A Tandem Route to the Synthesis of Carbazolo[1,2-*b*]carbazoles

T. Krishna Chaitanya, Rajagopal Nagarajan*

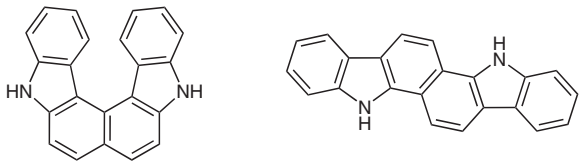
School of Chemistry, University of Hyderabad, Hyderabad 500046, India
Fax +91(40)23012460; E-mail: rnsc@uohyd.ernet.in

Received 25 June 2011

Abstract: A simple and facile synthesis of carbazolo[1,2-*b*]carbazole derivatives via Michael addition of 2-methylindole, condensation of methyl group with the carbonyl, dehydration followed by aromatization by heating in hydrothermal oven is reported.

Key words: carbazolocarbazoles, tandem cyclization, tetrahydrocarbazole, carbazole, π-donor complexes

Carbazole derivatives have been attracting increasing interest of synthetic chemists for many years.[1] A broad range of carbazole alkaloids with interesting structural motifs and useful biological applications such as pyridocarbazoles,[2] pyranocarbazoles,[3] furocarbazoles,[4] indolocarbazoles, benzocarbazoles, etc.,[5] which have a heteroarylcarbazole skeleton, have been isolated from diverse natural sources. This initiated the development of many novel and efficient synthetic methods for these heteroarylcarbazole derivatives.



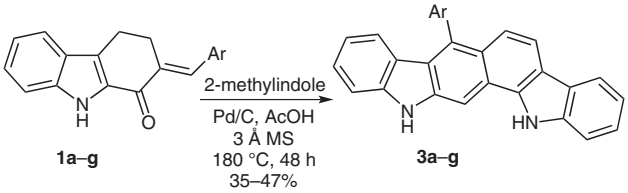
carbazolo[3,4-*c*]carbazole carbazolo[2,1-*a*]carbazole

Figure 1 Carbazolocarbazoles

Carbazolocarbazoles are a new class of heteroarylcarbazoles where a carbazole is fused with another carbazole at various positions. These molecules are little explored, and very few reports are available in the literature, though they are reported to form stronger π-donor complexes.[6] Carbazolo[3,4-*c*]carbazole and tetranitro fluorenone are reported to form a strong electron-donor–acceptor complex (EDA complex).[7] The synthesis of carbazolocarbazoles is less explored and very few reports are available for the synthesis. Zander et al. have reported the synthesis of carbazolo[3,4-*c*]carbazoles and carbazolo[2,1-*a*]carbazoles from dinaphthols, phenyl hydrazine, and sodium bisulfite (Figure 1).[8] A series of carbazolo[2,1-*a*]carbazoles were prepared from Fischer indole synthesis of 4-oxo-1,2,3,4-tetrahydrobenzocarbazole derivatives by Kirsch et al.[9] Haider and coworkers reported the synthesis of carbazolo[3,2-*b*]carbazoles in lower yields.[10] In this context, development of an efficient methodology for the synthesis of these derivatives is highly desirable.

Synthesis of heterocycles employing tandem reactions is one of the most economical and desirable synthetic strategies.[11] Tandem processes are well explored in the literature and development of new tandem processes is of continuous synthetic interest. In continuation of our interest in the development of efficient methodologies for new heteroarylcarbazole derivatives,[12] we wish to report here a simple and efficient route for the synthesis of carbazolo[1,2-*b*]carbazole derivatives.

