Pharmaceutical organic chemistry

Alcohol – Lecture 4

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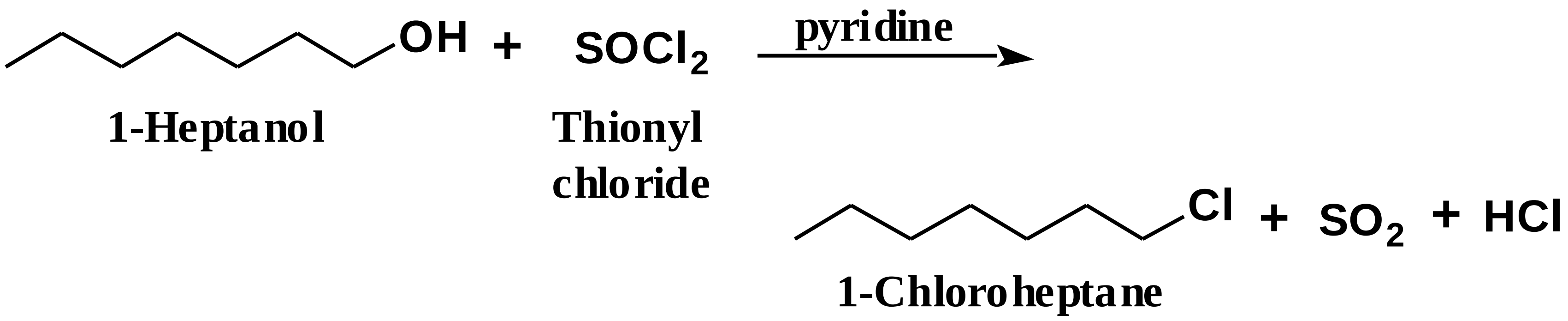
Reaction with $SOCl_2$

Thionyl chloride is the most widely used reagent for the conversion of 1° and 2° alcohols to alkyl chlorides

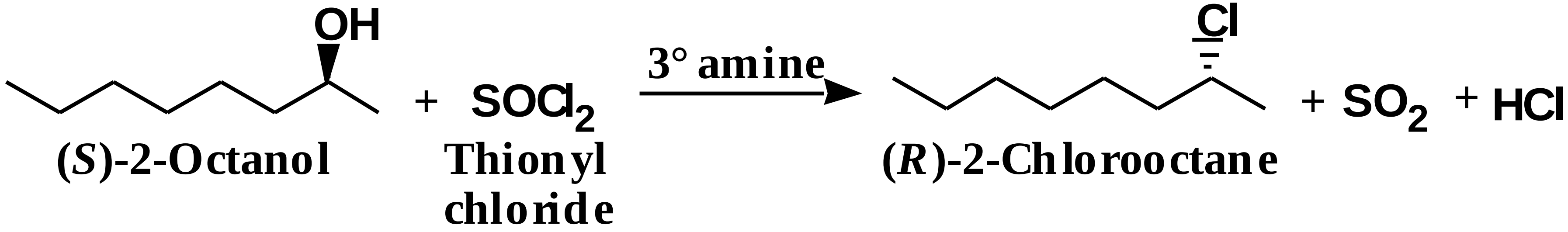
- a base, most commonly pyridine or triethylamine, is added to catalyze the reaction and to neutralize the HCl



Reaction with $SOCl_2$

Reaction of an alcohol with $SOCl_2$ in the presence of a 3° amine is stereoselective

- it occurs with inversion of configuration



Inversion of configuration in the S_N2 reaction

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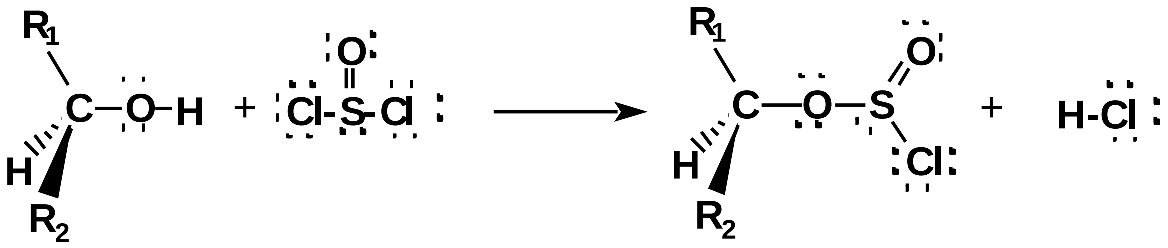
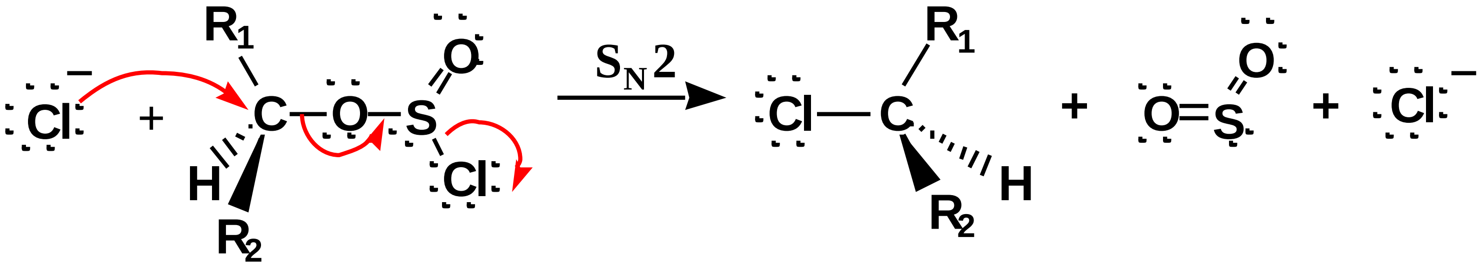
Reaction with $SOCl_2$

