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Rapid and efficient thiocyanation of phenols, indoles and anilines in 1,1,1,3,3,3-hexafluoro-2-propanol under ultrasound irradiation

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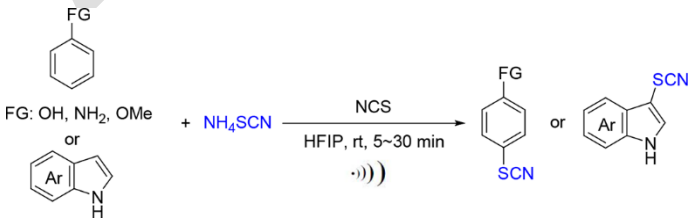
ABSTRACT

An efficient ultrasound-promoted thiocyanation of phenols, indoles and anilines in the presence of *N*-chlorosuccinimide (NCS) and NH_4SCN using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the solvent has been developed. The major features of the present protocol include the mild reaction conditions, short reaction times, good to excellent yields and broad substrate scope. Moreover, scale-up synthesis can be achieved and the solvent can be easily recovered and reused.

GRAPHICAL ABSTRACT



KEYWORDS: 1,1,1,3,3,3-hexafluoro-2-propanol; thiocyanation; ultrasound irradiation; green chemistry

1. Introduction

Aryl thiocyanates have been receiving considerable attention since thiocyano groups widely exist in natural products and pharmaceutical ingredients.[1,2] The thiocyano groups often serve as useful blocks for the preparation of valuable sulfur-containing compounds, and can be readily transformed into other useful functional groups.[3–13] Thereby, the introduction of a thiocyano group into a molecule is of great importance and still remains a challenge. Over the past decades, a series of synthetic protocols have been developed for thiocyanation of arenes.[14–25] However, the reported procedures still associated with some disadvantages such as the use of a large excess of strong oxidizing agents, the use of the expensive metal catalysts, long reaction times or unsatisfactory yields.

Recently, we focused on developing mild, efficient and green electrophilic thiocyanation protocols.[26] The utilization of *N*-thiocyanatosuccinimide, XSCN (X = halogen), which was generated *in situ* from from *N*-halosuccinimide and an inorganic thiocyanate has proven to be successful.[27,28] However, for the cheap and readily available NCS/NH_4SCN combination, it showed relatively lower reactivity compared with the NBS/NH_4SCN combination. This phenomenon may be ascribed to the strong N−Cl bond. An additive such as thiourea was thus required to accelerate the reaction rate through hydrogen bonding. It is well known that HFIP has

some unique properties such as high hydrogen bonding donor ability, high ionizing power, low nucleophilicity and good solvation capability with water, making them popular as green solvent in organic transformations.[29,30] We envisioned that HFIP can activate NCS via hydrogen bonding, thereby facilitating the cleavage of N−Cl bond and the formation of ClSCN. In another aspect, the utilization of ultrasound irradiation in organic synthesis has been received much attention since it involves energy conservation and generates minimal waste. Particularly, better yields and chemoselectivity can be achieved under milder reaction conditions within shorter reaction times.[31–35] Herein, we report a rapid and efficient thiocyanation protocol using NCS/NH_4SCN combination in HFIP under ultrasound irradiation (Scheme 1).

2. Results and Discussion

Initially, phenol **1a** and ammonium thiocyanate were selected as the substrates to optimize the reaction conditions. The results are summarized in **Table 1**. The solvents were vital for this reaction. Reactions in acetonitrile, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,4-dioxane, and methanol afforded the product **2a** in only trace yield. Switching the solvent to tetrahydrofuran (THF), dichloromethane (DCM), ethyl acetate (EtOAc) and 2,2,2-trifluoroethanol (TFE) afforded the desired products in 60%, 86%, 52%, and 81% yield, respectively (entries 2, 3, 7 and 9). Pleasingly, it was found that the reaction proceeded very quickly in HFIP under ultrasonic irradiation, giving the desired product in 90% yield after 5 minutes (entry 10). These results suggested that both dissolving capacity and hydrogen bonding donor ability of the solvent played

