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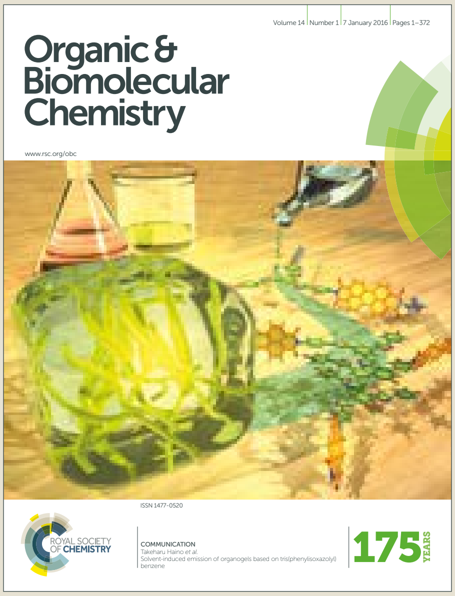

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Visible-Light Mediated Sulfonylation of Thiols *via* Insertion of Sulfur Dioxide

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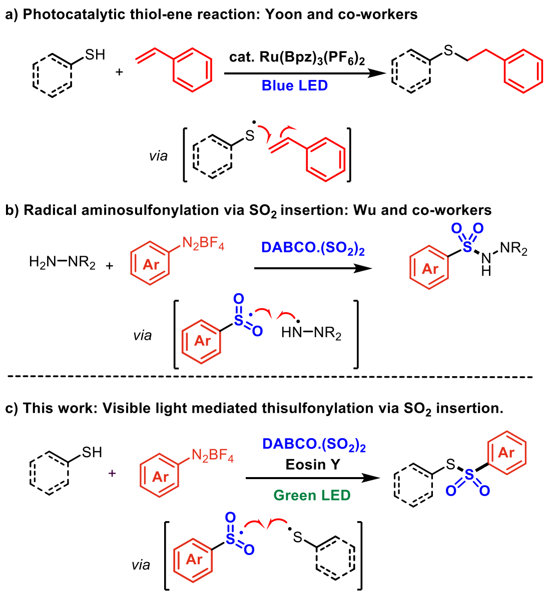
Akshay M. Nair, Shreemoyee Kumar, Indranil Halder and Chandra M. R. Volla*[a]

A simple and efficient visible-light mediated synthesis of thiosulfonates *via* a radical-radical coupling sulfenyl radicals and arylsulfonyl radicals was developed. The reaction of thiols, aryldiazonium tetrafluoroborates and DABSO proceeds at room temperature using 5 mol% Eosin Y. The reaction displays wide functional group tolerance and delivered the unsymmetrical thiosulfonates in good to excellent yields.

The abilty to adapt variable oxidation states enables sulfur to form valuable functional groups like mercapto, thioethers, sulfoxides sulfones and sulfonamides. Consequently, sulfur could be found in the core of a variety of syntheticallly and comercially important molecules like active pharmaceutical ingredients, pesticides, and various advanced materilas.[1] As a result, efficient synthesis of oganosulfur compounds and incorporation of sulfur into organic molecules has intrigued both synthetic and medicinal chemists.[2] The escalating concerns regarding sustainability and energy efficiency in the recent years has seen the emergence of visible-light photocatalysis as a powerful tool in synthetic organic chemistry.[3] These reactions permit the generation of organic radicals under mild catalytic conditions, bypassing the use of stochiometric radical initiators or oxidants. The seminal work by Yoon on visible light mediated thiol-ene reactions (Scheme 1a),[4] paved way for numerous reports on photocatalytic radical C-S bond formations using thiols.[5] However, the formation of S-heteroatom bonds using photocatalalysis remains unexplored apart from, photocatalytic dimerization of thiols reported by Noel and co-workers[6a] and visible light mediated synthesis of thiophosphates from thiols and diaryl phosphine oxides illustrated by Zhang and co-workers.[6b]

On the other hand, the fixation of sulfur dioxide into small molecules has gained a lot interest in the synthetic community.[7] Willis and co-workers introduced DABSO: a charge transfer complex of SO_2 and DABCO, as a bench stable and easy to handle source of sulfur dioxide.[8] They developed an elegant amino sulfonylation reaction using DABSO under palladium catalysis.[8a] Subsequently, Wu pioneered the use of DABSO to generate arylsulfonyl radicals,[9,10] demonstrating an elegant radical amino sulfonylation raction (Scheme 1b).[10a] Since then, arylsulfonyl radical generation from DABSO has been extensively studied for the construction of S-N,[10a-e] S-C[10f-k] and S-P bonds.[10l] However, the formation S-S bonds using DABSO remains elusive until recently. In a recent report Yang and co-workers described TFA mediated synthesis of thiosulfonates using diazonium salts and DABSO.[11]



Scheme 1: Overview of the work.

