INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

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Research Article

IODINE CATALYZED DIRECT REGIOSELECTIVE 3-SULFENYLATION OF INDOLES USING DIARYL DISULFIDES

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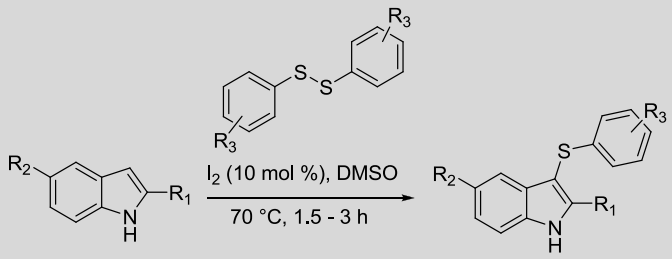
ABSTRACT

The present paper reports a facile and simple method for synthesis of structurally diverse 3-sulfenylindole derivatives by direct sulfenylation of indoles using diaryl disulfides in the presence of molecular iodine as a catalyst. The sulfenylation proceeds well in both dichloromethane and dimethylsulfoxide. The reaction proceeds much faster in good yield in DMSO at 70 °C, as compared to dichloromethane at room temperature or in acetonitrile under reflux conditions and without iodine no conversion was observed. With 5 mol% of iodine, a reasonable conversion was observed in dichloromethane as compared to acetonitrile at room temperature and under reflux conditions while 10 mol% gave an excellent conversion in DCM and DMSO. The simplified procedure has several merits in terms of ease of operation, mild conditions, excellent yields, atom economy and regioselectivity. The method would find wide spread application in synthesis of bioactive compounds bearing simple and substituted 3- sulfenyl moiety.

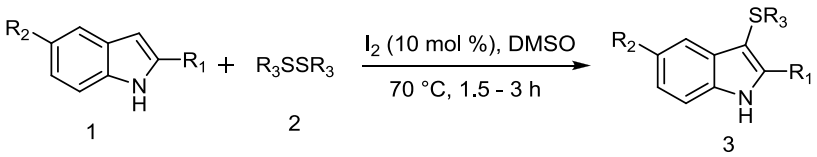


Keywords: Iodine, diphenyl disulfide, indole, sulfenyl indole, catalytic.

1. INTRODUCTION

The indole nucleus is an important heterocycle often encountered in a variety of bioactive compounds and therapeutic agents.[1] In particular, 3-thioindoles have received considerable interest as they are of therapeutic value in the treatment of diseases such as HIV,[2] Cancer,[3] obesity,[4] heart disease,[5] and allergies.[6] A variety of sulfenylating agents such as sulfonium salts,[7] quinone mono-O,S-acetals,[8] sulfonyl hydrazides,[9] sulfinates,[10] disulfides,[11] sulfenyl halides,[12] *N*-thioimides,[13] thiols,[14] and arylsulfonylchlorides[15] have been used to introduce sulfenyl moiety on indoles. Also, oxidant-promoted thiocyanation with ammonium thiocyanate[16] and conversion of 3,3′-dithiobisindoles by treatment with metallated aromatics or heterocycles[17] provide facile access to 3-sulfenylindoles. The reported methods suffer in terms of expensive sulfur component, accessibility, stability, use of

harsh conditions and incompatibility with sensitive functional groups.[18-25] The procedure reported by Jin-Heng Li *et al.* for direct sulfenylation using disulfides employ $FeCl_3$/catalytic I_2 system and the procedure requires heating in acetonitrile at 80 ^oC for a period of 36 h.[26a] On similar lines, Wei *et al.* have reported direct sulfenylation of indoles uisng iodine/DMSO system in dimethyl carbonate as a solvent with emphasis on the role of DMSO as oxidant[26b] for regeneration of iodine. As part of our ongoing project on the design and synthesis of different biologically active sulfenylindoles, we required an efficient and mild method to have an easy access to this skeleton using easily available bench top reagents on a large scale. In view of the current green chemistry scenario, iodine/disulfide system has several attributes in terms of availability, stability, atom economy and easy to handle reagent and hence this reagent system was explored for possible simplification and acceleration of the reaction. Herein, we report that, sulfenylation using catalytic iodine/diaryl disulfide proceeds with or without DMSO as oxidant to provide facile access to a wide variety of 3- sulfenylindoles in good to excellent yield (Scheme 1).



Scheme 1: Direct sulfenylation of indoles using disulfide/iodine

2. MATERIALS AND METHODS

2.1 RESULTS AND DISCUSSION

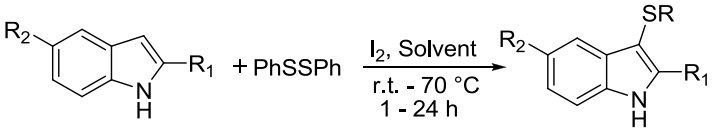
To begin with, sulfenylation using iodine and diphenyl disulfide was investigated with different mol%. of iodine in different solvents at different temperatures (Table 1).

Table 1: Iodine-catalyzed sulfenylation of Indoles

Entry	mol% of Iodine	Solvent	Time (h)	Temperature (°C)	% conversion
1	0	ACN	48	r.t.	0
2	0	-	48	r.t.	0
3	5	ACN	24	r.t.	30
4	5	ACN	24	reflux	35
5	5	DCM	10	r.t.	70
6	10	DCM	3	r.t.	95
7	10	DMSO	2	r.t.	100
8	10	DMSO	1	70	100

As is obvious from the Table 1, the reaction proceeds much faster in good yield in dimethyl sulfoxide (DMSO) at 70 °C, as compared to dichloromethane (DCM) at room temperature or in acetonitrile (ACN) under reflux conditions. As expected, without iodine no conversion was observed (Table 1 and entry 1 & 2). With 5 mol% of iodine, a reasonable conversion was observed in dichloromethane as compared to acetonitrile at room temperature and under reflux conditions while 10 mol% gave an excellent conversion in DCM and DMSO (Table 1, entry 6,7). It is remarkable to note that reaction proceeded in a quantitative fashion in DMSO at 70 °C within an hour. With 10 mol% iodine the reaction proceeds well in DCM (entry 6), it appears that the role of DMSO as oxidant for regeneration of iodine is not be essential. However, DMSO seems to promote the sulfenylation reaction in terms of time and yield (entry 7 and 8). Having set the conditions, different substituted indoles were investigated in DCM and DMSO at room temperature and at 70°C and the results are presented in Table 2. Sulfenylation with simple indole proceeded at r.t. in both the solvents in good yield while methyl indole required heating in DMSO for good conversion (Table 2 & entry 1). Similarly, other substituted indoles bearing different functional groups required heating at 70 °C in DMSO for good conversion (entries 3-7).

