First Example of C-3 Alkylation of Indoles with Activated Azetidines Catalyzed by Indium(III) Bromide

J. S. Yadav,* B. V. Subba Reddy, G. Narasimhulu, G. Satheesh

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India
Fax +91(40)27160512; E-mail: yadavpub@iict.res.in

Received 22 September 2009

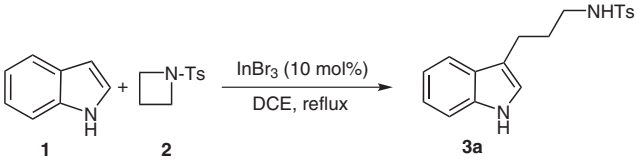
Abstract: Indoles undergo smooth alkylation with *N*-tosylazetidines in the presence of indium(III) bromide in dichloroethane under mild conditions to produce the corresponding C-3 substituted indole derivatives in good to high yields and with high selectivity. This is the first report on the alkylation of indoles with activated azetidines.

Key words: indoles, indium(III) bromide, activated azetidine, C-3 alkylation

The indole nucleus is one of the most relevant structures in medicinal chemistry.[1] Substituted indoles are widely found in nature and are considered as 'privileged scaffolds' since they are capable of binding to many receptors with high affinity.[2] Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years.[3,4] In particular, 3-substituted indoles are important building blocks for the synthesis of various biologically active molecules. Consequently, there is a continuing interest in the development of improved methods for the synthesis of 3-substituted indoles.[5,6] Particular focus is devoted to developing new methods to couple indoles and pyrroles with various electrophiles such as electron-deficient systems, aziridines, enol ethers, cyclic acetals, and allylic acetates.[5–7] However, there have been no previous reports on the C-3 alkylation of indoles with azetidines.

Recently, indium tribromide has received increasing attention as a water-tolerant, green Lewis acid catalyst for organic synthesis demonstrating highly chemo-, regio-, and stereoselective results.[8] Compared to conventional Lewis acids, it has advantages of water stability, recyclability, operational simplicity, strong tolerance to oxygen, and nitrogen-containing substrates and functional groups, and it can often be used in catalytic amounts.[9]

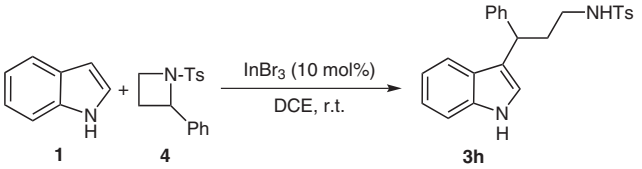
Following our interest in catalytic uses of indium tribromide,[10,11] we herein report a novel method for the C-3 alkylation of indoles with *N*-azetidines using a catalytic amount of $InBr_3$ under mild conditions. We first attempted the coupling of indole (**1**) with *N*-tosylazetidine (**2**). The reaction was carried out using 10 mol% anhydrous $InBr_3$ in dichloroethane, and went to completion in 4.5 hours at reflux temperature giving product *N*-(3-1*H*-indol-3-yl)propyl-4-methylbenzenesulfonamide (**3a**) in 80% yield (Scheme 1).



Scheme 1

Similarly, *N*-tosylazetidine reacted smoothly with various other indoles such as 5-bromo-, 2-methyl-, 7-ethyl-, 5-methyl-, and 2-ethoxycarbonyl derivatives to produce the corresponding C-3 alkyl indoles (entries 2–6, Table 1).

In addition, *N*-ethylindole also participated in this reaction (entry 7, Table 1). This result provided incentive for further studies with other substituted azetidines. Interestingly, 2-phenyl-*N*-tosylazetidine also participated well in this reaction. For example, treatment of indole (**1**) with 2-phenyl-*N*-tosylazetidine (**4**) in the presence of 10 mol% $InBr_3$ at room temperature gave *N*-(3-1*H*-indol-3-yl)-3-phenylpropyl)-4-methylbenzenesulfonamide (**3h**) in 82% yield (Scheme 2).

