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Potassium Thiocyanate as Source of Cyanide for the Oxidative α-Cyanation of Tertiary Amines

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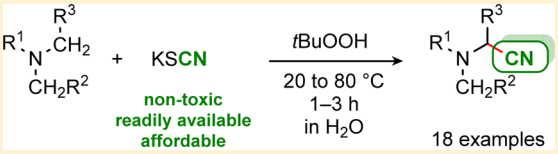
Supporting Information

ABSTRACT: Oxidation at the sulfur of the safe-to-handle potassium thiocyanate releases cyanide units that are trapped in the presence of co-oxidized tertiary amines to form α-amino nitriles. These cyanations work in aqueous solutions and do not require a catalyst, nor do they form toxic byproducts.



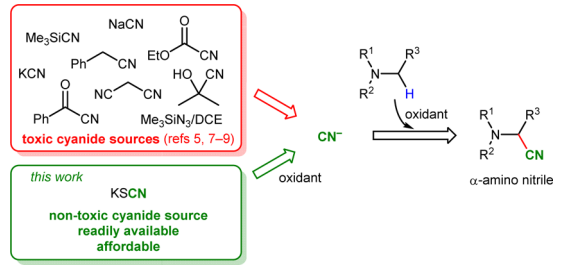
Oxidation of thiocyanate salts can be directed in a way that cyanide ions accumulate. This cyanide formation is of interest in mining industries where waste waters and tailings with high concentrations of thiocyanate salts are generated during the cyanidation of sulfur-containing metal ores. Several technical oxidation processes have, therefore, been developed for the recycling of CN^- from SCN^- with the goal to minimize costly loss of cyanide during the treatment of the ores as well as to reduce deleterious effects of SCN^- on aquatic ecosystems.[1,2] Also, in organisms, peroxidases can catalyze the oxidative degradation of thiocyanate to cyanide.[3] Such peroxidase activities, for example, complicate the correct forensic analysis of human tissue[3d−f] and disturb the relation of blood cyanide concentration with the amount of excreted hydrogen cyanide in breath.[3c] Furthermore, peroxidase-catalyzed production of CN^- from SCN^- has been discussed to contribute to the metabolic formation of toxic dicyano aurate (I) in patients treated with medicinal gold complexes.[3g] In addition, the mechanism of the pH dependent thiocyanate oxidation by H_2O_2 to form cyanide according to eq 1 has been studied in some detail.[4]

$$3H_2O_2 + SCN^- \rightarrow HSO_4^- + HCN + 2H_2O \qquad (1)$$

We previously showed that CH-cyanation adjacent to the nitrogen of a broad range of tertiary amines can be achieved by using $FeCl_2$ as the catalyst, *t*BuOOH as the oxidant, and Me_3SiCN as the CN source.[5] We then hypothesized that, under analogous reaction conditions, combining oxidizable SCN^- salts with oxidizable tertiary amines could provide access to α-amino nitriles[6] which is particularly appealing because a nontoxic CN source could be used (Scheme 1 and Table S1, Supporting Information).[5,7−10]

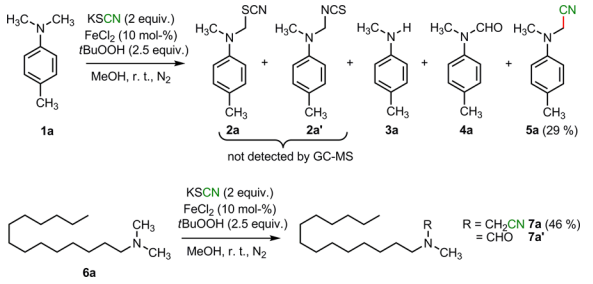
The reaction of *N*,*N*-dimethyl-*p*-toluidine (**1a**) with 2 equiv of potassium rhodanide in the presence of catalytic amounts of $FeCl_2$ (10 mol %) and 2.5 equiv of *t*BuOOH produced neither the thiocyanated amine **2a** nor the thermodynamically more stable isothiocyanate isomer **2a′** (Scheme 2, upper part). Instead, a mixture of *N*-methyl-*p*-toluidine (**3a**), *N*-methyl-*N*-(*p*-tolyl)formamide (**4a**), and the α-amino nitrile **5a** formed with low selectivity (ratio in the crude product: 33/24/43, as determined by GC-MS analysis).

Scheme 1. Synthesis of α-Amino Nitriles by Oxidative Coupling of Cyanide with Tertiary Amines[a]



[a]DCE = 1,2-dichloroethane.

Scheme 2. Formation of α-Amino Nitriles 5a and 7a by Oxidative Coupling of KSCN with the Amines 1a and 6a[a]



[a]5.5 M *t*BuOOH in decane was used as the oxidant.

The presence of **5a** in the crude product mixture confirmed that not only the aniline derivative **1a** but also the thiocyanate ion was oxidized under the reaction conditions. After purification by column chromatography, **5a** was obtained in 29% yield. Analogously, and even more promising, the oxidative cyanation of dimethyltetradecylamine (**6a**) with KSCN generated α-amino nitrile **7a** in an isolated yield of 46% (Scheme 2, lower part). *N*-Methyl-*N*-tetradecyl-formamide

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(**7a**′) was formed as a byproduct of the oxidation of **6a**, but the selectivity for the formation of **7a** (ratio in the crude product: **7a**/**7a**′ = 84/16, as determined by GC-MS) was already encouraging. Further optimization of the cyanation of amine **6a** by thiocyanate was carried out to improve the practicability and selectivity of the reaction (Table 1).

