Unexpected C2-Arylation of 1-(Pyridin-2-yl)indole-3-carboxaldehyde Mediated by Copper

Charlène Sagnes, Guy Fournet, Benoît Joseph*

Laboratoire de Chimie Organique 1, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, UMR-CNRS 5246, Université Claude Bernard - Lyon 1, Bâtiment Curien, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France
Fax +33(4)72431214; E-mail: benoit.joseph@univ-lyon1.fr

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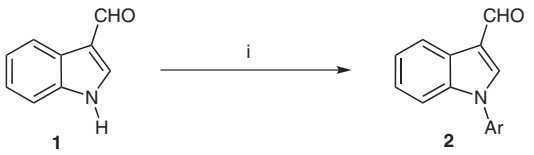
Abstract: The C2-arylation of 1-(pyridin-2-yl)indole-3-carboxaldehyde with aryl iodides was carried out in the presence of Cu_2O in basic medium. This simple and efficient method led to the preparation of 1,2-diarylindole derivatives.

Key words: indole, arylation, copper, pyridine

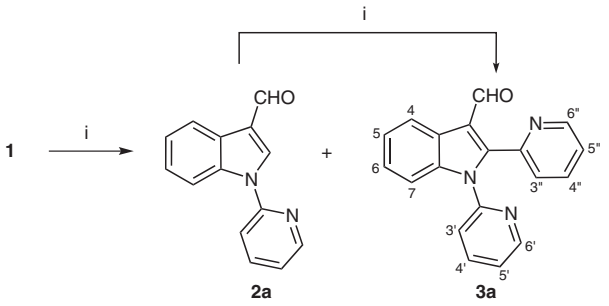
N-Arylindole derivatives are widely used as pharmaceuticals[1] or agrochimicals.[2] The transition-metal-catalyzed formation (copper or palladium) of C–N bond is the simplest way to reach these compounds.[3,4] Originally, the classical Ullmann reaction with aromatic amines required high temperature (140 °C or more) and stoichiometric amount of copper in the presence of a base in polar high-boiling-point solvent.[5] Since this time, milder conditions have been reported for the synthesis of *N*-arylindoles, involving a catalytic amount of copper and a large scope of ligands such as aliphatic diamines,[6] substituted 1,10-phenantroline,[7] amino acid (L-proline),[8] and different oximes or Schiff bases.[9] For our part, we became interested in the synthesis of *N*-arylindole-3-carboxaldehydes as starting material of potent serotoninergic ligands. The N-arylation reaction was performed in the presence of commercial indole-3-carboxaldehyde (**1**), Cu_2O (0.1 equiv), aryl iodide (2 equiv), and K_2CO_3 (2 equiv) in DMF at 153 °C for three days to afford N-arylated indoles **2** (Scheme 1). These reaction conditions were chosen in consideration of its advantages.[10,11] The method is easy to handle, the presence of a ligand is not required, and Cu_2O is described as an interesting copper source, due to its low cost and its insensitivity to light and air.

When 2-iodopyridine was used as the aryl halide, 1-(pyridin-2-yl)indole-3-carboxaldehyde (**2a**)[12] was obtained in 65% yield but biarylated product **3a**[13] was also isolated in 20% yield (Scheme 2). The preparation of **3a** from **1** was improved when 0.3 equivalent of Cu_2O was used. In this case, compound **2a** and **3a** were obtained in 16% and 41% yield, respectively.



Scheme 1 *Reagents and conditions*: (i) ArI (2 equiv), Cu_2O (0.1 equiv), K_2CO_3 (2 equiv), DMF, 153 °C, 3 d; Ar: Ph (74%), 3-pyridinyl (70%), 4-MeC_6H_4 (64%), 2-MeC_6H_4 (26%).

Similarly, the synthesis of **2a** was performed according to the literature methodology.[14] A solution of the indole-3-carboxaldehyde sodium salt was stirred with 2-fluoropyridine in DMF at 110 °C for 18 hours to afford **2a** in 86% yield. Then, compound **2a** was engaged in the arylation reaction (Cu_2O: 0.1 equiv, 2-iodopyridine: 2 equiv) to obtain the C2-arylated product **3a**.[15] We were pleased to isolate **3a** in 84% yield (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) 2-iodopyridine (2 equiv), Cu_2O (0.1 equiv), K_2CO_3 (2 equiv), DMF, 153 °C, 3 d. From **1**: **2a** (65%); **3a** (20%). From **2a**: **3a** (84%).

