Multifunctionalization of Indoles: Synthesis of 3-Iodo-2-sulfonyl Indoles

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The selective multifunctionalization of indoles by using thiosulfonates, trimethyl sulfoxonium iodide (Me_3SOI), and H_2O_2 was studied. The reaction of thiosulfonates with Me_3SOI and H_2O_2 produced sulfonyl radicals and an iodination reagent, both of which were incorporated in indoles to form 3-iodo-2-sulfonyl indoles under carefully controlled conditions. The related reaction mechanism and the substrate scope of 3-iodo-2-sulfonyl indoles are presented.

Keywords: Sulfonylation, Indole, Iodination, Thiosulfonate, Multifunctionalization

Introduction

Sulfonylated indoles are useful building blocks in therapeutic agents and drugs.[1] Apart from the development of a variety of synthetic methods involving the incorporation of a sulfonyl group in indole derivatives, the use of efficient sulfonylating agents for the synthesis of sulfonylated indoles has been investigated; sulfonyl chloride, sodium sulfinates, and sulfonyl hydrazides are commonly employed for 2- or 3-sulfonylation of indoles.[2,3] In particular, for the synthesis of 2-sulfonyl indoles, sodium sulfinates and sulfonyl hydrazides are commonly used under oxidation conditions involving I^- or I_2. It is known that the reaction of iodine with sulfonyl precursors produces sulfonyl radicals that promote the coupling reaction of the sulfonyl group with indoles in a radical manner. Although iodine is a good halogenation reagent,[4] the incorporation of the iodo group in sulfonylated indoles is rare.1c Therefore, the development of protocols for promoting the site-selective introduction of both sulfonyl and iodo groups in indoles would be useful, since iodo- and sulfonyl-functionalized indoles can be used as useful building blocks in transition metal catalysis.[5]

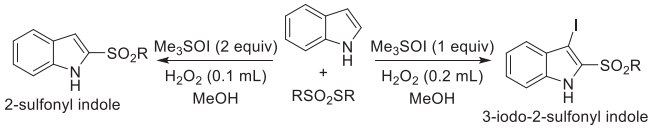
Our research group has been rigorously studying the sulfonylation of organic compounds by using thiosulfonates,[6] which are synthesized via the copper-catalyzed aerobic oxidation of thiols.[7] In the presence of I^- or I_2, thiosulfonates are converted to sulfonyl iodides. These sulfonyl iodides promoted the formation of C-S bonds, leading to the incorporation of sulfonyl groups in the organic compounds. In this study, the combination of thiosulfonates, trimethyl sulfoxonium iodide (Me_3SOI), and H_2O_2 induced the selective C2- and C3-multifunctionalization of indoles. The judicious variation of the reaction conditions helped control the product distribution, affording 3-iodo-2-sulfonyl indoles over 2-sulfonyl indoles selectively (Scheme 1).

Experimental

General Procedure for the Synthesis of 3-Iodo-2-sulfonyl indole. Trimethylsulfoxonium iodide (55.1 mg, 0.25 mmol) was added to a mixture of *S*-phenyl benzenesulfonothiolate (125.2 mg, 0.50 mmol) and indole (29.3 mg, 0.25 mmol) with 0.5 mL methanol in a 5 mL round-bottom flask under N_2 atmosphere. The solution was stirred at 0 °C for 1 min. Then, 0.2 mL hydrogen peroxide (34.5 wt % in H_2O) was slowly added to the reaction mixture at 0 °C for 10 min. The reaction was stirred at room temperature for 16 h. The reaction mixture was extracted with aqueous sodium thiosulfate solution and dichloromethane. The organic layer was dried with sodium sulfate, concentrated, and purified by column chromatography on a silica gel column eluting with 5% ethyl acetate in hexane.

