

Highly Chemoselective NH- and O-Transfer to Thiols Using Hypervalent Iodine Reagents: Synthesis of Sulfonylimides and Sulfonamides

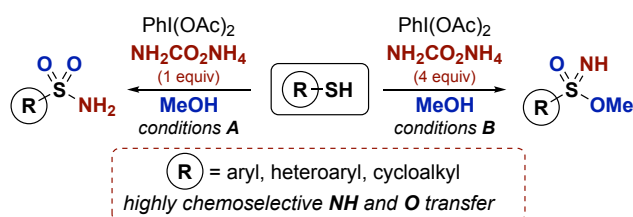
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Supporting Information Placeholder



ABSTRACT: Aryl thiols can be selectively converted to sulfonylimides or sulfonamides with 3 new S–X connections being made selectively in one-pot. Using hypervalent iodine reagents in the presence of ammonium carbamate, NH- and O-groups are transferred under mild and practical conditions. Reducing the loading of ammonium carbamate changed the product distribution, converting the sulfonylimide to the sulfonamide. Studies into the possible intermediate species are presented, suggesting that multiple pathways may be possible via sulfinate esters, or related intermediates, with each species forming the same products.

Functional groups that contain S–O and S–N linkages comprise some of the most useful motifs used in medicinal chemistry.¹ Sulfonamides are the most common and are widely found in marketed drug compounds. Recently, sulfoximines have emerged as valuable groups for medicinal chemistry as chiral alternatives to sulfones,² and have progressed into clinical trials in several compounds.³ These have seen considerable synthetic advances in recent years,⁴ with developments in sulfoxide imination⁵ and sulfide imination, followed by oxidation.⁶ Sulfonylimidamides, aza-analogues of sulfonamides, have also become recently appreciated for potential in medicinal and agrochemistry.⁷ Related sulfonylimides are less studied,⁸ and are more reactive at S through displacement of the alkoxide. This has led to application as sulfoximine precursors on reaction with organometallics,⁹ and in materials science as monomers for polymerization.¹⁰ They are also reactive by S_N2 at the alkoxy carbon with the sulfur group as an effective leaving group affording a sulfonamide.^{11,12}

Here, we report the selective formation of sulfonylimides through a highly chemoselective NH, O and OR transfer to aryl thiols using hypervalent iodine reagents. A modified set of conditions affords sulfonamides, proceeding through the sulfonylimide as an intermediate. Preliminary studies into the order of atom transfer are presented, suggesting multiple pathways could afford the same products.

We recently reported facile conditions for the transfer of NH groups to sulfoxides to form NH-sulfoximines, using bisacetox-iodobenzene and ammonium carbamate (Figure 1).¹³ These

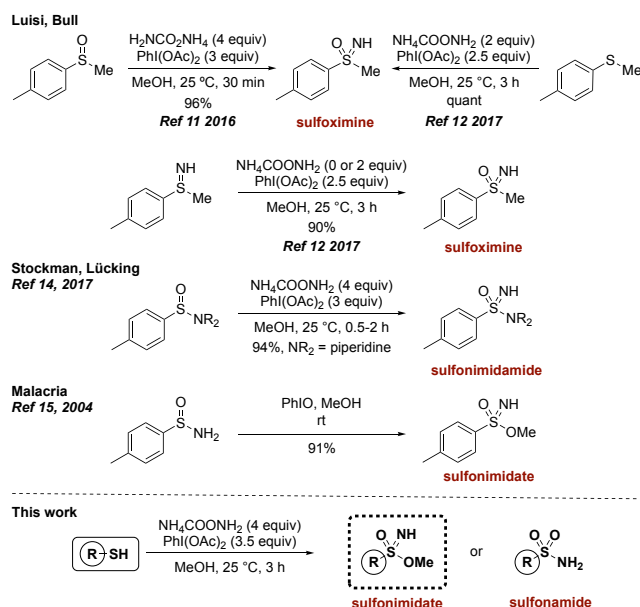


Figure 1. NH and O transfer to S-groups to form sulfoximines, sulfonylimidamides, and this work, sulfonylimides/sulfonamides.

