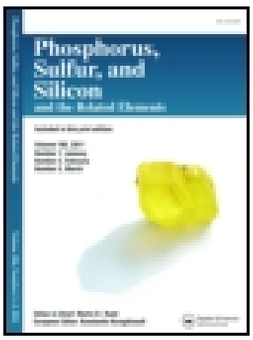

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Catalyst-Free Synthesis of 3-(1-Arylsulfonylalkyl)indoles via Three-Component Reaction of Indoles, Carbonyls, and Arenesulfinic Acids

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Abstract

A catalyst-free three-component reaction of indoles, carbonyls, and arenesulfinic acids performed at room temperature provides direct access to biologically important 3-(1-arylsulfonylalkyl)indoles. This process features mild conditions, low cost, broad substrate scope, and high yields, and mechanistically bis(indolyl)methanes were identified as the key intermediates.

Keywords

Multicomponent reaction; indole functionalization; sulfinic acids

INTRODUCTION

The indole nucleus is a privileged structural motif that has been found in a vast number of alkaloid natural products and of synthetic molecules with significant biological activities,[1-4] and is therefore addressed as "The Lord of the Rings" of aromatic compounds.[5] On the other hand, sulfones are well known for their ability to inhibit various types of enzymatic processes and for their broad spectrum of medicinal applications.[6,7] As a consequence, the introduction of a sulfonyl functionality in the indole system to form, say, 3-(1-arylsulfonylalkyl)indole derivatives, is a common practice in drug design.[8-12] Moreover, they are versatile synthons in organic synthesis and have further scope for a wide range of synthetic transformations.[13-16,19-21,23-25]

3-(1-Arylsulfonylalkyl)indoles are generally synthesized through acid-promoted/catalyzed Friedel-Crafts reaction of indoles with α-amido sulfones, which are, in advance, prepared from carbamates, aldehydes, and sodium sulfinates.[17-20] A complementary indirect entry to these sulfonyl heterocycles is nucleophilic substitution reaction of pre-functionalized 3-alkyl indoles with sodium sulfinates, of which the substrate scope is rather limited.[21,22] Not long ago, Petrini *et al.* disclosed an elegant and straightforward synthesis of 3-(1-arylsulfonylalkyl)indoles via multicomponent reaction (MCR) from simple starting materials, yet in his condensation 50 mol% of Brønsted acid was needed as promoter.[23-25] Given the proven importance of sulfonyl indoles, there is still an urgent need for mild and economic protocols for their preparation.

In a step- and atom-economical manner, MCR is a powerful tool for rapid construction of molecular complexity.[26,27] As the electron-rich indole nucleus exhibits an enhanced reactivity toward electrophiles, we speculated that arenesulfinic acids, though a kind of weak acid, might serve dual roles as nucleophile and acid promoter in MCRs of indoles. Herein, we report the successful execution of this scheme, and present a catalyst-free synthesis of 3-(1-arylsulfonylalkyl)indoles via three-component reaction of indoles, carbonyls, and arenesulfinic acids, which is mild, efficient, and cost-effective.

RESULTS AND DISCUSSION

At the outset of the present study, 1*H*-indole **1a**, benzaldehyde **2a**, and *p*-toluenesulfinic acid **3a** were employed as model substrates to screen reaction conditions (Table 1). <**Table 1**> When the MCR was conducted with CH_2Cl_2 as solvent and without any catalyst, target 3-(phenyl(tosyl)methyl)indole **4a** was produced in 76% yield within 1 h (entry 1, note c). Though the yield did not increase appreciably with prolonged reaction time, heating, or addition of 10 mol% of H_2SO_4, an excellent yield of 91% was achieved by using higher loading of **3a** (entry 1). These could be rationalized by the instability of sulfinic acids.[28,29] A series of control experiments confirmed that it made little difference that various Brønsted acids (entry 2), including H_2SO_4, *p*-toluenesulfonic acid (TsOH),[23-25] trifluoromethanesulfonic acid (TfOH), and

