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Letter

Copper-Mediated Direct Cyanation of Heteroarene and Arene C–H Bonds by the Combination of Ammonium and DMF

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Supporting Information

ABSTRACT: A copper-mediated cyanation of heteroarene and arene C–H bonds has been developed, where ammonium iodide and DMF served as a safe cyanating combination. This procedure shows a broad substrate scope, allowing the facile access of 2-cyano indole, 1-cyano carbazole, 2-cyano pyrrole, and 2-cyano 1-pyridinyl benzene in high yields with good functional group tolerance.

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A romatic nitriles are common structural motifs in natural products, agrochemicals, herbicides, pharmaceuticals, and dyes.¹ Moreover, the nitrile moiety serves as an effective precursor and a valuable intermediate to access numerous functional groups such as acids, amines, amidines, amides, aldehydes, carboxylic, ketones, and their derivatives.² Traditionally, the Sandmeyer reaction of diazonium salt³ and the cyanation of aryl halides⁴ represent powerful strategies to access aromatic nitriles (Scheme 1a). Compared with the aforementioned procedures, the direct C–H cyanation features high reaction efficiency and atom economy. As such, much



effort had been paid in the transition-metal-catalyzed direct C–H cyanation, including the nondirecting (Scheme 1b)⁵ and directing group assisted versions (Scheme 1c).⁶ Except the toxic cyanation sources, various cyanation sources, such as MeCN, N-cyano-N-phenyl-p-toluenesulfonamide (NCTS), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), azobis-(isobutyronitrile) (AIBN), and others were developed in transition-metal-catalyzed direct cyanation of aromatic compounds. Notably, the application of the combination of DMF (or DMSO) and ammonium, developed by Chang,⁷ Jiao,⁸ and our group,⁹ served as simple and safe cyanation sources in direct C-H cyanation (Scheme 1d). However, this strategy was ultimately limited in access of 3-cyano indoles and 2-cyano 1-pyridinyl benzenes. Nevertheless, the development of such a safe combination in direct C-H cyanation was far below as expected.

Herein, we wish to report the application of NH₄I and DMF as a cyanation source to access 2-cyano indoles, 1-cyano carbazole, 2-cyano pyrroles, and 2-cyano 1-pyridinyl benzenes.

Initially, we tested the reaction of 1-(pyrimidin-2-yl)-1*H*indole (**1a**) and NH₄I catalyzed by Pd(OAc)₂ (5 mol %) in the presence of Cu(OAc)₂ as the additive in DMF at 130 °C for 12 h under O₂ atmosphere. Fortunately, 1-(pyrimidin-2-yl)-1*H*indole-2-carbonitrile **2a** was isolated in 76% yield (Table 1, entry 1). No reaction took place in the presence of either Pd(OAc)₂/NaOAc or [Cp*RhCl₂]₂/NaOAc (entries 2 and 3). In the absence of Pd(OAc)₂, product **2a** was also isolated in 84% yield (entry 4), indicating copper salt played an important role, and Pd(OAc)₂ was not required during this transformation. After a series of copper sources were surveyed, such as CuBr₂ (50%), CuBr (52%), CuSO₄·SH₂O (0%), and Cu(OTf)₂ (43%), Cu(OAc)₂ was the best (entries 5–8). To

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Table 1. Selected Results for Screening the Optimized Reaction Conditions a



entry	cat.	additive $(x equiv)$	temp (°C)	yield (%) ^b
1	$Pd(OAc)_2$	$Cu(OAc)_2$ (2)	130	76
2	$Pd(OAc)_2$	NaOAc (2)	130	0
3	[Cp*RhCl ₂] ₂	NaOAc (2)	130	0
4		$Cu(OAc)_2(2)$	130	84
5		$CuBr_2(2)$	130	50
6		CuBr (2)	130	52
7		$CuSO_4 \cdot 5H_2O(2)$	130	0
8		$Cu(OTf)_2(2)$	130	43
9		$Cu(OAc)_2(1)$	130	91, 76 ^c , 0 ^d
10		$Cu(OAc)_2(1)$	120	77
11		$Cu(OAc)_2(1)$	110	56
12		$Cu(OAc)_2(1)$	80	0
13		$Cu(OAc)_2(1)$	130	90 ^e , 93 ^f
14		$Cu(OAc)_2(1)$	130	0 ^g
15		$Cu(OAc)_2(1)$	130	0 ^{<i>h</i>}
16		$Cu(OAc)_2(1)$	130	90 ^{<i>i</i>}

