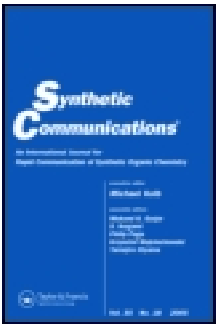

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Thiocyanation of Aromatic and Heteroaromatic Compounds using Ammonium Thiocyanate and I_2O_5

Jing Wu [a], Guaili Wu [a] & Longmin Wu [a]
[a] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, China

Version of record first published: 11 Jul 2008.

To cite this article: Jing Wu, Guaili Wu & Longmin Wu (2008): Thiocyanation of Aromatic and Heteroaromatic Compounds using Ammonium Thiocyanate and I_2O_5, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:14, 2367-2373

To link to this article: http://dx.doi.org/10.1080/00397910802139254

Synthetic Communications®, 38: 2367–2373, 2008
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802139254

Thiocyanation of Aromatic and Heteroaromatic Compounds using Ammonium Thiocyanate and I_2O_5

Jing Wu, Guaili Wu, and Longmin Wu
State Key Laboratory of Applied Organic Chemistry, Lanzhou University,
Lanzhou, China

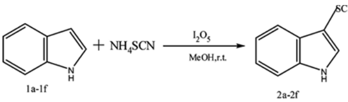
Abstract: Thiocyanation of indoles, pyrrols, and anilines has been efficiently achieved using ammonium thiocyanate as a thiocyanation agent and I_2O_5 as an oxidant.

Keywords: Ammonium thiocyanate; Iodine pentoxide (I_2O_5); Thiocyanation

As part of our ongoing program on the oxidative thiocyanation of aromatic and heteroaromatic compounds,[1] we have particularly extended the substrate scope for oxidants. We have paid more attention to safe, benign, economic, commercially available, and environmentally friendly oxidants. One of the candidates is iodine pentoxide (I_2O_5), which has been referred to as a mild oxidant.[2] I_2O_5 generally offers advantages for performing reactions at room temperature and providing a large margin of safety. Although I_2O_5 has been extensively used in industry,[3] it has rarely been employed in organic synthesis. The few examples are the aromatization of dihydropyridines and pyrazolines[2a] in water and the oxidation of alcohols to the corresponding aldehydes and ketones in water.[2b] In the present work, I_2O_5 was employed as an oxidant in the oxidative thiocyanation of indoles, pyrrols, and anilines in methanol at room temperature. The corresponding monothiocyanated compounds were obtained in various yields. A representative reaction is shown in Scheme 1 using indole **1a** as a substrate.

Received October 12, 2007

Address correspondence to Longmin Wu, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China. E-mail: nlaoc@lzu.edu.cn



Scheme 1. Thiocyanation of indoles using I_2O_5.

Upon treatment of **1a** with ammonium thiocyanate in the presence of I_2O_5 in methanol at room temperature, 2-methyl-3-thiocyano indole **2a** was obtained in 95% yield (Scheme 1). A variety of indoles were examined under similar conditions (Table 1). Table 1 shows that the monothiocyanation uniquely occurred highly regioselectively at the 3-position of the indole ring or at the *para*-position of anilines. A strong electron-withdrawing group NO_2 at the benzene ring of indoles, such as in **1e**, led to a low yield of monothiocyanated compound (Table 1). Pyrrol **1g** gave monothiocyanated pyrrol too, but at position 2. Anilines **1h–k** were easily oxidized to highly polar by-products, most likely dimers.

In short, this work demonstrated an alternative method for the thiocyanation of indoles, pyrrols, and anilines with ammonium thiocyanate as a thiocyanation agent and I_2O_5 as an oxidant.

