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Graphene oxide (GO)-catalyzed multi-component reactions: green synthesis of library of pharmacophore 3-sulfenylimidazo[1,2-*a*]pyridines†

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The green carbocatalyst graphene oxide (GO) has been successfully utilized for selective and expedient synthesis of biologically important motifs imidazo[1,2-*a*]pyridines, and 3-sulfenylimidazo[1,2-*a*]pyridines *via* one-pot multi-component reactions (MCR). Diversity in small heterocyclic molecular synthesis has been demonstrated with tolerance of broad range of functional groups establishing the generality of the reaction and as well as demonstrating preparation of libraries of potential pharmacophores. The reactions are believed to proceed *via* selective and tandem reactions in the presence of GO and NaI (as the additive), and the catalyst GO was found to be easily recoverable and recyclable with appreciable conversions.

Introduction

Imidazo[1,2-*a*]pyridines represent an important N-bridged and fused bicyclic scaffolds finding versatile applications in pharmaceuticals and organic functional materials.[1] The heterocyclic motif occurs in various clinical drugs including alpidem, necopidem, zolpidem, saripidem, olprinone, miroprofen, zolimidine and anti-HIV drugs GSK812397, a few representative examples are shown in Fig. 1.[2] Its anticancer,[3a] antiviral,[3b,c] antimicrobial,[3d] anti-rhinoviral,[3e,f] antiulcer[3g] activities are responsible for its wide applications in medicinal chemistry. This moiety has also been used in material sciences.[4] Further functionalized N-bridged fused bicyclic imidazo[1,2-*a*]pyridines, such as 3-sulfenylimidazo[1,2-*a*]pyridines, (Fig. 1) are also of considerable therapeutic value against a variety of diseases and do find broad spectrum uses in pharmaceutical industries.[5]

In spite of enormous applications, most of the imidazo[1,2-*a*]-pyridine derivatives are not commercially available and hence its synthesis from easily available substances has remained in the focus of synthetic organic and pharmaceutical chemists. Most synthetic procedures involve the reaction of 2-aminopyridine with a variety of chemicals like acetophenones, α-haloketones, α-diazoketones, α-tosyloxyketones, nitroalkenes, suitably substituted alkyne derivatives *etc.*[6] The reactions are usually done through condensation, tandem reactions or in a multi-component approach in the presence of Brønsted or Lewis acids or other metal catalysts. For example, protic acid,[7a,b] Lewis acids[7c–e] or metal catalysts like Cu(I) salts,[7f–h] Cu(I)/Cu(II),[7i,j] Cu(I)/Zn(II),[7k] Cu(II)/Fe(III)[7l] systems have been employed for the synthesis of imidazo[1,2-*a*]pyridine derivatives.

Among several approaches, $CeCl_3 \cdot 7H_2O$/NaI-catalyzed multicomponent tandem procedure,[7c] has emerged possibly as a powerful methodology. However, modern green practices demand for eco-friendly procedures without metal toxicity, contamination with the product and final disposal. As such, the need for metal-free, non-toxic and easily available or prepared catalysts are attractive targets for green and sustainable synthesis. In this perspective, carbon materials like GO has emerged as an efficient and promising carbocatalyst.[8] Large surface area, bio-compatibility, inertness, and outstanding electronic, optical, thermal & mechanical properties make GO as an versatile material, which is obtained from low-cost and easily available starting materials.[9] The presence of multiple functionalities such as epoxide, hydroxyl and carboxyl groups (Fig. 2) account for its acidic nature (pH 4.5 at 0.1 mg mL^{-1}),[10] and strong oxidizing property.[11] Harnessing these unique qualities over the last few years, GO has been finely exploited as a metal-free and robust carbocatalyst in various synthetic processes like hydration of alkyne,[12] selective oxidation of thiols and sulphides,[11c] oxidation of olefins to diones, methyl benzenes to aldehydes, diarylmethanes to ketones,[11d] oxidative coupling of amines to imines,[11e] Friedel–Craft addition of indole to α,β-unsaturated ketones *etc.*[11f] From our laboratory, we successfully developed controlled use of this carbocatalyst in one-pot sequential dehydration–hydrothiolation of *sec*-aryl alcohols,[13a] as well as chemoselective thioacetalization of aryl aldehydes.[13b]

Considering the vast applicability of GO as the carbocatalyst in C–H oxidation, C–C and C–heteroatom bond-forming

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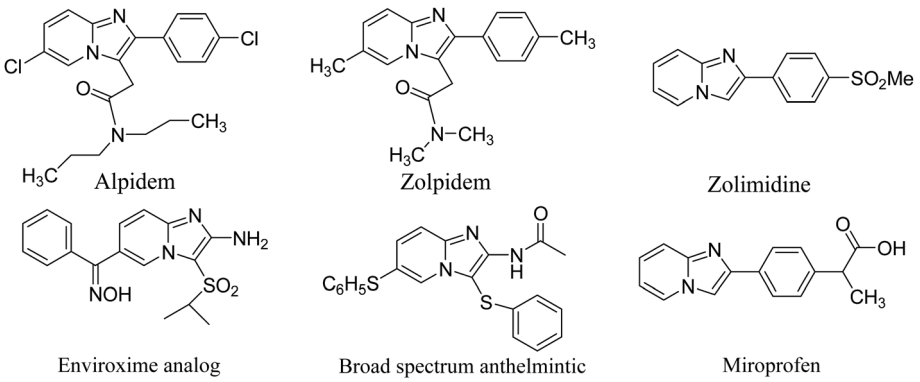


Fig. 1 Representative examples of imidazo[1,2-*a*]pyridine-based drugs.

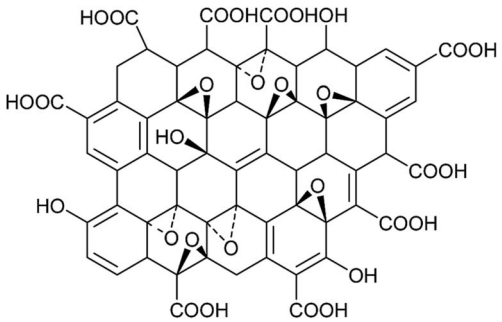


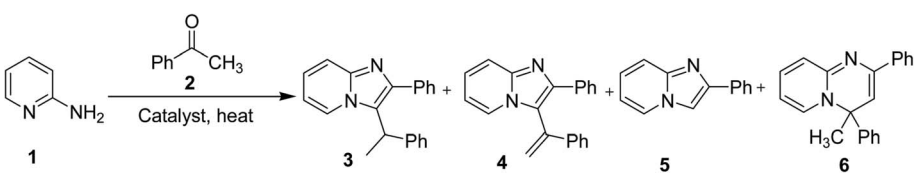
Fig. 2 Schematic presentation of graphene oxide (GO).

reactions,[11f,14] and our previous findings on one-pot diverse reactions to prepare complex molecules,[13a] we wanted to explore further GO-catalyzed synthesis of complex heterocycles of biological relevance. We describe herein highly selective metal-free synthetic protocol for imidazo[1,2-*a*]pyridines from the reaction of 2-aminopyridine and acetophenone, and an efficient one-pot MCR procedure using aryl/alkyl thiol as the third component leading to the synthesis of 3-sulfenylimidazo [1,2-*a*]pyridines in the presence of a catalytic combination of GO and NaI.

Results and discussion

Direct reaction of 2-aminopyridine (**1**) and acetophenone (**2**) can produce a number of possible products like 3-(1-phenylethane)-2-phenyl (**3**), 3-(1-phenylethene)-2-phenyl (**4**) and 2-phenyl (**5**) substituted imidazo[1,2-*a*] compounds and 4-methyl-2,4-diphenyl-4*H*-pyrido[1,2-*a*]pyrimidine (**6**), either *via* ketimine intermediate or *via* Ortoleva-King type reaction intermediate (Scheme 1).[7a] Among metal-free catalytic conditions, Kurteva *et al.* demonstrated *p*TSA-catalyzed selective formation of **3** from a mixture of 2-aminopyridine (**1**) and acetophenone (**2**) at 210 °C.[7b] Hitherto, there are no metal-free conditions developed that can furnish selectively a single product other than **3**.

As GO has been shown to act as an efficient carbocatalyst for both oxidation and acid-catalyzed reactions,[11–13] we presume that the use of GO in this reaction might play an active role. We thus conducted experiments taking equimolar quantities of 2-aminopyridine and acetophenone in the presence of catalytic amounts of GO under varying reaction conditions. The results are presented in Table 1. Initial attempt of heating a mixture of reactants **1** (1 mmol) and **2** (1 mmol), the catalyst GO (100 mg) in acetonitrile (1 mL) at 80 °C did not afford any product (entry 1). However, the same reaction in the presence of an additive (NaI, 10 mol%) did produce a single product **5** in good yield (82%, entry 2). It is interesting to observe that other possible products **3**, **4** & **6** (Scheme 1) were not formed and the compound **5** was obtained as the sole product (HPLC analysis of the reaction mixture before purification). Being encouraged by this finding, we tried to optimize other facets of the reaction. For example, varying the quantity of GO, it was found that 50 mg of GO is the minimal requirement to obtain >80% isolated yield of **5** (entries 3, 4). Reactions performed in different solvents such ethanol or water were not productive either (entries 6, 7), but the same reaction carried out in toluene afforded the single product **5** in excellent yield (entries 8, 9). As seen from the results, the additive NaI does have a significant role in the catalytic process, and possibly in the selective formation of **5**.



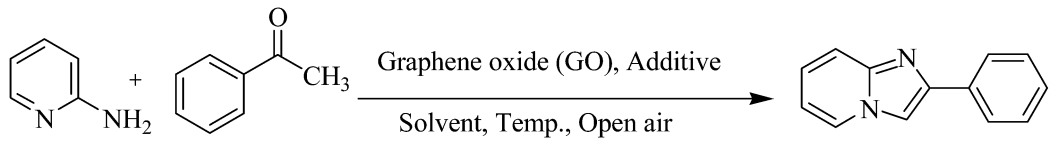
Scheme 1 Possibility of formation of different products from 2-aminopyridine and acetophenone

Decreasing its quantity below 10 mol% afforded the product **5** either in low yields or not formed at all (entries 5, 10 and 1). In the absence of GO, lowering of temperature or carrying out the reactions under N_2 resulted in rather poor yields of the desired product (entries 10–12). Use of other alkali metal salts such as KI or KBr acted less efficiently as compared to NaI (entries 13, 14). Thus the optimized condition established at our hand is as in entry 8, with the combination of GO (50 mg $mmol^{-1}$) and the additive, especially NaI (10 mol%), in solvent toluene, can produce selectively the product **5** in excellent yield. When we scaled up the reaction up to 3–5 mmols of the starting compounds in the presence of GO (50–100 mg), appreciable conversions (67–88%) were achieved (entries 15–17). This signifies that proportionate increase in the quantity of the catalyst (50 mg of GO $mmol^{-1}$) is not an essential factor. Among the solvents tried for the reaction, non-polar toluene performed best, polar aprotic solvent like acetonitrile can also perform the reaction, but protic and polar solvents like ethanol or water were not suitable for this conversion. Among other greener solvents,[15] the reaction works as well in ethyl acetate (entry 18).

Next, the scope of this selective one-pot condensation-cyclization reaction was examined employing the optimized condition and the results are summarized in Table 2. It can be seen that diverse functional groups attached with the aromatic moiety of both reaction partners did not have significant influence in the course of the reaction and in all cases the desired imidazo[1,2-*a*]pyridine derivatives were obtained as the sole product and in good to excellent yields. We studied with amino pyridines substituted with $-CH_3$ and –Cl, while the acetophenones bearing $-C_2H_5$, –Cl, –Br or –I afforded the corresponding product in a highly selective manner (Table 2, compounds **5a–i**). All reactions were carried out under open air and at 80 °C.

The electrophilic addition to imidazo[1,2-*a*]pyridine ring system is ought to be facile and likely to take place at C-3 position. Since thiol addition would lead to important pharmacophores,[16,7c] we performed a three-component reaction involving 2-aminopyridine, acetophenone and benzenethiol in the presence of GO and NaI. Indeed the thiophenol is suitably reactive to add to imidazo[1,2-*a*]pyridine in a selective manner yielding the 2-phenyl-3-(phenylthio)*H*-imidazo[1,2-*a*]pyridine (**8a**) in 84% isolated yield. Based on this observation, we performed the GO/NaI-catalyzed MCR of broad range of functionalized aminopyridines, acetophenones and arylthiols to generate a library of potential heterocyclic scaffolds, 3-sulfenylimidazo[1,2-*a*]pyridines (**8**). In general, the reaction occurred fairly smoothly producing the corresponding 3-

Table 1 Optimization of the reaction conditions[a]

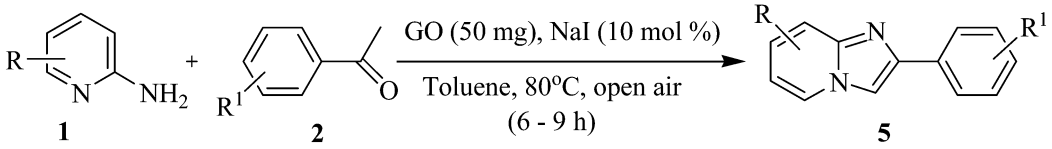


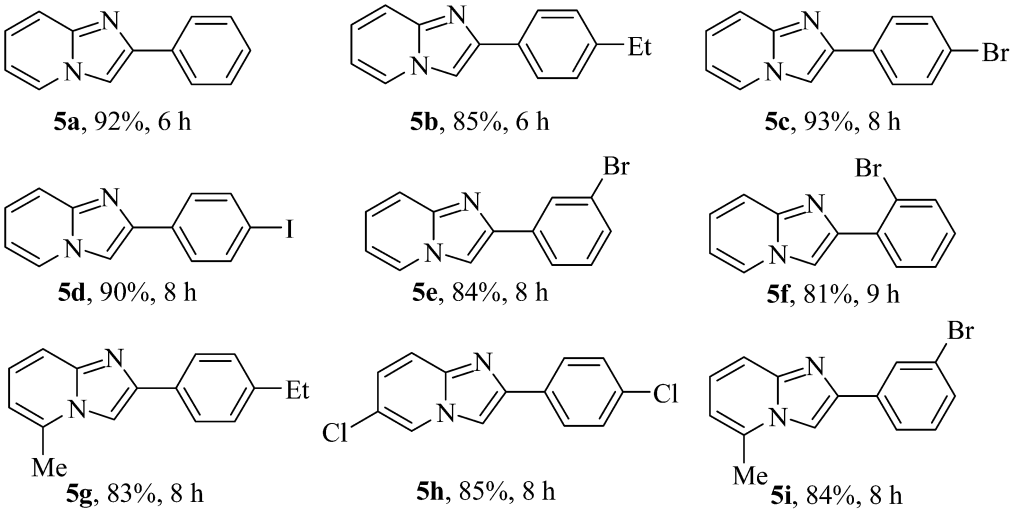
1 **2** **5**

Entry	GO (mg)	Additive (salt/mol%)	Solvent	Temp. (°C)	Time (h)	**5**[b] (yield %)
1	100	Nil	CH_3CN	80	8	No product
2	100	NaI/10	CH_3CN	80	8	82
3	50	NaI/10	CH_3CN	80	14	81
4	30	NaI/10	CH_3CN	80	20	20
5	50	NaI/5	CH_3CN	80	24	65
6	50	NaI/10	EtOH	80	24	40
7	50	NaI/10	H_2O	80	24	No product
8	**50**	**NaI/10**	**Toluene**	**80**	**6**	**92**
9	50	NaI/20	Toluene	80	6	92
10	50	NaI/10	Toluene	60	15	55
11	Nil	NaI/10	Toluene	80	24	No product
12[c]	50	NaI/10	Toluene	80	24	Trace
13	50	KI/10	Toluene	80	15	57
14	50	KBr/10	Toluene	80	15	34
15[d]	50	NaI/10	Toluene	80	8	67
16[e]	100	NaI/10	Toluene	80	8	88
17[f]	**100**	**NaI/10**	**Toluene**	**80**	**8**	**81**
18	50	NaI/10	Ethyl acetate	Reflux	12	84
19	50	NaI/10	2-Propanol	80	15	48

[a] General reaction conditions: mixture of 2-aminopyridine (1 mmol), acetophenone (1 mmol), GO and NaI in solvent (1 mL) was stirred with a magnetic spin bar at temperatures/times. [b] Yield represents pure product isolated after purification. [c] Reaction was carried out under N_2 blanket. [d] Reaction was carried out with 3 mmol of **1** & **2**. [e] Reaction was performed in 3 mmol scale. [f] Reaction was performed in 5 mmol scale.