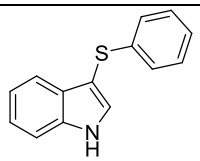
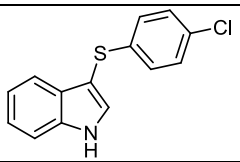
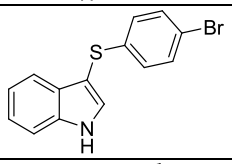
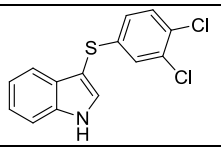
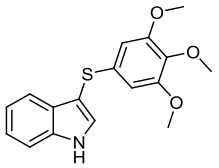
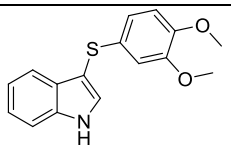
Table 2: Iodine-catalyzed sulfenylation of Indoles

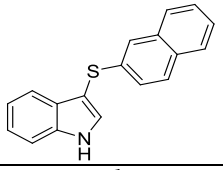
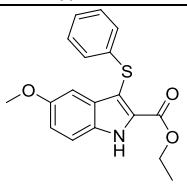
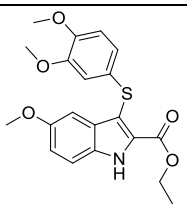
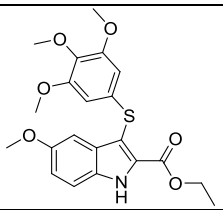
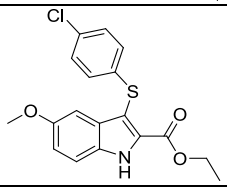
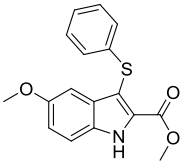
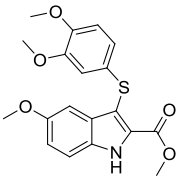
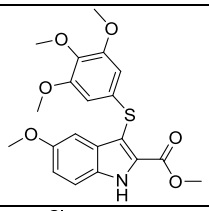
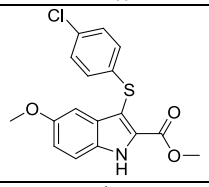
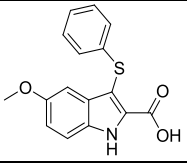


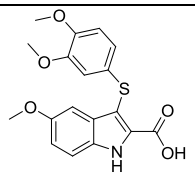
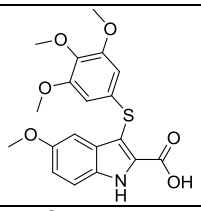
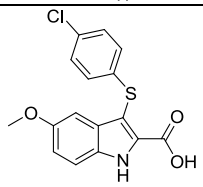
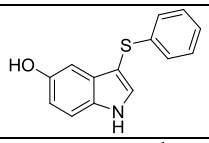
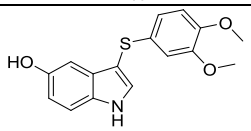
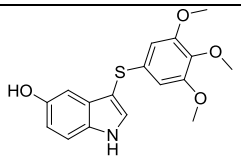
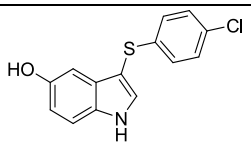
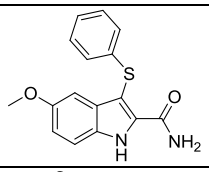
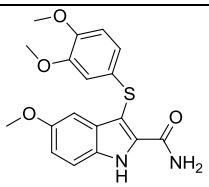
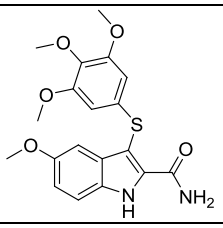
Entry	R_1	R_2	Reaction conditions					
			DCM, r.t.		DMSO, r.t.		DMSO, 70 °C	
			Time (h)	% conversion	Time (h)	% conversion	Time (h)	% conversion
1	H	H	3	95	2	100	1	100
2	Me	H	10	60	5	70	2	100
3	CO_2Et	OMe	24	10	24	20	3	100
4	H	OH	24	Trace	24	20	1.5	100
5	CO_2H	OMe	24	5	24	10	2.5	100
6	$CONH_2$	OMe	24	Trace	24	Trace	3	100
7	CO_2Et	Cl	24	7	24	12	2.5	100

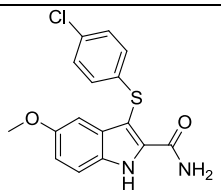
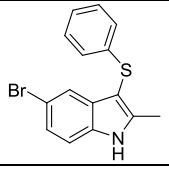
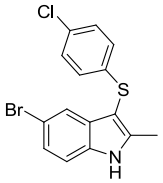
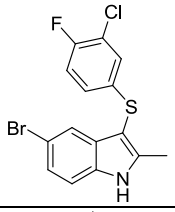
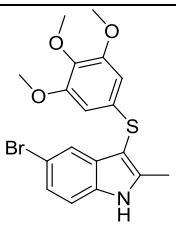
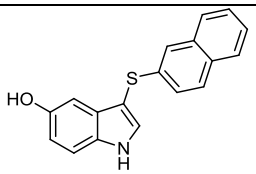
Though the conversion was observed at room temperature in DCM and DMSO, the yields were less than 20% even after 24 h but at 70 °C quantitative conversion was observed in 2 h. Next we studied the reaction conditions with different substituted disulfides and the results are presented in Table 3. As expected the reaction proceeded extremely well to afford the respective sulfenylindoles in good yield. The functional groups on the indole moiety and disulfide are well tolerated and yield the corresponding sulfenyl product in good to excellent yield.

