

Ethers and Epoxides

Chapter Summary

Ethers have two organic groups, either alkyl or aryl, connected to a single oxygen atom (R–O–R'). In common names, the two organic groups are named and followed by the word *ether*, as in *ethyl methyl ether*, $\text{CH}_3\text{CH}_2\text{OCH}_3$. In the IUPAC system, the smaller **alkoxy group** is named as a substituent on the longer carbon chain. For the preceding example, the IUPAC name is *methoxyethane*.

Ethers have much lower boiling points than the corresponding isomeric alcohols because ethers cannot form intermolecular hydrogen bonds with themselves. They do, however, act as Lewis bases to form hydrogen bonds with compounds containing an –OH group (alcohols or water).

Ethers are excellent solvents for organic compounds. Their relative inertness makes them good solvents in which to carry out organic reactions.

Alkyl or aryl halides react with magnesium metal in **diethyl ether** or **tetrahydrofuran (THF)** to form **Grignard reagents, R–MgX**. Ethers stabilize these reagents by coordinating with the magnesium. Grignard reagents react with water, and the –MgX is replaced by –H, or if D_2O is used, by –D. Alkyl halides also react with lithium to form organolithium reagents.

Diethyl ether is prepared commercially by intermolecular dehydration of ethanol with sulfuric acid. The **Williamson ether synthesis**, another route to ethers, involves preparation of an alkoxide from an alcohol and a reactive metal, followed by an $\text{S}_{\text{N}}2$ displacement between the alkoxide and an alkyl halide.

Ethers can be cleaved at the C–O bond by strong protonic (HBr) or Lewis (BBr_3) acids. The products are alcohols and/or alkyl halides.

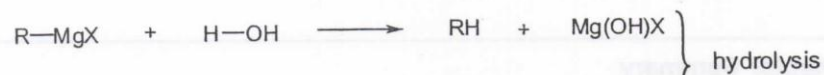
Epoxides (oxiranes) are three-membered cyclic ethers. The simplest and commercially most important example is **ethylene oxide**, manufactured from ethylene, air, and a silver catalyst. In the laboratory, epoxides are most commonly prepared from alkenes and organic peroxy acids.

Epoxides react with nucleophiles to give products in which the ring has opened. For example, acid-catalyzed hydration of ethylene oxide gives **ethylene glycol**. Other nucleophiles (such as alcohols) add similarly to epoxides, as do Grignard reagents and organolithium reagents. The reactions with **organometallic reagents** (RMgX and RLi) are useful two-carbon chain-lengthening reactions.

Cyclic ethers with larger rings than epoxides include **tetrahydrofuran (THF)**, **tetrahydropyran (THP)**, and **dioxane**. Large-ring cyclic polyethers, called **crown ethers**, can selectively bind metal ions, depending on the ring size.

Reaction Summary

Grignard Reagents

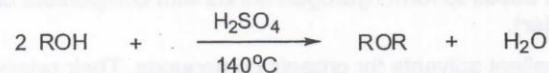


} hydrolysis

Lithium Reagents



Ether Preparation



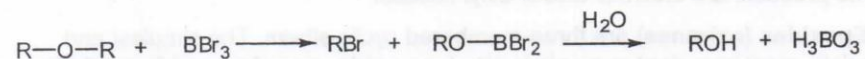
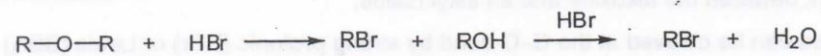
(best for primary alcohols; gives symmetric ethers)



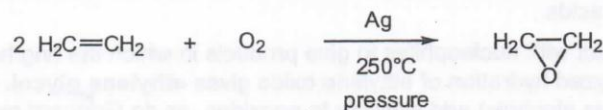
} Williamson synthesis

(best for R' = primary)

