Chemoselective Oxidation of Sulfides to Sulfoxides with Urea-Hydrogen Peroxide Complex Catalysed by Diselenide

Philip C. Bulman Page,a\* Benjamin R. Buckley,b\* Claire Elliott,b Yohan Chan,a Nicolas Dreyfus,c Frank Markend.

a School of Chemistry, University of East Anglia, Norwich Research Park, Norwich, Norfolk NR4 7TJ, UK.

b Chemistry Department, Loughborough University, Ashby Road, Loughborough, Leicestershire, LE11 3TU, UK.

c Lilly Research Centre, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, KT13 8JT, UK.

d Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK.

Fax: 00 44 1603 592008

E-mail: p.page@uea.ac.uk

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Dedication - To Prof Steven Victor Ley for the occasion of his 70th birthday

**Abstract:** A highly selective catalytic oxidation system has been developed for the conversion of sulfides to the corresponding sulfoxides using urea–hydrogen peroxide as stoichiometric oxidant in the presence of a catalytic quantity of diphenyl diselenide.

**Key words:** Sulfoxidation, urea–hydrogen peroxide, Diphenyl diselenide, Oxidation, Catalysis.

**Introduction**

Selective sulfur oxidation to sulfoxides, without over-oxidation to sulfones, remains an important process, and can be problematic in the production of pharmaceutical intermediates. Most known processes are non-catalytic, and suffer from the generation of considerable waste streams derived from the oxidant. Much of this waste is unrecoverable inorganic material resulting from the use of standard oxidation reagents, which typically contain stoicheiometric quantities of metals. Use of such stoicheiometric oxidizing reagents, with the concomitant production of inorganic waste, inevitably brings inherent environmental disadvantages and safety hazards.

We were interested in seeking greener variants of traditional sulfur oxidation reactions, in which the requirement for addition of a traditional inorganic stoicheiometric oxidant would be eliminated. We reasoned that this aim would be achieved in a catalytic system driven by hydrogen peroxide or an equivalent as the reoxidant in the presence of a suitable catalyst.

The complex urea-hydrogen peroxide (UHP), a solid soluble in organic solvents, provides a valuable alternative to the use of anhydrous hydrogen peroxide solutions.1 UHP was first prepared in the early 1900’s 2 and its structure elucidated much later.3 UHP has been used for the oxidation of a number of functional groups.4 Its reactivity is, however, limited, and when used on its own the reaction mixtures are commonly heated.5 UHP is also used for the *in situ* preparation of peracids from the corresponding anhydrides,6 in particular trifluoroperacetic acid.7 The majority of oxidations using UHP are catalysed either by a variety of metal complexes, such as copper(II) salens,8 polyoxotungstates,9 methyltrioxorhenium,10 or by using organocatalysts, such as ketones,11 or biocatalysis.12 Metal-catalysed enantioselective versions have also been developed for epoxidation 13 and sulfur oxidation.14

Diselenides have long been known to act as catalysts for the oxidation of various species by, for example: hydrogen peroxide for dihydroxylation,15 the Baeyer-Villiger reaction,16 and other oxidations;17 t-butyl hydroperoxide for the oxidation of allylic alcohols;18 and iodoxybenzene for the oxidation of steroidal alcohols and ketones to the corresponding enones;19 and have been used in conjunction with UHP as the reoxidant for catalysed oxidative processes,20 but do not appear to have been used previously in conjunction with UHP directly to promote oxidation.

**Results and Discussion**

The oxidation of sulfides using UHP can be driven thermally,5b or using a catalyst,21 with most examples involving a metal-based system.22 However, most of these methodologies report the formation of the corresponding sulfone. We have found that sulfides may be selectively oxidized to sulfoxides in excellent yields using a catalytic quantity (≤1.0 mol%) of diphenyl diselenide (reacting presumably through the perseleninic acid or anhydride)23 and urea–hydrogen peroxide complex (UHP) as the stoicheiometric oxidant (Scheme 1, Table 1).



Scheme 1

**Table 1.** Oxidation of sulfides to the corresponding sulfoxides using UHP and catalytic Ph2Se2.a

|  |  |  |  |
| --- | --- | --- | --- |
| Entry | Substrate | Conv/%b | Yield/%c |
| 1 |  | >99 | 97d |
| 2 |  | >99 | 99e |
| 3 |  | <5f | <5 |
| 4 |  | 95 | 73 |
| 5 |  | 97 | 80 |
| 6 |  | >99 | 96 |
| 7 |  | 96 | 90 |
| 8 |  | >99 | 66g |
| 9 |  | 73 | 68 |
| 10 |  | 96 | 68 |
| 11 |  | >99 | 89 |
| 12 |  | >99 | 74 |
| 13 |  | >99 | 92 |
| 14 |  | 92 | 69 |
| 15 |  | 99 | 74 |

aStandard conditions: Sulfide, Ph2Se2 (1.0 mol%), UHP (1.0 eq), CH2Cl2, 24 h.

b Conversions were evaluated by comparison of the methylene signals in the 1H NMR spectra α to sulfur in both the sulfide and sulfoxide.

c Isolated yield.

d Reaction complete in 7 h.

e Reaction run using Ph2Se2 (0.1 mol%).

f Reaction run in the absence of Ph2Se2.

g Reaction complete in 20 minutes.