Table 3: Iodine-catalyzed sulfenylation of Indoles

Entry	R_1, R_2	Aryl-	Product	Time (h)	% Yield
1.	H, H	Phenyl		1	98
2.	H, H	4- Chlorophenyl		1	97
3	H, H	4- Bromophenyl		1	97
4	H, H	2,4- Dichlorophenyl		1	95
5	H, H	3,4,5-Trimethoxyphenyl		1.2	96
6	H, H	3,4- Dimethoxyphenyl		1.2	95

7	H, H	2 -Naphthyl		1	96
8	CO_2Et, OMe	Phenyl		3	95
9	CO_2Et, OMe	3,4- Dimethoxyphenyl		3	95
10	CO_2Et, OMe	3,4,5-Trimethoxyphenyl		3	93
11	CO_2Et, OMe	4-Chlorophenyl		3	94
12	CO_2Me, OMe	Phenyl		3	95
13	CO_2Me, OMe	3,4- Dimethoxyphenyl		3	94
14	CO_2Me, OMe	3,4,5-Trimethoxyphenyl		2.5	93
15	CO_2Me, OMe	4- Chlorophenyl		2.5	96
16	CO_2H, OMe	Phenyl		2.5	92

17	CO_2H, OMe	3,4- Dimethoxyphenyl		2.5	91
18	CO_2H, OMe	3,4,5-Trimethoxyphenyl		2.5	90
19	CO_2H, OMe	4-Chlorophenyl		2.5	93
20	H, OH	Phenyl		1.5	91
21	H, OH	3,4- Dimethoxyphenyl		1.5	90
22	H, OH	3,4,5-Trimethoxyphenyl		1.5	90
23	H, OH	4-Chlorophenyl		1.5	90
24	$CONH_2$, OMe	Phenyl		3	92
25	$CONH_2$, OMe	3,4- Dimethoxyphenyl		3	90
26	$CONH_2$, OMe	3,4,5-Trimethoxyphenyl		3	91

27	$CONH_2$, OMe	4-Chlorophenyl		3	93
28	Me, Br	Phenyl		0.5	95
29	Me, Br	4-Chlorophenyl		0.5	94
30	Me, Br	3-Chloro-4-fluorophenyl		0.5	93
31	Me, Br	3,4,5-Trimethoxyphenyl		0.5	94
32	H, OH	2 –Naphthyl		1.5	92

2.2 General Procedure

A mixture of an indole (0.4 mmol), a disulfide (0.24 mmol) and I_2 (10 mol%) in DMSO (2 mL) was stirred at 70 °C for 0.5-3 h until complete consumption of the starting material, as monitored by TLC. After completion of the reaction, 5% sodium thiosulfate solution (5 mL) was added and extracted with dichloromethane (2x15 mL). The combined organic extracts were washed with brine solution and dried over anhydrous sodium sulfate and evaporation of solvents under the reduced pressure afforded 90-98% yield of product. The pure product was obtained by passing through a 100-200 mesh silica gel column chromatography using chloroform and ethyl acetate as eluent to afford the sulfenylindole product.

3-(Phenylthio)-1H-indole (entry 1)

Off white solid; m.p.: 151-153 °C. IR (KBr): cm^{-1} 3397, 3109, 3080, 2923, 2853, 1564, 1547, 1451, 1364, 1088, 1024, 790, 818, 751, 518. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03-7.19 (m, 5H), 7.28 (d, 2H, *J* = 7.6 Hz), 7.45 (d, 1H. *J* = 8.0 Hz), 7.5 (d, 1H, *J* = 2.5 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 8.41 (br, 1H). EI MS: m/z (rel.abund.%) 224, ($[M-1]^+$, 100).

3-(4-Chlorophenylthio)-1H-indole (entry 2)

Off white solid; m.p.: 142-144 °C. IR (KBr): cm^{-1} 3392, 3107, 3086, 2922, 2853, 1563, 1545, 1451, 1364, 1087, 1023, 780, 808, 751, 518. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, 2H, *J* = 8.8 Hz), 7.11 (d, 2H, *J* = 8.8Hz), 7.17 (m, 1H), 7.29 (d, 1H. *J* = 8.0 Hz), 7.45 (d, 1H, *J* = 8.4 Hz), 7.49 (d, 1H, *J* = 2.4 Hz), 7.57 (d, 1H, *J* = 8.0 Hz), 8.42 (br, 1H). EI MS: m/z (rel.abund.%) 258, ($[M-1]^+$, 100), 260 (Cl).

3-(4-Bromophenylthio)-1H-indole (entry 3)
Off white solid; m.p.: 146-148 °C. IR (KBr): cm^{-1} 3395, 3107, 3086, 2923, 2852, 1563, 1547, 1450, 1364, 1088, 1025, 790, 818, 751, 528. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (d, 2H, *J* = 8.4 Hz), 7.15-7.19 (m, 1H), 7.24-7.29 (m, 3H), 7.44 (d, 1H. *J* = 8.4 Hz), 7.49 (d, 1H, *J* = 2.8 Hz), 7.56 (d, 1H, *J* = 8.0 Hz), 8.41 (br, 1H). EI MS: m/z (rel.abund.%) 302 (M^+, 98(Br)), 304 ($[M+2]^+$, 100).

