

Ligand-Free Cu-Catalyzed Cyanation of Aryl Halides with $K_4[Fe(CN)_6]$ in Water

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Abstract: A simple methodology for Cu-catalyzed cyanation of aryl halides with $K_4[Fe(CN)_6]$ was developed with water as the solvent in conjunction with ligand-free $Cu(OAc)_2 \cdot H_2O$ as the catalyst. The suggested methodology is applicable to cyanation of a wide range of aryl iodides and activated aryl bromides, and allows the catalyst to be reused six times with a very slight change in the catalytic activity.

Keywords: Cyanation, aryl halide, ligand-free catalyst, water solvent.

Aromatic nitriles represent an important class of compounds since they not only constitute key components of a range of pharmaceuticals, agrochemicals, dyes and so on [1], but also can easily be transformed into various classes of compounds such as nitrogen-containing heterocycles, aldehydes, amines, amidines, acids, and acid derivatives [2]. One of the most convenient methods for the synthesis of aryl nitriles is the direct reaction between aryl halides and copper cyanide (the Rosenmund-von Braun reaction) [3]. However, such a strategy does not meet today's criteria of sustainable synthesis owing to stoichiometric amounts of metal waste, which has prompted chemists to develop some transition metal-catalyzed methods by using palladium [4], nickel [5] or copper [6] compounds as the catalysts, and KCN [7], Me_3SiCN [8], $Zn(CN)_2$ [4b,c] or $K_4[Fe(CN)_6]$ [9] as the cyanating agents.

Clearly so far, palladium complexes have dominated as catalysts in the transition metal-catalyzed cyanation of aryl halides [4], whereas inexpensive copper catalysts always receive scant attention. As was described in previous literatures [6,10], the first case for copper-catalyzed cyanation of aryl halides was reported by Buchwald and co-workers [11], who used 10 mol % CuI and 100 mol % expensive *N,N'*-dimethylethylenediamine (DMEDA) as the catalyst system. Subsequently, only a few catalyst systems have been developed such as DMEDA/ $Cu(BF_4)_2 \cdot 6H_2O$ [12], 1,10-phenanthroline/ CuI or Cu_2O [13], 1-alkylimidazoles/ CuI or $Cu(BF_4)_2 \cdot 6H_2O$ [6,14], ethylenediamine/ $Cu(OAc)_2 \cdot H_2O$ [15].

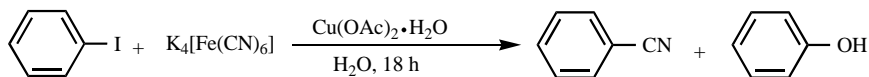
All the above-mentioned methods for Cu-catalyzed cyanation of aryl halides require the use of ligands and hazardous organic solvents. From environmental and economic perspectives, both the use of ligand-free catalyst systems and the replacement of organic solvent by water are still desirable [16]. Thus our attention has been drawn to

developing a more economical and environmentally benign procedure for Cu-catalyzed cyanation of aryl halides using water as the solvent, ligand-free copper salt as the catalyst, and nontoxic $K_4[Fe(CN)_6]$ as the cyanide source under microwave heating [16h]. We found that the reactions could proceed effectively without an assistance of microwave, and report our results here.

In our initial study, cyanation of iodobenzene was chosen as a model reaction to demonstrate the catalytic effectiveness of ligand-free $Cu(OAc)_2 \cdot H_2O$ with water as the solvent under argon (Table 1, entries 1-9). According to a related report [12], the use of Na_2CO_3 was necessary for facilitating copper-catalyzed cyanation. However, in the case of using Na_2CO_3 as the base, the desired cyanation product was herein obtained in only 21% yield, accompanied by a considerable amount of phenolic and benzoic acid products (Table 1, entry 1). The replacement of Na_2CO_3 by some bases such as K_2CO_3 , $K_3PO_4 \cdot 3H_2O$ and KF , did not improve the cyanation to a satisfactory extent (Table 1, entries 2-4). These disappointing results prompted us to use tetrabutylammonium bromide (TBAB) as an additive to improve the reaction. To our delight, such a modification to this procedure allowed the cyanation reaction to proceed in high yields in the case of using KF as the base (Table 1, entry 8). We tried eliminating toxic KF from the reaction system and this modification did not cause a decrease in the yield of benzonitrile, revealing that the use of the base was unnecessary (Table 1, entry 9). In order to further improve this cyanation protocol to allow it more easy-handling, the reaction was carried out without any inert gas protection (Table 1, entries 10-12). The results showed that the presence of oxygen had a negative effect on the reaction (Table 1, entry 10).