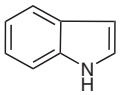
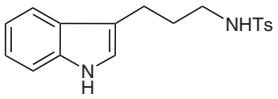
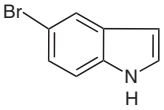
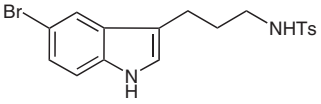
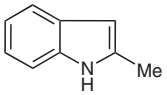
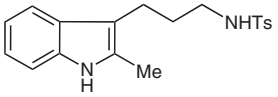
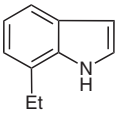
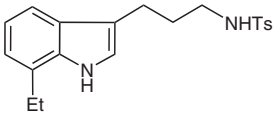
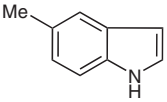
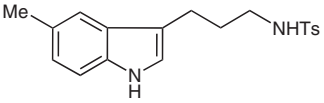
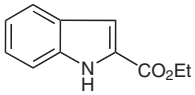
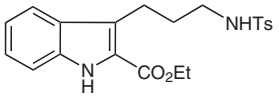
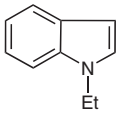
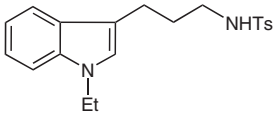
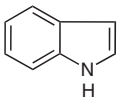
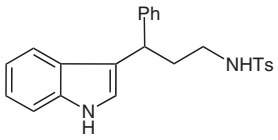
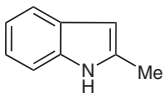
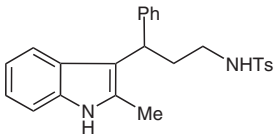
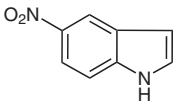
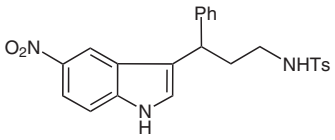
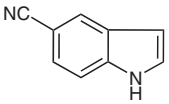
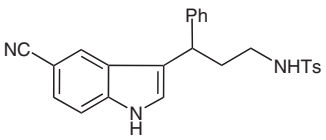
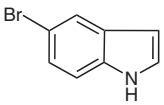
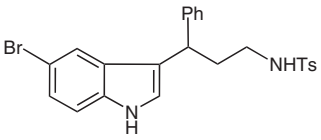


Scheme 2

In the case of 2-phenyl-*N*-tosylazetidine, the corresponding ring-opened product **3h** was obtained by preferential attack of indole at the benzylic position (entries 8–11, Table 1). Because of the stability of the benzylic carbocation, the ring-opening of azetidine is highly regioselective (entries 8–11, Table 1). Both electron-rich as well as electron-deficient indoles reacted effectively with *N*-tosylazetidines under these reaction conditions. In the absence of catalyst, the reaction failed to give the desired product. The products were characterized by NMR and IR spectroscopy and mass spectrometry. The advantages of this procedure include mild conditions as well as convenience and easy workup. This method is effective even with unprotected indoles. There was no considerable difference in

SYNLETT 2009, No. 5, pp 0727–0730
Advanced online publication: 26.2.2009
DOI: 10.1055/s-0028-1087957; Art ID: D33408ST

Table 1 C-3 Alkylation of Indoles with *N*-Tosylazetidines

Entry	Indole	Azetidine	Product[a]	Time (h)	Yield (%)[b]
1				4.5	80
2				6.0	75
3				5.0	80
4				5.0	74
5				4.5	80
6				5.5	70
7				4.0	80
8				2.0	82
9				1.5	84
9				3.0	73
10				2.5	74
11				2.0	78

[a] Products were characterized by MS, ^{1}H NMR, and IR spectroscopy.
[b] Yield refers to pure products after chromatography.

