

## Chapter 23. Alpha Substitution of Carbonyl Compounds.

### 1. Enolates.

- a) Carbonyl compounds are *acidic* at the  $\alpha$  C, can be deprotonated by bases to give *enolates*.
  - i) Ketones and aldehydes have  $pK_a = 18-20$ , about as acidic as alcohols. Acidity of simple carbonyls is directly related to energy of carbonyl: the lower in energy, the less acidic. So aldehydes are more acidic than ketones. Acetone, a typical ketone, has  $pK_a = 20$ .
  - ii) Two carbonyl groups are even better than one. Generally 1,3-dicarbonyl compounds have  $pK_a$  of 9-14, more acidic than alcohols. Diethyl malonate has  $pK_a = 13$ , ethyl acetoacetate and malononitrile have  $pK_a = 11$ , ethyl cyanoacetate and 2,4-pentanedione have  $pK_a = 9$ .
- b) Choice of base for deprotonation of carbonyl compounds.
  - i) Simple carbonyl compounds can be completely and irreversibly deprotonated by a strong base in an aprotic solvent. The base most widely used for this purpose, LDA, is derived by deprotonating *i*-Pr<sub>2</sub>NH ( $pK_a \approx 37$ ) with BuLi. LDA will deprotonate ketones, esters, or 3° amides in this way.
  - ii) LDA deprotonates unsymmetrical ketones on less hindered side (steric hindrance).
  - iii) Limitations to LDA:
    - Not useful for aldehydes and acyl chlorides — side reactions occur.
    - Not useful for deprotonating CH<sub>3</sub>COX (methyl ketones, acetonitrile, ethyl acetate, other esters and amides of acetic acid) — side reactions occur.
    - With 1° or 2° amides, deprotonates N.
  - iv) A moderate base such as EtO<sup>-</sup> cannot deprotonate a simple carbonyl compound irreversibly. However, a small amount of enolate is generated when NaOEt (or another alkoxide) is added to a ketone or ester in EtOH (or another alcohol), and this small amount of enolate can react with some electrophiles. EtO<sup>-</sup> deprotonates ketones on *more* substituted side — reversible deprotonation, so two different enolates are in equilibrium, and more substituted enolate is lower in energy.
  - v) 1,3-Dicarbonyl compounds are completely and irreversibly deprotonated by moderate bases such as NaOEt. LDA is not used for 1,3-dicarbonyl compounds (overkill).
- c) *Enolates are nucleophilic at the former  $\alpha$  C.* Reaction of an enolate with an electrophile gives a carbonyl compound with a new bond.
- d) Ketones and aldehydes with  $\alpha$ -stereocenters racemize readily under acidic or basic conditions.

### 2. Enols.

- a) Carbonyl compounds are in equilibrium with *enols*. Enols and carbonyl compounds are *tautomers*.
- b) Carbonyls are converted to the enols under both acidic and basic conditions.
  - i) Under acidic conditions, protonation, then deprotonation. Any strong acid in a protic solvent such as EtOH or H<sub>2</sub>O can be used. (Sometimes no solvent is used.)
  - ii) Under basic conditions, deprotonation to give an *enolate*, then protonation. The base is

typically  $\text{HO}^-$  in  $\text{H}_2\text{O}$ ,  $\text{EtO}^-$  in  $\text{EtOH}$ , or  $t\text{-BuO}^-$  in  $t\text{-BuOH}$ .

