Synthesis of 3-(Arylthio)indoles and Related Compounds by Reactions of Metalated Aromatics or Heterocycles with Protected 3,3′-Dithiobisindoles

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Abstract: An efficient and practical strategy for the synthesis of new 3-(arylthio)indoles and related compounds has been developed, involving cleavage of readily available protected 3,3′-dithiobisindoles with metalated aromatics or heterocycles.

Key words: indoles, thioindoles, sulfides, lithiation, Grignard reagents

There has been considerable interest in the chemistry of 3-(arylthio)indoles and closely related 3-sulfonylindoles, as several compounds belonging to these classes have been demonstrated to possess interesting biological effects. The 3-(arylthio)indole **1** serves as an excellent example of such a molecule, as it is not only an inhibitor of tubulin polymerization, but is also capable of inhibiting growth of human breast cancer cells.[1] Identification of the sulfone **2** as a potent anti-HIV compound[2] have triggered further studies of similar 3-sulfonylindoles against HIV-1 variants possessing resistance mutations.[3] In addition, 3-thioindole derivatives may also be encountered in nature, as illustrated by the alkaloid echinosulfone A (**3**)[4] (Figure 1).

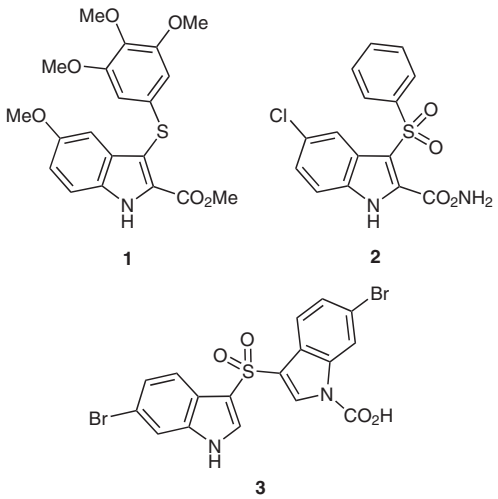

Figure 1 Some biologically active 3-(arylthio)indoles (**1**, **2**) and the natural product echinosulfone A (**3**)

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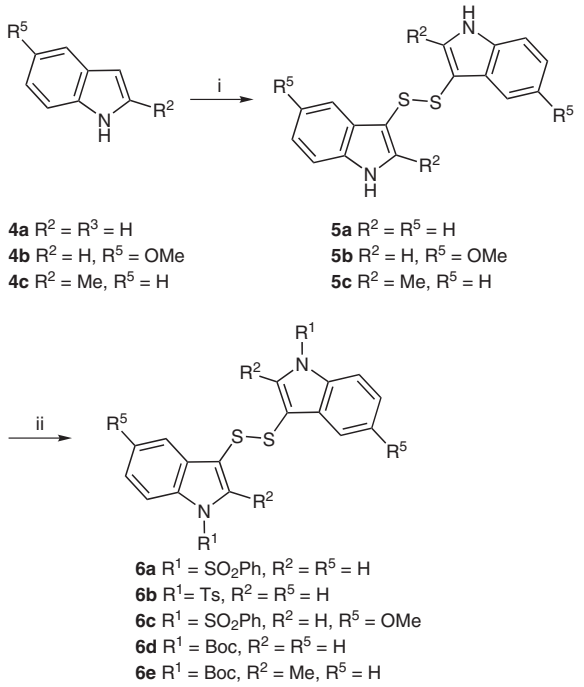
Consequently, there are several different strategies towards 3-(arylthio)- or 3-(alkylthio)indoles available involving, for example, such diverse sulfenylating reagents as disulfides,[5] thiols in the presence of oxygen,[6] quinone-*O*,*S*-acetals,[7] sulfenyl chlorides generated in situ,[8] and *N*-thioalkyl- or *N*-thioarylphthalimides.[9] Some direct approaches to 3-sulfonylindoles rely on sulfonation using chlorosulfonic acid[10] or sulfonyl chlorides.[11] Even though some of these routes have been implemented for the preparation of specific targets, many problems associated with using very reactive, unstable, or not readily available reagents have yet to be overcome. Our preliminary results have demonstrated that 3-(arylthio)indoles and related heterocyclic derivatives are easily available in good yields by cleavage of readily available protected 3,3′-dithiobisindoles with metalated aromatics or heteroaromatics.[12] Herein, we present the full details of this investigation, as well as further potentially useful developments demonstrating the scope of this approach.

Since our approach required access to substantial amounts of protected 3,3′-dithiobisindoles, the initial efforts were directed towards development of viable routes to such compounds. It is well established that 3,3′-dithiobisindoles are formed upon exposure of indoles to thiourea in the presence of iodine in a basic medium.[13] However, this approach appeared to suffer from generally poor yields, and it was therefore necessary to optimize the conditions. After some experimentation, we found that passing a stream of air through the reaction mixture leads to a considerable improvement in yields, probably by promoting the oxidative process giving rise to disulfide formation. Thus, treatment of the indoles **4a–c** under these modified conditions afforded the disulfides **5a–c** in good yields. Interestingly, the 3,3′-dithiobisindoles **5a**,**b** proved to be remarkably stable towards basic reaction conditions, as treatment thereof with benzenesulfonyl chloride or *p*-toluenesulfonyl chloride in the presence of potassium hydroxide and a phase-transfer catalyst[14] provided the protected derivatives **6a–c** in 60–72% yield (Scheme 1). However, initial attempts to protect the disulfides **5a** or **5c** under standard conditions using di-*tert*-butyl dicarbonate in the presence of DMAP as the catalyst in anhydrous THF[15] gave disappointing results. The formation of considerable amounts of side products which presumably originated from cleavage of the disulfide linkage could be discerned in the crude mixture apart from the desired protected disulfides. In contrast, when the disulfides **5a** or **5c**

were exposed to di-*tert*-butyl dicarbonate and potassium carbonate in anhydrous DMF, the protection proceeded smoothly giving the products **6d–e** in 82% and 88% yield, respectively (Scheme 1). This completed our syntheses of a small series of 3,3′-dithiobisindoles incorporating both base sensitive and acid labile protecting groups.



