Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

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Recommended texts:

1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588, 2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

B] 1,3-bifunctional (1,3-diX) compounds and α , β -unsaturated carbonyl compounds:

The following is a summary of the retrosynthetic strategies one can adopt commonly when the target molecule contains two heteroatom-based functional groups placed at an 1,3-relation. The α , β -Unsaturated carbonyl compounds can be traced back to 1,3-bifunctional compounds as well, so we include those here. These target molecules are consonant systems, so umpolung strategy will not be necessary in general, but depending upon the availability of the SEs, one might adopt such a method (entry 4 and 5).

1.
$$R_1 \stackrel{OH}{\underset{R_2}{\longleftarrow}} R_3 \stackrel{H-O-C-C}{\underset{Aldol}{\longleftarrow}} \underset{Aldol}{\overset{O}{\underset{R_1}{\longleftarrow}}} R_2 + \underset{d^2}{\overset{O}{\underset{R_3}{\longleftarrow}}} \underset{h \text{ base}}{\overset{O}{\underset{R_3}{\longleftarrow}}}$$

β-hydroxyketone TM

- Classic aldol target

2.
$$R_1$$
 R_2 R_2 R_1 R_2 R_2 R_3 R_3 R_4 R_3 R_4 R_5 R_5 R_7 R_8 R_8 R_8 R_8 R_8 R_8

β-diketo (1,3-diketo) TM revised to β-hydroxyketone TM

- Classic aldol target

Whenever attempting cross-aldol - must take necessary precautions to avoid mixture of products. Most suitable if one component lacks α -H and is also more electrophilic than the other.

lacks α -H, more electrophilic than acetophenone

3.
$$R_1$$
 R_2
 R_1
 R_2
 R_1
 R_2
 R_2
 R_1
 R_2
 R_2
 R_1
 R_2
 R_2
 R_2
 R_2
 R_3
 R_4
 R_4
 R_5
 R_5
 R_5
 R_5
 R_7
 R_7

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- Saha et al. Volume 5 (ISBN 9788193853085)

All cases use d² synthon - make use of suitable enol equivalent

B] 1,3-bifunctional (1,3-diX) compounds and α,β -unsaturated carbonyl compounds (contd.):

These target molecules are consonant systems, so umpolung strategy will not be necessary in general, but depending upon the availability of the SEs, one might adopt such a method (entry 4 and 5).

both synthons illogical

4.
$$R_1$$
 R_2 R_3 R_3 R_3 R_4 R_5 R

$$\overset{\mathsf{R_1}}{\underset{\mathsf{R_2}}{\longleftarrow}} \overset{\mathsf{RCO_3H}}{\underset{\mathsf{umpolung}}{\longleftarrow}} \mathsf{R_1} \overset{\mathsf{O}}{\underset{\mathsf{R_2}}{\longleftarrow}}$$

acyl anion equivalents

5.
$$R_1$$
 R_2 R_2 R_2 R_3 R_4 R_2 R_4 R_5 R_4 R_5 R_5 R_6 R

illogical nucleophile logical nucleophile

epoxide ring-opening has to be regioselective

$$R_1$$
 R_2
 R_2
 R_1
 R_2

In basic medium, epoxide ring suffers nucleophilic attack from the less hindered side - regioselectivity in epoxide ring-opening okay.

$$R_1 \xrightarrow{O}$$
 R_2

$$\stackrel{\mathsf{R}_1}{\rightleftharpoons}$$
 + $\mathsf{RCO_3H}$

Note how both the electrophilic and nucleophilic synthons are illogical in strategies 4 and 5

B] 1,3-bifunctional (1,3-diX) compounds and α , β -unsaturated carbonyl compounds (contd.):

6.
$$R_1$$
 R_3 R_3 R_4 R_5 R_5 R_5 R_5 R_5 R_5 R_6 R_7 R_8 R_8 R_8 R_8 R_9 R

Cross-aldol - must take necessary precautions to avoid mixture of products.

Most suitable if one component lacks $\alpha\textsc{-H}$ and is also more electrophilic than the other.

