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A Metal-Free Sulfenylation and Bromosulfenylation of Indoles: Controllable Synthesis of 3-Arylthioindoles and 2-Bromo-3-arylthioindoles

Dayun Huang,[a] Jiuxi Chen,[a,*] Weixing Dan,[a] Jinchang Ding,[a,b] Miaochang Liu,[a] and Huayue Wu[a,*]

[a] College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, People's Republic of China
Fax: (+86)-577-8836-8280; phone: (+86)-577-8836-8280; e-mail: jiuxichen@wzu.edu.cn or huayuewu@wuz.edu.cn
[b] College of Light Industry, Wenzhou Vocational and Technical College, Wenzhou 325035, People's Republic of China

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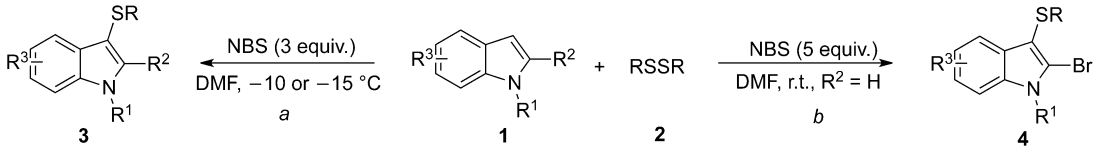
Abstract: An efficient metal-free sulfenylation of indoles with disulfides has been developed, leading to 3-arylthioindoles in moderate to excellent yields. Furthermore, bromosulfenylation of indoles with disulfides has been realized for the first time providing a new family of 2-bromo-3-arylthioindole derivatives in good yield by the one-pot construction of C–S and C–Br bonds. It is noteworthy that the system enables the use of both the RS moieties in RSSR and shows a broad functional group tolerance.

Keywords: 3-arylthioindoles; 2-bromo-3-arylthioindoles; bromosulfenylation; metal-free conditions; sulfenylation

In synthetic organic chemistry, the impact of organosulfur chemistry, especially in the area of heterocyclic chemistry, has led to a resurgence of interest in this field since sulfur-containing groups in heterocyclic compounds can serve as important auxiliary functions in synthetic sequences.[1] The substituted indole nucleus is prevalent in numerous natural products and is extremely important in medicinal chemistry.[2] Among the numerous indole derivatives known, 3-arylthioindole and its derivatives have recently attracted considerable attention due to their therapeutic value.[3] Most recently, Silvestri and co-workers reported that indolylarylsulfones have been used as HIV-1 non-nucleoside reverse transcriptase inhibitors.[4] The importance of 3-arylthioindoles has resulted in the development of two synthetic routes for their preparation. One route involves the introduction of substituents by direct sulfenylation of a preexisting indole ring,[5–8] whereas the other route involves the cyclization reactions of 2-alkynylanilines[9] or *N*,*N*-dialkyl-2-iodoanilines.[10] One of the first methods described above involves the direct sulfenylation of indoles using excess thiol.[5] However, the use of highly volatile and unpleasant smelling free thiols can lead to serious environmental and safety issues and can also limit the scalability of such processes in all of the reported methods. Undesirable side reactions resulting from the oxidation of thiols represent a further drawback to these methodologies. To minimize or eliminate the problems typically encountered, improved protocols for the synthesis of 3-arlythioindoles from the direct sulfenylation of indoles with disulfides using stoichiometric quantities of strong base[6a,b] or transition metal catalysts[6c,d] have been developed. Furthermore, the direct sulfenylation of indoles according to alternative methods have been reported using sulfenylating agents, such as *N*-thioarylphthalimides[7] and quinone mono-*O*,*S*-acetals.[8]

Recently, palladium[9a] and copper[9b] catalyzed annulations of 2-alkynylanilines with disulfides have been developed. Larock and co-workers reported that 3-arylthioindoles were synthesized by the Pd/Cu-catalyzed coupling of *N*,*N*-dialkyl-2-iodoanilines with terminal alkynes, followed by $(n\text{-Bu})_4$NI-induced electrophilic cyclization in the presence of arylsulfenyl chlorides.[10] However, the methods were restricted to the use of toxic and unstable sulfenyl halides as the reaction partners in the presence of a transition metal catalyst. As a result, the development of direct and concise methods for synthesizing 3-arylthioindoles under mild conditions using stable and readily available materials remains a challenging area for exploration.