Step 1: formation of an alkyl chlorosulfite



An alkyl chlorosulfite

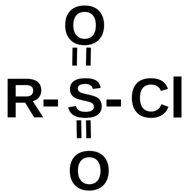
Step 2: nucleophilic displacement of this leaving group by chloride ion gives the chloroalkane



Alkyl Sulfonates

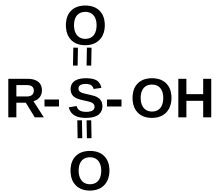
Sulfonyl chlorides are derived from sulfonic acids

- sulfonic acids, like sulfuric acid, are strong acids



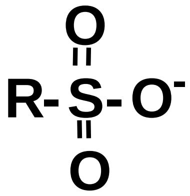
$$\mathrm{R{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}Cl}$$

A sulfonyl chloride



$$\mathrm{R{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}OH}$$

A sulfonic acid (a very strong acid)

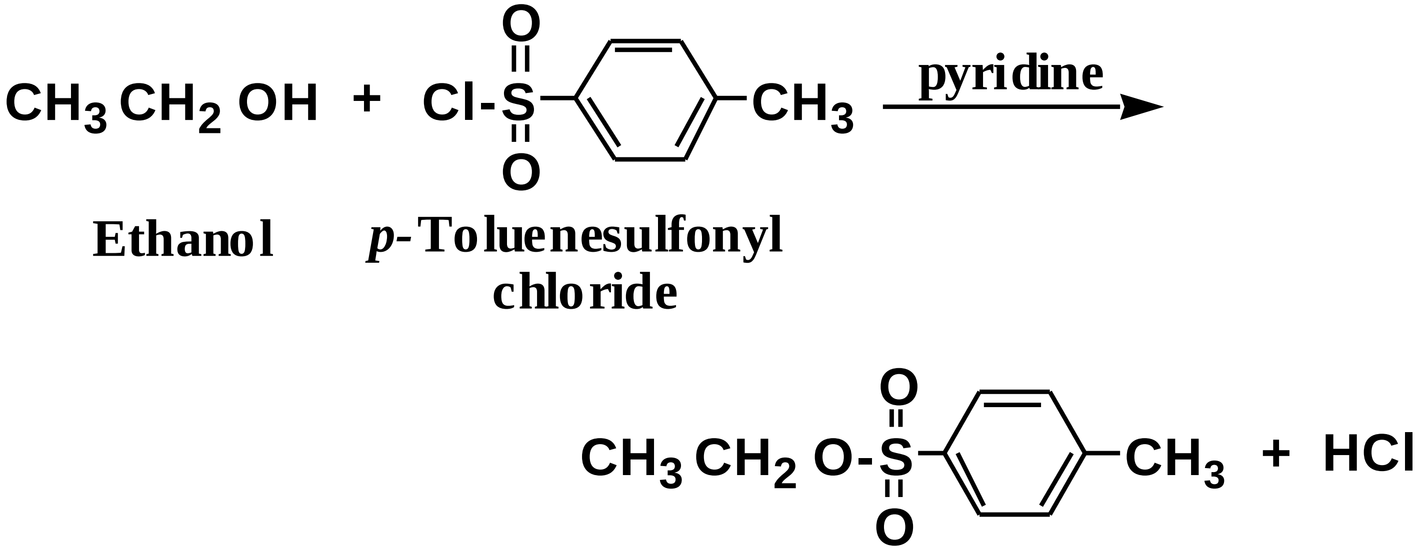


$$\mathrm{R{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}O^{-}}$$

A sulfonate anion (a very weak base and stable anion; a very good leaving group

Alkyl Sulfonates

A commonly used sulfonyl chloride is *p*-toluenesulfonyl chloride (Ts-Cl)



