

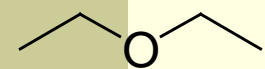


Chapter 18: Ethers and Epoxides; Thiols and Sulfides

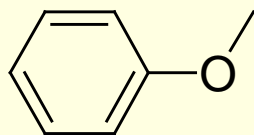


Ethers and Their Relatives

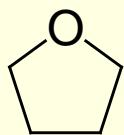
- An **ether** has two organic groups (alkyl, aryl, or vinyl) bonded to the same oxygen atom, $R-O-R'$
- Diethyl ether is used industrially as a solvent
- Tetrahydrofuran (THF) is a solvent that is a cyclic ether
- *Thiols* ($R-S-H$) and *sulfides* ($R-S-R'$) are sulfur (for oxygen) analogs of alcohols and ethers



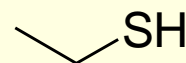
Diethyl ether



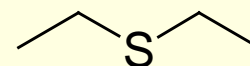
Anisole



Tetrahydrofuran



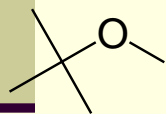
Ethanethiol



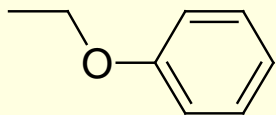
Ethylsulfanyl-ethane

Naming Ethers

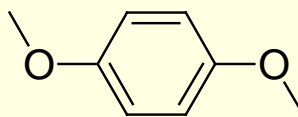
- Simple ethers are named by identifying the two organic substituents and adding the word *ether*
- If other functional groups are present, the ether part is considered an alkoxy substituent



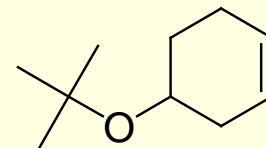
t-butyl methyl ether



ethyl phenyl ether



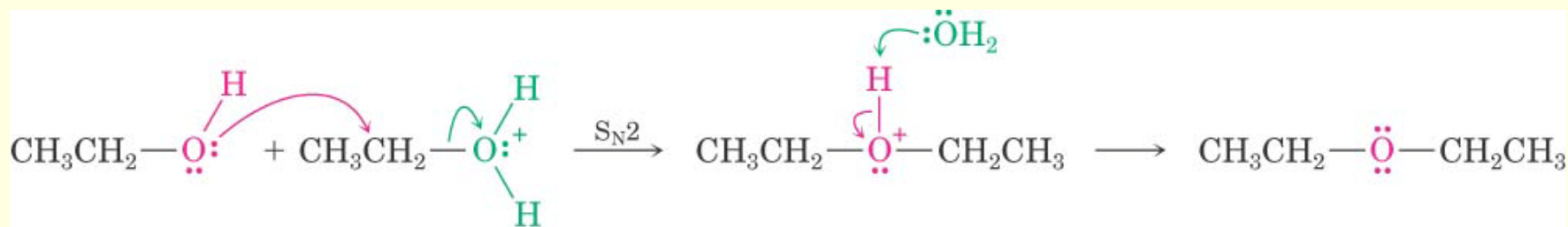
p-dimethoxybenzene



4-tert-butoxy-1-cyclohexene

Structure, Properties, and Sources of Ethers

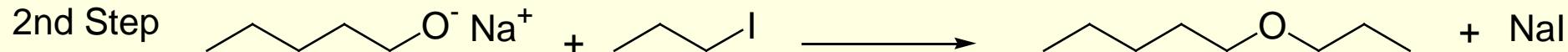
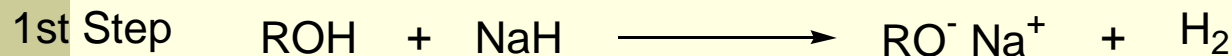
- R–O–R ~ tetrahedral bond angle (112° in dimethyl ether)
- Oxygen is sp^3 -hybridized
- Oxygen atom gives ethers a slight dipole moment
- Diethyl ether prepared industrially by sulfuric acid-catalyzed dehydration of ethanol – also with other primary alcohols



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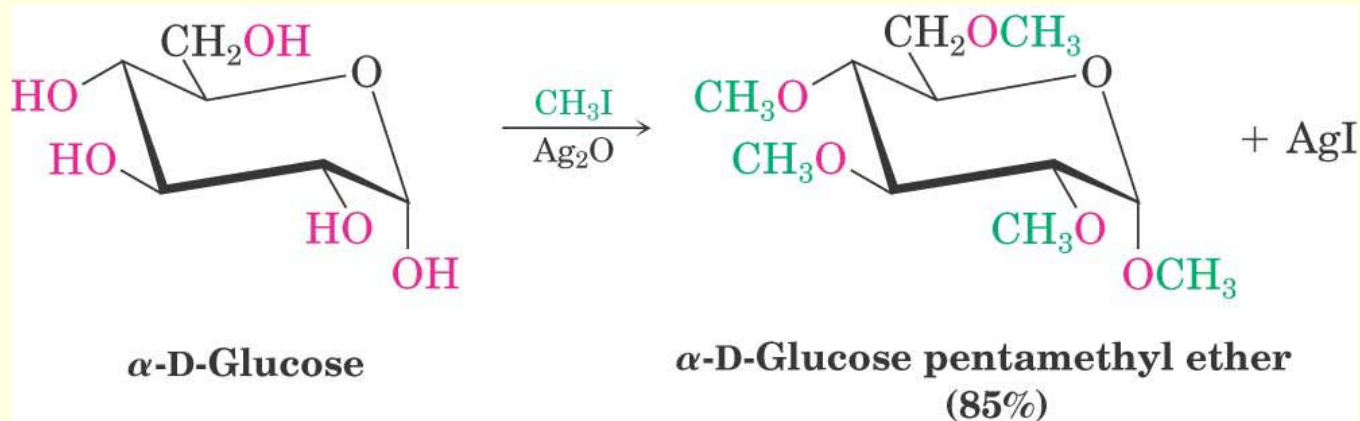
The Williamson Ether Synthesis

- Reaction of metal alkoxides and primary alkyl halides and tosylates
- Best method for the preparation of ethers
- Alkoxides prepared by reaction of an alcohol with a strong base such as sodium hydride, NaH



