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Cu-Catalyzed Cyanation of Indoles with Acetonitrile as a Cyano Source

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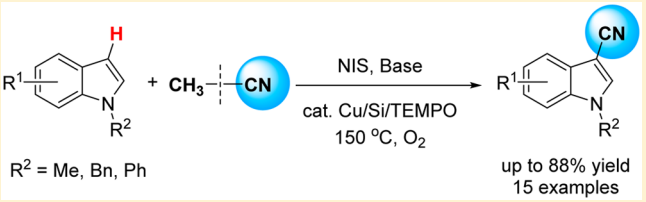
Supporting Information

ABSTRACT: Cu-catalyzed cyanation of indoles with acetonitrile for the synthesis of 3-cyanoindoles has been developed. The 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 a sequential iodination/cyanation process in one pot. This reaction furnishes 3-cyanoindoles in moderate to good yields and tolerates a series of functional groups. Moreover, low-cost copper catalysts and hazardless acetonitrile as a cyano source feature the practicability of this reaction.



Indole nitriles display wide 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 to a broad range of functional groups, for example, aldehydes, amines, amidines, tetrazoles, amides, and their carboxyl derivatives.[3]

Significant progress has been made in the the syntheses 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) multistep organic transformation.[8] Despite these advances, simple and straightforward access to 3-cyanoindoles remains desirable.

Because of the attraction of a direct C−H functionalization protocol that avoids the need for prefunctionalization of substrates, the development of transition metal-catalyzed C−H activation has witnessed stupendous growing in the past few 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 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 limits its applicability. Recently, the investigation of combined cyano sources as an alternative strategy has attracted considerable attention, and significant progress has been made in this field.[10a−c,11a,13]

Acetonitrile is a common solvent that features readily available, inexpensive, abundant, and hazardless properties.[14] In connection with our ongoing project on the cleavage of acetonitrile, we have recently determined that unactivated acetonitrile can serve as an attractive cyano source via copper-catalyzed C−CN bond cleavage under a Cu/Si or Cu/Si/TEMPO system.[15] The Li and Zhu groups discovered that a Cu/Ag system is also suitable for acetonitrile C−CN bond cleavage.[16] Notably, we found that the Cu/Si system for the C−H cyanation of indoles exclusively occurred at the 2-position of indoles with acetonitrile to yield 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 the common solvent acetonitrile as the cyano source. Herein, we report catalytic tandem cyanation of indoles with acetonitrile as a cyano source under a 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 the CN^+ cation.[15] Therefore, we envisioned the sequential iodination/cyanation process for the cyanation of indoles. A series of parameters, such as

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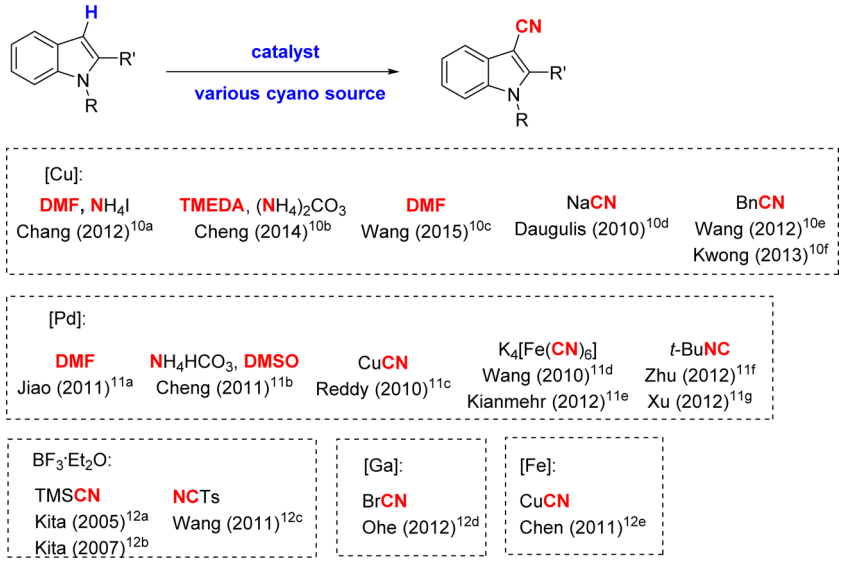
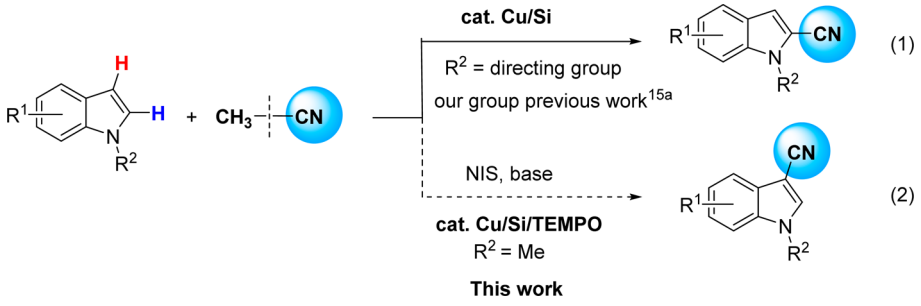
Scheme 1. Synthesis of 3-Cyanoindoles via C−H Cyanation



