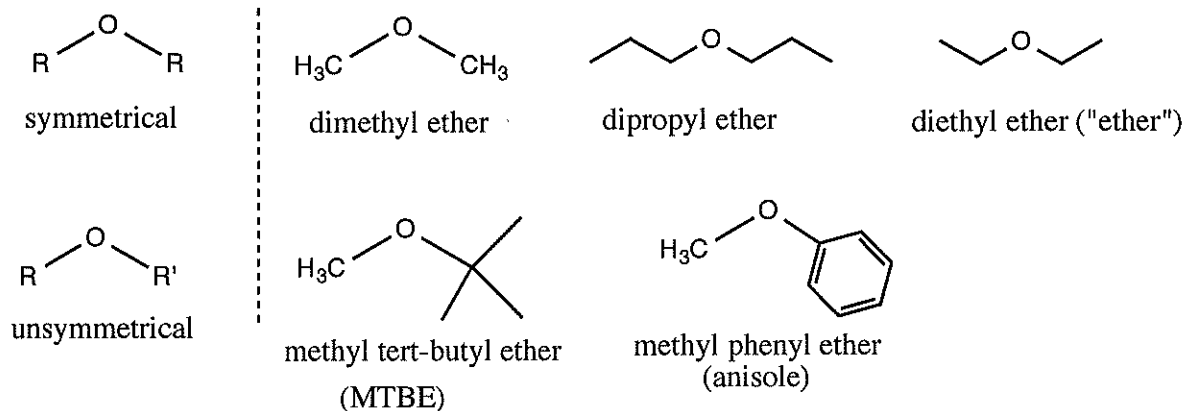


Chapter 14: Ethers and Epoxides

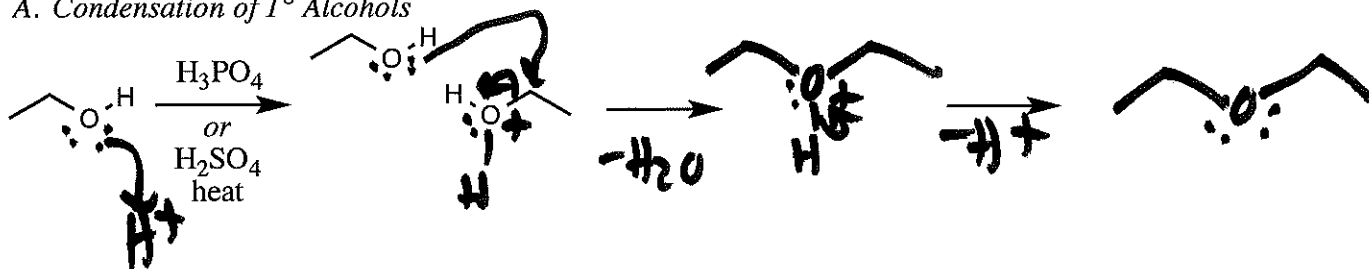
[Chapter 9 Sections: 9.9-9.10; Chapter 14 Sections 14.1-14.3, 14.5-14.6, 14.8, 14.10 (reaction with nucleophiles only)]

