Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: *Asymmetry* 16 (2005) 2681–2683
Tetrahedron: Asymmetry

Bienzymatic synthesis of chiral heteroaryl-methyl-sulfoxides

Fabio Pezzotti, Krzysztof Okrasa and Michel Therisod*

LCBB, ICMMO, bat. 420, Université Paris-Sud, F-91405 Orsay, France

Received 27 June 2005; accepted 8 July 2005
Available online 15 August 2005

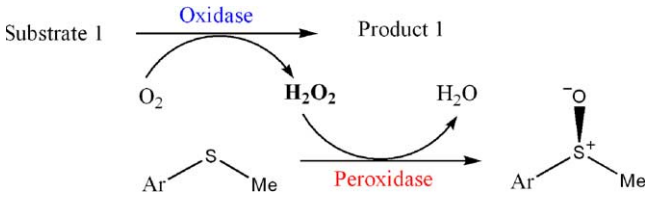
Abstract—Several chiral heteroaryl-methyl-sulfoxides were prepared from the corresponding sulfides by an oxidation process catalysed by an oxidase/peroxidase bienzymatic system.

1. Introduction

Chiral sulfoxides have been extensively used as auxiliaries in asymmetric synthesis.[1–4] Their preparation is well documented, by either chemical,[5–8] microbiological[9–11] or enzymatic methods.[12–17] Heteroaryl-alkyl-sulfoxides can offer an advantage over dialkyl-sulfoxides or alkyl-aryl-sulfoxides by having an additional chelating centre of potential interest in asymmetric catalysis.

We previously reported the enantioselective preparation of various aryl-methyl-sulfoxides by bienzymatic methods making use of an oxidase producing hydrogen peroxide, immediately consumed by a peroxidase from *Coprinus cinereus* to oxidise a sulfide (Scheme 1).[18,19]

The two main advantages of the process, when compared to the direct addition of hydrogen peroxide into the reaction medium are



Scheme 1. Bienzymatic catalysed synthesis of (*S*)-aryl-methyl-sulfoxides.

- An increased operational stability of the peroxidase, known to be inactivated by hydrogen peroxide acting as a 'suicide substrate'.[20]
- An increased enantiomeric excess obtained on the products, since non-enzymatic spontaneous oxidation of the sulfide is avoided.

2. Results and discussion

We herein report the preparation of several chiral heteroaryl-methyl-sulfoxides by a similar method, in which hydrogen peroxide is produced by glucose oxidase acting on glucose, and immediately used by the peroxidase for an asymmetric oxidation of the sulfide.[28] Some sulfides derived from electron-deficient heterocycles were completely unreactive (Scheme 2).

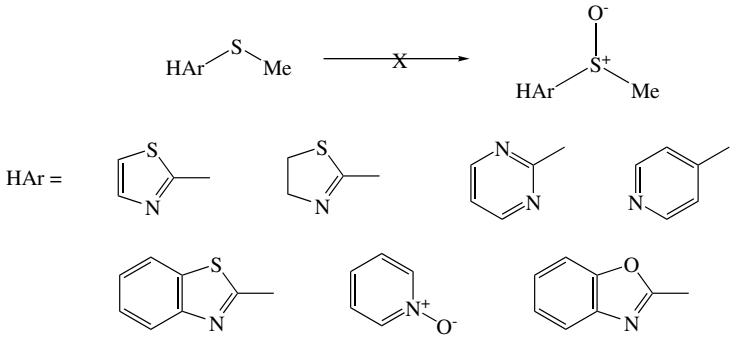
Conversely, sulfides bearing electron-rich heterocycles (Scheme 3) were readily oxidised, giving the sulfoxides as sole products, with good enantiomeric excess (Table 1).

2-Methylthiopyridine and 3-methylthiopyridine (in contrast to 4-methylthiopyridine, which was not oxidised) had an intermediate behaviour: the corresponding sulfoxides were obtained more slowly, and with lower ees (entries 3 and 4).

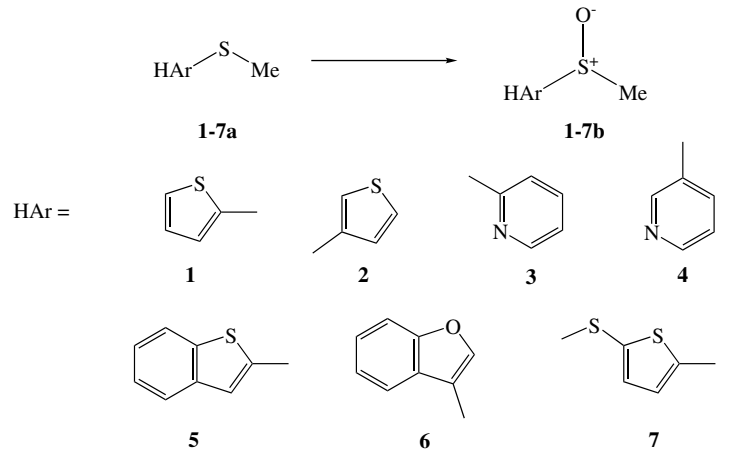
No sulfone or side-products were detected. Interestingly, the bis-sulfide **7a** (entry 7) was only mono-oxidised, while the chemical oxidation by one molar equivalent of sodium periodate always gave a mixture of mono- and di-oxidised products (Scheme 4).