Ether Cleavage

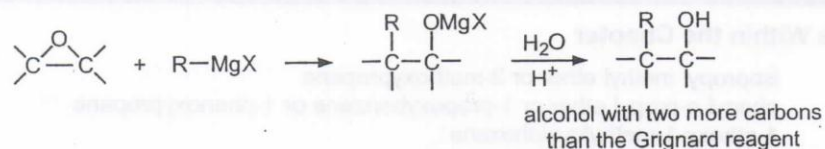
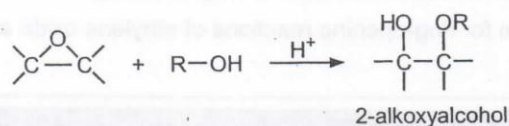
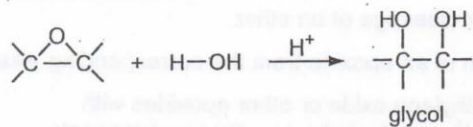


Ethylene Oxide



Other Epoxides



Epoxide Ring Openings**Learning Objectives**

1. Know the meaning of: ether, alkoxy group, Grignard reagent, organolithium reagents; organometallic compound, ether cleavage.
2. Know the meaning of: epoxide, oxirane, organic peroxy acid, nucleophilic addition to epoxides, diethylene glycol.
3. Know the meaning of: cyclic ether, tetrahydrofuran, furan, tetrahydropyran, dioxane, crown ethers.
4. Given the name of an ether or epoxide, write its structure, and vice versa.
5. Given the molecular formula, draw the structures of isomeric ethers and alcohols.
6. Compare the boiling points and solubilities in water of isomeric ethers and alcohols.
7. Write an equation for the preparation of a given Grignard reagent, and be able to name it.
8. Write an equation for the reaction of a given Grignard reagent with H₂O or D₂O.
9. Write an equation, using the appropriate Grignard reagent, for the preparation of a specific deuterium-labeled hydrocarbon.
10. Write an equation for the preparation of a given organolithium reagent.
11. Write equations for the reaction of organolithium reagents with water or epoxides.
12. Write equations for the preparation of a symmetrical and an unsymmetrical ether.
13. Write equations for the preparation of an ether using a Williamson synthesis.
14. Write the equation for the cleavage of an ether by a strong acid (HBr, HI, H₂SO₄) or a Lewis acid (BBr₃).

15. Write the steps in the mechanism for cleavage of an ether.
16. Write an equation for the preparation of an epoxide from the corresponding alkene.
17. Write equations for the reaction of ethylene oxide or other epoxides with nucleophiles such as H^+ , and H_2O , H^+ and alcohols, or a Grignard reagent.
18. Write the steps in the mechanism for ring-opening reactions of ethylene oxide and other epoxides.

ANSWERS TO PROBLEMS

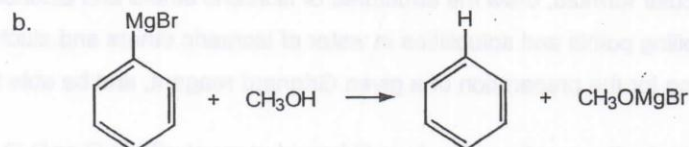
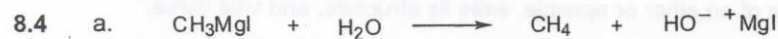
Problems Within the Chapter

- 8.1 a. isopropyl methyl ether or 2-methoxypropane
 b. phenyl *n*-propyl ether or 1-propoxybenzene or 1-phenoxypropane
 c. 1-ethoxy-1-methylcyclohexane

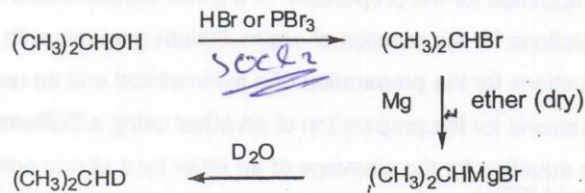


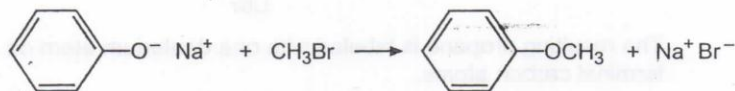
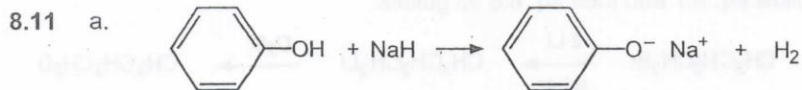
- 8.3 $\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1,4-butanediol
 $\text{CH}_3\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH}$ 3-methoxy-1-propanol
 $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_3$ 1,2-dimethoxyethane

The compounds are listed in order of decreasing boiling point. The fewer the hydroxyl groups, the fewer the possibilities there are for intermolecular hydrogen bonding, and the lower the boiling point.



