Objectives

After completing this section, you should be able to

1. write an equation to illustrate the acidic cleavage of an ether.
2. identify the products formed when a given ether is cleaved by a strong acid.
3. identify the reagent needed to bring about cleavage of a given ether.
4. deduce the structure of an unknown ether, given the products of acidic cleavage of the ether.
5. write the detailed mechanism for the acidic cleavage of a given ether.

Study Notes

There are a number of points in this section that require additional explanations.

First, if an excess of HI (or HBr) is used in the cleavage reaction, the alcohol formed is converted by a nucleophilic substitution reaction to the appropriate alkyl halide:

$$\text{ROH} + \text{HI} \rightarrow \text{R} \text{I} + \text{H}_2\text{O}$$

In view of this substitution, some textbooks simplify the overall cleavage process as:

$$\text{R} \text{O} \text{-} \text{R'} + 2\text{HI} \rightarrow \text{R} \text{I} + \text{R'} \text{I} + \text{H}_2\text{O}$$

Second, we should consider in detail how certain ethers (those containing tertiary alkyl, benzyl or allyl groups) cleave by an $S_{N1}$ mechanism:

\[
\begin{align*}
\text{O} & \quad + \text{HI} \quad \leftrightarrow \quad \text{O}^{\text{H}} & + & \text{I}^{-} \\
\text{E1} & \quad \text{elimination of H}^{+} \\
\text{S}_{N1} & \quad \text{attack by I}^{-} \\
\text{addition of HI} & \quad \\
\end{align*}
\]

\[
\begin{align*}
\text{C} & \quad + \text{CH}_3\text{OH} \\
\end{align*}
\]
Finally, notice that an aryl alkyl ether will always produce a phenol and an alkyl halide, never an aryl halide and an alcohol. This is because we rarely see a nucleophile attacking an aromatic ring carbon in preference to an aliphatic carbon:

As phenols do not undergo nucleophilic substitution reactions, even if an excess of HX is used, the products from the cleavage of an aryl alkyl ether are a phenol and an alkyl halide. Diaryl ethers are not cleaved by acids.

The most common reaction of ethers is cleavage of the C–O bond by strong acids. This may occur by S<sub>N</sub>1 or E1 mechanisms for 3º-alkyl groups or by an S<sub>N</sub>2 mechanism for 1º-alkyl groups. Some examples are shown in the following diagram. The conjugate acid of the ether is an intermediate in all these reactions, just as conjugate acids were intermediates in certain alcohol reactions.

The first two reactions proceed by a sequence of S<sub>N</sub>2 steps in which the iodide or bromide anion displaces an alcohol in the first step, and then converts the conjugate acid of that alcohol to an alkyl halide in the second. Since S<sub>N</sub>2 reactions are favored at least hindered sites, the methyl group in example #1 is cleaved first. The 2º-alkyl group in example #3 is probably cleaved by an S<sub>N</sub>2 mechanism, but the S<sub>N</sub>1 alternative cannot be ruled out. The phenol formed in this reaction does not react further, since S<sub>N</sub>2, S<sub>N</sub>1 and E1 reactions do not take place on aromatic rings. The last example shows the cleavage of a 3º-alkyl group by a strong acid. Acids having poorly nucleophilic conjugate bases are often chosen for this purpose so that E1 products are favored. The reaction shown here (#4) is the reverse of the tert-butyl ether preparation described earlier.
Objectives

After completing this section, you should be able to

1. explain what is meant by “protecting” a functional group during an organic synthesis.
2. describe one common method for protecting the hydroxy group of an alcohol, and give an example of its use (e.g., in the preparation of a Grignard reagent).

Often during the synthesis of complex molecules on functional group in a molecule interferes with an intended reaction on a second functional group on the same molecule. An excellent example is the fact that a Grignard reagent can't be prepared from halo alcohol because the C-Mg bond is not compatible with the acidic -OH group.

When situations like this occurs chemists circumvent eh problem by protecting the interfering functional group. Functional group protection involves three steps:

1. Blocking the interfering functionality by introducing a protecting group.
2. Performing the intended reaction.
3. Removing the protecting group and reforming the original functional group.

There are several methods for protecting an alcohol, however, the most common is the reaction with a chlorotrialkysilane, Cl-SiR₃. This reaction forms a trialkylsilyl ether, R'O-SiR₃. Chlorotrimethylsilane is often used in conjunction with a base, such as triethylamine. The base helps to form the alkoxide anion and remove the HCl produced by the reaction.

General Reaction

Example
The silyl ether protecting group can be removed by reaction with an aqueous acid or the fluoride ion.

\[
\text{H₃C} \quad \overset{\text{H₂O}^+}{\text{Silyl Ether}} \quad \xrightarrow{\text{H₂O}^+} \quad \text{H₃C} \quad \overset{\text{OH}}{\text{OH}} \quad \overset{\text{H₂O}^+}{\text{H₃C} \quad \overset{\text{SiOH}}{\text{OH}}}
\]

By utilizing a protecting group a Grignard reagent can be formed and reacted on a halo alcohol.

1) Protect the Alcohol

\[
\text{HOCH₂CH₂Br} \quad \overset{\text{(CH₃)₃SiCl}}{\text{(CH₃)₃SiOCH₂CH₂Br}} \quad \overset{\text{(CH₃)₃SiOCH₂CH₂Br}}{\text{(CH₃)₃SiOCH₂CH₂Br}} \quad \overset{\text{(CH₃)₃SiOCH₂CH₂MgBr}}{\text{(CH₃)₃SiOCH₂CH₂MgBr}}
\]

2) Form the Grignard Reagent

3) Perform the Grignard Reaction

4) Deprotection

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