3-Iodo-2-(phenylsulfonyl)-1H-indole (1c). The representative experimental procedure was applied to *S*-phenyl benzenesulfonothioate (125.2 mg, 0.50 mmol) with indole (29.3 mg, 0.25 mmol) to obtain **1c** as yellow solid in 53% (50.8 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.82 (s, 1H), 8.13 (d, J = 7.6 Hz, 2H), 7.59–7.62 (m, 1H), 7.52 (t, J = 7.9 Hz, 2H), 7.48 (d, J = 8.3 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.24 (q, J = 7.6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): 140.32, 136.14, 133.99, 133.79, 131.38, 129.35, 128.00, 127.24, 123.21, 122.42, 112.72, 65.25 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{14}H_{10}NO_2SI$, calcd: 382.9477, found: 382.9478. FTIR (neat, cm^{-1}): 3325, 2922, 1319, 1144, 724 cm^{-1}. Mp (°C): 148–149 °C.

2-((4-Fluorophenyl)sulfonyl)-3-iodo-1H-indole (2c). The representative experimental procedure was applied to *S*-(4-fluorophenyl) 4-fluorobenzenesulfonothioate (143.1 mg, 0.50 mmol) with indole (29.3 mg, 0.25 mmol) to obtain **2c** as yellow solid in 52% (51.5 mg) yields. ^{1}H NMR ($CDCl_3$,



Scheme 1. Chemoselective synthesis of sulfonylated indoles.

600 MHz): δ 9.76 (s, 1H), 8.14 (q, *J* = 4.1 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 8.3 Hz, 2H) ppm. ^{13}C NMR (CDCl3, 151 MHz): δ 166.01 (d, *J* = 257.3 Hz) 136.37, 136.16, 133.66, 131.41, 131.00 (d, *J* = 8.758 Hz), 127.42, 123.28, 122.59, 116.74 (d, *J* = 23.3 Hz), 112.75, 65.38 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{14}H_9FNO_2SI$, calcd: 400.9383, found: 400.9380. FTIR (neat, cm^{-1}): 3326, 2923, 1589, 1491, 1323, 1141 cm^{-1}. Mp (°C): 142 °C.

3-Iodo-2-tosyl-1H-indole (3c). The representative experimental procedure was applied to *S*-(*p*-tolyl) 4-methylbenzenesulfonothioate (139.2 mg, 0.50 mmol) with indole (29.3 mg, 0.25 mmol) to obtain **3c** as brown solid in 10% (9.9 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.64 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.24 (q, *J* = 8.0 Hz, 1H), 2.40 (s, 3H) ppm. ^{13}C NMR (CDCl3, 151 MHz): δ 145.12, 137.39, 135.95, 134.29, 131.41, 129.95, 128.08, 127.09, 123.19, 122.36, 112.59, 64.76, 21.75 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{15}H_{12}NO_2SI$, calcd: 396.9634, found: 396.9634. FTIR (neat, cm^{-1}): 3318, 2923, 1492, 1320, 1144, 678 cm^{-1}. Mp (°C): 155 °C.

3-Iodo-5-methyl-2-(phenylsulfonyl)-1H-indole (4c). The representative experimental procedure was applied to *S*-phenyl benzenesulfonothioate (125.2 mg, 0.50 mmol) with 5-methylindole (32.8 mg, 0.25 mmol) to obtain **4c** as yellow solid in 52% (51.6 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.67 (s, 1H), 8.11 (d, *J* = 8.3 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 9.6 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 2.44 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): 140.45, 134.50, 133.88, 133.56, 132.15, 131.54, 129.29, 129.24, 127.94, 122.34, 112.38, 64.63, 21.50 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{15}H_{12}NO_2SI$, calcd: 396.9634, found: 396.9631. FTIR (neat, cm^{-1}): 3324, 2920, 1309, 1143, 753 cm^{-1}. Mp (°C): 189 °C.

5-Fluoro-3-iodo-2-(phenylsulfonyl)-1H-indole (5c). The representative experimental procedure was applied to *S*-phenyl benzenesulfonothioate (125.2 mg, 0.50 mmol) with 5-fluoroindole (33.8 mg, 0.25 mmol) to obtain **5c** as brown solid in 32% (31.6 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.12 (s, 1H), 8.12 (d, *J* = 8.3 Hz, 2H), 7.60–7.62 (m, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.39 (q, *J* = 4.4 Hz, 1H), 7.11 (t, *J* = 9.0 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 159.11 (d, J = 240.09 Hz), 140.02, 135.25, 134.20, 132.80, 131.99 (d, *J* = 10.57 Hz), 129.45, 128.05, 116.64 (d, *J* = 27.18 Hz), 114.24, 107.75 (d, *J* = 24.16 Hz), 64.18 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{14}H_9FNO_2SI$, calcd: 400.9383, found: 400.9385. FTIR (neat, cm^{-1}): 3330, 2923, 1498, 1310, 1141, 600 cm^{-1}. Mp (°C): 175 °C.

