Microwave-assisted *N*-Arylation of Indoles *via* C(sp^2)–N(sp^2) Bond Formation by Aromatic Nucleophilic Substitution Reactions

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Microwave-assisted nucleophilic aromatic substitution on aryl halides with different indoles is described. Moderate to good yields are obtained in short reaction time (25 – 40 min) when coupling indoles with fluoro- and chloro-substituted aryl halides under catalyst-free conditions.

Key words: N-Arylindoles, Aryl Halides, Microwave, S_NAr Reaction, Cross-coupling

Introduction

The *N*-arylindole subunit is an important species in many biologically active and pharmaceutically important compounds, which display antiestrogen [1], analgesic [2], antiallergy [3], antimicrobial [4], and neuroleptic activity [5]. Although the traditional copper-catalyzed coupling of an aryl halide with a heteroatom-based nucleophile, the Ullmann-type coupling reaction, has remained a standard method for the construction of *N*-arylindoles, it requires high temperatures, generally 140 °C or more, and often the use of two or more equivalents of the aryl halide to obtain optimal yields. Buchwald reported some improved *N*-arylation of indoles, but still using expensive palladium or copper [6]. Another reaction of the CuOAc catalyzed *N*-arylation of indoles has been reported recently [7]. On the other hand, the nucleophilic aromatic substitution of aryl halides, activated by electron-withdrawing substituents, with indoles represents yet another route to *N*-arylindoles for certain substrate combinations. Smith has described the *N*-arylation of indole by aromatic nucleophilic substitution, however, this S_NAr reaction was catalyzed by 18-crown-6 at high temperature (120 °C), and no examples of reactions of substituted indoles were reported [8]. Maiorana described *N*-arylation of indoles by aromatic nucleophilic substitution on haloarenes, but using chromium tricarbonyl complexes [9]. Therefore, a simple and general method for S_NAr reactions, including easy work-up and a wide scope of substrates, for the preparation of *N*-arylindoles is highly desirable.

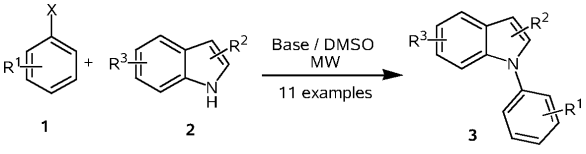


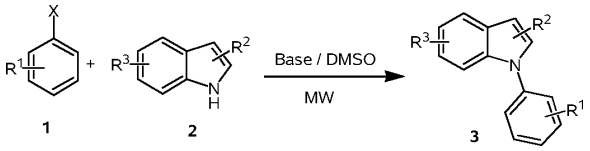
Fig. 1. Microwave-assisted synthesis of *N*-arylindoles *via* C(sp^2)–N(sp^2) bond formation.

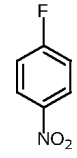
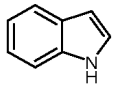
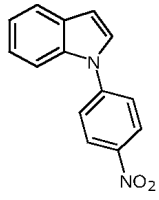
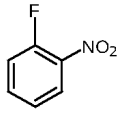
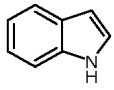
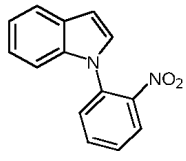
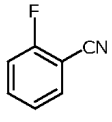
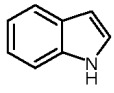
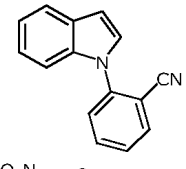
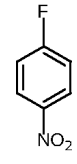
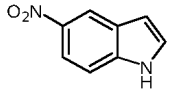
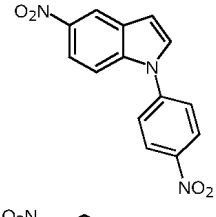
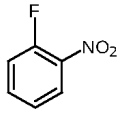
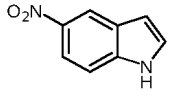
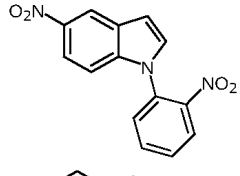
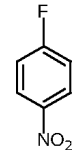
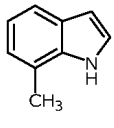
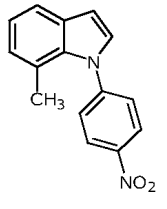
Compared to traditional processing of organic synthesis, microwave-enhanced chemistry saves significant time, very often improves yields and has attracted considerable attention in the past decade [10, 11]. To the best of our knowledge, however, the catalyst-free *N*-arylation of a variety of 3-, 5- and 7-substituted indoles with aryl halides by S_NAr reaction using high-speed microwave techniques has not been reported. In continuation of our research interest in the use of microwave irradiation [11], herein, we wish to describe our studies on the microwave-assisted construction of *N*-arylindoles *via* C(sp^2)–N(sp^2) bond formation by S_NAr reaction at an irradiation power of 420 W (Fig. 1).

