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Copper-Mediated Cyanation of Aryl Halide with the Combined Cyanide Source

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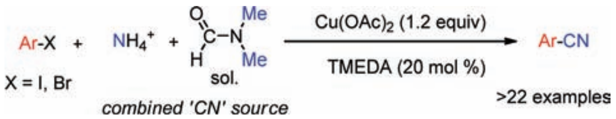
ABSTRACT



A simple copper-mediated cyanation of aryl halide with the combination of ammonium bicarbonate and *N,N*-dimethylformamide as a cyanide source is achieved, providing nitriles in moderate to good yields. This new approach represents an exceedingly practical and safe method for the synthesis of aryl nitriles.

The cyanation reaction plays an important role in organic synthesis because nitriles are versatile building blocks in the synthesis of natural products, pharmaceuticals, and agricultural chemicals.[1] Moreover, nitriles may be facilely transformed to a series of functional groups, such as amines, aldehydes, amidines, tetrazoles, and amides.[2] The Sandmeyer and Rosenmund–von Braun reactions are traditional methods to access nitriles.[3] However, the reactions suffer from the toxicity of a cyanide source at high temperature with prolonged times and multiple procedures. The industrial method involves ammoxidation of toluene derivatives with oxygen, at 300–550 °C under high pressure.[4]

The transition-metal-catalyzed direct cyanation of arene C–H bonds represents a graceful method to access aryl nitriles.[5] In 2006, Yu described the Cu-catalyzed cyanation of 2-arylpyridine C–H bonds using TMSCN and CH_3NO_2.[6] Encouraged by Yu's works, we reported a Pd-catalyzed direct cyanation of 2-arylpyridine C–H bonds with CuCN and a cascade bromination/cyanation reaction of the C–H bond using $K_3Fe(CN)_6$.[7] Subsequently, Wang and Reddy reported the Pd-catalyzed direct cyanation of an indole C–H bond, respectively.[8]

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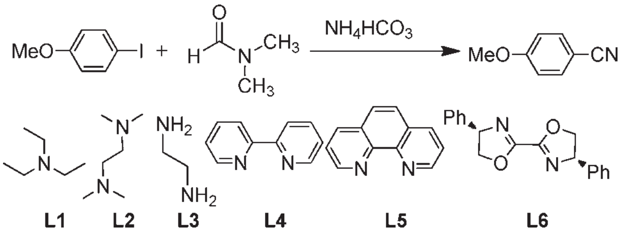
Nevertheless, the requirement of the chelation group would limit the substrate scope.

Recently, the transition-metal-catalyzed cyanation of aryl halides,[9] borons,[10] or mesylates[11] provides a promising alternative to the cyanating reactions. Yet, except for $K_4[Fe(CN)_6]$ and $K_3[Fe(CN)_6]$,[12] the toxicity of the cyanide source of MCN (M = Cu, K, Zn, TMS), acetone cyanohydrin,[13] would greatly decrease the utility of the aforementioned transformations. Therefore, the development of a new and safe cyanide source in the cyanation reaction with a broad substrate scope remains an extremely attractive but challenging task for organic chemists.

Recently, Chang reported the Pd-catalyzed chelation-assisted cyanation of a 2-arylpyridine C–H bond using the combination of ammonia and DMF as a safe cyanide source.[14] Subsequently, we demonstrated the Pd-catalyzed cyanation of an indole C–H bond with the combination of NH_4HCO_3 and DMSO.[15] Very recently, Jiao described a direct cyanation of indoles and benzofurans in which DMF was disclosed for the first time as a source of –CN.[16] However, the requirement of a chelation group and employment of an expensive palladium catalyst are required. Hideo described the conversion of aromatic bromides and aromatics into aromatic nitriles via aryllithiums or Grignard reagents and their DMF adduct in the presence of equivalents of I_2 and ammonia.[17] Herein, we report a novel and facile strategy to obtain aryl nitriles starting from commercially available aryl halides and the combination of DMF and NH_4HCO_3 as a safe cyanide source based on the well-developed copper-mediated cyanation.

