

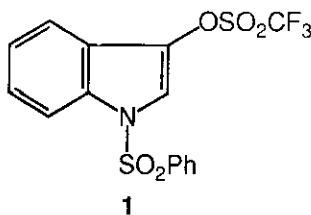
SYNTHESIS OF 1-(PHENYLSULFONYL)INDOL-3-YL
TRIFLUOROMETHANESULFONATE‡

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Abstract - The synthesis of the potentially useful intermediate 1-(phenylsulfonyl)indol-3-yl trifluoromethanesulfonate (triflate) (**1**), via several approaches to the corresponding indoxyl **6**, is described. Of these, the direct oxidation of 1-(phenylsulfonyl)indole (**2**) with magnesium monophtalate (MMPP) in refluxing acetic acid is the most concise route to **6**.

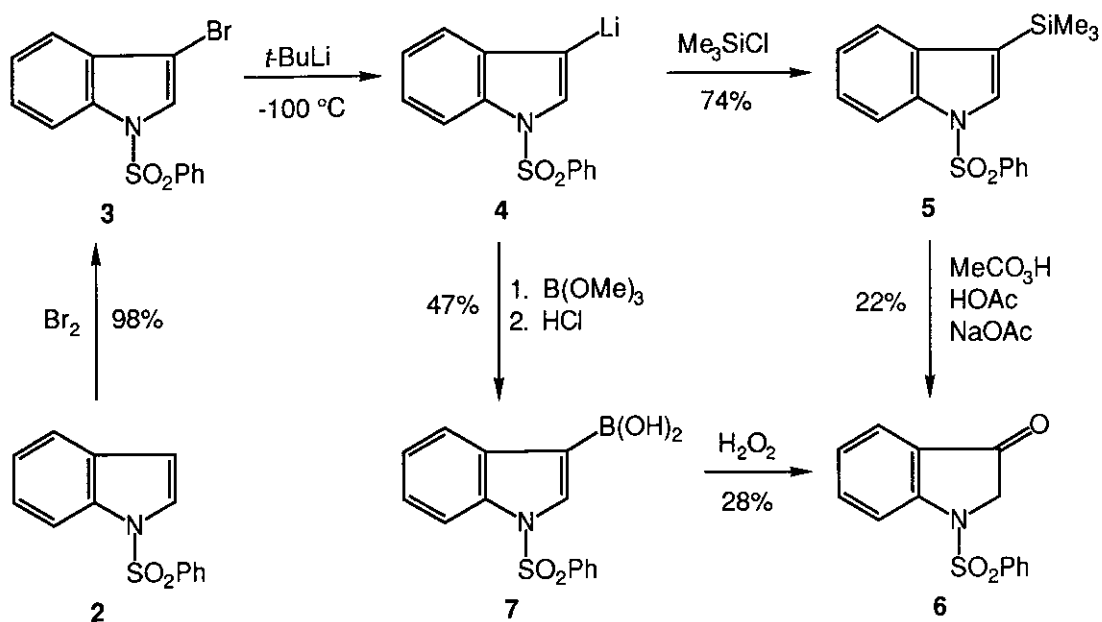
We¹ and others² have shown that 3-haloindoles are useful intermediates in the synthesis of indoles and indole alkaloids via halogen-metal exchange or palladium-catalyzed cross-coupling technologies. In an effort to improve upon and extend the latter methodology, in particular, we sought to prepare an *N*-protected 3-indolyl triflate. In the present paper we describe the synthesis of 1-(phenylsulfonyl)indol-3-yl trifluoromethanesulfonate (triflate) (**1**) via the corresponding indoxyl derivative.