Results and Discussion

From the results shown in Table 1 it can be seen that a range of indoles, including those with electron-deficient and electron-rich substitutents, can be used in this C(sp^2)–N(sp^2) cross-coupling S_NAr reaction with activated aryl halides (*X* = F, Cl, Br) in the presence of K_2CO_3 or Cs_2CO_3 under microwave irradiation. For

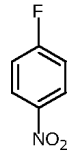
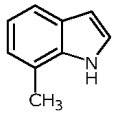
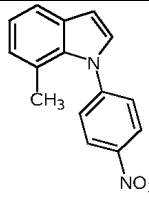
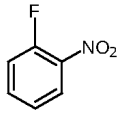
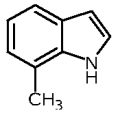
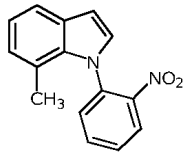
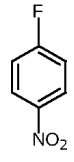
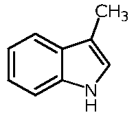
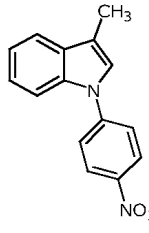
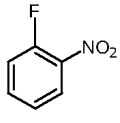
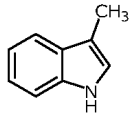
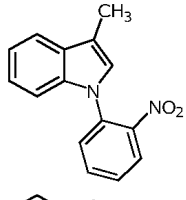
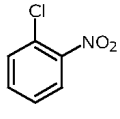
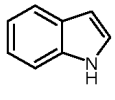
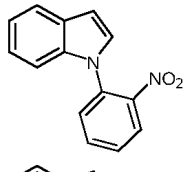
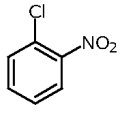
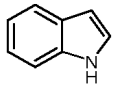
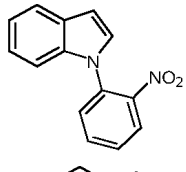
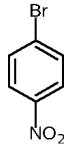
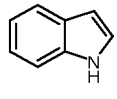
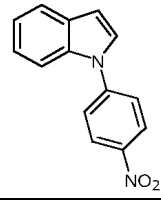
Table 1. Microwave-assisted synthesis of *N*-arylated indoles[a].



Entry	Aryl halides (**1**)	Indoles (**2**)	*N*-Arylindoles (**3**)	Base	Time[b] (min)	Yield (%)
a				K_2CO_3	6×5	79
b				K_2CO_3	6×5	71
c				K_2CO_3	7×5	52
d				K_2CO_3	6×5	94
e				K_2CO_3	5×5	91
f				K_2CO_3	6×5	NR[c]

example, 4-fluoronitrobenzene (0.5 mmol) was coupled with indole (0.55 mmol) in DMSO (2 mL) at an irradiation power of 420 W mediated by K_2CO_3 (1.5 mmol) for 6×5 min, *N*-(4-nitrophenyl)indole being obtained in 79 % yield (entry a). It is noteworthy that in our reaction the electron-poor 5-nitroindole could smoothly be coupled with 4-fluoronitrobenzene and 2-fluoronitrobenzene (entries d and e), the corresponding yields being 94 % and 91 %, respectively. A steric effect was observed for this reaction. Although K_2CO_3 was a good base for combining the activated fluoroarenes with indole, 5-nitroindole or 3-methylindole (entries a – e, i, j), it was ineffective in the coupling reaction with 7-methylindole. For example, when

Table 1 (continued).