Over the past few years, intermolecular direct C2-arylation of indoles via cross-coupling of C2–H bond with aryl halide in the presence palladium[16] and rhodium[17] catalysts has received considerable attention. To our knowledge, one example of C2-arylation of indole with diaryliodine(III) reagents mediated by $Cu(OTf)_2$ was reported in a recent work.[18] For our part, we next explored the scope of this coupling reaction.

We investigated a first set of experiments using various indole-3-carboxaldehyde derivatives [1-methylindole-3-carboxaldehyde, 1-phenylindole-3-carboxaldehyde, 1-(pyridin-3-yl)indole-3-carboxaldehyde, and 1-(methylsulfonyl)indole-3-carboxaldehyde] in the presence of 0.1 equivalent of Cu_2O and 2 equivalents of 2-iodopyridine. The C2-arylated derivatives were isolated in low yield (11–23%). Thus, the presence of the 2-pyridinyl group at the N-position is crucial to promote the C2-arylation in fair yield.

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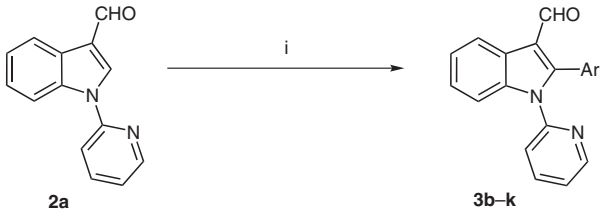
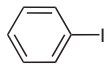
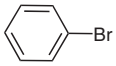
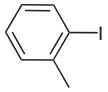
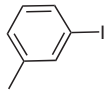
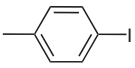
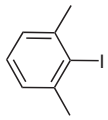
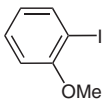
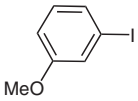
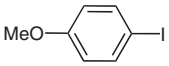
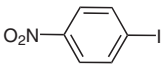
The model compound **2a** was then treated with various substituted aromatic halides to afford 2-aryl-1-(pyridin-2-yl)indole-3-carboxaldehydes **3b–k** in 4–88% yield (Scheme 3, Table 1).



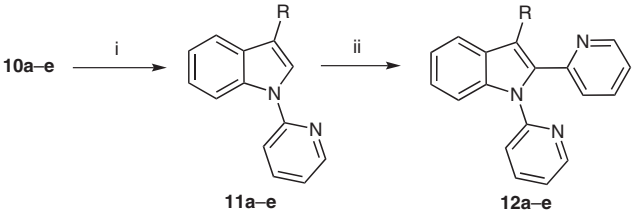
Scheme 3 *Reagents and conditions*: (i) ArX (2 equiv), Cu_2O (0.1 equiv), K_2CO_3 (2 equiv), DMF, 153 °C, 3 d (see Table 1).

Table 1 C2-Arylation of **2a**

Entry	ArX	Compd	Yield (%)
1		**3b**[19]	79
2		**3c**	4
3		**3d**	65
4		**3e**	84
5		**3f**[20]	77
6		**3g**	80
7		**3h**	71
8		**3i**	88
9		**3j**	60
10		**3k**	35

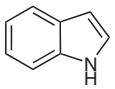
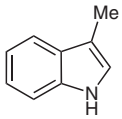
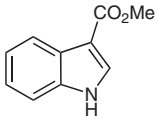
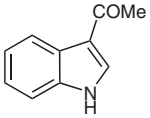
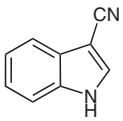
As shown in Table 1, higher yield was obtained when aryl iodide was used (compare entries 1 and 2). In our hands, bromobenzene gave poor yield. Electron-donating groups on *ortho*-, *meta*-, or *para*-position of the aryl iodide gave fair yields (entries 3–5 and 7–9). The use of bulky 2-iodo-1,3-dimethylbenzene (entry 6) led also to the desired with 80% yield. The presence of an electron-withdrawing group (entry 10) had a dramatic effect on the efficiency of the reaction. In this last example, compound **3k** was isolated in 35% yield.

In a second time, different functional groups at the C3-position of indole were tested (Scheme 4). N-arylation of indoles **10a–e** was first performed to give derivatives **11a–e** in good yield (Table 2).[14,21,22] The C2-arylation for **11a–c** did not occurr in the presence of Cu_2O and 2-iodopyridine in basic medium. For compounds **11d** and **11e**,[23] the same reaction afforded the compounds **12d** and **12e**[24] in 11–87% yield (Table 2). The arylation conditions require an aldehyde or nitrile group at the C3-position of indole.



