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Facile Method for Thiocyanation of Activated Arenes Using Iodic Acid in Combination with Ammonium Thiocyanate

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Abstract: A facile method for direct thiocyanation of activated arenes using iodic acid in combination with ammonium thiocyanate is described.

Keywords: Activated arenes, ammonium thiocyanate, iodic acid, thiocyanation

Aromatic thiocyanation of activated arenes is an important synthetic transformation and is frequently used as an intermediate step in synthesis of various heterocyclic compounds.[1] In addition, thiocyanate functionality can be easily transformed into other functionality such as thiophenols by reduction with aluminium hydride,[2] and it can be used as a cyanide-free source for the cyanation of aryl boronic acid.[3] Utility of thiocyanates in synthesis of sulfur-containing thiosulfonates, which were coupled fruitfully to the 5,6-dihydropyran-2-one ring to give products that showed excellent HIV protease activity, has been demonstrated.[4]

A number of protocols are available to achieve thiocynation of aromatic and heteroaromatic compounds, such as oxone/ammonium thiocyanate,[5a] iodine/ammonium thiocyanate,[5b] ferric chloride/ammonium thiocyanate,[5c] *N*-thiocyanatosuccinimide,[6a] ceric ammonium nitrate/ammonium thiocynate,[6b] Selectfluor®/sodium cyanate,[6c] acidic K-10 clay/ammonium thiocyanate,[6d] phenyliodine(III) bis(trifluoroacetate)

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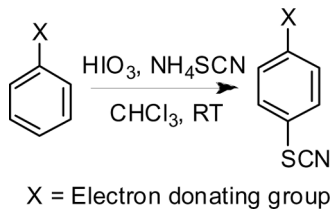
(PIFA)/trimethylsilylisothiocyanate (TMS-NCS),[7a] $PhICl_2$/PbSCN,[7b] and diacetoxyiodobenzene/ammonium thiocyanate.[7c] However, these methods suffer from one or the other drawbacks and hence there is scope for new methods.

In particular, reaction systems based on hypervalent iodine compounds such as PIFA/TMS-NCS,[7a] $PhICl_2$/PbSCN,[7b] and diacetoxyiodobenzene/ammonium thiocyanate[7c] used for this transformation also suffer from drawbacks of either being expensive and moisture sensitive[7a] requiring hazardous reagents,[7b] or being unsuitable for phenols and indole.[7c] Iodic acid (HIO_3) is a readily accessible crystalline solid and is employed as an oxidant for many synthetic transformations, such as oxidation of sulfides,[8a] iodination,[8b] and nitrosation.[8c] This reagent has several advantages: it is nontoxic, easy to handle, and cost-effective.

In continuation of our work on the development of useful synthetic methodologies using hypervalent iodine compounds,[9] we report a new combination of iodic acid with ammonium thiocyanate as an effective reagent system for thiocyanation of activated arenes. Scheme 1.

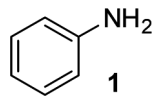
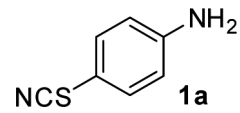
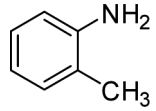
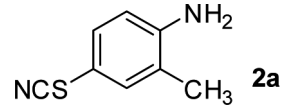
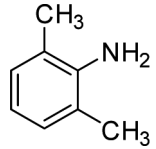
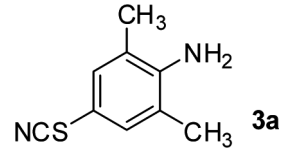
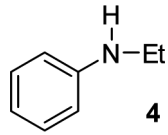
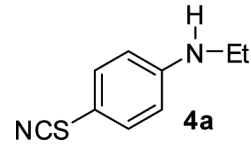
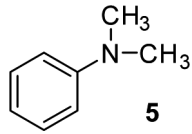
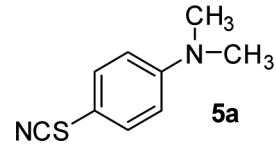
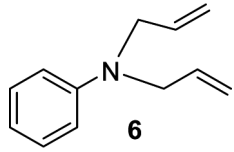
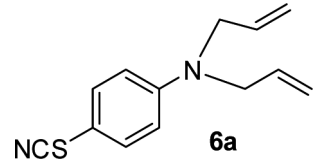
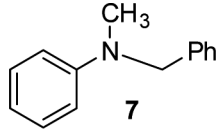
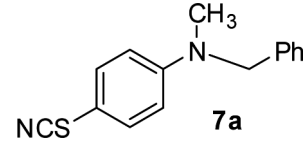
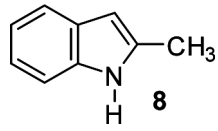
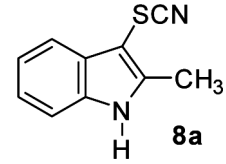
Reaction conditions were optimized using *N,N*-dimethylaniline as a model substrate. It was treated with 1 equiv of iodic acid in combination with a stoichiometric amount of ammonium thiocyanate at room temperature in acetonitrile as a solvent, and the corresponding 4-thiocyanato-*N,N*-dimethylaniline was isolated with excellent regioselectivity in 60% yield. Investigations were carried out by changing the solvent and increasing the molar ratios of iodic acid and ammonium thiocyanate in relation to *N,N*-dimethylaniline. The best results were obtained with 1.5 equiv of iodic acid and 2.2 equiv of ammonium thiocyanate in chloroform as solvent. Other hypervalent iodine compounds, such as Dess–Martin periodinane (DMP), o-iodoxylbenzoic acid (IBX), and HIO_4 in combination with ammonium thiocyanates, were also studied using chloroform as solvent, and only HIO_4 was found to be viable for this transformation.

