SHORT COMMUNICATION

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Practical Access to Aromatic Thiocyanates by CuCN-Mediated Direct Aerobic Oxidative Cyanation of Thiophenols and Diaryl Disulfides

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Dedicated to Professor Alexandre Alexakis on the occasion of his retirement

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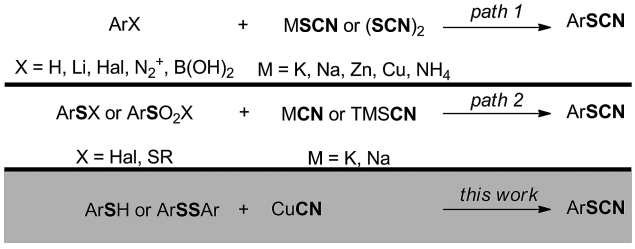
The practical and mild aerobic oxidative CuCN-mediated cyanation of thiophenols and diaryl disulfides was investigated. The reaction was performed in air at room temperature and reached aromatic thiocyanates in moderate to good yields starting from a broad range of diversely functionalized substrates.

Introduction

Organic thiocyanates are important synthetic intermediates for the preparation of various sulfur-containing compounds, such as thiols, sulfides, disulfides, thioesters, thiocarbamates, and sulfur heterocycles, and they are also constituents of biologically active compounds.[1] Compared to alkyl thiocyanates, which are generally easily prepared from alkyl halides and potassium or ammonium thiocyanate, aryl thiocyanates are more difficult to access. Besides the synthetic applications mentioned above, aryl thiocyanates have been used as reagents for the cyanothiolation of alkynes.[2] Two main strategies are currently used to prepare these compounds: the first one (Scheme 1, path 1) consists in the reaction of various non-sulfur aromatic substrates (arenes or aryl metal, aryl halides, aryl diazonium salts, or arylboronic acids) with a thiocyanating agent such as a thiocyanate salt or thiocyanogen.[3] The second one (Scheme 1, path 2) is based on the nucleophilic attack of a cyanide (KCN, NaCN, or TMSCN) on a substrate bearing an electrophilic sulfur (aryl disulfides, aryl sulfenyl, or sulfonyl derivatives).[4] All these procedures require high temperatures or the presence of a metal catalyst, and the main drawback of the second strategy represents the use of highly toxic and moisture-sensitive cyanation agents. An additional approach making use of electrophilic CN sources has been developed but is infrequently used.[5] Although CuCN was already used as the cyanide source for the formation of a C–CN bond[6] and very recently for a N–CN bond,[7] no example of sulfur cyanation by this reagent has been described to date.



Scheme 1. Methods for the synthesis of aryl thiocyanates.

Herein, we report an efficient S-cyanation of aromatic thiols and disulfides by CuCN at room temperature and by using oxygen as the oxidant[8] (Scheme 1).

Results and Discussion

Preliminary studies were conducted on thiophenol (**1a**) as a model substrate. Acetonitrile was chosen as the solvent and molecular oxygen (air) was chosen as the oxidant for obvious practical reasons. In the first place, we wanted to know if a ligand was required; no reaction was observed in its absence (Table 1, entry 1). Then, the influence of the copper ligand was evaluated (Table 1, entries 2–7). Different usual ligands were screened, and it appeared that only two of them allowed the cyanation to take place, namely, *N*-methylimidazole and *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine (TMEDA; Table 1, entries 6 and 7). TMEDA turned out to be the best ligand, as the reaction was complete after 18 h and thiocyanate **3a** was obtained in a good yield of 94%, whereas *N*-methylimidazole drove the reaction only to a poor yield of 25% of the targeted compound along

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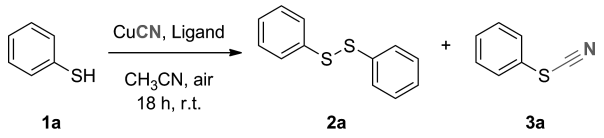
with a large amount of diphenyl disulfide (**2a**). Ligands such as triphenylphosphine, acetylacetone, pyridine, and 1,10-phenanthroline were unable to promote the reaction, and in these cases only disulfide **2a**, the product of thiophenol oxidation, was recovered after 18 h reaction.

Table 1. Screening of ligands for the copper-mediated oxidative cyanation of thiophenol.[a]



Entry	Ligand	Conv. [%][b]	Ratio **2a**/**3a**[b]	Yield **3a** [%][c]
1	none	0	–	–
2	PPh_3	100	100:0	–
3	acetylacetone	100	100:0	–
4	pyridine	100	100:0	–
5	1,10-phenanthroline	100	100:0	–
6	*N*-methylimidazole	100	54:46	25[d]
7	TMEDA	100	0:100	94

[a] Conditions: thiophenol (**1a**, 1 equiv.), CuCN (2 equiv.) in CH_3CN (0.3 M) and the ligand (2 equiv. for bidentate and 4 equiv. for monodentate) in an open vessel for 18 h at room temperature. [b] Determined by GC–MS analysis. [c] Yield of isolated product. [d] 83% based on recovered disulfide.