A logical precursor to triflate **1** is the *N*-protected indoxyl **6**.³ Initial attempts to synthesize **6** involved the oxidation procedures indicated in Scheme 1. Thus, treatment of the readily available 3-bromo-1-(phenylsulfonyl)indole (**3**) with *t*-BuLi generates 3-lithio-1-(phenylsulfonyl)indole (**4**).¹ Quenching this species with chlorotrimethylsilane followed by oxidation of silane **5** according to the procedure of Kuwajima and Urabe⁴ produced the target 1-(phenylsulfonyl)indoxyl (**6**) albeit in only 22% yield. No better was a sequence involving the preparation and oxidation of 1-(phenylsulfonyl)indol-3-ylboronic acid (**7**), following the method of Hawthorne,⁵ which afforded **6** in low yield. The structure of **6** is supported by elemental analysis and spectral data. In particular, the ir spectrum of **6** exhibits an aryl ketone carbonyl stretch at 1726 cm⁻¹ and the ¹H nmr spectrum displays a singlet at δ 4.14 for the methylene group.

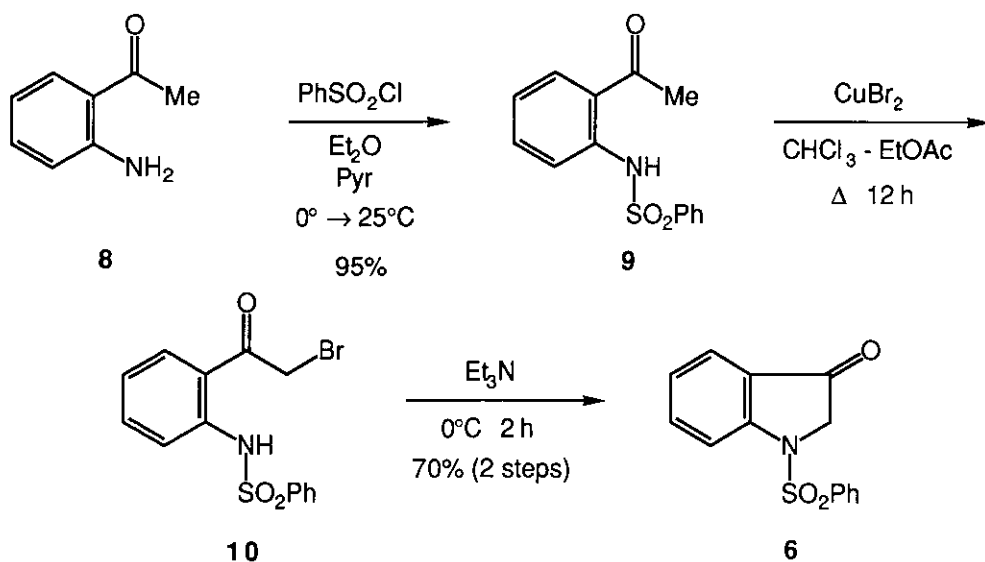
‡We dedicate this paper to the memory of Dr. Tetsuji Kametani.

