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One-pot thiol-free synthetic approach to sulfides, and sulfoxides selectively†

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A facile and efficient thiol-free one-pot method for direct synthesis of sulfides and sulfoxides under green conditions without using any metal catalyst is reported. For this purpose, we used benzyl bromides as starting materials in the presence of potassium thioacetate (PTA) and Oxone® which are low-cost, and readily accessible chemicals. This method is highly compatible with a variety of functional groups and delivered a series of sulfides, bis-sulfides, and sulfoxides in good yields. The selective formation of sulfoxides over sulfones is discussed *via* a mechanism.

Introduction

Organosulfur compounds constitute a significant part of organic synthesis[1] because they are useful in medicinal chemistry,[2] materials science,[3] and natural product syntheses.[4] Thioethers (sulfides) have found attractive applications in the pharma industry.[5] For example, Montelukast (Singulair) is a drug prescribed for allergies and asthma.[6] Ranitidine is a well-known drug utilized in histamine-2 blockers[7] (Fig. 1). Additionally, benzyl sulfides are used as near infra-red (NIR) fluorescent probes for targeted cancer imaging.[8] Given the versatility in the utilization of organosulfur compounds, searching for a better and more sustainable synthetic method seems like a necessity.

A common strategy to prepare organosulfur compounds, especially sulphides, is to use thiols as starting materials.[9] The synthesis of sulfides from thiols is promoted by the ease of their availability and high reactivity.[10] However, thiols often restrict the direct synthesis of desired sulfides due to inherent disadvantages such as awfully irritating smell and side effects concerning health.[11]

Our group has been engaged in the design of organosulfur compounds using a green reagent such as rongalite.[12] Some of these sulfur compounds are reported as useful synthons in C–C bond formation and metathesis.[13] Generally, thioacetate anions are reacted with halides or alcohol derivatives to prepare thioacetates[14] which are purified first. Then, in the next step, the thioacetates are converted to thiols.[15] Afterwards, the thiols are transformed further to desired unsymmetrical sulfides.[9] We questioned whether an easier, shorter, and odorless protocol can be realized for the preparation of sulfides. Gratifyingly, here we present a synthetic strategy that combines the aforementioned three steps in one-pot. Our methodology converts benzyl halides into unsymmetrical sulfides *via* a one-pot operation. This strategy avoids the formation of byproducts, usage of transition metal catalysts, and toxic solvents. The reaction time is short and the purification is docile. The substrate scope is quite large and the yields are good to excellent. The advantages of this methodology are; avoiding the usage of thiols hence environmentally benign, reducing the number of steps in overall sequence, and employing inexpensive reagents. A library of benzyl sulfides is easily prepared with this strategy.

Several odorless reagents such as Na_2S, rongalite, NaHS, KSCN, potassium ethylxanthate, and potassium thioacetate are available for the preparation of sulfur-based compounds. By utilizing sodium sulfide/rongalite, only symmetrical sulfides[16]/sulfones[17] are prepared from halides and these reagents are further explored.[18] Sodium hydrosulfide (NaHS), highly hygroscopic and difficult to handle, is a source for HS^- which leads to the formation of thiols and hence adding one more step towards preparing sulfides.[19] KSCN leads to thiocyanate

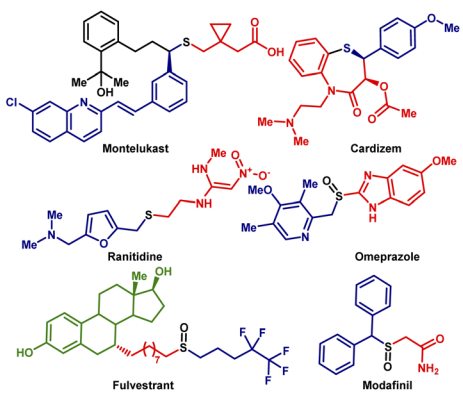

Fig. 1 Representative biologically active organosulfur compounds.

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products as well as isothiocyanate products.[20] Potassium ethyl xanthate leads to sulfides in two steps under heating conditions and several byproducts were observed as reported by Fochi *et al.*[21] Therefore, in light of these limitations, we have chosen potassium thioacetate as our reagent due to its capacity of preparing versatile sulfides without involving thiols in a single-pot at room temperature as explored in this manuscript.

