Metal free mono- and 2,3-bis-sulfenylation of indoles in water with sodium sulfinates as a sulfur source

Changqing Liu,[a,b] Jian Fan,[a] Manyi Wu,[a] Jiahui Chen,[a]

Yiming Zhao,[a] Meihua Xie[a,*]

ABSTRACT An iodine-PPh_3 mediated sulfenylation of indoles in water with stable and odorless sodium sulfinates as the sulfur source is described. The reaction could afford monosulfenylated indoles in moderate to excellent yields under metal free conditions. Moreover, double C-H sulfenylation of indoles at 2- and 3-positions has also been achieved by using excess sodium sulfinates under the optimized reaction conditions.

KEYWORDS indole, sodium sulfinate, sulfenylation

Introduction

Sulfur-containing moieties exist in a variety of biologically and medicinally active molecules and introduction of a sulfur moiety into organic molecules is one of the major research areas in organic synthesis.[1] Among them, sulfenylated indoles show potent activities such as inhibition of tubulin polymerization and cell growth, and have a great therapeutic value in the treatment of cancer, HIV, heart disease, allergies and bacterial diseases (Fig 1).[2] Numerous synthetic methods to access sulfenylated indoles have been successfully established by exploiting disulfides, [3] sulfenyl halides,[4] thiols,[5] and arylsulfonyl chlorides,[6] many of which have disadvantages such as unpleasant odors, air and moisture sensitive, high cost, or difficult to prepare. In this regard, development of new and practical methods to synthesize sulfenylated indoles is in great demand. During recent years, sodium sulfinates have been widely used in organic synthesis as the sulfur source for its nature of stability, odorlessness and safety.[7] However, the usage of sodium sulfinates for the synthesis of sulfenylated indoles is rare until now.[8] Especially, double C-H

[a]Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, College of Chemistry and Materials Science, Anhui Normal University, Wuhu, 241000, China.
[b]Department of Chemistry, Bengbu Medical College, Bengbu, 233030, China
[*]E-mail: xiemh@mail.ahnu.edu.cn

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cjoc.201800164

sulfenylation in indoles with sodium sulfinates to give 2,3-bis-sulfenyl indoles remains elusive.

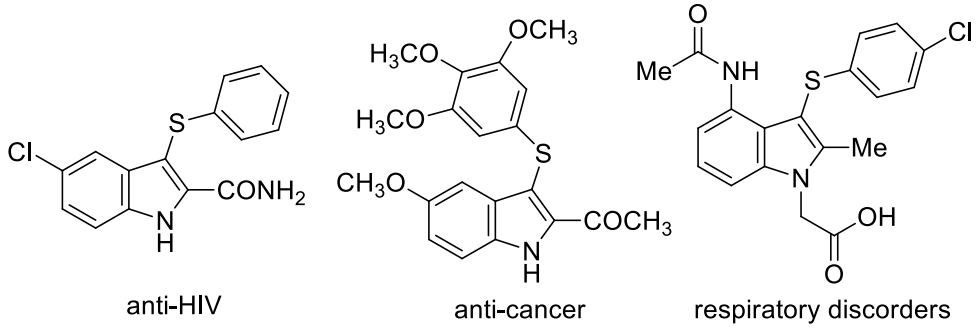


Fig 1 Examples of biologically active 3-(arylsulfanyl)indoles

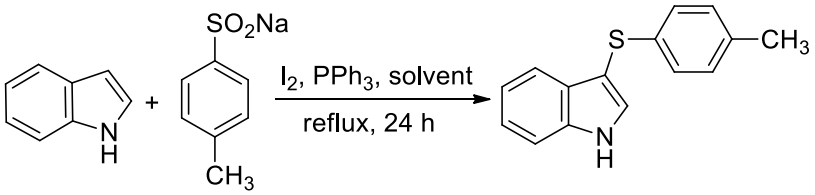
On the other hand, reactions for organic synthesis that are performed in aqueous conditions have attracted tremendous attention and are becoming some of the most exciting research areas. [9] With regard to the green chemistry and environmental protection, it is still challenging and highly desirable to develop efficient methods for the synthesis of sulfenylated indoles from simple and readily available starting materials under environmentally benign reaction conditions. To the best of our knowledge, there are no reports in literature describing the metal-free sulfenylation of indoles using sodium sulfinates in aqueous medium. Herein, we wish to present an efficient metal-free synthesis of mono- and 2,3-bis-sulfenylindoles with sodium sulfinates as sulfur sources in water. Various indoles and sodium sulfinates participated in the reaction to afford the corresponding products in moderate to excellent yields.

Results and discussion

At the outset of our study, we focused our investigation on indole (**1a**) as a model reactant and the experimental results are compiled in Table 1. To our delight, the desired product **3a** was isolated in 55% yield by treatment of indole (**1a**) and sodium *p*-toluenesulfinate (**2a**, 1 equiv.) in the presence of 2.0 equiv. of PPh_3 and 1.0 equiv. of I_2 in refluxing CH_2Cl_2 for 24 h (Table 1, entry 1). A number of organic solvents were examined (Table 1, entries 2-10) and the results show that 1,2-dichloroethane gave the best efficiency in terms of product yield (83% yield). Surprisingly, product **3a** was isolated in 82% yield when the green and cheap medium of water was used as the reaction solvent (Table 1, entry 11). Considering the environmental benign and sustainable process in organic synthesis, we chose water as the solvent for the further optimization. Screening of the

amount of PPh_3 or I_2 showed that less PPh_3 or I_2 resulted in a poor yield (Table 1, entries 12 and 14) and increasing the amount of PPh_3 or I_2 did not improve the yield of **3a** (Table 1, entries 13 and 15). In these cases, **3a** was obtained as the sole sulfenylated product when indole reacts with 1.0 equiv. sodium sulfinate. While **3a** was obtained only in 52% yield along with the formation of 22% yield of 2,3-bis-sulfenylindoles **4a** when 1.5 equiv. sodium *p*-toluenesulfinate was used (Table 1, entry 16). Lower yield of **3a** was obtained when the reaction was conducted in air (Table 1, entry 17). Thus, the suitable reaction conditions selected for 3-sulfenylation of indoles are the following: indole (1 equiv.), sodium sulfinate (1 equiv.), I_2 (1 equiv.), and PPh_3 (2 equiv.) in water at refluxing temperature under argon atmosphere.

Table 1 Optimization of reaction conditions for 3-sulfenylation of indoles[a]



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

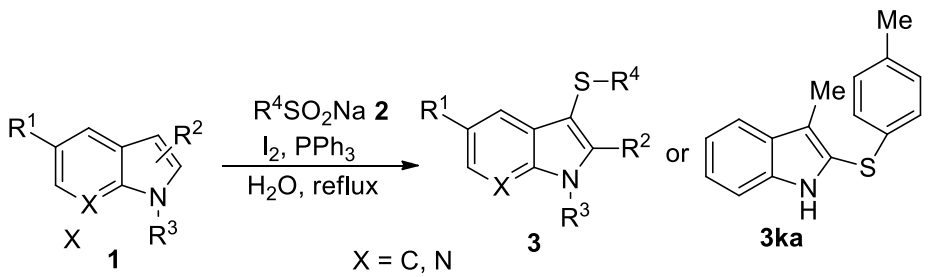
Entry	**2a** (equiv.)	I_2 (equiv.)	PPh_3 (equiv.)	solvent	Yield (%)[b]
1	1	1	2	CH_2Cl_2	55
2	1	1	2	THF	23
3	1	1	2	toluene	26
4	1	1	2	1,4-dioxane	59
5	1	1	2	CH_3CN	42
6	1	1	2	$ClCH_2CH_2Cl$	83
7	1	1	2	acetone	Trace
8	1	1	2	ethyl acetate	25
9	1	1	2	DMF (100 ^oC)	80
10	1	1	2	DMSO (100 ^oC)	72
11	1	1	2	H_2O	82
12	1	1	1.5	H_2O	46

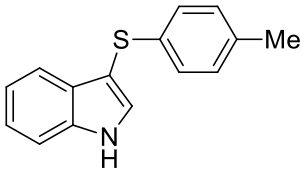
13	1	1	2.5	H_2O	80
14	1	0.5	2	H_2O	18
15	1	1.5	2	H_2O	76
16[c]	1.5	1.5	3	H_2O	52
17[d]	1	1	2	H_2O	70

[a]Reaction conditions: **1a** (0.25 mmol), sodium *p*-toluenesulfinate, I_2 and PPh_3 in 2 mL of solvent. [b]Isolated yield based on **1a**. [c]2,3-bis-sulfenylindoles **4a** was isolated in 22% yield. [d]Under air.