Organic thiosulfonates belong to an important class of organosulfur compounds as they display an array of biological activities including antibacterial, antiviral and antifungal.[12] Additionally, their synthetic utility as a source of both sulfenyl and sulfonyl groups has been well documented.[13] Consequently, the synthesis of thiosulfonates has gained widespread attention. Synthesis of these thiosulfonates from various precursors like

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[a] *Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai-400076, India. E-mail: chandra.volla@chem.iitb.ac.in*

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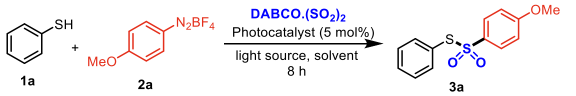
disulfides, sodium sulfinates, and sulfonyl hydrazides have been achieved.[14] Despite the progress in this field, concerns such as poor yields, sustainability, use of metals, stoichiometric oxidants and high temperatures have limited their widepread utilization. As a result, it is desirable to develop mild and selective protocols for accessing thiosulfonates and herein, we report an Eosin Y catalyzed visible light mediated thiosulfonylation for the synthesis of thiosulfonates using DABSO as sulfur dioxide source (Scheme 1c). We envisioned that the arylsulfonyl radical generated from the aryldiazonium salts and DABSO could be coupled with photocatalytically generated sulfenyl radicals to access various unsymmetrical thiosulfonates. To the best of our knowledge, photocatalytic synthesis of thiosulfonates starting from easily available precursors has not been reported.

Table 1. Optimization of the reaction conditions[a]



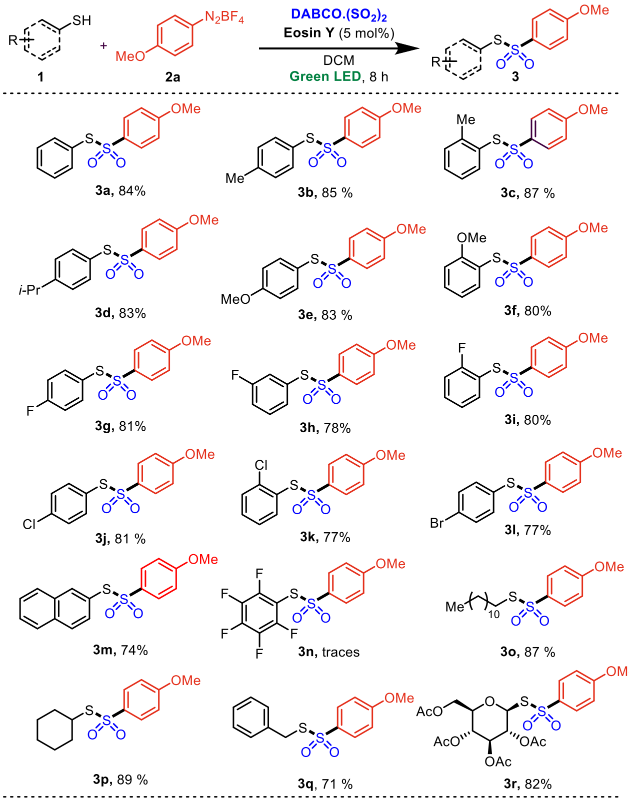
Sr.No	Photocatalyst	light	solvent	Yield (%)[b]
1	-	-	MeCN	16
2	-	-	DMF	<5
3	-	-	DMSO	12
4	-	-	DCM	25
5	-	-	THF	15
6[c]	-	-	DCM	35
7[d]	-	-	DCM	32
8	Rhodamine B	Green LED	DCM	78
9	Eosin Y	Green LED	DCM	87 (84)[e]
10	Eosin B	Green LED	DCM	64
11	Fluorescein	Green LED	DCM	35
12	Rose Bengal	Green LED	DCM	64
13	Eosin Y	Blue LED	DCM	76
14	Eosin Y	White LED	DCM	71
15	Eosin Y	-	DCM	26
16	-	Green LED	DCM	30

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv.), DABSO (1 equiv.), photo catalyst (5 mol %), solvent (2 mL), RT, 8 h, under air. [b]NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c]Reaction was performed at 70 °C. [d]Reaction was performed at 90 °C,. [e]Isolated yields in parenthesis.

