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Sulfuryl Fluoride Promoted Thiocyanation of Alcohols: A Practical Method for Preparing Thiocyanates

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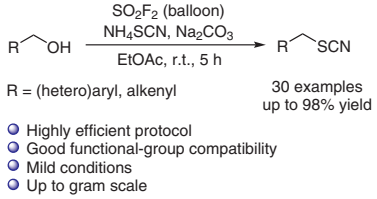

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Abstract A novel SO_2F_2-promoted thiocyanation method for the one-step synthesis of thiocyanates through C–O bond cleavage of readily available alcohols with ammonium thiocyanate as the thiocyanating agent was developed. The method avoids the use of additional catalyst, and a variety of (hetero)arene, alkene and aliphatic alcohols reacted with high efficiency in ethyl acetate under mild conditions to afford the corresponding thiocyanates in excellent to quantitative yields with broad functional-group compatibility.

Key words sulfuryl fluoride catalysis, alcohols, thiocyanation, ammonium thiocyanate, thiocyanates

Organic thiocyanate compounds are versatile intermediates in organic synthesis, and are widely used in syntheses of pharmaceuticals, dyes, natural products, and agrochemicals; they are also used as biologically active molecules. The favorable physiochemical profile and chemical stability of organic thiocyanates combine to propel the thiocyanate group to the forefront among the functional groups employed in the design of modern bioactive molecules. The resulting molecules, which are used in many applications, include the histone deacetylase inhibitor psammaplin B,[1] the *Trypanosoma cruzi* growth inhibitor (4-phenoxyphenoxy)ethyl thiocyanate,[2] and the nematocidal agent thiocyanatin A (Figure 1).[3] Furthermore, given the wide range of functions that thiocyanates perform in synthetic chemistry, further conversions of such thiocyanates are essential to increasing their utility.[4] As such, efficient methods for the construction of alkyl thiocyanates, especially from readily available starting materials, are of great significance in organic synthesis.

Because of the versatile applications of thiocyanates, many routes for their synthesis have been reported in the literature in recent years. One of the most frequently adopted methods for the preparation of alkyl thiocyanates is the nucleophilic substitution of alkyl halides or pseudohalides with thiocyanate salts (Scheme 1a).[5] However, this strategy has certain limitations because of the need for prior installation at a predetermined position of a halogen atom that is not an essential part of the target molecule. In recent years, the functionalization of thiols has become a highly attractive strategy for assembling alkyl thiocyanates. There is no doubt that direct thiocyanation of thiols is a more efficient and attractive alternative to the use of alkyl thiocyanates because of its high economy of steps and atoms (Scheme 1b).[6] However, most of the above-mentioned procedures suffer from such drawbacks as a need for photocatalysts or ligands or their high cost. In 2009 and 2014, Azadi and Asgharzadeh reported that cross-coupling of alcohols with NH_4SCN to give thiocyanates, providing a more convenient protocol for the synthesis of these compounds (Scheme 1c).[7] Regrettably, however, this reaction requires an additional trivalent phosphorus reagent (Ph_2PCl) and relatively harsh reaction conditions.

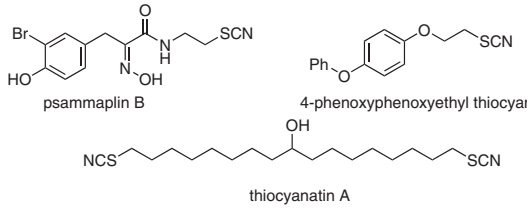

Figure 1 Representative bioactive alkyl thiocyanates

Sulfuryl fluoride (SO_2F_2)[8] is an inexpensive and stable reagent that has attracted significant attention in recent years due to its use in sulfonyl(VI) fluoride ion-exchange (SuFEx) systems.[9] Since 2014, SO_2F_2 has been widely used in other chemical transformations in addition to its application in SuFEx-based click reactions. Qin and co-workers re-

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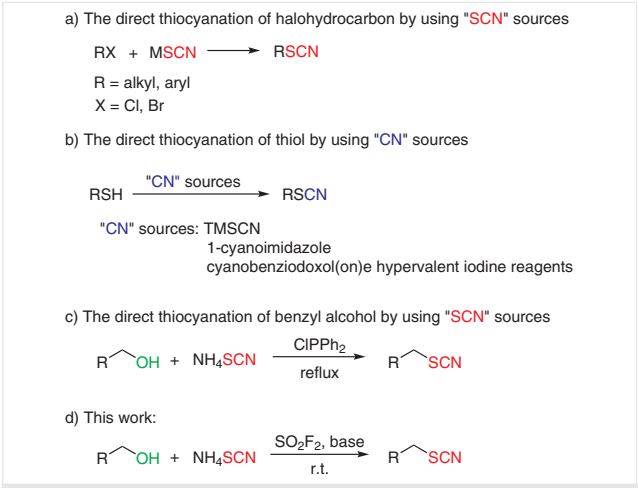
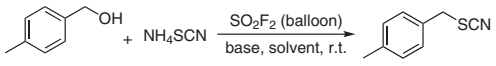


