Malonic Ester Synthesis

6 step synthesis

disubstituted carboxylic acid

1. NaOEt
2. E+Br
3. NaOEt
4. MeBr
5. H_3O^+
6. heat

can use different alkyl halide also

can also use different alkyl halide

most acidic H's
Conjugate Addition Reactions

- two electrophilic sites on $\alpha,\beta$-unsaturated carbonyls

\[
\begin{align*}
\text{Nu} & \\
\text{Nu} & \\
\text{Nu} & \\
\end{align*}
\]

1,4-addition
thermodynamic product
(more stable - carbonyl-containing)

1,2-addition
kinetic product
(forms faster)

Many different nucleophiles and conditions will favor either
1,2- or 1,4-addition

Weak nucleophiles ($\text{CN}^-$, $\text{NH}_2\text{R}$, $\text{R-S}^-$) add
reversibly to

$\Rightarrow$ 1,4-product accumulates
(thermodynamic)
Stronger nucleophiles (R-Li, LiAlH₄) add irreversibly to carbonyl, so 1,2-product (kinetic) accumulates.

**Michael Addition**

\[
\text{CH₃CH} = \text{CHCH₃} + \text{CH₃COCH₃} \xrightarrow{\text{NaOH, H₂O}} \text{CH₃CH} = \text{CHCH₃} \text{CH₃COCH₃}
\]

α,β-unsaturated ketone

C-C bond formed; important reaction

Weak N₃O favors 1,4-addition
Robinson Annulation

Useful variant of Michael addition

* Michael addition then aldol → form a ring

\[
\begin{align*}
\text{O} & \quad + \quad \text{NaOH} \quad \xrightarrow{\text{H}_2\text{O}} \\
\text{C} & \quad \text{H} \quad \text{O} & \quad \xrightarrow{\text{Michael add'n}} \\
\text{C} & \quad \text{H} \quad \text{O} & \quad \xrightarrow{\text{Aldol rxn}} \\
\text{C} & \quad \text{H} \quad \text{O} & \quad \xrightarrow{\text{Michael add'n}} \\
\text{C} & \quad \text{H} \quad \text{O} & \quad \xrightarrow{\text{H}_2\text{O} - \text{H}} \\
\text{C} & \quad \text{H} \quad \text{O} & \quad \xrightarrow{\text{Aldol (intramolecular)}} \\
\end{align*}
\]
Submit a Single-sided Copy to the Office
DO NOT STAPLE

1,2-Addition, C-C formation

\[ \text{strong } \ce{Nu^+} \]

\[ \text{weaker } \ce{Nu^+} \]

\[
\begin{align*}
\text{CH}_3\text{MgBr} & \quad \text{OR} \\
\text{CH}_3\text{Li} & \quad \text{H}_2\text{O}
\end{align*}
\]

1,4-Addition, C-C formation

\[ \text{strong } \ce{Nu^+} \]

add carbon to carbonyl functional group

\[ \text{weaker } \ce{Nu^+} \]

add carbon to \( \delta \)-carbon
Chapter 23 - Amines

- Classified based on # of "R" groups on N

\[ \text{NH}_3 \] - ammonia - no R

\[ \text{CH}_3-\text{NH}_2 \] - primary

\[ \text{CH}_3/\text{N-H} \] - secondary

\[ \text{N} \] - tertiary also tertiary

Amine Geometry

- Tetrahedral due to electron pair (pyramidal in shape)

\[ \text{interconvert} \]

- Rapidly interconvert between enantiomers

- Can only freeze enantiomers at very cold temperatures (for most cases)

Interconvert via flat intermediate

\[ \text{interconvert via} \]

\[ \text{flat intermediate} \]