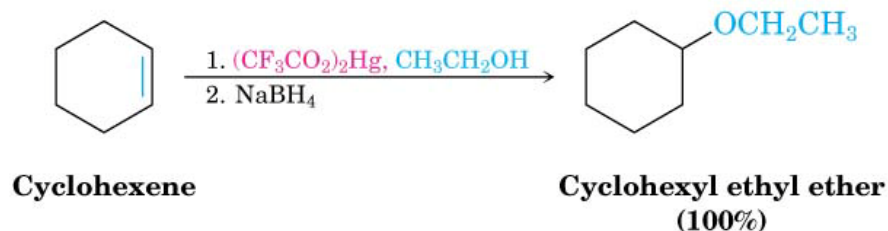
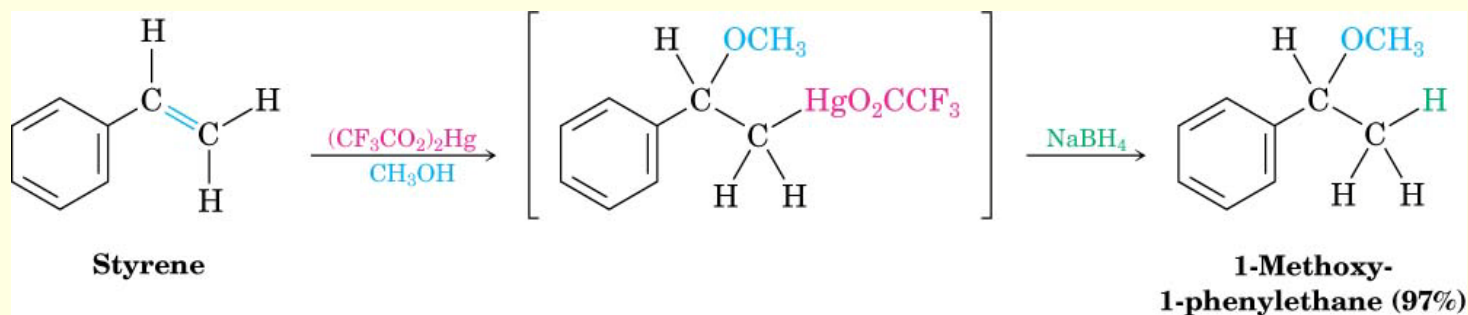
Silver Oxide-Catalyzed Ether Formation

- Reaction of alcohols with Ag_2O directly with alkyl halide forms ether in one step
- Glucose reacts with excess iodomethane in the presence of Ag_2O to generate a *pentaether* in 85% yield



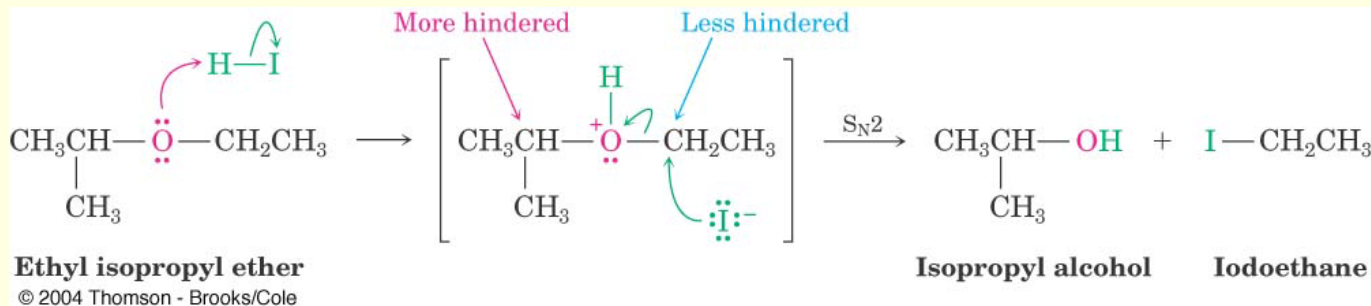
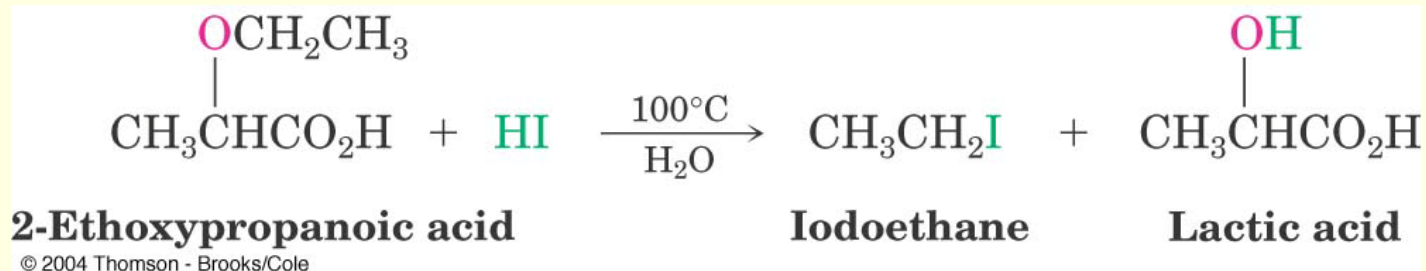
Alkoxymercuration of Alkenes

- React alkene with an alcohol and mercuric acetate or trifluoroacetate
- Demercuration with NaBH_4 yields an ether
- Overall Markovnikov addition of alcohol to alkene