Table 1. Optimization of the Oxidative α-Cyanation of Dimethyltetradecylamine (6a) by Potassium Thiocyanate[a]

entry	$FeCl_2$ [mol %]	solvent	equiv KSCN	oxidant/conditions	yields of **7a** [%]
1	10	MeOH	2	*t*BuOOH[b]/under N_2, 16 h	46
2	10	MeOH	2	*t*BuOOH[b]/air, 16 h	47
3	10	MeOH	3	*t*BuOOH[b]/air, 16 h	51
4	10	MeOH	3	aq *t*BuOOH[c]/air, 5 h	51
5	20	MeOH	3	aq *t*BuOOH[c] /air, 6 h	50
6	100	MeOH	3	aq *t*BuOOH[c] /air, 6 h	43
7	—	MeOH	3	aq *t*BuOOH[c] /air, 6 h	52
8	—	MeOH	3	aq *t*BuOOH[d] /air, 3 h	57
9	—	MeCN	3	aq *t*BuOOH[d] /air, 3 h	60
10	—	H_2O	3	aq *t*BuOOH[d] /air, 4 h	61
11	—	—	3	aq *t*BuOOH[d] /air, 45 min	61
12	—	—	4	aq *t*BuOOH[d] /air, 45 min	62
13	—	—	**4**	**aq *t*BuOOH[d]/air, 1.5 h**	**66**
14	—	—	5	aq *t*BuOOH[e]/air, 45 min	64

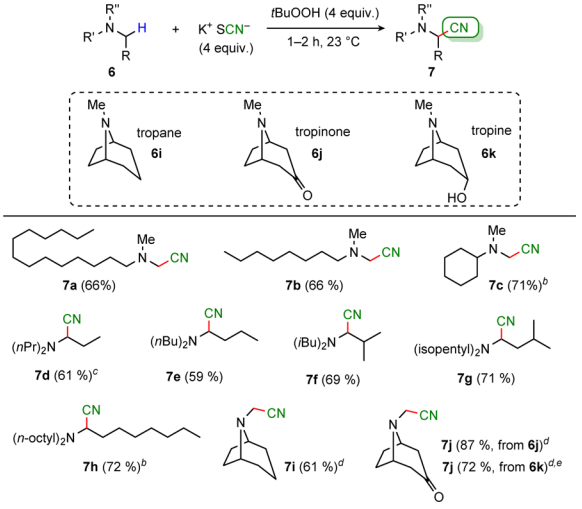
[a]At ambient temperature (ca. 23 °C), solvent volume: 2 mL; yields refer to isolated product after column chromatography. [b]2.5 equiv of *t*BuOOH (5.5 M solution in decane). [c]2.5 equiv of aqueous *t*BuOOH (= 70/30 w/w mixture of *t*BuOOH and water). [d]4 equiv of aq *t*BuOOH. [e]6 equiv of aq *t*BuOOH.

Entries 1−2 of Table 1 show that exclusion of moisture did not affect the yield of **7a**, which enabled us to continue working without a protecting N_2 atmosphere. Increasing the excess of thiocyanate from 2 to 3 equiv slightly increased the yield of **7a** from 47% to 51% (entry 3). After changing the solvent of the oxidant *t*BuOOH from decane to water, the yield of **7a** remained unaffected while the reaction time could be reduced from 16 to 5 h (entry 4). Surprisingly, the yield of **7a** decreased gradually when the amount of $FeCl_2$ was increased from 10 to 20 to 100 mol % (entries 4−6), which led us to study the oxidative cyanation reaction in the absence of $FeCl_2$. Comparison of entry 7 with entries 4−6 shows that $FeCl_2$ was not necessary for the formation of **7a** from **6a** and KSCN. We, therefore, continued the optimization without using a catalyst.

Owing to the consumption of the oxidant *t*BuOOH by interaction with the amine *and* the thiocyanate ions, a further increase in the amount of oxidant seemed to make sense. Thus, the use of 4 equiv of *t*BuOOH was beneficial for the yield of **7a** (57%, entry 8) and further shortened the reaction time from 6 to 3 h. Similar yields of **7a** (57−61%) were obtained after comparable reaction times (3 to 4 h) when the reaction was carried out in methanol, acetonitrile, or water. However, the fastest conversion of **6a** to **7a** was achieved when the reactants were not diluted by any added solvent, which reduced the reaction time from 3 h (entries 8−10) to 45 min (entry 11). Further increase of the excess of potassium thiocyanate or the oxidant *t*BuOOH slightly improved the isolated yields of **7a** (entries 12 and 14). An optimum of 66% for the yield of **7a** was found at a reaction time of 90 min when 4 equiv of *t*BuOOH and 4 equiv of KSCN were used (entry 13). Under the conditions of entry 13, also, the selectivity **7a**/**7a**′ had increased to 95/5 in favor of the cyanation product **7a** (GC-MS of the crude material). Hence, entry 13 was defined as standard for testing the scope of the double oxidative cyanation with further amines.

