The Synthesis of Naphtho[*a*]carbazoles and Benzo[*c*]carbazoles

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Abstract: The synthesis of naphtho[*a*]carbazoles and benzo[*c*]carbazoles from indole precursors using a reaction mediated by potassium *t*-butoxide and light is described. The indole precursors were prepared utilizing Suzuki coupling methodology.

Key words: carbazoles, indoles, naphtho[*a*]carbazoles, benzo[*c*]carbazoles, Suzuki coupling

Carbazoles display a range of biological activities making them attractive compounds to synthetic and medicinal chemists.[1–3] As a result, in the past two decades numerous carbazole alkaloids and synthetic analogues, many of them possessing useful pharmacological properties, have been studied. Some of the most important compounds with proven chemotherapeutic value belong to the ellipticine class (e.g. **1**).[4,5] In this class of compound a heteroaromatic ring is fused to the *b*-face of the carbazole. However, there is a growing number of carbazoles that contain aromatic or heteroaromatic rings fused to the *a*- or *c*-face of the carbazole nucleus. For example, the synthetic naphtho[*a*]carbazole **2**[6] is a potential candidate for cancer treatment as a result of DNA intercalative binding properties[7] and the well-known indole/naphthalene bioisostery,[8] while benzo[*c*]carbazole **3**[9] shows promising profiles for intra-cyclin dependent kinase selectivity (Figure 1).

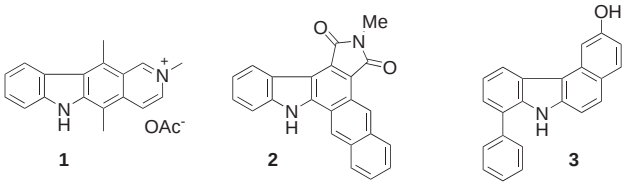


Figure 1

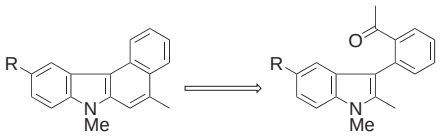
In these laboratories we have developed novel methodology for the synthesis of benzo[*a*]carbazoles and pyrido[2,3-*a*]carbazoles.[10,11] This methodology utilizes a novel light- and base-assisted cyclization reaction to form a centrally-positioned aromatic ring. We have previously demonstrated that the synthesis of benzo[*a*]carbazoles can be accomplished by our novel ring-forming reaction, in which the last step is the construction of the C-5/C-6 bond (Figure 2).[11] Therefore we wished to explore the generality of this reaction. In particular we wished to extend this method to the synthesis of naphtho[*a*]-fused carbazoles as well as carbazoles containing rings fused on the *c*-face. In this paper we disclose our results on the extension of our work on the synthesis of benzo[*a*]carbazoles to include naphtho[*a*]carbazoles as well as to the synthesis of a benzene ring fused on the *c*-face to afford benzo[*c*]carbazoles.

Benzo[*a*]carbazoles

Figure 2

Treatment of the readily available *N*-methyl-2-bromoindole-3-carbaldehyde **4**[11] with three different boronic acids **5a**–**c**[12] under aqueous Suzuki coupling reaction conditions afforded the desired biaryl compounds **6**, **7** and **8** in good yields (Scheme 1).[13] Exposure of each of these substrates to our novel ring forming reaction conditions (*t*-BuOK, DMF, hv) afforded the desired naphtho-fused carbazoles **9**, **10** and **11** in fair to good yields (56–85%).[14,15]

As depicted in the retrosynthesis in Figure 3, we planned to synthesize benzo[*c*]carbazoles **12** from indoles such as **13** containing a substituted aromatic ring at the 3-position. A carbonyl-containing substitutient is required *ortho* to the biaryl linkage on the benzene ring, and on the indole nucleus a methyl substituent at the 2-position is necessary. The biaryl linkage could be formed using Suzuki coupling methodology.



12a, R=H
12b, R=OMe

13a, R=H
13b, R=OMe

Figure 3

In order to achieve the synthesis of **13a**,**b**, suitable precursors **14a** and **14b** for the Suzuki coupling reaction were prepared (Scheme 2). Exposure of 2-methylindole **15a** to molecular bromine followed by protection of the indole nitrogen by N-methylation afforded **14a** in good yield. The synthesis of methoxyindole **14b** was accomplished from **15b**, but in this case the bromination of **15b** was accomplished with *N*-bromosuccinimide (NBS), as the use

