EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Iodine-Catalyzed Mono- and Bis-Sulfenylation of Indoles in PEG400 via a facile Microwave-Assisted Process

Authors: Rajjakfur Rahaman and Pranjit Barman

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701293

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701293

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201701293

WILEY-VCH

Iodine-Catalyzed Mono- and Bis-Sulfenylation of Indoles in PEG_{400} via a facile Microwave-Assisted Process

Rajjakfur Rahaman[a] and Pranjit Barman[a]*

Abstract: An iodine-catalyzed versatile green method for the synthesis of mono- and 2,3-bis-sulfenyl indoles has been presented. Various indoles can react with alkyl or aryl sodium sulfinates using hydrogen peroxide as an oxidizing agent in PEG_{400} under microwave conditions. This simple method enabled the rapid synthesis of mono- and 2,3-bis-sulfenylindoles with good to excellent yields under metal free conditions. The notable features of this protocol include environmental friendliness, odorless and short reaction time, easy operation, mild reaction conditions and excellent functional group tolerance.

Introduction

The sulfur bearing indoles represent a class of very important organosulfur heterocyclic compounds as they are present in many biologically and pharmaceutically important molecules.[1] According to known results, 3-sulfenylindoles have attracted researchers considerably because of their greater therapeutic value in the treatment of several diseases (Figure 1), such as cancer (**1**),[2] HIV (**2**),[3] vascular (**3**),[4] heart disease,[5] respiratory disorders (**4**),[6] bacterial infections[7] and allergies.[8] They have also inhibitory effect of both tubulin polymerization and of cancer cells.[9] In the last few decades, a number of significant methods have been developed for the synthesis of 3-sulfenylindoles. During the synthetic efforts a variety of thiolating reagents have been used as the reaction partners. For example, sulfenyl halides,[10] arylsulfonyl chlorides,[11] sulfonium salts,[12] quinine mono-O,S-acetals,[13] N-thioimides,[14] and sulfinic acids,[15] thiols,[16] disulfides,[17] sulfonyl hydrazides,[18] sulfinic acid salts,[19] and bunte salts.[20] Nevertheless, many of these sulfenylating reagents are either difficult to prepare, toxic, expensive or air and moisture sensitive. Moreover, the existing methodologies have some practical limitations such as long reaction time, harsh reaction conditions, high temperature, excess additives and transition metal catalysts, suffers from a narrow substrate scope or yield hazardous by-products.

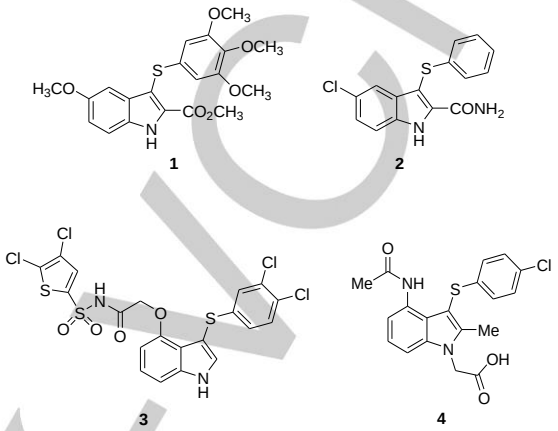


Figure 1. Some biologically active 3-arylthioindoles.

Although numerous methods have been successfully demonstrated to construct structurally diverse mono-sulfenyl indoles, double sulfenylation of indole has not been well documented to date. Moreover, methods that can accomplish bis-sulfenylation of indoles at 2- and 3-positions have remained elusive. Earlier, only 3-sulfenylation of indoles was done with the help of microwave-irradiation.[21] We also reported two protocol for the synthesis of 3-sulfenylindoles with sulfonyl hydrazides and sulfinic acids under microwave-irradiation.[22] However, with the same protocol bis-sulfenylated product was not observed. Previously, Hamel et al. first reported the bis-sulfenylation of indoles using sulfenyl chlorides as sulfur source.[23,10b] In addition Sangit Kumar and co-workers described persulfate mediated mono- and bis-sulfenylation of indoles with equivalent amount of iodine using disulfides as thiolating agent.[17h] Recently, Wang's group disclosed the double sulfenylation of indoles using thiols as sulfenylating agent with excess amount of iodine.[16i] While these methodologies rely on the harsh reaction conditions with excess catalyst loading and long reaction time to achieve bis-sulfenylation, developing new and straightforward methods enabling selective bis-sulfenylation of indole under milder conditions is highly desirable. Thiols and disulfides showed excellent activities in sulfenylation of indoles, but they have some practical limitations. Thiols are toxic, volatile and foul smelling, whereas disulfides are expensive and moisture sensitive. In addition, the main problem of using disulfide as the thiolating reagent is that disulfide needs to be prepared via oxidative coupling of thiols; an extra operational step which causes low atom economy.[24] Therefore, we wanted to explore a way to attain the desirable requirement of atom economy and relative safety. So, our aim is to develop a new methodology for the synthesis of 2,3-bis-sulfenylindoles which avoid limitations of existing methods (Scheme 1).

Recently, sodium arylsulfinates have been widely applied as the sulfur sources under reduction conditions for the

[a] Department of Chemistry, National Institute of Technology Silchar
Silchar 788010, India
E-mail: barmanpranjit@yahoo.co.in
http://www.nits.ac.in/departments/chem/chem.php

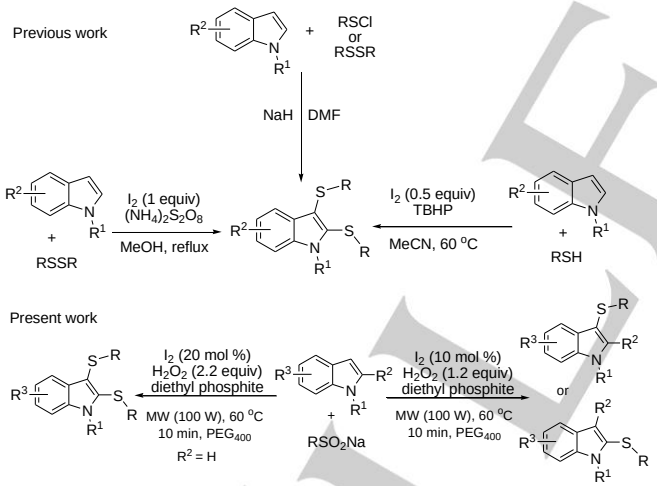
Supporting information for this article is given via a link at the end of the document.

construction of C–S bonds.[25] These are stable to air and moisture, odorless and easy-to-handle sulfur compounds; notably, the reaction generates environmentally benign by-products, as expected.