The reactions were carried out simply by stirring in dichloromethane solution at room temperature for up to 24 hours.24 In the absence of diphenyl diselenide, conversion to sulfoxide was slow (entry 3). Our standard conditions used 1% diphenyl diselenide, but we were able to reduce the loading of the diselenide to 0.1 mol% and still achieve excellent yields of the sulfoxides at room temperature, with reactions complete within 24 h (Entry 2). The reaction tolerates a wide range of functional groups, for example the electron-rich alkene in entry 13, where no epoxide was observed, and the ketone in entry 9, where Baeyer-Villiger reaction was not observed**.** The presence of electron-rich aryl substituents (entry 8, reaction complete in 20 min) accelerates sulfoxidation, while electron-poor systems deactivate the process (entries 5,6, although the reactions are complete after 24 h). The reaction is extremely simple to carry out, and over-oxidation to the corresponding sulfone is not observed.

**Conclusion**

We have developed a highly selective catalytic oxidation system free of heavy metals for the conversion of sulfides into the corresponding sulfoxides using urea–hydrogen peroxide (UHP) in the presence of catalytic diphenyl diselenide without formation of the corresponding sulfones. This simple system requires no special preparation and can be carried out simply by stirring in solution at room temperature.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(24) General Procedure for the oxidation of sulfides using urea–hydrogen peroxide and diphenyl diselenide: Urea–hydrogen peroxide (2 mmol) was dissolved in dichloromethane (2 mL), and the solution stirred at room temperature. A solution of diphenyl diselenide (1 mol%) and sulfide (2 mmol) in dichloromethane (2 mL) was added to the urea–hydrogen peroxide solution. The mixture was stirred at room temperature for 24 hours or until complete conversion to sulfoxide was observed by TLC. Extraction was carried out with dichloromethane (3 x 5 mL), after the addition of water (5 mL), and the combined organic solutions were washed with brine (50 mL), dried (MgSO4), filtered, and the solvents removed under reduced pressure. Sulfoxide products were purified where necessary by column chromatography. Sulfoxide from thiochroman-4-one: Yellow oil; νmax (cm-1) 1694, 1585, 1325, 1282, 1237, 1182, 1120, 1080, 1039, 854; 1H NMR (400 MHz, CDCl3): δH 2.86-2.97 (1 H, m), 3.43-3.56 (3 H, m), 7.65-7.68 (1 H, m), 7.75-7.79 (1 H, m), 7.87 (1 H, dd, *J* 8.1, 7.6 Hz), 8.14 (1 H, dd, *J* 8.0, 7.6 Hz) ppm; 13C NMR (100 MHz, CDCl3): δC 30.3, 46.6, 128.5, 128.9, 132.1, 134.6, 145.5, 192.1. Sulfoxide from 4-fluorothioanisole: Yellow oil; νmax (cm-1) 3096, 3062, 2996, 1655, 1641, 1046 (S=O), 958, 834 (C-F); 1H NMR (400 MHz, CDCl3): δH 2.73 (3 H, s), 7.21-7.26 (2 H, m), 7.66-7.69 (2 H, m) ppm; 13C NMR (100 MHz, CDCl3): δC 44.0, 117.0, 125.5, 130.1, 141.2. Sulfoxide from 2-chloroethyl ethyl sulfide: Yellow oil; νmax (cm-1) 1653, 1455, 1301, 1127, 1020, 864; 1H NMR (400 MHz, CDCl3): δH 1.37 (3 H, t, *J* 7.6 Hz), 2.76-2.86 (2 H, m), 3.04-3.08 (2 H, m), 3.89-4.00 (2 H, m) ppm; 13C NMR (100 MHz, CDCl3): δC 6.7, 37.0, 46.0, 54.0. Sulfoxide from furfuryl methyl sulfide: Yellow oil; νmax (cm-1) 2972, 2916, 1423, 1033, 933, 744; 1H NMR (400 MHz, CDCl3): δH 2.52 (3 H, s), 4.06 (2 H, q, *J* 13.92 Hz), 6.40 (2 H, m), 7.39 (1 H, dd, *J* 2.0 Hz) ppm; 13C NMR (100 MHz, CDCl3): δC 37.9, 52.2, 111.2, 143.5, 143.9.

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Philip C. Bulman Page

School of Chemistry

University of East Anglia

Norwich Research Park

Norwich

Norfolk NR4 7TJ, UK

Fax: 00 44 1603 592008

Tel: 00 44 1603 591061

E-mail: p.page@uea.ac.uk

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