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ARTICLE

Metal- and base-free syntheses of aryl / alkylthioindoles by the iodine-induced reductive coupling of aryl / alkyl sulfonyl chlorides with indoles

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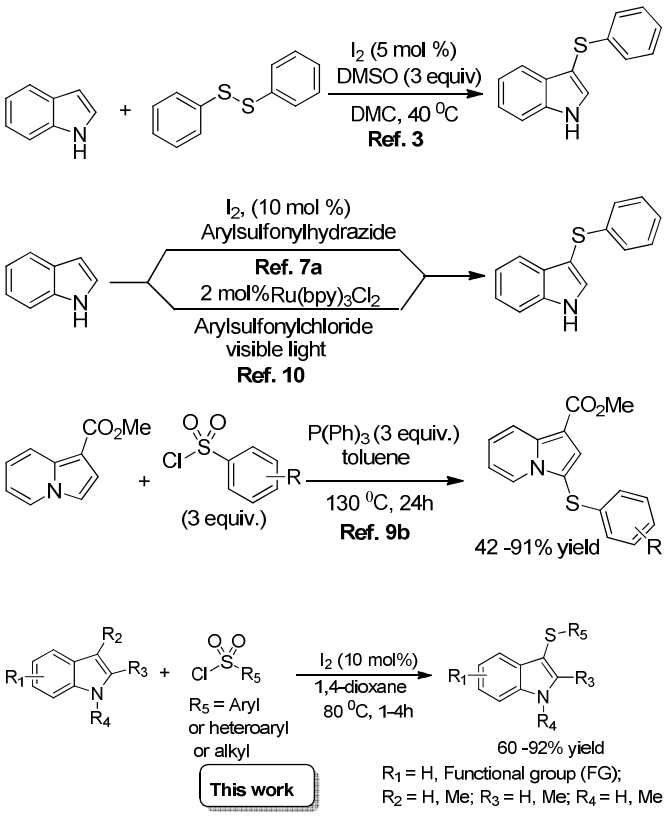
Abstract An Iodine-catalysing process for an efficient and scalable sulfenylation protocol for indoles employing aryl-/ alkyl sulfonyl chlorides has been developed. A series of sterically and electronically divergent aryl-/ alkyl sulfonyl chlorides were participated in the sulfenylation of C(sp^2)-H bonds, resulting in a high to excellent yield of indole 3-sulfenylether molecules. It is noteworthy that indole-3-thiomethyl ether is efficiently generated with methanesulfonyl chloride as an electrophile, indicating the potential of this methodology.

Introduction

Indole sulfenylether molecules are the basic motif of numerous pharmaceutically active molecules due to their inherent potential biological activity.[1] They are also important precursors of functional materials that enable the realisation of novel properties.[2] The critical importance of these scaffolds has resulted in the development of various synthetic methods. Thus far sulfenylating agents for the thiolation of C(sp^2)-H bonds have included disulfides,[3] sodium sulfinates,[4] sulfenyl halides,[5] *N*-thioarylphthalimides,[6] and sulfonyl hydrazides,[7] catalyzed by metal-free salts such as iodine or metal salts (Scheme 1). In spite of the availability of various thiolating agents[8] for the sulfenylation of indole C(sp^2)-H bonds, a limitation remains with regard to accessing these precursors due to the multistep synthesis process required. The thiolation can be achieved in principle, by means of aryl-/ alkyl-/ heteroarylsulfonyl chlorides as a sulphur source. Aryl-/ alkyl-/ heteroarylsulfonyl chlorides are remarkably stable, inexpensive and mostly commercially available. Fairly recently, aryl-/ alkyl-/ heteroarylsulfonyl chlorides[9a] as a sulphur source were assessed by means of reductive coupling with indolizines, indoles, electron-rich benzenes[9b] and H-phosphonates.[9c] On the other hand, visible light-induced sulfenylation of indoles and *N*-methylindoles with arylsulfonyl chlorides was also discovred.[10]



Scheme 1. Prior art in the sulfenylation of indole C(sp^2)-H bonds.

Previous work:

Interestingly, in all cases an excess of one of the reactant is essential for transformation to be observed, resulting in the concomitant quantitative production of corresponding oxidizing substrate as a by-product.[11] Furthermore, sulfonyl chlorides

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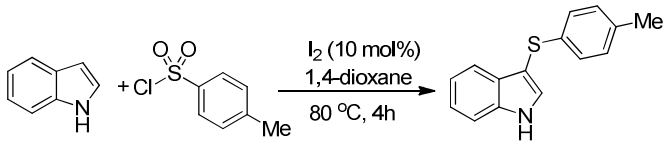
have been employed in excess to improve the yields of corresponding sulfenylether molecules.