Table 2 Reaction of different 2-aminopyridines with different acetophenones to synthesise imidazo[1,2-*a*]pyridines[a,b]





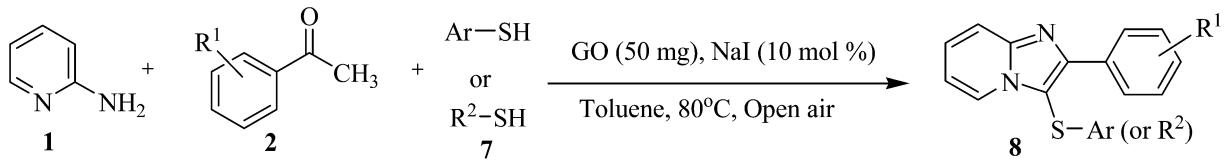
[a] A mixture of **1** (1 mmol), **2** (1 mmol), GO (50 mg), NaI (10 mol%) in toluene (1 mL) was stirred at 80 °C in open air. [b] Yield represents pure product isolated by column chromatography.

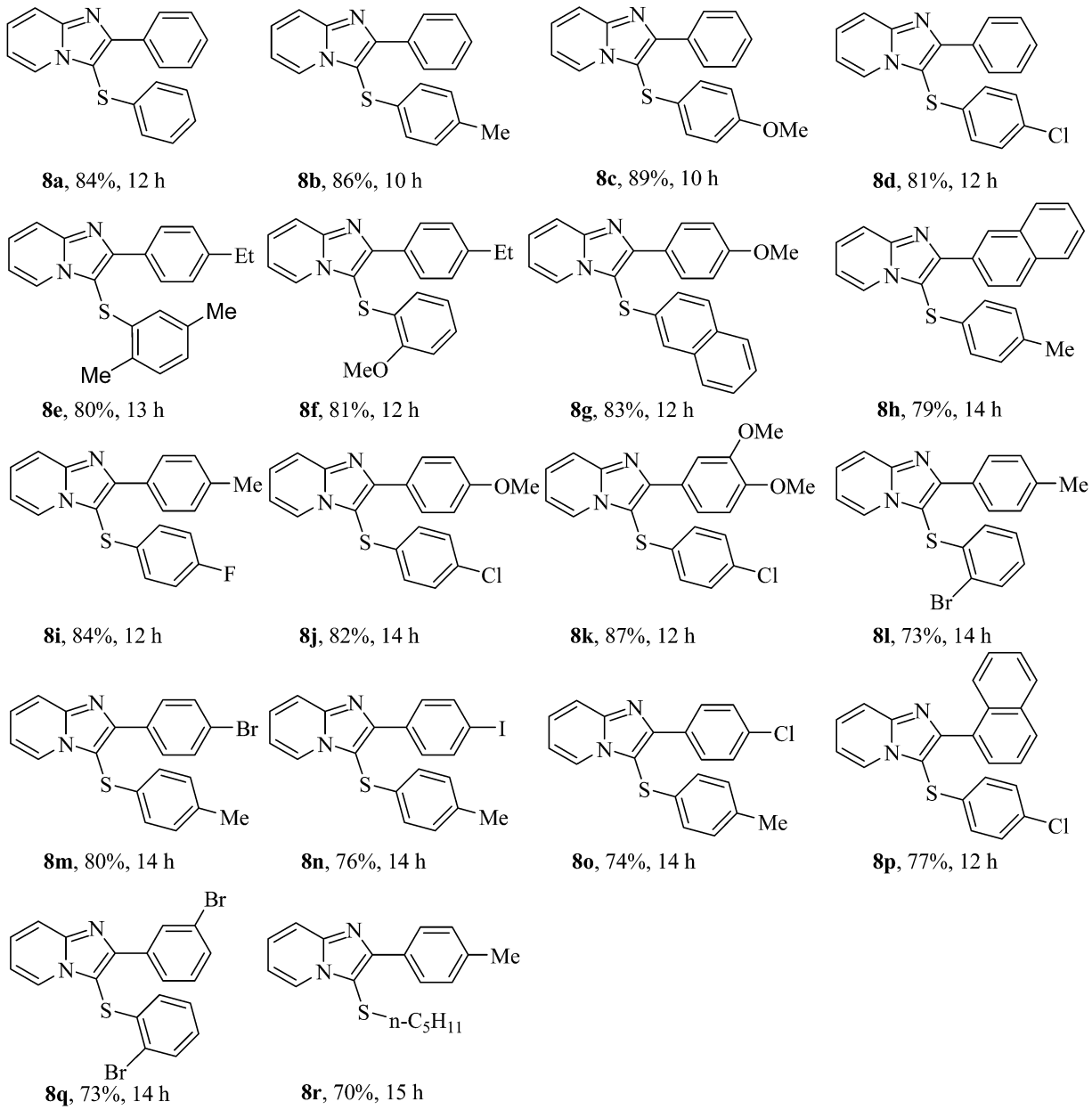
sulfenylimidazo[1,2-*a*]pyridine derivatives in 70–89% isolated yields. Critically, a marginal effect of the presence of *ortho*-substituent in thiophenol has been observed affording slightly lower yields of **8e**, **8f**, **8l**, **8q**), possibly due to steric encumbrance. However, there was no significant electronic effect of the substituents present in either benzenethiol or acetophenone observed. Aliphatic thiol also worked efficiently to afford the corresponding heterocyclic scaffold (**8r**). In general, the present MCR procedure using the catalytic combination of GO and NaI was found to be effective with diverse functional groups, as listed in the Table 3.

Catalytic performance is often measured by its life-cycle. After recovering the GO from the first batch of reaction by simple filtration, it was washed successively with ethyl acetate, water and acetone and finally dried under vacuum. The recovered free-flowing GO black powder was reused along with fresh NaI for three consecutive batches under similar reaction conditions giving nearly same yield in each batch (Table 4, 84–80%). In order to see any changes of the catalyst, we compared the FT-IR spectra of GO before and after use, and found no significant changes in characteristic absorption bands (Fig. 3). The absorption bands for various functional groups of graphene oxide remain unchanged during the course of the reaction. Isolation of the product in comparable yield in each run suggest the active sites of the surface of GO remain unaffected.

Previous mechanistic considerations suggest for two possible mechanistic pathways, *viz. via* ketimine or Ortoleva-King type intermediate.[7a,b] Since the reaction condition results in the formation of the bicyclic imidazo[1,2-*a*]pyridine **5** selectively, the reaction might proceed *via* Ortoleva-King type intermediate and possibly not through the formation of ketimine. Control experiments in the absence of GO (Table 1, entry 11) and under N_2 (Table 1, entry 12), afforded no product or trace conversion respectively signifying that the oxidation of iodide to iodine is likely to be possible in the presence of GO under aerobic condition. Based on our experimental observations, we propose that initially NaI is oxidized under aerobic condition to I_2 in the presence of GO and then acetophenone is iodinated to phenacyl iodide **9** (Scheme 2). Liberation of I_2 vapour is realized on mixing of GO with NaI in a blank test and without the presence of either of the components, the reaction is unsuccessful. Subsequently, phenacyl iodide **9** is attacked by the lone-pair pyridine nitrogen electrons to form the Ortoleva-King type intermediate **10**, which is eventually on dehydration afforded bicyclic imidazo[1,2-*a*]pyridine **5**. In the presence of thiol, compound **5** presumably undergoes hydrothiolation entirely in anti-Markovnikov fashion **11**, which is then oxidized to the desired 3-sulfenylimidazo[1,2-*a*]pyridines (Scheme 2). While GO has been shown to catalyze oxidation under aerobic condition, the active sites of the GO surface consisting of carboxylic acids may also help in acid-catalyzed reactions. In the present study, presumably the primary role of GO is to

Table 3 Preparation of library of 3-sulfenylimidazo[1,2-*a*]pyridines from multi-component reaction of 2-aminopyridines, acetophenone and thiol under the optimized reaction condition[a,b]





[a] A mixture of **1** (1 mmol), **2** (1 mmol), GO (50 mg), **7** (1.2 mmol), NaI (10 mol%) in toluene (1 mL) was stirred at 80 °C in open air. [b] Yield represents isolated product by column chromatography.

promote the oxidation of NaI to I_2 as well as that of the hydrothiolated intermediate **11** efficiently, resulting in the formation of 3-sulfenylimidazo[1,2-*a*]pyridines **8**.

Conclusion

In summary, we have demonstrated that catalytic amounts of graphene oxide in combination with NaI can efficiently perform

Table 4 Recyclability of GO in three-component tandem reaction of 2-aminopyridine, acetophenone and thiophenol[a]

Entry	Yield[b] (%)
1st run	84
2nd run	83
3rd run	84
4th run	80

[a] 2-Aminopyridine (1 mmol), acetophenone (1 mmol), thiophenol (1.2 mmol), GO (50 mg), NaI (10 mol%) in toluene was stirred at 80 °C. [b] Yield represents isolated pure product.

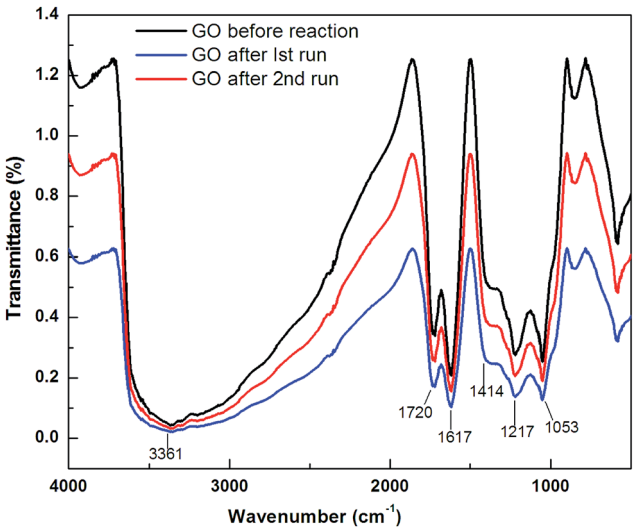


Fig. 3 Comparative FT-IR spectra of GO before use (black), after 1st run (blue) and 2nd run (red).

the reaction of 2-aminopyridine and acetophenone leading to the selective formation of important pharmacophore imidazo [1,2-*a*]pyridine. The same catalytic system can further carry out one-pot multi-component reactions, established with the formation of another class of important scaffolds 3-thiophenyl imidazo[1,2-*a*]pyridine. Both reactions are highly selective, metal-free, tolerant with diverse functional groups, and the carbocatalyst can be recovered and reused. The GO-catalyzed multi-component tandem reactions and application to important pharmaceutically active scaffolds are hitherto unknown and reported for the first time. Further applications of this sustainable and easily available carbonaceous material are expected to come out in the synthesis of diverse complex molecules of importance in pharmaceutical chemistry and material sciences.

Experimental section

All chemicals were purchased from commercial suppliers (Sigma-Aldrich) and used without further purification. NMR spectra were recorded on Varian AV-300 spectrometer using $CDCl_3$ solvent. Chemical shifts (δ) are reported in ppm and referenced to TMS for ^{1}H NMR and residual solvent signals for ^{13}C NMR as internal standard. Coupling constants (J) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, q = quartet, qnt = quintet, m = multiplet. Melting points were determined by heating in open capillary tube.

Preparation of graphene oxide (GO)

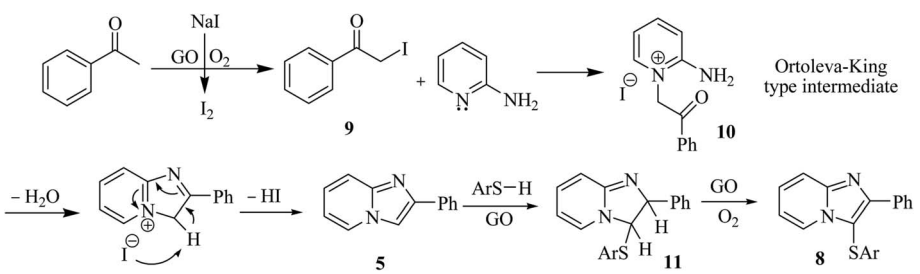
GO was prepared according to the modified Hummers method,[9c,17] and our previously reported conditions (see ESI, S1†).[13a]

General procedure for the synthesis of imidazo[1,2-*a*] pyridines (Table 2, 5a–5i)

To a solution of 2-aminopyridine (1 mmol), acetophenone (1 mmol) in toluene (1 mL) was added GO (50 mg) followed by NaI (15 mg, 10 mol%). The reaction mixture was then stirred using a small spin bar at 80 °C under an open air for the time indicated in Table 2. After completion of the reaction (monitored by tlc), the catalyst was filtered off, washed with ethyl acetate (3 × 3 mL) and the combined organic layer was washed with H_2O, dried (anhy. Na_2SO_4) and concentrated under vacuum. The residue was purified by passing through a short path of silica gel and elution with 9 : 1 light petroleum/ethyl acetate to afford the desired imidazo[1,2-*a*]pyridine (**5a–5i**). All products were characterized by ^{1}H- & ^{13}C-NMR spectral data and comparison with their melting points with the literature value, wherever reported (see ESI, S2†).

