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An Efficient Method for Thiocyanation of Aromatic and Heteroaromatic Compounds using Cyanuric Chloride and Ammonium Thiocyanate under Conventional and Nonconventional Conditions

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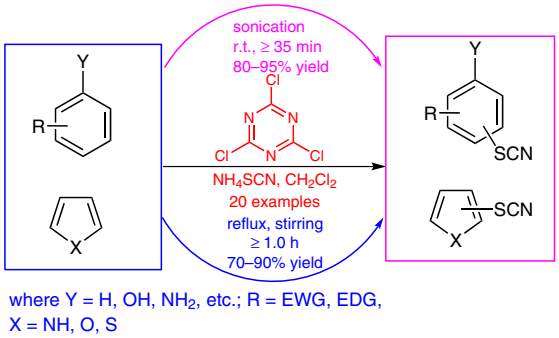

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Abstract Highly efficient thiocyanation of aromatic and heteroaromatic compounds has been accomplished by using cyanuric chloride $(NCCl)_3$/NH_4SCN in dichloromethane under conventional and ultrasonic-assisted conditions. Sonicated reactions reached completion with reduced reaction times. The protocol involves a simple workup.

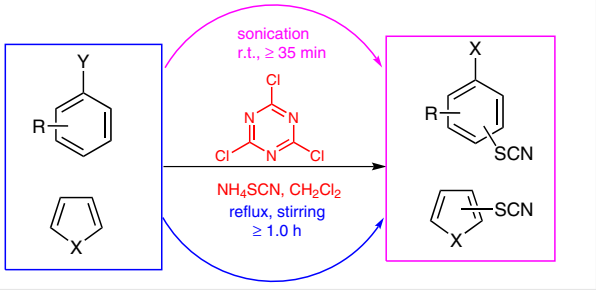
Key words aromatic compounds, heteroaromatic compounds, thiocyanation, cyanuric chloride, sonication

Electrophilic thiocyanation is a useful way of introducing a C–S bond into aromatic or heteroaromatic substrates because nucleophilic attack of the thiocyanate ion at an aromatic nucleus through displacement reactions is not an easy way to form thiocyanated compounds.[1–5] The thiocyanate group can be easily converted into other functional groups such as sulfide,[6–9] aryl nitrile,[10] thiocarbamate,[11] and thionitrile.[12] Several useful thiocyanation protocols have been developed for C–S bond formation using thiocyanate.[13–20] An efficient microwave (MW) assisted protocol[13] developed by Varma et al. promoted nucleophilic substitution of alkyl halides or tosylates with alkali azides, thiocyanates, or sulfinates in aqueous media, and the reaction tolerated a range of functionalities. A novel and highly selective method has been accomplished by Iranpoor and coworkers[14] to convert alcohols, thiols, carboxylic acids, silyl ethers, and silyl carboxylates into their corresponding thiocyanates by using triphenylphosphine, diethylazodicarboxylate, and NH_4SCN. Ionic liquids[15] [bmim][X] (X = Cl, Br, I, OAc, SCN) were developed as highly efficient reagents by Liu et al. for nucleophilic substitution reactions of sulfonate esters. This protocol is highly attractive because ionic liquids do not require additional solvents for activation. In addition, ionic liquids can be readily recycled. A cross-coupling reaction of arylboronic acids with KSCN has been developed by Sun et al.[16] Copper acetate has been used as a catalyst in the presence of 4-methylpyridine (serving both as ligand and base) under 0.2 MPa of molecular oxygen. Yadav's research group[19,20] developed two different protocols with economically viable laboratory desktop reagents such as $FeCl_3$ and SCN for the α-thiocyanation of ketones and potassium thiocyanate, and anhydrous $FeCl_3$ to produce dithiocyanate derivatives from olefins under mild conditions. The versatility of the thiocyanate group has stimulated further exploration into the use of several other reagents for thiocyanation of aromatic and heteroaromatic compounds.[21–40] Noteworthy reagents include: bromine/potassium thiocyanate (only for indoles),[31] *N*-thiocyanato succinimide (only for 5-methoxy-2-methylindole and accompanied by two bisthiocyanates),[32] cerium(IV) ammonium nitrate (CAN),[33] acidic montmorillonite K10 clay,[34] iodine/methanol, oxone,[35] diethyl azodicarboxylate,[36] (IL-$OPPh_2$),[37] potassium peroxydisulfate-copper(II),[38] (KSCN/H_2O_2), (KSCN/H_5IO_6)[39] and boron sulfonic acid (BSA)[40] as a new catalyst and KSCN/H_2O_2 for efficient regioselective thiocyanation of indoles and N,N-disubstituted anilines. Recently, we have reported the use of ammonium metavanadate[41] and zeolite H-SDUSY powder (CBV720)[42] for efficient thiocyanation of aromatic and heteroaromatic compounds in acetonitrile medium.