Results and discussion

With our continued interest in developing a copper-catalysed sulfenylation process,[12] herein we describe our finding regarding the synthesis of aryl / alkylthioindoles by the iodine-induced reductive coupling of aryl / alkyl sulfonyl chlorides with indoles.

Table 1. Evaluation of optimized conditions for the synthesis of 3-(*p*-tolyl)thioindole.[a]



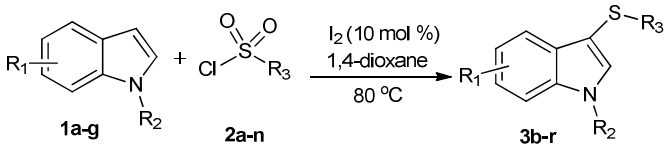
1a **2a** **3a**

entry	catalyst (10 mol%)	solvent	3a (% yield)[e]
1	CuI	dioxane	64
2	I_2	dioxane	54[b]
3	**I_2**	**dioxane**	**86**[c,g]
4	I_2	dioxane	65[d]
5	I_2	dioxane	60[f]
6	I_2	CH_3CN	64
7	I_2	DMF	40
8	I_2	$(CH_2Cl_2)_2$	30
9	I_2	DMSO	15
10	$(n\text{-}Bu)_4NI$	dioxane	40
11	KI	dioxane	20
12	ICl	dioxane	82
13	*N*-iodosuccinimide	dioxane	72

a) All reactions were carried out unless otherwise stated on the 1 mmol scale using 2 mmol of **1a** and 1 mmol of **2a** in 3 ml of dioxane heated to 80 °C for 4 h in open air.
b) The reaction was carried out with 1.0 equiv. **1a** and 1.1 equiv. of **2a**.
c) The reaction was carried out with 2.0 equiv. **1a** and 1.0 equiv. of **2a**.
d) The reaction was carried out with 1.0 equiv. **1a** and 2.0 equiv. of **2a**.
e) Isolated yield, but not optimized. Yields based on the disappearance of **2a**.
f) The reaction was carried out with 5 mol% of catalyst at 80 °C.
g) This reaction was also carried out at 10 mmol scale.

Initially, we chose indole **1a** and *p*-toluenesulfonyl chloride **2a** as the test substrates. At the outset, in the presence of 10 mol% of CuI in dioxane **1a** (1.0 equiv.) and **2a** (1.1 equiv.) reacted smoothly at 80 °C for 4h to afford the expected 3-(*p*-tolyl)thioindole **3a** at a 64% yield (Table 1, entry 1). As we intended to develop a metal-free sulfenylation process, we replaced CuI with iodine. With 10 mol% of I_2, the same reaction under otherwise identical conditions resulted in **3a** at a 55% isolated yield (Table 1, entry 2). Under typical conditions, the molar ratios of reactants have shown considerable influence on the product yield (**3a)**. Using 1.0 equiv. of **1a** and 1.1 equiv. of **2a** yielded the desired product at 55%, whereas, loading 2.0 equiv. of **1a** and 1.0 equiv. of **2a** improved the yield of the desired product (Table 1, entries 2 and 3, respectively). Loading 1.0 equiv. of **1a** and 2.0 equiv. of **2a**[13] furnished a lower yield of **3a** (Table 1, entry 4). The screening of various solvents indicated that 1,4-dioxane is the only preferable medium for this transformation (Table 1, entries 3 and 6-9).

Table 2. Scope of sulfenylation with the functional group substituted indoles and aryl- alkyl sulfonyl chlorides.[a]



1a-g **2a-n** **3b-r**

Entry	R_1	R_2	R_3	Time (h)	% yield[b]
1	H	H	Ph	4	**3b**, 85
2	H	H	2,5-Me-Ph	4	**3c**, 85
3	H	H	4-Cl-Ph	4	**3d**, 81
4	H	H	3,5-Cl-4-Me-Ph	3	**3e**, 78
5	H	H	4-Br-Ph	4	**3f**, 80
6	H	H	5-F-2-Me-Ph	3	**3g**, 77
7	H	H	3-CF_3-Ph	2	**3h**, 77
8	H	H	4-I-Ph	4	**3i,** 82
9	H	Me	4-Me-Ph	4	**3j**, 75
10	H	H	3-NO_2-Ph	1.5	**3k**, 76
11	H	H	4-NO_2-Ph	1	**3l**, 72
12	5-Bromo	H	4-Me-Ph	3	**3m,** 84
13	5-Iodo	H	4-Me-Ph	3	**3n,** 82
14	5-Methoxy	H	4-Me-Ph	3	**3o,** 87
15	H	H	Bn	4	**3p**, 76
16	H	H	Me	3	**3q,** 72
17	H	H	*n*-Bu	3	**3r,** 71
18	5-CN	H	4-Me-Ph	4	NR[c]
19	H	Ts	4-Me-Ph	4	NR[c]

a) All reactions were carried out on the 2 mmol scale using **1a-1g** (2.0 equiv.), **2a-n** (1.0 equiv.), I_2 (10 mol%) in dioxane heated at 80 °C in open air.
b) Isolated yield, but not optimized.
c) NR = No reaction.