Microwave-assisted organic synthesis (MAOS) has attained the status of a new and fascinating discipline in the current green chemistry scenario.[26] Microwave-assisted synthesis has reduced reaction times dramatically. By reducing unwanted side reactions compared to conventional heating methods, it has increase product purities and yields.[27]

Molecular iodine and its salts recently have emerged as a promising alternative to catalyse oxidative sulfenylation due to their ease of handling, commercial availability, low toxicity, mild reaction conditions, high efficiency, and transition metal free features.[28] Several methodologies have demonstrated impressive advancements of I_2-catalyzed sulfenylation of heterocyclic compounds and C−C unsaturated bonds.[29]

Recently, some polymer media such as polyethylene glycol (PEG) are being used as new solvents in organic synthesis.[30] PEG_{400} is a viscous sustainable liquid soluble in water and many organic solvents. This medium has the advantage of being non-toxic, nonvolatile, non-irritating, odorless, and neutral and is used in a variety of pharmaceuticals and medications. In our effort to benign protocols, we have continuously tried to promote the use of non-toxic media and transition metal free conditions.[31] Herein, we wish to report a green protocol for the synthesis of mono- and bis-sulfenylation of indoles with sodium sulfinates under microwave irradiation (Scheme 1).



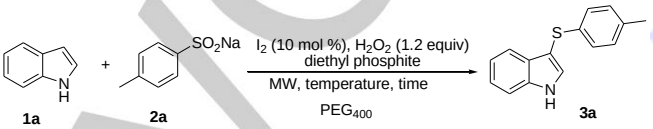
Scheme 1. Different routes for the synthesis of 2,3-bis-sulfenylation of indoles.

Results and Discussion

At the outset of this study, we employed indole **1a** sodium *p*-toluenesulfinate **2a** as the model substrate in the presence of hydrogen peroxide, diethyl phosphite as reagent and iodine as the catalyst in PEG_{400} (Table 1). When the reaction was carried out for 3 min, **3a** was obtained in only 50 % yield (entry 1). The reaction was carried out for reaction times of 3, 5, 8, and 10 min. The reaction delivered the desired product in almost quantitative yield in 10 min (Table 1, entry 4).

Afterward, we tested the effect of temperature and influence of the microwave irradiation power in various levels. However, at 60 °C and 100 W provided the desired product **3a** in 95 % yield. Increasing the power from 100 to 120 W did not affect the reaction since the product **3a** was obtained in the same yield (Table 1, entry 7). However, on decreasing the power to 80 W the yield decreased considerably (Table 1, entry 8). A temperature higher or lower than 60 °C was deleterious to the reaction (Table 1, entries 5 and 6). Moreover, we examined the reaction under conventional heating in oil bath and at room temperature giving the desired product **3a** only 50 % and 35 % but required a very long reaction time (Table 1, entries 9 and 10)

Table 1. Optimization of microwave parameters.[a]



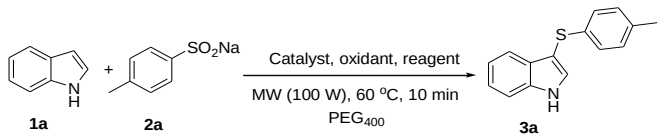
1a **2a** **3a**

Entry	MW (W)	*T* (°C)	Time (min)	Yield (%)[b]
1	100	60	3	50
2	100	60	5	65
3	100	60	8	80
4	**100**	**60**	**10**	**95**
5	100	70	10	80
6	100	50	10	70
7	120	60	10	95
8	80	60	10	60
9	-	60	24 h	50[c]
10	-	r.t.	48 h	35[d]

[a] Reaction conditions: indole **1a** (0.5 mmol), sodium *p*-toluenesulfinate **2a** (0.6 mmol), catalyst (0.05 mmol; 10 mol %), oxidant (0.6 mmol), reagent (1.5 equiv.), solvent (2 mL), 60 °C, 10 min. [b] Isolated yield. [c] Conventional heating (open vessel). [d] Reaction performed without microwave irradiation at room temperature (closed vessel).

After that, catalyst loading was screened to improve the yield of the product. An increase in the mol % of I_2 to 10 brought about a reasonable rise in the yield to 85 % (Table 2, entry 2). However, further increase of I_2 concentration did not enhance the yield of product (Table 2, entry 3). Higher yield was observed when **2a** was employed in slight excess amount (Table 2, entry 4). Different types of iodine containing catalysts including NIS, KI and nBu$_4$NI were investigated in the model reaction, and found that these catalysts hardly facilitate the reaction (Table 2, entries 12-14). Screening a range of oxidants such as DMSO, *t*BuOOH, $K_2S_2O_8$, and O_2 revealed that H_2O_2 is more effective than these oxidants (Table 2, entries 8-11). Moreover, there was no product formation observed in the absence of iodine and diethyl ether (Table 2, entries 15 and 17). The best molar ratio of indole/sodium *p*-toluenesulfinate was found to be 0.5/0.6 (Table 2). Therefore, the standard reaction conditions for the synthesis of 3-sulfenylindoles were obtained: indole **1a** (0.5 equiv.), sodium *p*-toluenesulfinate **2a** (0.6 equiv.), I_2 (0.05 equiv.; 10 mol %), diethyl phosphite (1.5 equiv.) in PEG_{400} (2 mL) at 60 °C and 100 W for 10 min.

