Oxidation of a 4-substituted chiral oxazoline using MCPBA and NO_2

R. Alan Aitken* and David P. Armstrong

School of Chemistry, University of St Andrews, North Haugh,
St Andrews, Fife, KY16 9ST, UK
E-mail: raa@st-and.ac.uk

Dedicated to Gurnos Jones on the occasion of his 70th birthday

(received 10 Feb 00; accepted 20 Aug 00; published on the web 28 Aug 00)

DOI: http://dx.doi.org/10.3998/ark.5550190.0001.301

Abstract

Oxidation of the chiral oxazoline 1 using 1.6 equivalents of MCPBA gives mainly the corresponding ring-opened nitroso compound 4 isolated as its dimer 5 together with an *E/Z* mixture of the isomeric oximes 2 and 3. Upon treatment of 1 with an excess of NO_2 the product is the alkyl nitrate 23.

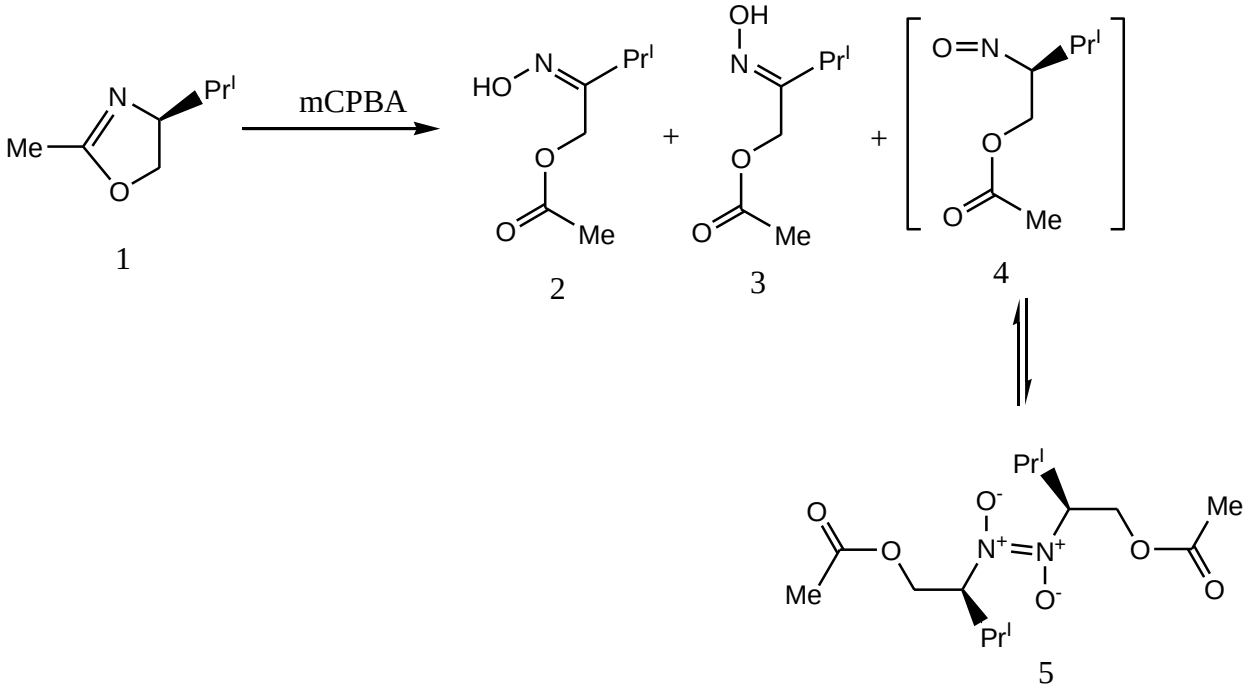
Keywords: Oxazolines, oxidation, MCPBA, ring-opening