trifluoroacetic acid (TFA), or Lewis acids (entry 3), such as $BF_3 \cdot Et_2O$, $FeCl_3$, $SnCl_4$, and Br_2,[30] were additionally added at the loading of 10 mol%. It should be noted that *p*-toluenesulfinic acid **3a** used in these transformations was freshly prepared and carefully washed with water to ensure complete removal of H_2SO_4.[29] Next, we evaluated several solvents in comparison with CH_2Cl_2 and found that with CH_3CN as solvent, product **4a** was delivered in 86% yield after a longer reaction time of 4 h (entry 4), whereas the use of ethyl acetate (entry 5), tetrahydrofuran (THF, entry 6), *N*,*N*-dimethylformamide (DMF, entry 7), ethanol (entry 8) or toluene (entry 9) led to incomplete MCRs even after 24 h, in which only moderate yields of **4a** were furnished. During all these reactions, noticeable amounts of bis(indolyl)methane derivative **Ia** were always observed.

<Table 2>

Having developed optimized reaction conditions (Table 1, entry 1), we subsequently explored the scope of this MCR with respect to the three components, and the results are summarized in Table 2. It proved that while indoles **1** bearing a phenyl (entry 2) or alkyl group (entry 3) at 2-position reacted with benzaldehyde **2a** and *p*-toluenesulfinic acid **3a** smoothly to provide the corresponding sulfones **4b,c** in excellent yields, ethyl indole-2-carboxylate gave product **4d** in only 33% yield even when the reaction was run with 3 equivalents of **3a** at reflux temperature for 12 h (entry 4). A range of electron-rich and electron-deficient indoles substituted at C(5)-C(7) all

worked well in the MCR, giving expected products **4e,f,h,i** in high to excellent yields (entries 5, 6, 8, and 9), except in the case concerning 5-nitroindole, which gave product **4g** only in a moderate yield even after the temperature was elevated to 82 °C and 3 equivalents of **3a** were employed (entry 7). Target sulfonyl indole **4j** was delivered in 93% yield from *N*-methylindole (entry 10), whereas the MCR carried out with *N*-phenylsulfonylindole did not proceed even under those enhanced conditions (entry 11). The poor or non-reactivity of indole-2-carboxylate (entry 4), 5-nitroindole (entry 7), and *N*-phenylsulfonylindole (entry 11) was readily rationalized by their far more electron-deficient characteristic. Then, other carbonyls **2** were tested. It was found that both selected aromatic aldehydes bearing either electron-donating (entries 12-14) or -withdrawing substituents (entries 15-18) at para, meta, or ortho positions, and a heteroaromatic one (entry 19) reacted efficiently with **1a** and **3a** to provide desired products **4k-r** in high to excellent yields. Aliphatic paraformaldehyde also underwent the same reaction to give product **4s** in 85% yield (entry 20). Notably, electrophile **2** could be cyclohexanone as well, and the corresponding sulfone **4t** was obtained in a high yield (entry 21). Finally, the scope of arenesulfinic acids **3** was investigated, and it proved that **3** having either a phenyl (entry 22) or an electron-deficient aromatic group (entry 23) were good substrates too, giving desired sulfonyl derivatives **4u,v** in high to excellent yields. The irregular and often enough relatively much longer reaction times in many cases (entries 6, 8-10, 14, and 18, for instance), reflected the poor

solubility of related intermediate bis(indolyl)methanes **I** generated during reactions.

<Scheme 1>

In an effort to ascertain the role of the key bisindole derivatives **I**, the reaction of indole **1a**, cyclohexanone, and *p*-toluenesulfinic acid **3a** under optimized conditions was quenched after 1 h, affording bisindole **Ib** in 78% yield, along with sulfonyl product **4t** in 13% yield (Scheme 1a). Then, 3,3'-(phenylmethylene)bisindole **Ia** was prepared and utilized to reacted with sulfinic acid **3a** (Scheme 1b). As might be expected, the reaction proceeded rapidly and within 1 h compound **4a**, the same product obtained in corresponding MCR, was delivered in 94% yield.