1,3,5-Triazine derivatives have a wide range of applications, and the chemistry of these compounds has been the subject of several reviews.[43–48] Cyanuric chloride or 2,4,6-trichloro-1,3,5-triazine (TCTA) has emerged as an activating agent for carboxylic acids.[44] It is employed for the effective conversion of alcohols and carboxylic acids into alkyl and acyl chlorides, respectively.[45] Cyanuric chloride gives Gold's reagent [$Me_2NCH{=}NCH{=}NMe_2^+Cl^-$] upon heating with *N*,*N*-dimethylformamide (DMF). Gold's reagent is a versatile reagent for aminoalkylations and is a precursor of heterocy-

cles.[46,47] Cyanuric chloride can also be used as an alternative to oxalyl chloride in the Swern oxidation.[49] A perusal of the literature reveals several reports on the use of TCTA as an environmentally friendly reagent.[50,51] We have recently reported its use for the preparation of the Vilsmeier–Haack reagent, replacing oxychlorides such as $POCl_3$, and successfully used it for the synthesis of quinoline derivatives from acetanilides.[52]

Encouraged by these results, we chose to explore the application of TCTA for the thiocyanation of aromatic and heteroaromatic compounds using ammonium thiocyanate under conventional and nonconventional conditions such as sonication (Scheme 1).[53–56] On this point, an efficient and novel method for thiocyanation of aromatic and heteroaromatic compounds using trichloroisocyanuric acid/ammonium thiocyanate/wet SiO_2 has been recently reported by Akhlaghinia et al.[57]



Scheme 1 Cyanuric chloride/NH_4SCN triggered thiocyanation of aromatic compounds

The data presented in Table 1 show that the most suitable conditions employ a 1:1:1 molar ratio of aromatic substrate/cyanuric chloride/ammonium thiocyanate. Under these conditions, a wide range of organic compounds such as benzene, arenes, phenols, anisoles, anilines, naphthalene, and heteroaromatic compounds underwent thiocyanation, as shown in Table 2. Products were analyzed spectroscopically, and all data were consistent with our earlier reports.[41,42]

The data presented in Table 2 show that benzene and a range of substituted aromatic compounds were thiocyanated selectively under the optimized conditions. *Ortho*-disubstituted substrates underwent thiocyanation at the *para*-position, whereas *para*-disubstituted substrates underwent thiocyanation at the *ortho*-position (entries 3 and 4). Phenols, anisoles, and anilines also followed a similar trend (entries 5–13). Phenol underwent thiocyanation at the *ortho*-position, whereas 4-bromophenol afforded 4-bromo-2-thiocyanatophenol. Heteroaromatic compounds such as thiophene, indole, and pyrrole were also easily transformed into the monothiocyanated products. However, reaction time did not correlate with the presence of electron-donating or electron-withdrawing substituents. The by-product

Table 1 Effect of Solvent and Concentration of the Catalyst

Solvent	TCTA (mol)	Phenol		Aniline		Pyrrole	
		Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
CH_2Cl_2	0.001	10.0	20	10.0	20	10.0	20
CH_2Cl_2	0.010	6.0	50	6.0	45	6.0	40
CH_2Cl_2	0.100	4.0	60	4.0	60	4.0	60
CH_2Cl_2	0.300	1.0	90	1.0	90	1.0	92
DCE	0.100	4.0	60	4.0	60	4.0	60
DCE	0.300	1.0	80	1.0	75	1.0	85
$CHCl_3$	0.300	6.0	30	6.0	35	6.0	30
THF	0.300	10.0	35	10.0	35	10.0	30
MeCN	0.300	10.0	35	10.0	35	10.0	30

was easily removed by washing with water. The reaction times and yields are comparable with those obtained using trichloroisocyanuric acid (TCICA) with ammonium thiocyanate and wet SiO_2.[57]

