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COMMUNICATION

Copper-Catalyzed Cyanation of Disulfides by Azobisisobutyronitrile Leading to Thiocyanates[†]

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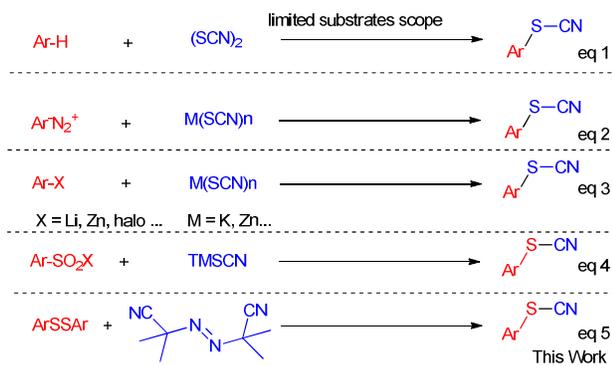
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The copper-catalyzed cyanation of disulfides by azobisisobutyronitrile (AIBN) was developed, leading to thiocyanates in moderate to good yields. The procedure tolerates a series of functional groups, such as chloro, nitro, methyl and methoxycarbonyl in the phenyl ring of disulfide. 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 anion.

Aryl thioncyanates are not only subunits of biological activity compounds¹ but also versatile intermediates leading to sulfonyl cyanides, sulfonic acids, sulfonylchlorides, thiocarbamates, thioesters, sulfides and relative heterocycles.² Moreover, thiocyanate served as the cyanation reagent with boronic acid.³

Scheme 1 The Pathways Leading to Aryl Thiocyanates.



Intriguingly, less attention has been paid in the synthesis of aryl thiocyanate. The thiocyanation of arene suffered from limited substrates scope (eq 1, Scheme 1).⁴ The reaction of diazonium salts with metal thiocyanate, known as Gattermann-Sandmeyer reaction, required careful control the reaction conditions (eq 2, Scheme 1).⁵

The reaction between aryl metal (or halo) represented a versatile pathway leading to aryl thiocyanate (eq 3, Scheme 1).⁶ Alternatively, the cyanation of organosulfur compounds provided a complement of the aforementioned transformation. For example, Saito reported the reaction between arenesulfonates (or arenesulfonyl chlorides) with cyanotrimethylsilane toward aryl thiocyanate (eq 4, Scheme 1).⁷ However, the toxicity of cyanide would dramatically decreased the practicability of such a transformation. Fortunately, the cyanation reaction using cyanide source other than metal cyanide was well developed in C-cyanation.⁸ Han reported the seminal copper-mediated direct cyanation of arene C-H bond by azobisisobutyronitrile (AIBN).⁹ The cyanation of hetero atom other than carbon atom was less studied or reported before. Inspired by our recently developed copper-mediated *N*-cyanation reaction,¹⁰ herein, we wish to report a fundamentally different pathway leading to thiocyanate: copper-catalyzed thiocyanation of diaryl disulfide by azobisisobutyronitrile (AIBN) (eq 5, Scheme 1). This procedure is featured with: 1) compared with the procedures in eqs 2 and 3, less halo-containing waste was produced; 2) AIBN served as less toxic cyanide source in comparison with the procedure in eq 4.

We started our study by using the combination of ArSSAr (Ar = 4-MeOC₆H₄-, 0.1 mmol), AIBN (0.15 mmol), CuO (10 mol %), and K₂CO₃ (0.1 mmol) in MeCN (2 mL) under O₂ at 100 °C as the model reaction. To our delight, the arylthionate was isolated in 27% yield (Table 1, entry 1). Replacing CuO with CuCl₂, the yield increased to 47% (Table 1, entry 2). CuSO₄ 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 copper was essential for the reaction (Table 1, entry 5).¹¹ The solvent was also crucial for this transformation. Toluene, DCM, CCl₄ 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 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).