Seminal existing pathways for sulfide preparation involving benzyl and alkenyl/alkyl moieties are presented in Fig. 2.[15c,22] It is observed from the literature that synthetic strategies for Csp^3–S–Csp^3 type of sulfides/sulfoxides are much less explored as compared to Csp^2–S–Csp^2 and Csp^2–S–Csp^3 sulfides[23]/sulfoxides[24] despite having significant applications (Fig. 1). Our work focuses on the less explored area of unsymmetrical Csp^3–S–Csp^3 hybridized organosulfur derivatives. The main theme of our strategy involves a one-pot operation and thus avoiding three steps used for converting bromides to sulfides through thioacetates and thiols. Instead, we directly obtain diverse sulfides from halides *via* a straightforward route in benign solvents such as methanol or water. The application of our method is demonstrated by preparing sulfide derivatives containing the core units of biologically active compounds and to our delight, the unsymmetrical sulfides were obtained in good yields.

Other classes of organosulfur compounds include sulfoxides and sulfones. Sulfoxides, along with their biological applications,[25] are useful as catalysts and chiral ligands in asymmetric syntheses,[26] and hence preparation of sulfoxides is an equally attractive task. Sulfoxides have been prepared extensively from sulfides[27] and control is needed to avoid the formation of sulfone.[28] To the best of our knowledge, no report is available where halides are directly converted into unsymmetrical Csp^3–S–Csp^3 hybridized sulfoxides in a single-pot without involving thiols and avoiding four steps of isolation and purification. To this end, the latter part of this article deals with the expansion of our procedure towards the selective preparation of sulfoxides instead of sulfones[29] from halides by aqueous Oxone® in the same pot.

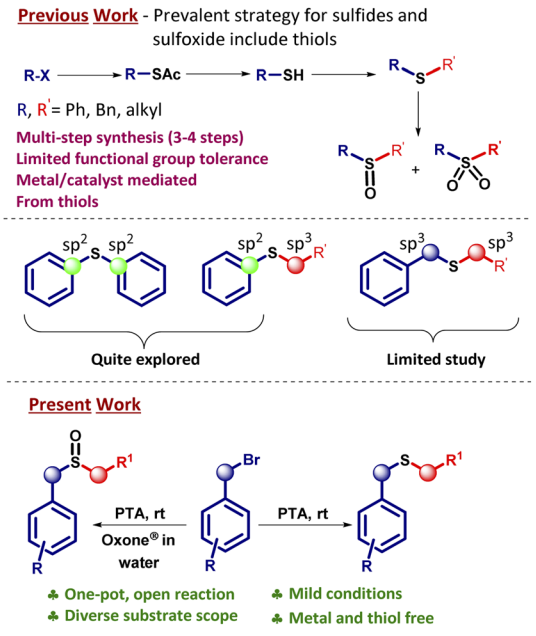


Fig. 2 General overview of the preparation of organosulfur compounds (sulfide, sulfoxide, and sulfone).

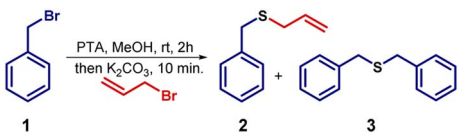
Results and discussion

Reaction development and optimization

To realize the one-pot strategy shown in Fig. 2, benzyl bromide was reacted with potassium thioacetate (PTA) in methanol. The reaction proceeds *via* S_N2 type of substitution with thioacetate at the benzylic position. After 2 h, potassium carbonate was added to the same reaction mixture to deprotect $-COCH_3$ group and generate sulfide (S^-) nucleophile. Then, sp^3 hybridized primary electrophile ($R–CH_2–X$) was added to this reaction mixture and delivered the desired product. Table 1 summarizes the optimization details with respect to the amount of base and solvent used for the conversion of **1** into **2**. As we increased the equiv. of the base, we observed a drastic increase in the yield and up to 3 equiv. of potassium carbonate is required (Table 1, entries 1–5) to get maximum yield.

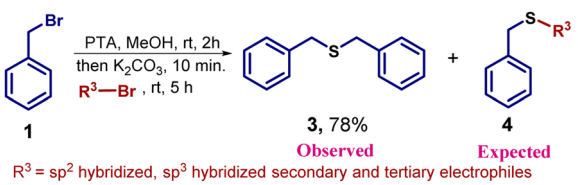
If the addition of halide is exempted after transferring K_2CO_3 in the reaction pot, then, compound **3** is obtained as a sole product. We also found that non-polar and aprotic solvents such as dichloroethane, dichloromethane, toluene, and diethyl ether are not suitable.