<Scheme 2>

On the basis of the above results, a plausible mechanism is outlined in Scheme 2. Initially, well-established condensation of indole **1** with carbonyl compound **2** took place under the acidic conditions and bis(indolyl)methane **I** was first generated,[30] which was known to undergo acid-promoted elimination of a molecule of indole **1** to give vinylogous iminium ion **III** via protonated intermediate **II**.[23,31] At last, **III** was captured by arenesulfinic acid **3** through conjugate addition and sufone **4** was produced.

CONCLUSION

In conclusion, we have developed a catalyst-free and efficient method for the synthesis of

ACCEPTED MANUSCRIPT

3-(1-arylsulfonylalkyl)indoles via MCR of indoles, carbonyls, and arenesulfinic acids, and a mechanism is proposed in which bis(indolyl)methanes were identified as the key intermediates. This reaction is associated with low cost, mild conditions, flexible substitution patterns, and potential synthetic and biomedical utility of the products.

EXPERIMENTAL

General

All chemicals were purchased from commercial sources and used without treatment, unless otherwise indicated. Sulfinic acids **3**[29] and 3,3'-(phenylmethylene)bisindole **Ia**[30] were prepared by reported methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a Bruker Avance II-400 spectrometer. High-resolution mass spectra (HRMS) were obtained using a Bruker MicroTOF II Focus spectrometer (electrospray ionization, ESI). Thin-layer chromatography (TLC) was carried out using silica gel GF254 plates. **4a**,[17-20] **4b**,[32] **4c**,[18-20,23] **4e,k,l,o,p**,[19] **4j**,[17-19] and **4q**[20] are known compounds and their spectral data can be found in literatures. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for the novel products (Figures S 1 – S 24)

General Procedure for Synthesis of Sulfones 4 (4f as Example)

A 25-mL flask was charged with a magnetic stirring bar and *p*-toluenesulfinic acid **3a** (312 mg, 2.0 mmol), followed by addition of CH_2Cl_2 (5.0 mL). After the mixture had been stirred for 1 min to fully dissolve **3a**, 5-bromoindole (196 mg, 1.0 mmol) and benzaldehyde **2a** (0.112 mL, 1.1 mmol) were added, and the resulting solution was stirred at room temperature for 1 h. After 5-bromoindole was consumed, as indicated by TLC, the reaction mixture was quenched with saturated aqueous K_2CO_3 solution (20.0 mL), and extracted with CH_2Cl_2 four times. The solvent of the extract was removed, and the residue was purified by column chromatography (silica gel, petroleum ether–dichloromethane–ethyl acetate = 8:1:1, v/v) to afford sulfone **4f** as a pink crystal (379 mg, 86% yield).

Ethyl 3-(phenyl(tosyl)methyl)-1*H*-indole-2-carboxylate (4d): White crystal; mp 187–188 °C (dec); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.29 (s, 3H), 4.22-4.34 (m, 2H), 7.15-7.24 (m, 4H), 7.29-7.41 (m, 6H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 8.23 (d, *J* = 8.4 Hz, 1H), 11.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 161.5 (*C*O_2Et), 144.8 (ArC), 136.9 (ArC), 135.9 (ArC), 133.7 (ArC), 130.1 (2ArC), 129.7 (2ArC), 129.0 (2ArC), 128.7 (ArC), 128.5 (2ArC), 125.9 (ArC), 125.7 (ArC), 125.6 (ArC), 124.2 (ArC), 121.2 (ArC), 114.1 (ArC), 113.4 (ArC), 67.6 (CH), 61.4 (CH_2), 21.4 (CH_3), 14.6 (CH_2*C*H_3); HRMS (ESI-TOF) Calcd for $C_{25}H_{24}NO_4S^+$ ($[M+H]^+$) 434.1421. Found 434.1422.