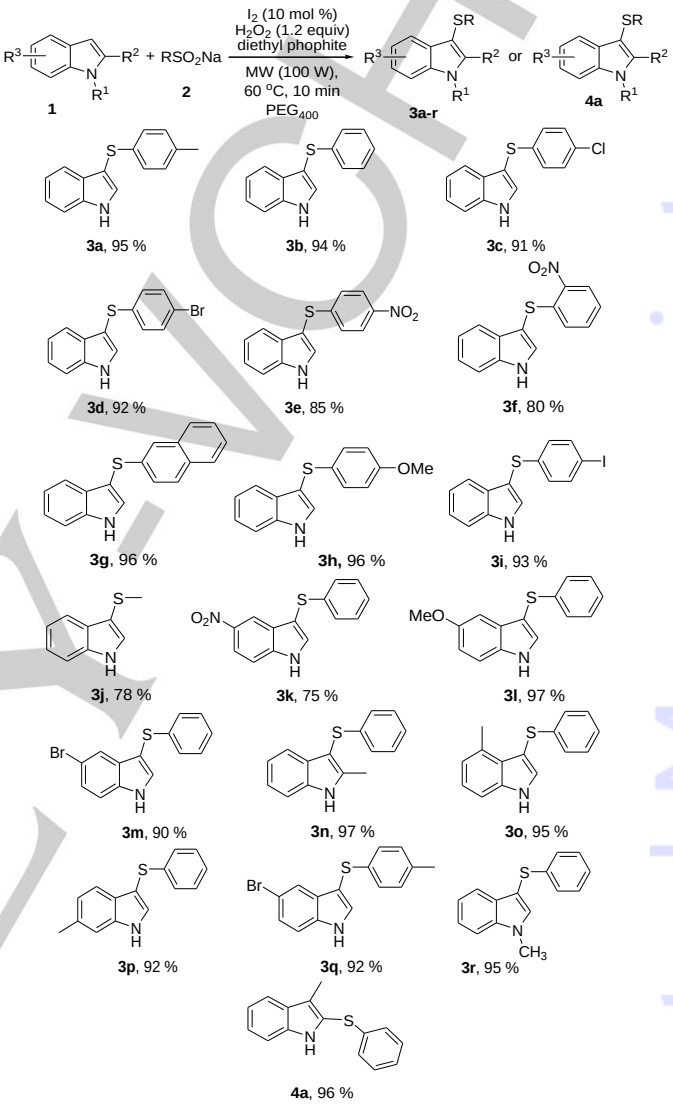
Table 2. Optimization of reaction conditions.[a]



Entry	1a/2a	Catalyst (Equiv)	Reagent (Equiv)	Oxidant (Equiv)	Yield (%)[b]
1	0.5/0.5	I_2 (0.025)	R1	H_2O_2 (0.6)	65
2	0.5/0.5	I_2 (0.05)	R1	H_2O_2 (0.6)	85
3	0.5/0.5	I_2 (0.1)	R1	H_2O_2 (0.6)	85
4	**0.5/0.6**	**I_2 (0.05)**	R1	**H_2O_2 (0.6)**	**95**
5	0.5/0.6	I_2 (0.05)	R2	H_2O_2 (0.6)	0
6	0.5/0.6	I_2 (0.05)	R3	H_2O_2 (0.6)	55
7	0.5/0.6	I_2 (0.05)	R4	H_2O_2 (0.6)	15
8	0.5/0.6	I_2 (0.05)	R1	DMSO (0.6)	75
9	0.5/0.6	I_2 (0.05)	R1	*t*BuOOH (0.6)	45
10	0.5/0.6	I_2 (0.05)	R1	$K_2S_2O_8$ (0.6)	35
11	0.5/0.6	I_2 (0.05)	R1	O_2	25
12	0.5/0.6	NIS (0.05)	R1	H_2O_2 (0.6)	55
13	0.5/0.6	KI (0.05)	R1	H_2O_2 (0.6)	50
14	0.5/0.6	*n*Bu_4NI (0.05)	R1	H_2O_2 (0.6)	45
15	0.5/0.6	–	R1	H_2O_2 (0.6)	0
16	0.5/0.6	I_2 (0.05)	R1	–	trace

[a] Reaction conditions: indole **1a**, sodium *p*-toluenesulfinate **2a**, catalyst (0.05 mmol; 10 mol %), oxidant (0.6 mmol), diethyl phosphite (1.5 equiv.), solvent (2 mL), 100 W, 60 °C, 10 min; R1 = $(C_2H_5O)_2POH$, R2 = $(PhO)_3P$, R3 = PhPO(OH)H, R4 = $PhPO(OH)_2$. [b] Isolated yield based on **1a**.

After establishing suitable reaction conditions (Table 2, entry 4), limitations and generality of the proposed method were investigated as shown in Scheme 2. First, the substrate scope of sodium sulfinates towards indole (Scheme 2, **3a–3i**) was examined. The electronic nature of the substrates was shown to have little influence on the reaction efficiency, and sodium sulfinates with electron-donating and electron-withdrawing groups were smoothly reacted with the indole to form their corresponding sulfenylated product in moderate to excellent yields (Scheme 2). The sodium sulfinates with electron-donating groups like –Me, –OMe on the phenyl ring gave the desired products with higher yields than those with electron-withdrawing groups (–Cl, –Br, and $–NO_2$). Sodium sulfinates with strong electron-withdrawing substituents such as $–NO_2$ group produced the desired 3-sulfenylindoles with lower yield (Scheme 2, **3e** and **3f**). To our delight, besides aromatic sodium sulfinates, aliphatic sodium sulfinates were also suitable for this transformation, which produces the corresponding products with moderate yield (Scheme 2, **3j**). Furthermore, we turned our attention to the scope of the different indoles derivatives with a variety of sodium sulfinates coupling partners (Scheme 2, **3k–3r**). Indoles bearing electron donating groups such as –Me and –OMe were produced the desired products in better yields than those with electron withdrawing groups like –Cl, –Br. Nevertheless, indoles with $–NO_2$ group gave poor results probably due to its strong electron withdrawing effect, which could deactivate the C3 position (Scheme 2, **3k**). As for substitution patterns, it was found that C2 substituted electron donating indoles delivered relatively higher yield compared with their 4- or 6-analogue (Scheme 2, **3n**–**3p**). *N*-Substituted indoles also gave the corresponding desired products with high yields without any difficulties (Scheme 2, **3s**). When C3 position occupied by alkyl groups such as –Me, C2 position of the indole ring becomes the active reaction site (Scheme 2, **4a**).