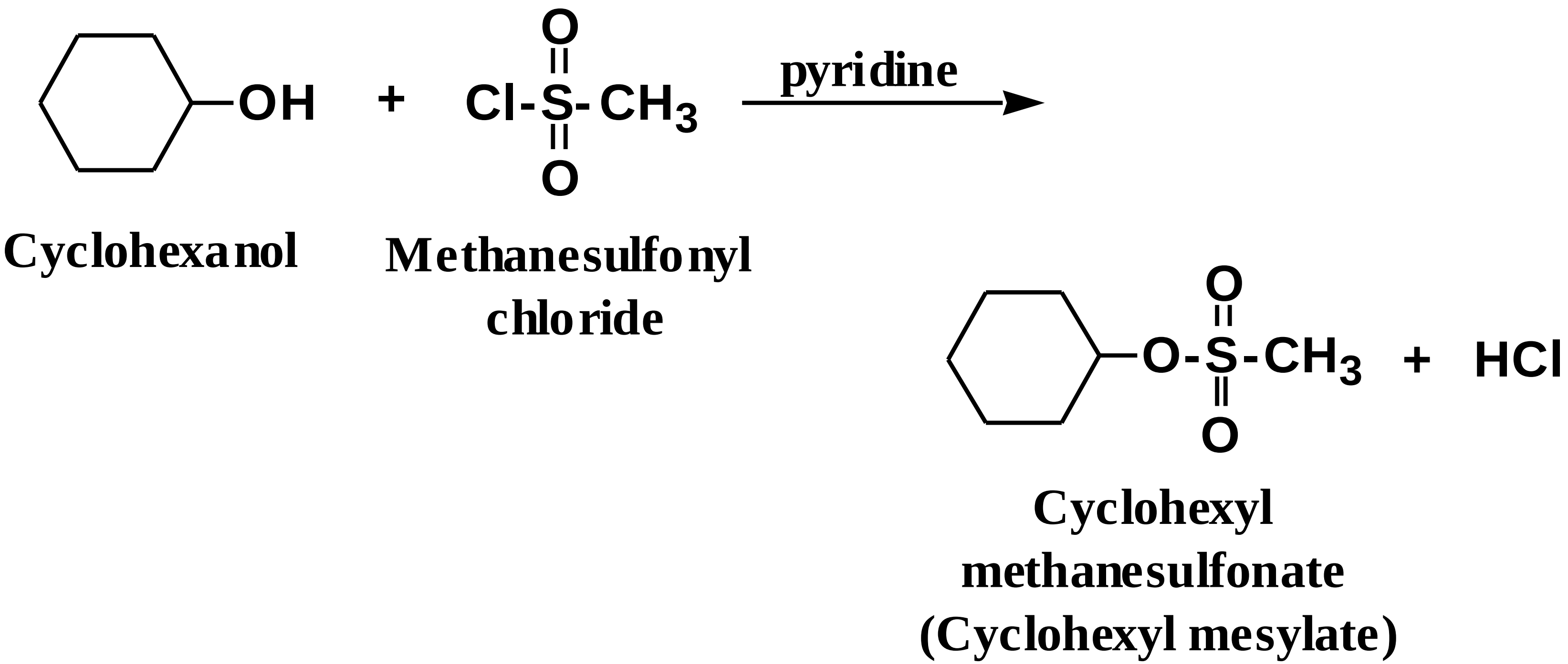
Ethanol

***p*-Toluenesulfonyl chloride**

Ethyl *p*-toluenesulfonate (Ethyl tosylate)

Alkyl Sulfonates

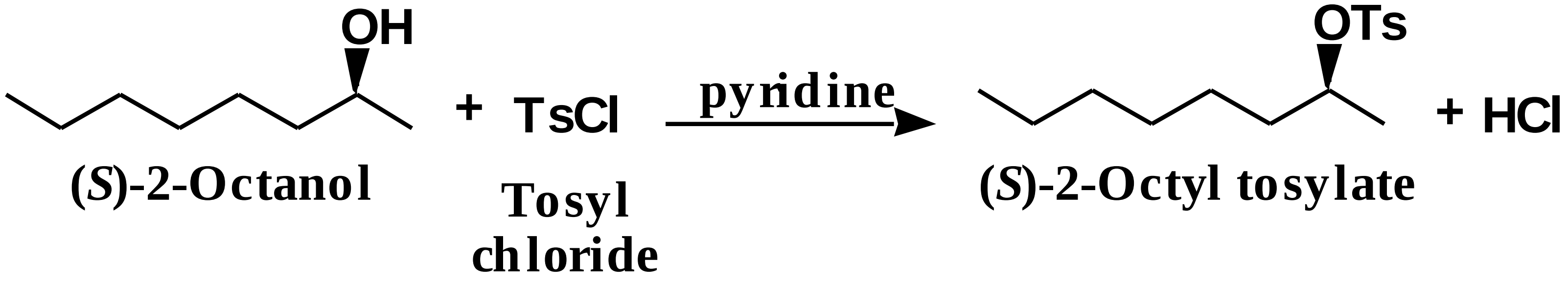
Another commonly used sulfonyl chloride is methanesulfonyl chloride (Ms-Cl)



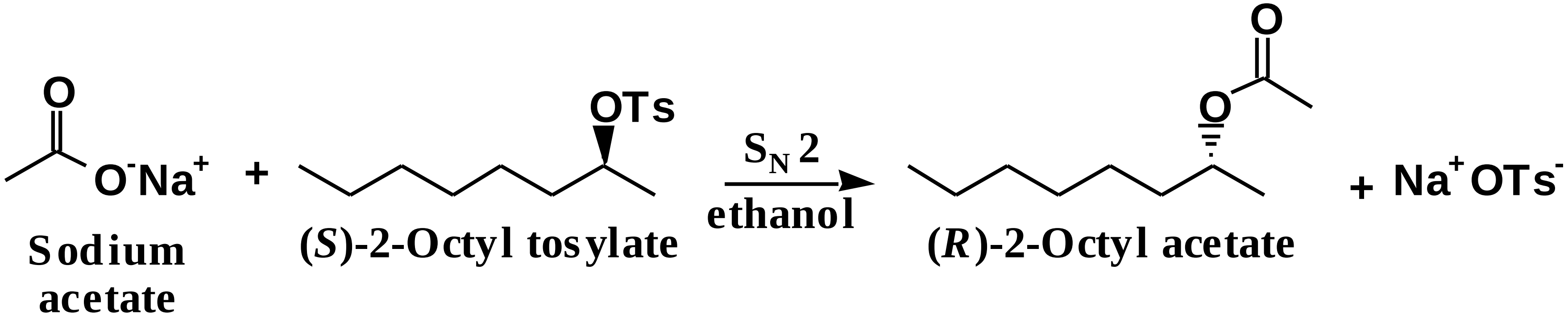
Alkyl Sulfonates

This two-step procedure converts (*S*)-2-octanol to (*R*)-2-octyl acetate

Step 1: formation of a *p*-toluenesulfonate (Ts) ester



Step 2: nucleophilic displacement of tosylate



Dehydration of ROH

An alcohol can be converted to an alkene by acid-catalyzed dehydration (a type of β-elimination)

- 1° alcohols must be heated at high temperature in the presence of an acid catalyst, such as H_2SO_4 or H_3PO_4
- 2° alcohols undergo dehydration at somewhat higher temperatures
- 3° alcohols often require temperatures at or slightly above room temperature

