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

C] 1,4-bifunctional compounds:

The following is a summary of the retrosynthetic strategies one can commonly adopt when the target molecule contains two heteroatom-based functional groups placed at an 1,4-relation. These target molecules are dissonant systems, so umpolung strategy will be necessary.

1. $\begin{array}{c} O \\ R_1 \end{array} \begin{array}{c} O \\ O \\ O \end{array} \end{array} \begin{array}{c} A_2 \end{array} \begin{array}{c} A_2 \\ \hline A_1 \\ \hline A_2 \end{array} \begin{array}{c} A_2 \\ \hline A_3 \\ \hline A_4 \end{array} \begin{array}{c} A_2 \\ \hline A_5 \\ \hline A_7 \end{array} \begin{array}{c} A_2 \\ \hline A_8 \end{array} \begin{array}{c} A_2 \\ \hline A_8 \end{array} \begin{array}{c} A_8 \\ \hline A_8 \\ \hline A_8 \end{array} \begin{array}{c} A_8 \\ \hline A_8 \\ \hline A_8 \end{array} \begin{array}{c} A_8 \\ \hline A_8$

4. Nitroalkane anions are excellent Michael donors2. Demasking nitro to carbonyl (4)

by McMurry reaction, TiCl₃, H₃O

2. R₁ OH FGI R₁ \xrightarrow{O} \xrightarrow{N} $\xrightarrow{1,3}$ C-C \xrightarrow{O} $\xrightarrow{\oplus}$ \xrightarrow{O} \xrightarrow{O} \xrightarrow{O} \xrightarrow{O} \xrightarrow{A} \xrightarrow{O} \xrightarrow{A} Aldol or Mannich

Demasking nitro to carbonyl by McMurry reaction, $TiCl_3$, H_3O

C] 1,4-bifunctional compounds (contd.):

The following is a summary of the retrosynthetic strategies one can commonly adopt when the target molecule contains two heteroatom-based functional groups placed at an 1,4-relation. These target molecules are dissonant systems, so umpoluing strategy will be necessary.

4. $R_1 \xrightarrow{O} R_2 \Longrightarrow R_1 \xrightarrow{O} + \bigoplus_{O} R_2 \Longrightarrow X \xrightarrow{\text{umpolung}} X^{\oplus} + \bigoplus_{O} R_2$ $1,4-\text{dicarbonyl} \qquad \qquad d^2 \text{(logical)} \qquad a^2 \text{(illogical)} \qquad \alpha-\text{halocarbonyl}$

halogenation at the α -position may include regioselectivity issue

specific enol equivalent is needed for the d² synthon otherwise Darzen's reaction would take over...

desired outcome:

enolate acting as
$$R_1$$
 R_2 R_2 R_2 R_1 R_2 R_2 R_1 R_2

possible side reaction:

to minimise this, we must reduce the basicity of the enolate; we need specific enol equivalents

regioselctivity)

more subst. end

C] 1,4-bifunctional compounds (contd.):

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C] 1,4-bifunctional compounds (contd.):

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8. R₁ Me FGI hydration (Markovnikov regioselctivity)

1,4-dicarbonyl TM, one side is ketomethyl

However, conjugate addition of alkynide ion may prove to be problematic; thus "a" is a better choice.

9. R_1 R_2 R_2 R_3 or FGI, reduction 1,4-diol TM

Note:

$$R_1$$
 $\xrightarrow{\text{OH}}$ R_2 $\xrightarrow{\text{FGA}}$ R_1 R_2 R_3 R_4 R_4 R_5

adding a triple bond - in that sense we can call this transform a functional group addition (FGA)

The C-C can be accessed by reducing a triple bond - in that sense we can call this transform a functional group interconcersion (FGI).

