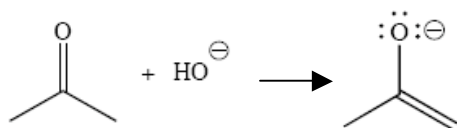


Enolates, Enols and Enamines

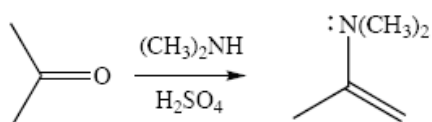
Structure, Reactivity, General formation

Enolate



Enolate = negative charge on oxygen with adjacent C-C double bond

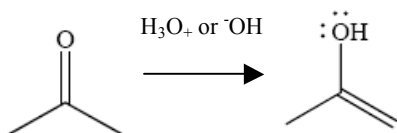
Enamine



Enamine = NR_2 group adjacent C-C double bond

Reacts in similar way as enolates

Enol

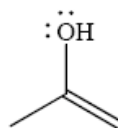
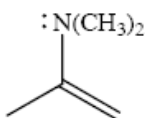
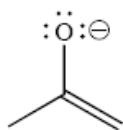


Enol = hydroxyl group with adjacent C-C double bond

Alkene + alcohol = enol

Order of Decreasing Nucleophilic reactivity

ENOLATE > ENAMINE > ENOL



*electron-rich pi bond is a source of nucleophilic character in all three

Enolate is nucleophilic due to...

- Oxygen's small atomic radius
- Formal negative charge

Detractors to nucleophilicity:

- Oxygen is more electronegative than N

Enamine is moderately nucleophilic due to...

- N (EN=3) is less electronegative than oxygen (EN =3.5)

Enol is moderate nucleophile due to...

- Additional electron density from oxygen of hydroxyl group

When looking at which **side is favored** (products or reactants):

- ☑ Equilibrium favors side with **WEAKER** acid/base pair
- ☑ Weakest acid and weakest base should be on **SAME** side
- ☑ When comparing pKa values, juxtapose just the acids or just the bases
Side with larger pKa value (weaker acid) favored in equilibrium
Remember that differences in pKa values reflect a difference quantity of 10^x

Example: compound H-A (pKa=3) + base \rightarrow compound A (pKa=10) + H-base
equilibrium lies to the **RIGHT** by factor of 10^7

Some Useful pKa values (from more acidic \rightarrow basic)

H₂SO₄ (pKa = -9)

H₃O⁺ (pKa = -1.8)

B-diketone (pKa = 9)

HCN (pKa = 9.1)

CH₃OH (pKa = 15.5)

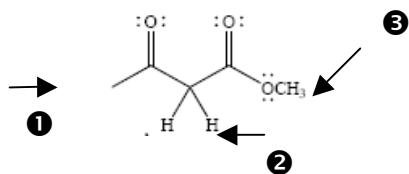
H₂O (pKa = 15.7)

CH₃COCH₃ (pKa = 19)

CH₃COOCH₃ (pKa = 25)

LDA-H (pKa = 36)

How do we know which proton to deprotonate?



- ☑ Deprotonate **most acidic** proton \rightarrow usually leads to the most **stable** enolate
 1. Draw all resonance contributors of formed enolate for each case
 2. Pick hydrogen that results in enolate with the most number of **IMPORTANT** resonance contributors
- ☑ Example:
 1. 3 possible choices to take away a hydrogen
 - ❶ H from terminal methyl group on the left
2 important resonance contributors
 - ❷ H from CH₂ in-between 2 carbonyls
3 important resonance contributors
***MOST ACIDIC HYDROGEN**
 - ❸ H from methyl attached to oxygen
2 important resonance contributors

Why do enolates, enamines, enols form in the first place?

- ☑ **Enolates** stabilized by conjugated product (stability gained by delocalization of electron density)
- ☑ **Enamines** stabilized by *similar conjugation*
- ☑ **Enols:** although keto tautomer more stable than enol tautomer, enols may be stabilized by H-bonding, conjugation, or gained aromaticity

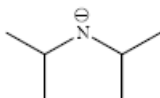
In enolate formation, **strong** bases used \rightarrow why don't they undergo S_N2 since good bases are usually good nucleophiles?