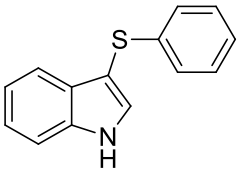
With the optimal reaction conditions established, the reactions of variously substituted indoles and sodium sulfinates were investigated to demonstrate the scope and generality of this method. The results are summarized in Table 2. Sodium sulfinates **2a-2c** reacted smoothly with indole **1a** to produce the corresponding 3-sulfenylated indoles (Table 2, **3aa-3ac**). Indoles with electron-donating substituents such as phenyl (Table 2, **3ba-3bd**) and methyl (Table 2, **3ca-3cc** and **3da-3dc**) gave higher yields in comparison to indole. Various functional groups, such as methoxyl (Table 2, **3ea-3ec**), fluoro (Table 2, **3fa-3fc**), ester (Table 2, **3ha**), and ketone (Table 2, **3ia**), on the aromatic ring of indoles were well tolerated under the standard conditions. More importantly, 3-sulfenylated indoles with ester (Table 2, **3ga-3gc**) or amide (Table 2, **3ja**) groups on the heterocycle might be of anti-HIV activity. [10] It should be noted that 7-azaindol and pyrrole could also conduct this reaction smoothly to give the corresponding products **3la** and **3ma** in 83% and 35% yields, respectively. 2-Sulfenylated indole **3ka** could be isolated in 53% yield when 3-methyl indole was used. Unfortunately, *N*-tosylindole could not be tolerated in this reaction, indicating that this reaction involved a nucleophilic process of indoles.

Table 2 Synthesis of monosulfenylindole **3** with sodium sulfinate in water[a]

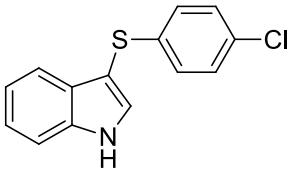




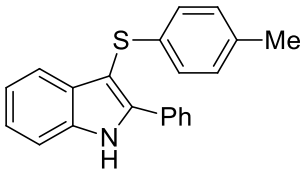
3aa, 82%



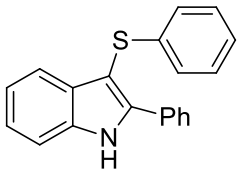
3ab, 85%



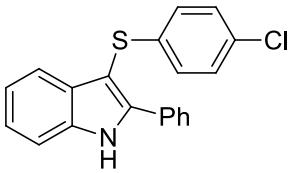
3ac, 94%



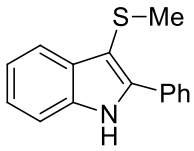
3ba, 96%



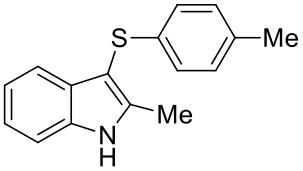
3bb, 96%



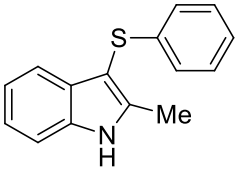
3bc, 95%



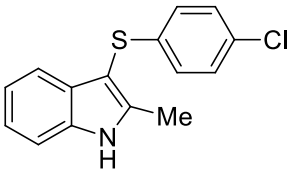
3bd, 94%



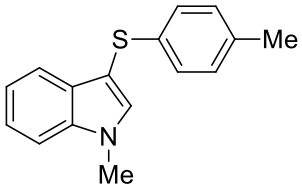
3ca, 98%



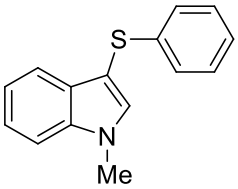
3cb, 98%



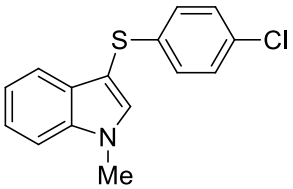
3cc, 97%



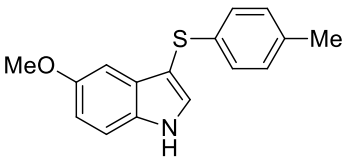
3da, 98%



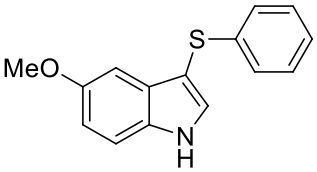
3db, 95%



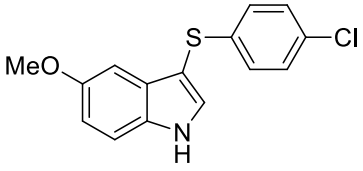
3dc, 90%



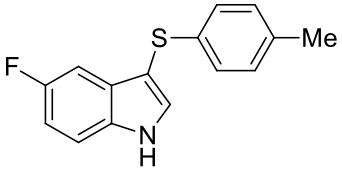
3ea, 52%



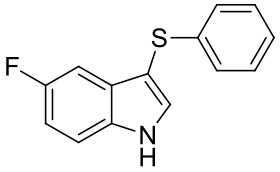
3eb, 48%



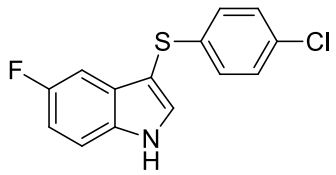
3ec, 61%



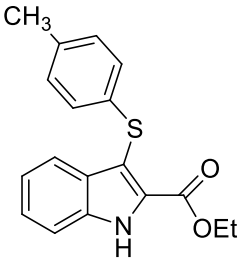
3fa, 94%



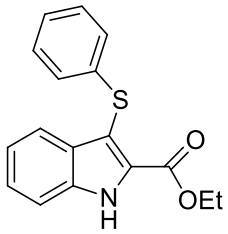
3fb, 98%



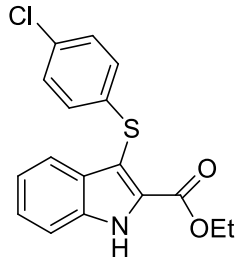
3fc, 82%



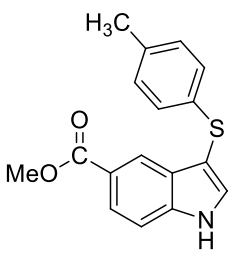
3ga, 85%



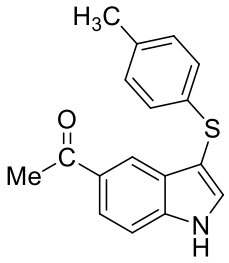
3gb, 80%



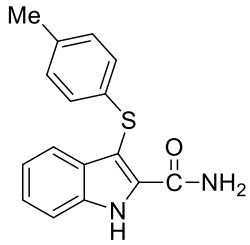
3gc, 60%



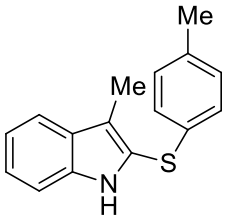
3ha, 75%



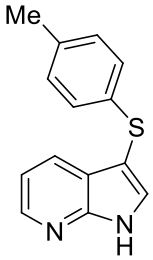
3ia, 60%



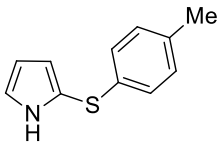
3ja, 92%



3ka, 53%



3la, 83%



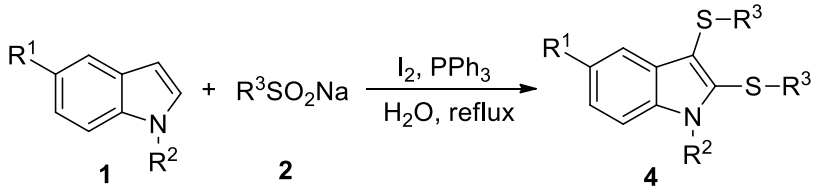
3ma, 35%

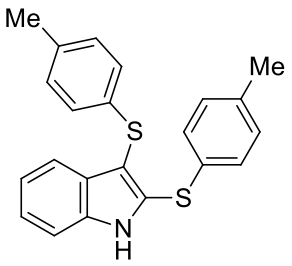
[a]Reaction condition: **1** (0.25 mmol), **2** (0.25 mmol), I_2 (0.25 mmol), PPh_3 (0.5 mmol), H_2O (2 mL), Ar, reflux; Isolated yield based on **1**.