In a brief survey of an alternative source of iodine applied as a catalyst, the yield of **3a** decreased (Table 1, entry 2). Further, when the reaction was conducted under strict anaerobic conditions, only a trace amount of **3a** was isolated (Table 1, entry 10-13). The reaction carried out with 5 mol% of iodine resulted in **3a** at an inferior yield (Table 1, entry 5).
With the optimal conditions in hand, the scope of the substrate was surveyed. These results are shown in Table 2.

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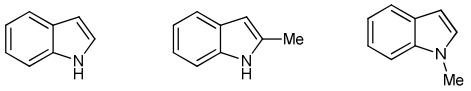
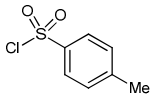
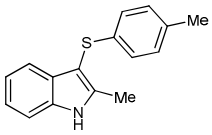
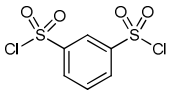
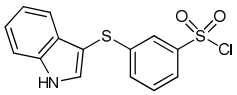
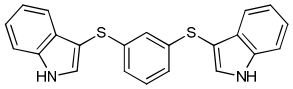
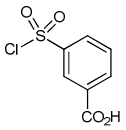
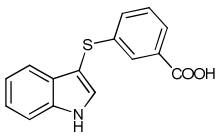
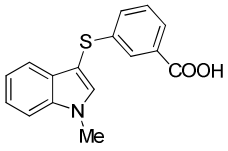
Table 3. Further scope of the sulfenylation reaction.[a]



1a **4a** **1b**

Arylsulfonyl chloride	product	% yield[b]
 **2a**	 **5a**	76
 **2aa**	 **5b**	64
2aa	 **5c**	78
 **2ab**	 **5d**	81
2ab	 **5e**	84

a) All reactions were carried out on the 2 mmol scale using **1a, 1b and 4a** (2.0 equiv.), **2a, 2aa and 2ab** (1.0 equiv.), I_2 (10 mol%) in dioxane heated at 80 °C in open air.
b) Isolated yield, but not optimized.

According to the results, the electron-donating and electron–withdrawing functional groups on the phenyl ring of sulfonyl chloride were compatible under the standard protocol and reacted with equal efficiency. On the other hand, the reaction efficiency was slightly sensitive to the electronic properties of the indole moiety. For instance, 5-cyanoindole failed to give the expected sulfenylation product, while 5-bromo- and 5-iodoindole did react under these conditions providing the desired product **3m** and **3n**, respectively at a very good yield, (Table 2, entry 11, and 12). Further, the halo-containing coupled product of arylthioindoles facilitates potential applications of further functionalization by a cross-coupling reaction. Remarkably, 3-NO_2-, and 4-NO_2-substituted phenylsulfonyl chlorides remain viable in this protocol disregarding the electronic effects and furnishing the desired products of **3k** and **3l** at high yields (Table 2, entries 10 and 11). 2-nitrobenzenesulfonyl chloride was also reacted with indole, but the effort to isolate the product which formed failed due to rapid decomposition. Under set conditions, *N*-methylindole was also an effective substrate for coupling with **2a** to give the sulfenylation product **3j** at a high yield (Table 2, entry 9), but the *N*-tosyl protected indole did not undergo a coupling reaction (Table 2, entry 19).

Next, we examined the alkyl sulfonyl chlorides, as these compounds are seldom employed due to their inherent reduced reactivity and rapid decomposition. To our delight, our method gave 3-alkylthioethers **3q** and **3r** at a good yield using methanesulfonyl chloride **2m** and butanesulfonyl chloride **2n** with **1a** (Table 2, entries 16 and 17). 2-Methylindole **4a** was also reacted with *p*-toluenesulfonyl chloride **2a** under typical conditions and gave the corresponding 3-thioether **5a** at a high yield (72%). It was gratifying to find a reaction between the 1,3-benzenedisulfonyl chloride **2aa** with **1a** (2 equiv), that provided an acceptable yield (64%) of mono-indolylsulfenyl ether **5b.** on the other hand, when **2aa** treated with 4 equiv of **1a**, di-indolylsulfenyl ether **5c** was formed at a high yield (78%) (Table 3). Significantly, a highly polar carboxylic acid substituted arylsulfonylchloride **2ab** performed well with **1a** and **1b** under the standard protocol, affording carboxylic acid possessing thioindole **5d** and **5e** at an 81% and 84% yield, respectively (Table 3). Several control experiments were carried out to understand this transformation. Indole **1a** and *p*-toluenesulfonyl chloride **2a** was heated to 80 °C for 4h. No trace of the desired product **3a** was observed and only the starting materials were recovered. In another experiment, with 10 mol% of iodine, one equiv. each of **1a** and **2a** were individually reacted under optimized conditions. In both cases, the recovery of the starting materials was realized, indicating the necessity of all reaction partners in order to forward the reaction. The reaction of **1a** and **2a** with one equivalent of TEMPO under standard protocol resulted in **3a** as exclusive product and no trace of TEMPO-coupled products were observed suggesting ionic mechanism rather than radical mechanism.

