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Cyanation of indoles with benzyl cyanide as the cyanide anion surrogate

Lianpeng Zhang, Qiaodong Wen, Jisong Jin, Chen Wang, Ping Lu *, Yanguang Wang *

Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China

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ABSTRACT

A copper-mediated direct cyanation of indoles with benzyl cyanide as the cyanide anion surrogate has been achieved. The cascade reaction furnished 3-cyanoindoles under mild reaction conditions in good to excellent yields with various functional groups tolerance.

1. Introduction

The importance of indole derivatives comes from their unique presence in natural products and pharmaceutical compounds. Among this field, 3-cyanoindoles particularly functioned as the key intermediates in the preparations of the most fascinating indole containing compounds. For instance, based on the versatile transformations of cyano group, they are useful in the synthesis of indolyl 1,2,4-triazoles[1] and 3,5-bis(indolyl)-1,2,4-thiadiazoles[2] as potent and selective anticancer agents, indole oxadiazoles as 5-HT3 antagonists,[3] and oxadiazole-5-carboxamide as inhibitors of glycogen-synthase-kinase-3 (GSK-3).[4] Beyond of these, modification of the N–H bond of 3-cyanoindoles also leads to a great amount of indole containing compounds with special bioactivities, such as indole-3-carbinol analogues,[5] oncrasin-1 analogues as inhibitors of the *C*-terminal domain of RNA polymerase II,[6] 1*H*-benzylindole derivatives as HIV-integrase inhibitors,[7] and indole-fused piperazinones and piperazines acting as antagonists of the histamine 3 (H3) receptor.[8] Further, it is noticeable that 3-cyanoindoles play a key role in the construction of tremendous natural products, such as strychnos alkaloids.[9] Therefore, the development of new methods leading to simple and rapid introduction of cyano group onto the 3-position of indole remains a challenge in the organic synthesis.

Traditional methods for the preparation of 3-cyanoindoles include two strategies. One is related to the 1C chemistry in which the cyano group of 3-cyanoindole derives from the relevant aldehyde,[10] aldoximine,[11] hydroxymethyl,[12] and ester.[13] Another one is the direct installation of cyano group through activation of C–H bond of 3-hydroindole or C–X bond of 3-haloindole, which is catalyzed by transition metals. Among these advance methods, cyano source can be a single component, such as MCN (with extremely toxic),[14] $K_2Fe(CN)_4$ (with solubility obstacle),[15] acetone cyanohydrin (with stability problem),[16] malononitrile,[17] TMSCN,[18] nitromethane,[19a] DMF[19b] and so on. Combinations of DMF+NH_3,[20] DMSO+NH_4HCO_3,[21] and DMF+NH_4HCO_3,[22] providing 'C' and 'N', respectively, can also be efficiently used for cyanation of Ar–H or Ar–X.

Encouraged by our previous works on benzyl cyanide as an operator-benign cyanation reagent that could be used for palladium-catalyzed cyanation of Ar–X,[23] and copper-catalyzed cyanation of Ar–H with directing group,[24] we were interested in exploring the cyanation of electron-rich aromatics with benzyl cyanide through C–H bond activation without directing group. We herein report the detail of this effort.

2. Results and discussion

In our primary investigation, indole was selected as the substrate and tested. As we expected, 3-cyanoindole (**3a**) was isolated in 75% yield when indole (**1a**) reacted with 2 equiv of benzyl cyanide (**2a**) in the presence of 2 equiv of CuI under air in DMF at 100 °C for 34 h (Scheme 1). With the above result, we optimized the reaction conditions (Table 1). By screening the copper sources, CuI presented the best among CuI, CuBr, and CuCl (Table 1, entries 1–3). Other Cu(I) source, such as Cu_2O, provided only a detectable product although

* Corresponding authors. Tel./fax: +86 571 87952543; e-mail addresses: pinglu@zju.edu.cn (P. Lu), orgwyg@zju.edu.cn (Y. Wang).

