Objectives

After completing this section, you should be able to

1. discuss the reactions of alcohols that have been introduced in previous units. These reactions include
   a. conversion of alcohols into alkyl halides.
   b. conversion of alcohols into tosylates.
   c. dehydration of alcohols to yield alkenes.
   d. conversion of alcohols into esters.

Study Notes

As you read through Section 17.6 you should be prepared to turn back to those earlier sections in which some of the reactions of alcohols were discussed:

- dehydration to alkenes—Section 8.1.
- conversion to alkyl halides—Section 10.5.

You may also wish to review the discussion of acidity constants, which can be found in Section 2.8.

Remember that when an alcohol reacts with tosyl chloride to form a tosylate, it is the O\text{-}H bond of the alcohol that is broken, not the C\text{-}O bond. This means that the absolute configuration of the carbon atom attached to the hydroxyl group remains unchanged throughout the reaction. The reading illustrates how this fact can be exploited to control the stereochemistry in an organic synthesis.

Finally, the reading shows the production of an ester from an alcohol and an acid chloride. In Section 21.3 we will discuss the Fischer esterification, a famous reaction that uses an alcohol and a carboxylic acid to form the ester.

Conversion of Alcohols into Alkyl Halides

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:

\[
R\:\text{OH} + H\:X \rightarrow R\:X + H_2O
\]

- The order of reactivity of alcohols is $3^\circ > 2^\circ > 1^\circ$ methyl.
- The order of reactivity of the hydrogen halides is $\text{HI} > \text{HBr} > \text{HCl}$ ($\text{HF}$ is generally unreactive).

The reaction is acid catalyzed. Alcohols react with the strongly acidic hydrogen halides $\text{HCl}$, $\text{HBr}$, and $\text{HI}$, but they do not react with nonacidic $\text{NaCl}$, $\text{NaBr}$, or $\text{NaI}$. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide and sulfuric acid:

\[
R\:\text{OH} + \text{NaX} \xrightarrow{H_2SO_4} R\:X + \text{NaHSO}_4 + H_2O
\]
Mechanisms of the Reactions of Alcohols with HX

Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation, in an $S_N1$ reaction with the protonated alcohol acting as the substrate.

The $S_N1$ mechanism is illustrated by the reaction tert-butyl alcohol and aqueous hydrochloric acid (H$_3$O$^+$, Cl$^-$). The first two steps in this $S_n1$ substitution mechanism are protonation of the alcohol to form an oxonium ion. Although the oxonium ion is formed by protonation of the alcohol, it can also be viewed as a Lewis acid-base complex between the cation (R$^+$) and H$_2$O. Protonation of the alcohol converts a poor leaving group (OH-) to a good leaving group (H$_2$O$^-$), which makes the dissociation step of the $S_N1$ mechanism more favorable.

In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.

When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and in the presence of halide ions, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, most of the carbocations react with an electron pair of a halide ion to form a more stable species, the alkyl halide product. The overall result is an $S_n1$ reaction.

Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations. Primary alcohols and methanol react to form alkyl halides under acidic conditions by an $S_N2$ mechanism.

In these reactions the function of the acid is to produce a protonated alcohol. The halide ion then displaces a molecule of water (a good leaving group) from carbon; this produces an alkyl halide:

Again, acid is required. Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves. Direct displacement of the hydroxyl group does not occur because the leaving group would have to be a strongly basic hydroxide ion:
We can see now why the reactions of alcohols with hydrogen halides are acid-promoted.

Carbocation rearrangements are extremely common in organic chemistry reactions and are defined as the movement of a carbocation from an unstable state to a more stable state through the use of various structural reorganizational "shifts" within the molecule. Once the carbocation has shifted over to a different carbon, we can say that there is a structural isomer of the initial molecule. However, this phenomenon is not as simple as it sounds.

The most common methods for converting 1º- and 2º-alcohols to the corresponding chloro and bromo alkanes (i.e. replacement of the hydroxyl group) are treatments with thionyl chloride and phosphorus tribromide, respectively. These reagents are generally preferred over the use of concentrated HX due to the harsh acidity of these hydrohalic acids and the carbocation rearrangements associated with their use.

