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 1 and applications in crop protection and medicinal chemistry. 2 They exhibit manifold reaction behavior, as reflected by Trost and Matsumi, who described N-nitrosulfoximines as ‘chemical chameleons’. 3 In general, substituents at the sulfoximidooyl group affect the properties of the respective molecules, 4 , 5 allowing, for example, fine-tuning of important parameters such as p K a 6 and solubility. 7 The N-substituent plays a key role in this context. Besides introducing it directly by sulfide or sulfoxide imidation, 4 , 8 it can be varied by functionalizing NH-sulfoximines 1 , which are readily accessible by various routes. 1 , 9 Most protocols involve deprotonated intermediates A , which react with electrophiles to give acylated, alkylated, or arylated products among others. 10 Alternative N-modification pathways via radicals B or cationic species C are rare.

In 2016 we introduced hypervalent iodine(III) compounds 2 with the vision to apply them synthetically as sulfoximidoyl transfer agents (Scheme 1). 11 , 12 To our delight, photocatalysis allowed activation of the central I–N bond of 2 leading to functionalizations of benzylic C–H bonds by the resulting sulfoximidoyl moieties. 10 , 13 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 2 react with terminal alkynes in the presence of a base affording N-alkynylated sulfoximines 3 . 11 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 5 . Products of type 5 were known, but the common synthetic procedures started from NH-sulfoximines 1 , which were either N-derivatized by deprotonation followed by treatment with electrophilic sulfur reagents (such as ArSCl) 14 or coupled with preformed 15 or thiol-derived disulfides 16 , 17 under metal catalysis. Thus, our new approach contrasted all previous ones.

Scheme 1 General reaction behavior of NH-sulfoximines 1 and access to target compounds 5 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-sulfenylsulfoximine 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>

* 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.

To achieve this result, the following parameters were important: First, the ratio of starting materials 2a and 4a had to be 1:4. Second, the solvent needed to be dichloromethane, and third, the reaction temperature had to be 50 °C.

With the optimized conditions in hand, the substrate scope was examined. The results for reactions performed on a 0.2-mmol scale with respect to 2a (in sealed tubes) are summarized in Scheme 2. First, various aromatic thiols were reacted with hypervalent iodine reagent 2a. All products 5aa–aj were obtained in good to high yields (52–91%). Electronic or steric effects induced by substituents on the thiophenol did not have an apparent impact on the reaction efficiency. Also ortho-substituted thiols reacted remarkably well as reflected by the results for products 5af–ah, which were isolated in yields of 81%, 80%, and 72%, respectively. Reactions of 2a with aliphatic thiols proved more difficult. Thus, 5ak and 5al stemming from couplings of 2a with 2-methylpropene-2-thiol (4k) and cyclohexanethiol (4l) were obtained in only 21% and 30%, respectively. Varying the structure of the hypervalent iodine reagent was possible too, and applying S,S-diphenyl and S-(4-fluorophenyl)-S-methyl derivatives 2b and 2c in reactions with thiophenol (4a) led to the corresponding products 5ba and 5ca in 77% and 46% yield, respectively. With tetrahydrothiophene derivative 2d as the coupling agent for 4a, only traces of the corresponding product 5da were observed. The attempt to use 1-sulfoximidoyl-1,2-benziodoxole 6 in the reaction with 4a remained unsuccessful.

Based on previous reports,¹¹,¹⁹,²⁰ we suggest the pathway depicted in Scheme 3 for the formation of N-sulfenylsulfoximines 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-sulfenylsulfoximines by electrophilic sulfoximidations of thiols with sulfoximidoyl-containing hypervalent iodine(III) reagents. Both N-(arylsulfonyl)- and N-(alkylsulfenyl)sulfoximines can easily be obtained under metal-free conditions.
Unless otherwise noted, all chemicals were purchased from commercial suppliers (Aкр, 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 VNMR 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 with a PerkinElmer Spectrum 100 spectrometer (EI, 70 eV). HRMS were recorded on a Finnigan SSQ Finnigan 7000 spectrometer (EI, 70 eV). Mass spectra were recorded with a PerkinElmer Spectrum 100 spectrometer (EI, 70 eV). HRMS were recorded on a Thermo Scientific LTQ Orbitrap XL spectrometer. NMR spectra were recorded on Agilent VNMRS 600, Agilent VNMRS 151 MHz, CDCl 3: δ = 7.94–7.92 (m, 2 H), 7.68–7.65 (m, 1 H), 7.59–7.56 (m, 2 H), 7.32–7.31 (d, J = 6.0 Hz, 2 H), 7.10–7.08 (m, 2 H), 3.26 (s, 3 H). 13C{1H} NMR (101 MHz, CDCl 3): δ = 141.2, 138.7, 133.7, 129.5, 128.5, 128.4, 125.1, 123.8, 43.8.

\[ \text{Scheme 3 Possible reaction pathway} \]

N-(4-Chlorophenylthio)-S-methyl-S-phenylsulfoximine (5ac)
Pale yellow oil; yield: 51 mg (87%).

