IBX: A Novel and Versatile Oxidant for Electrophilic Thiocyanation of Indoles, Pyrrole and Arylamines

Jhillu S. Yadav,* Basi V. Subba Reddy, B. Bala Murali Krishna

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India
Fax 0091 40 27160512; E-mail: yadav@iict.res.in

Received 17 June 2008; revised 16 August 2008

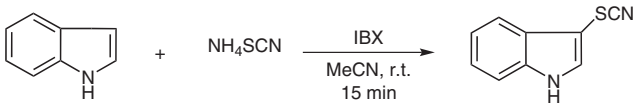
Abstract: The direct thiocyanation of indoles and pyrrole with ammonium thiocyanate has been achieved using *o*-iodoxybenzoic acid (IBX) under mild and neutral conditions to produce indol-3-yl and pyrrol-2-yl thiocyanates, respectively, in excellent yields and with high selectivity. This method is effective even with N-substituted arylamines for the preparation of aryl thiocyanates.

Key words: *o*-iodoxybenzoic acid, electrophilic substitution, indoles, aryl thiocyanates, heteroaryl thiocyanates

The electrophilic thiocyanation of aromatics and heteroaromatics is an important carbon–heteroatom bond-forming reaction in organic synthesis.[1] Aryl and heteroaryl thiocyanates are useful intermediates in the synthesis of sulfur-containing heterocycles.[2] They are useful building blocks for drugs and pharmaceuticals.[2b] In particular, aryl thiocyanates can be easily transformed into various sulfur-containing functional groups such as thiophenols, by reduction with lithium aluminum hydride, and aryl nitriles/disulfides, by aromatic Grignard reagents.[3] The thiocyanate functionality is used as a masked mercapto group. Thus, the direct thiocyanation of aromatic systems is of prime importance. Generally, aryl/heteroaryl thiocyanates have been prepared by electrophilic thiocyanation.[4] In contrast, only few reagents such as *N*-halosuccinimides, cerium(IV) ammonium nitrate, acidic K10 clay, iodine/methanol, iron(III) chloride, and Oxone have been utilized for the thiocyanation of indoles.[5,6] However, many of them require a large excess of strong oxidizing agents and toxic metal thiocyanates and often involve low conversions, especially in case of arylamines. Furthermore, some require high temperatures to obtain satisfactory results. In view of the versatility of the thiocyanate group in the fields of drugs and pharmaceuticals, the development of mild, convenient, and highly yielding protocols is desirable.

Recently, the use of hypervalent iodine reagents as oxidants in organic synthesis has attracted increasing interest due to their mild, selective, and environmentally benign oxidizing properties.[7] *o*-Iodoxybenzoic acid (IBX) is one of the most versatile oxidizing agents due its high efficiency, easy availability, mild reaction conditions, and its stability to moisture and air.[8] Wide functional group tolerance and high yielding reactions without over oxidation have made the use of IBX common for the oxidation of alcohols even in the presence of alkenes, sulfides, and amino groups[9] and in other elegant oxidative transformations.[10] Furthermore, there have been no examples of the use of IBX for the electrophilic thiocyanation of indoles.

In this article, we report a direct and metal-free approach to the thiocyanation of indoles, pyrrole, and arylamines using IBX in acetonitrile. First, we attempted electrophilic thiocyanation of 1*H*-indole (**1a**) with ammonium thiocyanate (**2**) using a stoichiometric amount of IBX. The reaction went to completion within 15 minutes at room temperature and the desired product, 3-thiocyanato-1*H*-indole (**3a**), was obtained in 95% yield (Table 1, entry 1; Scheme 1).



