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ULTRASOUND-ASSISTED *N*-ARYLATION OF INDOLES WITHOUT ANY CATALYST

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Dedicated to Professor Dr. Ryoji Noyori on the occasion of his 70th birthday

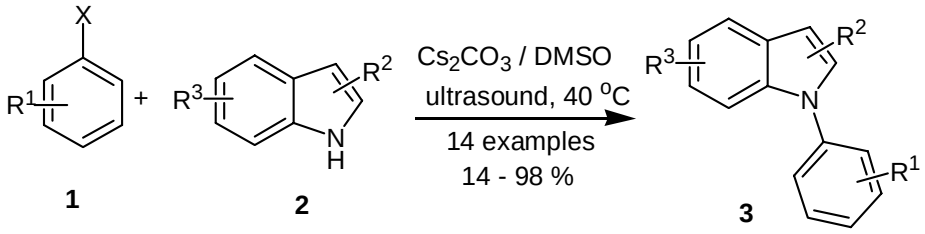
Abstract – An efficient method for the ultrasound-assisted *N*-arylation of indoles with haloarenes in an air atmosphere mediated by Cs_2CO_3 without any catalyst is reported. *N*-arylindoles are obtained in moderate to good yields while indoles cross-coupling with activated aryl halides (X = F or Cl).

INTRODUCTION

The synthesis of compounds bearing the *N*-arylindole subunit has gained widespread interest due to their key role in medically important species, such as those displaying antiestrogen,[1] analgesic,[2] antimicrobial,[3] neuroleptic,[4] antiallergy,[5] 5-HT_6 receptor antagonists,[6] and FTase inhibitors (FTIs) activity.[7] Although the 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 involves use of expensive chemicals, tedious work-up, and sensitive catalysts/ligands. Recently, the methods of palladium- [8] and copper- [9] catalyzed *N*-arylation of indoles have been reported. Meanwhile, the nucleophilic aromatic substitution (S_NAr) of aryl halides, activated by electron-withdrawing substituents, with indoles represent an alternate route to *N*-arylindoles for some substrate combinations. For example, Smith has described the *N*-arylation of indole by aromatic nucleophilic substitution reaction, which was catalyzed by 18-crown-6 at high temperature (120 ^oC), and non-substituted indole was investigated.[10] Maiorana described *N*-arylation of indoles by aromatic nucleophilic substitution on haloarene, using chromium tricarbonyl complexes.[11] While all of these methods are useful in its own right,

each suffers from one or more disadvantages including a lack of generality, the use of inert atmosphere and stoichiometric quantities of toxic and expensive reagents, or the need to employ harsh reaction conditions. Therefore, there is still a need for mild methods for the preparation of *N*-arylindoles.

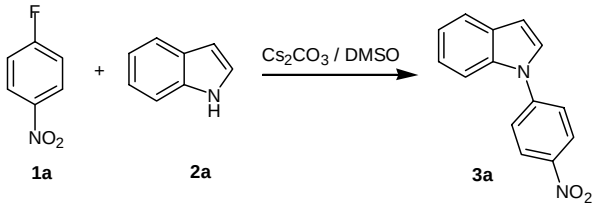
Ultrasound has been increasingly used in organic synthesis in last two decades. A large number of organic reactions can be carried out to result in higher yield, shorter reaction time and milder conditions under ultrasonic irradiation.[12] However, to the best of our knowledge, the ultrasound-assisted *N*-arylation of a wide range of indoles with aryl halides by S_NAr reactions without using any catalyst has not yet been reported. In continuation of our research interest in the use of ultrasonic irradiation,[13] herein, we firstly present our studies toward the coupling of different types of substituted indoles with haloarenes (X = F, Cl or Br) by S_NAr reactions under ultrasonic irradiation in an air atmosphere, which overcome a number of the above disadvantages (Scheme 1).



R^1 = NO_2, CN; X = F, Cl, Br; R^2 = Me; R^3 = Me, NO_2

Scheme 1

Table 1 Optimization studies[a]



Entry	Temp. (°C)	Time (h)	Conditions	Isolated yield (%)
1	20	8	ultrasound	49
2	30	2	ultrasound	94
3	40	1.5	ultrasound	98
4	50	1.5	ultrasound	99
5	40	2	silent	86

[a] All reactions were carried out with **1a** (1.0 mmol), **2a** (1.2 mmol) and Cs_2CO_3 (2.0 mmol) in DMSO (2 mL).

