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Regioselective thiocyanation of aromatic and heteroaromatic compounds using ammonium thiocyanate and oxone

Guaili Wu, Qiang Liu, Yinglin Shen, Wentao Wu and Longmin Wu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Guansu 730000, PR China

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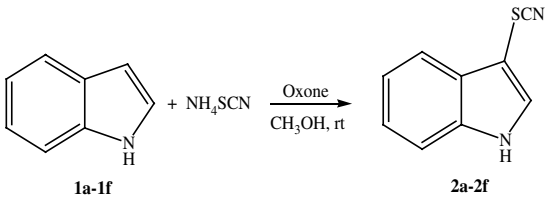
Abstract—An efficient and regioselective approach for the thiocyanation of indoles, pyrrole, aromatic amino compounds, and 2-methoxycarbazole has been developed using ammonium thiocyanate as a thiocyanation reagent and oxone as an oxidant.

Thiocyanation of aromatic and heteroaromatic compounds is one of the most important reactions in organic synthesis. The thiocyano substituted compounds are a useful kind of intermediates in the synthesis of sulfur-containing heterocycles, in which the thiocyanate group will be readily transformed into other sulfur-bearing functionalities.[1] They are particularly useful for producing drugs and pharmaceuticals.[2] In view of the versatility of thiocyanate group in heterocyclic construction,[3] it will be of significance to probe the thiocyanation of aromatic and heteroaromatic compounds. Several methods have been developed for the thiocyanation of arenes by using various reagents under certain conditions.[4,5] Yet, only a limited number of reagents, such as bromine/potassium thiocyanate (only for indoles),[5a] *N*-thiocyanatosuccinimide (only for 5-methoxy-2-methylindole and accompanied by two bisthiocyanates),[5b] ceric ammonium nitrate (CAN),[5c] acidic montK10clay,[5d] iodine/methanol,[2] etc., have been applied to the thiocyanation of indoles. However, these methodologies suffer from one or more drawbacks such as the less availability or hard preparation of starting materials,[5a,b] the requirement for a large excess of strong oxidizing reagents, the toxicity of metal thiocyanates, low yields for some compounds,[5c] and performances under certain special conditions.[5d] Hence, a requirement for developing alternative synthesis routines accessible to the thiocyanation of aromatic and heteroaromatic compounds is in high demand. In the present work, we will report a novel, efficient, and regioselective approach for the thiocyanation of aromatic and heteroaromatic compounds using ammonium thiocyanate as a thiocyanation reagent and oxone as an oxidant. The substrates studied were indoles, anilines, pyrrole, and carbazole. Using indoles as substrates, the reaction gave unique 3-thiocyano substituted indoles in high yield (Scheme 1 and Table 1).

In a typical experiment, a solution of 117 mg **1a** (1 mmol) and 114 mg ammonium thiocyanate (1.5 mmol) in 10 mL of methanol was treated with 924 mg oxone (1.5 mmol) and allowed to stir at room temperature until completion of the reaction, monitored by TCL. Consequently, it was diluted with water and extracted with 4×15 mL of dichloromethane (DCM). DCM was then evaporated and the residue was purified by column chromatography on silica gel (200–300 mesh, ethyl acetate/hexane) to afford the product as colorless crystallines. It was recrystallized from dichloromethane/hexane or ethyl acetate/hexane. The product was identified by ^{1}H and ^{13}C NMR, MS, IR, and element analysis.[6] IR spectrum showed the characteristic peak



1a-1f **2a-2f**

isolated yields of the products up to 98%

Scheme 1.

Keywords: Thiocyanation; Oxone; Ammonium thiocyanate.
* Corresponding author. Tel.: +86 931 8912500; fax: +86 931 8625657; e-mail: nlaoc@lzu.edu.cn

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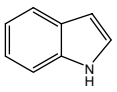
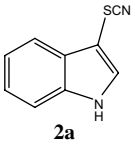
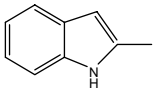
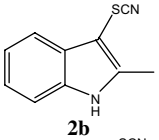
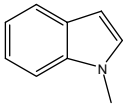
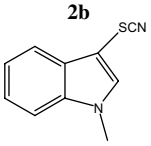
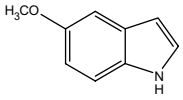
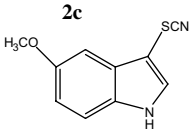
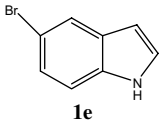
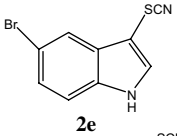
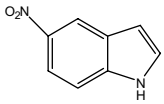
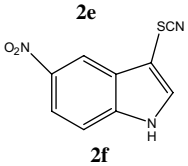
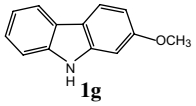
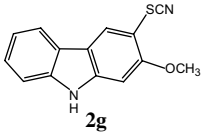
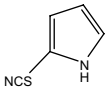
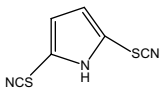
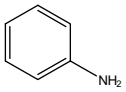
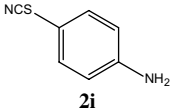
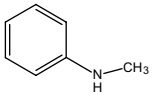
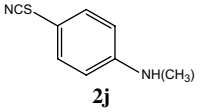
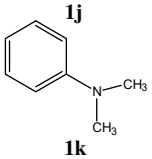
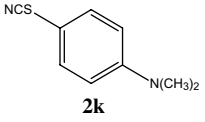
Table 1. Thiocyanation of aromatic and heteroaromatic compounds with oxone in methanol at room temperature

Substrate	Product	t^a (min)	Yield[b] (%)
 **1a**	 **2a**	43	98
 **1b**	 **2b**	12	90
 **1c**	 **2c**	30	96
 **1d**	 **2d**	21	98
 **1e**	 **2e**	25	91
 **1f**	 **2f**	18	94
 **1g**	 **2g**	30	97
 **1h**	 **2h$_a$** +  **2h$_b$**	15	**2h$_a$** 83 **2h$_b$** 8
 **1i**	 **2i**	25	63
 **1j**	 **2j**	30	71
 **1k**	 **2k**	23	80

[a] The reaction time.
[b] Isolated yields of the products after column chromatography.

of –SCN at 2160 cm^{-1} and the –C–S stretching at 702 cm^{-1}. The results are listed in Table 1.

The products (**2a–f**) from indoles (**1a–f**) showed that the mono-thiocyanation uniquely occurred at the 3-position of indole ring. As for 2-methoxycarbazole (**1g**), the mono-thiocyanation still took place at the 3-position of benzene ring. Pyrrole (**1h**) was also easily transformed into the mono-thiocyanated product (**2h$_a$**) within 23 min. The dithiocyanated product (**2h$_b$**) will be formed with a longer reaction time of 12 h. Therefore, under the properly controlled reaction time and amount of ammonium thiocyanate, only **2h$_a$** will be yielded.

The solvent effect on product yields was investigated using **1a** as a substrate. Both the yields and reaction times listed in Table 2 suggest that methanol appears to be very favorable for thiocyanations.

Potassium peroxymonosulfate is a cheap and readily accessible oxidizing reagent. It is commonly referred to as oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) and is a versatile oxidant for transformation of a wide range of functional groups.[7] These reactions generally occur at lower temperatures. Thus, they will provide a larger margin of safety. In addition, oxone is present as solid. It has an advantage of precise weighed amount of it being used in the reaction.