As summarized in Scheme 3, a series of aliphatic tertiary amines **6** was selectively α-cyanated to form **7a**−**h**. Reactions of

Scheme 3. Generation of α-Amino Nitriles from Tertiary Amines and Potassium Thiocyanate[a]



[a]Reaction conditions: amine (1 mmol), KSCN (4 equiv), aq *t*BuOOH (70% (*w*/*w*), 4 equiv), ambient temperature (ca. 23 °C); yields refer to isolated products after column chromatography. [b]4.5 M solution of *t*BuOOH in CH_2Cl_2 was used as oxidant. [c]With MeCN as solvent (0.5 mL). [d]With MeCN as solvent (2 mL) at 50 °C. [e]With 5 equiv of *t*BuOOH.

dimethylalkylamines $RNMe_2$ led to formation of 2-amino acetonitriles **7a**,**b** because of a selective cyanation at the NMe groups. Efficient oxidation of the very water-soluble amines cyclohexyldimethylamine (**6c**) and tripropylamine (**6d**) under standard conditions generated the corresponding amides instead of α-cyanated amines.[11] Cyanation of **6c** by KSCN could be achieved, however, by using a 4.5 M solution of *t*BuOOH in dichloromethane, which is a milder oxidizing agent as compared with 70% aq *t*BuOOH and provides a lower solubility for KSCN than purely aqueous reaction mixtures. Alternatively, small volumes of acetonitrile can be added to the reaction mixture when aq *t*BuOOH is used. In this way, **7d** was obtained from **6d** in a moderate yield of 61%.

Oxidative photogeneration of iminium ions from amines and subsequent trapping with trimethylsilyl cyanide has been reported to be an efficient method for the cyanation of a series of alkaloids.[9a] As tropinone (**6j**) was reported to undergo iron-catalyzed oxidative amidations by aldehydes with *t*BuOOH as the oxidant,[12] we set out to investigate whether cyanation of **6j** is possible with the reagent combination *t*BuOOH/KSCN. We found that neither tropane (**6i**) nor **6j** was converted under the standard conditions at ambient temperature. However, heating the acetonitrile solutions of **6i** and **6j** with KSCN and *t*BuOOH at 50 °C resulted in the selective formation of the α-amino nitriles **7i** and **7j** in 61% and 87% yield, respectively. In a

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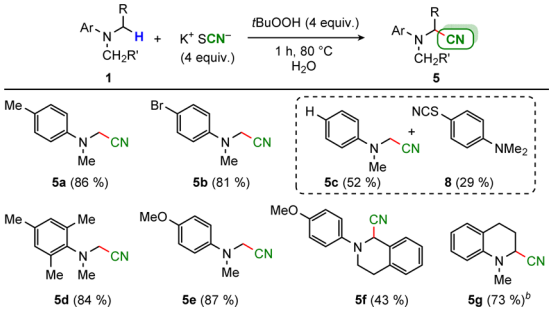
gram scale experiment, 10 mmol of tropinone (**6j**) gave **7j** in 85% yield. Crystals suitable for X-ray single crystal analysis were grown by slow evaporation of the solvent from a CH_2Cl_2 solution of **7j**.[13]

The cyanated alkaloid **7j** was also obtained from tropine (**6k**), which demonstrates that the secondary alcohol group of **6k** is oxidized to a ketone under the reaction conditions. The corresponding cyanation of atropine, which carries a primary hydroxyl group, however, turned out to be beyond the scope of the *t*BuOOH/KSCN cyanation method in this work.

We then studied the behavior of *N*,*N*-dialkylanilines under our reaction conditions (Scheme 4). After heating the reaction

Scheme 4. Generation of α-Amino Nitriles from Anilines and Potassium Thiocyanate[a]



[a]Reaction conditions: aniline (1 mmol), KSCN (4 equiv), 70% aq *t*BuOOH, 4 equiv), water (2 mL), 80 °C; yields refer to isolated products after column chromatography. [b]With MeCN as solvent (2 mL) at 50 °C for 2 h.

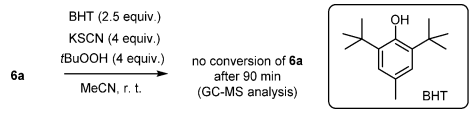
mixtures for 1 h at 80 °C, oxidative cyanation at one of the NMe groups of *para*-substituted *N*,*N*-dimethylanilines produced the corresponding α-amino nitriles **5a**,**b**,**d**,**e** with yields of 81% to 87%. Cyanation of the *N*-(*p*-anisyl)-tetrahydroisoquinoline (**1f**) was less efficient, but still gave solely the product of the cyanation reaction **5f** in 43% yield. Only in the reaction with the parent *N*,*N*-dimethylaniline (**1c**) was the formation of α-amino nitrile accompanied by the thiocyanation of the aromatic ring: After separation by column chromatography, **5c** and **8** were obtained in 52% and 29% yield, respectively. The formation of **8** is in accord with a recent report by Khazaei, Zolfigol, and co-workers that *N*,*N*-dialkylanilines react with KSCN and 30% aq. H_2O_2 to yield *para*-thiocyanated anilines.[14]

In contrast to the regioselectivity observed for **6a**-**c**, 1-methyl tetrahydroquinoline (**1g**) did not undergo cyanation at the NCH_3 group after warming at 50 °C for 2 h but was selectively cyanated at the NCH_2 group to give **5g**. Competing thiocyanation of the electron-rich aromatic ring of **1g** was not observed.

