

# 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 iodoform 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.

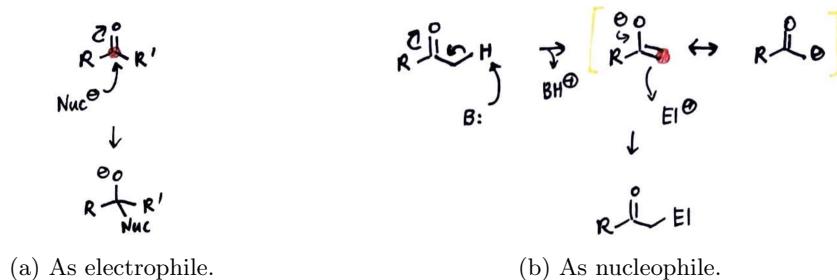


Figure 5.1: Carbonyl-based chemical reactions.

- 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.

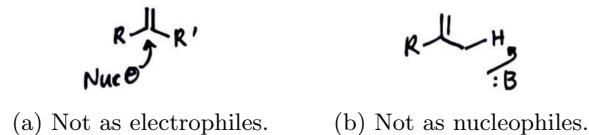


Figure 5.2: Alkenes do not react via carbonyl-analogous pathways.

- 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.

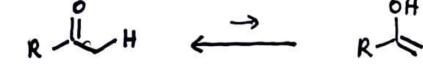


Figure 5.3: Keto-enol tautomerization.

- 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.

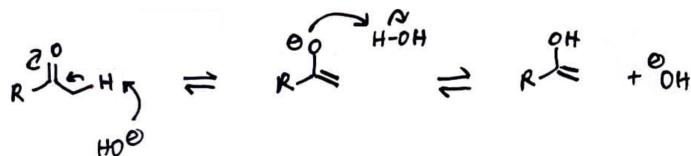
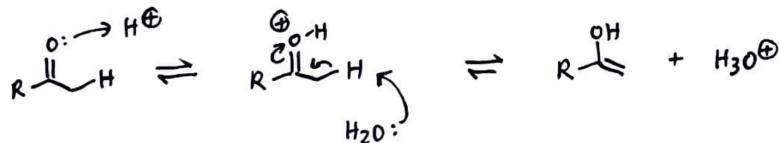
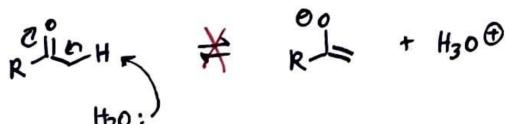


Figure 5.4: Keto-enol tautomerization mechanism (base-catalyzed).

- 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.

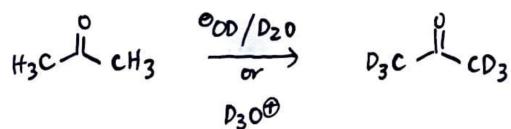


Figure 5.6: Isotopic labeling provides evidence for keto-enol tautomerization.

- 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.

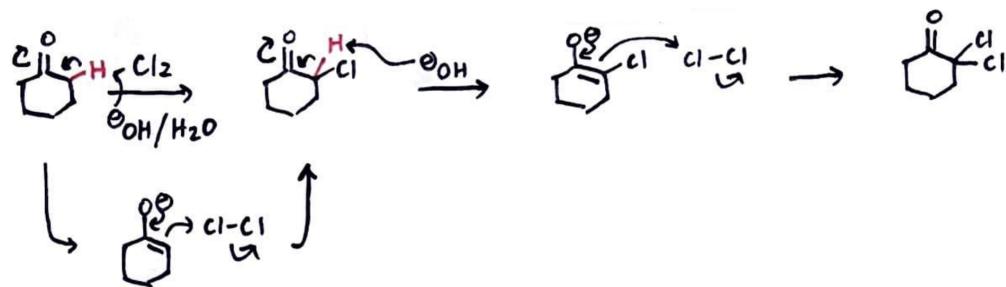


Figure 5.7:  $\alpha$ -halogenation mechanism (base-promoted).

- 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.

