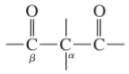
Chapter 19

Synthesis and Reactions of b-Dicarbonyl Compounds:

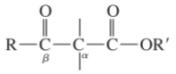
More Chemistry of Enolate Anions

ß-dicarbonyl compounds

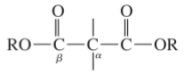
- Two carbonyl groups separated by a carbon
- Three common types



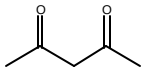
ß-diketone

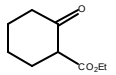


ß-ketoester



ß-diester

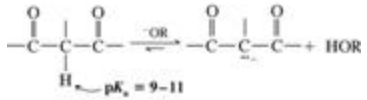


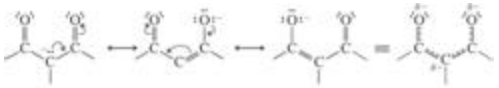


ß-dicarbonyl compounds

Protons on the a-carbon are acidic (pK_a = 9-10)

- Rresonance stabilization of the enolate by two carbonyl groups

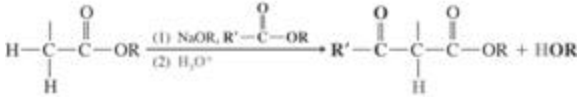




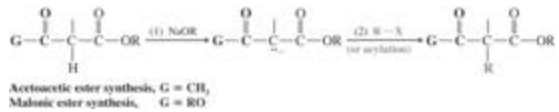
Contributing resonance structures Resonance hybrid

Why are ß-dicarbonyls useful?

1. Readily synthesized by the Claisen condensation

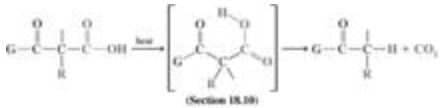


2. The acetoacetic ester and malonic acid syntheses use b-dicarbonyl compounds for carbon-carbon bond forming reactions



Acetoacetic ester synthesis, G = CH_3
Malonic ester synthesis, G = RO

- Usually conclude with decarboxylation of a b-keto acid

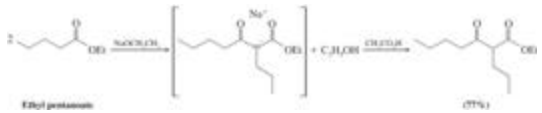


(Section 18.10)

The Claisen Condensation: Synthesis of b-Keto Esters

- Esters undergoes a Claisen condensation when treated with sodium alkoxide (ususally ethyl)
  - The product is commonly called acetoacetic ester

Sodioacetoacetic ester | (removed by distillation) | Ethyl acetoacetate (acetoacetic ester) (76%)



Ethyl pentanoate | (77%)

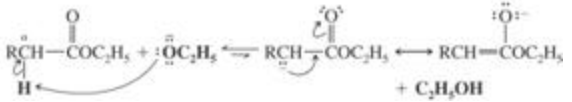
Claisen Condensation

- The overall reaction involves loss of an a hydrogen from one ester and loss of ethoxide from another

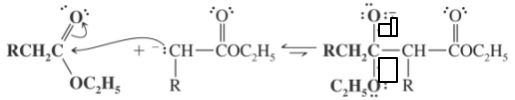
(R may also be H) | A b-keto ester

- Mechanism combines
  - enolate anion formation (Chapter 17)
  - nucleophilic addition-elimination at an ester carbonyl (Ch.18)

Step 1: formation of enolate

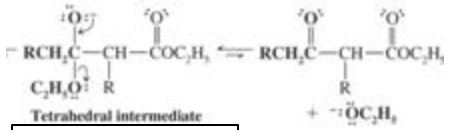


Step 2: addition of enolate nucleophile to ester carbonyl

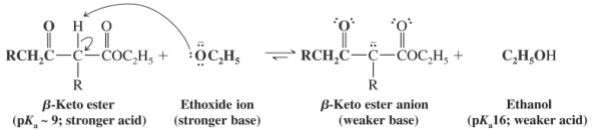


Nucleophilic addition | Tetrahedral intermediate

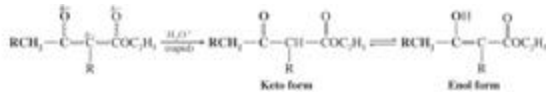
Step 3: elimination of alkoxide



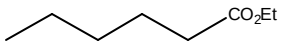
Step 4: formation of more stable enolate