Introduction

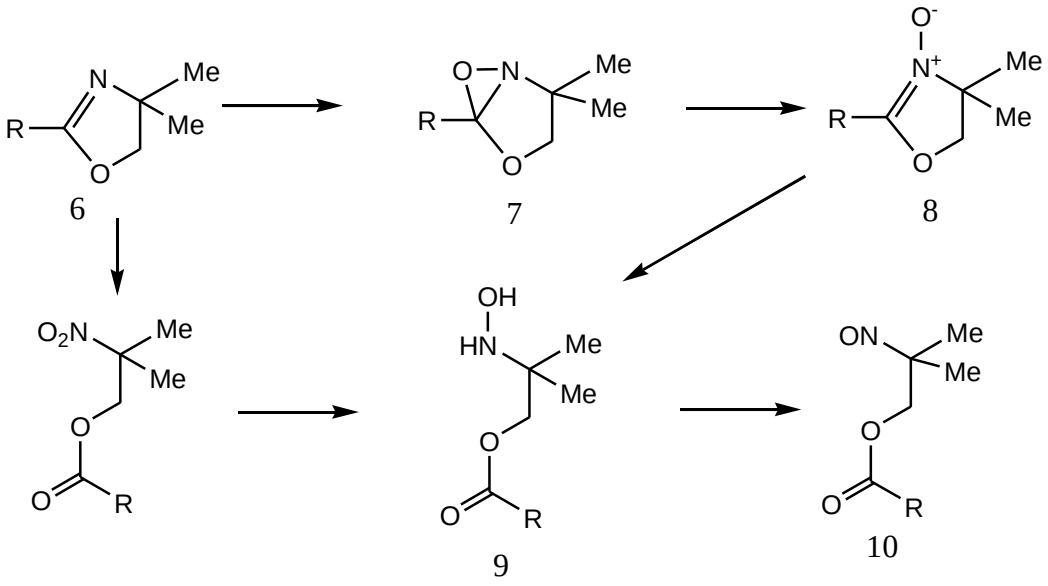
Some time ago we described the oxidation of a range of chiral 2-thiazolines (4,5-dihydrothiazoles) which was found to result in either *S*-oxidation to give thiazoline *S,S*-dioxides which were subject to subsequent hydrolytic ring-opening and disproportionation or else dehydrogenation to give thiazoles depending on the conditions used.[1] In no case was *N*-oxidation observed. On the other hand, 2-oxazolines (4,5-dihydrooxazoles) are known to undergo oxidation to the corresponding oxaziridines with MCPBA and these may be isomerised to the corresponding oxazoline *N*-oxides on silica gel.[2] The 4,4-dimethyloxazoline *N*-oxides formed in this way or by an alternative ring synthesis have been shown to be effective 1,3-dipoles.[3] Since we had available a range of chiral 4-substituted oxazolines used as precursors for the corresponding thiazolines,[1] we decided to examine oxidation of these in the hope that the *N*-oxides might prove to be useful chiral 1,3-dipoles for asymmetric synthesis. In this paper the results of oxidation of the representative oxazoline 1 with both MCPBA and the more unusual oxidant NO_2 are described.