Subsequently, our investigation was focused on the quantitative recovery and recycling of the catalyst. At the end of the reaction, 0.5 mL *n*-pentane was added to the reaction mixture, and a two-phase mixture is obtained. After the organic layer containing benzonitrile product was separated, the recovered aqueous phase containing the

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Table 1. Cyanation of Iodobenzene Catalyzed by $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}^{\text{a}}$ 

Entry	Base	TBAB (mmol)	Conversion (%) ^b	Yield of Benzonitrile (%) ^b	Yield of Phenol (%) ^b
1	Na_2CO_3	-	49	21	16
2	K_2CO_3	-	73	9	60
3	$\text{K}_3\text{PO}_4 \cdot 3\text{H}_2\text{O}$	-	69	16	38
4	KF	-	46	45	0
5	Na_2CO_3	1	68	41	11
6	K_2CO_3	1	82	9	68
7	$\text{K}_3\text{PO}_4 \cdot 3\text{H}_2\text{O}$	1	52	16	25
8	KF	1	91	90	0
9	-	1	93	92	0
10 ^c	-	1	81	80	0
11 ^{c,d}	-	1	94	92	0
12 ^{c,e}	-	1	96	95	0

^aReaction conditions: the reactions were performed under argon, other reaction conditions were shown in Reference [17]. ^bDetermined by GC analysis using *n*-tetradecane as an internal standard (average of two runs). ^cThe reactions were performed without inert gas protection. ^dReaction time: 22 h. ^eDMEDA (50 mol %) was additionally added.

catalyst could be reused five times with a very slight change in the catalytic activity (Fig. 1).

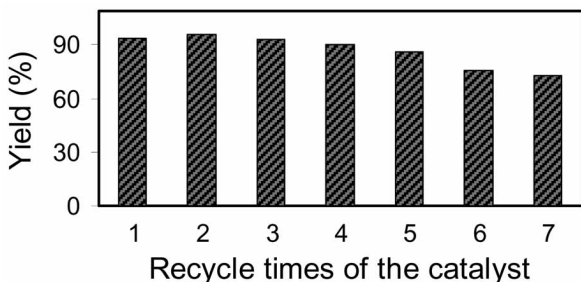
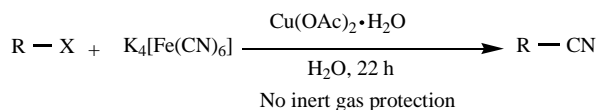


Fig. (1). Recycle of the catalyst for $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ -catalyzed cyanation of iodobenzene with $\text{K}_4[\text{Fe}(\text{CN})_6]$ under the reaction conditions as shown in entry 11, Table 1.

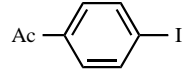
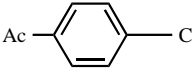
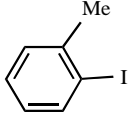
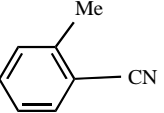
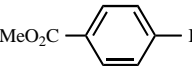
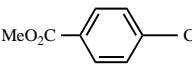
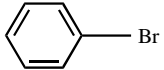
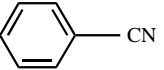
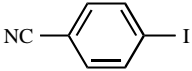
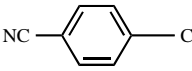

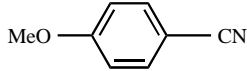
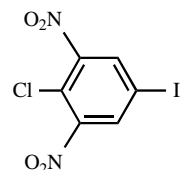
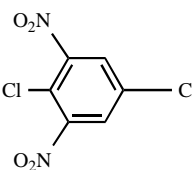
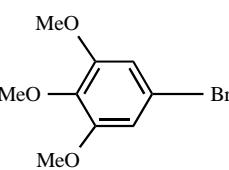
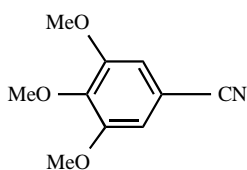
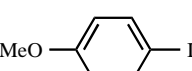
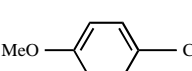
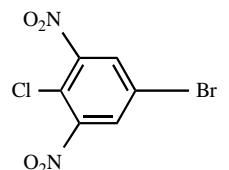
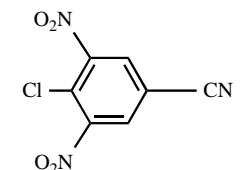
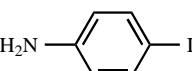
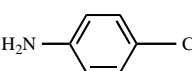
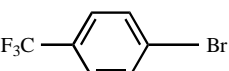
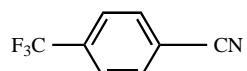
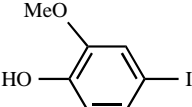
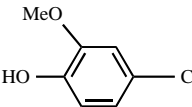
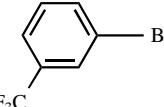
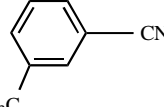
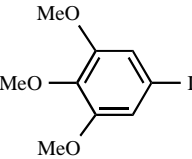
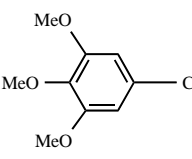
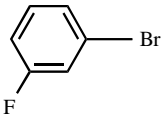
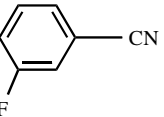
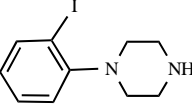
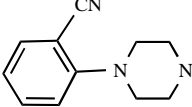
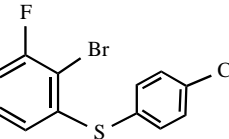
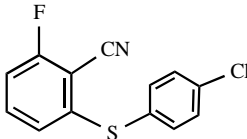
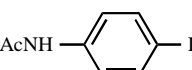
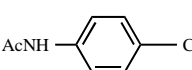
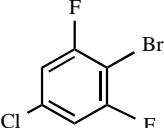
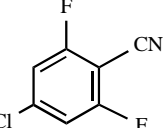
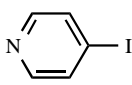
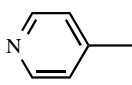
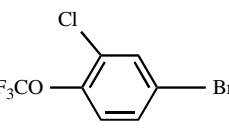
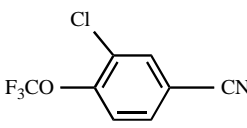
With the above results in mind, we decided to examine the scope and limitation of this cyanation protocol by testing a variety of representative aryl halides. In all cases the reactions were performed using water as the solvent in

