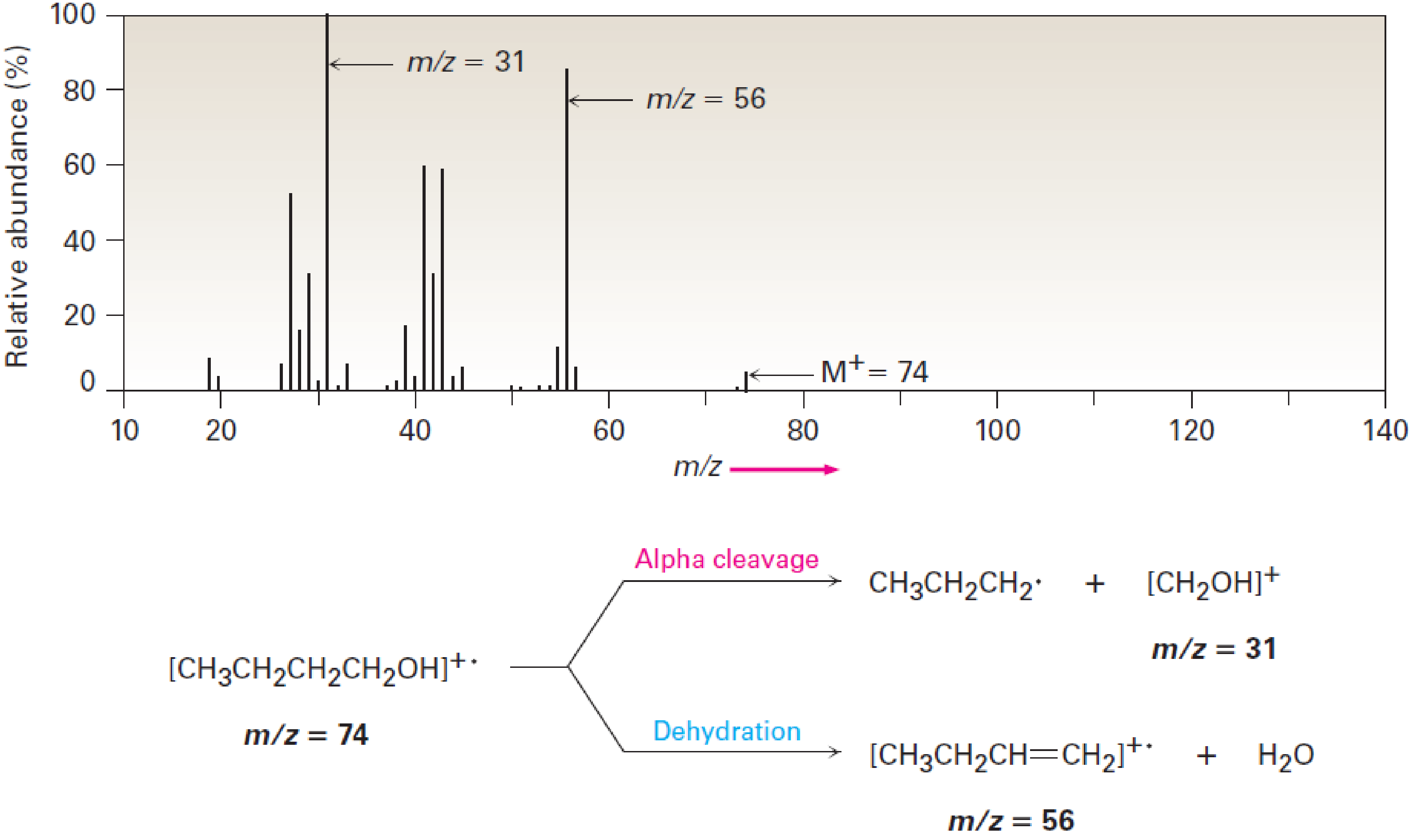

Figure 17.14 Mass spectrum of 1-butanol ($M^+ = 74$). Dehydration gives a peak at *m/z* = 56, and fragmentation by alpha cleavage gives a peak at *m/z* = 31.

REFERENCES

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