Electrophilic Sulfoximidations of Thiols by Hypervalent Iodine Reagents

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Abstract  
A new electrophilic sulfoximidation of thiols has been developed. Using sodium hydride as a base, the treatment of sulfoximidoyl-containing hypervalent iodine(III) reagents with thiols affords the corresponding N-sulfenylsulfoximines (N-thiosulfoximines) in good to excellent yields. A plausible mechanism is proposed.

Key words  
sulfoximidation, thiol, N-sulfenylsulfoximine, hypervalent iodine reagents, ligand exchange

Sulfoximines are monoaza analogues of sulfones with relevance for asymmetric synthesis and applications in crop protection and medicinal chemistry. They exhibit manifold reaction behavior, as reflected by Trost and Matsuzuka, who described N-nitrosulfoximines as 'chemical chameleons'. In general, substituents at the sulfoximidoyl group affect the properties of the respective molecules, allowing, for example, fine-tuning of important parameters such as $pK_a$ and solubility. The N-substituent plays a key role in this context. Besides introducing it directly by sulfide or sulf oxide imidation, it can be varied by functionalizing NH-sulfoximines, which are readily accessible by various routes. Most protocols involve deprotonated intermediates, which react with electrophiles to give acylated, alkylated, or arylated products among others. Alternative N-modification pathways via radicals or cationic species are rare.

In 2016 we introduced hypervalent iodine(III) compounds with the vision to apply them synthetically as sulfoximidoyl transfer agents (Scheme 1). To our delight, photocatalysis allowed activation of the central I–N bond of 2 leading to functionalizations of benzylidene C–H bonds by the resulting sulfoximidoyl moieties. In terms of the mechanism, the process was suggested to proceed via radicals such as B. While searching for new applications of iodine reagents 2, we began focusing on pathways via (formally) cationic species C. Until now, only one transformation reflecting such reactivity is known. In the respective reaction scheme, reagents react with terminal alkynes in the presence of a base affording N-alkynylated sulfoximines. After screening a series of other nucleophiles, we have now also discovered that deprotonated thiols were capable of reacting with 2 leading to N-sulfenylsulfoximines with the general structure. Products of type 5 were known, but the common synthetic procedures started from NH-sulfoximines, which were either N-derivatized by deprotonation followed by treatment with electrophilic sulfur reagents (such as ArSCl) or coupled with preformed or thiol-derived disulfides under metal catalysis. Thus, our new approach contrasted all previous ones.

Scheme 1  General reaction behavior of NH-sulfoximines and access to target compounds via iodine reagents 2
The initial studies were performed with S-methyl-S-phenyl derivative 2a and thiophenol (4a) as representative substrates. In dichloroethane (DCE), both compounds did not react at ambient temperature or at 70 °C, and only the starting materials were recovered (Table 1, entries 1 and 2). Also the addition of DBU, K₂CO₃, or KOt-Bu did not lead to a breakthrough, and at best, traces of the expected product 5aa were observed (Table 1, entries 3–5). The situation changed, when NaH was applied as base, and after a short optimization of the reaction conditions (Table 1, entries 6–11), N-sulfonylsulfimine 5aa was obtained in 91% yield (Table 1, entry 11).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>DCE</td>
<td>25</td>
<td>n.r.</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>DCE</td>
<td>70</td>
<td>n.r.</td>
</tr>
<tr>
<td>3</td>
<td>DBU (2.1)</td>
<td>DCE</td>
<td>25</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃ (2.1)</td>
<td>DCE</td>
<td>25</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>KOt-Bu (2.1)</td>
<td>DCE</td>
<td>25</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>NaH (2.1)</td>
<td>DCE</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>NaH (2.1)</td>
<td>DCE</td>
<td>50</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>NaH (2.1)</td>
<td>MeCN</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>NaH (2.1)</td>
<td>THF</td>
<td>50</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>NaH (2.1)</td>
<td>CH₂Cl₂</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>11b</td>
<td>NaH (4.2)</td>
<td>CH₂Cl₂</td>
<td>50</td>
<td>91</td>
</tr>
</tbody>
</table>

*a Reaction conditions (0.2-mmol scale): iodine reagent 2a, thiophenol (4a; 2 equiv), base, solvent (2 mL), sealed tube, 16 h. n.r. = no reaction, n.d. = not detected.

Based on previous reports,¹¹,¹⁹,²⁰ we suggest the pathway depicted in Scheme 3 for the formation of N-sulfonylsulfimines 5. First, thiol 4 is deprotonated by sodium hydride, and the resulting thiolate reacts with hypervalent iodine reagent 2 by tosylate substitution. This ligand exchange leads to the formation of a transient intermediate 7, which upon elimination of iodobenzene provides product 5.

