A Rapid Assembly of Furo[3,4-b] and Pyrrolo[3,4-b]carbazolones by Domino Wittig Diels–Alder Reaction

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Dedicated to Prof. R. S. Mali on his 70th birthday

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Abstract: Regioisomeric hexahydrofuro[3,4-b]carbazol-1-ones, hexahydropyrrolo[3,4-b]carbazol-1-ones, hexahydrofuro[3,4-b]carbazol-3-ones and hexahydropyrrolo[3,4-b]carbazol-3-ones were synthesized in 59% to 62% yields by domino Wittig Diels–Alder reactions from indole-3-carboxaldehyde and indole-2-carboxaldehyde and Wittig reagents. Further the corresponding carbazolelactones and carbazolelactams were obtained by oxidation with DDQ.

Key words: domino Wittig, Diels–Alder, furocarbazoles, pyrrolo-carbazoles

A large number of substituted carbazole alkaloids have been isolated1 from plants in last few decades. Both, natural and synthetic carbazoles display a wide range of biological activities which includes inhibition of CDK-5, antitumor, psychotropic, anti-inflammatory, antimicrobial, antihistamine, antibiotic, and antioxidative activities.2 Application of carbazoles in material science is also well documented.3 Consequently, the development of regioselective synthesis4 of functionalized tetrahydrocarbazole and carbazole scaffolds has gained paramount interest. A plethora of reviews5 is available on the synthesis of carbazole alkaloids.

The ubiquitous presence of a lactone and a lactam unit in many polycyclic antineoplastic agents6 prompted us to undertake the synthesis of carbazolelactones and carbazolelactams. Further impetus was provided by the cytotoxicity exhibited by the recently isolated 7-lactone carbazole against human leukemia cell line.6a

Domino reactions7 are of current interest for the synthesis of complex molecules. In continuation of our endeavors in domino methodologies,8 we report herein a facile synthesis of furo[3,4-b]carbazolones and pyrrolo[3,4-b]carbazolones using domino Wittig–Diels–Alder reaction sequence.9

Thus, when indole-3-carboxaldehyde (1), was subjected to domino Wittig Diels–Alder reaction protocol8e,10 with phosphorane 2a a mixture of two diastereomers, cis- and trans-3,3a,4,5,10,10a-hexahydro-1H-furo[3,4-b]carbazol-1-one (5a) was obtained in 1:1 ratio (HPLC) in 60% yield.

In this one-pot reaction first the Wittig reaction takes place to form E unsaturated ester 3a, which under the reaction conditions undergoes intramolecular Diels–Alder reaction to form 4a, which then rapidly isomerizes to 5a (Scheme 1).

The cis diastereomer was assumed to have arisen from the syn transition state while the trans from the anti transition state (Scheme 2). The formation of both the diastereomers in equal proportion suggests that the energy barrier between the two transition states is negligible. Interestingly, no dimeric product due to intermolecular Diels–Alder reaction was observed though the conjugated double bond in 3 can also behave as a dienophile. Compound 5a was then easily oxidized with DDQ to the required furo[3,4-b]carbazol-1-one. The success of this reaction prompted us to condense phosphorane 2b with 1 to obtain a mixture...
of diastereomers of 5b which were directly converted into 6b.

Having synthesized the furcocarbazolones 6a,b, our next aim was to prepare the corresponding pyrrolocarbazolones, for which 1 was reacted with the phosphorane 2c under similar reaction conditions. As expected a mixture of cis and trans fused 2-benzyl-2,3,3a,4,10,10a-hexahydro-pyrrolo[3,4-b]carbazol-1(5H)-one (5c) was formed which on oxidation gave 6c. With phosphorane 2d, a mixture of diastereomers of 5d was obtained, which on aromatization gave the carbazolone 6d (Table 1).

We next undertook the synthesis of carbazole lactones and lactams regioisomeric to 6a-d using indole-2-carboxaldehyde 7. Thus, when 7 was subjected to similar reaction conditions with 2a, a mixture of cis- and trans-3a,4,10,10a-tetrahydro-1H-furo[3,4-b]carbazol-3(5H)-one (10a) was obtained in 60% yield. Compound 10a was then easily oxidized to 11a using DDQ (Scheme 3). The reaction of 7 with phosphorane 2b, however, yielded an isomeric product 11b' in major amount. The formation of 11b' could be accounted from an allylic ester rearrangement of the Wittig product intermediate prior to the Diels–Alder reaction (as shown in Scheme 4).