Scheme 1 Strategies for the synthesis of thiocyanates

ported applications of SO_2F_2 in syntheses of a range of compounds, including heterocycles,[10a–e] nitriles,[10f–h] diarylmethanes,[10i] arylcarboxylic acids,[10j] alkynes,[10k] and amides.[10l–m] Our group recently reported a mild and practical method for efficiently converting aldehydes or aldoximes into the corresponding nitriles that is mediated by SO_2F_2 and a base in an economical and green manner.[11] Soon afterwards, we also reported the use of SO_2F_2 and a base as a simple catalyst system for effectively promoting Beckmann rearrangement of ketoximes into amides or lactams[12] and a cascade process for directly converting nitriles into cyanamides through a SO_2F_2-activated Tiemann rearrangement.[13] Inspired by our preliminary research results[14] and the unique properties of SO_2F_2, we surmised that SO_2F_2 might similarly be able to react with alcohols to form intermediate sulfonyl esters that should serve as excellent leaving groups. Here, we report a highly efficient, mild, and widely applicable SO_2F_2-promoted thiocyanation of alcohols with ammonium thiocyanate (NH_4SCN) at room temperature (Scheme 1d).

We chose 4-methylbenzyl alcohol (**1b**) as a model substrate to test the feasibility of our proposed cross-coupling of alcohols with thiocyanates (Table 1). To our delight, the desired product, 4-methylbenzyl thiocyanate (**2b**), was isolated in 70% yield under an SO_2F_2 atmosphere at room temperature when 3.0 equivalents of triethylamine (Et_3N) were employed with CH_3CN (Table 1, entry 1). Encouraged by this initial result, we performed a further screening of the reaction conditions with respect to the base and solvent (see the Supporting Information for a more detailed account of the optimization process). The examination indicated that the performance of inorganic bases was superior to that of organic bases (Table 1, entries 1–5). Interestingly, we found that the yields of **2b** decreased markedly when the organic and inorganic strong bases DBU and *t*-BuOK, respectively, were used (entries 2 and 3), whereas the use of Et_3N and Na_2CO_3 assisted the reaction more efficiently to generate the desired product **2b** in yields of 70 and 86%, respectively (entries 1 and 5). The solvents 1,4-dioxane, dimethyl sulfoxide, dichloromethane, and ethyl acetate were also screened (entries 6–9). Compared with CH_3CN, 1,4-dioxane and EtOAc were more effective for this transformation and promoted this reaction to provide product **2b** in yields of 91 and 92%, respectively (entries 6 and 9). Subsequently, increasing the loading of Na_2CO_3 to 4.0 equivalents gave **2b** in an excellent yield of 95% (entry 10). Note, however, that increasing the loading of Na_2CO_3 to 5.0 equivalents caused an obvious decrease in the yield of **2b** to 84% (entry 11). Furthermore, on decreasing the loading of NH_4SCN to 1.0 equivalents, product **2b** was obtained in almost quantitative (97%) yield (entry 12). Increasing the amount of NH_4SCN did not significantly improve the yield of this transformation, possibly because of the higher reactivity of thiocyanate (entries 10 and 12–14). Moreover, reducing the concentration of the substrate resulted in an inferior 84% isolated yield of **2b** (entry 15). Therefore, the optimal conditions for the reaction of alcohols with thiocyanates involve the use of Na_2CO_3 (4.0 equiv), and NH_4SCN (1.0 equiv) in EtOAc (2.0 mL) with stirring at room temperature under an SO_2F_2 atmosphere (SO_2F_2 balloon) for five hours, and these

Table 1 Optimization of the Reaction Conditions[a]



1b **2b**

Entry	Base (equiv)	Solvent	Isolated yield (%)
1	Et_3N (3.0)	CH_3CN	70
2	DBU (3.0)	CH_3CN	38
3	*t*-BuOK (3.0)	CH_3CN	58
4	K_2CO_3 (3.0)	CH_3CN	77
5	Na_2CO_3 (3.0)	CH_3CN	86
6	Na_2CO_3 (3.0)	1,4-dioxane	91
7	Na_2CO_3 (3.0)	DMSO	67
8	Na_2CO_3 (3.0)	CH_2Cl_2	21
9	Na_2CO_3 (3.0)	EtOAc	92
10	Na_2CO_3 (4.0)	EtOAc	95
11	Na_2CO_3 (5.0)	EtOAc	84
12[b]	Na_2CO_3 (4.0)	EtOAc	97
13[c]	Na_2CO_3 (4.0)	EtOAc	94
14[d]	Na_2CO_3 (4.0)	EtOAc	95
15[e]	Na_2CO_3 (4.0)	EtOAc	84