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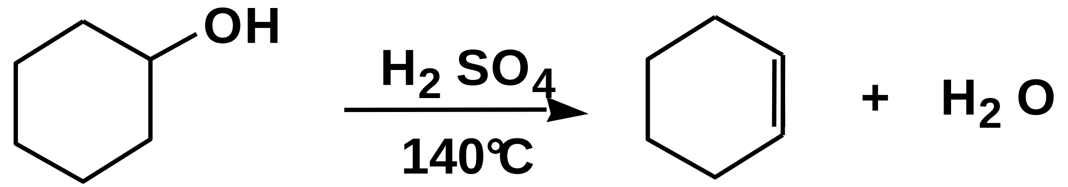
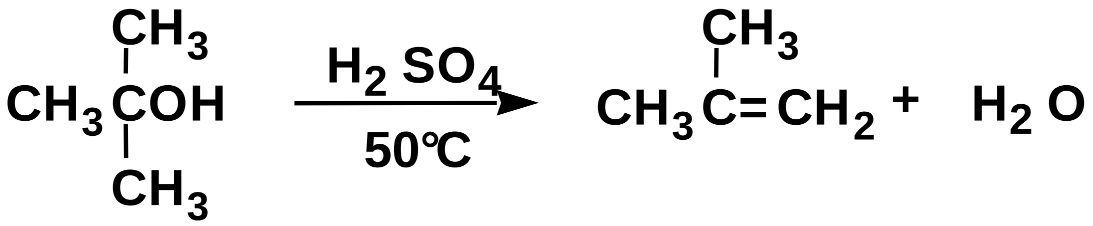
Dehydration of ROH

$$CH_3CH_2OH \xrightarrow[180°C]{H_2SO_4} CH_2{=}CH_2 + H_2O$$



Cyclohexanol

Cyclohexene



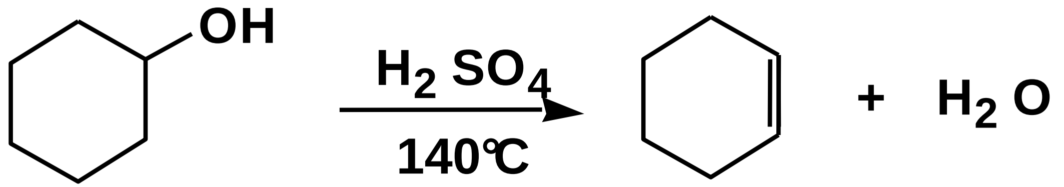
$$(CH_3)_3COH \xrightarrow[50℃]{H_2SO_4} CH_3\overset{CH_3}{\overset{|}{C}}{=}CH_2 + H_2O$$

2-Methyl-2-propanol
(*tert-* Butyl alcohol)

2-Methylpropene
(Isobutylene)

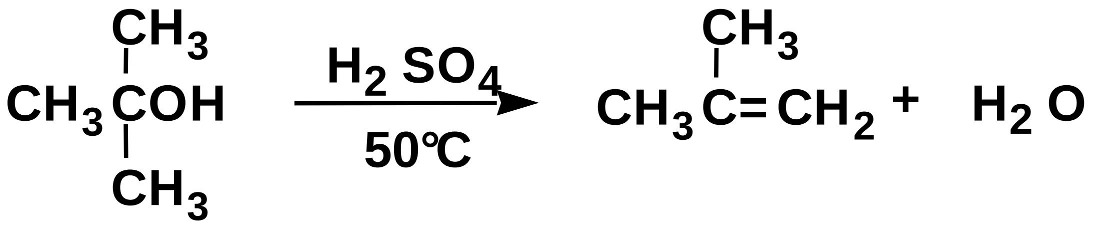
Dehydration of ROH

$$CH_3CH_2OH \xrightarrow[180^\circ C]{H_2SO_4} CH_2{=}CH_2 + H_2O$$



Cyclohexanol

Cyclohexene



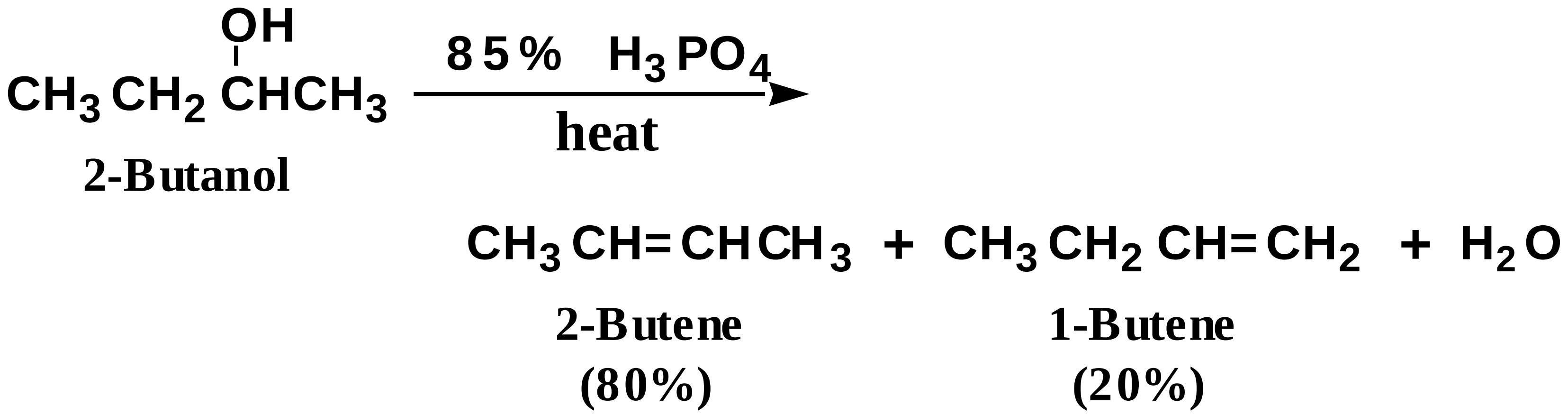
$$CH_3\underset{CH_3}{\overset{CH_3}{C}}OH \xrightarrow[50^\circ C]{H_2SO_4} CH_3\overset{CH_3}{C}{=}CH_2 + H_2O$$