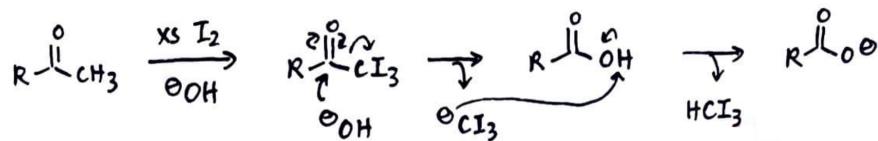
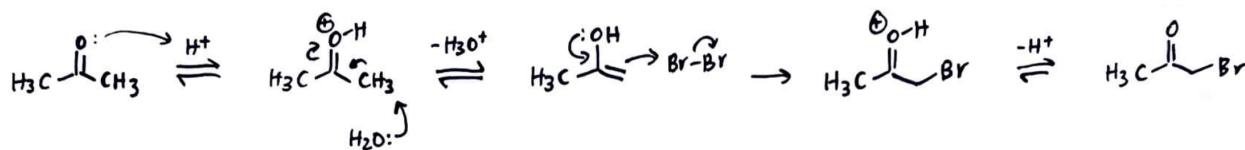


Figure 5.8: Iodoform reaction.

- 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.

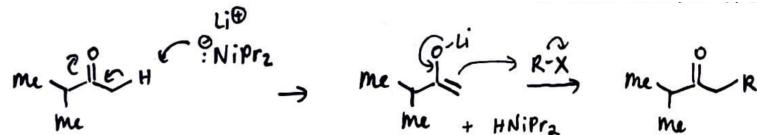
Figure 5.9:  $\alpha$ -halogenation mechanism (acid-catalyzed).

- 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.

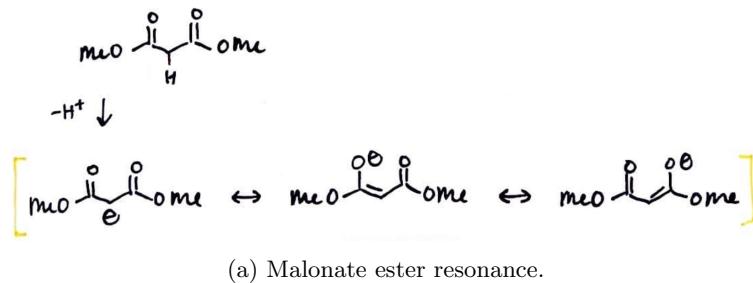


Figure 5.12:  $\alpha$ -alkylation with malonate esters.

- 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.

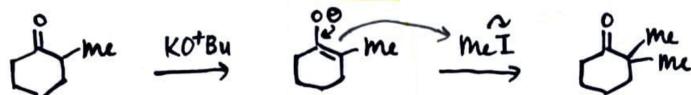


Figure 5.14: Thermodynamic enolate formation.

- 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.

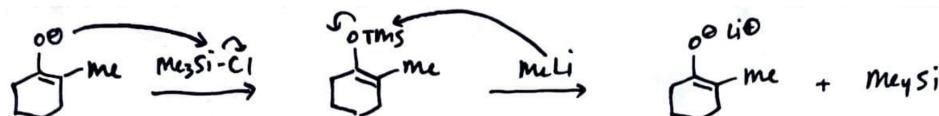


Figure 5.15: Trapping enolates as silyl enol ethers.

- 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.

## 5.30 Enolate Alkylation

11/18:

- We will not begin with a line-by-line review of last lecture; rather, we will clarify some things.
- Lecture 29 recap.
  - Recall kinetic vs. thermodynamic enolates (Figures 5.13 & 5.14).
  - When we use a strong, hindered base (like LDA), we abstract the unhindered proton to form the kinetic enolate.
    - This process is irreversible, and yields 100% of the kinetic enolate.
    - The process is irreversible because  $pK_a \approx 35$  for the conjugate acid of LDA (lithium diisopropylamide), so this conjugate acid cannot react backwards.
  - Use of a somewhat strong, somewhat bulky base (like  $\text{KO}^t\text{Bu}$  in  ${}^t\text{BuOH}$ ).
    - This process is highly reversible, so we'll abstract the unhindered proton first. But then the enolate can react backwards with  ${}^t\text{BuOH}$  to reform the ketone!
    - This process is highly reversible because  $pK_a \approx 19$  for  ${}^t\text{BuOH}$ , so this conjugate acid *can* react backwards.
    - However, when we eventually deprotonate the hindered proton, we form a more stable enolate that is *less likely* to react backwards.
    - Thus, the net result is that we form the *thermodynamic* enolate under these conditions.
  - Both of these enolates can then be trapped with  $\text{MeI}$  into the corresponding  $\alpha$ -alkylation product.

- Lecture outline.