Compared to the extensive investigation on the synthesis of 3-sulfenylindoles, synthesis of 2,3-bis-sulfenylindoles is sparse. As far as we know, there are no reports in the literature describing the direct 2,3-bis-sulfenylation of indoles using sodium sulfinates as sulfenylating agents in aqueous medium. In the course of the optimization of reaction conditions, we noted that a mixture of mono- and disulfenylindoles were yielded when indole reacted with 1.5 equiv. sodium sulfinate in the optimal reaction conditions (Table 1, entry 16). Encouraged by this result, we further investigated the reaction of indole with excess sodium sulfinate, hoping to provide a simple and convenient method for the synthesis of 2,3-bis-sulfenylindoles. Gratifyingly, 2,3-bis-sulfenylindoles **4** were obtained in moderate to excellent yields when indoles **1** were subjected to 2.5 equiv. sodium sulfinates **2** under the otherwise similar reaction conditions. The results are summarized in Table 3. The reaction tolerated a variety of indoles **1** and sodium

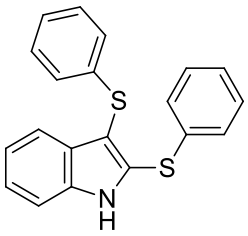
sulfinates **2**. Indole derivatives could be indole (Table 3, **4a**-**4c**), *N*-methylindoles (Table 3, **4d**-**4f**), 5-fluoroindole (Table 3, **4g**-**4i**), 5-methoxylindole (Table 3, **4j**-**4l**), methyl indole-5-carboxylate (Table 3, **4m**), and albeit *N*-tosylindole failed to participate in this reaction to give the desired product **4**. Several commercially available sodium sulfinates **2** such as sodium *p*-tolylsulfinate, sodium phenylsulfinate and sodium *p*-chlorophenylsulfinate could conduct this reaction successfully to give the desired products. The reaction of 3-sulfenylindole with sodium sulfinate was also investigated, hoping to install two different sulfur groups on indole. However, a mixture of two isomers was detected and it was difficult to isolate them from each other when the two sulfur groups on indole were different.

Table 3 Synthesis of 2,3-bis-sulfenylindoles **4** with sodium sulfinate in water[a]

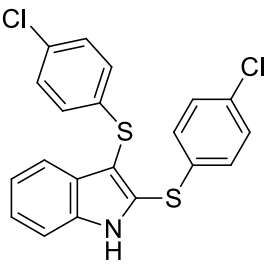




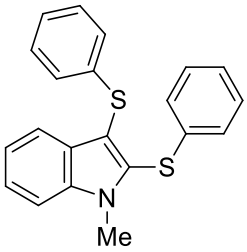
4a, 89%



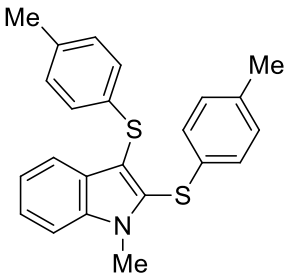
4b, 86%



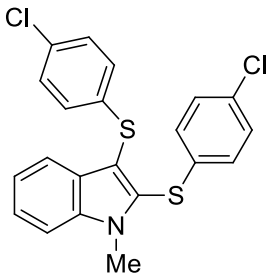
4c, 60%



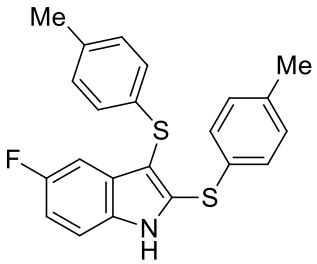
4d, 57%



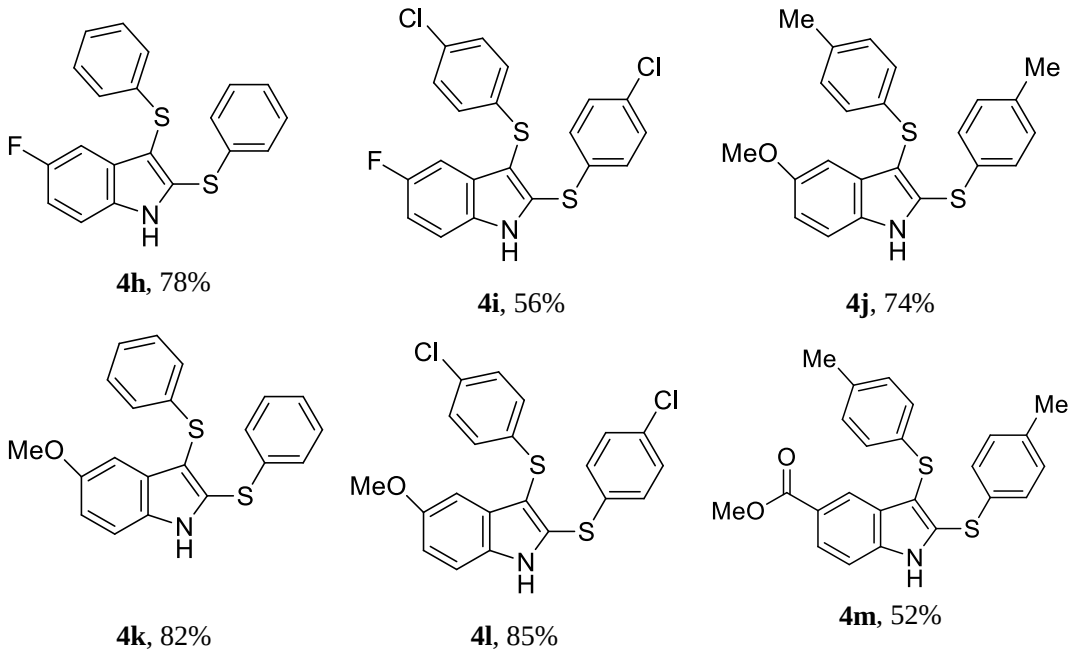
4e, 61%



4f, 47%

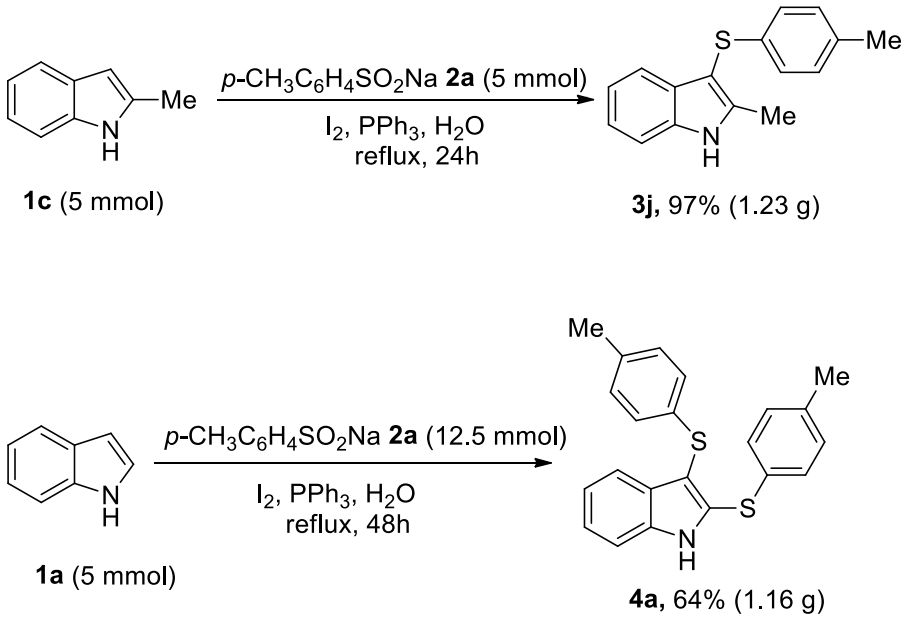


4g, 94%



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.625 mmol), I_2 (0.625 mmol), PPh_3 (1.25 mmol), H_2O (2 mL), Ar, reflux; Isolated yield based on substrate **1**.