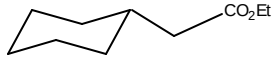


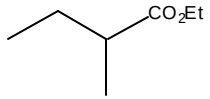
Step 5: neutralize



Which ester will not undergo Claisen condensation?

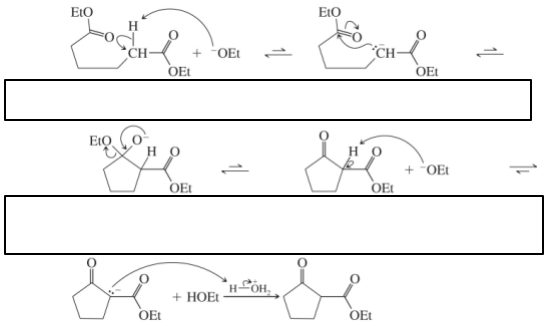
A. 

B. 

C. 

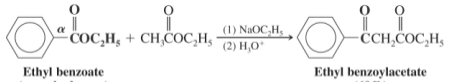
Dieckmann condensation: an intramolecular Claisen condensation

Useful for 5- and 6-membered rings
Cyclization of hexanedioic acid ester

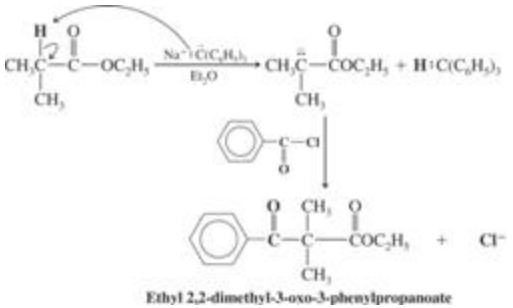


Crossed Claisen Condensations

- **Crossed Claisen condensations can lead to one major product when one of the two esters has no *a* hydrogen**



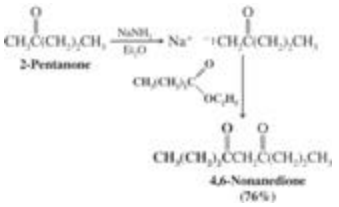
➡ Esters with one *a* hydrogen can react in Claisen condensations if they are deprotonated with a strong base and acylated with an acyl chloride



Ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate

Acylation of Other Carbanions

♦ Ketone enolates formed with strong bases can also be acylated to form *b*-dicarbonyl compounds



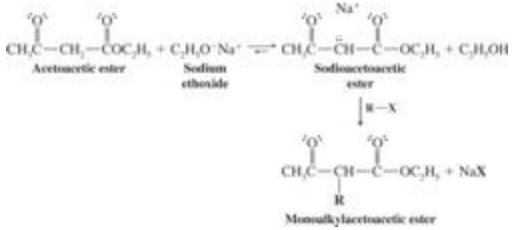
♦Note formation of the *kinetic* enolate

The Acetoacetic Ester Synthesis

♦ A route to synthesis of Methyl Ketones (Substituted Acetones)

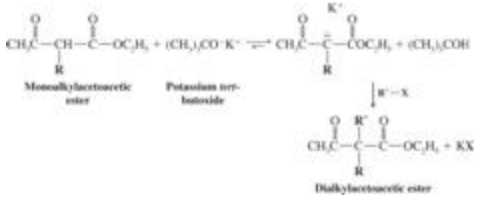
Step 1: Alkylation of the enolate derived from acetoacetic ester