1a **2** **3a** 95%

Scheme 1

This result provided an incentive to study further reactions with various indoles. Interestingly, several substituted indoles, such as 2-methyl- **1b**, 7-ethyl- **1c**, 5-methoxy- **1d**, 5-nitro- **1e**, and 5-bromo-1*H*-indole (**1f**) reacted effectively with ammonium thiocyanate (**2**) to furnish the corresponding 3-thiocyanatoindole derivatives **3b–f** (Table 1, entries 2–6). In addition, N-protected indoles, such as 1-benzyl- **1g** and 1-ethyl-2-phenyl-1*H*-indole (**1h**) also participated in this reaction (Table 1, entries 7 and 8). Like indoles, 1*H*-pyrrole (**1i**) was also easily transformed into the monothiocyanato pyrrole **3i** using this procedure. In this case, substitution took place at the 2-position (Table 1, entry 9); no bis-thiocyanation was observed. Next, we examined the reactivity of N-substituted arylamines in the thiocyanation. Interestingly, *N*-alkylanilines such as *N*-methyl- **1j**, *N*-ethyl- **1k**, *N*-benzyl- **1l**, *N*,*N*-dimethyl- **1m**, and *N*,*N*-diethylaniline (**1n**) underwent smooth electrophilic thiocyanation under similar reaction conditions to produce 4-thiocyanatoanilines (Table 1, entries 10–14).

In all cases, the reactions took place rapidly at room temperature with high regioselectivity. As the solvent, acetonitrile appeared to give the best results. No oxidation of indole was observed under the reaction conditions. The

SYNTHESIS 2008, No. 23, pp 3779–3782
Advanced online publication: 06.11.2008
DOI: 10.1055/s-0028-1083636; Art ID: Z14008SS

products were characterized by ^{1}H NMR, IR, and mass spectrometry and also by comparison with authentic samples.[5,6] Mechanistically, the reaction may proceed via the electrophilic substitution of indole by thiocyanogen ($^+$SCN) formed in situ from IBX and ammonium thiocyanate (Scheme 2).

Table 1 IBX-Promoted Thiocyanation of Indoles, Pyrrole, and Arylamines with Ammonium Thiocyanate

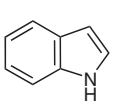
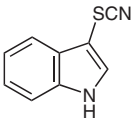
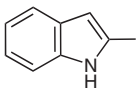
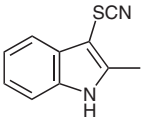
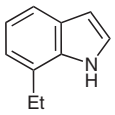
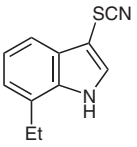
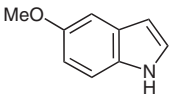
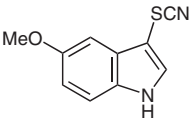
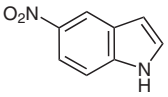
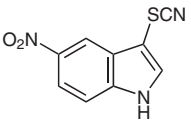
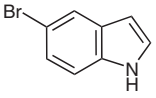
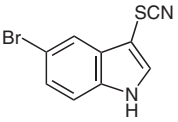
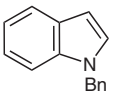
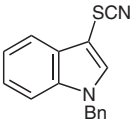
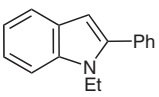
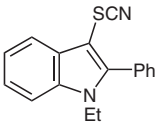
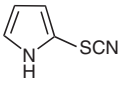
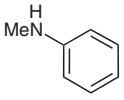
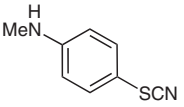
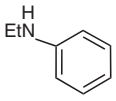
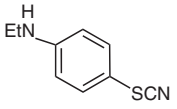
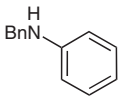
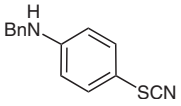
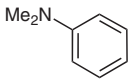
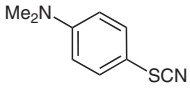
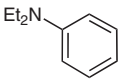
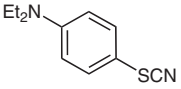
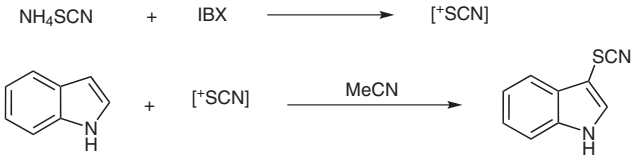
Entry	Substrate	Product[a]		Time (min)	Yield[b] (%)
1		**1a**		**3a**	10	95
2		**1b**		**3b**	5	91
3		**1c**		**3c**	10	94
4		**1d**		**3d**	5	91
5		**1e**		**3e**	20	85
6		**1f**		**3f**	15	90
7		**1g**		**3g**	10	95
8		**1h**		**3h**	15	90
9		**1i**		**3i**	10	84
10		**1j**		**3j**	10	92
11		**1k**		**3k**	10	95

Table 1 IBX-Promoted Thiocyanation of Indoles, Pyrrole, and Arylamines with Ammonium Thiocyanate (continued)

Entry	Substrate	Product[a]		Time (min)	Yield[b] (%)
12		**1l**		**3l**	10	90
13		**1m**		**3m**	10	95
14		**1n**		**3n**	10	93

[a] The products were characterized by NMR, IR, and MS.
[b] Yield refers to pure products after purification.