General procedure for the multi-component synthesis of 3-sulfenylimidazo[1,2-*a*]pyridines (Table 3, 8a–8r)

To a solution of 2-aminopyridine (1 mmol), acetophenone (1 mmol) and thiol (1.2 mmol) in toluene (1 mL), were added GO



Scheme 2 Proposed mechanism for the formation of 3-sulfenylimidazopyridine *via* Ortoleva-King type intermediate.

(50 mg), and NaI (15 mg, 10 mol%). The reaction mixture was stirred with magnetic spin bar at 80 °C for the time indicated in Table 3. After completion of the reaction (monitored by tlc), the catalyst was filtered off and the catalyst washed with ethyl acetate (3 × 3 mL) and the combined filtrate was washed with H_2O and then dried (anhy. Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography over silica gel and elution with light petroleum/ethyl acetate (19 : 1–9 : 1) to obtain the desired 3-sulfenylimidazo[1,2-*a*]pyridine (Table 3, **8a–8r**) in pure form. All products were characterized by ^{1}H-& ^{13}C-NMR spectral data and comparison of melting points with their literature values, wherever reported (see ESI, S2†).

Acknowledgements

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Unprecedented amidation of 'transient' aryl thioaldehydes by *N,N*-dimethylformamide under basic conditions†

Basudeb Basu* and Samir Kundu

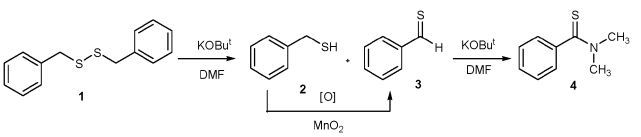
An unprecedented reaction of *N,N*-dimethylformamide (DMF) with 'transient' aryl thiobenzaldehydes, derived from diaryl disulfides under basic conditions, is reported. The unique role of DMF has been generalized to construct a simple method for the synthesis of *N,N*-dimethyl aryl thioamides. A plausible mechanism for this transformation is discussed.

N,N-dimethylformamide (DMF) is commonly used as a polar organic solvent, and has a high boiling point and a low evaporation rate. The structure of DMF is believed to be a combination of two resonating forms, as evidenced by its IR and NMR spectra. DMF contains two functionalities – the amide and the aldehyde functionalities.[1] In reagent chemistry, DMF is used as a reagent in the Vilsmeier–Haack reaction to introduce formyl groups into electron-rich arenes in the presence of $POCl_3$. It is believed that the combination of DMF and $POCl_3$ produces an electrophilic iminium cation, which undergoes an electrophilic aromatic substitution reaction, followed by hydrolysis of the arene–iminium ion intermediate to form the aryl aldehyde.[2] Besides these major functions, DMF can also act as a source of CO in metal-catalyzed carbonylation, and can be used as a source of NMe_2 units, Me_2NCO units, *etc.*[3]

Thiobenzaldehydes are generally very unstable compounds, except for some highly substituted aryl thioaldehydes.[4] Although several methods are known to produce aryl thioaldehydes, they are considered to be reactive intermediates and can be trapped by suitable reagents to afford stable products, *e.g.* cycloaddition with dienes,[5] condensation with hydrazine,[6] or addition of suitable amines.[7] Several authors have reported the generation of 'transient' thioaldehydes in reactions such as: (i) the formation of 'Bunte salts' (*S*-alkyl/aryl thiosulfates) in the presence of NEt_3;[5] (ii) photolytic Norrish type-II cleavage of phenacyl sulfides;[8a–c] (iii) the reaction of dibenzyl disulfides in the presence of Na_2CO_3 in DMF;[6] (iv) the reaction of phosphonium ylides with elemental sulfur;[8d] or (v) fluoride-induced elimination of α-silyldisulfides,[8e] besides the classical Willgerodt–Kindler reaction under harsh conditions,[8f,g] or the use of Lawesson's reagent for S-transfer,[8h] and others.[8i,j]

We found that the reaction of dibenzyl disulfide in the presence of potassium *tert*-butoxide (KO^tBu) in DMF unexpectedly afforded *N,N*-dimethylthiobenzamide in 43% yield on heating to 100 °C. Based on literature reports,[6] it was presumed that dibenzyl disulfide underwent 1,2-elimination under basic conditions to form benzylthiol and thiobenzaldehyde, and that the latter could react with DMF to form *N,N*-dimethylthiobenzamide, as outlined in Scheme 1. Since one part of the dibenzyl disulfide produces benzylthiol, the reaction was also carried out in the presence of an oxidizing agent (MnO_2). It is interesting that the ultimate product, *N,N*-dimethylthiobenzamide, was then isolated in 91% yield. Changing the base and varying the temperature, however, did not result in any better practical observations. The optimization of the reaction conditions is presented in Table 1. Moreover, use of K_2CO_3 as the base did not result in the formation of thiobenzamide (Table 1, entry 4), although it has been reported that treatment of Na_2CO_3 with dibenzyl disulfide could form 'transient' thioaryl aldehyde.[6]

Since *N,N*-dialkyl aryl thioamides are important building blocks for the synthesis of diverse heterocyclic compounds of biological relevance,[9a–f] and also find applications in coordination chemistry and materials science,[9g–k] we were interested in



Scheme 1 Amidation of thiobenzaldehyde, derived from dibenzyl disulfide, in the presence of DMF under basic conditions.

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† Electronic supplementary information (ESI) available: ^{1}H- & ^{13}C-NMR spectral data for compounds **4a–4i** in Table 2, X-ray analysis data & ORTEP diagrams for compounds **4a** and **4d**, and scanned copies of NMR spectra for **4a–4i**. CCDC 994136 and 994137. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4nj00480a

Table 1 Optimization of the one pot thiobenzamide synthesis reaction[a]

Entry	Base	Oxidant	Temp. (°C)	Time (h)	Yield[b] (%)
1	KO^{t}Bu	Nil	100	4	43
2	**KO^{t}Bu**	**MnO_2**	**100**	**4**	**91**
3	NaH	Nil	100	4	39
4	K_2CO_3	Nil	100	15	Nil
5	KO^{t}Bu	MnO_2	rt	24	Nil
6	KO^{t}Bu	MnO_2	50	24	Nil
7	KO^{t}Bu	MnO_2	80	10	54

[a] Reactions were performed with dibenzyl disulfide (1 mmol), base (3.0 mmol), MnO_2 (1.5 mmol, for entries 2 and 5–7) and DMF (2 mL) in a sealed tube. [b] Isolated yields after passing through a short silica gel column.

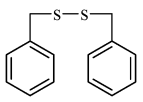
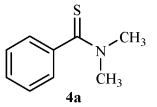
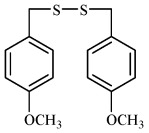
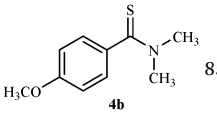
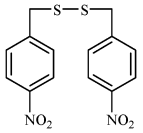
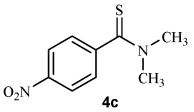
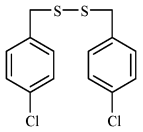
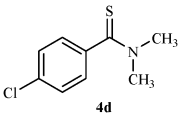
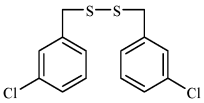
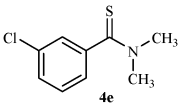
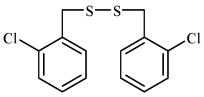
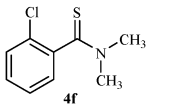
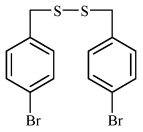
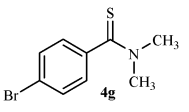
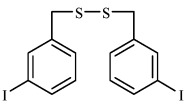
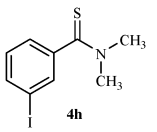
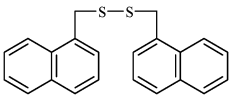
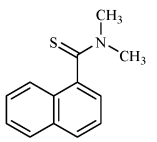
developing this simple and clean reaction as a general protocol for their synthesis. In this paper, we report our results, which establish that DMF plays a unique role in delivering the dimethylamino group (–NMe_2) to the reactive thiobenzaldehydes formed *in situ* to finally produce the corresponding *N,N*-dimethyl aryl thioamides.

The optimized reaction conditions, as shown in entry 2 (Table 1), were employed for a variety of diaryl disulfides. Table 2 shows that different substituents attached to the aromatic ring can survive the reaction conditions, resulting in the formation of thiobenzamides.

For example, electron-donating groups (–OMe), strongly electron-withdrawing groups (–NO_2) and different halides attached at the *ortho*, *meta* or *para* positions underwent clean reactions, affording the corresponding *N,N*-dimethyl aryl thioamides in good to excellent yields (Table 2, entries 2–8). This clearly reveals the tolerance of various substituents to the reaction conditions and establishes the generality of the reaction procedure. A similar reaction was performed with dinaphthyl disulfide to afford *N,N*-dimethyl 1-naphthyl thioamide in 87% isolated yield (entry 9).

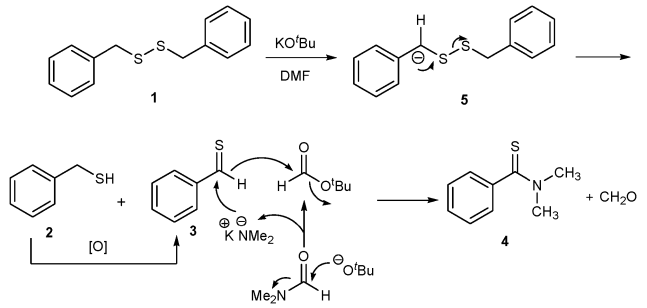
Regarding a plausible mechanism for this unique conversion, literature reports revealed that DMF can act as a source of the –NMe_2 group in reactions with acid chlorides, esters or anhydrides that involve attack of the acyl group by the nitrogen atom of DMF.[10] Further substitution by the –NMe_2 group has been reported for active halides such as benzyl chloride,[10a] or electron-deficient aryl chlorides, usually at high temperature.[11] On the other hand, Okuma and co-workers reported that thioaldehydes, prepared *in situ*, can undergo reactions with amines to produce the corresponding thioamides *via* the formation of aminals and subsequent reaction with H_2S, though secondary amines such as diisopropylamine or morpholine do not form thiobenzamides bearing *N*-diisopropyl or *N*-morpholino groups.[7] In our study, we believe that the dibenzyl disulfide produces a 'transient' thiobenzaldehyde, as evidenced by trapping it with $PhNHNH_2$ and isolating the addition product benzalazine.[6] Nasipuri suggested that a mixture of DMF and NaH can produce *N,N*-dimethylsodamide.[12a] In a recent report on the metal-catalyzed hetero cross-coupling reaction of aryl halides, DMF was shown to act as one of the coupling partners, and *N,N*-dimethyl aryl amines were believed to be formed *via* transmetalation with $KNMe_2$, which was generated under the

Table 2 Reactions of different diaryl disulfides with DMF[a]

Entry	Disulfide **1**	Time (h)	Product **4**	Yield[b] (%)
1		4	 **4a**	91
2		4	 **4b**	85
3		4	 **4c**	83
4		4	 **4d**	89
5		5	 **4e**	83
6		6	 **4f**	86
7		4	 **4g**	87
8		5	 **4h**	79
9		4	 **4i**	87

[a] Reaction conditions: disulfide (1 mmol), KO^{t}Bu (3.0 mmol), MnO_2 (1.5 eq.) in DMF (2 mL) in a sealed tube with gentle magnetic stirring at 100 °C for the time mentioned. [b] Isolated yields after passing through a short silica gel column.

reaction conditions.[12b] From this background and our observations, and considering that the reaction was carried out in a strongly basic medium, we propose the mechanism outlined in Scheme 2. The reaction starts with the formation of a benzyl carbanion, **5**, from dibenzyl disulfide **1**. The benzyl carbanion undergoes cleavage of the disulfide linkage, affording benzylthiol **2** and the 'transient' thiobenzaldehyde **3**. It should be mentioned that dibenzylsulfide decomposes in the presence of KO^{t}Bu in DMF, producing styrene through the formation of a benzyl carbanion and subsequent elimination of a sulfide ion.[13] DMF reacts with the base (–O^{t}Bu) to produce an amide ($KNMe_2$)



Scheme 2 Plausible mechanism involving attack of the thiobenzaldehyde by the dimethylamide anion.

that attacks at the thiocarbonyl carbon and eliminates hydride to eventually form *N,N*-dimethylthiobenzamide **4** and formaldehyde. Formation of thiobenzaldehyde **3** was confirmed by the isolation of benzalazine in 62% yield along with the thiobenzamide **4a** (18%),‡ and the fact that the reaction carried out in the presence of MnO_2 afforded a higher yield of thiobenzamide (43% to 91%) conforms to the mechanistic sequence (Scheme 2). A strong base is essential to produce the amide ($-NMe_2$) from DMF, and use of K_2CO_3 did not result in the formation of thiobenzamide (Table 1, entry 4), although generation of thiobenzaldehyde from dibenzyl disulfide using Na_2CO_3 in DMF has been reported.[6]

Most of the aryl thioamides were characterized by their FT-IR, ^{1}H-NMR and ^{13}C-NMR spectral data and melting points, which were compared with the reported compounds, where available. However, in order to establish the structures of the compounds unequivocally, at the beginning of our studies we performed single crystal X-ray structure determination for two compounds, *viz.*, *N,N*-dimethylthiobenzamide, **4a** and *N,N*-dimethyl 4-chlorophenylthioamide, **4d**. The single crystal X-ray diffraction analyses for thiobenzamides **4a** and **4d** not only confirmed their structures unambiguously but also revealed possible contacts between the sulfur atoms and the methyl hydrogen atoms. In the case of **4a**, there are possible contacts between the S and N-methyl H atoms, whereas for compound **4d**, there are Ar–H atoms that show contacts with the S atom of the amide (Fig. 1).

