One-Pot *N*-Arylation of Indoles Directly from *N*-Arylsulfonylindoles *via* Consecutive Deprotection and *S*$_N$Ar Reactions with Activated Aryl Halides

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An efficient one-pot step by step *t*-BuOK-mediated procedure for the synthesis of *N*-arylindoles has been developed in moderate to good yields. The protocol involves the consecutive deprotection of *N*-arylsulfonylindoles as latent indoles and subsequent *S*$_N$Ar reactions with activated aryl halides. This tandem reaction affords an efficient and convenient preparation of *N*-arylindoles that benefit from prior indoles protection by arylsulfonyl group, and can shorten a reaction sequence and improve synthetic efficiency.

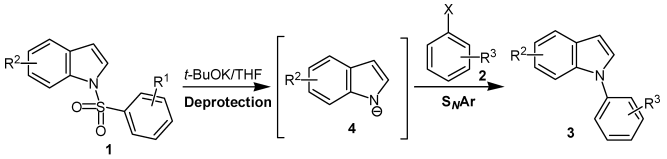
Key words *N*-arylindole; *N*-arylsulfonylindole; one-pot reaction

N-Arylindoles are known to be important subunits due to their key role in medically biological activities, such as those displaying antiestrogen,[1] analgesic,[2] antimicrobial,[3] neuroleptic,[4] antiallergy,[5] 5-HT$_6$ receptor antagonists,[6] FTase inhibitors (FTIs),[7] and anti-human immunodeficiency virus (HIV)-1 activities.[8] Although the development of new methodologies for the *N*-arylation of indoles catalyzed by palladium or copper has received much attention in recent years,[9—14] the nucleophilic aromatic substitutions (*S*$_N$Ar) of aryl halides, activated by electron-withdrawing substituents, with indoles represent an alternate route to *N*-arylindoles for certain substrate combinations.[15—17] Meanwhile, the fact that the strategic use of protective groups is a necessary and time-consuming tactic in organic synthesis is well-known; however, a merging of protective group chemistry with other transformations *via* one-pot step by step reaction that can shorten a reaction sequence and improve synthetic efficiency and convenience is always of great interest.[18—21] The arylsulfonyl groups are useful for protecting groups for the NH group of the indoles because of their robust behavior under a wide variety of reaction conditions.[22—25] Recently, many methods for the deprotection of *N*-tosylated indoles have been described, such as highly basic NaOH or KOH in alcohol,[26] tetra-*n*-butylammonium fluoride (TBAF) in refluxing tetrahydrofuran (THF),[27] and Mg in MeOH.[28] However, to the best of our knowledge, *N*-arylsulfonylindoles have never been used as latent indoles in the *S*$_N$Ar reactions with aryl halides to prepare *N*-arylindoles directly. In the meantime, Rubiralta *et al.* reported that the indolyl anion could be efficiently formed by the deprotection of *N*-benzenesulfonylindole in the presence of *t*-BuOK.[29] Consequently, as part of our program aimed at the development of one-pot step by step reactions,[30] in this paper we want to explore the synthesis of *N*-arylindoles directly from *N*-arylsulfonylindoles and activated aryl halides in the presence of *t*-BuOK for the first time. On the other hand, in order to examine the consecutive two reaction conditions for the deprotection of *N*-arylsulfonylindoles (**1**) and the *S*$_N$Ar reactions with activated aryl halides (**2**), respectively, a set of the experiments was performed as shown in Chart 1. Fortunately, we were pleased to find that *N*-arylindoles (**3**) could be obtained smoothly *via* the deprotection of **1** followed by direct *S*$_N$Ar reactions with **2** in the presence of *t*-BuOK.