Scheme 2

The scope and generality of this process is illustrated with respect to various indoles, pyrrole, and arylamines and the results are presented in Table 1. The effects of various oxidizing agents, such as Dess–Martin periodinane, (diacetoxyiodo)benzene, iodine/methanol, Oxone/methanol, and iron(III) chloride, were assessed in the thiocyanation of indole. Of these reagents, IBX was found to be the most effective oxidant in terms of conversion and reaction time.

In conclusion, IBX has proved to be an effective reagent for the electrophilic thiocyanation of indoles, pyrrole, and arylamines under extremely mild and neutral conditions. In addition to its simplicity and efficiency, this method affords the desired thiocyanates in excellent yields in short reaction times. This method can be used for the thiocyanation of even deactivated indoles in an efficient manner. This method provides a direct access to a wide range of heteroaryl thiocyanates.

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H and ^{13}C NMR spectra were recorded on Gemini-200 spectrometer (200 MHz) in $CDCl_3$ using TMS as an internal standard. MS were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed using E. Merck 60–120, mesh silica gel.

Thiocyanates 3; General Procedure

To a stirred soln of indole, pyrrole, or arylamine (1 mmol) and NH_4SCN (**2**, 2 mmol) in MeCN (10 mL), IBX (1.0 mmol) was added and the resulting mixture was stirred at r.t. for the appropriate time (Table 1). After completion of the reaction (TLC), the mixture was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried (anhyd Na_2SO_4),

concentrated in vacuo, and purified by column chromatography (silica gel, Merck, 60–120 mesh, EtOAc–hexane, 0.5:9.5) to furnish pure thiocyanate derivatives **3**.

3-Thiocyanato-1*H*-indole (3a)[5c]
Solid; mp 126–128 °C.

IR (KBr): 3343, 3043, 2920, 2157, 1413, 1233, 735, 663, 590 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.19–7.40 (m, 4 H), 7.73 (d, *J* = 8.1 Hz, 1 H), 9.0 (br s, 1 H, NH).

LC-MS: *m*/*z* = 197 [M + Na], 133, 113, 102, 59.3.

2-Methyl-3-thiocyanato-1*H*-indole (3b)
Solid; mp 104–106 °C.

IR (KBr): 3323, 2922, 2644, 2153, 1676, 1404, 740, 658, 549 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 7.15–7.38 (m, 3 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 8.45 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.9, 135.0, 128.6, 122.9, 121.5, 117.9, 112.0, 111.1, 29.6, 11.9.

LC-MS: *m*/*z* = 189 [M + 1], 179, 162, 131, 89, 59.3.

7-Ethyl-3-thiocyanato-1*H*-indole (3c)
Solid; mp 134–136 °C.

IR (KBr): 3305, 3109, 2965, 2930, 2155, 1421, 1123, 742, 593 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$, DMSO): δ = 1.35 (t, *J* = 7.3 Hz, 3 H), 2.92 (q, *J* = 7.3 Hz, 2 H), 7.05–7.20 (m, 2 H), 7.54 (d, *J* = 8.1 Hz, 1 H), 7.67 (s, 1 H), 11.70 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$, DMSO): δ = 134.2, 130.8, 127.4, 126.5, 120.6, 120.3, 114.5, 110.9, 88.9, 22.7, 13.2.

LC-MS: *m*/*z* = 225 [M + Na], 198, 155, 97.

5-Methoxy-3-thiocyanato-1*H*-indole (3d)
Solid; mp 124–126 °C.

