Enamine Reactions: 2-Acetylcylohexanone


Introduction:

Hydrogens on the [\(-\)]-carbon of ketones, aldehydes, and other carbonyl compounds are weakly acidic and are removed in a basic solution (Equation 1). Although resonance stabilizes the conjugate base \(A\) in such a reaction, the equilibrium is still unfavorable because of the high \(pK_a\) (about 20) of a carbonyl compound.

\[
\begin{align*}
\ce{R-O-R + OH^- &<=> [R-O-R^- + A] + H_2O} \\
\text{Typically, carbonyl compounds are alkylated (Equation 2) or acylated (Equation 4) only with difficulty in the presence of aqueous sodium hydroxide because of more important secondary side reactions (Equations 3, 5, and 6). In effect, the concentration of the nucleophilic conjugate base species (A in Equation 1) is low because of the unfavorable equilibrium (Equation 1), while the concentration of the completing nucleophile (OH\(^-\)) is very high. A significant side reaction occurs when hydroxide ion reacts with an alkyl halide by Equation 3 or acyl halide by Equation 5. In addition, the conjugate base can react with unreacted carbonyl compound by an aldol condensation reaction (Equation 6). Enamine reactions, described in the next section, avoid many of the problems described here.
\end{align*}
\]

Alkylation

\[
\begin{align*}
\ce{R-O-R + R-X &<=> R-O-R + X^-} \\
\text{Small Amount}
\end{align*}
\]

Acylation

\[
\begin{align*}
\ce{H-O^- + R-O-R + HO^- &<=> R-OH + R-O^-} \\
\text{Large Amount}
\end{align*}
\]

Aldol condensation

\[
\begin{align*}
\ce{R-O-R + R-O-R &<=> R-O-R + R-OH} \\
\text{Large Amount}
\end{align*}
\]
Formation and Reactivity of Enamines

Enamines are prepared easily from carbonyl compounds (for example, cyclohexanone) and a secondary amine (for example, pyrrolidine) by an acid-catalyzed addition-elimination reaction. An excess of the amine can be used to shift the equilibrium to the right:

\[
\text{Enamine} = \text{carbonyl compound} + \text{amine} \xrightarrow{\text{acid catalyst}} \text{amine} + \text{water}
\]

An enamine has the desirable property of being nucleophilic (carbon alkylation is more important than nitrogen alkylation) and is easily alkylated:

The key point is that the resonance hybrid B is like the resonance hybrid A shown in Equation 1. However, B has been produced under nearly neutral conditions so that it is the only nucleophile present.

Contrast this situation to the one in Equation 1 where hydroxide ion, present in a large amount, produces undesirable side reactions (Equations 3 and 5).

The alkylation step is followed by removal of the secondary amine by an acid-catalyzed hydrolysis:

Examples of Enamine Reactions
**Robinson Annelation (Ring-Formation) Reaction**

Reactions that combine the Michael addition reaction and aldol condensation to form a six-membered ring fused on another ring are well known in the steroid field. These reactions are known as **Robinson annelation** reactions.

Michael addition

\[
\text{C\text{H}_2\text{O}} \xrightarrow{\text{base}} \text{C\text{H}_2\text{O}}^- \xrightarrow{\text{H}^+} \text{C\text{H}_2\text{O}}
\]

Aldol condensation

\[
\text{C\text{H}_2\text{O}} \xrightarrow{\text{base}} \text{C\text{H}_2\text{O}}^- \xrightarrow{\text{H}^+} \text{C\text{H}_2\text{O}} \quad \xrightarrow{(2) \text{H}_2\text{O}} \text{C\text{H}_2\text{O}}
\]

Robinson annelation reactions can also be conducted by enamine chemistry. One advantage of enamines is that the unsaturated ketones are not easily polymerized under the mild conditions of this reaction. Base-catalyzed reactions often give large amounts of polymer.

**Pre-lab Question:**

1. The enamine formed from pyrrolidine and 2-methylcyclohexanone has the A structure. What reason can you give for the less substituted enamine being formed instead of the more substituted enamine B?

