

α -Substitution and Condensation Reactions of Enols and Enolate ions

Reading: Wade chapter 22, sections 21-1- 21-19

Study Problems: 22-62, 22-63, 22-64, 22-65, 22-67, 22-69, 22-70, 22-71, 22-73, 22-77, 22-81

Key Concepts and Skills:

- Show how enols and enolate ions act as nucleophiles; give mechanisms for acid and base-catalyzed alpha halogenation, explaining why multiple halogenation is common under basic conditions
- Show how alkylation and acylation of enamines and lithium enolates is used synthetically to make substituted ketones. Give mechanisms for these reactions
- Predict the products of aldol and crossed aldol reactions before and after dehydration of the aldol product, giving mechanisms for the acid and base-catalyzed processes.
- Predict the products of Claisen and crossed Claisen condensations, and propose mechanisms.
- Show how the malonic ester and acetoacetic ester synthesis are used to make substituted acetic acids and acetones
- Predict the products of Michael additions, and show how to use these reactions in synthesis. Show the general mechanism of the Robinson annulation, and use it to form cyclohexenone ring systems.

Lecture Topics:

I. General Form of Alpha Substitutions and Condensations

In alpha substitution, a proton on the carbon alpha to a carbonyl group is replaced by an electrophile; in a condensation, the electrophile is a carbonyl compound which can either undergo addition (aldehydes and ketones) or substitution (carboxylic acid derivatives).

Note that alpha substitution and carbonyl condensation are among the most useful carbon-carbon bond-forming reactions in chemistry.

II. Keto-Enol Tautomerism

Ketones and aldehydes are in equilibrium with their enol isomers. This phenomenon is known as tautomerism, and tautomers are isomers that interconvert by migration of a proton and the movement of a double bond. Note that tautomers are different compounds which are isolable in some circumstances; they are not resonance forms (which are different representations of the same structure).

Acids and bases catalyze the interconversion of keto and enol tautomers:

Since the enol contains an sp^2 hybridized alpha carbon, acid or base catalyzed keto-enol tautomerism can result in racemization of optically active ketones:

III. Acidity of Ketones and Aldehydes

Ketones and aldehydes are weak acids that react with bases to form enolates in equilibrium amounts. Note that when hydroxide or alkoxide bases are used, the equilibrium concentration of the enolate is small:

LDA is a strong amide base generated from the reaction of diisopropyl amine and butyllithium. Since the pK_a of diisopropylamine is 40, the lithium amide is easily able to quantitatively deprotonate ketones at the alpha position; since LDA is so sterically bulky, it will not add to the carbonyl carbon of ketones and aldehydes and is thus non-nucleophilic (yet highly basic).

IV. Reactions of Enols and Enolates with Electrophiles

A. S_N2 reactions of enolates

Enolates can nucleophilically attack unhindered alkyl halides and tosylates by the S_N2 mechanism. Alkylation usually takes place at the carbon of an enolate, allowing restoration of the strong C=O.

Enolate alkylation at carbon is a useful means of introducing carbon-carbon bonds next to the carbonyl group. For ketones, this process works particularly well if there is only one type of α hydrogen which can be abstracted by base:

For situations where multiple different protons can be abstracted, it is often possible to obtain products selectively by altering reaction conditions. Under thermodynamic conditions (high temperature), the more stable enolate is formed preferentially and will be alkylated; under kinetic conditions (low temperature), the least hindered proton will be abstracted, leading to a less substituted enolate that undergoes alkylation.

B. Enamines

The use of enamines instead of enols and enolates for α -alkylation of carbonyl compounds is a milder alternative to the use of strong bases such as LDA. Treatment of a ketone with a secondary amine under acidic, dehydrating conditions gives an enamine, whose second resonance form has a negative charge on carbon (indicating the primary site of nucleophilicity)

Enamines react with alkyl halides and tosylates by S_N2 reaction and with acyl chlorides by nucleophilic acyl substitution. The ketone can be regenerated by treatment of the enamine (or iminium ion) with aqueous acid. This process for ketone alpha alkylation is known as the **Stork Enamine Reaction**.

C. Bromine as an electrophile

α -Halogenation of ketones occurs under acidic or basic conditions. Under basic conditions, more than one halogen is often introduced at an alpha carbon atom; under acidic conditions, mono halogenation predominates.

The alpha halo ketone products can be used in the synthesis of α,β -unsaturated ketones. Treatment with base results in an E2 elimination:

Base-promoted α -halogenation often leads to the introduction of multiple halogen substituents. The reason is that α -haloketones are more acidic than ketones and are thus more readily enolized under basic conditions.

The **Haloform Reaction** takes advantage of the multiple brominations encountered under basic conditions to degrade methyl ketones to carboxylic acids. Treatment of a methyl ketone with excess bromine in the presence of base produces a tribromomethyl ketone; the CBr_3 group is a good leaving group, so attack of hydroxide at the carbonyl carbon results in nucleophilic acyl substitution:

The Hell-Vollhard-Zelinsky Reaction

The HVZ reaction involves conversion of carboxylic acids to α -bromo acids and acid derivatives.

Bromine and PBr_3 react with acids to form acyl bromides that readily enolize and trap bromine at the alpha carbon. Workup with water gives the α -bromo acid; workup with an alcohol gives the α -bromo ester.