In summary, we developed a new approach towards N-sulfonylsulfimines by electrophilic sulfimidations of thiolates with sulfoximidoyl-containing hypervalent iodine(III) reagents. Both N-(aryl)sulfenyl)- as well as N-(alkyl)sulfonyl)sulfimines can easily be obtained under metal-free conditions.
**Scheme 3** Possible reaction pathway

Unless otherwise noted, all chemicals were purchased from commercial suppliers (Abcr, Acros, Sigma Aldrich, Merck) and used without further purification. When required, solvents were dried according to general purification methods. The product mixtures were analyzed by TLC using silica gel plates (Merck-Schuchardt) with fluorescent indicator (λ = 254 nm). The purification of the products was performed by flash column chromatography using silica gel 60 (63–200 μm) from Merck. NMR spectra were recorded on Agilent VNMRS 600, Agilent VNMR 400 or Varian Mercury 300 in deuterated solvents. The IR spectra were recorded with a PerkinElmer Spectrum 100 spectrometer with an attached UATR device Diamond KRS-5; all IR data were collected by attenuated total reflectance (ATR). Mass spectra were recorded on a Finnigan SSQ Finnigan 7000 spectrometer (EI, 70 eV). HRMS were recorded on a Thermo Scientific LTQ Orbitrap XL spectrometer. Melting points (mp) were measured on a Büchi B-540 melting point apparatus.

### N-Thiosulfoximines Saa–da; General Procedure

Thiol 4 (0.80 mmol), NaH (0.80 mmol, 32 mg, wt = 60%), and CH₂Cl₂ (2.0 mL) were added to a flame-dried reaction tube (15 mL) equipped with a magnetic stirring bar, and the mixture was stirred at 50 °C for 4 h. Then, the hypervalent iodine(III) salt 2 (0.20 mmol) was added to the mixture in one portion. The resulting solution was stirred for 12 h at 50 °C and then cooled to r.t. Concentration under reduced pressure and subsequent purification of the product by column chromatography (silica gel, EtOAc/pentane 1:2) afforded N-thiosulfoximines 5.

**N-(Phenylthio)-S-methyl-S-phenylsulfoximine (5aa)**

Pale yellow viscous oil; yield: 48 mg (91%).

**1H NMR** (600 MHz, CDCl₃): δ = 7.95–7.93 (m, 2 H), 7.67–7.64 (m, 1 H), 7.60–7.56 (m, 2 H), 7.41–7.38 (m, 2 H), 7.27–7.25 (m, 2 H), 7.09 (t, J = 7.3 Hz, 1 H), 3.28 (s, 3 H).

**13C{1H} NMR** (151 MHz, CDCl₃): δ = 141.2, 138.7, 133.7, 129.5, 128.5, 128.4, 125.1, 123.8, 43.8.

**N-(4-Chlorophenylthio)-S-methyl-S-phenylsulfoximine (5ac)**

Pale yellow oil; yield: 45 mg (81%).

**1H NMR** (600 MHz, CDCl₃): δ = 7.97–7.94 (m, 2 H), 7.68–7.65 (m, 1 H), 7.60–7.56 (m, 2 H), 7.41–7.38 (m, 2 H), 7.27–7.25 (m, 2 H), 7.09 (t, J = 7.3 Hz, 1 H), 3.28 (s, 3 H).

**13C{1H} NMR** (151 MHz, CDCl₃): δ = 141.2, 138.8, 138.2, 135.3, 133.6, 129.4, 129.3, 128.4, 125.0, 43.7, 21.0.

**MS (EI):** m/z = 277 (13, M⁺), 261 (4), 140 (23), 125 (21), 123 (100), 91 (72).

**HRMS:** m/z calcd for [C₁₄H₁₂ClNOS₂ + H⁺]: 278.0688; found: 278.0668.

**N-(4-Fluorophenylthio)-S-methyl-S-phenylsulfoximine (5ad)**

Pale yellow oil; yield: 44 mg (73%).

**1H NMR** (600 MHz, CDCl₃): δ = 7.93–7.91 (m, 2 H), 7.65–7.63 (m, 1 H), 7.58–7.56 (m, 2 H), 7.43–7.41 (m, 2 H), 6.84–6.82 (m, 2 H), 3.78 (s, 3 H), 3.23 (s, 3 H).

**13C{1H} NMR** (151 MHz, CDCl₃): δ = 158.7, 138.9, 133.5, 132.7, 129.5, 129.4, 128.5, 121.3, 55.4, 43.9.

**MS (EI):** m/z = 281 (99, M⁺), 141 (6), 140 (100), 127 (8), 125 (4), 124 (8), 95 (15), 77 (38).

**HRMS:** m/z calcd for [C₁₄H₁₃FNOS₂ + H⁺]: 282.0417; found: 282.0420.

**N-(4-Methoxyphenylthio)-S-methyl-S-phenylsulfoximine (5ae)**

Pale yellow oil; yield: 45 mg (81%).

