Ferric(III) Chloride-Promoted Electrophilic Thiocyanation of Aromatic and Heteroaromatic Compounds[1]

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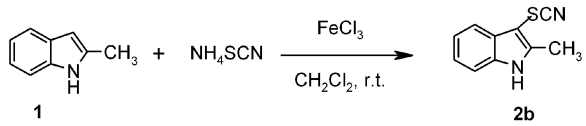
Abstract: Indoles, oxindoles and aromatic amino compounds undergo smooth thiocyanation with ammonium thiocyanate in the presence of anhydrous $FeCl_3$ in dichloromethane under mild conditions to afford the corresponding 3-indolyl and 4-aryl thiocyanates, respectively, in high yields with excellent selectivity. The use of ferric chloride makes it quite simple, more convenient and practical. This new method offers several advantages such as high conversions, cleaner reaction profiles, short reaction times, and the use of inexpensive and readily available catalyst.

Key words: thiocyanation, electrophilic substitution, aromatic systems, aryl thiocyanates

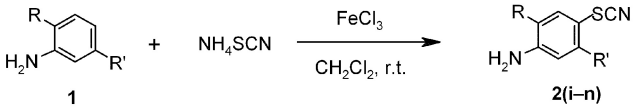
The electrophilic thiocyanation of aromatics and heteroaromatics is an important carbon–heteroatom bond formation in organic synthesis.[2] Aryl or heteroaryl thiocyanates are useful intermediates in the synthesis of sulfur containing heterocycles.[2a,3] Furthermore, aryl thiocyanates can be easily transformed into various sulfur functional groups[4] such as thiophenols by reduction with lithium aluminum hydride and aryl nitriles/disulfides by aromatic Grignard reagents. Thus, the direct thiocyanation of aromatic systems is of importance. Consequently, several methods have been developed for the thiocyanation of arenes using a variety of reagents under various reaction conditions.[2,5] In contrast, only a limited number of reagents such as *N*-halosuccinimides (NCS or NBS), ceric ammonium nitrate (CAN) and acidic K-10 clay have been reported for the thiocyanation of indoles.[6,7] However, many of these methods involve the use of strongly acidic or oxidizing conditions and toxic metal thiocyanates and permit only low conversions, especially in case of arylamines. Furthermore, some require high temperatures to obtain satisfactory results. Since organosulfur compounds have become increasingly useful and important in the field of drugs and pharmaceuticals, the development of simple, convenient and efficient approaches are desirable. Recently, $FeCl_3$ has emerged as a potential catalyst in effecting various organic transformations due to its high catalytic ability, ease of handling, economic viability, experimental simplicity and easy availability.[8]

In this article, we wish to disclose a simple, convenient and efficient protocol for the thiocyanation of indoles, oxindoles and arylamines using anhydrous $FeCl_3$ as an inexpensive and readily available catalyst. Initially, we have attempted the electrophilic thiocyanation of 2-methylindole (**1**) as a model substrate with two equivalents of ammonium thiocyanate using anhydrous $FeCl_3$ as novel oxidant. The reaction went to completion within three hours at room temperature and the product, 3-thiocyanatoindole (**2b**), was obtained in 92% yield (Scheme 1, Table 1, entry **b**).



Scheme 1

The high accelerating activity of $FeCl_3$ in the thiocyanation of 2-methylindole (**1**) encouraged us to study it in reactions with other indoles and arylamines. Interestingly, various substituted indoles, such as 5-methoxy-, 1-ethyl-2-phenyl, and *N*-benzylindole reacted efficiently with ammonium thiocyanate to afford the corresponding 3-thiocyanatoindole derivatives (Table 1, entries **a**–**e**). Like indoles, *N*-methyloxindole, *N*-benzyloxindole and isatin also worked well under similar conditions to give 5-thiocyanato derivatives (Table 1, entries **f**–**h**). Interestingly, the non-activated compound *N*-acetylindole (entry **o**) was also converted to the corresponding derivative in good yield. Moreover, treatment of arylamines such as aniline, 2-cholro-3-methylaniline, *N*,*N*-dimethylaniline, *N*-ethylaniline, 3-nitroaniline and 2,5-dichloroaniline with ammonium thiocyanate in the presence of anhydrous $FeCl_3$ resulted also in the formation of aryl thiocyanates in high yields (entries **i**–**n**, Table 1, Scheme 2).



