Expedient Synthesis of N-Fused Indoles through an Intramolecular [3+2]-Cycloaddition Approach

Subban Kathiravan, Raghavachary Raghunathan*

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India
Fax +91(44)22352494; E-mail: ragharaghunathan@yahoo.com

Received 18 November 2009

Abstract: A variety of N-fused indolo pyrrolo-pyrroles and pyrrolo-pyrrolizidines were synthesized by intramolecular 1,3-dipolar cycloaddition reaction of azomethine ylide generated from *N*-alkenylindole carbaldehyde which were prepared by the N-alkylation of indole 2-aldehyde with Baylis–Hillman bromides.

Key words: N-fused indoles, indolo pyrrolo-pyrroles, pyrrolo-pyrrolizidines 1,3-dipolar cycloaddition, azomethine ylides, Baylis–Hillman adducts

Many natural and synthetic biologically active compounds containing the indole skeleton are being used for therapeutic purposes.[1] N-Fused indoles, for example, mitomycin C[2] and cryptaustoline[3] possess the N-fused indole structure (Figure 1), exhibit antitumor[4] and tubulin polymerization inhibitory[5] activities. Pyrazino[1,2-*a*]indoles behave as 5-HT_{2c} receptor agonists[6] and are used for the treatment of hyperglycemia and other diseases.

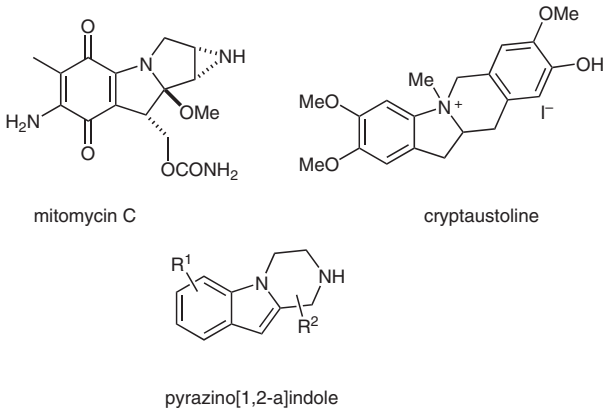


Figure 1 Biologically active N-fused indoles

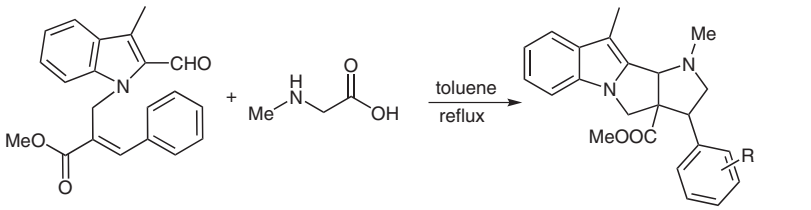
Despite the importance of N-fused indole derivatives, the synthesis of this class of compounds has not yet been fully developed: alkyl-chain elongation and ring closure on an existing indole platform have been reported by many research groups (e.g., by intermolecular alkylation,[7a] radical cyclization,[7b,c] and other methods[7d–f]). Transannulation reactions[8] also afford N-fused indoles.

Although many methods are available for the synthesis of N-fused indoles, many of them requires vigorous reaction conditions and use of expensive catalyst, which also results in poor yields of the products.[9] In recent years many transition-metal-catalyzed reactions have been reported.[10] However, the ring-closure strategy still posed many problems and most importantly, a multistep synthesis of the substrate is required regardless of the synthetic strategy selected.

Intramolecular [3+2] cycloaddition of azomethine ylides has been used widely to construct complex cyclic systems from relatively simple precursors. This mode of cycloaddition simultaneously constructs two carbon–carbon bonds and forms complex ring systems with regio- and stereocontrol.[11–14]

In continuation of our ongoing research program,[15] herein we describe an expedient synthesis of N-fused indoles by means of direct, intramolecular 1,3-dipolar cycloaddition of azomethine ylide from *N*-alkenylindole-2-carbaldehyde. Our strategy consists of N-alkylation of 3-methylindole with Baylis–Hillman bromides[16] and Vilsmeier–Haack formylation followed by intramolecular cycloaddition to afford N-fused indole derivatives.

Thus we have prepared the substrates **1a–g** by treating 3-methylindole with Baylis–Hillman adducts followed by



