

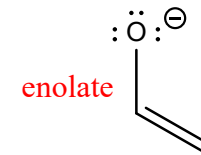
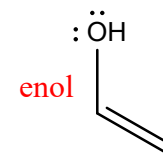
Organic Chemistry
Mechanistic Patterns
(Ogilvie)
Chapter 17
(sections 17.1 to 17.5
but not 17.4.2)



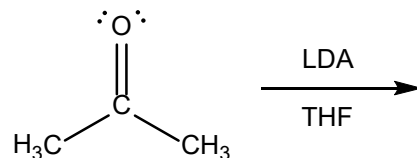
CHEMISTRY 2600

Topic #8: Enolates
Spring 2021
Dr. Susan Findlay

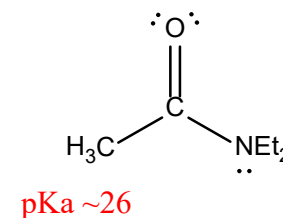
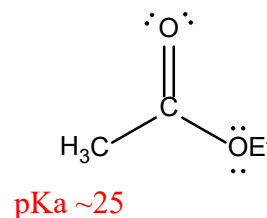
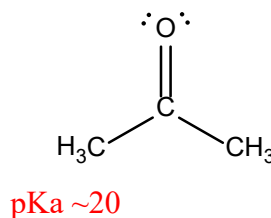
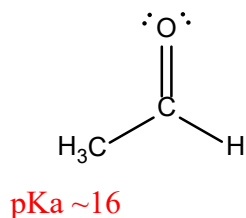
Preparation of Enolates



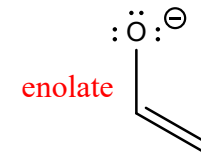
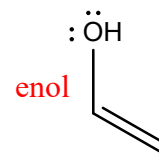
- Another important class of nucleophilic carbon atom is the **enolate** (the conjugate base of an enol). In CHEM 2500, you saw that the hydrogen atom α to a carbonyl group is quite acidic because the conjugate base is resonance-stabilized:



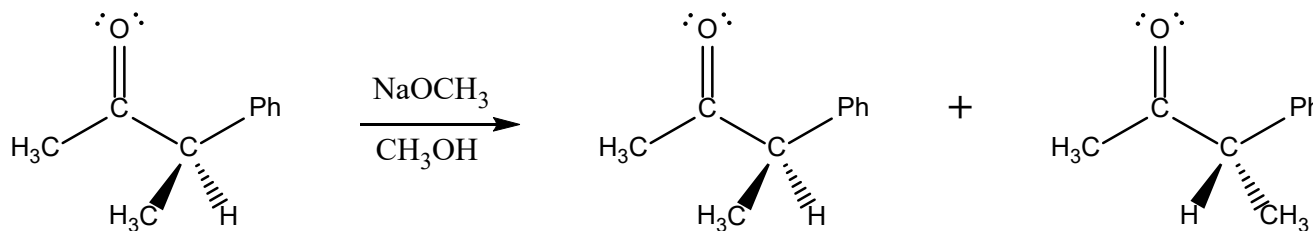
- Carbonyl groups with electron-donating groups attached (e.g. esters or amides) have less acidic α hydrogen atoms since electron-donating groups tend to destabilize anions (like the conjugate base):



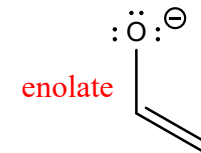
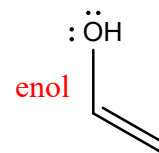
Enolates and Stereochemistry



