Chapter 11: Alcohols and Ethers

• Alcohols and Ethers: Structure and Properties (Sections 11.1-2)
• Important Alcohols and Ethers (Section 11.3)
• Synthesis of Alcohols from Alkenes (Section 11.4; Chapter 8)
• Reactions of Alcohols (Section 11.5)
• Old Acid Base Stuff (Section 11.6, Chapter 3)
• Alcohols into Alkyl Halides (Section 11.7)
• Alcohol Reactions w/ HX (Section 11.8)
• Alcohol Reactions w/ PBr₃, SOCl₂ (Section 11.9)
• Alcohol Derivatives as Leaving Groups (Section 11.10)
• Synthesis of Ethers (Section 11.11)
• Reactions of Ethers (Section 11.12)
• Epoxides: Synthesis and Opening (Sections 11.13 and 11.14)
• Anti 1,2 Dihydroxylation of Alkenes (Section 11.15)
Alcohols: General Nomenclature

- Methanol
- Ethanol
- 2-Propanol
- 2-methyl-2-propanol
- Benzyl alcohol
- 2-Propenol
- 2-Propynol
- Phenol
- m-Ethylphenol
- p-tert-Butylphenol
Use para/meta/ortho Designations to Describe Substituent Orientation in Disubstituted Benzene Rings, Just as in the Phenol Examples from Previous Slide
Ethers: General Nomenclature

- Ethyl methyl ether
- Diethyl ether
- tert-Butyl phenyl ether
- 2-Methoxypentane
- Dimethoxymethane
- 1,2-Diethoxyethane
- 1-Ethoxy-4-methylbenzene
- 1-Methoxy-4-methylbenzene (para-Methylanisole)
Naming Cyclic Ethers

- Oxacyclopropane (oxirane, ethylene oxide)
- Oxacyclobutane (oxetane)
- Oxacyclohexane (tetrahydropyran)
- Oxacyclopentane (tetrahydrofuran)
- 1,4-Dioxacycloclohexane (1,4-dioxane)

- Can Use Replacement Nomenclature (oxa → O replaces CH₂)
- Also Many Common Name (Acceptable to Use)
Alcohols and Ethers: Physical Properties

• Properties of Ethers Similar to Alkanes of Like Masses
  ➢ Diethyl ether (MW=74); Pentane (MW=72)
  ➢ Diethyl ether (BP=34.6 °C); Pentane (BP=36 °C)

• Alcohols Boil Much Higher than Comparable Ethers/Alkanes

• Related to Hydrogen Bonding of Alcohols (See Chapter 4)

• Alcohols form Hydrogen Bonding Networks w/ one Another

• Ethers Cannot Hydrogen Bond w/ one Another

• Ethers CAN H-Bond w/ H₂O and Alcohols (Soluble in These)

Properties of Some Alcohols/Ethers in Tables 11.1 and 11.2
Important Alcohols and Ethers

- Methanol (CH$_3$OH)
  - Often Called Wood Alcohol (Distilled From Wood)
  - Prepared Now via Catalytic Hydrogenation Reactions

- Ethanol (CH$_3$CH$_2$OH)
  - Made Through Fermentation of Sugars, in Alcoholic Drinks
  - Common Solvent in Organic Labs (Absolute Ethanol)

- Ethylene Glycol (HOCH$_2$CH$_2$OH)
  - Good Antifreeze: Low MW, High Boiling Point (197 °C)

- Diethyl Ether (CH$_3$CH$_2$OCH$_2$CH$_3$)
  - Low Boiling Point, Volatile, Highly Flammable Liquid
  - One of First Uses was as Surgical Anesthetic
  - Watch Out for Old Ether Containers (Peroxides!!)
Synthesizing Alcohols from Alkenes

• We’ve Looked at Several OH Synthesis Reactions in Ch. 8
  ➢ Acid-Catalyzed Hydration (Markovnikov)
    ➢ $\text{H}_3\text{O}^+ / \text{H}_2\text{O}$ OR warm, dilute $\text{H}_2\text{SO}_4, \text{H}_2\text{O}$
  ➢ Oxymercuration/Demercuration (Markovnikov)
    ➢ 1. $\text{Hg(OAc)}_2$ THF/$\text{H}_2\text{O}$  2. $\text{NaBH}_4, \text{NaOH}$
  ➢ Hydroboration/Oxidation (Anti-Markovnikov)
    ➢ 1. $\text{BH}_3 : \text{THF}$  2. $\text{H}_2\text{O}_2, \text{NaOH}$

