Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5335–5338

TETRAHEDRON LETTERS

Efficient nitrogen transfer from aldehyde-derived *N*-acyloxaziridines

Alan Armstrong,[a,*] Ian D. Edmonds[a] and Martin E. Swarbrick[b]

[a]*Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK*
[b]*Neurology & GI CEDD, GlaxoSmithKline, Medicines Research Centre, Stevenage, Herts SG1 2NY, UK*

Received 7 April 2003; revised 28 April 2003; accepted 9 May 2003

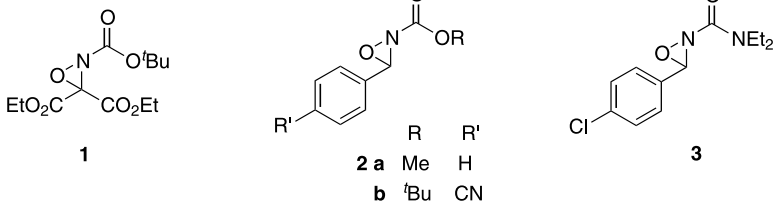
Abstract—The effect of solvent polarity on the reaction of 3-aryl-*N*-carboxamido- and 3-aryl-*N*-alkoxycarbonyl oxaziridines has been studied and an efficient procedure for high yielding sulfimidation developed by use of polar solvents. The first examples of asymmetric sulfimidation using novel chiral oxaziridines have been carried out with low diastereoselectivity (up to 30% de).

1. Introduction

The development of efficient reagents for transfer of electrophilic nitrogen to organic substrates is an important contemporary goal.[1] We have recently reported[2] that the ketomalonate-derived *N*-alkoxycarbonyloxaziridine **1** effects efficient amination of sulfides and applied this reagent to the preparation and subsequent [2,3]-sigmatropic rearrangement of allylic sulfimides. An asymmetric version of this process would provide a non-metal mediated alternative to the recent Mn-catalysed process reported by Katsuki[3] and allow access to valuable chiral amine derivatives. The configuration at the oxaziridine ring nitrogen would be expected to exert a major influence on asymmetric sulfimidation using chiral analogues of **1**. However, inversion at nitrogen is rapid, and there is likely to be little difference in energy between the two invertomers in ketone-derived oxaziridines, presenting a challenge for control of asymmetry in the amination reaction. Aldehyde-derived oxaziridines display a strong preference for the *N*-substituent to be *trans*- to the substituent on the ring carbon,[4–7] and so stereocontrol is likely to be more easily achieved. However, the *N*-alkoxycarbonyloxaziridines (e.g. **2a**) developed by Vidal and Collet and co-workers[4] afford a mixture of oxidation and amination products in reaction with heteroatom nucleophiles such as sulfides. In view of the potential stereochemical advantages of these compounds, we decided to investigate the variation of reaction conditions to promote amination over oxidation. Here we describe successful accomplishment of this goal, as well as the first examples of asymmetric sulfimidation using chiral oxaziridines.

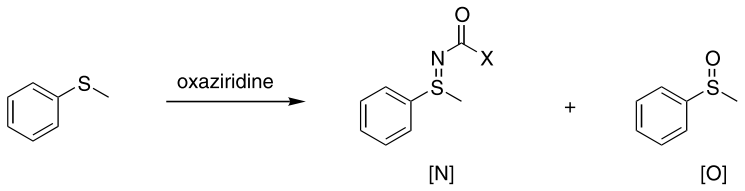
2. Results and discussion

Initial studies focused on the reaction of thioanisole with *N*-carboxamidooxaziridine **3** (Scheme 1), previously developed in the group for electrophilic amination of carbanions.[5] Collet and co-workers had reported[4] that oxaziridine **2a** afforded a mixture of sulfoxide and sulfimide, with the degree of amination increasing in more polar solvent and at lower temperature (entries 2–4 of Table 1). However, the range of



Keywords: oxaziridines; amination; sulfimides.
* Corresponding author. Fax: +44 (0)20 75945804; e-mail: a.armstrong@imperial.ac.uk

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01200-0



Scheme 1.