3-Iodo-5-methoxy-2-(phenylsulfonyl)-1H-indole (6c). The representative experimental procedure was applied to *S*-phenyl benzenesulfonothioate (125.2 mg, 0.50 mmol) with 5-methoxyindole (35.2 mg, 0.25 mmol) to obtain **6c** as yellow solid in 50% (50.1 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.66 (s, 1H), 8.10 (d, *J* = 8.3 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 1H), 7.03 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 3.85 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz: δ 156.09, 140.44, 133.88, 133.77, 131.93, 131.22, 129.30, 127.96, 119.26, 113.79, 102.81, 64.36, 55.83 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{15}H_{12}FNO_3SI$, calcd: 412.9583, found: 412.9580. FTIR (neat, cm^{-1}): 3319, 2924, 1497, 1319, 1143, 724 cm^{-1}. Mp (°C): 138 °C.

3-Iodo-5-methyl-2-tosyl-1H-indole (7c). The representative experimental procedure was applied to *S*-(p-tolyl) 4-methylbenzenesulfonothioate (139.2 mg, 0.50 mmol) with 5-methylindole (32.8 mg, 0.25 mmol) to obtain **7c** as yellow solid in 19% (19.5 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.32 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 3H), 7.23 (s, 1H), 7.20 (d, *J* = 9.0 Hz, 1H), 2.44 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 144.98, 137.51, 134.23, 134.11, 132.10, 131.60, 129.89, 129.10, 128.05, 122.39, 112.18, 64.19, 21.74, 21.49 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{16}H_{14}NO_2SI$, calcd: 410.9790, found: 410.9793. FTIR (neat, cm^{-1}): 3319, 2920, 1497, 1319, 1143, 680 cm^{-1}. Mp (°C): 160 °C.

5-Fluoro-3-iodo-2-tosyl-1H-indole (8c). The representative experimental procedure was applied to *S*-(p-tolyl) 4-methylbenzenesulfonothioate (139.2 mg, 0.50 mmol) with 5-fluoroindole (33.8 mg, 0.25 mmol) to obtain **8c** as brown solid in 4% (3.6 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.36 (s, 1H), 7.98 (d, *J* = 9.0 Hz, 2H), 7.37 (q, *J* = 4.8 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.13–7.16 (m, 2H), 2.41 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 159.07 (d, *J* = 241.6 Hz) 145.35, 137.06, 135.97, 132.35, 132.14, 132.11 (d, *J* = 9.1 Hz), 128.19, 116.46 (d, *J* = 27.2 Hz), 113.85 (d, *J* = 7.6 Hz), 107.90 (d, *J* = 25.7 Hz), 63.75, 21.78 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{15}H_{11}FNO_2SI$, calcd: 414.9539, found: 414.9539. FTIR (neat, cm^{-1}): 3310, 2918, 1497, 1142, 1320, 679 cm^{-1}. Mp (°C): 155 °C.

2-((4-Fluorophenyl)sulfonyl)-3-iodo-5-methyl-1H-indole (9c). The representative experimental procedure was applied to *S*-(4-fluorophenyl) 4-fluorobenzenesulfonothioate (143.1 mg, 0.50 mmol) with 5-methylindole (32.8 mg, 0.25 mmol) to obtain **9c** as yellow solid in 56% (57.6 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.64 (s, 1H), 8.11–8.13 (m, 2H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.23 (s, 1H), 7.16–7.21 (m, 3H), 2.44 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 165.90 (d, *J* = 257.5 Hz), 136.48 (d, *J* = 2.8 Hz), 134.50, 133.36, 132.29, 131.53, 130.90

(d, J = 10.1 Hz), 129.38, 122.35, 116.63 (d, J = 23.1 Hz), 112.39, 64.72, 21.51 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{15}H_{11}FNO_2SI$, calcd: 414.9539, found: 414.9541. FTIR (neat, cm^{-1}): 3325, 1588, 1491, 1320, 1139, 833 cm^{-1}. Mp (°C): 80 °C.

