Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7292

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Graphite oxide: a selective and highly efficient oxidant of thiols and sulfides†

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Received 6th July 2011, Accepted 19th August 2011
DOI: 10.1039/c1ob06102j

The selective oxidation of thiols to disulfides and sulfides to sulfoxides using graphite oxide (GO), a heterogeneous carbocatalyst obtained from low cost, commercial starting materials is described. The aforementioned oxidation reactions were found to proceed rapidly (as short as 10 min in some cases) and in good yield (51–100%) (19 examples). No over-oxidation of the substrates was observed, and GO's heterogeneous nature facilitated isolation and purification of the target products.

The oxidation of organosulfur compounds (*e.g.*, thiols and sulfides) is of great importance in synthesis, drug metabolism and the preparation of bioconjugates.[1,2] While a large number of methods have been developed for such purposes, a persistent challenge is over-oxidation. For example, disulfides, which may be obtained through the dimerization of thiols, can undergo further oxidation to their corresponding thiosulfinates, disulfoxides, sulfinyl sulfones or disulfones. Likewise, the oxidation of sulfides often leads to not only sulfoxides but also sulfones or sulfonic acids. To address these important issues, a wide range of sophisticated catalysts (frequently containing transition metals as the active species) has been developed.[2] Indeed, catalysts based on iron,[3,4] palladium,[5] and molybdenum,[6,7] among other metals, have led to reduced reaction times and improved selectivity for the target products. However, despite these advances, many metal-containing catalysts are inapplicable in pharmaceutical or biotechnological applications due to toxicity concerns and separation challenges. Thus, the development of highly active but metal-free oxidants for organosulfur compounds is of high value. Moreover, the use of heterogeneous catalysts enables the rapid and straightforward isolation of the target compounds, usually *via* filtration or distillation, as well as the recovery and reuse of the catalyst itself.[8,9]

We envisioned that many of the aforementioned challenges for accessing practical organosulfur oxidants may be addressed through the use of graphite oxide (GO). Often employed as a precursor to graphene-like materials,[12,13] GO may be synthesized by treating graphite with $K_2S_2O_8$ and P_2O_5, followed by $KMnO_4$ in concentrated H_2SO_4, and finally worked up in aqueous H_2O_2.[14] As a result of these strongly oxidizing conditions, a wide range of oxygen-containing functional groups is introduced to graphite's surface (Fig. 1).[10] Accordingly, GO is both highly acidic and a strong oxidizer,[10] and exhibits a propensity to undergo reduction when exposed to various chemical reagents.[10]

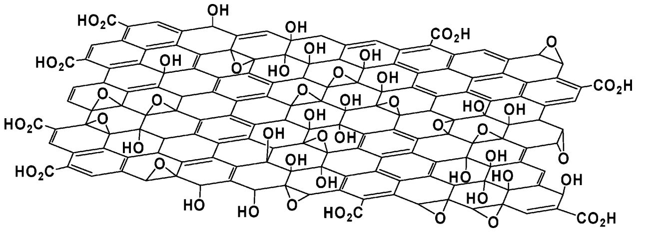

Fig. 1 Proposed structure of graphite oxide (GO) based on the Lerf–Klinowski model.[10,11]

Recently we reported that GO[10] is capable of heterogeneously facilitating a broad range of synthetic transformations including alcohol,[15,16] olefin,[15,17] and C–H oxidations,[17] alkyne hydrations,[15] and combinations thereof.[18] Though typically more challenging to prepare than GO, other acidic and oxidizing carbon materials (*e.g.*, graphite intercalation compounds (GICs) incorporating strong acids and oxidized carbon nanotubes) have also been used to facilitate chemical reactions, including carbonylations,[19] decarboxylation,[20] and dehydrogenations.[21] The use of metal-free carbons such as GO in synthesis takes advantage of their unique characteristics, including their biocompatibility,[22,23] heterogeneity, high surface area, and rich surface chemistry, as well as their low cost and ease of preparation.[24] As a result, GO and other "carbocatalysts"[25] may be distinguished from metallo- or organocatalysts used for similar purposes. Building upon GO's demonstrated oxidative properties,[15] we envisioned utilizing this material for the facile and selective preparation of disulfides and sulfoxides from thiols and sulfides, respectively.