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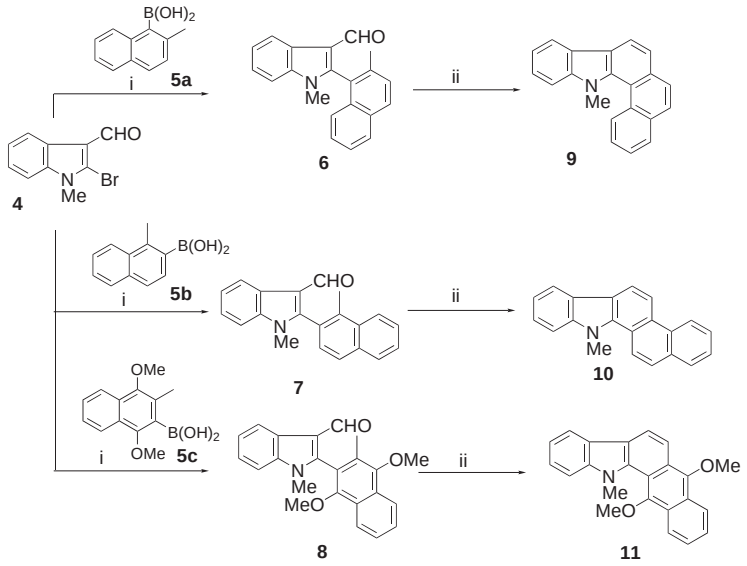
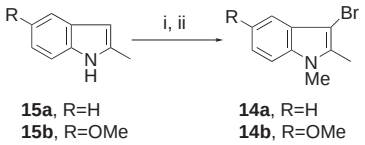


Scheme 1 *Reagents and conditions*: i, 10 mol% $Pd(PPh_3)_4$, DME/EtOH, 2 M aq Na_2CO_3, reflux 48 h; **6**, 99%; **7**, 86%; **8**, 60%. ii, *t*-BuOK, DMF, hν, 10 min; **9**, 85%; **10**, 56%; **11**, 86%.

of molecular bromine resulted in simultaneous bromination of the electron-rich aromatic ring. Both **14a** and **14b** were unstable and had to be used immediately in subsequent steps.

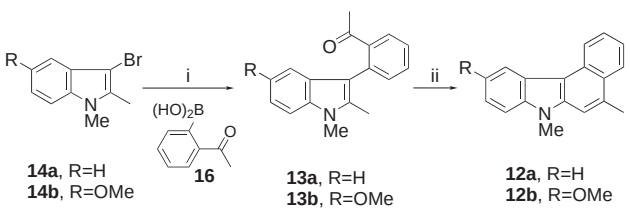


15a, R=H
15b, R=OMe

14a, R=H
14b, R=OMe

Scheme 2 *Reagents and conditions*: **15a**→**14a** i, Br_2, DMF, r.t., 99%; ii, $(MeO)_2SO_2$, NaH, THF, 18 h, 99%. **15b**→**14b** i, NBS, CH_2Cl_2, cat. SiO_2, 30 min, 99%; ii, $(MeO)_2SO_2$, NaH, THF, 48 h, 94%.

Treatment of both **14a** and **14b** under non-aqueous Suzuki coupling conditions with the commercially available boronic acid **16** resulted in the formation of the desired biaryl compounds **13a** and **13b** in good yields (Scheme 3). Exposure of **13a** and **13b** to potassium *t*-butoxide in the presence of light gave the desired benzo[*c*]carbazoles **12a** and **12b** in good yield.[16]



14a, R=H
14b, R=OMe

16

13a, R=H
13b, R=OMe

12a, R=H
12b, R=OMe

Scheme 3 *Reagents and conditions*: i, 20 mol% $Pd(PPh_3)_4$, DMF, K_3PO_4, 100 °C, 65 h, **13a**, 83%; **13b**, 80%. ii, *t*-BuOK, DMF, hν, 10 min, **12a**, 71%; **12b**, 70%.

Acknowledgment

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(12) **Typical Experimental Procedures:** The preparation of the three boronic acids was accomplished as follows: (a) **2-Methyl-1-naphthylboronic Acid 5a.** *n*-Butyllithium (1.2 M, 3.9 cm^3, 4.7 mmol) was added dropwise to a solution of 1-bromo-2-methylnaphthalene (1.01 g, 4.57 mmol) in THF (30 cm^3) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C, then $B(OMe)_3$ (1.39 g, 1.50 cm^3, 13.4 mmol) was added. The resulting mixture was stirred at –78 °C for a further 30 min and then allowed to warm to r.t. The reaction mixture was acidified with aq 10% HCl solution and extracted with Et_2O (3×30 cm^3). The organic layer was then dried with $MgSO_4$ and concentrated under vacuum to afford an off-white crystalline material, 2-methyl-1-naphthylboronic acid **5a** (0.74 g, 87%), which was used without further purification or characterization. (b) Budac, D.; Wan, P. *Can. J. Chem.* **1996**, *74*, 1447. (c) **1-Methyl-2-naphthylboronic Acid 5b.** *n*-Butyllithium (1.4 M, 2.1 cm^3, 2.9 mmol) was added dropwise to a solution of 2-bromo-1-methylnaphthalene (0.50 g, 2.3 mmol) in THF (15 cm^3) at –78 °C. The reaction mixture was then treated as described above and $B(OMe)_3$ (0.70g, 0.75 cm^3, 6.69 mmol) was added. An off-white crystalline material, 1-methyl-2-naphthylboronic acid **5b** (0.39 g, 93%) was produced, which was used without further purification or characterization. (d) Parham, W. E.; Reiff, H. E.; Swartzentruber, P. *J. Am. Chem. Soc.* **1956**, *78*, 1437. (e) **1,4-Dimethoxy-3-methyl-2-naphthylboronic Acid 5c.** 2-Bromo-1,4-dimethoxy-3-methylnaphthalene was prepared according to: Adams, R.; Geissman, T. A.; Baker, B. R.; Teeter, H. M. *J. Am. Chem. Soc.* **1941**, *63*, 528; this was then treated as described above to afford the desired boronic acid **5c**..

