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Metal-Free Trifluoromethylthiolation of Alkyl Electrophiles via a Cascade of Thiocyanation and Nucleophilic Cyanide–CF_3 Substitution

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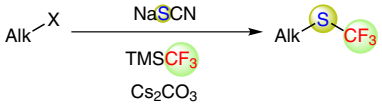

– simple and environmentally benign system
– one-pot protocol
– 22 examples in high yields

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Abstract A straightforward synthesis of alkyl trifluoromethyl thioethers was developed that starts from widely available alkyl halides or mesylates and the inexpensive reagents sodium thiocyanate and trimethyl(trifluoromethyl)silane. The alkyl electrophiles are converted in situ into the corresponding thiocyanates, which react with the nucleophilic Ruppert–Prakash reagent to give the corresponding trifluoromethyl thioethers via a Langlois-type CN–CF_3 substitution. This process enables the efficient introduction of the pharmaceutically meaningful trifluoromethylthio groups into functionalized molecules without the need of metal catalysts or expensive preformed trifluoromethylthiolating agents.

Key words trifluoromethylthiolation, alkyl halides, fluorine, nucleophiles, sulfur

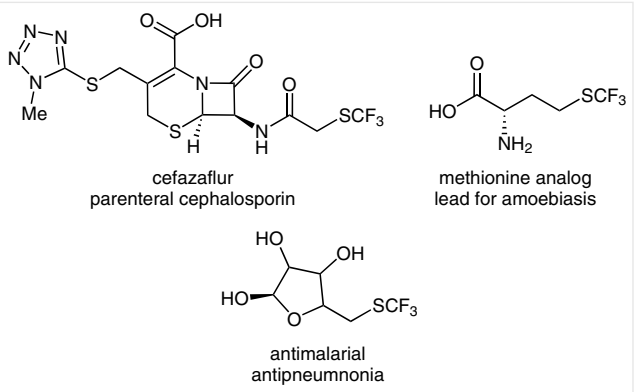


Figure 1 Biologically active alkyl trifluoromethyl thioethers

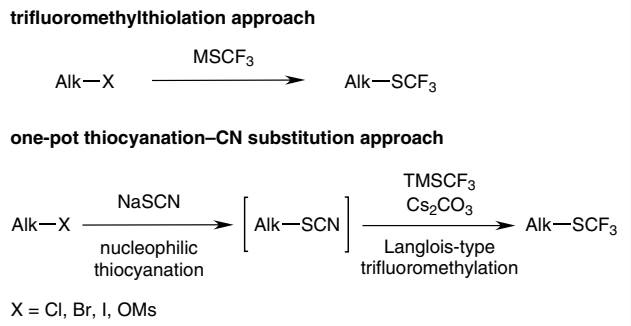
Around 40% of marketed agrochemicals and 25% of pharmaceuticals contain fluorine atoms. Fluorine-containing residues are central functionalities in bioactive compounds, because they induce higher lipophilicity and metabolic stability.[1] The unique properties of fluorinated groups have led to the development of a range of sustainable concepts for the late-stage introduction of trifluoromethyl groups.[2] In recent years, the focus has shifted towards the corresponding trifluoromethylthio groups,[3] since these enhance the lipophilicity of druglike molecules even more than their trifluoromethylated analog (Hansch constant 1.44 for SCF_3 vs. 0.88 for CF_3).[4] This property improves the bioavailability of drug molecules due to their more effective transport through lipid membranes.[3d,e]

The trifluoromethylthio moiety is a key functionality for example in the antibiotic cefazaflur, in a trifluoromethylthiolated methionine analogue with antimalarial properties, and in a ribose derivative with antipneumnonia activity (Figure 1).[3b,5]

Traditional strategies for the synthesis of trifluoromethylthio groups include halogen–fluorine exchange reactions of trihalomethyl thioethers,[6] as well as the trifluoromethylation of thiols, disulfides, and related compounds.[7] However, these methods are limited by substrate availability. Recently, various methods for the introduction of trifluoromethylthio groups into aromatic substrates via electrophilic,[8] nucleophilic,[9] radical,[10] or oxidative methods have been reported.[11] The synthesis of alkyl trifluoromethyl thioethers is less studied.[3e,12] Contemporary syntheses start from diazo compounds,[13] alcohols,[14] halides,[15] or carboxylic acids[16] or proceed via C–H activation following methods by Tang, Chen, Rüping, or Qing.[17] However, each of these methods calls for preformation of SCF_3 reagents.[18]

Efficient methods for the late-stage introduction of trifluoromethylthio groups into functionalized molecules based on widely available leaving groups and inexpensive, easy-to-use reagents are still highly sought-after.