Scheme 1 *Reagents and conditions*: (i) H_2NCSNH_2, I_2, NaOH, EtOH, H_2O, r.t., 18 h, then air, r.t., 8–9 h; (ii) $PhSO_2Cl$, Bu_4NHSO_4, KOH, CH_2Cl_2, 0 °C 1 h, then r.t., 1.5 h (for **6a–c**), or Boc_2O, K_2CO_3, DMF, r.t., 18 h (for **6d**,**e**).

Having secured access to the necessary disulfides **6a–e**, experiments probing their applicability as reagents for transfer of 3-thioindole units were undertaken (Table 1). For instance, in situ protection and lithiation of indole at the 2-position according to Katritzky,[16] followed by reaction of the resulting lithioindole with the disulfide **6a** gave the mono-protected 2,3′-thiobisindole **7** in a moderate yield (Table 1, entry 1). Likewise, lithiation of benzo[*b*]thiophene, and subsequent quenching with **6a** afforded the 3-thioindole **9** (Table 1, entry 3). Similar conditions were employed for metalation of thiophene and benzo[*b*]furan, providing additional 3-(thioheteroaryl)indoles after introduction of appropriate disulfides **6**. In the case of benzenoid aromatics lacking additional reactive functional groups, the substrates were first converted to their corresponding Grignard reagents by treatment with magnesium turnings in THF in the presence of catalytic amounts of iodine. The resulting organomagnesium species were thereafter treated with suitable 3,3′-dithiobisindoles **6**, affording a series of 3-(arylthio)indoles, as illustrated by formation of compound **17** (Table 1, entry 11). A further extension of the scope of this strategy was demonstrated by generation of functionalized organomagnesium reagents from ethyl 2-iodobenzoate or ethyl 4-iodobenzoate and *i*-PrMgCl,[17] followed by reactions with the disulfides **6a** or **6c**, providing the 3-(arylthio)indoles **23–25**, all featuring ester units (Table 1, entries 17–19). The full series of products originating from the reactions between different combinations of organometallic reagents and the disulfides **6a–e** under various conditions is summarized in Table 1.

NMR spectra were recorded on a Bruker DPX 300 operating at 300.1 MHz for ^1H and 75.5 MHz for ^{13}C, using the residual solvent signal as reference. IR spectra were acquired on a Thermo Nicolet Avatar 330 FT-IR instrument. The elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were determined in open capillary tubes on a Büchi B-545 melting point apparatus. Chemicals and solvents were obtained from commercial sources and used as received, except THF, which was distilled from sodium and benzophenone, and DMF, which was stored over activated 4Å molecular sieves. All reactions were performed under N_2. Chromatography was performed using silica gel (40–63 μm).

3,3′-Dithiobis(1*H*-indole) (5a)

This material was prepared using a modified literature procedure.[13a] A beaker was charged with indole (23.4 g, 0.2 mol), thiourea (45.6 g, 0.6 mol), EtOH (400 mL) and H_2O (200 mL). To the resulting stirred mixture were cautiously added I_2 (50.8 g, 0.2 mol) and NaOH pellets (30 g), followed by more H_2O (1 L). After stirring at r.t. for 18 h, a stream of air was passed through the mixture during 8–9 h. The crude product was collected by filtration, washed with plenty of H_2O, and was then allowed to dry. It was thereafter suspended in *i*-Pr_2O (150 mL), and stirred for ca 2 h. Filtration, washing with several small portions of *i*-Pr_2O, and drying gave **5a** (20.3 g, 68%) as a pale beige solid. The yield varied somewhat between different runs, but was typically around 60%; mp 216–219 °C (Lit.[13a] mp 227–229.5 °C).

IR (neat): 3413, 1491, 1451, 1400, 1235, 1097, 742 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.54 (br s, 2 H), 7.46–7.40 (m, 4 H), 7.31 (s, 2 H), 7.21–7.15 (m, 2 H), 7.08–7.03 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 136.6, 131.9, 128.4, 122.1, 120.0, 118.8, 112.2, 105.9.

MS (ESI–): *m*/*z* = 295 $[M - H]^-$.

3,3′-Dithiobis(2-methyl-1*H*-indole) (5b)

The procedure described above was used, employing 2-methylindole (13.1 g, 0.1 mol), and appropriate amounts of the reagents and solvents, to afford **5b** (11.7 g, 72%) as a cream-colored solid; mp 226–227.5 °C (Lit.[18] mp 230 °C).

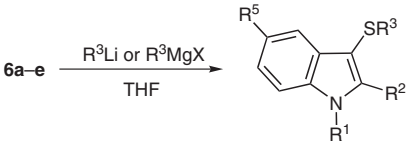
IR (neat): 3395, 1453, 1393, 1382, 1286, 1220, 733 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.44 (br s, 2 H), 7.34–7.30 (m, 4 H), 7.12–7.00 (m, 4 H), 1.74 (s, 6 H).

^{13}C NMR (DMSO-d_6): δ = 142.8, 135.5, 129.4, 121.4, 119.8, 117.9, 111.0, 102.4, 10.6.

MS (ESI–): *m*/*z* = 323 $[M - H]^-$.

Table 1 Reactions of Metalated Aromatics or Heteroaromatics with Disulfides **6a–e**



7–25

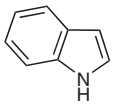
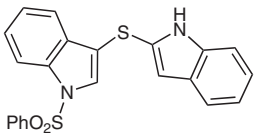
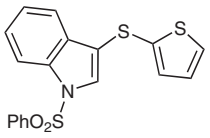
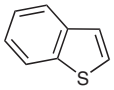
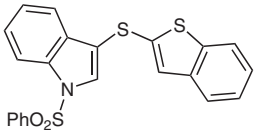
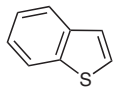
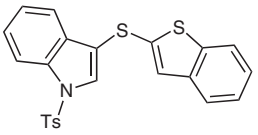
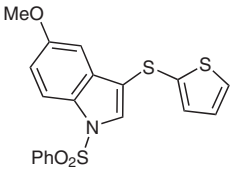
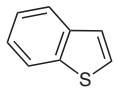
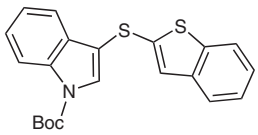
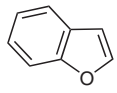
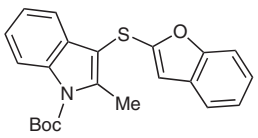
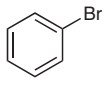
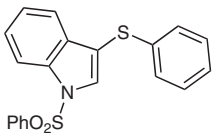
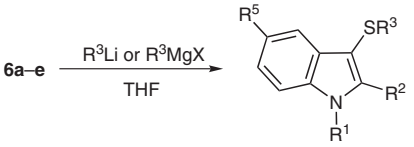
Entry	Substrate	Disulfide	Conditions[a]	Product	Yield (%)[b]
1		**6a**	A	 **7**	39
2		**6a**	B	 **8**	80
3		**6a**	B	 **9**	76
4		**6b**	B	 **10**	70
5		**6c**	B	 **11**	76
6		**6d**	B	 **12**	62
7		**6e**	B	 **13**	82
8		**6a**	C	 **14**	75