3-(3,4-Dichlorophenylthio)-1H-indole (entry 4)
Off white solid; m.p.: 105-107 °C. IR (KBr): cm^{-1} 3397, 3109, 3080, 2923, 2853, 1564, 1547, 1451, 1364, 1088, 1024, 818, 803, 751, 518. ^{1}H NMR (400 MHz, DMSO d_6): δ 6.96 (dd, 1H, *J* = 2.4 Hz, 8.4 Hz), 7.08-7.11 (m, 1H), 7.18-7.22 (m, 2H), 7.38 (d, 1H. *J* = 8.0 Hz), 7.45 (d, 1H, *J* = 8.4 Hz), 7.51 (d, 1H, *J* = 8.4 Hz), 7.83 (d, 1H, *J* = 2.8 Hz), 11.81 (s, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 101.57, 111.73, 119.33, 121.23, 123.35, 125.05, 127.12, 128.57, 128.60, 130.28, 130.95, 132.75, 136.48 and 139.82. EI MS: m/z (rel.abund.%) 291.88, ($[M-1]^+$, 100), 293.87 ($[M+1]^+$ 75). HRMS: Found mass 293.99110, calculated mass 293.99186, with M.F. $C_{14}H_{10}NCl_2S$.

3-(3, 4-Dimethoxyphenylthio)-1H-indole (entry 5)
White solid; m.p.: 137-139 °C. IR (KBr): cm^{-1} 3397, 3108, 3079, 2923, 2853, 1554, 1544, 1448, 1363, 1085, 1024. ^{1}H NMR (400 MHz, DMSO d_6): δ 3.63 (s, 3H), 3.65 (s, 3H), 6.53 (dd, 1H, *J* = 2.4 Hz, 8.4 Hz), 6.78-6.81 (m, 2H), 7.03-7.18 (m, 2H), 7.44 (dd, 2H. *J* = 8.0 Hz, *J* = 11.2 Hz), 7.72 (d, 1H, *J* = 2.8 Hz), 11.58 (s, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 55.50, 55.56, 101.57, 111.73, 119.33, 121.23, 123.35, 125.05, 127.12, 128.57, 128.60, 130.28, 130.95, 132.75, 147.65 and 149.07. EI MS: m/z (rel.abund.%) 284 ,($[M-1]^+$, 100). HRMS: Found mass 286.09212, calculated mass 286.09017, with M.F. $C_{16}H_{16}O_2NS$.

3-(3,4,5-Trimethoxyphenylthio)-1H-indole (entry 6)
Off white solid; m.p.: 139-142 °C. IR (KBr): cm^{-1} 3396, 3109, 3082, 2923, 2853, 1561, 1547, 1451, 1364, 1088, 1024, 818, 803. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.65 (s, 6H), 3.77 (s, 3H), 6.39 (s, 2H), 7.15-7.18 (m, 1H), 7.24 (d, 1H, *J* = 8.4 Hz), 7.42 (d, 1H, *J* = 8.4 Hz), 7.48 (d, 1H, *J* = 2.1 Hz), 7.64 (d, 1H, *J* = 7.3 Hz), 8.53 (s, 1H) (EI MS: m/z (rel.abund.%) 316, ($[M+1]^+$, 100).

3-(Naphthalene-2-ylthio)-1H-indole (entry 7)
White solid; m.p.: 177-179 °C. IR (KBr): cm^{-1} 3394, 3105, 3088, 2924, 2853, 1564, 1548, 1451, 1365, 1088, 1024, 809, 801, 751, 518. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-7.17 (m, 1H) 7.28-739 (m, 4H), 7.47 (d, 2H, *J* = 8.0 Hz), 7.56-7.66 (m, 4H), 7.72 (d, 1H. *J* = 7.2 Hz), 8.46 (br, 1H). EI MS: m/z (rel.abund.%) 276 ($[M+1]^+$, 100).

5-Bromo-2-methyl-3-(phenylthio)-1H-indole (entry 8)
Off white solid; m.p.: 156-159 °C. IR (KBr): cm^{-1} 3354.3, 3115.7, 3075.7, 2914.1, 2823.3, 1557.3, 1550.2, 1461.7, 1344.2, 1087.4, 1024.1, 809.2, 801.0, 762.1, 510.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 6.69-7.78 (m, 3 H), 7.12-7.25 (m, 4H), 7.65 (s, 1H), 10.11 (s, 1H). EI MS: m/z (rel.abund.%) 318 (M^+, 100), 320 ($[M+2]^+$, 98 (Br)).

5-Bromo-3-(4-chlorophenylthio)-2-methyl-1H-indole (entry 9)
White solid; m.p.: 153-155 °C. IR (KBr): cm^{-1} 3354, 3116, 3074, 2912, 2824, 1554, 1555, 1464, 1342, 1083, 1025, 801, 801, 762, 510. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H), 6.69-7.79 (m, 3 H), 7.11-7.25 (m, 3H), 7.66 (s, 1H), 10.12 (s, 1H). EI MS: m/z (rel.abund.%) 352 ($[M +2]^+$, 80), 354 ($[M+4]^+$, 100).

5-Bromo-3-(3-chloro-4-fluorophenylthio)-2-methyl-1H-indole (entry 10)
Pale pink solid; m.p.: 129-131 °C. IR (KBr): cm^{-1} 33574, 3112, 3072, 2922, 2834, 1559, 1553, 1466, 1344, 1080, 1030, 810, 807, 769, 520, 517. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H), 6.81-7.06 (m, 3H), 7.17-7.35 (m, 3H), 7.64 (d, J = 1.8 Hz, 1H), 8.35 (s, 1H). ^{13}C NMR (75 MHz, CDCl3): δ 12.14, 98.88, 112.24, 114.42, 116.70, 116.99, 121.26, 121.40, 121.64, 125.22, 125.31, 125.36, 127.25, 131.77, 134.06, 135.36, 135.41, 142.73, 154.34 and 157.61. HRMS: Found mass 369.94848, calculated mass 369.94690, with M.F. $C_{15}H_{11}NFClBrS$.