A series of arenes were subjected to thiocyanation under the optimized reaction conditions. Only activated arenes reacted to give thiocyanated products, and deactivated arenes failed to react. Even



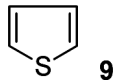
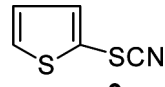
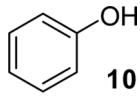
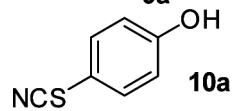
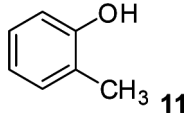
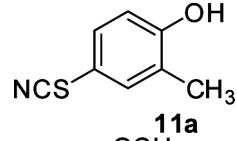
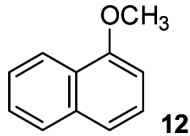
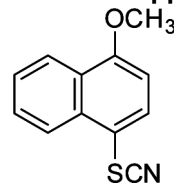
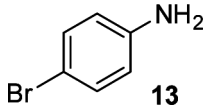
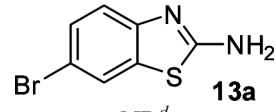
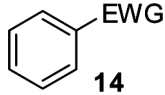
Scheme 1. Thiocyanation of activated arenes.

Table 1. Thiocyanation of arenes using iodic acid/ammonium thiocyanate[a]

Entry	Substrate	Product	Time (min)	Yield (%)[b]
1	 **1**	 **1a**	25	88
2	 **2**	 **2a**	20	90
3	 **3**	 **3a**	25	92
4	 **4**	 **4a**	30	88
5	 **5**	 **5a**	20	94
6	 **6**	 **6a**	25	90
7	 **7**	 **7a**	25	92
8	 **8**	 **8a**	35	84

(*Continued*)

Table 1. Continued

Entry	Substrate	Product	Time (min)	Yield (%)[b]
9	 **9**	 **9a**	25	87
10	 **10**	 **10a**	15	86
11	 **11**	 **11a**	25	92
12	 **12**	 **12a**	30	82
13	 **13**	 **13a**	35	84
14	 **14** EWG [c] = -NO_2, -COOH	NR[d]	360	—

[a]All products were characterized by ^{1}H NMR and IR, and their physical properties were compared with the reported values.
[b]Isolated yield.
[c]EWG = electron-withdrawing group.
[d]NR = no reaction.

though iodic acid is acidic in nature, aniline, *N,N*-dialkylatedbenzenamines, phenol, and anisole reacted efficiently and afforded the corresponding thiocyanato derivatives with good to excellent yields (Table 1, entries 1–5 and 10–12). Chemoselectivity was observed when *N*-benzyl-*N*-methylbenzenamine and *N,N*-diallylbenzenamine were reacted under the reaction conditions to give *N*-benzyl-*N*-methyl-4-thiocyanatobenzenamine and *N,N*-diallyl-4-thiocyanatobenzenamine, respectively (Table 1, entries 6 and 7) without affecting allylic and

benzylic positions. Heteroaromatic compounds including indole and thiophene thiocyanated under the reaction conditions and gave the corresponding thiocyanato derivatives (Table 1, entries 8 and 9). In the case of *p*-bromoaniline where *para* position was blocked, it reacted completely to give 2-amino-6-bromobenzothiozole in 84% yield as the sole product, indicating *ortho* thiocyanation followed by cyclization (Table 1, entry 13).

When the reaction was performed with electron-deficient aromatic substrates, such as nitrobenzene and benzoic acid, reaction did not occur (Table 1, entry 14). In all the cases, only single compounds were isolated, indicating that the method provides regioselective monothiocyanation.

In conclusion, we have developed a simple, efficient, and rapid method for regioselective thiocyanation of activated arenes including phenols, indoles, and anilines using a combination of iodic acid and ammonium thiocyanate. Because it is complementary to existing methods and the reagents are inexpensive, easily accessible, and less hazardous, the method may find wide utility.

