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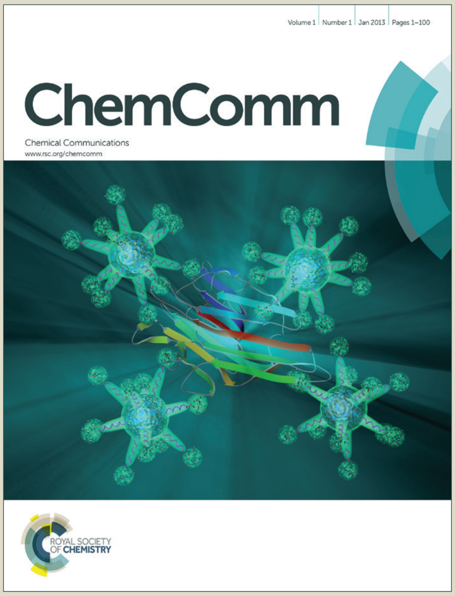

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ARTICLE TYPE

Copper-Mediated C3-Cyanation of Indole by the Combination of Amine and Ammonium

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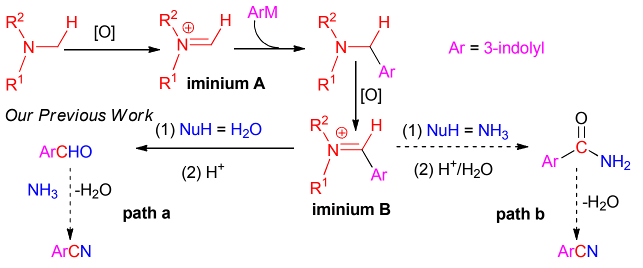
A copper-promoted C3-cyanation of both the free N-H and *N*-protected indoles by *N,N,N′,N′*-tetramethyl-ethane-1,2-diamine (TMEDA) and ammonium is achieved. Iminium ion acts as the intermediate for this transformation, which is sequentially electrophilically attacked by indole and H_2O followed by hydrolyzation to form the aldehyde. Then the reaction between aldehyde and ammonium afforded nitriles. The reaction employs O_2 as a clean oxidant with good efficiency and functional group tolerance. Thus, it represents a facile and safe procedure leading to 3-cyano indoles.

Indoles are ubiquitous structural motifs which are frequently found in innumerable natural products, biologically active molecules and medicinally relevant structures.[1] Among these frameworks, the 3-substituted indolyl moiety has immense importance on account of roles they play in various biologically active molecules. In particular, 3-cyanoindoles serve as versatile precursors of a number of antiviral, antibacterial and cytotoxic natural products.[2] Thereby, various strategies have been developed for the C3-cyanation of indoles.[3,4]

Apart from the traditional cyanide source such as NaCN,[3f] CuCN,[3g,3l] $K_4[Fe(CN)_6]$,[3b,3h] *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS),[3c] a variety of the state-of-the-art cyanide sources were developed for the cyanation of indoles. For example, in 2011, Jiao described the palladium-catalyzed cyanation of indoles by *N*, *N*-dimethyl formamide (DMF).[3d] And our group reported the palladium-catalyzed cyanation of indole C-H bonds with the combination of NH_4HCO_3 and DMSO as a safe cyanide source.[3e] Subsequently, Chang developed the copper-mediated cyanation of indoles with ammonium iodide and DMF.[3a] Wang and Kwong independently demonstrated the copper-mediated cyanation of indole using BnCN as the cyanide source.[3i,m]

Recently, we described a copper-catalyzed 3-formylation of indole C-H bonds using tertiary amines and molecular oxygen, involving iminium ion as the intermediate (Scheme 1).[5a] In this procedure, iminium intermediate **b** was trapped by H_2O as the nucleophile leading to the carbonyl compounds. Combining with our interest in the cyanation,[3e,6] we envisioned that the formed formylation products would be transformed to the nitrile in the presence of proper ammonium (Scheme 1, path a).[7] Alternatively, the new iminium intermediate **b** could be attacked by NH_3 rather than H_2O followed by hydrolyzation leading to amide as the precursor of nitrile, which could be converted to the nitrile by loss of one equivalent of H_2O (Scheme 1, path b). Herein, we report a safe and practical procedure for the copper-mediated cyanation of indole by the combination of amine and ammonium as a safe cyanide source.