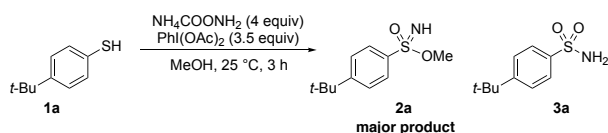
conditions provided a mild and functional group tolerant approach to the unprotected sulfoximine group. An intermediate iminoiodinane species was invoked as the reactive N-species. We then demonstrated that using sulfides, under essentially the same conditions, a chemoselective NH and O transfer occurred to generate sulfoximines directly.^{14,15} Applying the reaction

conditions to diphenyl sulfilimine gave the conversion to the sulfoximine with or without the nitrogen source. Reboul reported related mechanistic and synthetic work at a similar time, which indicated that the O atom derived from methanol or acetate.^{15a} Adopting these ammonium carbamate and bisacetoxiodobenzene conditions, Stockman and Lücking reported NH transfer to sulfenamides to form sulfonimidamides with chemoselective NH transfer.¹⁶ Previously, the oxidation of sulfenamides to methyl sulfonimidates was demonstrated by Malacria using iodobenzene in methanol to promote oxidation.¹⁷

Given the value of these compound classes, we were intrigued by the potential for chemoselective transfer of N and/or O atoms to S-functional groups starting at much lower oxidation levels. We intended to explore direct S–N and S–O bond formations from thiols targeting multiple bond formations in a single process to give valuable S-derivatives, and extend the N-transfer chemistry of hypervalent iodine reagents.^{18,19}

Initially, we examined 4-*tert*-butylbenzenethiol **1a** using a modification of our previously reported conditions (Scheme 1). We were delighted to find that a major product was formed corresponding to methyl sulfonimide **2a**. Primary sulfonamide **3a** was also formed as a minor product.

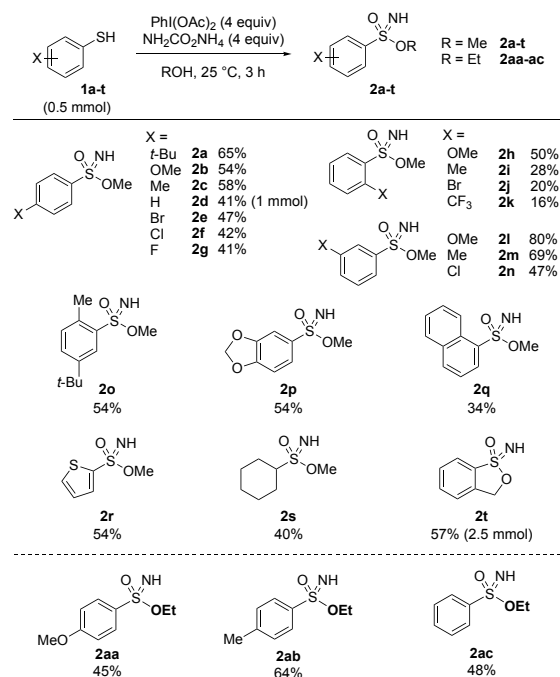
Scheme 1. Initial results forming sulfonimide and sulfonamide



We subsequently optimized this process, varying the reaction conditions and equivalents of reagents. It was clear through these studies that running the reaction with fewer equivalents of ammonium carbamate gave increasing amounts of the sulfonamide. The best conditions to form sulfonimide **2a** used 4 equivalents of ammonium carbamate and 4 equivalents bisacetoxiodobenzene. Unfortunately, despite considerable efforts to prevent formation of the sulfonamide product, it was always formed in small amounts and was inseparable by silica chromatography, hence the sulfonimide was not isolated cleanly. To improve separation and due to concern about the stability of the acid sensitive sulfonimide on silica, we examined various stationary phases.²⁰ Pleasingly, the use of neutral alumina was effective at removing the sulfonamide and afforded the pure sulfonimide. Under these conditions the scope of the reaction was assessed, varying the arylthiol component (Scheme 2).

