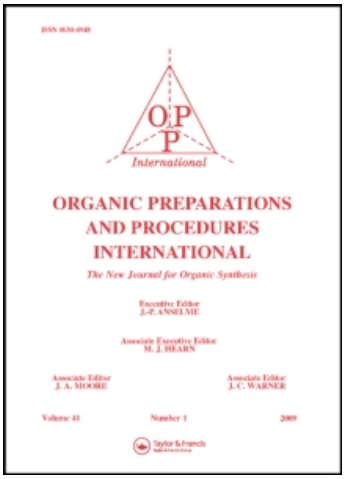

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SYNTHESES OF 2,3-DIHALO-1-(PHENYLSULFONYL)INDOLES

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SYNTHESES OF 2,3-DIHALO-1-(PHENYLSULFONYL)INDOLES

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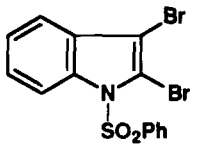
In connection with our studies on regioselective halogen-metal exchange[1] and radical reactions[2] of 2,3-dihalogenated indoles, we required efficient syntheses of several 2,3-dihalogenated *N*-protected indoles. Since *N*-unsubstituted 2-halo-, 3-halo-, and 2,3-dihalogenated indoles are unusually labile[3] and, in some cases, toxic,[4] the presence of an electron-withdrawing group on the nitrogen, such as *N*-phenylsulfonyl, is generally necessary to preserve these compounds for extended periods. This paper describes convenient syntheses of 2,3-dibromo- (**1**), 3-bromo-2-iodo- (**2**), and 2-bromo-3-iodo-1-(phenylsulfonyl)-indole (**3**).



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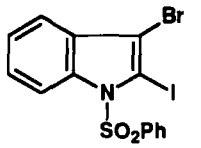

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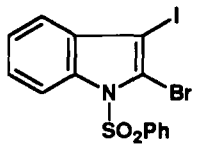
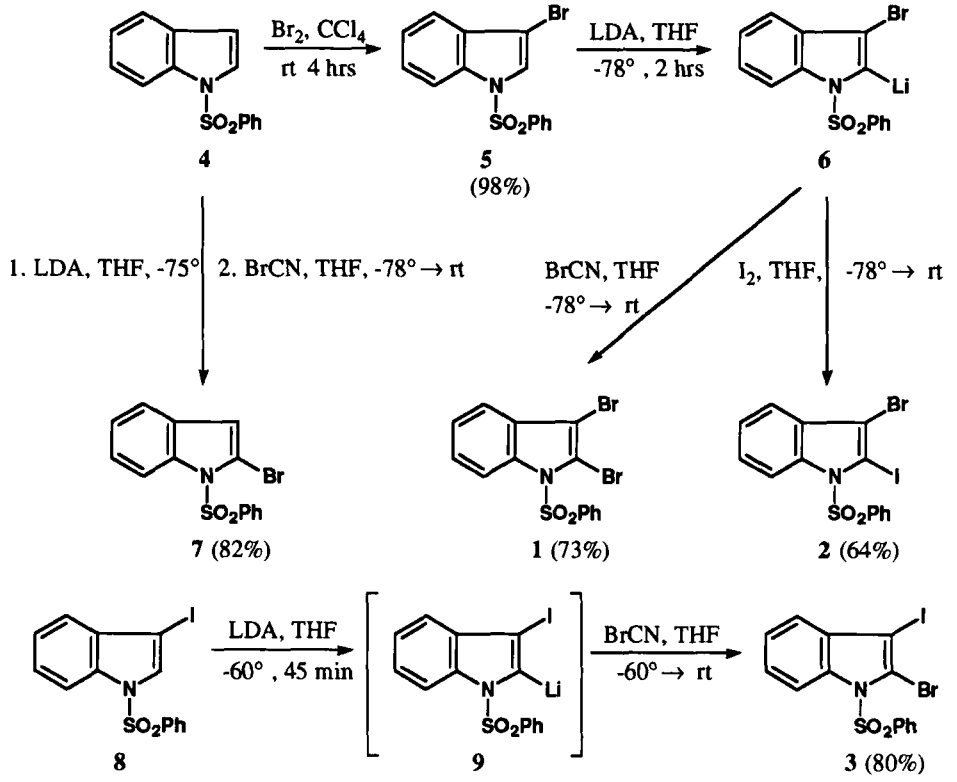