Table 1 Optimization table for the preparation of sulfide **2**[a]



S. no.	Solvent	K_2CO_3 (equiv.)	Time (h)	Yield[b] (%) (**2**/**3**)
1	MeOH	1	16	25/55
2	MeOH	1.5	12	37/42
3	MeOH	2	8	50/26
4	MeOH	2.5	8	68/09
5	**MeOH**	**3.0**	**3**	**78/00**
6	MeOH : H_2O (1 : 1)	3.0	10	61/14
7	H_2O	3.0	10	65/12

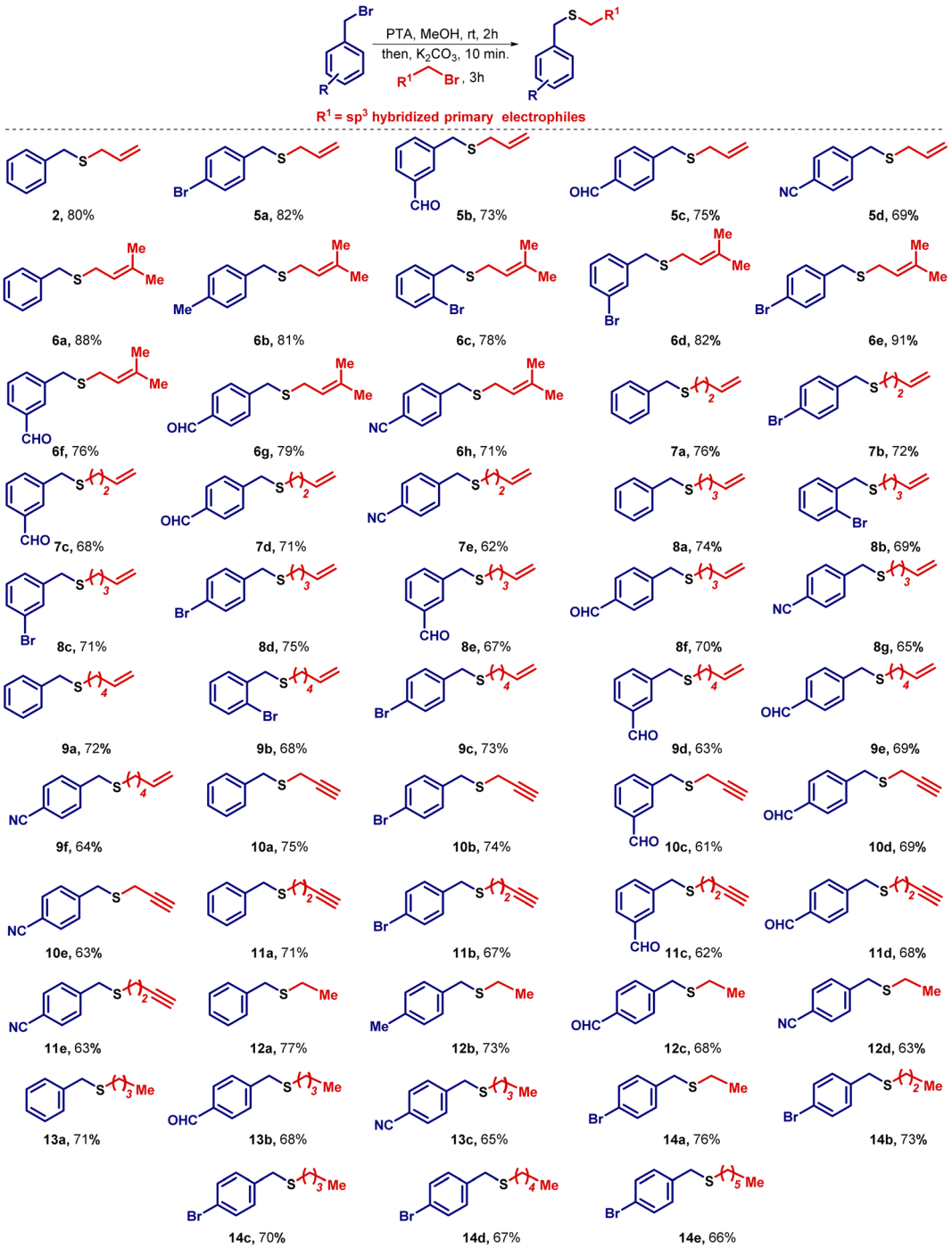
[a] Reaction conditions: compound **1** (0.87 mmol, 1 equiv.), PTA (0.87 mmol, 1 equiv.), MeOH (10 ml), K_2CO_3 (2.61 mmol, 3 equiv.), allylbromide (0.87 mmol, 1 equiv.) All reactions are performed at room temperature. [b] Isolated yield.