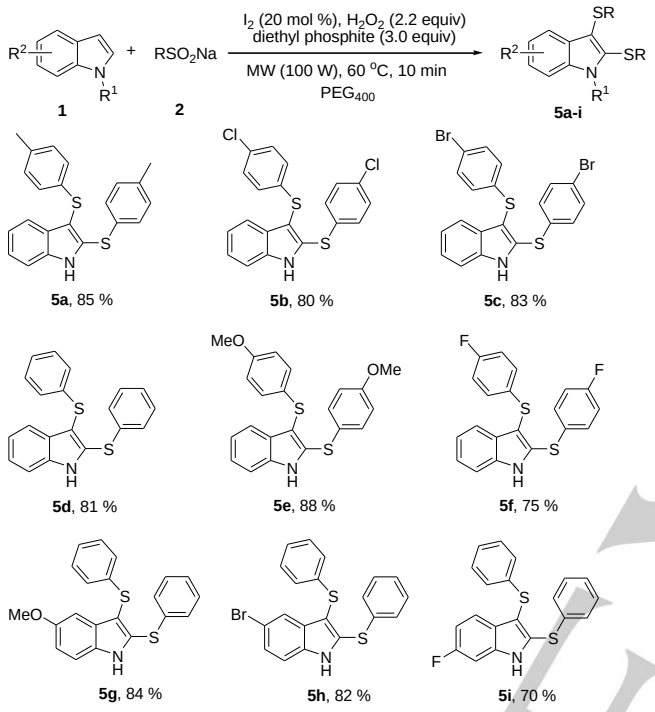


[a] Reaction conditions: indole **1** (0.5 mmol), sodium sulfinate **2** (0.6 mmol), I_2 (0.05 mmol; 10 mol %), H_2O_2 (0.6 mmol), diethyl phosphite (1.5 equiv.), PEG_{400} (2 mL), MW (100 W), 60 °C, 10 min.

Scheme 2. Substrates scope for the reaction of indoles **1** with thiols **2**.[a]

Assuming that 2,3-bis-sulfenyl indoles could be generated by a I_2/H_2O_2 mediated reaction in PEG_{400}. To testify our hypothesis, indole **1a** (0.5 equiv) and sodium *p*-toluenesulfinate **2a** (1.2 equiv) were selected as the model substrate in the presence of different kinds and loadings of oxidants and iodine-containing catalysts. Ultimately, 0.1 equiv (20 mol %) of I_2 and 2.2 equiv of H_2O_2 were found to be optimum for the maximum yield (85 %) of desired 2,3-bis-sulfenylindole **5a** (Scheme 3). It is noteworthy that both electron-donating and withdrawing groups were introduced into the 2,3-sulfenylation products by employing

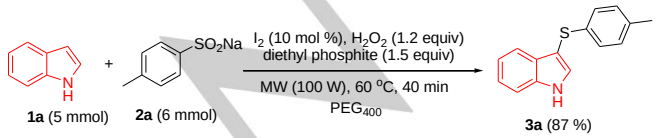
various sodium sulfinate and indoles bearing such groups on the aromatic ring to give the respective 2,3-bis-sulfenyl indoles in moderate to excellent yields (Scheme 3, **5a-i**). Sodium sulfinate containing electron-rich aromatic ring gave better result compared to electron-deficient aromatic ring (Scheme 3, **5a-f**). Substituents effects on indoles ring were also investigated. It was found that indoles with electron-donating groups delivered higher yield compared to the electron-withdrawing indoles (Scheme 3, **5g-i**).



[a] Reaction conditions: indole **1** (0.5 mmol), sodium sulfinate **2** (1.2 mmol), I_2 (0.1 mmol; 20 mol %), H_2O_2 (1.1 mmol), diethyl phosphite (3.0 equiv.), PEG_{400} (3 mL), MW (100 W), 60 °C, 10 min.

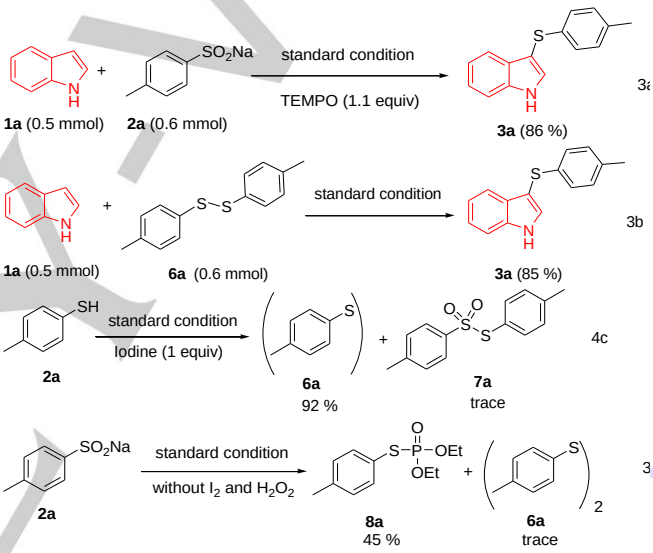
Scheme 3. 2,3-Bis-sulfenylation of indoles.[a]

Gram scale reaction was performed under the optimized reaction conditions as shown in scheme 4, which demonstrate practical usefulness of the new protocol. Thereby, the reaction between 1*H*-indole **1a** (5 mmol) and sodium *p*-toluenesulfinate **2a** (6 mmol) in the presence of I_2 (10 mol %) and H_2O_2 (6 mmol) afforded the desired product **3a** in 87 % yield, after 40 minute of reaction time.



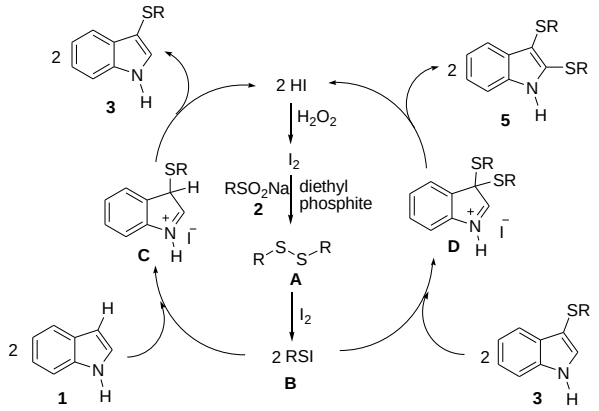
Scheme 4. Scale-up reaction between **1a** and **2a**.