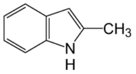
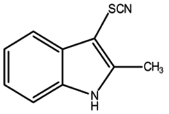
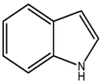
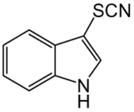
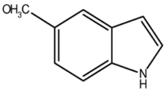
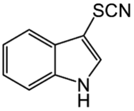
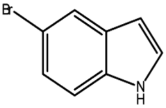
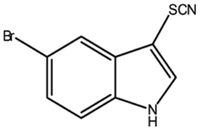
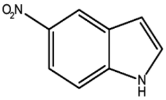
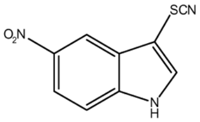
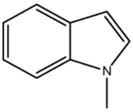
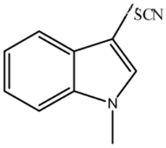
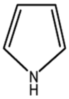
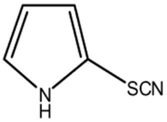
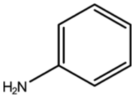
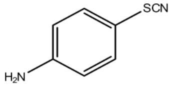
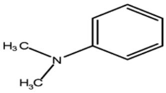
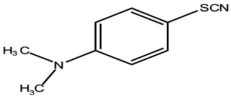
EXPERIMENTAL

Melting points were measured on a Yanagimoto melting-point apparatus and were uncorrected. IR spectra (KBr) were conducted on a Nicolet Nexus 670 Fourier-transform infrared spectroscopy (FT-IR) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 300 NMR spectrometer. ^1H chemical shifts (δ) were reported relative to TMS and ^{13}C to the peak of $CHCl_3$ (77.0 ppm) as an internal standard. Mass spectrometry electron impact (MS-EI) (70 eV) determinations were carried out on an HP 5985 A spectrometer. High resolution, mass spectrometry (HRMS-ESI) detections were run on a Bruker Daltonics Apex II 47e spectrometer with an ESI.

General Procedure for the Thiocyanation of Aromatic and Heteroaromatic Compounds

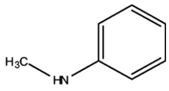
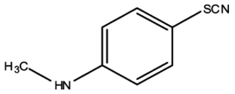
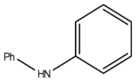
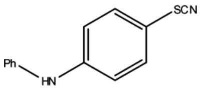
To a stirred methanol solution of 3 mmol of ammonium thiocyanate and 1 mmol of **1a**, 1 mmol of I_2O_5 was added. The resulting mixture was allowed to stir at room temperature for an appropriate time (Table 1). After completing conversion, as indicated by thin-layer

Table 1. Thiocyanation of aromatic and heteroaromatic compounds with ammonium thiocyanate and I_2O_5 in methanol at room temperature

Entry	Substrate **1**	Product **2**[a]	Time[b] (h)	Yield[c] (%)
a			0.25	95
b			0.33	93
c			2.5	94
d			0.33	96
e			8	61
f			0.4	86
g			0.1	62
h			0.2	59
i			3.6	93

(*Continued*)

Table 1. Continued

Entry	Substrate **1**	Product **2**[a]	Time[b] (h)	Yield[c] (%)
j			5	83
k			0.2	80

[a] All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[b] The reaction time. [c] Isolated by column chromatography.

chromatography (TLC), the reaction mixture was quenched with water. The reaction mixture was successively extracted with ethyl acetate, washed by $Na_2S_2O_3$, and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. The resulting product was purified by column chromatography on silica gel (200–300 mesh, ethyl acetate/hexane, 1 : 8) to afford pure **2a**. All products were identified by ^{1}H and ^{13}C NMR, MS, infrared spectroscopy (IR), and HRESI-MS.

Characterization Data for Products

2-Methyl-3-thiocyanatoindole (**2a**)

Solid, mp 96–98 °C. IR (KBr): ν_{max} cm^{-1} 3394, 2922, 2149, 1454, 739. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (s, 1H, NH), 7.69 (d, $J = 6.6$ Hz, 1H, arom), 7.30–7.22 (m, 3H, arom), 2.45 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 135.0, 128.5, 122.8, 121.4, 117.8, 112.3, 111.2, 88.3, 11.8. MS (EI) m/z (%): 188 (M^+, 100%), 161 (25), 155 (28), 94 (13), 77 (16). HRESI-MS m/z: Found $M + H = 189.0482$; $C_{10}H_8N_2S$ required $M + H = 189.0481$.