Entry	Aryl halides (**1**)	Indoles (**2**)	*N*-Arylindoles (**3**)	Base	Time[b] (min)	Yield (%)
g				Cs_2CO_3	8×5	62
h				Cs_2CO_3	8×5	46
i				K_2CO_3	7×5	83
j				K_2CO_3	7×5	94
k				K_2CO_3	8×5	NR
l				Cs_2CO_3	5×5	47
m				Cs_2CO_3	5×5	18

[a] All reactions were carried out with compounds **1** (0.5 mmol), **2** (0.55 mmol), and K_2CO_3 (1.5 mmol) or Cs_2CO_3 (1.0 mmol) in DMSO (2 mL) under microwave irradiation; [b] 6×5 means 6 times 5 min as reaction time; the progress of the reaction was checked by TLC at the end of each irradiation period; [c] NR = no reaction.

7-methylindole was coupled with 4-fluoronitrobenzene in the presence of K_2CO_3 for 6×5 min, no target compound was monitored by TLC as the nitrogen atom of 7-methylindole is strongly hindered (entry f).

However, when we chose Cs_2CO_3 as the base for the *N*-arylation of 7-methylindole with 4-fluoronitrobenzene and 2-fluoronitrobenzene, the corresponding yields were 62 % and 46 %, respectively (entries g and h).

Finally we investigated the microwave-assisted coupling of 2-chloronitrobenzene or 4-bromonitrobenzene with indole at an irradiation power of 420 W. Unfortunately, conditions employing K_2CO_3 as the base were inefficient for the cross-coupling reaction (entry k). However, *N*-(2-nitrophenyl)indole and *N*-(4-nitrophenyl)indole were obtained in 47 and 18 % yields, respectively, in the presence of Cs_2CO_3 (entries l and m).

Conclusion

In summary, we have described an efficient S_NAr reaction to synthesize *N*-arylindoles *via* C(sp^2)–N(sp^2) bond formation in the presence of K_2CO_3 or Cs_2CO_3 under a microwave irradiation power of 420 W. The reaction time was very short (25 – 40 min), and moderate to good yields (46 – 94 %) were achieved without any catalyst, when a wide substrate range of indoles were reacted with fluoro- and chloro-substituted aryl halides.

Experimental Section

The materials were used as purchased. Melting points were determined on a digital melting-point apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance DMX instrument (^{1}H: 400 MHz; ^{13}C: 100 MHz) using TMS as internal standard and $CDCl_3$ as solvent. HRMS and EIMS measurements were carried out with APEX II Bruker 4.7T AS and Thermo DSQ GC/MS instruments, respectively. Elemental analyses were determined with a Carlo-Erba 1106 CHN microanalyzer. Microwave irradiation was performed in a Galanz microwave oven, WG700CTL.

General procedure

To a mixture of activated aryl halide (*X* = F, Cl, Br, 0.5 mmol), indole (0.55 mmol) and K_2CO_3 (1.5 mmol) or Cs_2CO_3 (1.0 mmol) was added DMSO (2 mL). The reaction was found not to be sensitive to air and moisture, hence DMSO was used directly without any additional purification, and there was no need for inert atmosphere. The mixture was placed in a microwave oven and irradiated at a power of 420 W for the appropriate time as shown in Table 1. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to r. t. and poured into ice water (20 mL). Then 40 mL of EtOAc was added to the mixture, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with 4 mol/L HCl (3 × 20 mL), brine (1 × 40 mL) and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by preparative thin-layer chromatography (PTLC) or silica gel column chromatography to give the pure *N*-arylindoles. All compounds were characterized by ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), HRMS or elemental analysis, EIMS, and melting points.

Compounds ***3a*** *and* ***3m***: Yellow solid, m. p. 109 – 109.5 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (1H, d, *J* = 3.2 Hz), 7.21 (2H, m), 7.37 (1H, d, *J* = 3.6 Hz), 7.64 (4H, m), 8.39 (2H, d, *J* = 8.8 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.4, 127.0, 125.4, 123.3, 121.6, 121.5, 110.4, 110.1, 106.1. – GC/MS (EI, 70 eV): *m/z* (%) = 238 (100) $[M]^+$. – HRMS-ESI: *m/z* = 239.0818 (calcd. 239.0815 for $C_{14}H_{10}N_2O_2$, $[M+H]^+$).

