Objectives

After completing this section, you should be able to

1. write an equation to illustrate the industrial preparation of simple symmetrical ethers.
2. write an equation to illustrate the Williamson synthesis of ethers.
   a. identify the ether obtained from the reaction of a given alkyl halide with a given alkoxide ion.
   b. identify the reagents needed to prepare a given ether through a Williamson synthesis.
   c. identify the limitations of the Williamson synthesis, and make the appropriate choices when deciding how best to synthesize a given ether.
   d. write an equation to describe the formation of an alkoxide from an alcohol.
   e. identify silver(I) oxide as a reagent which can be used in a Williamson synthesis.
3. write an equation to show how an ether can be prepared by the alkoxymercuration-demercuration of an alkene.
   a. identify the product formed from the alkoxymercuration-demercuration of a given alkene.
   b. identify the alkene, the reagents, or both, needed to prepare a given ether by the alkoxymercuration-demercuration process.
   c. write the detailed mechanism of the reaction between an alkene, an alcohol and mercury(II) trifluoroacetate.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- alkoxymercuration
- oxymercuration
- Williamson ether synthesis

Study Notes

We studied oxymercuration as a method of converting an alkene to an alcohol in Section 8.4. “Alkoxymercuration” is a very similar process, except that we are now converting an alkene into an ether. The two processes are compared below.

<table>
<thead>
<tr>
<th></th>
<th>oxymercuration</th>
<th>alkoxymercuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>we react</td>
<td>alkene</td>
<td>alkene</td>
</tr>
<tr>
<td>with</td>
<td>water</td>
<td>an alcohol</td>
</tr>
<tr>
<td>in the presence of</td>
<td>Hg(O_2CCH_3)_2</td>
<td>Hg(O_2CCF_3)_2</td>
</tr>
<tr>
<td>followed by treatment with</td>
<td>NaBH_4</td>
<td>NaBH_4</td>
</tr>
<tr>
<td>to produce an</td>
<td>alcohol</td>
<td>ether</td>
</tr>
</tbody>
</table>

Review the mechanism of the oxymercuration reaction in Section 8.4, paying particular attention to the regiochemistry and the stereochemistry of the reaction. The mechanism is identical to alkoxymercuration.
Ethers are usually prepared from alcohols or their conjugate bases. One important procedure, known as the Williamson Ether Synthesis, proceeds by an $S_{N}2$ reaction of an alkoxide nucleophile with an alkyl halide. Reactions #1 and #2 below are two examples of this procedure. When applied to an unsymmetrical ether, as in this case, there are two different combinations of reactants possible. Of these one is usually better than the other. Since alkoxide anions are strong bases, the possibility of a competing E2 elimination must always be considered. Bearing in mind the factors that favor substitution over elimination, a $1^\circ$-alkyl halide should be selected as a preferred reactant whenever possible. Thus, reaction #1 gives a better and cleaner yield of benzyl isopropyl ether than does reaction #2, which generates considerable elimination product.

\[
\text{H}_3\text{C}-\text{CH}_2\text{OH} + \text{CH}_3\text{CH}_2\text{Br} \xrightarrow{\text{NaOH}} \text{H}_3\text{C}-\text{CH}_2\text{O}-\text{CH}_2\text{CH}_3 + \text{NaBr}
\]

A second general ether synthesis, alkoxymercuration, is patterned after the oxymercuration reaction. Reactions #3 and #4 are examples of this two-step procedure. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the acetate (trifluoroacetate anion is a poorer nucleophile than acetate). The mechanism of alkoxymercuration is similar to that of oxymercuration, with an initial anti-addition of the mercuric species and alcohol being followed by reductive demercuration.

Acid-catalyzed dehydration of small $1^\circ$-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. As shown in the following two equations, the success of this procedure depends on the temperature. At 110° to 130 °C an $S_{N}2$ reaction of the alcohol conjugate acid leads to an ether product.

\[
\text{CH}_3\text{CH}_2\text{OH} + \text{H}_2\text{SO}_4 \xrightarrow{110° \text{ to } 130 °C} \text{CH}_3\text{CH}_2\text{O}-\text{CH}_2\text{CH}_3 + \text{H}_2\text{O}
\]

At higher temperatures (over 150 °C) an E2 elimination takes place.

\[
\text{CH}_3\text{CH}_2\text{OH} + \text{H}_2\text{SO}_4 \xrightarrow{150 °C} \text{CH}_2\text{=CH}_2 + \text{H}_2\text{O}
\]

This reaction cannot be employed to prepare unsymmetrical ethers. It is because a mixture of products is likely to be obtained.

Exercises
Questions

Q18.2.1

When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

Q18.2.2

How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a)

(b)

(c)

(d)

(e)
Q18.2.3

Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Q18.2.4

Ether C from problem 26 can also be prepared from an alkene and an alcohol, draw these two. (There are two possibilities for the alcohol and alkene)

Q18.2.5

Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [J. Org. Chem., 2016, 81 (20), pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)

Q18.2.6

What reagents would you use to perform the following transformations?

(a)

(b)
Q18.2.7

Predict the product of the following.

\[
\text{HO-\text{O-CH}_2\text{-OH}} \xrightarrow{\text{H}_2\text{SO}_4 \text{ (conc.)}}
\]

Q18.2.8

If the following epoxide were subjected to a general nucleophile, Nu, what would be the major product?

Solutions

S18.2.1

The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions from occurring. The electrophile should have the characteristics of a good Sn2 electrophile, preferably primary to minimize any elimination reactions from occurring.

S18.2.2

The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

(a)
Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e)

\[ \text{OH} + \text{OH} + \text{H}_2\text{SO}_4 \text{(conc.)} \]

S18.2.3

S18.2.4
While both are possible, the top route is likely easier because both starting materials are a liquid.

S18.2.5

S18.2.6

(a)

(b)

Note the cis addition

(c)

An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.
Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.

S18.2.7

The result is the production of dioxane, a common solvent.

S18.2.8

The regiochemistry is determined by the slight electron withdrawing effect of the adjacent benzene ring. The stereochemistry is determined by the stereospecific Sn2 mechanism.

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