We envisioned that the nucleophilic displacement of the CN group in thiocyanates by CF_3 using $TMSCF_3$, as originally reported by Langlois et al., might be the key towards such a process.[7e] If this transformation could be combined in one pot with a straightforward synthesis of the alkyl thiocyanates from alkyl halides or pseudohalides, the overall protocol would allow accessing valuable trifluoromethyl thioethers without the need for preformed trifluoromethylthiolation reagents (Scheme 1).



Scheme 1 Strategies to access alkyl trifluoromethyl thioethers

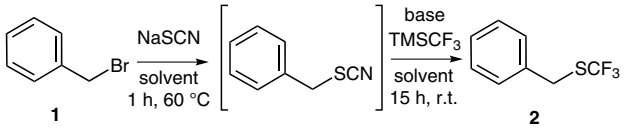
In the context of our work on di- and trifluoromethylation methods,[19] we discovered that for the synthesis of aryl di- and trifluoromethyl thioethers the envisioned approach is viable starting from diazonium salts.[20] However, since the nucleophilic substitution of alkyl halides with thiocyanate salts requires substantially higher temperatures than do Sandmeyer processes, it was doubtful whether the sensitive Ruppert–Prakash reagent would tolerate this initial reaction step.

In order to probe the viability of our projected approach, we started with benzyl bromide (**1**) as a model substrate and investigated its nucleophilic substitution with sodium thiocyanate, with addition of the trifluoromethylating agent $TMSCF_3$ following complete formation of the alkyl thiocyanate (Table 1). In order to combine both steps to a true one-pot procedure, it was crucial to identify solvents and conditions that would be equally effective for both steps.

The nucleophilic substitution of bromide with sodium thiocyanate was found to proceed best in polar aprotic solvents such as DMF. GC analysis revealed that full conversion was reached within one hour at 60 °C. However, when adding $TMSCF_3$ and TBAF, the reagent combination described by Langlois, the trifluoromethylation proceeded rather sluggishly and gave an unsatisfactory 20% yield (Table 1, entry 1). In THF, reported to be the optimal solvent for trifluoromethylations,[7e] the thiocyanation was slower, and the yield of the trifluoromethylation remained low (Table 1, entry 2). This suggests that the sodium bromide released in the thiocyanation step may interfere with the trifluoromethylation step.

Systematic studies revealed that the choice of the base had a profound effect on the reaction outcome (Table 1, entries 3–5). Using Cs_2CO_3, near-quantitative yields were achieved in the stepwise procedure (Table 1, entry 5). Acetonitrile was found to be the optimal solvent with regard to yield and reaction rate, but DMF and THF can be used as well (Table 1, entry 6). The amounts of base and trifluoromethylation reagent could be reduced to 1.0 equivalent of Cs_2CO_3 and 1.2 equivalents of $TMSCF_3$, respectively, without affecting the reaction outcome (Table 1, entries 7 and 8).

Table 1 Optimization of the Reaction Conditions[a]

