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Radical N-cyanation of sulfoximine through acetonitrile C—CN cleavage

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ABSTRACT

A new strategy for the N-cyanation of sulfoximine via radical process has been developed, leading to the desired products in moderate to excellent yields with good functional group tolerance. This procedure provided an alternative pathway to C—CN bond activation of acetonitrile. In particular, 1,1,3,3-tetramethylguanidine also worked well in this procedure.

Sulfoximidoyl-containing derivatives have caught significant attention in organic chemistry and have been widely applied in crop protection and medicinal chemistry.[1] Meanwhile, they have also been proven to be successful reaction partners as chiral auxiliaries[2] and ligands.[3] Thus, pursuing N-functionalization of sulfoximines continues to be a front-burner issue.[4] Moreover, the N—CN bonds are ubiquitous and frequently found in large numbers of biologically active molecules, natural products, and some medicinal structures.[5] So far, only a few studies on N-cyanation of sulfoximine have been conducted.[6] Therefore, N-cyanation of sulfoximine is still extremely appealing.

In the past years, it has been a challenging work to activate the C—C bond in modern organic chemistry.[7] Cleavage of C—CN bond is fascinating to serve as a cyanide source, yet challenging. In 1986, Murahashi discovered the Pd-catalyzed decarbonylation of acyl cyanides.[8] Since then advance in C—CN cleavage has been made, which was promoted by transition metal complexes, such as Pd,[9] Ni,[10] Rh,[11] Fe,[12] and others.[13] However, much attention was paid mainly to aromatic nitriles or acyl cyanides in these cases, which are easier to be cleaved compared to alkyl nitriles. To the best of our knowledge, only a few examples have been reported on the C—CN cleavage of acetonitrile. In 1998, Cheng's group reported on the C—CN bond cleavage of acetonitrile mediated by palladium and zinc species.[14] Afterward, Mascharak and co-workers discovered [Cu(dmppy)(en)] (en = ethylenediamine) could activate such a C—CN bond by heterolytic cleavage to form cyano anion and methyl cation fragments.[15] Subsequently, Lu reported copper(II) cryptate-mediated C—C bond activation of acetonitrile.[16] Recently, a Cu/Si system for the cyanation with acetonitrile has been documented by Shen.[17] In 2012, Li's group reported on the C—C bond cleavage of acetonitrile catalyzed by copper.[18] And Zhu's group reported cyanation of indoles using Cu/Ag system to activate the C—CN bond of acetonitrile in 2013.[19] Nevertheless, there is no report on acetonitrile serving as the radical precursor in N-cyanation reaction. We are confident of initiating a study that acetonitrile might be a suitable cyano radical source to access N-cyanation of sulfoximines, if the reaction conditions could be properly controlled. And that would provide an alternative option for more efficient synthesis of N-cyanation sulfoximines. Herein we report our success on this approach (see Scheme 1).

We used the sulfoximine **1a** as a model substrate to find suitable reaction conditions. Initially, we examined the reaction using **1a**, Cu_2O, and TBHP under O_2 in CH_3CN at 120 °C. To our delight, after 24 h, N-cyanation product **2a** was formed in 26% yield (Table 1, entry 1). Following this exciting result, other peroxides were tested (Table 1, entries 2–4). Delightedly, we achieved the desired product **2a** in 85% yield when using DTBP instead of TBHP (Table 1, entry 4). Then control experiments showed that, in the absence of DTBP, the reaction could not take place (Table 1, entry 5). While in the absence of Cu_2O, still we got the product **2a** in 8% yield (Table 1, entry 6). It represented that the reaction might

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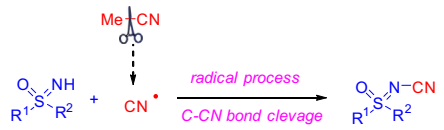
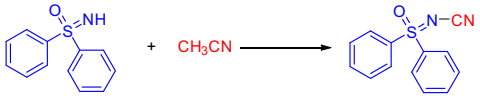


Scheme 1. N-cyanation of sulfoximine.