Oxidation of SCN^- by H_2O_2 has been described to generate $OSCN^-$ (or HOSCN) as a first intermediate that is easily further oxidized to finally yield SO_4^{2-} as the sulfur-containing product.[4d] Repeating the experiment in Table 1, entry 13, with subsequent treatment of the reaction solution with $BaCO_3$/HCl led to precipitation of a colorless powder that was collected by filtration and analyzed by X-ray powder diffraction, which clearly showed that $BaSO_4$ had precipitated (see Supporting Information) and thus clarified the fate of sulfur upon oxidation of SCN^- by *t*BuOOH.

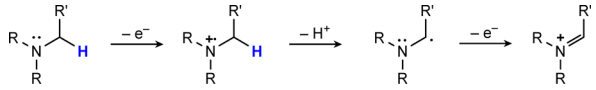
The important role of radical intermediates in the initial steps of the oxidative cyanation reactions in Schemes 3 and 4 is revealed by the ability of the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT, 2.5 equiv) to completely suppress the conversion of the tertiary amine **6a** (Scheme 5) under reaction conditions similar to those of Table 1, entries 9 or 13.

Scheme 5. Attempted Cyanation of 6a in the Presence of the Radical Scavenger BHT



The regioselective formation of the α-amino nitriles **7a**−**c**,**i**,**j** shows that oxidation at the methyl group adjacent to the nitrogen of the amine is highly preferred over a competing process at an NCH_2R or $NCHR_2$ group, which agrees with previous reports[5c,7h,i,k,o,u,z] but is just the opposite of the expectation based on the stabilities of structurally related amino-stabilized alkyl radicals or iminium ions. The reactivity order $NCH_3 > NCH_2R \gg NCHR_2$ agrees, however, with the regioselective photoadditions of tertiary amines to singlet stilbene,[15a,b] as well as with relative rates for the deprotonation of laser-flash photolytically generated amine radical cations by acetate,[15c] which both have been rationalized by stereoelectronic effects in the preferred transition state conformation.[15] We assume, therefore, that stereoelectronic effects during the deprotonation of the amine radical cations (Scheme 6) also control the regioselectivities under our reaction conditions.

Scheme 6. Oxidation of Tertiary Amines by Subsequent Electron−Proton−Electron Transfers



In oxidative couplings one of the substrate nucleophiles is converted to an electrophilic species that is then trapped by the other nucleophile.[16] In this work *both the electrophile and the nucleophile were generated in situ from oxidizable precursors*. The sulfur of SCN^- is used as a sacrificial group that safeguards the toxic nucleophile CN^- until its active form is released under the reaction conditions. To the best of our knowledge, this concept has only been applied once before: Wan and co-workers recently obtained α-amino nitriles from benzyl cyanide and tertiary amines with *t*BuOOH as the oxidant.[7aa] In that reaction, *t*BuOOH oxidized the benzyl cyanide to benzoyl cyanide and the tertiary amines to α-aminoalkyl radicals. Experimental and theoretical investigations led Wan and co-workers to propose that the radical intermediates then attack the CN triple bond of PhCOCN to form imine radical intermediates that eliminate a phenacyl radical to yield the α-amino nitriles. Whether analogous radical processes also operate in the oxidative removal of sulfur from SCN^- remains to be clarified. Alternatively, the intermediate α-aminoalkyl radicals could be further oxidized by *t*BuO· or HO· to yield iminium ions which are trapped by cyanide ions that are generated by oxidation of thiocyanate ions as suggested in eq 2.

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$$3t\text{BuOOH} + H_2O + SCN^- \rightarrow HSO_4^- + HCN + 3t\text{BuOH} \quad (2)$$

In summary, simultaneous oxidation of tertiary amines and thiocyanate ions by *tert*-butylhydroperoxide in various solvents generated α-amino nitriles under mild conditions without the use of catalysts or toxic CN sources. Contributing to a development of synthetic chemistry that is friendly to the environment and hazard-free to men, potassium thiocyanate is used for the first time in organic synthesis to replace toxic cyanation reagents.[10,17] It is also worth mentioning that the waste products of the presented reactions (that is, H_2O, $KHSO_4$, *t*BuOH, or KOCN from overoxidation of KSCN) are non-problematic with regard to safety and environmental aspects.[18]

EXPERIMENTAL SECTION

All reactions were carried out under air atmosphere. ^{1}H (300 or 400 MHz) and ^{13}C (75.5 or 100.6 MHz) NMR spectra of solutions in $CDCl_3$ were recorded on 300 or 400 MHz NMR spectrometers. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals (δ_H 7.26 and δ_C 77.16).[19] Abbreviations for signal couplings are s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The numbers of attached hydrogen atoms (C, CH, CH_2, or CH_3) were derived from additional gHSQC data. HRMS was performed on a mass spectrometer with sector field detector. Infrared spectra of neat substances were recorded on a FT-IR spectrometer equipped with an ATR probe (diamond).