* Corresponding author. Tel.: +33 (0)1 69 15 63 11; fax: +33 (0)1 69 15 72 81; e-mail: therisod@icmo.u-psud.fr

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.07.004



Scheme 2. Heteroaryl-methyl-sulfides insensitive to oxidation by the oxidase/peroxidase system.



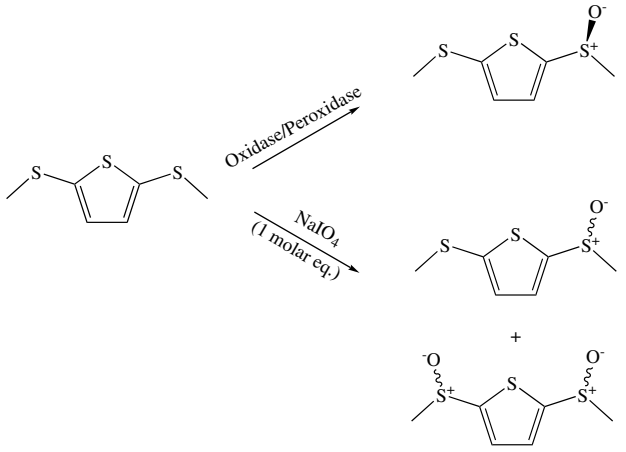
Scheme 3. Heteroaryl-methyl-sulfides oxidised by the bienzymatic oxidase/peroxidase system.

Table 1. Oxidation of sulfides **1**–**7a** into the corresponding sulfoxides **1**–**7b** catalysed by the bienzymatic oxidase/peroxidase system

Entry	Sulfide	% Conversion (20 h reaction)	ee (configuration)[a]	Ref.
1	**1a**	100	93 (−)-(*S*)	24
2	**2a**	100	85 (−)-(*S*)	22
3	**3a**	60	50 (−)-(*S*)	24
4	**4a**	40	41 (−)-(*S*)	27
5	**5a**	90	>99 (−)-(*S*)	—
6	**6a**	100	>99 (−)-(*S*)	—
7	**7a**	70	75 (−)-(*S*)	—

[a] Deduced from the sign of the specific rotation.

Some of these chiral sulfoxides (*R*)- or (*S*)-**1b**,[21–24] **2b**,[22] **3b**[22,24–26] and **4b**[27] have been previously described. These were individually prepared by the oxidation of the corresponding sulfide chemically,[26,27] with whole cells of microorganisms (fungi or bacteria)[21,22,24] or enzymatically (with chloroperoxidase[23,25] or cyclohexanone monooxygenase[25]). Compounds **5b**–**7b** have not been previously prepared, even as racemates.[28,29] Assuming the same enantioselectivity of the peroxidase for all the heteroaryl-methyl-sulfides, we propose an (*S*)-configuration for these new chiral sulfoxides.



Scheme 4. Chemical and bienzymatic sulfoxidation of 2,5-bis-methylsulfanyl-thiophene.

3. Conclusion

Enantioselective oxidation of heteroaryl-methyl-sulfides was realised using cheap industrial enzymes, available in large quantities from Novozymes, which make these syntheses easily possible on a large (several grams) scale.

Acknowledgements

We are grateful to Dr. Schneider, Dr. Danhus and Dr. Danielsen (Novozymes) for kindly supplying glucose oxidase and *C. cinereus* peroxidase. This work was supported by studentships to F.P. from the Mexican Government CONACyT and to K.O. from the French Government (BGF).