[a] Reaction conditions:**1b** (1.0 mmol), NH_4SCN (4.0 equiv), base, solvent (2.0 mL, 0.5 M), SO_2F_2 balloon, r.t., 5.0 h.
[b] NH_4SCN (1.0 equiv).
[c] NH_4SCN (2.0 equiv).
[d] NH_4SCN (3.0 equiv).
[e] EtOAc (5.0 mL, 0.25 M).

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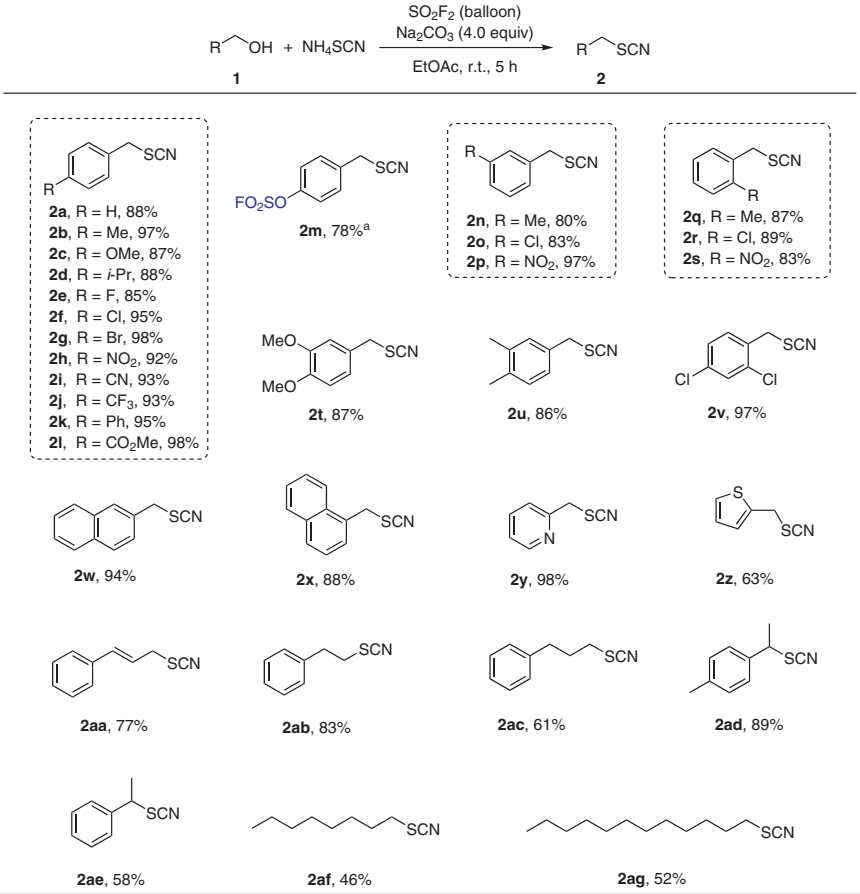
were chosen as the standard conditions for examinations of the functional-group tolerance and substrate scope of the reaction.

Having established the optimal conditions, we turned our attention to examining the substrate scope of this method (Scheme 2). Various substituted alcohols were successfully thiocyanated to give the corresponding alkyl thiocyanates. Gratifyingly, a broad range of *para*-substituted benzylic alcohols reacted smoothly to afford the corresponding thiocyanates in good to excellent yields with broad functional-group tolerance.[15] Benzylic alcohols bearing electron-donating (R = Me, OMe, *i*-Pr, Ph) substituents on the aromatic ring reacted smoothly to give the corresponding alkyl thiocyanates **2b–d** and **2k** in good to excellent yields. Moreover, substrates bearing an electron-withdrawing group such as F, Cl, Br, NO_2, CN, or CF_3 on the aromatic ring similarly afforded the products **2e–j** in yields of 85–98%. Of particular note was the effective reaction of sterically hindered *m*- and *o*-substituted benzylic alcohols, which provided the products **2n–s** in excellent yields. In the presence of triethylamine as base, 4-(hydroxymethyl)phenol gave the fluoridosulfate **2m** in 78% yield.[16] Furthermore, several polyfunctionalized benzylic alcohols and naphthylmethanols were also successfully converted into the corresponding thiocyanates **2t–v**, **2w**, and **2x** in moderate to excellent yields. Two heteroarylmethanols were also assessed: excitingly, the novel system showed promising activity for the thiocyanation of pyridin-2-ylmethanol and 2-thienylmethanol, giving the corresponding products **2y** and **2z** in yields of 98 and 63%, respectively. Moreover, cinnamyl and aliphatic alcohols underwent thiocyanation to give the corresponding thiocyanates **2aa–ac**, **2af**, and **2ag** in yields of 77, 83, 61, 46 and 52%, respectively. Notably, secondary benzylic alcohols also underwent thiocyanation to give the corresponding thiocyanates **2ad** and **2ae** in isolated yields of 89 and 58%, respectively.

