Objectives

After completing this section, you should be able to

1. write an equation to illustrate the formation of acetals.
2. identify the acetal formed from the reaction of a given aldehyde or ketone with a given alcohol.
3. identify the carbonyl compound, the alcohol, or both, needed to form a given acetal.
4. write a detailed mechanism for the reaction which occurs between an aldehyde or a ketone and an alcohol.
5. explain how an acid catalyst makes aldehydes and ketones more susceptible to attack by alcohols.
6. illustrate how the reversibility of the reaction between an aldehyde or a ketone and an alcohol can be used to protect a carbonyl group during an organic synthesis.

Key Terms

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

• acetal
• hemiacetal

Study Notes

This section presents a second example of the use of a protecting group. [The first was in the discussion of alcohols, Section 17.8.] Because of the reactivity of hydroxy groups and carbonyl groups, we often need to protect such groups during organic syntheses. When you are designing multi-step syntheses as part of an assignment or examination question, you must always keep in mind the possibility that you may need to protect such groups to carry out the desired sequence of reactions successfully.

In this organic chemistry topic, we shall see how alcohols (R-OH) add to carbonyl groups. Carbonyl groups are characterized by a carbon-oxygen double bond. The two main functional groups that consist of this carbon-oxygen double bond are Aldehydes and Ketones.

Introduction

It has been demonstrated that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diol. In a similar reaction alcohols add reversibly to aldehydes and ketones to form hemiacetals (hemi, Greek, half). This reaction can continue by adding another alcohol to form an acetal. Hemiacetals and acetals are important functional groups because they appear in sugars.

To achieve effective hemiacetal or acetal formation, two additional features must be implemented. First, an acid catalyst must be used because alcohol is a weak nucleophile; and second, the water produced with the acetal must be removed from the reaction by a process such as a molecular sieves or a Dean-Stark trap. The latter is important, since acetal formation is reversible. Indeed, once pure hemiacetal or acetals are obtained they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.
Formation of Hemi-acetals

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<table>
<thead>
<tr>
<th>Aldehyde or Ketone</th>
<th>Hemi-Acetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{C} = \text{O}) + ROH (\xrightarrow{\text{H}_3\text{O}^+}) HO C OR</td>
<td></td>
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</tbody>
</table>
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Example 19.10.1: Formation of Hemi-acetals

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\[
\text{HO-C-CH}_3 + \text{H}_3\text{O}^+ \rightarrow \text{HO-O-CH}_3
\]
```

Example 19.10.2: Hemi-acetal Reversibility

```
\[
\text{HO-O-CH}_3 + \text{Excess H}_2\text{O} \xrightarrow{\text{H}_3\text{O}^+} \text{C-CHO} + \text{HO-CH}_3
\]
```

Formation of Acetals

Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents (or an excess amount) of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. It is important to note that a hemiacetal is formed as an intermediate during the formation of an acetal.

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<td></td>
</tr>
</tbody>
</table>
```

Example 19.10.3: Formation of Acetals

```
\[
\text{HO-C-CH}_3 + 2 \text{HO-CH}_3 \xrightarrow{\text{H}_3\text{O}^+} \text{H}_3\text{C-O-C-CH}_3 + \text{H}_2\text{O}
\]
```

Example 19.10.4: Acetal Reversibility
Mechanism for Hemiacetal and Acetal Formation

The mechanism shown here applies to both acetal and hemiacetal formation

1) Protonation of the carbonyl

2) Nucleophilic attack by the alcohol

3) Deprotonation to form a hemiacetal

4) Protonation of the alcohol
5) Removal of water

6) Nucleophilic attack by the alcohol

7) Deprotonation by water
Acetals as Protecting Groups

The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride, alkyl and aryl reagents. If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented.

In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with esters and ketones.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)