Objectives

After completing this section, you should be able to

1. write an equation to illustrate the three-step Stork enamine reaction.
2. write a detailed mechanism for each of the three steps of the Stork enamine reaction.
3. identify the product formed, and the various intermediates (i.e., the enamine, the Michael-type adduct), in a given Stork enamine reaction.
4. identify the reagents needed to synthesize a given compound by a Stork enamine reaction.

Key Terms

• Stork enamine reaction

Study Notes

If we try to use a monoketone as a donor molecule in a Michael reaction, we will obtain a poor yield. An alternative route to the product that would be expected from such a synthesis is via the Stork enamine reaction. You may wish to review the formation of enamines (from ketones and secondary amines) before you proceed with this section; if so, review Section 19.8.

As previously seen, aldehydes and ketones react with \(2^\circ\) amines to reversibly form enamines.

Example

\[
\begin{align*}
\text{2}^\circ\text{Amine} & \quad + \quad \text{Ketone} \quad \xrightleftharpoons{\ \text{H}_2\text{O}^+\text{, }-\text{H}_2\text{O}} \quad \text{Enamine} \\
\end{align*}
\]

Reversible

Enamines act as nucleophiles in a fashion similar to enolates. Because of this enamines can be used as synthetic equivalents as enolates in many reactions. This process requires a three steps: 1) Formation of the enamine, 2) Reaction with an electrophile to form an iminium salt, 3) Hydrolysis
of the iminium salt to reform the aldehyde or ketone. Some of the advantages of using an enamine over and enolate are enamines are neutral, easier to prepare, and usually prevent the overreaction problems plagued by enolates. These reactions are generally known as the Stork enamine reaction after Gilbert Stork of Columbia University who originated the work.

![Chemical structures showing enamine formation and alkylation.]

Typically we use the following $2^\circ$ amines for enamine reactions:

- Pyrrolidine
- Piperidine
- Morpholine

Enamines undergo an $S_N2$ reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl.

Individual steps:

1) Formation of an enamine

2) $S_N2$ Alkylation
3) Reform the carbonyl by hydrolysis

All three steps together:

Enamine can react with acid halides to form β-dicarbonyls

1) Formation of the enamine

2) Nucleophilic attack
3) Leaving group removal

4) Reform the carbonyl by hydrolysis

All three steps together:

Enamines, like other weak bases, add 1,4 to enones. The end product is a 1,5 dicarbonyl compound.
Questions

Q23.11.1

Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

(a)

(b)

(c)

Q23.11.2

Propose a synthesis for the following compounds via an enamine.

(a)
Solutions
S23.11.1
S23.11.2

(a) cyclopentanone enamine + 2-cyanopropene

(b) cyclohexanone enamine + ethyl acrylate

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