The application of [5+2] cycloadditions in natural product synthesis

Reporter: Baochao Yang
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Index

• Introduction

• Main Contents
  • Oxidopyrylium-mediated [5+2]cycloaddition
  • Pyridinium and quinolinium-mediated [5+2] cycloadditions
  • Perezone-type [5+2] cycloadditions
  • [5+2] cycloadditions of vinyl cyclopropanes (VCPs)
  • [5+2] cycloadditions of five-carbon organometallic complexes

• Summary
Index

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• Main Contents
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  • Pyridinium and quinolinium-mediated [5+2] cycloadditions
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• Summary
Selected natural products containing seven-membered ring skeleton

Among them, the most famous molecule is Colchicine, which is a commonly used drug in the treatment of gout.
Main type of intermediates involved in [5+2] cycloadditions

Oxidopyrylium-mediated [5+2] cycloaddition

pyridinium- and quinolinium-mediated [5+2] cycloadditions

seven-membered rings via [5+2] cycloadditions

[5+2] cycloadditions of vinyl cyclopropanes (VCPs)

[5+2] cycloadditions of 3-acyloxy-1,4-enynes (ACEs)

formal [5+2] cycloadditions of vinylphenols, alkyldienes and arylanilines

[5+2] cycloadditions of five-carbon organometallic complexes

Main type of intermediates involved in [5+2] cycloadditions

From 2008 to 2021, Natural products were synthesized by [5+2] cycloaddition reaction as a key step.
Index

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• Summary
Oxidopyrylium-mediated [5+2] cycloaddition

Intramolecular [5+2] cycloaddition

$$\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et}$$

$$\text{R}^1$$  $$\text{R}^2$$  $$\text{R}^3$$

$$\text{O}$$

$$\text{R} = \text{H, Me, Bn, allyl}$$

$$\text{R'} = \text{OMe, F, Cl}$$

MeOTf, 40 °C;
CsF, 25 °C

R' = OMe, F, Cl

1,5-dipolar

40-90% yield

Intermolecular [5+2] cycloaddition

$$\text{R}^1$$  $$\text{R}^2$$  $$\text{R}^3$$

$$\text{R} = \text{Me, Bn}$$

$$\text{R}^2 = \text{H, F, Cl}$$

$$\text{R}^3 = \text{H, Me}$$

MeOTf, 40 °C

Me$_2$NPh, 25 °C

This is the first dearomative indole [5+2] cycloaddition with an oxidopyrylium ylide

Type II intramolecular [5+2] cycloaddition

Oxidopyrylium-mediated [5+2] cycloaddition

6, acetoxyxypyrane

MeCN
100 or 160 °C

7, bridged bicycle

7a, 90%
dr = 1.6:1

7b, 88%
dr = 1.3:1

7c, 92%
dr > 20:1

7d, 92%
dr > 20:1

7e, 90%
dr = 1.3:1

7f, 91%
dr = 1.7:1

7g, 61%
dr = 1.7:1

7h, 94%

Total synthesis of (±)-englerin

Oxidopyrylium-mediated [5+2] cycloaddition

Total synthesis of harringtononolide

Oxidopyrylium-mediated [5+2]cycloaddition

Oxidopyrylium-mediated [5+2] cycloaddition

Oxidopyrylium-mediated [5+2] cycloaddition

N. Kornblum, H. DeLaMare, *J. Am. Chem. Soc.* 1951, 73, 880.
Index

• Introduction

• Main Contents
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[5+2] cycloaddition of pyridinium and quinolinium ylides

Rh-catalyzed [5+2] cycloaddition of pyridinium ylides

\[ \text{Rh}^\text{II} \text{(esp)}_2 (\text{1.5 mmol}) \]

benzene

\[ \text{Rh}^\text{II} \text{(esp)}_2 \text{N}^\text{Ts} \]

\[ \text{Rh}^\text{II} \text{(esp)}_2 \text{N}^\text{Ts} \]

isolable azomethine

29a, 82%
29b, 80%
29c, 88%
29d, 83%

Gold-catalyzed [5+2] cycloaddition of quinolinium ylide

\[ R^1\text{C} = N\text{Ph} + R^2\text{C} = N\text{Ph} \rightarrow AuCl (5 \text{ mmol\%}) \rightarrow \text{THF, 25 }^\circ\text{C} \rightarrow R^1\text{C} = N\text{Ph} \text{NTs} + R^2\text{C} = N\text{Ph} \text{NTs} \]

isolable azomethine

1,4-diazepine

[5+2] cycloaddition of pyridinium and quinolinium ylides

Fischer indole synthesis

vellosimine \((R^1 = R^2 = H; 58\%)\) (43)

N-methylvellosimine \((R^1 = H, R^2 = Me; 52\%)\) (44)