5-Bromo-3-(phenyl(tosyl)methyl)-1*H*-indole (4f): Pink crystal; mp 169–170 °C (dec); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.30 (s, 3H), 6.28 (s, 1H), 7.17 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.28-7.34 (m, 4H), 7.56-7.61 (m, 4H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 11.54 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 144.5 (ArC), 135.9 (ArC), 134.5 (ArC), 134.3 (ArC), 130.6 (2ArC), 129.7 (2ArC), 129.3 (ArC), 129.0 (2ArC), 128.7 (2ArC), 127.5 (ArC), 124.5 (ArC), 121.5 (ArC), 114.0 (ArC), 112.3 (ArC), 106.8 (ArC), 66.4 (CH), 21.5 (CH_3); HRMS (ESI-TOF) Calcd for $C_{22}H_{19}BrNO_2S^+$ ($[M+H]^+$) 440.0314. Found 440.0312.

5-Nitro-3-(phenyl(tosyl)methyl)-1*H*-indole (4g): Light yellow solid; mp 200–201 °C (dec); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.27 (s, 3H), 6.53 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.30-7.35 (m, 3H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.65 (dd, *J* = 6.0, 7.6 Hz, 2H), 7.94-7.97 (m, 2H), 8.71 (d, *J* = 2.0 Hz, 1H), 12.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 144.5 (ArC), 141.4 (ArC), 139.0 (ArC), 135.8 (ArC), 134.1 (ArC), 130.6 (2ArC), 130.0 (ArC), 129.9 (2ArC), 129.6 (2ArC), 129.0 (2ArC), 128.8 (ArC), 126.9 (ArC), 117.3 (ArC), 116.9 (ArC), 112.6 (ArC), 110.0 (ArC), 66.1 (CH), 21.4 (CH_3); HRMS (ESI-TOF) Calcd for $C_{22}H_{19}N_2O_4S^+$ ($[M+H]^+$) 407.1060. Found 407.1042.

6-Chloro-3-(phenyl(tosyl)methyl)-1*H*-indole (4h): Pink crystal; mp 176–177 °C (dec); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.27 (s, 3H), 6.27 (s, 1H), 7.00 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.28-7.32 (m, 3H), 7.42 (d, *J* = 1.6 Hz, 1H), 7.59-7.63 (m, 4H), 7.71 (d, *J* = 8.4

Hz, 1H), 7.77 (d, *J* = 2.4 Hz, 1H), 11.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 144.3 (ArC), 136.3 (ArC), 136.1 (ArC), 134.3 (ArC), 130.6 (2ArC), 129.6 (2ArC), 128.9 (2ArC), 128.7 (2ArC), 127.1 (ArC), 126.7 (ArC), 126.3 (ArC), 120.7 (ArC), 119.8 (ArC), 111.6 (ArC), 107.4 (ArC), 66.8 (CH), 21.4 (CH_3); HRMS (ESI-TOF) Calcd for $C_{22}H_{19}ClNO_2S^+$ ($[M+H]^+$) 396.0820. Found 396.0823.

7-Methyl-3-(phenyl(tosyl)methyl)-1*H*-indole (4i): Pink crystal; mp 195–196 °C (dec); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.27 (s, 3H), 2.42 (s, 3H), 6.21 (s, 1H), 6.86 (s, 2H), 7.25-7.28 (m, 5H), 7.47-7.70 (m, 6H), 11.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 144.2 (ArC), 136.4 (ArC), 135.4 (ArC), 134.6 (ArC), 130.7 (2ArC), 129.7 (2ArC), 128.9 (2ArC), 128.6 (2ArC), 127.1 (ArC), 125.3 (ArC), 122.5 (ArC), 121.1 (ArC), 119.6 (ArC), 116.7 (ArC), 107.5 (ArC), 67.1 (CH), 21.4 (SO_2Ph-CH_3), 17.1 (C7-CH_3); HRMS (ESI-TOF) Calcd for $C_{23}H_{22}NO_2S^+$ ($[M+H]^+$) 376.1366. Found 376.1366.