To get insight into the reaction mechanism, some control experiments were performed (Scheme 5). First, a reaction between indole **1a** and sodium *p*-toluenesulfinate **2a** under the optimized conditions, in presence of TEMPO proceeds to form **3a** in 86 % yield, which indicates that the reaction does not proceed through a radical mechanism (Scheme 5a). Next, a reaction of disulfide **6a** with indole **1a** was performed under the standard conditions furnishing the sulfenylated product **3a** in 85 % yield (Scheme 5b). This experiment support that the reaction is proceed through a disulfide intermediate. The reaction of sodium *p*-toluenesulfinate **2a** under the standard conditions resulted in almost complete decomposition of the starting materials (Scheme 5c). The NMR study of this reaction has shown the formation of a disulfide intermediate (see the Supporting Information). However, the reaction of sodium *p*-toluenesulfinate **2a** without the use of iodine and H_2O_2, *S*-phenyl phosphorothioate **8a** was obtained as the major product (Scheme 5d).



Scheme 5. Control experiments.

On the basis of the literature precedence, control experiments and our observations, a plausible mechanism has been proposed (Scheme 6). Initially, disulfide **A** is generated from sodium sulfinate **2** in the presence of I_2 or H_2O_2 with diethyl phosphite.[32] Then, interaction between disulfide with I_2 may be formed the electrophilic RSI.[17f,18a,23a] The nucleophilic attack of indole **1** on sulfur atom of RSI can occur leading to the formation of an indolinium intermediate **C**. **C** undergoes aromatization to give the desired mono-sulfenylated indole **3** with the concomitant formation of HI. Thereafter, the second sulfenylation of indole occurs predominantly by initial addition at the 3-position of the indole ring, which leads to a 3,3-bis-substituted indolenium intermediate **D**.[17a,h,19a,b] Migration of one of the sulfide groups from 3 to 2 position forming an episulfonium species, and subsequent release of proton can give 2,3-bis-sulfenyl indole **5**. In the end, reaction between HI and H_2O_2 regenerates the catalyst I_2 with the formation of H_2O.



Scheme 6. Proposed reaction mechanism.

Conclusions

In summary, we have developed a very efficient and environment-friendly method for the synthesis of mono- and 2,3-bis-sulfenylindoles in a highly functional group compatible manner via I_2/H_2O_2-mediated reaction of indoles with odorless sodium sulfinates in PEG_{400}. The reaction is easy to perform and provides a convenient process for the synthesis of bioactive compound scaffolds. The synthetic protocol presented here has metal free, simple operation, short reaction time, and inexpensive I_2 catalyst, excellent yields, and broad substrate scope, which promises to be a greener alternative to earlier methods. Further studies on synthetic applications of this transformation are ongoing in our laboratories and the results will be disclosed in near future.

Experimental Section

To a mixture of indole **1** (0.5 mmol), sodium *p*-toluenesulfinate **2** (0.6 mmol), I_2 (0.05 mmol; 10 mol %), H_2O_2 (0.6 mmol), PEG_{400} (2 mL) were taken in a sealed glass tube and placed in the cavity of microwave apparatus. Then set parameters are as follows: microwave irradiation power 100 W, increasing time 5 min, target temperature 60 ºC, standing time 10 min, standing temperature 60 ºC. A maximum irradiation power of 100 W and 60 ºC temperature were applied for 10 min. When temperature reaches 60 ºC, the instrument automatically adjust to maintain a constant temperature. After 10 min (monitored through TLC), the reaction mixture was cooled to room temperature. Then diluted with distilled water and the organic layer was extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (15:1-9:1), which affords the desired product **3**.

Acknowledgements

The authors are thankful to the Director, NIT Silchar for financial support. MHRD, Govt. of India is acknowledged for the doctorate fellowship (MHRD GATE fellowship) received by R. F. R. Authors are also thankful to CSIR-NEIST Jorhat and SAIC, Tezpur University for spectral analysis.

Keywords: indole • mono-sulfenylation • 2,3-bis-sulfenylation • green solvent • microwave-assisted

[1] a) R. L. Sundberg, Indoles, Academic, London, **1996**; (b) A. R. Katritzky, A. F. Pozharskii, Handbook of Heterocyclic Chemistry, Pergamon, Oxford, **2000**; c) T. R. Garbe, M. Kobayashi, N. Shimizu, N. Takesue, M. Ozawa, H. Yukawa, *J. Nat. Prod.* **2000**, *63*, 596-598; d) A. Casapullo, G. Bifulco, I. Bruno, R. Riccio, *J. Nat. Prod.* **2000**, *63*, 447-451; e) B. Bao, Q. Sun, X. Yao, J. Hong, C. O. Lee, C. J. Sim, K. S. Im, J. H. Jung, *J. Nat. Prod.* **2005**, *68*, 711-715; f) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873-2920; g) M. C. van Zandt, M. L. Jones, D. E. Gunn, L. S. Geraci, J. H. Jones, D. R. Sawicki, J. Sredy, J. L. Jacot, A. T. Dicioccio, T. Petrova, A. Mischler, A. D. Podjarny, *J. Med. Chem.* **2005**, *48*, 3141-3152; h) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875-2911.

[2] G. La Regina, M. C. Edler, A. Brancale, S. Kandil, A. Coluccia, F. Piscitelli, E. Hamel, G. de Martino, R. Matesanz, J. F. D´ıaz, A. I. Scovassi, E. Prosperi, A. Lavecchia, E. Novellino, M. Artico, R. Silvestri *J. Med. Chem.* **2007**, *50*, 2865-2874.

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

[4] N. Zhou, W. Zeller, M. Krohn, H. Anderson, J. Zhang, E. Onua, A. S. Kiselyov, J. Ramirez, G. Halldorsdottir, T. Andresson, M. E. Gurney, J. Singh, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 123-128.