yields when comparing protected and unprotected indoles. No bisindoles were formed under these conditions. As solvent, dichloroethane appeared to give the best results. No bromination of indole was observed under the reaction conditions. The effects of various Lewis acids such as $InCl_3$, $InBr_3$, $ZrCl_4$, $BiCl_3$, $YbCl_3$, YCl_3, $SmCl_3$,

and $CeCl_3 \cdot 7H_2O$ were tested for this conversion. Of these catalysts, anhydrous $InBr_3$ was found to be the most effective in terms of conversion. Various metal triflates such as $Bi(OTf)_3$, $In(OTf)_3$, $Sm(OTf)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$ were found to be ineffective for this transformation. Various indium(III) reagents such as $InBr_3$, $InCl_3$, $In(OTf)_3$, and $In(ClO_4)_3$ were also screened for this conversion. Of these catalysts, indium tribromide was found to be most effective in terms of conversion and selectivity. For example, treatment of indole (**1**) with *N*-tosylazetidine (**2**) in the presence of 10 mol% of $InBr_3$ and 10 mol% of $InCl_3$ for 4.5 hours in refluxing dichloroethane afforded **3a** in 80% and 71% yields, respectively. The scope and generality of this process is illustrated in Table 1.[12]

In summary, anhydrous $InBr_3$ has proved to be a useful and highly efficient catalyst for the C-3 alkylation of indoles via ring opening of activated azetidines under mild conditions. In addition to its simplicity and efficiency, this method produces 3-alkylindoles in good yields. This method provides an access to a wide range of potentially valuable homotriptamine derivatives which will find extensive applications in organic synthesis.

Acknowledgment

G.N. and G.S. thank CSIR, New Delhi for the award of fellowships.

References and Notes

(1) (a) Sundberg, R. J. *Indoles*; Academic Press: San Diego, **1996**. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49. (c) Ninomiya, I. *J. Nat. Prod.* **1992**, *55*, 541.

(2) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Bird, C. W., Eds.; Pergamon Press: Oxford, **1996**, 207. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (d) Tois, J.; Franzen, R.; Koskinen, A. *Tetrahedron* **2003**, *59*, 5395.

(3) (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 550. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (c) Jensen, K. B.; Thorhange, J.; Hazel, R. G.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 160.

(4) (a) Yoshiaki, N.; Masato, Y.; Youichi, I.; Masnobu, H.; Sakae, U. *J. Am. Chem. Soc.* **2002**, *124*, 11846. (b) Wenkert, E.; Angell, E. C.; Ferreira, V. F.; Michelotti, E. L.; Piettre, S. R.; Sheu, J. H.; Swindell, C. S. *J. Org. Chem.* **1986**, *51*, 2343. (c) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199.

(5) (a) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109. (b) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594. (c) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165. (d) Yadav, J. S.; Reddy, B. V. S.; Singh, A. P.; Basak, A. K. *Tetrahedron Lett.* **2007**, *48*, 4169.

(6) (a) Campos, K. R.; Woo, J. C. S.; Lee, S.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 79. (b) Hong, K. B.; Lee, C. W.; Yum, E. K. *Tetrahedron Lett.* **2004**, *45*, 693. (c) Kohling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett.* **2003**, *5*, 3213. (d) Arcadi, A.; Bianchi, G.; Chiarini, M.; Anniballe, G.; Marinelli, F. *Synlett* **2004**, *6*, 944. (e) Yadav, J. S.; Reddy, B. V. S.; Aravind, S.; Narayana Kumar, G. G. K. S.; Srinivas Reddy, A. *Tetrahedron Lett.* **2007**, *48*, 6117.

(7) (a) Nenajdenko, V. G.; Karpov, A. S.; Balenkova, E. S. *Tetrahedron: Asymmetry* **2001**, *12*, 2517. (b) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Prabhakar, A.; Kunwar, A. C. *Tetrahedron Lett.* **2003**, *44*, 2221. (c) Yadav, J. S.; Reddy, B. V. S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* **2002**, *43*, 1565. (d) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G. *Tetrahedron Lett.* **2004**, *45*, 3673.

(8) (a) Zang, Z. H. *Synlett* **2005**, 711. (b) Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2005**, *46*, 6407.

(9) (a) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126. (b) Huang, J.-M.; Wong, C.-M.; Xu, F.-X.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 3375. (c) Harada, S.; Takita, R.; Ohshima, T.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2007**, 948.

