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Iodine/MeOH: a novel and efficient reagent system for thiocyanation of aromatics and heteroaromatics

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Abstract—Indoles, pyrroles, oxindoles and aromatic amino compounds undergo smooth thiocyanation with ammonium thiocyanate in the presence of molecular iodine in methanol under mild conditions to afford the corresponding 3-indolyl, 2-pyrrolyl and 4-aryl thiocyanates, respectively, in excellent yields with high selectivity. The reactions proceed rapidly at room temperature without heating or the use of strong Lewis acids.

The electrophilic thiocyanation of aromatics and heteroaromatics is an important carbon–heteroatom bond formation in organic synthesis.[1] Aryl or heteroaryl thiocyanates are useful intermediates in the synthesis of sulfur-containing heterocycles.[2] Furthermore, aryl thiocyanates can be easily transformed into various sulfur functional groups[3] such as thiophenols by reduction with lithium aluminium hydride and aryl nitriles/disulphides 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.[1,4] In contrast, only a limited number of reagents such as *N*-halosuccinimides (NCS or NBS), ceric ammonium nitrate (CAN) and acidic K10 clay have been reported for the thiocyanation of indoles.[5,6] However, many of these methods involve the use of a large excess of strong oxidizing agents and toxic metal thiocyanates and also involve low conversions especially in the case of aryl amines. 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. Owing to its unique catalytic properties, iodine has been extensively used as a catalyst for a plethora of organic transformations such as glycosidation, allylation, conjugate addition, cycloaddition, and many others.[7,8]

In this report, we wish to disclose a simple, convenient and efficient protocol for the thiocyanation of indoles, oxindoles, pyrroles and aryl amines using molecular iodine in methanol. Initially, we have studied the electrophilic thiocyanation of 2-methylindole **1** as a model substrate with 3 equiv of ammonium thiocyanate using a stoichiometric amount of iodine. The reaction went to completion within 20 min at room temperature and the product, 3-thiocyanato-indole **2a**, was obtained in 96% yield (Table 1, entry b, Scheme 1).

This remarkable catalytic activity of iodine in the thiocyanation of 2-methylindole prompted us to study it in reactions with other indoles and pyrroles. Interestingly, various substituted indoles, such as 7-ethyl-, 5-methoxy- and *N*-methyl-indoles, reacted efficiently with ammonium thiocyanate to afford the corresponding 3-thiocyanato-indole derivatives (Table 1, entries 2c–2e). Like indoles, oxindoles such as the *N*-phenyl- and *N*-benzyl-derivatives worked well under similar conditions to give 5-thiocyanato-oxindoles (Table 1, entries 2f–2g). Similarly, pyrrole and *N*-methylpyrrole also afforded the corresponding 2-thiocyanatopyrroles in excellent yields (Table 1, entries 3h–3i, Scheme 2).

In the case of pyrrole, a minor amount of 2,4-dithiocyanatopyrrole **4** was obtained along with the 2-thiocyanato derivative **3**. However, treatment of aryl amines

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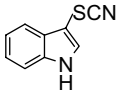
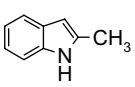
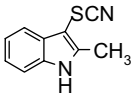
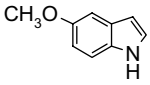
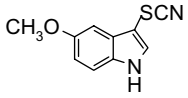
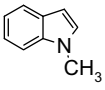
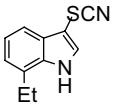
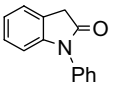
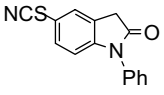
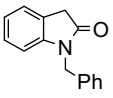
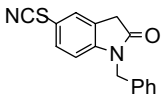
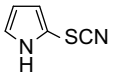
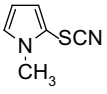
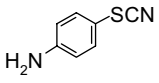
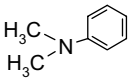
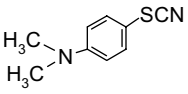
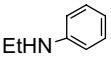
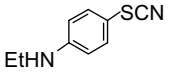
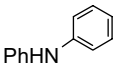
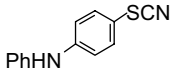
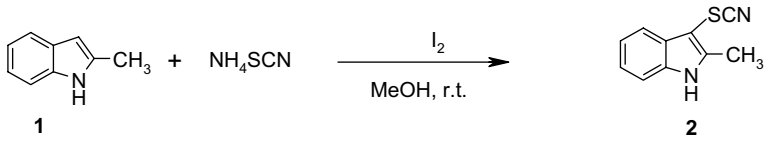
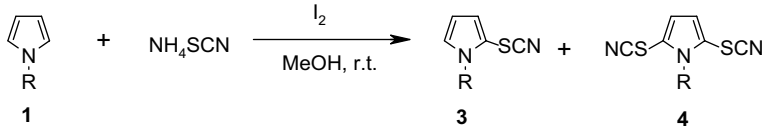
Table 1. Iodine-promoted thiocyanation of aromatic and heteroaromatic compounds