C.  $\alpha$ -alkylation.

- Enolate-forming bases.
- Enolates from esters (hard to form) and aldehydes (don't form).
- Enolate-alkylation electrophiles.
- Synthesis of  $\alpha$ -substituted acetic acid derivatives.
- Synthesis of  $\alpha$ -substituted 1,3-diols.

- We return to Topic C:  $\alpha$ -alkylation.
- Let's consider the properties of several strong bases.

<u>Base</u>	<u>Conjugate Acid (of Base)</u>	<u>pK<sub>a</sub> of Conjugate Acid</u>
NaOEt/EtOH	EtOH	~16
KOtBu/ <sup>t</sup> BuOH	<sup>t</sup> BuOH	~19
LDA/THF	iPr <sub>2</sub> NH	~35

Table 5.1: pK<sub>a</sub>'s of typical enolate-forming bases.

- The left column shows a base and the solvent in which you use it, not necessarily the base and its conjugate acid!
- It follows from the table that NaOEt and KO<sup>t</sup>Bu are reversible bases, and LDA is an irreversible base.
- The difference between the first two is that KO<sup>t</sup>Bu is bulkier and less nucleophilic.
  - So if we're worried about nucleophilic attack as a side reaction, use this!
- Otherwise, NaOEt is cheaper and more pleasant to work with.
- So what happens when we do enolate formation with different bases?
  - Suppose that the conjugate acid B<sub>1</sub>H has pK<sub>a</sub> > 22.
    - Then the reaction is irreversible.
    - Example: LDA!
  - Suppose that the conjugate acid B<sub>2</sub>H has 16 < pK<sub>a</sub> < 22.
    - This reaction is reversible.
    - Examples: NaOEt and KO<sup>t</sup>Bu!
  - Suppose that the conjugate acid B<sub>3</sub>H has pK<sub>a</sub> < 16.
    - Nothing happens! The base isn't strong enough.
  - Note: We'll read in Clayden et al. (2012) that we can use bases with pK<sub>a</sub> < 16 *if* we pair it with a Lewis acid.
    - Example: Trimethylsilyl chloride (TMSCl) and NEt<sub>3</sub>.
  - Generalizing this.
    - Consider the pK<sub>a</sub> of our  $\alpha$ -proton.
    - If the base is 3 pK<sub>a</sub> units weaker or stronger, we get reversible enolate formation.
    - If the base is more than 3 pK<sub>a</sub> units stronger, we get irreversible enolate formation.
    - If the base is more than 3 pK<sub>a</sub> units weaker, no reaction occurs because the base is too weak.

- Example: Consider methyl isopropyl ketone.
  - Use LDA to deprotonate at the methyl group and form the kinetic enolate.
  - Use  $\text{KO}^t\text{Bu}$  in  $t\text{BuOH}$  to form the thermodynamic enolate.
- How about forming enolates from esters?
  - We need LDA because  $pK_a \approx 25$  for the ester's  $\alpha$ -proton.
  - Indeed, esters have significantly less acidic  $\alpha$ -protons than ketones.
  - We also need low temperatures to prevent self-condensation.
- How about forming enolates from aldehydes?
  - For the purposes of this class, we'll say that aldehyde enolates don't exist.
  - In reality, aldehyde enolates *do* exist, but they are *so* reactive that even at low temperatures, there is lots of competitive self-condensation.
- We now return to alkylations of enolates in more depth.
  - There are parallels to  $\text{S}_{\text{N}}2$  reactivity here.
  - Enolates are more hindered than, for example, cyanide nucleophiles ( $\text{CN}^-$ ), azide nucleophiles ( $\text{N}_3^-$ ), etc.
    - They are also more basic.
  - For the purposes of 5.13...
    - We'll say that primary alkyl, methyl, benzyl, and allyl halides react with enolates to do  $\alpha$ -alkylation.
      - The TFs will discuss in recitation why benzyl and allyl halides are "activated!"
    - We'll also say that secondary alkyl halides do not react with enolates.
      - This is because it's more hindered, so we get more competitive elimination.
  - Tertiary, vinyl, phenyl, and neopentyl halides *never* react with enolates.
    - Note that neopentyl is bad (even though it's primary) because it's *super* bulky.
- We now discuss the synthesis of  $\alpha$ -substituted malonate esters.