3-((3,4-Dimethoxyphenyl)(tosyl)methyl)-1*H*-indole (4m): Light yellow solid; mp 180–181 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.65 (s, 3H), 3.74 (s, 3H), 5.56 (s, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.86-7.05 (m, 6H), 7.19 (dd, *J* = 6.0, 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.59 (s, 1H), 8.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2 (ArC), 148.6 (ArC), 144.3 (ArC), 135.6 (ArC), 135.4 (ArC), 129.3 (2ArC), 129.0 (2ArC), 127.0 (ArC), 125.8 (ArC), 124.8 (ArC), 122.9 (ArC), 122.4 (ArC), 119.9 (ArC), 118.4 (ArC), 113.2 (ArC),

111.5 (ArC), 110.9 (ArC), 107.4 (ArC), 68.9 (CH), 55.9 (OCH_3), 55.8 (OCH_3), 21.6 (CH_3); HRMS (ESI-TOF) Calcd for $C_{24}H_{24}NO_4S^+$ ($[M+H]^+$) 422.1421. Found 422.1425.

3-((4-Bromophenyl)(tosyl)methyl)-1*H*-indole (4n): Light pink crystal; mp 170–171 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 6.30 (s, 1H), 6.95-7.08 (m, 2H), 7.25-7.36 (m, 3H), 7.54-7.70 (m, 8H), 11.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (ArC), 136.1 (ArC), 135.9 (ArC), 134.0 (ArC), 132.8 (2ArC), 131.6 (2ArC), 129.7 (2ArC), 128.9 (2ArC), 127.3 (ArC), 125.8 (ArC), 122.1 (ArC), 122.0 (ArC), 119.5 (ArC), 119.1 (ArC), 112.0 (ArC), 106.6 (ArC), 66.2 (CH), 21.5 (CH_3); HRMS (ESI-TOF) Calcd for $C_{22}H_{19}BrNO_2S^+$ ($[M+H]^+$) 440.0314. Found 440.0317.

3-(Thiophen-2-yl(tosyl)methyl)-1*H*-indole (4r): Pinkish crystal; mp 196–197 °C (dec); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.30 (s, 3H), 6.59 (s, 1H), 6.97-7.00 (m, 2H), 7.09 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.21 (d, *J* = 3.2 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 5.2 Hz, 1H), 7.57-7.59 (m, 3H), 7.74 (d, *J* = 8.0 Hz, 1H), 11.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 144.4 (ArC), 136.5 (ArC), 135.9 (ArC), 135.5 (ArC), 130.1 (ArC), 129.6 (2ArC), 129.0 (2ArC), 127.8 (ArC), 127.14 (ArC), 127.12 (ArC), 126.6 (ArC), 122.0 (ArC), 119.6 (ArC), 119.5 (ArC), 112.0 (ArC), 107.0 (ArC), 63.1 (CH), 21.5 (CH_3); HRMS (ESI-TOF) Calcd for $C_{20}H_{18}NO_2S_2^+$ ($[M+H]^+$) 368.0773. Found 368.0789.

3-(Tosylmethyl)-1*H*-indole (4s): Red crystal; mp 158–159 °C; ^{1}H NMR (400 MHz,

DMSO-*d6*) δ 2.35 (s, 3H), 4.73 (s, 2H), 6.95-7.11 (m, 3H), 7.34-7.62 (m, 6H), 11.15 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 144.4 (ArC), 136.5 (ArC), 136.3 (ArC), 129.9 (2ArC), 128.5 (2ArC), 127.6 (ArC), 127.4 (ArC), 121.8 (ArC), 119.44 (ArC), 119.37 (ArC), 112.0 (ArC), 102.0 (ArC), 53.7 (CH_2), 21.5 (CH_3); HRMS (ESI-TOF) Calcd for $C_{16}H_{16}NO_2S^+$ ($[M+H]^+$) 286.0896. Found 286.0887.