Results and Discusion

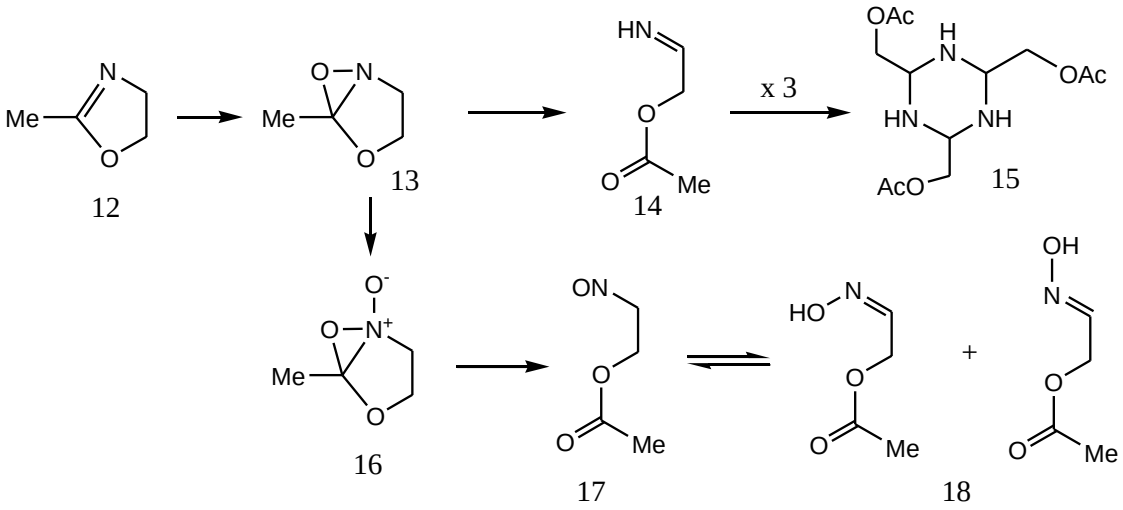
When a solution of the chiral oxazoline 1 in CH_2Cl_2 was treated with MCPBA (1.6 equiv.) at RT a deep blue-green colour developed which slowly faded. Work-up and chromatographic separation of the products gave, as minor products, the *Z* and *E* oximes 2 and 3 and as the major product the dimer 5 of the nitroso compound 4. The formation of dimers of this type from aliphatic nitroso compounds is well known,[4] and the yellow dimer 5 was found to dissociate to 4 in boiling toluene as indicated by formation of an intense blue colour which reverted to yellow upon cooling. Both attempted distillation and prolonged storage of 5 led to complete conversion into a mixture of 2 and 3 suggesting that these are the most thermodynamically stable isomers in this system. The formation of 5 would not be expected to result in racemisation and indeed it showed a substantial optical rotation although its enantiomeric purity was not readily confirmed.



It is of interest to compare our results with those found previously for the 4,4-disubstituted compounds 6 and the 4-unsubstituted compound 12. In the case of 6 (R = n-pentyl) reaction with MCPBA (1 equiv.) gave the oxaziridine 7 which was isomerised by silica gel to the oxazoline *N*-oxide 8. This could be hydrolysed to the hydroxylamine 9 which was then oxidised by MCPBA (1 equiv.) to the nitroso compound 10. In contrast to 4 this showed no tendency to dimerise presumably due to steric hindrance.[2] On the other hand, treatment of 6 with an excess of MCPBA led directly to the nitro compound 11 which could be reduced to 9 using zinc and ammonium chloride.

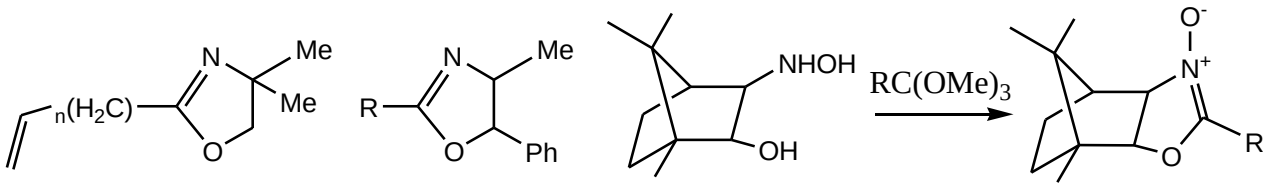


For the 4-unsubstituted compound 12, oxidation with MCPBA (1 equiv.) gave only partial oxidation to the oxaziridine 13 and it was found to be impossible to achieve complete reaction without further oxidation *via* 16 to give the ring-opened nitroso compound 17 which existed entirely as a mixture of the isomeric oximes 18.[5] When 13 was heated in solution it underwent ring-opening to give the cyclic trimer 15 of the imine 14.