In contrast, bromosulfenylation by the one-pot formation of C–S and C–Br bonds has been scarcely explored.[11] To the best of our knowledge, there are no



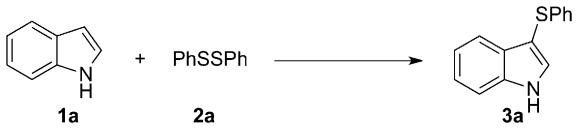
Scheme 1. Sulfenylation and bromosulfenylation of indoles with disulfides.

known reports of the bromosulfenylation of indoles in the literature.

As part of the continuing efforts in our laboratory towards the development of new methodologies using disulfides as sulfur sources,[12] we herein report a new route to 3-arylthioindoles (**3**) by regioselective sulfenylation of indoles (**1**) with disulfides (**2**) in the presence of *N*-bromosuccinimide (NBS) under metal-free conditions (Scheme 1, *a*). Furthermore, a new family of 2-bromo-3-arylthioindole (**4**) compounds has been synthesized by the one-pot construction of C–S and C–Br bonds (Scheme 1, *b*).

Initially, the reaction between indole (**1a**) and diphenyl disulfide (**2a**) was chosen as a model reaction to screen for the optimal reaction conditions (Table 1). Our investigation began with a model reaction run in the absence of NBS and no target product was detected (Table 1, entry 1). Next, the solvent effect was tested in the presence of NBS. Among all the solvents screened, traces or low yields of product were observed in CH_2Cl_2, 1,4-dioxane, acetone, CH_3CN, EtOH and DMSO (Table 1, entries 2–7). However, we were encouraged to find that the yield of the desired product 3-phenylthioindole (**3a**) was improved to 67% when DMF was employed as the solvent at room temperature (Table 1, entry 8). Encouraged by these promising results, we further adjusted the reaction parameters including reaction temperature and the loading amount of NBS. At the elevated temperatures, upon completion of the reaction, significant levels of side products were found in the product mixture, as indicated by TLC or GC-MS analysis. As a result, a decrease in the yield of **3a** was observed when the reaction was carried out at elevated temperatures (Table 1, entries 9 and 10). In contrast, we were pleased to discover that the yield of **3a** was dramatically improved at lower temperatures (Table 1, entries 11–15). The results indicated that the reaction could be conducted successfully to afford a 93% yield of **3a** in the presence of 3 equiv. of NBS at −15 °C (Table 1, entries 15–18).

Table 1. Screening for optimal reaction conditions.[a]



Entry	Temp. [°C]	Time [h]	Solvent	Yield [%][b]
1	25	0.5	DMF	NR[c]
2	25	0.5	CH_2Cl_2	trace
3	25	0.5	1,4-dioxane	trace
4	25	0.5	acetone	trace
5	25	0.5	CH_3CN	14
6	25	0.5	EtOH	17
7	25	0.5	DMSO	39
8	25	0.5	DMF	67
9	50	0.5	DMF	52
10	80	0.5	DMF	43
11	0	1.0	DMF	72
12	−5	1.5	DMF	78
13	−10	2.0	DMF	89
14	−20	2.5	DMF	92
15	−15	2.0	DMF	93
16	−15	2.0	DMF	63[d]
17	−15	2.0	DMF	81[e]
18	−15	2.0	DMF	89[f]

[a] *Reaction conditions*: **1a** (0.42 mmol), **2a** (0.2 mmol) and NBS (3 equiv., loading amount based on **2a**) in solvent (3 mL).
[b] Isolated yield.
[c] Without NBS (NR = no reaction).
[d] 2 equiv. of NBS.
[e] 2.5 equiv. of NBS.
[f] 3.5 equiv. of NBS.

With the optimized reaction conditions in hand, the scope and generality of the sulfenylation reaction was investigated using several structurally diverse indoles and disulfides. As shown in Table 2, a range of functional groups, including methyl, methoxy, fluoro, chloro, nitro and phenyl groups, was tolerated in this procedure.

First, we examined the reactions of indole (**1a**) with different disulfides and the results are summarized in Table 2. The electronic properties of the groups on the phenyl ring of indoles had little effect on the reaction. Generally, disulfides possessing electron-withdrawing groups gave the corresponding 3-arylthioindoles with higher yields than their electron-donating analogues (Table 2, entries 1–5). However, the steric hindrance had an obvious impact on the yields of the reaction. For example, the sulfenylation reactions of indole (**1a**) with the *para*-, *meta*- and *ortho*-fluorophenyl disulfides **2d**, **2e** and **2f**, respectively, were examined. Isolated yields of 96 and 91% were obtained for **3d** and **3e** were respectively, whereas the yield of **3f** was much lower at 62% (Table 2, entries 4-6).