Scheme 1

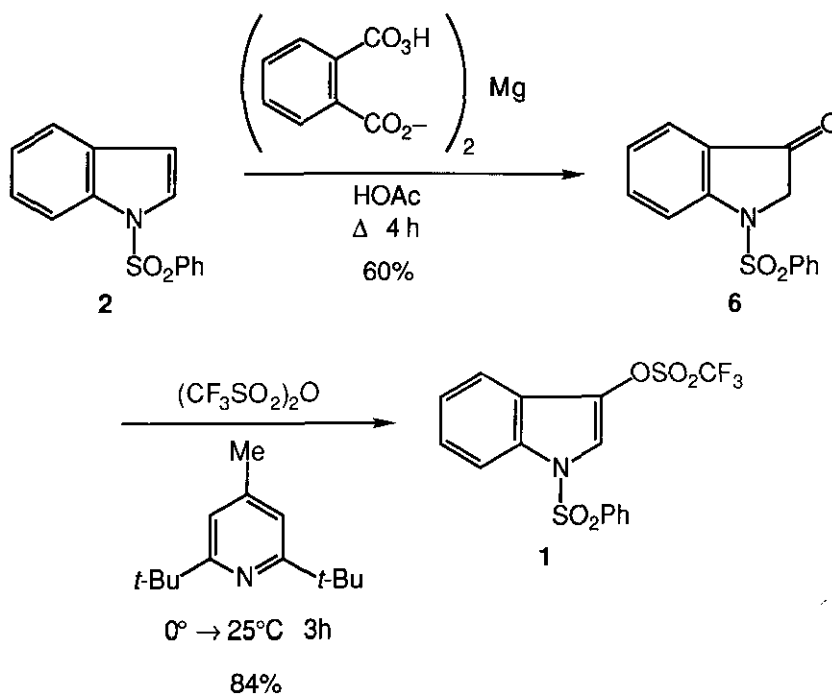


A superior synthesis of indoxyl **6** was realized in a procedure starting with 2-aminoacetophenone (**8**) (Scheme 2). Thus, phenylsulfonylation⁶ of **8** to give **9**, followed by bromination of the ketone group with cupric bromide⁷ gave the bromide **10** in good yield. Although **10** could be isolated and characterized, we found that simply exposing the reaction mixture to triethylamine afforded **6** in 70% overall yield from **9**. This synthesis of **6** suffers from the fact that 2-aminoacetophenone (**8**) is an expensive starting material.

Scheme 2



We then considered that a direct oxidation (epoxidation, rearrangement) of 1-(phenylsulfonyl)indole (**2**) might provide a feasible route to indoxyl **6**. Indeed, treatment of **2** with magnesium monopero-phthalate (MMPP) in refluxing acetic acid for two hours gave **6** in 60% yield. The reaction time is crucial since other products begin to form after two hours. In related chemistry, the oxidation of 1-tosylindole to the corresponding indoxyl with $\text{MoO}_5 \cdot \text{HMPA}$ has been reported but the yield is only 38%.⁸



After some experimentation, we found that the desired triflate **1** could be prepared in high yield from indoxyl **6** by treatment with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine.⁹ Pyridine could not be used in this regard. The indole triflate **1** is a stable crystalline solid whose structure is fully supported by analytical and spectral data. Our studies of the chemistry of **1** are underway and will be described in due course.

EXPERIMENTAL

The general techniques and procedures used in this research have been recently described.¹⁰

1-(Phenylsulfonyl)indole (2). The procedure of Illi was used.¹¹ To an ice-cold mixture of powdered sodium hydroxide (50.0 g, 1.25 mol) and tetra-*n*-butylammonium hydrogen sulfate (3.50 g, 10.3 mmol) in methylene chloride (500 ml) under argon was added solid indole (46.75 g, 0.40 mol) in one portion, followed by a solution of benzenesulfonyl chloride (63.8 ml, 0.50 mol) in methylene chloride (300 ml) at

such a rate as to keep the internal temperature below 20 °C. The mixture was then vigorously stirred at room temperature for 2 h, filtered, and evaporated in vacuo to produce a thick orange oil. Trituration with 100 ml of boiling methanol followed by slow cooling yielded 92.79 g of white crystals, mp 77-79 °C (lit.¹¹ mp 78-79 °C). Concentration of the supernatant followed by slow cooling produced an additional 4.18 g of crystals. Total yield: 96.97 g (94%).

3-Bromo-1-(phenylsulfonyl)indole (3). This procedure represents an improvement over that described earlier.^{1c} 1-(Phenylsulfonyl)indole (2) (15.4 g, 60.0 mmol) was dissolved in dry carbon tetrachloride (120 ml), and a solution of bromine (10.1 g, 63.0 mmol) in dry carbon tetrachloride (50 ml) was added at room temperature over 15 min. The red solution was stirred for 4 h, and then poured into saturated aqueous NaHCO₃ (150 ml). The layers were separated, and the organic phase was washed successively with 10% aqueous Na₂S₂O₃ (100 ml), water (100 ml), brine (100 ml), and dried (Na₂SO₄) with decolorizing carbon added. Evaporation in vacuo yielded 19.7 g (98%) of 3 as pale yellow crystals: mp 119-120 °C (lit.^{1c} mp 122-123 °C).