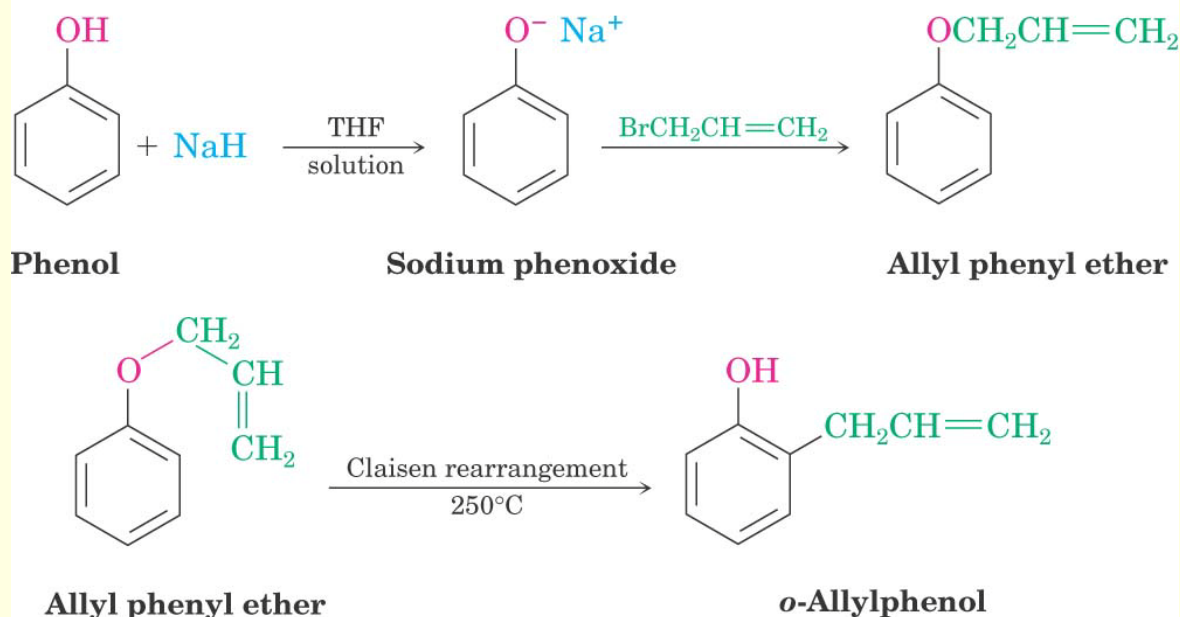
Reactions of Ethers: Acidic Cleavage

- Ethers are generally unreactive
- Strong acid will cleave an ether at elevated temperature
- HI, HBr produce an alkyl halide from less hindered component by S_N2 (tertiary ethers undergo S_N1)



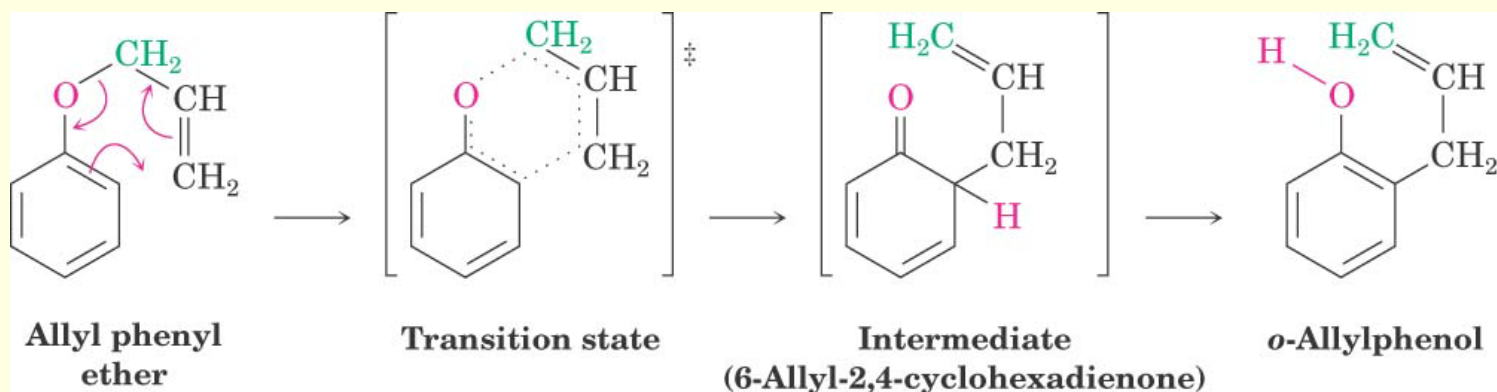
Reactions of Ethers: Claisen Rearrangement

- Specific to allyl aryl ethers, $\text{ArOCH}_2\text{CH}=\text{CH}_2$
- Heating to $200\text{--}250^\circ\text{C}$ leads to an *o*-allylphenol
- Result is alkylation of the phenol in an ortho position



Claisen Rearrangement Mechanism

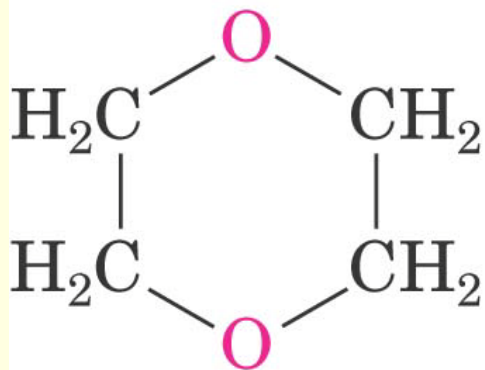
- Concerted pericyclic 6-electron, 6-membered ring transition state
- Mechanism consistent with ^{14}C labelling



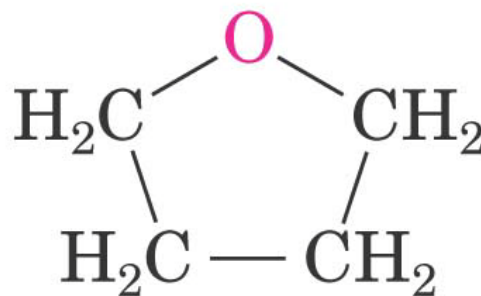
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Cyclic Ethers: Epoxides

- Cyclic ethers behave like acyclic ethers, except if ring is 3-membered
- Dioxane and tetrahydrofuran are used as solvents