Scheme 2. Cyanation of Indoles with Acetonitrile



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 h; the generated indole iodide was able to undergo catalytic cyanation with acetonitrile promoted by $Cu(OAc)_2$/1,10-phen (20 mol %) at 150 °C in one pot, giving the desired 3-cyanoindoles **2a** in 48% yield (Table 1, entry 2). To increase the solubility of KOH in acetonitrile, a trace amount of water (2.5 v%) was added to 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 a 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, we next examined a series of bases (entries 7−13). The observation revealed that *t*-BuOLi is slightly better than KOH and 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 at one time and then directly heated to 150 °C, achievement of one-pot tandem iodination/cyanation was observed, smoothly providing 3-cyanoindole in 81% yield (entry 13).

With the optimal conditions in hand, the scope and limitations for the cyanation of indoles was explored. As illustrated in Table 2, we found that both electron-rich and -deficient substituents on indole rings could be well-tolerated 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 indoles. For example, substrates bearing MeO (**1b**) and Me (**1c**) groups gave the desired 3-cyanoindoles **2b** and **2c** in 67−70% yields, respectively. The reactions of substrates **1d** and **1e** containing halogen atoms with acetonitrile performed smoothly to yield expected 3-cyanoindoles **2d** and **2e** in high yields (for F, 88% yield; for Cl, 79% yield), respectively, 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 undergoes cyanation within 5 days to form the corresponding 3-cyanoindole **2k** in 78% yield. By changing substitutents on the nitrogen atom, we found that 1*H*-indole with free NH did not undergo this reaction, whereas substrates with phenyl **1l** and benzyl groups **1m** and **1n** on the nitrogen atom led to the cyanation process. Interestingly, this Cu-catalyzed TEMPO system was also suitable for *N*-methyl-1*H*-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.

On the basis of our mechanistic studies regarding the cyanation of simple arenes and boronic acids reported by our

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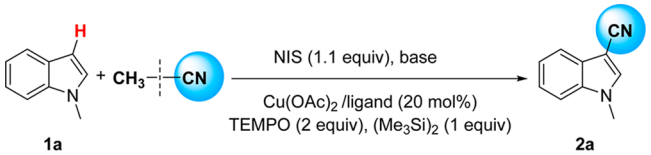
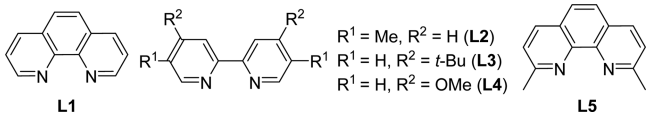
Table 1. Optimization of the Synthesis of 3-Cyanoindoles with Acetonitrile[a]



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 h, and it was then heated at 150 °C. [b]Isolated yield. [c]H_2O (2.5 v%, 30 uL). [d]Reaction was directly heated to 150 °C without adding water.

group,[15] a proposed reaction pathway was developed and is displayed in Scheme 3. Acetonitrile first reacts with TEMPO under the [Cu]/$(Me_3Si)_2$ system to release the cyanide anion by C−CN cleavage. The cyanide anion then takes part in the cyanation of 3-iodoindole **3**, starting from the iodination of indole **1** with NIS to yield desired 3-cyanoindole **2**.

