ORGANIC
LETTERS

2012
Vol. 14, No. 15
3924–3927

Copper-Mediated Selective Cyanation of Indoles and 2-Phenylpyridines with Ammonium Iodide and DMF

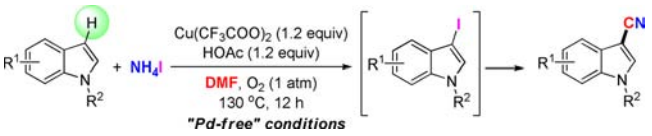
Jinho Kim, Hyunwoo Kim, and Sukbok Chang*

Department of Chemistry and Molecular-Level Interface Research Center, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 305-701, Korea

sbchang@kaist.ac.kr

Received June 19, 2012

ABSTRACT



Copper-mediated regioselective cyanation of indoles and 2-phenylpyridines was developed by using ammonium iodide and DMF as the combined source of a cyano unit under *"Pd-free" conditions.* Mechanistic studies indicate that the reaction of indoles proceeds through a two-step sequence: electrophilic initial iodination and then cyanation. The cyanation has a broad substrate scope, high functional group tolerance, and excellent regioselectivity.

Nitrile is a key building unit in organic synthesis to serve as a versatile precursor for various functional groups such as aldehydes, amines, amidines, tetrazoles, amides, or other carboxy derivatives.[1] In particular, aryl or heteroaromatic nitriles are widely utilized in synthetic chemistry or in industry for the manufacture of pharmaceuticals, agrochemicals, or dyes.[2] Sandmeyer reaction[3] and Rosenmund–von Braun's procedures[4] are conventional methods to prepare these nitrile compounds using CuCN as the cyanating reagent. In recent decades, cyanation of aryl (pseudo)halides[5] with anionic cyano sources such as MCN (M = K, Na, or Zn), TMSCN, or $K_3Fe(CN)_6$ was shown to be readily mediated by metal species including palladium, nickel, or copper complexes.[6–10] In addition, certain organic precursors such as acetone cyanohydrin $(CH_3)_2CH(OH)(CN)$[11] or nitromethane CH_3NO_2[12] were often employed to provide the cyano unit in metal-catalyzed cyanation reactions.[13]

Along this line, we recently discovered that the cyano unit "CN" could be generated *in situ* from aqueous ammonia and *N*,*N*-dimethylformamide (DMF) under copper-mediated oxidative conditions.[14] This novel procedure was utilized in the palladium-catalyzed direct C–H cyanation

---

(1) (a) *The Chemisty of the Cyano Group*; Rappoport, Z., Ed.; Interscience: London, 1970. (b) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Fucntional Group Preparations*; VCH: New York, 1989.

(2) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substance: Synthesis, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, 2001.

(3) (a) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633. (b) Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251. (c) Galli, C. *Chem. Rev.* **1988**, *88*, 765.

(4) (a) Rosenmund, K. W.; Struck, E. *Ber. Dtsch. Chem. Ges.* **1919**, *2*, 1749. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(5) (a) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779. (b) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049.

(6) For the transition metal catalyzed cyanations using KCN, see: (a) Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985. (b) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224. (c) Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *17*, 2837. (d) Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2005**, *11*, 2483.

(7) For the transition metal catalyzed cyanations using NaCN, see: (a) Okano, T.; Iwahara, M.; Kiji, J. Y.; Sakakibara, F.; Okuda, A. *Synlett* **1998**, 243. (b) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890.

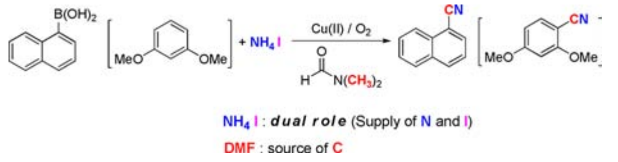
(8) For the transition metal catalyzed cyanations using $Zn(CN)_2$, see: (a) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887. (b) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193. (c) Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984. (d) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441. (e) Jensen, R. S.; Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Tetrahedron Lett.* **2005**, *46*, 8645. (f) Buono, F. G.; Chidambaram, R.; Mueller, R. H.; Waltermire, R. E. *Org. Lett.* **2008**, *10*, 5325. (g) Martin, M. T.; Liu, B.; Cooley, B. E., Jr.; Eaddy, J. F. *Tetrahedron Lett.* **2007**, *48*, 2555.

(9) For the transition metal catalyzed cyanations using TMSCN, see: (a) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1986**, *51*, 4714. (b) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50.