10-methoxy-vellosimine \((R^1 = OMe, R^2 = H; 63\%)\) (45)

[5+2] cycloaddition

Aggarwal’s chiral ketene equivalent

oxidopyridinium

[5+2] cycloaddition of pyridinium and quinolinium ylides

Aggarwal's chiral ketene equivalent

oxidopyridinium

vellosimine ($R^1 = R^2 = H; 58\%$) (43)
$N$-methylvellosimine ($R^1 = H, R^2 = Me; 52\%$) (44)
10-methoxy-vellosimine ($R^1 = OMe, R^2 = H; 63\%$) (45)

[5+2] cycloaddition of pyridinium and quinolinium ylides

Ring expansion

Index

• Introduction

• Main Contents
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  • Perezone-type [5+2] cycloadditions
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Perezone to Pipitzol Transformation

Oxidative dearomatization-induced (ODI) [5+2] cascade reaction

**Reagents and Conditions:**
- OAc
- Pb(OAc)_3
- Pb(OAc)_2
- CHCl_3, -40 °C

**Equation:**

\[ \text{53 dipole umpolung} \]

**Products:**

- 56
- 57

**Yields:**

- 57a, 61%
- 57b, 54%
- 57c, 52%
- 57d, 65%

**References:**

Oxidative dearomatization-induced (ODI) [5+2] cascade reaction

Perezone-type [5+2] cycloaddition

Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetylpseurata C, and Pseurata C

Perezone-type [5+2] cycloaddition

enone formation

stereoselective diketone reduction

ODI-[5+2] cycloaddition

1,2-acyl migration

1,2-addition

Eschenmoser-Tanabe fragmentation

1. IBX, DMSO
2. H₂O₂, NaOH
85% (2 steps)

1. H₂NCONHNH₂•HCl, NaOAc
2. Pb(OAc)₄

Eschenmoser-Tanabe fragmentation

Perezone-type [5+2] cycloaddition

Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetylpseurata C, and Pseurata C
Perezone-type [5+2] cycloaddition

Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetylpseurata C, and Pseurata C

Perezone-type [5+2] cycloaddition

Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetylipseurata C, and Pseurata C

1. L-Selectride
2. methylene blue
O₂, hv, MeCN; then TCCA

singlet oxygen ene reaction

Perezone-type [5+2] cycloaddition

Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetyl pseurata C, and Pseurata C

1. L-Selectride
2. methylene blue
   O₂, hv, MeCN; then TCCA

singlet oxygen ene reaction

ene reaction

allylic hydroperoxide

O-O

[4+2] [2+2]

Index

• Introduction
• Main Contents
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  • Perezone-type [5+2] cycloadditions
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[5+2] cycloaddition of vinyl/allenyl cyclopropanes

In 2017, Yu group discovered that vinylcyclopropane can react with allene by rhodium(I)-catalyzed intramolecular [5+2] cycloaddition to synthesize the challenging bicyclo[4.3.1]decane skeleton.

[5+2] Cycloaddition of vinyl cyclopropanes

[5+2] cycloaddition of vinyl/allenyl cyclopropanes

[5+2] Cycloaddition of vinyl cyclopropanes

[5+2] cycloaddition of vinyl/allenyl cyclopropanes

Hetero-[5+2] cycloaddition of vinyl aziridines and vinyl oxiranes

(E) or (Z) - 95 up to 99% ee


96, up to 99% ee
chirality-transfer strategy

98 (X = C(CO₂Me)₂, R¹ = Ph, R² = R³ = Me), 72%
99 (X = C(CO₂Me)₂, R¹ = Me, R² = Me, R³ = H), 75%
100 (X = NTs, R¹ = Ph, R² = H, R³ = nPr), 72%


[5+2] Cycloaddition of vinyl cyclopropanes

Index

• Introduction

• Main Contents
  • Oxidopyrylium-mediated [5+2] cycloaddition
  • Pyridinium and quinolininium-mediated [5+2] cycloadditions
  • Perezone-type [5+2] cycloadditions
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[5+2] Cycloadditions of 5-carbon organo-metallic complexes

This process can be considered as a novel “interrupted Nazarov” cyclization, in which the cationic intermediate is intercepted prior to the electrocyclization.

[5+2] Cycloadditions of 5-carbon organo-metallic complexes

[5+2] Cycloadditions of 5-carbon organo-metallic complexes

furanether B (129)
[5+2] Cycloadditions of 5-carbon organo-metallic complexes

Index

• Introduction

• Main Contents
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• Summary
This seminar mainly introduce five kinds of strategies to synthesize 7-membered ring and its application in natural product. As you can see, every strategy has unique feature, but these two strategies are most commonly used in total synthesis.
Thank you!
Scheme 23. [5 + 2] Cycloaddition via Group Elimination

- **Scheme Details:**
  - Reaction sequence:
    1. Reaction with Br₂ in MeOH to form the intermediate.
    2. Hydrolysis with H₂O⁺.
    3. Cyclization with Ac₂O in pyridine to form 73.

