Nickel-Catalyzed Three-Component [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

Selective Synthesis of Multisubstituted Cycloheptadienes

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{R}^1 \equiv \text{R}^2 \\
\text{R}^1 & \quad \text{R}^2 \\
\text{Cat. Ni}^0 & \quad \rightarrow
\end{align*}
\]


Michel Grenon

April 1\textsuperscript{st}, 2006
Presentation Outline

☐ Other Transition-Metal Catalyzed Cycloadditions for the Construction of Seven-Membered Rings

  • [6+1] Cycloaddition of arenes with α-diazo carbonyl compounds
  • [5+2] Cycloaddition of vinylcyclopropanes with alkynes
  • [4+3] Cycloaddition of dienes with TMM derivatives

☐ Previous Examples of Transition-Metal Catalyzed(Mediated) [3+3+2] Cycloadditions for the Construction of Seven-Membered Rings

  • Iridium-mediated allyl/alkyne [3+2+2] cycloaddition
  • Cobalt-mediated allyl/alkyne [3+2+2] cycloaddition
  • Nickel and Rhodium-catalyzed [3+2+2] cycloaddition of alkenyl Fischer carbene complexes and allenes

☐ Nickel-Catalyzed Intermolecular [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

☐ Future Work
Transition-Metal Catalyzed [6+1] Cycloaddition (Buchner Reaction)

von E. Doering, W.; Laber, G.; Vonderwahl, R.; Chamberlain, N. F.; Williams, R. B. 


Substituted arenes give mixtures of isomeric products


Transition-Metal Catalyzed [5+2] Cycloaddition

Formation of a metallacycle, followed by a strain-driven cleavage of the cyclopropane ring and a reductive elimination to the cycloheptadiene.

An increase in reaction rate is also observed when the reactions are performed in CF$_3$CH$_2$OH.

<table>
<thead>
<tr>
<th>entry</th>
<th>react. cond</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>R$_3$</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A, 20 min</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>B, 2 d</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>B, 2 d</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>B, 16 h</td>
<td>H</td>
<td>Me</td>
<td>CO$_2$Me</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>B, 7 d</td>
<td>H</td>
<td>Me</td>
<td>TMS</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>C, 30 min</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>82</td>
</tr>
</tbody>
</table>

A: 0.5 mol % [RhCl(PPh$_3$)$_3$], 0.5 mol % AgOTf;
B: 10 mol % [RhCl(PPh$_3$)$_3$];
C: 10 mol % [RhCl(PPh$_3$)$_3$], 10 mol % AgOTf.

Transition-Metal Catalyzed [4+3] Cycloaddition

\[
\text{Pd(PPh}_3\text{)}_4 \text{ (7 mol\%)} \quad \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \\
\text{dppe (1.5 mol\%)} \quad \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \\
\text{Dioxane, } \Delta, 8 \text{ h} \quad 98\%
\]

Trost, B. M.; Nanninga, T. N.; Chan, D. M. T. *Organometallics* **1982**, *1*, 1543

\[
\text{Pd(OAc)}_2 \text{ (5 mol\%)} \quad \text{CO}_2\text{CH}_2\text{CH}_2\text{Ph} \\
\text{P(OiPr)}_3 \text{ (35 mol\%)} \quad \text{CO}_2\text{CH}_2\text{CH}_2\text{Ph} \\
\text{THF, } \Delta, 8 \text{ h} \quad 88\%
\]

Minor amounts of [3+2] cycloadduct observed

Freezing the diene in a cisoid conformation favors the formation of the seven-membered ring


Previous Examples of [3+2+2] Cycloadditions

Iridium-mediated allyl/alkyne [3+2+2] cycloaddition

\[
\begin{align*}
&\text{Me} & \text{Ir} & \text{Me} & + \text{OTf} \\
\xrightarrow{\text{Ph} \equiv \equiv \text{Ph}} & \text{Me} & \text{Ir} & \text{Ph} & + \text{OTf} \\
& \text{CH}_2\text{Cl}_2, 0 \, ^\circ \text{C to rt, 24 h} & 56\% \\
& \text{Ph} \equiv \equiv \text{Me} & \text{Me} & \text{Ir} & + \text{OTf} \\
& \text{CH}_2\text{Cl}_2, 0 \, ^\circ \text{C to rt, 24 h} & \text{ca. 40\% (3:1)} \\
\end{align*}
\]

Similar results with phenylacetylene

\[
\begin{align*}
&\text{Me} & \text{Ir} & \text{Me} & + \text{OTf} \\
\xrightarrow{\text{Me} \equiv \equiv \text{Me}} & \text{Me} & \text{Ir} & \text{Me} & + \text{OTf} \\
& \text{CH}_2\text{Cl}_2, 0 \, ^\circ \text{C to rt, 12 h} & 78\% \\
\end{align*}
\]

Stoichiometric reaction, and poor selectivities are obtained for unsymmetrical alkynes

Previous Examples of [3+2+2] Cycloadditions

Cobalt-mediated allyl/alkyne [3+2+2] cycloaddition

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{i}} \text{Co} & \xrightarrow{\text{ii}} \text{alkyne} \\
\text{i: } & \text{R} = R' = H \\
\text{ii: } & \text{R} = H, R' = \text{Me}
\end{align*}
\]

Conditions: i: (C₅Me₅)Co(C₂H₄)₂ (1), TfOH, Et₂O, −78 °C→RT, 4h
ii: (C₅Me₅)Co(C₂H₄)₂ (1), hexane, 65 °C, 4–12 h; then step i.