Table 1  Product of Domino Wittig–Diels–Alder Reaction and Oxidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Phosphorane</th>
<th>Product 5/10</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product 6/11</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tr>
<td>1</td>
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<td>2a</td>
<td>5a</td>
<td>60</td>
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<td>62</td>
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<td>1</td>
<td>2b</td>
<td>5b</td>
<td>61</td>
<td>6b</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2c</td>
<td>5c</td>
<td>62</td>
<td>6c</td>
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</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2d</td>
<td>5d</td>
<td>61</td>
<td>6d</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>2a</td>
<td>10a</td>
<td>61</td>
<td>11a</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>2b</td>
<td>10b</td>
<td>57</td>
<td>11b</td>
<td>58&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>2c</td>
<td>10c</td>
<td>62</td>
<td>11c</td>
<td>28</td>
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<tr>
<td>8</td>
<td>7</td>
<td>2d</td>
<td>10d</td>
<td>61</td>
<td>11d</td>
<td>34</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield.
<sup>b</sup> The ratio of 11b/11b' (0.2:1.0) was determined by 1H NMR.
Scheme 2  Transition states involved in Diels–Alder reaction. 

Scheme 3  Synthesis of carbazolones using indole-2-carboxaldehyde

Scheme 4  Probable mechanism for the formation of 11b' 

For obtaining hexahydropyrrolo[3,4-b]carbazol-3-ones, 7 was treated with phosphorane 2c,d. With phosphorane 2c, a mixture of diastereomers (cis- and trans-fused) of 2-benzyl-1,2,3a,4,10a-hexahydropyrrolo[3,4-b]carbazol-3(5H)-one (10c) was formed. Phosphorane 2d provided the corresponding 2-benzyl-4-methyl-1,2,3a,4,10a-hexahydropyrrolo[3,4-b]carbazol-3(5H)-one (10d). The compounds 10c and 10d were aromatized to obtain 11c and 11d, respectively.

In conclusion we have demonstrated that the functionalized tetrahydrocabazoles can be rapidly assembled using domino Wittig and Diels–Alder reaction protocol. During this sequence, Wittig reaction, intramolecular Diels–Alder reaction and isomerization take place in a domino fashion.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toe/synlett.

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11a 

11a 

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(10) General Procedure for the Tandem Wittig–Diels–Alder Reaction for Preparation of Tetrahydrocarbazole Lactones (5a,b/10a,b) and Tetrahydrocarbazole Lactams (5c/10c): A solution of indole carboxaldehyde 1/7 (1 mmol) and phosphonate 2a–d (1.5 mmol) in diphenyl ether (10 mL) was refluxed under nitrogen atmosphere for 2–8 h. The crude mixture was subjected to column chromatography over silica gel and diphenyl ether was removed using hexanes as eluent. Further elution with 30–40% EtOAc and hexanes afforded the corresponding γ-lactones 5a,b/10a,b and γ-lactams 5c/10c. 

(11a) A mixture of tetrahydrocarbazoles 5a–d/10a–d (1 mmol) and DDQ (3 mmol) in dioxane (10 mL) was refluxed for 8 h. The reaction mixture was allowed to cool to ambient temperature and filtered. The filtrate was then concentrated under reduced pressure. The resulting residue was dissolved in EtOAc and washed with 2 N NaOH (20 mL) and H₂O (20 mL). The organic phase was dried over anhyd Na₂SO₄ and concentrated under reduced pressure. The resulting residue on purification using flash chromatography with hexanes–EtOAc (70:30) gave the oxidized products 6a–d/11a–d.

3,5-Dihydro-1H-furo[3,4-b]carbazol-1-one (6a): 1H NMR (300 MHz, DMSO): δ = 5.46 (s, 2 H), 7.21 (t, J = 7.8 Hz, 1 H), 7.49 (t, J = 7.8 Hz, 1 H), 7.53 (d, J = 8.1 Hz, 1 H), 7.62 (s, 1 H), 8.30 (d, J = 7.8 Hz, 1 H), 8.66 (s, 1 H), 11.78 (s, 1 H). 13C NMR (300 MHz, DMSO): δ = 69.85, 104.29, 111.83, 116.03, 118.12, 121.47, 122.56, 124.50, 127.28, 141.27, 144.80, 171.69. HRMS: m/z [M + Na] calcd for C₁₇H₁₄O₂N: 246.0531; found: 246.0524.