important roles in this reaction. Further increasing the amounts of ammonium thiocyanate and NCS to 1.5 equivalents led to a full conversion of phenol, giving the desired product **2a** in almost quantitative yield (entry 11). Moreover, slight decrease in the product yield was observed for when ammonium thiocyanate was replaced by NaSCN or KSN (entries 12 and 13). Expectedly, **2a** was not observed in the absence of NCS, indicating *N*-thiocyanatosuccinimide was the key intermediate (entry 14). Particularly, the reaction selectively took place at the *para* position, and nearly no chlorinated phenol was observed as the by-product. This results indicated that the reaction between NCS and NH_4SCN was much faster than the chlorination of phenol. Finally, only 37% yield of **2a** was obtained in the absence of ultrasonic irradiation (entry 15). This phenomenon was attributed that ultrasonic irradiation could greatly enhance the reaction rates via increasing the mixing between reactants and accelerating the diffusion of reactants and products.[36]

The thiocyanation reaction of various phenols under the optimized reaction conditions was then examined (**Table 2**). To our delight, phenols with electron-donating groups such as methyl, *tert*-butyl and methoxyl underwent the reaction smoothly to afford the corresponding products in excellent yields (90~99%). Anisole also showed good activity to give product **2k** in 95% yield. Notably, the thiocyanation reaction exclusively occurred at the *para* position. For the *meta*-substituted phenols, excellent yields could be obtained by prolonging the reaction time (**2g** and **2h**). Substrate bearing electron-withdrawing group such as bromo also survived the reaction conditions, delivering the desired product **2f** in 72% yield after 30 min. Moreover, the

thiocyanation of 1-naphthol took place at the 8-position of the naphthalene ring, resulting in product **2j** in 93% yield. Interestingly, a stable oxathioimine **2i** was isolated as the major product in 84% yield when using *p*-methylphenol as the substrate.[37]

Encouraged by these results, we next investigated the thiocyanation of indoles and anilines (**Table 3**). As seen from the results, a series of indoles and anilines showed good activities to provide the corresponding products in good to excellent yields. For indole derivatives, functional groups such as halo, alkoxy, alkyl, ester and nitro were well tolerated under the standard conditions, albeit substrates with electron-withdrawing groups afforded relatively lower yields (**5c**~**5g**). *N*-methyl indole also reacted smoothly to deliver the desired product in 93% yield, while *N*-Boc indole gave only trace amount of the desired product. Interestingly, when 3-methyl-1*H*-indole was employed as the substrate, both products **5l** and **5m** were observed in 24% and 47% yields, respectively. Generally, electrophilic thiocyanation at 3-position of 3-methyl-1*H*-indole could deliver product **5l**.[24,38] Meanwhile the thiocyanation reaction could also occur at the 2-position due to the steric hindrance. The 2-thiocyanated indole could be further attacked by succinimide anion or Cl^- to lose a CN^-. Then the generated 3-methyl-1*H*-indole-2-thiolate was protonated and rearranged to give the product **5m**.[26] Different aniline derivatives were then checked and excellent yields were obtained. It was worth noting that the thiocyanation reaction was regioselectively occurred at the *para* position. Similar with *ortho*-substituted phenols, the benzo[*d*]thiazol-2-amines **6g** and **6h** were isolated as the major products when using *para*-

substituted anilines as the substrates. This result was attributed that that *ortho*-thiocyanation reaction occurs at the first step, followed by the addition of hydroxyl or amino group to the thiocyanato group.[37] Moreover, *N*-substituted aniline derivatives such as *N*-methylaniline and acetanilide also showed good activities, affording the desired products **6f** and **6i** in good yields.

Furthermore, gram-scale synthesis of product **2a** was performed to show the practical application of the present protocol (Scheme 2). The reaction reacted well and afforded **2a** in 95% yield (10 mmol scale). Moreover, the solvent HFIP could be recovered via evaporation.