- **Product 73:**
  - Formed by cyclization after hydrolysis.

- **Dimerization Product 75:**
  - Formed by dimerization of the intermediate.

- **Yields:**
  - 42% (R₁ = R₂ = CO₂Me)
  - 35% (R₁ = H, R₂ = SO₂C₄F₉)
  - 69% (R₁ = H, R₂ = CHO)

- **References:**
  - Reactions involving MeO₂C=CNCO₂Me or similar.
  - Reaction conditions: 134 °C in CDCl₃ sealed tube.
Scheme 36. Intramolecular [5+2] cycloaddition of inverted 3-acyloxy-1,4-enynes and alkynes.
Fischer indole synthesis

R\textsuperscript{1}\textsuperscript{}-${\text{CH}}_{2}$-$R\textsuperscript{2}$ + R\textsuperscript{3} N=NH \rightarrow \text{arylhdydrazone}

\text{ene-hydrazines} \xrightarrow{\text{1. [3,3]} \; \text{2. -NH}_2\text{H}} \text{regioisomeric indoles}

\text{Substituted indole}
**Eschenmoser-Tanabe fragmentation**

Synthesis of cyclic alkyrones:

\[
\begin{align*}
\text{N-NHR} & \xrightarrow{\text{acid, base or heat}} \text{Cyclic alkyrone} \\
x = 1 \text{ or more} & \quad y = 0 \text{ or more}
\end{align*}
\]

- \( \text{N}_{2} \)

Synthesis of acyclic alkyrones and alkylnals:

\[
\begin{align*}
\text{N-NHR} & \xrightarrow{\text{acid, base or heat}} \text{Acyclic alkynal or alkyrone} \\
n = 0 \text{ or } 1 & \quad R^2 = \text{alkyl}
\end{align*}
\]

- \( \text{N}_{2} \)

\( R = \text{tosyl, 2,4-dinitrophenyl; } R^{1-2} = \text{H, alkyl; when } R^{2} = \text{H, then the product is an alkyanal, and when } R^{2} = \text{alkyl, then it is an alkyone} \)

**Explanation**

- **Base**

\[
\begin{align*}
\text{Ts} &= p\text{-toluenesulfonyl} \\
- \text{[Base-H]}^{\ominus} & \quad \text{Cyclic alkyrone}
\end{align*}
\]

\( + \text{N=N:} + \text{Ts}^{\ominus} \)
Eschenmoser-Tanabe fragmentation

\[
\begin{align*}
X & \rightarrow \text{C} = \text{N} = \text{N} + \text{X} = \text{C} = \text{O}
\end{align*}
\]

Table 1. \(\alpha,\beta\)-Epoxyketone derivatives and thermolysis products

<table>
<thead>
<tr>
<th>(\alpha,\beta)-Epoxyketone</th>
<th>Semi-carbazone</th>
<th>Oxadiazoline</th>
<th>Acetylenic carbonyl</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 R = H</td>
<td></td>
<td></td>
<td></td>
<td>44^a, 71^b</td>
</tr>
<tr>
<td>7 R = C(_6)H(_5)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>53^b</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 R = H</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 R = C(_6)H(_5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>13 X = O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 X = NC(_6)H(_5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td></td>
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<tr>
<td>15</td>
<td></td>
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</tr>
<tr>
<td>16 X = NH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 X = NC(_6)H(_5)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>20</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td>38^c, 64^b</td>
</tr>
</tbody>
</table>

Table 1. Optimization of the ODI-[5+2] Cycloaddition/Pinacol-Type 1,2-Acyl Migration Cascade\(^a\)

![Chemical structures and reactions](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant</th>
<th>solvent</th>
<th>(\text{yield (%)})^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pb(OAc)(_4^c)</td>
<td>CHCl(_3)</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>PhI(OAc)(_2)</td>
<td>CHCl(_3)</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>PhI(OAc)(_2)</td>
<td>TFE</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>PhI(OAc)(_2)</td>
<td>HFIP</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>PhI(CF(_3)CO(_2))(_2)</td>
<td>HFIP</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^a\)Unless stated otherwise, the reactions were performed with 12a (0.2 mmol) and oxidant (1.1 equiv) in solvent (4 mL) at 0 °C for 20 min.  
\(^b\)Isolated yields.  
\(^c\)Run at −40 °C for 10 min.  
TFE = 2,2,2-trifluoroethanol, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.