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

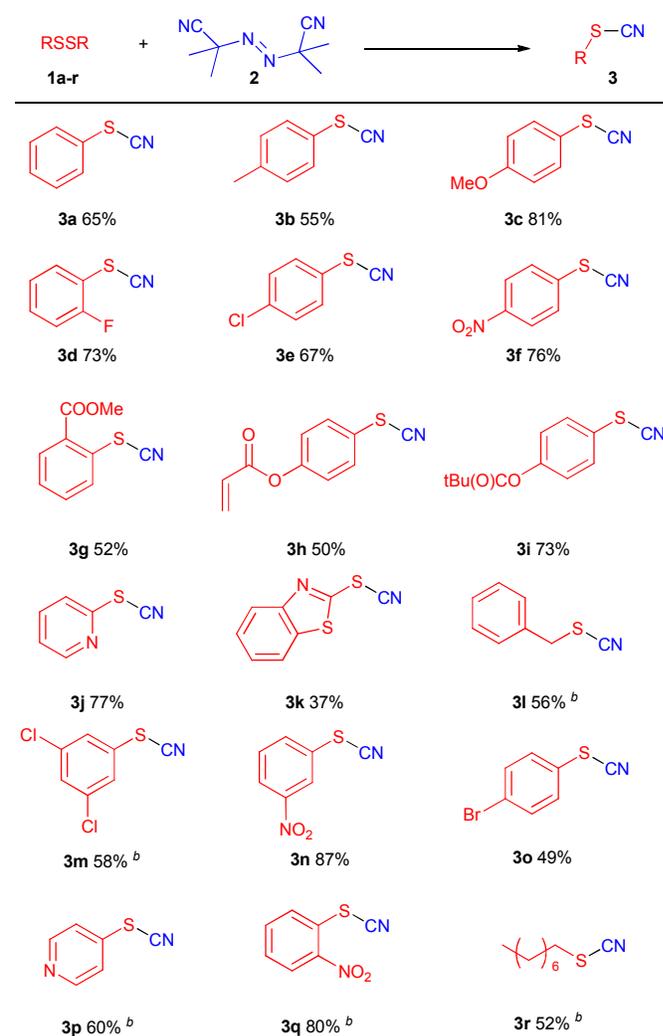
^a Reaction conditions: **1c** (0.1 mmol), AIBN (1.5 equiv), Cu catalyst (0.1 equiv), base (1.0 equiv), solvent (2.0 mL) under O_2 for 12 h, 100 °C, sealed tube. ^b Isolated yield. ^c Under N_2 . ^d Under air.

After the establishment of the optimized reaction condition, the scope of disulfides was studied, as shown in Figure 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-methoxy substrates provided the desired products in good yields (**3c** and **3f**). However, **3g** was isolated in moderate yields. The chloro and alkenyl groups survived well under the standard procedure (**3e**, **3h** and **3m**), which was applicable for further functionalization. Diaryl disulfide with free phenolic hydroxyl failed to deliver the thiocyanation product. However, after the protection of hydroxyl group, **3i** and **3h** were isolated in 73% and 50% yields. Particularly, the di-hetero aryl disulfide, such as 2,2'-dipyridyl disulfide, 2,2'-dithio-dibenzothiazole and 4,4'-dipyridyl disulfide worked under the standard procedure, providing **3j**, **3k** and **3p** in 77%, 37% and 60%

yields, respectively. Notably, dibenzyl disulfide was good reaction partners, 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, cyanide anion was detected by indicating paper (For detail, see Supporting Information). Further study revealed PhSSPh, $KHCO_3$ and O_2 were not essential for the *in situ* formation of cyanide anion. However, in the absence of CuI, no cyanide ion was detected (Table 2).

Figure 1. Scope of Disulfides.^a



^a Reaction conditions: disulfide **1** (0.1 mmol), AIBN **2** (0.15 mmol), $KHCO_3$ (0.1 mmol), CH_3CN (2.0 mL), O_2 , 100 °C, 12 h. ^b disulfide (0.1 mmol), CuI (0.02 mmol), AIBN (0.15 mmol), K_2CO_3 (0.15 mmol), CH_3CN (2.0 mL), O_2 , 75 °C, 12 h.

Next, in the presence of 0.5 mmol of TEMPO, the reaction was inhibited, indicating a radical pathway may be involved in the procedure (Scheme 2, eq 1). 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, eq 2), which was comparable with the result when two equivalents of CuI

was employed (Scheme 2, eq 3). Moreover, replacing CuI with PhSCu (10 mol%) under the standard procedure, phenyl thiocyanate was isolated in 53% yield (Scheme 2, eq 4). Furthermore, acetone was detected as byproduct in the procedure by GC-MS (Scheme 2).

