New Methods of Indole Formations and Applications in Total Synthesis

Palladium-Catalyzed Synthesis of 2-(Aminomethyl)indoles from Ethyl 3-(o-Trifluoroacetamidophenyl)-1-Propargyl Carbonate
Ilaria Ambrogio, Sandro Cacchi and Giancario Fabrizi
Org. Lett., 2006, ASAP

and

A New Modular Indole Synthesis. Construction of the Highly Strained CDEF Parent Tetracycle of Nodulisporic Acids A and B
Amos B. Smith, III, László Kürti and Akin H. Davulcu
Org. Lett., 2006, ASAP

Erick B. Iezzi, PhD
Current Literature
May 6, 2006
Why are these articles significant?

• New routes to functionalized indoles:
  - significant for natural product and pharmaceutical drug synthesis

• Cacchi’s group developed a simple approach to 2-(aminomethyl)indoles and the important class of 2-(piperazin-1-ylmethyl)indoles

• Smith’s group developed a new synthesis of tetracyclic indoles via a Stille cross-coupling/Buckwald-Hartwig union/cyclization
Synthesis and Functionalization of Indoles

• Classical methods (over last 100 years):
  - Fisher synthesis
  - Gassman synthesis
  - Madelung cyclization
  - Bischler synthesis

Bischler-Möhlau synthesis

• Palladium-catalyzed syntheses (over last 40 years):
  - industrial synthesis of acetaldehyde from ethylene (PdCl$_2$ and CuCl$_2$)
    launched a new area of research
    - fewer steps, less waste, etc.
Alkyne-Based Palladium-Catalyzed Assembly of Indoles

Mechanism

Example

Alkene-Based Palladium-Catalyzed Assembly of Indoles

Mechanism

Example

Palladium-catalyzed hydroarylation/cyclization of alkynes (Cacchi’s methodology)

• Used to construct heterocyclic rings:
  - butenolides
  - quinolines
  - chromenes
  - coumarins
  - chromanols

Palladium-Catalyzed Synthesis of 2-(Aminomethyl)indoles (Cacchi et al., ASAP)

* A new palladium-catalyzed cyclization of an acyclic alkyne to a free N-H functionalized indole!

Erick Iezzi @ Wipf Group 5/10/2006
Synthesis of 2-(piperazin-1-ylmethyl)indoles (Cacchi et al., ASAP)

- 2 privileged structures (indole and piperazine nuclei)
  - significant components in pharmaceutical chemistry (i.e., Clozapine)
  - formed in a single step

Two C-N bonds formed in a single operation

- Stepwise pathways (2 & 3 positions)

Synthesis of Starting Materials and Evaluation of Conditions for 2-(Piperazin-1-ylmethyl)indole Formation

**Equation 1:**

\[
\text{Ethyl chloroformate, CH}_2\text{Cl}_2, \text{Et}_3\text{N}, 0 \degree \text{C}, 2 \text{h} \rightarrow \text{NHCOCF}_3 \]

80% (4 steps)

**Table 1.** Examination of the Reaction of Ethyl 3-(a-Trifluoroacetimidophenyl)-1-propargyl Carbonate 1a with N-Ethylpiperazine 5a*.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst System</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield % of 6a*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$, PPh$_3$</td>
<td>THF</td>
<td>6</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>Pd($\text{dba}_3$, PPh$_3$</td>
<td>THF</td>
<td>6</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh$_3$)$_2$</td>
<td>MeCN</td>
<td>6</td>
<td>57*</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh$_3$)$_2$</td>
<td>DMF</td>
<td>6</td>
<td>54*</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh$_3$)$_2$</td>
<td>THF</td>
<td>1.5</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>Pd($\text{dba}_3$, dppf</td>
<td>THF</td>
<td>6</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>Pd($\text{dba}_3$, dppp</td>
<td>THF</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>PdCl$_2$(2-furyl)$_2$</td>
<td>THF</td>
<td>24</td>
<td>33</td>
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</tbody>
</table>

*Unless otherwise stated, reactions were carried out on a 0.159 mmol scale in 1 mL of solvent under argon at 80 °C by using 1 equiv of 1a, 3 equiv of 5a, 0.05 equiv of [Pd], 0.1 equiv of PPh$_3$, or 0.05 equiv of bidentate phosphine ligand. *Yields are given for isolated products. *With 0.05 equiv of Pd(PPh$_3$)$_2$. 
Evaluation of Functional Groups in 2-(Piperazin-1-ylmethyl)indole Formations

