Synthesis of Benzo[a]carbazole Derivatives from β-(2-Arylindolyl) nitroalkanes via Mn(OAc)₃-mediated Cyclization

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Diversely substituted benzo[a]carbazoles and related derivatives are important because of their interesting biological activities such as neuroprotective property, antitumor activity, and kinase inhibitory activity. Thus, various synthetic methods have been developed including Lewis acid-catalyzed annulation of 2-arylindoles with propargylic alcohol derivatives, double cascade cyclization of diynes catalyzed by gold, or palladium, and copper-catalyzed synthesis via α-C-arylation of ketones.

Recently, we also reported the synthesis of benzo[a]carbazoles from 2-arylindoles via sequential propargylation, propargyl–allenyl isomerization, and 6π-electrocyclization approach, as shown in Scheme 1. Various 5-benzyl- and 5-methylbenzo[a]carbazoles have been synthesized; however, 5-unsubstituted benzo[a]carbazoles could not be synthesized by the approach. In order to develop a synthetic method of 5-unsubstituted benzo[a]carbazoles, we decided to examine the reaction of β-(2-phenylindolyl) nitroalkane 3a by Mn(OAc)₃-mediated cyclization and subsequent elimination of nitrous acid, as shown in Scheme 1. A similar synthesis of a naphthalene ring via Mn(OAc)₃-mediated intramolecular oxidative coupling reaction between arene and nitroalkane moieties has already been reported in the previous studies.

The required starting materials 3a–3h were prepared from corresponding 2-arylindoles and β-nitrostyrenes according to the reported methods (see Appendix S1). Supporting information. As reported in our previous paper, the reaction of 3a was examined in ETOH (reflux, 24 h) in the presence of Mn(OAc)₃ (4.0 equiv). To our delight, 4a was obtained in a reasonable yield (56%) along with a low yield of 5-nitro derivative 5a (13%). The reactions in other solvents such as MeOH, n-propanol, n-butanol, and polyethylene glycol (PEG)-3400/BuOH were less effective when compared with ETOH. The reaction in AcOH showed the formation of many intractable side products. The use of CAN (cerium ammonium nitrate) in ETOH was completely ineffective. When we used lesser amount of Mn(OAc)₃ (3.0 equiv) in ETOH (reflux, 24 h), the yields of 4a (48%) and 5a (8%) decreased a little.

The synthesis of various benzo[a]carbazoles was carried out under the original reaction condition, and the results are summarized in Table 1. The reaction of 2-(p-methoxyphenyl)indole derivative 3b (entry 2) afforded 4b (50%) and 5b (14%). Similarly, the reaction of 5-methylnitro derivative 3c (entry 3) gave 4c (44%) and 5c (10%). The reaction of 2-(2-naphthyl)indole 3d (entry 4) afforded naphtho[2,3-a]carbazoles 4d (43%) and 5d (9%). The reactions of 2-(2-benzofuranyll)indole 3e (entry 5) and 2-(2-thienyl)indole 3f (entry 6) produced benzofuro[2,3-a]carbazole 4e (59%) and thieno[2,3-a]carbazole 4f (51%), respectively, in good yields. The isolation of the corresponding 5-nitro derivatives 5e and 5f failed in these entries. It is interesting to note that the reactions of thiophene derivative 3g (entry 7) and furan derivative 3h (entry 8) afforded 4g (33%) and 4h (15%) in lower yields than other entries, and the yields of 5g (23%) and 5h (20%) increased accordingly.

In order to synthesize ethyl benzo[a]carbazole-5-carboxylates 4i–4k (Scheme 2), the required starting materials 3i–3k were prepared according to the reported methods (see Appendix S1). The reaction of 3i under the standard reaction condition afforded ethyl benzo[a]carbazole-5-carboxylate 4i in good yield (73%) in short time (5 h). Similarly, the reaction of 3j (synlanti mixture) afforded 4j in good yield (82%). The reaction of 3k (synanti mixture) also afforded 4k in moderate yield (61%) for somewhat longer reaction time (12 h). As in our previous paper, Mn(OAc)₃-mediated radical cyclization was more effective with nitroalkanes bearing an ester moiety. A plausible reaction mechanism for the formation of 4a and 5a is suggested in Scheme 3. As in our previous synthesis of naphthalenes, Mn(OAc)₃-mediated radical cyclization of 3a afforded dihydrobenzo[a]carbazole intermediate I. A competitive elimination of nitrous acid from I and oxidation of I with Mn(OAc)₃ produced 4a and 5a, respectively.

In summary, a new synthetic method of benzo[a]carbazoles has been developed from β-(2-phenylindolyl)nitroalkanes via Mn(OAc)₃-mediated cyclization protocol. Various 5-unsubstituted benzo[a]carbazoles could be synthesized, when compared with previous approach to 5-benzylbenzo [a]carbazoles involving 6π-electrocyclization reaction.
Experimental

Typical procedure for the synthesis of 4a and 5a. A stirred solution of 3a (171 mg, 0.5 mmol) and Mn(OAc)$_3$ (536 mg, 2.0 mmol) in EtOH (2.0 mL) was heated to reflux for 24 h. The reaction mixture was filtered through a Celite pad and washed with ethanol. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 8:1), compounds 4a (82 mg, 56%) and 5a (22 mg, 13%) were obtained as pale yellow solids.