Scheme 1 Attempts to prepare unsymmetrical sulfide **4**.

Alternatively, another polar protic solvent *i.e.* water was tested to check the feasibility of the reaction. The reaction is facile in MeOH : water (1 : 1) combination as well as in water (Table 1, entry 6 and 7). However, the addition of water led to a slight reduction in the overall yield of the reaction as compared to the other optimized conditions (Table 1, entry 7).

Later on, we attempted sp^2 hybridized, and sp^3 hybridized secondary and tertiary electrophiles to deliver the desired compound **4**. In each case, we failed to detect the expected sulfide **4**. Instead, we observed a common product **3** in good yield. The possibility of secondary nucleophilic substitution reaction at a less hindered sp^3 hybridized center leads to the formation of unsymmetrical sulfide **4** (Scheme 1). So, it was concluded that this one-pot methodology is useful with reactive electrophiles such as primary alkyl halide to generate various sulfide derivatives.



Scheme 2 Synthesis of unsymmetrical sulfides containing unsaturated and saturated aliphatic side chains. Reaction conditions: compound **1** (0.87 mmol, 1 equiv.), PTA (0.87 mmol, 1 equiv.), MeOH (10 ml), K_2CO_3 (2.61 mmol, 3 equiv.), $R^1–CH_2–Br$ (0.87 mmol, 1 equiv.). All reactions are performed at room temperature.

Substrate scope

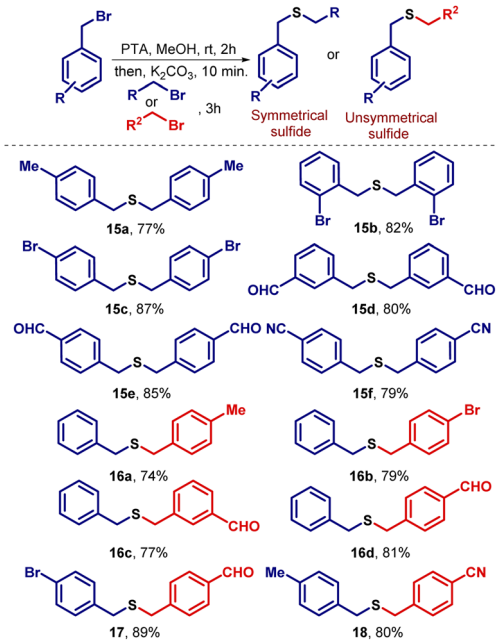
Having identified the optimal reaction conditions, the attention was turned towards establishing the generality of this transformation. To this end, benzyl bromide was reacted with several unsaturated halides and to our delight, the desired unsymmetrical sulfides were obtained in good to excellent yields. Noticeably, the aliphatic chain length of the halide has an inverse relationship with respect to the yield. As the number of methylene units ($-CH_2$) increases in the electrophile, a slight decrease in the yield was observed. After the preparation of unsymmetrical sulfides containing unsaturated aliphatic side chains, the attention was shifted towards the synthesis of unsymmetrical sulfides containing saturated alkane side chains. In this regard, various substituted benzyl bromides were treated with alkyl bromides of varying chain lengths to prepare unsymmetrical sulfides containing benzylic and aliphatic moieties (Scheme 2).

During the expansion of substrate scope, we observed that unsubstituted aromatic systems gave higher yields of the desired sulfides as compared to substituted aromatic systems (–EWG and –EDG). Additionally, we observed better yields when –Br is present in the benzylic system at different positions like *ortho*-, *meta*-, and *para*-positions, on the same sequence. Further, we also noticed slightly lower yields due to the presence of the *–m* effect group present in the aromatic system (–CHO, –CN group). In conclusion, the presence of an electron donating group in the benzylic system enhances the nucleophilicity of the sulfide ion, and hence favors relatively higher yields, whereas the presence of an electron withdrawing group decreases the nucleophilicity of sulfide ion and as a result, a slight reduction in the yields was observed. To study the role of chain length on the yields of sulfides, we kept the benzylic system constant and treated it with alkyl bromides of different chain lengths. We found that no drastic change in the final yields of the sulfides **9** was observed. Evidently, a slight decrease in the yields was observed as we go lower to higher carbon chains of the electrophiles. It is worth mentioning that if the series of sulfides **6b–6h** would have been prepared from thiols, the required thiol would be 3-methyl-2-butene-1-thiol which has a skunky beer smell.[30] This reason may be attributed to why these sulfides, nonetheless quite simple, have not been prepared before. The efficacy of this methodology is realized in the easy retrieval of such sulfides without utilizing smelly thiols (Scheme 2).

