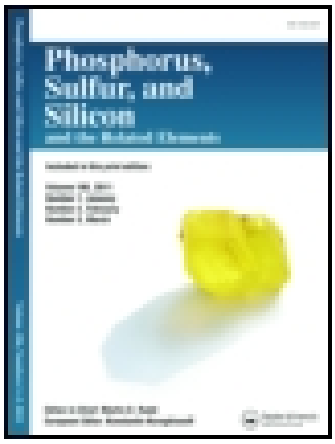

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$AlCl_3$-Promoted Thiocyanation Of N-Containing Aromatic And Heteroaromatic Compounds Under Solvent-Free Conditions

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$AlCl_3$-PROMOTED THIOCYANATION OF *N*-CONTAINING AROMATIC AND HETEROAROMATIC COMPOUNDS UNDER SOLVENT-FREE CONDITIONS

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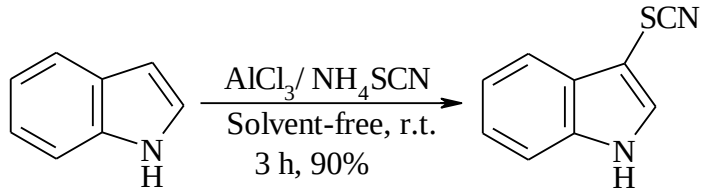
Abstract Aluminum chloride/Ammonium thiocyanate ($AlCl_3/NH_4SCN$) was found to be an effective system for the thiocyanation of some arylamines and indoles to afford the corresponding thiocyanated adducts at room temperature under solvent-free conditions. The efficacy of this combined reagent was also examined in the thiocyanation of pyrrole and isatin. A plausible mechanism of thiocyanation has also been suggested.



1a **2a**

Running title $AlCl_3$ THIOYANATION OF AROMATIC COMPOUNDS

Keywords Thiocyanation; Indole; $AlCl_3$; Solvent-free conditions

INTRODUCTION

The thiocyanation of aromatic and heteroaromatic compounds is an important transformation in both organic synthesis and pharmaceuticals.[1,2] Organic compounds containing the thiocyano group have been used as precursors for agrochemical, dyes, and drugs.[3] This moiety is a significant functionality in several anticancer agents.[4] Most applications of thiocyanate motif have been observed when it is used as a functional group on *N*-bearing (hetero)arene compounds. The thiocyanated *N*-containing chemicals have excessive key application. Nitrogen occurs in all living organisms, primarily in amino acids and thus proteins and in the nucleic acids (DNA and RNA).[5] Several methods for the thiocyanation of (hetero)aromatic systems using various reagents such as oxone/NH_4SCN,[6] *N*-thiocyanosuccinimde,[7] $FeCl_3/NH_4SCN$,[8] cerric ammonium nitrate (CAN)/NH_4SCN,[9] Montmorillonite K-10 clay/NH_4SCN,[10] Poly(4-diacetoxyiodo)styrene (PDAIS)/NH_4SCN,[11] acidic Al_2O_3/NH_4SCN,[12] $HCl/H_2O_2/KSCN$,[13] trichloroisocyanuric acid (TCCA)/NH_4SCN/wet SiO_2,[14] and citric acid/KSCN/H2O2[15] have been explored. Although the reported methods are efficient, but some of them have disadvantages including low yields, strongly acidic conditions, long reaction times, high temperatures and use of expensive and toxic reagent or solvent. So developing new protocols for thiocyanation of organic compounds is still in demand.