Potassium thiocyanate (99%) and aqueous *t*BuOOH (70 wt % *t*BuOOH in H_2O) were purchased.

Commercially available tertiary amines were used as received: Dimethyltetradecylamine (technical, ≥95%), dimethyl-*n*-octylamine (95%), cyclohexyldimethylamine (98%), tropinone (99%), tropane (98%), tripropylamine (≥98%), tributylamin (puriss. p.a., ≥99%), triisobutylamine (98%), triisopentylamine (≥95%), tri-*n*-octylamine (96%), tropine (98%), *N*,*N*,4-trimethylaniline (99%), *N*,*N*,2,4,6-pentamethylaniline (98%), 4-bromo-*N*,*N*-dimethylaniline (98%), dicyclohexylmethylamine (97%), and *N*,*N*-dimethylaniline (99%).

N,*N*-Dimethyl-*p*-anisidine was prepared as described in ref 20 and 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline was obtained by following a procedure reported in ref 21. Reductive formylation of quinoline with formic acid furnished 1-formyl-1,2,3,4-tetrahydroquinoline that was subsequently reduced with $LiAlH_4$ to 1-methyl-1,2,3,4-tetrahydroquinoline.[22]

Experimental Procedure A. A 10 mL round-bottom flask was charged with KSCN (0.40 g, 4.0 mmol) and the tertiary amine (1.0 mmol). Then, aqueous *t*BuOOH (70 wt % *t*BuOOH in H_2O, 0.55 mL, 4.0 mmol) or a 4.9 M solution of *t*BuOOH in CH_2Cl_2 (0.75 mL, 4.0 mmol) was added successively by syringe over a period of 5 min, and the suspension was stirred at room temperature for the indicated time. At the end of the reaction, the reaction mixture was poured on brine (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

Experimental Procedure B. KSCN (0.40 g, 4.0 mmol) and the tertiary amine (1.0 mmol) were dissolved in MeCN (2 mL). Then, aqueous *t*BuOOH (70 wt % *t*BuOOH in H_2O, 0.55 mL, 4.0 mmol) was added successively by syringe. The solution was stirred at 50 °C for the indicated time. After allowing the reaction mixture to cool to room temperature, the suspension was poured on brine (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

Experimental Procedure C. KSCN (0.40 g, 4.0 mmol) and the *N*,*N*-dialkylated aniline (1.00 mmol) were poured on water (2.00 mL), and aqueous *t*BuOOH (70 wt % *t*BuOOH in H_2O, 0.55 mL, 4.0 mmol) was added by syringe. The solution was stirred at 80 °C for 1 h. After allowing the reaction mixture to cool to room temperature, the suspension was poured on brine (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

*2-(Methyl(tetradecyl)amino)acetonitrile (**7a**).* Following General Procedure A, dimethyl-tetradecylamine **6a** (0.30 mL, 0.99 mmol) reacted with KSCN and aq *t*BuOOH for 1.5 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 2:1) to give **7a** (174 mg, 66%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86−0.90 (m, 3 H), 1.26 (br s, 22 H), 1.40−1.47 (m, 2 H), 2.35 (s, 3 H), 2.41−2.46 (m, 2 H), 3.53 (s, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 14.3, 22.8, 27.3, 27.6, 29.5, 29.6, 29.72, 29.74, 29.80, 29.82, 29.83, 32.1, 42.2, 45.3, 56.0, 114.8.

*2-(Methyl(octyl)amino)acetonitrile (**7b**).* Following General Procedure A, dimethyl-octylamine **6b** (0.20 mL, 0.97 mmol) reacted with KSCN and aq *t*BuOOH for 1.5 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 2:1) to give **7b** (117 mg, 66%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85−0.90 (m, 3 H), 1.27−1.29 (m, 10 H), 1.42−1.47 (m, 2 H), 2.35 (s, 3 H), 2.41−2.46 (m, 2 H), 3.52 (s, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 14.2, 22.8, 27.3, 27.6, 29.4, 29.5, 31.9, 42.2, 45.3, 56.0, 114.8.

*2-(Cyclohexyl(methyl)amino)acetonitrile (**7c**).* Following General Procedure A, *N*,*N*-dimethylcyclohexylamine **6c** (0.15 mL, 1.0 mmol) reacted with KSCN and *t*BuOOH (4.9 M in CH_2Cl_2) for 1.5 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 1:1) to give **7c** (108 mg, 71%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 23. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.11−1.34 (m, 4 H), 1.59−1.92 (m, 6 H), 2.29−2.39 (m, 1 H), 2.40 (s, 3 H), 3.58 (s, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 25.2, 25.9, 30.1, 39.2, 42.6, 61.3, 116.1; IR (neat/ATR probe): $\tilde{\nu}$ = 2923, 2850, 1660, 1448, 1436, 1421, 1292, 1268, 1232, 1180, 1128, 994, 896, 810, 724, 715 cm^{-1}.