➡ An S_N2 reaction with the ethyl acetoacetate enolate acting as the nucleophile



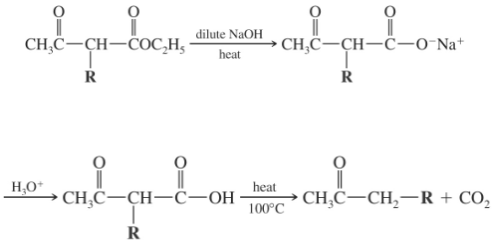
♦ A second alkylation can be performed

- A stronger base such as potassium *tert*-butoxide must be use to deprotonate the monoalkyl ester

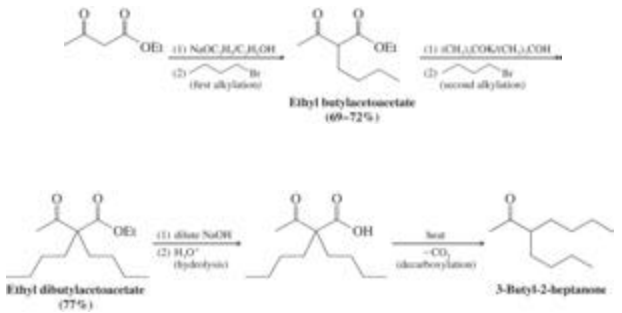


♦ **Step 2: Hydrolysis of the ester and heating of the resultant b-ketoacid causes decarboxylation**

- **The product is a substituted acetone derivative**



- **Example:**



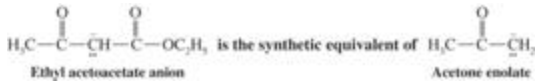
Ethyl butylacetoacetate (69–72%)

Ethyl dibutylacetoacetate (77%)

3-Butyl-2-heptanone

♦ **Ethylacetoacetate serves as *synthetic equivalent* of the acetone enolate**

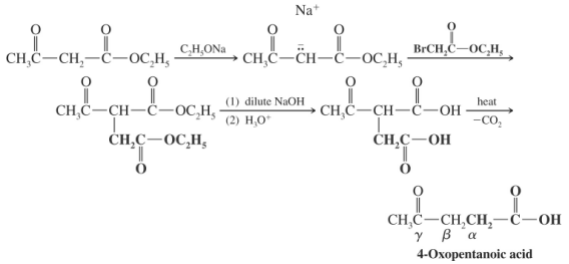
- **Activation by second carbonyl means milder conditions**



Ethyl acetoacetate anion **is the synthetic equivalent of** **Acetone enolate**

Variations on acetoacetic ester synthesis

♦ **a-halo esters plus the enolate produce g-keto acids**



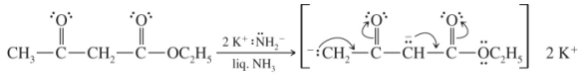
4-Oxopentanoic acid

Acylation of acetoacetic ester leads to ß-diketones

- **Use acyl halides or anhydrides**
  - The reaction is carried out in aprotic solvents such as DMF or DMSO because these will not destroy the acylating reagents

Acetoacetic Ester Dianion: Alkylation at the Terminal Carbon

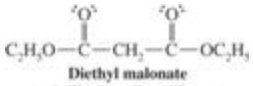
- Treating acetoacetic ester with two equivalents of a very strong base produces a dianion



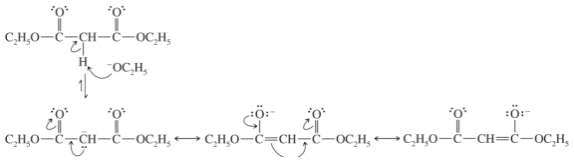
- Alkylation of the dianion occurs first at the terminal carbon
  - Terminal carbanion is more nucleophilic and more basic

