Copper-mediated N-arylation of electron-deficient pyrroles and indoles

Henri Bekolo[1]

Abstract: We have found that it is possible to N-arylate electron-deficient pyrroles and indoles having no carbonyl group α to the nitrogen ring in good to excellent yields under the Chan and Lam conditions using *N*-Ethyldiisopropylamine (DIEA) base as a substitute for triethylamine (TEA) and pyridine.

Key words: cupric acetate, arylboronic acid, N-arylation, pyrroles, indoles.

Résumé : Nous avons trouvé qu'il est possible de faire la N-arylation des pyrroles et des indoles pauvres en électrons ne possèdant pas de groupement carbonyle en position α de l'atome d'azote du noyau pyrrolique, avec de bons rendements, dans les conditions de Chan et Lam en remplaçant la triéthylamine (TEA) et la pyridine par la *N*-éthyldiisopropylamine (DIEA).

Mots-clés : acétate cuprique, acide arylboronique, N-arylation, pyrroles, indoles.

Introduction

The C–N bond forming reaction using stoichiometric (1–8) or catalytic (9–14) amounts of copper salt, a boronic acid, a nucleophile, and a base is a fast growing methodology that was pioneered by Chan and co-workers in its stoichiometric version (1, 2). Although various substrates have been efficiently N-arylated (15), the reaction outcome is somewhat unpredictable (8). To account for the successful N-arylation of electron-deficient pyrroles and indoles, it has been hypothesized that the presence of a carbonyl group α to the pyrrole ring nitrogen promotes the reaction and is, in part, a key to a successful reaction (5,6). Herein, we report good to excellent N-arylation yields of some commercially available electron-deficient pyrroles (Table 1, **1** and **2**) and indoles (Table 2, **5** and **6**) having no carbonyl group α to the pyrrole ring nitrogen.

Chan and Lam conditions for N-arylation of NH-containing heterocycles include a nucleophile, stoichiometric anhyd. $Cu(OAc)_2$, a boronic acid, and pyridine or Et_3N as a base in dichloromethane (DCM) at RT. Examples in the literature include the N-arylation of azoles (2), purines (3, 4), 2-pyridones and 3-pyridazinones (5). Closely related to this work is the N-arylation of indoles and pyrroles. Pyrrole itself has been N-arylated using catalytic copper salt in 89% yield (9), whereas, under stoichiometric $Cu(OAc)_2$ conditions, Lam et al. (2) and Srirangam and co-workers (6) reported less than 3% and 0% yields, respectively. In Lam et al. (2), indole itself was also reported to have been N-arylated in less than 3% yield.

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Considering the successful N-arylation of amides, imides, sulfonamides, and ureas (1), Mederski et al. (5) hypothesized that the presence of a carbonyl group at the C-2 position of pyrrole and indole derivatives activates the heterocyclic ring nitrogen, thereby contributing to the positive outcome of the N-arylation process. They demonstrated the concept by N-arylation of the electron-deficient ethyl pyrrole-2-carboxylate in 50% yield and of a series of 2-carboxyindoles in 21% to 50% yields.

Under similar conditions, excellent N-arylation yields of electron-deficient pyrroles were reported by Srirangam and co-workers (6). However, these remarkable yields were restricted to pyrroles having a carbonyl group at either the 2 or the 5 position. Ethyl pyrrole-3-glyoxalate, the only reported example of stoichiometric copper-mediated N-arylation of an electron-deficient pyrrole lacking a carbonyl group α to the ring nitrogen, exhibited very poor reactivity, yielding traces of expected products in three runs out of four and with only 25% of the expected product. According to the authors, the excellent yields with α-deactivated pyrroles "might in part be attributed to the chelation of carbonyl oxygen to the pyrrole nitrogen-Cu complex".

Although reasonable, the above hypothesis suggests the necessity of having a carbonyl group α to the pyrrole ring nitrogen to achieve synthetically useful yields of stoichiometric copper-mediated N-arylation of electron-deficient pyrroles and indoles. This prompted us to investigate the reactivity of electron-deficient pyrroles **1** and **2**, similar to ethyl pyrrole-3-glyoxalate, and indoles **5** and **6**.

