

Carbonyl Chemistry III: Reactivity at the Alpha Position

Section Agenda

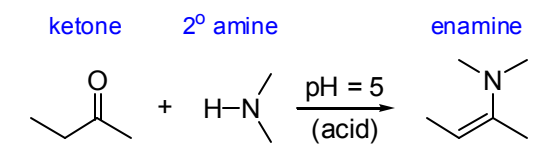
- 1) Exam II Fallout
- 2) Skill Drills – A New Feature of the PJB Show
- 3) Carbonyl Chemistry III Handout
- 4) Practice Problems + Handout
- 5) Thursday Office Hour, 8-9PM, Bauer Lobby

Exam II Results

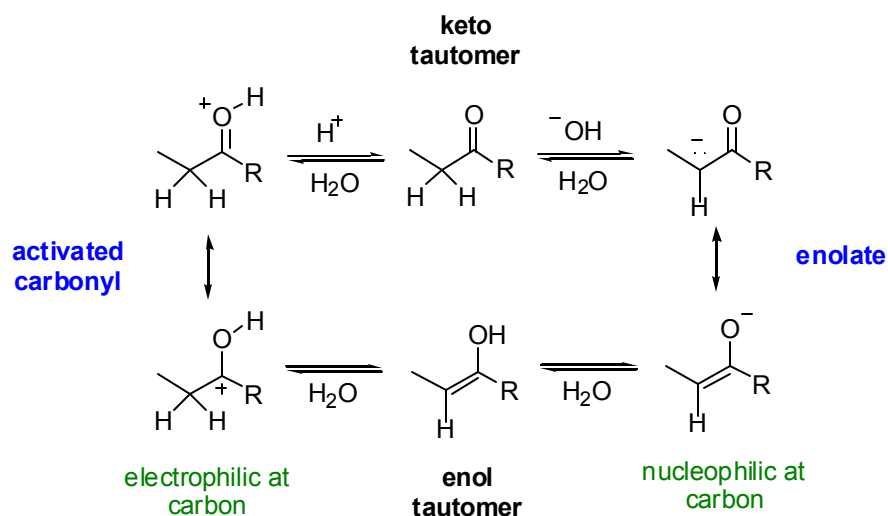
- I thought that this was a much easier exam. There was no Chem 206-like material and all of the mechanisms were straightforward. Thus, it is somewhat disturbing that the mean was lower and the standard deviation was smaller.
- Please take the midterms and study hard for them. It's a bad idea to count on the "resurrection final" to save you in this course. First, if you bomb it, you have nothing to fall back on. Second, if you don't keep up with the material by studying for midterms, what other mechanism do you have to learn it? Do you plan on cramming during reading period? Good luck. Third, I think the final is going to be a killer. At least, there is no way it will be as easy as exam II.
- Try to force yourself to work two database problems per night *with a pencil* on blank white paper and *without* the answers in front of you or nearby.

Skill Drill

Provide a mechanism for enamine formation:

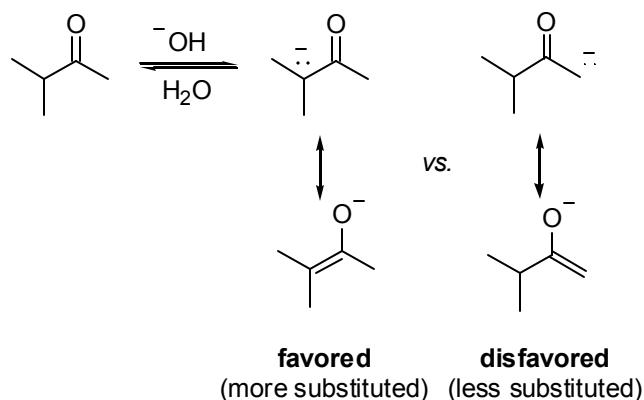


Carbonyl Chemistry at the Alpha Position

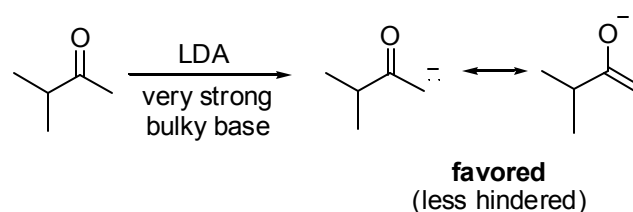


- Hydrogens on α -carbonyl carbons are acidic, so long as nothing prevents charge delocalization into the carbonyl group.
- Be careful! Just like there are two different (but similar) mechanisms for addition to carbonyl groups in acid and base, there are two different (but similar) mechanisms for tautomerization in acid and base.
- Due to the strong bond strength of a carbonyl group, the keto tautomer usually predominates in the equilibrium. The same is true for imines predominating over enamines.
- When a compound has more than one type of α hydrogen, the predominate enolate will be controlled by the method of deprotonation:

Thermodynamic Conditions



Kinetic Conditions



- Common bases: NaOH, NaOR (alkoxides)
- Thermodynamic conditions use bases where the deprotonation is reversible, so the enolates are in equilibrium
- Zaitsev's Rule: The stability of a double bond increases with increasing substitution
- Bulky bases (like LDA) deprotonate α -hydrogens from the less hindered/less substituted side. Deprotonation by very strong bases is irreversible as the pK_{a} s of amines are > 30 , so the enolates cannot equilibrate.
- In both cases, the structure with the charge on the oxygen is the more stable resonance form

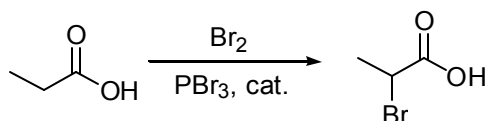
Reactions Involving Enolates

- We normally view carbonyl compounds as good electrophiles. When we convert them to enolates, they become good nucleophiles. Now the original ketone is capable of reacting with itself (e.g. aldol reaction). If you add another carbonyl compound, more reactions can occur (e.g. mixed aldols). Additional reactions are possible by introducing other nucleophiles and electrophiles.

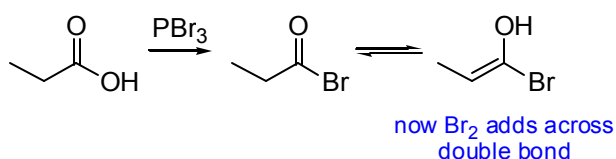
Additions Across an Enol Double Bond

Nucleophile: Enol π Bond; Electrophile: Bromine or Bromonium cation

Example: Hell-Volhard-Zelinsky



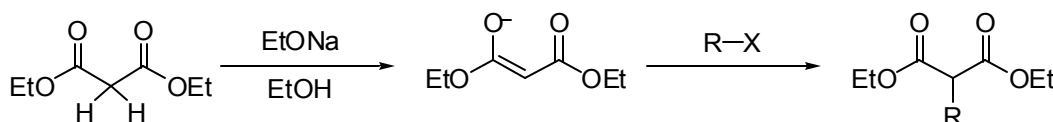
By way of:



- Review your olefin reactions from Chem 20

Malonic Ester Alkylation

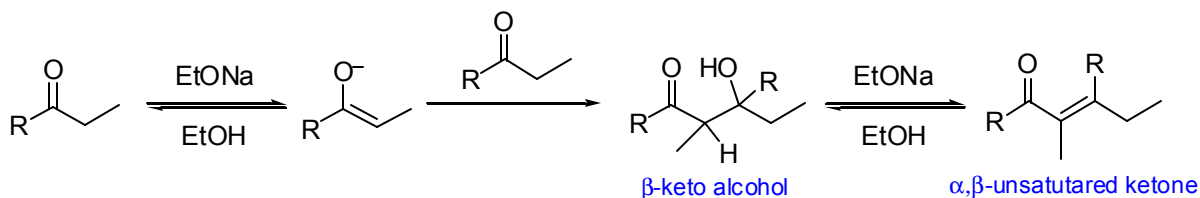
Nucleophile: Malonate anion; Electrophile: Alkyl halide



- The middle hydrogens are the most acidic, as the negative charge can be delocalized into two carbonyl groups.
- You typically use the alkoxide corresponding to the type of ester you are using, so the saponification side product is equivalent to the starting material

Aldol Additions & Aldol Condensation

Nucleophile: Ketone or Aldehyde enolate anion; Electrophile: Aldehyde or Ketone carbonyl group



- You can have "crossed" reactions if more than one type of aldehyde or ketone is present
- Watch out for "retro-aldols," where a β -keto alcohol can break apart

Relative Acidity of α -Hydrogens:

Malonic esters > Ketones ($2^\circ > 1^\circ > \text{Me}$) > Esters

Relative Electrophilicity of Carbonyl:

Formaldehyde > Aldehydes >> Ketones > Esters