3

Our preparation of **1** and **2** is summarized in Scheme 1. Following the procedure described earlier,[5] 1-(phenylsulfonyl)indole (**4**) was brominated under mild conditions to afford 3-bromo-1-(phenylsulfonyl)indole (**5**) in nearly quantitative yield. Regioselective C-2 lithiation of **5** was achieved with lithium diisopropylamide (LDA) (THF, -78°). Quenching this solution of the presumed 2-lithio-3-bromo-1-(phenylsulfonyl)indole (**6**) with cyanogen bromide or iodine afforded the desired compounds **1** or **2**, respectively, in very satisfactory yields of pure compounds. The conditions for the introduction of bromine using cyanogen bromide were initially explored with 1-(phenylsulfonyl)indole (**4**) to give 2-bromo-1-(phenylsulfonyl)indole (**7**) in 82% yield. Cyanogen bromide does not appear to have been frequently used as a source of "Br^+" with metalated species.[6] The synthesis of **3** was accomplished by treatment of 3-iodo-1-(phenylsulfonyl)indole (**8**)[7] with LDA (THF, -78°), followed by quenching the presumed anion **9** with cyanogen bromide to give **3** in 80% yield.

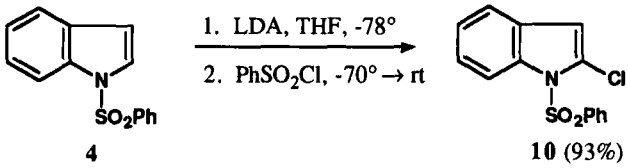
Since we had synthesized 2,3-diiodo-1-(phenylsulfonyl)indole earlier,[7] the present work completes the preparation of the four possible 2,3-dihalogenated (brominated/iodinated) 1-(phenylsul-

Scheme 1



fonyl)indoles. These compounds are all well-behaved solids. It may be noted that several substituted 2,3-dibromoindoles, as well as mixed 2,3-bromochloroindoles, are marine natural products.[8]

Although the preparation of *N*-protected chloroindoles will be described separately, it is interesting to note that the reaction between 2-lithio-1-(phenylsulfonyl)indole, as derived from **4** with LDA, and benzenesulfonyl chloride, affords 2-chloro-1-(phenylsulfonyl)indole (**10**) in 93% yield. Thus, benzenesulfonyl chloride may be a useful source of "Cl^+" with other metalated species.



EXPERIMENTAL SECTION

Melting points were determined with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 599 Infrared Spectrophotometer. Mass spectra were measured at 35 or 70 eV on a Finnigan 4023 mass spectrometer. Unless noted, ^{13}C and ^{1}H NMR spectra were recorded on a Varian XL-300 Fourier-transform NMR spectrometer (300

MHz), with tetramethylsilane as the internal reference; otherwise, spectra were measured on a Varian EM-360 spectrometer (60 MHz). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Samples for elemental analysis were prepared by recrystallization to constant melting point, followed by drying *in vacuo*; two recrystallizations were usually sufficient. Flash chromatography was performed using 230-400 mesh silica gel 60 from EM Science. Thin Layer Chromatography (TLC) was performed on 0.2 mm silica gel 60 F_{254} plastic plates from E. Merck. Tetrahydrofuran was distilled from sodium/benzophenone, and diisopropylamine was distilled from calcium hydride. Reactions were performed in oven-dried glassware fitted with a magnetic stirrer, thermometer, and inlet for dry Ar gas. A dry ice/acetone bath was used to achieve -78°, and -100° was achieved with a dry ice/acetone/liquid nitrogen bath. Alkyllithium reagents were titrated with diphenylacetic acid prior to use.

2,3-Dibromo-1-(phenylsulfonyl)indole (1).- To a stirred solution of 3-bromo-1-(phenylsulfonyl)-indole (1.54 g, 4.58 mmol) in dry THF (50 mL) under Ar at -78° was added a solution of LDA (2.1 mL of a 2.29 M solution in THF/heptane, 4.8 mmol) dropwise *via* a syringe. The solution was stirred for 40 min at that temperature. A solution of cyanogen bromide (0.627 g, 5.91 mmol) in dry THF (9 mL) was then rapidly added, and the reaction mixture was allowed to warm to rt overnight. It was then poured into 5% aqueous $NaHCO_3$ (50 mL) and extracted with Et_2O (2 x 50 mL). The combined organic layers were washed successively with H_2O (2 x 75 mL), brine (75 mL), and dried ($MgSO_4$). The solution was concentrated *in vacuo* to yield orange crystals. Flash chromatography (CH_2Cl_2) and collection of the sole high-Rf product yielded 2.09 g of white powder, which was recrystallized from Et_2O to yield 1.38 g (73%) of **1** as white crystals, mp 141-143°. IR (KBr): 1442, 1377, 1213, 1192, 1170, 1143, 1087, 737, 726, 692, 680, 589, 578 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.33-8.25 (m, 1 H), 7.92-7.83 (m, 2 H), 7.59-7.28 (m, 6 H). ^{13}C NMR ($CDCl_3$): δ 137.7, 136.5, 134.4, 129.3, 128.9, 127.1, 126.1, 124.6, 119.5, 115.3, 111.2, 106.7. MS *m/e*: 417, 415, 413, 274, 77 (100%).

