

Mild and Highly Chemoselective Oxidation of Thioethers Mediated by $\text{Sc}(\text{OTf})_3$

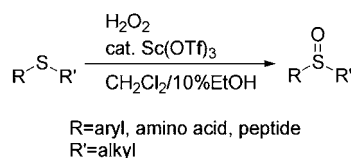
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ABSTRACT



Catalytic $\text{Sc}(\text{OTf})_3$ greatly increases the efficiency of hydrogen peroxide mediated monooxidation of alkyl–aryl sulfides and methyl cysteine containing peptides. The method is high yielding, compatible with many widely used protecting groups, suitable for solid-phase applications and proceeds with minimum over-oxidation.

Sulfoxides are important intermediates in the synthesis of many natural products.^{1,2} Their synthesis has been achieved by means of a wide range of oxidizing systems starting from the corresponding sulfides.^{3,4} Aqueous hydrogen peroxide is a particularly attractive oxidant since it is cheap, environmentally friendly, easy to handle and produces only water as a byproduct, which reduces purification requirements. Catalysts are often used to enhance the efficiency of the oxidation and metal salts (including chlorides, oxides, peroxides, acetates, and acetyl acetonates of Ti, V, Mo, W,⁵ Re,⁶ and Mn⁷) play a very important role as catalytic activators of hydrogen peroxide.³ The resulting metal-peroxo

derivatives are such powerful catalysts that over-oxidized byproducts are often observed especially with sulfides containing electron-rich double bonds.⁸

Lanthanides have never been explored in the oxidation of thioethers, yet these elements are receiving increasing attention in the literature,⁹ with applications in the fields of organic synthesis,¹⁰ coordination, and materials chemistry. Scandium triflate is a readily available reagent and behaves as an excellent Lewis acid catalyst for a wide range of organic transformations in both aqueous and organic media.¹¹ In this letter, the use of this catalyst for the highly chemoselective, hydrogen peroxide mediated, oxidation of thioethers to the corresponding sulfoxides is reported.

A range of thioethers were subjected to the developed reaction conditions to give sulfoxides with very high chemoselectivity and in excellent yields (even when using large excesses of oxidant). The method proved to be

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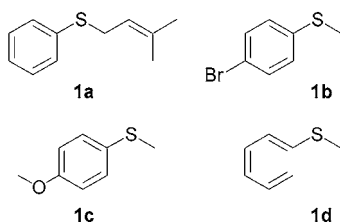


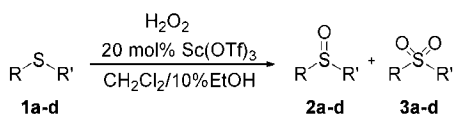
Figure 1. Sulfides tested for Sc(OTf)₃-catalyzed oxidation

extremely mild, worked in neutral conditions, and was compatible with many widely used protecting groups (allyl, trityl, Fmoc, Boc, *t*Bu esters and *t*Bu ethers). Hydrogen peroxide was used as a 60% solution in water.

The possibility of using excess oxidant and a binary solvent system rich in CH₂Cl₂ renders the method highly suitable for solid-phase applications.

Model thioethers **1a–d** (Figure 1) were first subjected to the oxidation conditions and the results are reported in Table 1.

Table 1. Oxidation of Sulfides Catalyzed by Sc(OTf)₃^a



entry	sulfide	H ₂ O ₂ ^b (equiv)	time (h)	yield (%) ^{c,12}	
				sulfoxide	sulfone
1	1a	1.2	5	95	3
2	1a	5	2	98	2
3	1b	1.2	5.5	94	2
4	1b	5	3	98	2
5	1c	1.2	2.3	98	2
6	1c	5	1.3	98	2
7	1d	1.2	6	97	2
8	1d	5	3	94	4

^a Reactions run at room temperature and *c* = 0.1 M, 0.1 mmol scale. ^b H₂O₂ was used as a 60% solution in water. ^c Determined by ¹H NMR.