- c) The equilibrium constant for the carbonyl  $\rightleftharpoons$  enol reaction usually lies far on the side of the carbonyl. (Cyclohexanone:  $K_{\text{eq}} = 10^{-6}$ ; acetone:  $K_{\text{eq}} = 10^{-8}$ .) *The lower in energy the carbonyl, the less enol is present at equilibrium.* Among simple carbonyl compounds, only ketones, aldehydes, and acyl chlorides have enough enol present at equilibrium to be detected chemically. Esters and amides have negligible amounts of enol present. However, all types of 1,3-dicarbonyl compounds have large amounts of enol present at equilibrium.
- d) Enols are *nucleophilic* at the C  $\beta$  to the HO group, i.e. at the former  $\alpha$  C. Reaction of an enol with an electrophile gives a protonated carbonyl compound.
- e) Although enols are formed under both acidic and basic conditions, *they are reactive intermediates under acidic conditions only.* Under basic conditions, the *enolate* is the reactive species.
3. Alkylation of enolates with alkyl halides. Forms C–C bonds!
- a) Alkylation of simple carbonyl compounds.
- Ketones are treated with LDA, then with  $1^\circ$  alkyl halide (iodide is best). Overall substitution of  $\alpha$  H of carbonyl with alkyl group.
    - $\text{RCH}_2\text{COR}'' + \text{LDA}$ , then  $\text{R}'\text{I} \rightarrow \text{RCHR}'\text{COR}''$ .
  - Mechanism of substitution is  $\text{S}_{\text{N}}2$  of enolate on alkyl halide.
  - Generally useful only for  $1^\circ$  alkyl iodides, allyl bromide, or benzyl bromide (latter two are particularly reactive toward  $\text{S}_{\text{N}}2$ ). For  $2^\circ$  alkyl halides, better to use the 1,3-dicarbonyl approach (see below).
  - Retrosynthesis: A C–C bond between the  $\alpha$  C and the  $\beta$  C of a carbonyl compound can be made from the simpler carbonyl compound and the alkyl iodide.
  - When NaOEt is used as base to alkylate simple carbonyl compounds, *multiple alkylations occur uncontrollably* because the base cannot discriminate between starting material and product as it goes around making small amounts of reactive enolates. This does not happen with LDA because all of the starting material is cleanly converted to enolate before the alkylation is carried out.
  - Not useful for aldehydes because of competing aldol reactions.
  - If the starting nucleophile is a  $\text{CH}_3\text{C}=\text{O}$  compound, better to use the 1,3-dicarbonyl approach (below); otherwise, aldol reactions can interfere with clean alkylation.
- b) Alkylation of 1,3-dicarbonyl compounds.
- $\text{CH}_2(\text{COR})\text{CO}_2\text{Et} + \text{NaOEt} \rightarrow \text{NaCH}(\text{COR})\text{CO}_2\text{Et}$ , then  $\text{R}'\text{Br} \rightarrow \text{R}'\text{CH}(\text{COR})\text{CO}_2\text{Et}$ .
  - Can be done twice.  $\text{R}'\text{CH}(\text{COR})\text{CO}_2\text{Et} + \text{NaOEt} \rightarrow \text{NaCR}'(\text{COR})\text{CO}_2\text{Et}$ , then  $\text{R}''\text{Br} \rightarrow \text{R}'\text{CR}''(\text{COR})\text{CO}_2\text{Et}$ .
  - The alkylating reagent can be  $1^\circ$  or  $2^\circ$  alkyl bromide, chloride, or iodide — much more general than alkylation of simple carbonyl compounds.
  - The  $\text{CO}_2\text{Et}$  group can be replaced with H! Use the Krapcho decarboxylation:  $\text{H}_2\text{O}$ , DMSO,

LiCl, heat.

v) Retrosynthesis: A ketone  $RCHR'COR''$  can be made from  $RCH(COR'')CO_2Et$  and  $R'Br$ .  
*Especially useful for making  $\alpha$ -substituted acetone derivatives.*

c) Clean monoalkylation of carbonyl compounds requires *complete* deprotonation of carbonyl compound: LDA for simple carbonyls,  $EtO^-$  for 1,3-dicarbonyls.

4. Reaction of enols with  $X_2$ :  $\alpha$ -Halogenation reactions.

a) Ketone +  $Br_2 \rightarrow \alpha$ -haloketone + HBr. Takes place under acidic conditions.  $Cl_2$  can be used, too. Enol is key intermediate. Reaction stops after first substitution (unlike under basic conditions) because the electron-withdrawing halogen makes the enol of the product less nucleophilic toward more  $X_2$ .

b) Hell-Volhard-Zelinskii reaction.  $RCH_2CO_2H + PBr_3, Br_2 \rightarrow [RCH_2COBr] \rightarrow RCHBrCOBr, + H_2O \rightarrow RCHBrCO_2H$ . Conversion of acid to acyl halide occurs first; the acyl bromide, unlike the acid, enolizes rapidly (because it is high in energy); the enol of the acyl bromide reacts with  $Br_2$ . Then aqueous work-up gives the  $\alpha$ -haloacid, or addition of alcohol gives the ester.

c) Why useful?

i)  $\alpha$ -Halogenation accomplishes umpolung at  $\alpha$  C! Addition of  $Nu^-$  (e.g.,  $^-CN, ^-N_3$ ) gives substitution reactions at  $\alpha$  C.

ii)  $\alpha$ -Haloketones are dehydrohalogenated with pyridine, heat to give  $\alpha,\beta$ -unsaturated ketones.

iii)  $\alpha$ -Chloroacetone is riot control agent (tear gas).