Considering the above results, a plausible reaction mechanism is delineated in Scheme 2, which will clearly require further experimentation. Initially, iodine induced substitution of chlorine atom of aryl- / alkyl sulfonyl chloride leads to putative intermediate [**A**] by eliminating ICl.[14] Then, subsequent Friedel-Crafts reaction of indole with [**A**] followed by HI exclusion via aromatization afford sulfone [**D**], which can undergo deoxygenation in the presence of HI to afford the desired indolylsulfenyl ether. Eventually, HOI can be oxidized in the presence of air to give I_2 and H_2O_2 (Scheme 3).

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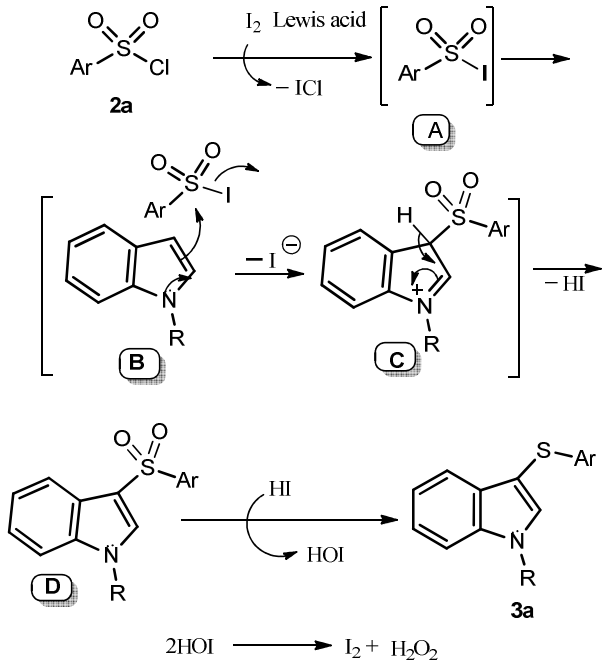
Scheme 2. Plausible mechanism for the observed transformation.



Conclusions

In conclusion, we have demonstrated an efficient cross-coupling reaction of indole with low-cost, and readily available, stable aryl- / alkyl sulfonyl chlorides through C(sp^2)-H bond activation for the syntheses of various 3-alkyl-/ arylthioethers. The sulfenylation process is initiated by a catalytic amount of I_2 without any combination of radical initiator. This process is remarkable in that stoichiometric reducing trivalent phosphorous compounds are avoided. To the best of our knowledge, this is the first report on sulfenylation wherein catalytic iodine acts as a reducing agent in combination with air and avoids the creation of oxides of phosphorous. Further work is in progress to broaden the scope of this methodology.

Acknowledgements

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Experimental section

General procedure:

spectra were recorded at 300, 400 & 500 MHz, and ^{13}C NMR 75 & 125 MHz in $CDCl_3$. The *J* values were recorded in hertz and abbreviations used were as follows: *s*-singlet, *d*-doublet, *m*-multiplet, br-broad, *dd*-doublet of doublet. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as an internal standard. The IR (FT-IR) spectra were measured using KBr pellet or as film. Mass spectral data were compiled using MS (ESI), HRMS mass spectrometers. Column chromatography was carried out using Silica gel 100-200 mesh (commercial suppliers).

The typical procedure for synthesis of 3-(*p*-Tolylthio)-1H-indole (3a): To a stirred solution of indole **1a** (2 mmol) in 1,4-dioxane (3 mL) was added sulfonylchloride, **2a** (1.0 mmol) and I_2 (10 mol%) successively. The resulting reaction mixture was heated at 80 ℃ for 4 h in open air. Subsequently, the reaction mixture was cooled down to ambient temperature, and the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel chromatography, eluting with hexane / ethyl acetate (10:0.5 to 5:1) to give the thioindole, **3a** at an 86% yield. White solid, Yield – 206 mg (86%), m.p. 124-126 ℃; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.38 (s, br, 1H), 7.61 (d, *J* = 7.93 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.27 – 7.24 (m, 1H), 7.17 – 7.14 (m, 1H), 7.04 – 6.96 (m, 4H), 2.25 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 136.4, 135.4, 134.6, 130.4, 129.4, 129.1, 126.2, 122.9, 120.8, 119.7, 111.5, 103.5, 20.8; **IR** (neat, cm^{-1}): 3405, 2922, 2853, 1892, 1490, 1453, 1088, 772, 744; **HRMS** (m/z): Calculated for C_{15} H_{13} N S (M-H) = 239.0768 found (M-H) = 239.0775.

