Synthesis of dispirocyclohexadiene bisoxindole from Morita-Baylis-Hillman carbonate of isatin

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Spiroproxindoles are found in numerous biologically interesting synthetic and natural substances. As a result, numerous synthetic methods of spiroproxindoles have been developed. Recently, dispirobisoxindoles have emerged as interesting target compounds due to their biological activities including antibacterial, anticaner, cholinesterase inhibitor, and anti-inflammatory activity, as shown in Fig. 1. There have been known many dispirobisoxindoles bearing carboxylic and heterocyclic linkers. Very recently, we reported the synthesis of dispirobisoxindoles bearing cyclohexane or cyclohexene links have been reported; however, dispirobisoxindole having cyclohexadiene linker has not been reported, to the best of our knowledge.

The derivatives of Morita-Baylis-Hillman (MBH) adduct of isatin could react with tertiary amines or phosphines to produce the corresponding nitrogen or phosphorous ylides after deprotonation. Most frequently, the ylides (see, ylide I in Scheme 1) were generated in situ by the reaction of MBH carbones and various tertiary amines or phosphines. The allylic ylide served a nucleophilic three-carbon unit, and various [3+2] and [3+4] cycloaddition reactions have been reported. In addition, the allylic ylide could be used as a nucleophile in S2 type reaction. We and other groups have reported S2 reactions of phosphorous ylides in many papers. In these respects, we reasoned that the ylide I might react with the MBH carbonate 1a to produce the conjugated triene 2a, after E2 elimination of amine or phosphine, as shown in Scheme 1. The trienes might be converted to dispirobisoxindole 3a via the isomerization of double bonds, followed by thermal 6π-electrocyclic ring closure (6π-ERC). At the outset of our experiment, the reaction of 1a and PPh3 (50 mol%) in benzene was examined, as shown in Table 1 (entry 1). We expected that the half of 1a would be converted to ylide I, and the ylide I would react with remaining 1a to produce the triene 2a. However, the reaction rate was slow, and 2a was obtained in moderate yield (56%, as a 5:1 mixture, vide infra) after 20 h in refluxing benzene. The reaction in refluxing toluene (entry 2) produced 2a in a similar yield (53%). It is interesting to note that the reaction of 1a and 4-(dimethylamino)pyridine (DMAP, 50 mol%, entry 3) afforded 2a in good yield (62%) in refluxing benzene in a short time (2 h). The yield of 2a was improved up to 73% when we used 10 mol% of DMAP (entry 4). The reactions in CH3 CN (entry 5) or 1,2-dichloroethane (entry 6) were similar to that of the reaction in benzene. The structure of the major triene was symmetric based on its 1H and 13C NMR spectra. The vinyl protons of the major triene appeared as a singlet at downfield (δ = 8.65 ppm) due to the anisotropy of the carbonyl group of isatin moiety, and the structure would be 2a-EEE. The minor triene was not symmetric in its 1H and 13C NMR spectra, and the two vinyl protons appeared at δ = 7.36 and δ = 8.79 ppm as doublets (J = 16.2 Hz). Thus, the structure of the minor triene would be 2a-EEZ.
Optimization of reaction conditions.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>2a (%)</th>
<th>3a-trans (%)</th>
<th>3a-cis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh3 (50 mol%), benzene, reflux, 20 h</td>
<td>56</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PPh3 (50 mol%), toluene, reflux, 15 h</td>
<td>53</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>DMAP (50 mol%), benzene, reflux, 2 h</td>
<td>62</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DMAP (10 mol%), benzene, reflux, 2 h</td>
<td>73</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>DMAP (10 mol%), CH2CN, reflux, 2 h</td>
<td>71</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>DMAP (10 mol%), CH2Cl2, reflux, 2 h</td>
<td>73</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>DMAP (10 mol%), ODCB, 120 °C, 30 h</td>
<td>11</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>DMAP (10 mol%), ODCB, 150 °C, 3 h</td>
<td>&lt;5</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>P(n-Bu3) (50 mol%), ODCB, 150 °C, 3 h</td>
<td>&lt;5</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>P(NMe3) (50 mol%), ODCB, 150 °C, 3 h</td>
<td>&lt;5</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>DBU (10 mol%), ODCB, 150 °C, 3 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>DABCO (10 mol%), ODCB, 150 °C, 3 h</td>
<td>&lt;5</td>
<td>23</td>
<td>29</td>
</tr>
</tbody>
</table>