^aReaction conditions: 1a (0.2 mmol), NH₄I (0.4 mmol), cat. (5 mol %), additive (x equiv), DMF (2 mL), O₂ (balloon), 12 h. ^bIsolated yield. ^cCu(OAc)₂ (0.5 equiv). ^dCu(OAc)₂ (0.2 equiv)/NaOAc (2.0 equiv). ^eNH₄I (0.3 mmol). ^fNH₄I (0.24 mmol). ^gNo NH₄I. ^hN₂. ⁱ1a (1.0 mmol), NH₄I (1.2 mmol), Cu(OAc)₂ (1.0 mmol), DMF (10 mL), O₂ (balloon), 130 °C, 12 h, in a 100 mL sealed Schlenk tube.

our delight, the yield dramatically increased to 91% with 1.0 equiv of $Cu(OAc)_2$ and decreased to 76% with 0.5 equiv of $Cu(OAc)_2$, No reaction took place under a catalytic amount of $Cu(OAc)_2$ (0.2 equiv) and NaOAc (2.0 equiv) as additive (entry 9). The yield reduced to 77% (120 °C, entry 10) and 56% (110 °C, entry 11) under elevated or lower temperature and resulted in no reaction under 80 °C (entry 12). The product **2a** was isolated in 90% (NH₄I, 1.5 equiv) and 93% (NH₄I, 1.2 equiv) yields, respectively (entry 13), and no reaction took place in the absence of NH₄I (entry 14). Moreover, the reaction was inhibited under N₂ atmosphere (entry 15). Furthermore, a 1 mmol scale reaction of **1a**, NH₄I, and DMF also ran smoothly under the standard conditions to afford **2a** in 90% yield (entry 16).

With the optimized reaction conditions established, first, the substrate scope of N-substituted indoles was evaluated As shown in Scheme 2, this procedure tolerated 3-methyl (2b, 94%) and 3-ethoxycarbonyl (2c, 89%) analogues well. 4-Methylindole worked well to afford 2d in 90% yield. A wide range of substrates with 5-substituents ran smoothly under the optimal condition (including methyl, methoxy, cyano, fluoro, chloro, bromo, benzyloxy) with yields ranging from 68 to 90% (2e-2k). Meanwhile, 6-substituted N-pyrimidine indoles took part in the cyanation to afford 2l (87%), 2m (82%), and 2n (90%). Importantly, N-pyridine indole was also a good reaction partner, and 1-(pyridin-2-yl)-1H-indole-2-carbonitrile (20) was obtained in 92% yield. Furthermore, in the case of methyl substituted pyridine as the directing group, 2cyanoindoles were isolated in excellent yields (2p-2r, 90-92%). Particularly, the halogen substituted groups in pyridine, such as chloro (2s, 88%) and fluoro (2t, 87%), survived well





"Reaction conditions: 1 (0.2 mmol), NH₄I (0.24 mmol), Cu(OAc)₂ (0.2 mmol), DMF (2 mL), O₂ (balloon), 130 $^{\circ}$ C, 12 h, in a sealed Schlenk tube, unless otherwise noted.

during this procedure. Notably, *N*-benzothiazole indole also worked well under the standard procedure to afford 1-(benzo[d]thiazol-2-yl)-1H-indole-2-carbonitrile (**2u**) in 71% yield.