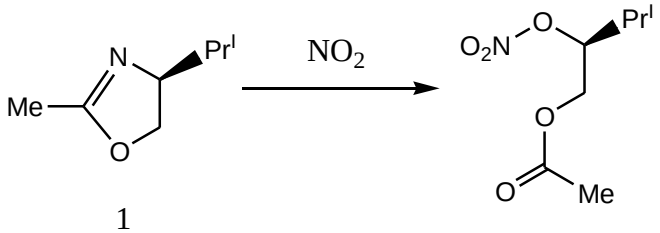
Langlois and coworkers have recently examined the synthetic utility of chiral oxazoline *N*-oxides. Although both the 4,4-dimethyl compounds 19 and the ephedrine-derived chiral compounds 20 could be oxidised to the corresponding oxaziridines, isomerisation of these to the *N*-oxides on silica was accompanied by a significant degree of hydrolysis to give the acyloxy hydroxylamines corresponding to 9 and the *N*-oxides were used for cycloaddition in impure

form.[6] In all later work, the camphor-derived compounds 22 have been formed directly by treatment of 21 with an ortho ester rather than by *N*-oxidation.[7] The *N*-oxide of 20 (R = Me) has also been prepared by oxygen transfer from a dihydroisoquinoline-derived oxaziridinium salt followed by acid-mediated isomerisation.[8]



It appears therefore that the oxazoline 1 is more similar to the 4-unsubstituted compound 12 in its behaviour with MCPBA in that reaction cannot be stopped at the monooxidation stage and ring-opening ensues. It is notable however that the nitroso dimer 5 is obtained as the major product in our case whereas 17 was not detected and immediately isomerised to the oximes 18. It might also be noted that similar ring-opening behaviour is observed for 2-alkylpyrroline *N*-oxides.[9]

Nitrogen dioxide is a rather interesting oxidant which has recently been used for a variety of systems such as 1,2,5-thiadiazoles[10] and phosphorus ylides.[11] Treatment of the oxazoline 1 with an excess of NO_2 in CH_2Cl_2 at RT led to formation of a green colour and, after evaporation and chromatographic purification, a product was isolated which appeared to be the ring-opened alkyl nitrate 23. It is not clear whether the nitrate ester function is derived from oxidation of the nitrite formed by rearrangement of the nitro compound similar to 11 or whether it has come from the NO_2. In view of the potentially explosive nature of this compound it was not investigated further.



1 23

In conclusion, it appears that in moving from 4,4-disubstituted oxazolines to the 4-monosubstituted chiral analogues, the oxidation behaviour becomes considerably more complex with the result that it is no longer a simple matter to obtain the oxazoline *N*-oxides of interest as chiral 1,3-dipoles.

Experimental Section

General Procedures. Infra red spectra were recorded as thin films on a Perkin Elmer 1420 instrument. NMR spectra were obtained for ^{1}H at 80 MHz using a Bruker WP80 instrument and for ^{13}C at 75 MHz using a Bruker AM300 instrument. All spectra were run on solutions in $CDCl_3$ with internal Me_4Si as reference. Chemical shifts are reported in ppm to high frequency of the reference and coupling constants *J* are in Hz. Mass spectra were obtained on an A. E. I. MS-902 spectrometer using electron impact at 70 eV. Optical rotations were determined on an Optical Activity AA1000 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}.
The chiral oxazoline 1 was prepared as described previously.[1]