Anal. Calcd for $C_{14}H_9Br_2NO_2S$: C, 40.51; H, 2.19; Br, 38.50; S, 7.72; N, 3.37

Found: C, 40.63; H, 2.18; Br, 38.42; S, 7.81; N, 3.41

3-Bromo-2-iodo-1-(phenylsulfonyl)indole (2). -To a stirred solution of LDA (prepared from diisopropylamine, 5.9 mL, 42.1 mmol, and *n*-BuLi, 27.5 mL of a 1.6 M solution in hexane, 44 mmol) in dry THF (500 mL) under Ar at -78° was added a solution of 3-bromo-1-(phenylsulfonyl)indole (**5**) (13.45 g, 40 mmol) in dry THF (50 mL) *via* a syringe. After stirring for 2 h at -78°, a solution of I_2 (11.17 g, 44 mmol) in dry THF (50 mL) was added at -78° *via* a syringe. The reaction was allowed to warm to rt overnight. The resulting yellow-orange solution was poured into 10% aqueous $Na_2S_2O_3$ (600 mL) and extracted with Et_2O (2 x 400 mL). The combined organic layers were divided in half, and each half was washed with H_2O (2 x 500 mL) and brine. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 16.45 g of orange-tan solid. The crude solid was washed with Et_2O (50 mL) and recrystallized three times from Et_2O to afford 11.78 g (64%) of **2** as a pale yellow solid, mp 148-150°. IR (KBr): 1583, 1190-1175, 1130-1075, 1015, 931, 746, 728, 685, 570 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.34-8.3 (m, 1 H), 7.92-7.87 (m, 2 H), 7.61-7.54 (m, 1 H), 7.49-7.41 (m, 3 H), 7.38-7.27 (m, 2 H). ^{13}C NMR (DMSO-d_6): δ 137.3, 136.8, 135.0, 129.9, 129.5, 126.7, 126.2,

124.9, 119.5, 115.3, 114.3, 87.7. MS *m/e*: 463, 461, 322, 320, 193, 191, 141, 125, 114.

Anal. Calcd for $C_{14}H_9BrINO_2S$: C, 36.39; H, 1.96; Br, 17.29; I, 27.46; N, 3.03; S, 6.94
Found: C, 36.49; H, 1.96; Br, 17.18; I, 27.56; N, 3.00; S, 7.02

2-Bromo-3-iodo-1-(phenylsulfonyl)indole (3). -To a stirred solution of LDA (prepared from diisopropylamine, 0.38 mL, 2.7 mmol, and *n*-BuLi, 1.4 mL of a 2.06 M solution in hexane, 2.9 mmol) in dry THF (30 mL) at -60° under Ar was added a solution of 3-iodo-1-(phenylsulfonyl)indole (**8**) (1.0 g, 2.6 mmol) in dry THF (10 mL) dropwise *via* a syringe. The solution was stirred for 45 min at -60°. A solution of CNBr (530 mg, 5 mmol) in dry THF (10 mL) was added dropwise *via* a syringe at -60°, resulting in a cloudy mixture. After warming to rt overnight, the mixture, which had become dark orange, was poured into H_2O and extracted with CH_2Cl_2 (80 mL, then 2 x 40 mL). The combined organic layers were washed with H_2O, and the H_2O was back-extracted with CH_2Cl_2. The organic layers were washed with brine and dried (Na_2SO_4). The solvents were concentrated *in vacuo* to give 1.28 g of a yellow-brown solid. Flash chromatography (CH_2Cl_2) and two recrystallizations from Et_2O yielded 970 mg (80%) of 2-bromo-3-iodo-1-(phenylsulfonyl)indole (**3**) as a white solid, mp 150-151°. IR (CH_2Cl_2): 1607, 1587, 1515, 1440, 1392, 1192, 1174, 1147, 1090, 1032, 940, 897, 787-687 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.28-8.24 (m, 1 H), 7.92-7.88 (m, 2 H), 7.61-7.54 (m, 1 H), 7.48-7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 137.8, 136.9, 134.4, 131.9, 129.3, 127.1, 126.0, 124.7, 121.9, 115.9, 115.2, 79.4. MS *m/e*: 463, 461, 322, 320, 195, 193, 141, 125, 114.