- Dramatic solvent effect (THF affords cyclopentadienyl complexes)
- Conditions: CH₂Cl₂, excess alkyne (3 to 10 equiv.), −78 °C to rt, 12 h
- Nucleophilic alkylation (Na-dimethylmalonate) of 3, followed by an oxidative decomplexation using [Cp₂Fe]⁺OTf affords substituted cycloheptadienes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allyl complex/precursor</th>
<th>Alkyne</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>H−H</td>
<td>3a (R, R' = H)</td>
<td>52 (66)</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>H−H</td>
<td>3b (R = H, R' = Me)</td>
<td>79 (85)</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>H−H</td>
<td>3c (R, R' = Me)</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>Ph−H</td>
<td>3d</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>'Bu−H</td>
<td>3e</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>2b</td>
<td>H−H</td>
<td>3f (n = 1)</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>2c</td>
<td>H−H</td>
<td>3g (n = 2, BF₄ salt)</td>
<td>59</td>
</tr>
</tbody>
</table>

Previous Examples of [3+2+2] Cycloadditions

Nickel and Rhodium-catalyzed [3+2+2] cycloaddition of alkenyl Fischer carbene complexes and allenes

![Chemical Structures]

Reaction affords the [3+2] cycloadduct when performed in toluene

Least substituted C=C bond of the allene inserts (head-to-head allene–allene coupling)

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>4 (%)α,b</th>
<th>5 (%)α</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-MeOCH₃</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>4a (53)</td>
<td>5a (55)</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>4b (40)</td>
<td>5b (61)</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>4c (52)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2-furyl</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>4d (56)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>5c (70)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>5d (55)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>5e (60)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>ferroceny</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>5f (63)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>5g (71)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>H</td>
<td>-(CH₂)₅-</td>
<td>Me</td>
<td>5h (64)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>5i (52)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>5j (50)</td>
<td></td>
</tr>
</tbody>
</table>

Done with Ni(cod)₂

Previous Examples of [3+2+2] Cycloadditions

Nickel and Rhodium-catalyzed [3+2+2] cycloaddition of alkenyl Fischer carbene complexes and allenes

Least substituted C=C bond of the allene inserts (head-to-tail allene–allene coupling)

Reversible metalla-[4+2] cycloaddition gives IV, which evolves to the more stable V

Done with [Rh(cod)Cl]₂

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>4 (%)a,b</th>
<th>5 (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-MeOC₆H₄</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>4a (53)</td>
<td>5a (55)</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>4b (40)</td>
<td>5b (61)</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>4c (52)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2-furyl</td>
<td>H</td>
<td>Me</td>
<td>Mc</td>
<td>4d (56)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>5e (70)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>H</td>
<td>Me</td>
<td>Mc</td>
<td>5d (58)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>5e (60)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>ferroceny1</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>5f (63)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Mc</td>
<td>Me</td>
<td>Mc</td>
<td>Me</td>
<td>5g (71)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>H</td>
<td>(CH₂)₅</td>
<td>Me</td>
<td>5h (64)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>5i (55)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>5j (50)</td>
<td></td>
</tr>
</tbody>
</table>

Nickel-Catalyzed Intermolecular [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

Other phosphines [P(Bu)₃, P(Cy)₃, P(t-Bu)₃, dppe] were less effective
Other catalysts [RhCl(PPh₃)₃, CpCo(PPh₃)₂, CpCp(CO)₂] were not effective

Good results obtained with sterically hindered terminal alkynes (entries 1–9)

Nickel-Catalyzed Three-Component [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

Selective Synthesis of Multisubstituted Cycloheptadienes

Nickel-Catalyzed Intermolecular [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

\[
\text{CO}_2\text{Et} \quad \text{Ni(cod)}_2 (10 \text{ mol\%})
\]

\[
\text{TMS} \quad \text{PPh}_3 (20 \text{ mol\%})
\]

\[
\text{R} \quad \text{Toluene, rt, dropwise addition of reagents}
\]

\[
\text{CO}_2\text{Et} \quad \text{TMS}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOCH₂</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>TBDMSOCH₂</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>PhCH₂</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>n-C₆H₁₃</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>p-MeOCH₆H₄</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>p-CF₃CH₆H₄</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>HO(CH₃)₂C</td>
<td>69</td>
</tr>
</tbody>
</table>

- DMF can also be used, but not THF, Et₂O or CH₂Cl₂
- Terminal alkyne doesn't need to be bulky in order to get good regioselectivities (see different R groups)
- Other alkynes; (4 equiv.) (4 equiv.) (4 equiv.) (4 equiv.)
  - TBDMS
  - BDMS
  - t-Bu
  - Pr

Nickel-Catalyzed Intermolecular [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

Future Work

- Extend this reaction to other cyclopropylmethylene derivatives

- Extend this reaction to cyclobutylmethylene derivatives

- Attempt to apply this methodology to the synthesis of complex natural products

(Feasible? Beilstein search resulted in no hits.)