Scheme 1. Design plan



Based on our reports on the cyanation reaction with the combined cyano source,[3e,6e] we initiated the present study by using *N*-methyl indole (**1a**) with TMEDA and NH_4HCO_3 as a suitable model reaction. To our delight, the first glimpse of success was obtained by using 1.3 equivalents of $CuCl_2$ under O_2 in xylene at 110 °C, delivering the target product **2a** in 37 % yield within 12 h (Table 1, entry 1). Encouraged by this promising result, other solvent such as chlorobenzene, polyethylene glycol (PEG) and dimethyl sulfoxide (DMSO) were tested, giving the desired product in moderate yields (49% to 61%, entries 2-4). The copper species was critical for the cyanation efficiency. When CuI was employed instead of $CuCl_2$, the yield dropped sharply to 24%, while no cyanated product **2a** was obtained employing $Cu(OAc)_2$ (entries 5 and 6). As for the source of ammonium, aqueous ammonia did not produce any target product while ammonium sulfate delivered a moderate yield (entries 7 and 8). Gratifyingly, ammonium carbonate afforded the desired product **2a** in 83% yield (entry 9). Under air, the yield dramatically decreased and the procedure did not work under N_2 (entry 9). However, attempt to develop a catalytic system failed, which is at least partly due to the strong coordination of ammonia with the metal to form a catalytically unreactive complex.[8] The blank experiment demonstrated that the reaction did not run in the absence of copper or TMEDA (entries 10 and 11).

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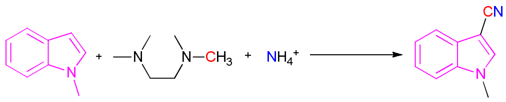
In our reported palladium-catalyzed procedure on the cyanation of indole, the C atom in the cyano group derived from the methyl of DMSO at elevated temperature (150 °C) and it failed to work under 110 °C.[3e] However, this current procedure enables the cyanation to be taken place in a relative mild conditions (110 °C). Moreover, except DMSO, this approach also worked in PhCl, PEG and xylene. These results revealed, in compare with our previously reported cyanation of indole by DMSO and ammonium,[3e] a different reaction pathway may be involved.

Table 1. Selected results of screening the optimal conditions.



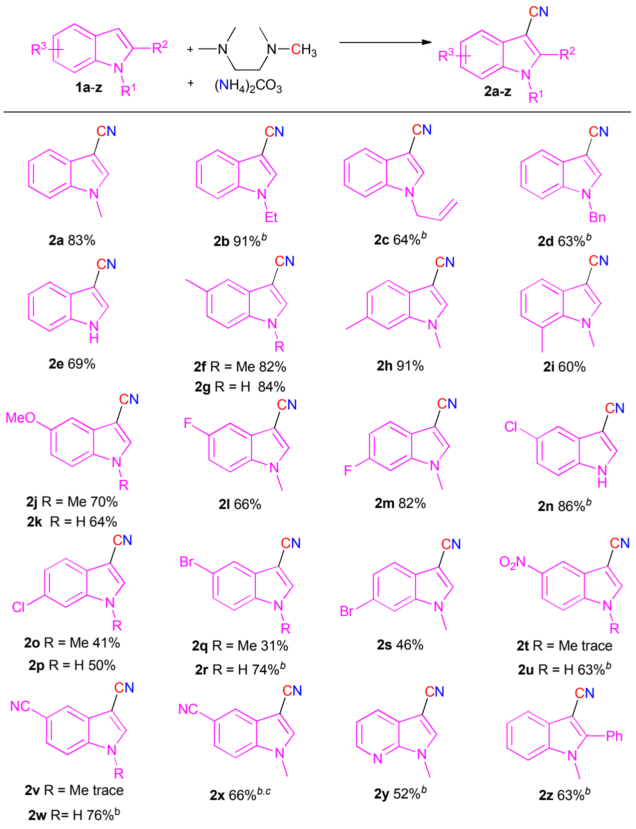
Entry	Copper	NH$_4^+$	Solvent	Yield(%)[a]
1	Cu(Cl$_2$	NH$_4$HCO$_3$	xylene	37
2	Cu(Cl$_2$	NH$_4$HCO$_3$	PhCl	49
3	CuCl$_2$	NH$_4$HCO$_3$	PEG	47
4	CuCl$_2$	NH$_4$HCO$_3$	DMSO	61
5	CuI	NH$_4$HCO$_3$	DMSO	24
6	Cu(OAc)$_2$	NH$_4$HCO$_3$	DMSO	0
7	CuCl$_2$	NH$_3$·H$_2$O	DMSO	0
8	CuCl$_2$	(NH$_4$)$_2$SO$_4$	DMSO	51
9	CuCl$_2$	(NH$_4$)$_2$CO$_3$	DMSO	83(< 5)[b](< 1)[c]
10	-	(NH$_4$)$_2$CO$_3$	DMSO	< 1
11	CuCl$_2$	(NH$_4$)$_2$CO$_3$	DMSO	< 1

[a] Reaction conditions: *N*-methyl-indole **1a** (0.2 mmol), TMEDA (0.5 mmol, 2.5 equiv), ammonium salt (0.8 mmol, 4.0 equiv), copper source (0.26 mmol, 1.3 equiv.) and O$_2$ (1 atm.), in solvent (0.5 mL), 110 °C for 12 h. [b] Under air. [c] Under N$_2$ [d] No TMEDA.

