Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1117–1119
Tetrahedron Letters

The synthesis of indolo- and pyrrolo[2,1-*a*]isoquinolines

Charles B. de Koning,* Joseph P. Michael, Rakhi Pathak and Willem A. L. van Otterlo

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits 2050, 2050 Johannesburg, South Africa

Received 27 October 2003; revised 24 November 2003; accepted 5 December 2003

Abstract—The synthesis of fused isoquinolines from *N*-benzyl protected indoles and pyrroles is described. For example, treatment of *t*-butyl-2-(2-formyl-3,4-dihydro-1-naphthalenyl)-3-methyl-1*H*-indole-1-carboxylate with KOBu^t in DMF provided 14-methyl-8-phenylbenzo[*h*]indolo[2,1-*a*]isoquinoline in good yield. Analogous *N*-benzylpyrrole precursors could similarly be cyclized to give pyrrolo[2,1-*a*]isoquinolines.

The synthesis of isoquinolines and tetrahydroisoquinolines as well as their derivatives has occupied scientists for decades. The interest in these compounds is largely owing to their biological properties.[1–4] For example, papaverine **1** is a well-known isoquinoline alkaloid that is a prescription vasodilator (Fig. 1). The chemistry and biology of the related compounds, the tetrahydroisoquinolines, has recently been reviewed.[5] Furthermore, compounds that have featured in our work are the naphthylisoquinolines,[6] of which compound **2** is an example.[7–10]

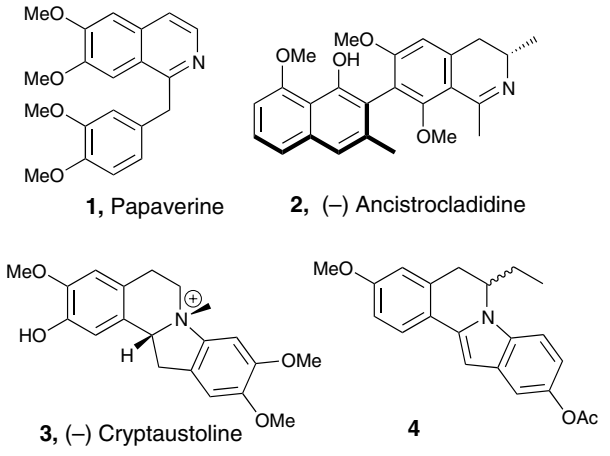


Figure 1. Examples of isoquinolines.

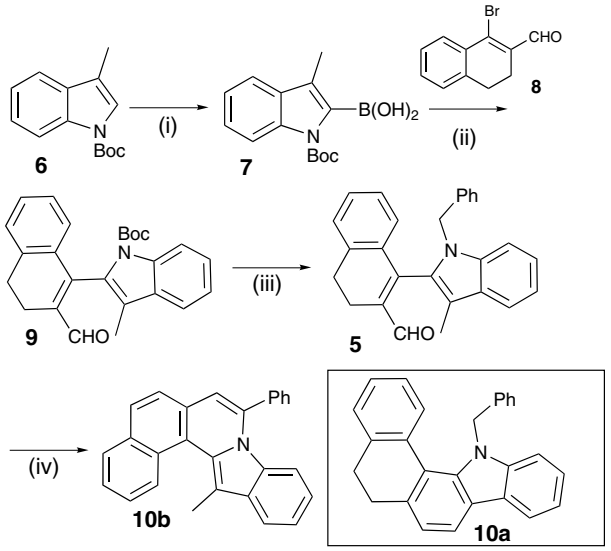
Examples of additional rings fused to the isoquinoline nucleus are also found in Nature, for example, the dibenzopyrrocoline alkaloid cryptaustoline **3**.[11] Synthetic compounds of this type are also documented to show biological activity. For example, compound **4** shows steroid hormone receptor binding affinity.[12] As a result, new methods to synthesize these types of molecules and their fused analogues are needed.

During the course of our work on the synthesis of benzo- and naphtho-fused carbazoles[13] we had reason to synthesize the *N*-benzyl protected indole **5**[14] from the Boc-protected indole **6** (Scheme 1). Reaction of **6** with *n*-BuLi and trimethyl borate followed by work-up with aqueous acid afforded boronic acid **7**, which was only stable if kept in a diethyl ether solution after work-up. Boronic acid **7** was then reacted with dihydronaphthalene **8** in the presence of catalytic $Pd(PPh_3)_4$ under Suzuki coupling reaction conditions to afford the desired coupled product **9**.[15] Exposure of **9** to the Lewis acid $AlCl_3$ yielded the intermediate deprotected indole, treatment of which with benzyl bromide gave the required benzyl-protected **5**.