To test our hypothesis, thiophenol **1a** and 4-methoxyphenyldiazonium tetrafluoroborate **2a** were chosen as the model substrates and indeed their reaction with 1eq. DABSO in MeCN at rt, provided the desired thiosulfate **3a** albeit in lower yield, 16% after 8h (Table 1, entry 1). In order to improve the reaction profile, we screened a variety of solvents for the reaction (entries 2-5) and found DCM to be superior of all, giving a best yield of 25%. No significant amplification in yield was observed by increasing the reaction temperature (entries 6-7).[15] Since we were sanguine about the slick formation of arylsulfonyl radical from diazonium salts and DABSO, we envisaged that facilitating the formation of sulfenyl radicals could ameliorate the reaction profile. Visible-light photocatalysis has manifested itself as an revered tool for the generation of sulfur centred radicals from thiols.[5] Carrying out studies in that facet, we were delighted to see a substantial amplification in the yield of **3a** (78%), when the reaction was carried out under irradiation by green LED using 5 mol % of rhodamine B as photocatalyst (entry 8). Following this, an array of organic photocatalysts was screened for the reaction (entries 8-12) and Eosin Y was found to be most effective providing 87 % of **3a** (isolated yield of 84%). Varying the light source from green to either blue or white LEDs led to slightly lower yields (entries 13 and 14). The combination of Eosin Y as photocatalyst and green LED as light source was found to be crucial, as the reaction fared poorly in the absence of either (entries 15 and 16).

With the optimized conditions in hand, we tested the scope of various diversely functionalized thiols with 4-methoxy phenyldiazonium tetrafluoroborate **2a** (Table 2). Thiophenols having substituents like methyl, *iso*-propyl and methoxy at different positions of the aromatic ring proceeded well under the standard conditions giving excellent yields of their corresponding products (**3b-3f**, 80-87%). Halogenated thiophenols were also found to be amenable substrates in the reaction affording the corresponding functionalized thiosulfonates in good yields (**3g-3l**). *Ortho*-substituted thiophenols also displayed similar reactivity profile as that of their *meta* and *para* counterparts indicating no appreciable steric effect giving **3c**, **3f**, **3i** and **3k** in 77-87% . While 2-napthylthiol **1m** gave the corresponding product **3m** in 74%, no conversion was observed when highly electron deficient *penta*-fluorothiophenol **1n** was employed.

Table 2. Substrate scope of the thiols with **2a**

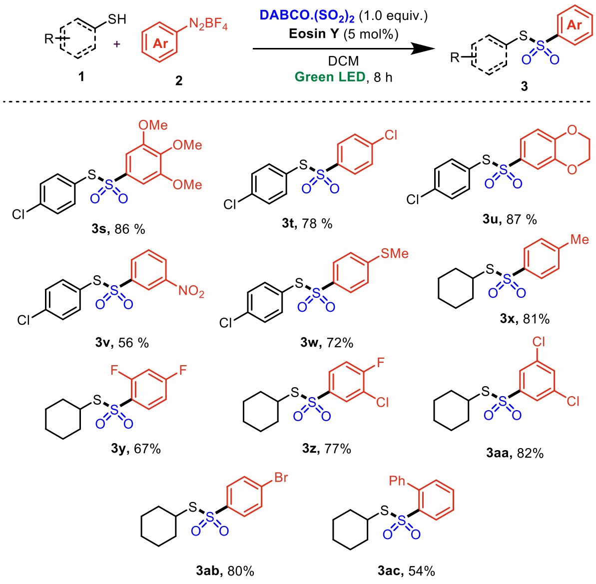


[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.5 equiv.), DABSO (1 equiv.), Eosin Y (5 mol %), DCM (2 mL), RT, 8 h, under air.