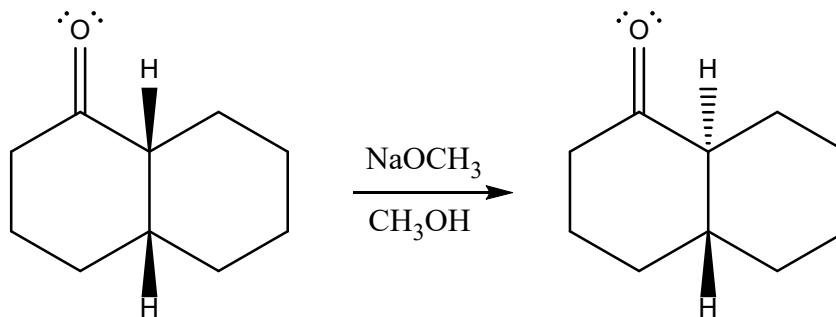
- Because enolates are planar, treatment of a carbonyl compound with any base strong enough generate an enolate – no matter how temporarily – affects any chirality center α to the carbonyl.
- This can lead to racemization of an enantiopure compound if that is the only chirality center:



Enolates and Stereochemistry

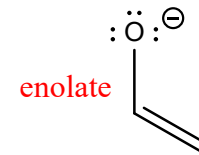
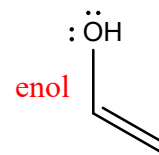


- It can lead to epimerization if there are other chirality centers in the molecule:



Epimers are isomers that differ by configuration of only one chirality center. They are a special case of diastereomers.

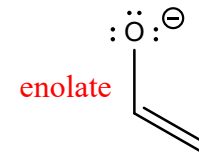
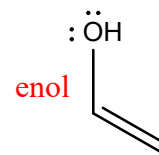
Enolates as Nucleophiles



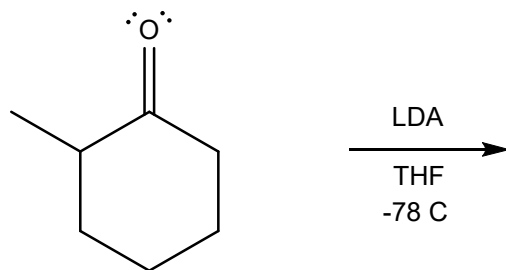
- Given that the hydrogen atoms α to carbonyls have $pK_a \sim 16-26$, deprotonation with alkoxides (pK_a of conjugate acid ~ 15) is reversible. That's why they were chosen for the examples on the previous page.
- If complete deprotonation is desired, a stronger base must be chosen. A common choice is LDA (pK_a of conjugate acid ~ 35).
- This generates a nucleophilic carbon atom that can be used in a variety of reactions including S_N2 and additions to polar pi bonds.
e.g.



Enolates as Nucleophiles

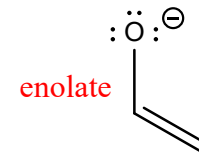
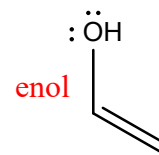


- If there is more than one type of α -hydrogen (and therefore more than one potential enolate), the kinetic enolate can be favoured by use of a strong bulky base at low temperature:

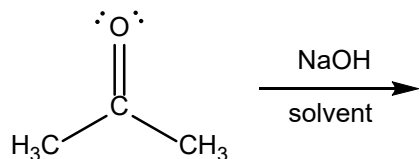


- Why is this the kinetic enolate?
- The enolate with the more substituted double bond is the thermodynamic enolate. It is formed under conditions which favour the system reaching equilibrium (higher temperature, weaker base, etc.)

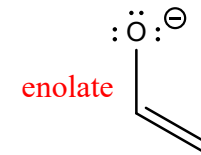
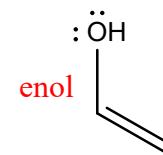
Enolates in Aldol Reactions



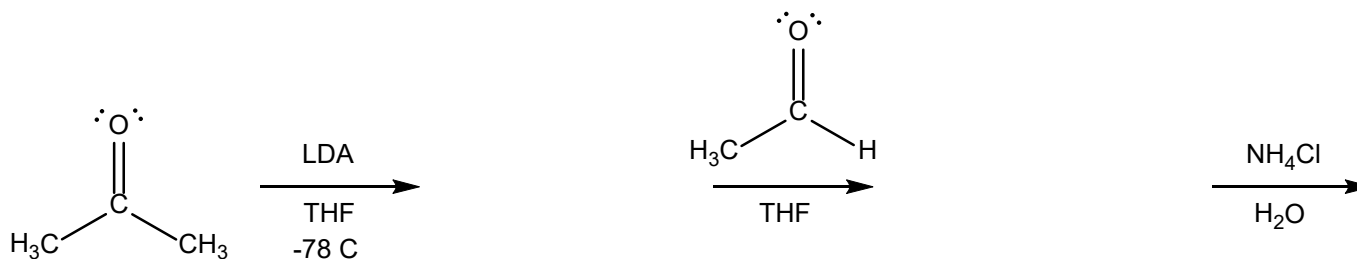
- Enolate formation is the reason why heating acetone with a small amount of moderate-to-strong base (NaOH or stronger) results in a tarry mess. Consider what happens when no external electrophile is added, leaving neutral acetone molecules as the only available electrophiles:



Enolates in Aldol Reactions

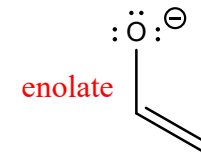
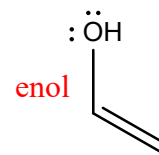


- While the reaction on the previous page isn't hugely useful, this chemistry can be put to good use with some careful planning:
 - Make sure to use a strong enough base that the enolate forms fully, leaving no electrophilic ketone or aldehyde. It is often helpful to prepare the enolate at low temperature.
 - Once the enolate has completely formed, add a reactive electrophile. Aldehydes are better electrophiles than ketones, so they're usually a better choice. If the aldehyde has no α hydrogen, even better! (Reacting an enolate from a ketone with an aldehyde having no α -hydrogen is called a **Claisen-Schmidt reaction**.)
 - After adding the electrophile, the solution may be allowed to warm.

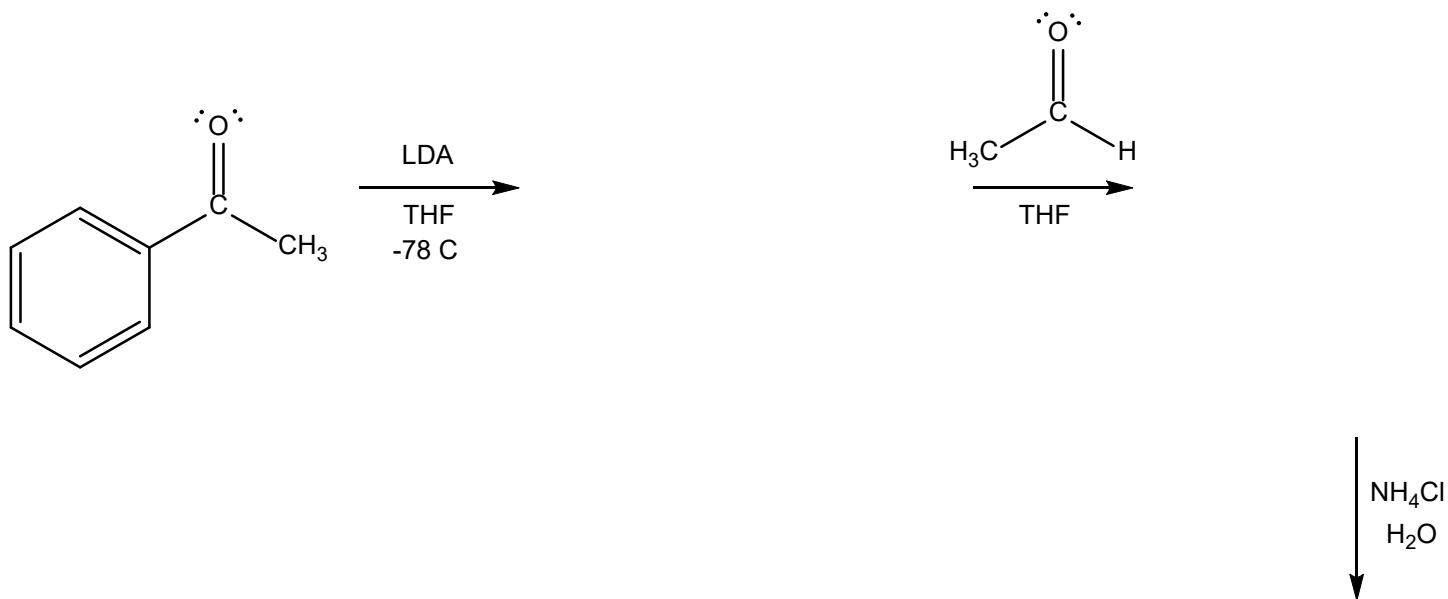


- And we've extended our carbon chain!

