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Practical access to aromatic thiocyanates by CuCN-mediated direct aerobic oxidative cyanation of thiophenols and diaryl disulfides.

Thomas Castanheiro, Mihaela Gulea,* Morgan Donnard* and Jean Suffert*[a]

Dedicated to Pr Alexandre Alexakis on the occasion of his retirement

Abstract: We report a practical and mild aerobic oxidative CuCN-mediated cyanation of thiophenols and diaryl disulfides. The reaction is performed under air at room temperature and reaches aromatic thiocyanates in moderate to good yields starting from a broad range of diversely functionalized substrates.

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 are also constituents of biologically active compounds.¹ Compared to alkyl thiocyanates, which are generally easily available 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 (path 1, Scheme 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 (path 2, Scheme 1) is based on the nucleophilic attack of a cyanide (KCN, NaCN, or TMSCN) on a substrate bearing an electrophilic sulfur (aryl disulfides, aryl sulfonyl 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 bond⁶ and very recently for a N-CN bond,⁷ no example of sulfur cyanation by this reagent was 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 using oxygen as oxidant⁸ (Scheme 1).

Preliminary studies were conducted on thiophenol **1a** as a model substrate. Acetonitrile was chosen as solvent and molecular oxygen (air) as oxidant for obvious practical reasons. In first place we controlled if a ligand was required and no reaction was observed in the absence of it (Table 1, entry 1). Then the influence of the copper ligand was evaluated (Table 1, entries 2–7). Different usual ligands have been screened and it appeared that only two of them allowed the cyanation to take place, namely *N*-methylimidazole and *N,N'*-tetramethylethylenediamine (Table 1, entries 6 and 7). TMEDA turned out to be the best ligand as the reaction was complete after 18h and thiocyanate **3a** was obtained in a good 94% yield whereas *N*-methylimidazole drove only to a poor 25% yield of the targeted compound along with a large amount of diphenyl disulfide **2a**. Ligands such as triphenylphosphine, acetylacetone, pyridine or 1,10-phenanthroline were unable to promote the reaction and only disulfide **2a**, product of thiophenol oxidation, was recovered after 18h reaction.

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

Entry	Ligand	Conv (%) ^[a]	Ratio 2a:3a ^[a]	Yield 3a (%) ^[b]
1	No ligand	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	<i>N</i> -methylimidazole	100	54:46	25 ^[c]
7	TMEDA	100	0:100	94

[a] Determined by GC/MS analysis. [b] Isolated yield. [c] 83% based on recovered disulfide.

Conditions: 1 equiv. of thiophenol **1a**, 2 equiv. of CuCN in CH₃CN (0.3M) and 2 (bidentate) or 4 (monodentate) equiv. of ligand in an open vessel for 18h at room temperature.

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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 an equivalent efficiency. It has been confirmed by the transformation of diphenyl disulfide **2a** into thiocyanate **3a** in a similar yield (88%) as the reaction performed on thiophenol. Remarkably, we noticed that the use of sodium thiolate salts as substrate considerably accelerated the reaction. For example, sodium phenylthiolate was converted into thiocyanate **2a** after 1h in comparable yield (92%). The effect of the solvent on the cyanation of diphenyl disulfide has been then investigated (Figure 1) and has been shown to be dramatic. Toluene, methanol, and 1,4-dioxane appeared incompatible with the reaction while *N,N*-dimethylformamide, tetrahydrofuran, and dichloromethane allowed the reaction to take place but drove after 18h to the targeted thiocyanate **3a** in modest yields (respectively 36%, 41% and 51%).

Figure 1. Relative efficiency of Copper-mediated oxidative cyanation of diphenyl disulfide in various solvents.

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 (Scheme 2). Complete consumption of the disulfides was controlled after 18h by GC/MS or TLC.

Methyl-substituted substrates such as *p*-tolylthiocyanate **3b** and 2,4-dimethylthiocyanate **3c** were synthesized in good yields of 74% and 71%. Diversely chlorinated or fluorinated disulfides (**2d**, **2e**, and **2f**) furnished the desired thiocyanate in yields up to 95% (4-fluorophenyl thiocyanate **3e**) while brominated ones (**2g** and **1h**) appeared less reactive, probably for electronic reasons, and drove to corresponding thiocyanates (**3g** and **3h**) in 40-50% yields. Electron-withdrawing substituents such as nitro group lower the reactivity of the disulfide, so disadvantaging the formation of the desired product. Thus, thiol **1i** was cyanated into **3i** in a poor 13% yield after 18h at 80°C while only disulfide **2i** was recovered when the reaction was performed at room temperature. Amide substituent appeared compatible with the transformation as thiol **1l** was converted into thiocyanate **3l** in reasonable 63% yield. However, we also demonstrated that the reaction was particularly sensitive to the steric hindrance of 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%) than parent 4-substituted compounds. So, thiols **1h** and **1l** gave **3h** and **3l** in 51% and 61% respectively.

Conditions: 1 equiv. of thiol or 0.5 equiv. of diphenyl disulfide, 2 equiv. of CuCN in acetonitrile (0.3M) and 2 equiv. of TMEDA in an open vessel for 18h at room temperature. ^[a] Performed at 80 °C for 18h; yield evaluated by NMR.

Scheme 2. Scope of copper-mediated cyanation of thiophenols and diaryl disulfides.

As expected, a free hydroxyl group on the substrate (**1m**) damaged the reaction (**3m**, 24%) while the corresponding *o*-methylated derivative **1n** gave good result (**3n**, 63%). Gratifyingly, substrates bearing a pyridyl group (**2o** and **2p**), that can unfavorably chelate copper species, were efficiently converted into thiocyanate **3o** and **3p** in yields up to 94%.

We propose a tentative mechanism based on experimental observation as well as reported mechanistic studies on copper chemistry with thiols.^{9,10} The first step when starting from the thiol **1a** is the complete conversion, almost instantaneously, into the corresponding disulfide **2a** as demonstrated by a GC/MS analysis of the reaction mixture after 5 min. Cuprous cyanide could then perform an oxidative addition into the S-S bond to form copper(III) intermediate **4a** that could undergo a reductive elimination in order to furnish the desired thiocyanate **3a** as well

as copper(I) thiolate **5a**. To finish, two molecules of this Cu(I) salt could generate under aerobic conditions a molecule of disulfide **2a** along with copper oxide species (observed black powder).

Scheme 3. Plausible reaction pathway.

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

Experimental Section

General procedure: To a solution of TMEDA (0.3 ml, 2 mmol) in acetonitrile (3 ml) was added CuCN (179 mg, 2 mmol) and then the disulfide (0.5 mmol) or the thiophenol (1 mmol). The reaction was stirred overnight, at room temperature, under air. The reaction mixture was then filtered through celite pad. The filtrate was evaporated and the crude product was directly purified on 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 ^1H NMR, ^{13}C NMR.

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Keywords: thiocyanate • copper • aerobic oxidative coupling • disulfide • cyanation

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SHORT COMMUNICATION

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