Malonic Ester Synthesis: Synthesis of Substituted Acetic Acids

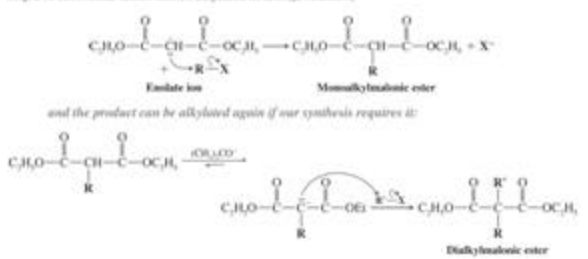
- A reaction directly analogous to the acetoacetic ester synthesis
- Except product is a substituted acetic acid



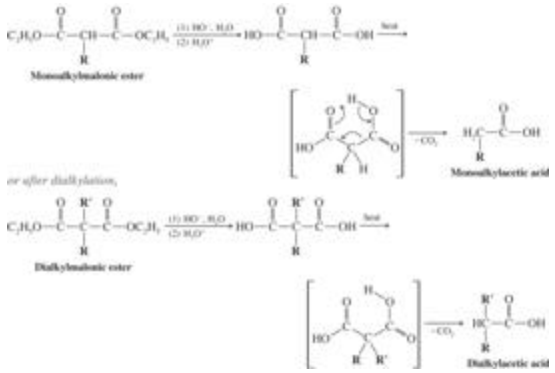
Step 1: formation of the stabilized anion



Step 2: the anion is mono- or dialkylated using S_N2 reactions

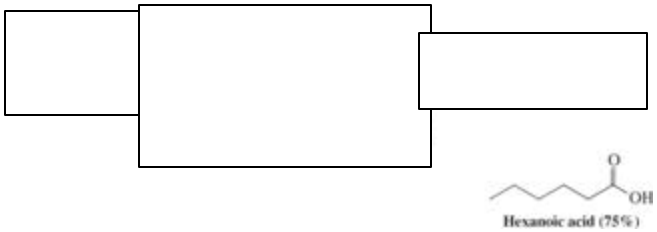


Step 3: alkylated product is hydrolyzed and decarboxylated

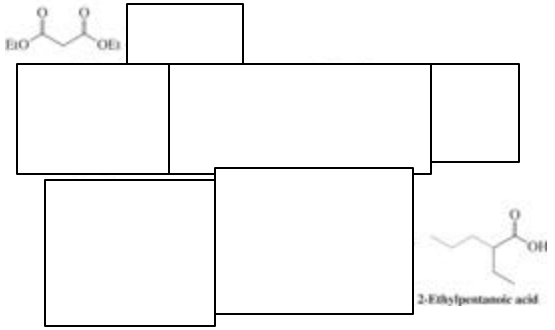


- **Diethylmalonate anion is the synthetic equivalent of acetic acid dianion**

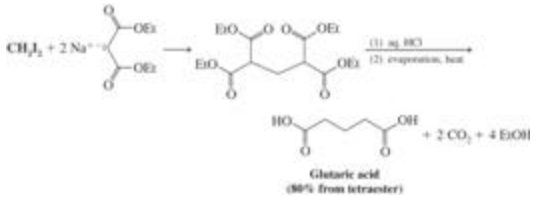
Example: malonic ester systhesis of hexanoic acid



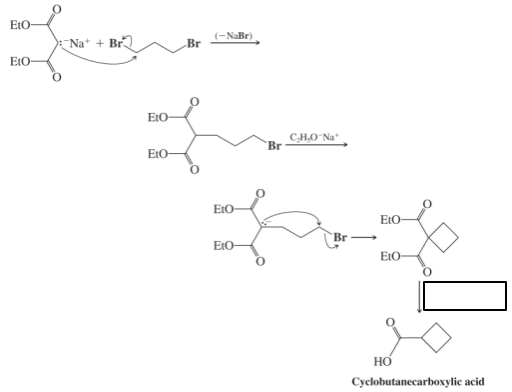
Malonic ester synthesis of 2-ethylpentanoic acid



- **Variation: By using two molar equivalents of malonate anion and a dihalide, a dicarboxylic acid is obtained**



- **Dihalides of 2 to 5 carbons can react to form rings by dialkylation of one molar equivalent of malonate**