5-Fluoro-2-((4-fluorophenyl)sulfonyl)-3-iodo-1H-indole (10c). The representative experimental procedure was applied *S*-(4-fluorophenyl)-4-fluorobenzenesulfonothioate (143.1 mg, 0.50 mmol) with 5-fluoroindole (33.8 mg, 0.25 mmol) to obtain **10c** as red solid in 40% (40.8 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.65 (s, 1H), 8.12–8.14 (m, 2H), 7.39 (q, J = 4.1 Hz, 1H), 7.21 (t, J = 8.6 Hz, 2H), 7.15 (t, J = 8.6 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 166.07 (d, J = 258.8 Hz), 159.14 (d, J = 239.9 Hz), 136.00, 135.26, 132.54, 132.07 (d, J = 10.1 Hz), 131.07 (d, J = 10.1 Hz), 116.87 (d, J = 5.74 Hz), 116.71, 114.02 (d, J = 10.1 Hz), 107.92 (d, J = 24.6 Hz), 64.28 (d, J = 6.04 Hz) ppm. HRMS *m/z* (EI, $[M]^+$): $C_{14}H_8F_2NO_2SI$, calcd: 418.9289, found: 418.9291. FTIR (neat, cm^{-1}): 3319, 1589, 1492, 1142, 1083, 834, 683 cm^{-1}. Mp (°C): 165 °C.

3-Methyl-2-(phenylsulfonyl)-1H-indole (11d). The representative experimental procedure was applied to *S*-phenyl benzenesulfonothioate (125.2 mg, 0.50 mmol) with 3-methylindole (32.8 mg, 0.25 mmol) to obtained **11d** as white solid in 53% (36.1 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.08 (s, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 6.9 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.40 (d, J = 8.3 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 2.54 (t, J = 14.8 Hz, 3H) ppm. ^{13}C NMR (CDCl3, 151 MHz): δ 142.03, 136.09, 133.40, 129.43, 129.23, 128.40, 127.02, 126.34, 120.88, 120.86, 119.00, 112.35, 9.05 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{15}H_{13}NO_2S$, calcd: 271.0667, found: 271.0669. FTIR (neat, cm^{-1}): 3343, 1307, 1150, 628 cm^{-1}. Mp (°C): 140 °C.

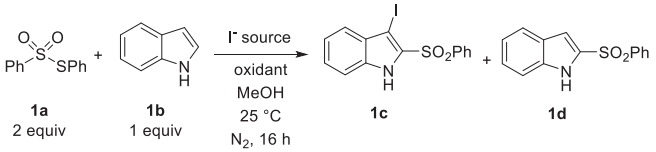
1-Methyl-2-(phenylsulfonyl)-1H-indole (12d). The representative experimental procedure was applied to *S*-phenyl benzenesulfonothioate (125.2 mg, 0.50 mmol) with *N*-methylindole (32.8 mg, 0.25 mmol) to obtained **12d** as red solid in 54% (53.6 mg) yields. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.95–7.96 (m, 2H), 7.70 (d, J = 8.3 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.35–7.38 (m, 2H), 7.30 (d, J = 9.0 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (CDCl3, 151 MHz): δ 141.36, 139.60, 134.84, 133.48, 129.40, 127.72, 125.83, 125.29, 122.95, 121.27, 110.91, 110.33, 31.08 ppm. HRMS *m/z* (EI, $[M]^+$): $C_{15}H_{13}NO_2S$, calcd: 271.0667, found: 271.0668. FTIR (neat, cm^{-1}): 1317, 1153 cm^{-1}. Mp (°C): 125 °C.

