H$_2$O$_2$/Tf$_2$O System: An Efficient Oxidizing Reagent for Selective Oxidation of Sulfanes

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Abstract: A versatile procedure for the oxidation of sulfanes to sulfoxides without any overoxidation to sulfones has been reported. It is noteworthy that the reaction tolerates oxidatively sensitive functional groups and that the sulfur atom is selectively oxidized.

Key words: sulfoxides, chemoselectivity, environmentally friendly, triflic anhydride

The selective oxidation of sulfanes to sulfoxides remains a challenge and is of interest because of the importance of sulfoxides as synthetic intermediates for the construction of various chemically and biologically active molecules.\(^1\)

To date, the most important method of preparation involves the oxidation of sulfanes. Various oxidizing agents are used for this purpose,\(^2\)–\(^14\) and unfortunately, most of these reagents are not satisfactory for medium to large-scale operations for several reasons. The first reason is that the low content of the effective oxygen that is available for the oxidation, generation of environmentally unfavorable by-products, and high cost. Another reason is that overoxidation of the sulfoxides to sulfones during the oxidation of sulfanes. Indeed selective oxidation of sulfanes to sulfoxides remains a challenging task, and constitutes an active research on its own, particularly with the emphasis on ‘green chemistry’. In this direction, use of aqueous hydrogen peroxide as oxidizing agent is highly preferred in view of an effective oxygen content (47%), cleanliness that produces only harmless water by reaction,\(^15\) safety in storage and operation, and the low cost of production transportation.\(^16,17\) This feature has already stimulated the development of useful procedures for H$_2$O$_2$ oxidation. In continuation of our recent work on the oxidation of sulfanes,\(^18\) we disclose that H$_2$O$_2$/Tf$_2$O system can be used for the gentle and efficient selective oxidation of a wide range of sulfanes. The route for the synthesis of sulfoxides is shown in Scheme 1.

Several solvents including acetonitrile, ethanol, acetone, and 1,4-dioxane were investigated during the course of this study. The best results based on yields and times of the reaction were achieved using ethanol.

Initially, we performed a set of preliminary experiments on benzyl phenyl sulfane as a model substrate using 30% aqueous hydrogen peroxide in the presence of different amount of triflic anhydride (Tf$_2$O) in ethanol at room temperature. The results are depicted in Table 1. A ratio of 1:2:0.5 sulfane/H$_2$O$_2$/Tf$_2$O was found to be optimum for complete conversion of sulfanes into sulfoxides.

### Table 1  Effect of Tf$_2$O on the H$_2$O$_2$ Oxidation of Benzyl Phenyl Sulfane\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tf$_2$O (mmol)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>97</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were performed with benzyl phenyl sulfane (1 mmol), and H$_2$O$_2$ (2 mmol) for 7 min, at r.t.
\(^b\) Isolated yield.

To extend the scope of the reaction and to generalize the procedure, we investigated the sulfoxidation of diaryl, dibenzyl, aroyl benzyl, dialkyl, and heterocyclic sulfanes under optimized reaction conditions (Table 2). Both sulfanes bearing electron-donating and electron-withdrawing substituents gave the desired sulfoxides in excellent yields. Even a much deactivated sulfane was converted into the sulfoxide (Table 2, entry 14). All the reactions occurred with complete selectivity for sulfoxide formation, no overoxidation products such as sulfones were detected in the reaction mixtures. The chemoselectivity of the procedure was noteworthy. Under these conditions, various functional groups including amine and olefin groups were tolerated (Table 2, entries 17 and 18). These substrates selectively underwent oxidation at the sulfur atom without undergoing further structural changes in their functional groups.

We also have monitored competitive oxidation of sulfanes in the presence of ester, aldehyde, alcohol, and oxime. The results are demonstrated in Scheme 2.
These observations clearly show that the method is applicable for the selective oxidation of sulfanes in the presence of the previously mentioned functional groups and can be considered as a useful practical achievement for this transformation. The proposed mechanism for the oxidation of sulfane to the corresponding sulfoxide is shown in Scheme 3.

In conclusion, we have found that the H₂O₂/Tf₂O system is an excellent and convenient oxidizing reagent for the oxidation of sulfanes to sulfoxides without any overoxidation to sulfones in almost quantitative yields. It is noteworthy that the reaction tolerates oxidatively sensitive functional groups and that the sulfur atom is selectively oxidized. Thus, the use of H₂O₂/Tf₂O system is a good addition to the existing methodologies for the oxidation of sulfanes.

Melting points were determined in a capillary tube and are not corrected. ¹H NMR spectra were recorded on a Bruker 200 spectrometer using TMS as internal standard. IR spectra were recorded on a Shimadzu IR-470 spectrophotometer using KBr pellets.

In a round-bottomed flask (50 mL) equipped with a magnetic stirrer, a solution of sulfane (2 mmol) in EtOH (10 mL) was prepared. H₂O₂ (30%, 4 mmol, 0.4 mL) and Tf₂O (1 mmol, 0.17 mL) were added and the mixture was stirred at r.t. for the time indicated in Table 2. The progress of the reaction was monitored by TLC (eluent: n-hexane–EtOAc, 7:3). When the starting sulfane had completely disappeared, the mixture was quenched by adding H₂O (10 mL). The product was extracted with EtOAc (4 × 5 mL) and the combined extracts were dried (MgSO₄). The filtrate was evaporated and the corresponding sulfoxide was obtained as the only product (Table 2).

