Objectives

After completing this section, you should be able to

1. write an equation to illustrate the formation of a Grignard reagent.
2. write a general equation to represent the reaction of an aldehyde or ketone with a Grignard reagent.
3. write the detailed mechanism for the reaction of an aldehyde or ketone with a Grignard reagent.
4. identify the product formed from the reaction of a given aldehyde or ketone with a given Grignard reagent.
5. identify the carbonyl compound, the Grignard reagent, or both, needed to prepare a given alcohol.
6. write the equation to describe the reaction of an ester with a Grignard reagent.
7. identify the product formed from the reaction of a given ester with a given Grignard reagent.
8. discuss the limitations of Grignard reagent formation, and determine whether a given compound can be used to form such a reagent.

Study Notes

Before you begin this section, you may wish to review Section 10.6 which discusses the formation of Grignard reagents. Grignard reagents are among the most frequently used reagents in organic synthesis. They react with a wide variety of substrates; however, in this section, we are concerned only with those reactions that produce alcohols. Notice that in a reaction involving a Grignard reagent, not only does the functional group get changed, but the number of carbon atoms present also changes. This fact provides us with a useful method for ascending a homologous series. For example:

\[
\begin{align*}
\text{CH}_3\text{OH} & \xrightarrow{\text{SOCl}_2} \text{CH}_3\text{Cl} \xrightarrow{\text{Mg\ ether}} \text{CH}_3\text{MgCl} \xrightarrow{1.1\text{CHO, } 2\text{H}_2\text{O}} \text{CH}_3\text{CH}_2\text{OH}
\end{align*}
\]

One important route for producing an alcohol from a Grignard reagent has been omitted from the discussion in the reading. It involves the reaction of the Grignard reagent with ethylene oxide to produce a primary alcohol containing two more carbon atoms than the original Grignard reagent.

As mentioned in the reading, both organolithium and Grignard reagents are good nucleophiles. They also act as strong bases in the presence of acidic protons such as –CO$_2$H, –OH, –SH, –NH and terminal alkyne groups. Not only do acidic protons interfere with the nucleophilic attack on the carbonyl of these organometallic reagents, if the starting materials possess any acidic protons, reagents cannot be generated in the first place. They are also the reason these reactions must be carried out in a water-free environment.

Another limitation of preparing Grignard and organolithium reagents is that they cannot already contain a carbonyl group (or other electrophilic multiple bonds like C\$\text{O}\$ C\$\text{N}\$ C\$\text{S}\$ N\$\text{O}\$ S\$\text{O}\$) because it would simply react with itself.

A summary of the methods used to prepare alcohols from Grignard reagents is provided below.
Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.

Both Grignard and Organolithium Reagents will perform these reactions

Addition to formaldehyde gives 1° alcohols

Addition to aldehydes gives 2° alcohols
Addition to ketones gives 3° alcohols

Example 17.5.1

Mechanism for the Addition to Carbonyls

The mechanism for a Grignard agent is shown. The mechanism for an organometallic reagent is the same.
1) Nucleophilic attack

\[
\begin{align*}
\text{R} & \quad \text{MgX} \\
\text{C} & \quad \text{O} \\
\text{[MgBr]} & \quad \text{R}
\end{align*}
\]

2) Protonation

\[
\begin{align*}
\text{C} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{R} & \quad \text{C} \\
\text{R} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{R} & \quad \text{C} \\
\text{R} & \quad \text{OH} \\
\text{H}_2\text{O} & \quad +
\end{align*}
\]

Grignard reagents convert esters to \(3^\circ\) alcohols

In effect, the Grignard reagent adds twice.

\[
\begin{align*}
\text{O} & \quad \text{C} \\
\text{C} & \quad \text{O} \\
\text{R} & \quad \text{O} \\
\text{R'} & \quad \text{1) } 2 \text{R''MgBr} \\
\text{2) } \text{H}_3\text{O}^+ & \quad \text{OH} \\
\text{R} & \quad \text{C} \\
\text{R'} & \quad \text{H} \\
\text{H}_2\text{O} & \quad +
\end{align*}
\]

Ester

\[
\begin{align*}
\text{R} & \quad \text{C} \\
\text{R'} & \quad \text{R'} \\
\text{3}^\circ \text{ Alcohol}
\end{align*}
\]

Example 17.5.2

\[
\begin{align*}
\text{C} & \quad \text{O} \\
\text{C} & \quad \text{O} \\
\text{C} & \quad \text{O} \\
\text{CH}_3 & \quad \text{1) } 2 \text{CH}_3\text{CH}_2\text{MgBr} \\
\text{2) } \text{H}_3\text{O}^+ & \quad \text{OH} \\
\text{CH}_2\text{CH}_3 & \quad +
\end{align*}
\]

Limitation of Organometallic Reagents

Edit section

As discussed above, Grignard and organolithium reagents are powerful bases. Because of this they cannot be used as nucleophiles on compounds which contain acidic hydrogens. If they are used they will act as a base and deprotonate the
acidic hydrogen rather than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used are: alcohols, amides, 1° amines, 2° amines, carboxylic acids, and terminal alkynes.

Exercises

Questions

Q17.5.1

If allylmagnesium chloride were added to a solution of the following compound and then worked-up with acid, the product would contain a chiral center. Would the product be a racemic mixture or an enatiomerically pure product? Draw both enantiomers.

Q17.5.2

What combination of carbonyl compound and grignard (use MgBr) reagent would yield the following alcohols (after workup)?

(a)
Q17.5.3

Fill in the blanks of the following reaction scheme.

Solutions

S17.5.1

The result would be a racemic mixture of the following.

\( s \) enantiomer \hspace{1cm} \( r \) enantiomer
S17.5.2

(a)  
\[
\text{\begin{tikzpicture}
  \node (a) at (0,0) {O};
  \node (b) at (-1,-1) {\text{MgBr}};
  \node (c) at (-3,-2) {\text{BrMg}};
  \end{tikzpicture}}
\]

(b)  
\[
\text{\begin{tikzpicture}
  \node (a) at (0,0) {\text{CO}};
  \node (b) at (-1,-1) {\text{BrMg}};
  \end{tikzpicture}}
\]

(c)  
\[
\text{\begin{tikzpicture}
  \node (a) at (0,0) {\text{CO}};
  \node (b) at (-1,-1) {\text{BrMg}};
  \end{tikzpicture}}
\]

(d)  
\[
\text{\begin{tikzpicture}
  \node (a) at (0,0) {\text{MgBr}};
  \node (b) at (1,-1) {\text{O}};
  \end{tikzpicture}}
\]

S17.5.3

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