Reaction of oxazoline 1 with MCPBA

A solution of the oxazoline 1 (4.2 g, 3.3 mmol) in CH_2Cl_2 (200 cm^3) was stirred at RT while a solution of *m*-chloroperbenzoic acid (9.0 g, 5.2 mmol) in CH_2Cl_2 (150 cm^3) was added slowly. After stirring for 1-2 h a blue-green colour developed which subsequently faded. After 17 h, the mixture was washed with saturated aqueous sodium carbonate (6 x 50 cm^3), dried and evaporated. Chromatography of the residue on silica eluting with hexane-diethyl ether (4:1) gave a (3:2) mixture of *(Z)*- and *(E)*-2-hydroxyimino-3-methyl-1-butyl acetate (2 and 3) (0.28 g, 5%) as a colourless liquid. (Found: C, 53.0; H, 8.5; N, 8.8. $C_7H_{13}NO_3$ requires C, 52.8; H, 8.2; N, 8.8%) ν_{max} /cm^{-1} 3700-2700 (br, OH), 1750 (C=O), 1650 (C=N), 1565, 1450, 1370, 1220, 1050, 950 and 750; *m/z* 159 (M, 3%), 139 (2), 129 (2), 99 (62), 84 (9), 69 (96) and 43 (100).
***(Z)*-2-hydroxyimino-3-methyl-1-butyl acetate (2)** δ_H 10.2-9.5 (1 H, br s, OH), 5.00 (2 H, s, CH_2O), 2.65 (1 H, septet, *J* 8, C*H*Me_2), 2.10 (3 H, s, COC*H*$_3$) and 1.13 (6 H, d, *J* 8, Me); δ_C 170.7 (C=O), 160.4 (C=N), 58.0 (CH_2O), 30.6 (CO*C*H_3), 20.8 (*C*HMe_2) and 19.9 (2 Me).
***(E)*-2-hydroxyimino-3-methyl-1-butyl acetate (3)** δ_H 10.2-9.5 (1 H, br s, OH), 4.70 (2 H, s, CH_2O), 3.40 (1 H, septet, *J* 8, C*H*Me_2), 2.08 (3 H, s, COC*H*$_3$) and 1.13 (6 H, d, *J* 8, Me); δ_C 170.6 (C=O), 159.5 (C=N), 62.3 (CH_2O), 25.9 (CO*C*H_3), 20.8 (*C*HMe_2) and 18.6 (2 Me).
Further elution using hexane-diethyl ether (1:1) gave *(E)-(2S)*-2-azo-3-methylbut-1-yl acetate *N*,*N'*-dioxide (5) (3.07 g, 58%) as a yellow liquid. (HRMS: found M, 318.1803. $C_{14}H_{26}N_2O_6$ requires *M*, 318.1791) [α] -9.0 (*c* 1.6, $CHCl_3$); λ_{max} /nm (EtOH) 292 (log ε 5.0) and 205 (log ε 5.02); ν_{max} /cm^{-1} 1750 (C=O), 1470, 1440, 1380, 1370, 1230, 1200, 1130, 1040 and 840; δ_H 5.45 (2 H, td, *J* 8, 4, CHN), 4.58 (2 H, half AB pattern of d, *J* 12, 4, CH_2O), 4.35 (2 H, half AB pattern of d, *J* 12, 8, CH_2O), 2.27 (2 H, octet, *J* 8, C*H*Me_2), 2.00 (6 H, s, COC*H*$_3$), 1.05 (6 H, d, *J* 6, Me) and 0.95 (6 H, d, *J* 8, Me); δ_C 170.2 (C=O), 70.7 (CHN), 61.6 (CH_2O), 28.2 (CO*C*H_3), 20.5 (*C*HMe_2), 19.5 (Me) and 16.4 (Me); *m/z* 319 (M, 5%), 318 (M, 2), 298 (6), 228 (8), 184 (3), 160 (35), 139 (50), 129 (27), 118 (12), 100 (38), 90 (7) and 69 (100).

Effect of heat upon dimer 5

Attempted Kugelrohr distillation of 5 (0.5 g) gave a mixture of the *(Z)*- and *(E)*-oximes 2 and 3 (0.32 g), bp (oven temperature) 195 °C at 0.9 Torr.
Heating a solution of 5 (0.20 g) in toluene (10 cm^3) under reflux led to rapid formation of the monomeric nitroso compound 4 as indicated by a change from yellow to blue but upon cooling the colour reverted to yellow.
Storage of 5 at RT for 3 months resulted in complete conversion into a mixture of the *(Z)*- and *(E)*-oximes 2 and 3.