Results and discussion

To our knowledge, DIEA has not been reported in experimental screenings as an optimal base in the Cu-mediated arylation of heteroatoms with arylboronic acids. DIEA was tested in the synthesis of the *N*-arylpyrrole **1a** (Table 1), which we isolated in 70% yield. TEA and pyridine did not

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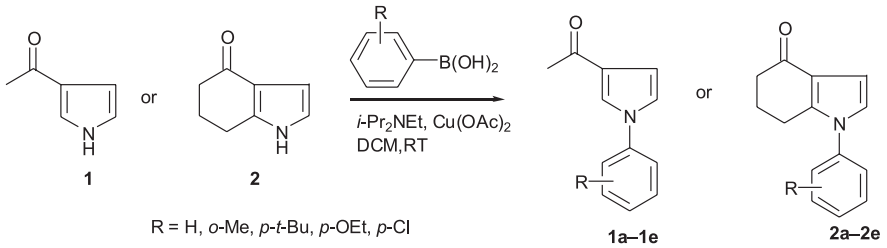
Table 1. $Cu(OAc)_2$-mediated N-arylation of **1** and **2** with $ArB(OH)_2$.



Product	Time (days)	Product yield (%)[a]	Recovered pyrrole **1** (%)[a]	Product[b]	Product yield (%)[a]	Time (days)
1a R = H	3	70	12	**2a** R = H	70	9
	3	25[c]	45			
	3	0[d]	69			
1b R = *o*-Me	5	70	0	**2b** R = *o*-Me	70	7
1c R = *p*-*t*-Bu	5	56	18	**2c** R = *p*-*t*-Bu	60[e]	14
1d R = *p*-OEt	14	50	23	**2d** R = *p*-OEt	60	14
1e R = *p*-Cl	5	47	38	**2e** R = *p*-Cl	43	6

[a]Isolated yields.
[b]Run on the 0.5 mmol scale in DMF. For **2b**, DCM (2 mL) was used; for **2e**, DCM was used.
[c]Et_3N was used instead of DIEA.
[d]Pyridine was used instead of DIEA.
[e]The reaction is cleaner in DCM.

efficiently promote the formation of **1a**. With this result, we decided to test the nonnucleophilic base DIEA with a range of *N*-arylpyrroles (Table 1). The expected products were isolated, along with the remaining starting pyrroles, phenolic by-products (up to 19%) that were already observed by Lam et al. (2), and symmetrical biaryls (up to 16%) that were also reported as side products by Lam et al. (14). These biaryls, characterized as dimers from arylboronic acids, most likely arose from the well-established $Cu(OAc)_2$-mediated oxidative dimerization of arylboronic acids (16).

Trisubstituted pyrrole **3** and tetrasubstituted pyrrole **4** (Fig. 1) were reacted with phenylboronic acid under our standard reaction conditions and found to be poor coupling partners. The reaction mixture with pyrrole **3** turned intensely red over time. After a 10-day reaction, 20% of the starting pyrrole **3** was recovered and 7% of the expected product **3a** (Fig. 1) was isolated (17), along with unidentified reddish by-products. Based on TLC analysis, pyrrole **4** did not react at all, even after a longer reaction time of 14 days.

The dramatic difference in reactivity between pyrroles **1** and **3** or **2** and **4** with phenylboronic acid may be accounted for by the methyl group steric hindrance at the α positions of **3** and **4** as copper-catalyzed coupling reactions are well-known to be extremely sensitive to steric effects in the nitrogen nucleophile. Pyrrole itself was reacted with phenylboronic acid in the dark for three days. The expected *N*-phenylpyrrole was isolated in 4% yield (9). We did not have an electron-rich pyrrole to test.

In this work, $Cu(OAc)_2$ is suspected to oxidize pyrrole anions as dark reddish unidentified by-products formed throughout the preparation of *N*-arylpyrroles. This hypothesis is supported by the fact that $Cu(OAc)_2$ is known to oxidize lithium enolates at temperatures as low as –78 °C (18).