Synthetic organic chemists, when they want to convert an alcohol into a better leaving group, have several methods to choose from. One common strategy is to convert the alcohol into an alkyl chloride or bromide, using thionyl chloride or phosphorus tribromide:

\[
\begin{align*}
\text{OH} & \quad + \quad \text{S} & \quad \rightarrow \quad \text{Cl} & \quad + \quad \text{SO}_2 (g) \\
\text{OH} & \quad + \quad \text{PBr}_3 & \quad \rightarrow \quad \text{Br} & \quad + \quad \text{H}_3\text{PO}_4
\end{align*}
\]

Despite their general usefulness, phosphorous tribromide and thionyl chloride have shortcomings. Hindered 1º- and 2º-alcohols react sluggishly with the former, and may form rearrangement products, as noted in the following equation.

Below, an abbreviated mechanism for the reaction is displayed. The initially formed trialkylphosphite ester may be isolated if the HBr byproduct is scavenged by base. In the presence of HBr a series of acid-base and S_N2 reactions take place, along with the transient formation of carbocation intermediates. Rearrangement (pink arrows) of the carbocations leads to isomeric products.

Reaction of thionyl chloride with chiral 2º-alcohols has been observed to proceed with either inversion or retention. In the presence of a base such as pyridine, the intermediate chlorosulfite ester reacts to form an "pyridinium" salt, which
undergoes a relatively clean $S_N2$ reaction to the inverted chloride. In ether and similar solvents the chlorosulfite reacts with retention of configuration, presumably by way of a tight or intimate ion pair. This is classified as an $S_{NI}$ reaction (nucleophilic substitution internal). The carbo-cation partner in the ion pair may also rearrange. These reactions are illustrated by the following equations. An alternative explanation for the retention of configuration, involving an initial solvent molecule displacement of the chlorosulfite group (as SO$_2$ and chloride anion), followed by chloride ion displacement of the solvent moiety, has been suggested. In this case, two inversions lead to retention.

Example 17.6.1: Conversion of Alcohols to Alkyl Chlorides

There's one important thing to note here: see the stereochemistry? It's been inverted. *(white lie alert – see below)* That's an important difference between ($\text{SOCl}_2$) and TsCl, which leaves the stereochemistry alone. We'll get to the root cause of that in a moment, but in the meantime, can you think of a mechanism which results in inversion of configuration at carbon?

**Mechanisms**

Since the reaction proceeds through a backside attack ($\text{SN}_2$), there is inversion of configuration at the carbon

The mechanism for formation of acid chlorides from carboxylic acids is similar. The conversion of carboxylic acids to acid chlorides is similar, but proceeds through a [1,2]-addition of chloride ion to the carbonyl carbon followed by [1,2]-elimination to give the acid chloride, ([SO$_2$Cl]) and ([HCl])

The PBr$_3$ reaction is thought to involve two successive $S_N2$-like steps:
Notice that these reactions result in inversion of stereochemistry in the resulting alkyl halide.

**Conversion of Alcohols into Tosylates**

Alternatively, we can transform an alcohol group into sulfonic ester using *para*-toluene sulfonyl chloride (Ts-Cl) or methanesulfonyl chloride (Ms-Cl), creating what is termed an organic **tosylate** or **mesylate**:

Good leaving group

Again, you'll have a chance to work a mechanism for tosylate and mesylate formation in the chapter 12 problems. Notice, though, that unlike the halogenation reactions above, conversion of an alcohol to a tosylate or mesylate proceeds with retention of configuration at the electrophilic carbon.

Chlorides, bromides, and tosylate / mesylate groups are excellent leaving groups in nucleophilic substitution reactions, due to resonance delocalization of the developing negative charge on the leaving oxygen.

The laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules such as cholesterol and β-carotene - was accomplished by first converting the alcohol into an organic tosylate (step 1), then displacing the tosylate group with an inorganic pyrophosphate nucleophile (step 2) (*J. Org. Chem* 1986, *51*, 4768).
Example 17.6.2

Predict the structures of A and B in the following reaction:

The importance of sulfonate esters as intermediates in many substitution reactions cannot be overstated. A rigorous proof of the configurational inversion that occurs at the substitution site in Sn2 reactions makes use of such reactions. An example of such a proof is displayed below.

**Dehydration of Alcohols to Yield Alkenes**

One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.
The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

- 1° alcohols: 170° - 180°C
- 2° alcohols: 100°– 140 °C
- 3° alcohols: 25°– 80°C

If the reaction is not sufficiently heated, the alcohols do not dehydrate to form alkenes, but react with one another to form ethers (e.g., the Williamson Ether Synthesis).

Alcohols are amphoteric; they can act both as acid or base. The lone pair of electrons on oxygen atom makes the –OH group weakly basic. Oxygen can donate two electrons to an electron-deficient proton. Thus, in the presence of a strong acid, R—OH acts as a base and protonates into the very acidic alkyloxonium ion $\text{+OH}_2^-$ (The pKa value of a tertiary protonated alcohol can go as low as -3.8). This basic characteristic of alcohol is essential for its dehydration reaction with an acid to form alkenes.

Mechanism for the Dehydration of Alcohol into Alkene

Different types of alcohols may dehydrate through a slightly different mechanism pathway. However, the general idea behind each dehydration reaction is that the –OH group in the alcohol donates two electrons to H$^+$ from the acid reagent, forming an alkyloxonium ion. This ion acts as a very good leaving group which leaves to form a carbocation. The deprotonated acid (the nucleophile) then attacks the hydrogen adjacent to the carbocation and form a double bond.

Primary alcohols undergo bimolecular elimination (E2 mechanism) while secondary and tertiary alcohols undergo unimolecular elimination (E1 mechanism). The relative reactivity of alcohols in dehydration reaction is ranked as the following

Methanol < primary < secondary < tertiary

Primary alcohol dehydrates through the E2 mechanism. Oxygen donates two electrons to a proton from sulfuric acid H$_2$SO$_4$, forming an alkyloxonium ion. Then the nucleophile HSO$_4^-$ back-side attacks one adjacent hydrogen and the alkyloxonium ion leaves in a concerted process, making a double bond.
Secondary and tertiary alcohols dehydrate through the E1 mechanism. Similarly to the reaction above, secondary and tertiary \(-\text{OH}\) protonate to form alkylloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the \(\text{HSO}_4^-\) ion) then abstracts a proton from an adjacent carbon, forming a double bond. Notice in the mechanism below that the alkene formed depends on which proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. Recall the general rule that more substituted alkenes are more stable than less substituted alkenes, and \(\text{trans}\) alkenes are more stable than \(\text{cis}\) alkenes. Therefore, the \(\text{trans}\) diastereomer of the 2-butene product is most abundant.

**Dehydration reaction of secondary alcohol**

The dehydration mechanism for a tertiary alcohol is analogous to that shown above for a secondary alcohol.

The E2 elimination of 3º-alcohols under relatively non-acidic conditions may be accomplished by treatment with phosphorous oxychloride (POCl\(_3\)) in pyridine. This procedure is also effective with hindered 2º-alcohols, but for unhindered and 1º-alcohols an \(\text{S}_2\) chloride ion substitution of the chlorophosphate intermediate competes with elimination.

Examples of these and related reactions are given in the following figure. The first equation shows the dehydration of a 3º-alcohol. The predominance of the non-Zaitsev product (less substituted double bond) is presumed due to steric hindrance of the methylene group hydrogen atoms, which interferes with the approach of base at that site. The second example shows two elimination procedures applied to the same 2º-alcohol. The first uses the single step POCl\(_3\) method, which works well in this case because \(\text{S}_2\) substitution is retarded by steric hindrance. The second method is another example in which an intermediate sulfonate ester confers halogen-like reactivity on an alcohol. In every case the anionic leaving group is the conjugate base of a strong acid.
Conversion of Alcohols into Esters

Acid chlorides react with alcohols to form esters

\[
\text{Acid Chloride} + \text{Alcohol} \rightarrow \text{Ester} + \text{HCl}
\]

Example 17.6.3

Exercises

Questions

Q17.6.1

Draw the expected product of the reaction of cyclohexanol with the following reagents.