All other 3-aryl and alkyl thioindole were prepared employing above typical procedure.

3-(Phenylthio)-1H-indole (3b): White solid, m.p. 150-152 ℃; Yield - 191 mg (85%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.47 (s, br, 1H), 7.61 (d, *J* = 7.9 Hz,1H), 7.49 – 7.43 (m, 2H), 7.28 – 7.25 (m, 1H), 7.18 – 7.03 (m, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 139.2, 130.7, 128.6, 125.8, 124.7, 123.0, 120.9, 119.6, 111.5; **IR** (neat, cm^{-1}): 3401, 3057, 2922, 2852, 1580, 1476, 1234, 1083, 770, 739; **HRMS** (m/z): Calculated for: C_{14} H_{11} N S (M+K) = 264.0249, found (M+K) = 264.0238.

3-((2,5-Dimethylphenyl)thio)-1H-indole (3c): White solid, m.p. 125-127 ℃; Yield - 215 mg (85%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.42 (s, br, 1H), 7.63 – 7.57 (m, 1H), 7.45 – 7.40 (m, 2H), 7.29 – 7.23 (m, 1H), 7.19 – 7.13 (m, 1H), 7.04 – 6.99 (m, 1H), 6.82 – 6.75 (m, 1H), 6.57 (s, 1H), 2.46 (s, 3H), 2.04 (s, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 137.7, 136.5, 135.8, 131.4, 130.7, 129.7,129.2, 125.9, 125.4, 122.9, 120.7, 119.7, 111.5, 102.4, 21.0, 19.4; **IR** (neat, cm^{-1}): 3412, 2926, 2857, 1896, 1520, 1456, 1075, 778, 734; **HRMS** (m/z): Calculated for C_{16} H_{15} N S (M-H) = 252.0842, found (M-H) = 252.0846.

3-(4-Chlorophenylthio)-1H-indole (3d): White solid, m.p. 129-131 ℃; Yield - 210 mg (84%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.42 (s, br, 1H), 7.56 (dd, *J* = 7.93 Hz, *J* = 0.76 Hz, 1H), 7.46 (d, *J* = 2.59 Hz, 1H), 7.43 (d, *J* = 8.24 Hz, 1H),7.29 – 7.24 (m, 1H), 7.18 – 7.15 (m, 1H), 7.12 – 7.09 (m, 2H), 7.02 – 6.99 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 137.8, 136.5, 130.7, 130.5, 128.7, 127.1, 123.2, 121.0, 119.5, 111.6, 102.4; **IR** (neat, cm^{-1}): 3405, 2921, 2851, 1472, 1090, 1008, 812, 746; **HRMS** (m/z): Calculated for: C_{14} H_9 N S Cl (M-H) = 258.0144, found (M-H) = 258.0150.

3-((3,5-Dichloro-4-methylphenyl)thio)-1H-indole (3e): White solid, m.p. 142-145 ℃; Yield - 239 mg (84%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.51 (s, br, 1H), 7.58 – 7.45 (m, 3H), 7.34 – 7.27 (m, 1H), 7.22 – 7.15 (m, 1H), 6.93 (d, *J* = 8.51 Hz, 1H), 6.41 (d, *J* = 8.71 Hz, 1H), 2.50 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 137.8, 136.6, 134.5, 131.3, 131.0, 130.7, 128.8, 127.3, 123.9, 123.3, 121.2, 119.5, 111.7, 101.3, 17.7; **IR** (neat, cm^{-1}): 3405, 2923, 2863, 1894, 1488, 1463, 1091, 774; **HRMS** (m/z): Calculated for C_{15} H_{10} N Cl_2 S (M-H) = 305.9906, found (M-H) = 305.9921.

3-(4-Bromophenylthio)-1H-indole (3f): White solid, m.p. 141-143 ℃; Yield - 242 mg (80%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.47 (s, br, 1H), 7.56 (d, *J* = 7.93 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.30 – 7.15 (m, 4H), 6.97 – 6.93 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 138.5, 136.5, 131.6, 130.7, 128.7, 127.3, 123.2, 121.0, 119.4, 118.2, 111.7, 102.1; **IR** (neat, cm^{-1}): 3389, 3053, 2921, 2851, 1889, 1469, 1406, 1235, 1083, 1004, 808, 744; **HRMS** (m/z): Calculated for C_{14} H_9 N S Br (M-H) = 301.9639, found (M-H) = 301.9645.