**1H NMR** (600 MHz, CDCl₃): δ = 7.97–7.94 (m, 2 H), 7.68–7.65 (m, 1 H), 7.60–7.56 (m, 2 H), 7.41–7.38 (m, 2 H), 7.27–7.25 (m, 2 H), 7.09 (t, J = 7.3 Hz, 1 H), 3.28 (s, 3 H).

**13C{1H} NMR** (151 MHz, CDCl₃): δ = 141.2, 138.7, 133.7, 129.5, 128.5, 128.4, 125.1, 123.8, 43.8.

**N-(2-Methylphenylthio)-S-methyl-S-phenylsulfoximine (5af)**

Pale yellow oil; yield: 45 mg (81%).

**1H NMR** (600 MHz, CDCl₃): δ = 7.97–7.94 (m, 2 H), 7.66–7.62 (m, 1 H), 7.58–7.54 (m, 2 H), 7.31–7.27 (m, 1 H), 7.02–6.95 (m, 2 H), 3.27 (s, 3 H), 2.14 (s, 3 H).

**13C{1H} NMR** (151 MHz, CDCl₃): δ = 140.7, 138.8, 133.6, 132.1, 129.4, 129.4, 128.4, 126.2, 124.3, 43.8, 18.8.

**MS (EI):** m/z = 277 (91, M⁺), 137 (20), 125 (29), 124 (44), 123 (14), 91 (14), 77 (31).

**HRMS:** m/z calcd for [C₁₃H₁₀NOS₂ + H⁺]: 278.0668; found: 278.0670.

**N-(2-Bromophenylthio)-S-methyl-S-phenylsulfoximine (5ag)**

Yellow oil; yield: 55 mg (80%).
IR (ATR): 3458, 3058, 2926, 2669, 2325, 2097, 1915, 1738, 1570, 1438, 1316, 1211, 1092, 982, 912, 735 cm⁻¹.

\(^1^H\) NMR (600 MHz, CDCl₃): \(\delta = 7.98–7.95\) (m, 2 H), 7.67–7.65 (m, 2 H), 7.61–7.57 (m, 2 H), 7.36–7.32 (m, 2 H), 6.95–6.91 (m, 1 H), 3.31 (s, 3 H).

\(^{13}C\{^1H\} \text{ NMR (101 MHz, CDCl}_3\): \(\delta = 7.98–7.95\) (m, 2 H), 7.67–7.65 (m, 2 H), 7.61–7.57 (m, 2 H), 7.36–7.32 (m, 2 H), 6.95–6.91 (m, 1 H), 3.31 (s, 3 H).

HRMS: \(m/z\) calcd for [C₁₃H₁₂BrONS₂ + Na⁺]: 358.0696; found: 358.0696.

HRMS: \(m/z\) calcd for [C₁₃H₁₃FNOS₂ + H⁺]: 282.0417; found: 282.0417.

Colorless oil; yield: 50 mg (77%).

IR (ATR): 3458, 3058, 2926, 2669, 2325, 2097, 1915, 1738, 1570, 1438, 1316, 1211, 1092, 982, 912, 735 cm⁻¹.

\(^1^H\) NMR (600 MHz, CDCl₃): \(\delta = 7.96–7.94\) (m, 2 H), 7.64–7.60 (m, 1 H), 7.59–7.56 (m, 2 H), 3.14 (s, 3 H), 1.38 (s, 9 H).

HRMS: \(m/z\) calcd for [C₁₃H₁₃FNOS₂ + H⁺]: 282.0417; found: 282.0417.

IR (ATR): 3458, 3058, 2926, 2669, 2325, 2097, 1915, 1738, 1570, 1438, 1316, 1211, 1092, 982, 912, 735 cm⁻¹.

\(^1^H\) NMR (600 MHz, CDCl₃): \(\delta = 7.96–7.94\) (m, 2 H), 7.64–7.60 (m, 1 H), 7.59–7.56 (m, 2 H), 3.14 (s, 3 H), 1.38 (s, 9 H).

HRMS: \(m/z\) calcd for [C₁₃H₁₃FNOS₂ + H⁺]: 282.0417; found: 282.0417.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610369.
References


(17) For the preparation of sulfoximines with N–SCF3 groups, which were prepared by reacting NBr-sulfoximines with AgSCF3, see: Bohnen, C.; Bolm, C. *Org. Lett.* 2015, 17, 3011.

(18) In these experiments, combinations of 4a (2 equiv) and NaH (2.1 equiv) were applied; satisfying results were not achieved in DCE at r.t. or 50 °C or in CH2Cl2 at 50 °C.