- 8.5 Yes. There are no acidic protons in the starting alkyl bromide.
- 8.6 We must first convert the alcohol to an alkyl halide before we can make the Grignard reagent.





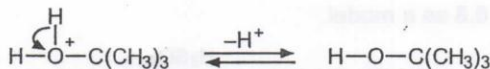
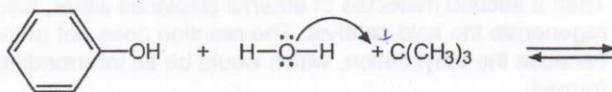
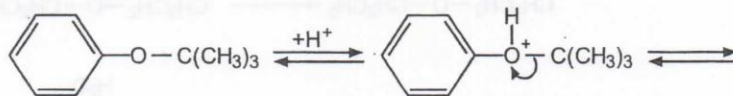
We cannot use the alternative combination because the second step would fail; aryl halides do *not* undergo S_N2 reactions.



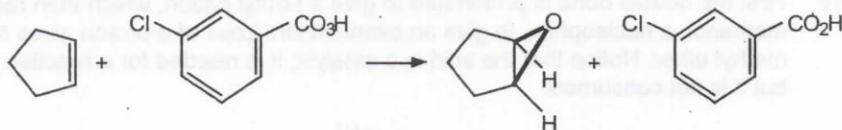
We cannot use the alternative combination because the second step would fail; tertiary halides do *not* undergo S_N2 reactions:



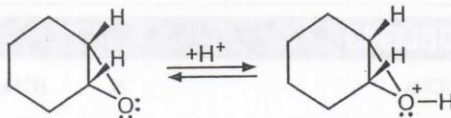
8.12 The reaction occurs by an S_N1 mechanism (review Sec. 6.6). The C–O bond to the *t*-butyl group cleaves to give an intermediate *t*-butyl cation that is much more stable than a phenyl cation.



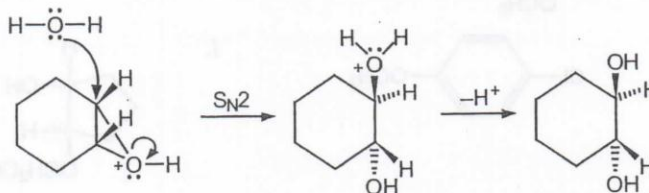
8.13 Follow eq. 8.18 as a guide.



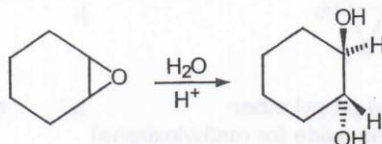
8.14 In the first step, the epoxide oxygen is protonated by the acid catalyst:



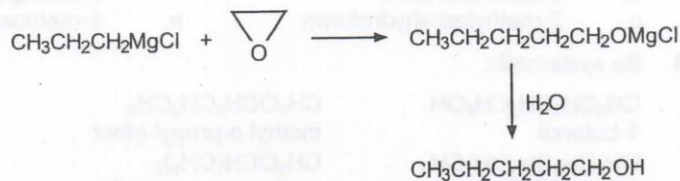
In the second step, water acts as a nucleophile in an S_N2 displacement:



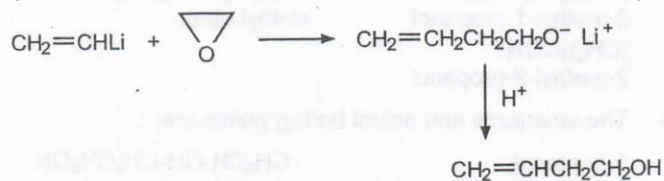
The product is *trans*-1,2-cyclohexanediol:



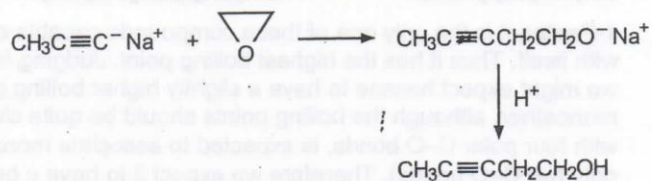
8.15 a. Follow eq. 8.21.



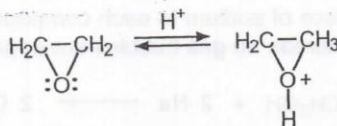
b. Follow eq. 8.22.



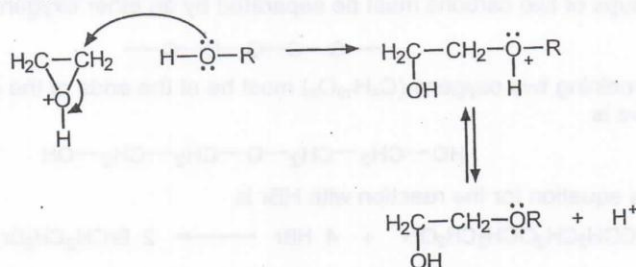
c. Acetylides (see eq. 3.53) are organometallic reagents. They react with epoxides as would a Grignard reagent or an organolithium reagent.



8.35 First the ethylene oxide is protonated by the acid catalyst:

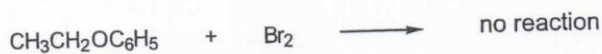
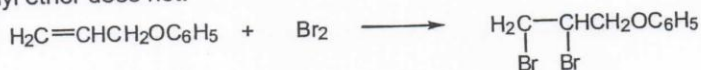


The alcohol or glycol then acts as a nucleophile in an $\text{S}_\text{N}2$ displacement, which occurs quite easily because the epoxide ring opens in the process, thus relieving the strain associated with the small ring:

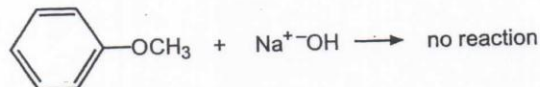
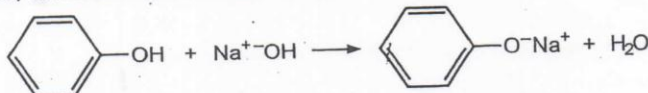


For eq. 8.20, $\text{R} = -\text{CH}_3$ or $-\text{CH}_2\text{CH}_2\text{OH}$

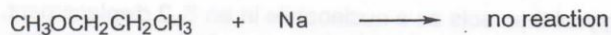
- 8.36 a. By analogy with crown ethers, it is the ether oxygens of nonactin and monensin that are expected to bind to the metal cations. The carboxylate and alcohol oxygens in monensin, and the ester oxygens in nonactin, might also be involved.
- b. Nonactin is cyclic and probably has a cavity size that is only conducive to complexation of sodium cation. Monensin is acyclic, more flexible than nonactin, and probably can fold in a manner that accommodates larger potassium ions.
- 8.37 a. Add a little of each compound to concentrated sulfuric acid, in separate test tubes. The ether is protonated and dissolves, whereas the hydrocarbon, being inert and less dense than sulfuric acid, simply floats on top.
- b. Add a little bromine in carbon tetrachloride to each ether. The allyl phenyl ether, being unsaturated, quickly decolorizes the bromine, but the ethyl phenyl ether does not.



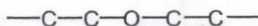
- c. Add each compound to a little 10% aqueous sodium hydroxide. The phenol dissolves, whereas the ether is inert toward the base.



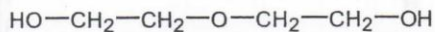
- d. Add a small piece of sodium to each compound. The alcohol liberates a gas (hydrogen), whereas no gas bubbles are apparent in the ether.