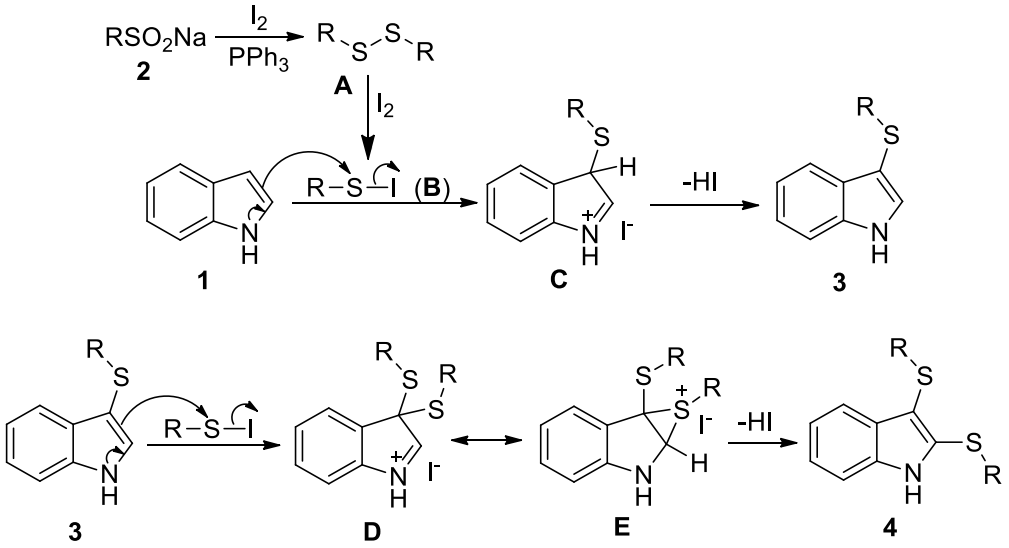
To demonstrate the potential applications of the sulfenylation of indole, we scaled up the reaction to 5 mmol (Scheme 1). The desired product 3-sulfenylindol **3j** and 2,3-bis-sulfenylindole **4a** could be afforded in 97% yield (1.23 g) and 64% yield (1.16 g), respectively.



Scheme 1 Gram-scale experiment

Based on the experimental results and the previous work [8], a plausible reaction mechanism

is shown in Scheme 2. Firstly, in the presence of I_2 and PPh_3, sodium sulfinate **2** was reduced to disulfide **A**, which was checked by GC-MS. Then **A** reacts with I_2 to give electrophilic sulfenyl iodide **B**, which would attack to indole **1** to form intermediate **C**. Subsequent deprotonation of intermediate **C** gives the desired monosulfenylated indole **3**. The second sulfenylation of indole might proceed by the similar mechanism of the reported literature.[4b,4c and 8a] Product **4** might occur by initial attack on the 3-position of the indole ring to give rise to 3,3-bis-substituted indolenium intermediate **D**, followed by migration of one of the sulfide group from 3-position to 2-position to generate an episulfonium species **E**. Finally, release proton of intermediate **D** affords 2,3-bis-sulfenylindole **4**.



Scheme 2 A plausible reaction mechanism for mono- and bis-sulfenylation of indole

Conclusions

In summary, we have developed a simple and convenient protocol to access monosulfenylated and 2,3-bis-sulfenylated indoles in good to excellent yields. The method not only could proceed without metal catalyst and organic solvent, but also has successfully employed the stable, readily accessible and ordorless sodium sulfinate as sulfenylating agents. Compared to the reported routes, this protocol displays broad substrate scope and several functional groups such as methoxyl, fluoro, ester, ketone, and amide on indole rings are well tolerated. Moreover, the reaction can be extended to 7-azaindole and pyrrole. Synthetically, the protocol could be scaled up to 5 mmol with good efficiency, which makes this reaction practical and attractive.

Experimental

General procedure for the synthesis of 3-sulfenylated indoles 3

Under argon atmosphere, a Schlenk flask equipped with a condenser was charged with 0.25 mmol of indole, 0.25 mmol of sodium sulfinate, 0.25 mmol (63.5 mg) of I_2, 0.5 mmol (131 mg) of PPh_3 and 2 mL of water. The reaction mixture was stirred at refluxing temperature until complete consumption of starting material **1** (monitored by TLC) and then cooled to room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic extracts were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether = 1/10) to give product **3**.

3-(*p*-Tolylthio)-1*H*-indole (3aa).[3e] White solid; m.p. 122-123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.47-7.41 (m, 2H), 7.25 (t, J = 8.2 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 7.00 (q, J = 8.1 Hz, 4H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.9, 135.9, 135.2, 131.0, 130.0, 129.5, 126.7, 123.4, 121.3, 120.1, 112.1, 103.7, 21.3; IR (KBr): ν (cm^{-1}) 3423, 1492, 1453, 1405, 1335, 1239, 1098, 1007, 800, 746; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{15}H_{14}NS$: 240.0841, found: 240.0849.

3-(Phenylthio)-1*H*-indole (3ab).[3e] White solid; m.p. 145-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.50-7.43 (m, 2H), 7.29-7.25 (m, 1H), 7.19-7.05 (m, 6H); ^{13}C NMR (125 MHz, d^6-DMSO): δ 140.1, 137.6, 133.3, 129.7, 129.5, 126.2, 125.6, 123.0, 121.0, 119.2, 113.2, 100.1; IR (KBr): ν (cm^{-1}) 3407, 1576, 1475, 1456, 1408, 1232, 1024, 746; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{14}H_{12}NS$: 226.0685, found: 226.0682.

3-((4-Chlorophenyl)thio)-1*H*-indole (3ac).[3e] White solid; m.p. 126-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.49-7.40 (m, 2H), 7.30-7.28 (m, 1H), 7.20-7.00 (m, 5H); ^{13}C NMR (125 MHz, d^6-DMSO): δ 139.3, 137.7, 133.5, 130.2, 129.6, 129.3, 127.7, 123.1, 121.1, 119.1, 113.3, 99.6; IR (KBr): ν (cm^{-1}) 3396, 1647, 1505, 1473, 1453, 1405, 1383, 1095, 1011, 811, 745; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{14}H_{11}ClNS$: 260.0295, found: 260.0298.

2-Phenyl-3-(*p*-tolylthio)-1*H*-indole (3ba).[8e] Dark purple oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.60 (d, J = 6.6 Hz, 2H), 7.52 (d, J = 7.5 Hz, 1H), 7.30-7.23 (m, 4H), 7.13 (t, J =

7.1 Hz, 1H), 7.08-7.01 (m, 1H), 6.90-6.82 (m, 4H), 2.11 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 142.5, 136.4, 136.2, 135.0, 131.9, 131.8, 130.3, 129.3, 129.2, 128.8, 126.3, 123.9, 121.7, 120.5, 111.9, 100.2, 21.5; IR (KBr): ν (cm^{-1}) 3404, 1488, 1442, 1395, 1324, 1084, 805, 741, 694; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{21}H_{18}NS$: 316.1154, found: 316.1153.

2-Phenyl-3-(phenylthio)-1*H*-indole (3bb).[3b] Faint yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.60 (d, *J* = 6.7 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.30-7.27 (m, 3H), 7.23 (s, 1H), 7.15 (t, *J* = 7.1 Hz, 1H), 7.08-7.00 (m, 5H), 6.95-6.90 (m, 1H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 142.6, 139.8, 136.4, 131.8, 131.6, 129.4, 129.3, 129.2, 128.7, 126.0, 125.2, 123.9, 121.7, 120.4, 111.8, 99.7; IR (KBr): ν (cm^{-1}) 3407, 3057, 1581, 1477, 1452, 1442, 1397, 1320, 1297, 1224, 739, 693; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{20}H_{16}NS$: 302.0998, found: 302.0996.

3-((4-Chlorophenyl)thio)-2-phenyl-1*H*-indole (3bc). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.66 (d, *J* = 6.7 Hz, 2H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.41-7.34 (m, 4H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.08-7.05 (m, 2H), 6.98-6.96 (m, 2H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 142.7, 138.4, 136.4, 131.7, 131.4, 130.9, 129.5, 129.4, 129.3, 128.6, 127.3, 124.0, 121.8, 120.3, 111.9, 99.3; IR (KBr): ν (cm^{-1}) 3407, 1476, 1452, 1444, 1087, 1008, 816, 740, 692; HRMS (APCI) $[M + H]^+$: m/z calcd for $C_{20}H_{15}ClNS$: 336.0608, found: 336.0616.

3-(Methylthio)-2-phenyl-1*H*-indole (3bd). Purple solid; m.p. 97-98 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.85 (t, *J* = 7.6 Hz, 3H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.43-7.40 (m, 2H), 7.25-7.21 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 140.2, 136.1, 132.4, 131.4, 129.1, 128.8, 128.6, 123.5, 121.1, 120.1, 111.6, 105.3 20.2; IR (KBr): ν (cm^{-1}) 3431, 1655, 1450, 1440, 1392, 1224, 772, 736, 696; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{15}H_{14}NS$: 240.0841, found: 240.0845.