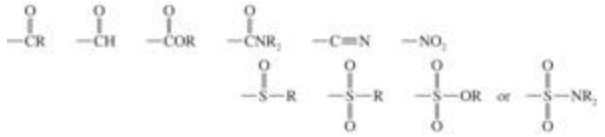
Reactions of Other Active Methylene Compounds

- **Compounds in which the hydrogen atoms of a methylene (-CH_2-) group are made acidic by two attached electron-withdrawing groups**

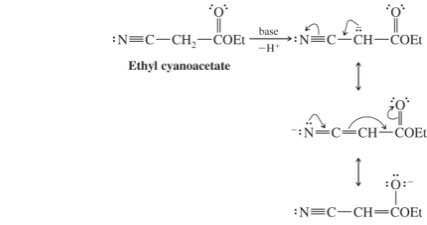
$$Z—CH_2—Z'$$

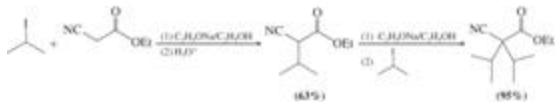
- **As with aldol condensations, a wide variety of electron-withdrawing groups can produce enhanced a hydrogen acidity**

Z, Z '=



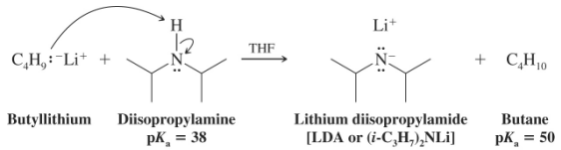
Example: Alkylation of ethyl cyanoacetate

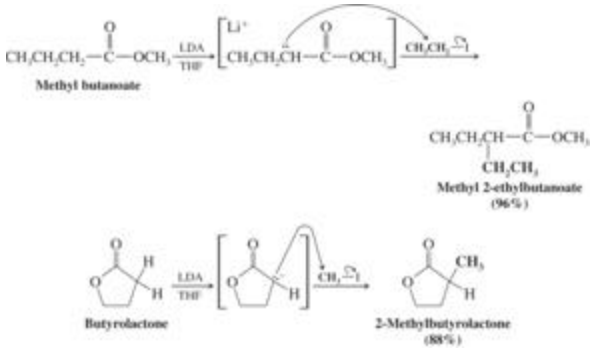




Direct Alkylation of Esters and Nitriles

- **Lithium diisopropyl amide (LDA) may be used for direct alkylation of esters and nitriles**
  - **Strong base rapidly converts all of ester or nitrile molecules into enolates so no Claisen condensation occurs**
  - **Bulky base will not react as a nucleophile at the ester carbonyl or nitrile carbon**

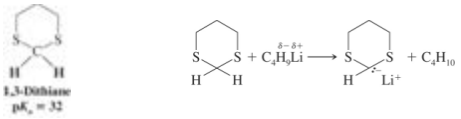




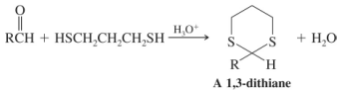
Alkylation of 1,3-Dithianes

Protons on the carbon between the sulfur atoms of a 1,3-dithiane are moderately acidic

- **Strong bases convert the dithiane to its anion**



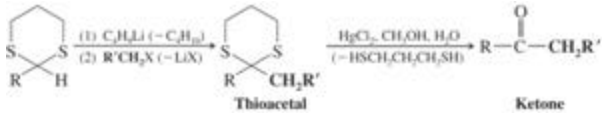
- **Dithianes are 6-membered ring thioacetals**
  - **Readily prepared from an aldehyde and the 1,3- dithiol**



Dithioacetal anion = synthetic equivalent of aldehyde carbonyl anion

An aldehyde can be converted to a ketone:

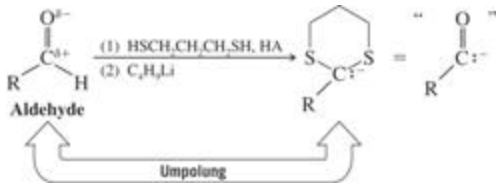
1. **by preparing the thioacetal from the aldehyde**
2. **alkylating the corresponding 1,3-dithiane anion**
3. **hydrolyzing the thioacetal**



Dithioacetal anion = synthetic equivalent of aldehyde carbonyl anion

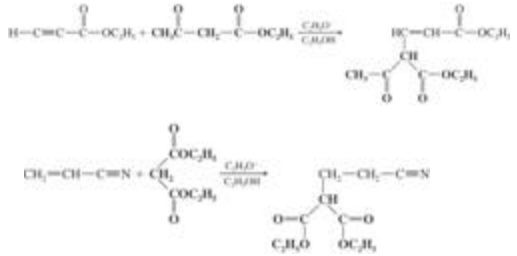
The reversal of the polarity of the carbonyl carbon in this series of reactions is called *umpulong*

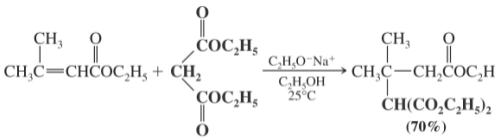
- **An aldehyde carbonyl carbon normally has a d+ charge and is electrophilic**
- **In dithioacetal alkylation, the equivalent of the aldehyde carbon is nucleophilic**



Michael Addition Reactions

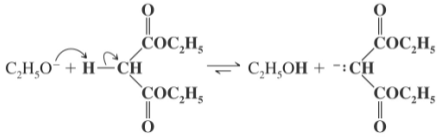
- **Conjugate addition of an enolate to an *a*,*b*-unsaturated carbonyl compound**
- **Michael additions take place with a wide variety of active methylene and *a*,*b*-unsaturated compounds**





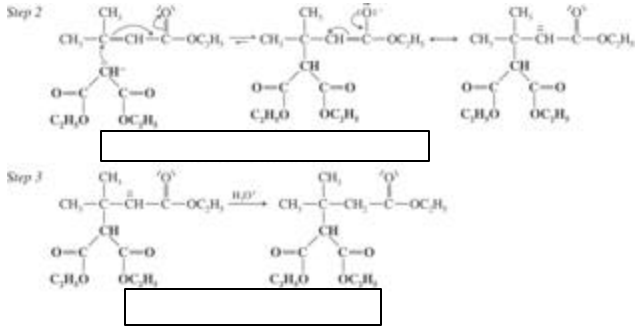
Mechanism:

Step 1



Step 2

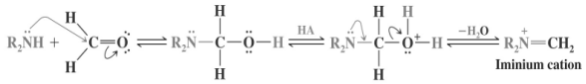
Step 3



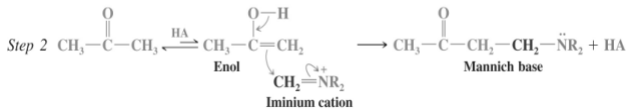
Recall that with weaker bases (like these stabilized enolates), 1,4-addition is favored

Mechanism for the Mannich Reaction

Step 1: addition of amine to carbonyl leads to iminium cation



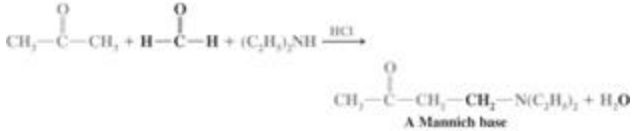
Step2: enolate of carbonyl reacts with iminium ion



Product is a ß-aminoketone (also called a Mannich base)

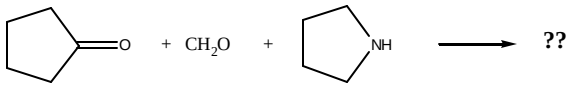
The Mannich Reaction

- **Compounds which can form enols react with imines or iminium ions derived from formaldehyde**
  - **Primary or secondary amines can be used to form the corresponding formaldehyde imines or iminium ions**

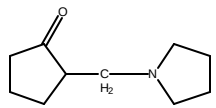


Net effect: adding – CH_2-NR_2 to the a-position of a carbonyl

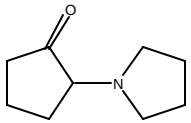
What is the product?