We initiated our investigation by examining the reaction of *p*-iodoanisole with DMF and NH_4HCO_3 (Table 1). Fortunately, the cyanation product was obtained in 12% yield with the combination of **1a**, NH_4HCO_3, and $CuBr_2$ in DMF (entry 1, Table 1). The reaction efficiency was improved by using **L2** as a ligand (entry 2, Table 1). Gratifyingly, **2a** was formed in 85% yield when 1.2 equiv of $Cu(OAc)_2$ was employed in the presence of **L2** (entry 4, Table 1). Other coppers, such as $CuCl_2$, $Cu(TFA)_2$, and $CuSO_4$, resulted in low efficiencies (entries 3, 5, 6, Table 1). In the absence of copper, the employment of an oxidant, such as DDQ, $K_2S_2O_8$, and $PhI(OAc)_2$, inhibited the reaction (entry 7, Table 1). The influence of ligands was also investigated, and the employment of 20 mol % of **L2** was found to be the best, providing the product in excellent yields for all the above transformations (entries 8–13, Table 1). Meanwhile, reaction in dioxane, DMSO, and CH_3NO_2 or with NH_4I and $(NH_4)_2S_2O_3$ resulted in low efficiencies or no reaction (entries 14–16, Table 1).[18] Importantly, this transformation is very practical, as the expensive palladium catalyst or a large excess of ammonia is not required.

Table 1. Selected Results of Screening the Optimal Conditions[a]



entry	Cu source	ligand	yield (%)
1	$CuBr_2$	--	12
2	$CuBr_2$	**L2**	46
3	$CuCl_2$	**L2**	29
4	$Cu(OAc)_2$	**L2**	85 (80)[b]
5	$Cu(TFA)_2$	**L2**	63
6	$CuSO_4$	**L2**	21
7	--	**L2**	0[c]0[d]0[e]
8	$Cu(OAc)_2$	**L1**	51
9	$Cu(OAc)_2$	**L3**	29
10	$Cu(OAc)_2$	**L4**	61
11	$Cu(OAc)_2$	**L5**	62
12	$Cu(OAc)_2$	**L6**	58
13	$Cu(OAc)_2$	--	46
14	$Cu(OAc)_2$	**L2**	46[f](0)[g]
15	$Cu(OAc)_2$	**L2**	0[h]
16	$Cu(OAc)_2$	**L2**	<5[i](26)[j]

[a] Reaction conditions: **1a** (0.2 mmol), NH_4HCO_3 (1.5 equiv), copper (1.2 equiv), ligand (20 mol %), under air, dry DMF (1 mL), 150 °C in a sealed tube for 22 h. [b] O_2. [c] DDQ. [d] $K_2S_2O_8$. [e] $PhI(OAc)_2$. [f] NH_4I. [g] $(NH_4)_2S_2O_3$. [h] Dioxane. [i] DMSO. [j] CH_3NO_2.

With the optimized reaction conditions in hand, we applied this new protocol to a range of aryl iodides, as shown in Figure 1.

A series of functional groups, such as methoxy, benzyloxy, acetyl, free phenolic hydroxyl, and free acetamido were compatible with the reaction conditions, and the cyanation products were isolated in good yields. The electronic properties of the substituents on the phenyl ring of aryl iodides had some effect on the reaction. Generally, the aryl iodides possessing electron-donating groups gave slightly higher yields than those possessing electron-withdrawing groups (**2a**–**2h** vs **2n**–**2p**, Figure 1). Importantly, various substitutents at the *para*, *meta*, and *ortho* position

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(18) For the effect of other solvents and ammonium salt, see Supporting Information for details.

(19) Commercially available DMF (carbonyl-^{13}C, 99%) and $^{15}NH_4Cl$ (^{15}N 99%) were employed.