5-Bromo-2-methyl-3-(3,4,5-trimethoxyphenylthio)-1H-indole (entry 11)
White solid; m.p.: 165-168 °C. IR (KBr): cm^{-1} 3294, 3126, 3094, 2915, 2834, 1543, 1547, 1454, 1345, 1089, 1027, 821, 810. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H), 3.67 (s, 6H), 3.78 (s, 3H), 6.27 (s, 2H), 7.17-7.27 (m, 2H), 7.70 (s, 1H), 8.51 (s, 1H). ^{13}C NMR (75 MHz, CDCl3): δ 12.14, 55.97, 60.83, 99.20, 102.80, 112.20, 114.04, 121.35, 124.98, 132.00, 134.01, 135.44, 142.59 and 153.41. HRMS: Found mass 408.02841, calculated mass 408.02635, with M.F. $C_{18}H_{19}O_3NBrS$.

Ethyl 5-methoxy-3-(phenylthio)-1H-indole-2-carboxylate (entry 12)
White solid; m.p.: 144-146 °C. IR (KBr): cm^{-1} 3305, 3071, 2986, 2939, 2903, 2831, 2699, 1936, 1879, 1682, 1582, 1507, 1476, 1454, 1439, 1438, 1340, 1258, 1207, 1169, 1120, 1058, 1024, 966, 687. 1H NMR (400 MHz, $CDCl_3$): 1H NMR (400 MHz, CDCl3): δ 1.28 (t, 3 H, J = 7.2 Hz), 3.73 (s, 3 H), 4.36 (q, 2 H, J = 7.2 Hz), 6.97 (d, 1H, J = 2.0 Hz), 7.10 (dd, 1H, J = 2.0 Hz, 8.8 Hz), 7.06-7.10 (m, 1H), 7.15-7.20 (m, 4H) 7.33 (d, 1H, J = 8.8 Hz), 9.29 (s, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 14.12, 55.54, 61.35, 101.18, 109.46, 113.09, 118.00, 125.17, 127.08, 128.67, 129.06, 130.82, 130.86, 137.93, 155.28 and 161.26. HRMS: Found mass 350.08369, calculated mass 350.08214, with M.F. $C_{18}H_{17}O_3NNaS$.

Ethyl 3-(4-chlorophenylthio)-5-methoxy-1H-indole-2-carboxylate (entry 13)
Off white solid; m.p.: 166-168 °C. IR (KBr): cm^{-1} 3279, 3073, 2981, 2936, 2906, 2833, 1682, 1507, 1474, 1453, 1418, 1254, 1209, 1166, 1010, 813. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, 3 H, *J* = 7.2 Hz), 3.78 (s, 3 H), 4.34 (q, 2 H, J = 7.2 Hz), 7.02-7.23 (m, 5H), 7.29 (s, 1H), 7.33-7.44 (m, 1H), δ 9.27 (s, 1H). ^{13}C NMR (75 MHz, CDCl3): δ 14.33, 55.99, 61.42, 101.01, 108.72, 113.20, 128.11, 128.15, 128.78, 129.25, 130.73, 130.83, 130.92, 136.71, 155.49 and 161.03. HRMS: Found mass 362.06196, calculated mass 362.06177, with M.F. $C_{18}H_{17}O_3NCl$.

Ethyl 3-(3,4-dimethoxyphenylthio)-5-methoxy-1H-indole-2-carboxylate (entry 14)
White solid; m.p.: 138-140 °C. IR (KBr): cm^{-1} 3300, 2984, 2930, 2903, 2830, 2252, 1682, 1625, 1581, 1503, 1452, 1254, 1233, 1208, 1168, 1024, 810, 729. ^1H NMR (400 MHz, DMSO d_6): δ 1.9 (t, 3 H, *J* = 7.2 Hz), 3.65 (s, 6 H), 3.68 (s, 3H), 4.34 (q, 2 H, *J* = 7.2 Hz), 6.68 (dd, 1H, *J* = 2.0 Hz, 8.4 Hz), 6.79 (d, 1H, *J* = 1.6 Hz), 6.83 (d, 1H, *J* = 8.4 Hz), 6.93 (d. 1H, *J* = 1.6 Hz), 6.96 (d. 1H, *J* = 2.4 Hz), 7.39 (d, 1H. *J* = 8.8 Hz), 12.12 (s, 1H). ^{13}C NMR(400 MHz, DMSO d_6): δ 14.28, 55.50, 55.86, 55.93,61.28, 101.29, 111.34, 111.60, 112.44, 113.04, 117.83, 121.31, 128.14, 128.27, 130.36, 130.90, 147.65, 149.07, 155.05 and 161.23. HRMS: Found mass 388.12361, calculated mass 388.12187, with M.F. $C_{20}H_{22}NO_5S$.

Ethyl 5-methoxy-3-(3,4,5-trimethoxyphenylthio)-1H-indole-2-carboxylate (entry 15)
White solid; m.p.: 147-149 °C. IR (KBr): cm^{-1} 3309, 2980, 2930, 2902, 2830, 2252, 1685, 1635, 1591, 1513, 1453, 1261, 1243, 1218, 1170, 1024, 815, 739, 635. ^1H NMR (500 MHz, $CDCl_3$ and DMSO d_6): δ 1.34 (t, 3H, *J* = 7.1 Hz), 3.67 (s, 6H), 6.74 (s, 6H), 4.37 (q, 2 H, *J* = 7.1 Hz), 6.44 (s, 2H), 6.93-6.96 (m, 2H), 7.42 (d, 1H, *J* = 9.1 Hz), 11.35 (s, 1H). EI MS: m/z (rel.abund.%) 416, ($[M-1]^+$, 100).

Methyl 5-methoxy-3-(phenylthio)-1H-indole-2-carboxylate (entry 16)
Off white solid; m.p.: 206-209 °C. IR (KBr): cm^{-1} 3305, 3072, 2988, 2941, 2834.1, 2699, 1933, 1879, 1682, 1582, 1507, 1476, 1454, 1439, 1438, 1340, 1258, 1207, 1169, 1120, 1023, 969, 687, 518. ^1H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3 H), 3.95 (s, 3 H), 6.96 (d, 1H, J = 2.0 Hz), 7.10 (dd, 1H, J = 2.0 Hz, 8.8 Hz), 7.05-7.10 (m, 1H), 7.15-7.20 (m, 4H) 7.33 (d, 1H, J = 8.8 Hz), 9.31 (s, 1H). EI MS: m/z (rel.abund.%) 312, ($[M-1]^+$, 100).