Sulfoxide **2a** was obtained with exceptionally low amounts of sulfone and free of epoxy byproducts even in the presence of a large excess of oxidant (Table 1, entries 1 and 2).¹³

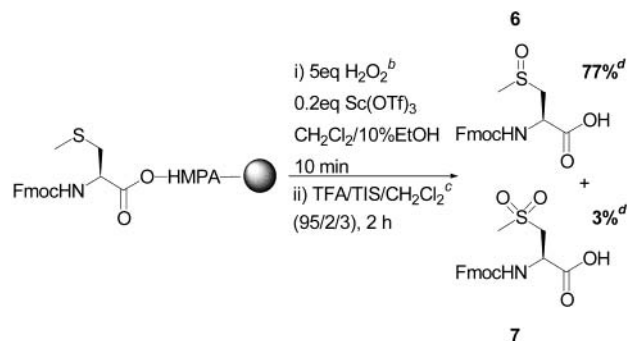
Our longstanding interest in the synthesis of dehydro-peptides^{2b,14} via oxidation/elimination of peptide-sulfoxides led to an investigation of the scope of the oxidation conditions with protected cysteine derivatives **4a–d** (Table 2, entries 1–8), synthesized in solution according to standard amino acid/peptide chemistry protocols (see Supporting Information).

(12) In the absence of catalyst, conversions to sulfoxides **2a**, **2b**, and **2d** were in the range 53–76% after 24 h in the presence of 5 equiv of 60% hydrogen peroxide. Sulfoxide **2c** was formed in a yield >98% after 20 h (see Supporting Information for details of uncatalyzed reactions).

The study of the methyl cysteine derivatives clearly indicates the high efficiency and total chemoselectivity of the method: no temperature control was required and no sulfone was observed even when large excesses of hydrogen peroxide were used. The conditions proved to be compatible with widely used protecting groups in peptide/organic synthesis (Fmoc, Boc, *t*Bu). As observed for alkyl–aryl sulfides, the allylic double bond (Table 2, entries 5 and 6) survived the oxidizing conditions. Peptide sulfoxides **5a–d** were isolated in high yields (91–96%). Of outstanding interest was the observed chemoselectivity of two differently protected cysteine residues (SMe and STrt, Table 2, entries 3 and 4).

To investigate further the scope and limitations of the method, polymer-supported Fmoc-*S*-methyl-L-cysteine was oxidized under the newly developed conditions (Scheme 1) and showed clean and efficient oxidation.

Scheme 1. Oxidation of Solid-Supported Fmoc-(L)-Cys(Me)-OH (HMPA = hydroxymethylphenoxyacetic acid)^a



^a Loading of 0.89 mmol g⁻¹. ^b H₂O₂ was used as a 60% solution in water. ^c TFA = trifluoroacetic acid; TIS = triisopropylsilane. ^d Based on RP-HPLC analysis, ELS detector.

The nature of the catalytic species is not yet clear and no reports have been found in the literature concerning the elucidation of the nature of complexes between scandium derivatives and hydrogen peroxide, although lanthanide metals, in combination with hydrogen peroxide, are known to accelerate greatly the hydrolysis of phosphates (including RNA) in aqueous systems.¹⁵

⁴⁵Sc-NMR spectroscopy has been used in the past to study the coordination chemistry of scandium¹⁶ and it was thought

(13) Recently, a new synthetic mixed metal oxide, LiNbMoO₆, was used in combination with H₂O₂ to overcome the low chemoselectivity offered by common oxidizing systems in the oxidation of sulfides containing electron-rich double bonds.⁸ Under carefully controlled conditions (stoichiometric hydrogen peroxide, 0 °C) sulfones were observed in the reaction mixture (3–14%) together with the expected sulfoxides. Compound **2a** was obtained together with 14% of sulfone **3a**.