Table 2. Sulfenylation of indoles with disulfides.[a]

Entry	Indole (**1**) R^1	R^2	R^3	Disulfide (**2**) R	Yield [%][b] (Product)
1	H	H	H (**1a**)	Ph (**2a**)	93 (**3a**)
2	H	H	H (**1a**)	*p*-MeC_6H_4 (**2b**)	84 (**3b**)
3	H	H	H (**1a**)	*p*-ClC_6H_4 (**2c**)	91 (**3c**)
4	H	H	H (**1a**)	*p*-FC_6H_4 (**2d**)	96 (**3d**)
5	H	H	H (**1a**)	*m*-FC_6H_4 (**2e**)	91 (**3e**)
6	H	H	H (**1a**)	*o*-FC_6H_4 (**2f**)	62 (**3f**)
7	CH_3	H	H (**1b**)	Ph (**2a**)	92 (**3g**)
8	CH_3	H	H (**1b**)	*p*-MeC_6H_4 (**2b**)	81 (**3h**)
9	CH_3	CH_3	H (**1b**)	*p*-FC_6H_4 (**2d**)	90 (**3i**)
10	H	CH_3	H (**1c**)	Ph (**2a**)	97[c] (**3j**)
11	H	CH_3	H (**1c**)	*p*-MeC_6H_4 (**2b**)	90[c] (**3k**)
12	H	CH_3	H (**1c**)	*p*-ClC_6H_4 (**2c**)	85[c] (**3l**)
13	H	CH_3	H (**1c**)	*p*-FC_6H_4 (**2d**)	93[c] (**3m**)
14	H	CH_3	H (**1c**)	*p*-$NO_2C_6H_4$ (**2g**)	98[c] (**3n**)
15	H	Ph	H (**1d**)	Ph (**2a**)	81[c] (**3o**)
16	H	H	5-CH_3 (**1e**)	Ph (**2a**)	92[d] (**3p**)
17	H	H	6-CH_3 (**1f**)	Ph (**2a**)	81[d] (**3q**)
18	H	H	7-CH_3 (**1g**)	Ph (**2a**)	93[d] (**3r**)
19	H	H	5-MeO (**1h**)	Ph (**2a**)	80[d] (**3s**)
20	H	H	6-F (**1i**)	Ph (**2a**)	68[d] (**3t**)

[a] *Reaction conditions*: **1** (0.42 mmol), **2** (0.2 mmol) and NBS (0.6 mmol) in DMF (3 mL) for 2 h at −15 °C.
[b] Isolated yield.
[c] At room temperature.
[d] At −10 °C.

Next, the sulfenylation reactions of disulfides with several substituted indoles were explored. Pleasingly, it was observed that *N*-containing heterocycle-substituted indoles, such as *N*-methylindole (**1b**) (Table 2, entries 7–9), 2-methylindole (**1c**) and 2-phenylindole (**1d**) (Table 2, entries 10–15) did not cause any difficulties for this transformation.

Benzo-substituted indoles (**1e**–**1h**) possessing electron-donating groups on the phenyl ring provided the corresponding 3-arylthioindoles (**3p**–**3s**) in good yields (Table 2, entries 16–19). However, benzo-substituted indoles containing an electron-withdrawing group on the benzene ring, such as 6-fluoroindole (**1i**), afforded the corresponding desired product **3t** in 68% yield (Table 2, entry 20), indicating a preference of the methodology for electron-donating groups on benzo-substituted indoles. To further confirm the structure of the product, an X-ray diffraction analysis was performed. The crystal structure of compound **3t** as a representative example is shown in Figure 1.[13a]

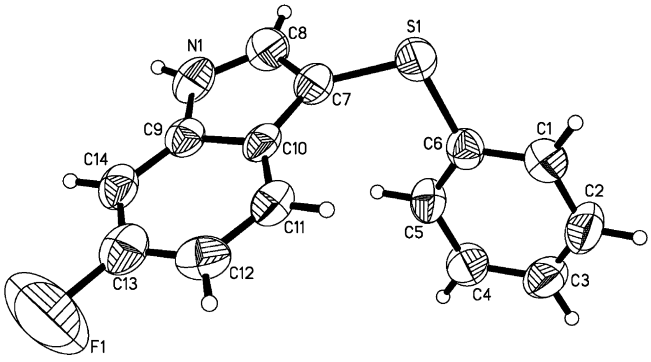


Figure 1. X-ray structure of **3t**.