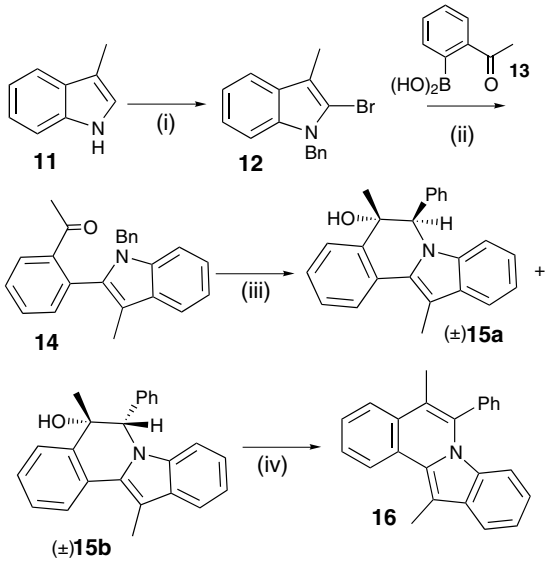
Utilizing our well-developed reaction conditions[16,17] for the formation of aromatic rings (KOBu^t, *hv*, DMF, 80 °C), we treated **5** in this manner. However none of the expected naphtho[*a*]carbazole **10a** was isolated, but isoquinoline **10b** was obtained instead.[18] Clearly the base is abstracting an *N*-benzyl proton and the resulting anion is condensing with the electrophilic aldehyde to

Keywords: Isoquinolines; Potassium *t*-butoxide.
* Corresponding author. Tel.: +27-11-7176724; fax: +27-11-7176749; e-mail: dekoning@aurum.chem.wits.ac.za

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.020



Scheme 1. Reagents and conditions: (i) (a) *n*-BuLi, THF, −78 °C, (b) $B(OMe)_3$, THF, −78 °C, (c) H_3O^+, extract into Et_2O; (ii) 10% $Pd(PPh_3)_4$, aq Na_2CO_3/DME, (Et_2O removed by bubbling N_2 through reaction mixture), 96% (two steps); (iii) (a) $AlCl_3$, CH_2Cl_2, rt, 2 h, 100%; (b) BnBr, 50% aq NaOH, DMF, 53%; (iv) KOBu^t, DMF, *hv*, 80 °C, **10a**, 0%, **10b**, 65%.



Scheme 2. Reagents and conditions: (i) (a) NBS, CCl_4, 3 h, 98%; (b) aq NaOH, BnBr, 66%; (ii) 10% $Pd(PPh_3)_4$, aq Na_2CO_3/DME, 64%; (iii) KOBu^t, DMF, *hv*, 80 °C, **15a**, 26%, **15b**, 74%; (iv) **15b**, 15 mol% TsOH, CH_2Cl_2, rt, 24 h, 79%.

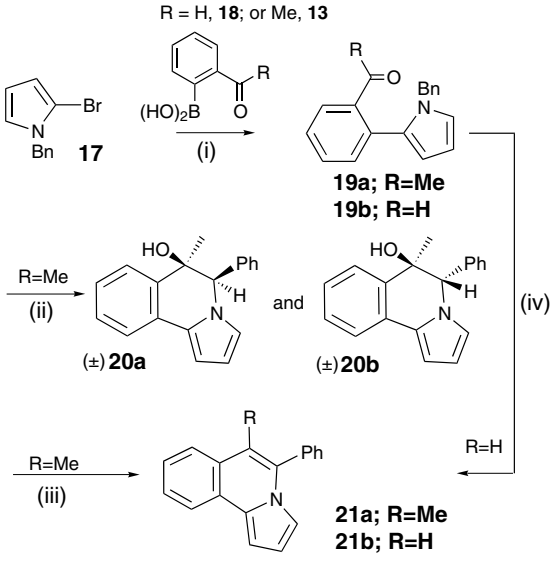
afford the fused isoquinoline **10b** after aromatization of the putative dihydronaphthalene intermediate.

We decided to test the generality of this reaction by synthesizing a number of indole and pyrrole analogues. As a first step we realized that an obvious extension to this methodology would be to exchange the functional groups of the substrates required for the coupling reaction. Therefore bromoindole **12** was synthesized using published chemistry from commercially available 3-methylindole **11**.[19] Suzuki coupling of **12** with the commercially available boronic acid **13** gave the desired precursor **14** on which to attempt the ring forming reaction (Scheme 2). Exposure of **14** to KOBu^t in DMF and a light source afforded the ring-closed alcohols **15a** and **15b** as diastereoisomers (~1:3 ratio). The major diastereoisomer was shown to be **15b** by nOe spectroscopy. Exposure of **15b** to 15 mol% TsOH afforded the dibenzopyrrocoline **16** in very good yield.