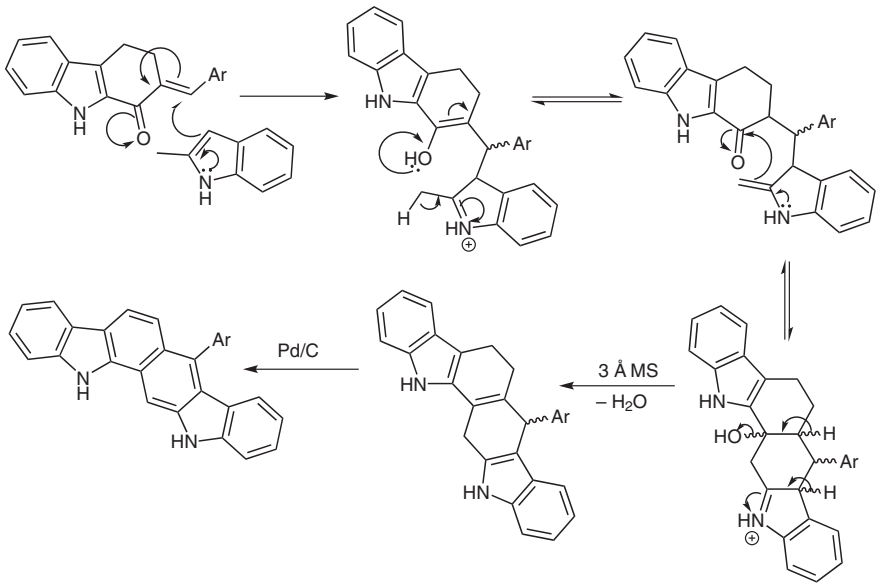
We envisioned that 2-alkylindoles on condensation with the chalcones of 1-ketotetrahydrocarbazole followed by aromatization can provide the desired products. We employed various solvent systems like water, DMF, DMSO; but we found negligible conversion of starting materials. When we conducted the reaction in acetic acid, we were successful in obtaining the products in moderate yields (Scheme 1). The role of the acid is explained in the mechanism. Aryl chalcones of 1-ketotetrahydrocarbazole[13] on reacting with 2-methylindole in the presence of palladium charcoal in acetic acid upon heating at 180 °C in a hydrothermal oven for 48 hours provided the carbazolo[1,2-*b*]carbazole derivatives in moderate yields.[14] When we carried out the reaction without Pd/C, product formation was not observed.



Scheme 1 Synthesis of carbazolo[1,2-*b*]carbazoles

The products are well characterized by NMR spectroscopy. In the ^{1}H NMR spectra, the absence of peaks in the aliphatic region and two singlets around δ = 12 and 11 ppm, which correspond to the two NH protons clearly indicate the formation of desired products. A sharp singlet at δ = 8.5 ppm corresponds to the CH at 1-position, indicating the complete aromatization of the product. Electron-withdrawing substituents on the aryl ring of chalcones gave better yields. When we carried out the reactions with 4-cyano and 4-nitro aldehydes, we obtained a complex mixture of products. Reaction with 2-benzylindole employing

SYNLETT 2011, No. 17, pp 2559–2561
Advanced online publication: 06.10.2011
DOI: 10.1055/s-0030-1289514; Art ID: B11911ST



Scheme 2 Proposed mechanism for carbazolocarbazoles

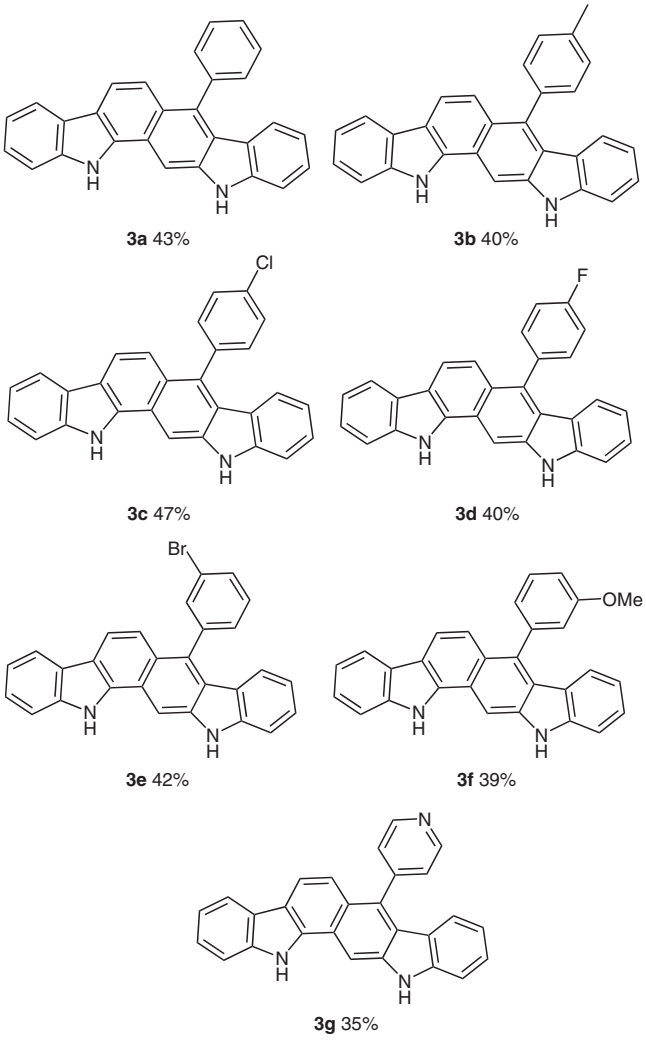


Figure 2 Carbazolo[1,2-*b*]carbazoles

similar conditions did not yield the product and starting materials were recovered.