Results and Discussion

The coupling reaction of *S*-phenyl benzenesulfonothiolate **1a** with an indole **1b** was examined under the conditions listed in Table 1. The reaction of **1a** and **1b** in the presence of Me_3SOI (1 equiv) and H_2O_2 (0.1 mL) in MeOH (0.5 mL) produced the 3-iodo-2-sulfonyl indole **1c** in 33% yield and the 2-sulfonyl indole **1d** in 26% yield (entry 1). Increasing the amount of H_2O_2 (0.2 mL) dramatically changed the selectivity of the reaction toward **1c** (entry 2). On the other hand, increasing the amount of Me_3SOI (2 equiv) completely changed the reaction route to form **1d** in 57% yield and **1c** in 4% yield (entry 3). The reaction temperature was increased to 65 °C for determining the key factors controlling the formation of **1c** and **1d**, but the major product remained the same (entries 4 and 5). Replacing the iodide source Me_3SOI with KI provided a mixture of **1c** (23% yield) and **1d** (18% yield) (entry 6). The use of NaI and tetrabutylammonium iodide (TBAI) as iodide sources produced **1c** with 25% and 29% yield, respectively (entries 7 and 8). Next, the effect of oxidants was examined. *Tert*-Butyl hydrogen peroxide (TBHP) was employed to form **1c** with 15% yield (entry 9). di-*tert*-Butyl peroxide (DTBP) and oxygen did not promote the desired reaction (entries 10–11). In the absence of oxidants, the reaction did not proceed at room temperature, but product **1d** was isolated with 10% yield along with 3-sulfenylated indole **1e** 60% yield at 65 °C (entry 12).[8] In the absence of an iodide source, no desired product was observed (entry 13). In addition to MeOH, toluene, dichloromethane, DMF, DMSO, CH_3CN, and THF were examined for the formation of **1c** using conditions of entry 2; the reactions in CH_3CN and in THF afforded **1c** with 20% and 11% yields, respectively, but other solvents did not promote the formation of either **1c** or **1d**.

After the optimization results were obtained, the substrate scope of the reaction was investigated (Table 2). The reaction conditions of entries 2 and 3 of Table 1 were employed for synthesizing 3-iodo-2-sulfonyl indoles (Method A) and 2-sulfonyl indoles (Method B), respectively. In the case of the formation of 3-iodo-2-sulfonyl indoles (Method A), the electronic effect of thiosulfonates and indoles was observed. The electron-donating group of thiosulfonates induced the formation of product **3c** in lower yield than **1c** or **2c** (entries 1–3). 5-Substituted indoles containing an electron donor and an electron acceptor were examined. Electron-rich indoles were converted to the desired products **4c** and **6c** with yields higher than the fluoro-substituted product **5c** (entries 4–6). The electronic effect of the indole was not as critical as the effect of substituents of thiosulfonates (entries 7–10). The reactions of 4-methyl substituted thiosulfonates with 5-methyl substituted indole and 5-fluoro substituted indole showed diminished yields, which was due to the low reactivity of 4-methyl substituted thiosulfonates (entries 7 and 8). The reactions of 4-fluoro substituted thiosulfonates with 5-methyl indole and 5-fluoro indole showed higher yields than results of entries 7 and 8 (entries 9 and 10). The reaction of 3-methyl indole with thiosulfonates afforded 2-sulfonyl indoles **11d** with Methods A and B, because the iodination position is blocked by the methyl group (entry 11). Although *N*-methyl indole was exposed to conditions

Table 1. Optimization for the formation of 3-iodo-2-sulfonyl indole **1c**.



Entry	I^- source (equiv)	Oxidant (mL)	Temp. (°C)	Yield (1c)	Yield (1d)
1	Me_3SOI (1)	H_2O_2 (0.1)[a]	25	33%	26%
2	Me_3SOI (1)	H_2O_2 (0.2)[a]	25	53%	—
3	Me_3SOI (2)	H_2O_2 (0.1)[a]	25	4%	57%
4	Me_3SOI (1)	H_2O_2 (0.2)[a]	65	40%	—
5	Me_3SOI (2)	H_2O_2 (0.1)[a]	65	—	36%
6	KI (1)	H_2O_2 (0.1)[a]	25	23%	18%
7	NaI (1)	H_2O_2 (0.1)[a]	25	25%	—
8	TBAI (1)	H_2O_2 (0.1)[a]	25	29%	—
9	Me_3SOI (1)	TBHP (0.16)[b]	25	15%	—
10	Me_3SOI (1)	DTBP (0.21)[c]	25	—	—
11	Me_3SOI (1)	O_2	25	—	—
12	Me_3SOI (1)	—	25	—	—(10%)[d]
13	—	H_2O_2 (0.1)[ass]	25	—	—

[a] H_2O_2 in water (34.5 wt %).
[b] TBHP in water (70 wt %).
[c] DTBP 98%.
[d] 65 °C. Reaction conditions: **1a** (0.5 mmol) and **1b** (0.25 mmol) in MeOH (0.5 mL) were subjected to the indicated reaction conditions.