Nomenclature and Types of Ethers

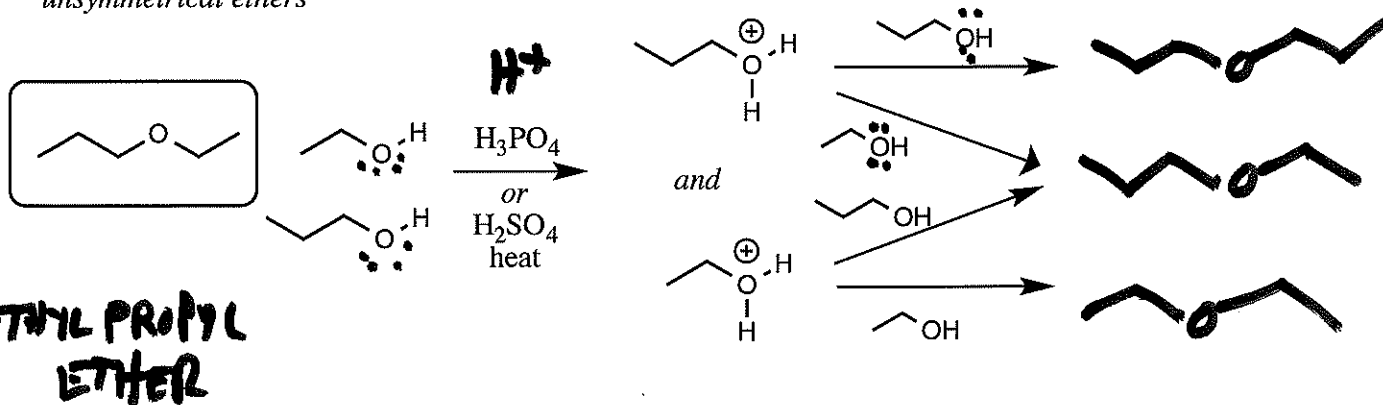


Synthesis of Ethers

A. Condensation of 1° Alcohols

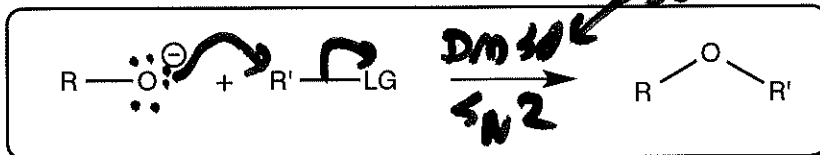


- a "condensation" reaction is one in which water is liberated
- this is an $\text{S}_{\text{N}}2$ reaction on a primary substrate in which the OH group is converted into a good leaving group via protonation to form a molecule of water
- the reaction is convenient for making symmetrical ethers from 1° alcohols but not for making unsymmetrical ethers

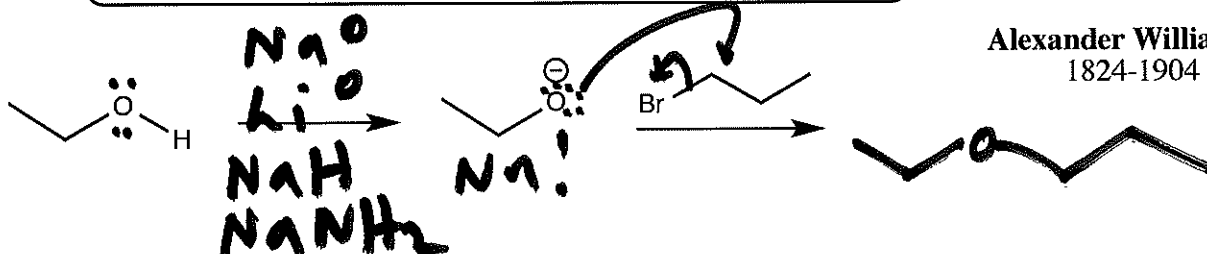


- attempted formation of an unsymmetrical ether via condensation generally results in the formation of three different products