Table 1
The optimization of reaction conditions[a]



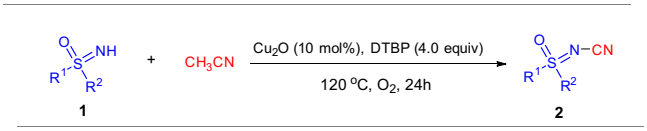
Entry	Catalyst	Oxidant	Temp (°C)	Yield[b] (%)
1	Cu_2O	TBHP	120	26
2	Cu_2O	$K_2S_2O_8$	120	<1
3	Cu_2O	BPO	120	<1
4	Cu_2O	DTBP	120	85 (80)[c] (<1)[d]
5	Cu_2O	—	120	<1
6	—	DTBP	120	8
7	CuF_2	DTBP	120	48
8	CuBr	DTBP	120	75
9	CuI	DTBP	120	40
10	CuCN	DTBP	120	46
11	$Fe(acac)_2$	DTBP	120	<1
12	AgF	DTBP	120	19
13	Cu_2O	DTBP	100	<1
14	Cu_2O	DTBP	110	41
15	Cu_2O	DTBP	130	79

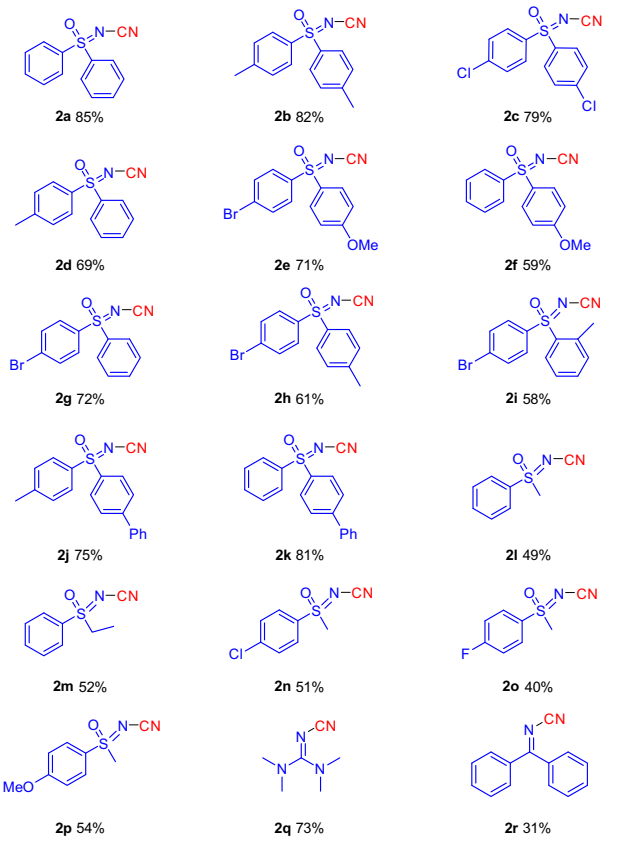
[a] Reaction conditions: **1a** (0.1 mmol), oxidant (0.4 mmol), catalyst (10 mol %), CH_3CN (1.5 mL) at 120 °C for 24 h under O_2 in a sealed tube. (TBHP = *tert*-butyl hydroperoxide, BPO = benzoyl peroxide, DTBP = di-*tert*-butyl peroxide.)
[b] Isolated yield.
[c] Under air.
[d] Under N_2.

proceed via a radical process. Thereafter, reactions were conducted under air and N_2. Sharply in contrast, N-cyanation product **2a** was formed in 80% yield under air while the reaction just did not take place under N_2 (Table 1, entry 4). Based on that, we could make a conclusion that O_2 participated in this procedure. Subsequently, other copper(I) and copper(II) salts such as CuF_2, CuBr, and CuI were also tested in the procedure and provided the desired product **2a** in 48%, 75%, and 40% yields, respectively, (Table 1, entries 7–9). It is significant and meaningful that when CuCN was tested, product **2a** was formed only in 46% yield (Table 1, entry 10), which ruled out the possibility that CN anion is the active compound in this reaction. No conversion occurred when $Fe(acac)_2$ was used as the catalyst (Table 1, entry 11), while **2a** was formed in 19% yield in the presence of AgF (Table 1, entry 12). Different temperatures had also been tested in this procedure. No reaction took place at 100 °C (Table 1, entry 13), while **2a** was formed in 41% and 79% yields at 110 °C and 130 °C, respectively, (Table 1, entries 14 and 15).