Afterward, we tried a similar strategy with benzylic systems as electrophiles and prepared symmetrical (**15a–f**) and unsymmetrical (**16–18**) sulfides containing dibenzylic moieties in good yields (Scheme 3). Higher yields were observed here as compared to when aliphatic systems as electrophiles were employed for the preparation of sulfides (Scheme 2). Next, we turned towards the preparation of bisbenzylthio systems. In this regard, several dibromides were successfully converted into bis(benzylthio) derivatives (**19–24**) in good to excellent yields (Scheme 4). The single-crystal structures for **20a** and **21b** are presented in Fig. 3.

Sulfoxide preparation

To prepare sulfoxide and sulfone derivatives *via* a single-pot operation starting with benzyl bromide **1**, we tried the

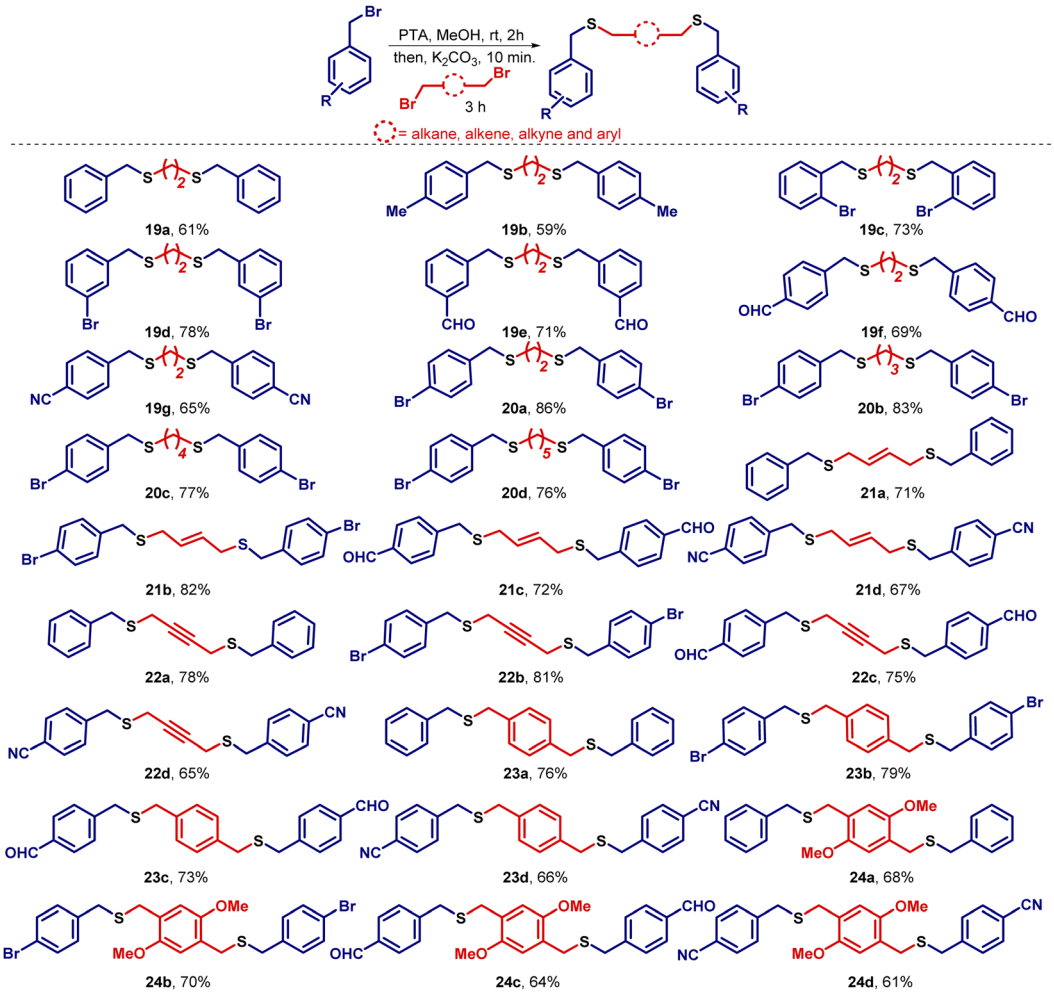


Scheme 3 Synthesis of symmetrical and unsymmetrical sulfides containing aromatic rings. Reaction conditions: compound **1** (0.87 mmol, 1 equiv.), PTA (0.87 mmol, 1 equiv.), MeOH (10 ml), K_2CO_3 (2.61 mmol, 3 equiv.), R/R^2-CH_2-Br (0.87 mmol, 1 equiv.). All reactions are performed at room temperature.

oxidation sequence with Oxone® (Scheme 5). In this regard, we used Oxone® in water and after careful monitoring of the reaction mixture by thin-layer chromatography and by NMR data, we found the selective formation of sulfoxides in a one-pot operation. By using different equivalents of Oxone® (0.5 to 1.5 equiv.), we noticed a mixture of compounds **2**, **25** (trace amount), and **26a** were formed. By increasing the equivalents of Oxone® from 1.5 to 2.2 equiv., the formation of compound **26a** was increased