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Copper-promoted cyanation of aryl iodides with *N*,*N*-dimethyl aminomalononitrile ☆

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ABSTRACT

A copper-promoted cyanation of aryl iodides has been successfully developed by using *N*,*N*-dimethyl aminomalononitrile as the cyanide source with moderate toxicity and better stability. This reaction features broad substrate scope, excellent reaction yields, readily available catalyst, and simple reaction conditions.

Benzonitrile, as a key structural unit, widely exists in a number of pharmaceutically active molecules [1] (Fig. 1). At the same time, aryl nitriles are also a kind of versatile synthetic intermediates as they can be easily converted into aldehydes, carboxylic acids, ketones and other products [2]. Therefore, the development of efficient synthetic methodologies toward this type of compound has attracted broad attention of synthetic chemists leading to a variety of reaction patterns. Among these methods, the direct cyanation of aryl halides, since its first report by Pongratz in 1927, has become one of the most commonly used strategies for the preparation of aryl cyanides [3].

Although metal cyanides such as MCN (M = K [4], Cu [5], Na [6] or Zn [7]), $K_4[Fe(CN)_6]$ [8] are usually used as cyanide sources for such a transformation, their toxicity is a significant safety concern for large scale applications. While reactions employing less toxic cyanide reagents have been developed, these processes often require conditions not suited for large scale preparation. Accordingly, different organic cyano reagents or their surrogates with less toxicity and easier operability have been applied to this reaction in recent years [9] such as dimethylmalononitrile (DMMN) [10], 2-methyl-2-phenyl malononitrile (MPMN) [11], butyronitrile [12], malononitrile [13], acetonitrile [14], ethyl (ethoxymethylene) cyanoacetate [15], amides [16] (Scheme 1, upper part). Nevertheless, corresponding procedures still suffer disadvantages like harsh reaction conditions, the use of expensive catalysts, ligands or additives, and synthetically complex cyanide reagents. Therefore, it is still highly desirable to search for alternative strategies using readily available cyano reagents with low-toxicity and better stability. In our previous work, a direct synthetic strategy for the synthesis of *N*,*N*-disubstituted aminomalononitriles has been successfully developed [17]. Based on the structural characteristics of such type of compound, in particular, the presence of two cyano and one amine groups, their synthetic utilities were then investigated,

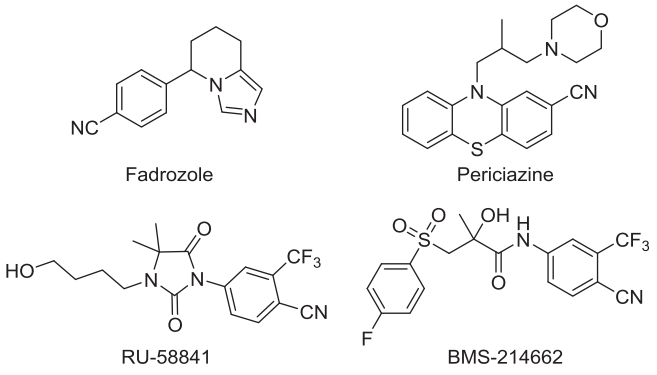

Fig. 1. Selected pharmaceutically active molecules with a benzonitrile moiety.