In conclusion, Cu-catalyzed cyanation of indoles with acetonitrile has been discovered. This C−H functionalization of indoles involves sequential iodination/cyanation in one pot. The Cu/TEMPO/$(Me_3Si)_2$ system displays efficient activity for the cyanation of indoles and acetonitrile C−CN cleavage, giving the corresponding 3-cyanoindole 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 catalysts and bound 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 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 to the tube. The reaction was stirred at 150 °C 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). ^{1}H 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); mp 105−106 °C. ^{1}H 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). ^{1}H 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); mp 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); mp 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); mp 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); mp 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); mp 160−161 °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); mp 202−203 °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,

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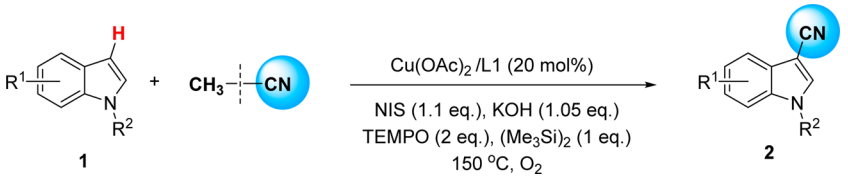
Table 2. Cu-Catalyzed Cyanation of Indoles with Acetonitrile[a]



2a, 81% (48 h) **2b**, 70% (45 h) **2c**, 67% (45 h) **2d**, 88% (45 h)

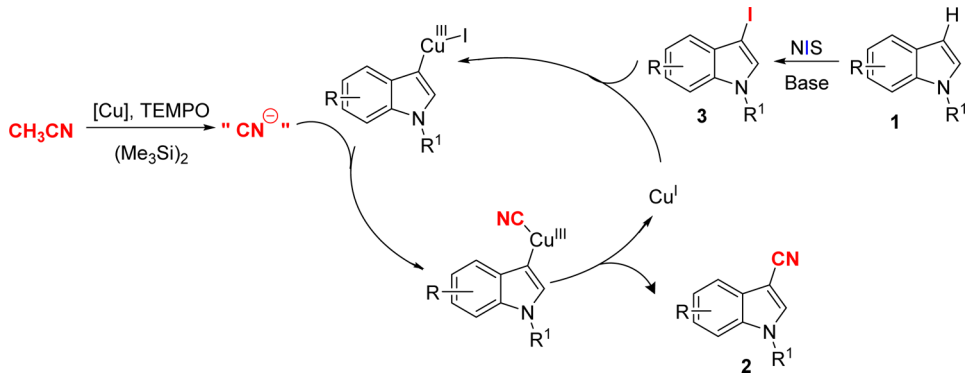
2e, 79% (48 h) **2f**, 37% (4 d) **2g**, 38% (4 d) **2h**, 37% (34 h)

2i, 37% (4 d) **2j**, 61% (2 d) **2k**, 73% (5 d) **2l**, 71% (2 d)

2m, 85% (3.5 d) **2n**, 56% (4 d) **2o**, 80% (46 h)

[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. Isolated yield.

Scheme 3. Proposed Reaction Pathway



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); mp 102−103 °C. ^1H 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); mp 104−105 °C. ^1H 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); mp 115−116 °C. ^1H 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); mp 66−67 °C. ^1H 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

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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). ^1H 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-F} = 238.3 Hz), 136.5, 135.1, 132.4, 129.4, 128.9 (d, J_{C-F} = 7.4 Hz), 127.3, 115.6, 113.0 (d, J_{C-F} = 26.3 Hz), 112.3, 112.2, 105.4 (d, J_{C-F} = 24.7 Hz), 86.5 (d, J_{C-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); mp 87−88 °C. ^1H 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]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01419.

Copies of ^1H NMR and ^{13}C NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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