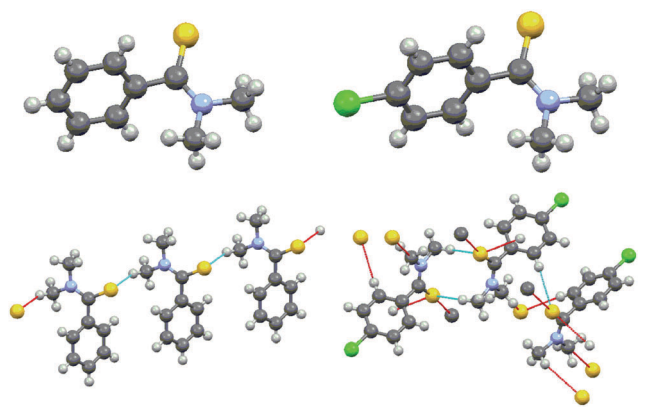


Fig. 1 Single crystal X-ray structures of thiobenzamides **4a** (left, top) and **4d** (right, top); possible contacts or bonding for compounds **4a** (left, bottom) and **4d** (right, bottom); ellipsoids set at 50% probability; all H atoms are shown.

In conclusion, a completely new process involving amidation of 'transient' thiobenzaldehydes using *N,N*-dimethylformamide, which bears both amide and aldehyde functionalities, has been established under catalyst-free conditions. The reaction possibly proceeds with the formation of *N,N*-dimethyl potassium amide ($KNMe_2$) and subsequent attack at the thiocarbonyl carbon atom, which is reported for the first time. Since aryl thioamides are an important class of compounds, this reaction using inexpensive DMF could not only replace the common Willgerodt–Kindler (WK) reaction, but also inspire diverse reactions that involve DMF beyond its use as a solvent.

Experimental

Materials and instrumentation

Chemicals were either purchased from commercial suppliers and used without further purification or prepared in the laboratory. IR spectra were recorded on an FT-IR spectrophotometer (8300 Shimadzu), using Nujol mulls for liquid compounds and KBr pellets for solid compounds. NMR spectra were recorded on a Varian AV 300 spectrometer, using $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm and referenced to TMS for ^{1}H and residual solvent signals for ^{13}C, as internal standards. Coupling constants (J) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity are used as follows: s = singlet, d = doublet, t = triplet, m = multiplet. Melting points were determined by heating in an open capillary tube, and were not corrected. Single crystal X-ray structure determinations were carried out on a Bruker Nonius Smart Apex II Diffractometer from IIT, Guwahati.

General Procedure for the synthesis of 4a–4i

To a solution of diaryl disulfide **1** (1 mmol) in freshly distilled DMF (2 mL) were added KO^{t}Bu (3 mmol) and MnO_2 (1.5 eq.), and the reaction mixture was heated at 100 °C with magnetic stirring in a screw-capped sealed tube for 4–6 h. The mixture was then cooled, diluted with water (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined ethereal extracts were dried (anhydrous Na_2SO_4) and concentrated to afford the product in almost pure form. However, for spectroscopic characterization (FT-IR, ^{1}H- and ^{13}C-NMR), the product was passed through a short silica gel column. All products (**4a–i**) gave satisfactory spectral analytical data and melting points (solid compounds), which compared well with those reported in the literature (see ESI† for ^{1}H- and ^{13}C-NMR spectral data and scanned copies of spectra).

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Notes and references

‡ A similar reaction was carried out in the presence of hydrazine hydrochloride (3 equiv.). After the reaction, TLC of the reaction mixture showed two spots corresponding to thiobenzamide (R_f = 0.43) and benzalazine (R_f = 0.21) in ethyl acetate–light petroleum (1 : 4). Both compounds were easily isolated by column chromatography over silica gel and characterized by NMR spectroscopy and comparison with melting point data.

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Silica: An efficient catalyst for one-pot regioselective synthesis of dithioethers

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Abstract

The development of a silica-promoted highly selective synthesis of 1,2 or 1,3-dithioethers via solvent-free one-pot tandem reactions of an allyl bromide with excess thiol at room temperature is described. The choice of silica gel, either pre-calcined or moistened with water, exhibited notable regioselectivity in the formation of dithioethers. Plausible mechanistic routes were explored and postulated.

Introduction

Organosulfur compounds are important building blocks for the synthesis of various biologically active molecules [1-3]. Versatile applications of organosulfur compounds are known in fields such as the pharmaceutical, the polymer, the pesticide and the food-processing industry [4-8]. For example, organosulfur compounds in garlic are often used in food-processing industries as flavouring and preservative agents and are also used as herbal medicine [4]. Dithioethers are commonly employed as ligands in preparing metal-coordination complexes and also as spacers in metal-organic frameworks [9-14]. For example, vicinal dithioether-based zirconium and titanium complexes have been used for alkene polymerization and hydroamination [15-18]. Chiral dithioethers have been prepared and their iridium complexes have been employed in asymmetric hydrogenation [18]. Vicinal dithioethers are generally synthesised either by the metal-catalyzed addition of disulfides to alkenes [19,20] or by the traditional nucleophilic substitution of 1,2-dihalides with suitable thiols/thiolates [21,22]. They are also prepared by consecutive hydrothiolation of alkynes, both under nucleophilic and radical-induced conditions [22,23]. On the other hand, 1,3-dithioethers can be prepared by the nucleophilic substitution of compounds bearing suitable leaving groups at 1,3-positions of alkyl chains [21]. Because of their versatile applications, a great number of procedures have been developed to synthesize bis(thioethers) with varying degrees of success and a variety of limitations [19-31].

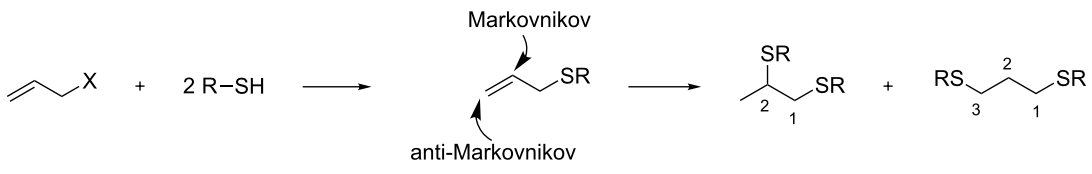
Over the last decade, organic synthesis has taken a major turn towards developing reaction conditions that are environmentally friendly and sustainable [32-36]. Mesoporous inorganic

oxides, which often facilitate various organic reactions, are considered suitable to promote eco-friendly chemical processes [36]. Organic reactions with a high selectivity under eco-friendly and sustainable conditions are attractive features in terms of the concepts of Green chemistry. Previously, we have developed silica-promoted facile and highly selective methods for N and S-alkylations/acylation from amines or thiols, respectively [37,38]. An equimolar mixture of a benzenethiol and allyl bromide on treatment with silica afforded allyl(phenyl)sulfane in excellent yield. Since alkenes are also known to undergo 'click' addition with thiols [39,40], excess use of thiols could effectively produce dithioethers, and based on a regioselective addition one could achieve either vicinal or 1,3-dithioethers in one-pot consecutive substitution–hydrothiolation processes (Scheme 1). Although both reactions are well-known, a search in the literature surprisingly revealed no general one-pot protocols for the preparation of dithioethers from allylic substrates. Recently, Banerjee and co-workers reported on the simple synthesis of thioethers by silica NPs, where a single example of a reaction of an allyl bromide and excess benzenethiol was studied [41,42]. The reaction was carried out in the presence of silica NPs and water, and they isolated 1,3-dithioether by an anti-Markovnikov addition. However, there is no report on the metal-free hydrothiolation of allylic substrates in a Markovnikov fashion to afford 1,2-dithioethers in one-pot reactions. In this paper, we wish to report our investigations on the reaction of allyl halides with excess thiols promoted by silica gel, which finally constitutes distinct protocols for one-pot, solvent-free substitution and regioselective additions to produce either 1,2 or 1,3-dithioethers.

Results and Discussion

Following our previous experience [37,38], we first attempted the magnetic stirring of a mixture of allyl bromide and benzenethiol in a 1:2.5 ratio by using pre-calcined silica gel at room temperature that indeed led to the formation of 1,2-dithioether in 91% yield. On the other hand, if silica gel moistened with a few drops of water was used for the same reaction, the regioselective anti-Markovnikov addition product, i.e., 1,3-dithioether, (1-(3-(phenylthio)propylthio)benzene) was obtained in 83% yield. In both cases, a minimal amount of diphenyldisulfide (5–10%) was formed [43,44], which was easily separable from the reaction mixture by column chromatography. Since the choice of silica led to the production of highly regioselective products, we wanted to optimize both conditions to establish them as general protocols. Table 1 shows the optimization of the reactions of different allylic substrates with benzenethiol. Silica gel (directly from the container, commercially available) was used either pre-activated by heating at 100 °C under vacuum for 1 h and then cooled under vacuum for use under conditions A or moist with water (0.1 mL water for 0.5 g of silica) for use under conditions B. It was observed that allyl bromide or allyl iodide underwent sequential substitution–addition reactions entirely regioselectively with comparable yields (Table 1, entries 1–5), whereas allyl chloride showed varying results under conditions A or B, and allyl acetate did not undergo any desired reaction, but merely produced the disulfide from oxidative dimerization of the thiol (Table 1, entries 6–8). Allyl tosylate, however, produced the desired thioethers in a regioselective manner, but with relatively low yields (Table 1, entries 9 and 10). Interestingly, allylphenylsulfane or allyl phenyl ether entirely followed an anti-Markovnikov addition, under both conditions, A and B (Table 1, entries 11–14).

With the two distinct conditions, we examined the scope of these one-pot tandem reactions of allyl bromide with a variety of thiols under both conditions. The results are presented in Table 2. Arylthiols bearing different functional groups like CH_3, OCH_3, Cl or F were reacted with allyl bromide in the presence of pre-calcined and dry silica affording good to excellent yields of the corresponding 1,2-dithioethers (Table 2, entries 1, 3, 5, 7, 9, 11 and 17). 2-Naphthylthiol also underwent a similar regioselective Markovnikov addition, resulting in the corresponding 1,2-dithioether in 82% yield (Table 2, entry 18). Extending the protocol to aliphatic thiols, such as *n*-pentylthiol and cyclohexylthiol also afforded regioselective dithioether in good yields (Table 2, entries 13 and 15). In all the cases, we observed 100% Markovnikov addition products and no anti-Markovnikov products were detected. We now turned our attention to the other conditions B – the use of moist silica gel. Again, a variety of aromatic thiols, including those that were used for the conditions A, were employed to react with allyl bromide in the presence of silica moist with a few drops of



Scheme 1: Sequential substitution-addition reactions of thiols with allyl halides leading to the formation of 1,2 or 1,3-dithioethers.

Table 1: Optimization of one-pot sequential substitution–hydrothiolation of allylic substrate with excess benzenethiol over silica at room temperature.

Entry	CH_2=CH-CH_2-X	Conditions[a]	Time (h)	Product[b]/Yield[c] (%)
1	X = Br	A	6	1,2-dithioether/77
2	X = Br	A	11	1,2-dithioether/91
3	X = Br	B	20	1,3-dithioether/83
4	X = I	A	12	1,2-dithioether/89
5	X = I	B	20	1,3-dithioether/85
6	X = Cl	A	15	1,2-dithioether/57
7	X = Cl	B	30	diphenyldisulfide/83
8	X = OAc	A	24	diphenyldisulfide/90
9	X = OTs	A	8	1,2-dithioether/75
10	X = OTs	B	22	1,3-dithioether/68
11[d]	X = SPh	A	5	1,3-dithioether/83
12[d]	X = SPh	B	12	1,3-dithioether/80
13[d]	X = OPh	A	6	3-phenoxythioether/89
14[d]	X = OPh	B	14	3-phenoxythioether/82
15	X = Br	Neat mixture	20	no dithioether is formed

[a]Conditions A: allylic compound and PhSH (1:2.5 mmol) over pre-calcined dry silica gel (0.5 g); conditions B: allylic compound and PhSH (1:2.5 mmol) over moistened silica gel (0.5 g). [b]In each case 5–10% diphenyldisulfide was formed except in entries 6–8. [c]Yield refers to isolated pure product and no other constitutional isomer was detected. [d]Thiol (1.2 mmol) was used for entries 11–13.

Table 2: Regioselective one-pot synthesis of 1,2 and 1,3-dithioethers using dry (pre-calcined) or moistened silica gel at room temperature.

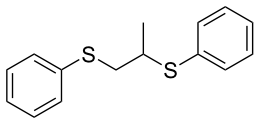
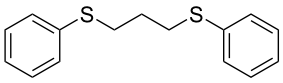
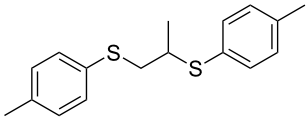
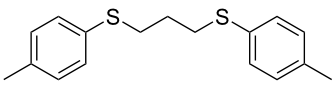
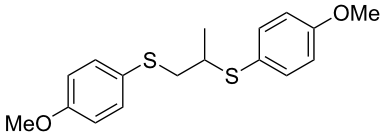
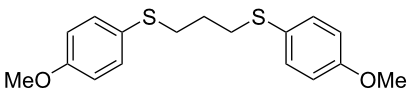
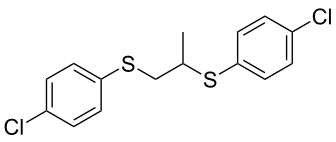
Entry	Thiol	Conditions[a]	Time (h)	Product	Yield[b] (%)
1	C_6H_5-SH	A	10		91
2	C_6H_5-SH	B	22		81
3	4-(H_3C)C_6H_4-SH	A	6		87
4	4-(H_3C)C_6H_4-SH	B	20		78
5	4-(H_3CO)C_6H_4-SH	A	6.5		78
6	4-(H_3CO)C_6H_4-SH	B	18		76
7	4-(Cl)C_6H_4-SH	A	6		83

Table 2: Regioselective one-pot synthesis of 1,2 and 1,3-dithioethers using dry (pre-calcined) or moistened silica gel at room temperature. (continued)