As a next step, we thought it would be useful to see if the same type of chemistry could be performed on pyrrole derivatives. The synthesis of the required bromopyrrole **17** was achieved using literature procedures.[20,21] Suzuki coupling of this with either the boronic acid **13** or the aldehyde equivalent **18** resulted in the formation of both desired precursors **19a** (R = Me) and **19b** (R = H). Exposure of **19a** to KOBu^t in DMF afforded a diastereomeric mixture of alcohols **20a** and **20b** (ratio ~2.5:1). The major product **20b** was dehydrated under acidic conditions to give the desired product **21a**.

At this stage, we decided to attempt these reactions in the absence of light. Subjecting substrate **5** to the same reaction conditions as described before but without the light source resulted in the formation of the identical product **10b** in a similar yield. In the same manner when **19b** was treated with KOBu^t in the absence of light, **21b** was produced, presumably by way of the analogous alcohol (Scheme 3).

In conclusion, we have been able to synthesize both indolo- and pyrrolo[2,1-*a*]isoquinolines starting from simple *N*-benzylated indoles or pyrroles that possess a suitable substituent on C-2 of the indole nucleus. We are currently looking at ways to utilize this methodology for the synthesis of isoquinoline or dibenzopyrrocoline natural products.



Scheme 3. Reagents and conditions: (i) 10% $Pd(PPh_3)_4$, aq Na_2CO_3/DME, **19a**, 82%, **19b**, 52%; (ii) KOBu^t, DMF, *hv*, 80 °C, **20a**, 56%, **20b**, 23%; (iii) R = Me, 15 mol% TsOH, CH_2Cl_2, rt, 24 h, **21a**, 74%; (iv) R = H, KOBu^t, DMF, 80 °C, **21b**, 68%.

Acknowledgements

This work was supported by the National Research Foundation (NRF, GUN 2053652), Pretoria, and the University of the Witwatersrand (University Research Council).