GENERAL EXPERIMENTAL PROCEDURE

A Substrate (5 mmol) was added immediately in one portion to a stirred red-colored suspension of iodic acid (1.32 g, 7.5 mmol) and ammonium thiocyanate (0.836 g, 11 mmol) in 15 mL of chloroform. The reaction mixture was stirred at room temperature until complete consumption of starting material was observed by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was diluted by adding chloroform (30 mL) and was washed with saturated solution of sodium bicarbonate (2×30 mL) and brine solution (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude thiocyanato product. Pure product was obtained after column chromatography (silica gel, mesh size 60–120, eluent ethyl acetate–hexane 10:90).

SPECTRAL DATA FOR THIOCYANATO COMPOUNDS

2-Methyl-4-thiocynatobenzeneamine 2a

Solid, mp 70–71°C (lit.[10a] 70–71°C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.75 (bs, 2H), 6.43–6.62 (m, 2H), 7.18–7.52 (m, 1H) ppm. IR (KBr): ν_{max} 3354, 3243, 2145 (-SCN), 1628, 1592, 1492, 1298, 821 cm^{-1}.

2,6-Dimethyl-4-thiocyanatobenzenamine 3a

Solid, mp 85–87°C (lit.[10b] 87–88°C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.44 (s, 6H), 3.87 (bs, 2H), 6.62 (s, 1H), 7.22 (s, 1H) ppm. IR (KBr): ν_{max} 2928, 2147 (-SCN), 1615, 1592, 1460, 1288 cm^{-1}.

***N*-Ethyl-4-thiocyanatobenzenamine 4a**

Solid, mp 54–55°C (lit.[6d] 52–53°C). IR (KBr): ν_{max} 3388, 29755, 2156 (-SCN), 815, 775 cm^{-1}. ^{1}H NMR (60 MHz, $CDCl_3$): δ = 3.02 (s, 6H), 6.60 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H) ppm.

***N,N*-Dimethyl-4-thiocynatobenzeneamine 5a**

Solid, mp 72–72°C (lit.[5a] 72–74°C). IR (KBr): ν_{max} 3382, 3095, 2159 (-SCN), 1685, 1465, 1295, 765 cm^{-1}. ^{1}H NMR (60 MHz, $CDCl_3$): δ = 3.02 (s, 6H), 6.60 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H) ppm.

***N,N*-Diallyl-4-thiocyanatobenzenamine 6a**

Oil.[1] H NMR (60 MHz, $CDCl_3$): δ 3.78–3.97 (m, 4H), 4.96–5.26 (m, 4H), 5.55–6.06 (m, 2H), 6.63 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 9.0 Hz, 2H) ppm. IR (KBr): ν_{max} 3082, 2916, 2148 (-SCN), 1641, 1591, 1504, 1238, 811 cm^{-1}. Elemental analysis calcd. for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.82; H, 6.15; N, 12.18.

***N*-Benzyl-*N*-methyl-4-thiocyanatobenzenamine 7a**

Solid, mp 68–70°C. ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.07 (s, 3H), 4.57 (s, 2H), 6.69 (d, J = 9.0 Hz, 2H), 7.05 (s, 5H), 7.39 (d, J = 9.0 Hz, 2H) ppm. IR (KBr): ν_{max} 3014, 2144 (-SCN), 1599, 1460, 1023, 824 cm^{-1}. Elemental analysis calcd. for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01. Found: C, 70.85; H, 5.54; N, 10.98.

2-Methyl-3-thiocyanato-1*H*-indole 8a

Solid, mp 101–102°C (lit.[5c] 102–103°C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.50 (s, 3H), 7.70–7.75 (m, 3H), 7.69–7.64 (m, 1H), 8.56 (bs, 1H) ppm. IR (KBr): ν_{max} 3323, 3061, 2152 (-SCN), 1614, 1583, 1408, 1228, 741 cm^{-1}.

2-Thiocyanatothiophene 9a

Oil (lit.[7c] oil). ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.50–8.12 (m, 3H) ppm. IR (neat): ν_{max} 3012, 2158 (-SCN), 1412, 1215, 850, 728 cm^{-1}.

2-Methyl-4-thiocyanatophenol 11a

Solid, mp 70–72°C (lit.[10c] 71–72°C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.24 (s, 3H), 6.14 (brs, 1H), 6.64–7.25 (m, 3H) ppm. IR (KBr): ν_{max} 3378, 2925, 2159 (-SCN), 1597, 1495, 1275, 815 cm^{-1}.

1-Methoxy-4-thiocyanatonaphthalene 12a

Solid, mp 104–106°C (lit.[7a] 106–107°C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.08 (s, 3H), 6.71–6.75 (m, 1H), 7.62–8.29 (m, 5H) ppm. IR (KBr): ν_{max} 2978, 2152 (-SCN), 1591, 1271, 1063, 807, 771 cm^{-1}.

2-Amino-6-bromobenzothiazol 13a

Solid, mp 212–213°C (lit.[10d] 213–214°C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.93–5.31 (bs, 2H), 7.32–7.85 (m, 3H) ppm. IR (KBr): ν_{max} 3320, 3430, 1605 cm^{-1}.

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