

Chapter 18

Carbonyl Compounds' α -Carbons

18.1 Reactions at the α -Carbon of Carbonyl Compounds 1

4/19:

- Comparing Units 1-3.
 - Units 1 and 2 were about nucleophiles adding to electrophilic carbonyls.
 - Unit 3 talks about carbonyls as nucleophiles (when they've been deprotonated at the α -position).
- **Enolate:** The class of molecules that resonate between a carbonyl with a carbanion at the α -position and a deprotonated, negatively charged enol. *Structure*

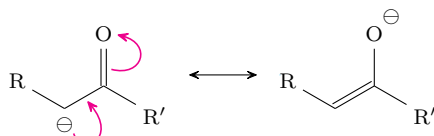
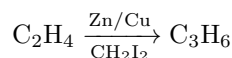


Figure 18.1: Enolate.

- We care about enolates as a way to form C–C bonds.
- Our current list of C–C bond forming reactions includes...
 1. Wittig.
 - Combines an ylide and a carbonyl electrophile.
 2. Friedel-Crafts.
 - Combines an arene and a carbonyl electrophile.
 3. Cyanide nucleophile.
 - Combines HCN or a CN^- source and a carbonyl electrophile.
 4. Organometallics: Grignards, lithiates, and alkyl anions.
 - Combine carbanions and a carbonyl electrophile.
 5. Diels-Alder.
 6. **Simmons Smith cyclopropanation.**
- Simmons Smith cyclopropanation.
- General form.



- This reaction is commonly taught in CHEM 22000 or CHEM 22100; the fact that it was not our year does not now make it our responsibility on tests.

- The takeaway from this refresher of C–C bond forming reactions is that of the six ways we know to make C–C bonds, four involve carbonyls (and in all of these, the carbonyl role plays as an electrophile).
 - As mentioned above, Unit 3 is about flipping this paradigm, i.e., making carbonyls into nucleophiles.
- pK_a 's.
 - Deprotonating an O–H bond: Recall that acetic acid ($pK_a \approx 15$) is 10^{10} times more acidic than ethanol ($pK_a \approx 5$) due to resonance stabilization of the conjugate base in the former.
 - Deprotonating a C–H bond: A hydrogen on the 1-carbon of propane ($pK_a \approx 50$) is 10^{25} - 10^{30} times more acidic than a hydrogen on acetone ($pK_a \approx 20$ -25) once again due to resonance stabilization (note that deprotonated acetone constitutes an enolate).
- Enolates have two main modes of reactivity.

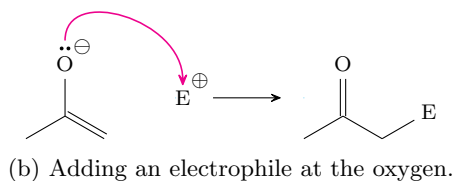
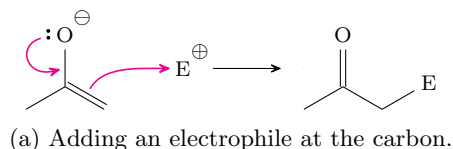


Figure 18.2: Reactions of enolates and electrophiles.

- We will focus on the mode in Figure 18.2a because we're most interested in making new bonds to carbon.
- If $E^+ = H^+$, then we can either generate a ketone (via Figure 18.2a) or an **enol** (via Figure 18.2b).
- **Enol**: The class of molecules containing adjacent alkene and alcohol functional groups. *Structure*

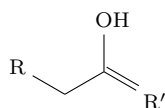
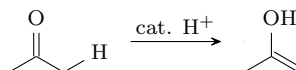


Figure 18.3: Enol.

- **Tautomers**: Two constitutional isomers that rapidly interconvert. *Etymology* from Greek **taut** "same" and **mer** "part."
- Example: Enols and ketones are tautomers.
- Enol formation (acid-catalyzed).
- General form.



- Mechanism.

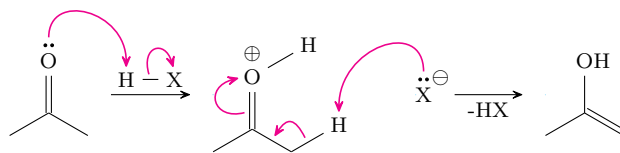
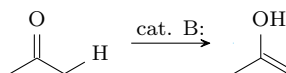


Figure 18.4: Acid-catalyzed enol formation mechanism.

- Enol formation (base-catalyzed).
- General form.