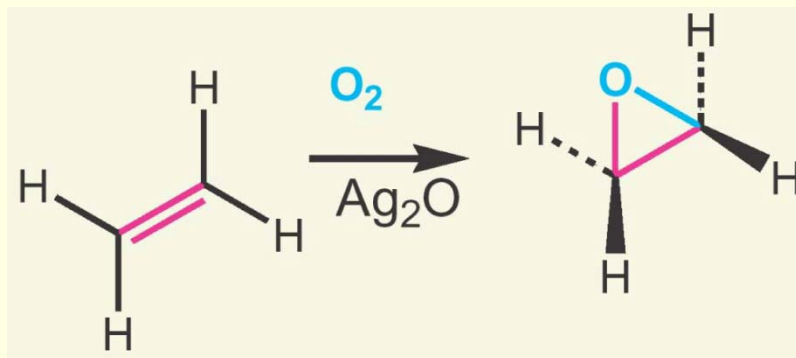
1,4-Dioxane



Tetrahydrofuran

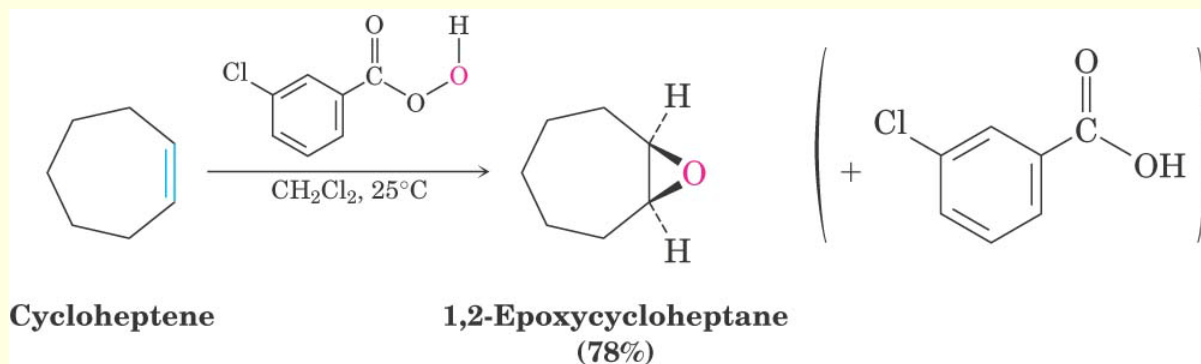
Epoxides (Oxiranes)

- Three membered ring ether is called an oxirane (root “ir” from “tri” for 3-membered; prefix “ox” for oxygen; “ane” for saturated)
- Also called epoxides
- Ethylene oxide (oxirane; 1,2-epoxyethane) is industrially important as an intermediate
- Prepared by reaction of ethylene with oxygen at 300 °C and silver oxide catalyst

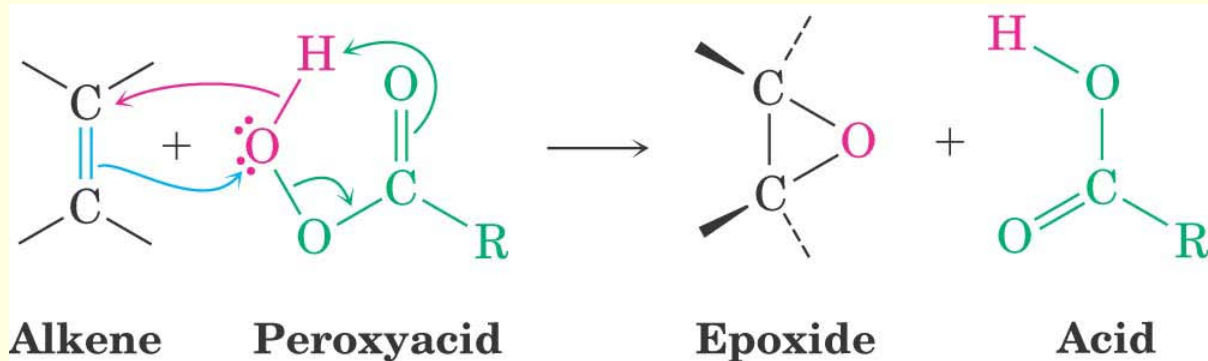


Preparation of Epoxides Using a Peroxyacid

- Treat an alkene with a peroxyacid



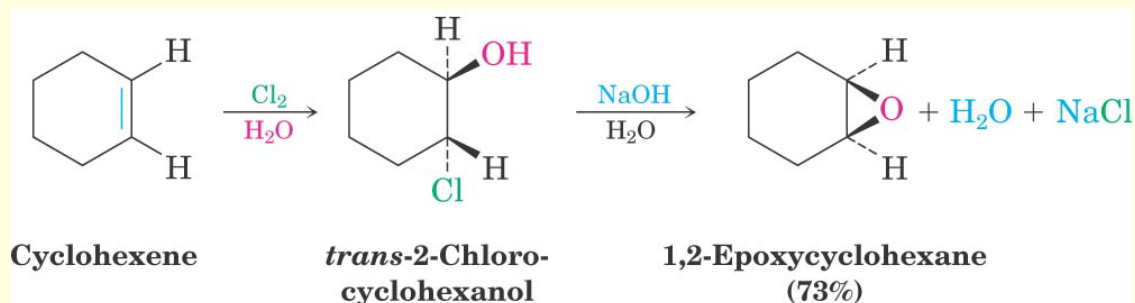
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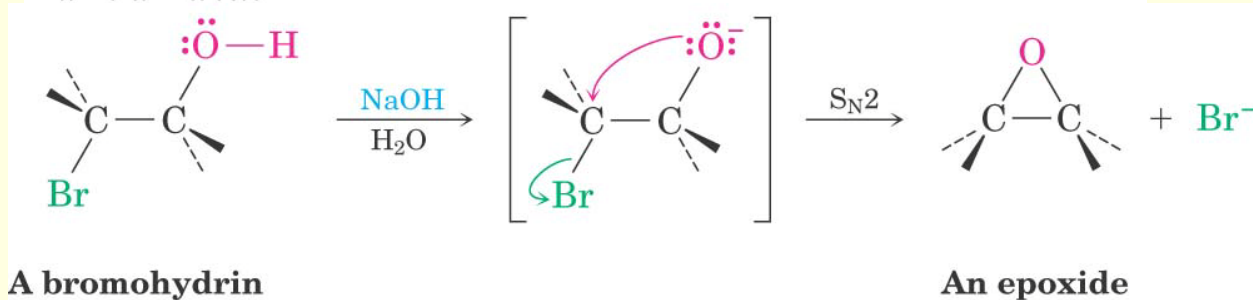
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Epoxides from Halohydrins

- Addition of HO-X to an alkene gives a halohydrin
- Treatment of a halohydrin with base gives an epoxide
- Intramolecular Williamson ether synthesis