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3-((5-fluoro-2-methylphenyl)thio)-1H-indole (3g): White solid, m.p. 136-138 ℃; Yield - 198 mg (77%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.44 (s, br, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.20 – 7.16 (m,1H), 6.85 – 6.79 (m, 1H), 6.64 – 6.59 (m, 1H), 2.06 (s, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 157.6 (d, J_{C-F} = 241.6 Hz), 136.4, 133.8 (d, J_{C-F} = 2.7 Hz), 131.0, 129.2, 128.5, 127.0 (d, J_{C-F} = 7.3 Hz), 125.6 (d, J_{C-F} = 16.4 Hz), 123.1, 120.9, 119.5, 114.8 (d, J_{C-F} = 21.8 Hz), 111.6, 101.1, 20.7; **IR** (neat, cm^{-1}): 3412, 2934, 2863, 1882, 1492, 1453, 1168, 764; **HRMS** (m/z): Calculated for C_{15} H_{12} F N S (M-H) = 256.0590, found (M-H) = 256.0592.

3-((3-(Trifluoromethyl)phenyl)thio)-1H-indole (3h): White solid, m.p. 130-132 ℃; Yield - 226 mg (77%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.47 (s, br, 1H), 7.57 (d, J = 7.93 Hz, 1H), 7.49 (d, J = 2.59 Hz, 1H), 7.44 (d, J = 8.24 Hz, 1H), 7.39 (s, 1H), 7.30 – 7.26 (m, 2H), 7.24 – 7.15 (m, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 140.9, 136.5, 131.0 (q, J_{C-F} = 31.8 Hz), 130.9, 129.0, 128.7, 123.8 (q, J_{C-F} = 272.5 Hz), 123.3, 122.3, (d, J_{C-F} = 3.6 Hz), 121.4 (d, J_{C-F} = 3.6 Hz), 121.1, 119.3, 111.7, 101.4; **IR** (neat, cm^{-1}); **HRMS** (m/z): Calculated for C_{15} H_{10} F_3 N S (M-H) = 292.0402, found (M-H) = 292.0411.

3-((4-iodophenyl)thio)-1H-indole (3i): White solid, m.p. 135-137 ℃; Yield - 288 mg (82%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.44 (s, br, 1H), 7.58 – 7.54 (m, 1H), 7.48 – 7.41 (m, 4H), 7.30 – 7.25 (m, 1H), 7.20 – 7.14 (m, 1H), 6.84 – 6.80 (m, 2H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 139.5, 137.5, 136.4, 130.7, 128.9, 127.6, 123.2, 121.0, 119.4, 111.6, 102.0, 88.9; **IR** (neat, cm^{-1}): 3312, 2876, 2753, 1882, 1496, 1455, 1076, 994, 752; **HRMS** (m/z): Calculated for C_{14} H_{10} N I S (M-H) = 349.9495, found (M-H) = 349.9494.

1-Methyl-3-(*p*-tolylthio)-1H-indole (3j): White solid, m.p. 86-88 ℃; Yield - 190 mg (83%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.46 (d, J = 8.4 Hz, 2H), 7.26 – 7.21 (m, 5H), 7.14 (d, J = 8.1 Hz, 2H), 2.42 (s, 3H), 2.38 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 144.5, 142.0, 140.4, 136.5, 130.2, 129.3, 127.6, 124.6, 29.7, 21.5; **IR** (neat, cm^{-1}): 3412, 2946, 2845, 1894, 1490, 1463, 1088, 772;**HRMS** (m/z): Calculated for C_{11} H_{18} O_3 N S (M+H) = 253.0925, found (M+H) = 253.0931.

3-((3-Nitrophenyl)thio)-1H-indole (3k): White solid, m.p. 135-137 ℃; Yield - 205 mg (84%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.57 (s, br, 1H), 7.93 – 7.86 (m, 2H), 7.57 – 7.54 (m, 2H), 7.48 (d, J = 8.24 Hz, 1H), 7.36 (d, J = 7.93 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.21 – 7.16 (m, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 136.4, 135.4, 134.6, 130.4, 129.4, 129.1, 126.2, 122.9, 120.8, 119.7, 111.5, 103.5, 20.8; **IR** (neat, cm^{-1}): 3506, 2923, 2873, 1867, 1556, 1490, 1454 1353, 1088, 782, 762; **HRMS** (m/z): Calculated for C_{14} H_9 O_2 N_2 S (M-H) = 269.0379, found (M-H) = 269.0390.