Some control experiments were then conducted to gain insight into this reaction. For example, when a radical inhibitor 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was added to the mixture, the reaction still proceeded smoothly without obviously decreasing of the yield of **2a**, indicating that the reaction did not involve a radical pathway. According to previous literature and our experiment results,[26–28] a plausible reaction mechanism was proposed in Scheme 3. First, reaction of NCS and NH_4SCN generated *N*-thiocyanatosuccinimide. The addition of $^+$SCN to phenol provided intermediate **A**, which was attacked by **B** to deliver the final product **2a** via deprotonation. In these processes, HFIP was a good solvent, and meanwhile, could activate NCS via hydrogen bonding to accelerate the formation of *N*-thiocyanatosuccinimide, namely the SCN cation. In another aspect, the utilization of ultrasonic irradiation also greatly enhanced the reaction rate.

3. Conclusion

In summary, we have developed a facile and efficient thiocyanation reaction of phenols, indoles and anilines using NCS/NH_4SCN combination in HFIP under ultrasonic irradiation. In the present protocol, HFIP not only worked as a good solvent but also greatly accelerated the formation of SCN cation via activation of NCS through hydrogen bonding. Mild reaction conditions, good to excellent yields, as well as broad substrate scope were the major features of the present protocol. Moreover, gram-scale synthesis could be achieved, demonstrating its practical use in organic synthesis.

4. Experimental

4.1 Apparatus and analysis

All reagents were obtained from local commercial suppliers and used without further purification. The progress of the reaction was monitored by TLC using analytical-grade silica gel plates (GF254) under UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded $CDCl_3$ or DMSO-d_6 at 300 MHz and 75 MHz (Bruker Avance) instrument respectively, using TMS as internal standard. Chemical shifts are given in parts per million (δ, ppm) and the coupling constants J are given in Hz. Mass spectrometry was performed on an LCMS-2010 EV (Shimadzu) instrument with an ESI source. High-resolution mass spectrometry (HRMS) was performed on a TOF MS instrument with an ESI source. The sonication was performed in a CD-4831 ultrasonic cleaner (with a frequency of 50 kHz and a nominal power 170 W; Codyson Co. Ltd., China). The reaction temperature of the water bath was controlled at room temperature (25 ^{o}C).

4.2 General procedure for thiocyanation of phenols, indoles and anilines

To a solution of *N*-chlorosuccinimide NCS (1.5 mmol, 200.3 mg) in HFIP (5 mL) was added ammonium thiocyanate (1.5 mmol, 114.2 mg) at room temperature. The mixture was stirred for 5 min. Then phenol (indole or aromatic amine) (1 mmol) was added immediately, and the mixture was placed in an ultrasound bath (monitored by TLC). After reaction, the HFIP was removed via evaporation. The residue was extracted with ethyl acetate and washed with water. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate to afford the pure desired product. (**CAUTION**: HFIP is highly toxic and corrosive. It should be used in a fume cupboard with all appropriate precautions taken.)

4.3 Selected spectral data

5-methylbenzo[d][1,3]oxathiol-2-imine (2i):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.99 (d, J = 1.0 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 149.0, 134.2, 127.5, 123.6, 121.9, 110.7, 21.0. HRMS (ESI) calcd. for C_8H_8NOS [M + H] + 166.0321, found 166.0329.

8-Thiocyanatonaphthalen-1-ol (2j):

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.34 – 8.17 (m, 2H), 7.88 (d, J = 8.1 Hz, 1H), 7.77 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.62 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 6.98 (d, J = 8.1 Hz,

1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.3, 136.6, 133.8, 128.7, 125.9, 125.8, 124.3, 123.3, 112.4, 108.7, 107.5. HRMS (ESI) calcd. for $C_{11}H_8NOS$ [M + H] + 202.0321, found 202.0315.

