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

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Supporting Information Placeholder

ABSTRACT: Aryl thiols can be selectively converted to sulfonimidates 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 sulfonimidate 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.
conditions to diphenyl sulfilimine gave the conversion to the sulfoximine with or without the nitrogen source. Rebold reported related mechanistic and synthetic work at a similar time, which indicated that the O atom derived from methanol or acetate.\textsuperscript{13,14} Adopting these ammonium carbamate and bisacetoxyiodobenzene conditions, Stockman and Lücking reported NH transfer to sulfinimides to form sulfonimidamides with chemoselective NH transfer.\textsuperscript{15} Previously, the oxidation of sulfanimides to methyl sulfonimidates was demonstrated by Malacria using iodosobenzene in methanol to promote oxidation.\textsuperscript{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.\textsuperscript{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 sulfonimidate 2a. Primary sulfonamide 3a was also formed as a minor product.

**Scheme 1. Initial results forming sulfonimidate 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 sulfonimidate 2a used 4 equivalents of ammonium carbamate and 4 equivalents bisacetoxyiodobenzene. 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 sulfonamide was not isolated cleanly. To improve separation and to concern about the stability of the acid sensitive sulfonimidate on silica, we examined various stationary phases.\textsuperscript{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, sulfonimidate 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 sulfonimidate 2r in good yield.

Cyclohexanethiol was also suitable, furnishing sulfonimidate 2s in 40% yield. Interestingly, the use of 2-mercaptobenzylalcohol gave the cyclic sulfonimidate 2t through intramolecular reaction of the benzyl alcohol in preference to the methanol solvent.\textsuperscript{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 sulfanamides.

At the same time, we optimized conditions for the direct formation of sulfonimidates from the thiols (Scheme 3).\textsuperscript{22} Running the reaction with only 1 equivalent of ammonium carbamate, and extending the reaction time to 24 h, at 25 ºC, gave full conversion from the thiol to the sulfonamide, via the sulfonimidate.\textsuperscript{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. Sulfonimides 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 sulfonimidate 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, sulfonimidate 2l was treated with other nucleophiles (Scheme 4).

Treating the isolated sulfonimidate 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 sulfonimidate 2b with morpholine gave sulfonimidamide 6 in high yield with displacement at the sulfur center (Scheme 4b).
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 sulfinate ester species. Only when investigating cyclohexanethiol as the substrate was another intermediate detected in the MS trace, which was putatively assigned as cHexS(NH)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, sulfonamides are selectively formed from thiols using ammonium carbamate and bisacetoxynidobenzene in methanol. Conversion to sulfonimidates occurs in the presence of lower ammonia concentrations and extended reaction times through substitution of the alkoxy group. Disulfides, sulfinites and sulfonamides are all suitable precursors to sulfonimidates 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 \(^1\)H and \(^{13}\)C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.
ACKNOWLEDGMENTS


We gratefully acknowledge The Royal Society for a University Research Fellowship (to J.A.B.) and EPSRC [CfA to J.A.B. (EP/J001538/1), Impact Acceleration Account (EP/K503733/1), DTA Studentship (to S.S.J.C. and E. B.)]. This research was supported by the project Laboratorio Sistema code PONa300369 financed by MIUR, the University of Bari.

REFERENCES
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\begin{align*}
\text{RSH} & \quad \text{PhI(OAc)}_2 \quad \text{NH}_2\text{CO}_2\text{NH}_4 \quad \text{MeOH} \quad \text{conditions A} \\
\text{R} & \quad \text{NH} \\
\text{R} & \quad \text{O} \\
\text{R} & \quad \text{OMe}
\end{align*}
\]

\[
\begin{align*}
\text{RSH} & \quad \text{PhI(OAc)}_2 \quad \text{NH}_2\text{CO}_2\text{NH}_4 \quad \text{MeOH} \quad \text{conditions B} \\
\text{R} & \quad \text{NH} \\
\text{R} & \quad \text{O}
\end{align*}
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\(\text{R} = \text{aryl, heteroaryl, cycloalkyl}\)  

*highly chemoselective NH and O transfer*