B. Williamson Ether Synthesis: General Method for Ether Synthesis

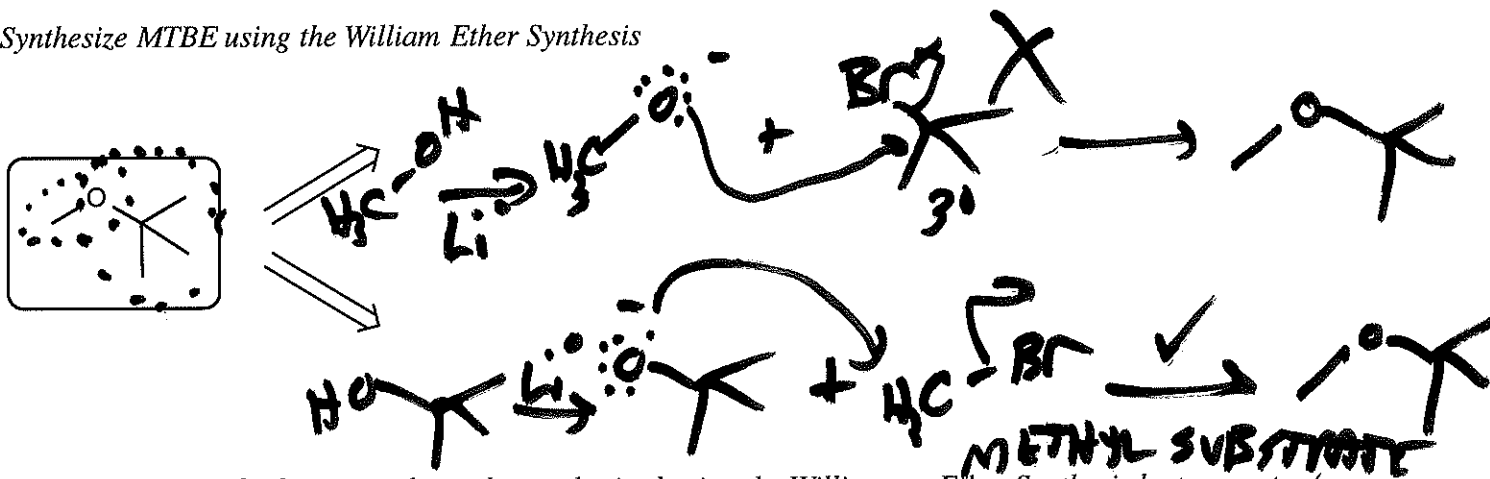


Alexander Williamson
1824-1904



- alcohols can be easily deprotonated to form strong nucleophiles
- addition of the deprotonated alcohol (alkoxide) to an alkyl halide results in an SN2 reaction
- this method can be used to synthesize both symmetrical and unsymmetrical ethers
- since it is an SN2 reaction, it has the same limitations as any other SN2 reaction!

Synthesize MTBE using the William Ether Synthesis

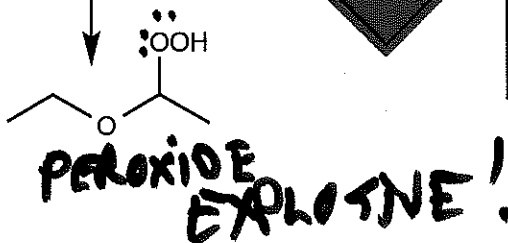
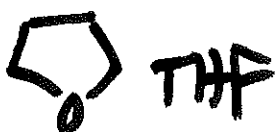
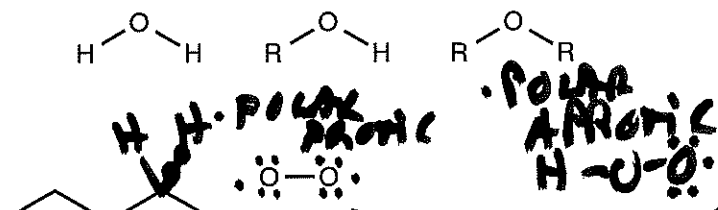


- unsymmetrical ethers can always be synthesized using the Williamson Ether Synthesis by two routes (one half serving as the nucleophilic alkoxide and the other as the alkyl halide substrate)
- generally, the better route is one in which the alkyl halide half is methyl, 1° or 2° (it can NOT be 3° or a benzene ring!)

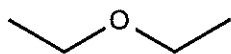
Problems: 1,2,3,6,7

Properties of Ethers

- unlike water or alcohols, ethers are unable to engage in intermolecular hydrogen bonds
- therefore, although ethers are polar they have very low solubility in water