In a preliminary experiment, thiophenol (25 mg) was treated with GO (75 mg) at 100 °C in $CHCl_3$ (0.3 mL) for 10 min in a sealed vessel. After workup by dissolution of the crude reaction mixture in $CHCl_3$ (50 mL) followed by filtration of the heterogeneous carbon and removal of the volatile solvent, the thiol was determined by ^1H NMR spectroscopy ($CDCl_3$) to have been quantitatively converted to diphenyldisulfide.[26] Compared to previously reported oxidative couplings of thiols using metal catalysts (*e.g.*, high surface area iron metal–organic frameworks; MOFs),[4] appreciably less time was required (10 min *versus* several hours) to

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob06102j

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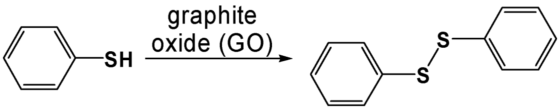
Table 1 Optimization of the GO-catalyzed oxidation of thiophenol[a]



Entry	Carbon (loading)	Reaction temperature (°C)	Reaction time	Conversion[b] (%)
1	—	100	10 min	3.5
2	GO (300 wt%)	100	10 min	100
3	GO (300 wt%)	100	20 min	98
4	GO (300 wt%)	100	30 min	94
5	GO (300 wt%)	100	60 min	96
6	GO (20 wt%)	100	10 min	81
7	GO (60 wt%)	100	10 min	100
8	GO (60 wt%)	40	10 min	5
9	GO (60 wt%)	60	10 min	22
10	GO (60 wt%)	80	10 min	86
11	Graphite (60 wt%)	100	10 min	7
12	Activated carbon (60 wt%)	100	10 min	10
13	Hydrazine-reduced graphene oxide[c] (60 wt%)	100	10 min	23

[a] Reaction conditions: thiophenol (25 mg), carbon (type and amount indicated), and $CDCl_3$ (0.3 mL) were combined in sealed 7.5 mL vial for the time and temperature indicated. [b] Conversion of thiophenol to diphenyldisulfide was monitored by ^1H NMR spectroscopy ($CDCl_3$) using 1,4-dinitrobenzene as an internal standard. [c] Prepared according to previously reported methods (see ESI†).

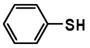
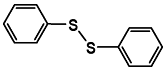
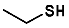
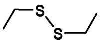
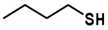
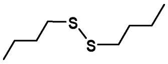
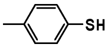
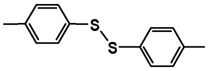
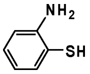
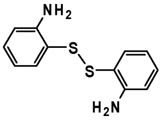
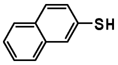
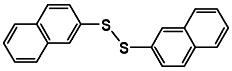
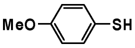
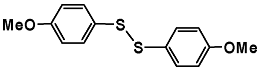
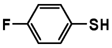
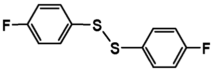
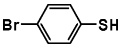
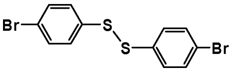
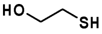
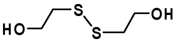
achieve quantitative reaction using GO under similar temperatures and catalyst loadings. After observing quantitative conversion in only a few minutes, subsequent efforts were directed toward optimizing the reaction times, GO loadings, and reaction temperatures employed. Minimal changes in the conversion were observed upon increasing the reaction time (Table 1, entries 2–5). While 20 wt% GO afforded 81% of the target product (entry 6), increasing the loading to 60 wt% GO was found to be sufficient to drive the oxidation reaction to quantitative conversion (entry 7).[27] We also found that variations in the reaction temperature (ranging from 40–100 °C) had a significant effect on the isolated yield of the disulfide product (entries 7–10). At low temperatures, minimal yield of product was obtained; however, a quantitative conversion was generally observed at reaction temperatures at or above 100 °C. Indicating that the observed reactivity was due to GO's unique chemical properties, only minimal yields of the disulfide product were obtained when natural flake graphite, activated carbon, or hydrazine-reduced graphene oxide[28] were substituted for GO (entries 11–13). Likewise, only a low yield of diphenyldisulfide (3.5%; entry 1) was obtained in the absence of a carbon promoter under otherwise identical conditions (100 °C, 10 min).