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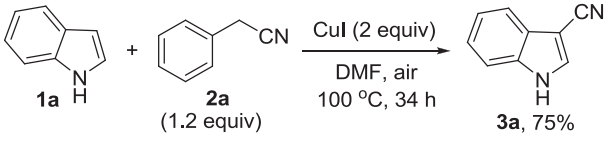
indole was completely consumed after 34 h (Table 1, entry 4). Cu(II) did not work for this transformation (Table 1, entries 5 and 6). By screening the solvents, DMF was found to be the optimal among polar aprotic solvents, such as DMF, DMAc, DMSO, HMPA, and NMP (Table 1, entries 7–10). Acetonitrile, toluene, *p*-xylene, and 1,4-dioxane did not work for this reaction with the recovery of indole (Table 1, entries 11–14). By decreasing the amount of CuI to 1.2 equiv, 80% yield of **3a** was observed (Table 1, entry 15). Further decreasing the amount of CuI to 1 equiv, indole was consumed completely after reaction and **3a** was isolated in 70% yield (Table 1, entry 16). When the amount of CuI dropped to 0.5 equiv, yield of **3a** was decreased to 36% with a 52% recovery of indole (Table 1, entry 17). When the reaction was carried out with the stoichiometric amount of iodine and catalytic amount of CuI, only trace amount of **3a** could be detected by TLC (Table 1, entry 18). The optimal amount of benzyl cyanide was found to be 1.2 equiv (Table 1, entries 15 and 17–19). Finally the optimal reaction temperature and reaction time were selected to be 100 °C and 34 h (Table 1, entries 15 and 20–23). When the reaction was conducted under nitrogen, no desired product was detected with the recovery of indole (Table 1, entry 24). When the reaction was carried out without benzyl cyanide, 3-formylindole and indolo[2,1-*b*]quinazoline-6,12-dione[25] were isolated in 16% and 46% yields, respectively (Scheme 2).



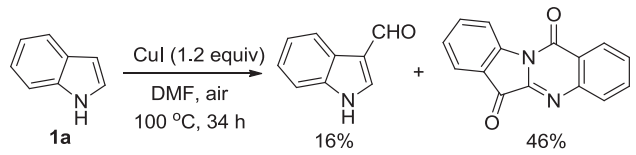
Scheme 1. Cu-catalyzed cyanation of indole with benzyl cyanide.

Table 1
Optimization of the reaction conditions[a]

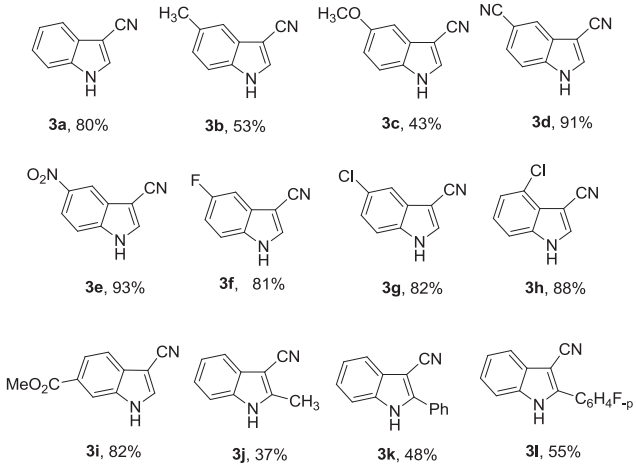
Entry	Catalyst (equiv)	Solvent	Benzyl cyanide (equiv)	Temp (°C)	Time (h)	Yield[b] (%)
1	CuI (2.0)	DMF	1.2	100	34	75
2	CuBr (2.0)	DMF	1.2	100	34	33
3	CuCl (2.0)	DMF	1.2	100	34	27
4	Cu_2O (2.0)	DMF	1.2	100	34	Trace
5	$CuBr_2$ (2.0)	DMF	1.2	100	34	0
6	$Cu(OAc)_2$ (2.0)	DMF	1.2	100	34	0
7	CuI (2.0)	DMAc	1.2	100	34	59
8	CuI (2.0)	DMSO	1.2	100	34	54
9	CuI (2.0)	HMPA	1.2	100	34	35
10	CuI (2.0)	NMP	1.2	100	34	30
11	CuI (2.0)	CH_3CN	1.2	81	34	0
12	CuI (2.0)	Toluene	1.2	100	34	0
13	CuI (2.0)	*p*-Xylene	1.2	100	34	0
14	CuI (2.0)	1,4-Dioxane	1.2	100	34	0
15	CuI (1.2)	DMF	1.2	100	34	80
16	CuI (1.0)	DMF	1.2	100	34	70
17	CuI (0.5)	DMF	1.2	100	34	36
18	CuI (0.5)+I_2 (1.0)	DMF	1.2	100	34	Trace
19	CuI (1.2)	DMF	1.5	100	34	80
20	CuI (1.2)	DMF	1.0	100	34	75
21	CuI (1.2)	DMF	1.2	120	34	75
22	CuI (1.2)	DMF	1.2	80	34	45
23	CuI (1.2)	DMF	1.2	100	24	62
24	CuI (1.2)	DMF	1.2	100	36	80
25	CuI (1.2)	DMF	1.2	100	34	0[c]