Interestingly, it appeared that the full conversion of thiol **1a** into disulfide **2a** was almost instantaneous, presumably catalyzed by copper salts, and we envisioned that the reaction could be performed on the disulfide itself with equivalent efficiency. This was confirmed by the transformation of **2a** into thiocyanate **3a** in a yield (88%) similar to that obtained in the reaction performed with thiophenol. Remarkably, we noticed that the use of sodium thiolate salts as the substrates considerably accelerated the reactions. For example, sodium phenylthiolate was converted into thiocyanate **2a** after 1 h in comparable yield (92%). The effect of the solvent on the cyanation of diphenyl disulfide was then investigated (Figure 1) and was shown to be dramatic. Toluene, methanol, and 1,4-dioxane appeared incompatible with the reaction, whereas DMF, THF, and CH_2Cl_2 allowed the reaction to take place but drove it, after 18 h, to targeted thiocyanate **3a** in modest yields (36, 41, and 51%, respectively).

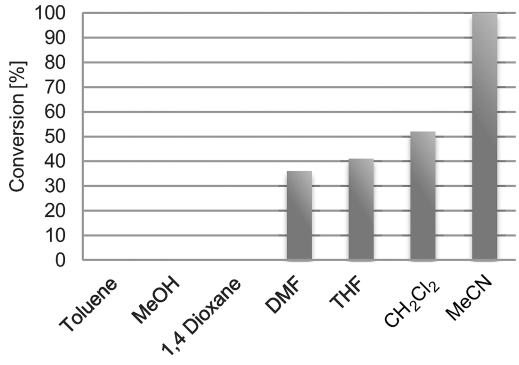
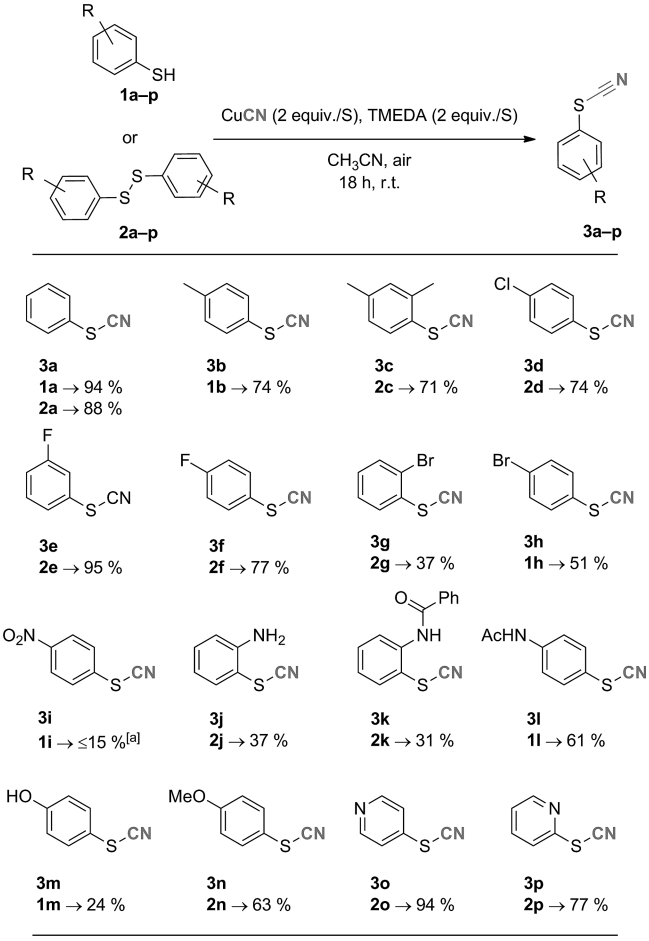


Figure 1. Relative efficiency of copper-mediated oxidative cyanation of diphenyl disulfide in various solvents after 18 h.

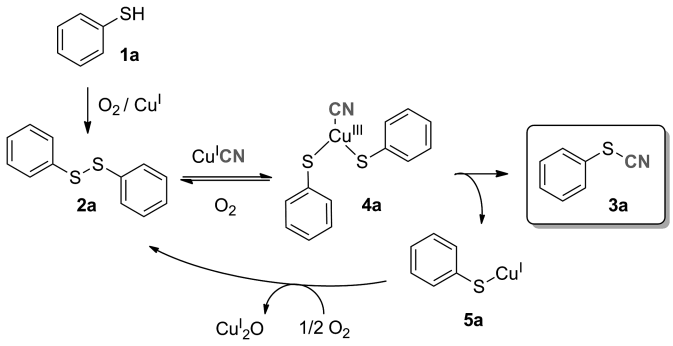
With the optimized conditions in hand, we investigated the scope of the reaction by performing the copper-mediated cyanation on representative aromatic thiols and diaryl disulfides (Table 2). Complete consumption of the disulfides was controlled after 18 h by GC–MS or TLC.