* Substrate 1a was used (0.5 mmol).
* a Isolated yield.
* A mixture of 2a-EEE/2a-E EZ (ca. 5:1 in all cases).
* b The carbonate group of 1a was cleaved, and the MBH alcohol was formed.

However, the formation of 3a was not observed in any trace amount in the above entries (entries 1–6). Thus, we examined the reaction of 1a at elevated temperature in the presence of DMAP (entry 7). To our delight, a slow formation of 3a was observed when we raised the reaction temperature to 120 °C. Actually, 3a was obtained in moderate yield (60%) in 1,2-dichlorobenzene (ODCB) for a long time (30 h). The yield of 3a was improved up to 73% at 150 °C (entry 8) in short time (3 h). However, the yield of 3a was low (30%) by using PPh3 (entry 9). The use of P(n-Bu3) was found to be completely ineffective (entry 10). The carbonate moiety of 1a was cleaved, and the formation of the alcohol derivative of 1a was observed. The use of hexamethylphosphorous triamide (HMPT, entry 11) showed a similar result to that of PPh3.

1,8-Diazabicyclo[4.4.0]undec-7-ene (DBU, entry 12) also cleaved the carbonate moiety of 1a. It is interesting to note that the use of 1,4-diazabicyclo[2.2.2]octane (DABCO, entry 13) gave 3a in moderate yield (52%).

In a controlled experiment, the reaction of 2a-EEE in ODCB at 150 °C (3 h) afforded 3a-trans (44%) and 3a-cis (51%). Similarly, the reaction of 2a-EEZ gave 3a-trans (50%) and 3a-cis (45%). The results stated that configuration of the second double bond (E-form) must be isomerized, in part, to Z-form and produced 2a-EEZ or 2a-E EZ, as shown in Scheme 2. During isomerization of the second double bond, the configuration of first double bond might be also isomerized in part. The generated 2a-E EZ and 2a-EEZ could be converted to 3a-cis and 3a-trans, respectively, by disrotatory 6π-electrocyclization reaction, which is thermally allowed by the Woodward-Hoffman rules. The double bond isomerization of 2a-EEE/2a-EEZ to 2a-E EZ/2a-EEZ might proceed thermally, as reported by Baldwin; however, an isomerization via addition/elimination process of moisture could not be ruled out completely. Actually, 2a-EEE was converted slowly into 2a-EEZ in the presence of DMAP or PPh3 in ODCB even at lower temperature (100 °C). When we elevated the reaction temperature to 120 °C the isomerization of 2a-EEE to 2a-E EZ was accelerated, and a typical equilibrium ratio (2a-EEE/2a-EEZ = 5:1) reached after 3 h; however, 6π-electrocyclization also competitively proceeded slowly and produced the final product 3a to some extent. The isomerization of 2a-EEZ to 2a-EEE occurred more rapidly, and the formation of a 5:1 mixture of 2a-EEE/2a-E EZ was observed within 1 h when the pure 2a-EEZ was heated to 120 °C in ODCB.