Having established efficient conditions for the cyanation of indole, we turned our attention to investigate the scope of indoles and the results were summarized in Figure 1. Firstly, to our delight, substrates with different *N*-protected groups could be smoothly transformed into the desired products in good to excellent yields (**2a-2d**). Electron-donating groups such as methoxy (**2j**), methyl (**2f-2i**) and electron-withdrawing groups such as chloro (**2n-2p**), and bromo (**2q-2s**) on the aromatic moiety could also be tolerated. These results were particularly striking because halogen functional groups remained intact under the standard procedure, offering handles for other valuable manipulations (**2n-2s**).

Importantly, in sharply contrast with their *N*-methyl analogues, the free (N-H) indoles, which did not work in Jiao's,[3d] Chang's,[3a] kwong's[3m] and our previously reported procedures,[3e] generally perform more efficiently under this system (**2q** *vs* **2r**), which was unambiguously demonstrated by the substrates bearing a strong electron-withdrawing groups such as nitro and cyano on the 5-position (**2t** *vs* **2u**, **2v** *vs* **2w**). Particularly, the heteroaryl indoles, such as *N*-methyl-1*H*-pyrrolo[2,3-b]pyridine **1y**, could be successfully converted to the desired product **2y** in 52% yield. Treatment of 1-*H*-indole-5-carbaldehyde with 5.0 equivalents of (NH$_4$)$_2$CO$_3$ under the standard conditions generating **2x** in 66% yield, where the formyl was in situ transformed into cyano group. Notably, under this procedure, when C2 position of indole was blocked by a phenyl, it did not interfere with this transformation, as evidenced by a good isolated yield (63%) of the **2z**. In terms of yields, the 6- methyl-substituted substrate is superior to the 5- and 7-substituted analogues (**2f**, **2h** and 2**i**).

Figure 1. Copper-mediated C3 cyanation of indole C-H bond[a]



[a] Reaction conditions: indole **1** (0.2 mmol), TMEDA (0.5 mmol, 2.5 equiv), (NH$_4$)$_2$CO$_3$ (0.8 mmol, 4.0 equiv), CuCl$_2$ (0.26 mmol, 1.3 equiv), O$_2$ (1 atm.), in DMSO (0.5 mL) under 110 °C for 12 h. [b] 24 h. [c] 1*H*-indole-5-carbaldehyde and 5.0 equiv of (NH$_4$)$_2$CO$_3$ was used.

In order to gain some detail of this transformation, a series of control experiments were conducted. The formyl group was found to be converted into cyano group (Figure 1, **1x**), and 3-cyano indole was isolated in 75% yield when 3-formyl indole was subjected to the standard reaction conditions. However, the amide could not transform into nitrile under the standard procedure (Scheme 2, eq 1). This result ruled out the possibility of amide as the intermediate in this procedure. Replacing DMSO with ^{13}C-DMSO, no ^{13}C enriched motifs was found in the cyanation product (Scheme 2, eq 2). However, ^{15}N was found in the cyano group by replacing (NH$_4$)$_2$CO$_3$ with ^{15}NH$_4$Cl (Scheme 2, eq 3). Addition of TEMPO (50 mol %) as a radical scavenger or 1,4-diazabicyclo[2,2,2]octane (DABCO) (50 or 100 mol %) as the singlet oxygen inhibitor did not inhibit this procedure. Furthermore, an iminium ion salt was detected from the model reaction of **1a** by HRMS (for detail, see Supporting Information). We also tested the cuprate of the indole C-H bonds (Scheme S2). All the phenomena were in consistent with our reported 3-formylation of indole.[5a]

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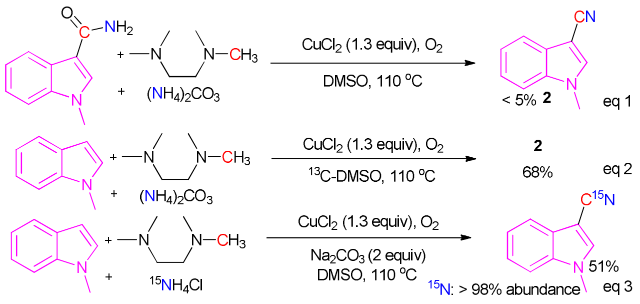
Based on the above experiments and earlier reported literature,[5a,9] we believe the iminium cation was the intermediate in this procedure, and the path a in Scheme 2 is favored.

Scheme 2. Preliminary mechanism study



In conclusion, we developed a copper-mediated C3-cyanation of indole with TMEDA and $(NH_4)_2CO_3$ as the combined cyanide source with good functional group tolerance. This procedure employed O_2 as a clean terminal oxidant. Thus, it provided a practical approach to access 3-cyano indoles.

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Notes and references

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