1-(Phenylsulfonyl)-3-(trimethylsilyl)indole (5). A solution of 3 (3.4 g, 10 mmol) in dry THF (100 ml) under argon was cooled to -100 °C. *t*-Butyllithium (13.2 ml of a 1.55 M solution in pentane, 20.5 mmol) was rapidly introduced via syringe, with liquid nitrogen being added to the cooling bath to maintain a temperature less than -90 °C. The mixture was stirred for 5 min, and neat chlorotrimethylsilane (1.52 ml, 12 mmol) was quickly added. After warming to room temperature overnight, the solution was poured into saturated aqueous NaHCO₃ (150 ml) and methylene chloride (100 ml). The aqueous layer was extracted with methylene chloride (50 ml), and the combined organic phases were washed with water (100 ml), brine (150 ml), dried (Na₂CO₃), and evaporated in vacuo to yield an orange oil (3.76 g). Flash chromatography over silica gel with 2:1 methylene chloride/hexane yielded 2.43 g (74%) of pure 1-(phenylsulfonyl)-3-(trimethylsilyl)indole (3) as colorless crystals, identified by tlc comparison with a known sample.^{1a}

1,2-Dihydro-1-(phenylsulfonyl)-3*H*-indol-3-one (6) from (5). A 32% solution of peracetic acid in acetic acid (1.75 ml, 7.36 mmol) and sodium acetate (0.23 g, 28.0 mmol) were stirred in methylene chloride (6 ml) under argon at 0 °C, and a solution of 5 (0.60 g, 1.82 mmol) in 6 ml of methylene chloride was added dropwise via syringe. The reaction mixture was stirred for 4 h at 0 °C, then for 5 days at room temperature. An additional 1.75 ml of peracid solution followed by stirring for two days failed to complete the reaction. Methylene chloride (25 ml) was then added, and the mixture was poured into 10% aqueous Na₂S₂O₃ (50 ml). The layers were separated, and the organic layer was washed successively with saturated aqueous NaHCO₃ (50 ml), water (50 ml), brine (70 ml), dried (Na₂SO₄), and evaporated in vacuo to yield a dark oil. Flash chromatography over silica gel with 2:1 hexane/ethyl acetate yielded 0.11 g (22%) of indoxyl 6: mp 128-130 °C dec; ir (KBr) 1726, 1609, 1477, 1463, 1455, 1366, 1205, 1169,

1153, 964, 762, 606, 569 cm^{-1} ; uv (EtOH) λ_{max} 218 nm; ms m/z 273 (M^+), 132 (100), 77; ^1H nmr (CDCl_3) δ 8.04 (d, 1H, $J = 8.4$ Hz), 7.89-7.80 (m, 2H), 7.71-7.56 (m, 3H), 7.53-7.44 (m, 2H), 7.21-7.14 (m, 1H), 4.14 (s, 2H); ^{13}C nmr (CDCl_3) δ 194.5, 153.4, 137.3, 136.4, 134.0, 129.5, 127.0, 125.0, 124.4, 124.2, 115.8, 56.0. Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{NO}_3\text{S}$: C, 61.53; H, 4.06; N, 5.12; S, 11.73. Found: C, 61.49; H, 4.09; N, 5.09; S, 11.70.

1,2-Dihydro-1-(phenylsulfonyl)-3H-indol-3-one (6) from (3). A solution of **3** (4.0 g, 12 mmol) in dry THF (100 ml) under argon was cooled to -100 $^\circ\text{C}$. *t*-Butyllithium (20 ml of a 1.25 M solution in pentane, 25 mmol) was rapidly introduced via syringe, with liquid nitrogen being added to the cooling bath to maintain an internal temperature below -90 $^\circ\text{C}$. The mixture was stirred for 5 min, and neat trimethylborate (1.70 ml, 15 mmol) was quickly added. After warming to room temperature overnight, the orange solution was treated with 3M HCl (25 ml) and extracted with methylene chloride (2x50 ml). The combined organic layers were washed with water (3x50 ml), brine (50 ml), dried (MgSO_4) with decolorizing carbon added, and evaporated in vacuo to produce a brown oil. Trituration with chloroform caused the precipitation of the boronic acid **7** as a white powder (1.68 g, 47%), which was collected and suspended in ether (35 ml). To this was added 15% H_2O_2 and the two-phase mixture was vigorously stirred until the boronic acid was dissolved. The ether layer was removed, evaporated in vacuo, and the residue was taken up in methylene chloride and eluted through a short silica gel column with methylene chloride. Evaporation of the eluent yielded 0.15 g (13%) of crude **6**, identified by tlc comparison with a known sample: mp 122-127 $^\circ\text{C}$ dec.