Never use formaldehyde in a cross-aldol, it is super-electrophilic, will react multiple times leading to misery. For TMs like MVK that bear the H₂C=C-C=O fragment, adopt Mannich. However, there may be regioselectivity issues as the Mannich reaction proceeds through enol, which forms at the more substituted side in case of an unsymmetrical ketone.

8.
$$\begin{array}{c} R_2 & O \\ R_1 & OH \end{array} \begin{array}{c} \hline \\ OH \\ OH \end{array} \begin{array}{c} \hline \\ elimination \\ \hline \\ \alpha,\beta\text{-unsaturated acid} \end{array} \begin{array}{c} \hline \\ OH \\ OEt \\ \hline \\ OH \\ \hline \end{array} \begin{array}{c} OH \\ OEt \\ \hline \\ R_1 & OH \\ \hline \end{array} \begin{array}{c} \hline \\ R_2 \\ \hline \\ OH \\ \hline \end{array} \begin{array}{c} OH \\ OEt \\ \hline \\ OH \\ \hline \end{array} \begin{array}{c} OH \\ OEt \\ \hline \\ OH \\ OH \\ \hline \end{array} \begin{array}{c} OH \\ OEt \\ \hline \\ OH \\ OH \\ \hline \end{array} \begin{array}{c} OH \\ OH \\ OH \\ \end{array} \begin{array}{c} OH \\ \end{array}$$

For α,β -unsaturated carboxylic acids, we can use Perkin or Knoevenagel reactions as well; Perkin can be used with aromatic variant only:

Accessing 1,3-dioxygenated target molecules depends mostly upon two important reactions, aldol and aldol-like reactions, and Claisen condensation. The product of aldol or aldol-like reaction may be transformed into α,β -unsaturated carbonyl compounds.

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B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

the 1,3-dicarbonyl will remain in the basic solution as the conjugate base, so acid work-up is necessary.

2. PhPh PhPh

1,3-dicarbonyl, β-diketo TM

Claisen condensation b/w ketone enolate and ester
- must avoid self-condensation of ester

Aldol reaction b/w ketones can be easily reversed, but reaction b/w ketone enolate and ester cannot.

$$\begin{array}{c|c}
 & b & O \\
\hline
 & a \\
\hline
 & 1,3-diCO
\end{array}$$

$$\begin{array}{c}
 & 1,3-diCO \\
\hline
 & CO_2Et
\end{array}$$

$$CO_2Et$$
 CO_2Et CO_2Et CO_2Et

CO₂Et

CO₂Et

diethyl phthalate
- a symmetrical diester

 $\downarrow 0$ $\downarrow 0$ $\downarrow 0$

pinacol, an 1,2-bifunctional compound, accessed from radical coupling of two acetone molecules

Two 1,3-diO relationship in TM route 'a' is better, greater simplification, lesser number of steps

compounds containing *t*-butyl group can be accessed from pinacol-pinacolone rearrangement

doubly activated

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

4.

revised TM is an 1,3-dicarbonyl

(not a 1,3-dicarbonyl, so why are we dealing with this here?! Let's see... alkylation of ketone is not a synthetically viable reaction, unless one uses v. strong base, like LDA)

1,2 C-C CO₂Et

$$\begin{array}{c}
CO_2Et \\
+ Me-I
\end{array}$$

(a decarbonylation will be necessary with DEO)

** via reverse-Claisen!

FGA 5. hydrolysisdecarboxylation

 α,α' -dialkylated ketone

_1,2 C-C

Enamine strategy would also work:

heat

Mel mechanism ?!

1. Mel 2. H₃O[⊕] Me

the other regioisomer suffers from 1,3-allylic strain

NaOEt, EtOH -CO₂Et heat CO₂Et ⊝ OEt CO₂Et work-up CO₂Et + EtOH

alkylation of enamine with SN2 reactive electrophiles is excellent

B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

Strategy 'a' does not work as it involves...

