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Combined Directed *Ortho* and Remote Metalation–Cross-Coupling Strategies. General Method for Benzo[*a*]carbazoles and the Synthesis of an Unnamed Indolo[2,3-*a*]carbazole Alkaloid

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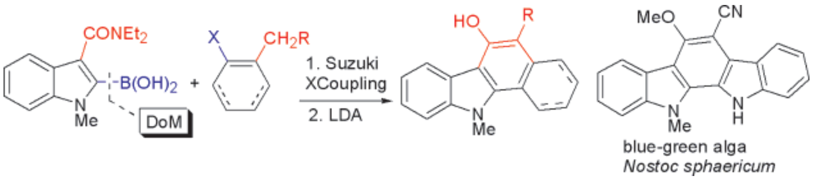
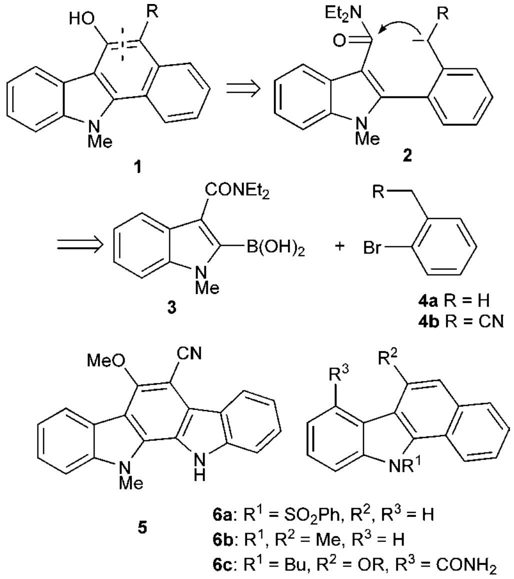
ABSTRACT



An efficient route to benzo[*a*]carbazoles via a metalation–cross-coupling sequence has been demonstrated (Scheme 2) and its application to the synthesis of the antitumor and antiviral alkaloid 6-cyano-5-methoxy-12-methylindolo[2,3-a]carbazole (5) has been achieved.

We report a general and efficient directed *ortho* and remote metalation (DoM)−Suzuki−Miyaura cross-coupling strategy to benzo[*a*]carbazoles (**1**, Scheme 1) and its application to the synthesis of the indolo[2,3-*a*]carbazole alkaloid **5**.[1] While the benzo[*a*]carbazoles, and benzannulated carbazoles in general,[2] are rarely found as natural products, these structural motifs have elicited considerable biological attention as demonstrated by derivatives **6** which show antitumor (leukemia, renal, colon)[3] and antinflammatory[4] activity. Furthermore, synthetic interest in the indolo[2,3-*a*]carbazoles and related bis-indolylmaleimide natural products has been fueled by the discovery of significant and diverse bioactivity such as inhibition of protein kinases and nerve growth factor, as well as platelet aggregation, antitumor, antiallergic,

Scheme 1



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[1] Knubel, G.; Larsen, L. K.; Moore, R. E. *J. Antibiot.* **1990**, *43*, 1236.

[2] (a) Gribble, G. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1990; Vol. 39, p 239. (b) For pyridocarbazole synthesis, see: Gribble, G. W. *Synlett* **1991**, 289. (c) For an excellent, comprehensive review, see: Knolker, H. J.; Reddy, K. R. *Chem Rev.* **2002**, *102*, 4303.

[3] Pindur, U.; Lemster, T. *Recent Res. Devel. Org. Biorg. Chem.* **1997**, 33.

[4] Beight, D. W.; Kinnick, M. D.; Lin, H.; Morin, J. M.; Richett, M. E.; Sall, D. J.; Sayer, J. S. US patent WO 2002050034; *Chem. Abstr.* **2002**, *137*, 47114.

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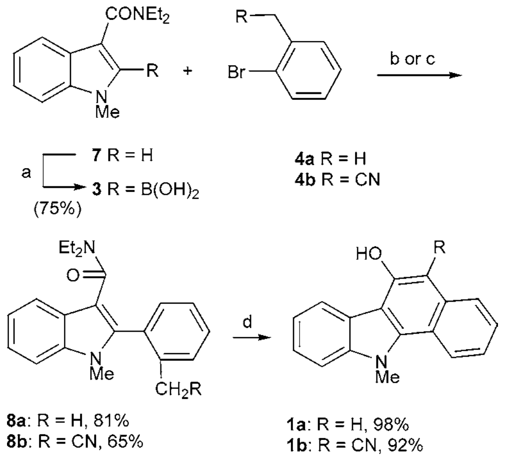
antiinflammatory, antiviral, and antihypertensive properties, among others.[2a] Our route takes advantage of readily available indole and aryl building blocks, the regioselectivity inherent in D*o*M-mediated cross-coupling, and an effective terminal remote metalation step,[5] which, in combination, has considerable scope for the uncomplicated construction of rings systems represented by **1**[6] and **5** and suggests potential for the preparation of similar heteroaromatics.