• Now Let’s Consider Some Reactions of Alcohols
Reactions of Alcohols

- Lone Pairs on Alcohols: Lewis Bases, Nucleophiles
- Note Bond Polarizations: C, H are $\delta^+$ and O is $\delta^-$
- Alcohol Carbon Not Particularly Electrophilic (HO$^-$ Bad LG)
- Protonation of Alcohol $\rightarrow$ H$_2$O; Good Leaving Group
Reactions of Alcohols

- Protonation of Alcohol $\rightarrow$ H$_2$O; Good Leaving Group
- Presence of Good Leaving Group Makes C$_{OH}$ Electrophilic
- OH$_2^+$ More Electron Withdrawing than OH; More Polarized
- Can Observe $S_{N1}$ or $S_{N2}$ Reactions (Depends on Alcohol Class)
Reactions of Alcohols

- Protonation of Alcohol $\rightarrow$ H$_2$O; Good Leaving Group
- Another Alcohol Molecules Can React, Get Protonated Ether
- Subsequent Deprotonation $\rightarrow$ Ether Product (Symmetric Here)
- Reaction is CONDENSATION of Two Alcohols
Converting Alcohols into Alkyl Halides

- **Converting a Primary Alcohol to a Chloride**
  - OH
  - React with conc. HCl at 25 °C
  - Result: Cl⁻ + H₂O

- **Converting a Primary Alcohol to a Bromide**
  - OH
  - React with conc. HBr at Reflux
  - Result: Br⁻

- **Converting a Tertiary Alcohol to a Bromide**
  - OH
  - React with PBr₃ at -10 to 0 °C
  - Result: Br⁻ + H₃PO₃

- **Converting an Aryl Alcohol to a Chloride**
  - OH
  - React with SOCl₂ in pyridine
  - Result: Cl⁻ + SO₂ + HCl

- **Converting a Secondary Alcohol to a Chloride**
  - OH
  - React with SOCl₂ in pyridine
  - Result: Cl⁻ + SO₂ + HCl

- **Converting a Secondary Alcohol to a Chloride**
  - OH
  - React with SOCl₂ in pyridine
  - Result: Cl⁻ + SO₂ + HCl

- **Converting a Secondary Alcohol to a Chloride**
  - OH
  - React with SOCl₂ in pyridine
  - Result: Cl⁻ + SO₂ + HCl

- **Converting a Secondary Alcohol to a Chloride**
  - OH
  - React with SOCl₂ in pyridine
  - Result: Cl⁻ + SO₂ + HCl
HX Reactions with Alcohols (3°, 2°)

Step 1

\[
\text{OH} \quad \text{H} \quad \Theta \quad \text{OH}_2 \quad \Theta \quad + \quad \text{H}_2\text{O}
\]

Step 2

\[
\Theta \quad \text{OH}_2 \quad \Theta \quad \text{Cl} \quad + \quad \text{H}_2\text{O}
\]

Step 3

\[
\Theta \quad \text{Cl} \quad \rightarrow \quad \Theta \quad \text{Cl}
\]
HX Reactions with Alcohols (1°, MeOH)

As Seen Previously, Protonation Makes Good Leaving Group

Presence of Nucleophile (Br) Allows for Substitution Reaction

Can also Add Lewis Acid to Help (esp. ZnCl₂ w/ Cl⁻)
Alcohol Reactions w/ $\text{PBr}_3$, $\text{SOCl}_2$

- P and S Atoms are Electrophilic Sites, O acts as Nucleophile
- Low Temperatures w/ $\text{PBr}_3$ Prevent C Skeleton Rearrangement
- $\text{PBr}_3$ Reaction Choice Reagent for $1^\circ$, $2^\circ$ OH $\rightarrow$ $1^\circ$, $2^\circ$ Br
- $\text{SOCl}_2$ Good Reagent for $1^\circ$, $2^\circ$ OH $\rightarrow$ $1^\circ$, $2^\circ$ Cl
- Reaction Usually Run with Added Amine Base (Consume HCl)
- $\text{SOCl}_2$ Reactions Also Typically Don’t Involve Rearrangements
- Will Later See $\text{SOCl}_2$ Replaces OH of Carboxylic Acid with Cl
Leaving Groups: OH Derivatives

- Make OH Better as Leaving Group (Replace H, Bond to O)
- This General Class is Called the Sulfonate Ester Class
- Prepared By Reacting Alcohol w/ a Sulfonyl Chloride and Base
- Formation of Derivatives does not Alter C—O Stereochemistry