Table 1 Reactions of Metalated Aromatics or Heteroaromatics with Disulfides **6a–e** (continued)



7–25

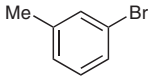
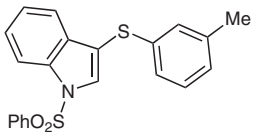
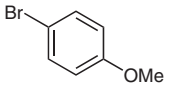
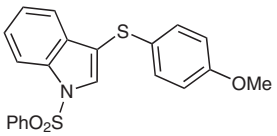
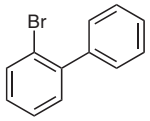
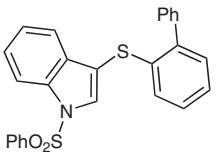
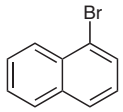
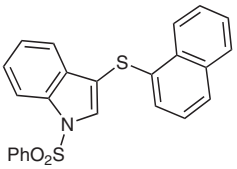
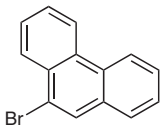
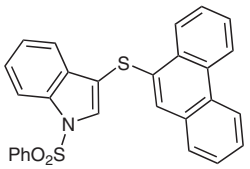
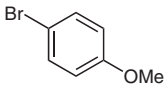
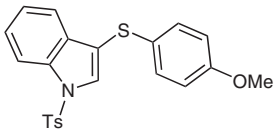
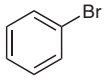
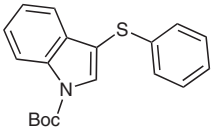
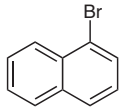
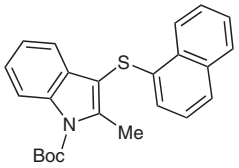
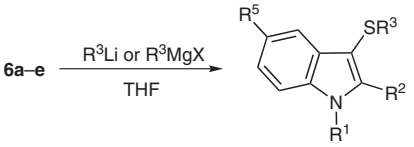
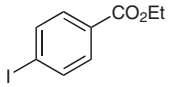
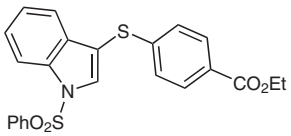
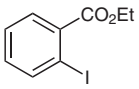
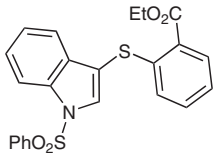
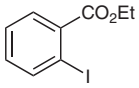
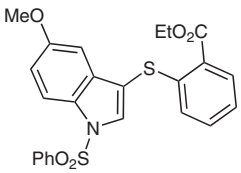
Entry	Substrate	Disulfide	Conditions[a]	Product	Yield (%)[b]
9		**6a**	C	 **15**	90
10		**6a**	C	 **16**	77
11		**6a**	C	 **17**	76
12		**6a**	C	 **18**	88
13		**6a**	C	 **19**	62
14		**6b**	C	 **20**	83
15		**6d**	C	 **21**	76
16		**6e**	C	 **22**	59

Table 1 Reactions of Metalated Aromatics or Heteroaromatics with Disulfides **6a–e** (continued)



7–25

Entry	Substrate	Disulfide	Conditions[a]	Product	Yield (%)[b]
17		**6a**	D	 **23**	39
18		**6a**	D	 **24**	69
19		**6c**	D	 **25**	75

[a] Reagents and conditions; A: (i) *n*-BuLi, THF, –78 °C, (ii) CO_2 (g), –78 °C, (iii) *t*-BuLi, –78 °C, (iv) **6a**, –78 °C to r.t.; B: (i) *n*-BuLi, THF, –78 °C, (ii) **6a–e**, –78 °C to r.t.; C: (i) Mg, I_2 (cat.), THF, reflux, (ii) **6a** or **6d**,**e**, 0 °C to r.t.; D: (i) *i*-PrMgCl, THF, –20 to 0 °C, (ii) **6a** or **6c**, –78 °C to r.t.

[b] Yield of purified products.

3,3′-Dithiobis(5-methoxy-1*H*-indole) (5c)

Application of the procedure above, using 5-methoxyindole (7.35 g, 50 mmol) and appropriate amounts of the reagents and solvents, furnished **5c** (5.65 g, 63%) as an off-white solid; mp 146–148 °C (Lit.[13b] mp 146–148 °C).

IR (neat): 3400, 3290, 1483, 1456, 1437, 1283, 1200, 1163, 1025, 918, 844, 802, 793 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.42 (br s, 2 H), 7.35 (s, 2 H), 7.31 (d, *J* = 8.7 Hz, 2 H), 6.76 (dd, *J* = 8.7, 2.3 Hz, 2 H), 6.68 (d, *J* = 2.3 Hz, 2 H), 3.50 (s, 6 H).

^{13}C NMR (DMSO-d_6): δ = 154.2, 132.4, 131.3, 129.2, 112.8, 112.5, 105.8, 100.1, 54.7.

MS (ESI–): *m*/*z* = 355 $[M - H]^-$.

3,3′-Dithiobis(1-phenylsulfonyl-1*H*-indole) (6a)

A stirred suspension of finely powdered KOH (12.5 g, 0.22 mol) in CH_2Cl_2 (155 mL) was cooled to 0 °C, followed by sequential addition of the disulfide **5a** (14.8 g, 50 mmol), and Bu_4NHSO_4 (0.88 g, 2.6 mmol). To this mixture, was added a solution of $PhSO_2Cl$ (16.0 mL, 0.125 mol) in CH_2Cl_2 (25 mL) at 0 °C during 1 h and 15 min. The resulting mixture was stirred at 0 °C for 1 h, and thereafter at r.t. for 1.5 h, whereupon it was filtered, and the filter cake was washed with several portions of CH_2Cl_2 (4 × 25 mL). Evaporation of the combined filtrates and washings gave a solid residue, which was crystallized from MeCN (with active charcoal), to give **6a** (20.9 g, 72%) as pinkish crystals; mp 165–166.5 °C.