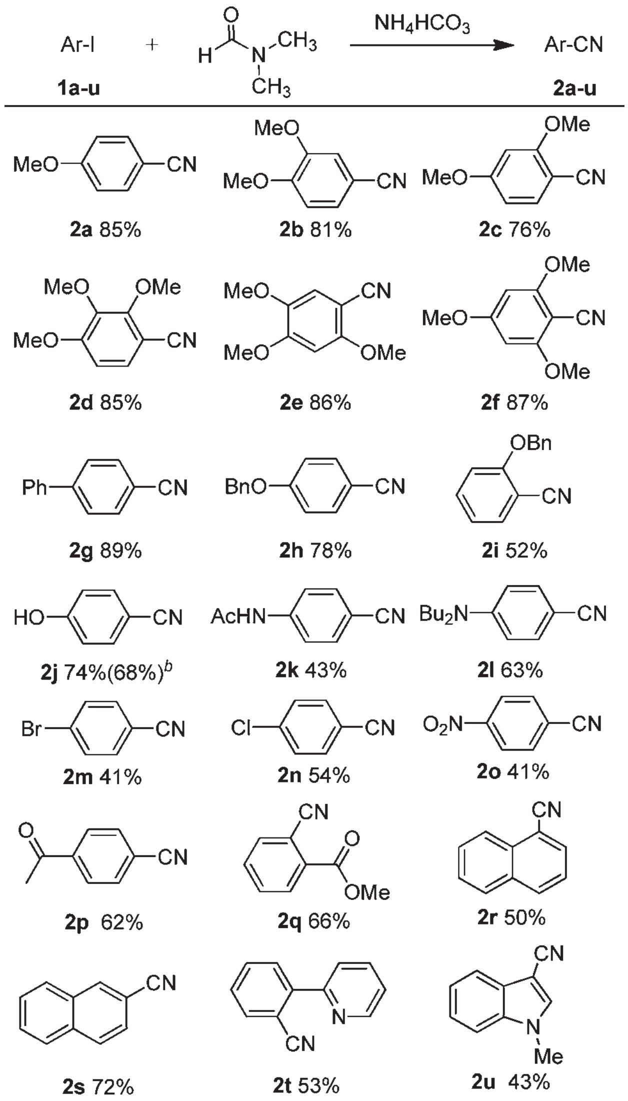


Figure 1. Copper-mediated cyanation of aryl iodides. [a]Reaction conditions: **1a**−**u** (0.2 mmol), NH_4HCO_3 (1.5 equiv), $Cu(OAc)_2$ (1.2 equiv), **L2** (20 mol %), under air, dry DMF (1 mL), 150 °C in a sealed tube for 22 h. [b]*p*-Iodophenyl acetate.

were all cyanated smoothly under the standard procedures. The cyanation of mono-, di-, and trimethoxy phenyl iodides furnished the corresponding products in excellent yields, and the order of activity is tri > di in terms of yields (**2b**−**2f**, Figure 1). Meanwhile, the hindrance on the phenyl ring of aryl iodides had a slight effect on the efficiency (**2h** vs **2i** and **2s** vs **2r**, Figure 1). Fortunately, free phenolic hydroxyl group survived well in the standard procedure, leading to **2j** in excellent yield. Intriguingly, when *p*-iodophenyl acetate was subjected to the procedure, a 68% yield of **2j** was isolated. Notably, the acetamido (**2k**) and dialkylamino (**2l**) groups tolerated this transformation, and importantly, *N*-containing substrates, such as 2-(2-iodophenyl)pyridine and 3-iodo-1-methyl-1*H*-indole, were also good reaction partners, providing **2t** and **2u** in 53% and 43% yield, respectively. Disappointingly, the alkyl, alkenyl, and alkynyl iodides did not work under the standard reaction conditions.

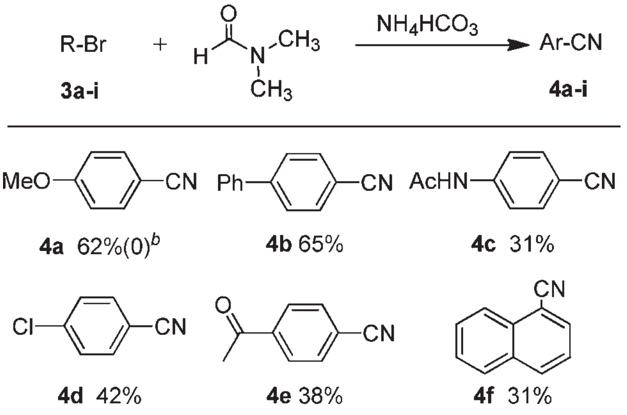
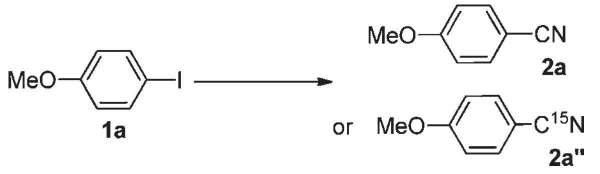