[a] Reaction conditions: **1a** (0.5 mmol), solvent (3 mL), air.
[b] Isolated yield.
[c] Under N_2.

With the optimized reaction conditions in hand, we tested the scope of indoles (Scheme 3). A variety of functional groups tolerated this reaction. Indoles with substituent on 5-position were firstly investigated. With the electron-donating nature of 5-substituent, **3b** and **3c** were obtained in relatively lower yields. Conversely, substituents with electron-withdrawing property benefitted the reaction. Thus, **3c**, **3d**, **3e**, and **3f** were obtained in good to excellent yields (81–93%). By altering 5-chloroindole to 4-chloroindole, a higher yield of **3h** was observed. With the ester group on 6-position of indole, **3i** was isolated in 82% yield. It was noticeable that cyanation still occurred smoothly on 3-position of 2-substituted indoles. Beyond of these, this transformation could be operated in gram scale. For example, 1.13 g (7 mmol) of 5-nitroindole was cyanated to give 1.15 g of 5-nitroindole-3-carbonitrile (**3e**) in 88% yield.



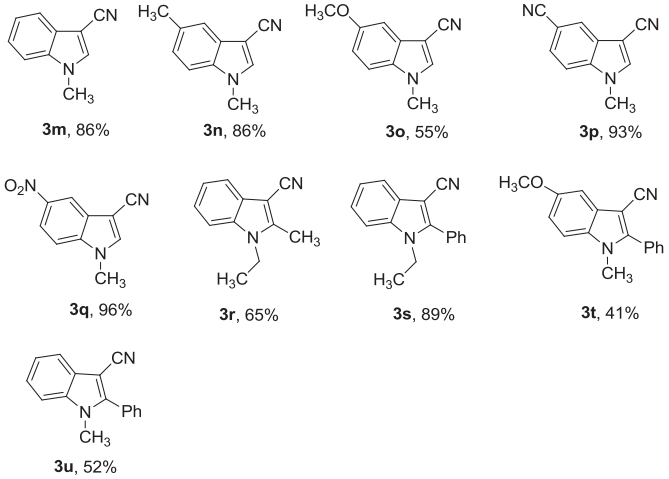
Scheme 2. Reaction of indole without benzyl cyanide.



Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), CuI (0.6 mmol), air, 100 °C, DMF (3 mL), 34 h.

Scheme 3. Structures and yields of prepared 3-cyanoindoles.