Anal. Calcd for $C_{14}H_9BrINO_2S$: C, 36.39; H, 1.96; Br, 17.29; I, 27.46; N, 3.03
Found: C, 36.51; H, 1.97; Br, 17.32; I, 27.56; N, 3.02

2-Lithio-1-(phenylsulfonyl)indole. -To a solution of lithium diisopropylamide (LDA) (8.40 mmol) prepared from diisopropylamine (9.00 mmol) and *n*-BuLi (1.58 M in hexane; 8.40 mmol) in dry THF (20 mL) under Ar at -75° was added dropwise *via* a syringe over 5 min a solution of **4** (8.01 mmol) in dry THF (22 mL), keeping the internal temperature below -60°. The mixture was stirred for 1.5 hr below -70° and then allowed to warm slowly to 5° over 1 hr. The resulting bright-red solution was cooled to -78° and then treated with the electrophiles as described below.

2-Bromo-1-(phenylsulfonyl)indole (7). -A magnetically stirred solution of 2-lithio-1-(phenylsulfonyl)indole (15.5 mmol) in dry THF (55 mL) at -78° under Ar was treated rapidly *via* a syringe with a solution of cyanogen bromide (1.87 g, 17.1 mmol) in dry THF (10 mL). The mixture was allowed to warm to rt overnight, poured into H_2O (150 mL), and extracted with CH_2Cl_2 (4 x 100 mL). The combined extracts were washed with H_2O (1 x 75 mL), and brine (2 x 125 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford 5.50 g of a dark oil. Flash chromatography over silica gel with 1:1 CH_2Cl_2/hexane gave 4.29 g (82%) of analytically pure **7** as a colorless solid, mp 50-53°. IR (neat film): 3050, 1583, 1525, 1438, 1375, 1272, 1180, 1117, 1079, 1000, 799, 738, 718, 677, 645 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.40-8.15 (m, 1 H), 8.15-7.70 (m, 2 H), 7.70-7.10 (m, 6 H), 6.68 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 134.2, 133.9, 129.2, 129.0, 127.0, 126.0, 124.8, 124.6, 123.9, 119.8, 119.5, 115.1. MS *m/e*: 337, 335 (M^+), 196, 194, 141, 115, 77 (100%). UV (95% EtOH): λ_{max} 214, 251, 283 (sh) nm.

Anal. Calcd for $C_{14}H_{10}BrNO_2S$: C, 50.01; H, 3.00; N, 4.17; S, 9.54; Br, 23.77
Found: C, 49.03; H, 2.81; N, 4.25; S, 9.66; Br, 24.35

2-Chloro-1-(phenylsulfonyl)indole (10).- A magnetically stirred solution of 2-lithio-1-(phenylsulfonyl)indole (11.7 mmol) in dry THF (40 mL) at -70° under Ar was treated neat *via* a syringe with benzenesulfonyl chloride (2.27 g, 12.8 mmol). The mixture was allowed to warm slowly to rt overnight, poured into 3% aqueous $NaHCO_3$ (200 mL), and extracted with CH_2Cl_2 (3 x 125 mL). The combined extracts were washed with H_2O (1 x 200 mL) and brine (2 x 200 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a light amber oil which was homogeneous by TLC (R_f, 0.56, PhH). Drying at 42°/0.4 Torr provided 3.16 g (93%) of **10** as a light tan solid, mp 57-59°. Flash chromatography over silica gel with 1:1 Et_2O-hexane gave the analytical sample as an off-white solid, mp 58-60°. IR (KBr): 1590, 1545, 1485, 1477, 1450, 1382, 1211, 1207, 1187, 1118, 1087, 1015, 816, 755, 728, 686, 661, 595, 577, 538, 433 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.32-8.06 (m, 1 H), 7.98-7.63 (m, 2 H), 7.60-6.88 (m, 6 H), 6.44 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 138.0, 136.3, 133.9, 129.0, 128.2, 126.7, 124.7, 124.5, 123.9, 119.9, 114.7, 110.1. MS *m/e*: 293, 291 (M^+), 152, 150, 141, 123, 115, 77 (100%). UV (95% EtOH): λ_{max} 216, 250, 285 (sh) nm.

Anal. Calcd for $C_{14}H_{10}ClNO_2S$: C, 57.64; H, 3.46; N, 4.80; S, 10.99; Cl, 12.15
Found: C, 57.48; H, 3.48; N, 4.76; S, 11.08; Cl, 12.14

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