(a) CrO₃, H₂SO₄, H₂O (b) Dess-Martin Periodinane (c) SOCl₂ (d) NaH and 1-bromoethane (e) PBr₃
Q17.6.2
Starting with cyclohexanol, describe how you would prepare the following?

(a) cyclohexyl acetate (b) 1-allylcyclohexan-1-ol (c) cyclohexene (d) ethoxycyclohexane

Q17.6.3
In cyclohexanone, a ketone, indicate the polarity of the bond between oxygen and carbon.

Q17.6.4
In the dehydration of 1-methylcyclohexanol, which product is favored?

\[
\text{CH}_3\text{C}_6\text{H}_9\text{OH} \xrightarrow{\text{H}_2\text{SO}_4, \text{Heat}} \text{CH}_3\text{C}_6\text{H}_8\text{CH}=\text{CH}_2
\]

Q17.6.5
In the dehydration of this diol the resulting product is a ketone. Draw the mechanism of its formation. (Hint a rearrangement occurs)

\[
\text{HOCH}_2\text{OH} \xrightarrow{\text{H}_2\text{SO}_4, \text{Heat}} \text{COCH}_2\text{CH}_3
\]

Q17.6.6
Draw the mechanism of the reaction of thionylchloride with cyclohexanol, given below.

\[
\text{OH} \xrightarrow{\text{SOCl}_2} \text{Cl}
\]

Q17.6.7
Draw an arrow pushing mechanism for the acid catalyzed dehydration of the following alcohol, make sure to draw both potential mechanisms. Assume no rearrangement for the first two product mechanisms. Which of these two would likely be the major product? If there was a rearrangement, draw the expected major product.
Q17.6.8

The following epoxide can be transformed into an alcohol using a grignard reagent, take for example allylmagnesium chloride. Draw the product of the treatment of this epoxide with this grignard after being worked up with H\textsubscript{2}O. Note the stereochemistry and also remember that benzylic carbons are good Sn2 electrophiles.

Q17.6.9

As seen in the previous example, there are many examples of chiral compounds containing alcohols. One common example of these are sugars, is the given the following sugar, allitol, also chiral?

Solutions

S17.6.1

(a)

(b)
S17.6.2

a. This can be seen as a transesterification, acid and some other ester would be needed to form cyclohexylacetate
b. First, oxidize the alcohol to a ketone, take for example Dess-Martin Periodinane, then use an allyl grignard to form 1-allylcyclohexan-1-ol
c. Alcohols can dehydrate to form alkenes under acidic conditions, so using anhydrous acid and heat would yield cyclohexene
d. The alcohol can also be a nucleophile, perform a halogen substitution, using 1-X ethane, to yield ethoxycyclohexane

S17.6.3

Oxygen is more electronegative than carbon creating the polar bond. This is the basis for the carbon's electrophilicity.

S17.6.4

The more substituted alkene is favored, as more substituted alkenes are relatively lower in energy.

S17.6.5
This is also known as the Pinacol rearrangement.

Note how the carbocation after the rearrangement is resonance stabilized by the oxygen.
The major product of this mechanism would be the more highly substituted alkene, or the product formed from the red arrows.

Note the secondary carbocation adjacent a tertiary carbon center, if there were a hydride transfer (rearrangement) to form a tertiary carbocation the following would be the major product. The minor product being the same product as the one formed from the red arrows.

This compound actually has a plane of symmetry, the plane parallel to the carbon chain/backbone. So, it is not chiral, also called a meso compound.

**Contributors and Attributions**

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