Methyl 3-(4-chlorophenylthio)-5-methoxy-1H-indole-2-carboxylate (entry 17)
Off white solid; m.p.: 209-211 °C. IR (KBr): cm^{-1} 3278, 3073, 2981, 2936, 2906, 2833, 1682, 1507, 1474, 1453, 1418, 1254, 1209, 1166, 1010, 819, 723. ^1H NMR (300 MHz, $CDCl_3$ and DMSO d_6): δ 3.74 (s, 3H), 3.89 (s, 3H), 6.89 (d, 1H, *J* = 2.3 Hz), 6.97 (dd, 1H, *J* = 2.5, *J* = 8.9 Hz), 7.00 – 7.08 (m, 2H), 7. 09 – 7.20 (m, 2H), 7.45 (d, 1H , *J* = 8.9 Hz,), 11.73 (s, 1H). ^{13}C NMR (75 MHz, CDCl3): δ 55.58, 55.99, 101.01, 108.72, 113.20, 128.11, 128.15, 128.78, 129.25, 130.73, 130.83, 130.92, 136.71, 155.49 and 161.03. HRMS: Found mass 348.04913, calculated mass 348.04621, with M.F. $C_{17}H_{15}O_3NClS$.

Methyl 3-(3,4-dimethoxyphenylthio)-5-methoxy-1H-indole-2-carboxylate (entry 18)
Off white solid; m.p.: 140-143 °C. IR (KBr): cm^{-1} 3320, 2974, 2950, 2903, 2834, 2251, 1679, 1634, 1579, 1503, 1452, 1271, 1233, 1208, 1168, 1024, 810, 729, 508. ^1H NMR (500 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 3.94 (s, 3H), 6.72, (d, 1H, *J* = 8.3 Hz), 6.83 (dd, 1H, *J* = 2.1, *J* = 8.4 Hz), 6.90-6.91 (m, 2H), 6.99 (dd, 1H, *J* = 2.1, *J* = 9.4 Hz), 7.30 (d, 1H, *J* = 9.4 Hz), 9.09 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.13, 55.53, 55.90, 55.96, 101.42, 111.67, 112.71, 113.04, 117.96, 121.60, 127.83, 128.09, 130.25, 130.97, 147.81, 144.12, 155.10 and 161.63. HRMS: Found mass 374.10827, calculated mass 374.10657, with M.F. $C_{19}H_{21}O_5NS$.

Methyl 5-methoxy-3-(3,4,5-trimethoxyphenylthio)-1H-indole-2-carboxylate (entry 19)
Off white solid; m.p.: 146-149 °C. IR (KBr): cm^{-1} 3388, 2980, 2930, 2902, 2830, 2252, 1675, 1634, 1581, 1513, 1453, 1261, 1243, 1218,

1170, 1024, 825, 735, 637, 528. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 6H), 3.74 (s, 3H), 3.79 (s, 3H), 3.95 (s, 3H), 6.48 (s, 2H), 6.92 (d, 1H, *J* = 2.4 Hz), 7.02 (dd, 1H, *J* = 2.5 Hz, *J* = 9.0 Hz), 7.33 (d, 1H, *J* = 8.9 Hz), 9.23(s, 1H). EI MS: m/z (rel.abund.%) 404,($[M+1]^+$, 100).

5-Methoxy-3-(phenylthio)-1H-indole-2-carboxylic acid (entry 20)

Pale yellow solid; m.p.: 213-215 °C. IR (KBr): cm^{-1} 3271, 3052, 2927, 2577, 1668, 1623, 1511, 1429, 1250, 1230, 1207, 1169, 1017, 739, 692. ^{1}H NMR (400 MHz, DMSO d_6): δ 3.64 (s, 3 H), 6.79 (d, 1H, *J* = 2.4 Hz), 6.94 (dd, 1H, *J* = 2.4 Hz, 9.2 Hz), 7.04-7.1 (m, 3H), 7.2-7.23 (m, 2H), 7.41 (d, 1H. *J* = 9.2 Hz), 12.19 (s, 1H), 13.2 (br, 1H). ^{13}C NMR (100 MHz, DMSO d_6): δ 55.14, 100.09, 105.56, 116.53, 114.19, 124.96, 126.19, 131.24, 130.57, 129.90, 128.83, 138.03, 154.59 and 161.74. HRMS: Found mass 322.05182, calculated mass 322.05084, with M.F. C_{15} H_{16} O_3NNaS.

3-(4-Chlorophenylthio)-5-methoxy-1H-indole-2-carboxylic acid (entry 21)

White solid; m.p.: 226-229 °C. IR (KBr): cm^{-1} 3371, 3052, 2927, 2577, 1668, 1623, 1511, 429, 1250, 1230, 1207, 1169, 1017, 739, 692. ^{1}H NMR (300 MHz, $CDCl_3$ and DMSO d_6): δ 3.61 (s, 3 H), 6.75 (d, 1H, *J* = 2.0 Hz), 6.82 (dd, 1H, *J* = 2.1, Hz, *J* = 8.8 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 6.99 (d, H, *J* = 8.6 Hz), 7.32 (d, 1H, *J* = 8.8 Hz), 11.31 (s, 1H). ^{13}C NMR (75 MHz, CDCl3): δ 55.99, 101.01, 108.72, 113.20, 128.11, 128.15, 128.78, 129.25, 130.73, 130.83, 130.92, 136.71, 155.49 and 162.15. HRMS: Found mass 334.03084, calculated mass 334.03078, with M.F. $C_{16}H_{13}O_3NClS$.