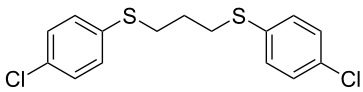
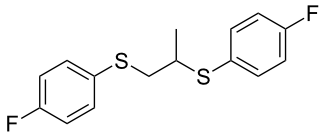
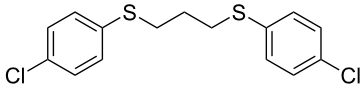
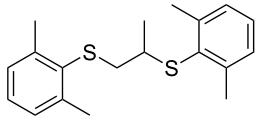
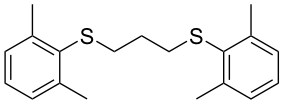
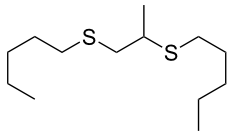
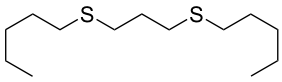
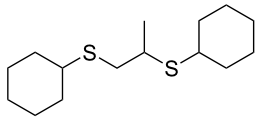
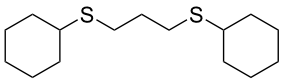
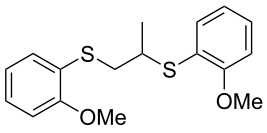
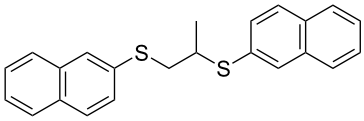
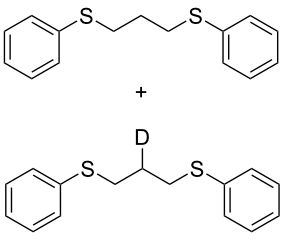
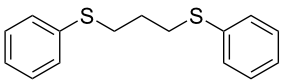
8	4-(Cl)C_6H_4-SH	B	15		87
9	4-(F)C_6H_4-SH	A	8		80
10	4-(F)C_6H_4-SH	B	16		84
11	2,6-$(CH_3)_2$)C_6H_3-SH	A	8		74
12	2,6-$(CH_3)_2$)C_6H_3-SH	B	20		77
13	*n*-C_5H_{11}-SH	A	9		67
14	*n*-C_5H_{11}-SH	B	16		71
15	Cy-SH	A	10		65
16	Cy-SH	B	18		67
17	2-(H_3C)C_6H_4-SH	A	7		71
18	2-$C_{10}H_7$-SH	A	9		82
19[c]	C_6H_5-SH	B	22		

Table 2: Regioselective one-pot synthesis of 1,2 and 1,3-dithioethers using dry (pre-calcined) or moistened silica gel at room temperature. (continued)

20	C_6H_5-SH	A[d]	15		82

[a]Conditions A: allylic compound and PhSH (1:2.5 mmol) over pre-calcined dry silica gel (0.5 g); conditions B: allylic compound and PhSH (1:2.5 mmol) over moist silica gel (0.5 g). [b]Yield refers to isolated pure product; in each case 5–10% diphenyldisulfide was formed and isolated. [c]D_2O (0.5 mL for 0.5 g silica gel) was used instead of H_2O. [d]Mixture of silica and sodium silicate (1:1 w/w; 0.5 g for 1 mmol of allyl bromide) was used after drying under vacuum.

water, and we isolated entirely regioselective 1,3-dithioethers (Table 2, entries 2, 4. 6, 8, 10 and 12). The same selectivity was observed in the reaction of aliphatic thiols (acyclic or alicyclic), viz. *n*-pentane-1-thiol and cyclohexanethiol, with allyl bromide to afford the corresponding 1,3-dithioethers in 71% and 67% yield, respectively (Table 2, entries 14 and 16). In these cases, we did not detect any Markovnikov addition products. Thus, moistened silica gel turns out to be effective for sequential substitution reactions, and entirely anti-Markovnikov addition, while pre-calcined dry silica gel could efficiently give rise to only Markovnikov addition products. The reactions over dry silica gel appear to be faster than the procedure using moist silica. Moreover, the 1,2-dithioethers are formed in slightly better yields than the corresponding 1,3-analogues. We also experienced that aromatic thiols, under both conditions A and B, give better yields than aliphatic thiols.

We assume that the nature of the silica surface and its possible interactions with thiols is responsible for the notable regioselectivity in the hydrothiolation of allylsulfane. It is known that amorphous or mesoporous silica consists of silanol groups and siloxane bridges that determine its surface properties, and the concentration of these OH groups depends mostly on the actual process of calcinations [45-47]. Based on Zhuravlev's physicochemical model of silica surface [45], it may be presumed that the moistened silica surface is covered with a single layer or multilayer of adsorbed water, which might disappear during the calcination process. Since allylphenylsulfane on hydrothiolation affords the anti-Markovnikov product under both conditions A and B (Table 1, entries 11 and 12), we presume that there might be an influence of the generated acid in the first step under dry conditions A. In the absence of water, the generated HBr in the first step might activate the double bond and subsequent assistance by the neighbouring sulfur atom coupled with the stability of the secondary carbocation lead to the Markovnikov addition resulting in the exclusive formation of 1,2-dithioether (Scheme 2, conditions A). On the other hand, the moist silica consisting of a single layer or multilayered adsorbed water promotes thiols to bind with allylsulfane, and the subsequent addition takes place in an anti-Markovnikov approach (Scheme 2, conditions B).

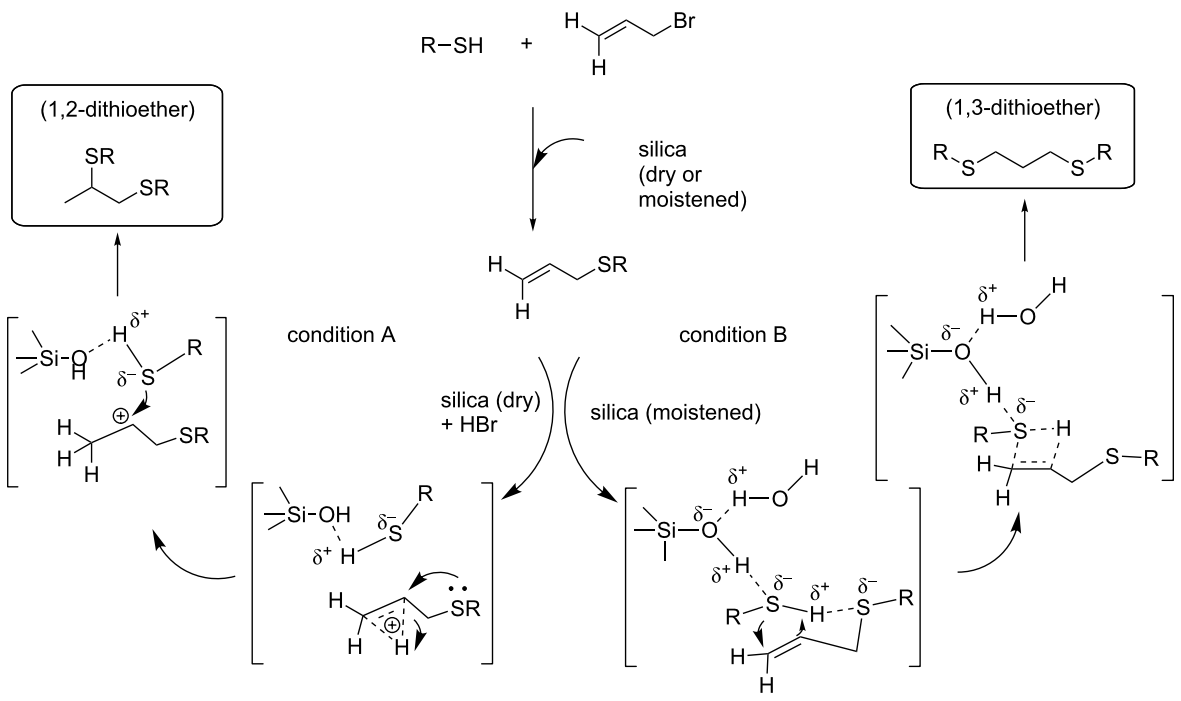
In order to find evidence for the role of silica adsorbed water, we conducted the following experiments: (i) the reaction was carried out under conditions A in the presence of an exogenous base (sodium silicate; see Experimental), which leads to the formation of anti-Markovnikov product only (1,3-dithioether) (Table 2, entry 20); (ii) reactions under conditions B with varying quantities of H_2O (0.5 mL and 1.0 mL) did not exhibit any significant changes producing only 1,3-dithioethers in quantities; (iii) dry HCl gas was passed through pre-calcined silica and was used for the hydrothiolation of allylphenylsulfane, exclusively yielding an Markovnikov addition product (1,2-dithioether); (iv) an experiment was carried out with silica moistened with D_2O (Table 2, entry 19), which afforded a mixture of 1,3-bis(phenylthio)propane and [2-D]1,3-dithioether as seen from the ^{1}H NMR spectrum of the mixture and calculated to be in the ratio of 1:3.9. In the ^{13}C NMR spectrum, the deuterated carbon appeared as a triplet at δ 27.96, J = 20 Hz (see Supporting Information File 1). This observation supports that conditions B might occur through an initial thiol proton exchange with D_2O (PhS–H → PhS–D).

Conclusion

We have demonstrated that the choice of silica gel, either dry or moistened, could lead to highly selective pathways for the preparation of different dithioethers. The sequential reactions in one-pot protocols are robust, neutral, metal-free and notably selective with a broad range of substrates. The diverse reactivity of silica gel in the formation of vicinal or 1,3-dithioethers might not only spur the adaptation of existing procedures for selective dithioether preparation but also attract novel applications. Further utilizations of this diverse reactivity are currently being explored in our laboratory.

Experimental

All chemicals were purchased from commercial suppliers and used without further purification. IR spectra were recorded on



Scheme 2: Plausible mechanisms for the regioselective formation of vicinal and 1,3-dithioethers by using dry or moistened silica gel.

an FTIR spectrophotometer (8300 Shimadzu) using Nujol mulling for liquid compounds and KBr pellets for solid compounds. NMR spectra were recorded on a Varian AV-300 spectrometer with $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm and referenced to TMS for ^{1}H NMR spectra and residual solvent signals for ^{13}C NMR spectra as internal standards. Coupling constants (*J*) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, q = quartet, qnt = quintet, m = multiplet. Melting points were determined by heating in an open capillary tube. High resolution mass spectra (HRMS) were performed in a Micromass Q-TOF Spectrometer under ESI (positive mode) by the services at the Indian Association for the Cultivation of Science, Kolkata.

Calcination: Commercially available silica gel (Merck, India; Grade: TLC; HF_{254}) was heated under vacuum at 100 °C for 1 h, cooled, and then be used for the reaction or stored in a glass-stoppered flask for at least two weeks.

Moistened silica: Commercially available silica gel (Merck, India; Grade: TLC; HF_{254}) was mixed with water and used for the reactions. For column chromatography: silica (60–120 μm) (Thomas Baker, India), and for TLC, Merck plates coated with silica gel 60, F_{254} were used.

General procedure for Table 2 (route A or B)

Route A: A mixture of allyl bromide (1 mmol) and thiol (2.5 mmol) was mixed with pre-calcined dry silica gel (Table 2, for entries 1, 3, 5, 7, 9, 11, 13, 15, 17 and 18)

Route B: A mixture of allyl bromide (1 mmol) and thiol (2.5 mmol) was mixed with silica gel (0.5 g), moistened with two drops of water, (Table 2, for entries 2, 4, 6, 8, 10, 12, 14 and 16), and stirred magnetically by using a spin bar for the respective times listed in Table 2. The reaction was monitored by TLC. After completion the product was purified by column chromatography over silica gel. Elution with light petroleum or mixtures of ethyl acetate/light petroleum (see Supporting Information File 1) furnished the desired dithioether. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS data.

Procedure for the reaction using a mixture of silica and sodium silicate under conditions A (Table 2, entry 20)

Equal quantities of silica gel and sodium silicate (1 g each) were mixed, dried under vacuum at 100 °C for 1 h, cooled, and used for the reaction. The mixture (500 mg) was stirred in water (10 mL) and its pH was measured to be 12.7. A mixture of allyl bromide (1 mmol) and benzene thiol (2.5 mmol) was thoroughly mixed with the mixture of dry silica gel and sodium sili-

cate (500 mg), and the solid reaction mixture stirred for 15 h at room temperature. After the reaction, the product was purified by column chromatography (82% yield) and characterized as 1-(3-(phenylthio)propylthio)benzene (1,3-dithioether).

Supporting Information

Supporting information features FTIR, ^{1}H NMR, ^{13}C NMR and HRMS data for 1,2 and 1,3-dithioethers (Table 2, entries 1–19) and ^{1}H NMR and ^{13}C NMR spectra for compounds listed in Table 2, entries 1–19.

Supporting Information File 1

Characterization data for compounds listed in Table 2, entries 1–19.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-5-S1.pdf]

Supporting Information File 2

^{1}H NMR and ^{13}C NMR spectra for compounds listed in Table 2, entries 1–19.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-5-S2.pdf]

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Graphene oxide as a carbocatalyst: the first example of a one-pot sequential dehydration–hydrothiolation of secondary aryl alcohols†

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An efficient and mild one-pot graphene oxide (GO)-catalyzed sequential dehydration–hydrothiolation reaction has been developed for the first time from a mixture of secondary aryl alcohols and thiols. The resulting unsymmetrical thioethers were prepared under metal-free conditions. The catalyst can be reused for five runs with appreciable conversions.

Introduction

Harnessing the efficiency of graphene oxide (GO) as a carbocatalyst for various synthetic reactions is a recently sought after challenge.[1] GO possesses a rich chemical functionality, is slightly acidic (pH 4.5 at 0.1 mg mL^{-1}),[2] and has long been recognized as having strong oxidizing properties.[1c,3] Fig. 1 represents the schematic structure of functionalized graphene oxide (FGO).[4]

Recent reports from Bielawski and coworkers, and subsequently from other groups, have revealed an intriguing new direction for the metal-free catalytic use of GO in organic reactions.[5] However, the application of GO and other chemically modified graphenes (CMGs) as catalysts in synthetic chemistry remains essentially unexplored. Bielawski and coworkers have reported the GO-facilitated oxidation of benzylic alcohols to the corresponding aldehydes or ketones with varying yields.[5a] The oxidation was carried out using 200 wt% GO and heating at 100 °C for 24 h. From their observations, it was noted that diphenylmethanol afforded a >98% conversion to the corresponding ketone, while 1-phenylethanol gave only 26% acetophenone. They also observed minimal oxidation of benzyl alcohol to benzaldehyde with low catalyst loadings or reaction temperatures. Interestingly, the oxidation reactions of alcohols did not proceed under a N_2 atmosphere. GO as an oxidation catalyst has also been used in the conversion of amines to imines.[5f] The use of GO as a metal-free catalyst is a growing area of interest, and the present work represents a unique example of the diverse reactivity of this material to afford complex products.