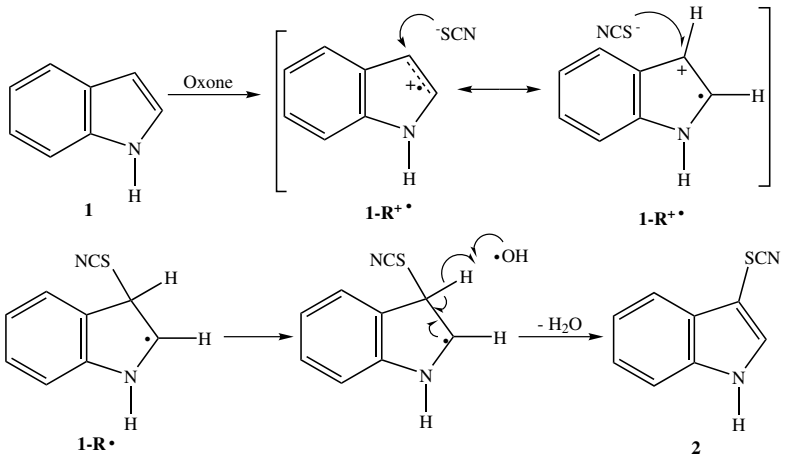
Aromatic amino compounds (**1i** and **k**) were readily converted to the mono-thiocyanated products (**2i** and **k**) with high *para*-selectivity. Since aromatic amino compounds could be oxidized, some highly polar by-products, easily dissolvable in water, were formed. It led to a decreased yield of thiocyanated products.

In order for the reaction mechanism to be proposed, the reduction potential of oxone and the oxidation potential of indole and ammonium thiocyanate were determined in anhydrous methanol.[8] The reduction and oxidation potentials of oxone and indole were estimated to be +0.325 V and −1.050 V, respectively. Yet, ammonium thiocyanate exhibited no oxidation potential. So, it might be assumed that oxone oxidized indole rather than ammonium thiocyanate. The oxidation occurs at the C–C double bond on the hetero-, five-membered ring of indole, giving a cation radical of indole (**1-R**$^{+\cdot}$), which was stabilized by a resonance effect. It was followed by nucleophilic attack of $^{-}$SCN at the 3-position. The radical (**1-R**$^{\cdot}$) so formed then undergoes a 3-H-abstraction by $^{\cdot}$OH generated from oxone[9] during its reduction, affording the end product, as depicted in

Table 2. Solvent effects on the thiocyanation of **1a**

Solvent	Time[a] (h)	Yield[b] (%)
Methanol	0.7	98
Acetonitrile	8	98
Tetrahydrofuran	48	97
Dichloromethane	48	53
Carbon tetrachloride	48	0

[a] The reaction time.
[b] Isolated yields of the products after column chromatography.



Scheme 2.

Scheme 2. Otherwise, the effect of solvent on the thiocyanation indicates that polar solvents highly favor the thiocyanation. It implies that: (a) a development of charge separation or a formation of ionic species most likely occur, and (b) the nucleophilicity of $^{-}$SCN may be enhanced.

This approach, due to the commercial availability of reagents, mild reaction conditions, and good yields of mono-thiocyanation products, makes it accessible to organic preparations.