NBS is well known as a highly useful and easy to handle brominating reagent.[14] Thus, we assumed that a new family of 2-bromo-3-arylthioindoles (**4**) could be generated by the sulfenylation and bromination reactions *via* the one-pot construction of C–S and C–Br bonds in the presence of NBS. In the following studies, the bromosulfenylation of 7-methylindole (**1g**) with diphenyl disulfide (**2a**) was conducted as a model reaction to screen for optimal reaction conditions. As expected, the product 2-bromo-7-methyl-3-phenylthioindole (**4f**) was observed by increasing the loading amount of NBS at elevated temperature. We found that the yield increased dramatically to 87% only

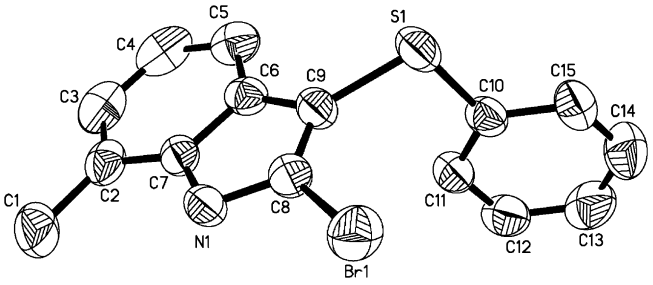
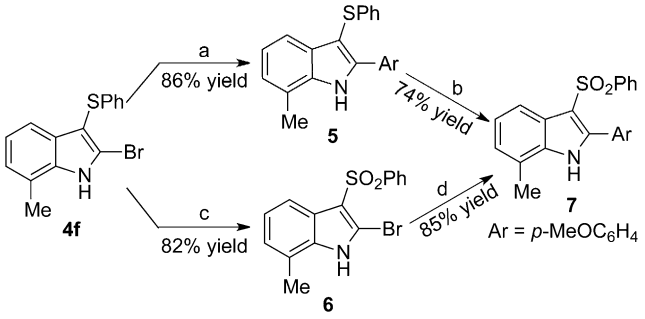


Figure 2. X-ray structure of **4f**.