Captivatingly, aliphatic thiols were found to be effective furnishing the corresponding thiosulfonates in excellent yields (**3o-3q**). Notably, when tetra-acetylated glucose thiol **1r** was employed, 82% of glycosylated thiosulfonate **3r** was obtained. It's worth a mention that these glycosylated thiosulfonates have been studied as precursors in glycoprotein synthesis.[16]

Subsequently, we expanded the scope of the developed protocol with various diazonium salts **2** using either *p*-chlorothiophenol **1j** or cyclohexane thiol **1p** (Table 3). Gratifyingly, diazonium salts bearing both electron withdrawing as well as donating substituents were found to be suitable substrates for the transformation. While, electron rich diazonium salts displayed good reaction profile, only moderate yields were obtained in case of electron deficient nitro substituent (**3v**, 56%). Unlike the case of thiophenols, steric factors seemed to have a marked effect in the case of diazonium salts, where lower yields were observed when *ortho* substituents were present **3y** (67%) and **3ac** (54%).

Table 3: Scope of aryldiazonium salts.



[a]Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv.), DABSO (1 equiv.), Eosin Y (5 mol %), DCM (2 mL), RT, 8 h, under air.

In order to improve the scope of the transformation, allyl tethered diazonium salt **4** was reacted with thiophenol **1a** under the standard condition and we were pleased to observe the formation the dihydrobenzofuran derived thiosulfonate **5a** in 79% (Scheme 2). While the formation of **5a** imparted significant synthetic importance to the developed protocol, it also provided basic insights into the reaction mechanism (see supporting information). The process involves an intramolecular 5-exo-cyclization of aryl radical followed by insertion of sulfur dioxide (*vide infra*). Consequently we tested various thiols for the aforementioned transformation and found that the reaction proceeds with good yields regardless of the electronic and steric aspects of the thiol.

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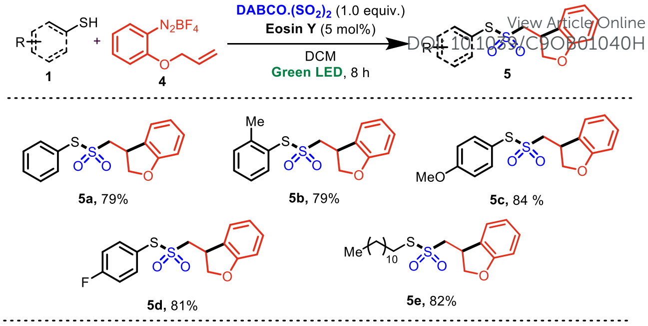
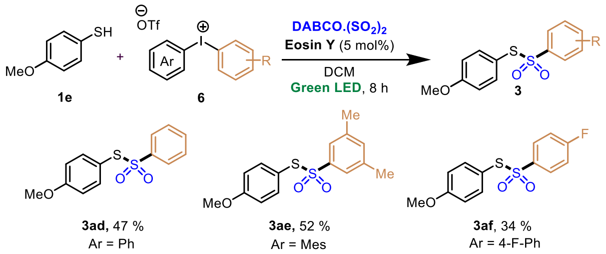


Scheme 2: Synthesis of dihydrobenzofuran-3-yl thiosulfonates.

The unique reactivity and low toxicity of diaryliodonium salts has led to their application as alternative arylating agents.[3c] Inspired by their utility in visible-light photoredox catalysis, thiol **1e** was reacted with the diphenyliodonium salt **6a** under the standard conditions and we observed the formation of the thiosulfonate **3ad** in a moderate yield of 47% (Scheme 3). It is worth mentioning that along with **3ad**, symmetrical thiosulfonate **3e** was isolated in 34%. These symmetrical thiosulfonate might be formed by the oxidation of the *in situ* generated disulphide. The absence of similar symmetrical thiosulfonates in the case of aryl diazonium salts implies their superior reactivity in compared to diaryliodonium salts in the visible light mediated thiosulfonylation.



Scheme 3: Three-component coupling of thiols, iodonium salts and SO_2.