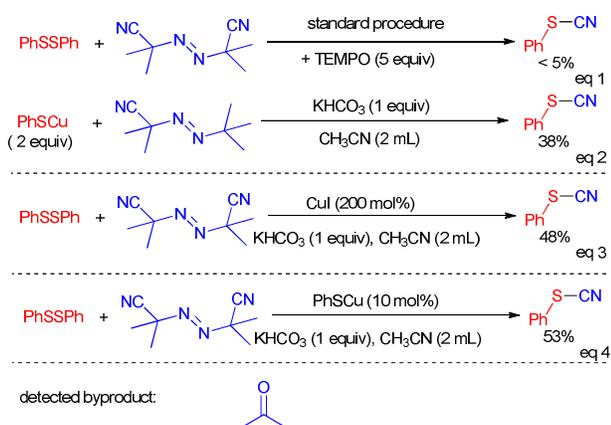
Table 2. Detecting of Cyanide Anion.

entry	PhSSPh	CuI	KHCO ₃	atmosphere	result
1	√	√	√	O ₂	+
2	×	√	√	O ₂	+
3	√	×	√	O ₂	-
4	√	√	×	O ₂	+
5	×	√	×	O ₂	+
6	×	√	×	N ₂	+
7	×	√	×	air	+

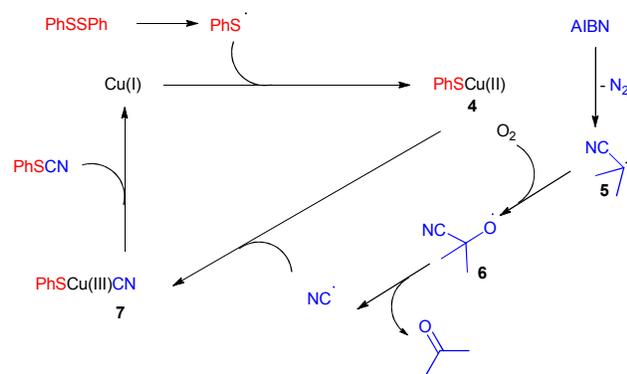
^a Detecting conditions: CuI (0.1 equiv). For detail, see Supporting Information. “+” means positive results; “-” means negative results.

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

Scheme 2. Preliminary Mechanism Study.



Scheme 3. The Proposed Mechanism.



In the presence of CuI, initially, the PhS• radical is formed by the homolytic cleavage of S-S bond. Then the formed PhS• radical reacts with Cu(I) to form a Cu(II) species 4. Meanwhile, the sequential cleavage of N=N bond in AIBN followed by the loss of

one equivalent of N₂ provides radical species 5, which is oxidized to radical species 6 by O₂. By the extrusion of one equivalent of acetone, radical species 6 converts to cyano radical. Subsequently, the single electron transferring between cyano radical and Cu(II) species 4 provides Cu(III) species 7. Finally, the reductive elimination of Cu(III) species 7 delivers the thiocyanation product and regenerates the Cu(I).

Conclusions

In conclusion, we have developed a copper-catalyzed cyanation of disulfides by AIBN leading to thiocyanates. This procedure employs O₂ 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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Notes and references

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[†] Electronic supplementary information (ESI) available: Detailed synthetic procedures and characterization of new compounds. See DOI: 10.1039/c000000x.

- (a) V. A. Kokorekin, A. O. Terent’ev, G. V. Ramenskaya, N. É. Grammatikova, G. M. Rodionova and A. I. Ilvovskii, *Pharm. Chem. J.*, 2013, **47**, 422; (b) M. Promkatkaew, D. Gleeson, S. Hannongbua and M. P. Gleeson, *Chem. Res. Toxicol.*, 2014, **27**, 51; (c) D. W. Roberts and A. O. Aptula, *Chem. Res. Toxicol.*, 2014, **27**, 240; (d) P. Jansa, L. Cêchova, M. Dračinský and Z. Janeba, *RSC Adv.*, 2013, **3**, 2650; (e) Y. Yasman, R. A. Edrada, V. Wray and P. Proksch, *J. Nat. Prod.*, 2003, **66**, 1512; (f) E. Elhalem, B. N. Bailey, R. Docampo, I. Ujváry, S. H. Szajnman and J. B. Rodriguez, *J. Med. Chem.*, 2002, **45**, 3984.
- (a) F. D. Toste, F. LaRonde and I. W. J. Still, *Tetrahedron Lett.*, 1995, **17**, 2949; (b) Z. P. Demko and K. B. Sharpless, *Org. Lett.*, 2001, **3**, 4091; (c) W. X. Zheng, A. Ariafard and Z. Y. Lin, *Organometallics*, 2008, **27**, 246; (d) R. J. Alaimo and S. S. Pelosi, *J. Med. Chem.*, 1974, **17**, 775; (e) F. Ke, Y.-Y. Qu, Z.-Q. Jiang, Z.-K. Li, D. Wu and X.-G. Zhou, *Org. Lett.*, 2011, **13**, 454; (f) For review, see: A. W. Erian and S. M. Sherif, *Tetrahedron*, 1999, **55**, 7957.
- Z. Zhang and L. S. Liebeskind, *Org. Lett.*, 2006, **8**, 4331.
- (a) S. G. Fridman, *Zh. Org. Khim.*, 1953, **23**, 116; (b) R. C. Elderfield and F. W. Short, *J. Org. Chem.*, 1952, **17**, 758.
- (a) R. G. Guy, In *The Chemistry of Cyanates and Their Thio Derivatives*, ed. S. Patai, 1977, Wiley, Chichester, 1977, Chapter 18;