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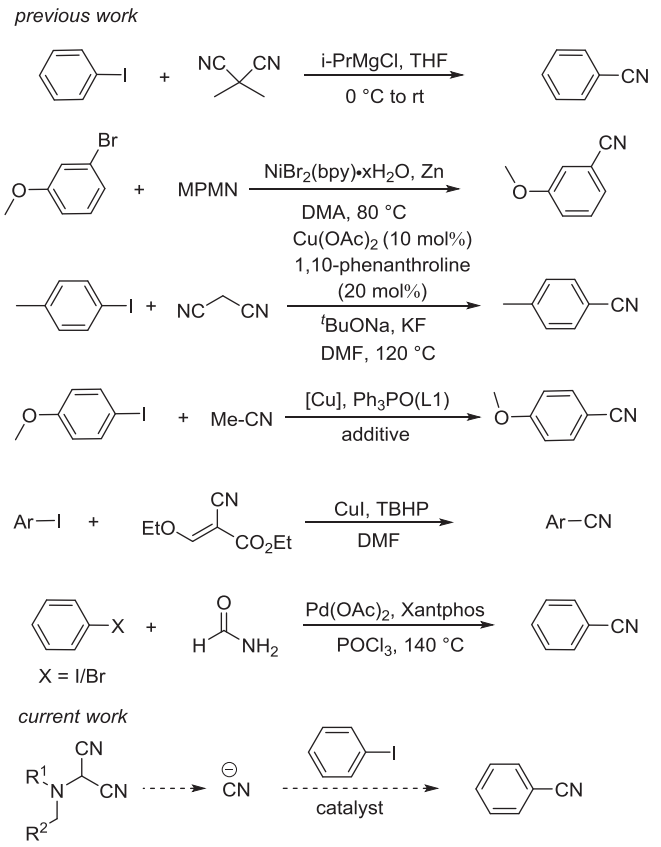


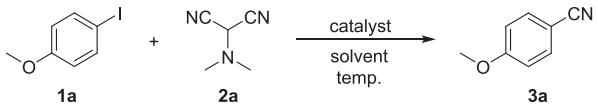
Scheme 1. Selected cyanation of aryl halides using organic cyano reagents.

leading to the development of several methodologies toward the construction of substituted pyrroles [18], pyrazoles [19], cyanoformamides [20], 1-cyano-bisindolylmethane [21], 2-substituted benzonitriles [22], and tertiary amides [23]. The above results and our understanding about the reactivity of *N*,*N*-disubstituted aminomalononitriles prompt us to further explore the synthetic utility of this type of synthetic precursor. Since it has been reported that C-CN bond could be dissociated under the activation of transition metals to form metallic cyano complexes [24], we anticipated whether it is possible to use *N*,*N*-disubstituted aminomalononitrile as a cyanide source to perform cyanation reaction with aryl halide to obtain substituted aryl cyanides (Scheme 1, lower part). Herein, as a systematic continuation of the *N*,*N*-disubstituted aminomalononitrile based synthetic methodology development, a copper promoted cyanation of aryl iodide with *N*,*N*-dimethyl aminomalononitrile is presented.

Following our original assumption, we first attempted the feasibility of this transformation was attempted by using 1-iodo-4-methoxybenzene **1a** and simple 2-(dimethylamino)malononitrile **2a** as the model substrates. As shown in Table 1, the first attempt using $Cu(OAc)_2$ as catalyst in DMF at 120 °C could afford the expected product **3a** in 39% yield (Table 1, entry 1). Next, different metal catalysts which have been used in the cyanation in previous work were applied to the reaction (Table 1, entries 2–6). Among them, the use of $PdCl_2$ and $Pd(OAc)_2$ did not promote the transformation at all (Table 1, entries 2–3), while, copper catalysts all promoted the reaction (Table 1, entries 4–6), and the best result was obtained under the catalysis of $Cu_3(PO_4)_2$ producing **3a** in a yield of 75%. Subsequently, further increasing the amount of $Cu_3(PO_4)_2$ to 0.2 equivalent could improve the yield of **3a** to 89% (Table 1, entry 7). Next, some other copper(II) catalysts were then screened, however, no better outcome was obtained compared with that of $Cu_3(PO_4)_2$ (Table 1, entries 8–12). After that, the reaction was carried out in different solvents, and only the use of DMSO could afford product **3a** in 57% yield [25]. We also tried to lower the reaction temperature, which clearly affected the reaction rate [25]. At 80 °C, only trace amount of product could be detected. Additionally, the reaction could also be carried out under dry air atmosphere to give a yield of 87% [25]. Therefore, using **2a** as the cyanide source under the catalysis of $Cu_3(PO_4)_2$ in DMF at 120 °C was selected as the optimal reaction conditions for the cyanation reaction (Table 1, entry 7). It should be noted that no extra ligand or additives were needed under the above conditions. Moreover, according to karber's method [25], the LD_{50} of **2a** for oral gavage in mice was also tested as 60 mg/kg [26], which is in the range of moderate toxicity and much lower than that of KCN or malononitrile.