[5] C. D. Funk, Nat. Rev. *Drug Discovery* **2005**, *4*, 664-672.

[6] D. Ainge, M. Butters, E. Merifield, R. Ramakrishnan, R. N. Rayapati, P. R. Sharma, C. Thomson, PCT Int. Appl. WO 2011004182 A1, January *13*, **2011**.

[7] S. S. Khandekar, D. R. Gentry, G. S. Van Aller, P. Warren, H. Xiang, C. Silverman, M. L. Doyle, P. A. Chambers, A. K. Konstantinidis, M. Brandt, R. A. Daines, J. T. Lonsdale, *J. Biol. Chem.* **2001**, *276*, 30024-30030.

[8] P. C. Unangst, D. T. Connor, S. R. Stabler, R. J. Weikert, M. E. Carethers, J. A. Kennedy, D. O. Thueson, J. C. Chestnut, R. L. Adolphson, M. C. Conroy, *J. Med. Chem.* **1989**, *32*, 1360-1366.

[9] a) G. La Regina, M. C. Edler, A. Brancale, S. Kandil, A. Coluccia, F. Piscitelli, E. Hamel, G. de Martino, R. Matesanz, J. F. D´ıaz, A. I. Scovassi, P. Ennio, A. Lavecchia, E. Novellino, M. Artico, R. Silvestri, *J. Med. Chem.* **2007**, *50*, 2865-2874; b) G. de Martino, M. C. Edler, G. La Regina, A. Coluccia, M. C. Barbera, D. Barrow, R. I. Nicholson, G. Chiosis, A. Brancale, E. Hamel, M. Artico, R. Silvestri, *J. Med. Chem.* **2006**, *49*, 947-954; c) G. de Martino, G. La Regina, A. Coluccia, M. C. Edler, M. C. Barbera, A. Brancale, E. Wilcox, E. Hamel, M. Artico, R. Silvestri, *J. Med. Chem.* **2004**, *47*, 6120-6123.

[10] a) M. Raban, L.-J. Chern, *J. Org. Chem.* **1980**, *45*, 1688-1691; b) P. Hamel, *J. Org. Chem.*, **2002**, *67*, 2854-2858.

[11] a) Q. Wu, D. Zhao, X. Qin, J. Lan, J. You, *Chem. Commun.* **2011**, *47*, 9188-9190; b) X.-F. Xia, S.-L. Zhu, D. Wang, Y.-M. Liang, *Adv. Synth. Catal.* **2017**, *359*, 859-865; c) Y. Zheng, F.-L. Qing, Y. Huang, X.-H. Xu, *Adv. Synth. Catal.* **2016**, *358*, 3477-3481; d) Z. Wu, Y.-C. Li, W.-Z. Ding T. Zhu, S.-Z. Liu, X. Ren, L.-H. Zou, *Asian J. Org. Chem*. **2016**, 5, 625-628.

[12] S. Jain, K. Shukla, A. Mukhopadhyay, S. N. Suryawanshi, D. S. Bhakuni, *Synth. Commun.* **1990**, *20*, 1315-1320.

[13] a) M. Matsugi, K. Murata, K. Gotanda, H. Nambu, G. Anilkumar, K. Matsumoto, Y. Kita, *J. Org. Chem.* **2001**, *66*, 2434-2441; b) M. Matsugi, K. Murata, H. Nambu, Y. Kita, *Tetrahedron Lett.* **2001**, *42*, 1077-1080.

[14] a) M. Tudge, M. Tamiya, C. Savarin, G. R. Humphrey, *Org. Lett.* **2006**, *8*, 565-568; b) E. Marcantoni, R. Cipolletti, L. Marsili, S. Menichetti, R. Properzi, C. Viglianisi, *Eur. J. Org. Chem.* **2013**, 132-140; c) C. C.

Silveira, S. R. Mendes, L. Wolf, G. M. Martins, *Tetrahedron Lett.* **2010**, *51*, 2014-2016.

[15] Liu, C.; Ding, L. *Org. Biomol. Chem.* **2015**, *13*, 2251-2254.

[16] a) Y. Maeda, M. Koyabu, T. Nishimura, S. Uemura, *J. Org. Chem.* **2004**, *69*, 7688-7693; b) K. M. Schlosser, A. P. Krasutsky, H. W. Hamilton, J. E. Reed, K. Sexton, *Org. Lett.* **2004**, *6*, 819-821; c) J. S. Yadav, B. V. S. Reddy, Y. J. Reddy, K. Praneeth, *Synthesis* **2009**, 1520-1524; d) J. A. Campbell, C. A. Broka, L. Gong, K. A. M. Walker, J.-H. Wang, *Tetrahedron Lett.* **2004**, *45*, 4073-4075; e) J. S. Yadav, B. V. S. Reddy, Y. J. Reddy, *Tetrahedron Lett.* **2007**, *48*, 7034-7037; f) G. Wu, J. Wu, J. Wu, L. Wu, *Synth. Commun.* **2008**, *38*, 1036-1043; g) Y. Liu, Y. Zhang, C. Hu, J.-P. Wana, C. Wen, *RSC Adv.* **2014**, *4*, 35528-35530; h) H. Zhang, X. Bao, Y. Song, J. Qu, B. Wang, *Tetrahedron* **2015**, *71*, 8885-8891; i) S. Yi, M. Li, W. Mo, X. Hu, B. Hu, N. Sun, L. Jin, Z. Shen, *Tetrahedron Lett*. **2016**, *57*, 1912-1916; j) T. Gensch, F. J. R. Klauck, F. Glorius, *Angew. Chem. Int. Ed*. **2016**, *55*, 11287-11291; k) P. Wang, S. Tang, P. Huang, A. Lei, *Angew. Chem. Int. Ed*. **2017**, *56*, 3009-3013; l) S. Song, Y. Zhang, A. Yeerlan, B. Zhu, J. Liu, N. Jiao, *Angew. Chem. Int. Ed*. **2017**, *56*, 2487-2491; m) F. Xiao, J. Tian, Q. Xing, H. Huang, G.-J. Deng, Y. Liu, *ChemistrySelect* **2017**, *2*, 428-431; n) Z.-H. Yang, Y.-L. An, Y. Chen, Z.-Y. Shao, S.-Y. Zhao, *Adv. Synth. Catal.* **2016**, *358*, 3869-3875.