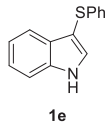
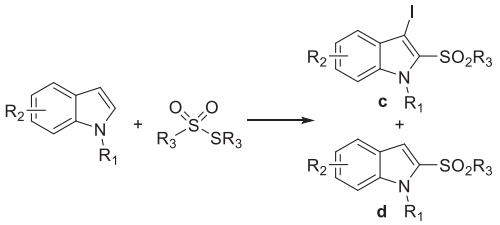


Table 2. Examples of 3-iodo-2-sulfonyl indoles and 2-sulfonyl indoles.



				Method A[a]		Method B[b]	
Entry	R1	R2	R3	Yield (c)	Yield (d)	Yield (c)	Yield (d)
1	H	H	Ph	53% (**1c**)	—	4% (**1c**)	57% (**1d**)
2	H	H	4-FPh	52% (**2c**)	—	5% (**2c**)	30% (**2d**)
3	H	H	4-MePh	10% (**3c**)	—	2% (**3c**)	29% (**3d**)
4	H	5-Me	Ph	52% (**4c**)	—	6% (**4c**)	54% (**4d**)
5	H	5-F	Ph	32% (**5c**)	—	—	45% (**5d**)
6	H	5-MeO	Ph	50% (**6c**)	—	11% (**6c**)	41% (**6d**)
7	H	5-Me	4-MePh	19% (**7c**)	—	3% (**7c**)	40% (**7d**)
8	H	5-F	4-MePh	4% (**8c**)	—	2% (**8c**)	11% (**8d**)
9	H	5-Me	4-FPh	56% (**9c**)	—	9% (**9c**)	44% (**9d**)
10	H	5-F	4-FPh	40% (**10c**)	—	6% (**10c**)	36% (**10d**)
11	H	3-Me	Ph	—	53% (**11d**)	—	55% (**11d**)
12	Me	H	Ph	—	54% (**12d**)	—	68% (**12d**)

[a] Method A: Indole (1 equiv, 0.25 mmol), thiosulphonate (2 equiv), Me_3SOI (1 equiv), and H_2O_2 (0.2 mL) in MeOH (0.5 mL) at r.t.
[b] Method B: Indole (1 equiv, 0.25 mmol), thiosulphonate (2 equiv), Me_3SOI (2 equiv), and H_2O_2 (0.1 mL) in MeOH (0.5 mL) at r.t.