3-((4-nitrophenyl)thio)-1H-indole (3l): Yellow solid, m.p. 174-175 ℃; Yield - 194 mg (84%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.92 (s, br, 1H), 7.95 (d, J = 9.0 Hz, 2H),7.52 – 7.46 (m, 3H), 7.28 (t, J = 8.1 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 9.0 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 150.0, 144.6, 136.5, 131.3, 128.3, 124.9, 123.7, 123.3, 121.2, 118.9, 112.0, 99.6; **IR** (neat, cm^{-1}): 3605, 3422, 2753, 1892, 1553, 1464, 1346, 1078, 784; **ESI-MS** (m/z): Calculated for C_{14} H_{10} O_2 N_2 S = 270, found (M-H) = 269.

5-Bromo-3-(p-tolylthio)-1H-indole (3m): White solid, m.p. 126-128 ℃; Yield - 266 mg (84%); **^{1}H-NMR** (300 MHz, $CDCl_3$+DMSO): δ 8.70 (s, br, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.26 – 7.24 (m, 1H), 7.01 – 6.96 (m, 4H), 2.25 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 135.0, 134.8, 133.9, 132.1, 130.3, 128.8, 125.4, 124.4, 120.8, 113.1, 112.8, 100.5, 20.2; **IR** (neat, cm^{-1}): 3744, 3611, 2922, 2852, 1696, 1509, 1454, 1219, 772, 657; **HRMS** (m/z): Calculated for C_{15} H_{11} N S Br (M-H) = 315.9795, found (M-H) = 315.9782.

5-iodo-3-(p-tolylthio)-1H-indole (3n): White solid, m.p. 132-134 ℃; Yield - 299 mg (82%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.46 (s, br, 1H), 7.51 (dd, J = 6.9 Hz, J = 1.7 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.0 (s, 4H), 2.26 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 135.5, 134.9, 134.8, 131.6, 131.4, 131.2, 129.6, 128.4, 126.2, 113.5, 102.9, 84.7, 20.8; **IR** (neat, cm^{-1}): 3645, 2924, 2853, 1692, 1512, 1453, 1098, 772, 646; **HRMS** (m/z): Calculated for C_{15} H_{11} N I S (M-H) = 363.9651, found (M-H) = 363.9665.

5-methoxy-3-(p-tolylthio)-1H-indole (3o): Brown oil; Yield - 234 mg (87%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.31 (s, br, 1H), 7.35 (d, J = 2.7 Hz, 1H), 7.24 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 7.03 – 6.99 (m, 2H), 6.98 – 6.95 (m, 2H), 3.76 (s, 3H), 2.23 (s, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 155.0, 135.6, 134.5, 131.3, 131.1, 129.9, 129.4,125.9, 113.5, 112.3, 102.7, 100.8, 55.7, 20.8; **IR** (neat, cm^{-1}): 3455, 2923, 2893, 1887, 1495, 1463, 1296, 1098, 772, 744; **HRMS** (m/z): Calculated for C_{15} H_{13} N S (M-H) = 253.0556, found (M-H) = 253.0561.

3-(Benzylthio)-1H-indole (3p): Yellow solid, m.p. 81-82 ℃; Yield - 182 mg (76%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.39 (s, br, 1H), 7.72-7.67 (m, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.25 – 7.14 (m, 5H), 7.10 – 7.04 (m, 2H), 6.95 (s, 1H), 3.85 (s, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 139.0, 136.2, 129.9, 129.2, 128.1, 126.7, 122.4, 120.3, 119.1, 111.5, 105.0,40.9; **IR** (neat, cm^{-1}): 3406, 2872, 1902, 1560, 1463, 1078, 736; **ESI-MS** (m/z): Calculated for C_{15} H_{13} N S = 239, found (M-H) = 238.

3-(Methylthio)-1H-indole (3q): Colorless oil; Yield - 117 mg (72%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.21 (s, br, 1H), 7.77 (d, J = 7.63 Hz, 1H), 7.36 (d, J = 8.10 Hz, 1H), 7.28 (d, J = 2.3 Hz, 1H), 7.26 – 7.18 (m, 2H), 2.37 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 134.2, 129.2, 127.8, 122.9, 121.0, 1118.9, 110.7, 105.1, 19.0; **IR** (neat, cm^{-1}): 3386, 2853, 1876, 1490, 1451, 1058, 776, 754; **ESI-MS** (m/z): Calculated for C_9 H_9 N S = 163, found (M-H) = 162.

3-(Butylthio)-1H-indole (3r): Yellow oil; Yield - 145 mg (71%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.26 (s, br, 1H), 7.77 (d, J = 7.93 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.27 – 7.24 (m, 1H), 7.17 – 7.14 (m, 1H), 7.04 – 6.96 (m, 4H), 2.25 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ **IR** (neat, cm^{-1}): 3345, 2934, 2835, 1876, 1478, 1433, 1068, 762, 745; **HRMS** (m/z): Calculated for C_{12} H_{14} N S (M-H) = 204.0842, found (M-H) = 204.0844.