To the best of our knowledge, there has been no report on the N-arylation under the Chan and Lam conditions of electron-deficient indoles having no carbonyl group at the C-2 position. Under the Chan and Lam conditions using DIEA, we have found that 3-acetylindole **5** and 5-nitroindole **6** lacking C-2 carbonyl groups undergo efficient N-arylations (Table 2).

When reacted with phenylboronic acid in the presence of DIEA, Et_3N, and pyridine, 3-acetylindole **5** exhibited similar reactivity as 3-acetylpyrrole **1**. That is, the use of DIEA as a base for the preparation of *N*-arylindole **5a** led to the isolation of **5a** in high yield (85%) after a two-day reaction (Table 2), whereas, the use of Et_3N for the same reaction resulted in low isolated yield of **5a** (35%) even after a longer reaction time of four days. The use of pyridine resulted in no formation of the expected product **5a**, as with a base-free reaction. For the most part, the balance of the material was likely the remaining 3-acetylindole **5**, as judged by TLC analysis. The use of DIEA was then extended to the synthesis of other *N*-arylindoles (Table 2), and we were pleased to find that the reactions proceeded uneventfully in high isolated yields. The 3-acetylindole series afforded higher product yields. Low yield (45%) of the expected product was observed for the synthesis of *N*-arylindole **6d**, in the case of which a thick mixture formed within 2 h under our standard reaction conditions that had to be diluted with an additional 3 mL of DCM. Extending the reaction time from 6 to 10 days did not improve the yield.

The modest reactivity of 4-chlorophenylboronic acid in both pyrrole and indole series reflects the known coupling partners dependency of the Cu–$ArB(OH)_2$ N-arylation reactions (1,8).

The electron-rich 5-methoxyindole was allowed to react with phenylboronic acid to assess its reactivity under our re-

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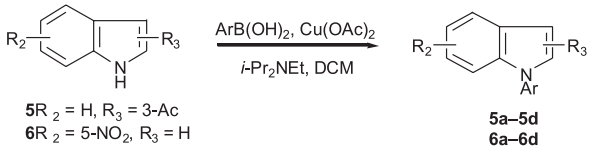
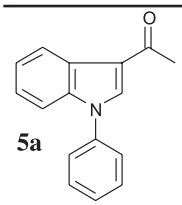
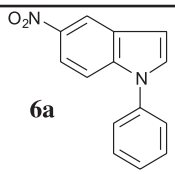
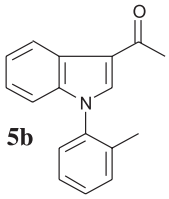
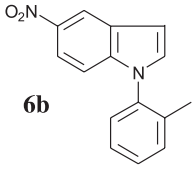
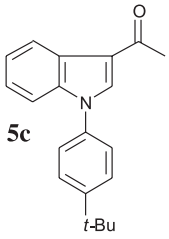
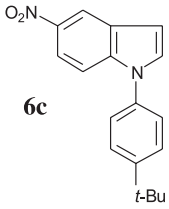
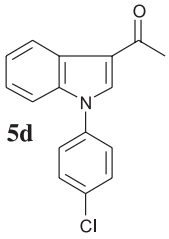
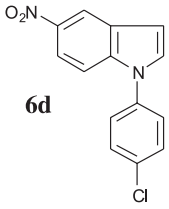
Table 2. $Cu(OAc)_2$–$ArB(OH)_2$ N-arylation of indoles **5** and **6**.



5R_2 = H, R_3 = 3-Ac
6R_2 = 5-NO_2, R_3 = H

5a–5d
6a–6d

N-arylindole	Yield (%)[a]	Time (days)	N-arylindole	Yield (%)[a]	Time (days)
 **5a**	100[b]	5	 **6a**	83	4
	85	2			
	35[c]	4			
	0[d]	2			
 **5b**	99	4	 **6b**	90	7
 **5c**	94	10	 **6c**	75[e]	10
 **5d**	65	8	 **6d**	45[e,f]	6

[a]Isolated yields.
[b]DMF was used instead of DCM.
[c]TEA was used instead of DIEA
[d]Pyridine was used instead of DIEA
[e]DCM (5 mL) was used for 1 mmol of **6**.
[f]The starting material **6** was recovered in 30% yield.

action conditions. After reacting for a week, the expected 5-methoxy-1-phenylindole was obtained in 7% isolated yield. The starting 5-methoxyindole was recovered in 70% yield. Under the same reaction conditions, the parent indole gave *N*-phenylindole (19) in 16% isolated yield, which is noteworthy. Indole was recovered in 76%.