Anhydrous $AlCl_3$ is probably the most commonly-used Lewis acid. This white relative non-toxic powder with LD50 = 3730 mg/kg is moisture-adsorbent. It has been extensively used as a strong Lewis acid in many organic reactions such as Friedel-Crafts reactions and Fries rearrangement.[16,17] Recently, $AlCl_3$ has been employed for some other transformations such as

the synthesis of 5-benzoylacenaphthene,[18] selective synthesis of 2-aryl-2*H*- and 4-aryl-4*H*-3,5-diformylpyrans,[19] asymmetric aldehydes arylation,[20] 1,4-dihydropyridines synthesis,[21] cycloadditions of activated cyclopropanes and aromatic aldehydes,[22] 1,2,3,4-tetrahydroquinolines synthesis,[23] and substituted guanidines synthesis.[24]

In continuation of research interest on thiocyanation of *N*-containing (hetero)aromatic organics,[25] herein we report $AlCl_3$ as a commercially available and low-cost promoter for thiocyanation of some *N*-containing heteroaromatics and *N*-activated arenes in the presence of NH_4SCN at room temperature under solvent-free conditions (Scheme 1 and Table 2).

RESULTS AND DISCUSSION

To investigate the optimized reaction condition, initial studies were performed by indole **1a** as a substrate model. The results are summarized in Table 1. Optimization of the temperature effect confirmed that room temperature condition is appropriate (entries 1, 2). By checking various amounts of NH_4SCN and $AlCl_3$, we attended that molar ratio $NH_4SCN/AlCl_3$ (2/1) afforded the best results (entries 2-5).The effect of solvent have also been examined .The data showed that the solvent-free condition is the most effective situation (entries 2, 6 and 7). In order to be sure about the promoting role of $AlCl_3$ in thiocyanation reaction, the model reaction was verified in the presence of 2 mmol of NH_4SCN without any $AlCl_3$ (entry 8). Comparison of the results affirmed the particular promoting activity of $AlCl_3$.

Therefore, performing the reaction with substrates (1 mmol), $AlCl_3$ (1 mmol) and NH_4SCN (2 mmol) at room temperature under solvent-free condition has been chosen as the optimized situation for our procedure. The result of different aromatic and heteroaromatic thiocyanation has

been summarized in Table 2. According to data on Table 2, indole **1a**, and its electron donating derivatives such as 2-methyl-indole **1b** and 1-methyl indole **1c** thiocyanated at their 3-position successfully. 5-bromoindole **1d** as an electron-withdrawing candidate of Indole derivatives yielded its corresponding 3-thioyanato-5-bromoindole **2d**. Isatin **1e** as another *N*-bearing heteroaromaitc thiocyanated at 5-position successfully. It must be mentioned that literature reports for isaitn thiocyanation is rare. Carbazole **1f** produced its correspondence 4-thiocyanato derivative prosperously. Pyrrole, as an example of heteroarene, created 2-thiocyanatopyrrole **2g**. This result also demonstrates the regioselectivity of the method as 2,5-dithiocyanatopyrrole hasn't been obtained. To display the efficacy of $AlCl_3$ for thiocyanation of a wide range of *N*-containing organic compounds, we accomplished the thiocyanation reaction with aniline as an *N*-activated aromatic example. 4-Thiocyantoaniline **2h** was the only product. In the next step, *N*-methylaniline, *N*,*N*-dimethylaniline and *N*,*N*-diethylaniline thiocyanated at their para position consequently (Table 2, **1i**-**1k**). Creation of 4-thiocyanato-2-iodoaniline **2l** demonstrates that thiocyanation of anilines occurred at para position selectively. Surprisingly, utilizing of 3-methylindole **1m** as another substrate, compound **2m** has been gained as the only product. Characterization of this compound, which followed by comparison of its spectral data with literature, [10,26] confirmed that it is an autoxidation product of skatole.

Although the tenuous mechanism of thiocyanation is not clear yet, but we have suggested a plausible mechanism for $AlCl_3$-promoted thiocyanation (Scheme 2). It seems that anhydrous $AlCl_3$ can create a complex with NH_4SCN to form **A**. Nucleophilic attack of indole **1a** to **A** which followed by a proton-release leads to the corresponding thiocyanated product **2a**. On the

other hand, $AlCl_3$ as a strong Lewis acid, can produce acid-base complexes with the nitrogen loan pair in *N*-containing heteroaromatics like indole and also arylamines like aniline (Scheme 2, **B** & **C**). It is obvious that the intermediate between aniline and $AlCl_3$ **B**, is more intensive than **C**. This Vigorous interaction captivate the nitrogen loan pair of aniline so tightly that the thiocyanating reaction of aniline **1h** hasn't progressed under solvent-free conditions. 4-Thiocyanatoaniline formation accelerated in the presence of CH_3OH as solvent. The solvent media may weaken the tight complex **C** and therefore nucleophilic attack of SCN^+ to the free form of aniline causes the product **2h**.