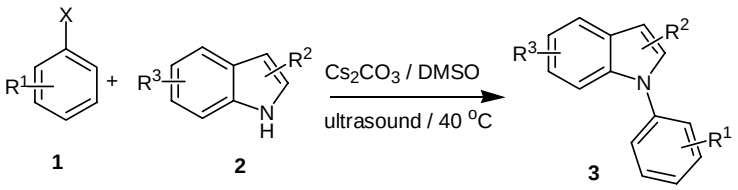
RESULTS AND DISCUSSION

At the beginning of our work we investigated the ultrasound-assisted coupling of 4-fluoronitrobenzene (**1a**) with indole (**2a**) for optimizing the reaction conditions, and the results were summarized in Table 1. In our previous paper, Cs_2CO_3 as the base and DMSO as the solvent under ultrasonic irradiation were found to be the most effective conditions for the cross-coupling of various phenols with activated fluoroarenes,[13] therefore in this paper Cs_2CO_3 and DMSO were used as the base and the solvent, respectively. Subsequently, we investigated the influence of temperature (such as at 20 ^oC, 30 ^oC, 40 ^oC and 50 ^oC) to this reactions under ultrasonic irradiation at an output power of 200 W, and found that the reaction temperature seems crucial. For example, the yield of 1-(4-nitrophenyl)indole （**3a**） was only 49 % after reaction at 20 ^oC even for 8 h (entry 1), but the yield was increased to 94 % after reaction at 30 ^oC for 2 h (entry 2), and the yield was increased to 98 % after reaction at 40 ^oC only for 1.5 h (entry 3). However, when the reaction temperature was above 40 ^oC, e.g. 50 ^oC , there was no obvious different between the yield and reaction time as compared to those of 40 ^oC (entry 4). On the contrary, while **1a** was reacted with **2a** at 40 ^oC for 2 h without any ultrasonic irradiation, **3a** was obtained in 86 % yield (entry 5). Evidently, Cs_2CO_3 as the base and DMSO as the solvent at 40 ^oC under ultrasonic irradiation were found to be the most effective conditions for this *N*-arylation of indoles.

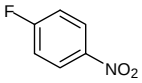
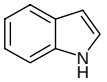
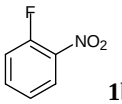
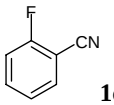
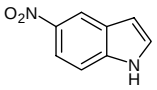
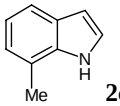
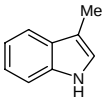
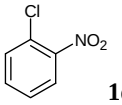
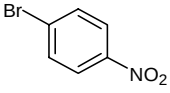
Based on the above findings, we further studied the coupling reaction of various indoles (**2a-d**) and haloarenes (**1a-e**) (X = F, Cl or Br) in the presence of Cs_2CO_3 under ultrasonic irradiation. From the results shown in Table 2, firstly, it can be seen in our reaction that a variety of indoles, having electron-deficient and electron-rich group, were effective for this C(aryl)-N cross-coupling S_NAr reaction with activated fluoroarenes. Good to excellent yields (55-98 %) were obtained. For example, when indole (**2a**) was coupled with 4-fluoronitrobenzene (**1a**) or 2-fluorobenzonitrile (**1c**) under ultrasonic irradiation at 40 ^oC in the presence of Cs_2CO_3 without any catalyst, the corresponding compounds 1-(4-nitrophenyl)indole （**3a**） and 1-(2-cyanophenyl)indole (**3c**) were obtained in 98 % yield for 1.5 h and 97 % yield for 2 h, respectively (entries 1, 3). But under the usual heating conditions, the KF-Al_2O_3/18-crown-6-catalyzed coupling indole with **1a** or **1c** needed long reaction time at 120 ^oC to give the same results.[10] Moreover, it is noteworthy in our reaction that the electron-poor indole (e.g. 5-nitroindole) could smoothly be coupled with **1a** or **1b** at 40 ^oC only for 1.5 h, and the corresponding yields were 82 % (**3d**) and 77 % (**3e**), respectively (entries 4, 5).

Distinct steric effect of aryl halides was observed in this cross-coupling S_NAr reaction. For instance, when 5-nitroindole was reacted with **1a** or **1b**, the corresponding yields of **3d** and **3e** were 82 % and 77 %, respectively (entries 4 vs. 5). Especially when 7-methylindole (**2c**) was coupled with **1a** or **1b**, the corresponding compounds 1-(4-nitrophenyl)-7-methylindole (**3f**) and 1-(2-nitrophenyl)-7-methylindole (**3g**) were obtained in 78 % and 55 % yields, respectively (entries 6 vs. 7). On the other hand, the steric