Table 1. Synthesis of benzo[a]carbazoles.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 3</th>
<th>Products 4/5 (%)</th>
<th>Entry</th>
<th>Substrate 3</th>
<th>Products 4/5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>4a (R = H, 56) 5a (R = NO$_2$, 13)</td>
<td>5</td>
<td>3e</td>
<td>4e (R = H, 59) 5e (R = NO$_2$, 0)$^b$</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>4b (R = H, 50) 5b (R = NO$_2$, 14)</td>
<td>6</td>
<td>3f</td>
<td>4f (R = H, 51) 5f (R = NO$_2$, 0)$^b$</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>4c (R = H, 44) 5c (R = NO$_2$, 10)</td>
<td>7</td>
<td>3g</td>
<td>4g (R = H, 33) 5g (R = NO$_2$, 23)</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>4d (R = H, 43) 5d (R = NO$_2$, 9)</td>
<td>8</td>
<td>3h</td>
<td>4h (R = H, 15) 5h (R = NO$_2$, 20)</td>
</tr>
</tbody>
</table>

$^a$ Conditions: Substrate 3 (0.5 mmol), Mn(OAc)$_3$ (4.0 equiv), EtOH, reflux, 24 h.  
$^b$ Failed to isolate.
solids. Other compounds were synthesized similarly, and the selected spectroscopic data of 4a, 5a, 4e and 4j are as follows.

**Compound 4a.** 56%; pale yellow solid, mp 208–210°C; IR (KBr) 3375, 1496, 1347, 1267 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.82 (d, J = 8.0 Hz, 1H), 7.03 (td, J = 8.0, 1.0 Hz, 1H), 7.40 (td, J = 8.0, 1.0 Hz, 1H), 7.53–7.59 (m, 6H), 7.63–7.70 (m, 2H), 7.95 (d, J = 7.5 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 9.12 (br s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 110.48, 115.00, 116.52, 120.15, 120.31, 120.86, 122.06, 123.81, 124.59, 125.40, 125.65, 127.55, 128.33, 128.85, 129.31, 132.06, 135.21, 136.52, 138.63, 141.16; ESIMS m/z 294 [M⁺+H].

**Compound 5a.** 13%; pale yellow solid, mp 208–210°C; IR (KBr) 3375, 1496, 1347, 1267 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.82 (d, J = 8.0 Hz, 1H), 7.03 (td, J = 8.0, 1.0 Hz, 1H), 7.40 (td, J = 8.0, 1.0 Hz, 1H), 7.53–7.59 (m, 6H), 7.63–7.70 (m, 2H), 7.95 (d, J = 7.5 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 9.12 (br s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 110.48, 115.00, 116.52, 120.15, 120.31, 120.86, 122.06, 123.81, 124.59, 125.40, 125.65, 127.55, 128.33, 128.85, 129.31, 132.06, 135.21, 136.52, 138.63, 141.16; ESIMS m/z 294 [M⁺+H].

**Compound 4e.** 59%; pale yellow solid, mp 218–220°C; IR (KBr) 3448, 1446, 1289, 1178 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.05 (td, J = 8.0, 1.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 2H), 7.45 (td, J = 8.0, 1.0 Hz, 1H), 7.50 (td, J = 8.0, 1.0 Hz, 1H), 7.52–7.60 (m, 4H), 7.66–7.72 (m, 4H), 8.02 (d, J = 7.5 Hz, 1H), 8.64 (br s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 110.96, 111.68, 113.11, 119.69, 120.56, 121.37, 121.55, 122.24, 123.06, 123.78, 124.77, 125.31, 125.60, 126.42, 127.50, 128.44, 129.59, 133.18, 139.71, 141.12, 141.35, 156.37; ESIMS m/z 334 [M⁺+H].

**Compound 4j.** 82%; pale yellow solid, mp 162–164°C; IR (KBr) 3340, 1694, 1369, 1227 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.98 (t, J = 7.0 Hz, 3H), 4.15 (q, J = 7.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.53–7.58 (m, 8H), 8.14–8.18 (m, 2H), 9.18 (br s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 13.73, 61.10, 111.00, 116.52, 120.03 (2C), 120.67, 121.85, 123.51, 124.10, 124.96, 125.77, 126.26, 126.55, 127.89, 128.31, 128.86, 129.37, 135.26, 135.64, 138.86, 139.12, 169.87; ESIMS m/z 366 [M⁺+H].

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Supporting Information. Additional supporting information including experimental procedure and spectroscopic data is available in the online version of this article.

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7. The reason for the formation of 5\(g\) or 5\(h\) in an increased yield is not clear at this stage.