When *N*-alkyl indoles were used as the substrates, yields of the cyanation products were significantly improved, especially in the case of 1-ethyl-2-phenyl-1*H*-indole (Scheme 4). From the pair of



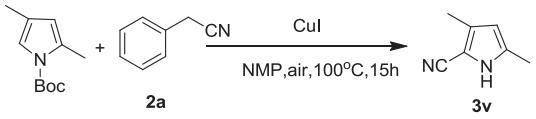
Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), CuI (0.6 mmol), air, 100 °C, DMF (3 mL), 34 h.

Scheme 4. Cyanation products of *N*-alkyl indoles.

the **3t** and **3u**, a preliminary conclusion could be made that the impact of the electronic effect on the reaction efficiency is larger than that of the steric effect.

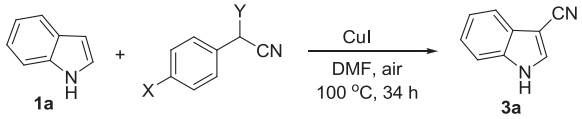
We also tested *N*-phenyl, *N*-acetyl, and *N*-tosyl indoles. All of these three substrates did not participate in the reaction with the quantitative recoveries of the starting materials.

Because of the importance of pyrrole in medicinal and material science, we tried the pyrrole as substrates. Unfortunately, no isolable cyanated products were obtained although pyrrole and 2,4-dimethylpyrrole consumed completely in NMP at 100 °C for 15 h. By decreasing the electron density of pyrrole, both *N*-tosylpyrrole and *N*-tosyl 2,4-dimethylpyrrole did not work with the recoveries of starting materials. *N*-Boc pyrrole could react, but no isolable product was obtained. To our delight, *N*-Boc 2,4-dimethylpyrrole could react to afford 5-cyano-2,4-dimethyl-pyrrole (**3v**)[26] in 94% yield (Scheme 5).



Scheme 5. Cyanation of *N*-Boc-2,4-dimethylpyrrole.

In order to have a good insight into the mechanism, we tested other cyanation reagents **2b**–**f** (Scheme 6). Substituted benzyl cyanides, either with electron-donating (**2b**) or with electron-withdrawing (**2c**), provided **3a** in lower yields than the naked benzyl cyanide (**2a**) did. The nature of the electron-withdrawing group on the para position of benzyl cyanide is beneficial to the copper-catalyzed benzylic C–H aerobic activation, but retarded the release of cyanide anion from cyanohydrin, which was obtained in situ from the oxidation of benzyl cyanides in the presence of copper. One support to this hypothesis is that **2e** could give **3a** in 81% yield. However, when benzaldehyde cyanohydrin (**2f**) was used as the surrogate of the cyanide anion, which should have the fastest rate of releasing cyanide anion in comparison with benzyl cyanides **2a**–**e** because the oxidation step from benzyl cyanide to **2f** was eliminated, **3a** was only isolated in 15% yield although indole was completely consumed after the reaction. Similarly, benzoyl cyanide provided **3a** in a trace amount. These might be ascribed to the relatively slow rate of the copper-catalyzed activation of C–H bond of indole. Therefore, it is obvious that balancing the rates of releasing cyanide anion and activating the indole C–H bond is critical to a successful transformation.



2a: X = H, Y = H
2b: X = OMe, Y = H
2c: X = NO_2, Y = H
2d: X = F, Y = H
2e: X = H, Y = Me
2f: X = H, Y = OH

X = H, Y = H, 80%
X = OMe, Y = H, 71%
X = NO_2, Y = H, 43%
X = F, Y = H, 22%
X = H, Y = Me, 81%
X = H, Y = OH, 15%

Scheme 6. Substituent effect of benzyl cyanides.

By tracking the reaction between **1a** and **2a** with gas chromatography, we observed the formation and disappear of 3-iodoindole (**4**) during the reaction process. As the time occurred about 12 h, about 70% of **4** was detected, while both indole and **3a** showed 15% only. The amount of **3a** kept going as the reaction proceeding and finally reached a maximum at 34 h (Fig. 1). **4** was isolated and characterized by its spectroscopy (see ESD). Under the established reaction conditions, **4** could be converted to **3a** with 82% yield.