   ![A and B structures](image)

**The Experiment**

In this experiment, pyrrolidine reacts with cyclohexanone to give the enamine. This enamine is used to prepare 2-acetylcyclohexanone.

\[
\text{Cyclohexanone} + \text{Pyrrolidine} \xrightarrow{\text{p-Toluenesulfonic acid}} \text{Enamine}
\]

\[
\text{Enamine} + \text{Acetic anhydride} \rightarrow \text{2-Acetylcyclohexanone}
\]

**Precautions and Instructions**

Pyrrolidine and acetic anhydride are toxic and noxious. You must measure and transfer these substances in a hood. If you are not careful, the entire room will be filled with vapors of pyrrolidine, and it will not be pleasant to work in the laboratory.

The enamine should be made during the first part of the laboratory period and used as soon as possible. Once the acetic anhydride has been added, the reaction mixture must be allowed to stand in your drawer for at least 48 hours to complete the reaction. The second period is used for the work-up and column chromatography. The yields in these reactions are low (less than 50%), partly due to reduced reaction periods necessary to fit the experiment into convenient 3-hour laboratory periods.
Procedure

Part A: Preparation of the Enamine

Obtain a 14/20 50-mL round-bottom flask, a 14/20 condenser and a microscale distillation kit from the stockroom. Place 3.2 mL of cyclohexanone into a preweighed 50-mL round-bottom flask and determine the weight of the material transferred. Add 15 mL of toluene and a stir bar to the flask, clamp the flask in a heating mantle (no sand) above a magnetic stirrer. Place about 0.1 g of p-toluenesulfonic acid monohydrate in the mixture. In your hood, transfer 4.0 mL of pyrrolidine to this flask using a 1 mL pipettor 4 times. Attach the water condenser. Move the apparatus to the back of the hood to minimize pyrrolidine vapors from entering the lab. Using a heating mantle, heat under reflux for 30 minutes with stirring.

Purification by Distillation

Allow the reaction to cool somewhat and assemble a simple distillation by inserting the microscale distillation head. Cool the receiving flask in an ice bath to prevent the noxious vapors of pyrrolidine from being released into the room. Distill the mixture until the temperature reaches 108 to 110°C (boiling point of toluene) and then stop the distillation. At this point most of the remaining pyrrolidine and water have been removed. The enamine and toluene solvent remain in the distilling flask. Be sure you save this liquid for the next step. Allow the reaction mixture in the distilling flask to cool to room temperature. Remove the flask and prepare 2-acetylcyclohexanone as described in the next section. Proceed to the next step during this laboratory period. Pour the distillate, containing pyrrolidine, toluene, and water, into a suitable waste container in your hood. Rinse out flask in hood drain.

Part B: Preparation of 2-Acetylcyclohexanone

Dissolve 3.2 mL of acetic anhydride in 5.0 mL of toluene in a small beaker. Add this solution to the enamine solution contained in the round-bottom flask. Place a glass stopper in the flask, swirl it for a few minutes at room temperature, and allow the mixture to stand for at least 48 hours.

In the next lab period, add 5.0 mL of water. Attach a condenser and heat the mixture under reflux for 30 minutes to convert the acetylated enamine product to the free ketone.

Purification and Isolation

Cool the flask to room temperature. Transfer the liquid to a separatory funnel. Add 5.0 mL of water, swirl, and separate the water layer. Extract the toluene layer with 10 mL of 6M hydrochloric acid, and finally 5.0 mL of water again. Transfer the organic layer into an Erlenmeyer flask and dry over 1 g of sodium sulfate. Decant the liquid into a 25-mL round-bottom flask and remove the toluene by simple distillation or by using a rotary evaporator (preferred). Stop the distillation when the temperature goes above 110°C. Transfer the remaining liquid into test tube and evaporate the toluene in a water bath at about 70°C, using a stream of nitrogen. Watch the liquid carefully during this procedure or your product may evaporate. When the toluene has all been removed, the volume of liquid will remain constant (2 to 2.5 mL). You will purify this yellow liquid residue by column chromatography.

Dissolve the crude product in 2.5 mL of methylene chloride and load it onto a previously prepared column containing 5.0 g alumina. Elute the product using methylene chloride (should take about 20 mL) or until all the colored material has eluted off the column. Combine all fractions and evaporate off the solvent to give the 2-acetylcyclohexanone as a yellow liquid. Identify the product by IR and NMR.

Manuscript R & D

1. The enolate formed from 2-methylcyclohexanone has the following structure. What is the structure of the other possible enolate, and why is it not as stable as the one shown here?