The substrate scope of this strategy was investigated under the optimized reaction conditions. Initially, diphenylsulfoximine derivatives were tested. Generally, various substituted groups (such as methyl, methoxy, chloro, and bromo groups) were all tolerated well and provided the corresponding N-cyanation products in moderate to excellent yields as shown in Table 2 under the standard procedure. For instance, **2b**, **2c**, **2e,** and **2k** were isolated in 82%, 79%, 71%, and 81% yields, respectively. To our delight, alkylphenylsulfoximines, arylimine, and guanidine also worked smoothly under the standard procedure delivering the N-cyanation products. For example, (*S*-methylsulfonimidoyl)benzene derivative provided the **2l** in 49% yield and (*S*-ethylsulfonimidoyl)benzene

Table 2
Scope of N-cyanation sulfoximines[a]



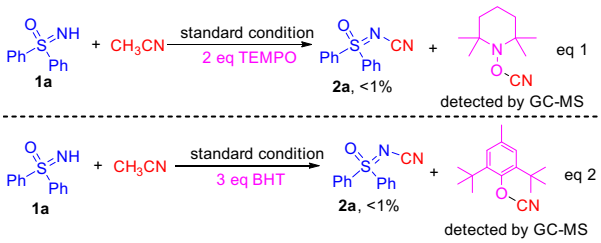


[a]Reaction conditions: **1a** (0.1 mmol), DTBP (0.4 mmol), Cu_2O (10 mol %), CH_3CN (1.5 mL) at 120 °C for 24 h under O_2 in a sealed tube.

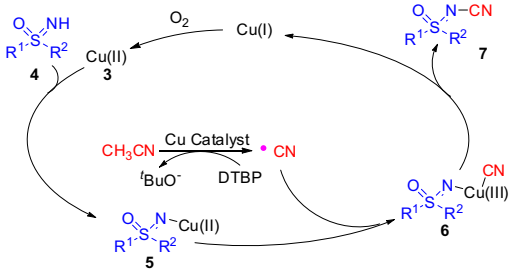
derivative provided the N-cyanation product **2m** in 52% yield. Meanwhile, we are glad to emphasize that substrates containing halogen also run smoothly (**2n**, **2o**), which provided an efficient route for further functionalizations. Interestingly, 1,1,3,3-tetramethylguanidine also worked well in this procedure, and gave the N-cyanation product in 73% yield (**2q**). Besides, benzophenone imine in this reaction led to the desired product in 31% yield (**2r**), which further extended the substrate scope.

More experiments were conducted to study the potential mechanism. Initially, the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) was added to this procedure, no desired product **2a** was formed, and the adduct TEMPO-CN was observed by GC–MS (Figs. S1 and S2 in Supplementary data). Meanwhile, product **2a** was not provided either when adding BHT (2,6-di-*tert*-butyl-4-methylphenol) to the reaction, and the adduct between BHT and cyanide was also detected by GC–MS (Figs. S3 and S4 in Supplementary data). These indicate that a radical pathway may be involved in this transformation (Scheme 2).

Based on the aforementioned experimental results, the possible mechanism is proposed shown in Scheme 3. Firstly, the catalyst Cu (I) is oxidized to Cu(II) by O_2. Then, the reaction between sulfoximines **4** and Cu(II) species **3** produces another Cu(II) species **5**. At the same time, cyano radical is formed via C—CN bond cleavage of acetonitrile promoted by catalyst copper and DTBP. Subse-



Scheme 2. Preliminary mechanistic studies.



Scheme 3. Proposed mechanism.

quently, cyano radical reacts with **5** and formed Cu(III) species **6**. Finally, reduction elimination of **6** provides the desired products **7** and regenerates Cu(I).

In conclusion, we have developed an alternative strategy for the N-cyanation of sulfoximines, which represents a significant and practical progress to N-cyanation reaction. The procedure featured a free-radical process, safe and cheap cyanide source, and good functional group tolerance.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.025.

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