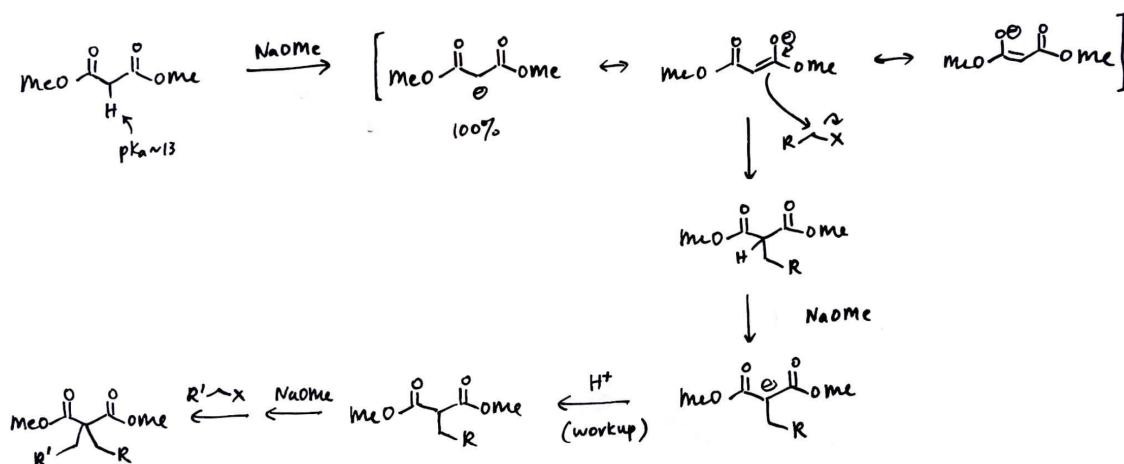
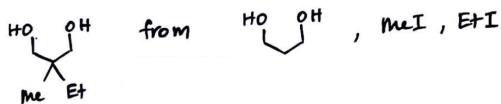


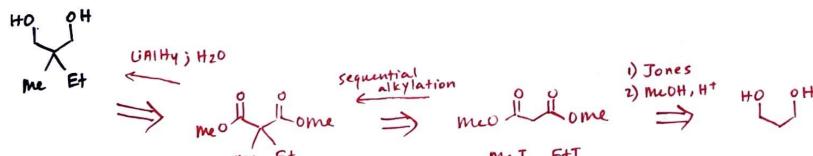
Figure 5.16: Malonate ester synthesis.

- Recall malonate esters from last class (see Figure 5.12a).
- Since these compounds have  $pK_a \approx 13$  at their  $\alpha$ -protons, NaOMe can do 100% deprotonation.
  - Note that we match the base to the ester: Dimethyl malonate should be paired with NaOMe in MeOH and diethyl malonate should be paired with NaOEt in EtOH.
  - This is because we'll have competitive transesterification (see Figure 4.32), so matching the base ensures that we don't get a mixture of products.
- Our deprotonated malonate ester can then attack some C–X bond, alkylating the  $\alpha$ -position.
- But we're still in basic solution, so our species will be deprotonated until water workup.
  - Do assume that we will *not* get competitive dialkylation.
  - However, alternatively, we could add more base and another C–X species to yield a dialkylated species.
- These reactions are collectively known as the **malonate ester synthesis**.

- TTQ: Given propane-1,3-diol, MeI, and EtI, make the product shown in Figure ??a.



(a) The desired molecule and starting materials.



(b) Retrosynthetic pathway.

Figure 5.17: TTQ: Synthesis of an  $\alpha$ -substituted 1,3-diol.

- You might get greedy and start thinking about how to deprotonate the middle carbon directly, but we can't do that; we have to go back to something more reasonable first.
- Indeed, we can do a malonate ester synthesis with sequential alkylations followed by LAH reduction to the diol!
- Tip: Whenever you see a 1,3-diol, you should ask yourself if a malonate ester can be used!
- Note that we make the malonate ester from the 1,3-diol via Jones oxidation (see Figure 4.6a) followed by Fischer esterification (see Figure 4.34).
- We now discuss a related process called the **acetoacetate synthesis**.

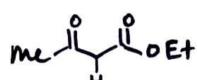


Figure 5.18: Ethyl acetoacetate.

- Here, we have a *ketone* next to an ester group.
  - The reason that one is an ethyl ester and the other is a methyl ester is historical; we are totally fine to use ethyl or methyl esters wherever, as long as we're consistent.
- $pK_a \approx 11$  for ethyl acetoacetate.