Encouraged by the successful results, we examined the synthesis of various dispirocyclohexadiene bisoxindoles 3b–3j by the reaction of MBH carbonates 1b–1j in the presence of DMAP (10 mol%) in ODCB at 150 °C. As shown in Table 2, the reactions of diversely substituted isatin derivatives 1b–1g afforded the...
corresponding products 3b-3g in good yields (68–80%). The ethyl ester derivatives 1h and 1i also gave 3h (77%) and 3i (79%) in good yields. The acetyl derivative 1j produced 3j in somewhat lower yield (66%) than other entries. As shown in Scheme 3, the triene 2a could be formed via an aerobic oxidation of phosphorous ylide I to the corresponding aldehyde II and a following Wittig olefination with remaining ylide I.19 A quantitative formation of ylide I was observed on TLC by the reaction of 1a and PPh₃ (100 mol%) in toluene at 80 °C within 30 min. When the reaction mixture was stirred at high temperature (100 °C) for 15 h under O₂ balloon atmosphere, 2a was isolated in moderate yield (61%, 5:1 mixture). As expected, dispirobisoxindole 3a could be synthesized in moderate yield (44%, cis/trans mixture) by carrying out the reaction of 1a with PPh₃ (100 mol%) in ODCB (80 °C, 30 min.) and elevating the reaction temperature to 150 °C for 3 h. Based on the experimental
In summary, various dispirocyclohexadiene bisoxindoles have been synthesized by thermal 6π-electrocyclization reaction of conjugated trienes derived in-situ from the Morita-Baylis-Hillman carbonates of N-methylisatins in good yields.

Acknowledgments

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17. CCDC 1530932 (3a-trans) and CCDC 1530933 (3a-cis) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

18. Typical procedure for the synthesis of 3a: A stirred solution of 1a (347 mg, 1.0 mmol) and DMAP (12 mg, 0.10 mol%) in ODCB (3.0 mL) was heated to 150°C for 3 h under N₂ balloon atmosphere. Removal of the volatiles and column chromatographic purification process (CH₂Cl₂/Et₂O, 10:1 to 3:1) afforded 3a-trans (78 mg, 34%) and 3a-cis (90 mg, 39%) as yellow solids. Other compounds were synthesized similarly, and the selected spectroscopic data of 3a are as follows. Compound 3a-trans: 34%; yellow solid, mp 258-260°C; IR (KBr) 1715, 1610, 1278 cm⁻¹; 1H NMR (CDCl₃, 500 MHz) δ 3.01 (s, 6H), 3.52 (s, 6H), 6.54 (d, J = 7.5 Hz, 2H), 6.91 (t, J = 7.5 Hz, 2H), 7.16 (t, J = 7.5 Hz, 2H), 7.20 (d, J = 7.5 Hz, 2H), 7.45 (s, 2H); 13C NMR (CDCl₃, 125 MHz) δ 26.3, 52.2, 56.5, 107.8, 122.0, 124.1, 127.0, 129.2, 133.1, 134.1, 144.0, 173.0; ESIMS m/z 459 [M+H].

Anal. Calcd for C₂₆H₂₂N₂O₆: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.43; H, 4.99; N, 5.97. Compound 3a-cis: 39%; yellow solid, mp 244-246°C; IR (KBr) 1722, 1609, 1281 cm⁻¹; 1H NMR (DMSO-d₆, 500 MHz) δ 2.84 (br s, 6H), 3.47 (s, 6H), 6.45 (br s, 2H), 6.74 (br s, 2H), 6.85 (d, J = 7.7 Hz, 2H), 7.25 (t, J = 7.7 Hz, 2H), 7.43 (s, 2H); 13C NMR (DMSO-d₆, 125 MHz) δ 26.2, 52.0, 56.4, 108.4, 121.2, 123.2, 125.5, 129.5, 132.8, 134.3, 144.2, 164.2, 172.3; ESIMS m/z 459 [M⁺H].

Anal. Calcd for C₂₆H₂₂N₂O₆: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.27; H, 5.02; N, 6.03. The protons at 6.45 and 6.74 ppm of 3a-cis appeared as broad singlets, presumably due to slow conformational equilibrium on the NMR time scale.

When we took the 1H NMR at 77°C, the proton at 6.74 ppm appeared as a triplet and the proton at 6.45 ppm as a broad doublet.

19. (a) For C=C double bond formation via aerobic oxidation of phosphorous ylide and a following Wittig reaction, see: Bestmann HJ, Pfuller H. Angew Chem Int Ed. 1972;11:508;
(b) Bestmann HJ, Kratzer O, Armes R, Maekawa E. Liebigs Ann Chem. 1973;760;
(c) Bestmann HJ, Kratzer O. Chem Ber. 1963;1899:96;