Finally, in order to show the superiority of $AlCl_3/NH_4SCN$ over other thiocyanating systems, the results of the present study for the synthesis of 3-thiocyanato-2-methylindole **2b** are compared with some other results reported in the literature in Table 3. The data have indicated that the recent procedure is a noteworthy route for thiocyanation.

CONCLUSION

In summary, $AlCl_3/NH_4SCN$ has been employed as a novel and highly efficient system for the thiocyanation reaction of *N*-bearing (hetero)aromatic compounds at room temperature under solvent-free conditions. $AlCl_3$ is commercially available, inexpensive and non-volatile chemical which is commonly found in organic laboratories and could be dehydrated by conventional heating. This non-corrosive, Lewis acid promotes NH_4SCN activation for the nucleophilic attack of substrates. Furthermore, the regioselectivity of the protocol has been also investigated in thiocyanation of pyrrole and anilines where the mono-thiocyanatopyrrole and para-

thiocyanatoanilines corresponding adduct has been gained. In addition, the absence of hazardous and non-green solvents and easy work-up in addition with wide-range thiocyanating power for different substrates are some other noteworthy advantages of the reported procedure.

EXPERIMENTAL

General

Chemicals and solvents were purchased from Merck, Aldrich and Alfa Aesar and used without further purifications except some liquid anilines which have been distilled before usage. Commercial $AlCl_3$ was heated and its sublimated anhydrous form was used. Melting points were determined using a Stuart Scientific apparatus and were uncorrected. All products were identified by their spectral data. IR spectra (KBr discs, 500-4000 cm^{-1}) were recorded using a Bruker FTIR model Tensor 27 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ solvent on a Brucker 400 MHz spectrometer. Mass spectra were obtained on Platform II spectrometer from Micromass; EI mode at 70 eV. The elemental analysis were determined using a Thermofinnigan Flash EA 1112 series instrument. Preparative layer chromatography (PLC) was carried out on 20×20 cm^2 plates, coated with a 1 mm layer of Merck silica gel PF_{254}, and prepared by applying the silica as slurry and drying in air. Yields refer to isolated products.

General procedure for thiocyanation of N-containing hetero(aromatic) compounds by $AlCl_3/NH_4SCN$ at room temperature under solvent-free condition

A mixture of substrates **1a-m** (1 mmol), anhydrous $AlCl_3$ (1 mmol) and NH_4SCN (2 mmol) was stirred at room temperature. The progress of the reaction was monitored by TLC (eluent: *n*-

hexane:EtOAc, 9:2). After completion (0.45-7 h), the residue was diluted with distillated water (20 mL) and extracted with chloroform (2 × 20 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The resulting crude product was purified by plate chromatography on silica gel (PLC) to afford the pure products **2a-m** (52-98%, Table 2). All the products were characterized by comparison of their spectroscopic data (FTIR, ^{1}H-NMR and Mass spectra) with those of the authentic samples in literature. The spectroscopic data of a selected compound **2l** is given below.

2-Iodo-4-thiocyanatoaniline (2l) Pale brown solid, mp 140 °C; IR (KBr, Cm^{-1}): υ= 3406 (NH_2), 3269 (NH_2), 2068 (SCN), 1599, 1486, 1285, 1108, 766 (N-H), 689 (C-S); ^{1}H-NMR ($CDCl_3$, ppm): δ= 4.39 (br s, 2H, NH_2), 6.77 (d, 1H, *J*= 8.47 Hz), 7.28 (dd, 1H, *J*= 8.46 & 2.14 Hz), 7.50 (d, 1H, *J*= 2.14 Hz) ppm; ^{13}C-NMR ($CDCl_3$, ppm): δ= 146.3. 133.7, 132.1, 119.6, 116.5, 112.1, 109.7; EI-MS (m/z, %) 276 [M^+] (86), 217 [M^+-HSCN] (45), 202 [M^+-SCN, -NH_2] (36), 91 [M^+-I, -SCN] (30), 77 [C_6H_5] (15); Anal. calcd. for C_7H_5NSI: C, 32.08; H, 1.92; N, 5.34 %, Found: C, 32.10; H, 1.95; N, 5.26 %.