Results and Discussion

Initially, the reaction rate of the deprotection of *N*-tosylindoles (R^2=H, Me, CN and NO$_2$) in the presence of *t*-BuOK to liberate the corresponding intermediates (**4**), the indolyl anions, was examined as shown in Table 1. It was found that the reaction rate of the deprotection of *N*-tosylindoles is very sensitive to electronic and steric effects of the substituents on the corresponding substrates. For example, the deprotection of *N*-tosylindole was essentially complete in 1 h at reflux (entries 1—4, 15, 16). The complete deprotection of *N*-tosyl-5-nitroindole and *N*-tosyl-5-cyanoindole, having electron-withdrawing substituents (*e.g.*, NO$_2$ and CN) on the indole's ring, was achieved only in 0.5 h at reflux (entries 5—7, 14). In contrast, when electron-rich substituent (*e.g.*, methyl group) was introduced on the 3-position of *N*-tosylindole, the corresponding deprotective rate could slow down sharply. For example, it took 12 h to give a 64% conversion of *N*-tosyl-3-methylindole to 3-methylindole at reflux (entries 9, 10).[31] But to our surprise, when methyl group was introduced on the 4- or 6-position of *N*-tosylindole, the corresponding deprotective rates were not affected in comparison to that of *N*-tosyl-3-methylindole, and the complete deprotection was finished in 1 h (entries 11, 12). Mainly due to steric effect, the deprotective rates of *N*-tosyl-2-methyl- and *N*-tosyl-7-methylindole were very slow, and no corresponding free indoles were formed even after 25 and 28 h, respectively (entries 8, 13).

Next, we investigated the synthesis of *N*-arylindoles *via* the deprotection of *N*-tosylindoles (R^2=H, Me, CN and NO$_2$) and sequent *S*$_N$Ar reactions with activated aryl halides (X=F, Cl and Br, R^3=CN and NO$_2$) in the presence of *t*-BuOK. *N*-Arylindoles (**3a**—**k**) were obtained in 14—94% yields (entries 1—7, 9—12, 14—16). As we all know that the cross-coupling of electron-deficient indoles with aryl halides was



R^1 = H, Me, NO$_2$, Et, Cl; R^2 = H, Me, CN, NO$_2$; R^3 = NO$_2$, CN; X = F, Cl, Br

Chart 1. The Synthetic Route of *N*-Arylindoles **3**

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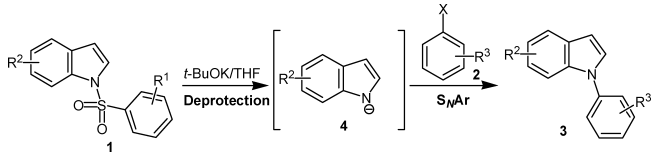
Table 1. *t*-BuOK-Mediated Construction of *N*-Arylindoles (**3**) from *N*-Arylsulfonylindoles (**1**) and Activated Aryl Halides (**2**)[a)]



Entry	1		2		Time (h)[b)]	Isolated yield of **3** (%)
	R^1	R^2	R^3	X		
1	4-Me	H	4-NO_2	F	1+2	**3a** (93)
2	4-Me	H	2-NO_2	F	1+3	**3b** (94)
3	4-Me	H	2-CN	F	1+2	**3c** (93)
4	4-Me	H	4-CN	F	1+0.5	**3d** (93)
5	4-Me	5-NO_2	2-NO_2	F	0.5+2.5	**3e** (88)
6	4-Me	5-NO_2	4-NO_2	F	0.5+2.5	**3f** (78)
7	4-Me	5-CN	2-NO_2	F	0.5+3.5	**3g** (87)
8	4-Me	2-Me	—	—	25[c)]	No reaction
9	4-Me	3-Me	4-NO_2	F	12[d)]+2	**3h** (49)
10	4-Me	3-Me	2-NO_2	F	12[d)]+2	**3i** (42)
11	4-Me	4-Me	2-CN	F	1+1	**3j** (91)
12	4-Me	6-Me	2-CN	F	1+1.5	**3k** (96)
13	4-Me	7-Me	—	—	28[c)]	No reaction
14	4-Me	5-NO_2	2-NO_2	Cl	0.5+8	**3e** (<18)
15	4-Me	H	2-NO_2	Cl	1+8	**3b** (34)
16	4-Me	H	4-NO_2	Br	1+12	**3a** (14)
17	H	H	4-NO_2	F	1+2	**3a** (91)
18	H	H	2-NO_2	F	1+2	**3b** (82)
19	H	H	2-CN	F	1+2	**3c** (83)
20	4-Cl	H	2-NO_2	F	1+3	**3b** (89)
21	4-Et	H	2-NO_2	F	0.5+2	**3b** (78)
22	3-NO_2	H	2-NO_2	F	1.5[e)]+3	**3b** (13)
23	H	5-NO_2	2-NO_2	F	0.5+3.5	**3e** (86)