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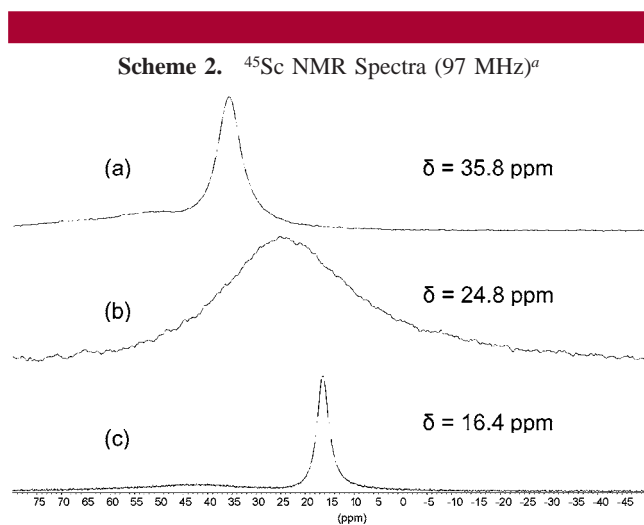
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Table 2. Oxidation of Cysteine Derivatives in the Presence of 20 mol % of Sc(OTf)₃^a

entry	amino acid/peptide	H ₂ O ₂ ^b (equiv)	time (min)	amino acid/peptide sulfoxide	yield (%) ^{c-e}
1	Fmoc-Cys(Me)-OMe (4a)	1.2	70	Fmoc-Cys((O)Me)-OMe (5a)	99
2		5	50		100
3	Boc-Phe-Cys(Me)-Cys(Trt)-OMe (4b)	1.2	15	Boc-Phe-Cys((O)Me)-Cys(Trt)-OMe (5b)	100
4		5	10		97
5	Boc-Phe-Cys(Me)-Ala-OAll (4c)	1.2	15	Boc-Phe-Cys((O)Me)-Ala-OAll (5c)	>99
6		5	5		98
7	Boc-Phe-Cys(Me)-Ser(<i>t</i> Bu)-O <i>t</i> Bu (4d)	1.2	15	Boc-Phe-Cys((O)Me)-Ser(<i>t</i> Bu)-O <i>t</i> Bu (5d)	98
8		5	10		96

^a Run at room temperature at a concentration $c = 0.1$ M, 0.1 mmol scale. ^b H₂O₂ was used as a 60% solution in water. ^c Determined by RP-HPLC, ELS detector. ^d No over-oxidation byproducts were observed. ^e See Supporting Information for results of uncatalyzed sulfoxidations.

that similar measurements could give insights into the nature of the actual catalytic species in the oxidation of thioethers. Sc(OTf)₃ gave rise to a strong signal at δ 35.8 ppm with a $w_{1/2} = 645$ Hz (Scheme 2, (a)).



^a Spectrum a: Sc(OTf)₃ (0.02 mM solution in CH₂Cl₂/10%EtOH). Spectrum b: Sc(OTf)₃ (0.02 mM solution in CH₂Cl₂/10%EtOH in the presence of 25 equiv of a 60% H₂O₂ solution in water). Spectrum c: Sc(OTf)₃ (0.02 mM solution in CH₂Cl₂/10%EtOH in the presence of 26.6 equiv of water).

Upon addition of 25 equiv of hydrogen peroxide (as in the standard protocol used for the oxidation of thioethers), the peak assigned to scandium triflate disappeared and was replaced by a new, broad ($w_{1/2} = 3015$ Hz) signal centered at δ 24.8 ppm (Scheme 2, (b)). When only water was added to the scandium triflate solution, a rather sharp signal ($w_{1/2} = 272$ Hz) was detected (Scheme 2, (c)) at higher field.

These data may suggest that a peroxo-derivative may be formed and could be the species responsible for the rate acceleration and chemoselectivities reported.

In summary, a new mild, neutral, and efficient method for the oxidation of sulfides to sulfoxides in high yields and chemoselectivities has been developed. Purification is often not needed, especially when using a small excess of oxidant. The method is suitable for solid-phase applications and is compatible with many widely used protecting groups in organic synthesis.

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Supporting Information Available: Description of experimental procedures and characterization of all compounds prepared in the study. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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