The possible mechanism for this tandem process is explained in Scheme 2. 2-Methylindole acts as a nucleophile to attack in Michael fashion on chalcone to give the addition product. In the presence of acid, the equilibrium of iminium intermediates of indole followed by aldol condensation of one of the intermediate enamine occurs. Elimination of a water molecule gives the tetrahydrocarbazole derivative, which undergoes aromatization in the presence of Pd/C to furnish the desired carbazolo[1,2-*b*]carbazole (Figure 2). The presence and position of substituent on aryl ring seems to have no effect on the reaction. All the substituents provided products in similar yields.

In conclusion, we report here a simple and facile synthesis of carbazolo[1,2-*b*]carbazole derivatives via Michael addition of 2-methylindole, condensation of the methyl group with the carbonyl, and elimination of a water molecule followed by aromatization. This tandem process is noteworthy as it involves easily accessible starting materials and provides carbazolocarbazoles in moderate yields.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We acknowledge DST for financial assistance (Project number: SR/S1/OC-70/2008) and for providing single-crystal X-ray diffractometer facility in our school. TKC thanks CSIR for Senior Research Fellowship.

References and Notes

(1) (a) Gribble, G. W. *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego (CA), **1990**, 239. (b) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (c) Cordell, G. A. *The Alkaloids*, Vol. 65; Academic Press: Amsterdam, **2008**. (d) Gribble, G. W. *Synlett* **1991**, 289. (e) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. *J. Org. Chem.* **1984**, *49*, 4518. (f) Knölker, H.-J. *Curr. Org. Chem.* **2004**, *1*, 309. (g) Knölker, H.-J. *Chem. Lett.* **2009**, *38*, 8.

(2) (a) Pindur, U.; Haber, M.; Sattler, K. *Pharmazie in unserer Zeit.* **1992**, 21. (b) Pelaprat, D.; Oberlin, R.; Le Guen, I.; Roques, B. R. *J. Med. Chem.* **1980**, *23*, 1330. (c) Lescot, E.; Muzard, G.; Markovits, J.; Belleney, J.; Roques, B. P.; Le Pecq, J.-B. *J. Med. Chem.* **1986**, *29*, 1731. (d) Karmakar, A. C.; Kar, G. K.; Ray, J. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1997. (e) Molina, P.; Fresneda, P. M.; Almendros, P. *Tetrahedron* **1993**, *49*, 1223. (f) Goodwin, S.; Smith, A. F.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 1903. (g) Woodward, R. B.; Iacobucci, G. A.; Hochstein, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 4434.

(3) (a) Chakraborty, D. P.; Das, K. C.; Chowdhury, B. K. *J. Org. Chem.* **1971**, *36*, 725. (b) Chakraborty, D. P.; Barman, B. K.; Bose, P. K. *Sci. Cult. (India)* **1964**, *30*, 445. (c) Dutta, N. L.; Quasim, C. *Indian J. Chem.* **1969**, *7*, 307. (d) Chakraborty, D. P.; Das, K. C. *Chem. Commun.* **1968**, 967. (e) Ray, S.; Chakraborty, D. P. *Phytochemistry* **1976**, *15*, 356. (f) Ito, C.; Nakagawa, M.; Wu, T.-S.; Furukawa, H. *Chem. Pharm. Bull.* **1991**, *39*, 1668. (g) Ito, C.; Nakagawa, M.; Wu, T.-S.; Furukawa, H. *Chem. Pharm. Bull.* **1991**, *39*, 2525. (h) Kumar, V.; Reisch, J.; Wickramasinghe, A. *Aust. J. Chem.* **1989**, *42*, 1375. (i) Ito, C.; Furukawa, H. *Chem. Pharm. Bull.* **1990**, *38*, 1548. (j) Wu, T.-S.; Wang, M.-L.; Wu, P.-L. *Phytochemistry* **1996**, *43*, 785. (k) Gruner, K. K.; Knölker, H.-J. *Org. Biomol. Chem.* **2008**, *6*, 3902. (l) Lebold, T. P.; Kerr, M. A. *Org Lett.* **2007**, *9*, 1883. (m) Gruner, K. K.; Hopfmann, T.; Matsumomto, K.; Jäger, A.; Katsuki, T.; Knölker, H.-J. *Org. Biomol. Chem.* **2011**, *9*, 2057.

(4) (a) Wu, T.-S.; Huang, S.-C.; Wu, P.-L. *Heterocycles* **1997**, *45*, 969. (b) Soós, T.; Timári, G.; Hajás, G. *Tetrahedron Lett.* **1999**, *40*, 8607. (c) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505. (d) Roques, B. P.; Florentin, D.; Callanquin, M. *J. Heterocycl. Chem.* **1975**, *12*, 195. (e) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541. (f) Hagiwara, H.; Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1998**, *46*, 1948. (g) Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. *Chem. Pharm. Bull.* **2001**, *49*, 881. (h) Bergman, J.; Pelcman, B. *Tetrahedron* **1988**, *44*, 5215. (i) Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Heterocycles* **2004**, *63*, 2393.