Ether as Anesthetic



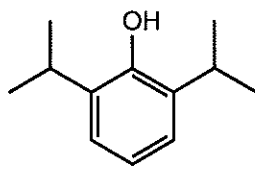
diethyl ether

1842

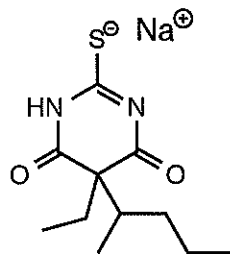


chloroform

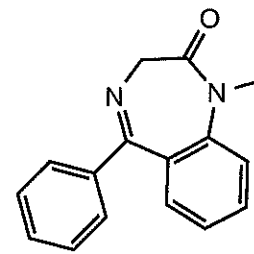
1847



propofol



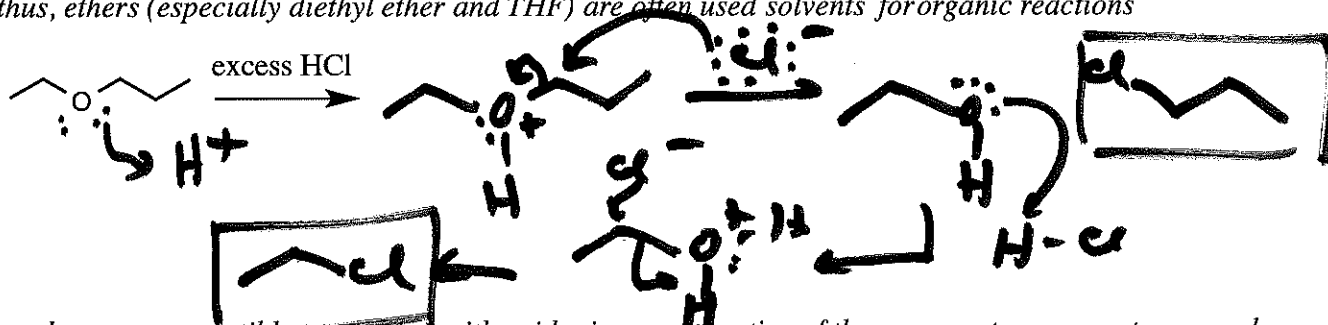
sodium thiopental
(sodium pentothal)



diazepam

Reactions of Ethers

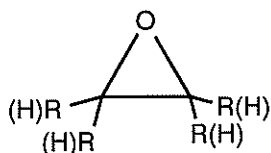
- ethers are generally very unreactive compounds, similar to alkanes. They do NOT react with strong bases, strong oxidizing agents or strong reducing agents
- thus, ethers (especially diethyl ether and THF) are often used solvents for organic reactions



- ethers are susceptible to reaction with acids since protonation of the oxygen atom generates a good leaving group for $\text{S}_{\text{N}}2$ attack by a nucleophile
- generally, both "halves" of the ether are converted to alkyl halides in the presence of HCl , HBr or HI

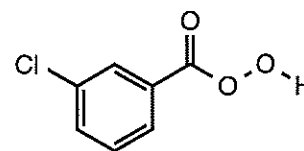
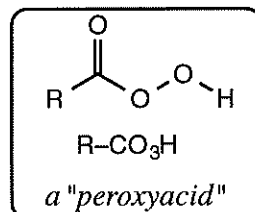
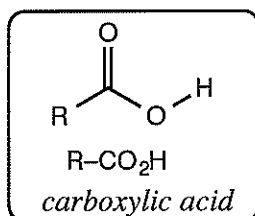
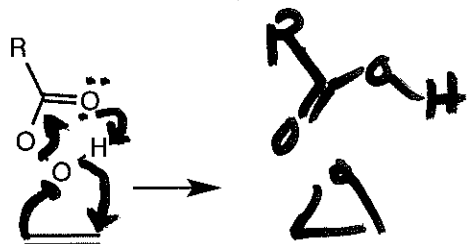
Problems: 7

