

# Unit 5

## Enolate Chemistry

### 5.29 Enols and Enolates

11/15:

- Grade cutoffs on Exam 3.
  - A: 85-100.
  - B: 70-84.
  - C: 63-69.
  - < C: < 57.
  - If you are considering dropping this class, the drop date is 11/20.
    - It does not count as a drop if you just stop showing up and stop submitting assignments.
    - Go to the Registrar's site and fill out an add/drop form.
  - If you are doing less well than you had hoped or expected, talk to your TFs about options!
    - You may be eligible for tutoring.
    - It is *your responsibility* to reach out for help.
- Fun (or scary) Friday: Prof. Buchwald sings the elements song!
- Announcement: Unit 5 study guide posted.
- We now begin the first of four lectures in Unit 5: Enols and enolates.
  - Readings: Chapters 20, 25, 26 of Clayden et al. (2012).
- Lecture outline.
  - A. Background.
    - Enolate definition.
    - Keto-enol tautomerization (base-catalyzed and acid-catalyzed).
    - Evidence: Deuterium exchange.
  - B.  $\alpha$ -halogenation of ketones.
    - Base-promoted mechanism (and complications).
    - The haloform reaction.
    - Acid-catalyzed mechanism.
  - C.  $\alpha$ -alkylation.
    - Lithium diisopropylamide.
    - Malonate ester synthesis.
    - Kinetic vs. thermodynamic enolates.

- We'll begin with Topic A: Background.
  - Defining enolates.

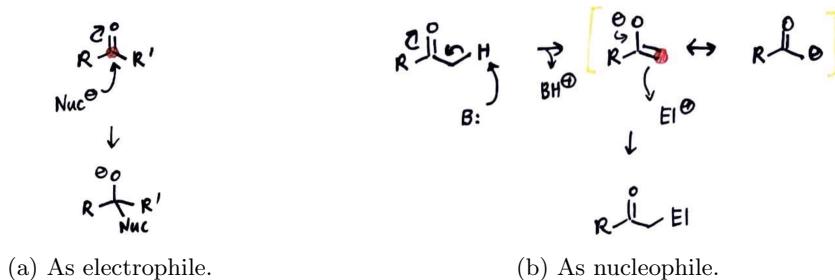


Figure 5.1: Carbonyl-based chemical reactions.

- Carbonyls have two important modes of reactivity.
  - We've already discussed how carbonyls can act as electrophiles (Figure 5.1a).
    - This yields a tetrahedral intermediate, as we've discussed.
  - The other mode of reactivity — which is new and our focus — is that we can deprotonate at the  $\alpha$ -carbon to make a nucleophilic species (Figure 5.1b).
    - The major resonance structure will be the oxygen-centered one (because oxygen is more electronegative).
    - However, most reactions we're interested in proceed at carbon.
  - Key concept: Oxygen *enables* this mode of reactivity stabilizing the negative charge.

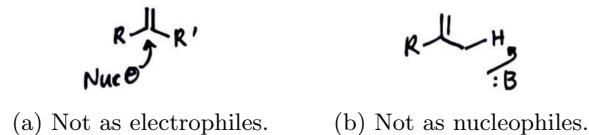


Figure 5.2: Alkenes do not react via carbonyl-analogous pathways.

- For the purposes of 5.13, analogous addition to alkenes (Figure 5.2a) and  $\alpha$ -deprotonation of alkenes (Figure 5.2b) is very rare.
  - Let's now discuss tautomers.



Figure 5.3: Keto-enol tautomerization.

- Ketones can tautomerize to **enols** (a portmanteau of alkene and alcohol).
  - The keto and enol form are known as **tautomers**.
  - The equilibrium favors the keto form by far (about a million to one; we'll only have 0.001% enol).

• Catalysts can speed up the interconversion, but they can't change the equilibrium.

  - Let's discuss the mechanism by which bases and acids speed this process up, though.

- Base-catalyzed keto-enol tautomerization mechanism.