Acknowledgements

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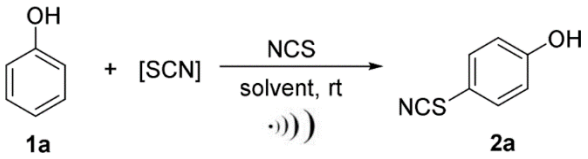
Table 1. Optimization of reaction conditions for thiocyanation of phenol.[a]

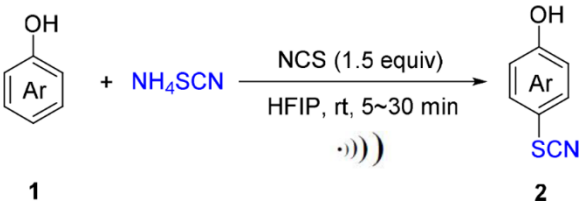


Entry	Solvent	SCN source (equiv)	NCS (equiv)	Time (min)	Yield (%)[b]
1	CH_3CN	NH_4SCN (1.2)	1.2	30	trace
2	THF	NH_4SCN (1.2)	1.2	30	60
3	DCM	NH_4SCN (1.2)	1.2	15	86
4	DMF	NH_4SCN (1.2)	1.2	30	trace
5	DMSO	NH_4SCN (1.2)	1.2	30	trace
6	dioxane	NH_4SCN (1.2)	1.2	30	trace
7	EtOAc	NH_4SCN (1.2)	1.2	30	52
8	MeOH	NH_4SCN (1.2)	1.2	30	trace
9	CF_3CH_2OH	NH_4SCN (1.2)	1.2	15	81
10	HFIP	NH_4SCN (1.2)	1.2	5	90
11	HFIP	NH_4SCN (1.5)	1.5	5	> 99

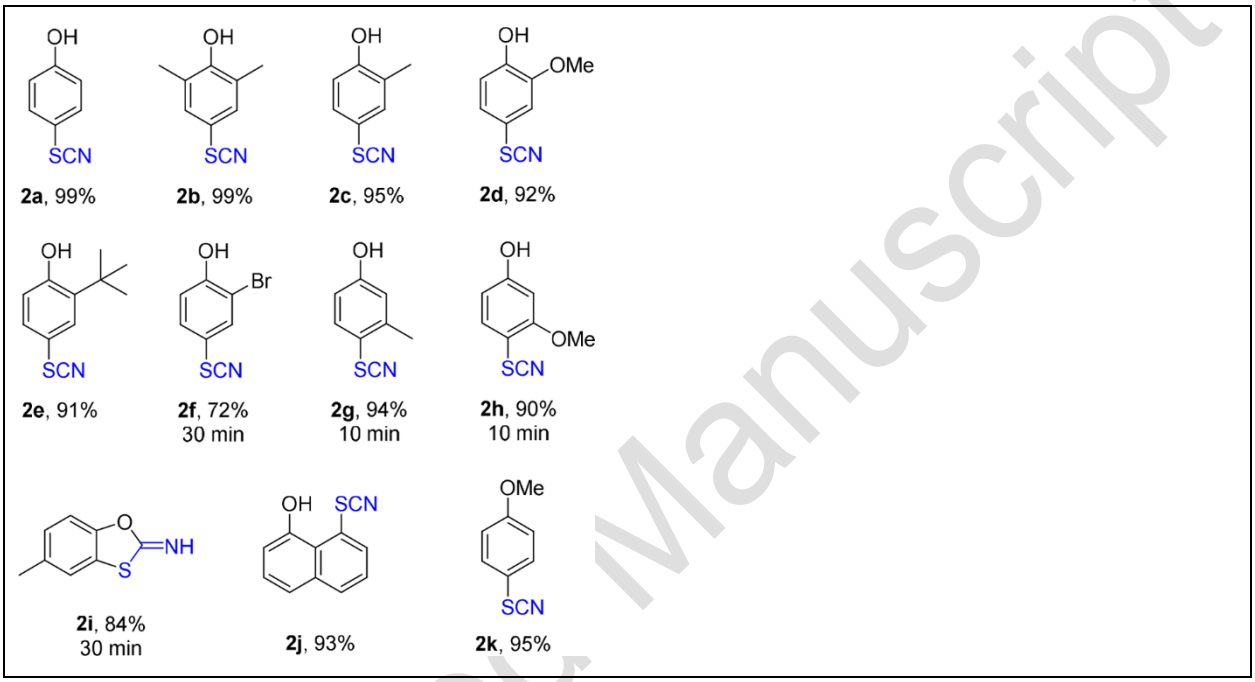
12	HFIP	NaSCN (1.5)	1.5	5	93
13	HFIP	KSCN (1.5)	1.5	5	95
14	HFIP	NH_4SCN (1.5)	-	30	no reaction
15	HFIP	NH_4SCN (1.5)	1.5	15	37[c]