- 8.38 Since the product has only two carbons and the starting material has four carbons, two groups of two carbons must be separated by an ether oxygen:



The remaining two oxygens ($\text{C}_4\text{H}_{10}\text{O}_3$) must be at the ends of the chain. The desired structure is

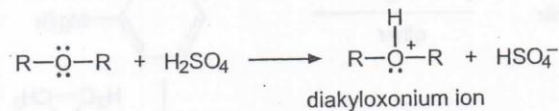


and the equation for the reaction with HBr is

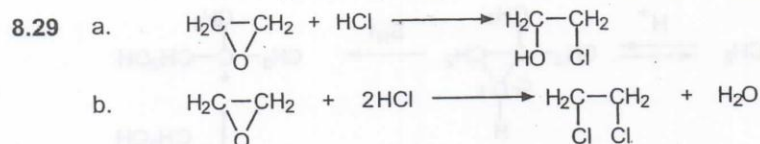
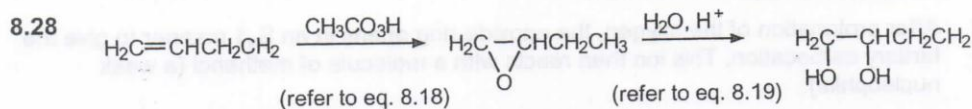
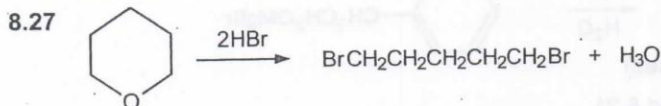


In this step the ether is cleaved, and the alcohol functions are also converted to alkyl halides.

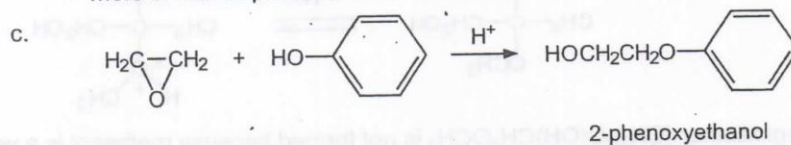
- 8.26 The oxygen of the ether can be protonated, and the resulting highly polar dialkyloxonium ion is soluble in sulfuric acid:



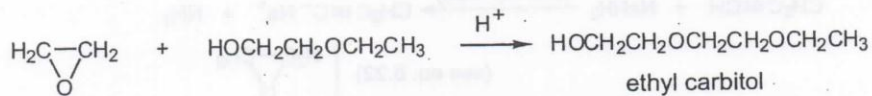
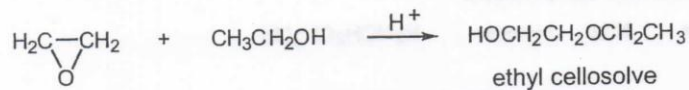
Alkanes have no unshared electron pairs and are not protonated by sulfuric acid and thus remain insoluble in it.

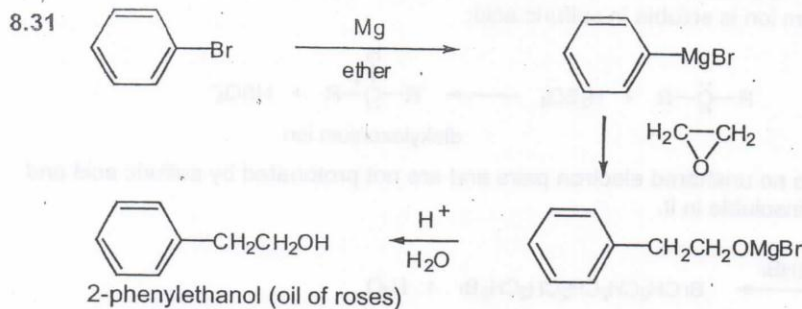


The 2-chloroethanol formed in part a reacts as an alcohol with the second mole of HCl to produce the dichloride.