Using the optimized experimental conditions described above (25 mg thiol, 15 mg GO, 0.3 mL $CHCl_3$, 100 °C, 10 min), we next explored the substrate scope of this method. As shown in Table 2, a wide range of thiols showed excellent conversion to their respective disulfides when treated with GO, and pure products were obtained after short reaction times by dissolution of the crude reaction mixtures in $CHCl_3$ (50 mL), filtration of the residual carbon, removal of the volatile solvent under vacuum, and purification *via* column chromatography in some cases. The reactivity of alkyl thiols (entries 2–3, 10) appeared slightly lower than that of aryl thiols (entries 1, 4–9), despite slightly longer reaction times (30 min *versus* 10 min), consistent with our previous observation that GO often exhibits higher activity toward arene-functionalized substrates.[15,17,18] As a further indicator of the preferential reactivity of aryl thiols over alkyl thiols, a 1 : 1 molar mixture of thiophenol and 1-butanethiol (total mass: 25 mg) was treated with GO (60 wt%) under optimized conditions (100 °C, 10 min). Using ^1H NMR spectroscopy, the crude product mixture (63% conversion) was found to contain a 1.0 : 5.0 : 2.9 molar ratio of dibutyldisulfide : butylphenyldisulfide : diphenyldisulfide, as well as unreacted 1-butylsulfide (34%) and a small amount of unreacted thiophenol (<5%).

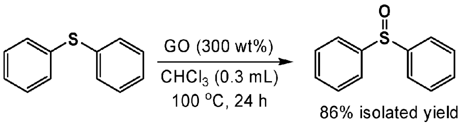
Perturbation of the electronic properties of aromatic thiols through the incorporation of electron-donating or -withdrawing substituents did not significantly affect the isolated yield of the desired product. For example, both electron rich (entries 4–7) and electron deficient thiols (entries 8–9) gave excellent isolated yields of the respective disulfides (94–99%). No over-oxidation (including N-oxidation, in the case of 2-aminothiophenol) was observed in any of the reactions performed, as has been observed with chromic potassium sulfate ($CrK(SO_4)_2 \cdot 12\ H_2O$) and other transition metal-based oxidation catalysts.[29] While this challenge has been addressed using more sophisticated metal species (*e.g.*, MOFs,[4] cobalt imidazoles or cobalt porphyrins,[30] and various bismuth species[31]) such catalysts often do not appear to show the breadth of reactivity that has been demonstrated with GO.

In an effort to expand GO's reactivity within the family of organosulfur species, we turned next toward exploring the oxidation of sulfides to their respective sulfoxides. In a preliminary experiment, diphenylsulfide was oxidized to diphenylsulfoxide in 86% isolated yield after 24 h at 100 °C (300 wt% GO) (Scheme 1); no other oxidation products were observed in the crude reaction mixture. In a similar manner to that described above, the reaction was optimized with respect to GO loading, reaction temperature, and reaction time (see ESI†). We found that GO loadings below 300 wt% were less effective in affording the desired products; however, no improvement in isolated yield was observed at higher loadings. Though the loadings used herein were higher than those typically used with metal catalysts,[1,29] GO's low cost and

Table 2 Oxidation of various thiols using GO[a]

Entry	Starting material	Product	Reaction time	Yield[b] (%)
1			10 min	100
2			30 min[c]	77
3			30 min[c]	90
4			10 min	95
5			10 min	96
6			10 min	97
7			10 min	97
8			10 min	99
9			10 min	94
10			30 min[c]	75

[a] All reactions were performed at 100 °C in sealed 7.5 mL vials using 25 mg thiol, 15 mg GO (60 wt%) and 0.3 mL $CHCl_3$ for the indicated reaction time. [b] Isolated yield after purification by column chromatography. [c] Relatively low yields (40–65%) were observed after 10 min; higher yields were obtained after 30 min.