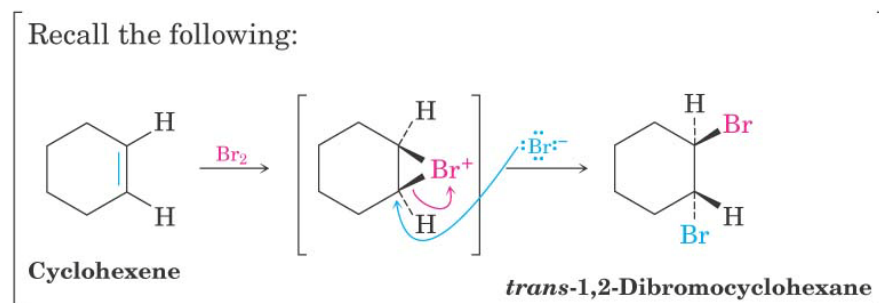
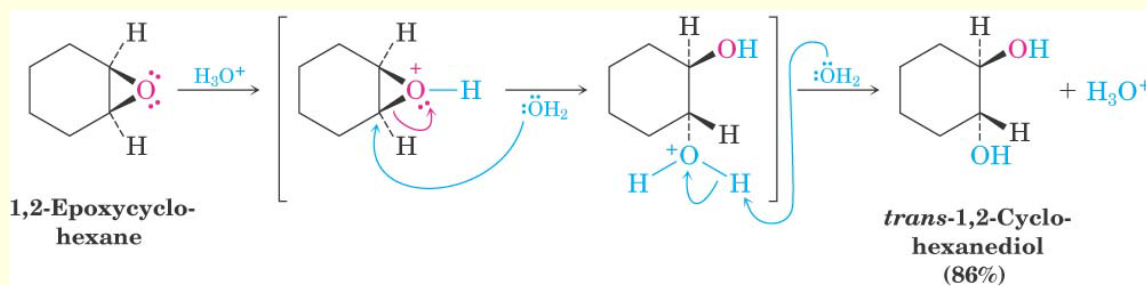
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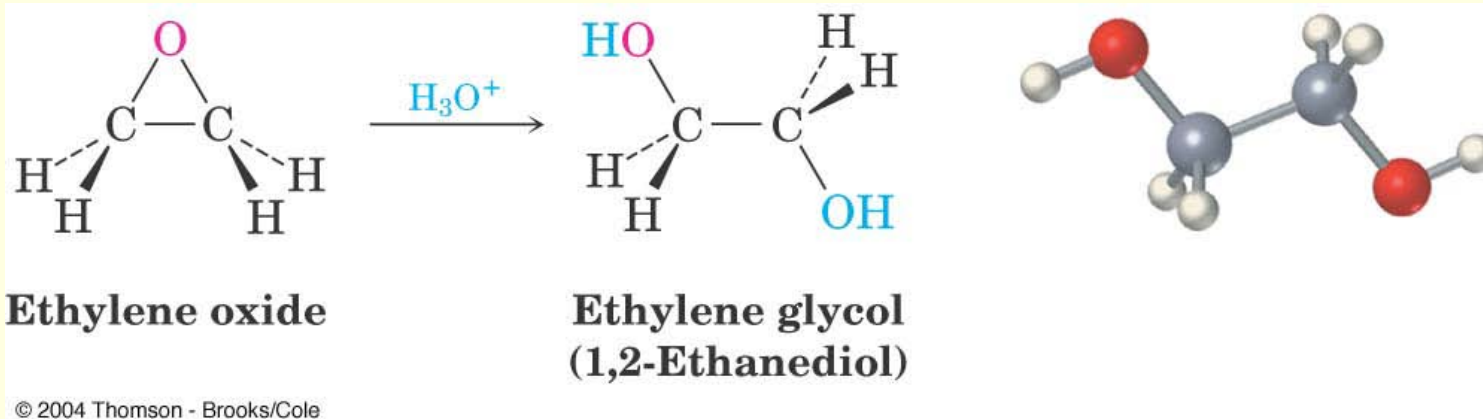
Ring-Opening Reactions of Epoxides

- Water adds to epoxides with dilute acid at room temperature
- Product is a 1,2-diol (on adjacent C's: *vicinal*)
- Mechanism: acid protonates oxygen and water adds to opposite side (trans addition)



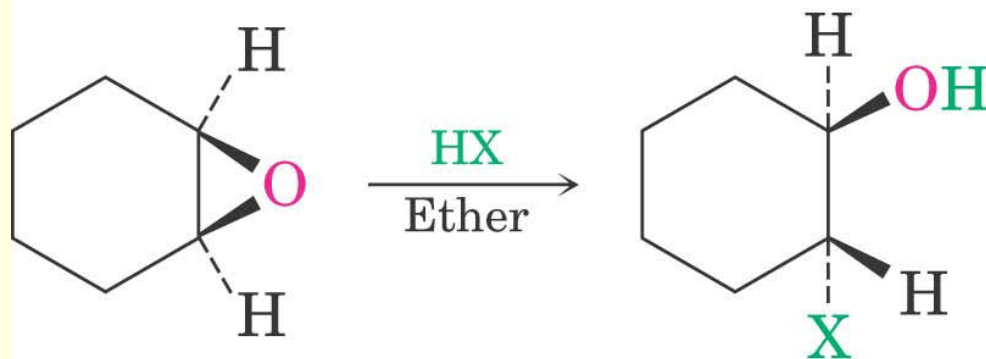
Ethylene Glycol

- 1,2-ethanediol from acid catalyzed hydration of ethylene
- Widely used as automobile antifreeze (lowers freezing point of water solutions)



