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Copper-catalyzed cyanation of disulfides by azobisisobutyronitrile leading to thiocyanates†

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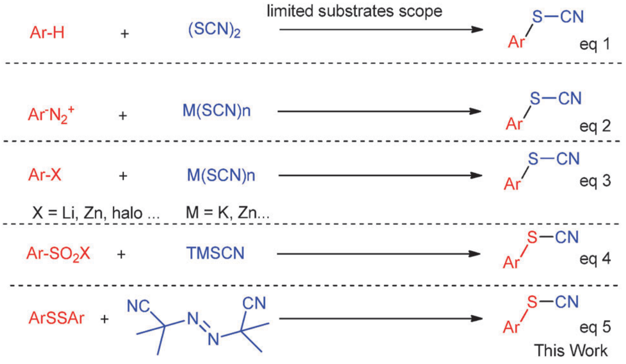
The copper-catalyzed cyanation of disulfides by azobisisobutyronitrile (AIBN) was developed, leading to thiocyanates in moderate to good yields. This procedure tolerates a series of functional groups, such as chloro, nitro, methyl and methoxycarbonyl in the phenyl ring of disulfides. Notably, it enables the use of two ArS units in $(ArS)_2$. CuI was found to be essential for the *in situ* formation of cyanide anions.

Aryl thiocyanates are not only the subunits of biologically active compounds[1] but also versatile intermediates leading to sulfonyl cyanides, sulfonic acids, sulfonylchlorides, thiocarbamates, thioesters, sulfides and related heterocycles.[2] Moreover, thiocyanate serves as the cyanation reagent with boronic acid.[3]

Intriguingly, less attention has been paid to the synthesis of aryl thiocyanate. Thiocyanation of arene suffered from limited substrate scope (eqn (1), Scheme 1).[4] The reaction of diazonium salts with metal thiocyanate, known as Gattermann–Sandmeyer reaction, required careful control of the reaction conditions (eqn (2), Scheme 1).[5] The reaction of the aryl metal (or halo) represented a versatile pathway leading to aryl thiocyanate (eqn (3), Scheme 1).[6] Alternatively, the cyanation of organosulfur compounds provided a complement of the aforementioned transformation. For example, Saito reported the reaction of arenesulfinates (or arenesulfonyl chlorides) with cyanotrimethylsilane to form aryl thiocyanates (eqn (4), Scheme 1).[7] However, the toxicity of cyanide would dramatically decrease the practicability of such a transformation. Fortunately, *C*-cyanation reaction using a cyanide source other than metal cyanide was well developed.[8] Han reported the seminal copper-mediated direct cyanation of an arene C–H bond by azobisisobutyronitrile (AIBN).[9] The cyanation of a heteroatom other than the carbon atom was less studied or reported before.



Scheme 1 The pathways leading to aryl thiocyanates.

Inspired by our recently developed copper-mediated *N*-cyanation reaction,[10] herein, we wish to report a fundamentally different pathway leading to thiocyanates: copper-catalyzed thiocyanation of diaryl disulfides by azobisisobutyronitrile (AIBN) (eqn (5), Scheme 1). This procedure is characterized by the following features: (1) compared with the procedures in eqn (2) and (3), less halo-containing waste was produced; (2) AIBN serves as a less toxic cyanide source in comparison with the procedure in eqn (4).

We started our study by using the combination of ArSSAr (Ar = 4-MeOC_6H_4–, 0.1 mmol), AIBN (0.15 mmol), CuO (10 mol%), and K_2CO_3 (0.1 mmol) in MeCN (2 mL) under O_2 at 100 °C as the model reaction. To our delight, arylthionate was isolated in 27% yield (Table 1, entry 1). Replacing CuO with $CuCl_2$, the yield increased to 47% (Table 1, entry 2). $CuSO_4$ was less efficient for this transformation (Table 1, entry 4) and CuI was the best, providing phenyl thiocyanate in 55% yield (Table 1, entry 3). In the absence of copper, the thiocyanation product was isolated in 10% yield, indicating that copper was essential for the reaction (Table 1, entry 5).[11] Solvent was also crucial for this transformation. Toluene, DCM, CCl_4 and MeOH all resulted in no reaction or low efficiency (Table 1, entries 6–9). Switching the base from K_2CO_3 to NaOH and K_3PO_4 slightly increased the yields to 61% and 65%, respectively (Table 1, entries 10 and 12). Fortunately, 81% yield was obtained by using $KHCO_3$ as base (Table 1, entry 13). Under air, the

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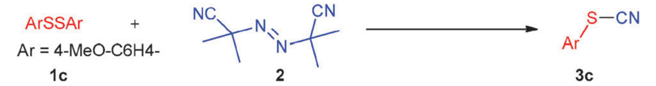
Table 1 Selected results for screening the optimized reaction conditions[a]



Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	CuO	K_2CO_3	MeCN	27
2	$CuCl_2$	K_2CO_3	MeCN	47
3	CuI	K_2CO_3	MeCN	55
4	$CuSO_4$	K_2CO_3	MeCN	25
5	—	K_2CO_3	MeCN	10
6	CuI	K_2CO_3	Toluene	<1
7	CuI	K_2CO_3	DCM	10
8	CuI	K_2CO_3	CCl_4	28
9	CuI	K_2CO_3	MeOH	<1
10	CuI	NaOH	MeCN	61
11	CuI	NaOAc	MeCN	39
12	CuI	K_3PO_4	MeCN	65
13	CuI	$KHCO_3$	MeCN	81 (<1)[c] (61)[d]
14	CuI	—	MeCN	<5
15	CuI	Et_3N	MeCN	10
16	CuI	DBU	MeCN	<5

[a] Reaction conditions: **1c** (0.1 mmol), AIBN (1.5 equiv.), Cu catalyst (0.1 equiv.), base (1.0 equiv.), solvent (2.0 mL) under O_2 for 12 h, 100 °C, sealed tube. [b] Isolated yield. [c] Under N_2. [d] Under air.

yield slightly decreased to 61% and no reaction took place under N_2 (Table 1, entry 13). In the absence of base, the procedure failed to produce any product (Table 1, entry 14). The organic bases, such as Et_3N and DBU, showed low efficiency (Table 1, entries 15 and 16).

After the establishment of the optimized reaction conditions, the scope of disulfides was studied, as shown in Fig. 1. This procedure tolerated chloro, nitro, methoxycarbonyl, methyl, bromo and acyl oxy groups. For diaryl disulfides, the reaction was not sensitive to the electron nature of the substrates, as both 4-nitro and 4-methyloxy substrates provided the desired products in good yields (**3c** and **3f**). However, **3g** was isolated in moderate yield. The chloro and alkenyl groups survived well under the standard conditions (**3e**, **3h** and **3m**), which were applicable for further functionalization. Diaryl disulfide with free phenolic hydroxyl failed to deliver the thiocyanation product. However, after the protection of the hydroxy group, **3i** and **3h** were isolated in 73% and 50% yields. Particularly, the di-hetero aryl disulfides, such as 2,2′-dipyridyl disulfide, 2,2′-dithio-dibenzothiazole and 4,4′-dipyridyl disulfide, worked under the standard conditions, providing **3j**, **3k** and **3p** in 77%, 37% and 60% yields, respectively. Notably, dibenzyl disulfide was a good reaction partner, and **3l** was isolated in 56% yield. Dioctyl disulfide provided the cyanation product **3r** in 52% yield.

Some experiments were conducted to gain some insight into the reaction. Firstly, the cyanide anion was detected using an indicating paper (for details, see ESI†). A further study revealed that PhSSPh, $KHCO_3$ and O_2 were not essential for the *in situ* formation of cyanide anions. However, in the absence of CuI, no cyanide ion was detected (Table 2).

Next, in the presence of 0.5 mmol of TEMPO, the reaction was inhibited, indicating that a radical pathway may be involved in the procedure (Scheme 2, eqn (1)). A stoichiometric amount of PhSCu(I) was subjected to the reaction, and the thiocyanation product was isolated in 38% yield in the presence of $KHCO_3$ in CH_3CN (Scheme 2, eqn (2)), which was comparable with the result when two equivalents of CuI were employed (Scheme 2, eqn (3)). Moreover, replacing CuI with PhSCu (10 mol%) under the standard conditions, phenyl thiocyanate was isolated in 53% yield (Scheme 2, eqn (4)). Furthermore, acetone was detected as the byproduct in the procedure by GC-MS (Scheme 2).