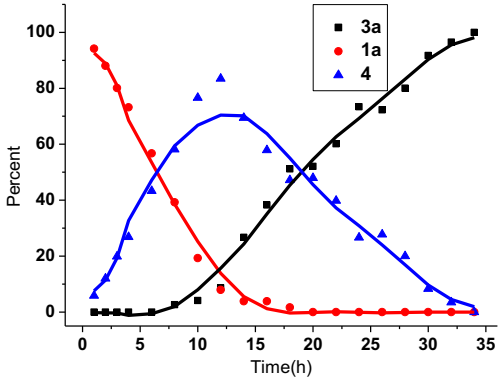
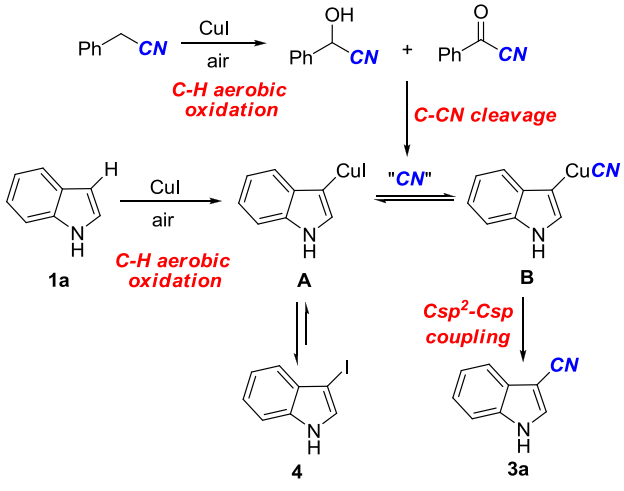


Fig. 1. Reaction profile of **1a** and **2a** (recorded by GC).

Based on these results, we proposed a possible mechanism for the formation of **3a** (Scheme 7). As we presented in our previous paper,[24] CN^- is released from benzaldehyde cyanohydrin and/or benzoyl cyanide in situ generated via a copper-catalyzed aerobic C–H oxidation of benzyl cyanide. Existence of free CN^- was indicated by the stripe test.[20] Meanwhile, C–H bond of indole is activated in the presence of Cu(I) and air that formed the key intermediated A. If reductive elimination of A occurs directly, 3-iodoindole is obtained. If A is further converted into B through anion exchange, followed by reductive elimination, **3a** is formed. It is interesting to note that formation of **4** is kinetically favored and it can be detected and isolated during the reaction, while formation of **3a** is thermodynamically favored.



Scheme 7. Possible mechanism for the formation of **3a**.

3. Conclusion

In conclusion, we developed a convenient method for the synthesis of 3-cyanoindoles from indoles using benzyl cyanide as

cyanation reagent. The cascade reaction involves a copper-catalyzed aerobic C–H oxidation, a C–CN bond cleavage, and a copper-catalyzed aerobic oxidative C–H functionalization without directing group. The cyanation reagent is environmentally benign and the reaction is palladium-free and ligand-free. Beyond of these advantageous, the reaction could be operated in gram scale. Further exploration of the copper-catalyzed cyanations and their applications are undergoing.

4. Experimental

4.1. General

Unless stated otherwise, reactions were conducted in flame-dried glassware using anhydrous solvents (dried by Molecular sieves 4 Å). Commercially available reagents and solvents were used as received. Flash column chromatography was performed using 200–300 mesh silica gel. Visualization on TLC was achieved by the use of UV light (254 nm). NMR spectra were obtained at 400 or 500 MHz for ^{1}H NMR and 100 or 125 MHz for ^{13}C NMR. Chemical shifts were quoted relative to tetramethylsilane (TMS) as internal standard and reported in parts per million. The following abbreviations were used to describe peak splitting patterns when appropriate: s=singlet, d=doublet, t=triplet, m=multiple. High-resolution mass spectra (HRMS) were recorded using TOF-EI.