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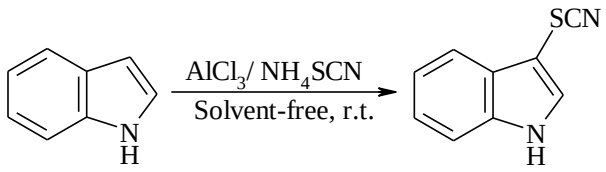
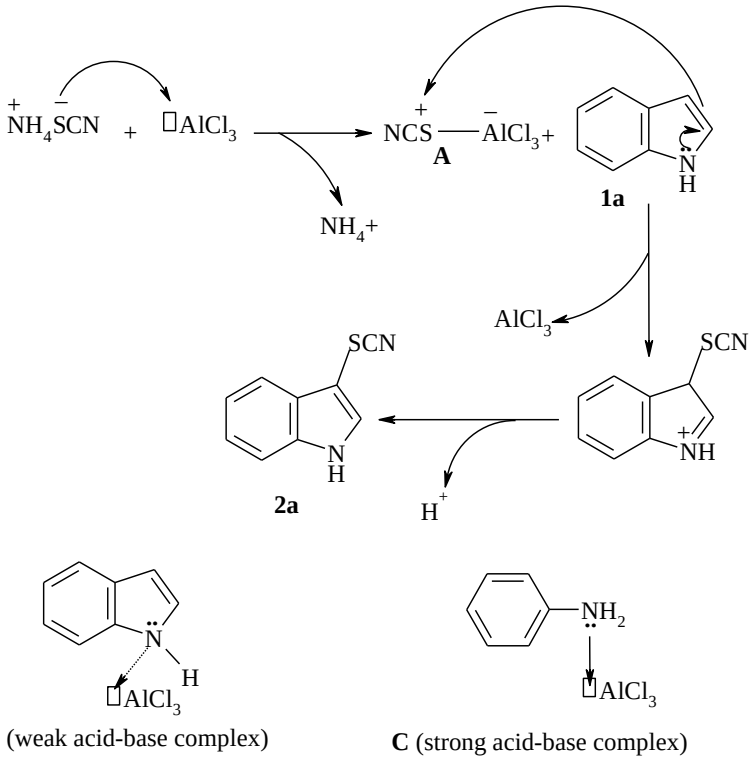


1a **2a**

Scheme 1



B (weak acid-base complex) **C** (strong acid-base complex)

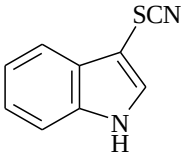
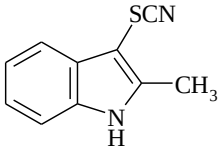
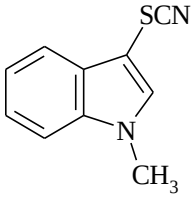
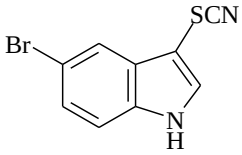
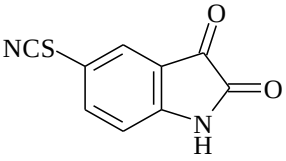
Scheme 2

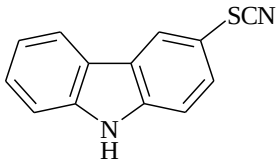
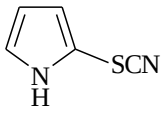
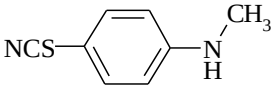
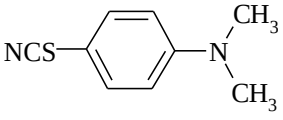
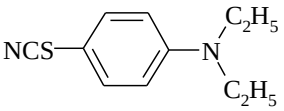
Table 1 Optimization of the reaction conditions for the synthesis of 3-thiocyanatoindole **2a**

