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

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. \[ R_1\text{CHO} \overset{1,4\text{-diCO}}{\xrightarrow{\text{Michael}}} R_1\text{CO} \overset{d^1}{\text{illogical}} + \overset{\alpha,\beta\text{-unsaturated carbonyl}}{\overset{a^3}{\text{CHO}}} \longrightarrow \text{Mannich or aldol as the case may be} \]

\[ R_1\text{CO} \overset{\text{NO}_2}{\xrightarrow{\text{umpolung}}} + \text{Base} \]

1. Nitroalkane anions are excellent Michael donors
2. Demasking nitro to carbonyl by McMurry reaction, TiCl_3, H_2O

2. \[ R_1\text{CH}_2\text{OH} \overset{\text{FGI}}{\xrightarrow{\text{1,3 C-C}}} R_1\text{CHO} \overset{d^1}{\text{illogical}} + R_1\text{C} \overset{a^3}{\text{CN}} \]

4-ketoacid TM

3. \[ R_1\text{CHO} \overset{\text{FGI}}{\xrightarrow{\text{1,4-diX}}} R_1\text{CHO} \overset{\text{NO}_2}{\xrightarrow{\text{Henry}}} R_1\text{CO} \overset{d^2}{\text{illogical}} + \overset{\text{1,3-diCO}}{\overset{\text{CO}_2\text{Et}}{\text{CO}_2\text{Et}}} \]

\[ \text{NO}_2 + \overset{\text{EtO}}{R_1\text{CH}_2\text{O}} \overset{\text{Base}}{\xrightarrow{\text{Henry}}} \overset{\text{Me}}{R_2} \]

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

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\[
\begin{align*}
R_1\text{C=O} &\xrightarrow{\text{halogenation at the}} R_1\text{C=O} + X\text{R}_2 \\
\text{R}_2 &\xrightarrow{\text{umpolung}} X + \text{R}_2\text{C}=\text{O}
\end{align*}
\]

- Halogenation at the \(\alpha\)-position may include regioselectivity issue.
- Specific enol equivalent is needed for the \(d^2\) syntho; otherwise Darzen's reaction would take over.

Desired outcome:

Possible side reaction:

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

\[
\begin{align*}
\text{R}_1\text{C}=\text{O} + \text{R}_2\text{C}=\text{O} &\xrightarrow{\text{enolate acting as}} \text{O}\text{R}_1\text{C}=\text{O} + \text{R}_2\text{C}=\text{O} \\
\text{R}_2 &\xrightarrow{\text{enolate acting as}} \text{O}\text{OH} + \text{BrR}_2
\end{align*}
\]

Glycidic ester

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5. symmetrical 1,4-dicarbonyl target
   - FGA
   - NaOEt (2 eqv.s)
   - I₂ (1 eqv.)
   - 1,4-diCO
   - a² component generated in situ
   - α-halocarbonyl derived from the same ketoester
   - NaOEt

6. 1,4-dio
   - FGI
   - 1,4-diO
   - a² component generated illogically
   - Wittig or related
   - Corey-Chaykovsky
   - umpolung

7. addition (Markovnikov regioselectivity)
   - 1,2 C-C
   - X

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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 umpolung strategy will be necessary.

8. $\text{Me} \quad \text{O} \quad \text{Me}$
   $\text{R}_1 \quad \text{O} \quad \text{R}_1$
   \[ \begin{align*}
   &\xrightarrow{\text{FGI, hydration (Markovnikov regioselectivity)}} \quad \xrightarrow{\text{1,2 C-C}} \\
   \text{1,4-dicarboxyl TM, one side is ketomethyl}
   \end{align*} \]

9. $\text{OH} \quad \text{OH}$
   $\text{R}_1 \quad \text{OH} \quad \text{R}_2$
   \[ \begin{align*}
   &\xrightarrow{\text{FGA or FGI, reduction}} \quad \xrightarrow{\text{H-O-C-C}} \\
   \text{1,4-diol TM}
   \end{align*} \]

Note:

- 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 interconversion (FGI).
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

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

Let us now consider a few examples:

1. **α,β-unsaturated cyclic ketone**
   
   1,4-diketo TM - unsymmetrical
   
   \[ \alpha,\beta \rightarrow \text{1,4-diCO} \]
   
   Condensation regioselectivity guided by formation of the more substituted C=C

2. Enamines react particularly well with SN2 reactive electrophiles
   
   (activation required for this d^2 synthet)
   
   Br\text{et} \rightarrow \text{BrCOEt} \rightarrow \text{BrCO} \rightarrow \text{BrOH} \rightarrow \text{BrH}
   
   H-V-Z umpolung + Br_2
   
   tetrasubstituted C=C, more favoured
   
   trisubstituted C=C, less favoured
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

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

Let us now consider a few examples:

3. \[
\begin{align*}
\text{CO}_2\text{Et} & \xrightarrow{\alpha,\beta} \text{CO}_2\text{Et} & \xrightarrow{1,4\text{-diCO}} & \text{CO}_2\text{Et} & \equiv & \text{Br} \\
\end{align*}
\]

need to install the Br at the less subst. side of the ketone, synthesis not straightforward.

