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Metal free sulfenylation and bis-sulfenylation of indoles: persulfate mediated synthesis†

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A method which avoids metal and halogen for the synthesis of 3-arylthioindoles from indoles and diaryl disulfides using ammonium persulfate in methanol has been presented. Moreover, double C–H sulfenylation of indoles at 2 and 3-positions has also been achieved using iodine and ammonium persulfate.

Thiolated indole moieties are an important class of organo-sulfur heterocyclic compounds having a greater therapeutic value in the treatment of HIV, cancer, cardiovascular, and bacterial diseases.[1,2] Among the various indole derivatives known, 3-arylthioindoles have attracted considerable interest (Chart 1).

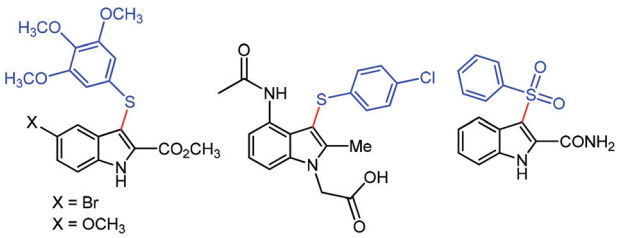

Chart 1 Biologically important 3-arylthioindoles.

As a result two synthetic routes have been developed to construct thiolated indoles. One route involves the introduction of substituents by direct sulfenylation of an existing indole ring,[3–13] whereas the other route involves the cyclization reactions of 2-alkynylanilines[14] or *N*,*N*-dialkyl-2-iodoanilines.[15] Most of the methodologies derived from the first synthetic route involve the usage of high boiling solvents such as DMSO[3] and DMF,[4] a strong base,[5] and the presence of transition metal catalysts[6] or halogenating reagents *N*-bromosuccinimide[4b] and trichloroisocyanuric acid[6e] to accomplish sulfenylation in indoles using arylsulfenyl halides,[7,13] aryl/alkyl thiols,[5a,6a,b,8] diaryl disulfides,[3,4c,6c,9] aryl-*N*-thioimides,[10] arylsulfonium salts,[11] and sulfonyl hydrazides[12] as a source of the organo-sulfur moiety. Most of the sulfur sources are either difficult to prepare or air and moisture sensitive and expensive.

The development of a methodology which involves mild reaction conditions, readily available reagents and substrates will be highly desirable for the synthesis of sulfenyl indoles. Mild reaction conditions enable installation of a wide range of functional groups such as ether, bromide, and most importantly functionalities having acidic protons such as hydroxyl, amine, and carboxylic acid which could be helpful in late stage transformation/functionalization for the synthesis of substituted sulfenyl indoles. Although many methods have been developed to construct sulfenyl indoles, synthesis of arylthiolated indoles having acidic proton functional groups (OH, NH_2, CO_2H *etc.*) has not been well documented to date. Also a methodology which can cause double C–H sulfenylation in indoles will be interesting because the double C–H sulfenylation in indoles has remained elusive. Recently, our group has launched a program to synthesize organo ethers, sulfur, selenium and tellurium compounds using new benign reaction conditions and reagents.[16] Here, in continuation of our work on organochalcogen chemistry, we present an economical and mild methodology for the regioselective synthesis of diversely substituted 3-sulfenyl indoles. Moreover, double C–H thiolation in indoles has been performed to give 2,3-bis-sulfenyl indoles.

Phenyl disulfide and indole were chosen as substrates in the presence of various oxidants such as hydrogen peroxide, *tert*-butyl hydroperoxide, potassium, and ammonium persulfates in methanol at reflux temperature to screen for the optimal reaction conditions (entries 1–5, Table 1). Among these, ammonium persulfate (2 equiv.) gave good yield of the sulfenylated product **1**. Increasing or decreasing oxidant loading resulted in a poor yield of **1**. A number of solvents like THF, dichloromethane, CH_3CN, DMF, and DMSO were examined; nonetheless, better yield could not be obtained (entries 6–10, Table 1).