Mesyl Group (Ms)

Tosyl Group (Ts)

Trifyl (Tf)
Leaving Groups: OH Derivatives

Sample Derivatizations. Note Retention of Stereochemistry in 2\textsuperscript{nd}
We’ve Already Seen Ether Synthesis by Alcohol Dehydration:

- Utility of this Reaction is Limited in its Scope:
  - Mixture of Ether/Alkenes with 2° Alkyl Groups
  - Exclusively Alkenes with 3° Alkyl Groups
  - Only Useful for Synthesis of Symmetric Ethers
    - $\text{ROH} + \text{R’OH} \rightarrow \text{ROR} + \text{R’OR} + \text{R’OR’}$
Williamson Synthesis of Ethers

Unsymmetrical Ethers From RONa + Halide, Sulfonate, etc.

- Utility of this Reaction is Much Greater Than Condensation:
  - Works with 1° and 2° Halides, Sulfonates, etc.
  - Still Exclusively Alkenes with 3° Alkyl Groups
  - Lower Temperatures Favor Substitution over Elimination
  - $S_N2$ Conditions Apply $\Rightarrow$ Prefer Unhindered Substrate
**Alkoxymercuration-Demercuration**

This Reaction is Analogous to Oxymercuration-Demercuration

- Using New Hg Salt Here (Triflate) → Can Use Hg(OAc)$_2$ Also
- Instead of H$_2$O in First Step, We Use an Alcohol
- Carbocation is Captured by Alcohol Molecule
- After Loss of Proton, Alkoxide is Added Instead of Alcohol
- See Chapter 8 for Mechanistic Details (Completely Parallel)
Protecting Groups: Alcohol Alkylation

- Alcohol Groups do not “Survive” Many Organic Reactions
- Alkylation (Ether Formation) Protects OH’s During Synthesis
- Can Remove the Protecting Group w/ Dilute Aqueous Acid
- Generally Dissolve Alcohol in Acid, THEN add Isobutylene
- Addition in this Manner Minimizes Isobutylene Dimerization
- Let’s See Why We Might Want to Use a Protecting Group
Protecting Groups: How They Work

Target Molecule:

Reagents: \( \ominus \text{Na}^+ \) and \( \text{Br} \)

We can't simply mix the reagents here: deprotonation occurs faster than alkylation (acid base reaction, think about pK\(_a\) differences)

So, we protect the alcohol as an ether first, and we can successfully alkylate:

1. \( \text{H}_2\text{SO}_4 \)
2. \( \text{CH}_2=\text{C(CH}_3)_2 \)

\( \ominus \text{Na}^+ \) + \( \text{Br} \) → \( \ominus \text{Na}^+ \) + \( \text{Br} \)
Protecting Groups: Silyl Ethers

- Silyl Ethers Stable Over a 4-12 pH Range (Acidic and Basic)
- Can Survive Conditions of Many Organic Reactions
- Typically Removed w/ Flouride Source (NBu₄F; aka TBAF)
- Silyl Ethers More Volatile Than Alcohols (GC Applications)
Ether Reactions w/ Strong Acids

- Ethers Can be Protonated by Strong Acids (Oxonium Ions)
- w/ 2 Equivalents of Acid (HX), Cleaved to 2 Eq. Alkyl Halide

- Protonation, $S_N2$, Protonation, $S_N2$
Ether Cleavage by HBr: Mechanism

- Two Equivalents of Ethyl bromide Produced (+ H₂O)
Synthesis of Epoxides

- Three-Membered Oxygen Containing Ring; Use Peroxy Acid
Some Peroxyacids

- Peroxyacetic acid (paracetic acid)
- Peroxyformic acid (performic acid)
- Peroxybenzoic acid (perbenzoic acid)

- Reactive, Often Unstable Species: Chemists use More Stable
Epoxide Opening: Acid-Catalyzed

- Epoxides Are Reactive to Opening Due to Ring Strain
- After Protonation, Opening is $S_N2$ Like Reaction (Anti)
- “Desire” to Relieve Ring Strain $\rightarrow$ Good Electrophiles
Epoxide Opening: Base-Catalyzed

- Epoxides Are Ethers That Can be Attacked by Bases
- Reactivity is Due to Ring Strain (Increases Electrophilicity)
- As in Acid Case, Opening is an $S_{N}2$ Reaction
- Can Open With Strong Base, Hydroxide and Alkoxide Usual