3-(1-Tosylcyclohexyl)-1*H*-indole (4t): White crystal; mp 184–185 °C (dec); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 0.85-2.09 (m, 10H), 2.31 (s, 3H), 6.93-7.18 (m, 7H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 11.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 144.1 (ArC), 137.2 (ArC), 132.8 (ArC), 130.2 (2ArC), 129.2 (2ArC), 129.0 (ArC), 126.8 (ArC), 121.7 (ArC), 121.2 (ArC), 119.5 (ArC), 112.2 (ArC), 106.9 (ArC), 69.5 (CQ), 25.3 (CH_2), 22.1 (CH_2), 21.5 (CH_3); HRMS (ESI-TOF) Calcd for $C_{21}H_{24}NO_2S^+$ ($[M+H]^+$) 354.1522. Found 354.1520.

3-(Phenyl(phenylsulfonyl)methyl)-1*H*-indole (4u): Light gray solid; mp 193–194 °C (dec); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.26 (s, 1H), 6.94 (td, *J* = 8.0, 0.8 Hz, 1H), 7.05 (td, *J* = 8.0, 0.8 Hz, 1H), 7.28-7.35 (m, 4H), 7.43 (dd, *J* = 7.6, 8.0 Hz, 2H), 7.55 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.60-7.65 (m, 3H), 7.70-7.72 (m, 3H), 11.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 139.0 (ArC), 135.7 (ArC), 134.3 (ArC), 133.9 (ArC), 130.7 (2ArC), 129.2 (2ArC), 128.8 (2ArC), 128.6 (2ArC), 127.3 (ArC), 125.9 (ArC), 122.0 (ArC), 119.4 (ArC), 119.1 (ArC), 112.0 (ArC), 106.7 (ArC), 66.9 (CH); HRMS (ESI-TOF) Calcd for $C_{21}H_{18}NO_2S^+$ ($[M+H]^+$) 348.1053. Found

348.1049.

3-((4-Chlorophenylsulfonyl)(phenyl)methyl)-1*H*-indole (4v): Pale reddish-brown solid; mp 198–199 °C (dec); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.30 (s, 1H), 6.94-7.08 (m, 3H), 7.31-7.36 (m, 4H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.64-7.71 (m, 5H), 11.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 138.9 (ArC), 138.0 (ArC), 135.8 (ArC), 134.2 (ArC), 130.8 (2ArC), 130.7 (2ArC), 129.3 (2ArC), 128.7 (2ArC), 127.4 (ArC), 126.1 (ArC), 122.0 (ArC), 119.5 (ArC), 119.1 (ArC), 112.0 (ArC), 106.5 (ArC), 67.1 (CH); HRMS (ESI-TOF) Calcd for $C_{21}H_{17}ClNO_2S^+$ ($[M+H]^+$) 382.0663. Found 382.0661.

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SUPPORTING INFORMATION

Supplementary data of this article can be accessed on the publisher's website, www.tandfonline.com/gpss

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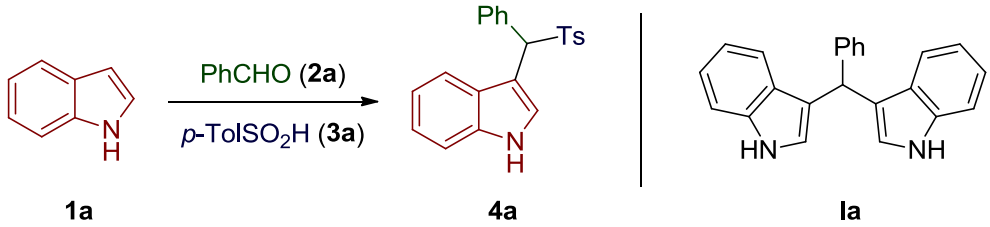
Table 1. Optimization of reaction conditions[a]



1a **4a** **Ia**

Entry	Solvent	Time (h)	Yield of **4a** (%)[b]
1	CH_2Cl_2	1	91 (76)[c]
2[d]	CH_2Cl_2	1	90-92
3[e]	CH_2Cl_2	1	89-92
4	CH_3CN	4	86
5	EtOAc	24	65
6	THF	24	55
7	DMF	24	62
8	EtOH	24	60
9	Toluene	24	66

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), **3a** (2.0 mmol), solvent (5.0 mL), room temperature.