IR (neat): 1443, 1369, 1259, 1199, 1173, 1123, 1105, 1092, 939, 757, 727 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.02–7.98 (m, 2 H), 7.91–7.88 (m, 4 H), 7.62–7.48 (m, 10 H), 7.42–7.36 (m, 2 H), 7.27–7.22 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 137.8, 135.3, 134.5, 130.6, 130.4, 129.8, 127.1, 125.9, 124.1, 120.6, 115.8, 113.8.

Anal. Calcd for $C_{28}H_{20}N_2O_4S_4$: C, 58.31; H, 3.50; N, 4.86. Found: C, 58.46; H, 3.58; N, 4.78.

3,3′-Dithiobis[1-(4-methylphenylsulfonyl)-1*H*-indole] (6b)

This compound was prepared according to the same procedure as for **6a** on a 25 mmol scale. Recrystallization from MeCN (using active charcoal) gave **6b** (10.0 g, 60%) as light yellow crystals; mp 153–155 °C.

IR (neat): 1444, 1363, 1170, 1122, 1109, 1089, 1039, 940, 740, 707 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.01–7.97 (m, 2 H), 7.79–7.75 (m, 4 H), 7.59–7.55 (m, 2 H), 7.54 (s, 2 H), 7.41–7.36 (m, 2 H), 7.31–7.22 (m, 6 H), 2.37 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 145.8, 135.3, 134.9, 130.6, 130.4, 130.4, 127.2, 125.7, 124.0, 120.5, 115.5, 113.9, 21.8.

Anal. Calcd for $C_{30}H_{24}N_2O_4S_4$: C, 59.58; H, 4.00; N, 4.63. Found: C, 59.67; H, 4.10; N, 4.60.

3,3′-Dithiobis(5-methoxy-1-phenylsulfonyl-1*H*-indole) (6c)
This compound was prepared according to the same procedure as for **6a** on a 12.5 mmol scale. Recrystallization from MeCN gave **6c** (5.55 g, 70%) as off-white crystals; mp 179–180 °C.

IR (neat): 1471, 1445, 1434, 1371, 1211, 1164, 1141, 1088, 1024, 960, 848, 723 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.87–7.83 (m, 6 H), 7.61–7.46 (m, 8 H), 6.98–6.94 (dd, *J* = 9.0, 2.5 Hz, 2 H), 6.88 (d, *J* = 2.5 Hz, 2 H), 3.62 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 157.2, 137.8, 134.5, 131.9, 131.2, 129.7, 129.7, 127.0, 115.7, 115.6, 114.9, 102.3, 55.6.

Anal. Calcd for $C_{30}H_{24}N_2O_6S_4$: C, 56.58; H, 3.80; N, 4.40. Found: C, 56.67; H, 3.94; N, 4.41.

3,3′-Dithiobis[1-(*tert*-butoxycarbonyl)-1*H*-indole] (6d)
Di-*tert*-butyl dicarbonate (6.0 g, 27.5 mmol) was dissolved in anhyd DMF (25 mL). To this solution was added the disulfide **5c** (3.70 g, 12.5 mmol), followed by K_2CO_3 (7.60 g, 0.11 mol). The resulting mixture was stirred at r.t. for 18 h, and was thereafter partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL). After separation of the layers, the aqueous phase was extracted with more CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and evaporated in vacuo to provide a solid residue, which was finally subjected to crystallization from MeCN to afford **6d** (5.09 g, 82%) as yellow crystals; mp 170 °C.

IR (neat): 1745, 1732, 1449, 1354, 1339, 1312, 1247, 1218, 1142, 1058, 743 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.20 (d, *J* = 8.3 Hz, 2 H), 7.58–7.56 (m, 4 H), 7.42–7.36 (m, 2 H), 7.29–7.24 (m, 2 H), 1.66 (s, 18 H).

^{13}C NMR ($CDCl_3$): δ = 149.1, 135.9, 131.2, 130.6, 125.4, 123.4, 120.3, 115.5, 114.2, 84.6, 28.3.

Anal. Calcd for $C_{26}H_{28}N_2O_4S_2$: C, 62.88; H, 5.68; N, 5.64. Found: C, 62.76; H, 5.75; N, 5.61.

3,3′-Dithiobis[1-(*tert*-butoxycarbonyl)-2-methyl-1*H*-indole] (6e)
This product was prepared as above using di-*tert*-butyl dicarbonate (12.0 g, 55 mmol), the disulfide **5c** (8.11 g, 25 mmol), and K_2CO_3 (15.2 g, 0.11 mol) in anhyd DMF (50 mL). Work-up as above, followed by crystallization from MeCN afforded **6e** (11.5 g, 88%) as yellow crystals; mp 168–170 °C.

IR (neat): 1734, 1449, 1366, 1354, 1315, 1297, 1256, 1214, 1152, 1106, 840, 745 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.13–8.10 (m, 2 H), 7.45–7.42 (m, 2 H), 7.32–7.26 (m, 2 H), 7.23–7.17 (m, 2 H), 2.22 (s, 6 H), 1.67 (s, 18 H).

^{13}C NMR ($CDCl_3$): δ = 150.3, 143.9, 136.0, 130.3, 124.5, 123.3, 119.4, 115.5, 113.0, 84.6, 28.4, 14.6.

Anal. Calcd for $C_{28}H_{32}N_2O_4S_2$: C, 64.09; H, 6.15; N, 5.34. Found: C, 64.26; H, 6.15; N, 5.32.