Analytical and spectral data of representative sulfoxides are given below.

### Benzyl Phenyl Sulfoxide

Mp 121–123 °C (Lit.¹⁹ mp 122–124 °C).

IR (KBr): 3430, 1643, 1506, 1410 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 7.55 (s, 5 H), 7.35–7.30 (m, 3 H), 7.25–7.20 (m, 2 H), 4.00 (d, J = 12.5 Hz, 1 H), 3.75 (d, J = 12.5 Hz, 1 H), 3.45 (s, 3 H), 1.90 (s, 3 H).

Scheme 2 [Reagents and conditions: substrates (1 equiv each), Tf₂O (0.5 equiv), H₂O₂ (2 equiv), EtOH, r.t.]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Time (min)</th>
<th>Yield (%)a,b,c</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Bn</td>
<td>7</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>4-O₂NC₆H₄CH₂</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>4-MeC₆H₄</td>
<td>Bn</td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>4-MeC₆H₄</td>
<td>4-MeC₆H₄CH₂</td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>4-MeC₆H₄</td>
<td>4-FC₆H₄CH₂</td>
<td>8</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>4-MeC₆H₄</td>
<td>4-O₂NC₆H₄CH₂</td>
<td>35</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>4-BrC₆H₄</td>
<td>Bn</td>
<td>15</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>4-BrC₆H₄</td>
<td>4-FC₆H₄CH₂</td>
<td>27</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>4-BrC₆H₄</td>
<td>4-MeC₆H₄CH₂</td>
<td>7</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>4-BrC₆H₄CH₂</td>
<td>Bn</td>
<td>9</td>
<td>94</td>
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<tr>
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<td>4-O₂NC₆H₄CH₂</td>
<td>20</td>
<td>93</td>
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<tr>
<td>12</td>
<td>4-ClC₆H₄</td>
<td>Bn</td>
<td>15</td>
<td>97</td>
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<tr>
<td>13</td>
<td>Bn</td>
<td>Bn</td>
<td>3</td>
<td>99</td>
</tr>
<tr>
<td>14</td>
<td>2,4-(NO₂)₂C₆H₄</td>
<td>Ph</td>
<td>60</td>
<td>70</td>
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<td>15</td>
<td>Ph</td>
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<td>16</td>
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<td>95</td>
</tr>
<tr>
<td>17</td>
<td>Ph</td>
<td>Bn</td>
<td>20</td>
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<tr>
<td>18</td>
<td>CH₂=CHCH₂</td>
<td>CH₂=CHCH₂</td>
<td>15</td>
<td>90</td>
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<tr>
<td>19</td>
<td>Bu</td>
<td>Bu</td>
<td>20</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 2 Oxidation of Sulfanes to Sulfoxides

### Scheme 3 Proposed mechanism for the oxidation of sulfane to the corresponding sulfoxide with aqueous H₂O₂ in the presence of Tf₂O

[Diagram showing the proposed mechanism]

These observations clearly show that the method is applicable for the selective oxidation of sulfanes in the presence of the previously mentioned functional groups and can be considered as a useful practical achievement for this transformation. The proposed mechanism for the oxidation of sulfane to the corresponding sulfoxide is shown in Scheme 3.

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### Dibenzyl Sulfoxide

Mp 130–132 °C (Lit.²⁰ mp 132–134 °C).

IR (KBr): 1026 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.70 (m, 4 H), 7.40 (m, 4 H), 7.30 (m, 8 H), 7.00 (d, J = 8.0 Hz, 2 H), 6.90 (d, J = 8.0 Hz, 2 H), 3.70 (s, 3 H), 1.90 (s, 3 H).

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$^1$H NMR (200 MHz, CDCl$_3$): $\delta = 3.83$ (d, $J = 12.8$ Hz, 2 H), 3.91 (d, $J = 12.8$ Hz, 2 H), 7.26–7.39 (m, 10 H).

Diphenyl Sulfoxide
Mp 70–72 °C (Lit.$^{21}$ mp 68 °C).
IR (KBr): 1038 cm$^{-1}$.
$^1$H NMR (200 MHz, CDCl$_3$): $\delta = 7.41–7.50$ (m, 6 H), 7.61–7.66 (m, 4 H).
Methyl Phenyl Sulfoxide
Mp 28–30 °C (Lit.$^{19}$ mp 28–30 °C).
IR (neat): 1050 cm$^{-1}$.
$^1$H NMR (200 MHz, CDCl$_3$): $\delta = 2.73$ (s, 3 H), 7.51–7.55 (m, 3 H), 7.65–7.70 (m, 2 H).
Dibutyl Sulfoxide
Mp 30–31 °C (Lit.$^{19}$ mp 30–31 °C).
IR (neat): 1022 cm$^{-1}$.
$^1$H NMR (200 MHz, CDCl$_3$): $\delta = 0.90$ (t, $J = 7.2$ Hz, 6 H), 1.36–1.50 (m, 4 H), 1.70 (quint, $J = 7.4$ Hz, 4 H), 2.57–2.67 (m, 4 H).

Acknowledgment
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References