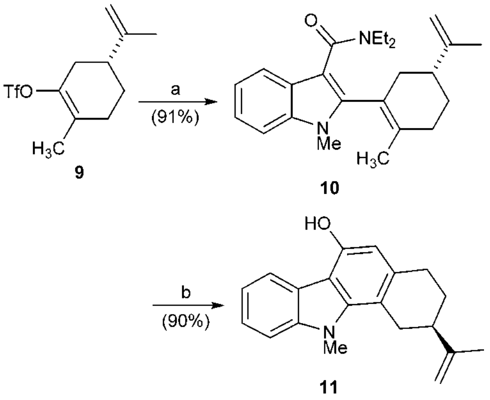
The general synthesis of benzo[*a*]carbazoles (**1**, Scheme 2) was initiated from the *N*-methylindolyl-3-carboxamide (**7**), which upon metalation under standard conditions (*s*-BuLi/-78 °C/THF/1 h) followed by quenching with trimethylborate and acidic workup afforded the boronic acid **3**. Without purification, **3** as the reactant in slight excess (1.1 equiv) was subjected to our standard Suzuki−Miyaura cross-coupling conditions[5] with commercially available bromobenzenes **4a**, **4b** to afford the amides **8a**, **8b**, respectively, in excellent yields. Although the boronic acid **3** underwent cross-coupling with 2-bromotoluene **4a** under condition (b) in good yield, this procedure, when adapted to the cross-coupling with **4b**, only led to the deboronation product **7** and the expected biaryl **8b** was not isolated. Condition (c) proved to be dependable as a general method for the preparation of biaryls **8b**. The key remote metalation−cyclization step of **8a**, **8b** was effected under optimized LDA (4−6 equiv) conditions[7] to afford the phenolic benzo[*a*]carbazoles **1a**, **1b** in high yields. As an extension of this concept to the deprotonation of a nontolyl, vinylogously γ-C−H acidic site, compound **10** (Scheme 3) was tested.

Scheme 2 [a]



[a] Key: (a) (i) *s*-BuLi, TMEDA, THF, -78 °C, 1 h, (ii) $B(OMe)_3$, -78 °C, 8 h, (iii) aq NH_4Cl; (b) $Pd(PPh_3)_4$, DME, Na_2CO_3, reflux, 12 h; (c) $Pd(PPh_3)_4$, DMF, K_3PO_4, 100 °C, 12 h; (d) (i) LDA, THF, 0 °C to rt, 4 h, (ii) aq NH_4Cl.

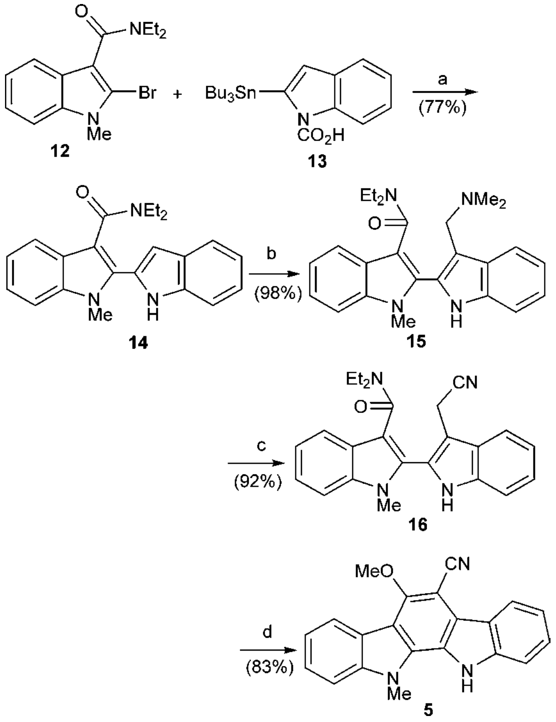
Scheme 3 [a]



[a] Key: (a) **3**, $Pd(PPh_3)_4$, DMF, K_3PO_4, 100 °C, 12 h; (b) (i) LDA, THF, 0 °C to rt, 4 h, (ii) aq NH_4Cl.

The indolyl terpenoid **10**, readily prepared by Suzuki cross-coupling of (+)-carvone enol triflate **9**[8] with **3**, proved to be a ready participant in the anionic cyclization reaction to afford the optically active tetrahydrobenzo[*a*]carbazole **11** in excellent yield.

Scheme 4 [a]



[a] Key: (a) 5 mol % $PdCl_2(PPh_3)_2$, EtOH, reflux, 2 h; (b) $CH_2N^+Me_2Cl^-$, 2 h; (c) (i) MeI, CH_3CN, rt, 10 min, (ii) KCN, DMF, 18-crown-6, rt, 1 h; (d) (i) LDA (4.0 equiv), THF, 0 °C to rt, 30 min, (ii) CH_2N_2, Et_2O, rt, 30 min.