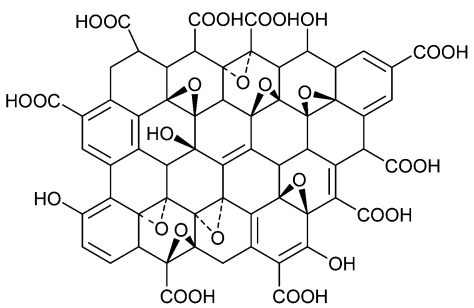

Fig. 1 Schematic representation of graphene oxide (GO).

Results and discussion

Considering that secondary aryl alcohols are prone towards dehydration, we envisaged that the course of the reaction might be altered and driven towards the dehydration depending on conditions such as low loadings of GO (wt%) and carrying out the reaction under mild conditions and N_2 atmosphere. Preliminary studies with 1-(2-naphthyl)ethanol revealed that the dehydration is indeed possible by heating a solution of toluene (N_2-bubbled) at 80–100 °C in the presence of GO (5–20 wt%), but not with an acceptable conversion (40–45%).‡ We reasoned that the dehydration may perhaps be driven if the resulting alkene is reacted immediately with some other reactant. As the combination of an alkene and a thiol represents an atom-economic 'click' reaction,[6] Bielawski and coworkers,[5b,g] reported the GO-catalyzed thiol oxidation to disulfide and also the

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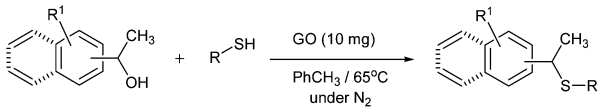
† Electronic supplementary information (ESI) available: Scanned copies of ^{1}H- and ^{13}C-NMR spectra for compounds **3a–o**, the anti-Markovnikov product (**3p**) and the FT-IR spectrum of graphene oxide (GO) before and after the reaction. See DOI: 10.1039/c3ra44712j

‡ The dehydration was accompanied by the recovery of the starting alcohol and some unidentified product. Another experiment was conducted taking a mixture of styrene and GO in toluene which showed partial decomposition after stirring for 12 h. All reactions were performed in screw-capped vials flushed with N_2 (see Experimental section for details).

polymerization of styrene under solvent-free conditions. Based on this background, we designed the experiments starting from a mixture of a secondary aryl alcohol and a thiol. Graphene oxide (GO) was synthesized by a variation of the Hummers method,[7a,b] and its FT-IR spectrum compared to the reported one[7c] (see ESI†).

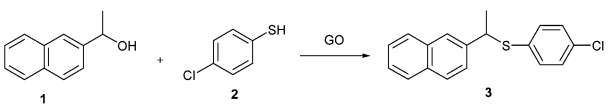
As summarized in Table 1, gentle magnetic stirring of an equimolar mixture of 1-(2-naphthyl)ethanol and 4-chlorobenzenethiol in toluene at different temperatures in the presence of varying amounts of GO produced diverse results. Initial stirring at up to 50 °C yielded no desired product except a certain amount of disulfide, formed by the oxidative dimerization of the thiol (entries 1 and 2). Increasing the reaction temperature and quantity of thiol however, gave the expected thiol-addition product (67–79%), characterized as [(4-chlorophenyl)(1-phenylethyl)sulfane], obtained through the sequential dehydration–hydrothiolation reaction in an entirely Markovnikov fashion (entries 3 and 4), with minimal amounts of diphenyldisulfide (8%). Further heating (80 °C) did not show significant improvement except slightly more disulfide formation (entry 5). Increasing or decreasing the amount of GO (wt%), or changing the solvent was not effective either (entry 6–10). The reactions carried out in DMF or without GO did not produce traces of the desired thioether (entries 11 and 12). Since these findings are new and thioethers are important building blocks for the synthesis of biologically active compounds,[8] we became interested in extending the reaction protocol, as in entry 4, with a variety of secondary aryl alcohols and thiols to finally create a general and practical method for the preparation of unsymmetrical thioethers *via* a one-pot GO-facilitated metal-free sequential dehydration–hydrothiolation reaction (Scheme 1). The preparation of thioethers from secondary aryl alcohols has been previously reported *via* Pd-catalyzed S_N1 reactions.[9]



Scheme 1 Graphene oxide (GO)-catalyzed one-pot sequential dehydration–hydrothiolation.

The first few examples in Table 2 represent the reaction of a mixture of 1-(2-naphthyl)ethanol and different aromatic thiols bearing Cl, Me, F and NH_2 groups (Table 2, entries 1–5). The reaction protocol was found to be successful, except in entry 5 with the NH_2 group, yielding the corresponding thioether in 67–79% yield along with 8–10% diaryldisulfide. However, the separation was easy by column chromatography over silica gel. A similar reaction sequence was also observed with 1-(1-naphthyl)ethanol and different arylthiols (entries 6 and 7). In the series of 1-phenylethanol, the variation of the functional groups in either the aryl moiety was also successful and the corresponding unsymmetrical thioethers were obtained in good yields (entries 8–10 and 12). However, the reaction with the aryl alcohol bearing a NO_2 group was unsuccessful, even after leaving the reaction for 24 h (entry 11). The disulfide was isolated along with the starting alcohol, 1-(3-nitrophenyl)ethanol. To broaden the scope of the reaction, we attempted a similar reaction sequence with aliphatic thiols. The reactions with both long chain and alicyclic thiols worked without any difficulty. Entries 13–17 demonstrate that the reactions did occur quite well giving the desired unsymmetrical thioethers in fairly good yields (68–81%), along with a minimal formation of the thiol-corresponding disulfides. It was observed that the presence of electron-donating groups in the aryl ring of the alcohol favoured the dehydration–hydrothiolation sequence.

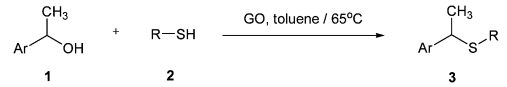
Table 1 Optimization of the sequential dehydration–hydrothiolation reaction conditions[a]



					Product yield[b] (%)		
Entry	GO (mg/wt%)	Solvent	Temp (°C)	Time (h)	**3**	Disulfide	2-Vinylnaphthalene
1	10/6	Toluene	rt	24	Nil	14	Nil
2	10/6	Toluene	50	24	Nil	22	Nil
3	10/6	Toluene	65	2	67	8	12
4	10/6	Toluene	65	2	79	8	Nil
5	10/6	Toluene	80	1.5	65	16	Nil
6	20/12	Toluene	65	1.5	47	23	Nil
7	5/3	Toluene	65	6	49	17	Nil
8	10/6	1,4-Dioxane	65	3.5	51	20	Nil
9	10/6	THF	65	3	48	22	Nil
10	10/6	MeCN	65	2	58	15	Nil
11	10/6	DMF	65	24	Nil	31	Nil
12	Nil	Toluene	65	24	Nil	10	Nil

[a] Reactions were performed with **1** (1 mmol), **2** (1 mmol) for entries 1–3 and **1** (1 mmol), **2** (1.2 mmol) for entries 4–11 in solvent (2 mL). [b] Isolated yield.

Table 2 Graphene oxide (GO)-catalyzed reaction of secondary aryl alcohols with different aromatic and aliphatic thiols[a]



Entry	Ar	R	Time (h)	Yield (%) **3**[b]
1	2-$C_{10}H_7$	4-ClC_6H_4	2	**3a:** 79
2	2-$C_{10}H_7$	4-$CH_3C_6H_4$	1.5	**3b:** 67
3	2-$C_{10}H_7$	2,6-$(CH_3)_2C_6H_3$	2	**3c:** 70
4	2-$C_{10}H_7$	4-FC_6H_4	2	**3d:** 77
5	2-$C_{10}H_7$	4-$NH_2C_6H_4$	3	Nil
6	1-$C_{10}H_7$	4-ClC_6H_4	2.5	**3e:** 72
7	1-$C_{10}H_7$	4-FC_6H_4	2.5	**3f:** 74
8	C_6H_5	4-$CH_3C_6H_4$	1.5	**3g:** 69
9	C_6H_5	C_6H_5	1.5	**3h:** 73
10	3,4-$(OCH_3)_2C_6H_3$	C_6H_5	2	**3i:** 78
11	3-$NO_2C_6H_4$	4-FC_6H_4	24	Nil
12	3,4-$(OCH_3)_2C_6H_3$	4-ClC_6H_4	2	**3j:** 78
13	2-$C_{10}H_7$	$CH_3(CH_2)_4$	2.5	**3k:** 68
14	2-$C_{10}H_7$	Cy	1	**3l:** 71
15	1-$C_{10}H_7$	$CH_3(CH_2)_6$	2	**3m:** 81
16	4-$CH_3C_6H_4$	$CH_3(CH_2)_4$	3	**3n:** 69
17	3,4-$(OCH_3)_2C_6H_3$	$CH_3(CH_2)_4$	3	**3o:** 80
18[c]		4-$CH_3C_6H_4$	2	Phenethyl(*p*-tolyl)sulfane **3p**: 82
19[d]		4-$CH_3C_6H_4$	4	**3p**: 74
20[e]		4-$CH_3C_6H_4$	7	**3p**: 77

[a] *Reaction conditions*: **1** (1 mmol), **2** (1.2 mmol), GO (10 mg) in toluene (2 mL), with gentle magnetic stirring in a screw-capped vial under N_2. [b] Isolated yield. [c] In the absence of GO. [d] In the presence of GO. [e] In the presence of graphite.

Table 3 Recyclability of GO in the carbocatalysis of the one-pot sequential dehydration–hydrothiolation of 1-(2-naphthyl)ethanol and 4-chlorobenzenethiol[a]

Entry	Yield[b] (%)	Yield[c] (%)
1st run	79	8
2nd run	79	8
3rd run	78	10
4th run	76	8
5th run	76	10

[a] Reaction conditions: alcohol (1 mmol) and thiol (1.2 mmol) in toluene (2 mL) at 65 °C. [b] Isolated yield of thioether (**3a**). [c] Isolated yield of disulfide.

In order to suggest a plausible mechanism and to test whether GO also catalyzes the hydrothiolation providing entirely the Markovnikov addition product, we performed experiments taking a solution of styrene and 4-tolylthiol in toluene under similar reaction conditions, both in the absence and presence of GO. It was interesting to observe that the resulting thioether **3p** was then obtained completely in an anti-Markovnikov fashion (Table 2, entries 18 and 19). Further reaction using graphite also gave **3p** by the anti-Markovnikov addition (entry 20). We initially observed the partial conversion of the aryl alcohol to styrene, when stirred with GO in the absence of any thiol, and stirring the mixture of styrene and GO in toluene showed a partial decomposition after 12 h.‡ Carrying out the experiments under an atmosphere of N_2 might suppress the possibility of polymerization,[5g] as well as the further oxidation of the disulfide to thione. Since we obtained the reverse addition product in other cases (*i.e.* the Markovnikov addition product), we presume that GO participates in the overall process, *i.e.* the one-pot dehydration–hydrothiolation reaction, *via* an acid-catalyzed Markovnikov addition.[8e]

The reusability of the GO as an heterogeneous carbocatalyst was also investigated with the same combination of reactants used for the optimization of the reaction conditions. The recovered GO from the first batch was washed with diethyl ether, dried and reused subsequently in four batches with appreciable conversions and without any loss of catalytic activity. In each run, a minimal formation of disulfide (8–10%) was noticed (Table 3). The FT-IR spectrum of the recovered GO (after the first run) was measured and displayed essentially the same absorptions, indicating no apparent changes in the functional groups of GO (see ESI†).

Conclusions

In summary, the present study has developed a new sequential dehydration–hydrothiolation reaction of mixtures of secondary aryl alcohols and thiols catalyzed by graphene oxide for the preparation of unsymmetrical thioethers. Benzyl alcohols are known to undergo oxidation and thiols are reported to produce disulfides under GO-catalyzed conditions. However, the

dehydration and subsequent regioselective hydrothiolation of the resulting alkene in this one-pot sequential reaction catalyzed by GO is new, straightforward and carried out under mild conditions. The catalytic role of graphene-based materials (GO) is a recent field, and metal-free catalysis under mild conditions is indeed promising and expected to reveal a host of new catalytic applications.

Experimental details

General information

All chemicals were purchased and used directly. For the column chromatography, silica (60–120 μm) (SRL, India) was used, and for tlc, Merck plates coated with silica gel 60, F_{254} were used. FT-IR spectra were recorded in a FT-IR-8300 SHIMADZU spectrophotometer. The NMR spectral data (^{1}H and ^{13}C NMR) were recorded in $CDCl_3$ on a Bruker AV 300, operating respectively at 300 MHz and 75 MHz. ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane serving as the internal standard (δ = 0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants (J) in Hz. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm).

Preparation of graphene oxide (GO)

GO was prepared according to the modified Hummers method.[7a,b] To ice-cold concentrated sulfuric acid (46 mL) was slowly added sodium nitrate (0.1 g) and then graphite powder (2 g) with vigorous magnetic stirring. After the complete addition of the graphite powder, potassium permanganate (6 g) was added to the reaction mixture very slowly, keeping the temperature within 0–5 °C to avoid any possible explosion. The mixture was allowed to stir at room temperature for 6 h forming a thick paste. It was diluted with double distilled water (92 mL) under stirring. The temperature of the solution was raised to about 90 °C and the mixture was allowed to stir for 30 min. Finally, 280 mL water was added followed by the slow addition of 3 mL H_2O_2 (30%). The colour of the solution changed from dark brown to yellow and the product was filtered off, washed repeatedly with water to remove all the acid. Finally, the brown solid was collected and dried at 60 °C under vacuum to obtain graphene oxide. The prepared GO was characterized by IR spectroscopy in KBr, and the spectrum was comparable to the literature data.[7c] IR (in KBr): 3359, 1719, 1618, 1411, 1218, 1052 cm^{-1}.

General procedure for the one-pot sequential dehydration–hydrothiolation reaction

To a solution of alcohol (**1**) (1 mmol) and thiol (**2**) (1.2 mmol) in toluene (2 mL) was added graphene oxide (10 mg), and the mixture was bubbled with N_2 gas for 2–3 min and immediately screw-capped to ensure the reaction mixture was under nitrogen atmosphere. The sealed tube was stirred with a magnetic spin bar at 65 °C for hours, as mentioned in Table 2. After the reaction, the catalyst was filtered off, washed with diethyl ether (3 × 5 mL) and the combined filtrates were concentrated to afford a mixture of thioether and disulfide. The crude mixture was separated by column chromatography over silica gel and elution with petroleum ether afforded the desired thioether in pure form.