Halohydrins from Epoxides

- Anhydrous HF, HBr, HCl, or HI combines with an epoxide
- Gives trans product

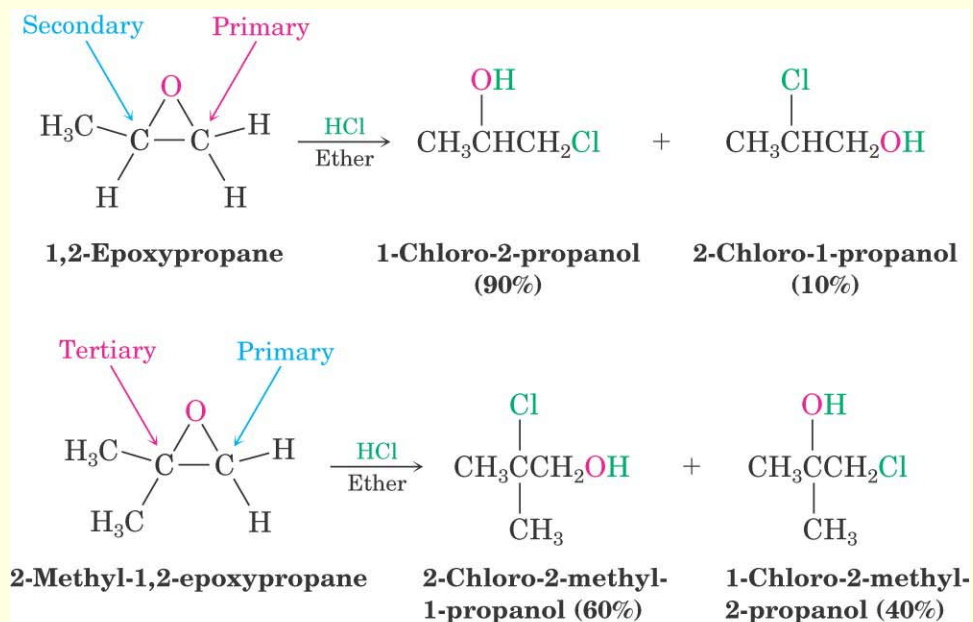


A trans 2-halocyclohexanol

where **X = F, Br, Cl, or I**

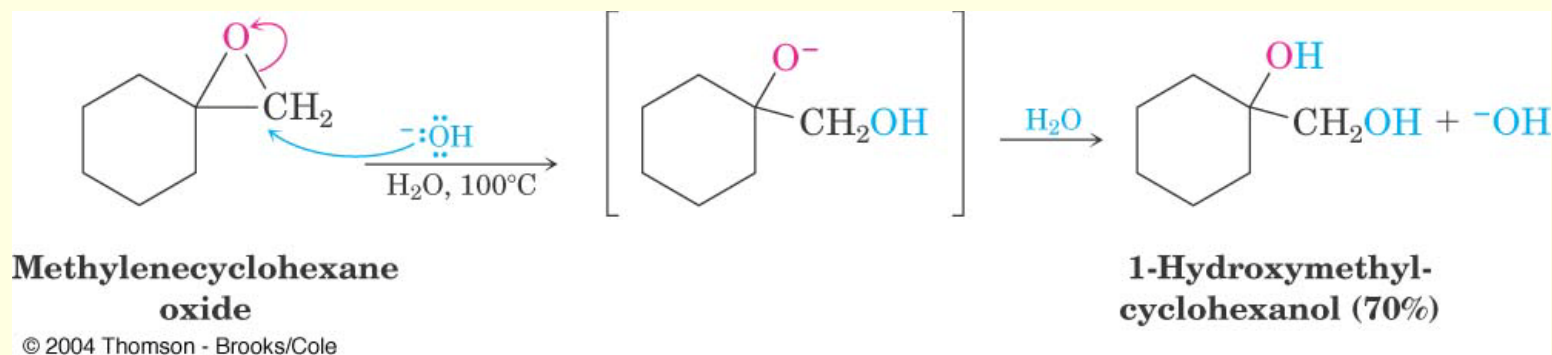
Regiochemistry of Acid-Catalyzed Opening of Epoxides

- Nucleophile preferably adds to less hindered site if primary and secondary C's
- Also at tertiary because of carbocation character (See Figure 18.2)



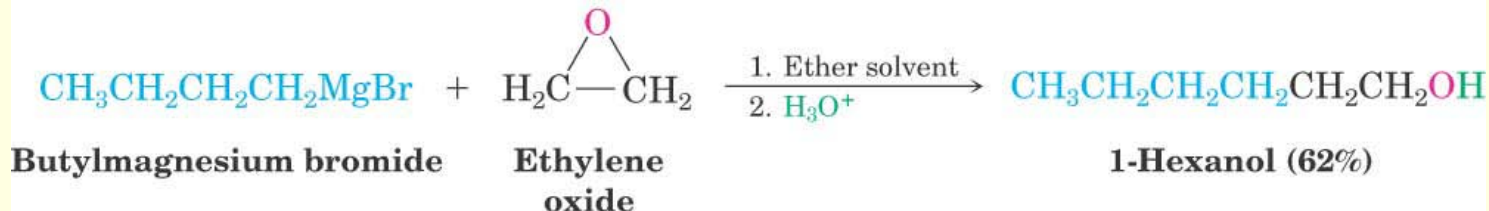
Base-Catalyzed Epoxide Opening

- Strain of the three-membered ring is relieved on ring-opening
- Hydroxide cleaves epoxides at elevated temperatures to give trans 1,2-diols



Addition of Grignards to Ethylene Oxide

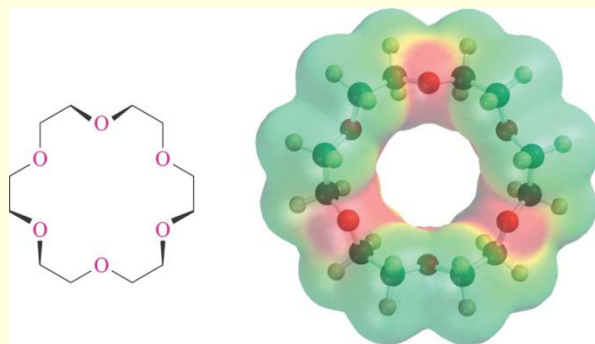
- Adds $-\text{CH}_2\text{CH}_2\text{OH}$ to the Grignard reagent's hydrocarbon chain
- Acyclic and other larger ring ethers do not react



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Crown Ethers

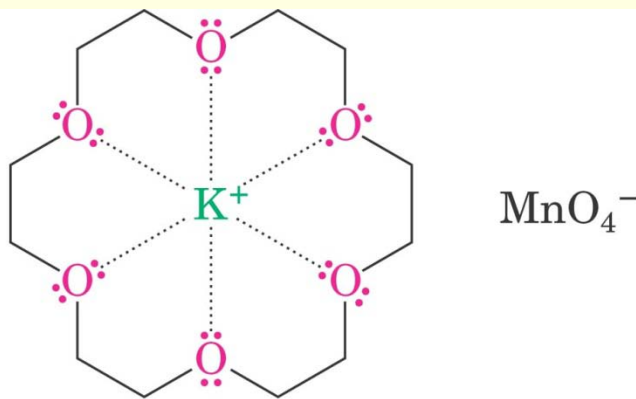
- Large rings consisting repeating (-OCH₂CH₂-) or similar units
- Named as *x*-crown-*y*
 - *x* is the total number of atoms in the ring
 - *y* is the number of oxygen atoms
 - 18-crown-6 ether: 18-membered ring containing 6 oxygens atoms
- Central cavity is electronegative and attracts cations