- Mechanism.

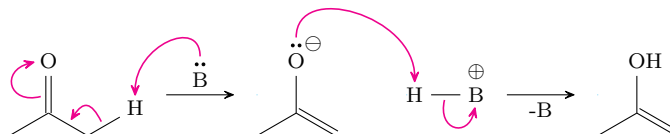


Figure 18.5: Base-catalyzed enol formation mechanism.

- If the base has a pK_a greater than that of the carbonyl, then the compound gets stuck at the enolate.
 - In other words, the enol will only form when the base is weak enough to do the initial deprotonation but not the reverse deprotonation, i.e., it can set up a keto-enol equilibrium but not stoichiometrically deprotonate the ketone.
- All of next lecture is on really strong bases and enolates.
- Levin also draws the reverse mechanism for both of these as per the principle of microscopic reversibility.
 - It follows that there is an equilibrium between a ketone and its enol.
- The position of the equilibrium depends largely on the resonance stability of both tautomers.
 - The equilibrium between 1-phenylpropan-1-one and (Z)-1-phenylprop-1-en-1-ol lies heavily on the side of the ketone.
 - Resonance between the carbonyl and the benzene ring favors the ketone.
 - The equilibrium between pentane-2,4-dione and (Z)-4-hydroxypent-3-en-2-one lies mostly on the side of the ketone.
 - An extra resonance form stabilizes the enol.
 - The equilibrium between cyclohexa-2,4-dien-1-one and phenol lies heavily on the side of the enol.
 - Aromaticity stabilizes the enol.
- Evidence for the existence of enols (which are usually present in such a small portion as to not be isolable).

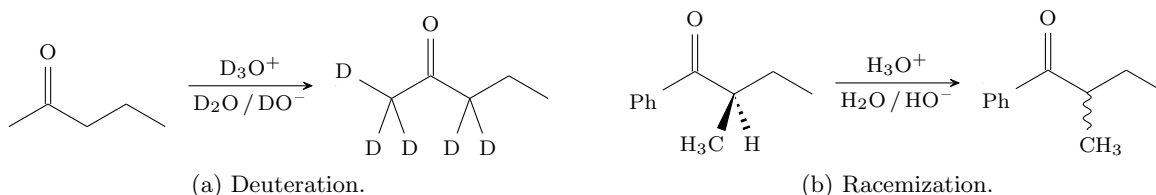


Figure 18.6: Evidence for the existence of enols.

1. Deuteration of carbonyl compounds (Figure 18.6a).

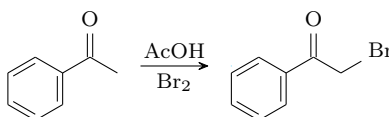
- Proves the existence of a process that is “washing in” the deuterium, but only at the α -positions.
- Note that D_2O / DO^- denotes basic deuterated water, and that only acidic or basic deuterated water is used at one time.

2. Racemization of compounds that are enantiopure at the α -position (Figure 18.6b).

- Thus, we're removing the hydrogen, forming an achiral intermediate, and then putting that hydrogen back but randomly this time.

- Halogenation of enols (acid-catalyzed).

- General form.



- Mechanism.

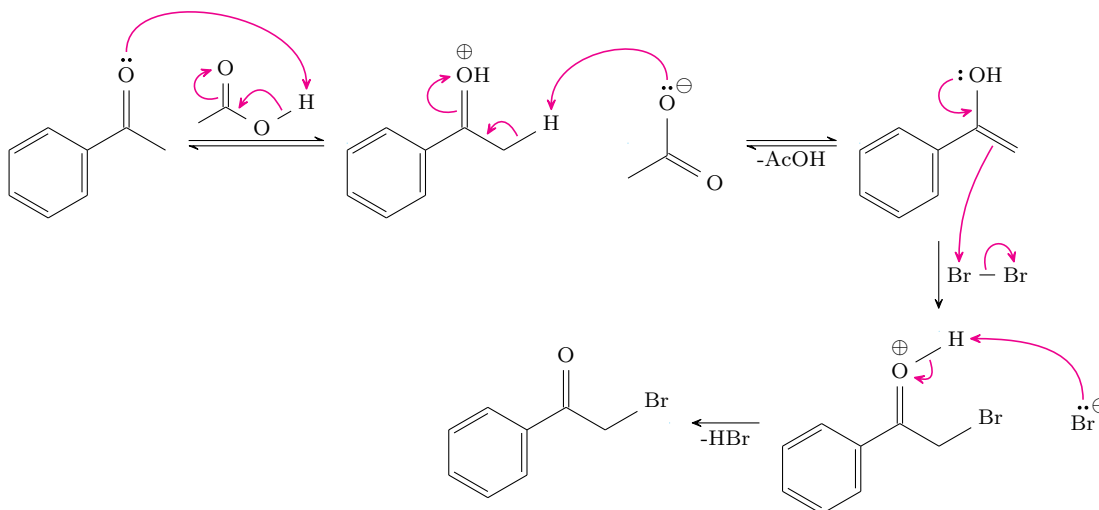
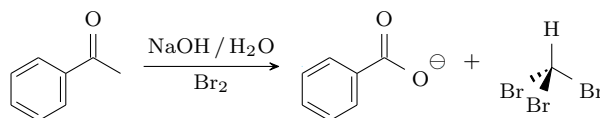