Scheme 4 *Reagents and conditions*: (i) NaH (1.5 equiv), 2-fluoropyridine (2 equiv), DMF, 110 °C, 18 h; (ii) 2-iodopyridine (2 equiv), Cu_2O (0.1 equiv), K_2CO_3 (2 equiv), DMF, 153 °C, 3 d (see Table 2).

Table 2 Arylation of **10** and **11**

10	Yield (%) of **11**	Yield (%) of **12**
 **10a**	**11a**[21] 94	–[a]
 **10b**	**11b**[22] 96	–[a]
 **10c**	**11c** 60	–[a]
 **10d**	**11d** 93	**12d** 11
 **10e**	**11e** 98	**12e** 87

[a] No reaction.

In a last part, we applied this arylation reaction under microwave dielectric heating as an alternative to the classical conductive heating. The reaction was first performed

with **1**, 2-iodopyridine (1 or 3 equiv), and Cu_2O (0.1 or 0.3 equiv) in DMF at 153 °C or 240 °C for 1–2 hours (Table 3).[25] At 153 °C, compound **2a** was the lone derivative observed and was isolated in 94% yield. In the presence of 3 equivalents of 2-iodopyridine and 0.3 equivalent of Cu_2O at 240 °C for 2 hours, 1,2-diaryl compound **3a** was obtained in 70% yield. The same reaction conditions were applied to **2a** and **10e** (Table 3). Again, the best yields were obtained when 0.3 equivalent of Cu_2O were used (2 equiv of 2-iodopyridine at 240 °C for 1 h).

Table 3 Arylation of **1**, **2a**, and **10e** under Microwave Conditions

Compd	Cu_2O (equiv)	2-Iodopyridine (equiv)	Temp (°C)	Time (h)	Compd, yield (%)
1	0.1	2	153	1	**2a**, 94
1	0.1	2	240	1	**2a**, 58; **3a**, 36
1	0.1	2	240	2	**2a**, 47; **3a**, 37
1	0.3	2	240	1	**2a**, 40; **3a**, 47
1	0.3	2	240	2	**2a**, 31; **3a**, 57
1	0.3	3	240	2	**2a**, 17; **3a**, 70
2a	0.1	1	240	1	**3a**, 28
2a	0.1	2	240	1	**3a**, 61
2a	0.3	2	240	1	**3a**, 81
10e	0.1	2	240	1	**11e**, 45; **12e**, 42
10e	0.1	2	240	2	**11e**, 29; **12e**, 55
10e	0.3	2	240	1	**11e**, 17; **12e**, 71

In conclusion, the outcome of the C2-arylation of the indole core depends of the presence of a 2-pyridinyl group at the N-position and an aldehyde (or nitrile) group at C3. By this route, 1,2-diaryl-3-formylindoles have been prepared in one or two steps in good yields. Further applications are now under investigation.

Acknowledgment

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References and Notes

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(12) **Analytical Data of 1-(Pyridin-2-yl)-1*H*-indole-3-carboxaldehyde (2a)**
Mp 114–115 °C (MeOH). IR (KBr): 3101, 3050, 2821, 1667, 1649, 1593, 1579, 1539, 1471, 1455, 1444, 1224, 1128, 1083, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.43 (m, 3 H, H-5, H-5′, H-6), 7.64 (d, 1 H, *J* = 8.3 Hz, H-3′), 7.95 (td, 1 H, *J* = 1.9, 7.7 Hz, H-4′), 8.02–8.05 (m, 1 H, H-4 or H-7), 8.38 (s, 1 H, H-2), 8.38–8.41 (m, 1 H, H-4 or H-7), 8.64 (dd, 1 H, *J* = 1.3, 4.7 Hz, H-6′), 10.16 (s, 1 H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.8 (CH), 115.7 (CH), 120.5 (C), 122.2 (CH), 122.3 (CH), 123.8 (CH), 125.1 (CH), 126.3 (C), 136.2 (C), 137.0 (CH), 139.0 (CH), 149.4 (CH), 150.9 (C), 185.4 (CO). ESI-MS: *m/z* = 223 $[M + H]^+$. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.99; H, 4.32; N, 12.55.