3-Thiocyanatoindole (**2b**)

Solid, mp 70–72 °C. IR (KBr): ν_{max} cm^{-1} 3395, 3178, 2156, 1412, 745. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.94 (s, 1H, NH), 7.82 (d, 1H, $J = 5.2$ Hz, arom), 7.34 (m, 4H, arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 131.2, 127.4, 123.6, 121.6, 118.3, 112.4, 112.2, 91.1. MS (EI) m/z (%): 174 (M^+, 100%), 148 (17), 142 (28), 120 (12), 77 (9). HRESI-MS m/z:

Found $M + NH_4 = 192.0591$; $C_9H_6N_2S$ required $M + NH_4 = 192.0590$.

5-Methoxy-3-thiocyanatoindole (**2c**)

Solid, mp 112–114 °C. IR (KBr): ν_{max} cm^{-1} 3337, 3119, 2155, 1487, 805. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 10.96 (s, 1H, NH), 7.83 (d, 1H, $J = 3$ Hz, arom), 7.47 (d, 1H, $J = 9$ Hz, arom), 7.21 (d, 1H, $J = 2.4$ Hz, arom), 6.94 (dd, 1H, $J = 2.1$ Hz, $J = 9$ Hz, arom), 3.89 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 159.2, 136.3, 135.0, 132.1, 117.2, 117.0, 114.9, 102.7, 93.5, 58.5. MS (EI) *m/z* (%): 204 (M$^+$, 100%), 189 (78), 161 (46), 135 (16), 75 (9). HRESI-MS *m/z*: Found $M + NH_4 = 222.0695$; $C_{10}H_8N_2SO$ required $M + NH_4 = 222.0696$.

5-Bromo-3-thiocyanatoindole (**2d**)

Solid, mp 124–125 °C. IR (KBr): ν_{max} cm^{-1} 3331, 2922, 2156, 1453, 801. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H, NH), 7.94 (s, 1H, arom), 7.56 (d, 1H, $J = 3$ Hz, arom), 7.42 (dd, 1H, $J = 9$ Hz, $J = 2.4$ Hz, arom), 7.32 (d, 1H, $J = 8.7$ Hz, arom). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 135.0, 133.6, 129.1, 125.6, 120.0, 114.2, 113.8, 110.6, 90.1. MS (EI) *m/z* (%): 252 (M$^+$, 58%), 173 (100), 149 (24), 93 (13), 75 (12). Anal. calcd. for $C_9H_5N_2SBr$: C, 42.68; H, 1.98; N, 11.07; S, 12.65; Br, 31.62. Found: C, 42.86; H, 1.96; N, 11.11; S, 12.72; Br, 31.74.

5-Nitro-3-thiocyanatoindole (**2e**)

Solid, mp 184–186 °C. IR (KBr): ν_{max} cm^{-1} 3287, 2924, 2155, 1491, 825. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 11.64 (s, 1H, NH), 8.65 (d, 1H, $J = 2.4$ Hz, arom), 8.18 (m, 2H, arom), 7.77 (d, 1H, $J = 9.6$ Hz, arom). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 144.0, 140.7, 137.3, 128.3, 119.4, 115.7, 114.4, 111.7, 95.2. MS (EI) *m/z* (%): 219 (M$^+$, 100%), 173 (61), 146 (58), 102 (8), 69 (19). HRESI-MS *m/z*: Found $M + Na = 241.9991$; $C_9H_5N_3SO_2$ required $M + Na = 241.9995$.

1-Methyl-3-thiocyanatoindole (**2f**)

Solid, mp 80–81 °C. IR (KBr): ν_{max} cm^{-1} 2923, 2150, 1513, 756. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82–7.79 (m, 1H, arom), 7.37–7.31 (m, 4H, arom), 3.77 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.0, 135.0, 128.3, 123.3, 121.5, 118.8, 11.9, 110.1, 89.6, 33.3. MS (EI) *m/z* (%): 188 (M^+, 100%), 173 (23), 156 (19), 94 (14), 77 (16). HRESI-MS *m/z*: Found M + H = 189.0484; $C_{10}H_8N_2S$ required M + H = 189.0481.