2-methyl-3-(p-tolylthio)-1H-indole (5a): White solid, m.p. 93-96 ℃; Yield - 192 mg (76%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.21 (s, br, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.19 – 7.15 (m, 1H), 7.13 – 7.09 (m, 1H), 6.95 (m, 4H), 2.49 (s, 3H), 2.23 (s, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 140.9, 135.6, 135.3, 134.2, 130.2, 129.4, 125.7, 122.0, 120.5, 118.9, 110.6, 99.6, 20.8, 12.0; **IR** (neat, cm^{-1}): 3415, 2892, 2763, 1952, 1560, 1463, 1078, 784, 753; **HRMS** (m/z): Calculated for C_{15} H_{13} N S = 239.0768, found = 239.0775.

3-((1H-indol-3-yl)thio)benzene-1-sulfonyl chloride (5b): White solid, m.p. 156-159 ℃; Yield - 207 mg (64%); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.62 (s, br, 1H), 7.75 – 7.72 (m, 1H), 7.70 – 7.66 (m, 1H), 7.56 – 7.53 (m, 2H), 7.48 (d, J = 8.21 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.21 – 7.17 (m, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 144.7, 143.3, 136.5, 131.7, 131.2, 129.7, 128.3, 123.5, 123.2, 122.7, 121.4, 119.1, 111.9, 100.3; **IR** (neat, cm^{-1}): 3505, 3312, 2921, 2845, 1553, 1370, 1290, 1092, 776.

1,3-bis((1H-indol-3-yl)thio)benzene (5c): White solid, m.p. 210-212 ℃; Yield - 290 mg (78%); **^{1}H-NMR** (300 MHz, $CDCl_3$+DMSO): δ 10.84 (s, br, 2H), 7.56 (s, 2H), 7.50 – 7.43 (m, 2H), 7.36 (d, J = 2.5 Hz, 2H), 7.24 – 7.16 (m, 2H), 7.11 – 7.03 (m, 2H), 6.89 (t, J = 7.7 Hz, 1H), 6.83 – 6.79 (m, 1H), 6.72 – 6.66 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$+DMSO): δ 139.7, 136.1, 130.9, 128.2, 128.0, 121.7, 121.6, 121.3, 119.5, 118.2, 111.4, 99.5; **IR** (neat, cm^{-1}): 3412, 2932, 2863, 1967, 1872, 1530, 1462, 1098, 792, 767; **HRMS** (m/z): Calculated for C_{22} H_{16} N_2 S_2 (M+H) = 373.0828, found (M+H) = 373.0826.

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3-((1H-indol-3-yl)thio)benzoic acid (5d): White solid, m.p. 183-186 ℃; Yield - 218 mg (81%); **^{1}H-NMR** (300 MHz, $CDCl_3$+DMSO): δ 10.94 (s, br, 1H), 7.81 (s, 1H), 7.73 – 7.61 (m, 1H), 7.55 – 7.45 (m, 3H), 7.24 – 7.04 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$+DMSO): δ 167.3, 139.7, 136.3, 131.2, 130.8, 129.1, 128.2, 127.9, 126.2, 125.4, 121.7, 119.6, 118.2, 111.6, 99.4; **IR** (neat, cm^{-1}): 3402, 2978, 2876, 1887, 1753, 1492, 1443, 1068, 768, 744; **HRMS** (m/z): Calculated for C_{15} H_{11} O_2 N S (M-H) = 268.0426, found (M-H) = 268.0427.

3-((1-methyl-1H-indol-3-yl)thio)benzoic acid (5e): White solid, m.p. 142-146 ℃; Yield - 238 mg (84%); **^{1}H-NMR** (300 MHz, $CDCl_3$+DMSO): δ 7.84 – 7.59 (m, 2H), 7.56 – 7.38 (m, 3H), 7.33 – 7.08 (m, 4H), 3.88 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$+DMSO): δ 167.2, 139.5, 136.9, 134.7, 130.8, 129.1, 128.8, 127.9, 126.2, 125.4, 121.9,119.8, 118.5, 109.3, 98.8, 32.5; **IR** (neat, cm^{-1}): 3305, 2972, 2845, 1892, 1745, 1490, 1453, 1413, 1294, 1076, 773; **ESI-MS** (m/z): Calculated for C_{16} H_{13} O_2 N S = 283, found (M-H) = 282.

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Electronic Supplementary Information (ESI) available: [Copies of ^{1}H and ^{13}C NMR spectras available free of charge via Internet]. See
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