and complete conversion of sulfide into sulfoxide **26a** was noticed. Earlier reports[28c] state that if the equivalent of Oxone® used is more than 1.5, then conversion to sulfone predominates however, in our case, even if Oxone® content was increased up to 3.0 equiv. sulfoxide was the only product obtained. This study led us to the conclusion that a controlled and easy one-pot reaction selectively provides sulfoxides as a major product directly from halides. In contrast, when we isolated and purified the sulfide **2**, then subjected to oxidation with Oxone® (3 equiv.) in water : methanol (1 : 1), sulfone **25** was found to be the major product (Scheme 5).

Substrate scope of sulfoxides

Having optimized the conditions to prepare sulfoxide in one-pot, we explored the substrate scope and studied other sulfoxides. Fortunately, we obtained diverse sulfoxides starting from benzyl bromides in a single step. Various unsymmetrical sulfoxides (**26–33**) prepared are included in Scheme 6. Benzyl sulfoxides (**32** and **33**) were obtained in good to excellent yields. A similar trend like sulfides was observed with respect to yield as discussed previously (Scheme 2).



Scheme 4 Synthesis of saturated and unsaturated bridges containing dithia molecules. Conditions: compound **1** (0.87 mmol, 1 equiv.), PTA (0.87 mmol, 1 equiv.), MeOH (10 ml), K_2CO_3 (2.61 mmol, 3 equiv.), dibromo derivative (0.44 mmol, 0.5 equiv.). All reactions are performed at room temperature.

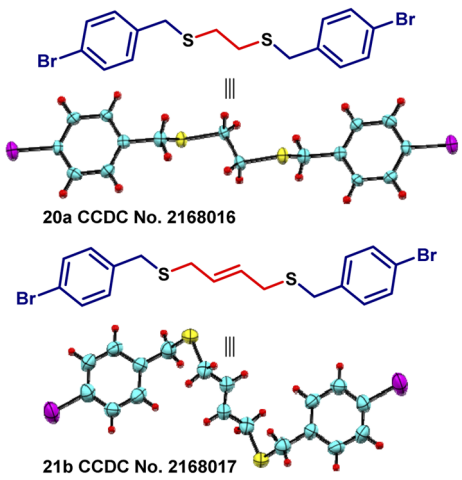
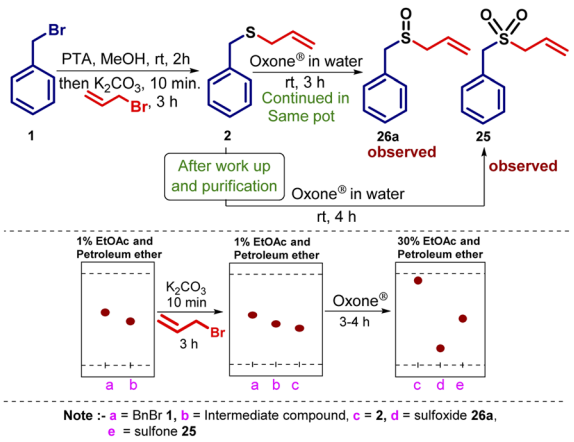


Fig. 3 Single-crystal structures of **20a** and **21b** (shown at 50% thermal ellipsoids).