2-Thiocyanatopyrrol (**2g**)

Colorless liquid. IR (KBr): ν_{max} cm^{-1} 3338, 3126, 2160, 1423, 738. ^1H NMR (300 MHz, $CDCl_3$): δ 8.97 (s, 1H, NH), 6.97 (m, 1H, arom), 6.65 (m, 1H, arom), 6.28 (dd, 1H, $J = 2.4$ Hz, $J = 5.7$ Hz, arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 124.4, 120.0, 111.1, 111.0, 102.7. MS (EI) *m/z* (%): 124 (M^+, 100%), 98 (47), 70 (33), 54 (26), 39 (46). HRESI-MS *m/z*: Found M + NH_4 = 142.0433; $C_5H_4N_2S$ required M + NH_4 = 142.0433.

4-Thiocyanatoaniline (**2h**)

Solid, mp 51–52 °C. IR (KBr): ν_{max} cm^{-1} 3374, 2922, 2151, 1494, 822. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 2H, $J = 8.7$ Hz, arom), 6.65 (d, 2H, $J = 8.7$ Hz, arom), 3.94 (s, 2H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8, 134.5 (2C), 116.0 (2C), 112.5, 109.2. MS (EI) *m/z* (%): 150 (M^+, 100%), 118 (38), 80 (25), 69 (20). HRESI-MS *m/z*: Found M + H = 151.0328; $C_7H_6N_2S$ required M + H = 151.0324.

N,*N*-Dimethyl-4-thiocyanatoaniline (**2i**)

Solid, mp 60–62 °C. IR (KBr): ν_{max} cm^{-1} 3373, 2921, 2144, 1513, 733. ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, 2H, $J = 8.7$ Hz, arom), 6.67 (d, 2H, $J = 8.7$ Hz, arom), 2.99 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.6, 134.4 (2C), 113.0 (2C), 112.6, 106.3, 40.1 (2C). MS (EI) *m/z* (%): 178 (M^+, 100%), 152 (28), 145 (55), 118 (16), 77 (13). HRESI-MS *m/z*: Found M + H = 179.0640; $C_9H_{10}N_2S$ required M + H = 179.0637.

N-Methyl-4-thiocyanatoaniline (**2j**)

Solid, mp 46–47 °C. IR (KBr): ν_{max} cm^{-1} 3409, 2930, 2151, 1513, 819. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, 2H, $J = 8.7$ Hz, arom), 6.58 (d, 2H, $J = 8.7$ Hz, arom), 4.20 (s, 1H, NH), 2.80 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.0, 134.5 (2C), 113.1 (2C), 112.7, 106.7, 29.9. MS (EI) *m/z* (%): 164 (M^+, 100%), 149 (31), 131 (32), 105 (25), 77 (23). HRESI-MS *m/z*: Found M + H = 165.0484; $C_8H_8N_2S$ required M + H = 165.0481.

N-Phenyl-4-thiocyanatoaniline (**2k**)

Solid, mp 58–60 °C. IR (KBr): ν_{max} cm^{-1} 3340, 3056, 2149, 1491, 747. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.31 (m, 4H, arom), 7.15–6.99 (m, 5H, arom), 6.04 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.03, 140.8, 134.0 (2C), 129.4 (2C), 122.9, 120.0 (2C), 117.0 (2C), 112.1, 111.1. MS (EI) m/z (%): 226 (M^+, 100%), 193 (17), 167 (31), 130 (25), 77 (32). HRESI-MS m/z: Found $M + H = 227.0641$; $C_{13}H_{10}N_2S$ required $M + H = 227.0637$.

ACKNOWLEDGMENT

Project 20572040 was supported by the National Natural Science Foundation of China.

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