2-Methyl-2-propanol
(*tert*- Butyl alcohol)

2-Methylpropene
(Isobutylene)

Dehydration of ROH

- where isomeric alkenes are possible, the alkene having the greater number of substituents on the double bond (the more stable alkene) usually predominates (Zaitsev rule)



$$\underset{\text{2-Butanol}}{CH_3CH_2\overset{\overset{OH}{|}}{C}HCH_3} \xrightarrow[\text{heat}]{85\%\ H_3PO_4} \underset{\substack{\text{2-Butene}\\(80\%)}}{CH_3CH{=}CHCH_3} + \underset{\substack{\text{1-Butene}\\(20\%)}}{CH_3CH_2CH{=}CH_2} + H_2O$$

Dehydration of ROH

Based on evidence of

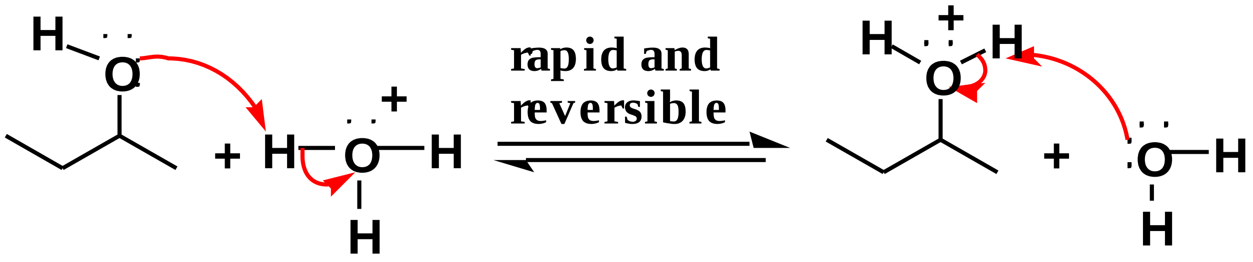
- ease of dehydration (3° > 2° > 1°)

Chemists propose a three-step mechanism for the dehydration of 2° and 3° alcohols

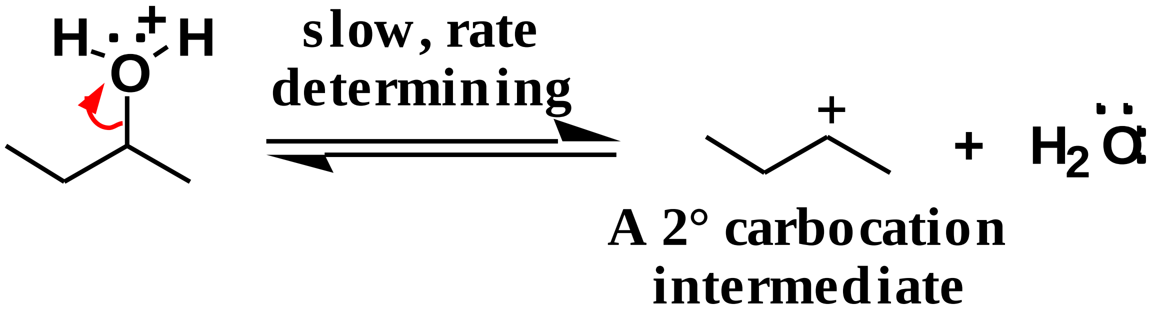
- because this mechanism involves formation of a carbocation intermediate in the rate-determining step, it is classified as E1

Dehydration of ROH

Step 1: proton transfer to the -OH group gives an oxonium ion

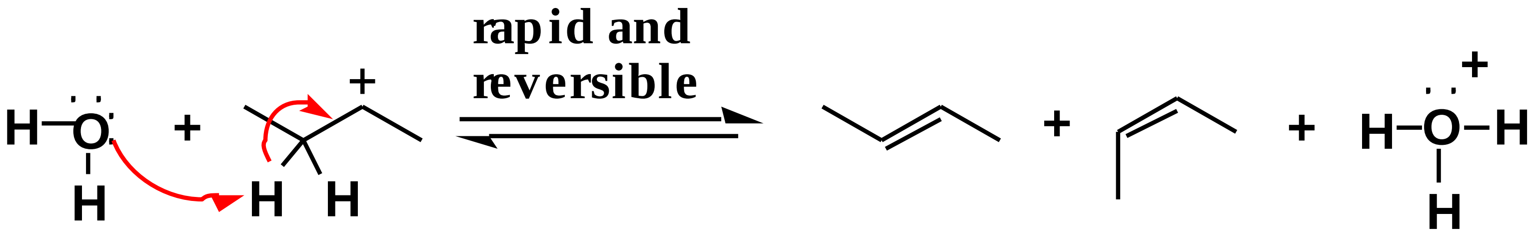


Step 2: loss of H_2O gives a carbocation intermediate



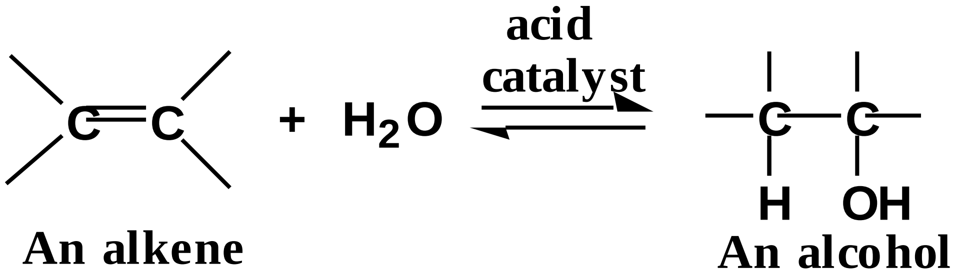
Dehydration of ROH

Step 3: proton transfer from a carbon adjacent to the positively charged carbon to water; the sigma electrons of the C-H bond become the pi electrons of the carbon-carbon double bond