[a] Reaction conditions: the mixture of **1a** (1 mmol), thiocyanate salt and NCS in a solvent (5 mL) was reacted under ultrasonic irradiation at room temperature. [b] Isolated yield. [c] In the absence of ultrasonic irradiation.

Table 2. Reaction scope for phenols.[a]

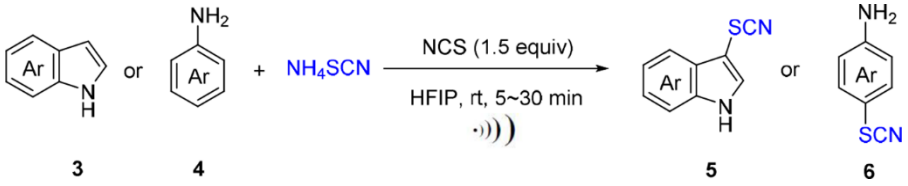


1 **2**

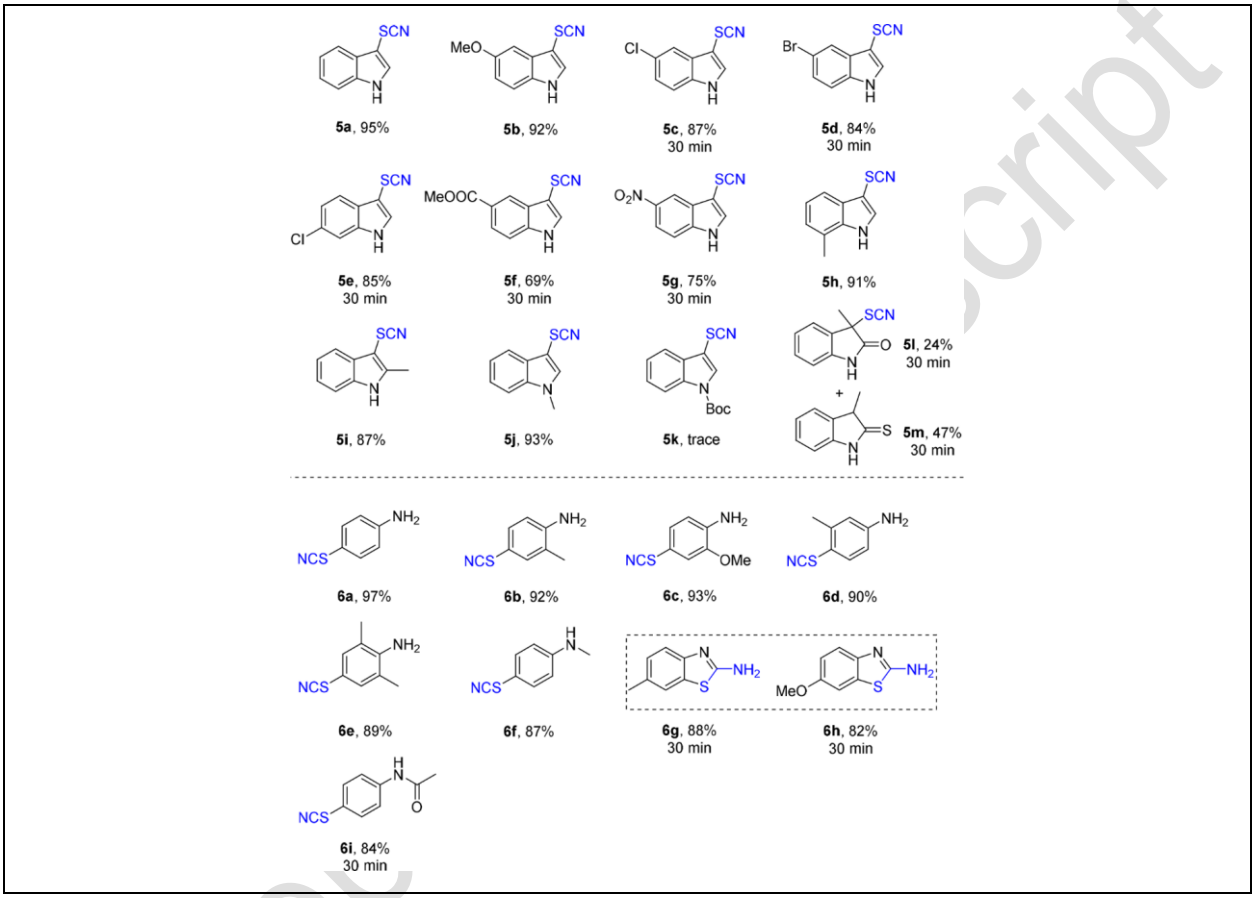


[a] Reaction conditions: **1** (1 mmol), NH_4SCN (1.5 mmol), NCS (1.5 mmol), HFIP (5 mL), room temperature, ultrasonic irradiation, 5 min, isolated yields.