2-(1-Phenylsulfonyl-1*H*-indol-3-yl)thio-1*H*-indole (7) (Conditions A, Table 1)
A solution of *n*-BuLi (2.5 M in hexanes, 1.0 mL, 2.5 mmol) was added dropwise to a solution of indole (234 mg, 2.0 mmol) in anhyd THF (10 mL) at –78 °C. The resulting solution was stirred at –78 °C for 30 min, followed by the introduction of dry CO_2 (g) during 10 min. The solvent was evaporated under reduced pressure (during that time the temperature was allowed to rise to 20 °C). N_2 was introduced into the vessel and the solid residue was dissolved in anhyd THF (10 mL), and cooled to –78 °C, followed by the dropwise addition (over 10 min) of *t*-BuLi (1.7 M in pentane; 1.4 mL, 2.4 mmol) at –78 °C. The mixture was stirred for 30 min at –78 °C, followed by the addition of **6a** (1.15 g, 2.0 mmol) dissolved in THF (10 mL) during 15 min. The temperature was allowed to rise to 20 °C over 17 h. AcOH (1 mL) was added and stirring was continued for 15 min, followed by the addition of sat. aq NH_4Cl (30 mL). The solution was extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with H_2O (30 mL), brine (30 mL), and dried (Na_2SO_4). Evaporation of the solvents gave a residue which was subjected to column chromatography using *n*-heptane–Et_2O (8:1) to provide **7** (310 mg, 39%) as off-white crystals; mp 198–201 °C.

IR (neat): 3380, 1443, 1364, 1340, 1170, 1130, 1112, 1089, 1047, 944, 789, 752, 741, 728 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.47 (s, 1 H), 8.16 (s, 1 H), 8.07–8.04 (m, 2 H), 7.95–7.93 (m, 1 H), 7.72–7.67 (m, 1 H), 7.61–7.56 (m, 3 H), 7.44–7.24 (m, 5 H), 7.10–7.05 (m, 1 H), 6.99–6.94 (m, 1 H), 6.60–6.59 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 137.4, 136.6, 134.9, 134.2, 130.2, 129.9, 129.8, 127.7, 126.9, 126.5, 125.6, 124.0, 121.9, 119.8, 119.7, 119.4, 113.4, 112.3, 111.0, 106.7.

Anal. Calcd for $C_{22}H_{16}N_2O_2S_2$: C, 65.32; H, 3.99; N, 6.93. Found: C, 65.06; H, 4.18; N, 6.73.

Metalation and Sulfenylation of Heterocyclic Compounds (Conditions B, Table 1)
A solution of *n*-BuLi (2.5 M in hexanes, 2.0 mmol) was added over 10 min to a solution of a suitable heterocyclic compound (2.0 mmol) in anhyd THF (10 mL) at –78 °C. The solution was stirred for 30 min at –78 °C, followed by the addition of a solution of the appropriate disulfide (2.0 mmol) in anhyd THF (10 mL) over 15 min at –78 °C. The mixture was allowed to warm to r.t. over 16 h and was thereafter quenched with sat. aq NH_4Cl (20 mL). The resulting mixture was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to column chromatography to give the products **8**–**13**.

1-Phenylsulfonyl-3-(thiophen-2-yl)thio-1*H*-indole (8)
Purification by column chromatography using *n*-heptane–EtOAc (6:1) followed by recrystallization from MeCN gave **8** as colorless crystals; mp 111–113 °C.

IR (neat): 1441, 1400, 1370, 1265, 1203, 1171, 1128, 1092, 942, 728 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.00–7.96 (m, 1 H), 7.90–7.86 (m, 2 H), 7.72 (s, 1 H), 7.66–7.62 (m, 1 H), 7.59–7.53 (m, 1 H), 7.48–7.42 (m, 2 H), 7.35–7.27 (m, 3 H), 7.20 (dd, *J* = 3.6, 1.3 Hz, 1 H), 6.94 (dd, *J* = 5.3, 3.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 138.1, 135.4, 134.3, 133.5, 132.8, 130.7, 129.6, 129.4, 128.6, 127.7, 127.1, 125.7, 124.0, 120.3, 116.1, 114.0.

Anal. Calcd for $C_{18}H_{13}NO_2S_3$: C, 58.20; H, 3.53; N, 3.77. Found: C, 58.37; H, 3.66; N, 3.76.

1-Phenylsulfonyl-3-(benzo[*b*]thiophen-2-yl)thio-1*H*-indole (9)
Purification by column chromatography using *n*-heptane–EtOAc (9:1 to 4:1) followed by recrystallization from MeCN gave **9** as white crystals; mp 140–143 °C.

IR (neat): 1444, 1377, 1266, 1174, 1129, 1109, 1090, 1047, 942, 749, 726 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.02–7.99 (m, 1 H), 7.93–7.90 (m, 2 H), 7.86 (s, 1 H), 7.65–7.56 (m, 4 H), 7.50–7.45 (m, 2 H), 7.39–7.23 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 141.4, 139.9, 138.0, 136.9, 135.4, 134.4, 130.8, 130.1, 129.6, 127.1, 126.4, 125.8, 124.7, 124.6, 124.2, 123.2, 122.0, 120.4, 114.0, 113.7.

Anal. Calcd for $C_{22}H_{15}NO_2S_3$: C, 62.68; H, 3.59; N, 3.32. Found: C, 62.61; H, 3.68; N, 3.25.

1-(4-Methylphenylsulfonyl)-3-(benzo[*b*]thiophen-2-yl)thio-1*H*-indole (10)

Purification by column chromatography using *n*-hexane–Et_2O (9:1) followed by recrystallization from MeCN gave **10** as white crystals; mp 134–137 °C.

IR (neat): 3122, 1445, 1422, 1365, 1263, 1201, 1167, 1130, 1111, 1088, 1016, 942, 822, 810, 741, 710 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.01–7.98 (m, 1 H), 7.87 (s, 1 H), 7.82–7.79 (m, 2 H), 7.65–7.62 (m, 2 H), 7.38–7.24 (m, 6 H), 2.37 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 145.6, 141.4, 139.9, 137.0, 135.3, 135.0, 130.8, 130.2, 127.2, 126.3, 125.7, 124.7, 124.5, 124.1, 123.2, 122.0, 120.3, 117.2, 113.9, 113.3, 21.8.

Anal. Calcd for $C_{23}H_{17}NO_2S_3$: C, 63.42; H, 3.93; N, 3.22. Found: C, 63.49; H, 3.89; N, 3.20.

5-Methoxy-1-phenylsulfonyl-3-(thiophen-2-yl)thio-1*H*-indole (11)

Purification by column chromatography using *n*-heptane–CH_2Cl_2 (9:1) followed by recrystallization from MeOH gave **11** as white crystals; mp 125–127 °C.