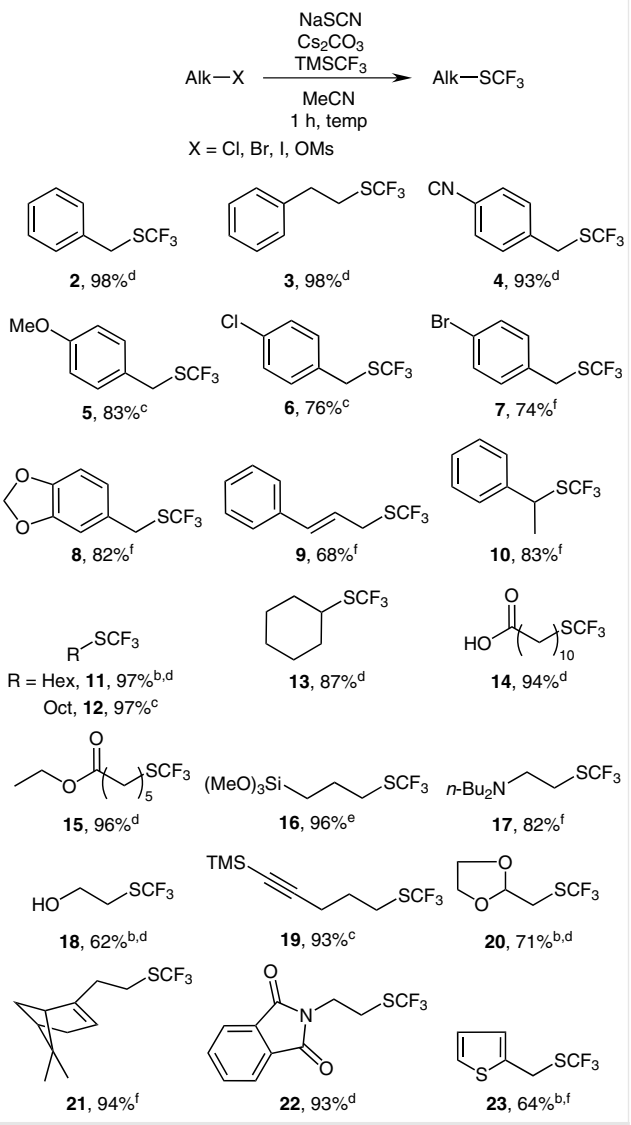


Entry	Base	Solvent	Yield (%)
1	TBAF	DMF	20
2	TBAF	THF	15
3	CsF	DMF	76
4	KF	DMF	80
5	Cs_2CO_3	DMF	99
6	Cs_2CO_3	MeCN	99
7[b]	Cs_2CO_3	MeCN	99
8[b,c]	Cs_2CO_3	MeCN	99
9[b–d]	Cs_2CO_3	MeCN	99
10[b–e]	Cs_2CO_3	MeCN	78
11[b–d,f]	Cs_2CO_3	MeCN	41

[a] Reaction conditions: benzyl bromide (0.5 mmol) and NaSCN (0.6 mmol) in solvent (1 mL), 60 °C, 1 h, then addition of base (1.0 mmol) and $TMSCF_3$ (1.0 mmol), 15 h, r.t. Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard.
[b] 0.5 mmol Cs_2CO_3.
[c] 0.6 mmol $TMSCF_3$.
[d] All reagents were added at the same time, and the mixture was stirred for 1 h at 60 °C.
[e] 0.25 mmol Cs_2CO_3.
[f] 0.1 mmol Cs_2CO_3.

We next probed whether under the optimal conditions the reagents for both steps could directly be combined. To our delight, the desired trifluoromethyl thioether **2** formed in quantitative yield when heating a mixture of **1** with 1.2 equivalents of sodium thiocyanate, 1.0 equivalent of Cs_2CO_3, and 1.2 equivalents of $TMSCF_3$ in acetonitrile to 60 °C for one hour (Table 1, entry 9). The reaction also proceeds with catalytic amounts of Cs_2CO_3 (Table 1, entries 10 and 11), since the released cyanate anions are able to desilylate the Ruppert–Prakash reagent as proposed by Langlois.[7e] However, full conversion was only obtained with equimolar amounts.

Having thus found a convenient and highly efficient trifluoromethylthiolation protocol, we went on to investigate its scope. Diversely substituted alkyl trifluoromethyl thioethers were synthesized in high yields from the corresponding alkyl halides (Scheme 2).[22]



Scheme 2 Trifluoromethylthiolation of alkyl halides and mesylates. [a] *Reagents and conditions*: alkyl electrophile (1.0 mmol), NaSCN (1.2 mmol), Cs_2CO_3 (1 mmol), $TMSCF_3$ (1.2 mmol) in MeCN (2 mL), 60–110 °C, 1 h, isolated yields (see Supporting Information). [b] Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard. [c] Starting from alkyl chloride. [d] Starting from alkyl bromide. [e] Starting from alkyl iodide. [f] Starting from alkyl mesylate.