(4-Chlorophenyl)(1-(naphthalene-6-yl)ethyl)sulfane (3a). White crystalline solid, mp 72–74 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (d, J = 7.2 Hz, 3H, CH_3), 4.43 (q, J = 6.9 Hz, 1H, CH), 7.10–7.19 (m, 4H ArH), 7.40–7.51 (m, 3H ArH), 7.58 (s, 1H ArH), 7.71–7.79 (m, 3H ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1, 48.4, 125.4, 125.7, 125.8, 126.1, 127.6, 127.7, 128.3, 128.8, 132.6, 133.1, 133.3, 133.9, 140.2.

(1-(Naphthyalen-6-yl)ethyl)(*p*-tolyl)sulfane (3b). White solid, mp 69–71 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.69 (d, J = 6.9 Hz, 3H, CH_3), 2.27 (s, 3H, $ArCH_3$), 4.42 (q, J = 6.9 Hz, 1H, CH), 6.99 (d, J = 8.1 Hz, 2H, ArH), 7.16–7.21 (m, 2H, ArH), 7.40–7.46 (m, 2H, ArH), 7.52 (dd, J = 8.4 and 1.8 Hz, 1H, ArH), 7.59 (s, 1H, ArH), 7.71–7.81 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1, 22.2, 48.6, 125.6, 125.69, 125.7, 126.0, 127.6, 127.8, 128.1, 129.4, 131.1, 132.6, 133.2, 137.4, 140.7.

2,6-Dimethylphenyl)(1-(naphthalene-6-yl)sulfane (3c). Pale yellow liquid ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.69 (d, J = 7.2 Hz, 3H, CH_3), 2.14 (s, 3H, $ArCH_3$), 2.27 (s, 3H, $ArCH_3$), 4.41 (q, J = 6.9 Hz, 1H, CH), 6.86 (dd, J = 7.5 and 1.2 Hz, 1H, ArH), 6.98 (d, J = 7.8 Hz, 1H, ArH), 7.09 (s, 1H, ArH), 7.37–7.42 (m, 2H, ArH), 7.48–7.51 (dd, J = 8.4 and 1.8 Hz, 1H, ArH), 7.58 (s, 1H, ArH), 7.67–7.76 (m, 3H, ArH) ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.2, 20.7, 22.1, 47.6, 125.5, 125.61, 125.64, 125.9, 127.5, 127.7, 128.0, 128.1, 129.9, 132.6, 133.2, 133.6, 133.9, 135.6, 136.9, 140.6.

(4-Fluorophenyl)(1-(naphthalene-6-yl)ethyl)sulfane (3d). White solid, mp 73–75 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.69 (d, J = 6.9 Hz, 3H, CH_3), 4.38 (q, J = 6.9 Hz, 1H, CH), 6.82–6.90 (m, 2H, ArH), 7.19–7.25 (m, 2H, ArH), 7.39–7.47 (m, 3H, ArH), 7.50–7.51 (m, 1H, ArH), 7.69–7.74 (m, 1H, ArH), 7.77–7.81 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.9, 49.1, 115.6, 115.8, 125.5, 125.8, 126.1, 127.6, 127.7, 128.2, 132.6, 133.1, 135.6, 135.8, 140.3, 160.9, 164.2.

(4-Chlorophenyl)(1-(naphthalene-8-yl)ethyl)sulfane (3e).[10] White crystalline solid, mp 96–98 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.73 (d, J = 6.9 Hz, 3H, CH_3), 5.10 (q, J = 6.9 Hz, 1H, CH), 7.10–7.18 (m, 4H, ArH), 7.36 (t, J = 7.5 Hz, 1H, ArH), 7.44–7.55 (m, 3H, ArH), 7.72 (d, J = 8.1 Hz, 1H, ArH), 7.82–7.85 (m, 1H, ArH), 8.16 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.9, 43.0, 122.9, 124.2, 125.3, 125.6, 126.1, 128.0, 128.8, 129.0, 130.7, 133.2, 133.4, 133.6, 133.9, 137.7.

(4-Fluorophenyl)(1-(naphthalene-8-yl)ethyl)sulfane (3f). White solid. mp 83–85 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.70 (d, J = 6.9 Hz, 3H, CH_3), 5.02 (q, J = 6.9 Hz, 1H, CH), 6.80–6.86 (m, 2H, ArH), 7.15–7.21 (m, 2H, ArH), 7.31–7.52 (m, 4H, ArH), 7.69 (d, J = 8.1 Hz, 1H, ArH), 7.79–7.82 (m, 1H, ArH), 8.16 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7, 43.4, 115.5, 115.8, 123.0, 124.2, 125.2, 125.5, 126.0, 127.8, 128.9, 129.49, 129.5, 130.7, 133.8, 135.5, 135.6, 137.9, 160.8, 164.1.

(1-Phenylethyl)(*p*-tolyl)sulfane (3g).[10] Colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (d, J = 7.2 Hz, 3H, CH_3), 2.29 (s, 3H, $ArCH_3$), 4.26 (q, J = 6.9 Hz, 1H, CH), 7.02 (d, J = 8.1 Hz, 2H,

ArH), 7.17–7.27 (m, 7H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1, 22.1, 48.3, 127.0, 127.3, 128.3, 129.4, 131.2, 133.2, 137.3, 143.3.

Phenyl(1-phenylethyl)sulfane (3h).[10] Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.63 (d, J = 6.9 Hz, 3H, CH_3), 4.34 (q, J = 6.9 Hz, 1H, CH), 7.19–7.31 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.3, 48.0, 127.1, 127.2, 128.4, 128.6, 132.5, 135.1, 143.2.

(1-(3,4-Dimethoxyphenyl)ethyl)(phenyl)sulfane (3i). Pale yellow solid, mp 53–55 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.61 (d, J = 6.9 Hz, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.30 (q, J = 6.9 Hz, 1H, CH), 6.72–6.75 (m, 1H, ArH), 6.79–6.82 (m, 2H, ArH), 7.17–7.31 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.2, 47.7, 55.6, 55.7, 110.3, 110.7, 119.1, 127.0, 128.5, 132.5, 135.0, 135.6, 147.9, 148.6.

(4-Chlorophenyl)(1-(3,4-dimethoxyphenyl)ethyl)sulfane (3j). Colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.60 (d, J = 6.9 Hz, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.26 (q, J = 6.9 Hz, 1H, CH), 6.73–6.80 (m, 3H, ArH), 7.18 (s, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.2, 48.1, 55.7, 55.8, 110.3, 110.7, 119.3, 128.7, 133.3, 133.5, 134.0, 135.3, 148.1, 148.7.

(1-(Naphthalen-6-yl)ethyl)(pentyl)sulfane (3k). Colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.82 (t, J = 6.9 Hz, 3H, CH_3), 1.19–1.28 (m, 4H, $-CH_2-CH_2-$), 1.45–1.52 (m, 2H, CH_2), 1.64 (d, J = 7.2 Hz, 3H, CH_3), 2.23–2.33 (m, 2H, S–CH_2), 4.11 (q, J = 6.9 Hz, 1H, S–CH-Ar), 7.42–7.49 (m, 2H, ArH), 7.53–7.57 (dd, J = 8.4 and 1.8 Hz, 1H, ArH), 7.68 (s, 1H, ArH), 7.78–7.83 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 22.2, 22.5, 29.0, 31.1, 31.2, 44.3, 125.4, 125.6, 125.7, 126.1, 127.6, 127.7, 128.4, 132.6, 133.2, 141.5.

Cyclohexyl(1-(naphthalene-6-yl)ethyl)sulfane (3l). Colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.43–1.73 (m, 9H, Cy–H), 1.61 (d, J = 6.9 Hz, 3H, CH_3), 1.99 (m, 1H, CyH), 2.35–2.39 (m, 1H, S–CyH), 4.21 (q, J = 7.2 Hz, 1H, S–CH-Ar), 7.42–7.49 (m, 2H, ArH), 7.56 (dd, J = 8.7 and 1.8 Hz, 1H, ArH), 7.70 (s, 1H, ArH), 7.79–7.83 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1, 25.7, 25.8, 25.9, 33.3, 33.9, 42.7, 42.75, 125.4, 125.6, 126.0, 127.6, 127.7, 128.3, 132.6, 133.3, 142.1.

Heptyl(1-(naphthalene-5-yl)ethyl)sulfane (3m). Colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84 (t, J = 6.6 Hz, 3H, CH_3), 1.17–1.27 (m, 8H, C_4H_8), 1.43–1.52 (m, 2H, CH_2), 1.72 (d, J = 7.2 Hz, 3H, CH_3), 2.35–2.41 (m, 2H, S–CH_2), 4.80 (q, J = 6.9 Hz, 1H, S–CH-Ar), 7.41–7.53 (m, 3H, ArH), 7.67–7.73 (m, 2H, ArH), 7.81–7.85 (m, 1H, ArH), 8.19 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 22.5, 28.76, 28.8, 29.4, 31.3, 31.6, 39.4, 123.0, 124.3, 125.4, 125.8, 127.4, 128.9, 131.0, 133.9, 139.3.

Pentyl(1-*p*-tolyiethyl)sulfane (3n). Colourless liquid ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (t, J = 6.9 Hz, 3H, CH_3), 1.21–1.29 (m, 4H, CH_2-CH_2), 1.45–150 (m, 2H, CH_2), 1.54 (d, J = 6.9 Hz, 3H, CH–CH_3), 2.24–2.34 (m, 5H, CH_2 & $ArCH_3$), 3.91 (q, J = 7.2 Hz, 1H, CH), 7.11 (d, J = 7.8 Hz, 2H, ArH), 7.21–7.24 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 21.0, 22.2, 22.6, 29.0, 31.1, 31.2, 43.7, 127.1, 129.0, 136.5, 141.1.

(1-(3,4-Dimethoxyphenyl)ethyl)(pentyl)sulfane (3o). Colourless liquid ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.83–0.88 (m, 3H, CH_3), 1.25–1.30 (m, 4H, CH_2-CH_2), 1.47–1.52 (m, 2H, CH_2), 1.54 (d, J = 7.2 Hz, 3H, CH_3), 2.26–2.34 (m, 2H, S–CH_2), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.92 (q, J = 7.2 Hz, 1H, CH–CH_3), 6.77–6.92 (m, 2H, ArH), 6.93 (d, J = 1.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 22.1, 22.7, 28.9, 31.0, 31.1, 43.8, 55.69, 55.7, 110.0, 110.6, 119.2, 136.6, 147.8, 148.9.

Phenethyl(*p*-toyl)sulfane (3p). Colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (s, 3H, CH_3), 2.88 (t, J = 7.2 Hz, 2H, CH_2-Ar), 3.08–3.13 (m, 2H, S–CH_2), 7.08–7.28 (m, 9H, ArH), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9, 35.67, 35.7, 126.3, 128.4, 128.44, 129.6, 130.0, 132.4, 136.1, 140.2.

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Research Article

In Quest of "Stereoselective Switch" for On-Water Hydrothiolation of Terminal Alkynes Using Different Additives and Green Synthesis of Vicinal Dithioethers

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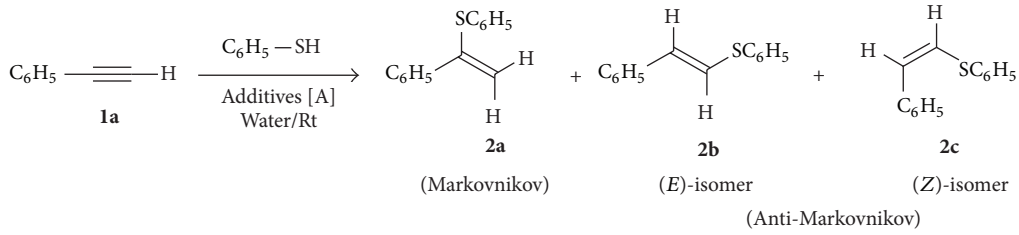
On-water hydrothiolation reaction between terminal alkyne and thiol has been probed in the presence of various additives. Aromatic alkynes yield corresponding 1-alkenyl sulfides, whereas aliphatic alkynes undergo double-addition yielding vicinal disulfides in good to excellent yields. Formation of 1-alkenyl sulfides proceeds with a high degree of regioselectivity (via anti-Markovnikov addition), and switching the stereoselectivity between *E*/*Z* isomers has been noticeably realized in the presence of different additives/promoters.

1. Introduction

Organosulfur compounds play a key role in biological processes, new materials, and chemical synthesis [1, 2]. 1-Alkenyl sulfides are important synthetic intermediates in total synthesis of many naturally occurring and biologically active compounds as well as versatile building blocks for many functionalized molecules [3–9]. The synthetic utility of alkenyl sulfides has been demonstrated in several reports by different research groups [10–17]. Increasing demand for alkenyl sulfides in material science, organic, and bioorganic chemistry has furthered the development of new synthetic methods [6, 18–21]. The addition of thiols to alkynes is considered as one of the straightforward methods to obtain vinyl sulphides either catalyzed by transition metal complexes [22–39], or base-promoted [40–44] and/or through free radicals [21, 45–48]. This reaction is often judged as a part of "click chemistry" and a process of high atom economy [49, 50]. Mechanistically, addition of thiols to alkynes is believed to occur (i) via radical pathway producing unselective mixture of (*E*/*Z*)-anti-Markovnikov vinyl sulphides, (ii) base-mediated nucleophilic addition giving all types of adducts, or (iii) transition-metal complex catalyzed processes yielding Markovnikov vinyl sulphides and (*E*) anti-Markovnikov vinyl sulphides (Scheme 1). Varying degrees of stereo- and regioselectivity and turnover are reported in the literature [22–48].

Additives are a kind of reagents whose effects are very much similar to catalysts. They have often shown a profound role in variety of organic reactions in terms of the rate of the reaction, yield of the product, or change in the course of the reaction [51, 52]. In hydrothiolation, most reports in the literature described the formation of thermodynamically more stable *E*-vinyl sulfide in considerable excess over the *Z*-isomer. On the other hand, hydrothiolation, particularly of aryl and benzyl thiols and catalyzed by transition-metal complexes, often produces a mixture of anti-Markovnikov *E*-alkenyl sulfide (*syn* addition) and Markovnikov adduct and thus suffers from poor regioselectivity. Among the transition metal catalysts, rhodium complexes, both in homogeneous and heterogeneous forms, have exhibited high catalytic activity [51, 52]. Recently, $In(OTf)_3$ has been shown to selectively catalyze both Markovnikov and anti-Markovnikov hydrothiolation of terminal alkynes [38]. However, transition metal complexes are generally expensive, their uses are not ecofriendly, and the course of the reaction might suffer deactivation due to the formation of strong metal-sulphur bonds [53]. More regioselective (anti-Markovnikov) on-water hydrothiolation processes have been reported in



Scheme 1: 1-Alkenyl sulphides from hydrothiolation of terminal alkynes.

the absence [45–48, 54] or presence of some additives like β-cyclodextrine [55]. Indeed, there are large varieties of reagents/catalysts that are used in the hydrothiolation of terminal alkynes with varying degrees of success in controlling stereo- and regioselectivity. However, many reports include expensive metal catalysts, nonaqueous solvents, and high temperature and moreover lack (*E/Z*)-stereoselectivity. In practice, there is no general guideline by which one can proceed to prepare a specific stereoisomer of a vinylic sulfide using this straightforward and atom-economic reaction under mild and environment-friendly conditions. Moreover, there are conditions that give rise to selective formation of the thermodynamically favoured (*E*)-alkenyl sulfide, it remains an unmet and elusive goal to develop optimum conditions that selectively produce (*Z*)-alkenyl sulfides under complete metal-free, base-free and on-water conditions. Since hydrothiolation of alkynes is a robust, atom-economic and highly useful synthetic method in C–S bond formation [6], we undertook a systematic investigation on the stereo- and regioselective addition of aliphatic and aromatic thiols to terminal alkynes in the presence of different additives in catalytic quantities under on-water conditions. We report herein our studies that constitute a rather broad guideline of "stereoselective switch" for the preparation of stereoselective (*E/Z*)-1-alkenyl sulfides.