- (b) M. Barbero, I. Degani, N. Diulgheroff, S. Dughera and R. Fochi, *Synthesis*, 2001, 585.
- 6 (a) Y.-F. Wang, Y. Zhou, J.-R. Wang, L. Liu and Q.-X. Guo, *Chin. Chem. Lett.*, 2006, **17**, 1283; (b) K. Takagi, H. Takachi and K. Sasaki, *J. Org. Chem.*, 1995, **60**, 6552; (c) K. Takagi, H. Takachi and N. Hayama, *Chem. Lett.*, 1992, 509; (d) N. Sun, H. Zhang, W. Mo, B. Hu, Z. Shen and X. Hu, *Synlett*, 2013, **24**, 1443.
- 7 (a) S. Kagabu, K. Sawahara, M. Maehara, S. Ichihashi and K. Saito, *Chem. Pharm. Bull.*, 1991, **39**, 784; (b) S. Kagabu, M. Maehara, K. Sawahara and K. Saito, *J. Chem. Soc., Chem. Commun.*, 1988, 1485.
- 8 (a) J. Jin, Q. Wen, P. Lu and Y. Wang, *Chem. Commun.*, 2012, **48**, 9933; (b) T.-J. Gong, B. Xiao, W.-M. Cheng, W. Su, J. Xu, Z.-J. Liu, L. Liu and Y. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 10630; (c) B. Liu, J. Wang, B. Zhang, Y. Sun, L. Wang, J. Chen and J. Cheng, *Chem. Commun.*, 2014, **50**, 2315; (d) G. Zhang, X. Ren, J. Chen, M. Hu and J. Cheng, *Org. Lett.*, 2011, **13**, 5004; (e) J. Kim and S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272; (f) S. Ding and N. Jiao, *J. Am. Chem. Soc.*, 2011, **133**, 12374; (g) X. Ren, J. Chen, F. Chen and J. Cheng, *Chem. Commun.*, 2011, **47**, 6725; (h) R. Wang and J. R. Falck, *Chem. Commun.*, 2013, **49**, 6516; (i) M. Chaitanya, D. Yadagiri and P. Anbarasan, *Org. Lett.*, 2013, **15**, 496; (j) G. Zhang, S. Chen, H. Fei, J. Cheng and F. Chen, *Synlett*, 2012, 2247; (k) X. Kou, M. Zhao, X. Qiao, Y. Zhu, X. Tong and Z. Shen, *Chem.—Eur. J.*, 2013, **19**, 16880; (l) C. Pan, H. Jin, P. Xu, X. Liu, Y. Cheng and C. Zhu, *J. Org. Chem.*, 2013, **78**, 9494; (m) L. Zhang, Q. Wen, J. Jin, C. Wang, P. Lu and Y. Wang, *Tetrahedron*, 2013, **69**, 4236; (n) Q. Wen, J. Jin, Y. Mei, P. Lu and Y. Wang, *Eur. J. Org. Chem.*, 2013, 4032.
- 9 H. Xu, P.-T. Liu, Y.-H. Li and F.-S. Han, *Org. Lett.*, 2013, **15**, 3354.
- 10 F. Teng, J.-T. Yu, Y. Jiang, H. Yang and J. Cheng, *Chem. Commun.*, 2014, 50, 8412.
- 11 K_2CO_3 contains 0.24 ppm of copper, as tested by ICP-MS.

Graphic Abstract

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