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Cu-catalyzed Cyanation of Indoles with Acetonitrile as A Cyano Source

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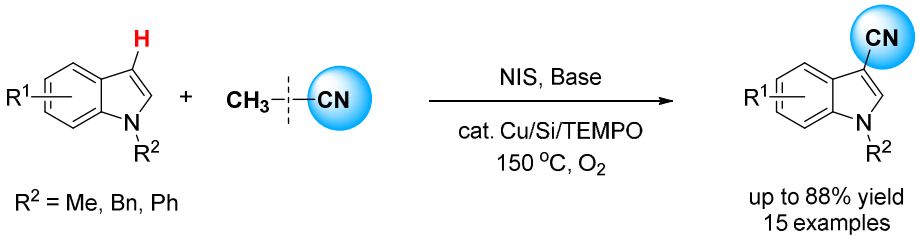


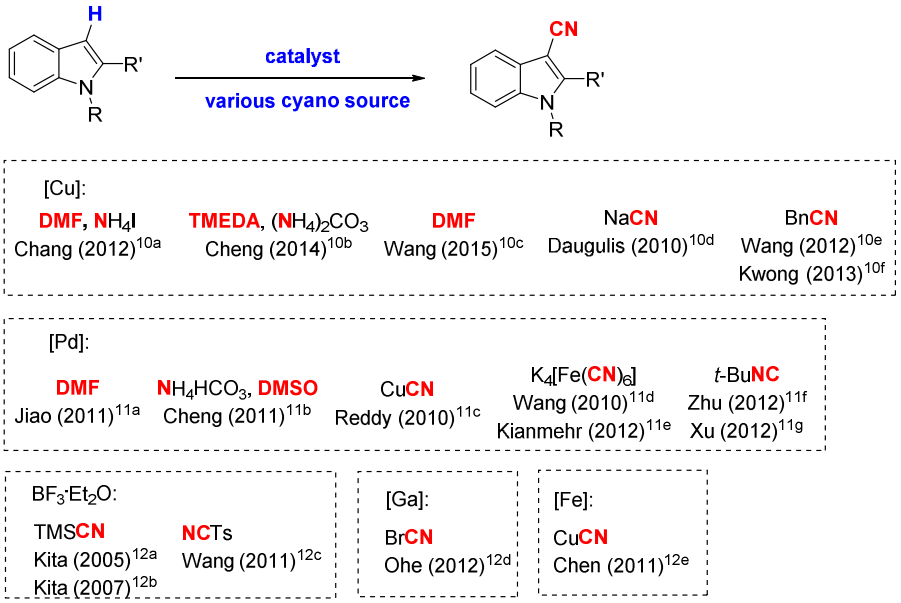
Abstract

Cu-catalyzed cyanation of indoles with acetonitrile for the synthesis of 3-cyanaindoles has been developed. Cu/TEMPO/$(Me_3Si)_2$ system has been identified to promote highly efficient and selective C−H cyanation of indoles by use of unactivated acetonitrile as a cyano source via sequential iodination/cyanation process in one pot. This reaction furnishes 3-cyanaindoles in moderate to good yields and tolerates a series of functional groups. Moreover, low-cost copper catalyst and hazardless acetonitrile as a cyano source feature the practicability of this reaction.

Indole nitriles display widely biological activities and exist in many dyes, herbicides, agrochemicals, pharmaceuticals and natural products as a backbone of their structural frameworks.[1] Notably, 3-cyanoindole is a key building block in

pharmaceutical syntheses, material science and fine chemistry.[2] Beyond these functions, the versatile cyano group can be easily transferred into a broad range of functional groups, for example, aldehydes, amines, amidines, tetrazoles, amides and their carboxyl derivatives.[3]

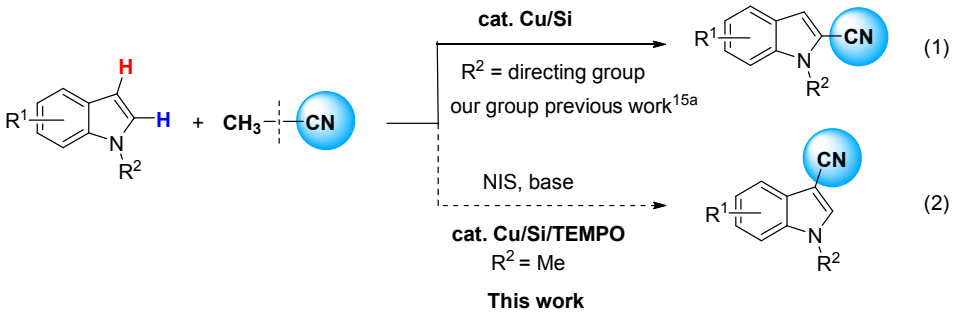
The significant progresses have been made in the development of the synthesis of 3-cyanoindoles. The classical methods include: 1) Sandmeyer[4] and Rosenmund-von Braun[5-6] reactions, in which stoichiometric and toxic CuCN is used as a cyanating reagent, 2) transition metal-catalyzed cyanation of aryl (pseudo)halides[7] and 3) multi-step organic transformation.[8] Despite these advances, the simple and straightforward access to 3-cyanoindoles remains desirable.



Scheme 1. The synthesis of 3-cyanoindoles via C−H cyanation

Due to the attraction of direct C−H functionalization protocol avoiding the need of prefunctionalization of substrates, the development of transition metal-catalyzed C−H activation has witnessed stupendous growing in the past decades.[9] Indole C−H cyanation is a direct pathway to form 3-cyanoindole promoted by Cu,[10] Pd[11] and other Lewis acids (Scheme 1).[12] In these procedures, the employment of cyano sources can

be classified as metal cyanides (NaCN, CuCN, TMSCN, $K_4[Fe(CN)_6]$), BnCN, *t*-BuNC, electrophilic CN^+ reagents (NCTs, BrCN), and the combined cyano sources (NH_4I/DMF, DMF, NH_4HCO_3/DMSO, TMEDA/$(NH_4)_2CO_3$) (Scheme 1). Nevertheless, almost all of these methods suffer from limitations. Metal cyanides are frequently used as cyanide sources. A significant problem is the high affinity of the cyanide ion for the transition metal, which often results in rapid deactivation of catalyst. Moreover, most of the cyano sources, in particular KCN, CuCN, and TMSCN, have notorious toxicity. Although $K_4[Fe(CN)_6]$ is exceptionally nontoxic, its slow solubility in organic solvent limited its applicability. Recently, the investigation of combined cyano sources as an alternative strategy has attracted considerable attention and a significant progress has been made in this field.[10a-c,11a,13]



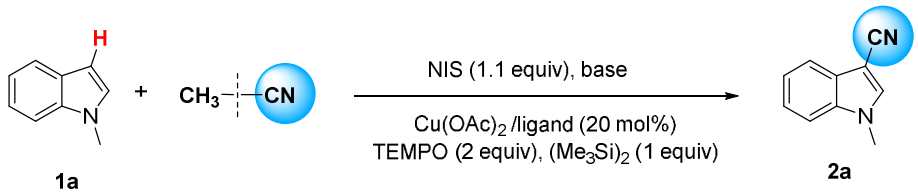
Scheme 2. The cyanation of indoles with acetonitrile.

Acetonitrile is a common solvent which features readily available, inexpensive, abundant and hazardless properties.[14] In connection with our ongoing project on the cleavage of acetonitrile, we have recently developed that unactivated acetonitrile could serve as an attractive cyano source via copper-catalyzed C−CN bond cleavage under Cu/Si or Cu/Si/TEMPO system.[15] Li and Zhu groups discovered that Cu/Ag system is also suitable for acetonitrile C−CN bond cleavage.[16] Notably, we found that Cu/Si system for the C−H cyanation of indoles was exclusively occurred at 2-position of indoles with acetonitrile to yield the corresponding 2-cyanoindoles, in which the directing group such as pyridine or pyrimidine on the nitrogen atom of indole controls

regioselectivity (Scheme 2, eq 1).[15a] We sought to develop a complementary method for the preparation of 3-cyanoindoles with common solvent, acetonitrile, as the cyano source. Herein, we report catalytic tandem cyanation of indoles with acetonitrile as a cyano source under Cu/Si/TEMPO system via an iodination process to exclusively furnish 3-cyanoindoles (Scheme 2, eq 2).

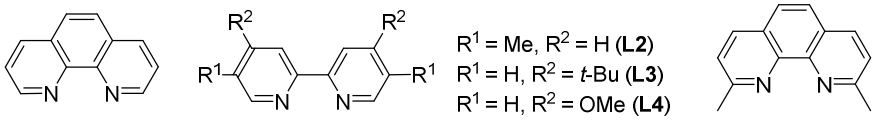
Initially, we chose *N*-methylindole **1a** as a model substrate. The direct cyanation of indole with CH_3CN was first studied in the presence of $Cu(OAc)_2$/1,10-phen, $(Me_3Si)_2$ and TEMPO. However, no reaction was observed under this system (Table 1, entry 1). We reasoned that electron-rich indoles facilitate electrophilic substitution reactions. On the contrary, Cu-catalyzed acetonitrile C−CN cleavage gives out the CN^- anion not CN^+ cation.[15] Therefore, we envisioned the sequential iodination/cyanation process for the cyanation of indoles. A series of parameters such as ligand, base, additive, and temperature were screened. To our delight, the iodination of *N*-methylindole **1a** was smoothly performed in the presence of NIS and KOH at room temperature for 2 hours; the generated indole iodide is able to undergo the catalytic cyanation with acetonitrile promoted by $Cu(OAc)_2$/1,10-phen (20 mol%) at 150 ^oC in one pot, giving the desired 3-cyanoindoles **2a** in 48% yield (Table 1, entry 2). In order to increase the solubility of KOH in acetonitrile, a trace amount of water (2.5 v%) was added into the reaction (entries 3-13). Under these conditions, various ligands were screened for the cyanation of indoles. It is found that these ligands **L1**-**L3** and **L5** have the similar effect on the transformation of indoles to provide **2a** in moderate yields (entries 2-4 and 6). With **L1** as a promising ligand in hand, a series of bases were next examined (entries 7-13). The observation revealed that *t*-BuOLi is slightly better than KOH, other bases such as *t*-BuONa, *t*-BuOK, KOAc, K_2CO_3, Na_2CO_3, and Cs_2CO_3 are inferior to KOH. Pleasingly, when all of the reagents were added in one time and then directly heated upon to 150 ^oC, the achievement of the one-pot tandem iodination/cyanation was observed, smoothly providing 3-cyanoindole in 81% yield (entry 13).

Table 1. Optimization for the synthesis of 3-cyanoindoles with acetonitrile[a]



1a 2a

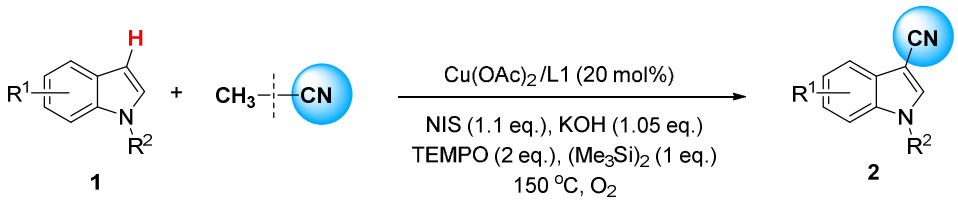
entry	ligand (20 mol%)	base (1.05 equiv)	**2a** (%)[b]
1	L1	none	n.r.
2	L1	KOH	48
3[c]	L2	KOH	41
4[c]	L3	KOH	50
5[c]	L4	KOH	15
6[c]	L5	KOH	47
7[c]	L1	*t*-BuOLi	56
8[c]	L1	*t*-BuONa	42
9[c]	L1	*t*-BuOK	32
10[c]	L1	KOAc	17
11[c]	L1	K_2CO_3	n.d.
12[c]	L1	Na_2CO_3	15
13[c]	L1	Cs_2CO_3	39
14[d]	L1	KOH	**81**

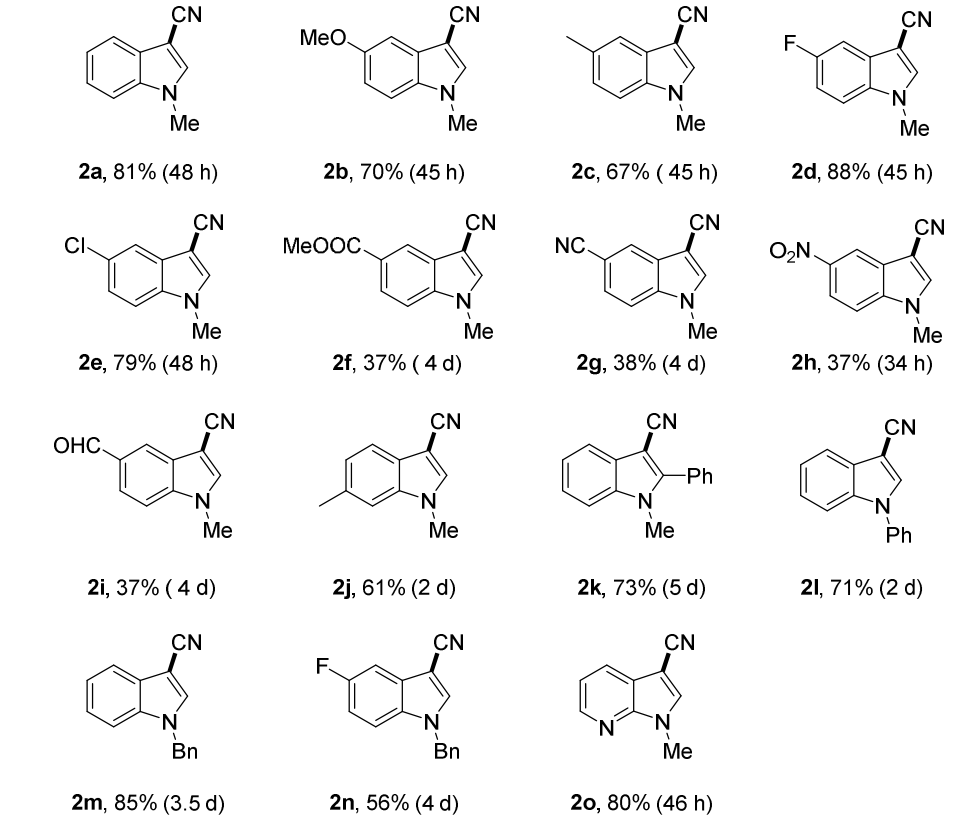


L1 L5

[a] Conditions: **1a** (0.2 mmol), NIS (1.05 equiv), base (1.1 equiv), $Cu(OAc)_2$ (20 mol%), ligand (20 mol%), $(Me_3Si)_2$ (1 equiv), TEMPO (2 equiv), CH_3CN (1.2 mL), O_2, 150 °C, 2 days. Reaction was run at room temperature for 2 hours, and then it was heated at 150 °C. [b] Isolated yield. [c] H_2O (2.5 v%, 30 uL). [d] Reaction was directly heated upon to 150 °C without adding water.

Table 2. Cu-catalyzed cyanation of indoles with acetonitrile[a,b]

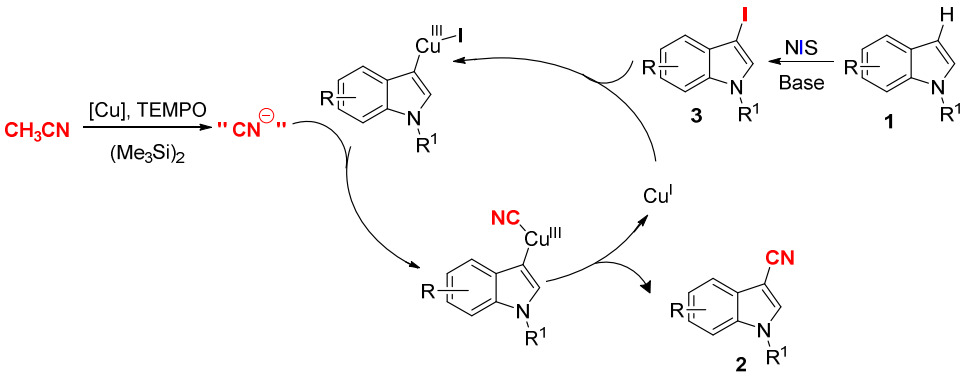




[a] Conditions: **1** (0.3 mmol), NIS (1.1 equiv), KOH (1.05 equiv), $Cu(OAc)_2$ (20 mol%), 1,10-phenanthroline (**L1**, 20 mol%), $(Me_3Si)_2$ (1 equiv), TEMPO (2 equiv), CH_3CN (1.2 mL), 150 °C, O_2. All of reactions were directly heated upon to 150 °C. [b] Isolated yield.

With the optimal conditions in hand, the scope and limitation for the cyanation of indoles has been explored. As illustrated in Table 2, we found that both electron-rich and -deficient substituents on indole rings could be tolerated well under this system, furnishing cyanated products exclusively at the 3-position of indole. It is observed that electron-rich group substituted substrates reacted more efficiently than

electron-deficient group substituted substrates, which is consistent with the rule of electrophilic iodination of indole. For example, substrates bearing MeO (**1b**) and Me (**1c**) groups gave the desired 3-cyanoindoles **2b-c** in 70-67% yields, respectively. The reactions of substrates **1d-e** containing halogen atoms with acetonitrile smoothly performed to yield the expected 3-cyanoindoles **2d-e** in high yields (for F, 88% yield; for Cl, 79% yield) which could be handled for further application. Electron-withdrawing substituents such as COOMe (**1f**), CN (**1g**), NO_2 (**1h**) and CHO (**1i**) were compatible under the standard conditions to give 3-cyanoindoles with moderate yields. When the 2-position of indole is occupied by a phenyl group, this substrate **1k** slowly undertaken cyanation within 5 days to form the corresponding 3-cyanoindole **2k** in 78% yield. By changing substitutents on nitrogen atom, we found that 1H-indole with free NH did not undergo this reaction, whereas substrates with phenyl **1l** and benzyl group **1m-n** on nitrogen atom led to the cyanation process. Interestingly, this Cu-catalyzed TEMPO system was also suitable for *N*-methyl-1H-pyrrolo[2,3-b]pyridine heteroaromatic ring (**1o**), providing the desired cyanated product **2o** in 80% yield. However, other heteroarenes such as benzofuran, benzothiophene, and *N*-methylpyrrole did not work under standard conditions.



Scheme 3. Proposed reaction pathway.

Based on our mechanistic studies regarding the cyanation of simple arenes and boronic acids reported by our group,[15] a proposed reaction pathway was displayed in Scheme 3. Acetonitrile first reacts with TEMPO under the [Cu]/$(Me_3Si)_2$ system to

release the cyanide anion by the C−CN cleavage. The cyanide anion then takes part in the cyanation of 3-iodo-indole **3** starting from the iodination of indole **1** with NIS to yield the desired 3-cyano-indole **2**.

In conclusion, Cu-catalyzed cyanation of indoles with acetonitrile has been discovered. This C−H functionlization of indoles involved sequential iodination/cyanation in one pot. Cu/TEMPO/$(Me_3Si)_2$ system displays efficient activity for the cyanation of indoles and acetonitrile C−CN cleavage, gives the corresponding 3-cyanaindole in moderate to good yields, and tolerates a series of functional groups, including OMe, Me, F, Cl, CHO, NO_2 and so on. Moreover, inexpensive copper catalyst and abound and hazardless acetonitrile as a cyano source make this system applicable.

■ EXPERIMENTAL SECTION

General Considerations. All solvents were dried and distilled before use according to the standard methods. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. Infrared (IR) spectra were recorded with a thin film on the KBr plate. High resolution mass spectra were obtained with a Q-TOF MS Spectrometer.

General procedure for copper-catalyzed cyanation of indoles with acetonitrile as the cyano source. An oven-dried Schlenk tube, which was equipped with a magnetic stir bar and charged with $Cu(OAc)_2$ (20 mol%, 11 mg), was evacuated and backfilled with oxygen three times. Under oxygen, 1,10-phenanthroline

(20 mol%, 11 mg), TEMPO (0.6 mmol, 94 mg), KOH (0.31 mmol, 17 mg), acetonitrile (1.2 mL), corresponding indole substrate (0.3 mmol), $(Me_3Si)_2$ (0.3 mmol, 44 mg) and NIS (0.33 mmol, 74 mg) were added into the tube. The reaction was stirred at 150 ^oC for the indicated time. Then, the mixture was cooled to room temperature, poured into saturated Na_2S solution (15 mL), and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography using petroleum ether/ethyl acetate as the eluent to give the corresponding cyanated product.

1-Methyl-1H-indole-3-carbonitrile (2a): brown oil (38 mg, 81% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H), 7.52 (s, 1H), 7.39-7.27 (m, 3H), 3.82 (s, 3H). IR (KBr) ν 3119, 2217, 1533, 1469, 1250, 1199, 1159, 1130, 744 cm^{-1}. MS (EI) m/z: 156 (M^+), 155, 141, 128, 114, 101, 88, 78, 28, 18.[10a]

5-Methoxy-1-methyl-1H-indole-3-carbonitrile (2b): yellow solid (39 mg, 70% yield); m.p. 105-106 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 8.8, 2.4 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H). IR (KBr) ν 3113, 2926, 2208, 1623, 1534, 1493, 1230, 1138, 825, 806 cm^{-1}. MS (EI) m/z: 186 (M^+), 171, 143, 128, 116, 101, 89, 18.[10a]

1,5-Dimethyl-1H-indole-3-carbonitrile (2c): brown oil (34 mg, 67% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.45 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 3.78 (s, 3H), 2.47 (s, 3H). IR (KBr) ν 3121, 2923, 2218, 1695, 1534, 1487, 1381, 1123, 806 cm^{-1}. MS (EI) m/z: 170 (M^+), 169, 155, 140, 127, 115, 101, 85,

18.[10a]

5-Fluoro-1-methyl-1H-indole-3-carbonitrile (2d): pale yellow solid (46 mg, 88% yield); m.p. 70-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.36 (d, *J* = 8.8, 1H), 7.32 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H), 3.85 (s, 3H). IR (KBr) ν 3125, 2214, 1629, 1533, 1490, 1190, 905, 858, 788 cm^{-1}. MS (EI) m/z: 174 (M^+), 159, 147, 132, 120, 87, 57, 18. [10a]

5-Chloro-1-methyl-1H-indole-3-carbonitrile (2e): yellow solid (45 mg, 79% yield); m.p. 96-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 1.2 Hz, 1H), 7.58 (s, 1H), 7.31 (d, *J* = 1.2 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 134.4, 128.6, 128.3, 124.4, 119.2, 115.1, 111.4, 85.2, 33.8. IR (KBr) ν 3115, 2212, 1728, 1704, 1620, 1534, 1319, 1246, 1146, 1098, 763 cm^{-1}. HRMS (ESI) Calcd for ($C_{10}H_7ClN_2 + Na^+$): 213.0195, found: 213.0191.

Methyl 3-cyano-1-methyl-1H-indole-5-carboxylate (2f): yellow solid (24 mg, 37% yield); m.p. 164-165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 1.6 Hz, 1H), 8.07 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.65 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H). IR (KBr) ν 3115, 2212, 1728, 1534, 1319, 1245, 1146, 743, cm^{-1}. MS (EI) m/z: 214 (M+), 183, 155, 128, 101, 91, 77, 28, 18. [10a]

1-Methyl-1H-indole-3,5-dicarbonitrile (2g): pale yellow solid (21 mg, 38% yield); m.p. 173-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.72 (s, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 3.92 (s, 3H). IR (KBr) ν 3113, 2224, 1702, 1535, 1138, 1122, 1062, 813 638 cm^{-1}. MS (EI) m/z: 181 (M^+), 180, 153, 139, 91, 28, 18. [10a]

1-Methyl-5-nitro-1H-indole-3-carbonitrile (2h): pale yellow solid (22 mg, 37% yield); m.p. 160-161 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.2 Hz, 1H), 8.27 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.75 (s, 1H), 7.49 (d, *J* = 9.0 Hz, 1H), 3.95 (s, 3H). IR (KBr) ν 3118, 2229, 1710, 1536, 1340, 1096, 1062, 815, 735 cm^{-1}. MS (EI) m/z: 201 (M^+), 171, 155, 143, 128, 101, 28, 18.[10a]

5-Formyl-1-methyl-1H-indole-3-carbonitrile (2i): pale yellow solid (21 mg, 37% yield); m.p. 202-203 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.29 (d, *J* = 0.8 Hz, 1H), 7.94 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.69 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 139.3, 137.5, 131.6, 127.8, 125.0 123.9, 114.9 111.4, 88.1, 34.2. IR (KBr) ν 3124, 2219, 1685, 1611, 1534, 1458, 1186, 1121, 1060, 809 621 cm^{-1}. HRMS (ESI) Calcd for ($C_{11}H_8N_2O$ + Na^+): 207.0534, found: 207.0525.

1,6-Dimethyl-1H-indole-3-carbonitrile (2j): deep yellow solid (31 mg, 61% yield); m.p. 102-103 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 1H), 7.45 (s, 1H), 7.17 (d, *J* = 0.6 Hz, 1H), 7.11 (dd, *J* = 8.2, 0.6 Hz, 1H), 3.79 (s, 3H), 2.51 (s, 3H). IR (KBr) ν 3115, 2210, 1625, 1533, 1467, 1386, 801 cm^{-1}. MS (EI) m/z: 170 (M^+), 155, 140, 128, 115, 101, 85, 77, 51, 39.[10a]

1-Methyl-2-phenyl-1H-indole-3-carbonitrile (2k): deep yellow solid (51 mg, 73% yield); m.p. 104-105 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.77 (m, 1H), 7.59-7.52 (m, 5H), 7.44-7.33 (m, 3H), 3.76 (s, 3H). IR (KBr) ν 3055, 2214, 1659, 1533, 1467, 1398, 1252, 811, 748, 700 cm^{-1}. MS (EI) m/z: 232 (M^+), 204, 190, 116, 102, 88, 77, 51.[10a]

1-phenyl-1H-indole-3-carbonitrile (2l) [10a]: white solid (46 mg, 71% yield); m.p. 115-116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 1H), 7.81 (s, 1H), 7.60-7.56 (m, 2H), 7.53-7.48 (m, 4H), 7.36-7.34 (m, 2H). IR (KBr) ν 3123, 2924, 2224, 1599, 1540, 1481, 1459, 1225, 736 cm^{-1}. MS (EI) m/z: 218 (M^+), 203, 190, 115, 109, 96, 77, 51.

1-Benzyl-1H-indole-3-carbonitrile (2m): yellow solid (59 mg, 85% yield); m.p. 66-67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.77 (m, 1H), 7.61 (s, 1H), 7.38-7.29 (m, 6H), 7.16-7.13 (m, 2H), 5.35 (s, 2H). IR (KBr) ν 3115, 3030, 2215, 1530, 1464, 1173, 1013 cm^{-1}. MS (EI) m/z: 232 (M^+), 216, 204, 191, 176, 102, 91, 65, 39.[10a]

1-Benzyl-5-fluoro-1H-indole-3-carbonitrile (2n): deep yellow oil (42 mg, 56% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.43 (dd, J = 8.4, 2.4 Hz, 1H), 7.39-7.34 (m, 3H), 7.29-7.27 (m, 1H), 7.15-7.13 (m, 2H), 7.04 (td, J = 12, 2.4 Hz, 1H), 5.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (d, $J_{C\text{-}F}$ = 238.3 Hz), 136.5, 135.1, 132.4, 129.4, 128.9 (d, $J_{C\text{-}F}$ = 7.4 Hz), 127.3, 115.6, 113.0 (d, $J_{C\text{-}F}$ = 26.3 Hz), 112.3, 112.2, 105.4 (d, $J_{C\text{-}F}$ = 24.7 Hz), 86.5 (d, $J_{C\text{-}F}$ = 4 Hz), 51.5. IR (KBr) ν 2215, 1528, 1540, 1485, 1392, 1183, 900, 703 cm^{-1}. HRMS (ESI) Calcd for ($C_{16}H_{11}N_2F$ + Na^+): 273.0804, found: 273.0810.

1-Methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (2o): pale yellow solid (38 mg, 80% yield); m.p. 87-88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, J = 4.8, 1.6 Hz, 1H), 8.08 (dd, J = 7.6, 1.2 Hz, 1H), 7.74 (s, 1H), 7.28-7.25 (m, 1H), 3.96 (s, 3H). IR (KBr) ν 3117, 2221, 1685, 1602, 1533, 1451, 1412, 1304, 1150, 772 cm^{-1}. MS (EI) m/z: 157 (M^+), 156, 129, 102, 88, 79, 64, 51, 28, 13.[10a]

Acknowledgments

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

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