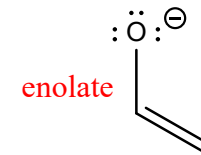
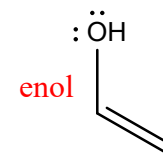
Enolates in Aldol Reactions



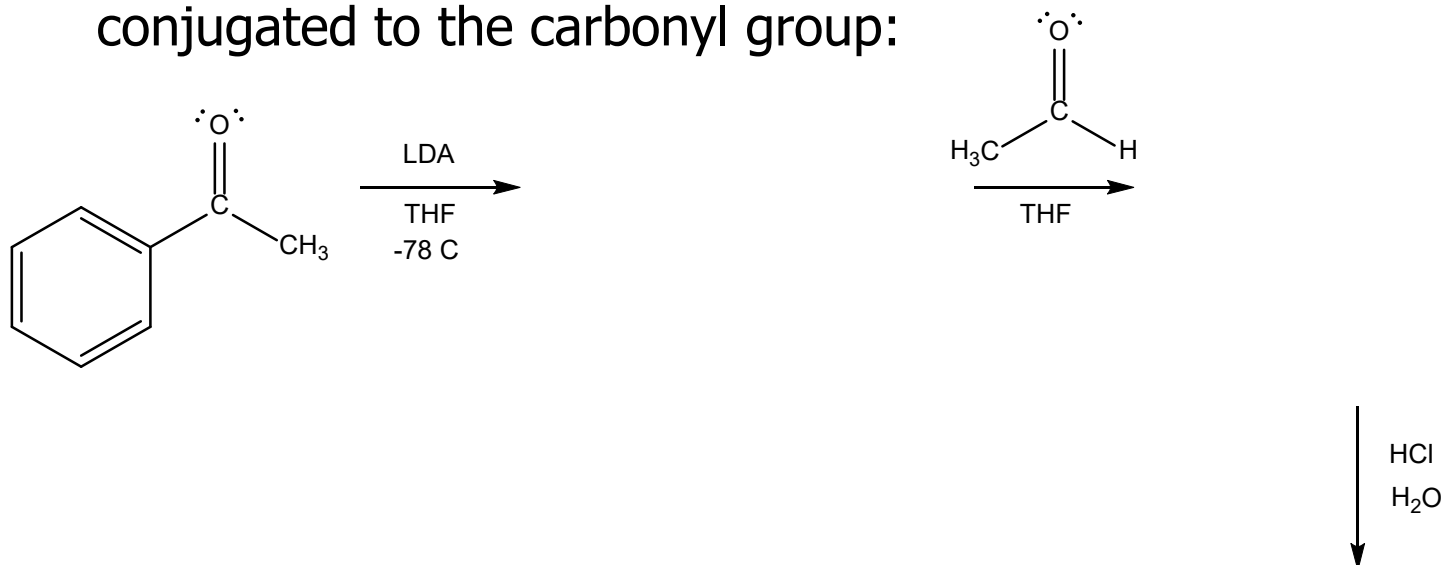
- This is an **aldol** reaction. It takes an **aldehyde** and converts it into an **alcohol** (while extending the carbon chain).