7. FGA
$$\xrightarrow{\text{EtO}_2\text{C}}$$
 $\xrightarrow{\text{CO}_2\text{Et}}$ $\xrightarrow{\text{I}_3\text{-diCO}}$ $\xrightarrow{\text{EtO}_2\text{C}}$ $\xrightarrow{\text{CO}_2\text{Et}}$ $\xrightarrow{\text{EtO}}$ $\xrightarrow{\text{OEt}}$ $\xrightarrow{\text{I}_3\text{-dicarbonyl}}$ $\xrightarrow{\text{I}_3\text{-dicarbonyl}}$ $\xrightarrow{\text{I}_3\text{-dicarbonyl}}$ $\xrightarrow{\text{EtO}_2\text{C}}$ $\xrightarrow{\text{CO}_2\text{Et}}$ $\xrightarrow{\text{EtO}}$ $\xrightarrow{\text{OEt}}$ $\xrightarrow{\text{I}_3\text{-dicarbonyl}}$ $\xrightarrow{\text{I}_3\text{-dica$

Exploiting the TM as a 1,2-dicarbonyl:

B] 1,3-bifunctional compounds and α , β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

1.5-dicarbonyl we'll do this later

Claisen condensation with ethoxide won't work for these TMs - either lacks the activated proton or the one present cannot be abstracted by a base such as ethoxide - final step in Claisen not possible.

as the C-H s-orbital and the C=O π^* orbitals are not parallel...

> ... we cannot deprotonate this proton with ethoxide

no acivated proton present

We have to use acidic condition (PPA, AcOH, heat) so that the reaction proceeds via an acylium ion. These are special cases. We will also use the keto acids as starting materials, and not the keto esters.

the ylide

β,γ-unsaturated ketone

β-hydroxy aldehyde

Point to be noted that it is difficult to keep a β , γ -unsaturated carbonyl compound's structural integrity intact. Given any chance, it isomerises to the more stable α,β -unsaturated carbonyl analogue. That, however, is not a problem here, as no α -hydrogen that can promote such isomerisation is available for this TM.

That is also precisely why we can safely implement the Wittig strategy. If a proton were present between the two carbonyl groups, Wittig reagent would have most likely abstracted it in an acid-base reaction.

- 1. Wittig reaction is chemoselective - attacks the more reactive aldehyde. and stereoselective, gives E-alkene with stabilised ylide.
- 2. Oxidation of secondary alcohol to keto in presence of aldehyde is done chemoselectively by PCC, CH₂Cl₂

enolisable H must be present for this isomerization to happen

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oxidation

B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

11.
$$\begin{array}{c} Ph \\ Ph \\ Ph \end{array} \begin{array}{c} \alpha,\beta \\ \text{aldol} \end{array} \begin{array}{c} Ph \\ Ph \\ \text{benzil} \\ \text{- 1,2-dicarbonyl} \end{array} \begin{array}{c} Ph \\ Ph \\ \text{Ph} \end{array} \begin{array}{c} \Rightarrow \text{ as demonstrated in example 6} \\ \end{array}$$

the more reactive component aldehyde cannot enolise - no self-condensation from that; moreover, the ketone enolises from one direction only, no regioselectivity issue as well

No control needed in the cross aldol.

β-hydroxy carbonyl

1,3-dicarbonyl

Alternative FGI strategy to revise TM to a 1,3-dicarbonyl will require chemoselective reduction of one of the C=O in the final synthesis step - problematic!

from benzaldehyde via benzoin

1,2-addition)

12.
$$\xrightarrow{\text{H-O-C-C}} \xrightarrow{\text{H-O-C-C}} \xrightarrow{\alpha,\beta} \xrightarrow{\text{IM aldol}} \xrightarrow{\text{Im aldol}} \xrightarrow{\text{Symmetrical TM}} \xrightarrow{\text{FGA}} \xrightarrow{\text{O H H O O}} \xrightarrow{\text{I,2 C-C}} \xrightarrow{\text{I,2 C-C}} \xrightarrow{\text{EtO}_2\text{C}} \xrightarrow{\text{EtO}_2\text{C}} \xrightarrow{\text{EtO}_2\text{C}} \xrightarrow{\text{EtO}_2\text{C}} \xrightarrow{\text{I,4 III}} \xrightarrow{\text{I,5-dicarbonyl - ?!}} \xrightarrow{\text{Symmetrical TM}} \xrightarrow{\text{Symmetr$$

but alternatives are available

B] 1,3-bifunctional compounds and α , β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

Control needed in the cross-aldol as the more reactive aldehyde can enolise in this case, so we must minimize its self-condensation. We have to use a stable enolate equivalent, enamine offers a good solution to the problem. Ketone symmetrical, no regioselectivity problem.