2. Materials and Methods

All compounds were identified by ^{1}H- and ^{13}C-NMR spectra, recorded on a Bruker AV300 spectrometer operating at 300 and 75 MHz, respectively, and supported by FT-IR spectra. All NMR spectra were measured in chloroform-d. Chemical shifts are given in δ (ppm) downfield from TMS. Analytical thin-layer chromatography (tlc) was performed on precoated aluminum plates from Merck silica gel 60 F_{254} as the adsorbent (layer thickness 0.25 mm). The developed plates were air-dried and exposed to UV light. Column chromatography was performed on silica gel (source: SRL India; 60–120 mesh).

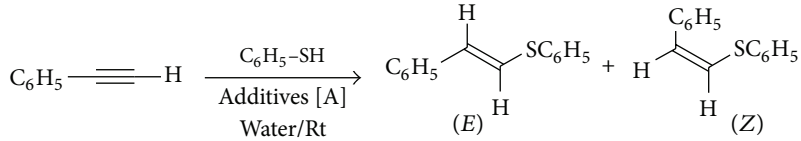
2.1. General Procedure for Monohydrothiolation of Alkynes. To a mixture of alkyne (1 mmol), thiol (1.1 mmol) in water (0.5 mL) was added to the additive (1 mmol) and stirred at room temperature (25–30°C) for 2–5 h (TLC). The reaction mixture was extracted with diethyl ether (3 × 10 mL), and the combined organic layer was washed with brine and then dried over Na_2SO_4. Evaporation of solvent under *vacuo* afforded an oily residue, which was passed through a short bed of silica gel, and NMR spectrum was recorded to evaluate the percent of (*E/Z*) isomers. NMR spectral data and scanned copies of selected NMR spectra are given in the Supplementary Material available online at http://dx.doi.org/10.1155/2014/358932 and are found to be in good agreement with those reported.

2.2. General Procedure for Dihydrothiolation of Alkynes. In a mixture of alkyne (1 mmol), thiol (2.2 mmol) in water (0.5 mL) was stirred for 5–9 h at room temperature (TLC). The reaction mixture was then extracted with diethyl ether (3 × 10 mL), and the combined organic layer was washed with brine and then dried over Na_2SO_4. Evaporation of solvent under *vacuo* afforded an oily residue, which was passed through a short bed of silica gel to afford 1, 2-disulfides in good to excellent yields. The products were identified on the basis of ^{1}H, ^{13}C NMR spectral data, and/or by comparison with the data reported in the literature. NMR spectral data and scanned copies of selected NMR spectra (^{1}H- and ^{13}C) are given in the Supplementary Material.

3. Results and Discussion

Preliminary studies on the influence of catalyst and/or promoter on hydrothiolation were studied with a model reaction of phenyl acetylene (**1a**) and benzenethiol in the presence of various homogeneous and heterogeneous additives/promoters under on-water conditions at room temperature. Screening of additives/promoters included inorganic salts, water-soluble organic molecules, amino acids, surfactants, or heterogeneous ion-exchange resins, and the results are summarized in Table 1. Since the hydrothiolated adducts are formed in varying ratios (*E/Z* ratios), the results in Table 1 have been arranged showing a gradual change in the formation of (*E*)-vinyl sulfide (**2b**) to the (*Z*)-isomer (**2c**). The screening shows that the *E/Z* ratio in favor of (*E*)-vinyl sulfide (87 : 13) is formed in the presence of NaCl (Table 1, entry 3), while the major (*Z*)-vinyl sulfide is obtained in the presence of a combination of amberlite resins (Cl) and $FeCl_3 \cdot 6H_2O$ (entry 23; *E/Z* ratio 22 : 78). The stereochemical outcome favouring the (*E*)-isomer is also seen when the reaction is carried out at higher temperature (65°C) and continued for longer reaction time (10 h) (entry 11; *E/Z* ratio 88 : 12). However, a specific observation may be noted from this study that the on-water additions do not give rise to the formation of any Markovnikov adduct; that is, in no case was the other regioisomer (**2a**) obtained. The NMR spectral data

Table 1: Role of additives in the addition of PhSH to phenylacetylene under on-water conditions at room temperature producing selectively anti-Markovnikov adducts[a].



Entry	Additive [A][b]	(*E*/*Z*) ratio[c, d]	Entry	Additive [A][b]	(*E*/*Z*) ratio[c, d]
1	Nil (neat)	83 : 17	13	CuI-Catechol violet	60 : 40
2	Nil (water)	80 : 20	14	Amberlite resins (Cl)	58 : 42
3	NaCl	87 : 13	15	n-Bu_4NBr	57 : 43
4	Sucrose	85 : 15	16	D-Glucose	56 : 44
5	CF_3COOH	78 : 22	17	CuI	52 : 48
6	$BF_3{\cdot}Et_2O$	76 : 24	18	Cholesterol	51 : 49
7	Catechol violet	75 : 25	19	CTAB	49 : 51
8	L-Proline	70 : 30	20	$FeCl_3{\cdot}6H_2O$	44 : 56
9	Glycin	69 : 31	21	Amberlyst resins (OH)	40 : 60
10	Starch	64 : 36	22	D-Glucose and $FeCl_3{\cdot}6H_2O$	35 : 65
11[e]	Water (65°C)	88 : 12	23	Amberlite resins (Cl) and $FeCl_3{\cdot}6H_2O$	22 : 78
12	Water (65°C)	64 : 36			

[a]Reaction conditions: phenyl acetylene (0.5 mmol), PhSH (0.55 mmol), water (1 mL), 2 h. [b]Additive [A] (2 mol %). [c]*E*/*Z* ratio was determined by ^{1}H NMR of the crude mixture. [d]Yield of the mixture of stereoisomers after chromatographic purification varies in the range 80–90%. [e]The reaction was continued for 10 h; all other reactions were carried out at room temperature unless otherwise mentioned.

of the unpurified products indicated only a mixture of **2b** and **2c,** and indeed there was no trace of **2a**.

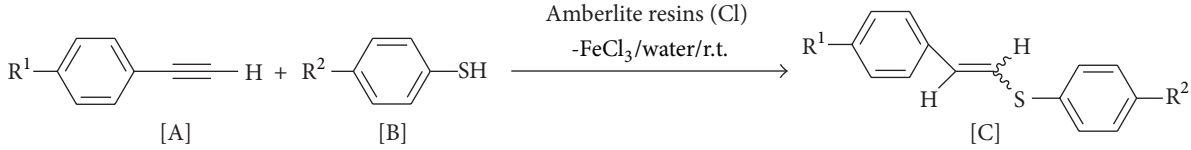
At this point, effect of functional groups in the aromatic moiety in either of the addition partners could be worth investigating. Since a combination of ion-exchange resins and ferric chloride showed a better selectivity towards the formation of (*Z*)-vinyl sulfide, this study was performed under similar conditions. The results are presented in Table 2. It is seen that both electron-donating and electron-withdrawing functional groups present on the aryl ring can give rise to the anti-Markovnikov hydrothiolation products in excellent yields (85–94%). The highest (*Z*)-selectivity was found in the reaction between phenyl acetylene and *p*-methoxybenzenethiol (Table 2, entry 4; *E*/*Z* 12 : 88), possibly due to the easy emulsification of the alkyne in water upon stirring, which might be supportive, in addition to the presence of the additive. On the other hand, presence of the electron-withdrawing group (fluorine) on the thiol part did not show any appreciable influence towards stereoselective addition yielding the (*E*)-isomer in major quantity (entries 6-7). It seems that there is not much electronic influence of the functional groups in the aryl ring of either of the addition partners; rather their stability in water in the presence of the additive might have some control towards *anti*-Markovnikov stereoselectivity.

Further studies of aryl acetylenes (terminal) with aliphatic thiols in the presence of one equivalent of D (+)-glucose showed a general trend in favour of the formation of (*Z*)-vinyl sulphides. For example, phenyl acetylene or *p*-tolyl acetylene undergoes hydrothiolation in the presence of *n*-alkyl thiols that afforded the corresponding 1-alkenyl sulphides with (*E*/*Z*) ratios (14 : 86). The results are summarized in Table 3.

Since there is significant reactivity difference between aliphatic and aromatic thiols [56, 57], we ought to investigate the stereochemical outcome in two other cases: hydrothiolation of (i) aliphatic terminal alkynes and aliphatic thiols and (ii) aliphatic terminal alkynes and aromatic thiols. It has been seen from previous reports that aliphatic alkynes undergo dihydrothiolation yielding *vicinal* disulfides only irrespective of the nature of the thiol [45, 54]. Thus, aliphatic terminal alkynes were subjected to hydrothiolation with aromatic and aliphatic thiols under on-water conditions. Seemingly, there was an influence of additives on this double-addition reaction. The results are presented in Table 4, which show that aliphatic terminal alkynes undergo double- additions yielding finally 1, 2-disulfides only in the presence or absence of D (+)-glucose.

With regard to the mechanism of hydrothiolation of terminal alkynes in water, the literature reports are of different views. For example, Bhadra and Ranu [54], in their studies on water-promoted regioselective hydrothiolation, ruled out the likeliness of a radical pathway as the reaction proceeds in the presence of dissolved oxygen. On the other hand, Jin et al. [45], hinted that the reaction probably proceeds through a radical mechanism under similar conditions. The latter group further observed that the reaction does not occur in the presence of galvinoxyl-free radical, although use of such radical quencher does not always prove radical mechanism [54, 55]. Our studies indeed demonstrated a role of additives in governing the stereoselectivity but the specific function of the additive, particularly in aqueous medium, and the mechanistic routes are not clear at this time. Furthermore, carrying out the reaction in the presence of radical initiator (AIBN) or light did not make the process faster appreciably. Several transition metal complexes are

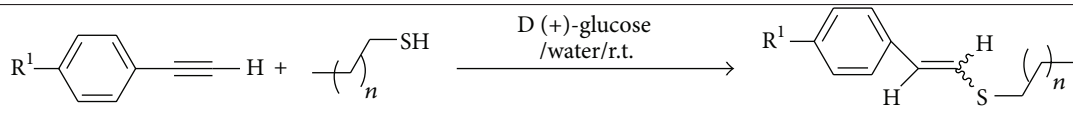
Table 2: Hydrothiolation of aryl thiol [B] to aryl acetylene [A] in (1.1 : 1) in water at room temperature.



Entry	[A]	[B]	Time (h)	Yield[a] (%) [C]	*E*/*Z* [C][b]
1	$R^1 = H$	$R^2 = H$	2.0	85	22 : 78
2	$R^1 = CH_3$	$R^2 = H$	3.5	91	40 : 60
3	$R^1 = CH_3$	$R^1 = CH_3$	2.5	88	29 : 71
4	$R^1 = H$	$R^1 = OCH_3$	3.0	93	12 : 88
5	$R^1 = CH_3$	$R^1 = OCH_3$	2.0	90	22 : 78
6	$R^1 = H$	$R^2 = F$	2.0	88	80 : 20
7	$R^1 = CH_3$	$R^2 = F$	2.0	94	39 : 61

[a]Yield represents the product [C] after purification by column chromatography. [b]*E*/*Z* ratio was determined by ^{1}H NMR of the crude mixture.

Table 3: Hydrothiolation aromatic terminal alkynes with aliphatic thiols.



Entry	[A]	[B]	Time (h)	Yield[a] (%) [C]	*E*/*Z* [C][b]
1	$R^1 = H$	$n = 3$	3.0	75	20 : 80
2	$R^1 = H$	$n = 5$	3.0	64	14 : 86
3	$R^1 = CH_3$	$n = 3$	4.5	79	14 : 86
4	$R^1 = CH_3$	$n = 5$	5.0	51	21 : 79

[a]Yield represents the product [C] after purification by column chromatography. [b]*E*/*Z* ratio was determined by ^{1}H NMR of the crude product mixture.

Table 4: Dihydrothiolation of aliphatic alkyne with thiols in water at room temperature.

Entry	[A]	[B][a]	Time (h)	Yield[b] (%) [C]
1[c]	$R^1 = CH_3\text{-}CH_2\text{-}CH_2$	$R^2 = Ph$	5	88
2	$R^1 = CH_3\text{-}CH_2\text{-}CH_2$	$R^2 = Ph$	5	76
3	$R^1 = CH_2OAc$	$R^2 = Ph$	6	79
4	$R^1 = CH_3\text{-}CH_2\text{-}CH_2$	$R^2 = CH_3(CH_2)_6$	9	58

[a][A] : [B] is 1 : 2.2. [b]Yield represents the product [C] after purification by column chromatography. [c]D (+)-Glucose (1 equiv) was added.

known to catalyze the process of hydrothiolation via radical intermediates leading to major anti-Markovnikov 1-alkenyl sulfides. In the absence of such metal complexes, it seems that stabilization of the reactive species by water as well as by the additive might govern the course of the reaction as well as the stereoselectivity.

4. Conclusions

In quest of finding "stereoselective switch" for the hydrothiolation of terminal alkynes under on-water conditions, our studies apparently revealed two types of additives that could lead to the stereoselective formation of the (*Z*)-1-alkenyl sulfides in substantial quantities depending on the nature of both reacting partners. Since most of the metal-free methods describe formation of the (*E*)-1-alkenyl sulfides in major amount, the present findings could steer in designing mild and green reaction conditions for stereoselective preparation of (*E*/*Z*) alkenyl sulphides under on-water conditions.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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