Dehydration of ROH

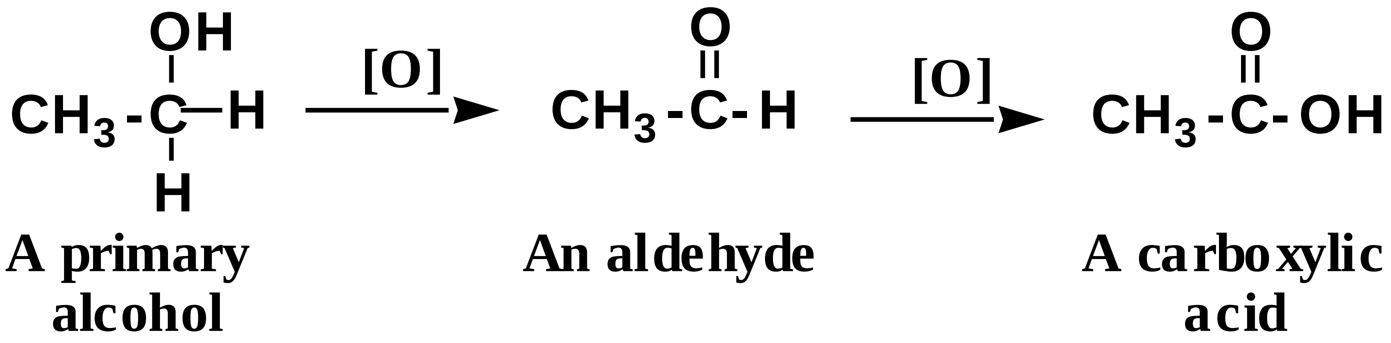
Acid-catalyzed alcohol dehydration and alkene hydration are competing processes



Oxidation of alcohols

Oxidation: 1° ROH

Oxidation of a primary alcohol gives an aldehyde or a carboxylic acid, depending on the experimental conditions



- to an aldehyde is a two-electron oxidation
- to a carboxylic acid is a four-electron oxidation

Oxidation of ROH

A common oxidizing agent for this purpose is chromic acid, prepared by dissolving chromium(VI) oxide or potassium dichromate in aqueous sulfuric acid