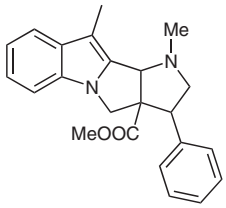
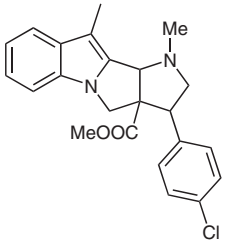
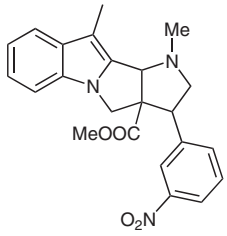
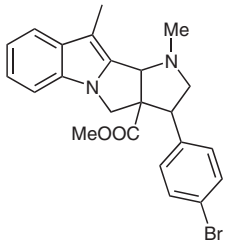
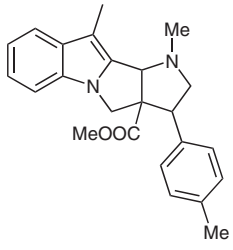
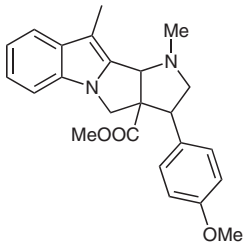
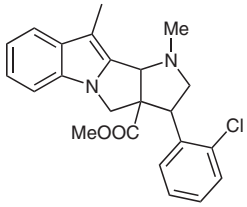
1a–g **2** **3a–g** (65–88%)
R = H, 4-Cl, 3-NO_2, 4-Br, 4-Me, 4-OMe, 2-Cl

Scheme 1 [3+2] Cycloaddition between precursor and sarcosine

SYNLETT 2010, No. 6, pp 0952–0954
Advanced online publication: 26.02.2010
DOI: 10.1055/s-0029-1219551; Art ID: G39210ST

formylation using Vilsmeier–Haack reaction (Scheme 1). The substrates thus prepared (**1a**–**g**) were treated with 1.5 equivalents of sarcosine in toluene and heated to reflux until the completion of the starting material as evidenced by TLC. The reaction completed in 7 h to afford N-fused indole derivatives **3a**–**g** in good yield (Table 1 entry 1). The conversion rate improved dramatically when the nitro substituent in the benzene ring was used, giving **3c** in 88% yield (Table 1 entry 3).

Table 1 Synthesis of N-Fused Indole Derivatives **3**

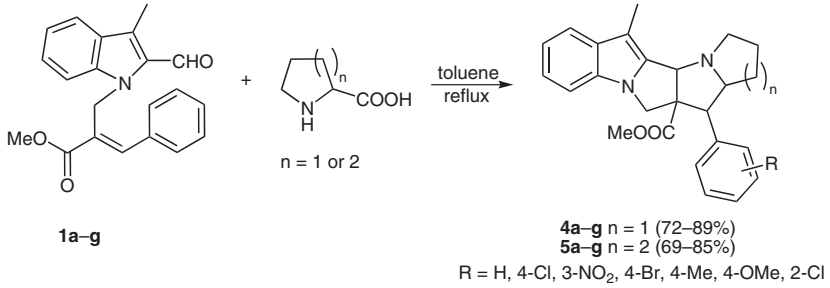
Entry	Precursor	Products	Time (h)[a]	Yield (%)[b]
1	**1a**	 **3a**	7	78
2	**1b**	 **3b**	6	80
3	**1c**	 **3c**	5	88
4	**1d**	 **3d**	5	85
5	**1e**	 **3e**	8	70
6	**1f**	 **3f**	6.5	65
7	**1g**	 **3g**	7	75

[a] Reaction time of the cycloaddition step.
[b] Yield obtained after column chromatography.

The structure and the regiochemistry of the cycloadducts were confirmed by spectral analysis.[17] The IR spectrum of **3a** showed a sharp peak at 1740 cm^{-1} for the ester carbonyl. The ^1H NMR spectrum of **3a** showed a singlet at δ = 1.843 ppm corresponding to NCH_3 protons. The methyl protons attached to indole unit showed a sharp singlet at δ = 2.60 ppm. The two NCH_2 protons appeared as multiplets in the range of δ = 3.25–3.38 and 3.71–3.81 ppm. The CH_2 protons attached to indole skeleton showed a sharp singlet at δ = 2.60 ppm. The proton attached to the ester carbonyl carbon appeared as a multiplet at δ = 4.07–4.18 ppm. A singlet at δ = 4.81 ppm was observed for the NCH proton. The off-resonance proton-decoupled ^{13}C spectrum of **3a** exhibited peaks at δ = 21.04, 39.66, and 67.95 ppm due to the CCH_3, NCH_3, and OCH_3 bonds. The ester carbonyl resonated at δ = 174.93 ppm. Finally, the structure of **3a** was confirmed by mass spectrometry, which showed a peak at *m/z* = 346.85 [M^+].

When secondary amino acids such as proline (n = 1) and pipecolinic acid (n = 2) were employed, the corresponding linearly fused pentacyclic pyrrolizidines and indolizidines were accessed (Scheme 2).

In summary, we have developed a new route to biologically and pharmacologically important N-fused indole derivatives. For the first time the efficient construction of the structurally novel indole derivatives has been synthesized via a highly stereoselective intramolecular [3+2]-cycloaddition reaction of azomethine ylides generated from functionalized *N*-alkyl-3-methylindole-2-carbaldehydes. Further studies are in progress to expand the reaction scope and to use ferrocene-substituted *N*-alkenylindole aldehydes for the synthesis of other novel heterocyclic systems, and will be reported in due course.



Scheme 2 [3+2] Cycloaddition between precursor and cyclic amino acid

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

Acknowledgment

S.K. thanks the Council of Scientific and Industrial Research (CSIR) for the award of Senior Research Fellowship (SRF). S.K. and R.R. thank DST-FIST New Delhi for NMR facility.