5. Aldol reaction.

a) We have already discussed reaction of enols and enolates with alkyl halides and elemental halogens. A third important class of electrophiles is carbonyl compounds.

b)  $2 RCH_2CHO + \text{cat. acid or base} \rightarrow RCH_2CH(OH)CHRCHO$ . Also works for ketones.

c) Requires  $\alpha$ -H's or can't occur! So PhCHO doesn't undergo the reaction.

d) Equilibrium reaction. Favors product for  $RCH_2CHO$ , but favors starting material for  $R_2CHCHO$  and ketones due to steric hindrance.

e) Both  $\alpha$ -alkylation and aldol reactions use carbonyl compound + base. How do we differentiate?

i)  $\alpha$ -Alkylation requires alkyl halide. In absence of alkyl halide, aldol can occur.

ii) Aldol reaction requires undepronated carbonyl compound. If all carbonyl compound is rapidly and completely deprotonated, aldol cannot occur.

iii) For simple carbonyls, slow addition of carbonyl to slight excess of LDA ensures that all carbonyl is deprotonated quickly and prevents aldol.

iv) On the other hand, for simple carbonyls,  $EtO^-$  generates small amounts of enolate in presence of excess of carbonyl, so  $EtO^-$  promotes aldol.

v) For 1,3-dicarbonyls,  $EtO^-$  deprotonates completely.

f) Forms new C-C bond!

g) Intramolecular aldol reactions.

6. Aldols can be dehydrated to give  $\alpha,\beta$ -unsaturated carbonyls.

- a) Occurs under either acidic or basic conditions.
- b) Can only occur if the aldol product has an  $\alpha$ -H. Possible for butyraldehyde or cyclohexanone aldol, but not for isobutyraldehyde aldol.
- c) For ketones, aldol reaction is unfavorable, but C–C bond-forming reaction can be driven toward completion by favorable dehydration. E.g. cyclohexanone. But not for diisopropyl ketone or isobutyraldehyde!

#### 7. Mixed aldol reactions.

- a) Two different ketones or aldehydes can give four different products upon aldol reaction.
- b) The mixed aldol reaction can proceed cleanly *if*:
  - i) One of the components is an aldehyde lacking  $\alpha$ -H's, e.g. PhCHO or CH<sub>2</sub>O, and the other is a carbonyl compound that is resistant to being an electrophile (ketone or ester).  
Cyclohexanone + PhCHO (dehydration follows), ethyl hexanoate + xs CH<sub>2</sub>O (gives two aldols).
  - ii) One component is deprotonated completely with LDA, and *then* the other component is added (*directed* aldol reaction). *Very* useful for esters as nucleophiles! Doesn't work well for aldehydes (aldol competes with LDA deprotonation).
  - iii) One of the components is a 1,3-dicarbonyl compound. A 1,3-dicarbonyl compound doesn't act as an electrophile, and it is so acidic that only it (and not the other carbonyl) is deprotonated.
  - iv) The reaction occurs in an intramolecular fashion. So 2,5-hexanedione, 2,6-heptanedione, and 6-oxohexan-2-one all cleanly undergo aldol-dehydration reactions. Regiochemistry questions.
- c) Possible to do mixed aldols with *esters* or *amides* as the nucleophiles using strategies (i) or (ii) above. Evans oxazolidinones for enantioselective aldol reactions.

#### 8. Retro-aldol reaction.

- a) A  $\beta$ -hydroxycarbonyl compound can undergo a retro-aldol reaction under acidic or basic conditions.
  - i) Under acidic conditions, protonate carbonyl O, cleave C–C bond to give enol and protonated carbonyl, do a couple of H<sup>+</sup> transfers and deprotonate.
  - ii) Under basic conditions, deprotonate OH, cleave C–C bond to give enolate and carbonyl, protonate enolate.
- b) Retro-aldol reaction often occurs to relieve strain.
- c) Decarboxylation of a  $\beta$ -keto acid is a retro-aldol reaction.

#### 9. Conjugate addition.

- a) Alkenes are usually nucleophilic, but when substituted with a carbonyl group they become electrophilic. Acrolein, MVK, and more highly substituted analogs.
- b) An  $\alpha,\beta$ -unsaturated ketone or aldehyde is electrophilic both at the carbonyl C and at the  $\beta$ -C.