IR (neat): 1609, 1471, 1444, 1436, 1371, 1303, 1210, 1161, 1104, 1087, 1026, 961, 841, 815, 802, 768, 752, 722 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.88–7.83 (m, 3 H), 7.67 (s, 1 H), 7.58–7.52 (m, 1 H), 7.47–7.41 (m, 2 H), 7.28 (dd, *J* = 5.3, 1.3 Hz, 1 H), 7.17 (dd, *J* = 3.6, 1.3 Hz, 1 H), 7.04 (d, *J* = 2.4 Hz, 1 H), 6.97–6.92 (m, 2 H), 3.80 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 157.1, 138.0, 134.2, 132.6, 131.8, 129.9, 129.7, 129.5, 129.4, 129.3, 127.7, 127.0, 115.9, 115.0, 114.9, 102.3, 55.8.

Anal. Calcd for $C_{19}H_{15}NO_3S_3$: C, 56.83; H, 3.77; N, 3.49. Found: C, 57.02; H, 3.67; N, 3.43.

1-(*tert*-Butoxycarbonyl)-3-(benzo[*b*]thiophen-2-yl)thio-1*H*-indole (12)

Purification by column chromatography using *n*-heptane–EtOAc (19:1) gave **12** as an off-white solid; mp 80–82 °C.

IR (neat): 1724, 1445, 1373, 1248, 1155, 1070, 808, 735 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.20 (d, *J* = 8.3 Hz, 1 H), 7.94 (s, 1 H), 7.71–7.68 (m, 1 H), 7.66–7.63 (m, 2 H), 7.39–7.24 (m, 5 H), 1.71 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 149.2, 141.2, 140.0, 138.1, 135.8, 130.6, 130.6, 125.5, 125.4, 124.6, 124.3, 123.6, 123.1, 122.0, 120.0, 115.6, 110.8, 84.8, 28.3.

Anal. Calcd for $C_{21}H_{19}NO_2S_2$: C, 66.11; H, 5.02; N, 3.67. Found: C, 66.15; H, 5.04; N, 3.67.

1-(*tert*-Butoxycarbonyl)-2-methyl-3-(benzo[*b*]furan-2-yl)thio-1*H*-indole (13)

Purification by column chromatography using *n*-heptane–CH_2Cl_2 (9:1 to 5:1) gave **13** as a colorless viscous oil which solidified upon standing; mp 96–98 °C.

IR (neat): 1727, 1446, 1351, 1368, 1334, 1317, 1334, 1215, 1157, 1116, 1060, 922, 854, 819, 760, 748 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.16–8.12 (m, 1 H), 7.75–7.72 (m, 1 H), 7.42–7.13 (m, 6 H), 6.63 (d, *J* = 0.9 Hz, 1 H), 2.89 (s, 3 H), 1.72 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 156.2, 150.7, 150.3, 143.1, 135.9, 130.3, 128.8, 124.5, 124.2, 123.5, 123.0, 120.3, 119.1, 115.7, 111.2, 108.8, 107.1, 84.8, 28.4, 15.3.

Anal. Calcd for $C_{22}H_{21}NO_3S$: C, 69.63; H, 5.58; N, 3.69. Found: C, 69.38; H, 5.80; N, 3.70.

Generation and Sulfenylation of Aromatic Grignard Reagents (Conditions C, Table 1)

A solution of the appropriate aryl halide (2.0 mmol) in THF (5 mL) was added dropwise to a suspension of Mg turnings (2.2 mmol) in anhyd THF (5 mL) at r.t. The mixture was heated at reflux for 1 h and was thereafter cooled to 0 °C, whereupon a solution of the suitable disulfide (2.0 mmol) in anhyd THF (10 mL) was added during 15 min at 0 °C. The mixture was allowed to warm to r.t. over 16 h and was thereafter quenched with sat. aq NH_4Cl (20 mL). Work-up as above, followed by column chromatography, afforded the products **14**–**22**.

1-Phenylsulfonyl-3-phenylthio-1*H*-indole (14)

Purification by column chromatography using *n*-heptane–Et_2O (9:1) followed by recrystallization from MeOH gave **14** as white crystals; mp 94–97 °C.

IR (neat): 1442, 1363, 1264, 1202, 1170, 1128, 1110, 1089, 1048, 1020, 943, 811, 728 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.07–8.04 (m, 1 H), 7.97–7.93 (m, 2 H), 7.85 (s, 1 H), 7.62–7.56 (m, 1 H), 7.51–7.45 (m, 3 H), 7.40–7.35 (m, 1 H), 7.27–7.11 (m, 6 H).

^{13}C NMR ($CDCl_3$): δ = 138.1, 136.2, 135.6, 134.3, 131.2, 130.9, 129.6, 129.2, 127.5, 127.1, 126.1, 125.7, 124.1, 120.7, 114.0, 112.4.

Anal. Calcd for $C_{20}H_{15}NO_2S_2$: C, 65.73; H, 4.14; N, 3.83. Found: C, 65.85; H, 4.15; N, 3.78.

1-Phenylsulfonyl-3-(3-methylphenyl)thio-1*H*-indole (15)

Purification by column chromatography using *n*-heptane–Et_2O (9:1) followed by recrystallization from MeCN gave **15** as white crystals; mp 120–121 °C.

IR (neat): 3155, 1444, 1364, 1265, 1205, 1171, 1163, 1129, 1111, 1090, 945, 785, 766, 729 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.06 (d, *J* = 8.3 Hz, 1 H), 7.96–7.92 (m, 2 H), 7.83 (s, 1 H), 7.62–7.56 (m, 1 H), 7.51–7.46 (m, 3 H), 7.40–7.34 (m, 1 H), 7.26–7.21 (m, 1 H), 7.10 (app t, *J* = 7.6 Hz, 1 H), 6.98–6.89 (m, 3 H), 2.24 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 139.0, 138.1, 135.9, 135.6, 134.3, 131.3, 130.8, 129.6, 129.0, 128.2, 127.1, 127.1, 125.7, 124.7, 124.1, 120.7, 113.9, 112.7, 21.5.

Anal. Calcd for $C_{21}H_{17}NO_2S_2$: C, 66.46; H, 4.52; N, 3.69. Found: 66.32; 4.58; 3.59.