After the optimal reaction conditions were setup (Table 1, entry 7), the generality of this transformation was then investigated. As shown in Table 2, the reaction was tolerant to a variety of aromatic

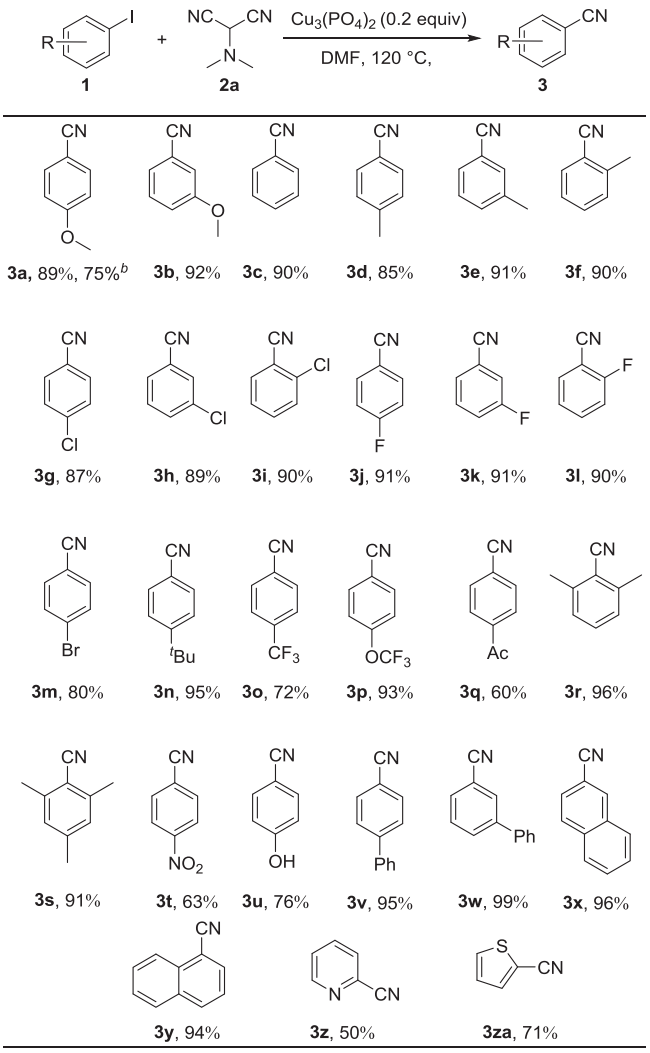
Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst	Temp.	Solvent	Yield[b]
1	$Cu(OAc)_2$	120 °C	DMF	39%
2	$PdCl_2$	120 °C	DMF	n.d.[c]
3	$Pd(OAc)_2$	120 °C	DMF	n.d.[c]
4	CuI	120 °C	DMF	20%
5	$Cu(OTf)_2$	120 °C	DMF	50%
6	$Cu_3(PO_4)_2$	120 °C	DMF	75%
7	$Cu_3(PO_4)_2$[d]	120 °C	DMF	89%
8	$Cu(OAc)_2$[d]	120 °C	DMF	50%
9	$Cu(OTf)_2$[d]	120 °C	DMF	52%
10	CuF_2[d]	120 °C	DMF	48%
11	$CuBr_2$[d]	120 °C	DMF	Trace
12	$CuSO_4$[d]	120 °C	DMF	41%