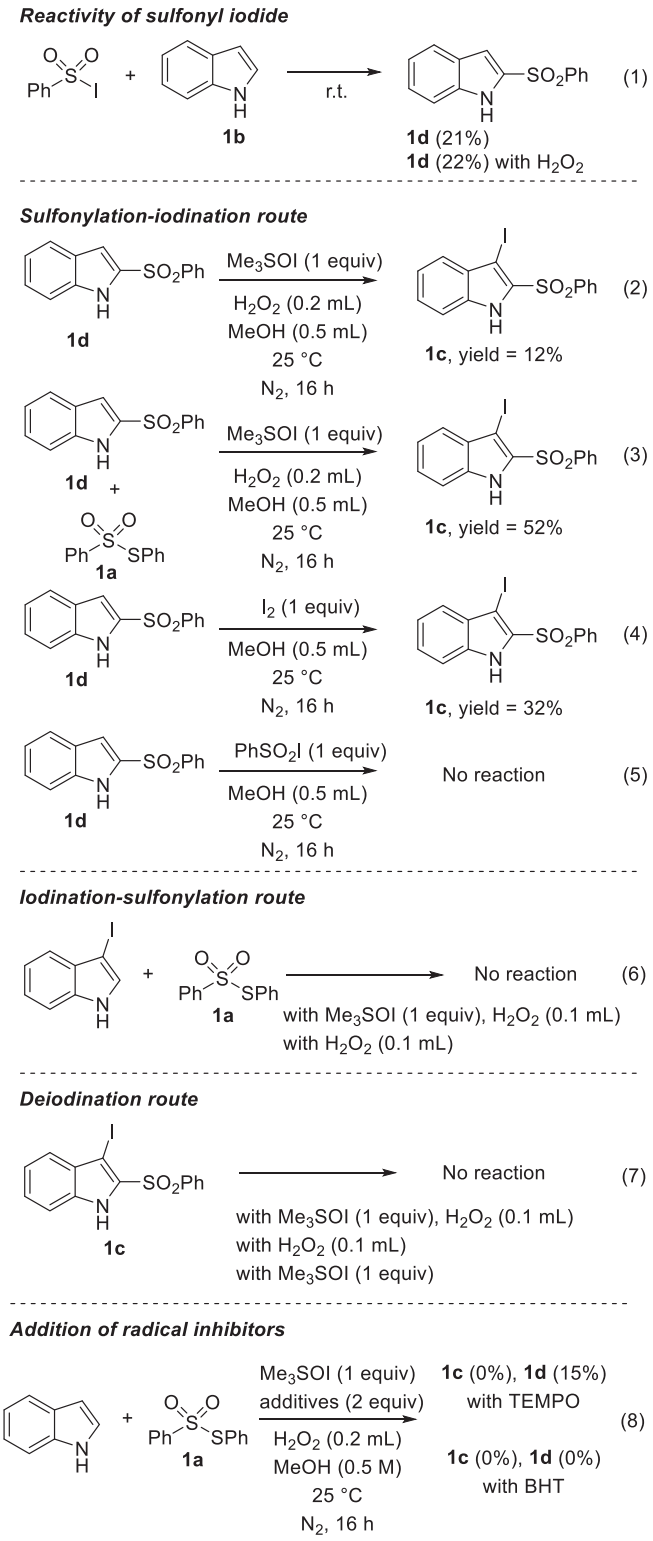
favorable for the formation of 3-iodo-2-sulfonyl indoles, only the 2-sulfonylation product **12d** was obtained in the absence of iodination (entry 12). *N*-sulfonyl indole was examined, but the desired sulfonylation product was not observed.

When reaction conditions favorable for the formation of 2-sulfonyl indoles (Method B) were employed, 2-sulfonyl indoles were isolated as the major product. 4-Fluoro and 4-methyl-substituted thiosulfonates participated in the reactions to form **2d** and **3d** with yields lower than **1d** (entries 2 and 3). The electronic properties of indoles for the formation of 2-sulfonyl indoles were not as important as the formation of 3-iodo-2-sulfonyl indoles (entries 4–10). The reaction of *N*-methyl indole afforded 2-sulfonyl indoles with a yield higher than obtained with Method A (entry 12).

Although the reaction optimization results showed the selective reaction conditions for the formation of **1c** or **1d**, the mechanism for the formation of **1c** or **1d** as the major product was not apparent. Control experiments were performed to investigate the mechanism, and they are described here (Scheme 2). Because past studies have reported the formation of sulfonyl iodide ($PhSO_2I$) from thiosulfonates and iodides, $PhSO_2I$ was reacted with the indole **1b**, and **1d** was obtained formation with 21% and 22% yield without H_2O_2 and with H_2O_2, respectively (Eq. (1)). In entry 12 of Table 1, thiosulfonate **1a** and Me_3SOI were employed in the absence of H_2O_2, and **1d** was not formed at r.t., but at an elevated temperature albeit with a low yield. On the basis of the results of Eq. (1) of Scheme 2 and entry 12 of Table 1, it was observed that in the absence of H_2O_2, a high $PhSO_2I$ concentration and a high temperature favored the formation of **1d** rather than **1c**.