Scheme 2

In the case of arylamines, the products were obtained with high *para*-selectivity. In all cases, the reactions proceeded smoothly at room temperature with high regioselectivity. The products were characterized by ^{1}H NMR, IR and mass spectroscopic data and also by comparison with authentic samples.[6,7] In the absence of catalyst, the reaction

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did not take place even after long reaction times (5–12 h). As solvent, dichloromethane appeared to give the best results. This method is very clean and free from side products. The efficacy of various oxidants such as DDQ, $Mn(OAc)_3 \cdot 2H_2O$, $Bi(NO_3)_3 \cdot 5H_2O$ and $PhI(OAc)_2$ was studied for this transformation. Among these reagents, anhydrous $FeCl_3$ was found to be a better catalyst in terms of mildness of the procedure, experimental simplicity, economic viability, and high degree of selectivity. No reaction was observed between indole and ammonium thiocyanate when other metal halides such as $InCl_3$, $ZrCl_4$, YCl_3, $BiCl_3$ and $YbCl_3$ were employed as catalysts. Similarly, metal triflates such as $Sc(OTf)_3$, $Yb(OTf)_3$, $In(OTf)_3$ and $Bi(OTf)_3$ also failed to give the desired products. These results clearly indicate that the reaction is successful only with anhydrous $FeCl_3$. Compared to conventional methods, high conversions were achieved by using this procedure. For example, treatment of indole with two equivalents of ammonium thiocyanate in the presence of 1.5 equivalents of $FeCl_3$ for four hours afforded the corresponding 3-thiocyanatoindole (**2a**) in 89% yield, whereas the same reaction using 1.5 equivalents of NBS after six hours gave the same product in 60% yield along with 5-bromoindole. Furthermore, our synthetic protocol utilizes inexpensive and readily available starting materials. The scope and generality of this process was illustrated with respect to various indoles and arylamines and the results are presented in Table 1.

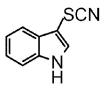
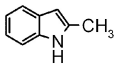
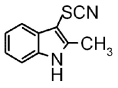
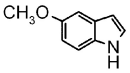
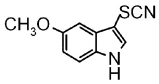
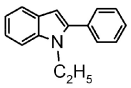
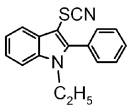
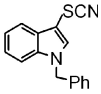
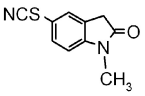
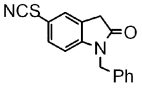
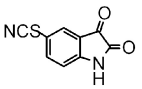
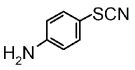
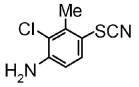
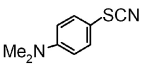
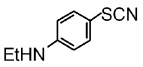
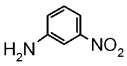
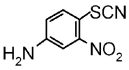
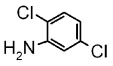
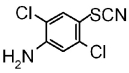
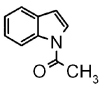
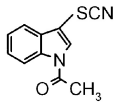
In summary, we have described a simple, convenient and efficient protocol for the thiocyanation of aromatics and heteroaromatics using anhydrous $FeCl_3$ as novel catalyst. The notable features of this procedure are mild reaction conditions, high conversions, greater regioselectivity, economic viability of the reagents and simple experimental/product isolation procedures which make it a useful and attractive alternative process for the preparation of aryl thiocyanates.

Melting points were recorded on a Büchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H and ^{13}C NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. TLC was monitored on 0.25 mm precoated silica gel plates (60F-254).

Thiocyanation of Aromatic and Heteroaromatic Compounds; General Procedure

To a stirred solution of NH_4SCN (1.5 mmol), and $FeCl_3$ (1.5 mmol) in CH_2Cl_2 (10 mL), was added the indole or arylamine (1.0 mmol) slowly and the reaction mixture was allowed to stir at r.t. for the appropriate time (Table 1). After complete conversion as indicated by 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 (Na_2SO_4), and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 1:9) to afford the pure thiocyanato derivative.

Table 1 $FeCl_3$-Promoted Thiocyanation of Heteroaromatic and Aromatic Compounds

Entry	Indole **1**	Product[a] **2**	Time (h)	Yield (%)[b]
a			3.5	86
b			3.0	92
c			4.0	87
d			4.5	85
e			4.0	82
f			5.0	80
g			3.0	85
h			4.5	83
i			4.0	86
j			3.5	82
k			3.0	85
l			3.5	87
m			4.0	80
n			3.5	85
o			5.0	81

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Isolated yields.

3-Thiocyanato-1*H*-indole (2a)
Solid; mp 125–127 °C.

IR (KBr): 3341, 3107, 2924, 2853, 2157, 1618, 1503, 1455, 1217, 758, 668, 589 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.23–7.45 (m, 4 H), 7.80 (d, 1 H, *J* = 8.0 Hz), 8.60 (br s, 1 H, NH).

EIMS: *m*/*z* (%): 174 (M^+, 30), 155 (25), 141 (30), 97 (20), 85 (27), 71 (36), 57 (94), 43 (100).