With the optimized reaction conditions in hand, a variety of indoles and diaryl disulfides were tested to determine the scope and limitations of this method. Results presented in

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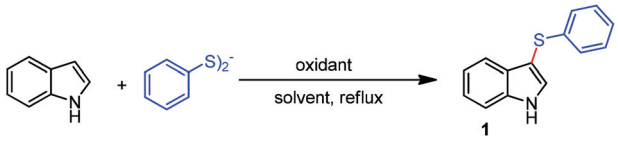
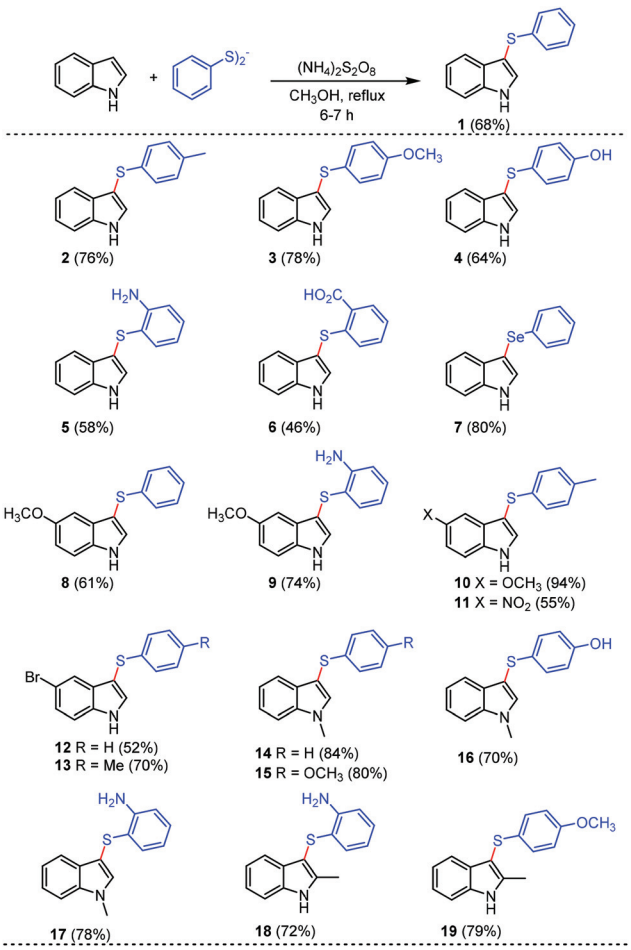
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra. CCDC 952234 (**21**) and 953902 (**11**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob41601a

Table 1 Optimization of the sulfenylation of indole[a]



Entry	Oxidant	Yield (%)	Entry	Solvent[b]	Yield (%)
1	H_2O_2	20	6	THF	22
2	^tBuOOH	25	7	CH_2Cl_2	35
3	Oxone	47	8	CH_3CN	43
4	$K_2S_2O_8$	61	9	DMF	Trace
5	$(NH_4)_2S_2O_8$	68	10	DMSO	Trace

[a] The reaction was carried out on a 1 mmol scale using 2 equiv. of indole, 1 equiv. of phenyl disulfide, and 2 equiv. of oxidant in 5 mL of CH_3OH at reflux (70 °C) temperature, unless otherwise noted. [b] 5 mL of solvent is used instead of CH_3OH.



Scheme 1 Synthesis of monosulfenyl indoles. The reaction was carried out on a 1 mmol scale using 2 equiv. of indole, 1 equiv. of phenyl disulfide, and 2 equiv. of $(NH_4)_2S_2O_8$ in 5 mL of CH_3OH at reflux (70 °C) temperature, unless otherwise noted.

Scheme 1 demonstrate that a series of diaryl disulfides underwent smooth transformations to give the structurally diverse sulfenyl indoles **1–19** in 46–94% yield.

At first, we examined the reaction of indole with substituted diaryl disulfides. Disulfides having electron donating groups like *para*-methyl, *para*-methoxy, *ortho*-amino, and *para*-hydroxy gave the respective sulfenylated products (**2–5**) with indole in good yields. Carboxylic acid containing diaryl disulfide also underwent this reaction smoothly with indole, resulting in 46% yield of **6**. Synthesis of hydroxyl substituted 3-arylthioindoles has not been explored to date, whereas amino and acid substituted 3-arylthioindoles are scarcely found in the literature.[13k,17] The present mild methodology gives access to a series of hydroxyl, amino, and acid substituted sulfenyl indoles **4–6**, **9** and **16–18**. Phenyl diselenide also reacted with indole under optimized reaction conditions in methanol to produce 3-selenylated indole **7** in 80% yield.