Figure 18.7: Acid-catalyzed halogenation of enols mechanism.

- Remember that only a tiny percentage of the enol will be formed in the equilibrium constituting the first two steps, but these few molecules formed will be piped through the rest of the reaction over time and will pull more through via Le Châtelier's principle.

- Haloform reaction.

- General form.



- This reaction essentially constitutes the base-catalyzed halogenation of enols.
- We can run this reaction with any halogen (not just bromine), hence the name “haloform reaction.”
- This is how chloroform is made!

- **Bromoform:** The right product of the haloform general reaction above. *Also known as tribromomethane.*
 - More generally, any trihalomethane has an old-school, common -form name. For example, we also have **chloroform** (trichloromethane) and **iodoform** (triiodomethane).
- Mechanism.

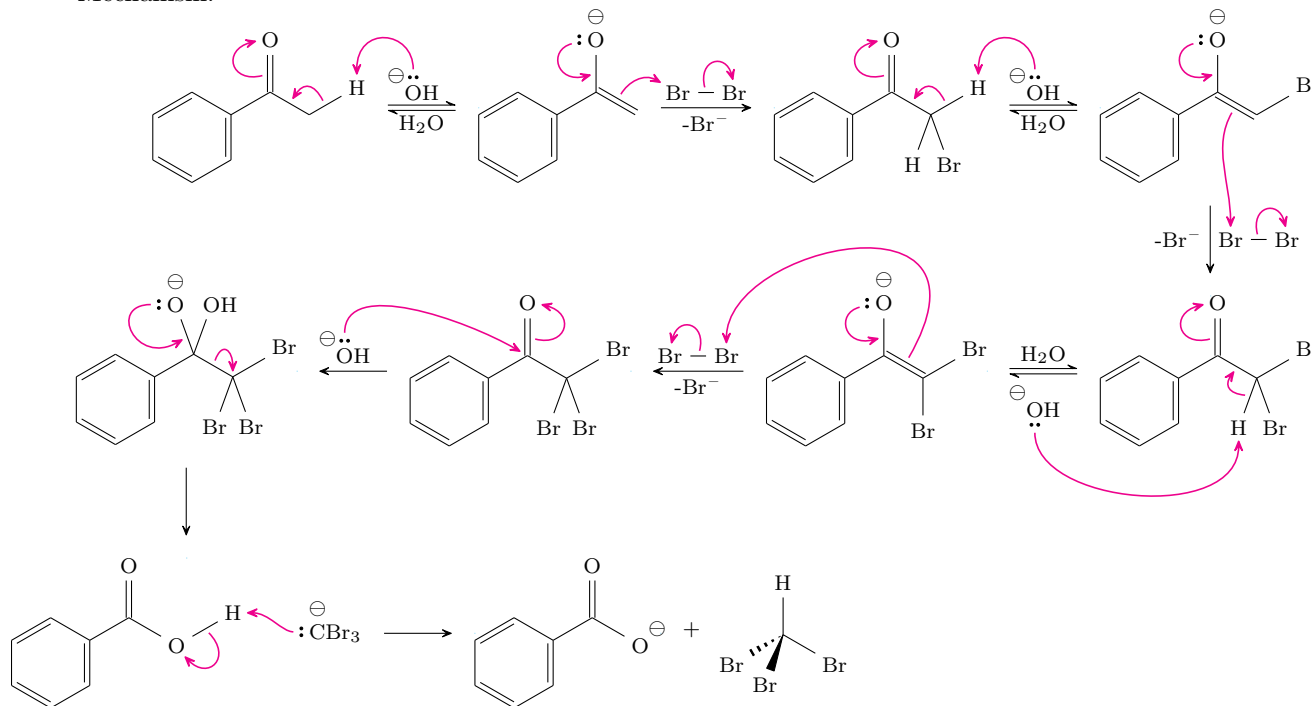
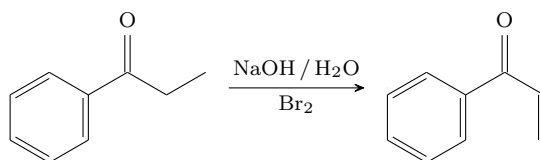


Figure 18.8: Haloform reaction mechanism.

- As with the acid-catalyzed version, only a little bit of the enol will be present at each stage, but Le Châtelier's principle is our friend here.
- Carbons are not usually good leaving groups, but with three strongly electron-withdrawing halogens, it will leave when the hydroxide is out of options in a last-ditch nucleophilic acyl substitution.
- Explaining the difference in the acid- vs. base-catalyzed halogenation of enols.
 - Consider the molecule which doubles as the product in the acidic mechanism and the second intermediate in the basic mechanism.
 - If we are to react this molecule further in the acidic mechanism...
 - The first step is protonation of the carbonyl.
 - The bromine (an EWG) *destabilizes* the positive oxygen.
 - Thus, the SM (which lacks the EWG bromine) reacts faster under acidic conditions. Therefore, all of it will react before any of the product reacts.
 - If we are to react this molecule further in the basic mechanism...
 - The first step is deprotonation at the α -carbon, resulting in an alkoxide anion.
 - The bromine (an EWG) *stabilizes* the negative oxygen.
 - Thus, the monobrominated species reacts faster under basic conditions. This favoritism is exacerbated by the addition of further bromines. Therefore, one molecule of the monobrominated species will react to completion before any more of the SM reacts.

- As further evidence, if we do the basic version with only 1 equivalent of bromine, we observe 1/3 carboxylate, a corresponding amount of bromoform, and 2/3 SM in the products.
- The haloform reaction doesn't always work.

Figure 18.9: β -hydrogens in the haloform reaction.

- When there are β -hydrogens, we generate an α, β -unsaturated ketone.
- This is because we'll brominate once (the α -hydrogens still have a far lower $\text{p}K_{\text{a}}$ than the β -hydrogens, so they attract the base) and then do an E2.
- Synthetically, the haloform reaction has uses most similar to the Baeyer-Villiger.

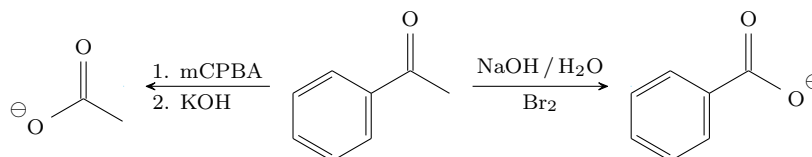


Figure 18.10: Synthetic uses of the haloform reaction.

- Suppose we have a ketone and want to create a carboxylate.
- The haloform reaction selectively cleaves methyl groups, installing an oxygen anion.
- The Baeyer-Villiger selectively inserts an ether into the bond to larger groups.
 - We can then cleave the larger group via the saponification mechanism.
- Note also that this reaction is useful as a C–C bond *cleaving* reaction.
 - We have even less of these than we do C–C bond forming reactions.
 - The only ones we have are periodate cleavage, ozonolysis, and the two techniques just described here.
- Midterm questions and review.
- Origin of selectivity for the Beckmann?
 - Discusses the transition state.
 - Goes into the σ^* orbital explanation.
 - Since σ^* is higher in energy than σ is low, filling σ^* breaks the bond.
 - The external lobe is significantly bigger than the internal (along the bond) lobe.
- The more sterically hindered the ketone, the harder it will be to do stuff to it.
- SOCl_2 releases HCl when there's no pyridine around.
 - We're only being graded on the presence of the organic products, though.
- In the Wolff-Kirshner, we do need both hydrogens in the hydrazone.
 - Modify notes!

- If we have some steps in the beginning of a mechanism and some steps in the end with a gap in between, we will get credit for what's on both sides.
- DPPA is paired with NEt_3 .
 - Modify notes!
- Ketal formation happens on ketones and aldehydes only (not carboxylic acid derivatives).
 - Modify notes!