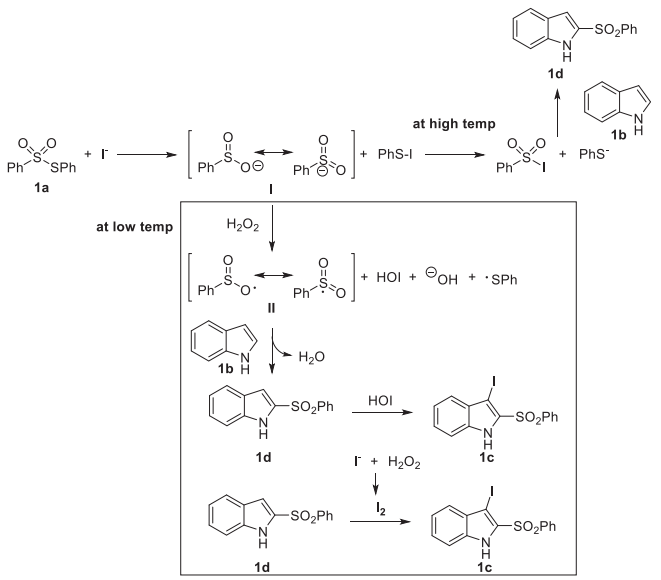
Next, the reaction route for the formation of **1c** was investigated. There are two possible routes: (1) 2-sulfonylation followed by 3-iodination and (2) 3-iodination followed by 2-sulfonylation. As shown in Eqs. (2)–(5), the 2-sulfonyl indoles **1d** underwent iodination to form **1c** under various conditions. The mixture of iodides and peroxides formed I_2, promoting the iodination of **1d**. This is supported by the result of Eq. (4). Interestingly, additional **1a** promoted the iodination of **1d** with considerably higher yield (Eq. (3)). Presumably, the presence of **1a** led to the formation of an efficient iodinating reagent under the indicated reaction conditions. Sulfonyl iodide did not participate in the iodination of **1d** (Eq. (5)), excluding the possibility of $PhSO_2I$ acting an iodinating reagent. Next, iodination and subsequent sulfonylation can be ruled out from the result of Eq. (6). The 3-iodo-2-sulfonyl indole **1c** did not undergo deiodination (Eq. (7)), which excluded the pathway converting **1c** to **1d**. The addition of radical inhibitors (TEMPO and BHT) retard the formation of **1c**. With TEMPO (2 equiv), only **1d** was isolated with 15% yield, and no sulfonylated indole was formed in the presence of BHT (2 equiv) (Eq. (8)).

On the basis of the control experiment results, a plausible reaction mechanism is proposed (Scheme 3). The



Scheme 2. Control experiments.

thiosulfonate **1a** reacts with Me_3SOI to afford $PhSO_2I$, which is instrumental in the formation of the 2-sulfonylated indole **1d** at an elevated temperature. At ambient temperature, sulfinate anion **I** is oxidized by H_2O_2 to form sulfonyl radical **II**, while sulfenyl iodide (PhSI) reacts with H_2O_2 to



Scheme 3. A plausible reaction mechanism.

form hypoiodous acid (HOI).[9] When **1b** is introduced, sulfonyl radical **II** reacts with **1b** to afford **1d**. Subsequently, **1d** is iodinated to form **1c**. For the iodination of **1d**, another route is possible. Under our reaction conditions, I_2 generated from I^- and H_2O_2 induced the iodination of **1d**. However, additional thiosulfonates increased the yield of **1c** (52%) to a value greater than the yield obtained with I_2 generated *in situ* (12%), indicating the presence of an efficient iodination reagent such as HOI. Overall, two factors determined the formation of **1c**: (1) the presence of excess thiosulfonate **1a** compared with I^- and (2) a large excess of oxidants (H_2O_2) promoted the 3-iodo-2-sulfonylation of indoles over the 2-sulfonylation of indoles.

Conclusion

We investigated the reaction conditions and efficient reagent combinations for the multifunctionalization of indoles. In the presence of H_2O_2, the combination of thiosulfonates (sulfonyl precursor) and Me_3SOI (iodo precursor) promoted the formation of 3-iodo-2-sulfonyl indoles. It was found that the complete conversion of 2-sulfonyl indoles to 3-iodo-2-sulfonyl indoles was promoted by the presence of excess thiosulfonates and H_2O_2. Control experiments supported the reaction mechanism proposed here.

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Supporting Information. The supporting information is available free of charge on the Bulletin of the Korean Chemical Society website: NMR spectra of 3-iodo-2-sulfonyl indoles. The NMR spectra of **1c-10c**, **11d**, and **12d** are found in Figures S1–S24.

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