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Optimized access to alkyl thiocyanates

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Abstract—Functionalized alkyl thiocyanates are synthesized in high yields from corresponding halides via in situ formation of tetra *n*-butylammonium thiocyanate. Use of this mild but efficient thiocyanation reagent limits the amounts of by-products.
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Alkyl thiocyanates are one of the most important synthetic intermediates for the preparation of sulfur-containing organic compounds. Not only natural products containing the thiocyanate group have attracted attention,[1] but this functional group can also be used as a masked mercapto group or a precursor for sulfur-containing heterocycle compounds. Yet the low nucleophilicity of the NCS- ion, compared to that of simple thiols, requires relatively harsh reaction conditions. To introduce the thiocyanate group into an organic molecule, the use of metal thiocyanate on organic halides or sulfonate has been generalized (usually K-SCN, Na-SCN or in situ formed $Zn(SCN)_2$).[2] However, the thiocyanate group is poorly stable when heated or submitted to acidic conditions. A simple chromatography on silica gel or a prolonged heating over 50°C can cause an intramolecular rearrangement to thermodynamically favored isothiocyanate isomers (this rearrangement occurs preferentially with primary thiocyanates, thus for such fragile compounds, heating or use of a dissociative solvent such as HMPA or DMF should be avoided).[3] Ammonium thiocyanate was also successfully used for such a halogen substitution, but this reagent is sensitive and explosion hazards have been reported.[4] This substitution could also be performed using trimethylsilyl isothiocyanate, but only on activated benzylic compounds using HMPA as solvent[5] or under activation with a stoichiometric amount of a strong Lewis acid such as $TiCl_4$.[6] In any case, high amounts of contaminating isothiocyanates were also formed. Thiocyanates can also be obtained from alcohols,[7] silyl ethers[8] or amines[9] using in situ formed electrophilic phosphorane $Ph_3P(SCN)_2$. However, the results are unreliable and not reproducible because of the low thermal stability of the required intermediate $(SCN)_2$. Once again various amounts of rearranged isothiocyanate by-product are observed. The toxicity of the starting material $Pb(SCN)_2$ is also a major drawback for this thiocyanation method.

Silica gel chromatography increases the amount of rearrangement by-products, so we aimed our efforts at finding a simple nucleophilic reagent with a higher reactivity than metal thiocyanate (as KSCN or NaSCN) and that would enable a straightforward experimental procedure in order to prevent aqueous treatment or silica gel chromatography.

Two recent papers have attracted our attention. In order to proceed to a nucleophilic substitution of an organic halide by an azide function,[10] the authors introduced the conjugated use of trimethylsilyl azide and a 'milder Lewis acid and silicon containing compounds activator' such as tetrabutylammonium fluoride. This use of $n\text{Bu}_4\text{NF}$ was also applied to the epoxide ring opening using trimethylsilyl isothiocyanate.[11] No mechanistic investigations were reported in these papers.

In order to extend this method to the nucleophilic substitution of organic halides, we tested the use of TMSNCS/n-Bu_4NF on benzyl bromide. We were

Keywords: thiocyanates; nucleophilic substitution; trimethylsilyl isothiocyanate.

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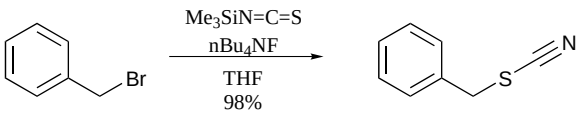
pleased to note that in THF and at room temperature, the substitution reaction occurred within minutes (quantitative yield in less than 1 h). No trace of rearrangement benzyl isothiocyanate was detected using GC/MS. As far as the reaction procedure is concerned, the resultant ammonium salts could be removed by filtration after successive precipitation with diethyl ether and pentane. Solvent evaporation yielded benzylthiocyanate of very high purity (>98% as checked by GC/MS), which could be used without further purification (Scheme 1).