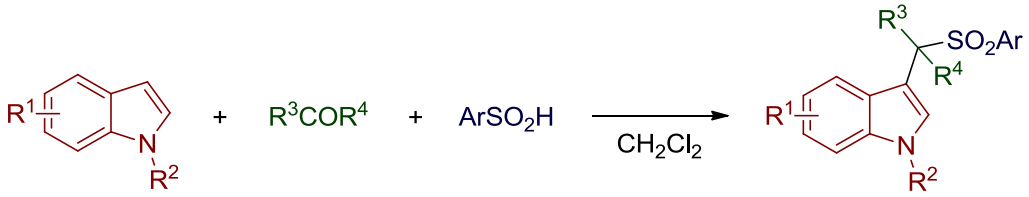
[b]Isolated yields.

[c]1.0 equivalent of **3a** was used.

[d]10 mol% of H_2SO_4, TsOH, TfOH, or TFA was additionally added as catalyst.

[e]10 mol% of $BF_3 \cdot Et_2O$, $FeCl_3$, $SnCl_4$, or Br_2 was additionally added as catalyst.

Table 2. Synthesis of 3-(1-arylsulfonylalkyl)indoles **4**[a]



1 2 3 4

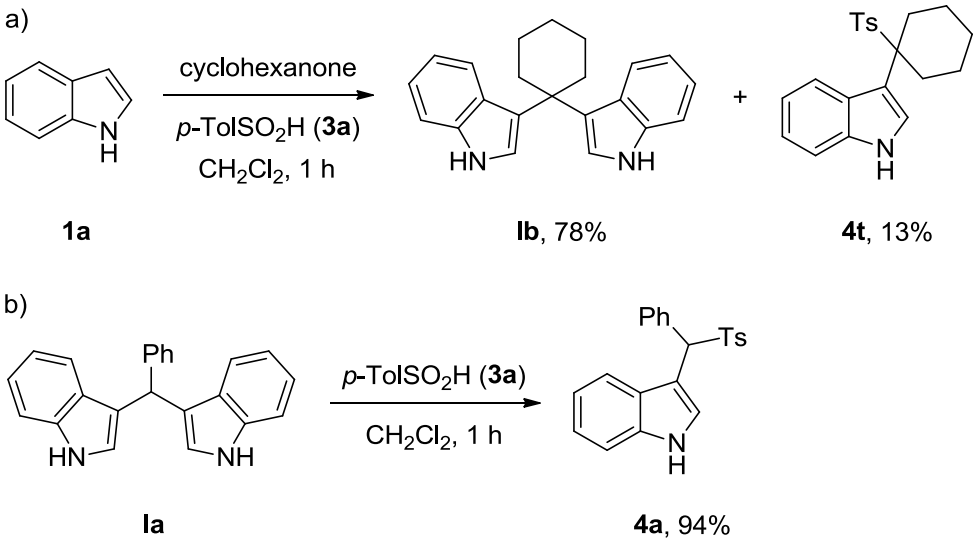
Entry	R^1	R^2	R^3	R^4	Ar	*t* (h)	**4**	Yield (%)[b]
1	H	H	Ph	H	4-MePh	1	**4a**	91
2	2-Ph	H	Ph	H	4-MePh	4	**4b**	95
3	2-Me	H	Ph	H	4-MePh	1	**4c**	97
4[c]	2-CO_2Et	H	Ph	H	4-MePh	24	**4d**	33
5	5-MeO	H	Ph	H	4-MePh	2	**4e**	82
6	5-Br	H	Ph	H	4-MePh	24	**4f**	86
7[c]	5-NO_2	H	Ph	H	4-MePh	24	**4g**	45
8	6-Cl	H	Ph	H	4-MePh	12	**4h**	90
9	7-Me	H	Ph	H	4-MePh	12	**4i**	90
10	H	Me	Ph	H	4-MePh	12	**4j**	93
11[c]	H	SO_2Ph	Ph	H	4-MePh	24		0
12	H	H	4-MePh	H	4-MePh	1	**4k**	94
13	H	H	4-MeOPh	H	4-MePh	1	**4l**	88