Reaction of oxazoline 1 with NO_2
A solution of the oxazoline 1 (3.0 g, 23.6 mmol) in CH_2Cl_2 (50 cm^3) was stirred at 0 °C while a solution of NO_2 (2.7 g, 60 mmol) in CH_2Cl_2 (50 cm^3) was added slowly. After the addition the mixture was stirred and allowed to warm to RT over 20 h. Evaporation gave a pale green liquid. Chromatography of this on silica using petroleum-diethyl ether (2:1) gave *(2S)*-3-methyl-2-nitrato-1-butyl acetate (23) (1.26 g, 28 %) as a pale yellow liquid, bp (oven temperature) 162 °C at 8 Torr. (HRMS: found M H, 192.0856. $C_7H_{13}NO_5$ requires *M H*, 192.0872) δ_H 5.25-4.95 (1 H, m, CHO), 4.40 (1 H, half AB pattern of d, *J* 12, 3, CH_2O), 4.10 (1 H, half AB pattern of d, *J* 12, 8, CH_2O), 2.05 (3 H, s, $COCH_3$), 2.05 (1 H, octet, *J* 8, $CHMe_2$) and 1.04 (6 H, d, *J* 8, Me); δ_C 170.6 (C=O), 85.4 (CHO), 62.4 (CH_2O), 28.9 ($COCH_3$), 20.6 ($CHMe_2$), 18.4 (Me) and 18.0 (Me); *m/z* 192 (M H, 25%), 174 (35), 156 (10), 132 (12), 129 (53), 114 (34), 85 (43), 69 (62) and 43 (100).

Acknowledgements

We thank EPSRC and ICI Pharmaceuticals, Alderley Park (now AstraZeneca) for a CASE studentship (DPA).

References

1. Aitken, R. A.; Armstrong, D. P.; Galt, R. H. B.; Mesher, S. T. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 935.
2. Keana, J. F. W.; Lee, T. D. *J. Am. Chem. Soc.* **1975**, *97*, 1273. (b) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1976**, *41*, 3237.
3. Ashburn, S. P.; Coates, R. M. *J. Org. Chem.* **1984**, *49*, 3127.(b) Ashburn, S. P.; Coates, R. M. *J. Org. Chem.* **1985**, *50*, 3076.
4. Emmons, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 6522. (b) Beckett, A. H.; Jones, G. R.; Coutts, R. T. *Tetrahedron* **1976**, *32*, 1267.
5. Aue, D. H.; Thomas, D. *J. Org. Chem.* **1974**, *39*, 3855.

6. (a) Kobayakawa, M.; Langlois, Y. *Tetrahedron Lett.* **1992**, *33*, 2353. (b) Bérranger, T.; André-Barrès, C.; Kobayakawa, T.; Langlois, Y. *Tetrahedron Lett.* **1993**, *34*, 5079.
7. (a) Dirat, O.; Berranger, T.; Langlois, Y. *Synlett* **1995**, 935. (b) Berranger, T.; Langlois, Y. *Tetrahedron Lett.* **1995**, *36*, 5523. (c) Dalko, P. I.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 2107. (d) Kouklovsky, C.; Dirat, O.; Berranger, T.; Langlois, Y.; Tran-Huu-Dau, M. E.; Riche, C. *J. Org. Chem.* **1998**, *63*, 5123. (e) Dirat, O.; Kouklovsky, C.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 6634. (f) Dirat, O.; Kouklovsky, C.; Langlois, Y.; Lesot, P.; Courtieu, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3197.
8. Hanquet, G.; Lusinchi, X. *Tetrahedron* **1994**, *50*, 12185.
9. Bapat, J. B.; Durie, A. *Aust. J. Chem.* **1984**, *37*, 211.
10. Dunn, P. J.; Rees, C. W.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1134.
11. Bestmann, H. J.; Kamberger, W.; Röder, T.; Zimmermann, R. *Liebigs Ann. Chem.* **1996**, 845 (b) Aitken, R. A.; Karodia, N. *Eur. J. Org. Chem.* **1999**, 251.