3-(3,4-Dimethoxyphenylthio)-5-methoxy-1H-indole-2-carboxylic acid (entry 22)

Off white solid; m.p.: 168-171 °C. IR (KBr): cm^{-1} 3311, 3073, 2995, 2954, 2833, 1676, 1623, 1581, 1508, 1458, 1437, 1388, 1327, 1208, 1047, 1026, 963, 790, 537. ^{1}H NMR (500 MHz, $CDCl_3$ and DMSO d_6): δ 3.71 (s, 3 H), 3.72 (s, 3 H), 3.79 (s, 3 H), 6.71 (d, 1H, *J* = 9.1 Hz), 6.79 (dd, 1H, *J* = 2.0 Hz, *J* = 8.1 Hz), 6.88 (s, 2H), 6.93 (dd, 1H, *J* = 3.0 Hz, *J* = 9.1 Hz), 7.39 (d, 1H. *J* = 9.1 Hz), 11.03 (s, 1H), ^{13}C NMR(400 MHz, DMSO d_6): δ 55.50, 55.86, 55.93, 101.29, 111.34, 111.60, 112.44, 113.04, 117.83, 121.31, 128.14, 128.27, 130.36, 130.90, 147.65, 149.07, 155.05 and 162.23. HRMS: Found mass 360.09070, calculated mass 360.09002, with M.F. $C_{18}H_{18}O_5NS$.

5-Methoxy-3-(3,4,5-trimethoxyphenylthio)-1H-indole-2-carboxylic acid (entry 23)

Off white solid; m.p.: 161-164 °C. IR (KBr): cm^{-1} 3331, 3173, 2995, 2958, 2837, 1677, 1628, 1587, 1509, 1459, 1437, 1388, 1327, 1208, 1047, 1024, 969, 799, 637. ^{1}H NMR (500 MHz, $CDCl_3$ and DMSO d_6): δ 3.66 (s, 6 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 6.40 (s, 2 H), 6.91-6.95 (m, 2H), 7.42 (d, 1H. *J* = 8.2 Hz), 11.27 (s, 1H) ^{13}C NMR (75 MHz, $CDCl_3$ and DMSO d_6): δ 55.13, 55.63, 60.31, 100.31, 104.41, 107.45, 113.58, 116.72, 129.37, 129.80, 131.12, 132.39, 135.50, 152.81, 154.51 and 162.03. HRMS: Found mass 390.10309, calculated mass 390.10118, with M.F. $C_{19}H_{20}O_6NS$.

5-Methoxy-3-(phenylthio)-1H-indole-2-carboxamide (entry 24)

White solid; m.p.: 218-220 °C. IR (KBr): cm^{-1} 3567, 3496, 3253, 2936, 2838, 2554, 1684, 1623, 1581, 1513, 1497, 1455, 1411, 1255, 1231, 1206, 1129. ^{1}H NMR (400 MHz, DMSO d_6): δ 3.70 (s, 3 H), 6.91-6.96 (m, 1H) 7.08 (d, 2H, *J* = 7.6 Hz), 7.12-7.15 (m, 1H) 7.23-7.27 (m, 2H), 7.46 (d, 1H, *J* = 8.8 Hz), 7.71 (s, 1H), 7.93 (s, 1H), 12.22 (s, 1H). ^{13}C NMR (100 MHz, DMSO d_6): δ 55.23, 99.56, 99.83, 114.18, 115.69, 125.69, 125.92, 129.20, 130.31, 130.60, 134.43, 136.79, 154.87 and 161.48. HRMS: Found mass 299.08632, calculated mass 299.08487, with M.F. $C_{16}H_{15}O_2N_2S$.

3-(4-Chlorophenylthio)-5-methoxy-1H-indole-2-carboxamide (entry 25)

Off white solid; m.p.: 242-245 °C. IR (KBr): cm^{-1} 3457, 3347, 3220, 2929, 2992, 2953, 2827, 1877, 1666, 1621, 1587, 1504, 1472, 1447, 1359, 1295, 1280, 1205, 1165, 808. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 5.74 (s, 1H), 7.03 (dd, *J* = 6.7, 2.6 Hz, 2H), 7.17 – 7.07 (m, 3H), 7.25 – 7.17 (m, 2H), 7.39 (dd, *J* = 9.3, 6.3 Hz, 1H), 8.11 (s, 1H), 9.70 (s, 1H^{13}C NMR (100 MHz, DMSO d_6): δ 55.28, 99.56, 99.83, 114.18, 115.70, 125.70, 126.00, 129.21, 130.30, 132.60, 134.73, 136.89, 154.87 and 161.48. HRMS: Found mass 333.04650, calculated mass 333.04590, with M.F. $C_{16}H_{14}O_2N_2ClS$.

3-(3,4-Dimethoxyphenylthio)-5-methoxy-1H-indole-2-carboxamide (entry 26)

White solid; m.p.: 234-236 °C. IR (KBr): cm^{-1} 3430, 3314, 3241, 2995, 2953, 2835, 1881, 1661, 1621, 1586, 1505, 1461, 1449, 1420, 1398, 1283, 1232, 1255, 1213, 1026, 961. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 3H), 3.78 (s, 3H),), 3.81 (s, 3H), 6.13 (s, 1H), 6.34-6.36 (m, 3H), 7.03 (d, *J* = 8.6 Hz, 2H), 7.45 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.20 – 8.14 (m, 1H), 10.31 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO

d_6): δ 55.50, 55.86, 55.93, 101.29, 111.34, 111.60, 112.44, 113.04, 117.83, 121.31, 128.14, 128.27, 130.36, 130.90, 147.65, 149.07, 155.05 and 161.48. HRMS: Found mass 359.10827, calculated mass 359.10657, with M.F. $C_{18}H_{19}O_4N_2S$.