References

1. Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760.
2. Solladie, G. *Heteroat. Chem.* **2002**, *13*, 443–452.
3. Krohn, K. *Org. Synth. Highlights* **1991**, 14–18.
4. Ruano, J. L. G.; Carretero, J. C.; Carreno, M. C.; Cabrejas, L. M. M.; Urbano, A. *Pure Appl. Chem.* **1996**, *68*, 925–930.
5. Capozzi, M. A. M.; Cardellicchio, C.; Naso, F. *Eur. J. Org. Chem.* **2004**, 1855–1863.
6. Kagan, H. B. In *Catalytic Asymmetric Synthesis*; Ojima, O., Ed.; Wiley-VCH: New York, 2000; pp 327–356.
7. Colonna, S.; Gaggero, N.; Carrea, G.; Pasta, P. In *Asymmetric Oxidation Reactions*; Katsuki, T., Ed.; Oxford University Press: Oxford, 2001; pp 227–235.
8. Lattanzi, A.; Scettri, A. *Curr. Org. Synth.* **2004**, *8*, 607–621.
9. Ricci, L. C.; Comasseto, J. V.; Andrade, L. H.; Capelari, M.; Cass, Q. B.; Porto, A. L. M. *Enzyme Microb. Technol.* **2005**, *36*, 937–946.
10. Holland, H. L.; Brown, F. M.; Kerridge, A.; Pienkos, P.; Arensdor, J. *J. Mol. Catal. B: Enzyme* **2003**, *22*, 219–223.
11. Ohta, H.; Okamoto, Y.; Tsuchihashi, G. *Chem. Lett.* **1984**, 205–208.
12. Trevisan, V.; Signoretto, M.; Colonna, S.; Pironti, V.; Strukul, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4097–4099.
13. Klibanov, A. M. *Curr. Opin. Biotech.* **2003**, *14*, 427–431.
14. Boyd, D. R.; Sharma, N. D.; Ljubez, V.; Byrne, B. E.; Sheperd, S. D.; Alle, C. C. R.; Kulakov, L. A.; Larkin, M. J.; Dalton, H. *Chem. Commun.* **2002**, 1914–1915.
15. Adam, W.; Mock-Knoblauch, C.; Saha-Moeller, C. R. *J. Org. Chem.* **1999**, *64*, 4834–4839.
16. Bakker, M.; van Rantwijk, F.; Sheldon, R. A. *Can. J. Chem.* **2002**, *80*, 622–625.
17. Waxman, D. J.; Light, D. R.; Walsh, C. *Biochemistry* **1982**, *21*, 2499–2507.
18. Okrasa, K.; Guibé-Jampel, E.; Therisod, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1077–1079.
19. Okrasa, K.; Falcimaigne, A.; Guibé-Jampel, E.; Therisod, M. *Tetrahedron: Asymmetry* **2002**, *13*, 519–522.
20. Valderrama, B.; Ayala, M.; Vazquez-Duhalt, R. *Chem. Biol.* **2002**, *9*, 555–565.
21. Boyd, D. R.; Sharma, N. D.; Gunaratne, N.; Haughey, S. A.; Kennedy, M. A.; Malone, J. F.; Allen, C. C. R.; Dalton, H. *Org. Biomol. Chem.* **2003**, 984–994.
22. Holland, H. L.; Turner, C. D.; Andreana, P. R.; Nguyen, D. *Can. J. Chem.* **1999**, *77*, 463–471.
23. van Deurzens, M. P. J.; Remkes, I. J.; van Rantwijk, F.; Sheldon, R. A. *J. Mol. Cat. A: Chem.* **1997**, *117*, 329–337, the absolute configuration however was not determined.
24. Boyd, D. R.; Sharma, N. D.; Haughey, S. A.; Kennedy, M. A.; McMurray, B. T.; Sheldrake, G. N.; Allen, C. C. R.; Dalton, H.; Sproule, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1929–1933.
25. Colonna, S.; del Sordo, S.; Gaggero, N.; Carrea, G.; Pasta, P. *Heteroat. Chem.* **2002**, *13*, 467–473.
26. Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.
27. Boussad, N.; Trfouel, T.; Dupas, G.; Bourguignon, J.; Queguiner, G. *Phosphorous Sulfur Silicon* **1992**, *66*, 127–137.
28. Typical procedure: all sulfides were prepared according to methods already described involving the deprotonation of the heterocycle by BuLi at −78 °C followed by reaction with methyl disulfide. The sulfide (1 mmol) was suspended in water (20 mL) followed by addition of D-glucose (1 mmol), glucose oxidase (10 U) and peroxidase (2 μmol). pH was adjusted to 7.5 by means of a pH-stat in order to neutralise the gluconic acid formed. After 20 h of reaction, the mixture was extracted with ethyl acetate and the organic phase evaporated. Degree of conversion was determined by NMR and GC. Enantiomeric excess was determined by HPLC on a Chiralcel OD-H column and by ^{1}H NMR with the addition of (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine as the chiral shifting agent.
29. Selected analytical data of compound **5b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.99 (s, 3H), 7.43 (m, 2H), 7.73 (s, 1H), 7.85 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 44.1, 122.7, 124.8, 125.1, 125.7, 126.2, 138.0, 140.8, 148.0. $[\alpha]_D = -18.7$ (*c* 8.4, EtOH). Compound **6b**: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.06 (s, 3H), 7.30 (s, 1H) 7.33 (t, $J = 7.5$, 1H), 7.45 (t, $J = 7.2$, 1H), 7.60 (d, $J = 8.2$, 1H), 7.69 (d, $J = 7.7$, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 38.9, 110.4, 111.6, 122.1, 123.6, 126.2, 126.6, 155.2, 155.9. $[\alpha]_D = -30.7$ (*c* 13.1, EtOH). Compound **7b**: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.54 (s, 3H), 2.89 (s, 3H), 6.97 (d, $J = 3.78$, 1H), 7.31 (d, $J = 3.86$, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 21.0, 44.2, 128.6, 130.1. $[\alpha]_D = -1.7$ (*c* 4.1, EtOH).