The data also show that reactions were sometimes sluggish at room temperature, and these required heating to reflux to achieve convenient reaction times. This prompted us to consider sonication. The pioneering work of Mason, Suslick, and others[53–56] has revealed that ultrasonication leads to cavitation, which induces very high local temperatures in the liquid and enhances mass transfer. In such cases, useful increases in reaction rate were observed (Table 2 entries 3, 4, 6, and 8)

In summary, we have developed a cyanuric chloride/ammonium thiocyanate triggered electrophilic thiocyanation of aromatic and heteroaromatic compounds in dichloromethane at room temperature and under sonication. Conversions that were sluggish at room temperature occurred smoothly at room temperature on sonication, with reduced the reaction times.

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Table 2 Thiocyanation of Aromatic and Heteroaromatic Compounds using Cyanuric Chloride /Ammonium Thiocyanate

Entry	Substrate	Product	Conventional heat reflux		Sonication at room temp.	
			Time (h)	Yield (%)	Time (min)	Yield (%)
1	benzene	thiocyanatobenzene	1	94	35	90
2	toluene	thiocyanatotoluene	1	90	40	87
3	*o*-xylene	1,2-dimethyl-4-thiocyanatobenzene	3	82	50	85
4	*p*-xylene	1,4-dimethyl-2-thiocyanatobenzene	3	80	55	83
5	phenol	2-thiocyanatophenol	1	90	35	92
6	4-bromophenol	4-bromo-2-thiocyanatophenol	3	83	40	90
7	anisole	1-methoxy-4-thiocyanatobenzene	2	85	40	87
8	1-methoxy-2-methyl benzene	1-methoxy-2-methyl-4-thiocyanatobenzene	4	95	60	90
9	aniline	4-thiocyanatoaniline	1	90	35	93
10	*o*-toluidine	2-methyl-4-thiocyanatobenzenamine	2	92	35	88
11	*o*-choloroaniline	2-choloro-4-thiocyanatoaniline	3	88	45	93
12	*N*-methylaniline	4-thiocyanato-*N*-methylaniline	3	88	45	93
13	*N*,*N*-dimethylaniline	4-thiocyanato-*N*,*N*-dimethylaniline	2	96	50	90
14	thiophene	2-thiocyanatothiophene	1	90	30	95
15	pyrrole	2-thiocyanato-1*H*-pyrrole	1	92	35	88
16	indole	3-thiocyanato-1*H*-indole	1	85	35	80
17	1-methylindole	1-methyl-3-thiocyanatoindole	1	80	30	80
18	naphthalene	thiocyanatonaphthalene	1	90	39	85
19	1-methoxynaphthalene	1-methoxy-4-thiocyanatonaphthalene	1	85	35	85
20	diphenylamine	dithiocyanatodiphenylamine	1	70	30	75

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(58) **Thiocyanation of Organic Compounds; Typical Procedure:** Phenol (32 mmol) was added to a mixture of cyanuric chloride (32 mmol) and ammonium thiocyanate (31.6 mmol) in CH_2Cl_2 (30 mL) and the mixture was heated to reflux with stirring. The progress of the reaction was monitored by TLC (*n*-hexane–EtOAc, 7:3). For ultrasonically assisted reactions, the reaction mixture was ultrasonicated in a TCL (BIO-Technics India) sonicator and the progress of the reaction was followed by TLC. Upon completion of the reaction, the mixture was filtered, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed. The residue was purified by chromatography on silica (*n*-hexane–EtOAc) to afford 2-thiocyanatophenol. Yield: 90% (thermal) and 92% (ultrasonication). ^{1}H NMR ($CDCl_3$): δ = 7.14 (d, *J* = 8.1 Hz, 1 H), 6.73 (m, *J* = 7.9 Hz, 2 H), 6.54 (d, *J* = 8.1 Hz, 1 H), 4.83 (s, 1 H). MS: *m*/*z* = 151.