The Claisen Rearrangement

Lecture Notes

Key Reviews:


[3,3]-Rearrangements:
The Claisen and Cope Reactions/Rearrangements

$\Delta$

[Claisen rearrangement]

[Claisen rearrangement]

[Cope rearrangement]
The Claisen Reaction: Initial Discovery

\[
\text{Bonds Broken} \quad \text{Bonds Formed}
\]

- 2 C=C
- 1 C=O

- 1 C=C
- 1 C=O
- 1 C=C

The Claisen Reaction: Initial Discovery

\[
\text{Bonds Broken} \\
\begin{align*}
2 & \text{ C=C} \\
1 & \text{ C-O}
\end{align*}
\]

\[
\text{Bonds Formed} \\
\begin{align*}
1 & \text{ C=C} \\
1 & \text{ C=O} \\
1 & \text{ C-C}
\end{align*}
\]

Reaction can be regarded as the sigmatropic homologation of an allylic alcohol, meaning the migration of a sigma bond across a conjugated pi system to a new position.

The Claisen Reaction: Why is it So Useful?

Key points:

1. Experimental procedures are very reliable
2. Compatible with a wide range of functional groups
3. Substrates are readily made, and the δ,γ-unsaturated product can be chemoselectively adjusted at either end (alkene or carbonyl) to give further materials
4. High stereoselectivity in formation of double bonds and chiral centers.
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4. **High stereoselectivity in formation of double bonds and chiral centers.**
**The Claisen Reaction: Substrate Preparation**

Potential drawbacks

Competing acid-catalyzed reactions with resident functional groups

If R is an alkyl group other than methyl, regiochemical problems in vinyl ether synthesis can occur

\[ R = \text{H, Me, alkyl} \]

The Claisen Reaction: Substrate Preparation

S. D. Burke and co-workers, Strategies and Tactics in Organic Synthesis 1987, 2, 57.
The Claisen Reaction: Substrate Preparation

\[
\text{OH} \quad \overset{\text{OEt}}{\underset{Hg(OAc)_2}{\longrightarrow}} \quad \left[ \begin{array}{c}
\text{OEt} \\
\text{HgOAc}
\end{array} \right]
\xrightarrow{\Delta} \left[ \begin{array}{c}
\text{O} \\
\text{[3,3]}
\end{array} \right] \quad \overset{\text{O}}{\longrightarrow} \quad \text{O}
\]

A much milder procedure for cases where substrates cannot tolerate acid and heat; in the case below it succeeded where others failed.

S. D. Burke and co-workers, Strategies and Tactics in Organic Synthesis 1987, 2, 57.
The Claisen Reaction: Substrate Preparation

O
MeO
2
C
H
H
Cl
OH
MeO
OMe
p-TsOH, Δ

In both cases the Claisen reaction occurs on the more accessible, convex face of the molecule.

KH, Br
CN
O
NC
O
Li, NH₃;
MeI
[3,3]

MeO₂C
H
H
Cl
MeO₂C
H
H
Cl

[3,3]

P. T. Lansbury, N. Y. Wang, J. E. Rhodes, Tetrahedron Lett. 1971, 12, 1829 and 1833
The Claisen Reaction: Substrate Preparation

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The Claisen Reaction: Substrate Preparation

Aromaticity can be broken through the Claisen rearrangement
The Claisen Reaction: Substrate Preparation

Aromaticity can be broken through the Claisen rearrangement
The Claisen Reaction: Stereochemical Considerations

Reactions proceed through chair-like transition states

The Claisen Reaction: Stereochemical Considerations

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The Claisen Reaction: Stereochemical Considerations

Reactions proceed through chair-like transition states

\[
\begin{align*}
\text{O} & \rightarrow \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \\
\text{O} & \rightarrow \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \\
\text{O} & \rightarrow \begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\end{align*}
\]

The Claisen Reaction: Stereochemical Considerations

Pre-existing chirality determines the stereoselectivity of the rearrangement.
The Claisen Reaction: Stereochemical Considerations

Pre-existing chirality determines the stereoselectivity of the rearrangement

As a general rule, unless there are strange geometrical constraints (i.e. the reaction proceeds in a chair, not a boat, transition state), E-olefins result from the Claisen rearrangement.
The Claisen Reaction: Stereochemical Considerations

Pre-existing chirality determines the stereoselectivity of the rearrangement

The Claisen Reaction: Stereochemical Considerations

Pre-existing chirality determines the stereoselectivity of the rearrangement

$X = H$, $E/Z = \sim 9:1$

$X = \text{OEt or NMe}_2$, $E/Z = >99:1$

Preference for equatorial position of substituents correlates with A-values

The Claisen Reaction: Stereochemical Considerations

Pre-existing chirality determines the stereoselectivity of the rearrangement, even if multiple substituents are present.