<table>
<thead>
<tr>
<th>entry</th>
<th>piperazine 5</th>
<th>time (h)</th>
<th>yield % of 6&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="402x54.jpg" alt="Image" /> 5a</td>
<td>1.5</td>
<td>6a 91</td>
</tr>
<tr>
<td>2</td>
<td><img src="414x466.jpg" alt="Image" /> 5b</td>
<td>2</td>
<td>6b 96</td>
</tr>
<tr>
<td>3</td>
<td><img src="136x150.jpg" alt="Image" /> 5c</td>
<td>24</td>
<td>6c 80</td>
</tr>
<tr>
<td>4</td>
<td><img src="132x466.jpg" alt="Image" /> 5d</td>
<td>3</td>
<td>6d 98</td>
</tr>
<tr>
<td>5</td>
<td><img src="136x150.jpg" alt="Image" /> 5e</td>
<td>6</td>
<td>6e 96</td>
</tr>
<tr>
<td>6</td>
<td><img src="136x150.jpg" alt="Image" /> 5f</td>
<td>6</td>
<td>6f 98</td>
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<tr>
<td>7</td>
<td><img src="136x150.jpg" alt="Image" /> 5g</td>
<td>2.5</td>
<td>6g 97</td>
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<tr>
<td>8</td>
<td><img src="136x150.jpg" alt="Image" /> 5h</td>
<td>3</td>
<td>6h 92</td>
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<table>
<thead>
<tr>
<th>entry</th>
<th>piperazine 5</th>
<th>time (h)</th>
<th>yield % of 6&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>9</td>
<td><img src="402x54.jpg" alt="Image" /> 5i</td>
<td>3</td>
<td>6i 94</td>
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<tr>
<td>10</td>
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<td>6j 58</td>
</tr>
<tr>
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<td>4</td>
<td>6k 85</td>
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<tr>
<td>12</td>
<td><img src="136x150.jpg" alt="Image" /> 5l</td>
<td>12</td>
<td>6l 78</td>
</tr>
<tr>
<td>13</td>
<td><img src="136x150.jpg" alt="Image" /> 5m</td>
<td>4</td>
<td>6m 81</td>
</tr>
<tr>
<td>14</td>
<td><img src="136x150.jpg" alt="Image" /> 5n</td>
<td>4</td>
<td>6n 80</td>
</tr>
<tr>
<td>15</td>
<td><img src="136x150.jpg" alt="Image" /> 5o</td>
<td>8</td>
<td>6o 92</td>
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<tr>
<td>16</td>
<td><img src="136x150.jpg" alt="Image" /> 5p</td>
<td>20</td>
<td>6p 88</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were carried out on a 0.159 mmol scale in 1 mL of THF under argon at 80 °C by using 1 equiv of 1a, 3 equiv of 5, and 0.05 equiv of Pd(PPh<sub>3</sub>)<sub>4</sub>. <sup>b</sup> Yields are given for isolated products.
Evaluation of Secondary Amines and Proposed Reaction Mechanism

Table 3. Palladium-Catalyzed Reaction of Ethyl 3-(α-Trifluoroacetamidophenyl)-1-propargyl Carbonate 1a with Secondary Amines

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>time (h)</th>
<th>yield % of 4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HN</td>
<td>1</td>
<td>4a 94(^c)</td>
</tr>
<tr>
<td>2</td>
<td>HN</td>
<td>1</td>
<td>4b 98</td>
</tr>
<tr>
<td>3</td>
<td>Et(_2)NH</td>
<td>2</td>
<td>4c 60(^d)</td>
</tr>
<tr>
<td>4</td>
<td>(i-Pr)(_2)NH</td>
<td>4</td>
<td>4d 45</td>
</tr>
</tbody>
</table>

Proposed mechanism

Not acidic enough
A New Modular Indole Synthesis. Construction of the Highly Strained CDEF Parent Tetracycle of Nodulisporic Acids A & B (Smith et al., ASAP)

Nodulisporanes:
- a novel class of indole diterpene alkaloids
- display potent insecticidal properties (i.e., fleas and ticks)
  - modulation of the invertebrate-specific glutamate-gated chloride ion channels

- Nodulisporic acid A – first reported by Merck in 1997 as a lead compound
  (potency, stability and pharmacokinetic profile was not optimal!)
Attempts to Synthesize the CDE Core via Known Indole Formations
(Smith et al., ASAP)

Reported approaches to CDE tricycle

Application of the Fisher Indole Synthesis

High strain in five-membered system!
Stille Cross-Coupling/Buchwald-Hartwig Union/Cyclization Tactic
(Smith et al., ASAP)

No reaction with 2.5 mol% cat.
Preparation of a Highly Substituted and Strained Indole Derived from (+)-Estrone and Construction of Diverse Indoles
Summary of New Indole Methodologies

• Cacchi’s group developed a simple approach to 2-(aminomethyl)indoles and 2-(piperazin-1-ylmethyl)indoles under mild conditions in a single operation
  - high product yields
  - application to functionalized indoles

• Smith’s group developed a new indole synthesis via a Stille/Hartwig-Buchwald coupling using mild conditions
  - application to structurally diverse indoles, especially novel tricyclic systems