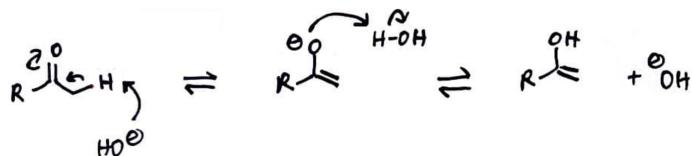
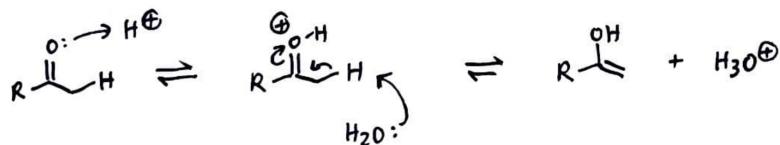
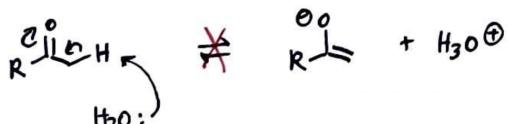


Figure 5.4: Keto-enol tautomerization mechanism (base-catalyzed).

- The  $\alpha$ -carbon of a ketone has  $pK_a \approx 20$ .
  - This is a good number to memorize, not because you'll ever be tested on it but because understanding relative  $pK_a$ 's will aid your chemical intuition.
- Hydroxide can speed up this process by deprotonating the  $\alpha$ -carbon.
  - Then we just protonate the oxygen.
- Recall that we still have  $K_{\text{eq}} \ll 1$ .
- Acid-catalyzed keto-enol tautomerization mechanism.



(a) Correct mechanism.



(b) Incorrect mechanism.

Figure 5.5: Keto-enol tautomerization mechanism (acid-catalyzed).

- We can either write the reagents equivalently as  $\text{H}^+/\text{H}_2\text{O}$  or  $\text{H}_3\text{O}^+$ .
- As we've been doing, we begin by protonating the carbonyl.
- Then the best base in solution comes and deprotonates the  $\alpha$ -carbon.
  - Water isn't a great base, but it's all we've got.
- Note that we do *not* do deprotonation first and protonation second, as drawn in Figure ??b.
  - Remember that anions cannot exist in acidic solution!
- So this is all great, but what if we don't believe Prof. Buchwald that tautomerization occurs?
  - It's good to question things in science!
  - Many times, we've assumed things that later experiments have proven incorrect.

- We can find evidence for enolization via an isotopic labeling study.

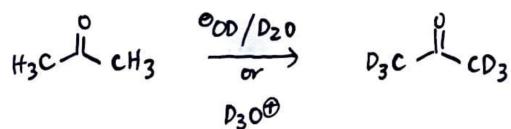


Figure 5.6: Isotopic labeling provides evidence for keto-enol tautomerization.

- If we dissolve acetone in basic deuterated water and deuterioxide (or acid), we will eventually obtain deuteroacetone.
- The mechanism proceeds analogously to Figure 5.4 or 5.5a, except that our reagents are all  $\text{DO}^-$  and  $\text{D}_2\text{O}$ .
  - In particular, we replace each of the six hydrogens one at a time with deuterium, eventually leading to the product.
  - We form the fully deuterated product instead of a H/D-mixed product because we assume that the concentration of deuterated acid or base and water is *much* greater than the concentration of acetone. This is similar to the swamping effect in Figure 4.31a.
- We now move onto Topic B:  $\alpha$ -halogenation of ketones.
  - We can do this with chlorine, bromine, or iodine.
- Base-promoted  $\alpha$ -halogenation mechanism.

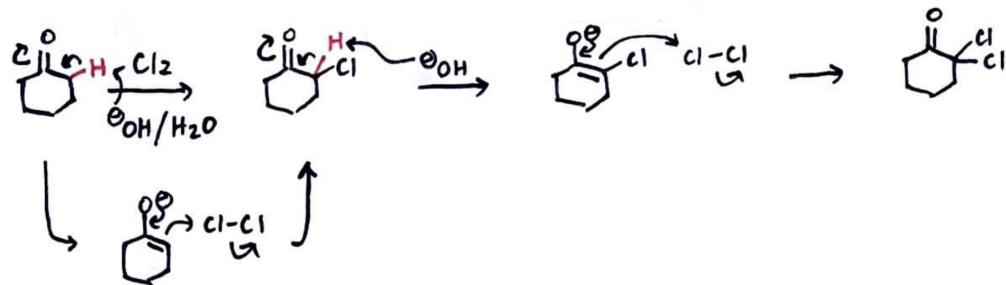


Figure 5.7:  $\alpha$ -halogenation mechanism (base-promoted).

- Imagine we mix cyclohexanone with chlorine gas under basic conditions. What's going to happen?
- We'll form a small amount of enolate, and then chlorinate to form  $\alpha$ -chlorocyclohexanone.
  - We declare victory!
  - Except that the world is a harsh place and — like in Figure 3.17a — we can get further reactivity.
- In particular, the hydrogen geminal to the  $\alpha$ -chlorine is now *more* acidic (proximity to an EWG, so anion is stabilized).
  - Thus, we can react again to get  $\alpha$ -dichlorocyclohexanone.
  - Thus, this reaction is not good... except in one case.