Epoxides: A Reactive Subclass of Ethers



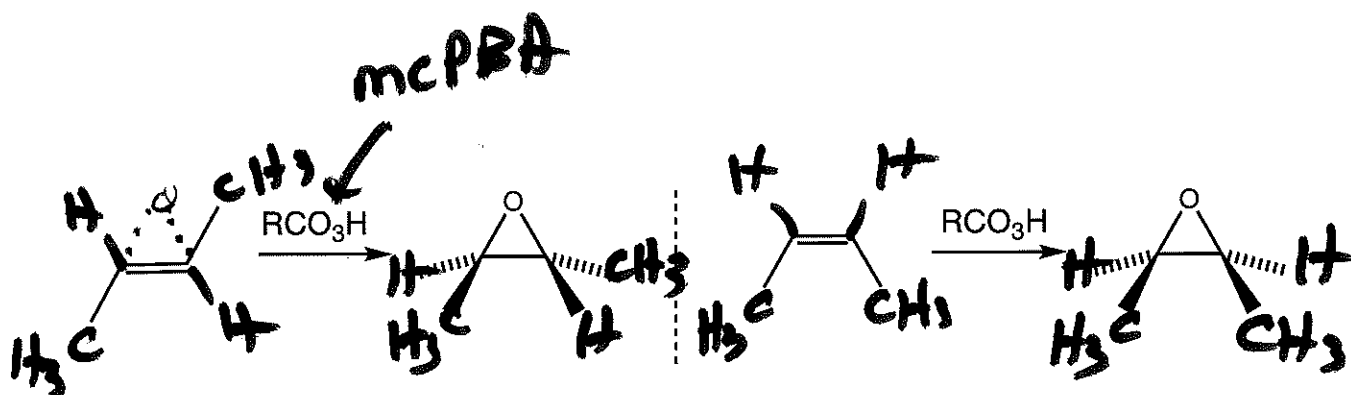
- epoxides are three-membered ring cyclic ethers
- epoxides are much more reactive than typical ethers
- because of the angle and torsional strain of cyclopropyl systems

A. Synthesis of Epoxides



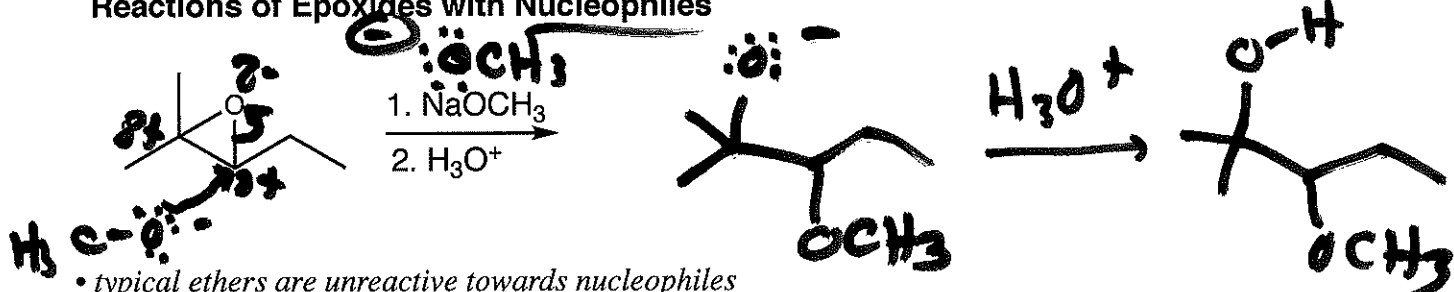
meta-chloroperoxybenzoic acid
(mCPBA)
most commonly used

- the reaction of an alkene with a peroxyacid (commonly mCPBA, but others also work) leads to formation of an epoxide in a single step
- the oxygen atom is added to the alkene on one face of the $\text{C}=\text{C}$ bond: syn addition