Next, the sulfenylation reaction of diaryl disulfides with variously substituted indoles was explored. The electronic properties of the groups attached to the indole have little effect on the outcome of the reaction as the yields of the sulfenyl indoles **8–19** remained nearly the same. Indoles with electron donating methoxy group and electron withdrawing 5-nitro and 5-bromo groups reacted with diaryl disulfides to give the sulfenyl indoles **8–13** in 52–94% yield. The structure of the synthesized 5-nitro-3-(*p*-tolylthio)-1*H*-indole **11** was also established by an X-ray single crystal structure study (Fig. 1).

Similarly, the sulfenylation reaction of substituted indoles with substituted disulfides was tested. *N*-Methyl indole reacted with *para*-methoxy, *para*-hydroxy, and *ortho*-aminophenyl disulfides to afford the sulfenyl indoles **14–17** in 70–84% yield. 2-Methyl indole also reacted smoothly with *para*-methoxy and *ortho*-aminophenyl disulfides resulting in the respective products **18** and **19** in 72 and 79% yield, respectively.

Assuming that 2,3-bis-sulfenyl indoles could be generated by a persulfate mediated reaction in methanol, we have conducted a model reaction with 1 mmol of phenyl disulfide, 1 mmol of indole and 2 mmol of ammonium persulfate under optimized reaction conditions. Unfortunately, varying the equiv. of persulfate and/or disulfide did not provide any 2,3-bis-sulfenyl indole. Interestingly, addition of iodine to the reaction mixture provided 2,3-bis-sulfenyl indole **20**. Varying

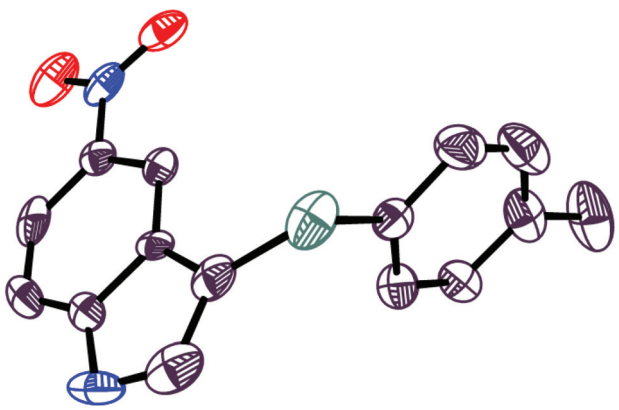
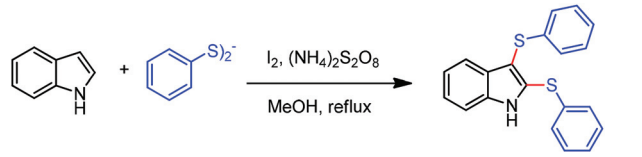
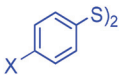
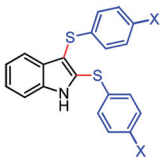
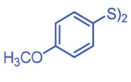
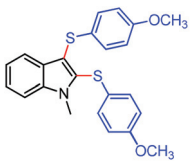


Fig. 1 X-Ray crystal structure of **11**.

Table 2 2,3-Bis-sulfenylation of indoles[a]



Entry	Indole	ArSSAr	Product	Yield (%)
1 2				**20** X = H (44) **21** X = OCH_3 (62)
3				**22** (71)

[a] The reaction was carried out on a 1 mmol scale using 1 equiv. of indole, 1 equiv. of phenyl disulfide, 1 equiv. of iodine and 2 equiv. of $(NH_4)_2S_2O_8$ in 5 mL of CH_3OH at reflux (70 °C) temperature, unless otherwise noted.

the loading of iodine yielded the mixture of mono and disulfenyl indoles and one equiv. of iodine was noticed to be optimum for the maximum yield (44%) of 2,3-bis-sulfenyl indole **20** (Table 2).