*2-(Dipropylamino)butanenitrile (**7d**).* Analogous to General Procedure A, tripropylamine **6d** (0.19 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH in acetonitrile (0.5 mL) for 2 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 40:1) to give **7d** (103 mg, 61%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, J = 7.3 Hz, 6 H), 1.04 (t, J = 7.4 Hz, 3 H), 1.38−1.56 (m, 4 H), 1.70−1.86 (m, 2 H), 2.31−2.40 (m, 2 H), 2.46−2.55 (m, 2 H), 3.47 (t, J = 7.8 Hz, 1 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 10.9, 11.8, 21.3, 25.5, 53.8, 56.6, 118.7.

*2-(Dibutylamino)pentanenitrile (**7e**).* Following General Procedure A, tributylamine **6e** (0.24 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 2 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 40:1) to give **7e** (124 mg, 59%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88−0.96 (m, 9 H), 1.27−1.51 (m, 10 H), 1.65−1.74 (m, 2 H), 2.29−2.38 (m, 2 H), 2.51−2.61 (m, 2 H), 3.57 (t, J = 7.7 Hz, 1 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 13.6, 14.1, 19.4, 20.5, 30.4, 34.1, 51.6, 54.5, 118.7.

*2-(Diisobutylamino)-3-methylbutanenitrile (**7f**).* Following General Procedure A, triisobutylamine **6f** (0.24 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1.5 h. The crude product was crystallized from H_2O to give **7f** (145 mg, 69%) as colorless crystals, mp. 61.0−61.5 °C. Known compound: the NMR spectroscopic data agree with those given in ref 5c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (d, J = 6.6 Hz, 6 H), 0.92 (d, J = 6.5 Hz, 6 H), 1.03 (d, J = 6.5 Hz, 3 H), 1.10 (d, J = 6.7 Hz, 3 H), 1.62−1.76 (m, 2 H), 1.85−1.98 (m, 1 H), 2.12 (dd, J = 12.9 Hz, J = 10.3 Hz, 2 H), 2.24 (dd, J = 12.9 Hz, J = 4.2 Hz, 2 H), 3.06 (d, J = 10.8 Hz, 1 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 19.9 (CH_3), 20.5 (CH_3), 20.8 (CH_3), 21.1 (CH_3), 26.3

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(CH), 29.4 (CH), 60.9 (CH_2), 63.0 (CH), 117.8 (C), the numbers of attached hydrogen atoms were derived from additional gHSQC data.

*2-(Diisopentylamino)-4-methylpentanenitrile (**7g**).* Following General Procedure A, triisopentylamine **6g** (0.29 mL, 0.95 mmol) reacted with KSCN and aq *t*BuOOH for 2 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 45:1) to give **7g** (170 mg, 71%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (d, J = 2.9 Hz, 6 H), 0.91 (d, J = 3.0 Hz, 6 H), 0.93 (d, J = 6.6 Hz, 6 H), 1.25−1.36 (m, 4 H), 1.53−1.66 (m, 4 H), 1.83 (sept, J = 6.7 Hz, 1 H), 2.28−2.37 (m, 2 H), 2.56−2.66 (m, 2 H), 3.66 (t, J = 7.7 Hz, 1 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 22.2, 22.45, 22.52, 23.2, 24.8, 26.2, 37.2, 40.8, 50.1, 52.9, 118.8.

*2-(Dioctylamino)nonanenitrile (**7h**).* Following General Procedure A, tri-*n*-octylamine **6h** (0.45 mL, 1.0 mmol) reacted with KSCN and *t*BuOOH (4.9 M in CH_2Cl_2) for 1.5 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 110:1) to give **7h** (273 mg, 72%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5c. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86−0.90 (m, 9 H), 1.23−1.45 (m, 34 H), 1.66−1.73 (m, 2 H), 2.30−2.36 (m, 2 H), 2.51−2.58 (m, 2 H), 3.55 (t, J = 7.8 Hz, 1 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz): δ 14.20, 14.24, 22.76, 22.81, 26.2, 27.4, 28.2, 29.1, 29.2, 29.5, 29.6, 31.9, 32.0, 32.1, 51.9, 54.7, 118.8.

*2-((1R,5S)-8-Azabicyclo[3.2.1]octan-8-yl)acetonitrile (**7i**).* Following General Procedure B, tropane **6i** (0.14 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc = 5:4) to give **7i** (96 mg, 61%) as a colorless viscous liquid. Known compound: ref 24. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34−1.78 (m, 8 H), 1.93−1.97 (m, 2 H), 3.27−3.29 (m, 4 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 16.2 (CH_2), 26.1 (CH_2), 31.0 (CH_2), 41.0 (CH_2), 60.5 (CH), 117.9 (C), the numbers of attached hydrogen atoms were derived from additional gHSQC data; IR (neat/ATR probe): $\tilde{\nu}$ = 2929, 2871, 1476, 1456, 1431, 1341, 1331, 1313, 1255, 1219, 1168, 1134, 1111, 1069, 1057, 1038, 980, 942, 874, 849, 821, 768, 720 cm^{-1}.