To study the scalability of this protocol 1.0 g of **1a** was reacted with of **2a** under standard conditions to furnish 2.05 g (81 %) of **3a** (scheme 4a). We found that **3a** could be utilized for selective sulfonylation of morpholine using NBS as an oxidant under basic conditions to obtain sulfonamide **7** in 86% yield.[12a] Base mediated benzylation of **3a** using Cs_2CO_3 led to the formation of sulfone **8** in 82% (scheme 4b).[12a] Furthermore, **3a** was demonstrated as an efficient source of sulfenyl group towards the formation of thiocarbamate **9** from *tert*-butylisonitrile in 87% (scheme 4c).[12e]

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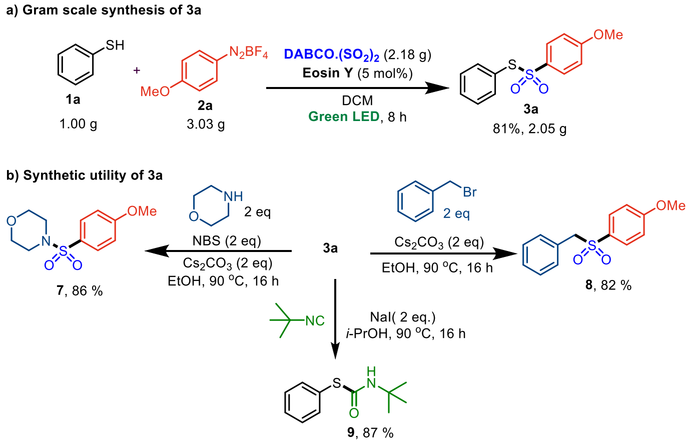
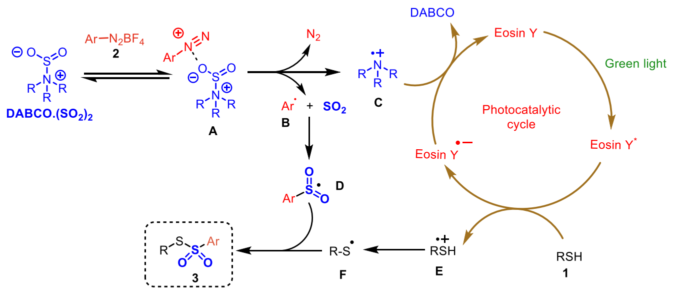


Scheme 4: Gram scale synthesis and synthetic utility.

In order to gain some insights on the reaction mechanism, control experiments with radical scavengers like TEMPO and BHT were conducted (see Supporting Information) and as expected, the desired product was not detected. Based on these preliminary mechanistic studies and previous literature, we propose the following plausible mechanism for the present transformation.[4,10] An electrostatic interaction between the aryldiazonium salt **2** and DABSO would generate the complex **A.** The subsequent homolytic cleavage of the N-S bond and the concomitant single electron transfer would result in the formation of the aryl radical **B**, SO_2 and the radical cation intermediate **C.** The aryl radical reacts with SO_2 to generate arylsulfonyl radical **D.** On the other hand Eosin Y, on visible light irradiation under goes excitation to generate eosin Y^* which then undergoes single electron transfer from the thiol to form eosin $Y^{\cdot -}$ and sulfenyl radical cation **E**. The more acidic radical cation **E** loses the proton and forms the sulfenyl radical **F,** which would then react with arylsulfonyl radical **D** to form the desired product **3**. Finally the single electron transfer to the radical cation intermediate **C** regenerates Eosin Y.



Scheme 5: Proposed mechanism.

Conclusions

In summary, we have developed a visible-light mediated synthesis of thiosulfonates via SO_2 insertion. The reaction proceeds *via* a radical-radial cross coupling of photoctalytically-generated sulfenyl radicals and the arylsulfonyl radical formed from DABSO and aryldiazonium salts or diaryliodonium salts. The protocol displayed good functional group tolerance and furnished good to excellent yields of the product. Furthermore, a cascade radical cyclization/radical-radical coupling of (2-allyloxy)-phenyldiazonium salts and thiols was demonstrated.

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15 At this juncture, to improve the yields Yang and co-workers chose to use 1 eq. of trifluoroacetic acid as an additive at 60 °C while we employed photocatalysis at room temperature. This also highlights the importance of exploring alternate solutions towards the same problem.

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