True that there is *some* formation of S_N2 products (nucleophilic attack on carbon)
BUT, **major product** is enolate formation due to...

1. **STERIC effects:** If base could easily snatch a hydrogen from one of the neighboring **less** sterically hindered atoms, it will and it won't work hard to get into the small groove (sterically unfavorable) for nucleophilic attack
2. **Proton transfer step:** much faster than having to wait for nucleophilic attack

Is there a way for there to be ALL enolate formation?

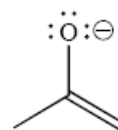
YES! Instead of just any old base, use sterically hindered base such as LDA (lithium diisopropyl amide)



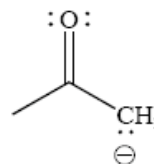
- Due to severe steric effects from LDA's 2 attached isopropyl groups, it cannot undergo S_N2 -type addition and can **ONLY** deprotonate carbonyl's less sterically hindered neighboring hydrogens
- LDA is a superior base so it readily takes an H atom **until no more left**

Enolates are Reactive Nucleophiles

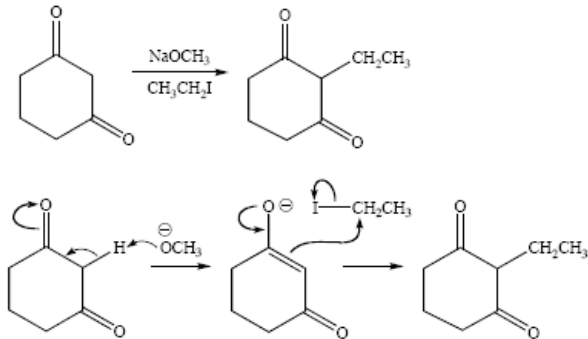
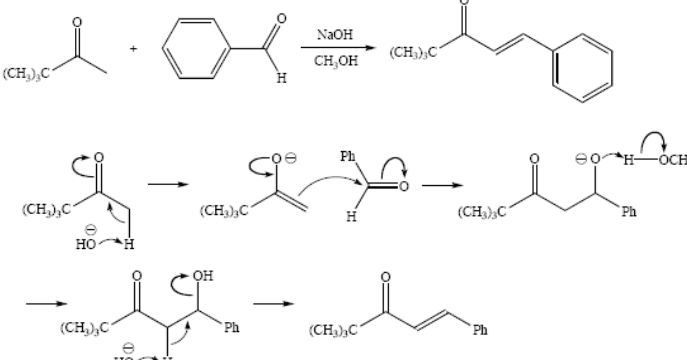
Although the major enolate contributor shows concentration of electron density on the electronegative oxygen,

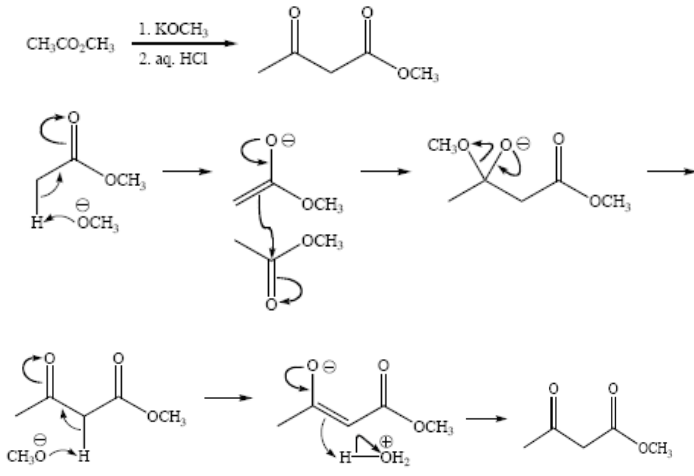


When it reacts with an electrophile, it behaves like the electron density is concentrated on C like so:



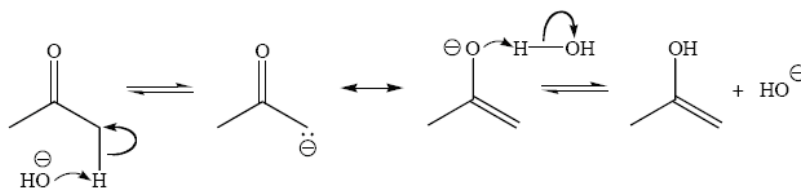
Enolates React with Alkyl Halides, Aldehydes/Ketones, Esters

Enolates react with...	Example Mechanism	Important things to remember
<p>1) Alkyl halides</p> <p>SN2/E2 pathways</p>	 <ol style="list-style-type: none"> -OCH₃ (base) deprotonates most acidic H (in-between 2 carbonyls gives most no. of significant res. contributors = most stable product), electrons of C-H bond made into pi bond, and electrons of original pi bond move to oxygen Nucleophilic pi bond attacks carbon of C-I bond in CH₃CH₂-I (alkyl halide) and superior leaving group I- leaves In same step, electrons on oxygen move back to remake pi bond Result is new C-C bond in-between 2 carbonyls 	<p>In step 2, this nucleophilic attack of enolate's pi bond is much like SN2 mechanism –</p> <p>Must follow the rules of SN2 reactions</p> <ul style="list-style-type: none"> ◆ (1) Electrophile cannot be tertiary ◆ (2) Good leaving group ◆ (3) Good nucleophile ◆ (4) Polar Solvent (aprotic preferred) <p>If these rules do not apply, no SN2 rxn</p> <ul style="list-style-type: none"> ◆ If electrophile is 3°, E2 reaction occurs → enolate is moderate base
<p>2) Aldehyde/ ketones</p> <p>Aldol reaction</p>	 <ol style="list-style-type: none"> -OH (base) deprotonates most acidic H (H of methyl group directly attached to carbon of carbonyl) of ketone, electrons of C-H bond made into pi bond, and electrons of original pi bond move to oxygen Nucleophilic pi bond attacks carbon of the other carbonyl molecule (aldehyde) and pi electrons of electrophile move to oxygen With presence of alcohol (CH₃OH, base), H₃O⁺ protonates oxygen with neg. charge (make into better leaving group) Leaving group OH leaves due to new conjugation gained by deprotonating adjacent H atom with base 	<p>Notice that -OR can leave if:</p> <ul style="list-style-type: none"> ◆ In tetrahedral adduct there is another oxygen with a negative charge ◆ The leaving of this group leads to favorable, stable conjugation <p>*The more conjugated the molecule can gain, the more readily OH can leave</p> <p>LOOK: we do not choose the H of the aldehyde because it can NOT be directly attached to carbonyl</p> <p>Originally named "aldol reaction" because this rxn originally thought to only occur between aldehydes and alcohol</p> <p>→ BUT it turns out that this reaction also occurs with ketones</p>