References and Notes

(1) Reviews on the synthesis of indoles: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Saki, N.; Annaka, K.; Fujita, A.; Sato, A. *J. Org. Chem.* **2008**, *73*, 4160.

(2) Hata, T.; Sano, Y.; Sugawara, R.; Matsukae, A.; Kanamori, K.; Shima, T.; Hoshi, T. *J. Antibiot, Ser. A* **1956**, *9*, 141.

(3) Ewing, J.; Hughes, G. K.; Ritchic, E.; Taylor, W. C. *Nature (London)* **1952**, *169*, 618.

(4) Yoda, N.; Hiayama, N. *J. Med. Chem.* **1993**, *36*, 1461.

(5) Goldbrunner, M.; Loidl, G.; Polossek, T.; Mannschreck, A.; Angerer, E. V. *J. Med. Chem.* **1997**, *40*, 3524.

(6) Bos, M.; Jenck, F.; Martin, J. R.; Moreau, J. L.; Mutel, V.; Sleight, A. J.; Widmer, U. *Eur. J. Med. Chem.* **1997**, *32*, 253.

(7) (a) Peters, R.; Waldmeier, P.; Joncour, A. *Org. Process Res. Dev.* **2005**, *9*, 508. (b) Caddick, S.; Aboutayab, K.; Jenkins, K.; West, R. I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 675. (c) Bennasar, M. L.; Roca, T.; Ferrando, F. *Org. Lett.* **2004**, *6*, 759. (d) Wang, S. F.; Chuang, C. P. *Tetrahedron Lett.* **1997**, *38*, 7597. (e) Shiue, J. S.; Fang, J. M. *J. Chem. Soc., Chem. Commun.* **1993**, 1277. (f) Ishikura, M.; Ida, W.; Yanada, K. *Tetrahedron* **2006**, *62*, 1015.

(8) Tsuboike, K.; Guerin, D. J.; Mennen, S. M.; Miller, S. J. *Tetrahedron* **2004**, *60*, 7367.

(9) (a) Liu, J.; Shen, M.; Zhang, Y.; Li, G.; Khodabocus, A.; Rodriguex, S.; Qu, B.; Farina, V.; Senanayake, C. H.; Lu, B. Z. *Org. Lett.* **2006**, *8*, 3573. (b) Takaya, J.; Udagawa, S.; Kusama, H.; Ieasawa, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4906; *Angew. Chem.* **2008**, *120*, 4984. (c) Lim, K. H.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T. S. *Tetrahedron Lett.* **2009**, *50*, 752. (d) Rogness, D. C.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4003.

(10) (a) Siebencicher, H.; Bytschkov, I.; Doye, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 3042; *Angew. Chem.* **2003**, *115*, 3151. (b) Perez-Serrano, L.; Dominguex, G.; Perez-Castells, J. *J. Org. Chem.* **2004**, *69*, 5413. (c) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 1138; *Angew. Chem.* **2009**, *121*, 1158.

(11) (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (c) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905.

(12) Pandey, T.; Sahoo, A. K.; Bagul, T. D. *Org. Lett.* **2000**, *2*, 2299.

(13) Vedejs, E.; Klapers, A.; Naidu, B. N.; Piotrowski, D. W.; Tucci, F. C. *J. Am. Chem. Soc.* **2000**, *122*, 5401.

(14) Coldham, I.; Crapnell, K. M.; Moseley, J. D.; Rabot, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 533.

(15) (a) Kathiravan, S.; Raghunathan, R. *Synlett* **2009**, 1126. (b) Purusothaman, S.; Raghunathan, R. *Tetrahedron Lett.* **2009**, *50*, 6848. (c) Suresh Babu, A. R.; Raghunathan, R.; Satiskumar, B. K. *Tetrahedron Lett.* **2009**, *50*, 2818. (d) Poornachandran, M.; Raghunathan, R. *Tetrahedron Lett.* **2005**, *46*, 7197.

(16) Basaviah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(17) **Synthesis of N-Fused Indole 3a – Typical Procedure**
A solution of **1a** (1 mmol) and sarcosine **2** (1.5 mmol) in toluene (10 mL) was stirred and heated at reflux for 6 h. After evoperation of the solvent under reduced pressure, the crude product was purified by short column chromatography on silica gel (hexane–EtOAc, 5:95) to provide the product in 78% yield as viscous colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (s, 3 H), 2.36 (s, 3 H), 2.60 (s, 2 H), 3.25–3.38 (m, 1 H), 3.71–3.81 (m, 1 H), 3.74 (s, 3 H), 4.07–4.15 (m, 1 H), 4.81 (s, 1 H), 7.03–7.53 (m, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.04, 39.66, 47.49, 49.65, 53.02, 59.33, 67.95, 104.52, 109.70, 118.91, 119.12, 121.26, 127.36, 128.51, 128.72, 132.08, 137.01, 138.46, 174.93. MS: *m/z* = 346.85 [M$^+$]. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 76.08; H, 6.62; N, 8.06. Found: C, 76.00; H, 6.57; N, 8.14.