IR (KBr): 3304, 3132, 2152, 1624, 1582, 1485, 1452, 1291, 1201, 1017, 803, 706 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 6.92 (d, *J* = 9.0 Hz, 1 H), 7.17 (d, *J* = 2.7 Hz, 1 H), 7.27 (d, *J* = 9.0 Hz, 1 H), 7.42 (d, *J* = 2.7 Hz, 1 H), 8.75 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 131.5, 130.7, 128.4, 114.4, 113.0, 112.2, 99.6, 91.1, 55.7.

LC-MS: *m*/*z* = 205 [M + 1], 181, 160, 141.

5-Nitro-3-thiocyanato-1*H*-indole (3e)[6a]
Solid; mp 206–208 °C.

IR (KBr): 3854, 3747, 3360, 2855, 2159, 1651, 1327, 1075, 660 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$, DMSO): δ = 7.63 (d, *J* = 8.5 Hz, 1 H), 7.93 (d, *J* = 1.5 Hz, 1 H), 8.13 (d, *J* = 8.5 Hz, 1 H), 8.61 (d, *J* = 1.0 Hz, 1 H), 12.43 (br s, 1 H, NH).

LC-MS: *m*/*z* = 242 [M + Na], 205, 133, 102, 85, 59.

5-Bromo-3-thiocyanato-1*H*-indole (3f)
Solid; mp 126–128 °C.

IR (KBr): 3310, 2924, 2855, 2640, 2362, 2152, 1679, 1576, 1265, 736, 673 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$, DMSO): δ = 7.31 (dd, *J* = 8.8, 1.4 Hz, 1 H), 7.40 (d, *J* = 8.8 Hz, 1 H), 7.69 (d, *J* = 2.9 Hz, 1 H), 7.81 (d, *J* = 1.4 Hz, 1 H), 11.86 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 92.3, 112.8, 114.1, 116.2, 121.9, 127.6, 130.4, 131.6, 137.2.

LC-MS: *m*/*z* = 276 [M + Na], 173, 146, 114, 59.

1-Benzyl-3-thiocyanato-1*H*-indole (3g)[6c]
Solid; mp 83–85 °C.

IR (KBr): 3431, 3119, 2926, 2149, 1509, 1450, 735 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.30 (s, 2 H), 7.09 (d, *J* = 6.8 Hz, 2 H), 7.21–7.38 (m, 6 H), 7.40 (s, 1 H), 7.80 (d, *J* = 6.8 Hz, 1 H).

LC-MS: *m*/*z* = 265 [M + 1], 227, 208, 197.

1-Ethyl-2-phenyl-3-thiocyanato-1*H*-indole (3h)
Solid; mp 108–110 °C.

IR (KBr): 3446, 3061, 2968, 2147, 1466, 1338, 745, 698, 616 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.3 Hz, 3 H), 4.18 (q, *J* = 7.3 Hz, 2 H), 7.30–7.81 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.1, 136.0, 130.5, 129.7, 129.5, 128.8, 123.5, 121.9, 119.1, 110.6, 39.8, 15.4.

LC-MS: *m*/*z* = 279 [M + 1], 252, 222, 102, 81.

2-Thiocyanato-1*H*-pyrrole (3i)
Liquid.

IR (neat): 3276, 3105, 1596, 1506, 1303, 815, 590 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 6.21 (m, 1 H), 6.59 (m, 1 H), 6.91 (m, 1 H), 9.22 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.1, 120.1, 111.1, 110.9, 102.6.

LC-MS: *m*/*z* = 125 [M + 1], 99, 66.

***N*-Methyl-4-thiocyanatoaniline (3j)**
Liquid.

IR (neat): 3412, 2893, 2819, 2150, 1596, 1513, 1329, 1183, 818, 673, 523 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$, DMSO): δ = 2.81 (s, 3 H), 4.03 (br s, 1 H, NH), 6.50 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.9, 134.2, 112.9, 112.6, 106.2, 29.6.

LC-MS: *m*/*z* = 165 [M + 1].