Enolates in Aldol Reactions

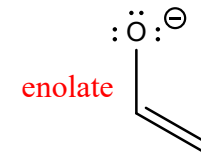
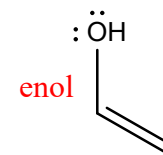


- If an aldol reaction is worked up under more acidic conditions, an elimination reaction is likely to follow, giving a double bond conjugated to the carbonyl group:

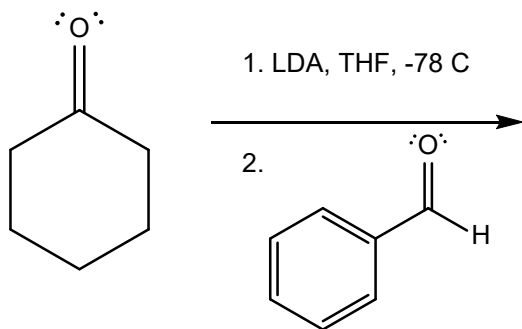


There is more thought put into work-up conditions than might immediately be apparent from a lab manual... 😊

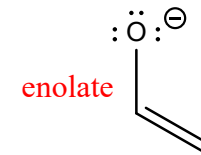
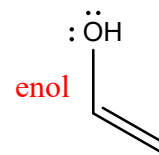
Enolates in Aldol Reactions



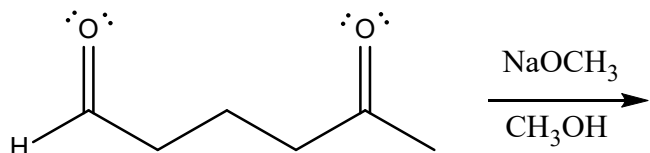
- What are the products of the following aldol reaction with
 - a. gentle work-up ($\text{NH}_4\text{Cl}_{(\text{aq})}$), or
 - b. acidic work-up ($\text{HCl}_{(\text{aq})}$):



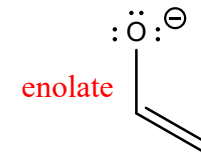
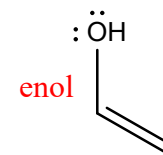
Enolates in Aldol Reactions



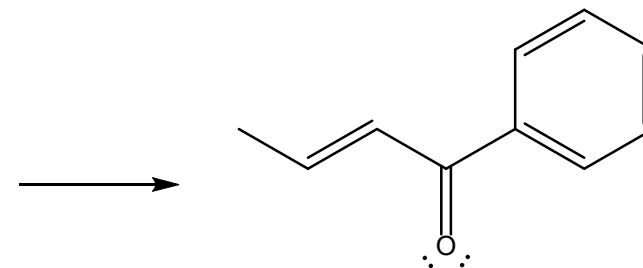
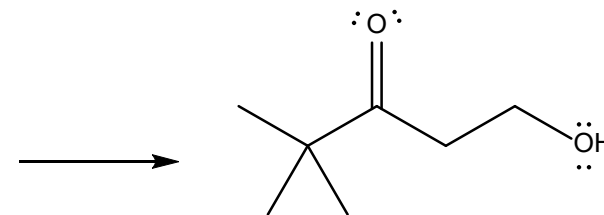
- It is possible to do intramolecular aldol reactions if both enolate and aldehyde are in the same molecule. For the reaction below,
 - Draw the three enolates which could be formed,
 - Draw the three products which could be formed, and
 - Identify which of the three products will be the major product.



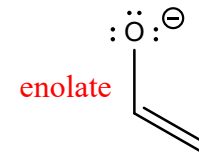
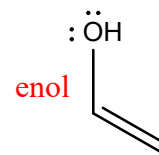
Enolates in Aldol Reactions



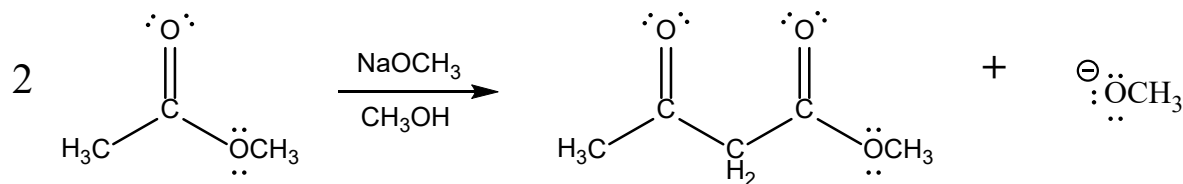
- How would you make the following compounds via aldol reactions?