14	H	H	3,4-$(MeO)_2$Ph	H	4-MePh	24	**4m**	88
15	H	H	4-BrPh	H	4-MePh	3	**4n**	92
16	H	H	4-ClPh	H	4-MePh	3	**4o**	90
17	H	H	2-ClPh	H	4-MePh	4	**4p**	91
18	H	H	4-NO_2Ph	H	4-MePh	24	**4q**	84
19	H	H	2-Thienyl	H	4-MePh	5	**4r**	82
20	H	H	H	H	4-MePh	24	**4s**	85
21	H	H	$(CH_2)_5$		4-MePh	6	**4t**	81
22	H	H	Ph	H	Ph	4	**4u**	86
23	H	H	Ph	H	4-ClPh	2	**4v**	95

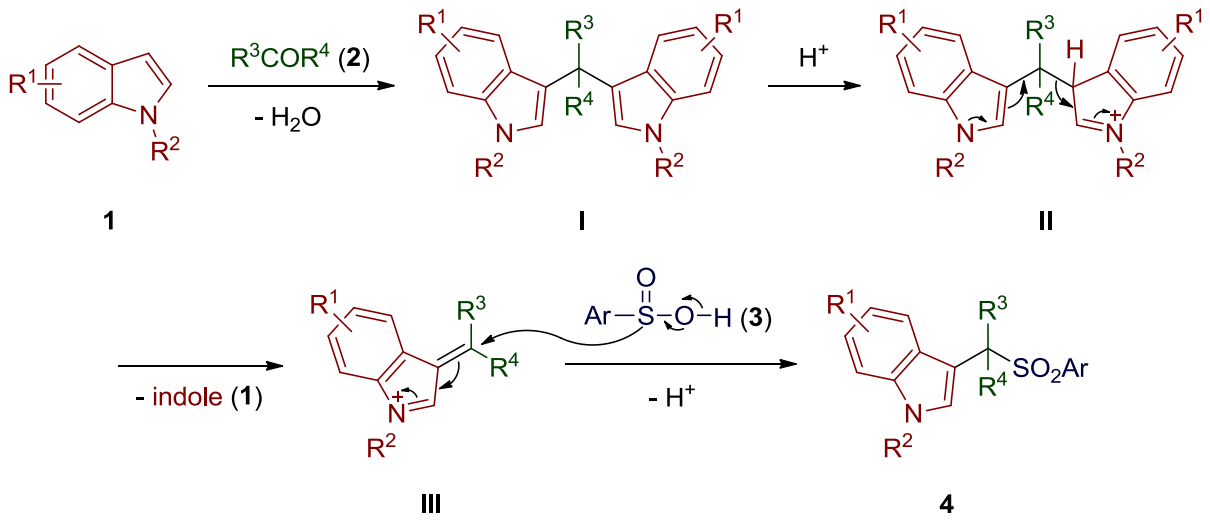
[a]Reaction conditions: **1** (1.0 mmol), **2** (1.1 mmol), **3** (2.0 mmol), CH_2Cl_2 (5.0 mL), room temperature.

[b]Isolated yields.

[c]The reaction was run at 82 °C with 3 equiv of *p*-toluenesulfinic acid **3a** which was added in three equal portions at one-hour intervals.



Scheme 1. Mechanistic investigations.



Scheme 2. Proposed mechanism.