4.2. General procedure for the synthesis of 3

A mixture of CuI (0.6 mmol), indoles (0.5 mmol) and benzyl cyanide (0.6 mmol) in DMF (3.0 mL) was stirred under air at 100 °C for 34 h and then cooled to room temperature. After the reaction mixture was quenched with 10 mL of water, it was extracted with DCM (3×10 mL). The combined organic layers were washed with the saturated aqueous solution of sodium chloride and dried over $MgSO_4$. The solution was concentrated under reduced pressure and purified by column chromatography to afford 3-cyanoindoles.

4.3. Characterization data

*4.3.1. 1H-Indole-3-carbonitrile (**3a**).*[27] Yield 80%; yellow solid; mp 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.78 (d, J=8.2 Hz, 1H), 7.76 (s, 1H), 7.48 (d, J=8.2 Hz, 1H), 7.39–7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 132.0, 127.1, 124.4, 122.5, 119.8, 116.0, 112.2, 87.5.

*4.3.2. 5-Methyl-1H-indole-3-carbonitrile (**3b**).* Yield 53%; white solid; mp 132–134 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.12 (s, 1H), 8.21 (s, 1H), 7.47 (d, J=8.4 Hz, 2H), 7.13(d, J=8.4 Hz, 1H), 2.45(s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 135.2, 134.5, 131.7, 128.0, 125.9, 118.9, 117.5, 113.6, 84.6, 22.0.

*4.3.3. 5-Methoxy-1H-indole-3-carbonitrile (**3c**).*[28] Yield 43%; white solid; mp 154–156 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.10 (s, 1H), 8.20 (s, 1H), 7.48 (d, J=8.8 Hz, 1H), 7.12 (s, 1H), 6.94 (d, J=8.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 156.2, 135.3, 131.0, 128.5, 117.6, 114.8, 100.7, 84.9, 56.3.

*4.3.4. 1H-Indole-3,5-dicarbonitrile (**3d**).* Yield 91%; yellow solid; mp 257–259 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.73 (s, 1H), 8.52 (s, 1H), 8.24 (s, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.69 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 138.3, 138.0, 127.3, 127.2, 125.0, 120.6, 116.1, 115.3, 105.1, 86.4.

*4.3.5. 5-Nitro-1H-indole-3-carbonitrile (**3e**).* Yield 93%; yellow solid; mp 186–188 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.86 (s, 1H), 8.56 (s, 1H), 8.49 (s, 1H), 8.17 (d, J=9.0 Hz, 1H), 7.77 (d, J=9.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 143.5, 139.4, 139.3, 127.0, 119.6, 116.0, 115.9, 114.8, 87.8.

*4.3.6. 5-Fluoro-1H-indole-3-carbonitrile (**3f**).*[29] Yield 81%; yellow solid; mp 151–153 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.34 (s, 1H), 8.35 (s, 1H), 7.60 (dd, J=8.9 Hz, J_{H-F}=4.6 Hz, 1H), 7.45 (dd, J=9.2 Hz, J_{H-F}=2.2 Hz, 1H), 7.18 (dd, J=9.2 Hz, J_{H-F}=2.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 160.4 (d, J_{C-F}=235 Hz), 137.1, 132.8, 128.2 (d, J_{C-F}=11 Hz), 116.8, 115.3 (d, J_{C-F}=9 Hz), 112.9 (d, J_{C-F}=26 Hz), 104.6 (d, J_{C-F}=24 Hz), 85.5.

*4.3.7. 5-Chloro-1H-indole-3-carbonitrile (**3g**).*[30] Yield 82%; white solid; mp 165–167 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.42 (s, 1H), 8.36 (s, 1H), 7.70 (s, 1H), 7.61 (d, J=8.8 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 137.0, 134.7, 128.8, 127.5, 124.5, 118.7, 116.7, 115.6, 85.1.