1-Phenylsulfonyl-3-(4-methoxyphenyl)thio-1*H*-indole (16)

Purification by column chromatography using *n*-heptane–Et_2O (9:1) followed by recrystallization from MeOH gave **16** as white crystals; mp 86–88 °C.

IR (neat): 1491, 1442, 1375, 1244, 1167, 1127, 1111, 1090, 1018, 943, 827, 739, 727 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.01 (d, *J* = 8.3 Hz, 1 H), 7.92–7.89 (m, 2 H), 7.71 (s, 1 H), 7.60–7.55 (m, 1 H), 7.49–7.44 (m, 3 H), 7.39–7.32 (m, 1 H), 7.27–7.18 (m, 3 H), 6.81–6.76 (m, 2 H), 3.77 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 159.0, 138.1, 135.6, 134.2, 131.1, 129.6, 129.2, 127.0, 125.9, 125.6, 124.0, 120.6, 115.0, 113.9, 55.5.

Anal. Calcd for $C_{21}H_{17}NO_3S_2$: C, 63.77; H, 4.33; N, 3.54. Found: C, 63.85; H, 4.38; N, 3.49.

1-Phenylsulfonyl-3-(biphenyl-2-yl)thio-1*H*-indole (17)

Purification by column chromatography using *n*-heptane–Et_2O (9:1) followed by recrystallization from MeOH gave **17** as white crystals; mp 128–130 °C.

IR (neat): 1443, 1366, 1263, 1172, 1126, 1110, 1090, 949, 742, 729 cm^{-1}.

^{13}C NMR ($CDCl_3$): δ = 8.03–8.00 (m, 1 H), 7.90–7.87 (m, 2 H), 7.69 (s, 1 H), 7.59–7.32 (m, 10 H), 7.26–7.15 (m, 3 H), 7.08–7.03 (m, 1 H), 6.84 (dd, *J* = 7.9, 0.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 141.0, 140.4, 138.0, 135.6, 135.0, 134.3, 131.3, 131.1, 130.5, 129.6, 129.5, 128.4, 128.1, 127.9, 127.5, 127.0, 125.9, 125.7, 124.1, 120.7, 114.0, 112.6.

Anal. Calcd for $C_{26}H_{19}NO_2S_2$: C, 70.72; H, 4.34; N, 3.17. Found: C, 70.83; H, 4.39; N, 3.14.

1-Phenylsulfonyl-3-(1-naphthyl)thio-1*H*-indole (18)

Purification by column chromatography using *n*-heptane–Et_2O (9:1) followed by recrystallization from MeCN gave **18** as white crystals; mp 134–136 °C.

IR (neat): 1441, 1371, 1267, 1203, 1173, 1130, 1112, 1088, 949, 788, 760, 722 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.45–8.42 (m, 1 H), 8.07 (dd, *J* = 8.3, 0.6 Hz, 1 H), 7.92–7.86 (m, 3 H), 7.79 (s, 1 H), 7.70 (d, *J* = 8.1 Hz, 1 H), 7.62–7.53 (m, 3 H), 7.49–7.44 (m, 3 H), 7.41–7.35 (m, 1 H), 7.28–7.12 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 138.0, 135.7, 134.3, 134.1, 132.7, 131.7, 131.1, 130.3, 129.6, 128.8, 127.2, 127.0, 126.7, 126.7, 126.5, 125.9, 125.7, 124.5, 124.1, 120.6, 114.0, 113.1.

Anal. Calcd for $C_{24}H_{17}NO_2S_2$: C, 69.37; H, 4.12; N, 3.37. Found: C, 69.41; H, 4.19; N, 3.40.

1-Phenylsulfonyl-3-(9-phenanthren-2-yl)thio-1*H*-indole (19)

Purification by column chromatography using *n*-heptane–Et_2O (9:1) followed by recrystallization from MeCN gave **19** as white crystals; mp 159–162 °C.

IR (neat): 1444, 1363, 1258, 1172, 1123, 1108, 1088, 1048, 946, 877, 812, 746, 729, 719, 701 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.75–8.72 (m, 1 H), 8.63 (d, *J* = 8.3 Hz, 1 H), 8.53–8.50 (m, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.92–7.89 (m, 2 H), 7.83 (s, 1 H), 7.77–7.66 (m, 2 H), 7.63–7.35 (m, 7 H), 7.23–7.20 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 138.1, 135.7, 134.3, 131.8, 131.2, 131.1, 131.0, 130.4, 130.4, 129.7, 129.6, 128.2, 127.3, 127.3, 127.2, 127.1, 127.1, 126.8, 125.8, 125.3, 124.2, 123.4, 122.8, 120.6, 114.1, 112.9.

Anal. Calcd for $C_{28}H_{19}NO_2S_2$: C, 72.23; H, 4.11; N, 3.01. Found: C, 72.18; H, 4.19; N, 2.97.

1-(4-Methylphenylsulfonyl)-3-(4-methoxyphenyl)thio-1*H*-indole (20)

Purification by column chromatography on silica using *n*-heptane–CH_2Cl_2 (19:1) followed by recrystallization from MeCN gave **20** as white crystals; mp 112–114 °C.

IR (neat): 1589, 1491, 1443, 1372, 1289, 1267, 1249, 1173, 1156, 1105, 1089, 1041, 1025, 941, 831, 812, 761, 744, 721, 712 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.02–7.98 (m, 1 H), 7.79 (d *J* = 8.4 Hz, 2 H), 7.71 (s, 1 H), 7.48–7.44 (m, 1 H), 7.37–7.31 (m, 1 H), 7.27–7.19 (m, 4 H), 6.78 (d, *J* = 9.0 Hz, 2 H), 3.77 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 158.9, 145.5, 135.6, 135.2, 131.1, 131.0, 130.2, 129.4, 127.1, 126.0, 125.5, 123.9, 120.5, 114.9, 114.5, 113.9, 55.5, 21.8.

Anal. Calcd for $C_{22}H_{19}NO_3S_2$: C, 64.52; H, 4.68; N, 3.42. Found: C, 64.60; H, 4.74; N, 3.36.

1-(*tert*-Butoxycarbonyl)-3-phenylthio-1*H*-indole (21)

Purification by column chromatography using *n*-heptane–EtOAc (19:1) gave **21** as light yellow oil.