Using 4-*tert*-butylbenzene thiol, sulfonimide **2a** was isolated in 65% yield. Various *para*-substituted examples were also successful (**2b–g**), with generally higher yields with more electron rich substrates. *ortho*-Substitution gave somewhat reduced yield for the corresponding sulfonimidates **2h–k** (Scheme 2). Better yields were obtained for *meta*-substituted aromatic sulfonimidates **2l–n**. More substituted aromatic thiols were found suitable for this transformation affording sulfonimidates **2o–q**. Electron-rich hetero-substituted thiols such as thiophene-2-thiol furnished the corresponding sulfonimide **2r** in good yield.

Scheme 2. Reaction scope forming sulfonimidates with aryl thiols



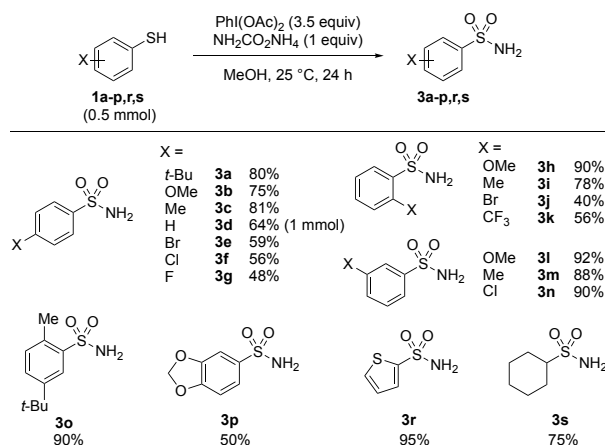
Cyclohexanethiol was also suitable, furnishing sulfonimide **2s** in 40% yield. Interestingly, the use of 2-mercaptobenzylalcohol gave the cyclic sulfonimide **2t** through intramolecular reaction of the benzylic alcohol in preference to the methanol solvent.²¹ Alternatively, running the reaction in EtOH afforded the corresponding ethyl sulfonimidates **2aa–ac**. This protocol provides much more facile access to alkyl aryl-NH-sulfonimidates than has previously been available, and avoids the preparation of sulfenamides.

At the same time, we optimized conditions for the direct formation of sulfenamides from the thiols (Scheme 3).²² Running the reaction with only 1 equivalent of ammonium carbamate, and extending the reaction time to 24 h, at 25 °C, gave full conversion from the thiol to the sulfonamide, via the sulfonimide.²³ For this reaction, the yields were higher than the sulfonimidates, and were again found to be dependent on the electronics of the aryl group. Sulfenamides **3a–n** were obtained in good to excellent yields from the corresponding aromatic thiols (Scheme 3). The protocol was successfully applied to thiols bearing poly-substituted aromatics (**3o,p**) as well as electron-rich heterocycle (**3r**) and alkyl moieties (**3s**).

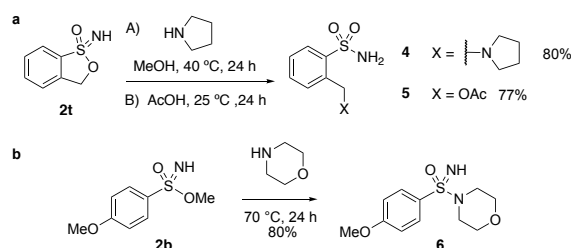
Cyclic sulfonimide **2t** did not significantly convert to the sulfonamide under the longer reaction conditions, perhaps representing stability of the cyclic system. Instead, and to provide insight to the mechanism, sulfonimide **2t** was treated with other nucleophiles (Scheme 4).

Treating the isolated sulfonimide **2t** with pyrrolidine in MeOH or with acetic acid gave ring opening to the sulfonamide products **4** and **5**, incorporating the nucleophile at the benzylic position. By contrast, treating the electron-rich 4-methoxyphenyl sulfonimide **2b** with morpholine gave sulfonimidamide **6** in high yield with displacement at the sulfur center (Scheme 4b).