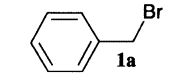
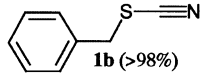
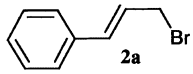
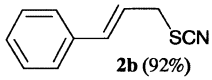
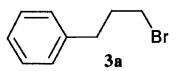
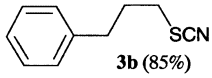
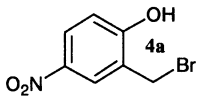
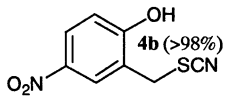
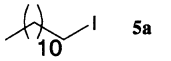
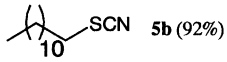
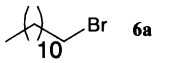
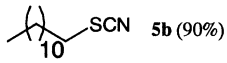
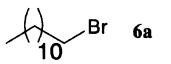
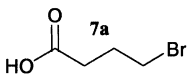
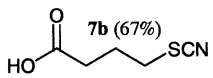
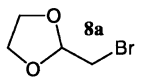
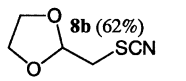
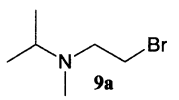
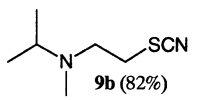
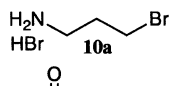
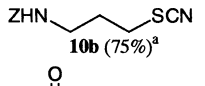
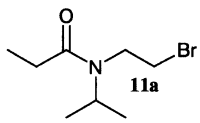
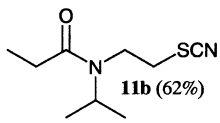
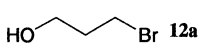
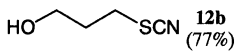
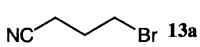
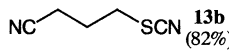
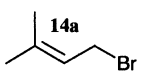
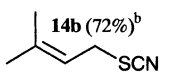
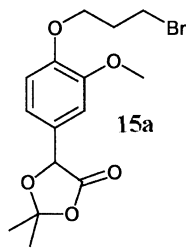
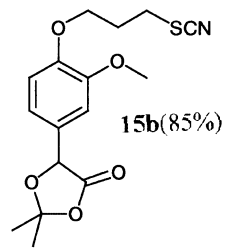
Scheme 1. Thiocyanation of benzyl bromide.

Mechanistic studies were then undertaken. In order to detect the active species, reaction product of a stoichiometric mixture of TMSNCS and *n*-Bu_4NF was analyzed. Not surprisingly, the tetrabutylammonium thiocyanate salt was detected as the major product. This salt was also formed and isolated using a previously described procedure (KSCN+*n*-Bu_4NBr).[12] Using this preformed salt, the reaction with primary alkylbromides proceeds smoothly in THF at room temperature, albeit at a slightly lower rate. Note that this salt is very hygroscopic and has to be freshly prepared and kept under a neutral atmosphere. The best yields were obtained with the in situ formation of tetrabutylammonium thiocyanate, requiring only 1.1 equiv. of each reactant instead of 1.5 equiv. of the commercially available salt (Aldrich or Fluka). We also experimentally checked that in both previously described reactions,[10,11] the active species were also the in situ formed tetrabutylammonium salts (azide or thiocyanate).

THF, DMF, and, to a lesser extent DME, acetonitrile and diethyl ether proved to be the best solvents for this reaction. Using either of the two methods, we could perform very mild thiocyanation of activated or unactivated primary bromides and iodides (Table 1). The reaction occurs at room temperature, and no trace of isothiocyanates was detected in GC/MS. The highest yields were obtained when a simple precipitation of resulting ammonium salts could be performed (with diethyl ether or pentane for iodides and pentane for bromides). When needed, flash chromatographies could be undertaken, lowering the yields to 65–85% (entries 8–12). A typical reaction procedure is illustrated for amide **11a**.[13]

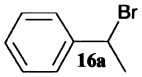
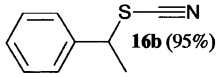
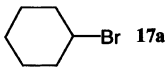
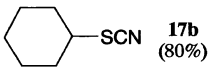
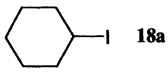
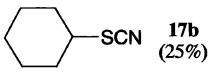
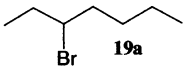
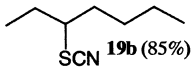
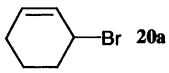
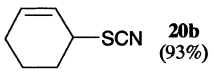
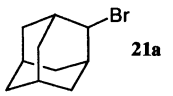
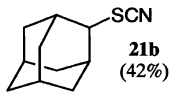
Not surprisingly, iodides are readily substituted, then bromides, and displacement of a chlorine atom is less favorable. Sensitive functions such as cyanides, phenols, aromatic nitrites, carboxylic acids, dioxolanes, and amides did not interfere in the reaction process. In any case, this procedure favorably competes with those using conventional thiocyanation procedures. Interestingly, high yields were obtained with alcohols (Table 1 entry 13) and amines (Table 1 entries 11 and 12), whereas other thiocyanation methods failed or gave <50% yields.

