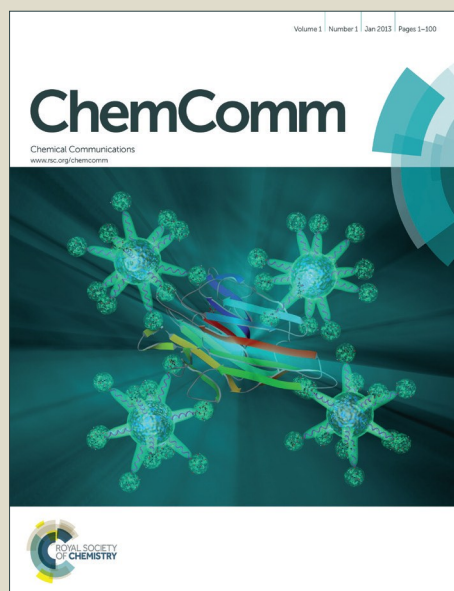


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Cu(NO₃)₂·3H₂O-Mediated Cyanation of Aryl Iodides and Bromides using DMF as a Single Surrogate of Cyanide

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Aryl nitriles were prepared through Cu(NO₃)₂·3H₂O-mediated cyanation of aryl iodides and bromides using DMF as a single surrogate of cyanide. Moreover, this protocol could be scalable and practice with operational benign.

Aryl nitriles are versatile intermediates in organic synthesis because they could be easily transferred into various valuable functional groups, such as carboxylic acids, amidines, and amines, or converted into heterocycles, such as pyrazoles,¹ triazoles,² and tetrazoles.³ Due to these practical transformations, development of new methodology leading to a cheap, safe, and feasible preparation method of aryl nitriles is still demanding, especially important in industry.

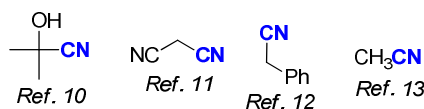
There are two classes of starting materials for the preparation of aryl nitriles. One is aryl halides,⁴ and the other is arenes in which the cyanation of arene happens through transition metal catalyzed C-H activation with/without directing group.⁵ Although the direct C-H functionalization is becoming more and more attractive and challengeable to organic chemists because of the exhilarating and fascinating mechanisms,⁶ aryl halides are still favourable because of their reaction orientation and broad availability.

Among the transition metal catalyzed cyanations of aryl halides, researches have been focusing on the discovery of metal catalysts and various operational benign cyanide sources. Although palladium catalyzed cyanations possessed high efficiencies, they still have drawbacks, such as expensive palladium catalysts as well as their special ligands required.⁷ Beside of this, palladium catalyst would be easily poisoned by the excess amount of cyanide anion due to the large affinity of cyanide anion to palladium.⁸ By comparison, copper salt is much cheaper and operational benign. In most cases, copper catalyzed or mediated cyanations could be conducted under air without specific ligands.^{5b} Metal cyanides are traditionally used "CN" sources, but with high toxicity. Organic cyanide surrogates slowly release cyanide anion during the reaction process surmounting the safety problem and are operational benign.⁹ These organic sources could be classified into two categories. One is "CN"-containing, the other is non-"CN"-containing in which C≡N triple bond forms as the reaction goes. Scheme 1 listed the organic cyanide surrogates which have been applied in copper-catalyzed or copper-mediated cyanations of aryl halides.

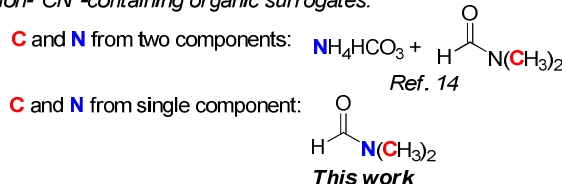
Herein, we would like to report a practical method for the preparation of aryl nitriles from aryl bromides / iodides in the presence of stoichiometric amount of Cu(NO₃)₂·3H₂O by using N,N'-

dimethylformamide (DMF) as a single surrogate of "CN" source (Scheme 1).

"CN"-containing organic surrogates:

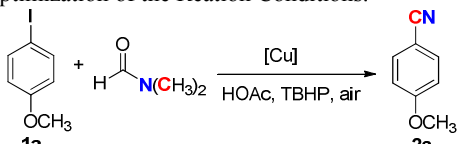


Non-"CN"-containing organic surrogates:



Scheme 1 Organic Cyanide Surrogates Applied in Cu-Catalyzed / Mediated Cyanations.

Initially, we tested the reaction of 4-iodoanisole (**1a**) and DMF in the presence of CuI, acetic acid, and TBHP under air at 130 °C for 48 h (Table 1, entry 1). 4-Cyanoanisole (**2a**) was indicated by GC in 45% conversion yield. Screening the copper sources, Cu(NO₃)₂·3H₂O was determined to be the optimal (Table 1, entries 1-12). Mediated by Cu(NO₃)₂·3H₂O, the conversion yield of **2a** was determined to be 73%, while the isolated yield of **2a** was obtained as 69% (Table 2, entry 8). Increasing or decreasing the amount of Cu(NO₃)₂·3H₂O, the yield of **2a** was dropped (Table 2, entries 13 and 14). Subsequently, the optimal amount of HOAc and TBHP was determined to be 4 and 2 equivalents (Table 1, entries 15-18). The yield was largely depended upon the reaction temperature and reaction atmosphere. The best yield was achieved by increasing the reaction temperature to 140 °C (Table 1, entries 19-20). Under nitrogen, the yield dropped to 19%, while the yield kept the same (89%) under oxygen (Table 1, entries 21-22). Without TBHP oxidant, the reaction worked, but with relatively lower yields (air: 34%; O₂: 78%, Table 1, entries 23 and 24). It was noticeable that the conversion yield of **2a** was 55% without HOAc (Table 1, entry 25). These two reactions indicated that the carbon source of "CN" did not come from HOAc or THBP. Thus, the optimal reaction conditions were established: running the mixture of ArX, Cu(NO₃)₂·3H₂O, HOAc, and TBHP (1:1.2:4:2) in DMF under air at 140 °C for 48 h (Table 1, entry 20).

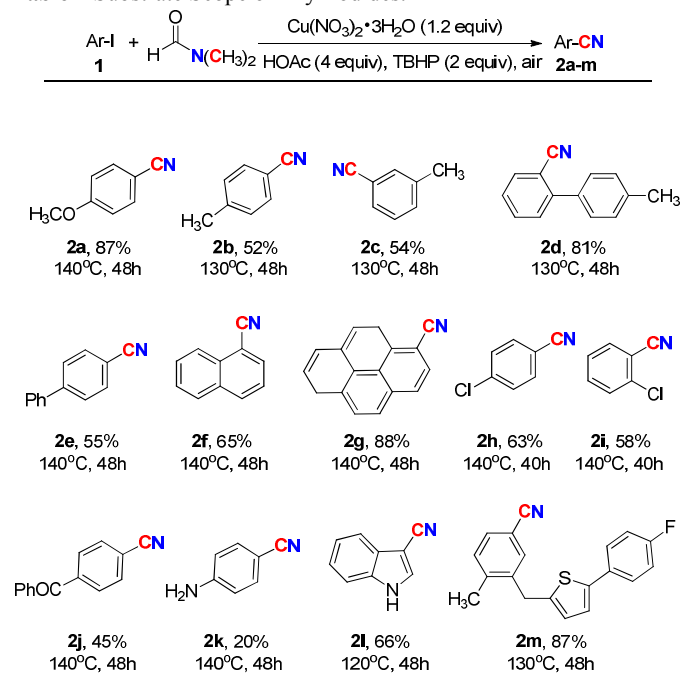
Table 1 Optimization of the Reaction Conditions.^a


entry	[Cu] (equiv)	HOAc (equiv)	TBHP (equiv)	Temp (°C)	Yield (%) ^b
1	CuI (1.2)	8	2	130	45
2	CuBr (1.2)	8	2	130	48
3	CuCl (1.2)	8	2	130	51
4	Cu ₂ O (1.2)	8	2	130	60
5	CuBr ₂ (1.2)	8	2	130	6
6	Cu(OAc) ₂ (1.2)	8	2	130	40
7	CuSO ₄ (1.2)	8	2	130	12
8	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	8	2	130	73 (69 ^c)
9	CuCl ₂ ·2H ₂ O (1.2)	8	2	130	12
10	CuO (1.2)	8	2	130	15
11	Cu(OTf) ₂ (1.2)	8	2	130	55
12	Cu (1.2)	8	2	130	61
13	Cu(NO ₃) ₂ ·3H ₂ O (1.0)	8	2	130	30
14	Cu(NO ₃) ₂ ·3H ₂ O (1.5)	8	2	130	70
15	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	4	2	130	74
16	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	12	2	130	22
17	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	4	1	130	51
18	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	4	3	130	73
19	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	4	2	120	54
20	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	4	2	140	89 (87 ^c)
21	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	4	2	140	19 ^d
22	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	4	2	140	89 ^e
23	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	4	—	140	34
24	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	4	—	140	78 ^e
25	Cu(NO ₃) ₂ ·3H ₂ O (1.2)	—	2	140	55

^a Reaction conditions: **1a** (0.5 mmol, 0.117 g) in DMF (3.0 mL) was stirred 48h under air. ^b Determined by GC analysis. ^c Yield of isolated product after column chromatography on silica gel. ^d N₂. ^e O₂.

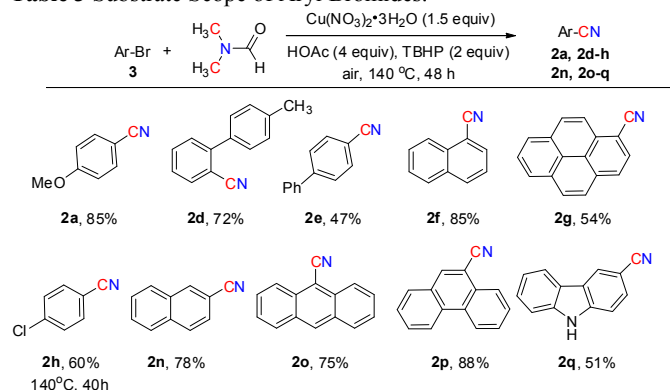
With the optimal reaction conditions in hand, we tested the substrate scope of aryl iodides (Table 2). A variety of substituents tolerated the reaction. With methyl substituted, 4-methylbenzonitrile (**2b**) and 3-methylbenzonitrile (**2c**) were isolated in 52% and 54% yields, respectively. The reaction temperature was slightly decreased in order to avoid the oxidation of methyl group in the presence of Cu(NO₃)₂ and oxidant. The similar treatment was applied to the preparation of **2d** which is a key intermediate in the manufacture of Sartan's drug. This cyanation method is also suitable to biphenyl, naphthalenyl, and pyrenyl iodides. Thus, **2e**, **2f**, and **2g** were obtained in yields of 55%, 65%, and 88%, respectively. When the substrate with both chlorine and iodine substituted, the reaction underwent chemoselectively. 4-Chlorobenzonitrile (**2h**) and 2-chlorobenzonitrile (**2i**) were produced in 63% and 58% yields, respectively, without the contaminant derived from the coupling with C-Cl bond. When the substrates contained active functional groups, such as, carbonyl (**2j**) and amino (**2k**), the reaction gave relatively lower yields. It was noticeable that 3-cyanoindole (**2l**) was

obtained in 66% yield without the protection on N-1 position. Finally, **2m**, having inhibitory activity against sodium-dependent glucose transporter (SGLT),¹⁵ was obtained in 87% yield. This protocol could be conducted in gram scale. Reaction of 2-(4-fluorophenyl)-5-(5-iodo-2-methylbenzyl)thiophene (2.04 g, 5.0 mmol), Cu(NO₃)₂·3H₂O (6.0 mmol), HOAc (20 mmol), and TBHP (10 mmol) in DMF (30 mL) under air at 140 °C for 48 h prepared 1.15 g of **2m** in 75% isolated yield.

Table 2 Substrate Scope of Aryl Iodides.^a

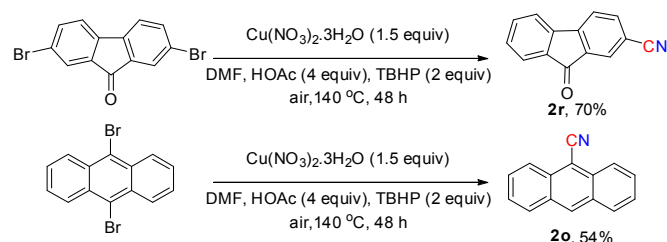
^a Reaction conditions: Aryl iodide (0.5 mmol), Cu(NO₃)₂·3H₂O (0.6 mmol), CH₃COOH (2.0 mmol), TBHP (1.0 mmol) in DMF (3 mL) was stirred under air. Yield of isolated product after column chromatography on silica gel.

Bond energy of C-Br is higher than that of C-I. Moreover, aryl bromides are more available and more economic than aryl iodides are. Therefore, we tested the possible cyanation of aryl bromides using this strategy. Under the reaction conditions established for aryl iodide, 1-bromonaphthalene (**3a**) was reacted and 1-naphthonitrile (**2f**) was isolated in 54% yield. By altering the amount of the catalyst, HOAc, and TBHP, the optimal yield (87% by GC, 85% by column chromatograph) was approached (see SI). It was indicated that increasing the amount of Cu(NO₃)₂·3H₂O to 1.5 equivalent benefitted the reaction conversion. Thus, a series of aryl bromides were tested (Table 3). Aryl bromides, with the fused structures, such as 1-naphthalenyl, 1-pyrenyl, 2-naphthalenyl, 9-anthracenyl, and 9-phenanthrenyl bromides provided corresponding aryl nitriles in yields varied from 54% to 88%. 1-Bromo-4-chlorobenzene gave **2h** in 60% yield with high chemoselectivity. Besides, 2-cyanocarbazole (**2q**) was obtained in 51% yield. The protection of N-H bond of the carbazole was not necessary. This protocol could also be conducted in gram scale. When 2-bromo-4'-methyl-1,1'-biphenyl (8 mmol, 1.98 g) was reacted in 40 mL DMF in the presence of CuI (1.5 equiv), HOAc (4 equiv), and TBHP (2 equiv) under air at 150 °C for 48 h, 1.21 g of **2d** was isolated in 78% yield. **2d** is a key intermediate in the preparation of several angiotensin II receptor antagonists used mainly for the treatment of hypertension.¹⁶

Table 3 Substrate Scope of Aryl Bromides.^{a,b}

^a Reaction conditions: ArBr (0.5 mmol), $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (0.75 mmol), HOAc (2.0 mmol), TBHP (1.0 mmol) in DMF (3.0 mL) was stirred under air. ^b Isolated yields.

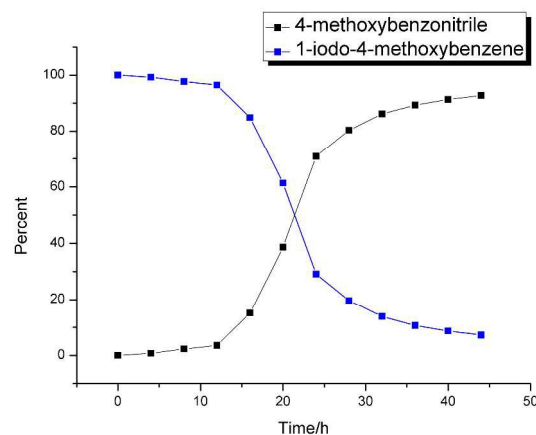
Cyanation of dibromoarenes, such as 2,7-bromofluorenone and 9,10-dibromoanthracene (Scheme 2), resulted in the formation of mono-cyanated products as major products. Thus, 2-cyanofluorenone (**2r**) and 9-cyanoanthracene (**2o**) were obtained in 70% and 54% yields, respectively. C-Br bond could be cleaved and replaced by hydrogen under these reaction conditions.

**Scheme 2** Cyanation of dibromoarenes.

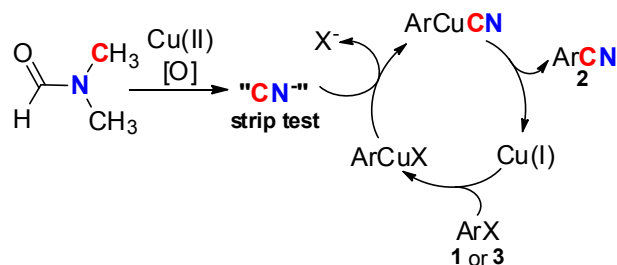
In order to understand the working mechanism of this transformation, we used the DMF with carbon-13 labelled on its carbonyl, the cyanated product did obtain, but without the carbon-13 involved (see SI). In combination of the aforementioned observation that carbon in “CN” group did not come from HOAc or TBHP (Table 1, entries 23-25), we concluded that the carbon in “CN” group came from the methyl of DMF. Therefore, DMF functioned as a single source for this cyanation. Although Jiao in 2011 disclosed DMF as a single source for the cyanation of indoles, the relatively complicated catalytic system was used which included the combination of 10 mol% $\text{Pd}(\text{OAc})_2$, 1.1 equiv CuBr_2 , 10 mol % FeCl_2 , 1.1 equiv TBAOAc, and 1.1 equiv K_2CO_3 .¹⁷

We then tested the existence of cyanide anion during the reaction process. Strip test showed that free cyanide anion formed during the reaction process (see SI).

Comparing the reaction profile (Figure 1) with those provided by Chang,^{14b-c} our reaction profile showed an S-curve (Figure 1). There was an induction period which lasted about 10h. After the induction period, aryl nitrile (**2a**) formed as the aryl iodide (**1a**) disappeared. The cross section appeared at 20 h, while the reaction finished in 45 h.

**Figure 1** Reaction Profile of Cu-Mediated Cyanation of ArI with DMF.

Referring to Chang's work¹⁸, we postulated a possible mechanism (Scheme 3). DMF was slowly oxidized in the presence of Cu(II) and oxidant and resulted in Cu(I) and cyanide anion. The cyanide anion was indicated by stripe test. As soon as the cyanide formed, it reacted with ArCuX . Finally, reductive elimination of ArCuCN provided ArCN in moderate to excellent yields.

**Scheme 3** Possible Mechanism.

Conclusions

In conclusion, we have developed a feasible method to prepare aryl nitriles from aryl iodides or bromides. The reactions were mediated by $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, while DMF functioned as a single source for “CN” group. Moreover, this method could be scalable and practice with operational benign.

Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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