The Claisen Reaction: Stereochemical Considerations

Many different ways to access chiral allylic alcohols:

\[
\begin{align*}
R_1^* \quad \text{OH} \\
\quad \quad \quad \quad \quad R_1 \quad R_2 \\
\end{align*}
\]

[3,3] Chiral pool building block

Resolution of achiral starting material

Asymmetric reduction of α, β-unsaturated system
The Claisen Reaction: Stereochemical Considerations

Many different ways to access chiral allylic alcohols:

- Chiral pool building block
- Resolution of achiral starting material
- Asymmetric reduction of $\alpha,\beta$-unsaturated system
The Roche Synthesis of α-Tocopherol

The Roche Synthesis of α-Tocopherol

\[ X = \text{OMe, OTBS, or NMe}_2 \]

97-99% e.e.
The Roche Synthesis of $\alpha$-Tocopherol

$97-99\%$ e.e.

[Repeat of process]

$94-99\%$ e.e.

$\alpha$-tocopherol

The Johnson Orthoester Claisen Rearrangement: A Useful Variant of the Claisen Reaction

The Johnson Orthoester Claisen Rearrangement: Key Stereochemical Difference from Eschenmoser Variant

Stereocontrol can become a concern with non-methyl alkyl chains

\[
\text{OH} \quad \text{EtO} \quad \text{OEt} \quad \Delta \quad \text{EtO} \quad \text{OEt} \quad \text{OEt}
\]
The Johnson Orthoester Claisen Rearrangement: Key Stereochemical Difference from Eschenmoser Variant

Stereocontrol can become a concern with non-methyl alkyl chains


\[
\begin{align*}
\text{OH} & \quad \text{EtO} \quad \text{OEt} \\
\text{EtO} & \quad \text{O} \quad \text{R} \\
\end{align*}
\]
The Johnson Orthoester Claisen Rearrangement: Key Stereochemical Difference from Eschenmoser Variant

Stereocontrol can become a concern with non-methyl alkyl chains

\[
\begin{align*}
\text{OH} & \quad \text{EtO} \quad \text{OEt} \\
\text{\( \Delta \)} & \quad \text{OEt} \\
\text{OEt} & \quad \text{EtO} \\
\text{R} & \quad \text{EtO} \\
\end{align*}
\]
Johnson Orthoester Claisen Rearrangements in Synthesis

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[Chemical structures and reactions are shown with step-by-step processes.

Johnson Orthoester Claisen Rearrangements in Synthesis

Johnson Orthoester Claisen Rearrangements in Synthesis

1. KOAc, 18-Crown-6
2. NaH, Me₂SO₄
3. PTSA (84% overall)

First example of a Claisen rearrangement creating a quaternary carbon next to a glycal oxygen

CH₃C(OMe)₃, toluene (1:20), propionic acid, 130 °C, 15 h

[Johnson-Claisen rearrangement]

The Eschenmosher Amide Acetal Rearrangement: A Useful Variant of the Claisen Reaction

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The Ireland-Claisen Rearrangement: Use of Enolates to Generate Well-Defined Precursors

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Key feature of chemistry is the ability to control enolate geometry to then control the formation of either syn- or anti-products

Work out the transition states for these on your own!

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A: syn-product
B: anti-product

Enolization conditions

<table>
<thead>
<tr>
<th>Enolization conditions</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA, 23% HMPA/THF</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>LDA, 45% DMPU/THF</td>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>LDA, THF</td>
<td>25</td>
<td>75</td>
</tr>
</tbody>
</table>

Remember: in cyclic systems boat-like transition states are possible. Here, the Z-enolate formed from the use of HMPA and DMPU likely goes through such a transition state. The standard chair should be favored with the formation of the E-enolate.

The Ireland-Claisen Rearrangement: Applications in Complex Molecule Synthesis

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The Ireland-Claisen Rearrangement:
Applications in Complex Molecule Synthesis

\[ \text{THPO} \quad \text{TBSO} \quad \text{TBS} \quad \text{O} \quad \text{OBn} \]

\[ \text{THPO} \quad \text{TBSO} \quad \text{OTBS} \quad \text{O} \quad \text{OBn} \]

\[ \text{xylene}, \Delta \]

[Brook rearrangement]

\[ \text{Z-enolate} \]

\[ [3,3] \quad (6:1 \text{ d.r.}) \]

ophiobolin C

The Carroll Rearrangement:
An Early Variant of the Claisen Reaction

The Buchi-Claisen Rearrangement: 
A Method for the Preparation of Certain Cyclohexenes

The Buchi-Claisen Rearrangement: A Method for the Preparation of Certain Cyclohexenes

The Buchi-Claisen Rearrangement: A Method for the Preparation of Certain Cyclohexenes

A Modified Buchi-Claisen Rearrangement: Large Ring Synthesis

The Danishefsky-Claisen Rearrangement: Combining the Virtues of the Buchi- and Ireland-Claisen Reactions