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(5) For application of this strategy to phenanthrenes, see: (a) Fu, J.-m.; Snieckus, V. *Can. J. Chem.* **2000**, *78*, 905. (b) Cai, X.; Brown, S.; Hodson, P.; Snieckus, V. *Can. J. Chem.* **2004**, *82*, 195.

(6) (a) For the primary routes to benzo[*a*]carbazoles (Fischer indole, Diels−Alder, Cr, Fe, Mo, and Pd-mediated, photochemical) and their evaluation, see ref 2c. For Rh-catalyzed alkyne cyclotrimerizations, see: Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281. (b) For an *N*-acyliminium approach from ditryptophans with implications for peptide transformations in vivo, see: Carter, D. S.; Van Vranken, D. L. *J. Org. Chem.* **1999**, *64*, 8537.

In approaches to the unnamed indolo[2,3-*a*]carbazole (**5**, Scheme 4) the antiviral and antitumor alkaloid isolated from a blue-green alga *Nostoc sphaericum*,[1] considerable, unsuccessful effort was expended in Suzuki−Miyaura cross-coupling reactions to establish the 2,2′-bisindolyl bond on differentially *N*-protected 3-substituted indole coupling partners. For example, cross-coupling between **3** and 2-bromoindolyl-3-acetonitrile failed presumably due to steric hindrance. As a result, we turned to the corresponding Stille tactic by combining the easily prepared 2-bromoindole carboxamide **12**[9] with the 2-stannylated *N*-carboxyindole **13**[10] to provide the bisindolyl derivative **14** in good yield. Treatment with Eschenmoser's salt **14** gave gramine **15**, which upon sequential reaction with MeI and KCN/18-crown-6 afforded the acetonitrile **16**. LDA-mediated cyclization of **16** followed by immediate methylation of the somewhat unstable phenol gave the natural product **5**.[11] The synthesis of **5** from indole proceeded in eight steps and 42% overall yield.

To conclude, an efficient and general protocol for the synthesis of benzo[*a*]carbazoles **1** following a merged directed *ortho* and remote metalation−Suzuki−Miyaura cross-coupling strategy has been demonstrated and, with variation to the Stille cross-coupling reaction, applied to the synthesis of the indolo[2,3-*a*]carbazole alkaloid **5**.[12] Expansion of the derived methodology for the construction of similar heteroaromatics and more complex indolo[2,3-*a*]carbazole alkaloids[2a,c] may be anticipated and is in progress.

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Supporting Information Available: Complete experimental details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) To a solution of LDA (2.50 mmol, in THF (20 mL), prepared from *n*-BuLi (1.0 mL, 2.50 M, 2.50 mmol), was added dropwise a solution of **8a** (0.60 g, 2.42 mmol) in THF (5 mL) at 0 °C, and the reaction mixture was stirred at rt for 30 min and quenched with a satd aq NH_4Cl solution (10 mL). The layers were separated, the aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane) to afford 0.58 g (98%) of **1a**: mp 120 °C dec; IR (KBr) 3505 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.73 (d, 1H, $J = 2.0$ Hz), 8.48 (d, 1H, $J = 2.0$ Hz), 7.69 (d, 1H, $J = 8.0$ Hz), 7.47−7.35 (m, 3H), 4.4 (s, 3H), 2.99 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 127.5, 125.3, 124.5, 123.1, 122.7, 122.4, 119.8, 109.2, 101.5, 33. 8; MS EI *m*/*z* (rel intensity) 247 (100), 218 (81), 201 (43), 91 (76); HRMS *m*/*z* calcd for $C_{17}H_{13}NO$, 247.0997, found 247.0997.

(8) For the preparation of enol triflates, see: Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.

(9) Prepared in 82% yield by NBS bromination of *N*,*N*-diethylindole-3-carboxamide, see: Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051.

(10) Hudkins, R. L.; Diebold, J. L.; Marsh, F. D. *J. Org. Chem.* **1995**, *60*, 6218.

(11) mp > 275 °C dec (lit.[1] mp > 280 °C dec). IR and NMR are identical to those reported. For details, see the Supporting Information.

(12) For previous syntheses, see: Hayashi, H.; Ohmoto, S.; Somei, M. *Heterocycles* **1997**, *45*, 1647 (two routes from indigo in 13% (six steps) and 5% (seven steps) overall yields respectively both of which involve a terminal nonregioselective *N*-methylation): Hayashi, H.; Suzuki, Y.; Somei, M. *Heterocycles* **1999**, *51*, 1233 (from indigo in 59% (six steps) overall yield). All routes involve interesting key central-ring closures via potentially electrocyclic processes, an anionic version of which for the cyclization of **15** may also be contemplated.