Alkyl mesylates, which are conveniently accessible from ubiquitous alcohols, are also suitable electrophilic precursors. The reaction is applicable to alkyl, benzyl and allyl electrophiles, and common functional groups, such as cyano, ether, carboxylic acid, ester, hydroxy, acetal, and amino are well-tolerated. In contrast to most metal-mediated trifluoromethylthiolations, chloro- and bromoarene moieties remain intact in this transformation, which opens up opportunities for further derivatization. Terminal alkynes are trimethylsilylated under the reaction conditions, but the TMS group can easily be cleaved by basic workup (**19**).[21]

All products were obtained in reasonable purity after aqueous workup and can be further purified by column chromatography. Compound **2** was isolated in 91% yield on a gram scale, demonstrating the scalability of the process.

In conclusion, a metal-free trifluoromethylthiolation of alkyl electrophiles via a cascade of thiocyanation and nucleophilic CN–CF_3 substitution has been developed. The key advantages of this approach, in which the sulfur and the CF_3 moiety originate from different sources, are the mild reaction conditions and the use of inexpensive, ready available reagents. As a result, this is suitable both for large-scale applications and late-stage trifluoromethylthiolations in drug discovery.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378702.

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(22) **General Procedure for the Trifluoromethylthiolation of Alkyl Thiocyanates Generated in situ**

An oven-dried 20 mL crimp-cap vessel with Teflon-coated stirrer bar was charged with Cs_2CO_3 (652 mg, 1.00 mmol) and NaSCN (100 mg, 1.20 mmol). MeCN (2 mL), $TMSCF_3$ (537 mg, 0.60 mL, 1.20 mmol), and the alkyl halide or mesylate (1.00 mmol) were added via syringe. The suspension was heated to the following temperatures, depending on the leaving group: primary alkyl bromides and iodides 60 °C; secondary alkyl bromides and primary chlorides 90 °C, and alkyl mesylates 110 °C. Stirring was continued until completion of the reaction was determined by GC and GC–MS. The resulting mixture was allowed to cool to r.t., diluted with Et_2O (20 mL), washed with H_2O (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure (700 mbar, 40 °C). Most compounds were obtained in pure form, for products with aromatic substituents the residue was purified by column chromatography (SiOH, Et_2O–pentane gradient).

[(Trifluoromethyl)thio]methylbenzene [CAS No.: 351-60-0] (2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 5 H), 4.15 (s, 2 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –41.47 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.0, 130.6 [q, ^1J(C,F) = 307.0 Hz], 128.9 (2 C), 128.8 (2 C), 128.0, 34.2 [q, ^3J(C,F) = 2.7 Hz] ppm. IR (neat): ν = 2922, 2853, 1463, 1378 cm^{-1}. MS (ion trap, EI, 70 eV): *m/z* (%) = 192 (23) [M$^+$], 91 (100), 69 (13). HRMS (EI-TOF): *m/z* calcd for $C_8H_7F_3S$: 192.0221; found: 192.0224.

11-[(Trifluoromethyl)thio]undecanoic Acid (14)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.88 (t, ^3J = 7.5 Hz, 2 H), 2.35 (t, ^3J = 7.5 Hz, 2 H), 1.72–1.60 (m, 4 H), 1.44–1.29 ppm (m, 12 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –41.3 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.5, 131.2 [q, ^1J(C,F) = 305.2 Hz], 34.1, 29.83 [q, ^3J(C,F) = 2.4 Hz], 29.34, 29.27, 29.25, 29.1, 29.0, 28.9, 28.5, 24.6 ppm. IR (neat): ν = 2927, 2856, 1709, 1464, 1414, 1113, 938, 756 cm^{-1}. MS (ion trap, EI, 70 eV): *m/z* (%) = 287 (12) [M$^+$ + H], 199 (73), 129 (44), 117 (91), 101 (9), 69 (24). HRMS (EI-TOF): *m/z* calcd for: $C_{12}H_{21}F_3O_2S$: 286.1214; found: 286.1230.