IR (ATR): 3459, 3064, 2923, 2662, 2331, 2100, 1739, 1496, 1391, 1211, 1089, 981, 816, 735, 683 cm\(^{-1}\).

1H NMR (600 MHz, CDCl 3): δ = 7.94–7.92 (m, 2 H), 7.69–7.66 (m, 1 H), 7.60–7.58 (m, 2 H), 7.33–7.31 (d, J = 6.0 Hz, 2 H), 7.23–7.21 (m, 2 H), 3.28 (s, 3 H).

13C{1H} NMR (151 MHz, CDCl 3): δ = 140.9, 138.5, 133.9, 130.6, 129.6, 128.6, 128.4, 125.1, 43.9.

MS (EI): m/z = 298 (95, M\(^+\)), 143 (88), 140 (48), 125 (84), 124 (100), 111 (21), 77 (81).

HRMS: m/z calcd for [C\(_{14}\)H\(_{15}\)ClNOS\(_2\) + H\(^+\)]: 298.0122; found: 298.0122.

N-(4-Fluorophenylthio)-S-methyl-S-phenylsulfoximine (5ad)
Yellow oil; yield: 29 mg (52%).

IR (ATR): 3459, 3302, 3059, 2660, 2323, 2090, 1911, 1739, 1584, 1481, 1390, 1216, 1091, 986, 832, 741, 692 cm\(^{-1}\).

1H NMR (600 MHz, CDCl 3): δ = 7.94–7.91 (m, 2 H), 7.69–7.65 (m, 1 H), 7.60–7.56 (m, 2 H), 7.41–7.37 (m, 2 H), 6.99–6.95 (m, 2 H), 3.27 (s, 3 H).

13C{1H} NMR (101 MHz, CDCl 3): δ = 161.2 (d, J\(_{CF} = 245.4\) Hz), 138.6, 136.8, 133.7, 129.5, 128.4, 127.0 (d, J\(_{CF} = 8.1\) Hz), 115.6 (d, J\(_{CF} = 22.2\) Hz), 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 [C\(_{14}\)H\(_{15}\)FNO\(_2\)S\(_2\) + H\(^+\)]: 282.0417; found: 282.0420.

N-(4-Methoxyphenylthio)-S-methyl-S-phenylsulfoximine (5ae)
Yellow oil; yield: 44 mg (73%).

IR (ATR): 3460, 3298, 3062, 2929, 2667, 2328, 2086, 1906, 1730, 1586, 1487, 1226, 1091, 986, 825, 740, 686 cm\(^{-1}\).

1H NMR (600 MHz, CDCl 3): 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 (101 MHz, CDCl 3): δ = 158.7, 138.9, 133.5, 132.7, 129.5, 129.4, 128.5, 114.3, 55.4, 43.9.

MS (EI): m/z = 293 (3, M\(^+\)), 154 (4), 140 (16), 139 (100), 125 (16), 124 (20), 107 (2), 77 (28).

HRMS: m/z calcd for [C\(_{14}\)H\(_{15}\)NO\(_2\)S\(_2\) + H\(^+\)]: 294.0617; found: 294.0618.

N-(2-Methylphenylthio)-S-methyl-S-phenylsulfoximine (5af)
Pale yellow oil; yield: 45 mg (81%).

IR (ATR): 3458, 3302, 3055, 2924, 2665, 2326, 2103, 1905, 1738, 1584, 1452, 1212, 1092, 986, 738, 685 cm\(^{-1}\).

1H NMR (600 MHz, CDCl 3): 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 (101 MHz, CDCl 3): δ = 140.7, 138.8, 133.6, 132.1, 129.4, 129.4, 128.4, 126.2, 124.5, 123.3, 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 [C\(_{14}\)H\(_{15}\)NO\(_2\)S\(_2\) + H\(^+\)]: 278.0668; found: 278.0670.

N-(2-Bromophenylthio)-S-methyl-S-phenylsulfoximine (5ag)
Yellow oil; yield: 55 mg (80%).
Supporting Information

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

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References


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

(18) In these experiments, combinations of 4a (2 equiv) and NaN3 (2.1 equiv) were applied; satisfying results were not achieved in DCE at r.t. or 50 °C or in CH2Cl2 at 50 °C.