- c) Any reactions that a ketone or aldehyde can undergo at the carbonyl C, an  $\alpha,\beta$ -unsaturated ketone or aldehyde can undergo at the  $\beta$ -C.
- d) Mechanism involves addition of nucleophile to  $\pi$  bond to form enolate and protonation of enolate to give product.
- e) How do you know a priori whether a nucleophile will attack the  $\beta$ -C (1,4-addition) or the carbonyl C (1,2-addition)? You don't. It's a matter of memorizing the reagents.
- Amines and  $\text{C}\equiv\text{N}$  usually do 1,4-addition (attack  $\beta$ -C). **Another way to make C–C bond!**
  - $\text{LiAlH}_4$  tends to do 1,2-addition, while  $\text{NaBH}_4$  can do either 1,2- or 1,4-addition, depending on the structure of the substrate. But  $\text{NaBH}_4$  *always* does 1,2-addition in the presence of  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ .
  - Grignard reagents can do either 1,2- or 1,4-addition. **Another way to make C–C bond!**  
However:
    - Grignard reagents *always* do 1,2-addition in the presence of anhydrous  $\text{CeCl}_3$ .
    - Dialkylcuprates (Gilman reagents),  $\text{R}_2\text{CuLi}$ , derived from alkyl halide  $\text{RBr}$  by addition of Li metal and then  $1/2 \text{ CuI}$ , do 1,4-addition preferentially to  $\alpha,\beta$ -unsaturated ketones. So  $\text{RCOCH}_2\text{CH}_2\text{R} \Rightarrow \text{RCOCH}=\text{CH}_2 + \text{RBr}$ . And remember  $\text{RBr} \Rightarrow \text{ROH}$ !
  - Good carbon acid, e.g.  $(\text{EtO}_2\text{C})\text{CHR}$ , also adds to electrophilic alkene, e.g.  $\text{CH}_2=\text{CH}-\text{COMe}$ , in the presence of catalytic amounts of base to give product of addition across the  $\pi$  bond of the alkene,  $(\text{EtO}_2\text{C})\text{CR}-\text{CH}_2-\text{CH}_2-\text{COMe}$ . Nucleophile can be any enolate, but works best with stabilized enolates, e.g.  $\alpha$ -cyanoesters,  $\beta$ -ketoesters, malonates, 1,3-diketones. *Must be at least one H on the  $\alpha$ -carbon!*
- f) Alkene *must* have electron-withdrawing group such as carbonyl attached if it is to undergo conjugate addition!

## 10. Enamines.

- Enols and enolates are nucleophilic at the alkene C not attached to O because a resonance structure can be drawn in which that C has a lone pair and a formal negative charge. Likewise, enamines,  $\text{R}_2\text{N}-\text{CR}=\text{CR}_2$  are also nucleophilic at the alkene C not attached to N.
- Enamines are intermediate in nucleophilicity between enols and enolates.
- Prepared from ketones or aldehydes and secondary amines, e.g.  $\text{CH}_3\text{COCH}_3 + \text{Et}_2\text{NH} \rightleftharpoons \text{Et}_2\text{NC}(\text{CH}_3)=\text{CH}_2$ , by removal of  $\text{H}_2\text{O}$ .
- Enamines are not widely used in synthesis any longer; they have been superseded by the use of enolates and LDA. However, enamines are the body's way of making ketones into nucleophiles at the  $\alpha$ -carbon. The body can't deprotonate ketones and aldehydes with a strong base, so it converts them into an enamine, which can undergo Michael or aldol reactions. Example: fructose biosynthesis.

## 11. Claisen and Dieckmann reactions: ester and ketone enolates react with esters. **Makes a C–C bond!**

- Mechanism
- Thermodynamics

- i) driven by deprotonation of product
  - ii) requires one full equivalent of base, unlike aldol reaction
  - iii) works only with esters with two  $\alpha$ -hydrogens: if product can't be deprotonated, doesn't go
  - c) Mixed Claisen works if one ester lacks  $\alpha$ -hydrogens (H-, Ph-, EtO<sub>2</sub>C-, EtO-CO<sub>2</sub>Et)
  - d) Dieckmann reaction is intramolecular Claisen (double Michael adduct as one example)
  - e) Retron is  $\beta$ -oxocarbonyl. Disconnect between  $\alpha$ -C and carbonyl C.
  - f) Multiple Claisens, plus reductions and eliminations, used to make polyketides like erythromycin. Thioesters are used instead of esters because thioesters are more electrophilic and more easily deprotonated.
  - g) Retro-Claisen can occur when  $\beta$ -keto ester with quaternary center between carbonyls is treated with NaOEt
12. Combining carbonyl condensation reactions in synthesis.
- a) The aldol and Michael reactions both form C-C bonds. Can use them in combination to effect powerful synthetic transformations.
  - b) The Robinson annulation: Michael, aldol, dehydration.