[17] a) X.-L. Fang, R.-Y. Tang, P. Zhong, J.-H. Li, *Synthesis* **2009**, 4183-4189; b) Z. Li, J. Hong, X. Zhou, *Tetrahedron* **2011**, *67*, 3690-3697; c) L.-H. Zou, J. Reball, J. Mottweiler, C. Bolm, *Chem. Commun.* **2012**, *48*, 11307-11309; d) W. Ge, Y. Wei, *Synthesis*, 2012, 934-940; e) W. Ge, Y. Wei, *Green Chem.* **2012**, *14*, 2066-2070; f) P. Sang, Z. Chen, J. Zoua, Y. Zhang, *Green Chem.* **2013**, *15*, 2096-2100; g) Ch. D. Prasad, S. Kumar, M. Sattar, A. Adhikary, S. Kumar, *Org. Biomol. Chem.* **2013**, *11*, 8036-8040; h) L.-M. Ye, J. Chen, P. Mao, X.-J. Zhang, M. Yan, *Tetrahedron Lett*. **2017**, *58*, 2743-2746; i) J. Sun, D. Z. Negrerie, Y. Du, *Adv. Synth. Catal.* **2016**, *358*, 2035-2040.

[18] a) F.-L. Yang, S.-K. Tian, *Angew. Chem. Int. Ed.* **2013**, *52*, 4929-4932; b) F.-L. Yang, Y. Gui, B.-K. Yu, Y.-X. Jin, S.-K. Tian, *Adv. Synth. Catal.* **2016**, *358*, 3368-3372; c) J.-P. Wan, S. Zhong, Y. Guo, L. Wei, *Eur. J. Org. Chem.* 10.1002/ejoc.201700910.

[19] P. Katrun, S. Hongthong, S. Hlekhlai, M. Pohmakotr, V. Reutrakul, D. Soorukram, T. Jaipetchb, C. Kuhakarn, *RSC Adv.* **2014**, *4*, 18933-18938.

[20] a) J. Li, Z.-J. Cai, S.-Y. Wang, S.-J. Ji, *Org. Biomol. Chem.* **2016**, *14*, 9384-9387; (b) H. Qi, T. Zhang, K. Wan, M. Luo, *J. Org. Chem.* **2016**, *81*, 4262-4268.

[21] a) W. Fan, Z. Yang, B. Jiang, G. Li, *Org. Chem. Front.*, **2017**, *4*, 1091-1102; b) J. B. Azeredo, M. Godoi, G. M. Martins, C. C. Silveira, A. L. Braga, *J. Org. Chem.* **2014**, *79*, 4125-4132; c) G. La Regina, V. Gatti, V. Famiglini, F. Piscitelli, R. Silvestri, *ACS Comb. Sci.* **2012**, *14*, 258-262.

[22] a) R. Rahaman, N. Devi, K. Sarma, P. Barman, *RSC Adv*. **2016**, *6*, 10873-10879; b) R. Rahaman, N. Devi, J. R. Bhagawati, P. Barman, *RSC Adv*. **2016**, *6*, 18929-18935.

[23] P. Hamel, P. Preville, *J. Org. Chem.* **1996**, *61*, 1573-1577.

[24] Y. Liu, H. Wang, C. Wang, J.-P. Wan and C. Wen, *RSC Adv.* **2013**, *3*, 21369-21372.

[25] a) F. Xiao, H. Xie, S. Liu, G.-J. Deng, *Adv. Synth. Catal.* **2014**, *356*, 364-368; b) Y.-m. Lin, G.-p. Lu, C. Cai, W.-b. Yi, *Org. Lett.*, **2015**, *17*, 3310-3313; c) Y. Gao, Y. Gao, X. Tang, J. Peng, M. Hu, W. Wu, H. Jiang, *Org. Lett.*, **2016**, *18*, 1158-1161; d) X. Xiao, M. Feng, X. Jiang, *Chem. Commun.*, **2015**, *51*, 4208-4211; e) Y. Ding, W. Wu, W. Zhao, Y. Li, P. Xie, Y. Huang, Y. Liu, A. Zhou, *Org. Biomol. Chem.* **2016**, *14*, 1428-1431; f) Y.-m. Lin, G.-p. Lu, G.-x. Wang, W.-b. Yi, *Adv. Synth. Catal.* **2016**, *358*, 4100-4105; g) Y.-m. Lin, G.-p. Lu, G.-x. Wang, W.-b. Yi, *J. Org. Chem*., **2017**, *82*, 382-389; h) Y. Yang, W. Li, C. Xia, B. Ying, C. Shen, P. Zhang, *ChemCatChem* **2016**, *8*, 304-307; i) Z.-b. Xu, G.-p. Lu, C. Cai, *Org. Biomol. Chem.* **2017**, *15*, 2804-2808; j) Y. Li, F. Zhu, Z. Wang, X.-F. Wu, *Chem. Asian J.* **2016**, *11*, 3503-3507.

[26] a) J. D. Moseley, C. O. Kappe, *Green Chem.* **2011**, *13*, 794-806; b) B. Gutmann, A. M. Schwan, B. Reichart, C. Gspan, F. Hofer, C. O. Kappe, *Angew. Chem. Int. Ed.* **2011**, *50*, 7636-7640.

