

Chemistry 204: Enolate Anions and Enamines

Brief review:

- aldehydes and ketones: nucleophilic addition

- carboxylic acid derivatives

Another important reaction of carbonyl compounds is α -substitution:

Keto-enol tautomerism

- aldehydes and ketones exist in solution as equilibrium mixture of two isomeric forms: keto form and enol form
- two isomers are called tautomers
- this acid or base-catalyzed equilibrium is called tautomerism

mechanism (base catalysis):

mechanism (acid catalysis)

Normally, with simple aldehydes and ketones, the keto tautomer predominates at equilibrium:

For β -diketones, the enol form contributes more to the keto-enol equilibrium and, in non-polar solvents, may predominate.

Although enols do occur as intermediates in certain organic reactions, we will concentrate on the use of **enolate anions**.

Acidity of α -protons: Enolate Anion Formation

How acidic are C-H bonds adjacent to a carbonyl or nitrile function?

Thus, enolate anions can be formed using appropriate bases:

This method for forming a solution of enolate anions is **most important** in organic chemistry!

If the C-H bond is adjacent to two C=O groups, the α -proton is **considerably** more acidic.

Reactivity of Enolate Anions

As shown above, enolate anions have two sites that are nucleophilic—the oxygen atom and the α -carbon.

Alkylation of Enolate Ions

- possibly most important reaction of enolate ions
- forms carbon-carbon bonds
- will discuss a number of important methods

The Malonic Ester Synthesis and the Acetoacetic Ester Synthesis

- alkylation, hydrolysis and decarboxylation of 1,3-diester and β -ketoesters
- general synthesis of structurally complex carboxylic acids and ketones

general reaction (malonic ester synthesis):

The monoalkylated malonic ester can be alkylated a second time:

How does the decarboxylation reaction occur?

general reaction (acetoacetic ester synthesis)

The decarboxylation takes place via a mechanism identical with that for the decarboxylation of a malonic acid:

Summary

Direct Alkylation of Ketones, Esters and Nitriles

Ketones, esters and nitriles can be alkylated directly. In these cases, one **must** use a **strong, sterically hindered** base to remove the α -proton.

strong: because these compounds are not very acidic

hindered: to prevent addition of the base to the carbonyl or the $\text{C}\equiv\text{N}$ function

A very useful base: lithium diisopropylamide (LDA)

Because these reactions proceed through a $\text{S}_{\text{N}}2$ mechanism, only reactive electrophiles (1° alkyl halides) work well in these reactions.

Carbonyl condensation reactions

Carbonyl condensation reactions are processes that take place between two carbonyl compounds.

Aldol condensation

- very important reaction involves enolate anion formation and carbonyl addition

mechanism:

If one attempts to carry out a “mixed” aldol condensation between two similar aldehydes, a complex mixture of products is formed.

What happens when aldol condensations are attempted with ketones? Here the equilibrium favors the ketones, not the aldol product.

This condensation can be “forced” towards product by heating to cause dehydration and to remove water as it is formed.

With certain highly electrophilic aldehydes, crossed aldol condensations are possible.

Crossed aldol condensations are also possible when one of the partners is quite acidic and is readily transformed into an enolate anion, while the other partner self-condenses slowly.

The aldol condensation is an important method for preparing α,β unsaturated aldehydes and ketones. These products are stabilized by partial delocalization of the π electrons.

Intramolecular aldol condensations of dicarbonyl compounds constitute a very important method for forming cyclic compounds. This is the **major** application of the aldol condensation.

The aldol condensation in molecule construction:

The Claisen condensation

- important reaction involving the condensation of an enolate derived from an ester with a neutral ester molecule. Somewhat analogous to the aldol condensation of aldehydes.

mechanism:

Mixed Claisen condensations are successful when one of the esters has no α -hydrogens.

One can also carry out a related condensation between a ketone and an ester. The pK_{A} of a ketone is lower than that of an ester. If an excess of ester is used, one can obtain primarily one product (a β -diketone).

Intramolecular Claisen condensations (Dieckmann condensations) are important reactions for the preparation of cyclic systems (particularly 5 and 6 membered rings). This is a **major application** of the Claisen condensation.