$$CrO_3 + H_2O \xrightarrow{H_2SO_4} H_2CrO_4$$

Chromium(VI) oxide

Chromic acid

$$K_2Cr_2O_7 \xrightarrow{H_2SO_4} H_2Cr_2O_7 \xrightarrow{H_2O} 2\,H_2CrO_4$$

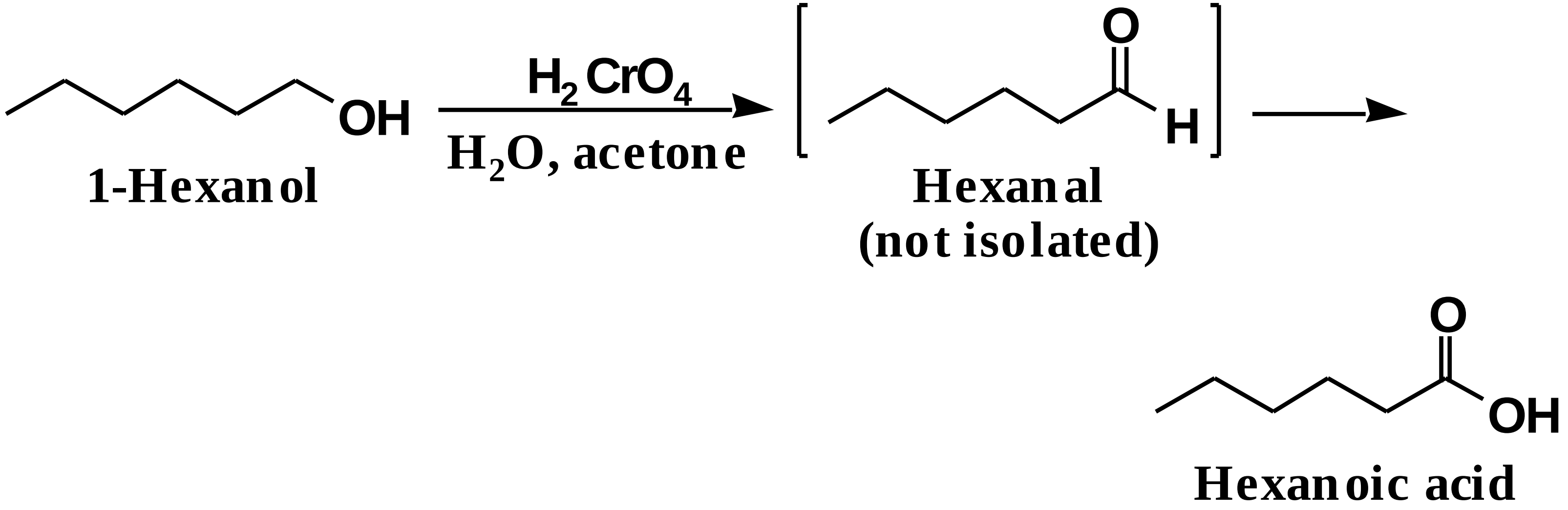
Potassium dichromate

Chromic acid

Oxidation: 1° ROH

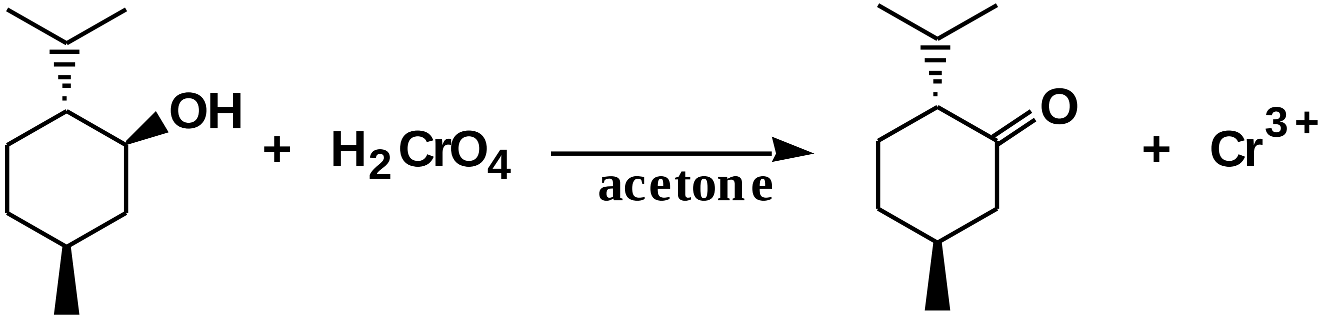
Oxidation of 1-octanol gives octanoic acid

- the aldehyde intermediate is not isolated



Oxidation: 2° ROH

2° alcohols are oxidized to ketones by chromic acid

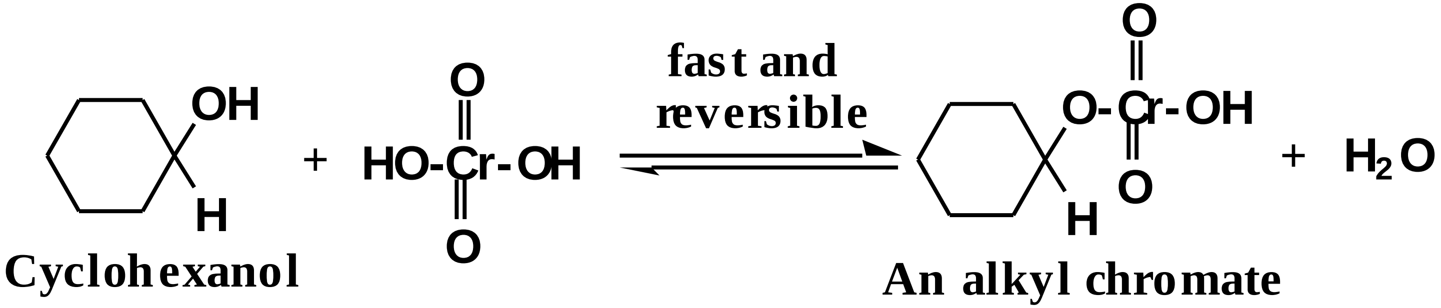


2-Isopropyl-5-methylcyclohexanol (Menthol)

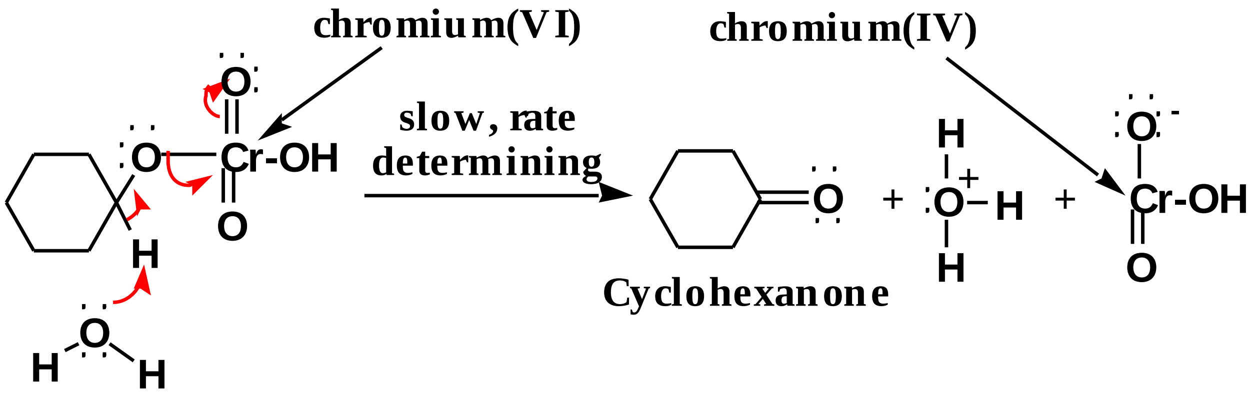
2-Isopropyl-5-methylcyclohexanone (Menthone)