(10) (a) Yadav, J. S.; Reddy, B. V. S.; Rao, K. V.; Raj, K. S.; Prasad, A. R.; Kumar, S. K.; Kunwar, A. C.; Jayaprakash, P. J.; Jagannath, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 5198. (b) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M. *Synlett* **2001**, 1781. (c) Yadav, J. S.; Reddy, B. V. S.; Baishya, G. *Synlett* **2003**, 396. (d) Yadav, J. S.; Reddy, B. V. S.; Swamy, T. *Synthesis* **2004**, 106.

(11) (a) Yadav, J. S.; Reddy, B. V. S.; Krishna, A. D.; Swamy, T. *Tetrahedron Lett.* **2003**, *44*, 6055. (b) Yadav, J. S.; Reddy, B. V. S.; Gakul, B. *Green Chem.* **2003**, *5*, 264. (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Parimala, G. *Synthesis* **2003**, 2390.

(12) **General Procedure**

To a stirred solution of indole (1 mmol) in DCE (3 mL) were added the *N*-tosylazetidine (1 mmol) and $InBr_3$ (0.1 mmol). The resulting mixture was stirred at reflux temperature for the appropriate time (Table 1).

After complete conversion as indicated by TLC, the solvent was removed by evaporation, and the residue was diluted with H_2O and extracted with EtOAc (2×10 mL). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The resulting product was purified by column chromatography on SiO_2 (Merck, 100–200 mesh) using EtOAc–hexane (3:7) as eluent to afford pure 3-alkenyl indole derivative.

Spectroscopic Data for Selected Products

***N*-1-[3-(1*H*-3-indolyl)propyl]-4-methyl-1-benzenesulfonamide (3a)**

Semisolid. IR (KBr): ν_{max} = 3405, 3054, 2923, 2853, 1598, 1455, 1322, 1156, 1091, 813, 771, 745 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.71–1.85 (m, 2 H), 2.38 (s, 3 H), 2.72 (t, *J* = 6.6 Hz, 2 H), 2.94 (q, *J* = 6.6 Hz, 2 H), 4.74 (br s, 1 H, NH), 6.85–7.30 (m, 6 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 2 H), 7.88 (br s, 1 H, ArNH). LC-MS: *m/z* = 351 [M + Na], 169, 139. HRMS: *m/z* calcd for $C_{18}H_{20}N_2O_2NaS$: 351.1143; found: 351.1131.

***N*-1-[3-(2-Methyl-1*H*-3-indolyl)propyl]-4-methyl-1-benzenesulfonamide (3c)**

Solid; mp 107–109 °C. IR (KBr): ν_{max} = 3397, 3290, 3054, 2923, 2856, 1596, 1462, 1322, 1156, 1091, 814, 745 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.65–1.72 (m, 2 H), 2.25 (s, 3 H), 2.40 (s, 3 H), 2.65 (t, *J* = 6.6 Hz, 2 H), 2.87 (q, *J* = 6.6 Hz, 2 H), 4.65 (t, *J* = 6.6 Hz, 1 H), 6.89–7.07 (m, 2 H), 7.10–7.30 (m, 4 H), 7.60 (d, *J* = 8.0 Hz, 2 H), 7.73 (br s, 1 H, ArNH): LC-MS: *m/z* = 381 [M + K], 365 [M + Na], 242, 197, 169, 139. HRMS: *m/z* calcd for $C_{19}H_{22}N_2O_2KS$: 381.1039; found: 381.1043.

***N*-1-[3-(2-Methyl-1*H*-3-indolyl)-3-phenylpropyl]-4-methyl-1-benzenesulfonamide (3i)**

Solid: mp 76–78 °C. IR (KBr): ν_{max} = 3380, 3026, 2924, 2855, 1601, 1457, 1323, 1156, 1092, 813, 753 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.30–2.35 (m, 2 H), 2.38 (s, 3 H), 2.84 (t, *J* = 5.2 Hz, 2 H), 4.23 (dd, *J* = 6.4, 9.4 Hz, 1 H), 4.57 (t, *J* = 6.0 Hz, 1 H), 6.85–7.24 (m, 10 H), 7.28 (d, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 8.3 Hz, 2 H), 7.84 (br s, 1 H, ArNH). LC-MS: *m/z* = 441 [M + Na], 139, 111. HRMS: *m/z* calcd for $C_{25}H_{26}N_2O_2NaS$: 441.1612; found: 441.1619.