Acknowledgment

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References and notes

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6. Data for the selected products: compound **2a**, solid, mp 72–73 °C; IR (KBr) ν_{max} 3344, 3389, 2158, 1453, 1416, 1234, 736, 667, 592 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 2H, $J = 9.9$ Hz, $J = 6.9$ Hz), 7.42 (m, 1H, $J = 9.9$ Hz, $J = 7.2$ Hz), 7.48 (d, 1H, $J = 3$ Hz), 7.08 (dd, 1H, $J = 5.7$ Hz, $J = 3$ Hz), 8.70 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 131.1, 127.5, 123.7, 121.8, 118.5, 112.2, 112.1, 91.52; MS (EI) *m/z* 174 (M^+), 148, 142, 120, 77, 45. Anal. Calcd for $C_9H_6N_2S$: C, 61.8; H, 3.5; N, 16.20; S, 18.4. Found: C, 62.0; H, 3.5; N, 16.1; S, 18.4. Compound **2d**, solid, mp 113–115 °C; IR (KBr) ν_{max} 3304, 3132, 2152, 1624, 1582, 1485, 1452, 1408, 1291, 1201, 1161, 1017, 803, 706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.900 (s, 3H), 6.926 (dd, 1H, $J = 2.4$ Hz, $J = 2.7$ Hz, $J = 9$ Hz), 7.17 (d, 1H, $J = 2.4$ Hz), 7.27 (d, 1H, $J = 9$ Hz), 7.42 (d, 1H, $J = 2.7$ Hz), 8.754 (s, 1H); ^{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; MS (EI) *m/z* 204 (M^+), 189, 178, 161, 134, 102. Anal. Calcd for $C_{10}H_8N_2OS$: C, 58.7; H, 3.5; N, 13.9; O, 7.9; S, 15.8. Found: C, 58.8; H, 3.9; N, 13.7; O, 7.8; S, 15.6. Compound **2g**, solid, mp 177–179 °C; IR (KBr) ν_{max} 3393, 2155, 1603, 1461, 1444, 1313, 1253, 1230, 1196, 1164, 769, 750 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 3.385 (s, 1H), 4.036 (s, 3H), 7.216 (t, 1H, $J = 7.5$ Hz), 7.28 (s, 1H), 7.38 (t, 1H, $J = 7.5$ Hz), 8.11 (d, 1H, $J = 8$ Hz), 8.11(d, 1H, $J = 8$ Hz), 8.34 (s, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 157.1, 143.0, 140.06, 125.6, 122.5, 119.9, 117.8, 111.7, 111.2, 101.8, 94.7, 56.3; MS (EI) *m/z* 254 (M^+), 239, 211, 153, 140, 127, 69, 63. Compound **2h$_a$**, colorless liquid, IR (KBr) ν_{max} 3336, 2160, 1531, 1423, 1120, 1076, 1029, 821, 737, 681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.273 (dd, H, $J = 3$ Hz, $J = 6.3$ Hz), 6.643 (m, 1H, $J = 1.5$ Hz, $J = 3.6$ Hz,$J = 3.9$ Hz), 6.968 (m, 1H, $J = 1.5$ Hz, $J = 3$ Hz, $J = 4.5$ Hz), 8.917 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.3, 120.1, 111.1, 110.9, 102.8; MS (EI) *m/z* 124 (M^+), 98, 70, 39. Compound **2h$_b$**, colorless solid, mp 99–102 °C; IR (KBr) ν_{max} 3273, 3124, 2161, 1522, 1415, 1386, 1229, 1101, 1032, 799, 689, 539, 403 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.487 (d, 2H, $J = 2.4$ Hz), 4.76 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 121.2 (2C), 110.9 (2C), 109.4 (2C); MS (EI) *m/z* 181(M^+), 123, 96, 69. Anal. Calcd for $C_6H_3N_3S_2$: C, 40.2; H, 1.3; N, 23.56; S, 34.91. Found: C, 39.7; H, 1.6; N, 23.2; S, 34.91. Compound **2i**, solid, mp 51–52 °C; IR (KBr) ν_{max} 3420, 3347, 3245, 2144, 1636, 1594, 1494, 1298, 1176, 823, 520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (br s, 2H, NH), 6.67 (d, 2H, $J = 8.7$ Hz), 7.32 (d, 2H, $J = 8.7$ Hz); ^{13}C NMR (75 Hz, $CDCl_3$) δ 148.8,

134.5 (2C), 116.0 (2C), 112.4, 109.4; MS (EI) m/z 150 (M^+), 124, 118, 106, 80, 65. Anal. Calcd for $C_7H_6N_2S$: C, 56.4; H, 4.1; N, 18.7; S, 20.8. Found: C, 56.0; H, 4.0; N, 18.7; S, 21.3.

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8. Redox potentials were measured in anhydrous methanol at ambient temperature using cyclic voltammetry performed on an electrochemical analyzer (model CHI 760B), which was connected to a PC with the Origin 6.0 software. One Pt flag was used as the working electrode, another Pt flag as the auxiliary electrode, and $HgCl_2$/Hg as the reference electrode. $NaClO_4$ was applied to a background electrolyte.
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