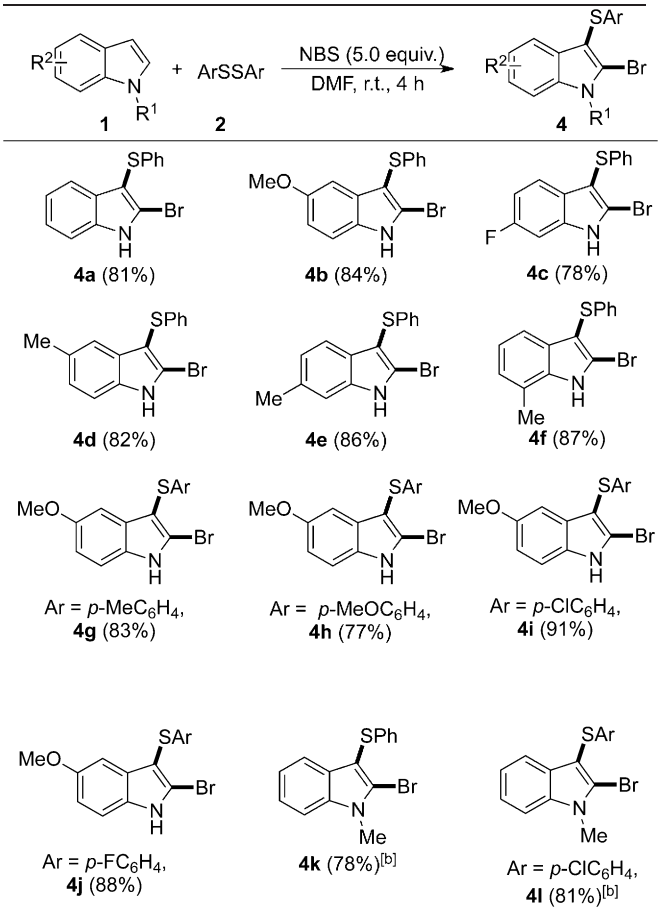


Scheme 2. Applications in organic synthesis. *Reaction conditions*: (a) or (d) *p*-$MeOC_6H_4B(OH)_2$ (1.3 equiv.), LiCl (2 equiv.), Na_2CO_3 (2.5 equiv.), $Pd(PPh_3)_4$ (0.04 equiv.), toluene/EtOH/H_2O = 1:1:1, 110 °C, 24 h; (b) or (d) *m*-CPBA (3 equiv.), $CHCl_3$, −10 °C, 30 min.

when 5 equiv. of NBS were added at room temperature. It is noteworthy that the structure of **4f** was unambiguously confirmed by an X-ray single-crystal diffraction analysis (Figure 2).[13b]

Similarly, we explored the synthesis of several structurally diverse 2-bromo-3-arylthioindoles (**4**). As shown in Table 3, the electronic properties of the groups on the phenyl ring had little impact on the reaction. The bromosulfenylation of indoles (**1**) with disulfides (**2**) proceeded smoothly to afford the corresponding desired 2-bromo-3-arylthioindoles (**4a**–**4j**) in good yields. It is noteworthy that *N*-substituted indoles, such as *N*-methylindole, also gave the corresponding desired products **4k** and **4l** in 78% and 81% yields, respectively.

Table 3. Bromosulfenylation of indoles with disulfides.[a]



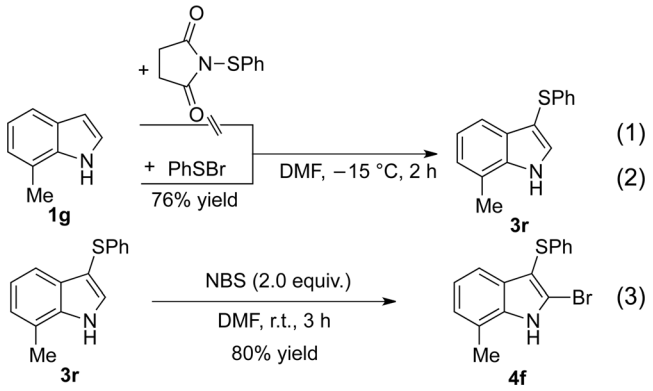
[a] *Reaction conditions*: **1** (0.45 mmol), **2** (0.2 mmol) and NBS (1.0 mmol) in DMF (3 mL) for 4 h at room temperature. Isolated yields in parentheses.

[b] For 6 h.

It is worthy of special mention that the above bromosulfenylation products are a new family of 2-bromo-3-arylthioindoles compounds **4** which leave the C−Br bond intact as an attractive handle for further synthetic elaboration. Similarly, the organosulfide compounds readily suffer oxidation. As shown in Scheme 2, the coupling and oxidation reactions of the product **4f**, as a representative example, were examined under the previously reported reaction conditions.[15,16] Pleasingly, 2-bromo-3-arylthioindole (**4f**) smoothly underwent Suzuki coupling with *p*-methoxyphenylboronic acid[15] and oxidation reaction of sulfide,[16] affording the corresponding products **5** and **6** in 86 and 82% yields, respectively. As a result, the two different methods have achieved their ultimate purpose in the synthesis of the potentially pharmacologically active[17] 2-aryl-3-phenylsulfonylindoles (**7**) from the 2-bromo-3-arylthioindoles **4** starting material.

Furthermore, the present synthetic route to 3-arylthioindoles and 2-bromo-3-arylthioindoles was successfully applied to the multigram-scale operations. For instance, the sulfenylation and bromosulfenylation of indole (21 mmol, 2.475 g) with diphenyl disulfide (10 mmol, 2.18 g) provided the desired products **3a** and **4a** in 85% and 76% yields, respectively.