a) A mixture of **1** (0.5 mmol) and *t*-BuOK (1.0 mmol) in anhydrous THF (2.5 ml) was stirred at refux under argon. When the deprotection of arylsulfonyl group of **1** was essentially complete and checked by TLC, **2** (0.5 mmol) was added to the above mixture, which continued to reflux under argon monitored by TLC. *b*) "1+2" means 1 h for the deprotection of arylsulfonyl group of **1** and 2 h for the sequent *SN*Ar reactions with **2**, respectively. *c*) No corresponding free indoles were monitored by TLC when the deprotection of *N*-tosyl-2-methylindole or *N*-tosyl-7-methylindole was after 25 and 28 h, respectively. *d*) Even after 12 h, the deprotection of *N*-tosyl-3-methylindole was partially complete and checked by TLC. *e*) Although the deprotection of *N*-(3-nitrobenzene)sulfonylindole was essentially complete for 1.5 h, many by-products were produced and checked by TLC analysis.

very troublesome because of the lower nucleophilicity of the corresponding anion at the indoles' nitrogen. But it is noteworthy in our reaction that it took only 3 h to obtain *N*-(2-nitrobenzene)-5-nitroindole (**3e**) and *N*-(4-nitrobenzene)-5-nitroindole (**3f**) in 88% and 78% yields, respectively, when *N*-tosyl-5-nitroindole was reacted with 2-fluoro- or 4-fluoronitrobenzene (entries 5, 6). *N*-(2-Nitrobenzene)-5-cyanoindole (**3g**) was also obtained in a 87% yield when *N*-tosyl-5-cyanoindole was reacted with 2-fluoronitrobenzene for 4 h (entry 7). When *N*-tosyl-3-methylindole was reacted with 2-fluoro- or 4-fluoronitrobenzene even after 14 h, the corresponding yields of **3h** and **3i** were only 49% and 42%, respectively, mainly because the deprotection of *N*-tosyl-3-methylindole to liberate the corresponding anion (**4**) was difficult due to electronic effect (entries 9, 10). As shown in Table 1, the activated fluoroarenes underwent *SN*Ar reactions with **4** much easier than those chloro and bromo analogues. For example, when the anion liberated from *N*-tosylindole was reacted with 2-fluoro- and 2-chloronitrobenzene, the corresponding yields of **3b** were 94% for 3 h and 34% for 8 h, respectively (entries 2 *vs.* 15); when the anion liberated from *N*-tosyl-5-nitroindole was reacted with 2-fluoro- and 2-chloronitrobenzene, the corresponding yields of **3e** were 88% for 2.5 h and <18% for 8 h, respectively (entries 5 *vs.* 14). Similarly, when the anion liberated from *N*-tosylindole was reacted with 4-fluoro- and 4-bromonitrobenzene, the corresponding yields of **3a** were 93% only for 2 h and 14% even for 12 h, respectively (entries 1 *vs.* 16).

Finally, the cross-coupling reactions of other *N*-arylsulfonylindoles (R^1=H, Cl, Et and NO_2; R^2=H and NO_2) with activated fluoroarenes in the presence of *t*-BuOK were also explored (entries 17—23). The deprotection of arylsulfonylindoles was essentially complete in the presence of *t*-BuOK in 1 h at reflux, and *N*-arylindoles were obtained in 78—91% yields. However, when *N*-(3-nitrobenzene)sulfonylindole was reacted with 2-fluoronitrobenzene, the corresponding yield of **3b** was only 13% (entry 22) because many byproducts were produced during the deprotection of *N*-(3-nitrobenzene)sulfonylindole.

Conclusion

In summary, we have developed an efficient procedure for the synthesis of *N*-arylindoles *via* the consecutive deprotection of *N*-arylsulfonylindoles and *SN*Ar reactions with activated aryl halides (X=F, Cl and Br) in the presence of *t*-BuOK. This one-pot tandem reaction affords an efficient and convenient preparation of *N*-arylindoles that benefit from prior indoles protection by arylsulfonyl group, and can shorten a reaction sequence and improve synthetic efficiency.

Experimental

All the solvents were of analytical grade and the reagents were used as purchased. Thin-layer chromatography (TLC) and silica gel column chromatography were used with silica gel 60 GF_{254} and 200—300 mesh, respectively (Qingdao Haiyang Chemical Co., Ltd.). Melting points were determined on an X-4 micromelting-point apparatus and uncorrected. Infrared (IR) spectra were recorded on a Thermo Nicolet Nexus FTIR-8700 spectrometer. ^{1}H-NMR spectra were recorded on a Bruker Avance DMX 400 MHz instrument using TMS as internal standard and $CDCl_3$ as solvent. HR-MS were carried out with APEX II Bruker 4.7T AS instrument.