18-Crown-6 ether

Uses of Crown Ethers

- Complexes between crown ethers and ionic salts are soluble in nonpolar organic solvents
- Creates reagents that are free of water that have useful properties
- Inorganic salts dissolve in organic solvents leaving the anion unassociated, enhancing reactivity



**$KMnO_4$ solvated by 18-crown-6
(this solvate is soluble in benzene)**

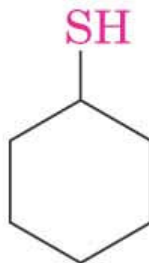
Thiols and Sulfides

- **Thiols (RSH)**, are sulfur analogs of alcohols
 - Named with the suffix *-thiol*
 - SH group is called “mercapto group” (“capturer of mercury”)

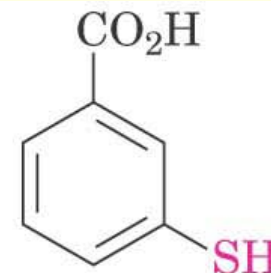


Ethanethiol

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Cyclohexanethiol



***m*-Mercaptobenzoic acid**

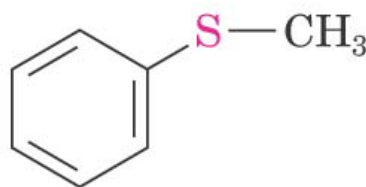
Sulfides

- **Sulfides (RSR')**, are sulfur analogs of ethers
 - Named by rules used for ethers, with *sulfide* in place of *ether* for simple compounds and *alkylthio* in place of *alkoxy*

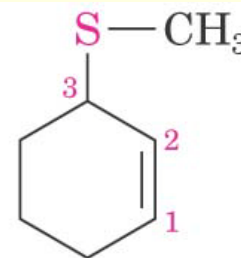


Dimethyl sulfide

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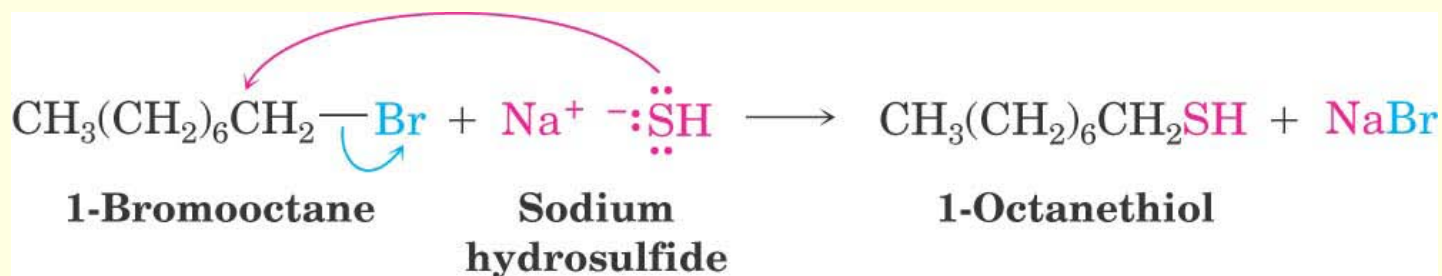
Methyl phenyl sulfide



3-(Methylthio)cyclohexene

Thiols: Formation and Reaction

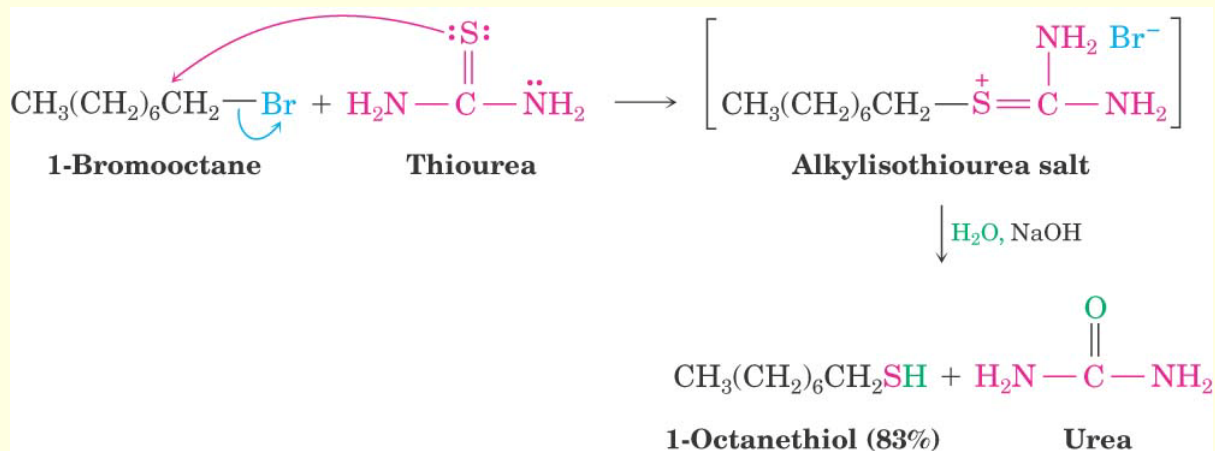
- From alkyl halides by displacement with a sulfur nucleophile such as -SH
 - The alkylthiol product can undergo further reaction with the alkyl halide to give a symmetrical sulfide, giving a poorer yield of the thiol



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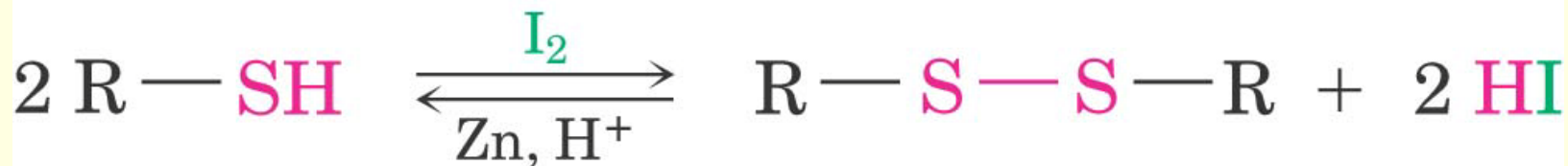
Using Thiourea to Form Alkylthiols