***N*-Ethyl-4-thiocyanatoaniline (3k)**
Solid; mp 52–54 °C.

IR (KBr): 3389, 2962, 2925, 2151, 1675, 1596, 1264, 736, 547 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 3.16 (q, *J* = 7.1 Hz, 2 H), 3.91 (br s, 1 H, NH), 6.52 (d, *J* = 8.6 Hz, 2 H), 7.36 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 134.6, 113.5, 112.6, 107.0, 37.9, 14.4.

MS (EI): *m*/*z* = 178 [M^+], 164, 150.

***N*-Benzyl-4-thiocyanatoaniline (3l)**
Solid; mp 68–70 °C.

IR (KBr): 3446, 2920, 2855, 2841, 2141, 1588, 1371, 1077, 805, 515 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 4.33 (s, 2 H), 4.38 (br s, 1 H, NH), 6.57 (d, *J* = 8.5 Hz, 2 H), 7.24–7.36 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.8, 138.1, 134.4, 128.6, 127.3, 127.1, 113.8, 112.4, 107.6, 47.4.

LC-MS: *m*/*z* = 241 [M + 1], 201, 181, 145, 122.

***N*,*N*-Dimethyl-4-thiocyanatoaniline (3m)**
Solid; mp 73–75 °C.

IR (KBr): 2972, 2931, 2151, 1591, 1507, 1271, 1196, 810, 670, 517 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.02 (s, 6 H), 6.65 (d, *J* = 8.6 Hz, 2 H), 7.41 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 134.2, 112.9, 112.4, 106.2, 40.0.

LC-MS: *m*/*z* = 178 [M$^+$], 153, 140, 92, 47.

***N*,*N*-Diethyl-4-thiocyanatoaniline (3n)**
Liquid.

IR (neat): 3405, 3061, 2923, 2853, 2150, 1593, 1590, 1330, 816, 697, 522 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 6.7 Hz, 6 H), 3.37 (q, *J* = 6.7 Hz, 4 H), 6.61 (d, *J* = 9.0 Hz, 2 H), 7.37 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.2, 134.8, 112.5, 104.8, 44.4, 12.3.

MS (EI): *m*/*z* = 206 [M$^+$], 191, 164, 137.

Acknowledgment

B.B.M.K. thanks CSIR, New Delhi for the award of a fellowship.

References

(1) Wood, J. L. *Org. React.* **1967**, *3*, 240.
(2) (a) Erian, A. W.; Sherif, S. M. *Tetrahedron* **1999**, *55*, 7957. (b) Guy, R. G. *The Chemistry of Cyanates and their Thio Derivatives*, Part 2; Patai, S., Ed.; John Wiley & Sons: New York, **1977**, Chap. 18, 819.
(3) (a) Toste, F. D.; Laronde, F.; Still, W. J. *Tetrahedron Lett.* **1995**, *36*, 2949. (b) Grant, M. S.; Snyder, H. R. *J. Am. Chem. Soc.* **1960**, *82*, 2742.
(4) (a) Kita, Y.; Takeda, T.; Mihara, S.; Whelan, B. A.; Thoma, H. *J. Org. Chem.* **1995**, *60*, 7144. (b) Kelly, T. R.; Kim, M. H.; Curtis, A. D. M. *J. Org. Chem.* **1993**, *58*, 5855.
(5) (a) Toste, F. D.; De Stefano, V.; Still, I. W. Jr. *Synth. Commun.* **1995**, *25*, 1277. (b) Nair, V.; George, T. G.; Nair, L. G.; Panicker, S. B. *Tetrahedron Lett.* **1999**, *40*, 1195. (c) Wu, G.; Liu, Q.; Shen, Y.; Wu, W.; Wu, L. *Tetrahedron Lett.* **2005**, *46*, 5831.
(6) (a) Chakrabarty, M.; Sarkar, S. *Tetrahedron Lett.* **2003**, *44*, 8131. (b) Yadav, J. S.; Reddy, B. V. S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* **2004**, *45*, 2951. (c) Yadav, J. S.; Reddy, B. V. S.; Krishna, A. D.; Reddy, Ch. S.; Narsaiah, A. V. *Synthesis* **2005**, 540.
(7) (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, **1997**. (b) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271.
(8) (a) Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (c) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409.
(9) Wirth, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 2812.
(10) (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 993. (b) Nicolaou, K. C.; Barn, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233.