- Let's now begin the synthesis.

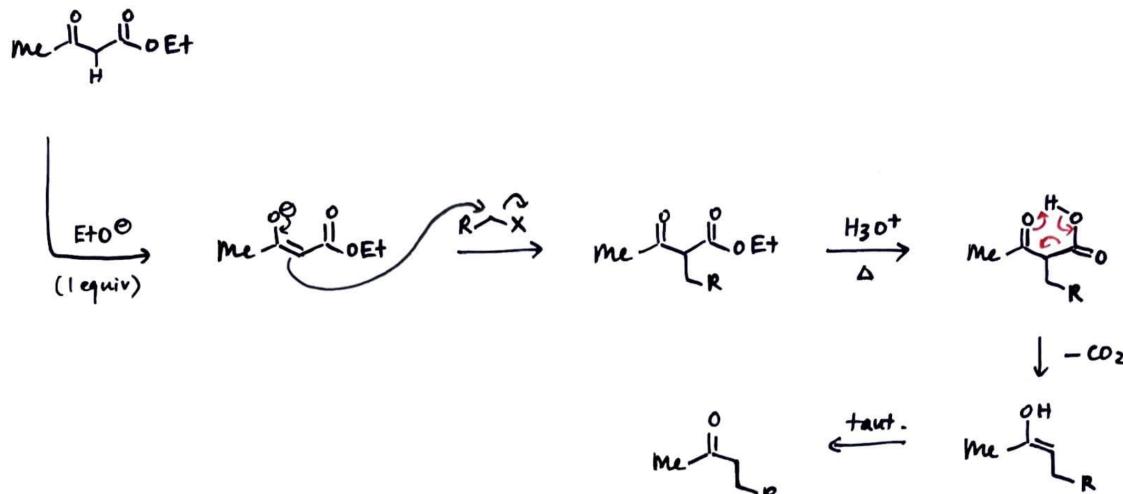
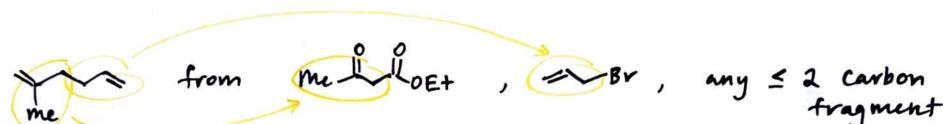
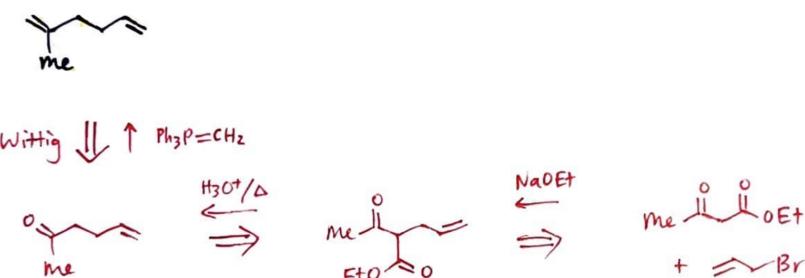


Figure 5.19: Acetoacetate synthesis.

- Adding 1 equivalent of  $\text{EtO}^-$  deprotonates to the enolate.
  - Note that the resonance will be primarily with the ketone, *not* the ester!
- Then we can do our alkylation.
  - We could even do a second alkylation, but we're just not going to show that here.
- Next step: We heat our intermediate in acid, which first gives ester hydrolysis to the  **$\beta$ -ketoacid**.
  - $\beta$ -ketoacids are known to undergo decarboxylation to yield enols!
- However, in acidic solution, our enol will quickly tautomerize to a ketone.
- Takeaway: This reaction is equivalent to enolate alkylation with LDA (see Figure 5.13).
  - However, LDA is pyrophoric and hence nasty to work with.
  - The acetoacetate synthesis, however, is **bucket chemistry** (easy, safe, and scalable).
- TTQ: Make 2-methylhexa-1,5-diene from ethyl acetoacetate, allyl bromide, any other reagent we want with two or fewer carbons, and any other non-carbon reagent.



(a) The desired molecule and starting materials.



(b) Retrosynthetic pathway.

Figure 5.20: TTQ: Using the acetoacetate synthesis.

- Match up the carbons as we've done previously.
- A Wittig would yield the product.
- Next step: We can go back to the acetoacetate.
- Next step: Do alkylation from the starting materials.