(5) (a) Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot.* **1995**, *48*, 535. (b) Bergman, J.; Janosik, T.; Wahlström, N. *Adv. Heterocycl. Chem.* **2001**, *80*, 1. (c) Bocchi, V.; Palla, G. *J. Chem. Soc., Chem. Commun.* **1983**, 1074. (d) Bocchi, V.; Palla, G. J. *Tetrahedron* **1984**, *40*, 3251. (e) Janosik, T.; Bergman, J. *Tetrahedron* **1999**, *55*, 2371. (f) Kistenmacher, A.; Mullen, K. *J. Heterocycl. Chem.* **1992**, *29*, 1237. (g) Noland, W. E.; Johnson, J. E. *Tetrahedron Lett.* **1962**, *14*, 589. (h) Bergmann, J.; Pelcmann, B. *Tetrahedron* **1988**, *44*, 5215. (i) Knölker, H.-J.; Reddy, K. R. *Tetrahedron* **2000**, *41*, 5035.

(6) (a) Fuchs, W.; Niszel, F. *Ber. Dtsch. Chem. Ges. B* **1927**, *60*, 209. (b) Curiel, D.; Más-Montoya, M.; Uruvakili, A.; Orenes, R. A.; Pallamreddy, H.; Molina, P. *Org. Lett.* **2010**, *12*, 3164.

(7) Zander, M.; Franke, W. H. *Chem. Ber.* **1969**, *102*, 2728.

(8) Icli, S.; Burgemeister, T.; Mannschreck, A.; Zander, M. *Org. Magn. Reson.* **1982**, *20*, 145.

(9) Dufour, F.; Kirsch, G. *J. Heterocycl. Chem.* **2008**, *45*, 161.

(10) Haider, N.; Käferböck, J.; Matyus, P. *Heterocycles* **1999**, *51*, 2703.

(11) (a) Liu, X.-Y.; Che, C.-M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3805. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (d) Ajamian, A.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 3754. (e) Wasilke, J.-C. S.; Obrey, J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (f) De Meijere, A.; Zezschwitz, P.; Brase, S. *Acc. Chem. Res.* **2005**, *38*, 413.

(12) (a) Sreenivas, D. K.; Nagarajan, R. *Tetrahedron* **2010**, *66*, 9650. (b) Ramesh, S.; Gaddam, V.; Nagarajan, R. *Synlett* **2010**, 757. (c) Meesala, R.; Nagarajan, R. *Tetrahedron Lett.* **2010**, *51*, 422. (d) Chaitanya, T. K.; Nagarajan, R. *Tetrahedron Lett.* **2007**, *48*, 2489. (e) Gaddam, V.; Nagarajan, R. *Org. Lett.* **2008**, *10*, 1975.

(13) (a) Kavitha, C.; Prasad, K. J. R. *J. Chem. Res., Miniprint* **2003**, 1025. (b) Vandana, T.; Velumani, K.; Prasad, K. J. R. *Heterocycl. Commun.* **2003**, *9*, 299.

(14) A mixture of 2-methylindole (1 mmol), chalcones (1 mmol), 3 Å MS (0.2 g), Pd/C (15 mg, 10%), and AcOH (10 mL) was stirred and loaded under nitrogen atmosphere in an autoclave (25 mL). The autoclave was heated at 180 °C for 48 h. After allowing to r.t., the reaction mixture was diluted with EtOAc, filtered through Celite, washed with 5% aq bicarbonate solution and H_2O, concentrated in vacuum. In TLC, the products show a characteristic blue fluorescence. The residue is purified by column chromatography to provide the desired carbazolocarbazole. Unreacted starting materials were recovered as nonpolar fractions.

9-Phenyl-2,14-dihydrocarbazolo[1,2-*b*]carbazole

Yield 43%; mp 176–178 °C. IR (KBr): ν_{max} = 3412, 1602, 1466, 1317, 740, 694 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.66 (s, 1 H), 10.82 (s, 1 H), 8.50 (s, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.56–7.64 (m, 4 H), 7.49 (d, *J* = 7.6 Hz, 2 H), 7.27–7.42 (m, 4 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 6.76–6.83 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 142.8, 139.2, 139.1, 138.6, 135.6, 133.2, 133.0, 132.2, 129.7, 127.2, 125.2, 124.6, 123.9, 122.6, 122.2, 122.1, 121.2, 120.0, 119.5, 118.9, 117.5, 116.7, 116.4, 111.8, 111.1, 100.6. MS (pos. Mode): *m/z* = 382. Anal. Calcd (%) for $C_{28}H_{18}N_2$: C, 87.93; H, 4.74; N, 7.32. Found: C, 87.85; H, 4.81; N, 7.26.