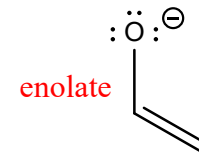
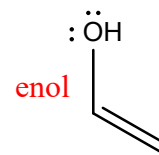
Claisen Condensations



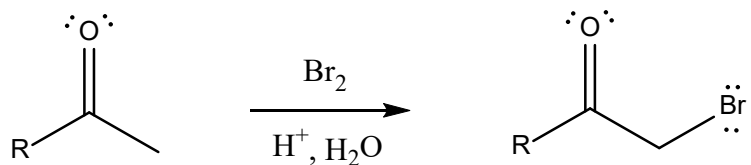
- Claisen condensations are very similar to aldol reactions except that an enolate is made from an ester, and the electrophile is also an ester (instead of an aldehyde).
- Propose a mechanism for the following reaction:



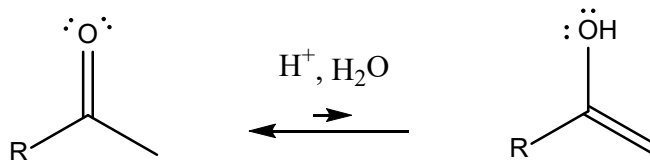
Enols as Nucleophiles



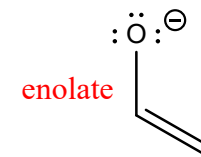
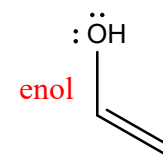
- While they are less nucleophilic than enolates, enols can also serve as nucleophiles. A classic example of this is the reaction between a carbonyl compound and a halogen in the presence of an acid catalyst:



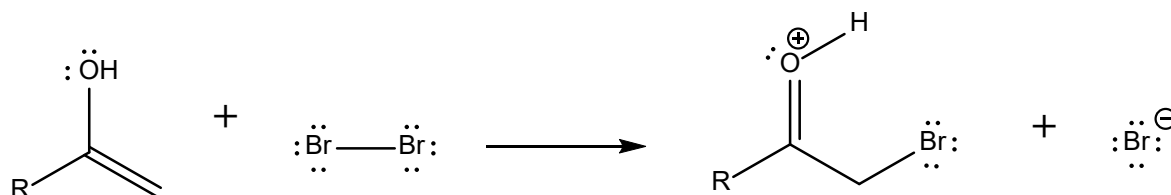
- While the majority of the starting material exists as the keto tautomer, at any moment in time, a small fraction exists as the enol tautomer:



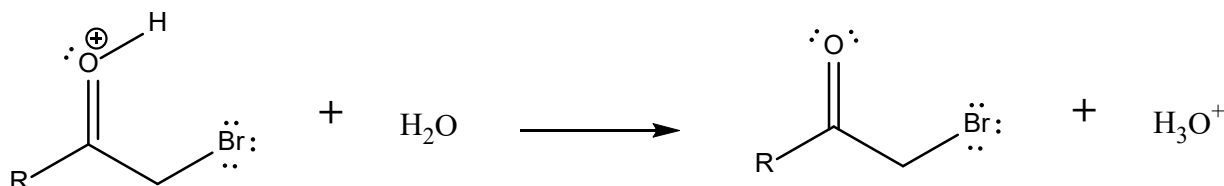
Enols as Nucleophiles



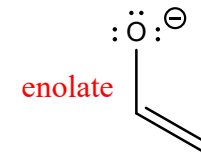
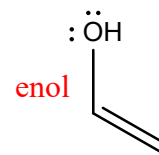
- The starting material in enol form can act as a nucleophile, attacking bromine:



- The resulting cation is deprotonated by water, giving an α -halo carbonyl compound:

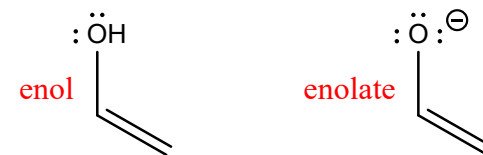


Enols as Nucleophiles

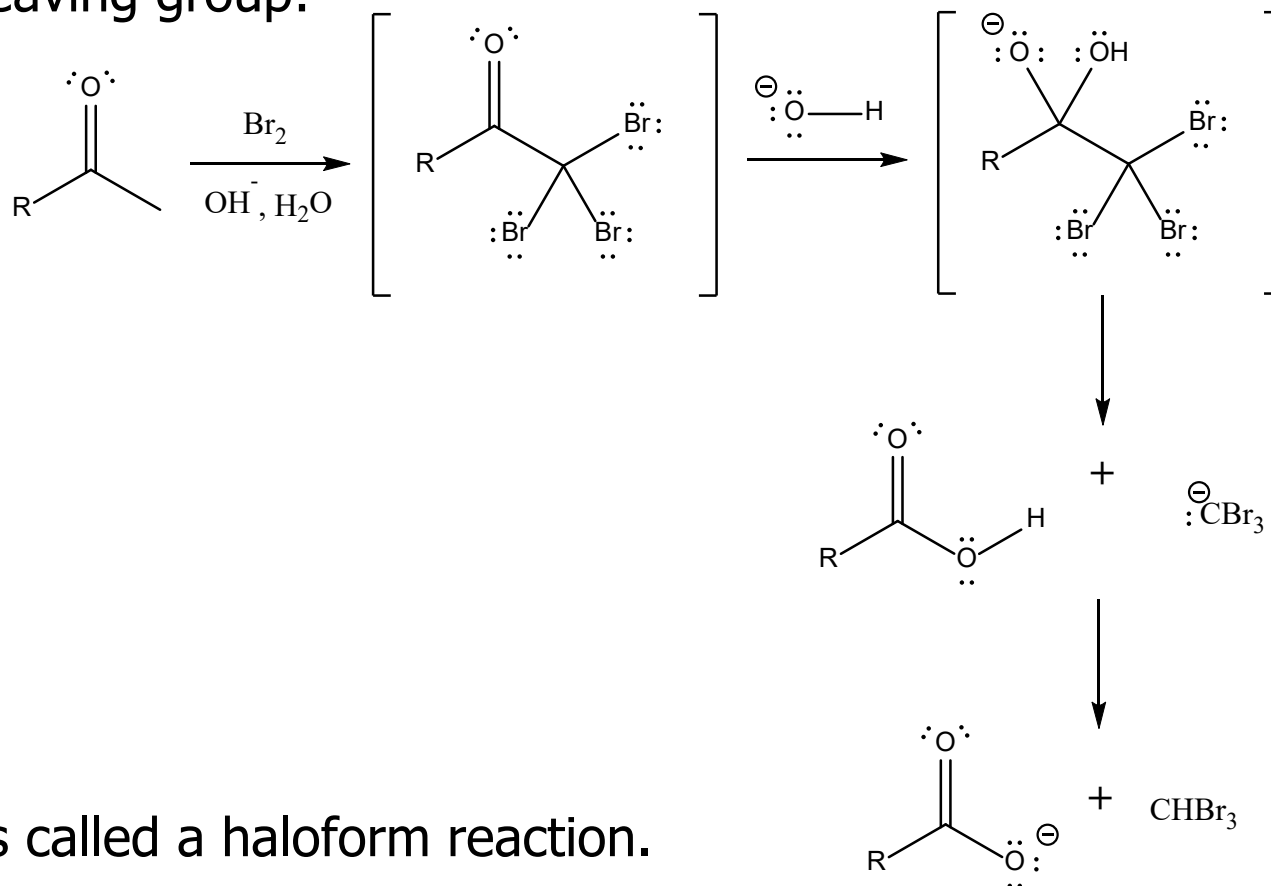


- While a small amount of the α -halo carbonyl compound will also exist in the enol tautomer, it does not attack another halogen molecule to give a doubly halogenated product. Why not?