To further increase the practicability of this procedure, a series of *N*-containing arenes were tested (Scheme 3). Once again, the cyanation ran smoothly for 1-(pyrimidin-2-yl)-pyrrole (4a, 78%; 4b, 89%). And *N*-(pyrimidin-2-yl) carbazole allowed the direct C-H cyanation at the 1-position (4c, 82%). Fortunately, benzo[h]quinoline underwent the C-H cyanation reaction to access cyano benzo[h]quinolone (4e) in 61% yield. As expected, 1-pyridinyl phene (4d, 78%), 2-(thiophen-2-yl)pyridine (4f, 90%), and 1-pyrazolyl benzene all worked well (4g, 64%) under the standard procedure.

To define the possible pathway of this reaction, some control experiments were carried out (Scheme 4). First, when NH_4HCO_3 instead of NH_4I reacted with 1a under the standard reaction condition, 2a was isolated in 85% yield. Thus, the involvement of six-membered copper-iodine intermediate m could be ruled out (Scheme 4a). Second, in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical scavenger, 2a was obtained in 72% yield, and no radical adduct was captured by GC-MS (for details, see Supporting Information). This result indicated the

Scheme 3. Scope of the Cyanation of Arenes and Heteroarenes^a



^aReaction conditions: 3 (0.2 mmol), NH₄I (0.24 mmol), $Cu(OAc)_2$ (0.2 mmol), DMF (2 mL), O₂ (balloon), 130 °C, 12 h, in a sealed Schlenk tube, unless otherwise noted.

Scheme 4. Mechanism Study



reaction did not proceed with a radical-involed pathway (Scheme 4b). Third, replacing NH₄I with ¹⁵NH₄Cl under the optimized reaction condition, the isotopic compound 2a' was isolated in 89% yield, and almost complete isotopic incorporation into the cyano moiety was observed by GC–MS and ¹³C NMR analysis (Scheme 4c) (for details, see Supporting Information). Thus, the N atom in the cyano group should be derived from ammonium. Fourth, replacing $Cu(OAc)_2$ with CuBr₂ or CuBr, **2a** also could be isolated in moderate yield (Table 1, entries 5 and 6), indicating the carbon atom in "CN" that came from DMF rather than $Cu(OAc)_2$. Finally, further research revealed that both $Cu(OAc)_2$ and O₂ were all essential for the in situ formation of cyanide for the combination of the NH4I and DMF (Table 2).

Based on aforementioned results and previous reports,^{60,7} a plausible mechanism is proposed (Scheme 5). First, after $Cu(OAc)_2$ coordinates with the N atom, the cleavage of the C2 C–H in 1a affords intermediate A. Meanwhile, DMF is oxidized to iminium species A1 by $Cu(OAc)_2$, proceeding with a single electron transfer step. Then, with the assistance of O_2 , the reaction of A1 and NH₃ leads to intermediate A2, which releases CN^- via the cleavage of the C–N bond. This

Table 2. Detection of CN⁻ by Indicator Paper^a

entry	NH_4I (0.24 mmol)	$Cu(OAc)_2$ (0.2 mmol)	atmosphere	results
1	\checkmark		O ₂	+
2	×		O ₂	_
3		×	O ₂	_
4			N_2	-
5			air	+

"Reaction conditions: the mixture was heated under 130 $^{\circ}$ C for 2 h in DMF (2 mL). "-" means negative result; "+" means positive result.

Scheme 5. A Plausible Mechanism



procedure was confirmed by the control experiments as depicted in Table 2. Afterward, the replacement of AcO⁻ with CN⁻ leads to intermediate **B**. Then, intermediate **B** was oxidized by O₂ to form Cu(III) intermediate **C**. Finally, the reductive elimination of Cu(III) intermediate **C** releases **2a** along with the generation of Cu(I), which may be oxidized to Cu(II) by O₂ to fulfill the catalytic cycle.

In conclusion, we have developed a copper-mediated direct C–H cyanation of heteroarenes and arenes, using NH_4I and DMF as a safe and efficient combined cyanide source. Both pyridinyl, pyrimidinyl, thiazolyl, and pyrazolyl served as efficient directing groups in this procedure. As such, this approach provides a novel route to access aromatic nitriles, such as pyrrole, carbazole, and benzene.

ASSOCIATED CONTENT

S Supporting Information

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Experimental procedures along with copies of spectra (PDF)

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