Table 3. Thiocyanation of indoles and anilines.[a]

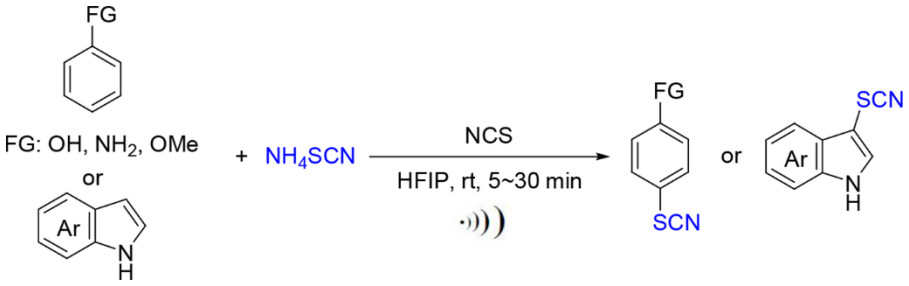


3 4 5 6

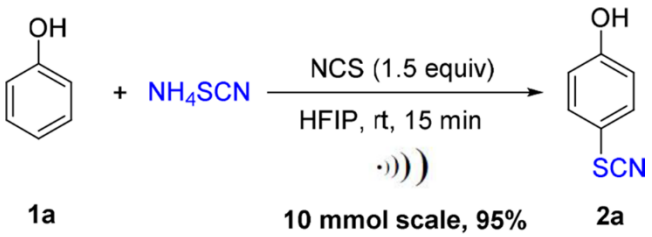


[a] Reaction conditions: **3** or **4** (1 mmol), NH_4SCN (1.5 mmol), NCS (1.5 mmol), HFIP (5 mL), room temperature, ultrasonic irradiation, 5 min, isolated yields.

Scheme 1. Ultrasound-promoted thiocyanation reactions in HFIP.



Scheme 2. Gram-scale synthesis of **2a.**



Scheme 3. Plausible mechanism.