Table 1. Formation of thiocyanates. The reaction was performed with 1.1 equiv. of TMSNCS and 1.1 equiv. of *n*Bu_4NF, substrate 0.1 M in THF. Yields of isolated thiocyanate

Entry	Halide	Temp. (time/h)	Thiocyanate (Yield/%)
1	 **1a**	rt (1)	 **1b** (>98%)
2	 **2a**	rt (1)	 **2b** (92%)
3	 **3a**	rt (1)	 **3b** (85%)
4	 **4a**	rt (1)	 **4b** (>98%)
5	 **5a**	rt (5)	 **5b** (92%)
6	 **6a**	rt (92)	 **5b** (90%)
7	 **6a**	40 (24)	 **5b** (85%)
8	 **7a**	40 (24)	 **7b** (67%)
9	 **8a**	70 (96)	 **8b** (62%)
10	 **9a**	rt (16)	 **9b** (82%)
11	 **10a**	rt (24)	 **10b** (75%)[a]
12	 **11a**	rt (16)	 **11b** (62%)
13	 **12a**	rt (24)	 **12b** (77%)
14	 **13a**	rt (18)	 **13b** (82%)
15	 **14a**	rt (2)	 **14b** (72%)[b]
16	 **15a**	rt (1)	 **15b**(85%)

[a] yield of the cbz derivative after carbobenzylation of the crude reaction mixture. [b] unstable when submitted to silicagel chromatography.

Table 2. Formation of secondary thiocyanates. Reaction was led with 1.5 equiv. of TMSNCS and 1.5 equiv. of nBu$_4$NF, substrate 0.1 M in THF. Yields of isolated thiocyanate

Entry	Halide	Temp. (time/h)	Thiocyanate (Yield/%)
1	 **16a**	rt (1)	 **16b** (95%)
2	 **17a**	60 (72)	 **17b** (80%)
3	 **18a**	60 (72)	 **17b** (25%)
4	 **19a**	60 (24)	 **19b** (85%)
5	 **20a**	rt (24)	 **20b** (93%)
6	 **21a**	100 (96) in DMF	 **21b** (42%)

As another example for the comparison with conventional thiocyanation methods, when dioxolanone **15a** was treated with potassium thiocyanate, the best yields (53%) were obtained by heating overnight at 118°C in methyl isobutyl ketone, whereas treatment with trimethylsilyl isothiocyanate and tetrabutylammonium fluoride at room temperature in THF gave an 85% yield in less than 1 h.

Substitution was then assayed using secondary halogen compounds (Table 2). Unexpectedly, iodide compounds gave mainly degradation products (Table 2, entry 3). Activated (allylic or benzylic) bromides were substituted in good yields (Table 2, entries 1 and 5), and unactivated bromides required moderate heating (60°C) and longer reaction times. In one case (Table 2, entry 6), higher reaction temperature was required (100°C, in DMF) leading to contamination with ca. 5% rearranged isothiocyanates (as estimated by GC/MS analysis of the crude reaction product). A modest 42% yield of pure thiocyanate **21b** was then isolated after careful flash chromatography.

In conclusion, we have developed an optimized thiocyanation method, which requires only a moderate reaction temperature, and a very easy isolation procedure, thus limiting the amount of undesired degradation products.

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13. A typical experimental procedure: Trimethylsilyl isothiocyanate (140 μL, 1.1 mmol) was added at room temperature to a solution of bromide **11a** (222 mg, 1.0 mmol, prepared using a conventional literature procedure from commercially available 2-aminoethanol) in dry THF (10 mL). Tetrabutylammonium fluoride (1.1 mL of a 1.0 M solution in THF) was then added dropwise. The reaction course was monitored by TLC, and after stirring for 16 h, THF was evaporated, and the reaction mixture was triturated with pentane. Filtration followed by removal of the solvants under vacuo yielded thiocyanate **11b** as a yellow oil (174 mg, 87% yield, 95% pure as estimated by GC/MS) which could either be used directly or submitted to flash chromatography on silica gel (CH_2Cl_2/MeOH, 98/2) yielding 124 mg (62%) of a pale yellow oil. IR λ (cm^{-1}): 2154 (SCN), 1639 (C=O); ^{1}H NMR (300.15 MHz, $CDCl_3$), δ, ppm: 1.15 (t, ^3J 7.5 Hz, 3H), 1.25 (d, ^3J 6.5 Hz, 6H), 2.39 (q, ^3J 7.5 Hz, 2H), 3.15 (t, ^3J 5 Hz, 2H), 3.55 (t, ^3J 5 Hz, 2H), 4.10 (quint, ^3J 6.5 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ, ppm: 9.44, 21.30, 26.87, 31.56, 41.24, 48.42, 53.49, 112.24 (SCN), 174.12; m/z (IC, NH_3,): 201 ($[M+H]^+$), 218 ($[M+NH_4]^+$).