3-[(Trifluoromethyl)thio]propyltrimethoxysilane (16)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.55 (s, 9 H), 2.88 (t, ^3J = 7.3 Hz, 2 H), 1.79 (qi, ^3J = 7.8 Hz, 2 H), 0.73 (t, ^3J = 8.3 Hz, 2 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –41.2 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.2 [q, ^1J(C,F) = 305.9 Hz], 50.5 (3 H), 32.5 [q, ^3J(C,F) = 1.5 Hz], 23.2, 8.3 ppm. IR (neat): ν = 2945, 2843, 1759, 1077, 809, 754 cm^{-1}. MS (ion trap, EI, 70 eV): *m/z* (%) = 264 (1)

[M+], 233 (12), 195 (63), 121 (13), 93 (100). HRMS (EI-TOF): *m/z* calcd for $C_7H_{15}O_3SiF_3S$: 264.0463; found: 264.0468.

_N_-{2-[(Trifluoromethyl)thio]ethyl}-_N_,_N_-dibutylamine (17)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.30 (t, ^3J = 7.1 Hz, 2 H), 2.74 (t, ^3J = 7.0 Hz, 2 H), 2.42 (t, ^3J = 7.2 Hz, 4 H), 1.43–1.37 (m, 4 H), 1.34–1.28 (m, 4 H), 0.92 (t, ^3J = 7.3 Hz, 6 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –41.4 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.6 [q, ^1J(C,F) = 306.8 Hz], 53.6 (2 C), 52.8, 29.3 (2 C), 28.8, 20.5 (2 C), 14.0 (2 C) ppm. IR (neat): ν = 2959, 2934, 2874, 1739, 1460, 1366, 1217, 1119, 748 cm^{-1}. MS (ion trap, EI, 70 eV): *m/z* (%) = 257 (3), 214 (44), 172 (66), 142 (100), 58 (41). HRMS (EI-TOF): *m/z* calcd for $C_{11}H_{22}NF_3S$: 257.1425; found: 257.1420.

1-Trimethylsilyl-5-(trifluoromethyl)thiopent-1-yne (19)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.01 (t, ^3J = 7.1 Hz, 2 H), 2.38 (t, ^3J = 6.8 Hz, 2 H), 1.90 (qi, ^3J = 7.0 Hz, 2 H), 0.15 (s, 9 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –41.1 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.0 [q, ^1J(C,F) = 306.1 Hz], 104.8, 86.2, 28.7 [q, ^3J(C,F) = 1.8 Hz], 28.3, 18.6, 0.0 (3 C) ppm. IR (neat): ν = 2960, 2176, 1685, 1432, 1250, 1107, 838, 758, 699 cm^{-1}. MS (ion trap, EI, 70 eV): *m/z* (%) = 240 (11) [M+], 171 (97), 129 (100). HRMS (EI-TOF): *m/z* calcd for $C_9H_{15}SiF_3S$: 240.0616; found: 240.0614.

(1*R*,5*S*)-[(Trifluoromethyl)thio]-2-{6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl}ethylene (21)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.31 (m, 1 H), 2.93–2.89 (m, 2 H), 2.41–2.38 (m, 1 H), 2.37–2.32 (m, 2 H), 2.26–2.23 (m, 2 H), 2.11–2.09 (m, 1 H), 2.02–1.99 (m, 1 H), 1.29 (s, 3 H), 1.16 (d, ^3J = 8.5 Hz, 1 H), 0.84 (s, 3 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –41.2 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.2, 132.2 [q, ^1J(C,F) = 306.1 Hz], 118.8, 40.6, 38.0, 36.6, 31.6, 31.2, 27.8 [q, ^3J(C,F) = 1.8 Hz], 26.2, 21.1 ppm. IR (neat): ν = 2917, 1434, 1366, 1104, 887, 794, 756 cm^{-1}. MS (ion trap, EI, 70 eV): *m/z* (%) = 250 (14) [M+], 105 (100), 121 (10). HRMS (EI-TOF): *m/z* calcd for $C_{12}H_{17}F_3S$: 250.1003; found: 250.0987; $[\alpha]_D^{20}$ –25.9 (*c* 1.00, Et_2O).