Table 1. Reaction of oxaziridines **1**, **2a**, **2b** and **3** with thioanisole

Entry	Oxaziridine	Solvent	Temp. (°C)	[N]:[O][a]
1	**1**	$CDCl_3$	19	90:10[b]
2	**2a**	$CDCl_3$	19	34:66[c]
3	**2a**	CH_3CN	19	48:52[c]
4	**2a**	CH_3CN	−35	67:33[c]
5	**3**	Toluene	19	<1:10[d]
6	**3**	Toluene	−40	1:3
7	**3**	Et_2O	19	1:5
8	**3**	THF	19	1:4
9	**3**	THF	−40	2:3
10	**3**	$CDCl_3$	19	1:2
11	**3**	Neat	19	1:2
12	**3**	CH_3CN	19	1:1.2
13	**3**	MeOH	19	3:1
14	**3**	MeOH	−30	7:1
15	**3**	60% MeOH (aq)	19	4:1
16	**3**	CF_3CH_2OH	19	10:1
17	**3**	CF_3CH_2OH	−40	>10:1
18	**2b**	$CDCl_3$	19	27:73[b]
19	**2b**	CH_3CN	−35	62:38[b]
20	**2b**	CF_3CH_2OH	19	5:1
21	**2b**	CF_3CH_2OH	−40	10:1

[a] Measured by integration of the SCH_3 peaks in the ^1H NMR spectrum of the crude reaction mixture.
[b] From Ref. 2.
[c] From Ref. 4.
[d] Sulfoxide isolated in 89% yield.

solvents used was limited, the most polar being acetonitrile which gave a 67:33 ratio of amination to oxidation at −35°C. Similar trends were observed with our *N*-carboxamidooxaziridine **3** (entries 5–17), but by investigating a wider range of solvent polarity, a remarkable reversal of chemoselectivity could be obtained. Almost exclusive oxidation was observed in toluene (entry 5), but using the highly polar 2,2,2-trifluoroethanol afforded almost exclusive amination (entries 16–17). Indeed, a good correlation between solvent polarity (quantified using $E_T(30)$ values[8]) and percentage amination was observed, with $R^2 = 0.99$.

In common with the results of Collet and co-workers, performing the reaction at low temperature increased the degree of amination (entries 5–6, 8–9, 13–14 and 16–17). Although Collet has only reported the use of *N*-methoxycarbonyloxaziridine **2a** for the amination of sulfides, we have previously shown[2] that the commercially available *N*-*tert*-butoxycarbonyl analogue **2b**, which affords sulfimides bearing the synthetically more useful Boc nitrogen protecting group, is an even less effective aminating agent in medium polarity solvents (compare entries 18–19 to 2–4). Again the use of 2,2,2-trifluoroethanol at low temperature results in efficient amination of thioanisole (entry 21).

These results suggest that the transition state for amination is more polar (and hence more stabilised by polar solvents) than that for oxidation.[9] Assuming the reaction proceeds by nucleophilic attack with N–O bond cleavage, these observations can be rationalised by comparing the developing alkoxy anion in the amination transition state with the much more stabilised developing charge on the carboxamido group in the oxidation transition state (Fig. 1).

These improved conditions for amination were exploited in the synthesis of a range of sulfimides (Scheme 2, Table 2) and, in contrast to many amination reagents, the sulfide was completely and cleanly converted to sulfimide (and sulfoxide) using only 1.05 equivalents of oxaziridine. *N*-Carboxamidooxaziridine **3** gave good to excellent yields of sulfimide in all cases, although introduction of bulky substituents on the sulfide decreased the ratio of amination to oxidation (entry 3). This steric effect was more pronounced with *N*-butoxycarbonyloxaziridine **2b**, resulting in lower yields of sulfimide.

Chiral sulfimides have considerable potential in stereoselective synthesis[10] and as such we were interested in developing an asymmetric variant of the above methodology. Preliminary work has focused on the use of a chiral amine auxiliary attached as an *N*-carboxamido substituent, namely oxaziridines **4a** and **4b**. Preparation of these novel oxaziridines is shown in Scheme 3. Conversion of commercially available (*R*,*R*)-bis-α-methylbenzylamine to its urea derivative was followed by titanium isopropoxide-mediated condensation with *p*-chlorobenzaldehyde.[11] Oxidation was achieved using biphasic basic *m*CPBA to afford a 1:3 mixture of separable diastereomers **4a** and **4b**.