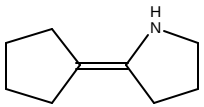
A.



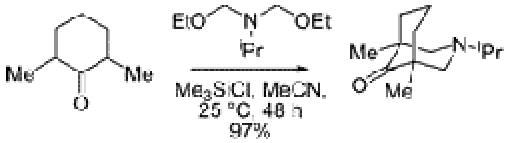
B.



C.

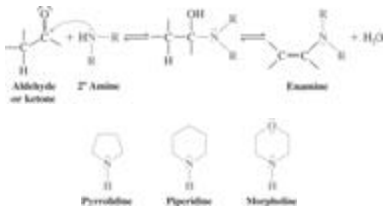


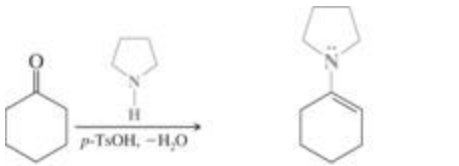
Example of Mannich reaction from recent literature



Stork Enamine Reactions

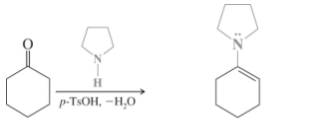
- **Aldehydes and ketones react with secondary amines to form enamines**
  - Cyclic amines are often used
  - The reaction is catalyzed by acid
  - Removal of water drives enamine formation to completion





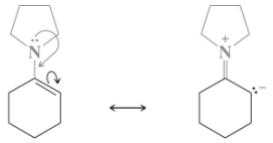
N-(1-Cyclohexenyl)pyrrolidine
(an enamine)

Typical enamine

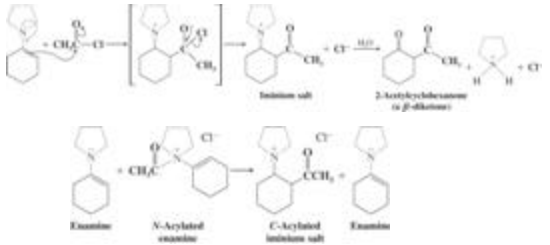


N-(1-Cyclohexenyl)pyrrolidine

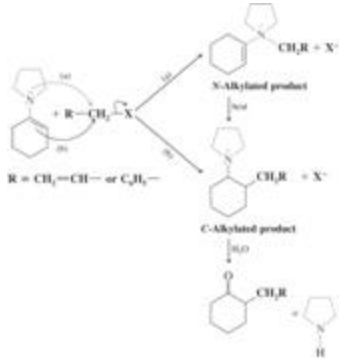
- **Enamines have a nucleophilic carbon and are the equivalent of ketone and aldehyde enolates**
  - The nitrogen of enamines is also nucleophilic



- **Enamines can be acylated, alkylated, or used in Michael reactions**
  - The iminium intermediate is then hydrolyzed by adding water
- ***C*-Acylation leads directly to β-diketones**
  - ***N*-acylated products can be formed, but they are unstable and act as acylating agents themselves**

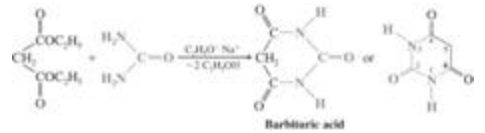


- **Alkylation of enamines can lead to some *N*-alkylation**
  - **The *N*-alkylated product can often be converted to the *C*-alkylated product by heating**



Barbiturates – simple organic molecules

Reaction of diethyl malonate with urea in the presence of sodium ethoxide produces barbituric acid



- **Barbiturates are derivatives of barbituric acid**
  - **Barbiturates are used in medicine as soporifics (sleep inducers)**