2-Methyl-3-thiocyanato-1*H*-indole (2b)
Solid; mp 102–103 °C.

IR (KBr): 3324, 2933, 2151, 1618, 1543, 1408, 1229, 740, 651 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 7.15–7.40 (m, 3 H), 7.70 (d, *J* = 8.1 Hz, 1 H), 8.48 (br s, 1 H, NH).

EIMS: *m*/*z* (%) = 188 (M^+, 100), 156 (18), 77 (14).

5-Methoxy-3-thiocyanato-1*H*-indole (2c)
Solid; mp 122–123 °C.

IR (KBr): 3375, 2983, 2155, 1687, 1385, 1459, 1291, 1035, 780 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 6.80 (dd, *J* = 8.5, 0.8 Hz, 1 H), 7.10 (d, *J* = 1.8 Hz, 1 H), 7.30 (d, *J* = 8.5 Hz, 1 H), 7.50 (d, *J* = 0.8 Hz, 1 H), 8.50 (br s, 1 H, NH).

EIMS: *m*/*z* (%) = 204 (M^+, 100), 178 (15), 149 (20), 122 (40), 107 (65), 47 (60).

1-Ethyl-2-phenyl-1*H*-3-indolyl Thiocyanate (2d)
Solid; mp 107–109 °C.

IR (KBr): 2969, 2359, 2341, 2149, 1458, 1467, 1445, 1390, 1340, 1198, 1074, 804, 770, 746, 700, 482 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 7.22–7.80 (m, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.4, 39.8, 110.6, 119.1, 121.9, 123.5, 128.8, 129.5, 129.7, 130.5, 136.0, 146.1.

EIMS*:* *m*/*z* (%) = 278 (M^+, 100), 264 (6), 250 (20), 237 (10), 224 (6).

HRMS: *m*/*z* calcd for $C_{17}H_{14}N_2S$: 278.0877; found: 278.0899.

1-Benzyl-1*H*-3-indolyl Thiocyanate (2e)
Solid; mp 82–84 °C.

IR (KBr): 3068, 2947, 2832, 2359, 2341, 2163, 1506, 1453, 1440, 1157, 732, 693 cm^{-1}.

^1H NMR (200 MHz $CDCl_3$): δ = 5.25 (s, 2 H), 7.35 (s, 1 H), 7.78 (d, *J* = 6.7 Hz, 1 H), 7.08 (d, *J* = 6.7 Hz, 2 H), 7.17–7.36 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 91.6, 111.3, 119.2, 121.8, 123.9, 127.2, 128.1, 128.8, 129.4, 134.3, 135.9, 136.9.

EIMS: *m*/*z* (%) = 264 (M^+, 69), 173 (6), 146 (10), 120 (8), 91 (100), 77 (8), 65 (74), 39 (30).

HRMS: *m*/*z* calcd for $C_{16}H_{12}N_2S$: 264.0721; found: 264.0712.

1-Methyl-5-thiocyanato-2-indolinone (2f)
Solid; mp 127–129 °C.

IR (KBr): 3074, 2953, 2924, 2359, 2151, 1726, 1695, 1605, 1493, 1364, 1345, 1106, 1060, 943, 908, 829, 716, 668 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.2 (s, 2 H), 3.53 (s, 2 H), 6.81–6.85 (d, *J* = 8.3 Hz, 1 H), 7.44–7.47 (d, *J* = 8.3 Hz, 1 H), 7.46 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 108.2, 110.4, 111.3, 115.9, 126.8, 129.1, 131.3, 133.5, 147.1, 174.2.

EIMS: *m*/*z* (%) = 204 (M^+, 10), 179 (6), 176 (36), 142 (10), 118 (42), 92 (6), 69 (8), 57 (20), 43 (20).

HRMS: *m*/*z* calcd for $C_{10}H_8N_2OS$: 204.0357; found: 204.0359.

1-Benzyl-5-thiocyanato-2-indolinone (2g)
Solid; mp 210–211 °C.

IR (KBr): 3422, 2923, 2853, 2126, 1719, 1654, 1466, 1364, 1321, 1220, 1026, 824, 769, 629 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.90 (s, 2 H), 3.80 (s, 2 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 7.40–7.65 (m, 8 H).

EIMS: *m*/*z* (%) = 280 (M^+, 30), 199 (10), 84 (70), 66 (100), 46 (20).

5-Thiocyanato-2,3-indolinedione (2h)
Solid; mp 203–204 °C.

IR (KBr): 3447, 2924, 2165, 1618, 1460, 771 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 7.05 (d, *J* = 8.1 Hz, 1 H), 7.65–7.75 (m, 2 H) 11.35 (br s, 1 H, NH).