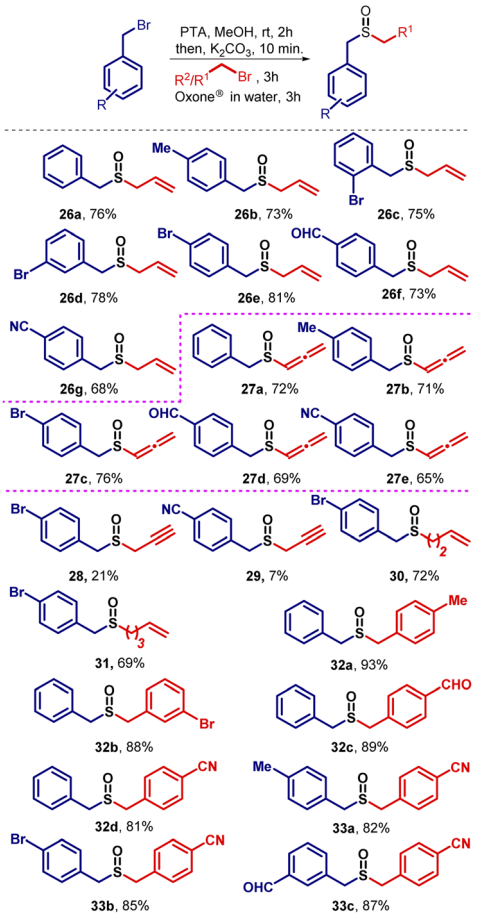
Allenes are useful synthons for several critical transformations.[31] Therefore, the preparation of such sulfoxides is a worthwhile exercise. There are reports which deal with sulfide allenyl derivatives.[32] However, sulfoxide allenyl derivatives are quite limited and were prepared *via* a multi-step synthetic protocol.[33] With this methodology, they are prepared quite easily. Allenyl sulfoxides were observed when the propargyl bromides were used as electrophiles. The expected sulfoxides **28** and **29** having propargyl group as a side chain were only isolated as minor products when the aromatic ring in benzyl bromide was substituted with a –Br and –CN group at *para*-position respectively (Scheme 6).

Mechanistic studies

Later on, we were concerned about the mechanism of sulfoxide formation instead of sulfone (Scheme 7) even if the equivalents of Oxone® were increased from the reported methods.[27c] In the first step, during the formation of intermediate **A**, the liberation of KBr is proposed. Here, KBr is playing a prominent role when we added Oxone® to generate sulfoxides. In the presence of KBr and Oxone®, the formation of potassium sulfate and



Scheme 5 TLC behavior during the selective formation of sulfoxides. Conditions: compound **1** (0.87 mmol, 1 equiv.), PTA (0.87 mmol, 1 equiv.), MeOH (10 ml), K_2CO_3 (2.61 mmol, 3 equiv.), allylbromide (0.87 mmol, 1 equiv.). Oxone® (1.91 mmol, 2.2 equiv.) in 10 ml H_2O. All reactions are performed at room temperature.



Scheme 6 One-pot preparation of sulfoxides. Conditions: compound **1** (0.87 mmol, 1 equiv.), PTA (0.87 mmol, 1 equiv.), MeOH (10 ml), K_2CO_3 (2.61 mmol, 3 equiv.), R^2/R^1–CH_2–Br (0.87 mmol, 1 equiv.). Oxone® (1.91 mmol, 2.2 equiv.) in 10 ml H_2O. All reactions are performed at room temperature.

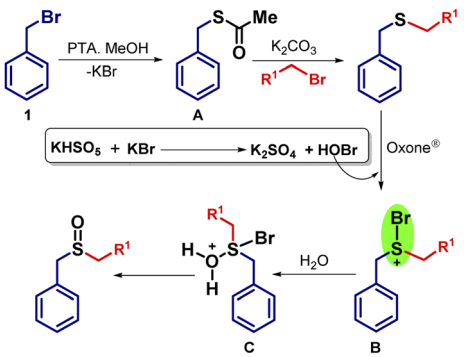
hypobromous acid (HOBr) takes place. From HOBr, bromine moiety is attached to sulfur atom and forms intermediate **B** containing S–Br bond which leads to the formation of intermediate **C** by reacting with water. Based on the mechanism as previously reported, we suggest that the formation of sulfur bromo bond is a key factor to reduce the reactivity of sulfur atom thus inhibiting further oxidation.[34] Because of this bond formation, only one oxygen atom can be attached to the sulfur atom and hence the formation of the sulfoxides (**26–33**) predominates in a one-pot reaction.