Figure 2. Copper-mediated cyanation of aryl bromides. [a]Reaction conditions: **3a**−**f** (0.2 mmol), NH_4HCO_3 (1.5 equiv), Cu(OAc)$_2$ (1.2 equiv), **L2** (40 mol %), under air, dry DMF (1 mL), 150 °C, 22 h. [b]*p*-Chloroanisole.

To broaden the scope of substrates used, we carried out reactions of aryl bromides with a combined cyanide source under the standard conditions as shown in Figure 2. The corresponding aryl nitriles were also afforded in moderate yields.

In the absence of any ammonium, only a trace of the cyanating product (< 1%) or no product was detected by GC-MS in DMF and NMP, respectively (entries 1, 4, and 5, Table 2). Under the standard procedures, replacing DMF with DMF ^{13}C-labeled on the carbonly[19] formed the normal product **2a** mostly. Moreover, **2a** was obtained in 12% yield when NMP was employed. These results

Table 2. Study on the "CN" Formation[a]



entry	ammonium	ligand	solvent	yield (%)
1	–	**L2**	DMF	<1
2	$NaHCO_3$	**L2**	DMF	<5[b]
3	NH_4HCO_3	**L2**	NMP	12
4	–	**L2**	NMP	0
5	–	**L4**	DMF	<1
6	NH_4Cl	**L2**	DMF	62
7	NH_4HCO_3	**L2**	$H^{13}CON(CH_3)_2$	79[c]
8	$^{15}NH_4Cl$	**L2**	DMF	56

[a] Reaction conditions: **1a** (0.2 mmol), Cu(OAc)$_2$ (1.2 equiv), ammonium (1.5 equiv), ligand (20 mol %), under air, dry solvent (1 mL), 150 °C in a sealed tube for 22 h. [b] $NaHCO_3$ (1.5 equiv). [c] DMF (0.25 mL).

indicated the C-atom in the "CN" may be derived from the methyl of DMF or NMP (entries 3, 7, Table 2). Chang also confirmed the combination of NMP and ammonia provided the cyanating product. Meanwhile, **1a** was allowed to react with $^{15}NH_4Cl$ to provide **2a″** under the standard conditions, and almost complete isotopic incorporation into the cyano moiety was observed, strongly indicating that ammonia serves as the nitrogen source of "CN" (entry 8, Table 2).

In the kinetic study, the reaction showed zero-order for ArI.[20] However, Paine confirmed it was first-order for ArI in the copper-mediated cyanation of ArI with CuCN in DMF.[21]

The cyanide indicator paper supports the formation of cyanide.[22] Similar to Chang's procedure, the CN^- is formed, which takes part in the cyanation as the copper-catalyzed cyanation of ArI.[23] However, the mechanism of the formation of the CN^- from the combination of DMF and NH_4HCO_3 in detail currently remains unclear.

In conclusion, we have demonstrated a new copper-mediated protocol for the generation of a cyano unit from two readily available precursors. The convenience of the methodology is promising for application in synthesizing a broad range of nitriles in bioactive natural products or other specific organic materials. Further mechanistic investigations are underway.

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Supporting Information Available. Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) See Supporting Information for details.

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(22) The CN^- was detected by indicator paper when the combination of NH_4HCO_3, DMF, and $Cu(OAc)_2$ was heated at 150 °C for 2 h. However, heating of NH_4HCO_3, DMF, and TMEDA or *p*-iodoanisole at 150 °C for 2 h did not produce any detectable CN^-. These results indicated the Cu played an important role in the *in situ* formation of CN^-. See Supporting Information for details.

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