(10) For the transition metal catalyzed cyanations using $K_3Fe(CN)_6$, see: (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388. (b) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508. (c) Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 2585. (d) Grossman, O.; Gelman, D. *Org. Lett.* **2006**, *8*, 1189. (e) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087.

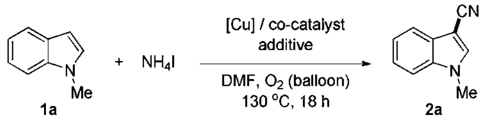
10.1021/ol301674m

Scheme 1. Cyanation of C−B and C−H Bonds with NH$_4$I/DMF



of 2-phenylpyridine and its derivatives.[15] Based on the labeling experiments, it was concluded that the carbon and nitrogen atom of the "CN" unit were originated from ammonia[16] and the *N*,*N*-dimethyl moiety of DMF, respectively.[17] With a slight modification by employing ammonium iodide instead of aqueous ammonia, we could extend this method for the cyanation of aryl boronic acids (their esters and borate salts) and electron-rich benzenes *without requiring a palladium catalyst*.[18] In this study, it was proposed that ammonium iodide has a dual role as a supplier of both an iodine and a nitrogen atom. Mechanistic studies revealed that *substrates are first iodinated and then iodoarenes intermediates are cyanated* under the copper-mediated conditions (Scheme 1). Since the position of the initial iodination of benzenes is controlled by the electrophilic aromatic substitution pathway,[19] we envisioned that the developed C−H cyanation protocol could also be applied to the reaction of indoles.[17a,c,20] Indoles are widely utilized in organic synthesis, medicinal chemistry, and materials science.[21] Therefore, facile and selective derivatization of indoles is highly important and desirable. In this regard, we describe herein a new entry of the regioselective C−H cyanation of indoles with the use of ammonium iodide and DMF.

Table 1. Optimization of Cu-Mediated Cyanation of **1a**[a]

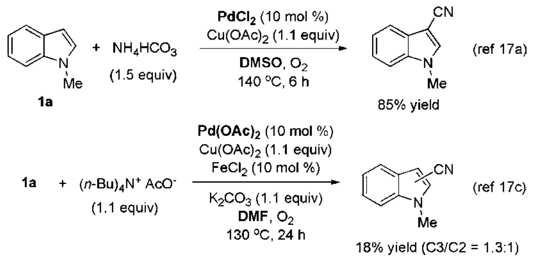


entry	[Cu] (equiv)	cocatalyst	additive (equiv)	yield (%)[b]
1	Cu(NO$_3$)$_2$·3H$_2$O (2.0)	–	HOAc (2.0)	0
2	Cu(ClO$_4$)$_2$·6H$_2$O (2.0)	–	HOAc (2.0)	0
3	Cu(OMe)$_2$ (2.0)	–	HOAc (2.0)	27
4	Cu(CH$_3$COO)$_2$ (2.0)	–	HOAc (2.0)	38
5	Cu(OTf)$_2$ (2.0)	–	HOAc (2.0)	0
6	Cu(CF$_3$COO)$_2$ (2.0)	–	HOAc (2.0)	62
7	Cu(CF$_3$COO)$_2$ (2.0)	PdCl$_2$[c]	HOAc (2.0)	54
8	Cu(CF$_3$COO)$_2$ (2.0)	Pd(OAc)$_2$[c]	HOAc (2.0)	61
9	Cu(CF$_3$COO)$_2$ (2.0)	–	TFA (2.0)	39
10[d]	**Cu(CF$_3$COO)$_2$ (1.2)**	–	**HOAc (1.2)**	**90**
11[d,e]	Cu(CF$_3$COO)$_2$ (1.2)	–	HOAc (1.2)	72

[a] Conditions: **1a** (0.3 mmol), NH$_4$I (2.0 equiv), additive, and [Cu] in DMF (1.5 mL). [b] ^{1}H NMR yield (internal standard: 1,1,2,2-tetrachloroethane). [c] Palladium species in 10 mol % was used. [d] NH$_4$I, copper, and additive were used in 1.2 equiv amounts for 12 h. [e] Under air balloon.

We initiated the present study with 1-methylindole (**1a**) as a model substrate using NH$_4$I (2 equiv) in DMF (Table 1). It was first found that the nature of copper species was critical for determining the cyanation efficiency. When copper(II) nitrate (2 equiv) was used, with which the cyanation of arylboronic acids and benzenes was highly efficient in our previous study,[18] the reaction was totally ineffective (entry 1). While the reaction progress was varied depending on the copper species examined (entries 2−5), copper(II) trifluoroacetate showed especially notable reactivity to afford 3-cyano-1-methylindole (**2a**) in 62% NMR yield (entry 6). Other isomeric compounds (e.g., 2-cyano-1-methylindole) were not observed in this reaction. The fact that *the presence of palladium catalysts such as PdCl$_2$ or Pd(OAc)$_2$ did not affect*

Scheme 2. Indole Cyanation Using Ammonium Salts and DMF



---

(11) (a) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661. (b) Park, E. J.; Lee, S.; Chang, S. *J. Org. Chem.* **2010**, *75*, 2760. (c) Schareina, T.; Zapf, A.; Cotté, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2011**, *353*, 777.