- Thiols can undergo further reaction with the alkyl halide to give dialkyl sulfides
- For a pure alkylthiol use thiourea ($\text{NH}_2(\text{C}=\text{S})\text{NH}_2$) as the nucleophile
- This gives an intermediate alkylisothiourea salt, which is hydrolyzed cleanly to the alkyl thiourea



Oxidation of Thiols to Disulfides

- Reaction of an alkyl thiol (RSH) with bromine or iodine gives a disulfide (RSSR)
- The thiol is oxidized in the process and the halogen is reduced



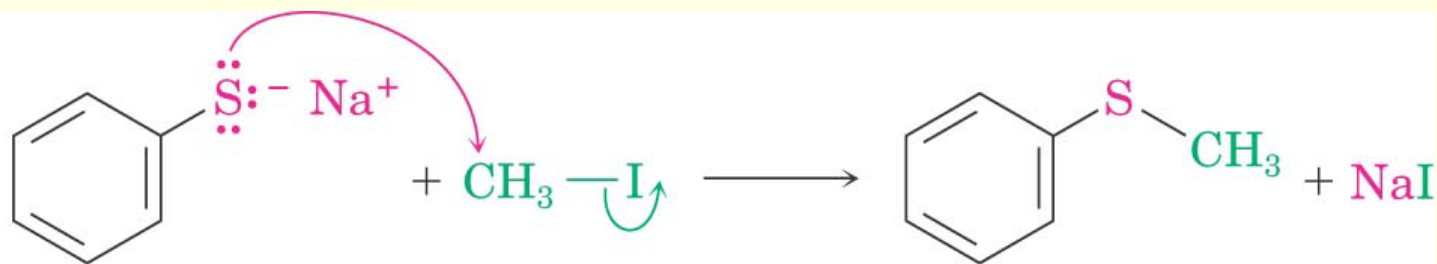
A thiol

A disulfide

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Sulfides

- **Thiolates (RS⁻)** are formed by the reaction of a thiol with a base
- Thiolates react with primary or secondary alkyl halide to give sulfides (RSR')
- Thiolates are excellent nucleophiles and react with many electrophiles

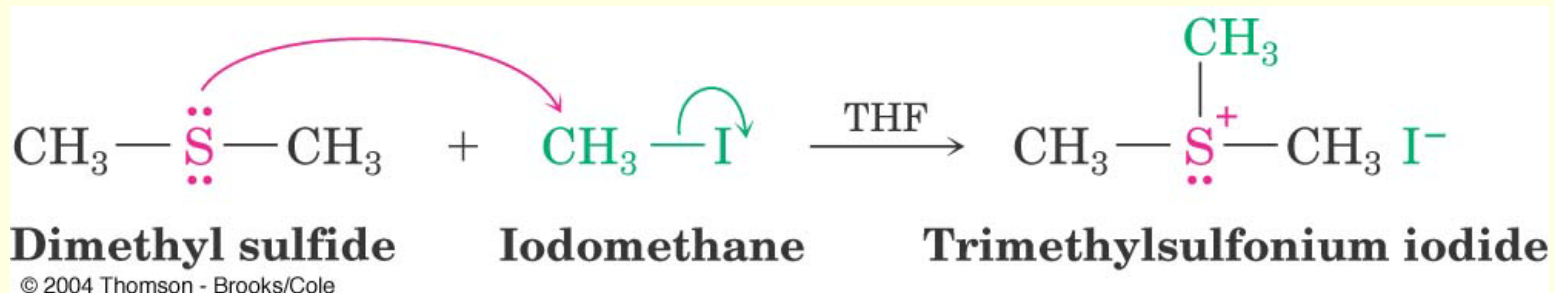


Sodium benzenethiolate

Methyl phenyl sulfide
(96%)

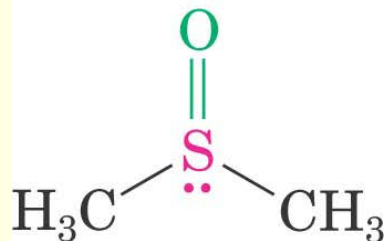
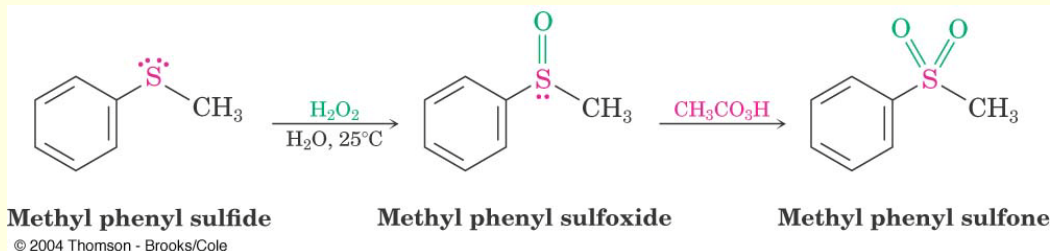
Sulfides as Nucleophiles

- Sulfur compounds are more nucleophilic than their oxygen-compound analogs
 - $3p$ valence electrons (on S) are less tightly held than $2p$ electrons (on O)
- Sulfides react with primary alkyl halides (S_N2) to give trialkylsulfonium salts (R_3S^+)



Oxidation of Sulfides

- Sulfides are easily oxidized with H_2O_2 to the sulfoxide (R_2SO)
- Oxidation of a sulfoxide with a peroxyacid yields a sulfone (R_2SO_2)
- Dimethyl sulfoxide (DMSO) is often used as a polar aprotic solvent



Dimethyl sulfoxide
(a polar aprotic solvent)

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Spectroscopy of Ethers

- **Infrared:** C–O single-bond stretching 1050 to 1150 cm^{-1} overlaps many other absorptions.
- **Proton NMR:** H on a C next to ether O are shifted downfield to δ 3.4 to δ 4.5
 - The ^1H NMR spectrum of dipropyl ether shows the these signals at δ 3.4
 - In epoxides, these H's absorb at δ 2.5 to δ 3.5 d in their ^1H NMR spectra
- **Carbon NMR:** C's in ethers exhibit a downfield shift to δ 50 to δ 80