Previously, the synthesis of 2,3-bis-sulfenyl indoles had been achieved by Hamel *et al.*[13g,h] utilizing aryl sulfenyl chlorides as the sulfur source. To the best of our knowledge, there are no reports in the literature on accomplishing the synthesis of 2,3-bis-sulfenyl indoles under mild reaction conditions and using readily available sulfur precursors. Herein, we have reported the synthesis of 2,3-bis-sulfenyl indoles exploiting diaryl disulfide substrates. Phenyl disulfide and *para*-methoxyphenyl disulfide reacted smoothly under the optimized reaction conditions to give the respective 2,3-bis-sulfenyl indoles **20–21** in moderate yields (Table 2, entries 1 and 2). 2,3-Bis-sulfenyl indole **21** was also characterized by a single X-ray crystal structure study (Fig. 2).

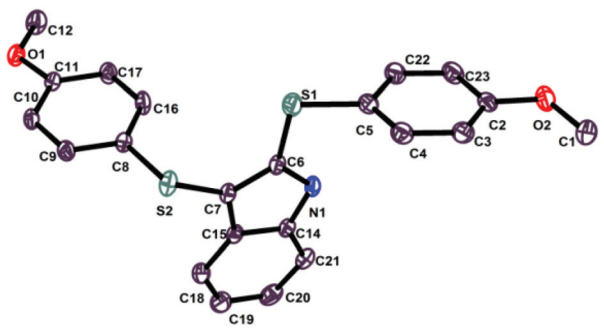
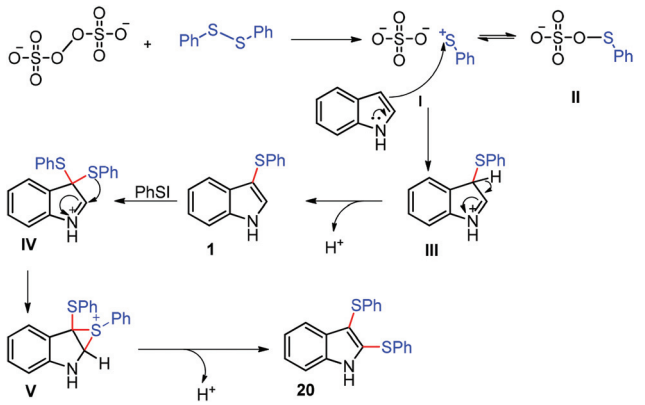


Fig. 2 X-Ray crystal structure of **21**.



Scheme 2 Proposed mechanism for 3- and 2,3-bis arylthiolation of indole.

We have also attempted the bis-sulfenylation reaction in *N*-methyl indole. *para*-Methoxy disulfide reacted with *N*-methyl indole in methanol and gave the respective 2,3-bis-sulfenyl indole **22** in 71% yield (Table 2, entry 3).

Based on the above experimental results and persulfate mediated reactions[16e,18,19] a possible mechanism has been depicted in Scheme 2.

First, ammonium persulfate reacts with diaryl disulfide to form aryl sulfenium ion intermediates **I** and **II**. The electrophilic aryl sulfenium ion could add on to the indole moiety to produce indole intermediate **III**, which may undergo deprotonation to give the desired monosulfenyl indole **1**. For the formation of 2,3-bis-sulfenyl indole **20**, the presence of iodine and persulfate is crucial in the reaction as iodine or persulfate alone is noticed to be ineffective for 2,3 C–H sulfenylation of indole. The formation of 2,3-bis thiolated product in the presence of iodine can be speculated by proposing a less hindered iodophenylthiolate intermediate, which may attack on the third position leading to 3,3-bis-substituted indolenium intermediate **IV**.[3c,6c,13h,m] Positive charge on nitrogen could enforce one of the phenylthio groups from position 3 to 2 forming an episulfonium species **V** and subsequent release of proton can give 2,3-bis-sulfenyl indole **20**.

In summary, a metal and halogen free, simple and mild method for the selective sulfenylation of indoles has been developed in methanol. The present methodology is not moisture sensitive and is carried out in the low boiling solvent methanol. In addition, both *N*-protected and unprotected indoles and disulfides with acidic protons such as amino, hydroxyl, and acid groups can be tolerated well in this methodology. Moreover, the methodology can be extended to synthesize 2,3-bis-sulfenyl indoles with the addition of stoichiometric amount of iodine, making use of diaryl disulfides as the sulfur source.

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