This efficient room temperature N-arylation of 3-acetylindole and 5-nitroindole complements the N-arylation methodologies for existing indoles that rely on the use of aryl halides as coupling partners at high temperature (19–34) and those that rely on the use of aryl bismuths (35) or arylboronic acids (5) as coupling partners at room temperature.

Conclusion

In conclusion, the reactivity of pyrroles **1** and **2**, indoles **5** and **6**, demonstrates that it is possible to achieve synthetically useful N-arylation yields of electron-deficient pyrroles and indoles having no carbonyl group α to the pyrrole ring nitrogen, under the Chan and Lam conditions using DIEA as a base.

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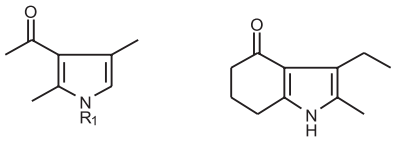
Fig. 1. Pyrroles **3**, **3a**, and **4**.



3 R_1 = H
3a R_1 = Ph

4

Experimental

Chemicals were purchased from commercial sources and used as received. The ^{1}H and ^{13}C NMR spectra were recorded on an AC Brucker 250 MHz spectrometer using $CDCl_3$ as solvent. The chemical shifts (δ) are reported in ppm. Melting points were determined on a Stuart Scientific SMP 3 capillary melting point apparatus and are uncorrected.

Typical procedure

In a sealed (glass cap and parafilm) oven-dried 25 mL flask, a mixture of pyrrole or indole (1.0 mmol), $ArB(OH)_2$ (2.5 mmol), anhyd. $Cu(OAc)_2$ (2.5 mmol), DIEA (99%, 2.5 mmol) in dry DCM (2 mL) was stirred at RT for the indicated time. DCM was removed under reduced pressure. Water (10 mL) and $HCCl_3$ (10 mL) were added. The aqueous layer was extracted with $HCCl_3$ (2 × 10 mL). The concentrated organic layer was purified by flash chromatography (FC) on silica gel.

Please see ref. 19 for analytical data on **6a** (FC: DCM–cyclohexane, 3:7).

Pyrrole 1a

FC: DCM–cyclohexane 1:1. Pale yellow oil. ^{1}H NMR δ: 7.66 (t-like, 1H, *J* = 1.84 Hz), 7.55–7.20 (m, 5H), 7.04 (m, 1H), 6.81–6.71 (m, 1H), 2.46 (s, 3H). ^{13}C NMR δ: 193.2, 139.4, 130.0, 129.1, 127.4, 120.7, 6.9.

Pyrrole 2a

FC: DCM 100%. Beige solid, mp 95 to 96 °C. ^{1}H NMR δ: 7.60–7.2 (m, 5H), 6.80 (d, 1H, *J* = 3.05 Hz), 6.69 (d, 1H, *J* = 3.05 Hz), 2.77 (t, 2H, *J* = 6.10 Hz), 2.51 (t, 2H, *J* = 6.40 Hz), 2.20–2.00 (m, 2H). ^{13}C NMR δ: 194.5, 143.3, 138.5, 129.3, 127.6, 124.6, 124.7, 123.0, 106.2, 37.6, 23.8, 22.9.

Pyrrole 1b

FC: DCM 100%. ^{1}H NMR δ: 7.40–7.10 (m, 5H), 6.73 (s-like, 2H), 2.43 (s, 3H), 2.19 (s, 3H). ^{13}C NMR δ: 193.4, 139.1, 131.1, 128.5, 128.4, 126.6, 126.5, 126.2, 123.7, 113.4, 109.2, 27.0, 17.5.