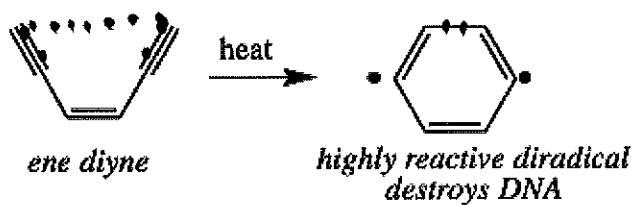
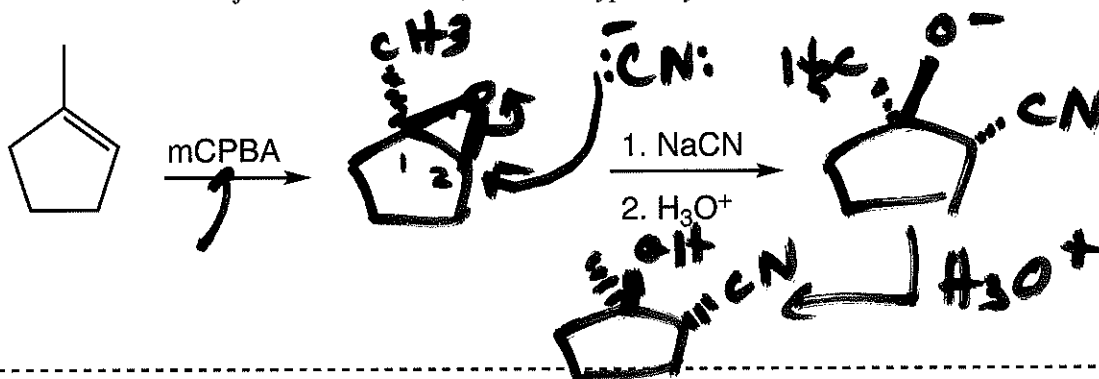


• epoxidations are stereospecific: a reaction in which the configuration of the product is dependent upon the configuration of the starting material

Reactions of Epoxides with Nucleophiles



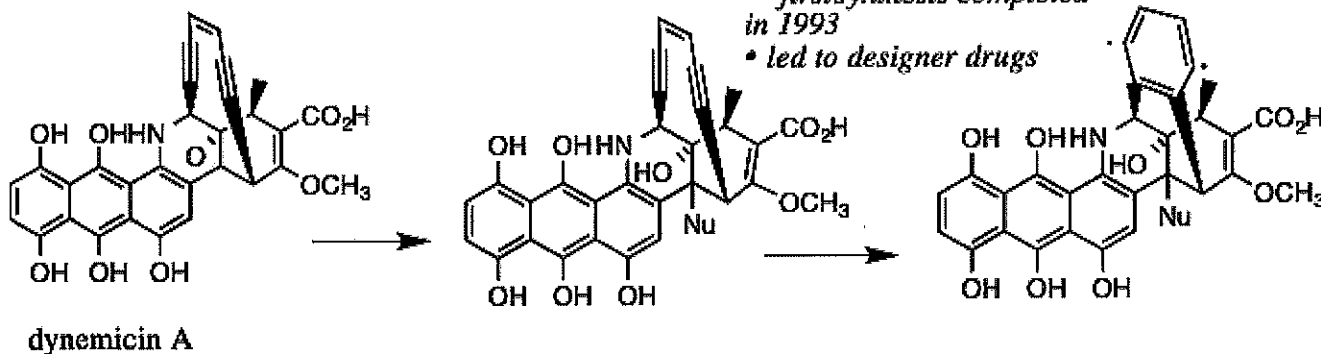
- typical ethers are unreactive towards nucleophiles
- epoxides are severely strained, they therefore react with nucleophiles in order to open the ring and release the strain
- since this is a version of an SN2 reaction, reaction typically occurs at the less substituted carbon atom



- dynemicin A first discovered in a bacteria found in Indian soil in the mid 80's
- most effective in leukemia, breast and lung cancer treatments
- first synthesis completed in 1993
- led to designer drugs



Stuart Schreiber
1956-



Chapter 14 *Essential Concepts*

1. Know how to name simple ethers
2. Know how to synthesize ethers using either the condensation method (for symmetrical ethers from 1° alcohols) or the general Williamson ether method. You should be able to synthesize ethers using alcohols as starting materials (i.e., know how to convert one alcohol to a nucleophilic alkoxide and the other to an electrophilic alkyl halide or tosylate)
3. Know the general properties of ethers and their role in the history of anesthetics
4. Know the mechanism for reaction of ethers with HX and be able to predict products
5. Be able to recognize the structure of a peroxy acid and know their stereospecific reaction with alkenes to form epoxides
6. Be able to predict the products of the reaction between epoxides and strong nucleophiles