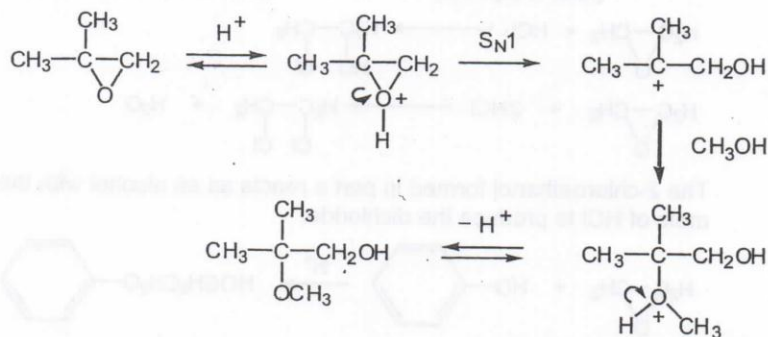
- 8.30 See eq. 8.20 for comparison.



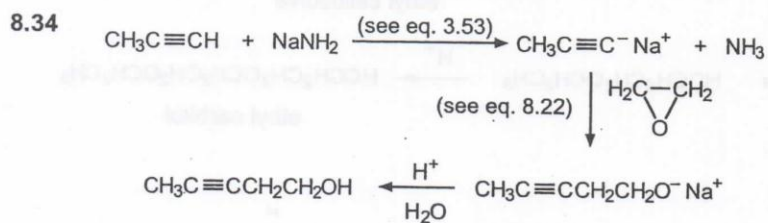
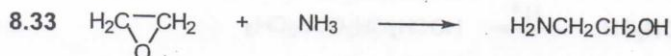


Compare with eqs. 8.4 and 8.21.

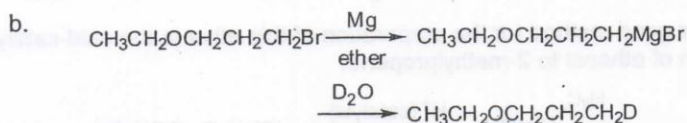
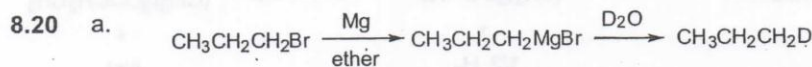
- 8.32 After protonation of the oxygen, the epoxide ring opens in an $\text{S}_{\text{N}}1$ manner to give the tertiary carbocation. This ion then reacts with a molecule of methanol (a weak nucleophile).



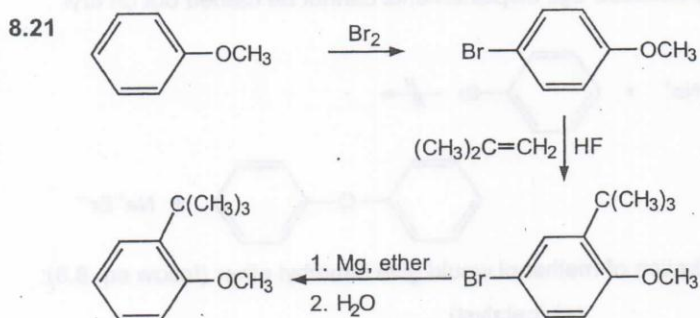
The regioisomer $(\text{CH}_3)_2\text{C}(\text{OH})\text{CH}_2\text{OCH}_3$ is *not* formed because methanol is a weak nucleophile and $\text{S}_{\text{N}}2$ attack on the protonated oxirane at the primary carbon cannot compete with the fast $\text{S}_{\text{N}}1$ process.



Regarding water solubility, 1,2-dimethoxyethane has two oxygens that can hydrogen-bond with water. The pentanol and the other ether have only one oxygen, and the hexane has none. We expect 1,2-dimethoxyethane to be the most soluble in water of these four compounds, and it is. In fact, the dimethoxyethane is completely soluble in water; 1-pentanol and ethyl *n*-propyl ether are only slightly soluble in water, and hexane is essentially insoluble in water.

