

# Chapter 18 Information

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1. The acidity of the alpha proton.
2. Keto-enol tautomerization in acid and in base. Stereochemical consequences. Recognize nonenolizable carbonyls as appropriate.
3. Halogenation in acid – adds once and stops (electron-withdrawing halogen lessens the ability of the carbonyl to be protonated).
4. Halogenation in base – haloform reaction. Functional group test for methyl carbonyl.
5. Aldol reaction.
  - a. Done in base at low temperature – get beta hydroxyl carbonyl.
  - b. Warm to rt or above, get dehydrated product (alpha-beta unsaturated carbonyl).
  - c. Crossed aldol with hydroxide will give all possible products. It's an equilibrium; only about 10% enolate at any given time.
  - d. Intramolecular cyclizations work fine with NaOH as base because of the stability of the product (great for 5 or 6 membered rings).
  - e. Use LDA as the base – get the kinetic enolate 100%. Crossed aldol now possible.
  - f. How do we get the thermodynamic enolate for aldols? Stork enamine synthesis. Can also use this for alkylation.
  - g. Hell-Vollhard-Zelinsky reaction – make alpha bromo carboxylic acids with  $\text{PBr}_3$ .
  - h. Alkylation of the alpha carbon using LDA works for methyl/primary carbons (competes with aldol)
6. The aldol reaction makes alpha-beta unsaturated carbonyls. What are those good for? (*Go back to 17.16.*)
  - a. Simple addition vs. conjugate addition
    - i. Simple addition: strongly basic nucleophiles (Grignards, acetylene anions, hydrides)
    - ii. Conjugate addition: weakly basic nucleophiles ( $\text{CN}$ , enolates,  $\text{LiCuR}_2$ , alcohols, amines)
  - b. Michael addition / Robinson annulations.
7. Claisen Condensation – this is an aldol-type reaction with esters. (Note that the initial product is the enolate of the beta dicarbonyl; acid hydrolysis as a second step neutralizes this.) An intramolecular Claisen is called a Dieckmann. These work well intramolecularly as well. Generally use the alkoxide base that corresponds with the ester so as to avoid transesterification; if doing a crossed Claisen, use LDA. Can also use LDA to alkylate an ester at the alpha position.
8. Decarboxylation of beta keto acids goes easily just by heating. Mechanism is an intramolecular electrocyclic rearrangement.
9. Malonic ester synthesis
10. Acetoacetic ester synthesis