- * Oxidation of primary alcohol to aldehyde
- must use high-valent Cr in non-aqueous solvent to prevent over-oxidation to carboxylic acids
- PCC in CH₂Cl₂ good option

FGI

followed by

esterification

Doing the cross-aldol with enamine strategy:

Can also use Li-enolate strategy:

B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

15. Me
$$CO_2$$
Et $\xrightarrow{\alpha,\beta}$ Me O + CO_2 Et CO_2 Et ester enolate

Control necessary as the more reactive aldehyde can enolise in this case, so we must minimize self-condensation. DEM is the preferred enolate equivalent here, as it enolises completely under the reaction condition.

This is the Knoevenagel reaction

Alternatively,

B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

16. Ph
$$\longrightarrow$$
 FGI \longrightarrow Ph \longrightarrow CO₂H \longrightarrow Ph \longrightarrow Ph \longrightarrow CO₂ \longrightarrow Ph \longrightarrow Ph

Final step of synthesis requires stereoselective reduction.

To access α,β -unsaturated acid / derivative:

- aromatic variant Perkin, Reformatsky, Knoevenagel
- aliphatic variant Reformatsky, Knoevenagel

17.
$$\alpha,\beta$$
 α,β β Me + α

With formaldehyde as the electrophilic partner of an aldol-type condensation, the chances of Tollens' condensation is high, so better use Mannich to access that TM.

aromatic ketone

B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

TM is a β -functionalized cyclohexanone

β-position of a carbonyl compound is electrophilic, need to use an enone to functionalize this β-position with a nucleophilic agent

19.
$$\stackrel{O}{\longrightarrow}$$
 $\stackrel{Me}{\longrightarrow}$ $\stackrel{1,2 \text{ C-C}}{\longrightarrow}$ $\stackrel{\bigcirc}{\longrightarrow}$ + Me_2CuLi

TM is a α,β -difunctionalized cyclohexanone

tandem conjugate addition-alkylation, functionalising both β - and α -position; the two methyls would be *trans* to each other.

2,3-dimethylcyclohexanone

One Me introduced as nucleophile at β -carbon (which is electrophilic), the other as electrophile at α -carbon (which is nculeophilic)

$$\underbrace{\begin{array}{c} \text{Seleno-Cope strategy} \\ \text{to install a double bond} \\ \text{between } \alpha\text{-and }\beta\text{-carbon} \end{array}}_{\text{between }\alpha\text{-and }\beta\text{-carbon}} \underbrace{\begin{array}{c} \text{Ph} \\ \text{Se} \end{array}}_{\text{selenylation}} \underbrace{\begin{array}{c} \text{Ph} \\ \text{selenylation} \end{array}}_{\text{heavision}} \underbrace{\begin{array}{c} \text{Me} \\ \text{Heavision} \\ \text{We} \\ \text{Selenylation} \end{array}}_{\text{heavision}} \underbrace{\begin{array}{c} \text{Me} \\ \text{Heavision} \\ \text{Heavi$$

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methylation of cyclohexanone Li-enolate / enamine derived from cyclohexanone

B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

21.
$$\xrightarrow{Q}$$
 $\xrightarrow{\alpha,\beta}$ \xrightarrow{Q} + \xrightarrow{H} ethyl vinyl ketone

Not a good choice, as Mannich reaction would afford the wrong regioisomer because it would proceed through the more stable, more subst. enol of 2-butanone. We cannot use the CH₂O directly as well, lest Tollens condensation intervenes. Way out??

Revised strategy:

more subst. enol in acid med.

b)
$$(just \ a \ ketone \ synthesis!)$$
 $(Cl + (Culi) \ culi)$ $(Cl + (Culi) \ culi)$

B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Try these yourself:

Propose another route (other than those shown!) for preparation of ethyl vinyl ketone.