Alcohol Synthesis

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Synthesis of Alcohols

- Alcohols can be synthesized from several functional groups.
- Nucleophilic substitution of OH⁻ on alkyl halide
- Hydration of alkenes
 - water in acid solution (not very effective)
 - oxymercuration demercuration
 - hydroboration oxidation

- Syn hydroxylation of alkenes
 - osmium tetroxide, hydrogen peroxide
 - cold, dilute, basic potassium permanganate
- Anti hydroxylation of alkenes
 - Peroxyacids followed byhydrolysis of epoxides



Synthesis of Alcohols from Alkenes

- Acid-Catalyzed Hydration of Alkenes
 - A reversible reaction with Markovnikov regioselectivity

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Alkene

Alcohol

- Oxymercuration-demercuration
 - Markovnikov addition which occurs without rearrangement

Oxymercuration

$$\sum_{C=C} \left(+ H_2O + Hg \left(\bigcirc \\ OCCH_3 \right)_2 \xrightarrow{THF} - \bigcirc \\ -C - \bigcirc \\ OCCH_3 \xrightarrow{I}_2 \xrightarrow{THF} + \bigcirc \\ HO \quad Hg - OCCH_3 \xrightarrow{I}_2 \xrightarrow{I}_1 \xrightarrow{I}_2 \xrightarrow{I}_1 \xrightarrow{I}_2 \xrightarrow{I}$$

Demercuration

$$-C - C - C - O + OH^{-} + NaBH_{4} \longrightarrow -C - C - C + Hg + CH_{3}CO^{-}$$

HO Hg - OCCH₃ HO H

Hydroboration-Oxidation

• Hydroboration (Anti-Markovnikov's addition)



• Halohydrin (Markovnikov's addition)



Oxidation of Alkenes: Syn 1,2-Dihydroxylation

Either OsO₄ or KMnO₄ will give cis 1,2 diols (glycols).

Both these reagents give "syn" diols i.e. addition of alcohols on same side.

Propene

1,2-Propanediol (propylene glycol)



Anti 1,2-Dihydroxylation of Alkenes via Epoxides

Opening of the following epoxide with water under acid catalyzed conditions gives the trans diol. (Will cover more in the ether chapter) The epoxide ring opening causes an "anti" addition of alcohols groups.



Anti 1,2-Dihydroxylation of Alkenes via Epoxides

Base-catalyzed reaction with strong nucleophiles (*e.g.* an alkoxide or hydroxide) occurs by an S_N^2 mechanism.

The nucleophile attacks at the least sterically hindered carbon of the epoxide.



A strong nucleophile such as an alkoxide ion or a hydroxide ion is able to open the strained epoxide ring in a direct S_N2 reaction.

Reduction of Carbonyls (R₂C=O)

Understanding Oxidation and Reduction

• In Hydrocarbons:





Alcohol Synthesis

Reduction of Carbonyls

- Reduction of a carbonyl compound in general gives an alcohol
- Note that organic reduction reactions add the equivalent of $\rm H_2$ to a molecule
- Aldehydes gives primary alcohols
- Ketones gives secondary alcohols
- Good reducing agent is sodium borohydride NaBH₄. Lithium aluminum hydride, LiAlH₄, is good but a little strong and hard to work with.

Aldehyde reduction





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Reduction of Acids and Esters

- Carboxylic acids and esters are reduced to give primary alcohols.
- LiAlH₄ is used because NaBH₄ is not effective, the former is stronger
- It is better to reduce esters and not acids.

Carboxylic acid reduction

Alcohols from Grignard Reagent

• Organometallic reagents

R – Li R-MgX R₂CuLi

- The carbon bonded to the metal is an anion carbonanion.
- Lithium reagents are most ionic (i.e. the carbonanion is the most negative) then magnesium and lastly the copper lithium reagents. Lithium reagents are most reactive and the least are the copper reagents (they offer more controlled reactions)
- The above reagents are made by treating alkyl halides with the metals. Reactions have to be done in moisture free environment since carbonanions formed are very reactive with water. (remember the carbon bonded is a carbonanion hence a strong base which reacts with acids)

$$\begin{array}{cccc} R \longrightarrow & \delta^{-} & \delta^{+} \\ R \longrightarrow & R \longrightarrow & R^{-} & MgX \\ & & & & & & \\ & & & & & & \\ & & &$$

Grignard Reagents with Aldehydes and Ketones

- General reaction O = 1. RMgX, ether OH = C R + HOMgX
- Reaction with water or alcohol

Mechanism with carbonyls



Grignard Reagents with Aldehydes and Ketones





Grignard Reagents with Aldehydes and Ketones



Grignard Reagents with Esters

- Esters give tertiary alcohols in which *two* alkyl substituents come from the Grignard reagent
- Grignard reagents do not add to carboxylic acids they undergo an acidbase reaction, generating the hydrocarbon of the Grignard reagent



Planning a Grignard Synthesis

- Example: Synthesis of 3-phenyl-3-pentanol
 - The starting material may be a ketone or an ester because it is a 3° alcohol
 - There are two routes that start with ketones (one is shown)



Using Lithium and Alkynide Reagents

- For both the reagents, starting material can be any carbonyl according to what is needed 1°, 2° or 3° alcohol.
- Organolithium reagents are similar to Grignard regents.

$$\begin{array}{cccc} & \overset{\delta-}{\mathbf{R}} : \overset{\delta+}{\mathrm{Li}} & + & \overset{\bullet}{\mathrm{C}} = & \overset{\bullet}{\mathrm{O}} : \overset{\bullet}{\overset{\bullet}{\ldots}} & \overset{\bullet}{\mathbf{R}} - \overset{\bullet}{\mathrm{C}} - & \overset{\bullet}{\mathrm{O}} : \overset{\bullet}{\mathrm{Li}} : \overset{\mathrm{H}_{3}\mathrm{O}^{+}}{\longrightarrow} & \overset{\bullet}{\mathbf{R}} - \overset{\bullet}{\mathrm{C}} - & \overset{\bullet}{\mathrm{O}\mathrm{H}} \\ \end{array}$$

$$\begin{array}{ccc} & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & &$$

• <u>Alkynide</u> ions will also have the alkyne group, in addition to the alcohol group that is being added from the carbonyl.

$$\mathbf{CH}_{\mathbf{3}}\mathbf{C} \equiv \mathbf{CH} \xrightarrow[-NH_3]{NaNH_2} \mathbf{CH}_{\mathbf{3}}\mathbf{C} \equiv \mathbf{CN}a$$



Examples



(2) NH_1Cl, H_2O

Key Words/Concepts

- Synthesis
 - From alkenes of alcohols
 - Of diols
 - Reduction of carbonlys
 - Using Grignard reagents and other organometallic reagents.