C] 1,4-bifunctional compounds (contd.):

Let us now consider a few examples:

1.
$$\xrightarrow{\alpha,\beta} \xrightarrow{\alpha,\beta} \xrightarrow{\alpha,\beta} \xrightarrow{\alpha,\beta} \xrightarrow{\alpha,\beta} \xrightarrow{\alpha,\beta} \xrightarrow{\alpha,\beta-\text{unsaturated}} \xrightarrow{\alpha,\beta-\text{unsymmetrical}} \xrightarrow{\alpha,\beta-\text{unsymmetrical}} \xrightarrow{\alpha,\beta-\text{unsymmetrical}} \xrightarrow{\alpha,\beta} \xrightarrow{\alpha,\beta}$$

2. OEt
$$\xrightarrow{1,4-\text{diCO}}$$
 OEt $\xrightarrow{\text{OEt}}$ $\xrightarrow{\text{FGI}}$ $\xrightarrow{\text{Br}}$ OH $\xrightarrow{\text{H-V-Z}}$ $\xrightarrow{\text{umpolung}}$ H OF $\xrightarrow{\text{cativation required for this d}^2 \text{ synthon}}$ $\xrightarrow{\text{C-N}}$ $\xrightarrow{\text{enamine}}$ $\xrightarrow{\text{C-N}}$ $\xrightarrow{\text{H-V-Z}}$ $\xrightarrow{\text{H-V-Z}}$ $\xrightarrow{\text{umpolung}}$ $\xrightarrow{\text{H-V-Z}}$ $\xrightarrow{\text{umpolung}}$ $\xrightarrow{\text{H-V-Z}}$ $\xrightarrow{\text{H-V-V-Z}}$ $\xrightarrow{\text{H-V-V-Z}}$ $\xrightarrow{\text{H-V-V-Z}}$ $\xrightarrow{\text{H-V-V-Z}}$ $\xrightarrow{\text{H-V-V-Z}}$ $\xrightarrow{\text{H-V-V-Z}}$

nitroalkane as acyl anion eqv.

condensation regioselectivity guided by formation of the more substituted C=C

enamines react particularly well with S_N2 reactive electrophiles

C] 1,4-bifunctional compounds (contd.):

Let us now consider a few examples:

3.
$$\begin{array}{c}
0 \\
\alpha,\beta \\
CO_2Et
\end{array}$$

$$\begin{array}{c}
\alpha,\beta \\
CO_2Et
\end{array}$$

$$\begin{array}{c}
0 \\
CO_2Et
\end{array}$$

$$\begin{array}{c}
\alpha^2 \\
0 \\
CO_2Et
\end{array}$$

$$\begin{array}{c}
0 \\
CO_2Et
\end{array}$$

condensation regioselectivity guided by formation of the more substituted C=C

For halogenation, we can't use

need to install the Br at the

less susbt. side of the ketone.

synthesis not straightforward.

- i) base haloform!
- ii) acid Br incorporated on the more substituted side!

How to solve this regioselectivity issue?

* Solutions to the regioselectivity problem:

iii)
$$\longrightarrow$$
 Hg(OAc)₂, H₂O, Br₂ \longrightarrow O Br

(This one is most interesting of the lot and as expected, has the most intricate mechanism. Try it; start just as you would for a Hg(II)-catalysed hydration of alkyne and then proceed from there.)

C] 1,4-bifunctional compounds (contd.):

Let us now consider a few examples:

4.
$$\xrightarrow{\text{0}} \xrightarrow{\text{1,4-diCO}} \xrightarrow{\text{0}} + \bigoplus_{\text{0}} \xrightarrow{\text{0}} \equiv \xrightarrow{\text{0}} \xrightarrow{\alpha,\beta}$$

$$\xrightarrow{\text{1}} \xrightarrow{\text{0}} + \bigoplus_{\text{0}} \xrightarrow{\text{0}} \xrightarrow{\text{0}} \xrightarrow{\alpha,\beta}$$

$$\xrightarrow{\text{NO}_2} \xrightarrow{\text{NaNO}_2}$$

$$+ \text{NaOMe}$$

5.
$$O_{2}H \xrightarrow{1,4-diO} O_{1}H \xrightarrow{a^{2}} O_{1}H \xrightarrow{a^{2}} O_{2}H = CO_{2}Et + NaOE$$

(racemic) $O_{1}H \xrightarrow{A_{2}C-CO_{2}H} O_{2}H = CO_{2}Et + NaOE$

$$O_{2}Et + NaOE$$

$$O_{3}Et + NaOE$$

$$O_{4}Et + NaOE$$

$$O_{5}EI + NaOE$$

$$O_{7}EI + R \xrightarrow{O_{7}O_{7}H} O_{7}H$$

6.
$$Prices Prices Pric$$

Enamine + α -haloketone strategy won't work here.