Compounds ***3b*** *and* ***3l***: Orange solid, m. p. 69 – 70 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (1H, d, *J* = 3.2 Hz), 7.11 (4H, m), 7.53 (2H, m), 7.68 (2H, m), 8.01 (1H, d, *J* = 8.4 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 133.6, 132.8, 129.7, 128.9, 128.3, 127.9, 125.4, 122.9, 121.3, 120.9, 109.4, 105.0. – GC/MS (EI, 70 eV): *m/z* (%) = 238 (100) $[M]^+$. – HRMS-ESI: *m/z* = 239.0818 (calcd. 239.0815 for $C_{14}H_{10}N_2O_2$, $[M+H]^+$).

Compound ***3c***: White solid, m. p. 96 – 96.5 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (1H, d, *J* = 3.6 Hz), 7.18 (2H, m), 7.33 (1H, d, *J* = 8.4 Hz), 7.40 (1H, d, *J* = 3.2 Hz), 7.46 (1H, m), 7.60 (1H, d, *J* = 8.4 Hz), 7.69 (2H, m), 7.83 (1H, d, *J* =7.6 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 134.5, 133.8, 129.3, 128.1, 127.4, 127.3, 122.8, 121.3, 121.1, 116.4, 110.2, 109.7, 105.0. – GC/MS (EI, 70 eV): *m/z* (%) = 218 (100) $[M]^+$. – HRMS-ESI: *m/z* = 219.0919 (calcd. 219.0917 for $C_{15}H_{10}N_2$, $[M+H]^+$).

Compound ***3d***: Yellow solid, m. p. 220 – 221 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (1H, d, *J* = 3.6 Hz), 7.53 (1H, d, *J* = 3.2 Hz), 7.61 (1H, d, *J* = 8.8 Hz), 7.70 (2H, d, *J* = 8.4 Hz), 8.18 (1H, dd, *J* = 8.8 Hz, *J* = 2.0 Hz), 8.46 (2H, d, *J* = 8.8 Hz), 8.66 (1H, d, *J* = 2.0 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 130.4, 129.4, 125.7, 124.4, 118.8, 118.5, 110.4, 107.5. – GC/MS (EI, 70 eV): *m/z* (%) = 283 (28) $[M]^+$. – $C_{14}H_9N_3O_4$ (283): calcd. C 59.36, H 3.18, N 14.84; found C 59.71, H 3.42, N 14.48.

Compound ***3e***: Orange solid, m. p. 104.5 – 106 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (1H, d, *J* = 3.2 Hz), 7.10 (1H, d, *J* = 9.2 Hz), 7.32 (1H, d, *J* = 3.2 Hz), 7.59 (1H, dd, *J* = 8.0 Hz, *J* = 0.8 Hz), 7.68 (1H, m), 7.81 (1H, m), 8.08 (2H, m), 8.63 (1H, d, *J* = 1.6 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 139.6, 134.1, 131.3, 130.0, 129.8, 128.2, 125.8, 118.5, 118.3, 109.6, 106.6. – GC/MS (EI, 70 eV): *m/z* (%) = 283 (100) $[M]^+$. – HRMS-ESI: *m/z* = 284.0592 (calcd. 284.0588 for $C_{14}H_9N_3O_4$, $[M+H]^+$).

Compound ***3g***: Yellow solid, m. p. 121 – 122 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09 (3H, s), 6.71 (1 H, d, *J* = 3.2 Hz), 7.01 (1 H, d, *J* = 7.2 Hz), 7.11 (2H, m), 7.49 (2H, dd, *J* = 6.8 Hz, *J* = 1.6 Hz), 7.54 (1 H, d, *J* = 8.0 Hz), 8.33 (2H, dd, *J* = 6.4 Hz, *J* = 1.6 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 130.3, 130.1, 127.3, 125.8, 124.2, 121.4, 119.3, 105.2, 20.4. – GC/MS (EI, 70 eV): *m/z* (%) = 252 (100) $[M]^+$. – $C_{15}H_{12}N_2O_2 \cdot 0.5H_2O$ (261): calcd. C 68.96, H 4.98, N 10.73; found C 69.28, H 4.57, N 11.20.