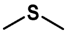
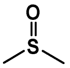
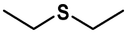
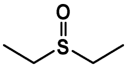
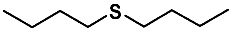
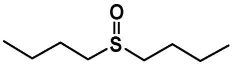
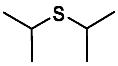
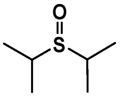
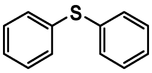
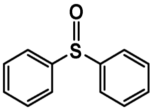
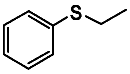
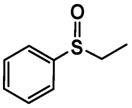
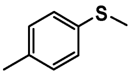
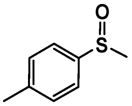
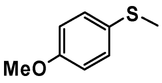
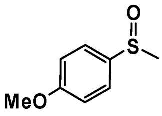
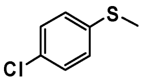
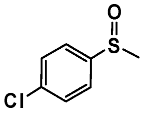
Scheme 1 Oxidation of diphenyl sulfide using GO.

heterogeneity make it a practical choice.[15] In addition to providing an economical, facile route to the target products, it was found that the spent catalyst, which had undergone partial deoxygenation (see below), was able to be reoxidized to GO using the same oxidation methods used with the graphite starting material. As observed in the aforementioned thiol coupling reactions, minimal reactivity was observed when carbons other than GO were used (*i.e.*, graphite, activated carbon, or hydrazine-reduced graphene oxide).

As summarized in Table 3, a broad range of sulfides was successfully converted to their corresponding sulfoxides using GO under optimized conditions (25 mg sulfide, 75 mg GO, 0.3 mL $CHCl_3$, 100 °C, 24 h). Excellent yields of the corresponding products were obtained in most cases after purification by column chromatography, including those that featured *S*-alkyl substituents. Variations in the electronic structure of the arene-substituted sulfides were found to have only a slight influence on the yield of the sulfoxide product. For example, an electron rich sulfide (*p*-methoxythianisole, entry 8) was oxidized in 96% isolated yield, whereas an electron deficient analogue (*p*-chlorothianisole, entry 9) was obtained in 81% yield under otherwise identical conditions. Compared to previously reported Ru and Fe catalysts (utilizing O_2 or H_2O_2 as the oxidant), GO provides increased yield and increased selectivity for the sulfoxide over the sulfone.[32,33]

To ascertain the fate of the GO used in the aforementioned oxidation reactions, the residual carbon was separated from a reaction mixture containing 25 mg thiophenol, 15 mg GO, 0.3 mL $CDCl_3$ after 10 min at 100 °C by filtration and the resulting material was characterized. Compared to the GO starting material, the FT-IR spectrum (KBr) of the recovered carbon exhibited attenuated stretching frequencies ascribed to the C–OH, C═O, and C–O moieties (see Fig. S3, ESI†). The FT-IR spectrum also revealed new signals that were attributed to the presence of aromatic and olefinic species. The deoxygenation of GO was

Table 3 Oxidation of various sulfides by using GO[a]

Entry	Starting material	Product	Yield[b]
1			89%
2			92%
3			90%
4			51%
5			86%
6			85%
7			75%
8			96%
9			81%

[a] All reactions were performed at 100 °C in sealed 7.5 mL vials using 25 mg sulfide, 75 mg GO (300 wt%) and 0.3 mL $CHCl_3$ for 24 h. [b] Isolated yield after purification by column chromatography.

later confirmed *via* X-ray photoelectron spectroscopy (XPS) and elemental combustion analysis (see Fig. S1–S2, Table S5, ESI†). For example, while the as-prepared GO exhibited a C : O ratio of 2.6 : 1 by XPS, the material recovered after reacting GO with thiophenol showed a C : O ratio of 9.2: 1.

In summary, GO was discovered to effectively facilitate the oxidation of thiols and sulfides to their corresponding disulfides and sulfoxides, respectively, and with good selectivity. In all cases studied herein, the necessary reaction times required were found to be relatively short (as brief as 10 min), the recovered yields were high, and purification of the product was facilitated by GO's heterogeneous nature. As such, the methods described provide a practical approach to the oxidation of sulfur compounds; one that does not lead to the over-oxidation often seen with metal catalysts used for similar purposes.[29,32,33]

Acknowledgements

This work was generously supported by the National Science Foundation (grant No. DMR-0907324) and the Robert A. Welch Foundation (grant No. F-1621).

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