Table 2. Scope of the copper-mediated cyanation of thiophenols and diaryl disulfides. Conditions: Thiol (1 equiv.) or diphenyl disulfide (0.5 equiv.), CuCN (2 equiv.) in acetonitrile (0.3 M) and TMEDA (2 equiv.) in an open vessel for 18 h at room temperature.



[a] Performed at 80 °C for 18 h; yield evaluated by NMR spectroscopy.

Methyl-substituted substrates such as *p*-tolylthiocyanate (**3b**) and 2,4-dimethylthiocyanate (**3c**) were synthesized in good yields of 74 and 71%, respectively. Diversely chlorinated and fluorinated disulfides **2d**, **2e**, and **2f** furnished the desired thiocyanates in yields up to 95% (4-fluorophenyl thiocyanate **3e**), whereas brominated substrates **2g** and **1h** appeared less reactive, probably for electronic reasons, and corresponding thiocyanates **3g** and **3h** were obtained in yields of 40–50%. Electron-withdrawing substituents such as a nitro group lowered the reactivity of the disulfide, which was disadvantageous to the formation of the desired product. Thus, thiol **1i** was cyanated into **3i** in a poor 13% yield after 18 h at 80 °C, whereas only disulfide **2i** was reco-



Scheme 2. Plausible reaction pathway.

vered upon performing the reaction at room temperature. An amide substituent appeared compatible with the transformation, as thiol **1l** was converted into thiocyanate **3l** in a reasonable 63% yield. However, we also demonstrated that the reaction was particularly sensitive to steric hindrance of the *ortho* substituents. Thus, substrates such as 2-bromo- (**2g**) and 2-benzamide (**2k**) diphenyl disulfides gave the corresponding cyanated products in notably lower yields (37 and 31%, respectively) than parent 4-substituted compounds. So, thiols **1h** and **1l** gave **3h** and **3l** in 51 and 61% yield, respectively.

As expected, a free hydroxy group on the substrate (see compound **1m**) was detrimental to the reaction (product **3m**, 24%), whereas corresponding *o*-methylated derivative **1n** gave a good result (product **3n**, 63%). Gratifyingly, substrates bearing a pyridyl group (see compounds **2o** and **2p**) that can unfavorably chelate copper species were efficiently converted into thiocyanates **3o** and **3p** in yields up to 94%.

We propose a tentative mechanism (Scheme 2) based on experimental observations and on reported mechanistic studies on copper chemistry with thiols.[9,10] The first step upon starting from thiol **1a** is the complete conversion, almost instantaneously, into disulfide **2a**, as demonstrated by GC–MS analysis of the reaction mixture after 5 min. Cuprous cyanide then performs oxidative addition into the S–S bond to form copper(III) intermediate **4a**, which undergoes reductive elimination to furnish desired thiocyanate **3a** as well as copper(I) thiolate **5a**. To finish, under aerobic conditions two molecules of this Cu^{I} salt generate a molecule of disulfide **2a** along with a copper oxide species (observed black powder).

Conclusions

In conclusion, we developed a practical and mild copper-mediated cyanation of thiophenols and diaryl disulfides. The reaction can be performed with the use of convenient cuprous cyanide as the CN source and is performed in air at room temperature; it leads readily to variously functionalized aromatic thiocyanates in moderate to very good yields. TMEDA and *N*-methylimidazole were determined to be efficient promoters of the reaction and acetonitrile was shown to be the best solvent. This method represents an interesting complement to existing syntheses of thiocyanates with synthetic potential in practical oxidative cyanation reactions. At the present time, further studies are under investigation to elucidate the mechanism of this transformation and to extend the scope of this approach to different valuable substrates.

Experimental Section

General Procedure: CuCN (179 mg, 2 mmol) and then the disulfide (0.5 mmol) or the thiophenol (1 mmol) were added to a solution of TMEDA (0.3 mL, 2 mmol) in acetonitrile (3 mL). The mixture was stirred overnight, at room temperature, in air. The mixture was then filtered through a Celite pad. The filtrate was evaporated, and the crude product was directly purified on a silica gel column or was washed with water and the product extracted with diethyl ether. The product was purified by flash chromatography (heptane/ethyl acetate).

Supporting Information (see footnote on the first page of this article): All experimental procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgments

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