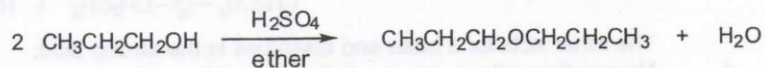


Note that the ether functional group can be tolerated in making a Grignard reagent (part b).

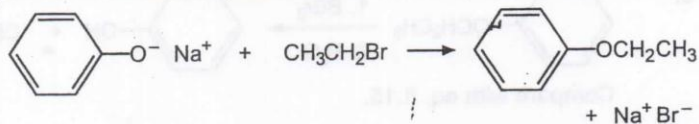


Direct Friedel-Crafts alkylation of anisole would give *p*-*t*-butylanisole, the sterically less hindered product. The bromine is therefore used to block the *para* position, then is removed when no longer needed. (For an activated substrate like anisole, a FeBr_3 catalyst is not required for step 1.)

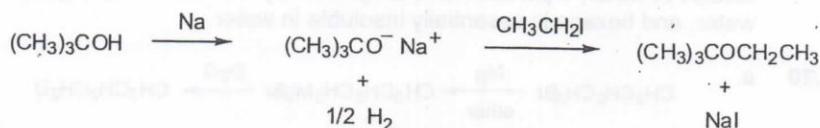
- 8.22 a. Since both alkyl groups are identical and primary, the dehydration route using sulfuric acid is preferred because it is least expensive and gives a good yield (see eq. 8.8).



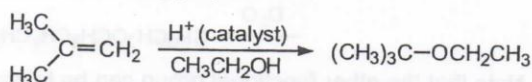
- b. The Williamson method is preferred. The sodium phenoxide can be prepared using NaOH instead of Na, because of the acidity of phenols:



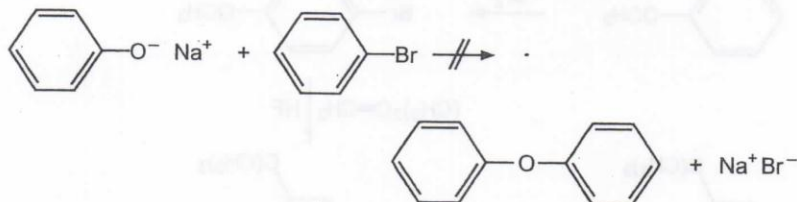
- c. The following Williamson ether synthesis is preferred. The alternate Williamson ether synthesis (the reaction between sodium ethoxide and *tert*-butyl iodide) would fail because dehydrohalogenation would be faster than substitution.



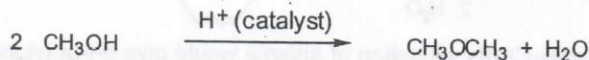
Another good method for the preparation of this ether is the acid-catalyzed addition of ethanol to 2-methylpropene:



- 8.23 The second step fails because $\text{S}_{\text{N}}2$ displacements cannot be carried out on aryl halides.



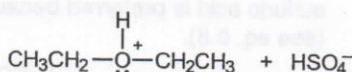
- 8.24 Acid-catalyzed dehydration of methanol would give dimethyl ether (follow eq. 8.8):



- 8.25 a. $\text{CH}_3\text{OCH}_2\text{CH}_2\text{CH}_3 + 2\text{HBr} \longrightarrow \text{CH}_3\text{Br} + \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{H}_2\text{O}$

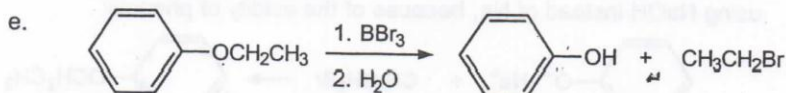
b. No reaction; ethers (except for epoxides) are inert toward base.

- c. $\text{CH}_3\text{CH}_2-\ddot{\text{O}}-\text{CH}_2\text{CH}_3 + \text{H}_2\text{SO}_4 \longrightarrow$



The ether acts as a base and dissolves in the strong acid.

- d. No reaction; ethers can be distinguished from alcohols by their inertness toward sodium metal.



Compare with eq. 8.15.