Scheme 3. Reaction scope forming sulfonamides with aryl thiols



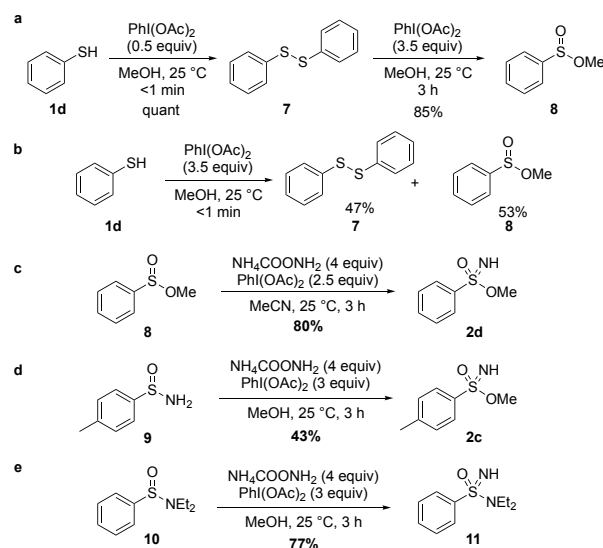
Scheme 4. Reaction of sulfonimides **2t** and **2b** with nucleophiles



To provide insight into the reaction mechanism and order of events, we next examined other sulfur functional groups under related reaction conditions. Treating PhSH with oxidant alone quantitatively formed diphenyl disulfide **7**.²⁴ The disulfide was converted to the methyl sulfinatate ester **8** with an excess of oxidant (Scheme 5a). A mixture of **7** and **8** was obtained on treating the thiol with 3.5 equivalents of oxidant in MeOH (Scheme 5b). Using methyl benzenesulfinate **8** as the substrate, sulfonimide **2d** was formed, using acetonitrile as the solvent (Scheme 5c). Importantly for the selectivity, the use of the reagents in the absence of the N-source did not give oxidation of the sulfinatate ester to the corresponding sulfonate ester. This provides a potentially valuable alternative route to sulfonimides from sulfinatate esters. In comparison to the Malacria method,¹⁷ applying our conditions to a primary sulfonamide **9** also formed sulfonimide **2c** with small quantities of the sulfonamide (Scheme 5d). As recently reported by Lücking and Stockman,¹⁶ we also observed NH transfer in the presence of N,N-disubstituted sulfonamides (Scheme 5e). This is in contrast to the oxidation observed for the NH_2 species.

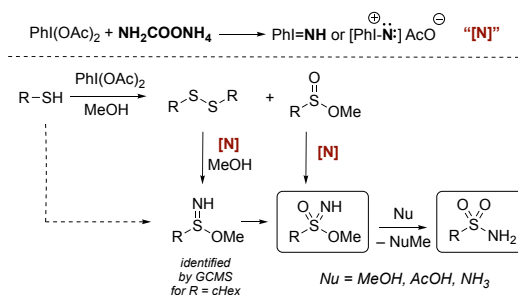
In terms of the source of the O-atom in the sulfonimides, it is likely to be the MeOH solvent or acetate. This is consistent with Reboul's proposal for sulfide oxidation to form sulfoximines,^{15a} which can also be compared with the conversion of sulfonimide to sulfonamide by nucleophilic substitution.

Scheme 5. Control reactions



To identify intermediate species, reactions using various sulfides were sampled and analyzed directly by GC and GCMS analysis. The reaction in all cases was fast, and intermediate species were not detected with the exception of the corresponding disulfide and sulfinatate ester species. Only when investigating cyclohexanethiol as the substrate was another intermediate detected in the MS trace, which was putatively assigned as $\text{cHexS}(\text{NH})\text{OMe}$. Based on these results and our prior studies, the sequence reported in Scheme 6 is proposed. It is likely that multiple pathways may be followed, but that these are selectively converted to the same product. However, the exact sequence of events remains unclear.

Scheme 6. Plausible reaction sequence



In conclusion, sulfonimides are selectively formed from thiols using ammonium carbamate and bisacetoxiodobenzene in methanol. Conversion to sulfonamides occurs in the presence of lower ammonia concentrations and extended reaction times through substitution of the alkoxy group. Disulfides, sulfinates and sulfonamides are all suitable precursors to sulfonimides under these reaction conditions. Further studies are underway in our laboratories to elucidate mechanistic pathways and exploit these simple reagents for selective transformations.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data and copies of ^1H and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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