2-Methyl-3-(*p*-tolylthio)-1*H*-indole (3ca).[3e] Yellow solid. m.p. 96-98 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.18-7.11 (m, 2H), 6.96 (s, 4H), 2.51 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 141.6, 136.2, 135.9, 134.9, 130.8, 130.0, 126.3, 122.6, 121.1, 119.4, 111.3, 100.1, 21.3, 12.5; IR (KBr): ν (cm^{-1}) 3396, 1542, 1488, 1453, 1399, 1287, 1224, 1087, 800, 748; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{16}H_{16}NS$: 254.0998, found: 254.0999.

2-Methyl-3-(phenylthio)-1*H*-indole (3cb).[3e] White solid; m.p. 113-114 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.54 (d, *J* = 7.1 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.25-7.12 (m, 4H),

7.05-7.02 (m, 3H), 2.51 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 141.8, 139.8, 135.9, 130.8, 129.3, 126.0, 125.1, 122.7, 121.2, 119.4, 111.3, 99.6, 12.5; IR (KBr): ν (cm^{-1}) 3404, 1657, 1636, 1561, 1476, 1457, 1437 1081, 743; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{15}H_{14}NS$: 240.0841, found: 240.0846.

3-((4-Chlorophenyl)thio)-2-methyl-1*H*-indole (3cc).[5f] Yellow solid; m.p. 88-89 ^oC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.14-7.00 (m, 4H), 6.86 (d, *J* = 8.0 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 141.7, 138.4, 135.9, 130.7, 130.5, 129.2, 127.2, 122.8, 121.3, 119.2, 111.3, 99.3, 12.5; IR (KBr): ν (cm^{-1}) 3400, 1468, 1406, 1381, 1290, 1093, 1015, 803, 743; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{15}H_{13}ClNS$: 274.0452, found: 274.0445.

1-Methyl-3-(*p*-tolylthio)-1*H*-indole (3da). Yellow solid; m.p. 112-113 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 12.0 Hz, 1H), 7.19-7.16 (m, 2H), 7.09-7.04 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 3.66 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.4, 134.9, 133.8, 133.4, 128.7, 128.4, 125.0, 121.4, 119.3, 118.7, 108.6, 100.0, 32.0, 19.8; IR (KBr): ν (cm^{-1}) 1487, 1330, 1257, 1229, 1081, 805, 741; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{16}H_{16}NS$: 254.0998, found: 254.0996.

1-Methyl-3-(phenylthio)-1*H*-indole (3db). Yellow solid; m.p. 74-75 ^oC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.5 Hz, 1H), 7.28-7.20 (m, 3H), 7.06-7.01 (m, 5H), 6.94 (d, *J* = 6.0 Hz, 1H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 136.5, 134.0, 128.7, 127.6, 124.6, 123.6, 121.5, 119.5, 118.6, 108.7, 99.3, 32.0; IR (KBr): ν (cm^{-1}) 1581, 1505, 1481, 1436, 1336, 1260, 1242, 738; HRMS (APCI) $[M + H]^+$: m/z calcd for $C_{15}H_{14}NS$: 240.0841, found: 240.0833.

3-((4-Chlorophenyl)thio)-1-methyl-1*H*-indole (3dc). Yellow solid; m.p. 115-116 ^oC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.41-7.25 (m, 3H), 7.19-7.09 (m, 3H), 7.00 (d, *J* = 8.2 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.2, 136.5, 134.0, 129.3, 128.4, 127.6, 125.9, 121.6, 119.6, 118.5, 108.8, 98.9, 32.1; IR (KBr): ν (cm^{-1}) 1508, 1475, 1369, 1242, 1008, 811, 747; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{15}H_{13}ClNS$: 274.0452, found: 274.0460.

5-Methoxy-3-(*p*-tolylthio)-1*H*-indole (3ea).[5f] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.39 (d, *J* = 2.6 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.05-6.95 (m, 5H), 6.89 (m, 1H), 3.77 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 136.0, 135.0, 131.8, 131.6,

130.4, 129.9, 126.4, 113.9, 112.8, 103.1, 101.2, 56.2, 21.3; IR (KBr): ν (cm^{-1}) 3415, 1484, 1288, 1204, 1169, 1030, 920, 806; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{16}H_{16}NOS$: 270.0947, found: 270.0938.

5-Methoxy-3-(phenylthio)-1*H*-indole (3eb).[3e] Yellow solid; m.p. 76-78 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.18-7.04 (m, 6H), 6.91 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 139.8, 131.8, 130.4, 129.1, 126.0, 125.1, 114.0, 112.9, 102.5, 101.2, 56.2; IR (KBr): ν (cm^{-1}) 3411, 1623, 1575, 1473, 1436, 1281, 1201, 1168, 1032, 737; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{15}H_{14}NOS$: 256.0791, found: 256.0785.

3-((4-Chlorophenyl)thio)-5-methoxy-1*H*-indole (3ec).[5f] White solid; m.p. 81-82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.13-7.10 (m, 2H), 7.01-6.98 (m, 3H), 6.92 (m, 1H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 138.3, 131.8, 130.9, 130.1, 129.2, 127.3, 114.1, 113.0, 102.1, 101.1, 56.2; IR (KBr): ν (cm^{-1}) 3357, 1472, 1278, 1207, 1158, 1087, 803; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{15}H_{13}ClNOS$: 290.0401, found: 290.0394.

5-Fluoro-3-(*p*-tolylthio)-1*H*-indole (3fa).[8d] White solid; m.p. 129-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.51 (t, J = 2.6 Hz, 1H), 7.34 (m, 1H), 7.25-7.24 (m, 1H), 7.03-6.98 (m, 5H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, d^6-DMSO): δ 158.5 (J_{F-C} = 232.4 Hz), 135.9, 135.2, 135.0, 134.2, 130.4, 130.2 (J_{F-C} = 9.9 Hz), 126.6, 114.5 (J_{F-C} = 9.6 Hz), 111.2 (J_{F-C} = 26.0 Hz), 103.8 (J_{F-C} = 23.6 Hz), 101.2 (J_{F-C} = 4.5 Hz), 21.2; IR (KBr): ν (cm^{-1}) 3419, 1484, 1261, 1157, 1088, 1026, 802; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{15}H_{13}FNS$: 258.0747, found: 258.0745.

5-Fluoro-3-(phenylthio)-1*H*-indole (3fb).[3b] White solid; m.p. 112-113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.52 (d, J = 2.5 Hz, 1H), 7.35 (m, 1H), 7.27-7.23 (m, 1H), 7.20-7.15 (m, 2H), 7.10-6.97 (m, 4H); ^{13}C NMR (125 MHz, d^6-DMSO): δ. 158.6 (J_{F-C} = 232.6 Hz), 139.7, 135.3, 134.2, 130.3 (J_{F-C} = 9.9 Hz), 129.8, 126.7, 125.8, 114.5 (J_{F-C} = 9.7 Hz), 111.3 (J_{F-C} = 25.9 Hz), 103.8 (J_{F-C} = 23.7 Hz), 100.4 (J_{F-C} = 4.5 Hz); IR (KBr): ν (cm^{-1}) 3415, 1573, 1484, 1449, 1262, 1155, 1023, 813, 734; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{14}H_{11}FNS$: 244.0591, found: 244.0593.

3-((4-Chlorophenyl)thio)-5-fluoro-1*H*-indole (3fc). White solid; m.p. 124-126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.53 (d, J = 2.6 Hz, 1H), 7.37 (m, 1H), 7.21 (m, 1H), 7.15-7.12

(m, 2H), 7.05-6.98 (m, 3H); ^{13}C NMR (125 MHz,d^6-DMSO): δ 158.6 ($J_{F\text{-}C}$ = 232.8 Hz), 138.9, 135.5, 134.2, 130.4, 130.0 ($J_{F\text{-}C}$ = 9.9 Hz), 129.7, 127.8, 114.6 ($J_{F\text{-}C}$ = 9.6 Hz), 114.4 ($J_{F\text{-}C}$ = 25.9 Hz), 103.7 ($J_{F\text{-}C}$ = 23.7 Hz), 99.9 ($J_{F\text{-}C}$ = 16.9 Hz); IR (KBr): ν (cm^{-1}) 3422, 1485, 1475, 1264, 1161, 1090, 1026, 865, 806; HRMS (APCI) [M+H]$^+$: m/z calcd for $C_{14}H_{10}ClFNS$: 278.0201, found: 278.0195.