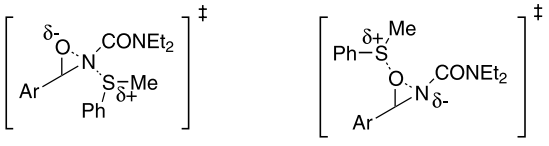
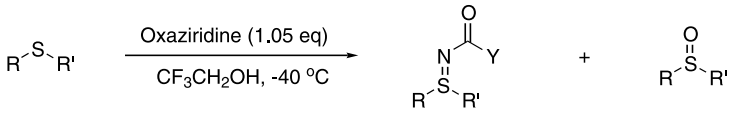


Figure 1. Possible transition states for amination and oxidation.

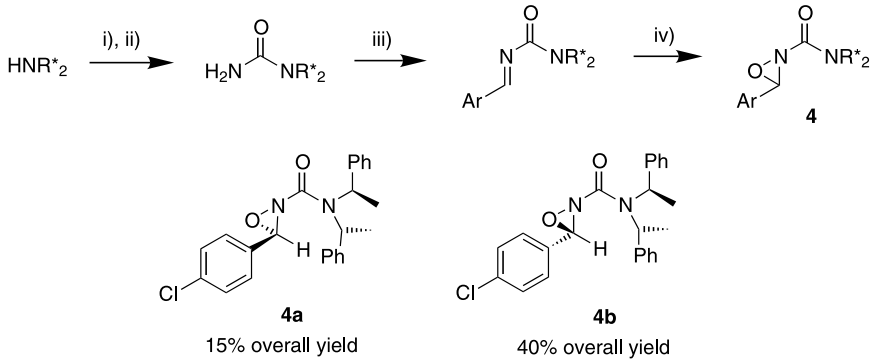


Scheme 2.

Table 2. Scope of the amination of sulfides

Entry	Oxaziridine	R	R′	[N]:[O][a]	Yield [N] (%)	Yield [O] (%)
1	**3**	Ph	Me	>10:1	99	–
2	**3**	Ph	Bn	>10:1	94	6
3	**3**	^{t}Bu	Me	3:1	72	–[b]
4	**2b**	Ph	Me	10:1	87	5
5	**2b**	Ph	Bn	3:1	75	22
6	**2b**	^{t}Bu	Me	1:1	49	–[b]

[a] Measured by integration of the SCH_2R peaks in the crude ^1H NMR spectrum.
[b] Volatile product not isolated.



Scheme 3. *Reagents and conditions*: (i) triphosgene (0.5 equiv.), Et_3N, DMAP, 93%; (ii) NH_3(g), Et_2O, 93%; (iii) *p*-chlorobenzaldehyde (1 equiv.), $Ti(O^iPr)_4$ (1.2 equiv.), THF; (iv) *m*CPBA (3 equiv.), K_2CO_3(aq), CH_2Cl_2, 63% for two steps.

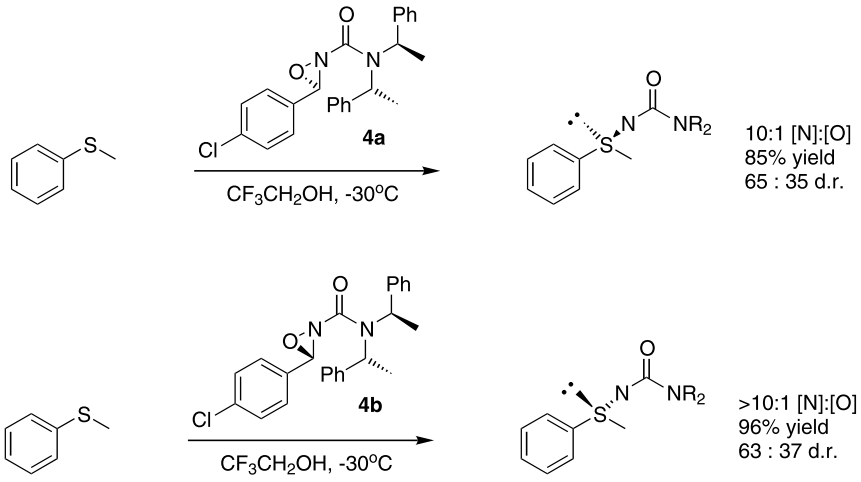
Since the ring carbon and nitrogen in these oxaziridines are both stereocentres, four diastereomers could potentially be formed. Two pairs of these could undergo interconversion by inversion at nitrogen, effectively resulting in *cis*- and *trans*-isomers. However, X-ray crystallography[12] of the separated diastereomers reveals that they are *trans*-isomers with opposite configurations at the ring carbons. The presence of only one set of peaks in the NMR spectra indicates that the *cis*-isomers are also not present in solution. Compounds **4a** and **4b** appear to represent the first reported examples of diastereomerically pure chiral non-racemic *N*-carboxamidooxaziridines.[13]