For halogenation, we can’t use
i) base - haloform!
ii) acid - Br incorporated on the more substituted side!

How to solve this regioselectivity issue?

* Solutions to the regioselectivity problem:

i) \[
\begin{align*}
\text{H} & \xrightarrow{1. \text{NaH}} \text{H} & \xrightarrow{2. \text{BuLi}} & \text{EAA diantion} \\
\text{less acidic proton} & \text{more acidic proton} & \text{Weiler alkylation strategy} & \text{(more reactive site of the dianion gets alkylated first, last-out-first-in!)} & \text{aq. acid work up}
\end{align*}
\]

bromination via:

ii) \[
\begin{align*}
\text{LDA, THF, I.t.} & \xrightarrow{\text{MeSiCl}} \text{OTMS} & \xrightarrow{\text{Br}_2} \text{Br} \\
\text{kinetic enolate formation} & \text{(mechanism?!)}
\end{align*}
\]

(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.)
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

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

Let us now consider a few examples:

4. $\text{RCO}_2\text{H} \xrightarrow{1,4\text{-diO}} \text{RCO}_2\text{H} + \text{RCO}_2\text{H} \equiv \text{RCO}_2\text{H} + \text{RCO}_2\text{H}

\text{NO}_2 \quad \text{X} \quad \text{NaOMe} \quad \text{NaNO}_2

\text{enamine will not form from the more substituted side.}

5. $\text{(racemic) CO}_2\text{H} \xrightarrow{1,4\text{-diO}} \text{CO}_2\text{H} + \text{H}_2\text{C-CO}_2\text{H} \equiv \text{CO}_2\text{Et} \quad \text{NaOE}_t

\text{FGI oxidation}

\text{epoxide ring-opening is in } \text{trans}-\text{orientation}

6. $\text{R-CO}\text{-Br} \xrightarrow{\text{FGI}} \text{R-CO}\text{-OH} \xrightarrow{1,4\text{-diO}} \text{R-CO}\text{OH} + \text{R-CO}\text{H} \equiv \text{R-CO}\text{OH} + \text{R-CO}\text{H}

\text{TM}

\text{Using EAA route we have the following observation:}

$\text{RCO}_2\text{Et} \xrightarrow{1. \text{NaOE}_t} \text{RCO}_2\text{Et} \xrightarrow{2. \text{in situ cyclisation}} \text{RCO}_2\text{Et}$

$\text{R-CO}\text{-Br} \xrightarrow{\text{HBr}} \text{RCO}_2\text{Et}$

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

Let us now consider a few examples:

7. \[ \text{Ph} - \text{COOH} \stackrel{FGI}{\longrightarrow} \text{Ph} - \text{CN} \stackrel{1,4-diX}{\longrightarrow} \text{Ph} - \text{COOH} + \text{CN} \]

- \( \alpha,\beta \)reiben
- \( \text{Ph} - \text{COH} + \text{H}_2\text{C} - \text{COOH} \]
- \( \text{H}_2\text{C} - \text{COOH} \)
- \( \text{NaOAc} \)

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

Use Perkin or Knoevenagel to access aromatic \( \alpha,\beta \)-unsaturated acid

8. \[ \text{cyclohexane} \stackrel{\alpha,\beta}{\longrightarrow} \text{cyclohexane} \]

- \( \text{a} \)
- \( \text{b} \)
- \( \text{1,4-diCO} \)

- \( \text{1-nitrocyclohex-1-ene} \)
- a Michael acceptor

- NO\(_2\) demasked via McMurry reaction

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

Let us now consider a few examples:

9.  
\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{CHO} & \quad \text{CHO} \\
\text{EtO}_2\text{C} & \quad \text{Me}
\end{align*}
\]

1,4-diCO

symmetrical 1,4-diketone

10.  
\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{NaOEt} & \quad \text{NaOEt} \\
\text{I}_2 (1 \text{ eqv.}) & \quad \text{I}_2 (1 \text{ eqv.}) \\
\text{NaOEt} (2 \text{ eqv.}) & \quad \text{NaOEt} (2 \text{ eqv.})
\end{align*}
\]

hydrolysis and decarboxylation

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 =CH_2. That's not a disconnection \textit{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.