- The iodoform reaction.

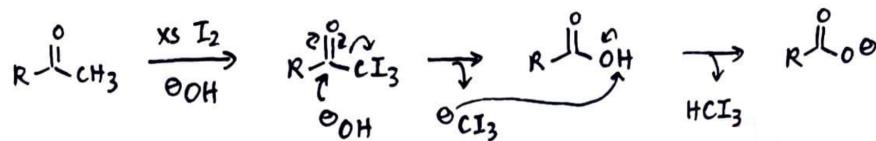
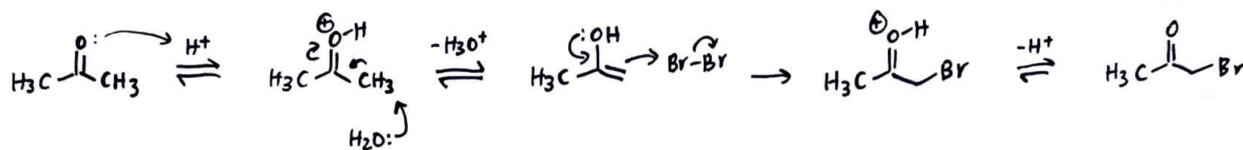


Figure 5.8: Iodoform reaction.

- In the first step, we have three successive iodinations to yield the triiodomethylketone.
- This is such a strong EWG and good leaving group that the triiodomethylketone acts kind of like an acid chloride.
  - In particular, we get an addition-elimination mechanism that kicks out the triiodomethanide anion.
  - This anion can then be protonated by the resultant carboxylic acid to yield iodoform ( $\text{HCl}_3$ ) and a stable carboxylate.
- Iodoform precipitates as a yellow solid.
  - In the olden days, it used to be a test for a ketone.
  - Before we had NMR, mass spec, and other kinds of spectroscopy, we had a bunch of test reagents that we would add to our compounds to determine what it was.
  - Essentially, if we had a compound and we didn't know what it was but thought it was a ketone, we could confirm or deny this by adding iodine and base to our mixture!
- What does it mean when Prof. Buchwald draws a circular arrow from a carbonyl  $\pi$ -bond back to it?
  - They use this in Clayden et al. (2012)!
  - This is a shorthand for the two-step addition-elimination process, in which electrons kick up in a first step and then kick back down in a second step.
  - This is similar to how we shorthand a two-step proton transfer as "PT!"
- So how do we make mono- $\alpha$ -haloketones, if that's our goal?
  - Use acid-catalyzed  $\alpha$ -halogenation!
- Acid-catalyzed  $\alpha$ -halogenation mechanism.

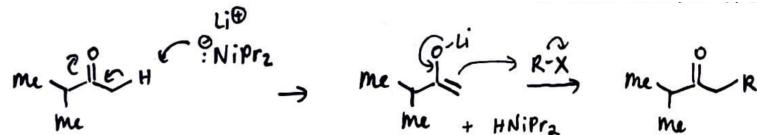
Figure 5.9:  $\alpha$ -halogenation mechanism (acid-catalyzed).

- Acids encourage the rate of formation of the enol.
- Then if we do this in the presence of bromine, we'll get  $\alpha$ -bromoacetone (following deprotonation).
- Now the product is *less* reactive than the starting material (because the bromine EWG stabilizes the carbonyl and disfavors protonation of it).
- Takeaway: Acid-catalyzed  $\alpha$ -halogenation is selective for monohalogenation.
- This process is used to synthesize a lot of medicines and drug molecules.

- We now move onto Topic C:  $\alpha$ -alkylation.
  - This is the heavy hitter; a really, really important reaction of ketones.
- General form.

Figure 5.10:  $\alpha$ -alkylation.

- Suppose we want to convert a ketone into a new compound where we've formed a C–C bond.
- The other reagent is a primary or secondary alkyl halide.
- Drawing a mechanism for this doesn't seem too bad at first.
  - We may deprotonate to the enolate and attack the alkyl halide to start.
  - But there is a complication.
    - We get lots of side reactions!
  - In 5.13, we're all about efficiency and elegance, so this is not good.
- There are several solutions to this issue, which we'll discuss presently.
- Solution 1: Use lithium diisopropylamide (LDA).

Figure 5.11:  $\alpha$ -alkylation with lithium diisopropylamide.

- See Figure 3.3b for the structure and synthesis of LDA.
- Helpful characteristics of LDA.
  - LDA is a strong base.
  - It is secondary and hence hindered (therefore a poor nucleophile).
  - The conjugate acid of LDA has  $\text{pK}_a \approx 35$ .
  - Thus, it will only deprotonate and not do any competitive addition chemistry!
- We begin with an essentially irreversible deprotonation to the enolate.
- This is followed by 100% conversion to the alkylated product.
- Using LDA is a relatively modern solution — only about 50 years old.
  - However, organic chemistry has been around for close to 250 years!
  - The roots of organic chemistry are in the old German dye industry, which morphed into the present-day pharmaceutical industry.
  - So how did people do this stuff before LDA? Via solution 2.

- Solution 2: Malonate ester synthesis.

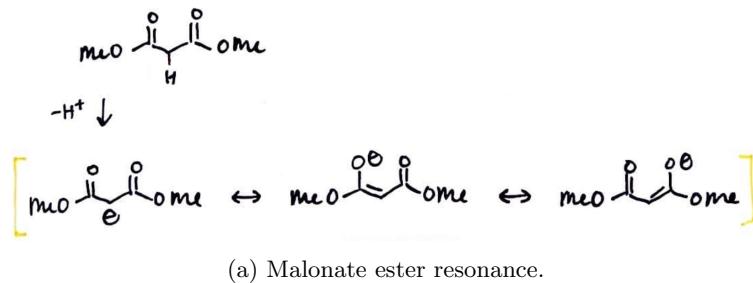


Figure 5.12:  $\alpha$ -alkylation with malonate esters.

- The starting material has esters on both sides (either ethyl or methyl; it doesn't matter).
- The important thing is that for the malonate ester,  $pK_a \approx 13$ .
  - In contrast, a regular ester has  $pK_a \approx 25$ .
  - Why this drastic difference in  $pK_a$ ?
    - The deprotonated malonate ester's anion has more resonance forms (two adjacent carbonyls into which to delocalize!) than the deprotonated ester (only one adjacent carbonyl).
  - This difference leads us to call the deprotonated malonate ester a **soft enolate**.
  - These characteristics make it very easy and safe to work with, so it's often used at scale.
- We'll now quickly introduce a topic that we'll also discuss more next time.
- Kinetic vs. thermodynamic enolates.
- Kinetic** (enolate): The enolate generated by deprotonation at the less-substituted position, all else being equal.
- Example: LDA (really big and bulky) will selectively form the kinetic enolate at the unsubstituted position of  $\alpha$ -methylcyclohexanone.



Figure 5.13: Kinetic enolate formation.

- This enolate could then be used — for example — to attack methyl iodide ( $\text{MeI}$ ) and alkylate.
- Note that this process would most likely form a mixture of stereoisomers.

- **Thermodynamic** (enolate): The enolate that is more stable.
- Example: Potassium *t*-butoxide ( $\text{KO}^t\text{Bu}$ ) has  $pK_a \approx 16-18$ , so it deprotonates  $\alpha$ -methylcyclohexanone reversibly until we get the more stable one.

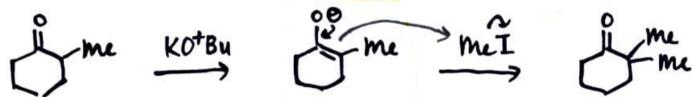


Figure 5.14: Thermodynamic enolate formation.

- Treating this with  $\text{MeI}$  then generates the  $\alpha$ -dimethylated form of cyclohexanone.
- You can add in  $\text{Me}_3\text{SiCl}$  to trap enolates as silyl enol ethers.

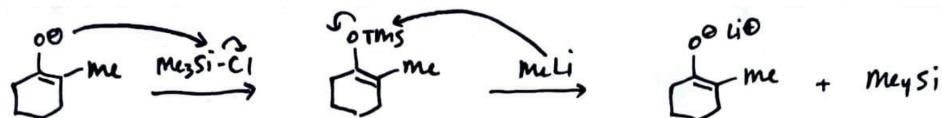


Figure 5.15: Trapping enolates as silyl enol ethers.

- This silyl protecting group could then be removed with  $\text{MeLi}$ , regenerating the enolate and yielding tetramethylsilane ( $\text{SiMe}_4$ ) as a byproduct.
- In the deprotection step, the methyl anion attacks the silicon atom in the TMS group, engaging in an  $S_N2$  displacement.