conjunction with ligand-free $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the catalyst and $\text{K}_4[\text{Fe}(\text{CN})_6]$ as the cyanide source. Although a protocol using $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in combination with DMEDA as the catalyst system was also effective (Table 1, entry 12), we preferred the methodology employing no additional ligand for economic reasons (Table 1, entry 11). Considering the fact that the procedure without inert gas protection is more easy-handling, we carried out the reaction without any inert gas protection regardless of the slight negative effect of oxygen on the reaction. As shown in Table 2, the cyanation reactions were able to tolerate a wide range of functional groups such as ketone carbonyl, ester, nitril, nitrile, methoxy, hydroxy groups and so on. 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 towards the copper catalyst [11]. Both electron-poor and electron-rich aryl iodides reacted well and gave moderate to high yields (Table 2, entries 1-16). Heteroaryl iodides are also suitable substrates for the cyanation reaction (Table 2, entries 13, 14).

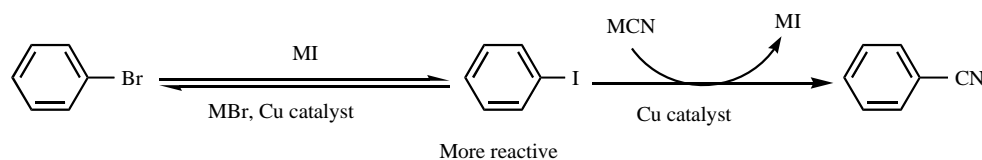
Table 2. $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ -Catalyzed Cyanation of Various Aryl Halides^a

Entry	Substrate	Product ^b	Yield (%) ^c	Entry	Substrate	Product ^b	Yield (%) ^c
1			92 ^d	14			86 ^d
2			85	15			83 ^d

(Table 2). Contd.....

Entry	Substrate	Product ^b	Yield (%) ^c	Entry	Substrate	Product ^b	Yield (%) ^c
3			92	16			87 ^d
4			75	17 ^e			6 ^d
5			67	18 ^e			11
6			81	19 ^e			12
7			95	20 ^e			86
8			69 ^e	21 ^e			79
9			86	22 ^e			83
10			92	23 ^e			71
11			77	24 ^e			53
12			93	25 ^e			91
13			82 ^d	26 ^e			82

^aReaction conditions were shown in Reference [17]. ^bAll compounds are known and characterized by comparison of ¹H-NMR and ¹³C-NMR data with that in the literature. ^cIsolated yield (average of two runs). ^dDetermined by GC analysis using *n*-tetradecane as an internal standard (average of two runs). ^e30 mol % KI was added.



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

The scope of the substrates was limited to aryl iodides. In order to extend the scope of the suggested protocol, 30 mol % KI was used as an additive to improve cyanation of aryl bromides. The KI-acceleration effect resulted possibly from the conversion of the aryl bromide into the more reactive aryl iodide followed by the cyanation of the resulting aryl iodide (Scheme 1). By applying this KI-accelerated protocol, some aryl bromides bearing strong electron-withdrawing groups provided the corresponding aromatic nitriles in moderate to excellent yields (Table 2, entries 20-26), whereas aryl bromides without electron-withdrawing substituents did not act as effective substrates (Table 2, entries 17-19). In the case of aryl bromides bearing chloro groups, bromo group was selectively cyanated (Table 2, entries 20, 24-26).

In conclusion, Cu-catalyzed cyanation of aryl halides with nontoxic $K_4[Fe(CN)_6]$ was improved to be more economical and environmentally friendly by the use of water solvent and ligand-free catalyst. The reactions can be performed without any inert gas protection, which makes them more easy-handling. In addition, the suggested methodology is applicable to cyanation of a wide range of aryl iodides and activated aryl bromides, and allows the catalyst to be reused six times with a very slight change in the catalytic activity.

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- [17] **General experimental procedure for cyanation reaction of aryl halides:** 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 iodide (1 mmol) were added to a flask containing H_2O (2 mL) without any inert gas protection. After being sealed, the flask was placed in an 180 °C oil bath and stirred for 22 h. Then the mixture was cooled to room temperature and the desired product was extracted with 3 × 5 mL of diethyl ether. 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.