(12) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(13) For the use of other cyanation sources, see: (a) Luo, F.-H.; Chu, C.-I.; Cheng, C.-H. *Organometallics* **1998**, *17*, 1025. (b) Sato, N.; Yue, Q. *Tetrahedron* **2003**, *59*, 5831. (c) Zhang, Z.; Liebeskind, L. S. *Org. Lett.* **2006**, *8*, 4331. (b) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 519. (c) Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 5608.

(14) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272.

(15) For the direct C−H bond functionalizations developed in this group, see: (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158. (d) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. (e) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899. (f) Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 3780. (g) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110.

(16) Our related works on the use of ammonia in synthetic methods: (a) Kim, J.; Chang, S. *Chem. Commun.* **2008**, 3052. (b) Kim, J.; Lee, S. Y.; Lee, J.; Do, Y.; Chang, S. *J. Org. Chem.* **2008**, *73*, 9454.

(17) For similar approaches for generating the cyano unit "CN" from ammonia and DMF (DMSO) under copper-mediated conditions, see: (a) Ren, X.; Chen, J.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 6725. (b) Zhang, G.; Ren, X.; Chen, J.; Hu, M.; Cheng, J. *Org. Lett.* **2011**, *13*, 5004. (c) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374.

(18) Kim., J.; Choi, J.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 2528.

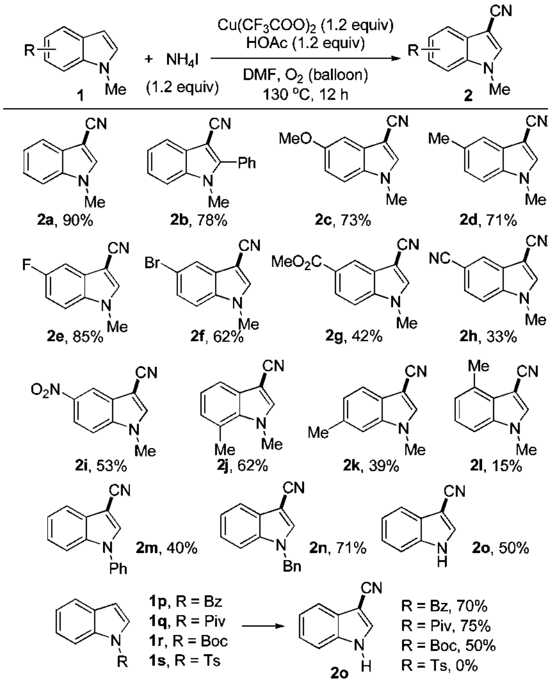
(19) (a) Jereb, M.; Zupan, M.; Stavber, S. *Chem. Commun.* **2004**, 2614. (b) Pavlinac, J.; Zupan, M.; Stavber, S. *Synthesis* **2006**, 2603.

(20) (a) Do, H.-Q.; Daugulis, O. *Org. Lett.* **2010**, *12*, 2517. (b) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 1052. (c) Reddy, B. V. S.; Begum, Z.; Reddy, Y. J.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 3334.

(21) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608.

the product yield and selectivity (entries 7−8) is especially significant in that Cheng and Jiao reported that palladium catalysts were essential in the cyanation of 1-methylindole (**1a**) under slightly different conditions (Scheme 2). While the product yield was decreased upon the use of trifluoroacetic acid instead of acetic acid (entry 9), it was found that the reaction efficiency could be improved by careful tuning of the molar ratio of the reactant, reagent, and additive. Indeed, the highest yield was obtained by using 1.2 equiv (relative to **1a**) of NH_4I, $Cu(CF_3COO)_2$, and HOAc each (entry 10). We assume that this result is related to the stability of an *in situ* generated intermediate, 3-iodo-1-methylindole (*vide infra*). Under air, the efficiency of the cyanation was decreased (entry 11).

Scheme 3. Copper-Mediated Cyanation of Indoles[a,b]

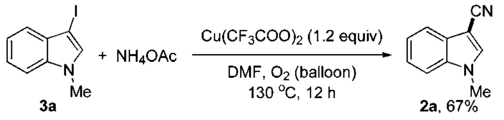


[a] Reaction conditions: **1** (0.3 mmol) and NH_4I (0.36 mmol) in DMF (1.5 mL) under O_2 at 130 °C for 12 h. [b] Isolated yields.

With encouraging conditions in hands, we next investigated the scope and limitations of our cyanation protocol (Scheme 3). First, it was observed that the reaction efficiency and regioselectivity were highly maintained even with substrates that do not bear a substituent at the 2-position of indoles (compare **2a** and **2b**). In contrast, in Jiao's system, the cyanation became quite sluggish with low selectivity when unsubstituted indoles at that position were subjected (Scheme 2).[17c] Second, the cyanation was not much influenced by the electronic nature of substrates as demonstrated by **2c**−**2i** although electron-deficient substituents slightly lowered the product yields. Third, an excellent level of functional group tolerance was observed and a wide range of labile groups were indeed intact under the present cyanation conditions (**2f**−**2i**). While the presence of a substituent at the 7-position did not affect the reaction efficiency (**2j**), indoles having the same group at the C6- or C4-position were cyanated in lower yields (**2k** and **2l**, respectively).

With regard to *N*-substituents, a range of different groups could be employed. *N*-Phenyl and *N*-benzylindole were cyanated exclusively at the 3-position in moderate to good yields (**2m** and **2n**, respectively). It is noted that cyanation of unprotected indole took place in an acceptable yield (**2o**), thus again demonstrating a high level of flexibility of the present protocol (**2m**−**2o**). In addition, cyanation of *N*-carbonyl group substituted indoles readily proceeded, but with concomitant decarbonylation leading to 3-cyano-1*H*-indole (**2o**) with varied yields. On the other hand, *N*-tosylindole (**1s**) did not undergo the cyanation. When 1,3-dimethylindole was subjected to the conditions, only decomposition occurred. In addition, no conversion was observed with benzofuran.

To gain mechanistic insights, a reaction profile was obtained in the cyanation of 1-methylindole (**1a**) under the standard conditions (Figure 1).[22] In analogy with our previous results in the cyanation of aryl boronic acids,[18] iodinated indole (**3a**) was initially observed to form in over 60% yield within 1 h. The cyanated product **2a** then started to generate gradually over time upon the decrease of **3a**, implying that an iodinated indole is indeed an intermediate in the present process. Besides, when an independently prepared iodoindole **3a** was subjected to the present copper-mediated oxidative conditions, 3-cyano-1-methylindole **2a** was obtained in 67% yield in the absence of acetic acid (eq 1).[17b] Thus, we have developed the regioselective cyanation of indoles with ammonium iodide and DMF *via sequential iodination and subsequent cyanation in the absence of a palladium catalyst*.



(1)

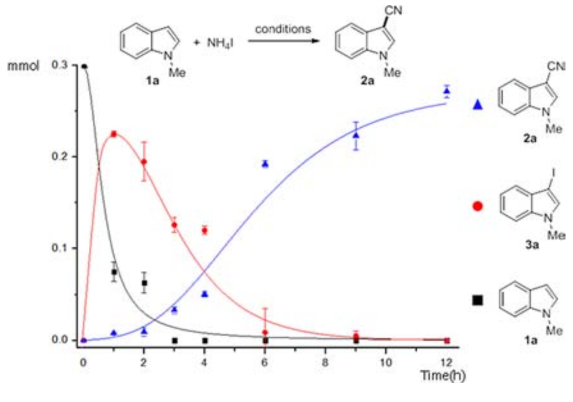


Figure 1. Reaction profile in the Cu-mediated cyanation of **1a**.

Recently, Yu et al. reported the direct cyanation of 2-phenylpyridines under copper-mediated conditions using TMSCN or nitromethane,[12] and a single electron transfer pathway was proposed to be responsible for this

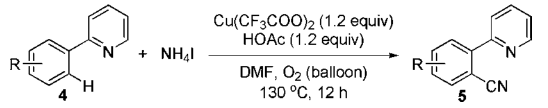
---

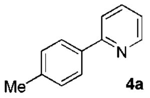
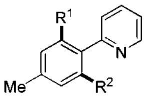
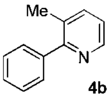
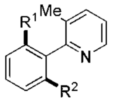
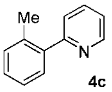
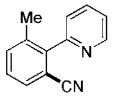
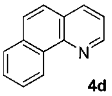
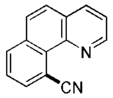
[22] See the Supporting Information for details.

process. Along this line, we also envisaged that cyanation of 2-phenylpyridines would be possible in a sequence of initial iodination followed by cyanation using the presently developed conditions without requiring palladium catalysts.[23] It should be mentioned that when *aqueous ammonia* and DMF were used in the direct cyanation of 2-phenylpyridines, a palladium catalyst was essential to achieve the rate-limiting C−H bond activation.[14]

We were pleased to observe that regioselective cyanation of 2-phenylpyridines was achieved under the current copper-mediated oxidative conditions *in the absence of palladium catalysts* (Table 2). When 2-phenylpyridine was subjected to the conditions, a mixture of mono- and bis-cyanated products was obtained with a similar ratio (entry 1). In contrast, sterically congested substrates were cyanated selectively to afford only monocyano products in high yields (entries 2−3). In addition, cyanation of benzoquinoline took place without difficulty (entry 4). It was observed that the cyanation did not take place when other ammonium salts (NH_4Cl or NH_4OAc) rather than NH_4I were employed under otherwise identical conditions, implying that the reaction proceeds via two sequential steps: initial iodination followed by cyanation.

Table 2. Copper-Mediated Cynation of 2-Phenylpyridines[a]

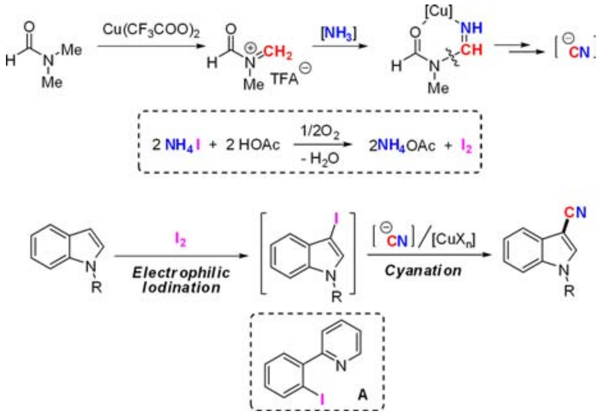


entry	substrate	product(s)[b]
1	 4a	 **5a**: R^1 = H, R^2 = CN, 32% **5aa**: R^1 = R^2 = CN, 40%
2	 4b	 **5b**: R^1 = H, R^2 = CN, 90% **5bb**: R^1 = R^2 = CN, <1%
3	 4c	 **5c**, 85%
4	 4d	 **5d**, 61%

[a] Reaction conditions: **4** (0.3 mmol) and NH_4I (0.36 mmol) in DMF (1.5 mL) under O_2 at 130 °C for 12 h. [b] Isolated yields.

Based on the present experimental studies and our precedent results,[14,18] a plausible pathway is proposed in Scheme 4.

Scheme 4. Proposed Pathway of the Present Cyanation



In analogy with the previous proposal,[14,18] a copper-mediated reaction of ammonia and DMF is postulated to provide a cyanide anion. In addition, it is assumed that ammonium iodide plays a dual role under the employed conditions: as a source of iodide for the formation of iodine molecule[24] and as a supplier of a nitrogen atom of the cyano unit. An electrophilic aromatic substitution is believed to involve the iodination of indoles to offer a 3-iodoindole intermediate. On the other hand, 2-phenylpyridine might undergo the iodination via a radical-cation pathway leading to an intermediate **A** based on the chelation assistance.[12,25] In both substrates, the subsequent cyanation step is proposed to operate utilizing a copper species.

In conclusion, we have developed a copper-mediated cyanation of indoles and 2-phenylpyridines using ammonium iodide and DMF under "*palladium-free*" conditions. The reaction proceeds via two sequential steps: initial iodination followed by cyanation. The direct C−H cyanation has a broad substrate scope, high functional group tolerance, and excellent regioselectivity.

Acknowledgment. This work was supported by the National Research Foundation (KRF-2008-C00024) and MIRC (NRF-2011-0001322). We thank Jiho Choi (KAIST) and Kwangmin Shin (KAIST) for their helpful discussions.

Supporting Information Available. Experimental details, and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(23) (a) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716. (b) Jia, X.; Yang, D.; Wang, W.; Luo, F.; Cheng, J. *J. Org. Chem.* **2009**, *74*, 9470.

(24) (a) Lyday, P. A. *Ullmann's Encyclopedia of Industrial Chemistry, 5th Completely Revised Edition*, Vol. A14; VCH: Weinheim, 1991; pp 388−389. (b) Mohan, K. V. V. K.; Narender, N.; Kulkarni, S. J. *Tetrahedron Lett.* **2004**, *45*, 8015.

(25) Biphenyl was not reacted under the present conditions.

The authors declare no competing financial interest.