General Procedure for the Preparation of the *N*-Arylindoles (3) *via* the Consecutive Deprotection of *N*-Arylsulfonylindoles (1) and *S*$_N$Ar Reactions with Activated Aryl Halides (2) in the Presence of *t*-BuOK A mixture of **1** (0.5 mmol) and *t*-BuOK (1.0 mmol) in anhydrous THF (2.5 ml) was stirred at reflux under argon. When the deprotection of arylsulfonyl group of **1** was essentially complete and checked by TLC for the appropriate time (Table 1), **2** (0.5 mmol) was added to the above mixture, which continued to reflux under argon. The progress of the reaction was monitored by TLC analysis. Then the reaction mixture was cooled to room temperature (rt), and the solvent was evaporated under reduced pressure to give the residue, which was purified by silica gel column chromatography to afford the pure *N*-arylindoles (**3a**—**k**). Compounds **3a**—**c**, **3e**—**f**, **3h**—**i** were characterized according to the procedures previously described.[8] The typical spectral data of compounds **3d**, **3g**, **3j**—**k** were as follows.

3d: White solid, mp 94—95 °C. IR cm^{-1}: 2219, 1600, 1510, 1455, 1344, 1315, 1210, 1174, 838, 763, 749, 729. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.75 (1H, d, J=3.2 Hz), 7.20 (2H, m), 7.34 (1H, d, J=3.2 Hz), 7.60 (3H, m), 7.69 (1H, d, J=8.0 Hz), 7.80 (2H, d, J=8.0 Hz). HR-MS m/z: 219.0914 $[M+H]^+$, Calcd 219.0917.

3g: Yellow solid, mp 186—187 °C. IR cm^{-1}: 2218, 1604, 1519, 1494, 1467, 1342, 1331, 1293, 1221, 1142, 1110, 905, 850, 810, 767, 742, 731. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.80 (1H, d, J=3.6 Hz), 7.13 (1H, d, J=8.4 Hz), 7.29 (1H, d, J=3.2 Hz), 7.41 (1H, d, J=8.8 Hz), 7.57 (1H, d, J=7.6 Hz), 7.67 (1H, m), 7.80 (1H, m), 8.03 (1H, s), 8.10 (1H, d, J=8.0 Hz). HR-MS m/z: 281.1029 $[M+NH_4]^+$, Calcd 281.1033.

3j: White solid, mp 89—91 °C. IR cm^{-1}: 2226, 1594, 1516, 1494, 1450, 1420, 1304, 1284, 1158, 1112, 922, 754, 719. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.60 (3H, s), 6.78 (1H, d, J=3.6 Hz), 7.00 (1H, d, J=6.0 Hz), 7.13 (2H, m), 7.40 (1H, d, J=3.2 Hz), 7.45 (1H, m), 7.60 (1H, d, J=7.6 Hz), 7.70 (1H, m), 7.82 (1H, dd, J=1.2, 8.0 Hz). HR-MS m/z: 233.1068 $[M+H]^+$, Calcd 233.1073.

3k: White solid, mp 89—90 °C. IR cm^{-1}: 2226, 1594, 1512, 1491, 1451, 1340, 1302, 1188, 1123, 924, 806, 773, 723. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.44 (3H, s), 6.70 (1H, d, J=3.2 Hz), 7.03 (1H, d, J=8.4 Hz), 7.13 (1H, s), 7.33 (1 H, d, J=3.6 Hz), 7.48 (1H, m), 7.56 (1H, d, J=8.0 Hz), 7.60 (1H, d, J=8.4 Hz), 7.72 (1H, m), 7.83 (1H, d, J=7.6 Hz). HR-MS m/z: 233.1071 $[M+H]^+$, Calcd 233.1073.

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References and Notes

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31) A mixture of *N*-tosyl-3-methylindole (0.5 mmol) and *t*-BuOK (1.0 mmol) in THF (2.5 ml) was stirred at reflux under argon for 12 h. After cooling, the solvent was evaporated under reduced pressure, and the residue was purified by preparative TLC to give 3-methylindole in a 64% yield.