(13) **Analytical Data of 1,2-Di(pyridin-2-yl)-1*H*-indole-3-carboxaldehyde (3a)**
Mp 127–128 °C (EtOAc–PE). IR (KBr): 3051, 3012, 2831, 1648, 1443, 1387, 1050, 754, 741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, 1 H, *J* = 7.9 Hz, H-3′ or H-3″), 7.27–7.44 (m, 5 H, H-3′ or H-3″, H-5, H-5′, H-5″, H-6), 7.54 (d, 1 H, *J* = 7,4 Hz, H-4 or H-7), 7.67–7.79 (m, 2 H, H-4′, H-4″), 8.53–8.60 (m, 3 H, H-4 or H-7, H-6′, H-6″), 10.18 (s, 1 H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.4 (CH), 117.7 (C), 122.1 (CH), 122.7 (CH), 123.1 (CH), 123.6 (CH), 124.0 (CH), 125.3 (CH), 125.4 (C), 126.8 (CH), 136.3 (CH), 137.4 (C), 138.4 (CH), 147.3 (C), 148.8 (C), 149.6 (CH), 149.9 (CH), 150.4 (C), 187.8 (CO). ESI-MS: *m/z* = 300 $[M + H]^+$. Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04. Found: C, 76.34; H, 4.43; N, 13.96.

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(15) **Typical Procedure**
In a sealed tube, a solution of **2a** (100 mg, 0.45 mmol, 1 equiv), Cu_2O (6.5 mg, 0.045 mmol, 0.1 equiv), 2-iodopyridine (101 μL, 0.90 mmol, 2 equiv), and K_2CO_3 (124 mg, 0.90 mmol, 2 equiv) in anhyd DMF (0.9 mL) was stirred at 153 °C for 3 d. The reaction was cooled to r.t., filtered through Celite, and the filtrate was concentrated in vacuo. The residue was diluted in EtOAc (20 mL). The organic layer was washed with a solution of 2.5% aq NH_4OH (2 × 20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude

product was purified by flash column chromatography (PE–EtOAc, 2:8 to 1:1) to provide **3a** (110 mg, 84%).

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(19) **Analytical Data of 2-Phenyl-1-(pyridin-2-yl)-1*H*-indole-3-carboxaldehyde (3b)**[26]
Mp 171–172 °C (EtOAc–PE). IR (KBr): 3065, 3043, 2836, 1652, 1466, 1454, 1384, 1225, 1082, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, 1 H, *J* = 7.9 Hz, H-3′), 7.30–7.43 (m, 8 H, H-5, H-5′, H-6, H_{arom}), 7.51 (d, 1 H, *J* = 7.5 Hz, H-4 or H-7), 7.68 (td, 1 H, *J* = 1.9, 8.0 Hz, H-4′), 8.50 (br d, 1 H, *J* = 6.9 Hz, H-4 or H-7), 8.65 (dd, 1 H, *J* = 1.3, 4.9 Hz, H-6′), 9.97 (s, 1 H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.6 (CH), 116.9 (C), 122.2 (CH), 122.4 (CH), 123.2 (CH), 123.9 (CH), 124.8 (CH), 125.5 (C), 128.5 (2 CH), 128.8 (C), 129.5 (CH), 131.1 (2 CH), 137.5 (C), 138.3 (CH), 149.6 (CH), 149.9 (C), 150.2 (C), 187.6 (CO). ESI-MS: *m/z* = 299 $[M + H]^+$. Anal. Calcd for $C_{20}H_{14}N_2O$: C 80.52; H, 4.73; N, 9.39. Found: C, 80.83; H, 4.85; N, 9.27.

(20) **Analytical Data of 1-(Pyridin-2-yl)-2-(4-methylphenyl)-1*H*-indole-3-carboxaldehyde (3f)**
Mp 206–207 °C (EtOAc–PE). IR (KBr): 3048, 2916, 2836, 1642, 1435, 1081, 747, 737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 6.92 (d, 1 H, *J* = 6.9 Hz, H-3′), 7.15 (d, 2 H, *J* = 8.0 Hz, H_{arom}), 7.26 (d, 2 H, *J* = 8.0 Hz, H_{arom}), 7.29–7.41 (m, 3 H, H-5, H-5′, H-6), 7.50 (dd, 1 H, *J* = 0.9, 7.4 Hz, H-4 or H-7), 7.68 (td, 1 H, *J* = 1.9, 7.7 Hz, H-4′), 8.48 (dd, 1 H, *J* = 1.1, 7.3 Hz, H-4 or H-7), 8.65 (dd, 1 H, *J* = 1.1, 4.9 Hz, H-6′), 9.95 (s, 1 H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 111.5 (CH), 116.7 (C), 122.1 (CH), 122.5 (CH), 123.1 (CH), 123.8 (CH), 124.7 (CH), 125.5 (C), 125.8 (C), 129.2 (2 CH), 131.0 (2 CH), 137.5 (C), 138.3 (CH), 139.7 (C), 149.6 (CH), 150.2 (C), 150.3 (C), 187.6 (CO). ESI-MS: *m/z* = 313 $[M + H]^+$. Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75, H, 5.16; N, 8.97. Found: C, 8.48; H, 4.97; N, 9.03.