*2-((1R,5S)-3-Oxo-8-azabicyclo[3.2.1]octan-8-yl)acetonitrile (**7j**) from tropinone (**6j**).* Potassium thiocyanate (4.0 g, 40 mmol) and tropinone **6j** (1.4 g, 10 mmol) were dissolved in acetonitrile (20 mL) and heated at 50 °C. The reaction was started by slow injection of aq *t*BuOOH (5.5 mL, 40 mmol, within ca. 5 min). The reaction mixture was then stirred at 50 °C for another 2.5 h, during which the mixture became more and more opaque. After allowing the reaction mixture to cool at ambient temperature, the suspension was poured on brine (60 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc = 4:5) to give **7j** (1.4 g, 85%) as a colorless solid (mp. 64.5−65 °C). Crystals suitable for X-ray single crystal analysis were obtained by slow evaporation of a dichloromethane solution of **7j**.[13] Known compound: ref 9a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.63−1.71 (m, 2 H), 2.09−2.13 (m, 2 H), 2.22−2.27 (m, 2 H), 2.61−2.68 (m, 2 H), 3.50 (s, 2 H), 3.59−3.60 (m, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 27.5 (CH_2), 40.2 (CH_2), 48.7 (CH_2), 59.7 (CH), 117.3 (C, CN), 208.1 (C, C═O), the numbers of attached hydrogen atoms were derived from additional gHSQC data; IR (neat/ATR probe): $\tilde{\nu}$ = 2955, 2886, 1709, 1473, 1411, 1341, 1234, 1194, 1152, 1134, 1101, 1008, 905, 842, 776, 726 cm^{-1}.

*2-((1R,5S)-3-Oxo-8-azabicyclo[3.2.1]octan-8-yl)acetonitrile (**7j**) from tropine (**6k**).* Analogous to General Procedure B, tropine **6k** (0.14 mL, 0.99 mmol) reacted with KSCN and 5 equiv of aq *t*BuOOH (0.69 mL, 5.00 mmol) for 2 h. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc = 4:5) to give **7j** (118 mg, 72%) as colorless crystals. ^{1}H and ^{13}C NMR spectra agree with those of **7j** that was obtained from **6j**.

*2-(Methyl(p-tolyl)amino)acetonitrile (**5a**).* Following General Procedure C, *N*,*N*,4-trimethylaniline **1a** (0.14 mL, 0.97 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 6:1) to give **5a** (133 mg, 86%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.33 (s, 3 H), 2.97 (s, 3 H), 4.12 (s, 2 H), 6.80−6.85 (m, 2 H), 7.14−7.17 (m, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 20.4, 39.4, 42.7, 115.3, 115.6, 129.7, 130.0, 145.7.

*2-((4-Bromophenyl)(methyl)amino)acetonitrile (**5b**).* Following General Procedure C, 4-bromo-*N*,*N*-dimethylaniline **1b** (0.20 g, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 20:1) to give **5b** (182 mg, 81%) as a colorless solid. Known compound: the NMR spectroscopic data agree with those given in ref 5a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.98 (s, 3 H), 4.14 (s, 2 H), 6.70−6.75 (m, 2 H), 7.37−7.42 (m, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 39.4, 42.3, 112.7, 115.2, 116.5, 132.4, 146.9.

*2-(Methyl(phenyl)amino)acetonitrile (**5c**) and N,N-dimethyl-4-thiocyanatoaniline (**8**).* Following General Procedure C, *N*,*N*-dimethylaniline **1c** (0.13 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The product mixture was separated by column chromatography (SiO_2, pentane/Et_2O = 15:1 → 15:2) to give **5c** and **8**.

*2-(Methyl(phenyl)amino)acetonitrile (**5c**).* 76 mg (52%), colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.01 (s, 3 H), 4.15 (s, 2 H), 6.87−6.98 (m, 3 H), 7.32−7.37 (m, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 39.2, 42.2, 114.8, 115.6, 120.1, 129.5, 147.8.

*N,N-Dimethyl-4-thiocyanatoaniline (**8**).* 52 mg (29%), colorless solid, mp 73−73.5 °C. Known compound: the NMR spectroscopic data agree with those given in refs 14,25. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.99 (s, 6 H), 6.66−6.69 (m, 2 H), 7.39−7.45 (m, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 40.3, 106.7, 112.7, 113.3, 134.6, 151.8.

*2-(Mesityl(methyl)amino)acetonitrile (**5d**).* Following General Procedure C, *N*,*N*,2,4,6-pentamethylaniline **1d** (0.18 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 2:1) to give **5d** (158 mg, 84%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.27 (s, 3 H), 2.29 (s, 6 H), 2.95 (s, 3 H), 3.93 (s, 2 H), 6.86 (s, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 19.0, 20.8, 40.4, 44.1, 117.7, 129.8, 136.0, 137.0, 144.3.

*2-((4-Methoxyphenyl)(methyl)amino)acetonitrile (**5e**).* Following General Procedure C, 4-methoxy-*N*,*N*-dimethylaniline **1e** (0.15 g, 0.99 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 2:1) to give **5e** (151 mg, 87%) as a colorless viscous liquid. Known compound: the NMR spectroscopic data agree with those given in ref 5a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.92 (s, 3 H), 3.78 (s, 3 H), 4.07 (s, 2 H), 6.88 (s, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 40.0, 44.0, 55.7, 114.9, 115.5, 117.8, 142.3, 154.4.