EIMS: *m*/*z* (%) = 204 (M^+, 20), 180 (80), 176 (35), 135 (30), 109 (10), 88 (100), 71 (60). 43 (50).

HRMS: *m*/*z* calcd for $C_9H_4N_2O_2S$: 203.9993; found: 203.9992.

4-Thiocyanatoaniline (2i)
Solid; mp 49–51 °C.

IR (KBr): 3345, 2923, 2143, 1635, 1593, 1390, 1297, 1176, 821 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.90 (br s, 2 H, NH_2), 6.60 (d, *J* = 8.1 Hz, 2 H), 7.45 (d, *J* = 8.1 Hz, 2 H).

EIMS: *m*/*z* (%) = 150 (M^+, 100), 125 (70), 91 (80), 76 (20).

2-Chloro-3-methyl-4-thiocyanatoaniline (2j)
Solid; mp 112–113 °C.

IR (KBr): 3382, 2148, 1632, 1578, 1461, 1394, 1302, 1109, 811, 593 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 3.85 (br s, 2 H, NH_2), 6.60 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.5, 114.0, 121.9, 131.5, 147.9.

EIMS: *m*/*z* (%) = 200 (M^+ + 2, 40), 198 (M^+, 100), 163 (55), 136 (20), 119 (15) 104 (15), 77 (23), 51 (15).

HRMS: *m*/*z* calcd for $C_8H_7N_2ClS$: 198.0018; found: 198.0009.

***N*,*N*-Dimethyl-4-thiocyanatoaniline (2k)**
Solid; mp 72–74 °C.

IR (KBr): 3382, 3094, 2978, 2843, 2158, 1685, 1461, 1295, 1040, 765 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.02 (s, 6 H), 6.60 (d, 2 H, *J* = 8.4 Hz), 7.40 (d, 2 H, *J* = 8.4 Hz).

EIMS: *m*/*z* (%) = 178 (M^+, 100), 153 (15), 140 (25), 92 (30), 47 (65).

***N*-Ethyl-4-thiocyanatoaniline (2l)**
Solid; mp 52–53 °C.

IR (KBr): 3388, 2971, 2153, 1595, 1509, 1406, 1329, 1220, 1150, 816, 770, 524 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.0 Hz, 3 H), 3.25 (q, *J* = 7.0 Hz, 2 H), 3.84 (br s, 1 H, NH), 6.60 (d, *J* = 8.3 Hz, 2 H), 7.45 (d, *J* = 8.3 Hz, 2 H).

EIMS: *m*/*z* (%) = 178 (M^+, 80), 163 (100), 105 (20).

3-Nitro-4-thiocyanatoaniline (2m)
Solid; mp 108–110 °C.

IR (KBr): 3475, 3218, 2126, 1643, 1526, 1483, 1434, 822, 764, 663, 622, 571 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 4.56 (br s, 2 H, NH_2), 6.95 (dd, *J* = 8.1, 2.3 Hz, 2 H), 7.60 (d, *J* = 2.3 Hz, 1 H), 7.65 (d, *J* = 8.1 Hz, 1 H).

EIMS: *m*/*z* (%) = 195 (M^+, 100), 150 (75), 122 (25), 106 (100), 84 (25) 69 (23), 57 (18), 41 (40).

2,5-Dichloro-4-thiocyanatoaniline (2n)
Solid; mp 116–118 °C.

IR (KBr): 3402, 3319, 2157, 1618, 1581, 1460, 1385, 1246, 1063, 863, 672 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 4.35 (br s, 2 H, NH_2), 6.85 (s, 1 H), 7.60 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 115.6, 116.2, 118.2, 131.8, 134.2, 135.8, 146.1.

EIMS: *m*/*z* (%) = 218 (M^+, 80), 183 (100), 157 (10), 148 (15), 69 (15), 52 (10).

HRMS: *m*/*z* calcd for $C_7H_4N_2Cl_2S$: 217.9472; found: 217.9467.

1-Acetyl-1*H*-3-indolyl Thiocyanate (2o)
Solid; mp 108–110 °C.

IR (KBr): 3132, 2951, 2358, 2147, 1729, 1529, 1441, 1376, 1311, 1213, 1152, 1040, 974, 928, 753 cm^{-1}.

^1H NMR (200 MHz $CDCl_3$): δ = 2.70 (s, 3 H), 7.40–7.50 (m, 2 H), 7.70–7.80 (m, 2 H), 8.45 (d, 1 H, *J* = 6.5 Hz).

EIMS: *m*/*z* (%) = 216 (M^+, 29), 174 (100), 146 (12), 120 (15), 77 (10), 43 (85).

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