Gram scale synthesis

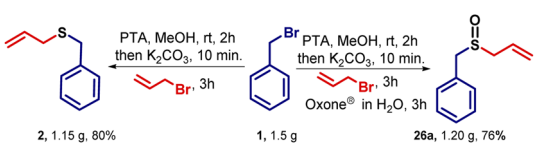
The methodology is tested for the gram-scale synthesis of sulfide and sulfoxide to demonstrate the synthetic utility of the developed reaction. When 1.5 g of benzyl bromide was used for gram-scale synthesis under the optimized conditions, then 1.15 g (80%) sulfide **2** and 1.20 g (76%) sulfoxide **26a** were obtained respectively, hence showing the scalability of our one-pot operation (Scheme 8).

Late stage functionalization

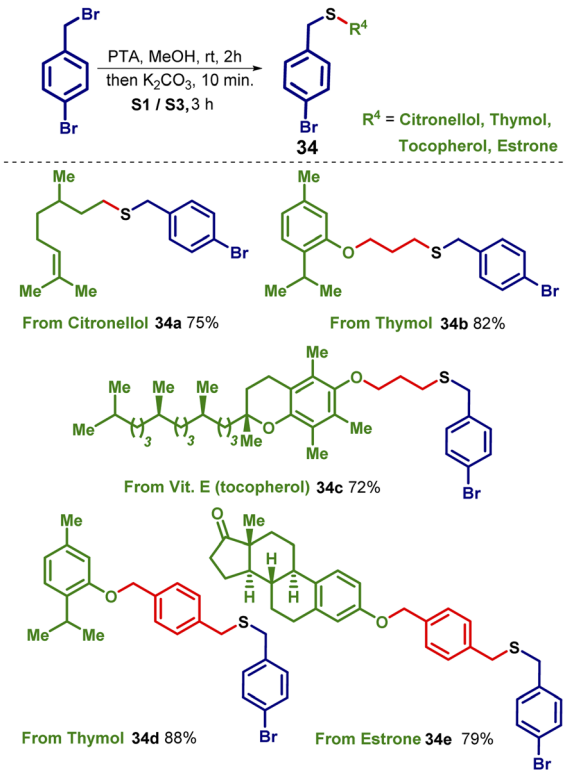
Given the importance of sulfide (thioether) in pharmaceuticals we speculated that combining the sulfide core with natural products or biologically active compounds will be a useful exercise as these products could be further useful in medicinal chemistry. Therefore, we carried out the preparation of sulfide derivatives starting with biologically active compounds by late-stage functionalization. After having bromoderivatives of citronellol, thymol, vitamin E (tocopherol), and estrone (refer ESI page S34†), we adopted the optimized conditions to prepare interesting sulfides **34** which are useful substrates for biological properties. Various derivatives prepared are listed in Scheme 9.



Scheme 7 Plausible mechanism for the formation of sulfoxides from benzyl halides in one-pot containing oxone–KBr combination.



Scheme 8 Gram-scale synthesis of sulfide **2** and sulfoxide **26a** in one-pot.



Scheme 9 Late-stage functionalization of biologically active compounds into sulfides.

Conclusions

To summarize, a wide range of sulfur-containing scaffolds are prepared efficiently. The preparation of sulfides/sulfoxides from halides that usually requires three to four steps has been achieved in a one-pot operation. This methodology involves a thiol-free path and hence much greener and odorless than the earlier reported methods. Potassium thioacetate has acted as an efficient surrogate for unsymmetrical Csp^3–S–Csp^3 type sulfides which are not much explored yet. Numerous benzylic sulfides and sulfoxides containing alkyl, alkenyl, alkynyl, and phenyl moieties are prepared and their structures are unambiguously established by spectral data. Selective preparation of sulfoxides and sulfone is also realized. Allenyl sulfoxides were prepared *via* facile one-pot operation which can be further utilized in several transformations. A series of sulfides containing biologically active scaffolds were prepared by late-stage functionalization.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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