*2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**5f**).* Following General Procedure C, 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **1f** (0.24 g, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 15:2) to give **5f** (114 mg, 43%) as a colorless solid. Known compound: the NMR spectroscopic data agree with those given in ref 5a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.88−2.96 (m, 1 H), 3.10−3.22 (m, 1 H), 3.39−3.48 (m, 1 H), 3.54−3.61 (m, 1 H), 3.79 (s, 3 H), 5.36 (s, 1 H), 6.88−6.94 (m, 2 H), 7.06−7.11 (m, 2 H), 7.20−7.33 (m, 4 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 28.8, 45.0, 55.66, 55.68, 114.9, 117.7, 121.1, 126.8, 127.2, 128.8, 129.6, 129.8, 134.5, 142.7, 155.8.

*1-Methyl-1,2,3,4-tetrahydroquinoline-2-carbonitrile (**5g**).* Following General Procedure B, 1-methyl-1,2,3,4-tetrahydroquinoline **1g** (0.15 g, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 7:1) to give **5g** (125 mg, 73%) as a colorless viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.24−2.34 (m, 2 H), 2.80−2.88 (m, 1 H), 3.02 (s, 3 H), 3.11−3.24 (m, 1 H), 4.28−4.31 (m, 1 H), 6.73−6.85 (m, 2 H), 7.05−7.21 (m, 2 H); ^{13}C{^{1}H} NMR ($CDCl_3$,

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75.5 MHz): δ 24.2 (CH_2), 25.6 (CH_2), 38.2 (CH_3), 51.8 (CH), 112.6 (CH), 118.2 (C, CN), 119.0 (CH), 121.8 (C), 127.6 (CH), 129.1 (CH), 143.4 (C), the numbers of attached hydrogen atoms were derived from additional gHSQC data; IR (ATR): $\tilde{\nu}$ = 3022, 2937, 2895, 2846, 2820, 1601, 1579, 1494, 1474, 1446, 1362, 1313, 1264, 1208, 1172, 1133, 1118, 1093, 1067, 1044, 1036, 995, 932, 831, 800, 746, 704 cm^{-1}. HRMS (EI, 70 eV) m/z: $[M]^{+\cdot}$ Calcd for $[C_{11}H_{12}N_2]^{+\cdot}$ 172.0995; Found 172.0985.

Formation of *N,N*-Dicyclohexylformamide. Following General Procedure A, *N,N*-dicyclohexylmethylamine (0.21 mL, 0.98 mmol) reacted with KSCN and aq *t*BuOOH for 1.5 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 2:1) to give *N,N*-dicyclohexylformamide (174 mg, 85%) as a colorless solid; mp 61−62 °C. Known compound (mp 62.5−63.5 °C).[26] ^1H NMR ($CDCl_3$, 600 MHz): δ 1.05−1.80 (m, 20 H), 2.99−3.03 (m, 1 H), 3.87−3.91 (m, 1 H), 8.16 (s, 1 H, CHO); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150.6 MHz): δ 25.3, 25.4, 25.9, 26.3, 30.4, 34.7, 52.4, 54.9, 161.7.

Precipitation of $BaSO_4$. A 10 mL flask was charged with KSCN (0.40 g, 4.0 mmol) and the amine **6a** (0.30 mL, 1.0 mmol). Then, aq *t*BuOOH (0.55 mL, 4.0 mmol) was added successively by syringe over a period of 5 min. The resulting suspension was stirred at room temperature for 1.5 h. At the end of the reaction, the reaction mixture was poured on deionized water (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was poured in a 100 mL Erlenmeyer flask, and $BaCO_3$ (1.0 g) and 2 M HCl (3 mL) were added. A colorless precipitate formed, which was separated by filtration and dried at 67 °C to give $BaSO_4$ (340 mg, 1.5 mmol) as a colorless powder that was analyzed by X-ray powder diffraction. Reflections of the precipitated solid agreed with those for $BaSO_4$[27] (Supporting Information, Figure S1).

Reaction of 6a in the Presence of Radical Scavenger 2,6-Di-*tert*-butyl-4-methylphenol (BHT). A mixture of KSCN (0.40 g, 4.0 mmol), the amine **6a** (0.30 mL, 1.0 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (0.55 g, 2.5 mmol) was dissolved in MeCN (2.00 mL) and aq *t*BuOOH (0.55 mL, 4.0 mmol) was added successively by syringe. The resulting suspension was stirred at room temperature for 1.5 h. Subsequently, the reaction mixture was poured on brine (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Analysis of the crude product mixture with GC/MS showed only signals of the substrate **6a**.

■ ASSOCIATED CONTENT

Supporting Information

Compilation of toxicity data for various CN sources (Table S1), X-ray powder diffraction of precipitated $BaSO_4$, X-ray data for **7j**, and copies of spectra of isolated products **5a-g**, **7a-j**, **8**, and Cy_2NCHO. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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