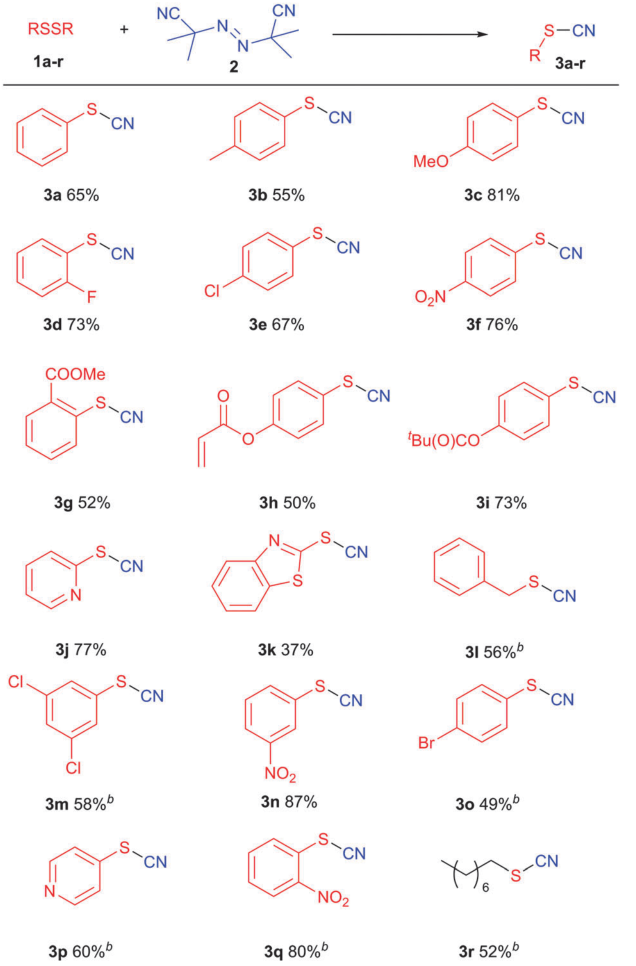
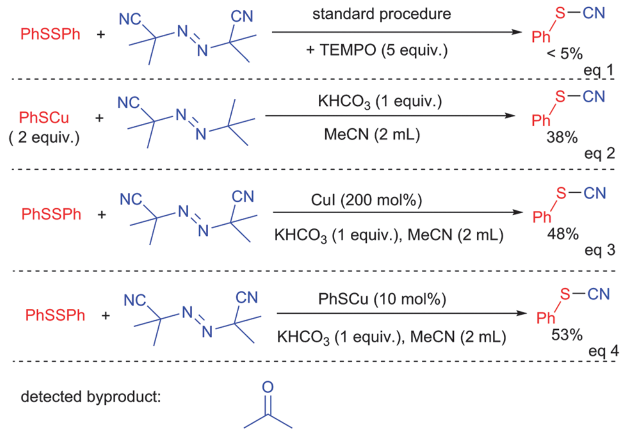


Fig. 1 Scope of disulfides.[a] [a] Reaction conditions: disulfide **1** (0.1 mmol), CuI (0.02 mmol), AIBN **2** (0.15 mmol), $KHCO_3$ (0.1 mmol), MeCN (2.0 mL), O_2, 100 °C, 12 h. [b] Disulfide **1** (0.1 mmol), CuI (0.02 mmol), AIBN (0.15 mmol), K_2CO_3 (0.15 mmol), MeCN (2.0 mL), O_2, 75 °C, 12 h.

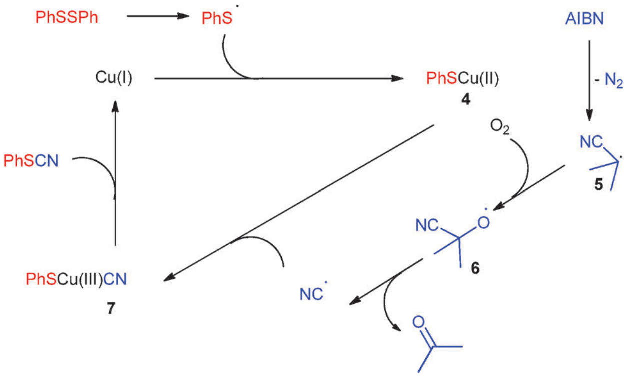
Table 2 Detection of cyanide anions[a]

Entry	PhSSPh	CuI	$KHCO_3$	Atmosphere	Results
1	√	√	√	O_2	+
2	×	√	√	O_2	+
3	√	×	√	O_2	−
4	√	√	×	O_2	+
5	×	√	×	O_2	+
6	×	√	×	N_2	+
7	×	√	×	Air	+

[a] Detection conditions: CuI (0.1 equiv.). For details, see ESI. "+" means positive results; "−" means negative results.



Scheme 2 Preliminary mechanism study.



Scheme 3 The proposed mechanism.

Based on these experimental results and Han's seminal work,[9] the proposed mechanism is outlined in Scheme 3.

In the presence of CuI, initially, the PhS• radical is formed by the homolytic cleavage of the S–S bond. Then the formed PhS• radical reacts with Cu(I) to form a Cu(II) species **4**. Meanwhile, the sequential cleavage of the N═N bond in AIBN followed by the loss of one equivalent of N_2 provides radical species **5**, which is oxidized to radical species **6** by O_2. By the extrusion of one equivalent of acetone, radical species **6** converts to the cyano radical. Subsequently, single electron transfer between the cyano radical and Cu(II) species **4** provides Cu(III) species **7**. Finally, reductive elimination of Cu(III) species **7** delivers the thiocyanation product and regenerates Cu(I).

In conclusion, we have developed a copper-catalyzed cyanation of disulfides by AIBN leading to thiocyanates. This procedure employs O_2 as the clean terminal oxidant and AIBN as a safe cyanide source. Thus, it represents a promising pathway to access thiocyanates and a key progress in cyanation reaction.

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