5-Methoxy-3-(3,4,5-trimethoxyphenylthio)-1H-indole-2-carboxamide (entry 27)

Off white solid; m.p.: 166-169 °C. IR (KBr): cm^{-1} 3445, 3336, 3247, 2935, 2828, 2227, 1995, 1655, 1590, 1498, 1449, 1407, 1308, 1277, 1232, 1207, 1131, 1053, 1003, 805. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 6H), 3.78 (s, 3H),), 3.81 (s, 3H), 6.13 (s, 1H), 6.35 (s, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 7.44 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.21 – 8.14 (m, 1H), 10.30 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO d_6): δ 55.09, 55.51, 6012, 99.80, 100.56, 103.12, 113.63, 115.84, 130.29, 130.42, 131.08, 132.99, 130.72, 153.01, 154.78 and 161.81. HRMS: Found mass 389.11827, calculated mass 389.11657, with M.F. $C_{19}H_{21}O_5N_2S$.

3-(Phenylthio)-1H-indol-5-ol (entry 28)

White solid; m.p.: 156-158 °C. IR (KBr): cm^{-1} 3545, 3422, 1621, 1591, 1577, 1475, 1464, 1437, 1437, 1409, 1206, 1179, 813, 803, 742, 689, 500. ^{1}H NMR (400 MHz, DMSO d_6): δ 6.67-6.71 (M, 2H), 6.98-7.01 (m,2H), 7.172-7.22 (m, 2H), 7.29 (d, 1H, *J* = 11.6 Hz), 7.63 (d, 1H, *J* = 3.6 Hz), 8.82 (s, 1H) 11.43 (br, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 97.82, 102.12, 11.45, 112.83, 124.58, 125.03, 128.78, 139.66, 130.98, 132.55, 139.39 and 151.66. HRMS: Found mass 242.06403, calculated mass 242.06341, with M.F. $C_{14}H_{12}ONS$.

3-(Naphthalene-2-ylthio)-1H-indol-5-ol (entry 29)

White solid; m.p.: 170-173 °C. IR (KBr): cm^{-1} 3402, 3394, 3108, 3055, 1620, 1588, 1486, 1464, 1181, 850, 816, 797. ^{1}H NMR (400 MHz, DMSO d_6): δ 6.69-6.74 (m, 2H), 7.21 (dd, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz), 7.32 (d, 1H. *J* = 8.4 Hz), 7.36-7.44 (m, 2H), 7.48 (d, 1H. *J* = 1.5 Hz), 7.65 (d, 1H. *J* = 8.0 Hz), 7.71 (d, 1H. *J* = 3.0 Hz), 7.75-7.81 (m, 2H), 8.81 (s, 1H), 11.46 (s, 1H). ^{13}C NMR (100 MHz, CDCl3): 97.77, 102.12, 112.51, 112.91, 122.45, 124.21, 125.12, 126.61, 127.60, 128.306, 129.64, 130.79, 131.03, 132.62, 133.27, 137.00 and 151.684. HRMS: Found mass 292.08014, calculated mass 292.07906, with M.F. $C_{18}H_{14}ONS$.

3-(4-Chlorophenylthio)-1H-indol-5-ol (entry 30)

White solid; m.p.: 144-147 °C. IR (KBr): cm^{-1} 3745, 3623, 1821, 1721, 1687, 1565, 1494, 1493, 1488, 1455, 1207, 1159, 853, 823, 743, 681, 500. ^{1}H NMR (400 MHz, DMSO d_6): δ 6.68 (d, 2H, *J* = 7.2 Hz), 6.99 (d, 2H, *J* = 8.4 Hz), 7.25-7.30 (m, 3H), 7.65 (d, 1H, *J* = 2.4 Hz), 8.84 (s, 1H), 11.45 (s, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 97.26, 101.97, 112.58, 112.95, 126.63, 128.72, 129.13, 129.40, 131.01, 132.67, 138.59 and 151.798. HRMS: Found mass 276.02673, calculated mass 276.02573, with M.F. $C_{14}H_{11}ONSCl$.

3-(3,4-Dimethoxyphenylthio)-1H-indol-5-ol (entry 31)

Brown solid; m.p.: 88-90 °C. IR (KBr): cm^{-1} 3402, 3351, 3001, 2932, 2836, 1584, 1501, 1463, 1438, 1251, 1226, 1177, 1136, 1021. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (S, 3h), 3.80 (s, 3 H), 6.75-6.93 (m, 2H), 6.81 (d, 1H, *J* = 1.5 Hz), 6.95-6.97 (m, 1H), 6.98 (d, 1H, *J* = 2.2 Hz), 7.28 (d, 1H, *J* = 7.1 Hz), 7.45 (d, 1H, *J* = 2.2 Hz), 8.31 (s, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 55.27, 55.53, 102.25, 110.52, 111.43, 111.91, 112.08, 113.33 113.86, 118.93, 123.15, 131.37, 148.69 and 151.37. HRMS: Found mass 302.08758, calculated mass 302.08509, with M.F. $C_{16}H_{16}O_3NS$.

3-(3,4,5-Trimethoxyphenylthio)-1H-indol-5-ol (entry 32)

Off white solid; m.p.: 184-186 °C. IR (KBr): cm^{-1} 3411, 3361, 3031, 2952, 2876, 1595, 1522, 1482, 1458, 1271, 1246, 1188, 1156, 1071, 692. ^{1}H NMR (300 MHz, $CDCl_3$ and DMSO d_6): δ 3.65 (s, 6 H), 3.73 (s, 3 H),6.34 (s, 2 H), 6.783-6.91 (m, 1H), 6.96 (s, 1 H), 7.27 (d, 1H, *J* = 8.6 Hz), 7.41 (s, 1 H), 10.41 (s, 1 H). EI MS: m/z (rel.abund.%) 332, ([M-1]$^+$, 100).

3. CONCLUSION

Sulfenylation using iodine/ disulfide reagent in DMSO at 70 ^{o}C provides facile access to a variety of 3-substituted indole derivatives in excellent yields. The merits of the developed procedure include functional group tolerance on the disulfide and indole moiety, excellent yields and short reaction time. The protocol would find wide spread application in organic synthesis for preparation of 3-sulfenyl bioactive indoles.

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