<p>3) Esters</p> <p>Claisen and Dieckmann Condensation Reactions</p>	 <ol style="list-style-type: none"> 1) -OCH_3 (base) deprotonates most acidic H (H of methyl group directly attached to carbon of carbonyl), electrons of C-H bond made into pi bond, and electrons of original pi bond move to oxygen 2) Nucleophilic pi bond attacks carbon of original carbonyl molecule (ester) and pi electrons of electrophile move to oxygen 3) Tetrahedral adduct formed and negative charge on oxygen → Is there a leaving group present? → YES! OCH_3 will leave due to electron repulsion 4) As OCH_3 leaves, electrons on oxygen move to make pi bond = product formed is B-ketoester <p>Deprotonation of H by base MUST occur</p> <ol style="list-style-type: none"> 5) React a SECOND time with base -OCH_3 deprotonating H, electrons of C-H bond moving next to carbonyl to form pi bond, and electrons of original pi bond moving up to oxygen 6) Pi bond attacks H of H_3O^+ and forms B-ketoester again <p>*acid drives equilibrium to the right (desired B-ketoester product)</p>	<p>Acid (H_3O^+) of aqueous HCl drives equilibrium to the right</p> <ul style="list-style-type: none"> → Yields desired B-ketoester product → If NO acid added, then equilibrium would go towards 2nd to last step <p>Claisen condensation: Condensations of 2 esters to form desired B-ketoester (intermolecular reaction)</p>
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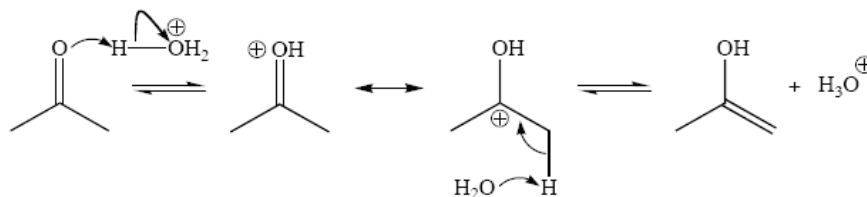
Enols can be Acid-catalyzed or Base-catalyzed

Base:



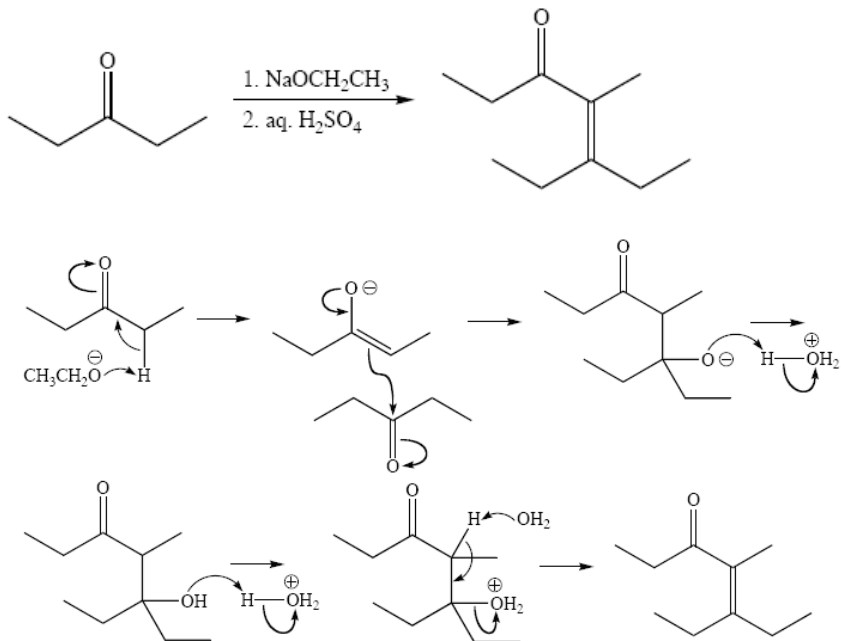
*Notice that the -OH is regenerated at the end (catalyst)

Acid:



*Notice that the -OH is regenerated at the end (catalyst)

Example of Self-Condensation:



- 1) $\text{-OCH}_2\text{CH}_3$ (base) deprotonates most acidic H (H's near carbonyl equally acidic), electrons of C-H bond made into pi bond, and electrons of original pi bond move to oxygen
- 2) Nucleophilic pi bond attacks carbon of another carbonyl molecule $\text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_3$ of 1st step (ketone) and pi electrons of electrophile move to oxygen
- 3) With presence of acid, H_3O^+ protonates oxygen with neg. charge twice so that there is a positive charge on oxygen (make into better leaving group)
- 4) Leaving group +OH_2 leaves as new conjugation gained by deprotonating adjacent H atom with water

* Images and examples in this study guide have been taken from Chemistry 14D Thinkbook, Fall 2006 by Hardinger and Organic Chemistry by Bruice