Ethyl 3-(*p*-tolylthio)-1*H*-indole-2-carboxylate (3ga). White solid; mp 116-117 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.50 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.13-7.10 (m, 3H), 6.98 (d, *J* = 8.0 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 136.3, 135.7, 134.5, 130.4, 129.9, 128.9, 128.3, 126.4, 122.2, 121.7, 112.5, 111.8, 61.9, 21.4, 14.7; IR (KBr): ν (cm^{-1}) 3314, 1677, 1505, 1490, 1329, 1253, 812, 744; HRMS (APCI) [M+H]$^+$: m/z calcd for $C_{18}H_{18}NO_2S$: 312.1053, found: 312.1058.

Ethyl 3-(phenylthio)-1*H*-indole-2-carboxylate (3gb). White solid; mp 113-114 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.17-7.15 (m, 4H), 7.14-7.12 (m, 1H), 7.09-7.06 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.9, 138.4, 136.3, 130.5, 129.2, 129.1, 127.6, 126.5, 125.7, 122.1, 121.9, 112.6, 110.9, 61.9, 14.6; IR (KBr): ν (cm^{-1}) 3316, 1674, 1508, 1493, 1331, 1261, 807, 742; HRMS (APCI) [M+H]$^+$: m/z calcd for $C_{17}H_{16}NO_2S$: 298.0896, found: 298.0893.

Ethyl 3-((4-chlorophenyl)thio)-1*H*-indole-2-carboxylate (3gc). White solid; mp 134-135 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.47 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.38-7.35 (m, 1H), 7.18-7.12 (m, 3H), 7.09-7.06 (m, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6, 137.0, 136.2, 131.5, 130.3, 129.3, 129.2, 128.8, 126.7, 122.1, 121.9, 112.6, 110.2, 61.9, 14.6; IR (KBr): ν (cm^{-1}) 3298, 1682, 1511, 1476, 1333, 1257, 809, 749; HRMS (APCI) [M+H]$^+$: m/z calcd for $C_{17}H_{15}ClNO_2S$: 332.0507, found: 332.0510.

Methyl 3-(*p*-tolylthio)-1*H*-indole-5-carboxylate (3ha). White solid; mp 166-167 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.40 (s, 1H), 7.98-7.96 (m, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.04-6.98 (m, 4H), 3.90 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 139.5, 135.5, 135.4, 132.3, 130.0, 129.3, 126.8, 124.8, 123.4, 122.9, 111.8, 105.8,

52.4, 21.3; IR (KBr): ν (cm^{-1}) 3285, 1692, 1612, 1292, 1209, 804, 744; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{17}H_{16}NO_2S$: 298.0896, found: 298.0891.

1-(3-(*p*-Tolylthio)-1*H*-indol-5-yl)ethanone (3ia). White solid; mp 144-145 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.25 (s, 1H), 7.94-7.92 (m, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.05-6.98 (m, 4H), 2.62 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.2, 139.7, 135.5, 135.3, 132.5, 131.1, 130.0, 129.2, 127.0, 123.4, 122.3, 112.2, 106.1, 27.1, 21.3; IR (KBr): ν (cm^{-1}) 3258, 1660, 1612, 1358, 1277, 907, 801; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{17}H_{16}NOS$: 282.0947, found: 282.0948.

3-(*p*-Tolylthio)-1*H*-indole-2-carboxamide (3ja). White solid; mp 102-103 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 10.45 (s, 1H), 8.29 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.35-7.32 (m, 1H), 7.18-7.15 (m, 1H), 7.03-6.99 (m, 4H), 6.26 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3, 136.4, 135.9, 132.9, 132.7, 130.6, 130.3, 127.1, 126.0, 122.1, 121.3, 113.0, 104.3, 21.3; IR (KBr): ν (cm^{-1}) 3182, 1647, 1564, 1486, 1348, 799, 744; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{16}H_{15}N_2OS$: 283.0900, found: 283.0904.

3-methyl-2-(*p*-tolylthio)-1*H*-indole (3ka). white solid; m.p. 79-81 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.29-7.20 (m, 2H), 7.17-7.11 (m, 1H), 7.04-6.97 (m, 4H), 2.40 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.8, 135.8, 133.2, 129.8, 128.5, 127.1, 123.3, 122.2, 119.5, 119.3, 110.8, 20.9, 9.4; IR (KBr): ν (cm^{-1}) 3380, 1716, 1699, 1683, 1656, 1049, 676; HRMS (ESI) $[M+H]^+$: m/z calcd for $C_{16}H_{16}NS$: 254.0998, found: 254.1004.

3-(*p*-Tolylthio)-1*H*-pyrrolo[2,3-b]pyridine (3la). White solid; mp 151-152 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 12.48 (s, 1H), 8.40 (d, *J* = 4.3 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.70 (s, 1H), 7.15-7.12 (m, 1H), 7.04-6.70 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 143.4, 135.5, 135.4, 132.3, 130.0, 129.0, 126.9, 122.7, 117.1, 102.3, 21.3; IR (KBr): ν (cm^{-1}) 3127, 1493, 1407, 1271, 797, 764, 512; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{14}H_{13}N_2S$: 241.0794, found: 241.0795

2-(*p*-Tolylthio)-1*H*-pyrrole (3ma). colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.06-7.05 (m, 2H), 7.02-7.00 (m, 2H), 6.98-6.97 (m, 1H), 6.84-6.82 (m, 1H), 6.31-6.30 (m, 1H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.1, 134.9, 129.8, 126.6, 124.1, 119.7, 114.8, 110.0, 21.2; IR (KBr): ν (cm^{-1}) 3419, 1486, 1041, 927, 806; HRMS (APCI) $[M+H]^+$: m/z calcd for

$C_{11}H_{12}NS$: 190.0685, found: 190.0686.

General procedure for the synthesis of 2,3-bis-sulfenylated indoles 4

A Schlenk flask equipped with a condenser was charged with 0.25 mmol of indole, 0.625 mmol of sodium sulfinate, 0.625 mmol (159 mg) of I_2, 1.25 mmol (327 mg) of PPh_3 and 2 mL of water under argon atmosphere. The reaction mixture was stirred at refluxing temperature until complete consumption of starting material **1** (monitored by TLC) and then cooled to room temperature. The reaction was then quenched with saturated $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether = 1/10) to give product **4**.

2,3-Bis-(p-tolylthio)-1*H*-indole (4a).[5e] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.29-7.18 (m, 4H), 7.15-7.02 (m, 5H), 6.96 (d, J = 7.9 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 137.1, 135.3, 135.0, 134.9, 131.2, 130.6, 130.5, 130.4, 129.9, 127.3, 123.9, 121.5, 120.1, 111.3, 108.7, 21.5, 21.3; IR (KBr): ν (cm^{-1}) 3392, 1490, 1442, 1393, 1337, 1332, 1229, 1084, 1013, 804, 742; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{22}H_{20}NS_2$: 362.1032, found: 362.1040.

2,3-Bis-(phenylthio)-1*H*-indole (4b).[5e] White solid; m.p. 85-86 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.35-7.21 (m, 7H), 7.18-7.06 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 137.3, 134.9, 134.0, 130.4, 130.1, 129.8, 129.2, 127.7, 127.0, 125.6, 124.3, 121.7, 120.4, 111.7, 109.6; IR (KBr): ν (cm^{-1}) 3384, 1580, 1480, 1442, 1227, 1083, 1019, 751; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{20}H_{16}NS_2$: 334.0719, found: 334.0718.

2,3-Bis-((4-chlorophenyl)thio)-1*H*-indole (4c). Yellow solid; m.p. 68-69 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.36-7.24 (m, 2H), 7.19-7.07 (m, 7H), 6.98 (d, J = 8.5 Hz,2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.3, 136.9, 133.8, 133.3, 133.2, 131.5, 131.1, 130.1, 129.9, 129.2, 128.3, 124.7, 122.0, 120.3, 111.8, 109.9; IR (KBr): ν (cm^{-1}) 3407, 1473, 1437, 1390, 1339, 1226, 1089, 1006, 811, 741; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{20}H_{14}Cl_2NS_2$: 401.9939, found: 401.9942.

5-Fluoro-2,3-bis-(*p*-tolylthio)-1*H*-indole (4d). White solid; m.p. 128-130 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.28-7.25 (m, 2H), 7.22-7.19 (m, 2H), 7.11 (d, J = 7.9 Hz, 2H),

7.04-6.90 (m,5H), 2.33 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, d^6-DMSO): δ 158.6 ($J_{F\text{-}C}$ = 233.7 Hz), 137.5, 136.3, 135.6, 134.8, 134.7, 131.8, 130.9, 130.6 ($J_{F\text{-}C}$ = 9.9 Hz), 130.5, 129.3, 127.3, 114.3 ($J_{F\text{-}C}$ = 9.5 Hz), 112.5 ($J_{F\text{-}C}$ = 26 Hz), 108.2 ($J_{F\text{-}C}$ = 4.6 Hz), 104.2 ($J_{F\text{-}C}$ = 23.6 Hz), 21.4, 21.3; IR (KBr): ν (cm^{-1}) 3442, 1489, 1433, 1259, 1100, 1024, 800; HRMS (APCI) [M+H]$^+$: m/z calcd for $C_{22}H_{19}FNS_2$: 380.0937, found: 380.0931.