Pyrrole 2b

FC: DCM 100%. ^{1}H NMR δ: 7.40–7.10 (m, 4H), 6.70 (d, 1H, *J* = 3.05 Hz), 6.62 (d, 1H, *J* = 3.05 Hz), 2.70–2.30 (m, 4H), 2.20–2.00 (m, 5H). ^{13}C NMR δ: 194.4, 144.2, 137.3, 135.2, 130.9, 128.9, 127.3, 126.7, 120.7, 105.6, 37.7, 23.7, 21.9, 17.1.

Pyrrole 1c

FC: DCM 100%. ^{1}H NMR δ: 7.63 (m, 1H), 7.45 (d, 2H, *J* = 8.55 Hz), 7.30 (d, 2H, *J* = 9.15 Hz), 7.00 (m, 1H), 6.74 (m, 1H), 2.44 (s, 3H), 1.37 (s, 9H). ^{13}C NMR δ: 193.4, 150.1, 137.1, 127.3, 126.5, 126.0, 124.1, 121.2, 120.6, 114.8, 110.4, 34.4, 31.2, 27.1.

Pyrrole 2c

FC: DCM 100%. ^{1}H NMR δ: 7.49 (d, 2H, *J* = 8.55 Hz), 7.24 (d, 2H, *J* = 8.52 Hz), 6.78 (d, 1H, *J* = 3.05 Hz), 6.67 (d, 1H, *J* = 3.05 Hz), 2.77 (t, 2H, *J* = 6.10 Hz), 2.51 (t, *J* = 6.4 Hz), 2.17–2.00 (m, 2H), 1.36 (s, 9H). ^{13}C NMR δ: 194.5, 150.8, 143.4, 135.9, 126.8, 124.7, 123.8, 123.1, 106.1, 37.5, 34.6, 31.5, 23.9, 22.5.

Pyrrole 1d

FC: DCM 100%. ^{1}H NMR δ: 7.55 (m, 1H), 7.25 (m, 2H), 6.90 (m, 3H), 6.70 (m, 1H), 3.97 (q, 2H, *J* = 4.87 Hz), 2.41 (s, 3H), 1.40 (t, 3H, *J* = 4.85 Hz). ^{13}C NMR δ: 193.3, 157.8, 132.8, 127.0, 122.4, 115.1, 110.1, 63.7, 27.0, 14.6.

Pyrrole 2d

FC: DCM 100%. ^{1}H NMR δ: 7.20 (d-like, 2H, *J* = 7.02 Hz), 6.98 (d-like, 2H, *J* = 6.71 Hz), 6.74 (d, 1H, *J* = 3.05 Hz), 6.65 (d, 1H, *J* = 3.05 Hz), 4.06 (q, 2H, *J* = 6.72 Hz), 2.71 (t, 2H, *J* = 6.10 Hz), 2.50 (t, 2H, *J* = 5.50 Hz), 2.20–2.05 (m, 2H), 1.45 (t, 3H, *J* = 6.72 Hz). ^{13}C NMR δ: 194.6, 158.4, 143.7, 131.4, 126.1, 121.3, 115.0, 105.9, 63.8, 37.7, 23.6, 22.8, 14.8.

Pyrrole 1e

FC: DCM 100%. ^{1}H NMR δ: 7.61 (m, 1H), 7.50–7.25 (m, 4H), 6.99 (m, 1H), 6.75 (m, 1H), 2.44 (s, 3H). ^{13}C NMR δ: 193.4, 138.2, 132.5, 129.8, 127.8, 123.8, 122.1, 121.1, 110.9, 27.1.

Pyrrole 2e

FC: DCM 100%. ^{1}H NMR δ: 7.55–7.40 (m, 2H), 7.32–7.20 (m, 2H), 6.77 (d, 1H, *J* = 3.05 Hz), 6.70 (d, 1H, *J* = 3.65 Hz), 2.75 (t, 2H, *J* = 6.10 Hz), 2.52 (t, 2H, *J* = 6.40 Hz), 2.20–2.05 (m, 2H). ^{13}C NMR δ: 194.4, 143.0, 137.0, 133.5, 129.5, 125.0, 122.8, 121.9, 106.6, 37.6, 23.8, 22.8.