Entry	Indole **1**	Product[a] **2**	Time (min)	Yield[b] (%)
a			50	85
b			20	96
c			30	89
d			45	87
e			30	83
f			25	92
g			30	90
h			35	85[c]
i			40	82[c]
j			25	80
k			20	87
l			20	85
m			35	83

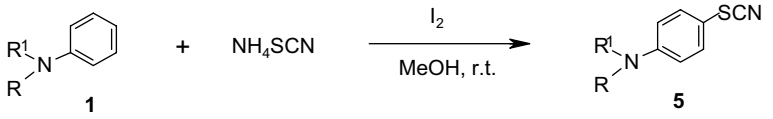
[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields.
[c] 10–15% bis-adducts were obtained.



Scheme 1.



Scheme 2.



Scheme 3.

such as aniline, *N*,*N*-dimethylaniline, *N*-ethylaniline, *N*-phenylaniline with ammonium thiocyanate in the presence of molecular iodine resulted in the formation of aryl thiocyanates in high yields (Table 1, entries 5j–5m, Scheme 3).

In the case of aryl amines, the products were obtained with high *para*-selectivity. In all cases, the reactions proceeded rapidly at room temperature with high regioselectivity. As solvent, methanol appeared to give the best results. The products were characterized by ^{1}H NMR, IR and mass spectroscopic data and also by comparison with authentic samples.[5,6] This method is very clean and free from side products. Among the various oxidants such as DDQ, $Mn(OAc)_3{\cdot}2H_2O$, $Bi(NO_3)_3{\cdot}5H_2O$ and $C_6H_5I(OAc)_2$ studied for this transformation, molecular iodine was found to be the most effective in terms of conversion and reaction rates. The scope and generality of this process is illustrated with respect to various indoles and aryl amines and the results are presented in Table 1.[9]

In conclusion, we describe a simple, convenient and highly efficient protocol for the preparation of aryl and heteroaryl thiocyanates through the electrophilic thiocyanation of aromatic and heteroaromatic compounds using molecular iodine as promoter.

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9. General procedure: To a stirred solution of ammonium thiocyanate (3 mmol), and iodine (1 mmol) in methanol (10 mL), the indole, aryl amine (1.0 mmol) or pyrrole (2 mmol) was added slowly in a dropwise manner and the mixture was allowed to stir at room temperature for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with

water (15 mL) and extracted with dichloromethane (2×15 mL). The combined extracts were washed with a 15% solution of sodium thiosulfate, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure thiocyanato derivative. Spectral data for selected products:

2c: 5-methoxy-3-thiocyanato-1*H*-indole[6] (see, Table 1): Solid, mp 122–123 °C, IR (KBr): υ 3375, 2983, 2155, 1687, 1385, 1459, 1291, 1035, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.98 (s, 3H), 6.80 (dd, $J = 8.5$, 0.8 Hz, 1H), 7.10 (d, $J = 1.8$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 1H), 7.50 (d, $J = 0.8$ Hz, 1H), 11.5 (br s, 1H, NH). EIMS: m/z (%): 204 M^+ (100), 178 (15), 149 (20), 122 (40) 107 (65), 47 (60).

3h: 2-Thiocyanato-1*H*-pyrrole[5b] (see, Table 1): Liquid, IR (KBr): υ 3285, 3105, 2152, 1596, 1506, 1330, 1183, 815 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.0 (s, 1H), 5.20 (s, 1H), 5.55 (s, 1H), 8.0 (br s, 1H, NH). EIMS: m/z (%): 124 M^+ (100), 99 (40), 66 (35).

5j: 4-Thiocyanatoaniline[5b] (see, Table 1): Solid, mp 49–51 °C, IR (KBr): υ 3345, 2923, 2143, 1635, 1593, 1390, 1297, 1176, 821 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.90 (br s, 2H, $-NH_2$), 6.60 (d, $J = 8.1$ Hz, 2H), 7.45 (d, $J = 8.1$ Hz, 2H). EIMS: m/z (%): 150 M^+ (100), 125 (70), 91 (80), 76 (20).

5k: *N*,*N*-dimethyl-4-thiocyanatoaniline[5a] (see, Table 1): Solid, mp 72–74 °C, IR (KBr): υ 3382, 2158, 1685, 1461, 1295, 1040, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.0 (s, 6H), 6.60 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H). EIMS: m/z (%): 178 M^+ (100), 153 (15), 140 (25), 92 (30). 47 (65).