Enols as Nucleophiles

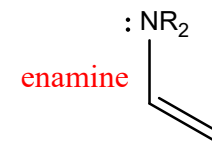
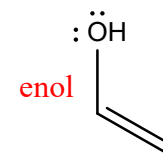


- This reaction can also be done under basic conditions (generating an enolate instead of an enol), but all of the α hydrogens are replaced by halogen atoms then CX_3 is displaced as a leaving group:

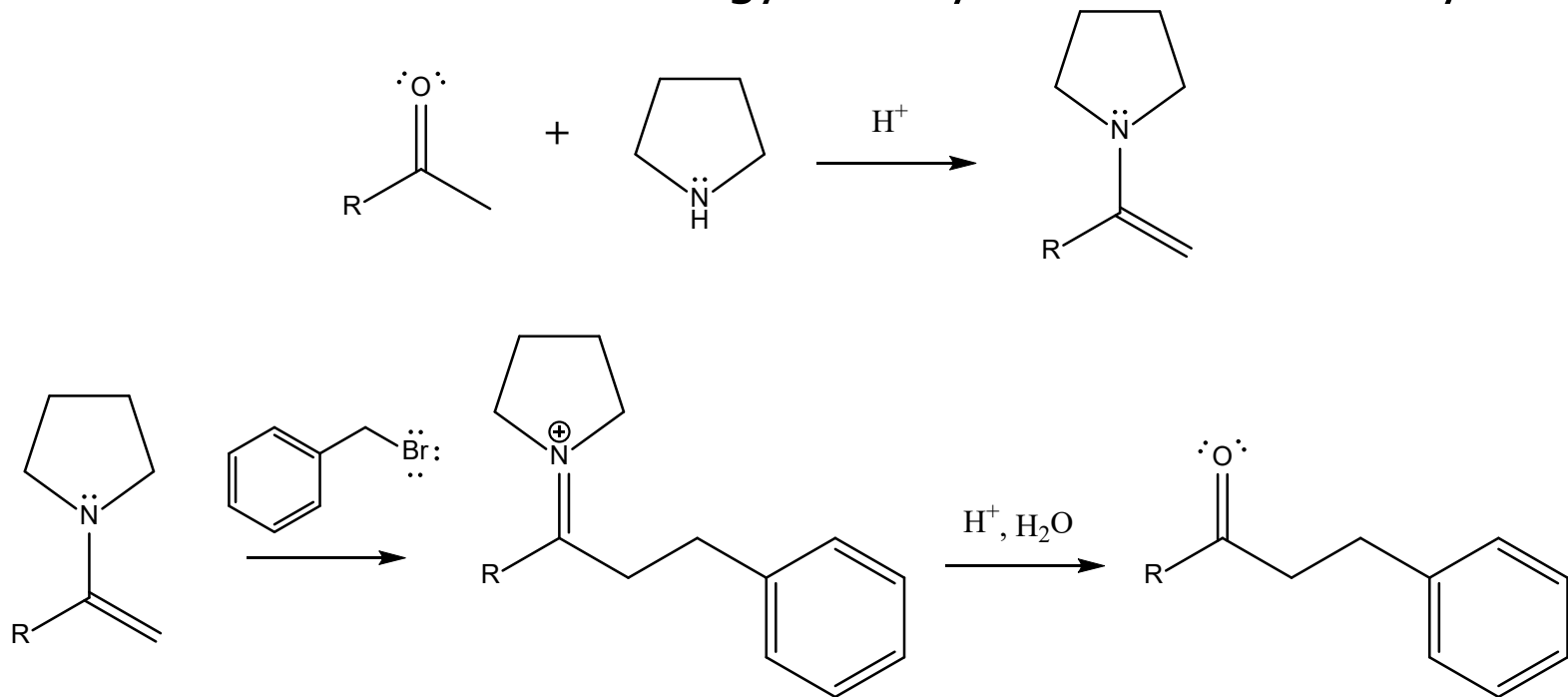


- This is called a haloform reaction.

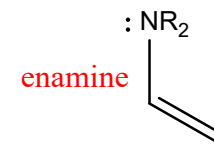
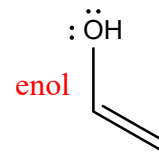
Enamines as Nucleophiles



- Enamines are better nucleophiles than enols (though not as good as enolates). Why?
- Formation of an enamine, alkylation then hydrolysis of the enamine is another strategy for alkylation α to a carbonyl:



Enamines as Nucleophiles



- How could you use an enamine strategy to prepare the following compound?