*4.3.8. 4-Chloro-1H-indole-3-carbonitrile (**3h**).*[31] Yield 88%; yellow solid; mp 223–225 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.55 (s, 1H), 8.41 (s, 1H), 7.65–7.40 (m, 1H), 7.30 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 137.6, 137.4, 125.3, 125.2, 124.5, 122.8, 117.2, 113.2, 84.6.

*4.3.9. Methyl 3-cyano-1H-indole-6-carboxylate (**3i**).* Yield 82%; white solid; mp 240–242 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 8.51 (s, 1H), 8.20 (s, 1H), 7.85 (d, J=8.4 Hz, 1H), 7.77 (d, J=8.4 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 167.5, 138.6, 135.6, 131.3, 125.5, 123.1, 119.5, 116.7, 115.7, 85.8, 53.1.

*4.3.10. 2-Methyl-1H-indole-3-carbonitrile (**3j**).*[32] Yield 37%; yellow solid; mp 208–210 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.12 (s, 1H), 7.55 (d, J=7.6 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H), 7.27–7.17 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 146.9, 135.7, 128.1, 123.6, 122.3, 118.6, 117.4, 113.0, 83.7, 13.5.

*4.3.11. 2-Phenyl-1H-indole-3-carbonitrile (**3k**).*[33] Yield 48%; white solid; mp 245–247 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.65 (s, 1H), 8.03 (d, J=7.6 Hz, 2H), 7.68 (m, 3H), 7.59 (d, J=7.4 Hz, 2H), 7.41–7.26 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 145.7, 136.5, 130.9, 130.3, 130.3, 129.3, 128.0, 124.9, 123.0, 119.4, 118.0, 113.6, 82.4.

*4.3.12. 2-(4-Fluorophenyl)-1H-indole-3-carbonitrile (**3l**).*[34] Yield 55%; white solid; mp 239–241 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.64 (s, 1H), 8.06 (dd, J=8.4 Hz, J_{H-F}=5.6 Hz, 2H), 7.68 (d, J=7.8 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.52 (dd, J_1=J_2=8.8 Hz, 2H), 7.32 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 165.1 (d, J_{C-F}=247 Hz), 144.8, 136.5, 130.4 (d, J_{C-F}=8 Hz), 129.2, 126.9 (d, J_{C-F}=3 Hz), 124.9, 123.0, 119.3, 117.9, 117.5 (d, J_{C-F}=21 Hz), 113.6, 82.4.

*4.3.13. 1-Methyl-1H-indole-3-carbonitrile (**3m**).*[15b] Yield 86%; white solid; mp 53–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J=7.8 Hz, 1H), 7.48 (s, 1H), 7.38–7.30 (m, 2H), 7.27 (d, J=11.2 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.6, 127.6, 123.7, 122.0, 119.5, 116.0, 110.4, 85.0, 33.5.

*4.3.14. 1,5-Dimethyl-1H-indole-3-carbonitrile (**3n**).*[21] Yield 86%; yellow solid; mp 80–82 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.27 (s, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.53 (s, 1H), 7.28 (d, J=8.4 Hz, 1H), 3.95 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 138.3, 135.2, 132.1, 128.3, 125.9, 119.1, 117.1, 112.1, 83.4, 34.3, 21.9.

*4.3.15. 5-Methoxy-1-methyl-1H-indole-3-carbonitrile (**3o**).*[15b] Yield 55%; yellow solid; mp 103–105 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.29 (s, 1H), 6.67 (d, J=8.8 Hz, 1H), 6.24 (s, 1H), 6.11 (d,

J=8.8 Hz, 1H), 2.98 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 156.5, 138.3, 131.8, 128.9, 117.2, 114.6, 113.3, 100.9, 83.6, 56.4, 34.4.