With the synthesis of the desired non-racemic oxaziridines accomplished, attention was then turned to their use in the amination of thioanisole (Scheme 4). These reactions proceeded with good chemoselectivity but only moderate diastereoselectivity (30% and 26% d.e. for **4a** and **4b**, respectively). Stereochemistry was determined by oxidation of the separate sulfimide diastereomers to the corresponding sulfoximines (precedented to proceed with retention of stereochemistry[10]) and comparison with authentic samples prepared by acylation of commercially available (*R*)- and (*S*)-*S*-methyl, *S*-phenyl sulfoximine. It is interesting to note that the two oxaziridine diastereomers gave opposite stereoselectivity. As might be expected this suggests that the ring carbon stereocentre, which also determines the stereocentre at the ring nitrogen, has much greater influence on selectivity than the auxiliary chirality.

In summary, we have reported an improved and efficient procedure for the amination of sulfides using aldehyde-derived *N*-alkoxycarbonyl and *N*-carboxamido oxaziridines. Use of polar solvents at low temperature promotes amination, whereas non-polar solvents at room temperature promote oxidation. The results with chiral non-racemic oxaziridines demonstrate the dominance of the ring carbon stereocentre in determining the stereoselectivity of the reaction. This is important information for ongoing studies aimed at improving the efficiency of asymmetric sulfimidation.

Acknowledgements

We are grateful to the EPSRC (GR/R54668) and GSK (CASE award to IDE) for their support of this work.



Scheme 4.

References

1. Reviews: (a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947–1980; (b) Greck, C.; Genet, J. P. *Synlett* **1997**, 741–748; (c) Mulzer, J.; Altenbach, H.-J. In *Organic Synthesis Highlights*; VCH: Weinheim, 1991; pp. 45–53; (d) Dembach, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281; (e) *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000.
2. Armstrong, A.; Cooke, R. *Chem. Commun.* **2002**, 904–905.
3. Murakami, M.; Uchida, T.; Saito, B.; Katsuki, T. *Chirality* **2003**, *15*, 116–123.
4. Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691–1709.
5. Armstrong, A.; Atkin, M. A.; Swallow, S. *Tetrahedron Lett.* **2000**, *41*, 2247–2251.
6. Armstrong, A.; Atkin, M. A.; Swallow, S. *Tetrahedron: Asymmetry* **2001**, *12*, 535–538.
7. Davis, F. A.; Lamendola, J., Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000–2005.
8. Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 98–110.
9. Crossover experiments indicate that this reaction is irreversible, i.e. under kinetic control.
10. Taylor, P. C. *Sulfur Rep.* **1999**, *21*, 241–280 and references cited therein.
11. Armstrong, J. D., III; Wolfe, C. N.; Keller, J. L.; Lynch, J.; Bhupathy, M.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 1531–1532.
12. We are grateful to Dr. A. J. P. White, Dept. of Chemistry, Imperial College London, for these structure determinations. Crystallographic data for compounds **4a** and **4b** (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 207422 (**4a**) and CCDC 207423 (**4b**).
13. For recent examples of chiral non-racemic *N*-alkoxycarbonyl oxaziridines see: Ref. 6: (a) Page, P. C. B.; Murrell, V. L.; Limousin, C.; Laffan, D. D. P.; Bethell, D.; Slawin, A. M. Z.; Smith, T. A. D. *J. Org. Chem.* **2000**, *65*, 4204–4207. For a 3,3-disubstituted chiral *N*-carboxamido oxaziridine prepared as a mixture of diastereomers, see: (b) Kostyanovsky, R. G.; Zakharov, K. S.; Zaripova, M.; Rudtchenko, V. F. *Tetrahedron Lett.* **1974**, 4207–4210.