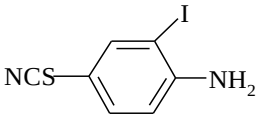
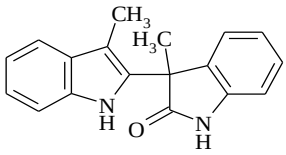
Entry	Condition[a]	Temperature (°C)	Time (h)	Yield[b] (%)
1	$AlCl_3$/NH_4SCN molar ratio (1/2)/ solvent-free	r.t.	3	90
2	$AlCl_3$/NH_4SCN molar ratio (1/2)/ solvent-free	50	3	90
3	$AlCl_3$/NH_4SCN molar ratio (1.5/2)/ solvent-free	r.t.	2	30
4	$AlCl_3$/NH_4SCN molar ratio (1/1)/ solvent-free	r.t.	4	45
5	$AlCl_3$/NH_4SCN molar ratio (0.5/2)/ solvent-free	r.t.	2.5	28
6	$AlCl_3$/NH_4SCN molar ratio (1/2)/ MeOH[c]	r.t.	3	75
7	$AlCl_3$/NH_4SCN molar ratio (1/2)/ CH_3CN[c]	r.t.	4	80
8	NH_4SCN (2 mmol)/ solvent-free	r.t.	6	20

[a]1 mmol of indole (**1a**) was used. [b]Isolated yields. [c]5 mL of solvent was used.

Table 2 Thiocyanation of aromatic and heteroaromatic compounds with NH_4SCN in the presence of $AlCl_3$ under solvent-free conditions at room temperature

Substrate		Product		Time (h)	Yield (%)	mp .(°C)
Indole	**1a**		**2a**	3	90	101-102[12]
2-Methylindole	**1b**		**2b**	1	98	99-101[12]
1-Methylindole	**1c**		**2c**	1.45	80	83-84[11]
5-Bromoindole	**1d**		**2d**	2.5	93	127-129[11]
Isatin	**1e**		**2e**	7	91	201[8]

Carbazole	**1f**		**2f**	6.5	87	90-92[10]
Pyrrole	**1g**		**2g**	6	52	Liquid[13]
Aniline	**1h**		**2h**	7	93[d]	51-52[8]
N-methylaniline	**1i**		**2i**	2	64	Liquid[14]
N,*N*-dimethylaniline	**1j**		**2j**	1	80	71-72[14]
N,*N*-diethylaniline	**1k**		**2k**	4.45	89	

						82[15]
2-Iodoaniline	**1l**		**2l**	2.5	71	140
3-Methylindole	**1m**		**2m**	0.45	67	198[26]

[a]All products were characterized by comparison of their spectroscopic data (IR, ^{1}H-NMR) with those reported in literature. [b]Yield of isolated product. [c] Reference of known compounds. [d] The reaction performed in the presence of 5 mL CH_3OH

Table 3 Comparison of some other procedures with the present work for the synthesis of 3-thiocyanato-2-methylindole **2b**[a]

Entry	Condition[a]	Time	Yield	Ref.
1	PDAIS/NH_4SCN molar ratio (1.2/2.5)/ CH_3CN/ r.t.	1	78	11
2	$FeCl_3$/NH_4SCN molar ratio (1.5/2.5)/ CH_2Cl_2/ r.t.	3	92	8
3	K-10 clay/NH_4SCN (2 g/3 mmol)/ solvent-free/ 80° C	3	92	10
4	CAN/NH_4SCN molar ratio (2.3/1.2)/ MeOH/ r.t.	0.25	84	9
5	$AlCl_3$/NH_4SCN molar ratio (1/2)/ solvent-free/ r.t.	1	98	This work

[a]1 mmol of 2-methylindole **1b** has been used.