Objectives

After completing this section, you should be able to

1. write an equation to describe the opening of an epoxide ring under mildly acidic conditions.
   a. identify the product formed from the hydrolysis of an epoxide.
   b. write the mechanism for the opening of an epoxide ring by an aqueous acid, paying particular attention to the stereochemistry of the product.
   c. identify the product formed when an epoxide ring is opened by a hydrogen halide under anhydrous conditions.
2. predict the major product from the acidic cleavage of a given unsymmetrical epoxide.
3. write an equation to illustrate the cleavage of an epoxide ring by a base.
   a. identify the product formed from the reaction of a given epoxide with given base.
   b. explain why epoxides are susceptible to cleavage by bases, whereas other cyclic ethers are not.

Study Notes

In the discussion on base-catalyzed epoxide opening, the mechanism is essentially $S_{N2}$. While oxygen is a poor leaving group, the ring strain of the epoxide really helps to drive this reaction to completion. Indeed, larger cyclic ethers would not be susceptible to either acid-catalyzed or base-catalyzed cleavage under the same conditions because the ring strain is not as great as in the three-membered epoxide ring.

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**Epoxide ring-opening reactions - $S_{N1}$ vs. $S_{N2}$, regioselectivity, and stereoselectivity**

The nonenzymatic ring-opening reactions of epoxides provide a nice overview of many of the concepts we have seen already in this chapter. Ring-opening reactions can proceed by either $S_{N2}$ or $S_{N1}$ mechanisms, depending on the nature of the epoxide and on the reaction conditions. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes solvolysis in basic methanol, ring-opening occurs by an $S_{N2}$ mechanism, and the less substituted carbon is the site of nucleophilic attack, leading to what we will refer to as product B:

\[
\text{basic ring-opening:}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{H}
\end{align*}
\]

\[
\text{Na}^+ \quad \text{OCH}_3
\]

\[
\begin{align*}
\text{HO} & \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{OCH}_3
\end{align*}
\]

product B

Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial $S_{N1}$ character, and the more substituted carbon is the site of attack. As a result, product A predominates.
These are both good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively).

Let us examine the basic, $\text{S}_2$ case first. The leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.

The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an $\text{S}_2$ mechanism.

What about the electrophile? There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an $\text{S}_2$ reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other $\text{S}_2$ reactions, nucleophilic attack takes place from the backside, resulting in inversion at the electrophilic carbon.

Probably the best way to depict the acid-catalyzed epoxide ring-opening reaction is as a hybrid, or cross, between an $\text{S}_2$ and $\text{S}_1$ mechanism. First, the oxygen is protonated, creating a good leaving group (step 1 below). Then the carbon-oxygen bond begins to break (step 2) and positive charge begins to build up on the more substituted carbon (recall the discussion from section 8.4B about carbocation stability).

Unlike in an $\text{S}_1$ reaction, the nucleophile attacks the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.
Attack takes place preferentially from the backside (like in an SN2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile attacks the more substituted carbon because it is this carbon that holds a greater degree of positive charge.

Example 18.6.1

Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

a. ethanol and a small amount of sodium hydroxide
b. ethanol and a small amount of sulfuric acid

Hint: be sure to consider both regiochemistry and stereochemistry!

Answer:

Anti Dihydroxylation

Edit section

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction described above. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is anti-hydroxylation of the double bond, in contrast to the syn-stereoselectivity of the earlier method. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which, of course, could be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.
Addition of HX

Epoxides can also be opened by other anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will attack the less substituted carbon and an $S_N 2$ like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in a $S_N 1$ like reaction.

Example 18.6.2

Exercises

Questions

Q18.6.1

Given the following, predict the product assuming only the epoxide is affected. (Remember stereochemistry)
Q18.6.2

Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

\[
\begin{array}{c}
\text{O} \\
1. \text{CH}_3\text{CH}_2\text{MgBr} \\
2. \text{H}_3\text{O}^+ \\
\end{array}
\]

Q18.6.3

Epoxides are often very useful reagents to use in synthesis when the desired product is a single stereoisomer. If the following alkene were reacted with an oxyacid to form an epoxide, would the result be a enantiomerically pure? If not, what would it be?

Solutions

S18.6.1

Note that the stereochemistry has been inverted

S18.6.2
First, look at the symmetry of the alkene. There is a mirror plane, shown here.

Then, think about the mechanism of epoxidation with an oxyacid, take for example \textit{m}CPBA. The mechanism is concerted, so the original \textit{cis} stereochemistry is not changed. This leads to "two" epoxides.

However, these two mirror images are actually identical due to the mirror plane of the \textit{cis} geometry. It is a meso compound, so the final result is a single stereoisomer, but not a single enantiomer.

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