IR (neat): 1734, 1448, 1354, 1311, 1246, 1218, 1149, 1060, 737 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.21 (d, *J* = 8.3 Hz, 1 H), 7.90 (s, 1 H), 7.52–7.49 (m, 1 H), 7.38–7.35 (m, 1 H), 7.27–7.09 (m, 6 H), 1.71 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 149.3, 137.2, 136.1, 131.4, 131.0, 129.1, 127.2, 125.7, 125.3, 123.5, 120.2, 115.6, 109.6, 84.6, 28.4.

Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 70.12; H, 5.88; N, 4.30. Found: C, 70.19; H, 5.94; N, 4.37.

1-(*tert*-Butoxycarbonyl)-2-methyl-3-(1-naphthyl)thio-1*H*-indole (22)

Purification by column chromatography using *n*-heptane–CH_2Cl_2 (9:1 to 5:1) gave **22** as a colorless viscous oil which solidified upon standing; mp 58–61 °C.

IR (neat): 1731, 1451, 1369, 1352, 1333, 1314, 1256, 1214, 1153, 1112, 788, 767, 745 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.52–8.48 (m, 1 H), 8.24–8.20 (m, 1 H), 7.89–7.86 (m, 1 H), 7.66–7.48 (m, 4 H), 7.36–730 (m, 1 H), 7.23–7.16 (m, 2 H), 6.86 (dd, *J* = 7.4, 1.1 Hz, 1 H), 2.82 (s, 3 H), 1.76 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 150.4, 143.9, 136.3, 134.7, 134.0, 131.0, 130.6, 128.7, 126.4, 126.3, 125.9, 125.5, 124.5, 124.1, 123.5, 123.1, 119.4, 115.7, 107.5, 84.8, 28.5, 15.2.

Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N, 3.60. Found: C, 74.08; H, 6.03; N, 3.52.

Generation and Sulfenylation of Functionalized Aromatic Grignard Reagents (Conditions D, Table 1)

A solution of *i*-PrMgCl (2.0 M in Et_2O, 1.2 mL, 2.4 mmol,) was added slowly (over ~10 min) to a solution of ethyl 2-iodobenzoate or ethyl 4-iodobenzoate (2.0 mmol) in anhyd THF (10 mL) at –20 °C. The mixture was stirred at –20 °C for 30 min, then allowed to warm to 0 °C over 30 min, and thereafter cooled to –78 °C. A solution of the appropriate disulfide (2.0 mmol) in THF (10 mL) was added over ~15 min at –78 °C. The resulting mixture was allowed to warm to r.t. over 16 h, and was subsequently treated with sat. aq NH_4Cl (25 mL). Work-up as above, followed by column chromatography gave the products **23**–**25**.

1-Phenylsulfonyl-3-(4-ethoxycarbonylphenyl)thio-1*H*-indole (23)

Purification by column chromatography using *n*-heptane–EtOAc (8:1) gave **23** as a light yellow viscous oil.

IR (neat): 2978, 1708, 1592, 1444, 1373, 1267, 1173, 1126, 1105, 1090, 1048, 1014, 944, 756, 745, 728, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.08–8.05 (m, 1 H), 7.97–7.94 (m, 2 H), 7.91 (s, 1 H), 8.83 (d *J* = 8.7 Hz, 2 H), 7.63–7.57 (m, 1 H), 7.53–7.47 (m, 2 H), 7.42–7.37 (m, 2 H), 7.26–7.21 (m, 1 H), 7.06 (d *J* = 8.7 Hz, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.3, 143.1, 138.0, 135.6, 134.5, 131.8, 130.9, 130.2, 129.7, 127.8, 127.1, 125.9, 125.9, 124.3, 120.5, 114.1, 110.4, 61.1, 14.5.

Anal. Calcd for $C_{23}H_{19}NO_4S_2$: C, 63.14; H, 4.38; N, 3.20. Found: C, 62.97; H, 4.37; N, 3.15.

1-Phenylsulfonyl-3-(2-ethoxycarbonylphenyl)thio-1*H*-indole (24)

Purification by column chromatography using *n*-heptane–EtOAc (9:1) gave **24** as a colorless viscous oil which solidified upon standing; mp 108–110.5 °C.

IR (neat): 1702, 1443, 1366, 1267, 1252, 1174, 1131, 1091, 1039, 944, 762, 752, 742, 728 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.08–8.02 (m, 2 H), 7.97–7.93 (m, 2 H), 7.90 (s, 1 H), 7.62–7.56 (m, 1 H), 7.51–7.46 (m, 2 H), 7.41–7.36 (m, 2

H), 7.25–7.19 (m, 1 H), 7.14–7.09 (m, 2 H), 6.69–6.66 (m, 1 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 1.45 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.6, 141.6, 138.0, 135.8, 134.4, 132.5, 132.3, 131.4, 131.3, 129.6, 127.1, 126.8, 126.6, 125.8, 124.5, 124.2, 120.7, 114.0, 111.9, 61.5, 14.5.

Anal. Calcd for $C_{23}H_{19}NO_4S_2$: C, 63.14; H, 4.38; N, 3.20. Found: C, 63.25; H, 4.32; N, 3.12.

5-Methoxy-1-phenylsulfonyl-3-(2-ethoxycarbonylphenyl)thio-1*H*-indole (25)

Purification by column chromatography using *n*-heptane–CH_2Cl_2 (4:1) gave **25** as white crystals; mp 114–117 °C.

IR (neat): 1704, 1460, 1446, 1434, 1372, 1267, 1250, 1212, 1164, 1140, 1100, 1090, 1029, 957, 851, 825, 810, 744, 724 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.06–8.03 (m, 1 H), 7.97–7.90 (m, 3 H), 7.84 (s, 1 H), 7.62–7.57 (m, 1 H), 7.53–7.46 (m, 2 H), 7.15–7.09 (m, 2 H), 6.99 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.83 (d, *J* = 2.5 Hz, 1 H), 6.67–6.64 (m, 1 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 3.70 (s, 3 H), 1.46 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.7, 157.4, 141.7, 138.0, 134.3, 133.1, 132.7, 132.6, 131.5, 130.3, 129.6, 127.1, 126.8, 126.5, 124.5, 115.4, 115.1, 111.8, 102.4, 61.5, 55.9, 14.6.

Anal. Calcd for $C_{24}H_{21}NO_5S_2$: C, 61.65; H. 4.53; N, 3.00. Found: C, 61.76; H, 4.62; N, 2.94.

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