1-[(2-Phenylsulfonamido)phenyl]ethanone (9). *o*-Aminoacetophenone (**8**) (20.3 g, 150 mmol) was dissolved in anhydrous ether (125 ml) under argon, and pyridine (18 ml, 224 mmol) was added. The solution was cooled to 0 $^\circ\text{C}$, and benzenesulfonyl chloride (20.0 ml, 157 mmol) was added dropwise. The mixture was stirred at this temperature for 1 h, after which the resulting precipitate was collected and washed with cold methanol, producing 7.11 g of analytically pure product. Concentration of the filtrate in vacuo and treatment with cold methanol yielded further product. Total yield 39.4 g (95%): mp 179-181 $^\circ\text{C}$; ir (KBr) 1654, 1582, 1498, 1456, 1447, 1397, 1361, 1334, 1310, 1298, 1253, 1184, 1168, 1160, 927, 773, 762, 721, 689, 633 cm^{-1} ; ms m/z 275 (M^+), 134 (100), 106, 92, 91, 77; ^1H nmr (CDCl_3) δ 7.91-7.76 (m, 3H), 7.73-7.67 (m, 1H), 7.56-7.39 (m, 4H), 7.11-7.03 (m, 1H), 2.55 (s, 3H); ^{13}C nmr (CDCl_3) δ 202.4, 139.9, 139.5, 134.9, 133.0, 131.9, 129.0, 127.2, 122.8, 122.5, 119.3, 28.4. Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_3\text{S}$: C, 61.07; H, 4.76; N, 5.09; S, 11.64. Found: C, 61.01; H, 4.76; N, 5.03; S, 11.57.

2-Bromo-1-[(2-phenylsulfonamido)phenyl]ethanone (10). Freshly-ground cupric bromide (2.12 g, 9.5 mmol) was added to a solution of **9** (1.38 g, 5.0 mmol) in 1:1 chloroform/ethyl acetate (15 ml). The dark-green mixture was refluxed for 12 h, slowly turning yellow when the reaction was completed; a small amount of decolorizing carbon was added, and the mixture was filtered to remove copper(I) salts. The

filtrate was evaporated in vacuo to yield an extremely hygroscopic yellow solid. Recrystallization from cold methanol under nitrogen yielded 0.883 g (53%) of **10** as pale yellow crystals: mp 98-101 °C; ir (KBr) 1649, 1578, 1495, 1456, 1449, 1389, 1343, 1263, 1161, 929, 751, 694, 630, 587 cm⁻¹; ms *m/z* 355, 353 (M⁺, 273, 260 (100), 196, 195, 133; ¹H nmr (CDCl₃) δ 7.88-7.76 (m, 3H), 7.73-7.68 (m, 1H), 7.56-7.38 (m, 4H), 7.13-7.05 (m, 1H), 4.36 (s, 2H); ¹³C nmr (CDCl₃) δ 195.0, 140.6, 135.7, 133.2, 131.6, 129.1, 127.1, 127.0, 123.0, 119.7, 119.6, 31.3. Anal. Calcd for C₁₄H₁₂BrNO₃S: C, 47.47; H, 3.41; N, 3.95; S, 9.05; Br, 22.56. Found: C, 47.74; H, 3.40; N, 3.88; S, 8.96; Br, 22.41.