5-Fluoro-2,3-bis-(phenylthio)-1*H*-indole (4e). White solid; m.p. 99-100 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.29-7.28 (m, 4H), 7.25-7.19 (m, 3H), 7.17-7.05 (m, 5H), 7.02-6.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1 ($J_{F\text{-}C}$ = 236.4 Hz), 138.0, 136.4, 134.0, 133.6, 131.3 ($J_{F\text{-}C}$ = 10.0 Hz), 130.7, 129.9, 129.2, 128.1, 127.0, 125.7, 112.7 ($J_{F\text{-}C}$ = 26.4 Hz), 112.4 ($J_{F\text{-}C}$ = 9.3 Hz), 108.9 ($J_{F\text{-}C}$ = 4.7 Hz), 105.2 ($J_{F\text{-}C}$ = 23.8 Hz); IR (KBr): ν (cm^{-1}) 3381, 1581, 1490, 1474, 1435, 1278, 1156, 846, 803, 739; HRMS (APCI) [M+H]$^+$: m/z calcd for $C_{20}H_{15}FNS_2$: 352.0624, found: 352.0626.

2,3-Bis-((4-chlorophenyl) thio)-5-fluoro-1*H*-indole (4f). White solid; m.p. 157-158 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.28 (m, 1H), 7.23-7.17 (m, 5H), 7.12-7.11 (m, 2H), 7.04-7.00 (m, 1H), 6.98-6.96 (m, 2H); ^{13}C NMR (125 MHz,d^6-DMSO): δ 158.5 ($J_{F\text{-}C}$ = 234.6 Hz), 137.5, 135.3, 134.9, 134.6, 132.5, 130.8, 130.7, 130.5 ($J_{F\text{-}C}$ = 10.0 Hz), 130.2, 129.7, 128.3, 114.7 ($J_{F\text{-}C}$ = 9.4 Hz), 113.1 ($J_{F\text{-}C}$ = 26.2 Hz), 107.7 ($J_{F\text{-}C}$ = 4.6 Hz) 158.5 ($J_{F\text{-}C}$ = 23.9 Hz); IR (KBr): ν (cm^{-1}) 3431, 1556, 1475, 1259, 1087, 1026, 803; HRMS (APCI) [M+H]$^+$: m/z calcd for $C_{20}H_{13}Cl_2FNS_2$: 419.9845, found: 419.9852.

5-Methoxy-2, 3-bis-(*p*-tolylthio)-1*H*-indole (4g). White solid; m.p. 142-143 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.25-7.16 (m, 3H), 7.08-6.95 (m, 7H), 6.86 (m, 1H), 3.78 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, d^6-DMSO): δ 155.3, 137.1, 135.4, 135.2, 133.9, 133.2, 132.7, 130.8, 130.5, 130.4, 129.3, 129.0, 114.6, 113.9, 107.9, 100.8, 56.1, 21.3, 21.2; IR (KBr): ν (cm^{-1}) 3396, 1624, 1488, 1421, 1284, 1208, 1172, 1014, 806; HRMS (APCI) [M+H]$^+$: m/z calcd for $C_{23}H_{22}NOS_2$: 392.1137, found: 392.1133.

5-Methoxy-2, 3-bis-(phenylthio)-1*H*-indole (4h). White solid; m.p. 91-92 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.18-7.15 (m, 5H), 7.13-7.07 (m, 5H), 7.04-7.00 (m, 2H), 6.87 (m, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 138.6, 135.1, 134.2, 132.4, 131.2, 129.8, 129.7, 129.2, 127.5, 126.8, 125.5, 115.0, 112.7, 109.0, 101.4, 56.2; IR (KBr): ν (cm^{-1}) 3373, 1623, 1580, 1487, 1425, 1281, 1205, 798; HRMS (APCI) [M+H]$^+$: m/z calcd for $C_{21}H_{18}NOS_2$: 364.0824,

found: 364.0818.

2,3-Bis-((4-chlorophenyl) thio)-5-methoxy-1*H*-indole (4i). White solid; m.p. 134-135 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.27-7.22 (m, 1H), 7.19-7.06 (m, 6H), 6.98-6.92 (m, 4H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 136.9, 133.7, 133.5, 133.4, 132.2, 131.3, 131.1, 130.9, 129.8, 129.2, 128.0, 115.5, 112.7, 109.2, 101.1, 56.2; IR (KBr): ν (cm^{-1}) 3307, 1633, 1579, 1474, 1425, 1289, 1165, 1087, 802; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{21}H_{16}Cl_2NOS_2$: 432.0045, found: 432.0041.

1-Methyl-2,3-bis(p-tolylthio)-1*H*-indole (4j). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.4 Hz, 1H), 7.30-7.30 (m, 2H), 7.15 (t, *J* = 6.8 Hz, 1H), 7.02-6.91 (m, 8H), 3.75 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 136.3, 135.0, 134.9, 134.8, 132.3, 130.0, 129.5, 129.3, 128.0, 127.1, 123.9, 121.0, 120.4, 111.4, 110.2, 31.2, 21.1, 21.0; IR (KBr): ν (cm^{-1}) 1490, 1445, 1326, 1220, 1087, 1011, 805, 744; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{23}H_{22}NS_2$: 376.1188, found: 376.1185.

1-Methyl-2,3-bis(phenylthio)-1*H*-indole (4k). White solid; m.p. 80-81 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 7.6 Hz, 1H), 7.31-7.22 (m, 2H), 7.09-7.01 (m, 8H), 6.96-6.94 (m, 3H), 3.69(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 134.8, 133.2, 128.1, 127.6, 126.3, 125.5, 125.1, 123.9, 122.9, 120.0, 119.3, 110.0, 109.2, 30.1; IR (KBr): ν (cm^{-1}) 1584, 1472, 1451, 1326, 1226, 1154, 744, 684; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{21}H_{18}NS_2$: 348.0875, found: 348.0871.

2,3-Bis((4-chlorophenyl)thio)-1-methyl-1*H*-indole (4l). White solid; m.p. 80-81 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.31-7.28 (m, 2H), 7.15-7.11 (m, 1H), 7.06-6.98 (m, 4H), 6.91-6.85 (m, 4H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 136.9, 134.2, 133.9, 132.4, 131.0, 129.4, 129.0, 128.8, 128.7, 127.9, 124.4, 121.4, 120.2, 110.8, 110.4, 31.2; IR (KBr): ν (cm^{-1}) 1475, 1333, 1232, 1081, 999, 808, 732; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{21}H_{16}Cl_2NS_2$: 416.0096, found: 416.0094.

Methyl 2,3-bis(*p*-tolylthio)-1*H*-indole-5-carboxylate (4m). White solid; mp 172-173 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.33 (t, *J* = 0.75 Hz, 1H), 7.91-7.89 (m, 1H), 7.28-7.26 (m, 3H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.05-7.03 (m, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 3.88 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 139.5, 138.8, 137.8, 135.5, 134.5, 132.0, 130.7, 130.3, 129.9, 129.1, 127.4, 125.0, 123.6, 122.4, 111.0, 108.9, 52.3, 21.4, 21.2; IR (KBr): ν

(cm^{-1}) 3273, 1689, 1490, 1440, 1291, 1246, 976, 807; HRMS (APCI) $[M+H]^+$: m/z calcd for $C_{24}H_{22}NO_2S_2$: 420.1086, found: 420.1081.

Acknowledgements

The authors are grateful to the National Natural Science Foundation of China (No. 20772001) and The Natural Science Foundation of the Higher Education Institutions of Anhui Province (KJ2018A0222) for financial support of this work.

Supporting Information

The supporting information for this article is available on the WWW under https://

References

[1] For selected reviews, see: (a) Feng, M. H,; Tang, B. Q.; Liang, S.; Jiang, X. F. *Curr. Top. Med. Chem.* **2016**, *16*, 1200-1216. (b) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596-1636. (c) Boyd, D. A. Angew. Chem., Int. Ed. 2016, 55, 15486-15502. (d) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534-1544.