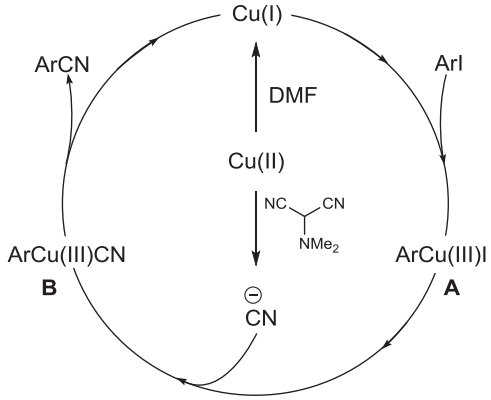
[a] Reaction conditions: 1-iodo-4-methoxybenzene **1a** (0.5 mmol, 1 equiv), 2-(dimethylamino)malononitrile **2a** (1 mmol, 2.0 equiv), catalyst (0.05 mmol 0.1 equiv), solvent (2 mL).
[b] Isolated yield.
[c] n.d. = not detected.
[d] Catalyst (0.1 mmol, 0.2 equiv) was used.

Table 2
Scope of the reaction.[a]



[a]Reaction conditions: 1 (0.5 mmol, 1 equiv), 2-(dimethylamino)malononitrile **2a** (1 mmol, 2.0 equiv), $Cu_3(PO_4)_2$ (0.1 mmol, 0.2 equiv), DMF (2 mL), 120 °C in a seal tube for 24 h.
[b]1g of **1a** was used.

iodides possessing different substituents with different electronic and steric properties, and most of the tested aromatic iodides gave good to excellent yields. Meanwhile all the substituents on the aromatic ring, such as halogen atoms (**3g** to **3m**), acetyl (**3q**) and nitro groups (**3t**), kept intact during the reaction. In particular, the presence of halogen atom, acetyl, nitro and hydroxyl (**3u**) group provided additional sites for subsequent derivatization. Moreover, in the case of substituted benzene iodide, no clear steric effect of the substituent was observed. For example, when substrates **1d**-**1l** with a methyl, chloro or fluoro atom substituent were subjected to this reaction, they all went through the transformation smoothly to give corresponding products in excellent yields regardless of the *ortho*, *meta*, or *para* position of the substituent on arene. Furthermore, the use of substrates **1r** and **1s** with two methyl groups at both the *ortho* positions of the iodo atom also afforded the desired products **3r** and **3s** in 96% and 91% yields, respectively. In contrast, the electronic effect of the substituent was observed. Selected examples like substrates **1a** and **1d** with electron donating group at the *para*-position could give products **3a** and **3d** in much higher yields than that of substrates **1q** and **1t** with a typical electron



Scheme 2. Plausible reaction mechanism.

withdrawing group at the same position. Additionally, iodobiphenyl, iodonaphthalene, 2-iodopyridine and 2-iodothiophene were also amenable to this reaction producing corresponding nitrile compounds **3v**-**3za** in moderate to excellent yields. It should be noted that aromatic bromide, chlorinate and phenyl trifluoromethanesulfonate were not applicable to this reaction, which is worth for further investigation. Besides, in order to demonstrate the potential practicability of this method, a gram-scale reaction of substrate **1a** was carried out to afford **3a** in 75% yield.

Based on the above results and related literature reports [27,28], a plausible reaction mechanism was proposed (Scheme 2). Initially, in the presence of DMF, the Cu(II) species could be reduced to the active Cu(I) species [27], which would form intermediate A through the oxidative addition of aromatic iodide [14a,27b,28]. Next, intermediate A underwent an anion exchange with the cyanide ion, which was generated from substrate **2a** under the promotion of Cu(II) catalyst [24], leading to the intermediate B. Finally, the reductive elimination of intermediate B would generate aromatic nitrile product and the active Cu(I) species for next cycle.

In summary, we have successfully developed a copper-promoted simple and efficient arylcyanation reaction that can be used to prepare various substituted arylcyanides with diverse functionality. Different from most of the known strategies, no additional ligand and additives were needed with current method. Further application of this reaction is ongoing in the same group.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152749.

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