To explore the synthetic utility of this SO_2F_2-promoted cross-coupling in the presence of Na_2CO_3, a gram-scale preparation of methyl 4-(thiocyanatomethyl)benzoate (**2l**), a synthetic precursor for the assembly of trifluoromethyl sulfides,[4e] was performed (Scheme 3). On extending the reaction time to nine hours under otherwise standard conditions, the reaction of methyl 4-(hydroxymethyl)benzoate (**1l**) proceeded smoothly, delivering the desired product **2l**



Scheme 2 Substrate scope for the thiocyanation of alcohols. *Reagents and conditions*: **1** (1.0 mmol), NH_4SCN (1.0 mmol, 1.0 equiv), Na_2CO_3 (4.0 mmol, 4.0 equiv), EtOAc (2.0 mL, 0.5 M), stirring, r.t., SO_2F_2 balloon. Isolated yields based on **1** are reported. [a] Et_3N (4 mmol).

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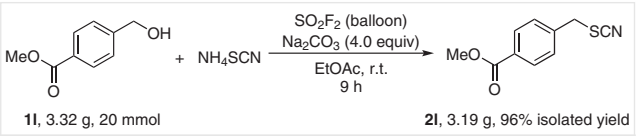
in 96% isolated yield, confirming that this method could serve as a valuable and convenient tool for practical applications in the laboratory.



1l, 3.32 g, 20 mmol **2l**, 3.19 g, 96% isolated yield

Scheme 3 Gram-scale synthesis of methyl 4-(thiocyanatomethyl)benzoate

In conclusion, an efficient, general, atom-economical method has been developed for the synthesis of thiocyanates from alcohols, catalyzed by readily available and inexpensive SO_2F_2. A wide range of alcohols underwent this transformation, producing the corresponding alkyl thiocyanates in modest to high yields with excellent functional-group compatibility and high efficiency. In addition, the reaction can be readily conducted on a gram scale in excellent yield.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707151.

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(15) **4-Methylbenzyl Thiocyanate (2b); Typical Procedure**
4-Methylbenzyl alcohol (**1b**; 1.0 mmol, 1.0 equiv), NH_4SCN (1.0 mmol, 1.0 equiv), Na_2CO_3 (4.0 mmol, 4.0 equiv), and EtOAc (2.0 mL, 0.5 M) were added sequentially to an oven-dried 30 mL reaction tube equipped with a stirrer bar. The tube was sealed

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with a plastic stopper and SO_2F_2 gas was introduced into the stirred mixture by slow bubbling from an SO_2F_2-filled balloon at r.t. for 5 h. The mixture was then diluted with H_2O and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to dryness. The residue was purified by chromatography (silica gel, EtOAc–PE) to give a yellow oil; yield: 158 mg (97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 2 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 4.13 (s, 2 H), 2.35 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 131.3, 129.8, 128.9, 112.1, 38.3, 21.2. HRMS (EI): *m/z* [M$^+$] calcd for C_9H_9NS: 163.0456; found: 163.0458.

(16) **4-(Thiocyanatomethyl)phenyl Fluoridosulfate (2m)**

4-(Hydroxymethyl)phenol (**1m**; 1.0 mmol, 1.0 equiv), NH_4SCN (1.0 mmol, 1.0 equiv), Et_3N (4.0 mmol, 4.0 equiv), and EtOAc (2.0 mL, 0.5 M) were added sequentially to an oven-dried 30 mL reaction tube equipped with a stirrer bar. The tube was sealed with a plastic stopper and SO_2F_2 gas was introduced into the stirred mixture by slow bubbling from an SO_2F_2-filled balloon at r.t. for 5 h. Workup as described above gave a colorless oil; yield: 193 mg (78%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.7 Hz, 2 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 4.16 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.1, 135.5, 131.1, 121.8, 111.2, 37.1. HRMS (EI): *m/z* [M$^+$] calcd for $C_8H_6FNO_3S_2$: 246.9773; found: 246.9796.

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