[2] (a) Golzar, N.; Nowrouzi, N.; Abbasi, M.; Mehranpour, A. M. *New J. Chem.* **2017**, *41*, 11921-11925. (b) He, L.; Li, X. W. *Tetrahedron* **2017**, *73*, 6138-6145. (c) Nuth, M.; Guan, H.; Zhukovskaya, N.; Saw, Y. L.; Ricciardi, R. P. *J. Med. Chem.* **2013**, *56*, 3235-3246. (d) Cianchi, F.; Cortesini, C.; Magnelli, L.; Fanti, E.; Papucci, L.; Schiavone, N.; Messerini, L.; Vannacci, A.; Capaccioli, S.; Perna, F.; Lulli, M.; Fabbroni, V.; Perigli, G.; Bechi, P.; Masini, E. *Mol. Cancer Ther.* **2006**, *5*, 2716-2726; (e) Ragno, R.; Coluccia, A.; La Regina, G.; De Martino, G.; Piscitelli, F.; Lavecchia, A.; Novellino, E.; Bergamini, A.; Ciaprini, C.; Sinistro, A.; Maga, G.; Crespan, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 3172-3184; (f) Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *27*, 209-238.

[3] (a) La Regina, G.; Gatti, V.; Famiglini, V.; Piscitelli, F.; Silvestri, R. *ACS, Comb. Sci.* **2012**, *14*, 258-262. (b) Sang, P.; Chen, Z. K.; Zou, J. W.; Zhang, Y. H. *Green Chem.* **2013**, *15*, 2096-2100. (c) Azeredo, J. B.; Godoi, M.; Martins, G. M.; Silveira, C. C.; Braga, A. L. *J. Org. Chem.* **2014**,

79, 4125-4130. (d) Prasad, C. D.; Kumar, S.; Sattar, M.; Adhikary, A.; Kumar, S. *Org. Biomol. Chem.* **2013**, *11*, 8036-8040; (e) Ge, W. L.; Wei, Y. Y. *Green Chem.* **2012**, ***14***, 2066-2070.

[4] (a) Chen, Y.; Cho, C. H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173-176. (b) Hamel, P. *J. Org. Chem.*, **2002**, *67*, 2854-2858. (c) Hamel, P.; Préville, P. *J. Org. Chem.* **1996**, *61*, 1573-1577.

[5] (a) Guo, W.; Tan, W.; Zhao, M. M.; Tao, K. L.; Zheng, L. Y.; Wu, Y. Q.; Chen, D. L.; Fan, X. L. *RSC Adv*. **2017**, *7*, 37739-37742. (b) Saima; Equbal, D.; Lavekar, A. G.; Sinha, A. K. *Org. Biomol. Chem*. **2016**, *14*, 6111-6118. (c) Liu, X. X.; Cui, H. H.; Yang, D. S.; Dai, S. C.; Zhang, G. Q.; Wei, W.; Wang, H. *Catal Lett*. **2016**, *146*, 1743-1748; (d) Yi, S. L.; Li, M. C.; Mo, W. M.; Hu, X. Q.; Hu, B. X.; Sun, N.; Jin, L. Q.; Shen, Z. L. *Tetrahedron Lett*. **2016**, *57*, 1912-1916; (e) Zhang, H. L.; Bao, X. Z.; Song, Y. M.; Qu, J. P.; Wang, B. M. *Tetrahedron* **2015**, *71*, 8885-8891. (f) Liu, Y. Y.; Zhang, Y.; Hu, C. F.; Wan, J. P.; Wen, C. P. *RSC Adv.* **2014**, *4*, 35528-35530.

[6] (a) Wu, Q.; Zhao, D. B.; Qin, X. R.; Lan, J. B.; You, J. S. *Chem. Commun*. **2011**, *47*, 9188-9190; (b) Kumaraswamy, G.; Raju, R.; Narayanarao, V. *RSC Adv*. **2015**, *5*, 22718-22723; (c) Chen, M.; Huang, Z. T.; Zheng, Q. Y. *Chem. Commun.* **2012**, *48*, 11686-11688.

[7] (a) Lin, Y. M.; Yi, W. B. *Chin. J. Org. Chem.* **2018**, *38*, 1207-1213. (b) Tang, Q. J.; Xie, P.; Wang, J.; Lin, J. J.; Feng, C. L.; Pittman Jr., C. U.; Zhou, A. H. *Tetrahedron* **2017**, *73*, 5436-5443. (c) Li, W. Y.; Yin, G. X.; Huang, L.; Xiao, Y.; Fu, Z. M.; Xin, X.; Liu, F.; Li, Z. Z.; He, W. M. *Green Chem.* **2016**, *18*, 4879-4883. (d) Yang, Y.; Li, W. M.; Xia, C. C.; Ying, B. B.; Shen, C.; Zhang, P. F. *ChemCatChem.* **2016**, *8*, 304-307. (e) Katrun, P.; Mueangkaew, C.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. *J. Org. Chem*. **2014**, *79*, 1778-1785. (f) Ding, Y. C.; Wu, W.; Zhao, W. N.; Li, Y. W.; Xie, P.; Huang, Y. Q.; Liu, Y.; Zhou, A. H. *Org. Biomol. Chem.* **2016**, *14*, 1428-1431. (g) Huang, X. H.; Wang, S. C.; Li, B. W.; Wang, X.; Ge, Z. M.; Li, R. T. *RSC Adv*. **2015**, *5*, 22654-22657. (h) Xiao, F. H.; Chen, H.; Xie, H.; Chen, S. Q.; Yang, L.; Deng, G. J. *Org. Lett.* **2014**, *16*, 50-53.

[8] (a) Rahaman, R.; Barman, P. *Eur J. Org. Chem.* **2017**, 6327-6334. (b) Ge, X.; Sun, F. L.; Liu, X. M.; Chen, X. Z.; Qian, C.; Zhou, S. D. *New J. Chem.* **2017**, *41*, 13175-13180. (c) Xiao, F. H.; Xie, H.; Liu, S. W.; Deng, G. J. *Adv. Synth. Catal.* **2014**, *356*, 364-368. (d) Katrun, P.; Hongthong, S.; Hlekhlai, S.; Pohmakotr, M.; Reutrakul, V.; Soorukram, D.; Jaipetch, T.; Kuhakarn, C. *RSC Adv*. **2014**, *4*, 18933-18938. (e) Rao, H. H.; Wang, P.; Wang, J. C.; Li, Z. F.;

Sun, X. Z.; Cao, S. L. *RSC Adv.* **2014**, *4*, 49165-49169.

[9] For recent representative examples, see: (a) Kitanosono, T.; Masuda, K.; Xu, P. Y.; Kabayashi, S. *Chem. Rev.* **2018**, *118*, 679-746. (b) Zhou, Z.; Duan, J. F.; Mu, X. J.; Xiao, S. Y. *Chin. J. Org. Chem.* **2018**, *38*, 585-593 (in chinese). (c) Wu, C.; Yang, P. P.; Fu, Z. M.; Peng, Y.; Wang, X.; Zhang, Z. Z.; Liu, F.; Li, W. Y.; Li, Z. Z.; He, W. M. *J. Org. Chem*. **2016**, *81*, 10664-10671. (d) Vamisetti, G. B.; Chowdhury, R.; Kumar, M.; Ghosh, S. K. *Org. Lett.*, **2016**, *18*, 1964-1967. (e) Li, W. Y.; Yin, G. X.; Huang, L.; Xiao, Y.; Fu, Z. M.; Xin, X.; Liu, F.; Li, Z. Z.; He, X. W. *Green Chem*. **2016**, ***18***, 4879-4883. (f) Pan, X. J.; Gao, J.; Liu, J.; Lai, J. Y.; Jiang, H. F.; Yuan, G. Q. *Green Chem.* **2015**, *17*, 1400-1403.

[10] Ragno, R.; Coluccia, A.; La Regina, G.; De Martino, G.; Piscitelli, F.; Lavecchia, A.; Novellino, E.; Bergamini, A.; Ciaprini, C.; Sinistro, A.; Maga, G.; Crespan, E,; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 3172-3184.

Metal free mono- and 2,3-bis-sulfenylation of indoles in water with sodium sulfinates as a sulfur source

Changqing Liu, Jian Fan, Manyi Wu, Jiahui Chen, Yiming Zhao, Meihua Xie*

An iodine-PPh_3 mediated sulfenylation of indoles in water with stable and odorless sodium sulfinates as the sulfur source is described. The reaction could afford monosulfenylated indoles in moderate to excellent yields under metal free conditions. Moreover, double C-H sulfenylation of indoles at 2- and 3-positions has also been achieved by using excess sodium sulfinates under the optimized reaction conditions.