Alpha Carbon Chemistry

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The α Carbon Proton

- Carbon next to carbonyl carbon is α carbon.
- Due to polarity the protons on alpha carbon are slightly acidic.



 After abstraction of proton by strong base, the resulting ion is resonance stabilized, however both structures can be isolated hence they are not resonance structures but isomers – called tautomers.



Resonance-stabilized anion

Keto-Enol Formation in Acids/Bases

 Carbonyl compounds can be converted to keto-enols depending on acidic or basic conditions, and the keto-enol are then interconvertible.



Keto-Enol Tautomers for Chiral Compounds

• If a carbon is chiral then chirality is lost.



pKa for Some Carbonyl Compounds

Table 22.1 Acidity Constants for Some Organic Compounds

Functional group	Example	pKa			
	0			0	
Carboxylic acid	СН3СОН	5	Aldehyde	сн ₃ ён	17
	0 0			0	
1,3-Diketone	CH ₃ CCH ₂ CCH ₃	9	Ketone	CH ₃ CCH ₃	19
	0 0			0	
3-Keto ester	CH ₃ CCH ₂ COCH ₃	11	Thioester	CH ₃ CSCH ₃	21
	0 0			0	
1,3-Diester	CH ₃ OCCH ₂ COCH ₃	13	Ester	CH ₃ COCH ₃	25
Alcohol	CH ₃ OH	16	Nitrile	CH ₃ C≡N	25
	0			O II	
Acid chloride	CH ₃ CCI	16	N,N-Dialkylamide	CH3CN(CH3)2	30
			Dialkylamine	HN(<i>i</i> -C ₃ H ₇) ₂	36

Bases Used for Keto-Enols

- The bases used for abstracting the acidic protons are strong bases but not good nucleophiles or they will carry out neucleophilic addition on the carbonyl carbon.
- Good bases are Lithium diisopropyl amide (LDA) and NaOH.

 $CH(CH_3)_2$ Li⁺ -NCH(CH₃)₂ Lithium diisopropylamide (LDA)

Stability of Keto-Enol Tautomers

OH

 Some tautomers are more stable than others. E.g. keto form of acetaldehyde and acetone than enols.



CH

Pentane-2,4-dione

(24%)



Resonance stabilization of the enol form

Reactions: α -Alkylation and α -Halogenation

- Once the α proton is abstracted a nucleophile is generated.
- This nucleophile can now do substitution reactions.



• (This is the basis of iodoform test of methyl ketones - next slide)



Acetophenone α-Bromoacetophenone (72%)
 Once bromination is achieved all substitution reactions or elimination reactions can be performed.

Reactions: Iodoform Test

• In presence of a strong base and KI, methyl ketones will give a positive test - a yellow ppt. (CHI₃).



Reactions: Aldol Reaction (Condensation Reaction)

- An aldehyde reacts with another aldehyde in presence of a strong base.
- One aldehyde forms the nucleophile from the base which then reacts with the second aldehyde (substrate)
- Water is formed as a result hence called condensation reaction.
- Product has the <u>aldehyde and alcohol</u> hence called <u>aldol</u>.
- The reaction is in equilibrium therefore reversible.



Aldol Mechanism



Dehydration of the Aldol Product

- If the aldol product is heated it will dehydrate to give an alkene.
- The alkene product is more stable due to conjugation with the carbonyl.



Reactions: Cross Aldol Reaction

- Aldol reactions can occur with two different aldehydes (cross aldol)
- Problem!! Some mixed products also form. (*How can you control that?*)

$$\begin{array}{c} O \\ CH_{3}CH + CH_{3}CH_{2}CH \xrightarrow{OH^{-}} CH_{3}CHCH_{2}CH + CH_{3}CH_{2}CHCHCH \\ H_{2}O \\ \end{array} \\ \begin{array}{c} OH^{-} \\ CH_{3} \\ \end{array} \\ \begin{array}{c} OH^{-} \\ OH^{-} \\ OH^{-} \\ \end{array} \\ \begin{array}{c} OH^{-} \\ OH^{-} \\ OH^{-} \\ \end{array} \\ \begin{array}{c} OH^{-} \\ OH^{-}$$

Reactions: Claisen-Schmidt Reaction

- This is the reaction between an aldehyde and ketone in presence of a strong base.
- This reaction works better if one of the compounds has no α hydrogen (*to avoid a mixture of products*)
- Write mechanism!



Reactions: Cyclization with Aldol Reaction

- If a molecule has two aldehyde groups, then an intramolecular aldol occurs.
- Reaction occurs preferentially at the less sterically hindered carbonyl.
- The ring formed is the more stable size.



Alpha Carbon Chemistry

Retrosynthesis of Aldol Products

• If the molecule has a carbonyl and alcohol separated by one carbon –then it is an aldol reaction product.



Aldol Products

- Aldol products can be used as such or reactions can be continued on with the new functional group created.
- One of the biggest advantage of Aldol reaction is a new C-C bond formation.
- Dehydration gives another advantage that an alkene is formed; so in addition to alcohol chemistry, alkene chemistry can also be carried out.

Reactions: Claisen Reaction

- These are similar to aldol but done using carboxylic esters.
- As with cross aldols, one can use different esters also.
 (Write the mechanism on your own)



a β -keto ester (75%)

Key Concepts

- α protons
- Keto enol tautomerism
- Substitution reaction at α carbon
- Iodoform reaction
- Aldol condensation
- Claisen-Schmidt reaction
- Intramolecular cyclization