(13) **1-Methyl-2-(2-methyl-1-naphthyl)-1*H*-indole-3-carbaldehyde 6.** A solution of 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde **4a** (see ref.[11]) (0.10 g, 0.42 mmol) in DME (2 cm^3) was deoxygenated by passing N_2 through the mixture for 5 min. The deoxygenated mixture was added to $Pd(PPh_3)_4$ (10 mol%, 0.048 g, 0.04 mmol) and stirred under N_2 for 10 min at r.t. A solution of 2-methyl-1-naphthylboronic acid **5a** (0.11 g, 0.59 mmol) in EtOH (1.5 cm^3) was deoxygenated and added to the reaction mixture. The mixture was stirred for a further 10 min. A deoxygenated 2 M aq Na_2CO_3 solution (3.0 cm^3, 6.0 mmol) was added and the reaction mixture stirred at r.t. for 5 min before being heated at reflux for 2 d. The mixture was cooled to r.t. and quenched with H_2O (20 cm^3). The organic material was extracted with CH_2Cl_2 (3×30 cm^3) and the solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography (2–10% EtOAc–hexane) to afford 1-methyl-2-(2-methyl-1-naphthyl)-1*H*-indole-3-carbaldehyde **6** as an off-white solid (0.13 g, 99%). Mp 146–147 °C. (Found: M^+ 299.1307, $C_{21}H_{17}NO$ requires M, 299.1310). IR ($CHCl_3$): ν_{max} =1655 (C=O) and 1579 (ArC=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 2.28 (3 H, s, $ArCH_3$), 3.42 (3 H, s, NCH_3), 7.23 (1 H, m, ArH), 7.35–7.51 (6 H, m, 6 × ArH), 7.91 (1 H, d, *J* = 8.0 Hz, ArH), 7.96 (1 H, d, *J* = 8.5 Hz, ArH), 8.48 (1 H, m, Ar-H) and 9.45 (1 H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5 ($ArCH_3$), 30.2 (NCH_3), 109.8, 122.3, 123.3, 123.8, 125.0, 125.7, 127.4, 128.1 (× 2) and 130.2 (ArCH), 116.4, 124.4, 125.3, 131.7, 133.6, 137.3, 137.6 and 149.4 (ArC), 186.0 (CHO). MS: *m/z* (%) = 299 (100) [M^+], 284 (38), 282 (55), 254 (19), 127.

(14) **11-Methyl-11*H*-naphtho[2,1-*a*]carbazole 10.** *t*-BuOK (0.12 g, 1.1 mmol), was added to 1-methyl-2-(1-methyl-2-naphthyl)-1*H*-indole-3-carbaldehyde **7** (0.085 g, 0.28 mmol) dissolved in dry DMF (10 cm^3), and the mixture was heated under N_2 at 80 °C while being irradiated with a high pressure mercury lamp through a quartz filter for 10 min. The reaction mixture was quenched with H_2O (50 cm^3) and extracted into Et_2O (3×50 cm^3). The organic layer was dried with $MgSO_4$ and filtered. It was then evaporated and subjected to column chromatography (5–20% EtOAc–hexane) to afford the product **10** (0.045 g, 56%) as an off-white solid. Mp 213–216 °C. (Found: M^+ 281.1209, $C_{21}H_{15}N$ requires 281.1204). IR ($CHCl_3$): ν_{max} = 1617 and 1572 (ArC=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 4.43 (3 H, s, NCH_3), 7.33 (1 H, m, ArH), 7.50–7.71 (4 H, m, 4 × ArH), 7.86 (1 H, d, *J* = 9.2 Hz, ArH), 7.94 (1 H, d, *J* = 7.6 Hz, ArH), 8.20 (1 H, d, *J* = 7.8 Hz, ArH), 8.35 (1 H, d, *J* = 8.7 Hz, ArH), 8.60 (1 H, d, *J* = 8.7 Hz, ArH), 8.71 (1 H, d, *J* = 9.2 Hz, ArH), 8.82 (1 H, d, *J* = 8.3 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.4 (NCH_3), 109.0, 114.8, 119.2, 119.5, 119.8, 121.0, 123.5, 125.3, 125.8, 126.1, 126.7 and 128.4 (ArCH), 120.7, 122.8, 129.7, 131.1, 131.2, 137.0 and 141.6 (ArC). MS: *m/z* (%) = 281 (100) [M^+], 266 (22), 252 (3), 140(2).

(15) This work is taken from the PhD of R. Pathak.

(16) This work is taken from the MSc of J. M. Nhlapo.