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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:

11. \[ \text{CO}_2\text{Et} \quad \text{CHO} \quad \text{Br} \quad \text{CHO} \]

\[ \text{ CO}_2\text{Et} \quad \text{H}_2\text{C} \quad \text{CHO} \quad \text{Br} \quad \text{CHO} \]

\[ \alpha\text{-haloaldehyde very difficult to handle} \]

\[ \text{ extremely reactive} \]

\[ ^* \text{ to stop the ozonolysis of the C=C at the aldehyde stage, we need a reductive work-up, use dimethyl sulfide} \]

12. \[ \text{Ph CO}_2\text{O} \quad \text{\gamma-lactone} \]

\[ \text{CO}_2\text{H} \quad \text{\gamma-hydroxyacid} \]

\[ \text{OH} \quad \text{hydrolysis} \quad \text{substitution} \]

\[ \text{Ph} \quad \text{Br} \quad \text{Markovnikov regioselectivity} \]

\[ \text{Ph} \quad \text{1,2 C-C} \]

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

Let us now consider a few examples:

13. \( \gamma \)-lactone \[ \xrightarrow{\text{C-O lactone}} \] \( \gamma \)-hydroxyacid \[ \xrightarrow{\text{FGI reduction}} \] 1,4-dioxygenated TM \[ \xrightarrow{\text{H-O-C-C \ + \ base}} \] CO\(_2\) + H\(_2\)C\(-\)C\(_{\text{=O}}\)

14. [levulinic acid, a \( \gamma \)-ketoacid aka 4-oxopentanoic acid] \[ \xrightarrow{1,4\text{-diCO}} \] acetyl cation \[ + \] acetyl anion \[ \xrightarrow{\text{CO\(_2\)Et + NaOEt}} \] CO\(_2\)Et \[ + \] NaOEt

[1,2 diX] \( \xrightarrow{\text{Br}} \) \( \xrightarrow{\text{Br}_2} \)

bromination in AcOH to access the \( \alpha \)-bromoacetone

15. [using Ivanov enolates derived from carboxylic acids] \[ \xrightarrow{1,2 \text{-C-C}} \] COOH \[ \xrightarrow{\text{LDA (2 eqv.)}} \] \( \text{H-O-C-C \ + \ Henry} \)

\[ \xrightarrow{\text{LDA (2 eqv.)}} \] \( \text{H-O-C-C \ + \ base} \)

nitro demasking with McMurry reaction

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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. \[
\begin{align*}
\text{Ph} & \quad \text{CO} \quad \text{Ph} \\
\text{Ph} & \quad \text{CO} \\
\end{align*}
\]

\[
\xrightarrow{1,4-\text{diCO}}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{CO} \quad \text{Ph} \\
\text{Ph} & \quad \text{CO} \\
\text{H} & \quad \text{OH} \\
\text{Ph} & \quad \text{CN} \\
\text{Ph} & \quad \text{CO} \quad \text{Ph} \\
\text{Ph} & \quad \text{CO} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{CN} \\
\text{NaCN} & \quad \text{NaOH} \\
\end{align*}
\]

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:

[C.1] \[
\begin{align*}
\text{CH}_2\text{CO}_2\text{H} \\
\end{align*}
\]
(two separate methods, other than the one shown)

[C.2] \[
\begin{align*}
\text{HO} & \quad \text{CH}_3\text{OH} \\
\end{align*}
\]

[C.3] \[
\begin{align*}
\text{C} & \quad \text{O} \\
\end{align*}
\]
(other than the methods shown)

[C.4] \[
\begin{align*}
\text{Me} & \quad \text{C} \quad \text{O} \\
\end{align*}
\]

[C.5] \[
\begin{align*}
\text{C} & \quad \text{O} \\
\end{align*}
\]

[C.6] \[
\begin{align*}
\text{C} & \quad \text{O} \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

(C.7) \[
\begin{align*}
\text{HOOC} & \quad \text{CH}_2\text{CH}_2\text{OH} \\
\end{align*}
\]

(C.8) \[
\begin{align*}
\text{CO} & \quad \text{CH}_3\text{Br} \\
\end{align*}
\]

(C.9) \[
\begin{align*}
\text{C} & \quad \text{O} \quad \text{Ph} \\
\end{align*}
\]

(C.10) \[
\begin{align*}
\text{C} & \quad \text{O} \\
\end{align*}
\]

(C.11) \[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CH}_2\text{CO}_2\text{Me} \\
\end{align*}
\]