*4.3.16. 1-Methyl-1H-indole-3,5-dicarbonitrile (**3p**).*[21] Yield 93%; yellow solid; mp 163–165 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.57 (s, 1H), 7.28 (s, 1H), 6.95 (d, J=8.6 Hz, 1H), 6.83 (d, J=8.6 Hz, 1H), 3.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 141.4, 138.4, 127.5, 127.1, 125.1, 120.5, 115.8, 113.9, 105.3, 85.4, 34.7.

*4.3.17. 1-Methyl-5-nitro-1H-indole-3-carbonitrile (**3q**).*[21] Yield 96%; yellow solid; mp 159–160 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.62 (s, 1H), 7.51 (s, 1H), 7.27 (d, J=8.0 Hz, 1H), 6.95 (d, J=8.0 Hz, 1H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 143.6, 142.5, 139.7, 127.1, 119.4, 116.1, 115.5, 113.5, 86.7, 34.9.

*4.3.18. 1-Ethyl-2-methyl-1H-indole-3-carbonitrile (**3r**).*[15b] Yield 65%; brown solid; mp 89–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=7.2 Hz, 1H), 7.33 (d, J=7.6 Hz, 1H), 7.30–7.24 (m, 2H), 4.16 (q, J=7.3 Hz, 2H), 2.58 (s, 3H), 1.38 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 135.3, 127.3, 123.0, 121.9, 119.2, 116.8, 109.9, 85.0, 38.8, 15.0, 11.8.

*4.3.19. 1-Ethyl-2-phenyl-1H-indole-3-carbonitrile (**3s**).* Yield 89%; yellow solid; mp 108–110 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.77 (d, J=8.2 Hz, 1H), 7.72 (d, J=7.8 Hz, 1H), 7.65 (m, 5H), 7.42 (dd, J_1=J_2=7.6 Hz, 1H), 7.35 (dd, J_1=J2=7.4 Hz, 1H), 4.25 (q, J=7.2 Hz, 2H), 1.24 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 166.9, 142.9, 141.8, 138.9, 134.8, 131.3, 128.6, 127.3, 126.4, 118.7, 115.4, 114.8, 112.7, 86.1, 34.2, 26.6.

*4.3.20. 5-Methoxy-1-methyl-2-phenyl-1H-indole-3-carbonitrile (**3t**).* Yield 41%; canary yellow solid; mp 253–255 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.71 (d, J=7.4 Hz, 2H), 7.65 (m, 3H), 7.15 (s, 1H), 7.04 (d, J=8.8 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 156.7, 148.5, 132.5, 130.8, 130.7, 129.9, 129.4, 128.5, 117.5, 114.9, 113.7, 100.7, 84.4, 56.4, 32.8; HRMS (EI) calcd for $C_{17}H_{14}N_2O$: 262.1106 ([M]$^+$), found: 262.1111.

*4.3.21. 1-Methyl-2-phenyl-1H-indole-3-carbonitrile (**3u**).*[15b] Yield 52%; white solid; mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J=8.0 Hz, 1H), 7.59–7.50 (m, 5H), 7.42 (d, J=8.0 Hz, 1H), 7.37 (dd, J_1=J_2=8.0 Hz, 1H), 7.33 (dd, J_1=J_2=8.0 Hz, 1H), 3.76 (s, 3H); s^{13}C NMR (100 MHz, $CDCl_3$) δ 148.21, 136.97, 130.02, 129.96, 129.14, 128.85, 127.70, 124.00, 122.55, 119.67, 116.76, 110.64, 85.67, 31.85.

*4.3.22. 3,5-Dimethyl-1H-pyrrole-2-carbonitrile (**3v**).*[26] Yield 94%; white solid; mp 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 5.80 (s, 1H), 2.25 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 137.0, 133.9, 115.1, 98.5, 69.9, 14.8, 14.2.

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Supplementary data

General experimental procedures, optimization of reaction conditions, kinetic data and copies of ^{1}H and ^{13}C NMR spectra for all products. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.03.089. These data include MOL files and InChiKeys of the most important compounds described in this article.

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