Indole 5a

FC: DCM 100%. Beige solid, mp 145 °C. ^{1}H NMR δ: 8.52–8.45 (m, 1H), 7.93 (s, 1H), 7.65–7.42 (m, 6H), 7.40–7.20 (m, 2H), 2.56 (s, 3H). ^{13}C NMR δ: 193.2, 138.2, 136.8, 134.6, 129.8, 129.7, 127.9, 126.4, 124.8, 124.7, 123.8, 122.9, 122.6, 118.4, 110.7, 27.5.

Indole 5b

FC: DCM 100%. Yellow solid, mp 117 to 118 °C. ^{1}H NMR δ: 8.50–8.40 (m, 1H), 7.81 (s, 1H), 7.55–7.15 (m, 6H), 7.02 (d, 1H, *J* = 7.30 Hz), 2.56 (s, 3H), 2.08 (s, 3H). ^{13}C NMR δ: 193.2, 137.8, 136.7, 135.5, 135.1, 131.3, 129.1, 127.8, 127.0, 125.6, 123.6, 122.7, 122.4, 110.7, 27.5, 17.3.

Indole 6b

FC: cyclohexane–DCM 6:4. ^{1}H NMR δ: 8.65 (d, 1H, *J* = 1.83 Hz), 8.10–8.00 (m, 1H), 7.50–7.20 (m, 5H), 7.04 (d,

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1H, J = 9.15 Hz), 6.85 (d, 1H, J = 3.05 Hz), 2.04 (s, 3H). ^{13}C NMR δ: 141.8, 139.5, 136.8, 135.4, 131.8, 131.3, 129.0, 127.7, 127.0, 118.0, 117.6, 110.3, 104.7, 17.3.

Indole 5c

FC: DCM–cyclohexane 2:8 then 1:1. ^{1}H NMR δ: 8.49 (d, 1H, J = 7.25 Hz), 7.93 (s, 1H), 7.65–7.20 (m, 7H), 2.58 (s, 3H), 1.46 (s, 9H). ^{13}C NMR δ: 193.4, 151.3, 137.2, 135.7, 134.9, 126.8, 124.5, 123.8, 123.0, 122.7, 118.4, 115.0, 111.0, 34.8, 27.6, 26.9.

Indole 6c

FC: DCM–cyclohexane 2:8. ^{1}H NMR δ: 8.63 (d, 1H, J = 2.25 Hz), 8.20–8.00 (m, 1H), 7.70–7.30 (m, 6H), 6.83 (d, 1H, J = 3.50 Hz), 1.40 (s, 9H). ^{13}C NMR δ: 131.4, 126.8, 124.2, 118.2, 117.7, 110.6, 105.3, 31.3.

Indole 5d

FC: DCM–cyclohexane 1:1. ^{1}H NMR δ: 8.50–8.40 (m, 1H), 7.89 (s, 1H), 7.60–7.20 (m, 7H), 2.60 (s, 3H). ^{13}C NMR δ: 134.3, 130.1, 126.1, 124.1, 123.2, 122.9, 110.6, 27.7.

Indole 6d

FC: DCM–cyclohexane 2:8. ^{1}H NMR δ: 8.63 (m, 1H), 8.20–8.05 (m, 1H), 7.60–7.35 (m, 6H), 6.87 (d, 1H, J = 3.00 Hz). ^{13}C NMR δ: 131.0, 130.2, 125.9, 118.3, 118.1, 110.3, 106.0.

5-Methoxy-1-phenylindole

FC: DCM–cyclohexane 3:7. ^{1}H NMR δ: 7.58–7.43 (m, 5H), 7.40–7.28 (m, 2H), 7.16 (d, 1H, J = 2.5 Hz), 6.94–6.84 (dd, 1H, J = 10 Hz, J = 2.5 Hz), 6.65–6.55 (m, 1H), 3.90 (s, 3H). ^{13}C NMR δ: 154.6, 140.0, 131.1, 129.8, 129.7, 128.4, 126.3, 124.1, 123.3, 118.9, 112.5, 111.4, 103.3, 102.7, 55.9.

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