Table 2 Ultrasound-assisted synthesis of *N*-arylindoles



1 **2** **3**

Entry	Aryl halides (**1**)	Indoles (**2**)	Time (h)	Isolated yield of **3** (%)
1	 **1a**	 **2a**	1.5	**3a** (98)
2	 **1b**	**2a**	2	**3b** (91)
3	 **1c**	**2a**	2	**3c** (97)
4	**1a**	 **2b**	1.5	**3d** (82)
5	**1b**	**2b**	1.5	**3e** (77)
6	**1a**	 **2c**	2.5	**3f** (78)
7	**1b**	**2c**	3	**3g** (55)
8	**1a**	 **2d**	2.5	**3h** (86)
9	**1b**	**2d**	3	**3i** (93)
10	 **1d**	**2a**	2	**3b** (55)
11	**1d**	**2b**	8	**3c** (50)
12	**1d**	**2c**	5	**3g** (23)
13	**1d**	**2d**	5.5	**3i** (41)
14	 **1e**	**2a**	11	**3a** (14)

effect among indoles was also obvious. when 4-fluoronitrobenzene was reacted with **2a** or **2c**, the corresponding yields of **3a** and **3f** were 98 % and 78 %, respectively (entries 1 vs. 6). Particularly when 2-fluoronitrobenzene was reacted with **2a** or **2c**, the corresponding compounds **3b** and **3g** were obtained in 91 % and 55 % yields, respectively (entries 2 vs. 7).

Later on, other haloarenes (X = Cl or Br, entries 10-14) have also been studied under our reaction conditions. As shown in Table 2, the fluoroarenes underwent S_NAr reactions with indoles much easier than those chloro and bromo analogues. For example, when **2a** was reacted with **1b** or **1d**, the corresponding yields were 91 % (entry 2) and 55 % (entry 10), respectively. Similarly, when 3-methylindole (**2d**) was reacted with **1b** or **1d**, the corresponding yields were 93 % for 3 h (entry 9) and 41 % for 5.5 h (entry 13), respectively. Especially when indole was reacted with 4-bromonitrobenzene (**1e**) (entry 14), even if the reaction time was prolonged to 11 h, the corresponding yield of **3a** was only 14 %.

In summary, we have described nucleophilic aromatic substitutions of some haloarenes (X = F, Cl or Br) with a wide range of indoles under ultrasonic irradiation without any catalyst in an air atmosphere. Especially when various indoles were reacted with activated fluoroarenes using sonication by S_NAr reactions, *N*-arylation indoles were achieved in good to excellent yields (55-98 %). Compared to the reported results,[10] advantages of the present procedure are as follows: (1) very lower reaction temperature (40 ^oC); (2) easy work-up and without inert atmosphere; (3) catalyst-free.

EXPERIMENTAL

The materials were used as purchased. Melting points were determined on a digital melting-point apparatus and uncorrected. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Avance DMX 400 MHz and 100 MHz instruments using TMS as internal standard and $CDCl_3$ as solvent. HR-MS and EI-MS were carried out with APEX II Bruker 4.7T AS and Thermo DSQ GC/MS instruments, respectively. Elemental analysis was executed on Carlo-Erba 1106 CHN microanalyzer. Sonication was performed in Ningbo SB-5200DT ultrasonic cleaner with the frequency of 40 KHz and an output power of 200 W. The size of the bath of the ultrasonic cleaner is 25 × 31 × 15 cm.

General Procedure for the preparation of *N*-arylindoles:

The mixture of the appropriate haloarene (1.0 mmol), the indole (1.2 mmol), anhydrous Cs_2CO_3 (2.0 mmol), and DMSO (2 mL) in 25 mL rockered flask in an air atmosphere, checked by TLC, was reacted using sonication at an output power of 200 W at 40 ^oC for an appropriate time as shown in Table 2. Then 40 mL ice water was added to the above mixture, and the latter was extracted by EtOAc (60 mL × 3). Subsequently the combined organic phase was washed by brine (40 mL), dried over anhydrous Na_2SO_4,

concentrated in vacuo, and purified by preparation TLC to give the pure *N*-arylation indoles.

Compound ***3a***: yellow solid, mp109-109.5 °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 $C_{14}H_{10}N_2O_2$, $[M+H]^+$).

Compound ***3b***: orange solid, mp 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, mp 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 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, mp 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) $[M]^+$; Anal. Calcd. for $C_{14}H_9N_3O_4$ (283): C 59.36, H 3.18, N 14.84; found C 59.71, H 3.42, N 14.48.

Compound ***3e***: orange solid, mp 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 ***3f***: yellow solid, mp 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) $[M]^+$; Anal. Calcd. for $C_{15}H_{12}N_2O_2 \cdot 0.5H_2O$ (261): C 68.96, H 4.98, N 10.73; found C 69.28, H 4.57, N 11.20.

Compound ***3g***: orange solid, mp 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 **3h***: yellow solid, mp 137-139 ^{o}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) $[M]^+$; Anal. Calcd. for $C_{15}H_{12}N_2O_2$ (252): C 71.42, H 4.76, N 11.11; found C 71.54, H 4.52, N 10.98.

*Compound **3i***: 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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