References and notes

1. Bentley, K. W. *Nat. Prod. Rep.* **2003**, *20*, 342–365.
2. Balasubramanian, M.; Scriven, E. F. V. Isoquinoline and its derivatives. In *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds, Vol IV: Heterocyclic Compounds, Parts F and G*; Sainsbury, M., Ed.; Elsevier: Amsterdam, 1998; pp 163–216.
3. Andreae, S. Isoquinolines (Benzo[*b*]pyridines). In *Heteroarenes II, Part 1*; Kreher, R.P., Ed.; Georg Thieme: Stuttgart, 1991; Vol. E7a, pp 571–740.
4. Kathawala, F. G. *Isoquinolines*; New York: Wiley, 1990.
5. Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.
6. For an extensive review see: Bringmann, G.; Pokorny, F. In *The Alkaloids. Chemistry and Pharmacology*; Cordell, G. A., Ed.; Academic: New York, 1995; Vol. 46, pp 127–271.
7. de Koning, C. B.; van Otterlo, W. A. L.; Michael, J. P. *Tetrahedron* **2003**, *59*, 8337–8345.
8. de Koning, C. B.; Michael, J. P.; van Otterlo, W. A. L. *Synlett* **2002**, 2065–2067.
9. de Koning, C. B.; Michael, J. P.; van Otterlo, W. A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 799–811.
10. For an approach to a 1,2-dihydroisoquinoline ring system using ruthenium-mediated isomerization and ring-closing metathesis see: van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B. *Synlett* **2003**, 1859–1861.
11. (a) Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. *Org. Lett.* **2000**, *2*, 1799–1801; (b) Meyers, A. I.; Sielecki, T. M. *J. Am. Chem. Soc.* **1991**, *113*, 2789–2790.
12. Ambros, R.; Schneider, M. R.; von Angerer, S. *J. Med. Chem.* **1990**, *33*, 153–160.
13. For example, see: de Koning, C. B.; Michael, J. P.; Nhlapo, J. M.; Pathak, R.; van Otterlo, W. A. L. *Synlett* **2003**, 705–707.
14. From the ongoing Ph.D of R. Pathak, University of the Witwatersrand.
15. *t*-Butyl-2-(2-formyl-3,4-dihydro-1-naphthalenyl)-3-methyl-1*H*-indole-1-carboxylate **9**: A solution of 1-bromo-3,4-dihydronaphthalene-2-carbaldehyde **8** (0.20 g, 0.84 mmol) in DME (4 cm^3) was deoxygenated by passing N_2 through the mixture for 5 min. The solution was then added to $Pd(PPh_3)_4$ (10 mol%, 0.096 g, 0.083 mmol) and stirred under N_2 atmosphere for 10 min at rt. A solution of 1-(*t*-butoxycarbonyl)-3-methyl-1*H*-indol-2-ylboronic acid **7** (1.5 equiv, 0.346 g, 1.26 mmol) in Et_2O (1.5 cm^3) was added to the reaction mixture, which was deoxygenated by bubbling N_2 through the solution. Presumably the Et_2O evaporated in the process. The mixture was then stirred for a further 10 min. A deoxygenated 2 M aqueous Na_2CO_3 solution (3.6 cm^3) was then added to the reaction mixture, which was stirred at rt for a further 5 min before being heated at reflux for 2 d. The mixture was cooled to rt and quenched with H_2O (20 cm^3) after which 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 (5–10% EtOAc–hexane) to afford the product **9** as a yellow solid (0.313 g, 96%). mp 141–142 °C (Found: M^+, 387.1830. $C_{25}H_{25}NO_3$ requires 387.1834); ν_{max} ($CHCl_3$)/cm^{-1} 1725 and 1660 (C=O) and 1616, 1599, 1559 (ArC=C); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.29 (9H, s, Boc), 2.10 (3H, s, CH_3), 2.72–2.82 (2H, m, CH_2), 2.96–3.00 (2H, m, CH_2), 6.78 (1H, d, $J = 7.8$ Hz, ArH), 7.08–7.11 (1H, m, ArH), 7.25–7.45 (4H, m, 4×ArH), 7.57 (1H, d, $J = 7.4$ Hz, ArH), 8.29 (1H, d, $J = 8.3$ Hz, ArH) and 9.70 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 9.3 ($ArCH_3$), 20.2 (CH_2), 27.1 (CH_2), 27.8 (Boc), 83.9 ($C(Me)_3$), 115.7 (CH), 119.1 (CH), 120.7 (C), 123.0 (CH), 125.4 (CH), 126.7 (CH), 126.9 (CH), 128.0 (CH), 129.8 (C), 130.2 (CH), 134.5 (C), 135.5 (C), 136.5 (C), 137.8 (C), 146.5 (C), 149.5 (CO) and 192.9 (CHO); *m/z* (EI) 387 (M^+, 47%), 287 (83), 273 (30), 272 (100), 270 (32), 269 (32), 258 (50), 130 (29) and 57 (62).
16. de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 787–797.
17. de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1705–1713.
18. 12-Methyl-6-phenylindolo[2,1-*a*]isoquinoline **10b**: $KOBu^t$ (0.119 g, 1.06 mmol), was added to **5** (0.105 g, 0.33 mmol) dissolved in dry DMF (10 cm^3). 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 with Et_2O (3×50 cm^3). The organic layer was dried ($MgSO_4$) and filtered. It was then evaporated and subjected to column chromatography (5–20% EtOAc–hexane) to afford the product **10b** (0.076 g, 65%) as a yellow solid. mp 96–98 °C (Found: M^+, 357.1518. $C_{27}H_{19}N$ requires 357.1518); ν_{max} ($CHCl_3$)/cm^{-1}, 1594 and 1551 (ArC=C), 1466, 1451 and 1388; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.55 (3H, s, CH_3), 6.53 (1H, s, Ar 5-H), 6.58 (1H, d, $J = 8.6$ Hz, ArH), 6.95–7.00 (1H, m, ArH), 7.29–7.34 (1H, m, ArH), 7.52–7.65 (8H, m, 8×ArH), 7.81 (1H, d, $J = 8.0$ Hz, ArH), 7.90 (1H, d, $J = 8.4$ Hz, ArH), 7.94 (1H, d, $J = 7.9$ Hz, ArH) and 8.32 (1H, d, $J = 8.3$ Hz, ArH); δ_C (75 MHz; $CDCl_3$) 14.5 ($ArCH_3$), 108.2 (C), 111.3 (CH), 114.0 (CH), 118.3 (CH), 120.8 (CH), 121.7 (CH), 124.1 (CH), 125.1 (CH), 125.5 (CH), 127.9 (CH), 127.9 (CH), 128.3 (CH), 128.9 (CH), 128.9 (C), 129.0 (CH), 129.2 (CH), 129.7 (C), 131.2 (C), 131.6 (C), 132.9 (C), 137.0 (C) and 139.1 (C); *m/z* (EI) 358 (36%), 357 (M^+, 100), 356 (54), 354 (21), 278 (11) and 171 (11).
19. Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 3103–3106.
20. Choi, D.-S.; Huang, S.; Huang, M.; Barnard, T. S.; Adams, R. D.; Seminario, J. M.; Tour, J. M. *J. Org. Chem.* **1998**, *63*, 2646–2655.
21. Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221–2225.