Compound ***3h***: Orange solid, m. p. 96.5 – 97 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (3H, s), 6.67 (1 H, d, *J* = 3.2 Hz), 6.92 (1 H, d, *J* = 6.8 Hz), 7.05 (2H, m), 7.49 (2H, m), 7.66 (2H, m), 7.97 (1H, dd, *J* = 8.0 Hz, *J* = 1.2 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.8, 132.6, 131.7, 130.0, 129.2, 125.2, 124.4, 120.8, 119.3, 104.4, 18.5. – GC/MS (EI, 70 eV): *m/z* (%) = 252 (95) $[M]^+$. – HRMS-ESI: *m/z* = 253.0973 (calcd. 253.0972 for $C_{15}H_{12}N_2O_2$, $[M+H]^+$).

Compound ***3i***: Yellow solid, m. p. 137 – 139 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (3H, s), 7.18 (1H, s), 7.24 (2H, m), 7.63 (2 H, d, *J* = 8.4 Hz), 7.64 (2H, d, *J* = 8.8 Hz), 8.36 (2H, d, *J* = 8.8 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 125.4, 124.4, 123.4, 122.6, 121.1, 119.7, 116.0, 110.4, 9.5. – GC/MS (EI, 70 eV): *m/z* (%) = 252 (100) $[M]^+$. – $C_{15}H_{12}N_2O_2$ (252): calcd. C 71.42, H 4.76, N 11.11; found C 71.54, H 4.52, N 10.98.

Compound ***3j***: Red liquid. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (3H, s), 6.90 (1H, s), 7.11 (3H, m), 7.43 (2H, m), 7.61 (2H, m), 7.94 (1H, dd, *J* = 8.0 Hz, *J* = 1.2 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 136.6, 133.5, 132.9, 129.6, 129.3, 127.6, 125.4, 125.1, 122.8, 120.3, 119.3, 114.3, 109.3, 9.5. – GC/MS (EI, 70 eV): *m/z* (%) = 252 (80) $[M]^+$. – HRMS-ESI: *m/z* = 253.0971 (calcd. 253.0972 for $C_{15}H_{12}N_2O_2$, $[M+H]^+$).

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[1] E. von Angerer, J. Strohmeier, *J. Med. Chem.* **1987**, *30*, 131 – 136.
[2] E. J. Glamkowski, J. M. Fortunato, T. C. Spaulding, J. C. Wilker, D. B. Ellis, *J. Med. Chem.* **1985**, *28*, 66 – 73.
[3] P. C. Unangst, M. E. Carethers, K. Webster, G. M. Janik, L. J. Robichaud, *J. Med. Chem.* **1984**, *27*, 1629 – 1633.
[4] A. G. Kamat, G. S. Gadaginamath, *Indian J. Chem.* **1994**, *33B*, 255 – 259.
[5] J. Perregaard, J. Arnt, K. P. Boegesoe, J. Hyttel, C. Sanchez, *J. Med. Chem.* **1992**, *35*, 1092 – 1101.
[6] a) D. W. Old, M. C. Harris, S. L. Buchwald, *Org. Lett.* **2000**, *2*, 1403 – 1406; b) J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 11684 – 11688.
[7] F. Bellina, C. Calandri, S. Cauteruccio, R. Rossi, *Eur. J. Org. Chem.* **2007**, 2147 – 2151.
[8] W. J. Smith III, J. S. Sawyer, *Tetrahedron Lett.* **1996**, *37*, 299 – 302.
[9] S. Maiorana, C. Baldoli, P. Del Buttero, M. Di Ciolo, A. Papagni, *Synthesis* **1998**, *5*, 735 – 738.
[10] a) D. S. Li, S. Komarneni, *Z. Naturforsch.* **2006**, *61b*, 1566 – 1572; b) E. K. Ahmed, M. A. Ameen, F. F. Abdel-Latif, *Z. Naturforsch.* **2005**, *60b*, 221 – 226; c) D. Bogdal, M. Lukasiewicz, J. Pielichowski, S. Bednarz, *Synth. Commun.* **2005**, *23*, 2973 – 2983.
[11] H. Xu, H. F. Li, *Z. Naturforsch.* **2007**, *62b*, 1183 – 1186.