1,2-Dihydro-1-(phenylsulfonyl)-3H-indol-3-one (**6**) from (**9**). A mixture of **9** (5.51 g, 20 mmol) and cupric bromide (8.71 g, 39 mmol) in 1:1 chloroform/ethyl acetate (60 ml) was refluxed for 12 h. A small amount of decolorizing carbon was added, and the mixture was filtered. The yellow filtrate was cooled to 0 °C and stirred under argon while triethylamine (2.85 ml, 20.5 mmol) was slowly added. The mixture was stirred at 0 °C for 2 h and filtered to remove the ammonium salt formed. The filter cake was extracted with ethyl acetate, and the filtrate was washed successively with 1M HCl (50 ml), water (50 ml), brine (50 ml), dried (Na₂SO₄), and evaporated in vacuo to yield bright red crystals. These were rinsed with cold ether to remove the bulk of the red color, and then recrystallized from ether to yield 3.70 g (70%) of **6**.

1,2-Dihydro-1-(phenylsulfonyl)-3H-indol-3-one (**6**) from direct oxidation of **2**. The protected indole **2** (2.57 g, 10.0 mmol) and 80% magnesium monopero-phthalate (6.18 g, 10.0 mmol) were dissolved in glacial acetic acid (50 ml), and the solution was refluxed for 2 h (bath temp. 125 °C). After cooling, the bulk of the solvent was removed by vacuum distillation, and methylene chloride (25 ml) and water (75 ml) were added. The resulting suspension was then treated with solid sodium bicarbonate until gas evolution ceased. The layers were filtered, separated, and the aqueous layer was extracted with methylene chloride (2x35 ml). The combined organic layers were washed with saturated aqueous NaHCO₃ (50 ml), water (50 ml), brine (70 ml), dried (Na₂SO₄), and evaporated in vacuo to yield a dark oil (3.71 g). Flash chromatography over silica gel with 5:1 methylene chloride/hexane yielded 1.64 g (60%) of **6**.

1-(Phenylsulfonyl)indol-3-yl trifluoromethanesulfonate (**1**) Freshly-recrystallized **6** (1.26 g, 4.61 mmol) was dissolved in methylene chloride (20 ml), and solid 2,6-di-*tert*-butyl-4-methylpyridine (0.977 g, 4.66 mmol) was added. The solution was cooled to 0 °C and stirred under argon while trifluoromethanesulfonic anhydride (0.84 ml, 4.99 mmol) was slowly added. After stirring for 1 h at this temperature and then for 3 h at room temperature, the mixture was evaporated in vacuo and the residue was triturated with pentane (25 ml). The resulting precipitate was collected and washed with pentane, and the combined supernatant liquids were washed successively with cold 1M HCl (25 ml), water (25 ml), brine (30 ml), dried (Na₂SO₄), and evaporated in vacuo to yield a yellow oil. Flash chromatography over

silica gel with methylene chloride yielded 1.57 g (84%) of analytically pure triflate **1** as a colorless oil which slowly crystallized upon standing at room temperature: mp 56-58 °C; ir (KBr) 1449, 1432, 1410, 1377, 1273, 1247, 1210, 1176, 1109 (broad), 869, 848, 740, 729, 681, 599, 574 cm⁻¹; ms *m/z* 405 (M⁺), 272, 141 (100), 103, 77, 76, 69; ¹H nmr (CDCl₃) δ 8.07 (d, 1H, J = 8.4 Hz), 7.95-7.89 (m, 2H), 7.77 (s, 1H), 7.59-7.40 (m, 5H), 7.30 (t, 1H, J = 7.5 Hz); ¹³C nmr (CDCl₃) δ 137.1, 134.4, 133.4, 132.6, 129.4, 126.8, 126.5, 124.4, 122.6, 118.6 (q, J = 322 Hz), 117.7, 116.6, 113.8. Anal. Calcd for C₁₅H₁₀F₃NO₅S₂: C, 44.44; H, 2.49; N, 3.46; S, 15.82. Found: C, 44.50; H, 2.49; N, 3.41; S, 15.87.

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