epoxide ring-opening is in *trans*-orientation

Using EAA route we have the following observation:

C] 1,4-bifunctional compounds (contd.):

3-mem ring

3-mem. ring,

no dehydration

Let us now consider a few examples:

7.
$$\xrightarrow{Ph} \xrightarrow{FGI} \xrightarrow{Ph} \xrightarrow{NC} CO_2H \xrightarrow{1,4-diX} \xrightarrow{Ph} \xrightarrow{COOH} \xrightarrow{+ \odot} CN$$

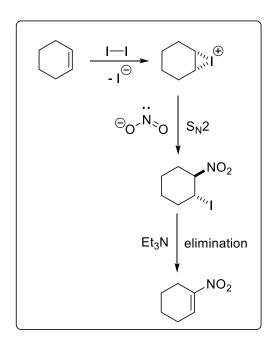
$$\downarrow \qquad \qquad \downarrow \qquad \qquad \qquad \qquad \downarrow \qquad \qquad \qquad$$

conjugate addition of cyanide is inevitable as it cannot add to COOH.

Use Perkin or Knoevenagel to access the aromatic α,β -unsaturated acid

bridged bicyclic system;

no dehydration



C] 1,4-bifunctional compounds (contd.):

Let us now consider a few examples:

$$\begin{array}{c|c}
O & I_2 \text{ (1 eqv.)} \\
\hline
CO_2Et & EtO_2C & O
\end{array}$$

$$\begin{array}{c|c}
O & CO_2Et \\
EtO_2C & O
\end{array}$$

$$\begin{array}{c|c}
O & CO_2Et \\
EtO_2C & O
\end{array}$$

One of the strategies used here is quite unique - the ozonolysis of a C=C to install a C=O group. In terms of retrosynthesis, this implies replacing a =O with =CH₂. That's not a disconnection per se. When this analysis is carried out to approach the dicarbonyl target, we are in fact using the reverse of a disconnection - we are joining up a bond in the revised target which will be broken during the synthesis.

This is called the *strategy of reconnection*.

regioselectivity issue)

C] 1,4-bifunctional compounds (contd.):

Oxidative cleavage of a C=C provides a useful route to 1,4-dicarbonyl targets. Here's another example of this concept at work:

* to stop the ozonolysis of the C=C at the aldehyde stage, we need a reductive work-up, use dimethyl sulfide

12.
$$Ph$$
 Ph
 CO_2H
 CO_2H
 Ph
 CO_2H
 CO_2H
 CO_2H
 CO_2H
 CO_2H
 CO_2H

C] 1,4-bifunctional compounds (contd.):

Let us now consider a few examples:

13.
$$C$$
-O lactone C -O, C -O lactone C -O, C -

bromination in AcOH to access the α-bromoacetone

15.
$$\begin{array}{c} \text{HOOC} \quad \text{O} \\ \text{1,4-diCO} \\ \text{HOOC} \quad \text{O} \\ \text{HOOC} \quad \text{O} \\ \text{HOOC} \quad \text{O} \\ \text{HOOC} \quad \text{O} \\ \text{OH} \\ \text{H-O-C-C} \\ \text{Hen} \\ \text{H-O-C-C} \\ \text{Hen} \\ \text{COOH} \\ \text{X} \\ \text{Wasing Ivanov enolates derived} \\ \text{from carboxylic acids} \\ \text{Hooc} \\ \text{H$$

enolate from carboxylic acid

C] 1,4-bifunctional compounds (contd.):

And finally, let us revisit a 1,4-dicarbonyl target once more. Again we use the d¹+a³ combination, but this time, our acyl anion equivalent is different from the one derived from nitroalkanes:

16.
$$Ph \xrightarrow{O} Ph \xrightarrow{O}$$

This is the Stetter reaction (mechanism?), using the cyanohydrin derived from the aromatic aldehyde as the umpoled reagent, an acyl anion equivalent. Possible side reaction is benzoin condensation which is reversible, so not a threat.

Try these yourself: