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Microwave-enhanced and ligand-free copper-catalyzed cyanation of aryl halides with $K_4[Fe(CN)_6]$ in water

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ABSTRACT

Copper-catalyzed cyanation of aryl halides was improved to be more economical and environmentally friendly by using water as the solvent and ligand-free $Cu(OAc)_2{\cdot}H_2O$ as the catalyst under microwave heating. The suggested methodology was applicable to a wide range of substrates including aryl iodides and activated aryl bromides.

Aromatic nitriles constitute the key components of numerous commercial compounds such as some natural products, pharmaceuticals, herbicides, and dyes.[1] They have also served as the intermediates for many synthetic targets including benzoic acid derivatives, benzylamines, benzaldehydes, and heterocycles.[2] As a result, the preparation of aromatic nitriles has attracted considerable attention. One of the most convenient methods for the synthesis of aryl nitriles is the Rosenmund–von Braun reaction (a direct reaction between aryl halide and CuCN).[3] However, such a strategy would lead to stoichiometric amounts of heavy metal waste, which has prompted people to develop some transition metal-catalyzed methods for the preparation of aryl nitriles.[4,5] Among various catalysts for the transition metal-catalyzed cyanation of aryl halides, palladium compounds have been widely investigated,[5,6] while less expensive copper catalysts received scanter attention. The first case for copper-catalyzed cyanation of aryl halides was reported by Pongratz and co-workers.[7] Subsequently, only a few effective catalytic systems were developed such as *N,N′*-dimethylethylenediamine (DMEDA)/CuI,[8] DMEDA/$Cu(BF_4)_2{\cdot}6H_2O$,[9] 1,10-phenanthroline/CuI,[10] 1-alkylimidazoles/CuI,[11] and ethylenediamine/$Cu(OAc)_2{\cdot}H_2O$.[12]

All the above-mentioned procedures for copper-catalyzed cyanation required the use of the ligands and organic solvents. Moreover, the reactions were quite sluggish. From environmental and economic perspectives, both the use of ligand-free catalytic systems and the replacement of organic solvent by water are still highly desirable goals.[13] Thus our attention was drawn to the development of an economical and environmentally benign method for the copper-catalyzed cyanation of aryl halides based on the use of water as the solvent, ligand-free $Cu(OAc)_2{\cdot}H_2O$ as the catalyst, and non-toxic $K_4[Fe(CN)_6]$ as the cyanide source. We report our results here.

Our investigation began with the cyanation of iodobenzene with $Cu(OAc)_2{\cdot}H_2O$ as the catalyst. Unfortunately, the desired product was obtained in only 38% yield, and a considerable amount of phenol by-product was detected (Table 1, entry 1). So our attention was turned to the optimization of the reaction conditions. After a series of copper salts were tested as the catalysts, it was found that $Cu(OAc)_2{\cdot}H_2O$ was optimal (Table 2, entries 1–9). Among the screened bases, KF turned out to be the most effective one (Table 2, entries 1 and 10–12). A similar phenomenon was described in a related report,[14] although KF was inefficient as the base in the case of using organic solvents, it was optimal for facilitating the cyanation with water as the solvent.

In order to improve further the reaction, tetrabutylammonium bromide (TBAB) was added into the reaction systems. To our delight, such a modification allowed the cyanation to proceed in high yield. As shown in Table 1, the cyanated product was obtained in 87% yield (Table 1, entry 16), and only trace amounts of other products were detected in the case of using TBAB and KF as the additives. Interestingly, a high yield was also obtained in the case of no addition of the base, revealing that the use of the base was unnecessary (Table 1, entry 17). It was also unnecessary to use an excess of $K_4[Fe(CN)_6]$, which suggested that all six cyanide ions bound to Fe could be transferred to the aryl group.

Subsequently, a variety of representative aryl halides were tested to determine the scope and limitation of the suggested

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0040-4039/$ - see front matter Crown Copyright © 2009 Published by Elsevier Ltd. All rights reserved.
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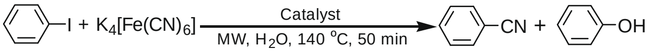
Table 1
Microwave-enhanced cyanation of iodobenzene catalyzed by various copper salts[a]

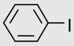
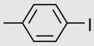
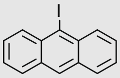
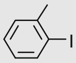
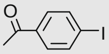
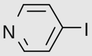
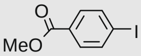
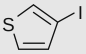
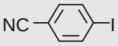
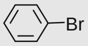
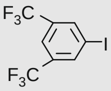
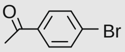
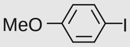
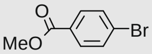
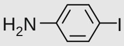
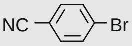
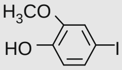
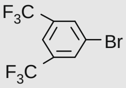
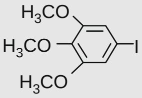
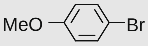
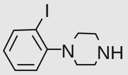
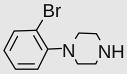
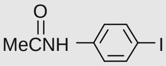
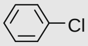


Entry	Catalyst	Base (1 mmol)	TBAB (mmol)	Conv.[b] (%)	Yield of benzonitrile[b] (%)	Yield of phenol[b] (%)
1	$Cu(OAc)_2\cdot H_2O$	Na_2CO_3	—	53	38	6
2	$CuCl_2\cdot 2H_2O$	Na_2CO_3	—	35	17	5
3	$Cu(NO_3)_2\cdot 3H_2O$	Na_2CO_3	—	23	11	4
4	$CuSO_4\cdot 5H_2O$	Na_2CO_3	—	15	7	6
5	$CuCO_3\cdot Cu(OH)_2$	Na_2CO_3	—	49	12	19
6	CuCN	Na_2CO_3	—	38	29	4
7	CuCl	Na_2CO_3	—	27	13	5
8	CuI	Na_2CO_3	—	47	22	3
9	CuBr	Na_2CO_3	—	35	18	7
10	$Cu(OAc)_2\cdot H_2O$	K_2CO_3	—	43	32	7
11	$Cu(OAc)_2\cdot H_2O$	K_3PO_4	—	48	13	15
12	$Cu(OAc)_2\cdot H_2O$	KF	—	52	50	0
13	$Cu(OAc)_2\cdot H_2O$	Na_2CO_3	1	87	66	8
14	$Cu(OAc)_2\cdot H_2O$	K_2CO_3	1	81	67	9
15	$Cu(OAc)_2\cdot H_2O$	K_3PO_4	1	92	70	13
16	$Cu(OAc)_2\cdot H_2O$	KF	1	89	87	0
17	$Cu(OAc)_2\cdot H_2O$	—	1	91	90	0
18	$Cu(OAc)_2\cdot H_2O$/ DMEDA	—	1	95	93	0

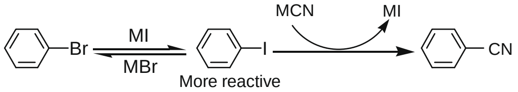
[a] Reaction conditions were shown in Ref. 15.
[b] Determined by GC analysis using *n*-tetradecane as an internal standard (average of two runs).

Table 2
Microwave-enhanced cyanation of various aryl halides catalyzed by $Cu(OAc)_2\cdot H_2O$[a]

$$Ar{-}X + K_4[Fe(CN)_6] \xrightarrow[\text{MW, TBAB, } H_2O\text{, 140 °C, 50 min}]{Cu(OAc)_2\cdot H_2O} Ar{-}CN$$

Entry	Substrate	Yield[b] (%)	Entry	Additive[c]	Substrate	Yield[b] (%)
1		86	13	—		81
2		93	14	—		95
3		85	15	—		89
4		66	16	—		77
5		87	17 18 19	— KI KI + DMEDA		4 7 89
6		89	20	KI		32
7		93	21	KI		61
8		72	22	KI		73
9		59	23 24	— KI		9 92
10		97	25 26	KI KI + DMEDA		11 95
11		87	27 28	KI KI + DMEDA		2 86
12		91	29	KI + DMEDA		0

[a] Reaction conditions were shown in Ref. 15.
[b] Isolated yield (average of two runs), the product was characterized by comparison of ^1H NMR and ^{13}C NMR data with those in the literature.
[c] KI (0.25 mmol) and DMEDA (0.5 mmol) were additionally used.



Scheme 1. Copper-catalyzed domino halide exchange-cyanation of bromobenzene.

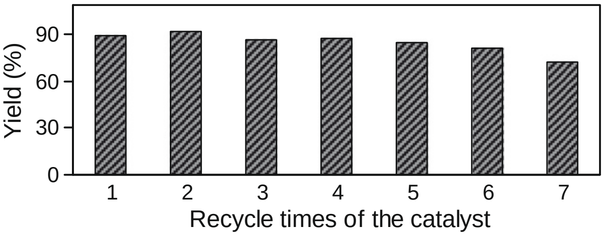


Figure 1. Reuse of the catalyst for $Cu(OAc)_2 \cdot H_2O$-catalyzed cyanation of iodobenzene under the reaction conditions as shown in entry 17, Table 1.

protocol. Although a protocol with DMEDA/$Cu(OAc)_2 \cdot H_2O$ as the catalytic system was also effective (Table 1, entry 18), we preferred the ligand-free methodology for economic reason (Table 1, entry 17). As summarized in Table 2, the cyanation of various aryl iodides gave the corresponding aromatic nitriles in moderate to excellent yields. In addition, the reactions were able to tolerate a wide range of functional groups such as ketone carbonyl, ester, nitryl, nitrile, methoxy, and hydroxy groups. Primary amido group was even well tolerated and did not suffer from N-arylation (Table 2, entry 8), which possibly resulted from the high affinity of the cyanide nucleophile toward the palladium catalyst.[8] The reactions appeared to be insensitive to the steric hindrance around the reaction site. For instance, 4-iodotoluene gave a yield of 81%, while 2-iodotoluene with a bigger steric hindrance around the reaction site also gave a high yield (Table 2, entries 13 and 14).

The cyanation of several aryl bromides gave very low yields (Table 2, entries 17 and 23), which urged us to use KI as an additive to improve the reaction. As shown in Table 2 (entries 20–22 and 24), the KI-accelerated protocol allowed several aryl bromides bearing electron-withdrawing groups to be cyanated in satisfying yields. According to a related report,[7] the KI-accelerated effect resulted possibly from a conversion of the aryl bromide into the more reactive aryl iodide (Scheme 1). Although aryl bromides bearing electron-donating groups did not act as the effective substrates (Table 2, entries 25 and 27), an additional use of DMEDA allowed the unactivated aryl bromides to be cyanated smoothly (Table 2, entries 19, 26, and 28).

Finally, our investigation was focused on the reuse of the ligand-free catalyst. When 0.5 mL *n*-pentane was added to the reaction mixture at the end of the reaction, a two-phase mixture was obtained. After the organic layer containing benzonitrile product was separated, the recovered aqueous phase containing the catalyst could be reused for six times with a very slight change in the catalytic activity (Fig. 1).

In conclusion, a practical and environmentally benign methodology for Cu-catalyzed cyanation of aryl halides was well developed with some main innovations: the use of water as the solvent and ligand-free $Cu(OAc)_2 \cdot H_2O$ as the catalyst under microwave heating. The suggested methodology was applicable to a wide range of substrates including aryl iodides and activated aryl bromides. In addition, the cyanated product could be quantitatively separated from the reaction mixture, and the recovered aqueous phase containing the catalyst could be reused for six times with a very slight change in the catalytic activity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.073.

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14. Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.
15. *Typical procedure for the cyanation of aryl halides:* In a 10 mL microwave tube copper salt (0.1 mmol), $K_4[Fe(CN)_6] \cdot 3H_2O$ (123 mg, 0.3 mmol), TBAB (323 mg, 1 mmol), and aryl halide (1 mmol) were placed. After adding water (2 mL), the vessel was sealed with a septum and was placed into the microwave cavity. Initial microwave irradiation of 600 W was used, the temperature being ramped from room temperature to the desired temperature of 140 °C. Once this was reached, the reaction mixture was held at this temperature until a total time of 50 min had elapsed. Then the mixture was cooled to room temperature and the desired product was extracted with diethyl ether (3×5 mL). Evaporation of the solvent was followed by the GC analysis of corresponding products. Then, the cyanation product was purified by column chromatography. All the products are known compounds and were identified by comparison of their ^1H NMR and ^{13}C NMR data with the literature data.