[27] Microwave Assisted Organic Synthesis, ed. J. P. Tierney, P. Lidstroem, Blackwell, Oxford, **2005.**

[28] a) X. Li, X. Xu, C. Zhou, *Chem. Commun.* **2012**, *48*, 12240-12242; b) X. Li, X. Xu, P. Hu, X. Xiao, C. Zhou, *J. Org. Chem.* **2013**, *78*, 7343-7348; c) X. Li, X. Xu, Y. Tang, *Org. Biomol. Chem.* **2013**, *11*, 1739-1742; d) F.-L. Yang, S.-K. Tian, *Angew. Chem. Int. Ed.* **2013**, *52*, 4929-4932; e) X. Li, X. Xu, X. Shi, *Tetrahedron Lett.* **2013**, *54*, 3071-3074; f) J. Zhang, Y. Shao, H. Wang, Q. Luo, J. Chen, D. Xu, X. Wan, *Org. Lett.* **2014**, *16*, 3312-3315; g) S. Tang, Y. Wu, W. Liao, R. Bai, C. Liu, A. Lei, *Chem. Commun.* **2014**, *50*, 4496-4499; h) L. T. Silva, J. B. Azeredo, S. Saba, J Rafique, A. J. Bortoluzzi, A. L. Braga, *Eur. J. Org. Chem.* **2017**, *32*, 4740–4748.

[29] a) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner, B. J. Nachtsheim, *Org. Lett*. **2011**, *13*, 3754-3757; b) M. Lamani, K. R. Prabhu, *J. Org. Chem*. **2011**, *76*, 7938-7944; c) J.-S. Tian, K. W. J. Ng, J.-R. Wong, T.-P. Loh, *Angew. Chem. Int. Ed*. **2012**, *51*, 9105-9109; d) T. Nobuta, N. Tada, A. Fujiya, A. Kariya, T. Miura, A. Itoh, *Org. Lett.* **2013**, *15*, 574-577; e) P. Finkbeiner, B. J. Nachtsheim, *Synthesis* **2013**, 979-999; f) G. Wang, Q.-Y. Yu, S.-Y. Chen, X.-Q. Yu, *Org. Biomol. Chem*. **2014**, *12*, 414-417; g) X.-F. Wu, J.-L. Gong, X. Qi, *Org. Biomol. Chem.* **2014**, *12*, 5807-5817; h) Y. Lv, Y. Li, T. Xiong, Y. Lu, Q. Liu, Q. Zhang, *Chem. Commun*. **2014**, *50*, 2367-2369; i) Q. Jiang, B. Xu, A. Zhao, J. Jia, T. Liu, C. Guo, *J. Org. Chem*. **2014**, *79*, 8750-8756; j) S. Tang, K. Liu, Y. Long, X. Gao, M. Gao, A. Lei, *Org. Lett*. **2015**, *17*, 2404-2407; k) D. Zhao, Q. Shen, J.-X. Li, *Adv. Synth. Catal*. **2015**, *357*, 339-344.

[30] a) D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345-3384; b) T. J. Dickerson, N. N. Reed, K. D. Janda, *Chem. Rev.* **2002**, *102*, 3325-3344; c) G. Chen, J. Weng, Z. Zheng, X. Zhu, Y. Cai, J. Cai, Y. Wan, *Eur. J. Org. Chem.* **2008**, 3524-3528; d) M. Huang, L. Wang, X. Zhu, Z. Mao, D. Kuang, Y. Wan, *Eur. J. Org. Chem.* **2012**, 4897-4901; e) U. P. Singh, *Synlett* **2012**, 2721-2722; f) E. Colacino, J. Martinez, F. Lamaty, L. S. Patrikeeva, L. L. Khemchyan, V. P. Ananikov, I. P. Beletskaya, *Coord. Chem. Rev.* 2012, *256*, 2893-2920; g) L. Ning, L. Chun, R. Xiaofeng, J. Zilin, *Adv. Chem. Res.* **2012**, *16*, 125-131. Publisher (Nova Science Publishers, Inc); h) R. Turgis, I. Billault, S. Acherar, J. Augé, M.-C. Scherrmann, *Green Chem.* **2013**, *15*, 1016-1029; i) M. S. Rao, M. Haritha, N. Chandrasekhar, M. V. B. Rao, M. Pal, *Tetrahedron Lett.* **2014**, *55*, 1660-1663; j) N. Mangarao, G. M. Basha, T. Ramu, R. Srinuvasarao, S. Prasanthi, V. Siddaiah, *Tetrahedron Lett.* **2014**, *55*, 177-179; k) M.-A. Hiebel, S. B. Raboin, *Green Chem.* **2015**, *17*, 937-944.

[31] a) R. Rahaman, N. Devi, P. Barman, *Tetrahedron Lett.* **2015**, *56*, 4224-4227; b) N. Devi, R. Rahaman, K. Sarma, P. Barman, *Eur. J. Org. Chem.* **2016**, 384-388; c) R. Rahaman, P. Barman, *Synlett* **2017**, 684-690; d) N. Devi, R. Rahaman, K. Sarma, T. Khan, P. Barman, *Eur. J. Org. Chem.* **2017**, 1520-1525.

[32] H. W. Pinnick, M. A. Reynolds, R. T. McDonaldJr, W. D. Brewster, *J. Org. Chem.* **1980**, *45*, 930-932.

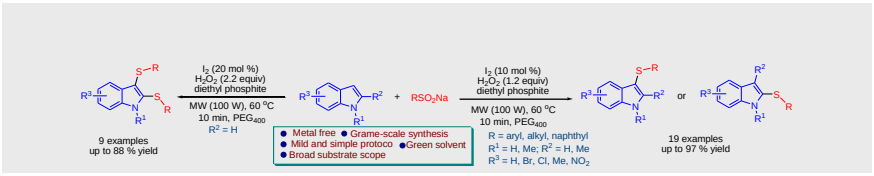
10.1002/ejoc.201701293

WILEY-VCH

Entry for the Table of Contents

Layout 2:

COMMUNICATION



Mono-sulfenylation and 2,3-Bis-sulfenylation

*Rajjakfur Rahaman, Pranjit Barman**

Page No. – Page No.

Iodine-Catalyzed Mono- and Bis-Sulfenylation of Indoles in PEG_{400} via a facile Microwave-Assisted Process

An I_2-catalyzed versatile green method for the synthesis of mono- and 2,3-bis-sulfenyl indoles with sodium sulfinates using H_2O_2 in PEG_{400} under microwave conditions has been presented. This simple method enabled the rapid synthesis of mono- and 2,3-bis-sulfenylindoles with good to excellent yields. The notable features of this protocol include environmental friendliness, odorless and short reaction time, easy operation and mild reaction conditions.