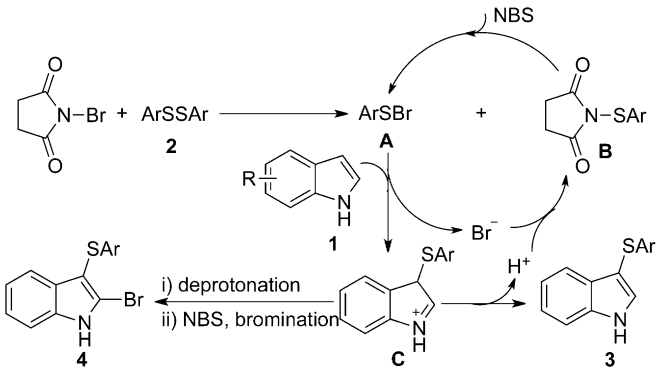
To elucidate the mechanism of the formation of 3-arylthioindoles and 2-bromo-3-arylthioindoles, the following control experiments were performed (Scheme 3). We found that 3-phenylthioindole was not detected by TLC or GC-MS analysis from the reaction of *N*-phenylthiosuccinimide[18] with **1g** [Eq.



Scheme 3. Control experiments.

(1)]. Benzenesulfenyl bromide was not isolated but prepared *in situ*, predominantly because benzenesulfenyl bromide is too reactive and unstable to be stored.[19] These results showed that the reaction of benzenesulfenyl bromide with **1g** proceeded smoothly to afford the corresponding desired 3-arylthioindole **3r** in 76% yield [Eq. (2)].[20] In contrast, 2-bromo-3-phenylthioindole (**4f**) was obtained in 84% yield by the bromination of 7-methyl-3-phenylthioindole (**3r**) [Eq. (3)].

On the basis of the above experimental results and relevant reports in the literature,[19,20] a possible mechanism for the formation of 3-arylthioindoles (**3**) and 2-bromo-3-arylthioindoles (**4**) was established as outlined in Scheme 4. First, the role of NBS as a promoter for the cleavage of disulfides **2** affords the reactive arylsulfenyl bromide (**A**) and *N*-(arylthio)succinimide (**B**). The arylsulfenyl bromide (**A**) species subsequently undergoes facile sulfenylation with indoles **1**, giving the desired product 3-arylthioindoles (**3**) along with a bromide anion. In the presence of NBS, the *N*-(arylthio)succinimide (**B**) can also be converted into the reactive arylsulfenyl bromide (**A**) by reaction with a bromide anion. As a result, the present process enables the use of both of the RS moieties in RSSR, which represents an atom-economical procedure for



Scheme 4. Plausible mechanism.

the synthesis of 3-arylthioindoles (**3**). Finally, bromination of 3-arylthioindoles (**3**) gave the corresponding 2-bromo-3-arylthioindoles (**4**).

In summary, we have developed a metal-free sulfenylation and bromosulfenylation of indoles with disulfides, namely a controllable synthesis of the corresponding 3-arylthioindoles and 2-bromo-3-arylthioindoles in moderate to excellent yields. The first reaction (sulfenylation) is a useful complement to the known literature protocols for preparing 3-arylthioindoles. The latter protocol (bromosulfenylation) gave a new family of 2-bromo-3-arylthioindoles and provides a simple method for the one-pot construction of C–S and C–Br bonds. Moreover, this technique also avoids the formation of 1 equiv. of RS waste that occurs when using a disulfide as the electrophilic sulfur source. Efforts to explore the detailed mechanism and further applications of the present system in other transformations using disulfide as a reaction partner are ongoing in our group.

Experimental Section

General Experimental Procedure for the Synthesis of 3-Arylthioindoles (3)

A mixture of indole **1** (0.42 mmol), disulfide **2** (0.2 mmol), and NBS (0.6 mmol) in DMF (3 mL) was stirred for 2 h at the respective temperature given in Table 2. After the completion of the reaction, as monitored by TLC and GC-MS analysis, the reaction mixture washed with water and extracted with ethyl acetate. The organic phase was separated and dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and the resulting residue was purified by flash column chromatography on silica gel (300–400 mesh) with petroleum ether-EtOAc as eluent to provide the products **3**.

General Experimental Procedure for the Synthesis of 2-Bromo-3-arylthioindoles (4)

A mixture of indole **1** (0.45 mmol), disulfide **2** (0.2 mmol), and NBS (1.0 mmol) in DMF (3 mL) was stirred for 4 h at room temperature as stated in Table 3. After the completion of the reaction, as monitored by TLC and GC-MS analysis, the reaction mixture washed with water and extracted with ethyl acetate. The organic phase was separated and dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and the resulting residue was purified by flash column chromatography on silica gel (300–400 mesh) with petroleum ether-EtOAc as eluent to provide the products **4**.

Acknowledgements

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