Chromic Acid Oxidation of ROH

- Step 1: formation of a chromate ester

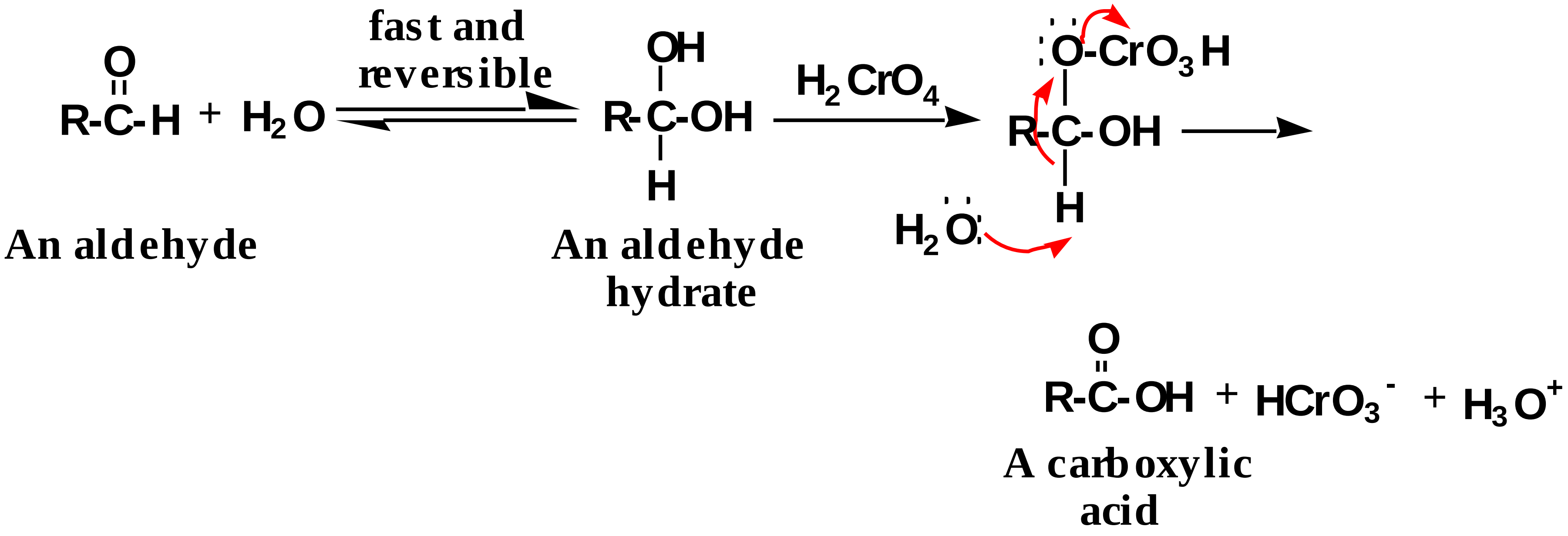


- Step 2: reaction of the chromate ester with a base, here shown as H_2O



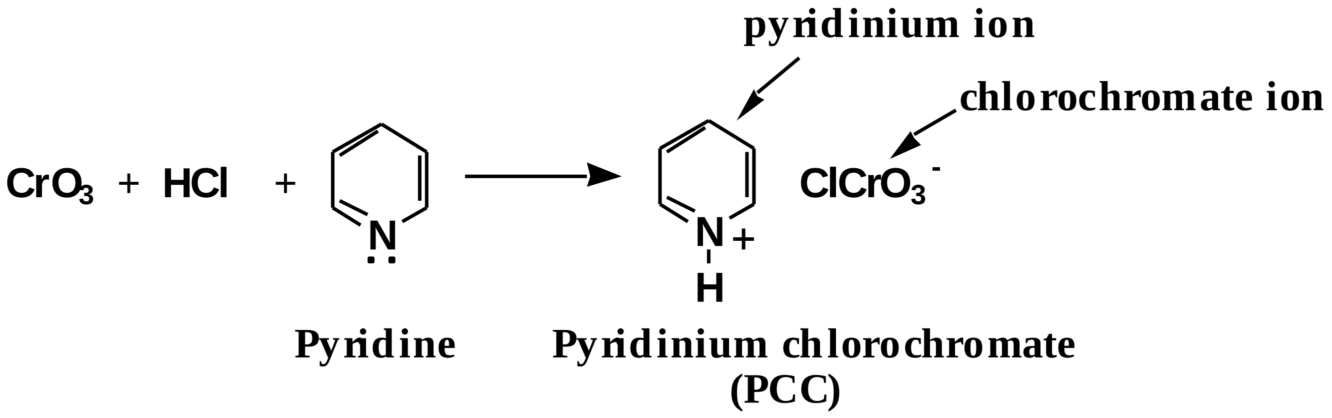
Chromic Acid Oxidation of RCHO

- chromic acid oxidizes a 1° alcohol first to an aldehyde and then to a carboxylic acid
- in the second step, it is not the aldehyde per se that is oxidized but rather the aldehyde hydrate



Oxidation: 1° ROH to RCHO

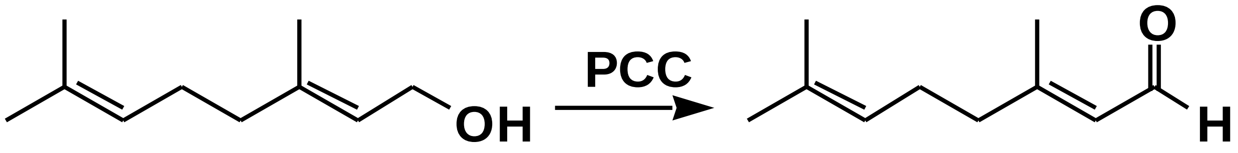
Pyridinium chlorochromate (PCC): a form of Cr(VI) prepared by dissolving CrO_3 in aqueous HCl and adding pyridine to precipitate PCC as a solid



- PCC is selective for the oxidation of 1° alcohols to aldehydes; it does not oxidize aldehydes further to carboxylic acids

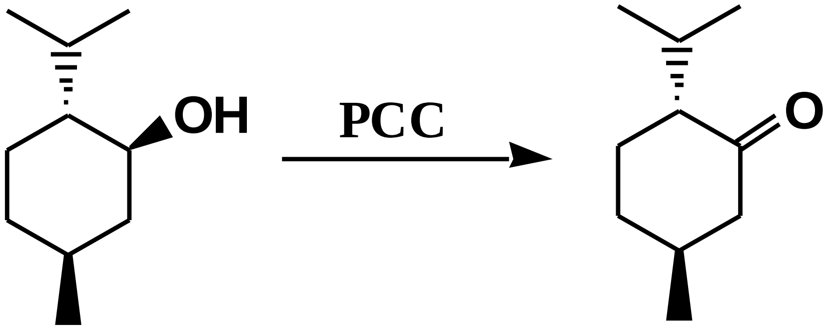
Oxidation: 1° ROH

- PCC oxidizes a 1° alcohol to an aldehyde



Geraniol Geranial

- PCC also oxidizes a 2° alcohol to a ketone



Menthol Menthone