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(23) **Analytical Data of 1-(Pyridin-2-yl)-1*H*-indole-3-carbonitrile (11e)**
Mp 150–151 °C (MeOH). IR (KBr): 3135, 3050, 2222, 1592, 1540, 1473, 1455, 1434, 1229, 1095, 735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.45 (m, 3 H, H-5, H-5′, H-6), 7.56 (d, 1 H, *J* = 8.1 Hz, H-3′), 7.83 (br d, 1 H, *J* = 7.5 Hz, H-4 or H-7), 7.93 (td, 1 H, *J* = 1.9, 7.5 Hz, H-4′), 8.10 (br d, 1 H, *J* = 7.1 Hz, H-4 or H-7), 8.23 (s, 1 H, H-2), 8.63 (dd, 1 H, *J* = 1.1, 4.9 Hz, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 89.8 (C), 113.4 (CH), 115.3 (C), 115.6 (CH), 120.0 (CH), 122.3 (CH), 123.4 (CH), 125.2 (CH), 128.7 (C), 133.3 (CH), 134.4 (C), 139.1 (CH), 149.5 (CH), 150.7 (C). ESI-MS: *m/z* = 220 $[M + H]^+$. Anal. Calcd for $C_{14}H_9N_3$: C, 76.70, H, 4.14, N, 19.17. Found: C, 76.72; H, 4.08; N, 19.25.

(24) **Analytical Data of 1,2-Di(pyridin-2-yl)-1*H*-indole-3-carbonitrile (11d)**
Mp 128–129 °C (CH_2Cl_2–PE). IR (KBr): 3065, 2213, 1589, 1569, 1467, 1448, 1435, 1393, 1225, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.41 (m, 5 H, H-3′ or H-3″, H-5, H-5′, H-5″, H-6), 7.50–7.53 (m, 1 H, H-4 or H-7), 7.82–7.89 (m, 4 H, H-3′ or H-3″, H-4 or H-7, H-4′, H-4″), 8.44 (br d, 1 H, *J* = 4.1 Hz, H-6′or H-6″), 8.51 (dd, 1 H, *J* = 1.1, 4.7, H-6′ or H-6″). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 89.3 (C), 112.1 (CH), 116.1 (C), 120.0 (CH), 122.0 (CH), 123.1 (CH), 123.4 (CH), 123.5 (CH), 124.9 (CH), 125.5 (CH), 127.6 (C), 136.8 (CH), 137.2 (C), 138.4 (CH), 144.8 (C), 148.2 (C), 149.5 (CH), 149.6 (CH), 150.7 (C). ESI-MS: *m/z* = 297 $[M + H]^+$. Anal. Calcd for $C_{19}H_{12}N_4$: C, 77.01, H, 4.08, N, 18.91. Found: C, 76.88; H, 4.27; N, 19.01.

(25) **Typical Procedure**
In a microwave vial with a magnetic stir bar was introduced indole-3-carboxaldehyde (100 mg, 0.68 mmol, 1 equiv), Cu_2O (10 mg, 0.07 mmol, 0.1 equiv), and K_2CO_3 (189 mg, 1.36 mmol, 2 equiv) in anhyd DMF (1.4 mL). After a purge with argon, 2-iodopyridine (153 μL, 1.36 mmol, 2 equiv) was added. The vial was sealed and heated at 240 °C under microwave irradiation (Biotage Initiator) for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was diluted in EtOAc (20 mL). The organic layer was washed with a solution of 2.5% aq NH_4OH (2 × 20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (PE–EtOAc, 2:8 to 1:1) to provide **2a** (88 mg, 58%) and **3a** (73 mg, 36%).

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