Intramolecular Epoxidation of Unsaturated Oxaziridines

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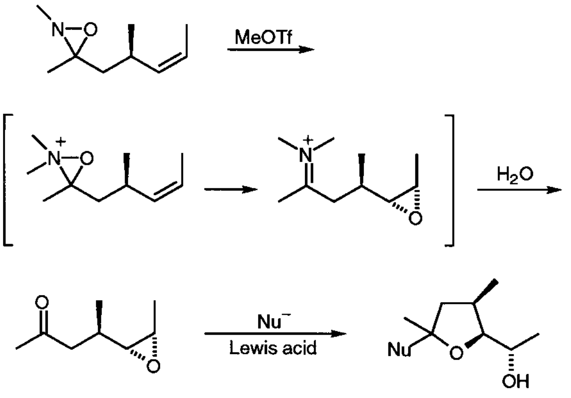
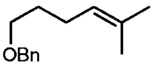
Abstract: Treatment of unsaturated oxaziridines with MeOTf results in intramolecular epoxidation, presumably *via* oxaziridinium salts. The method has been used to effect regioselective epoxidation of a non-conjugated diene.

Reactions in which regio- and stereoselectivity are controlled by ”internal delivery” of reagent are of great importance in organic synthesis.[1] In the area of alkene epoxidation, high selectivity has been accomplished by hydroxyl-directed processes.[1] As an alternative approach, we have been interested in the possibility of intramolecular oxygen delivery from carbonyl groups[2] and we have also begun an investigation of the possibility of intramolecular epoxidation with unsaturated oxaziridines. Oxaziridines have rarely been used for alkene epoxidation:[3] indeed, *N*-unsubstituted oxaziridines are reported to transfer nitrogen rather than oxygen to olefins.[4] However, introduction of electron withdrawing *N*-sulfonyl[3b] or *N*-phosphinoyl[5] groups does result in active epoxidants, and perfluorooxaziridines are also capable of oxygen transfer to olefins.[6] As a first stage in our investigations of intramolecular oxaziridine epoxidation, we were particularly attracted to the pioneering work of Hanquet and Luscini and co-workers[7] who demonstrated that *N*-quaternisation of oxaziridines leads to oxaziridinium salts which can efficiently transfer oxygen to alkenes.[8] We wondered whether an intramolecular version of this process (Scheme 1) might allow regio- and/or stereoselective alkene epoxidation, providing, after iminium hydrolysis, a stereocontrolled route to epoxycarbonyl compounds as precursors to oxygen heterocycles *via* rearrangement.[9] Here we report the realisation of the concept of intramolecular oxaziridinium epoxidation and demonstrate its use for the regioselective epoxidation of a non-conjugated diene.



Scheme 1

The first substrate to be examined was the unsaturated imine **2a**, prepared from the corresponding aldehyde **1a**[10] (Scheme 2 and Table 1). As a key requirement of the proposed sequence, selective oxidation of the imine in the presence of the alkene was necessary. There was surprisingly little precedent for this, although scattered examples of the use of *m*CPBA, usually at low temperature, were to be found in the literature.[11] We were pleased to find that Oxone® in CH_3CN / H_2O effected this transformation cleanly (Scheme 2, Table 1).[12, 13] Moreover, treatment of a 42 mM solution of the resulting oxaziridine **3a** in CH_2Cl_2 with MeOTf followed by brief exposure to aqueous $NaHCO_3$ afforded the epoxyaldehyde **4a** in moderate yield as the only isolated product.[13] A crossover experiment was then performed to demonstrate that the epoxidation process was indeed intramolecular: an equimolar mixture of **3a** and benzyl ether **5** in CH_2Cl_2 was treated with MeOTf followed by aqueous $NaHCO_3$. The benzyl ether **5** was recovered in good yield (73%), with no evidence of the corresponding epoxide, while **4a** was again the major product (39%). Since **5** would be expected to undergo intermolecular electrophilic epoxidation as least as quickly as **3a** or the unsaturated oxaziridinium salt derived from it (and probably faster than the latter due to the –*I* inductive effect of the oxaziridinium group), this suggests that the selective epoxidation of **3a** in this experiment is due to an intramolecular epoxidation process.



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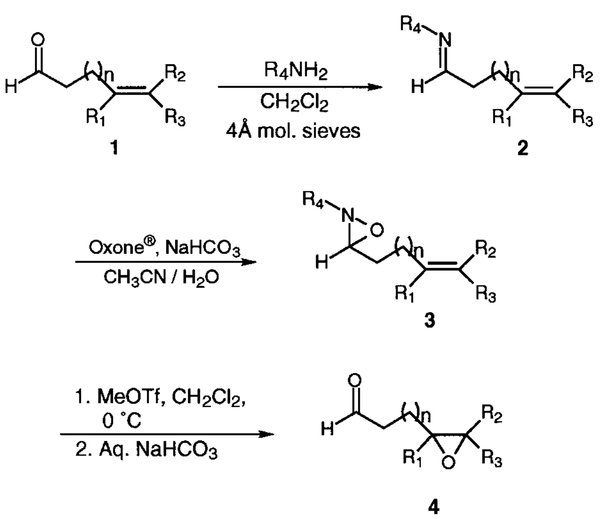
The homologue **1b**, with an extra carbon atom in the linking tether and potentially an eventual precursor to a tetrahydropyran rather than a tetrahydrofuran product, was investigated next (Table 1, entry 2). Application of the same reagent sequence again provided the epoxyaldehyde (**4b**, 41%), and a crossover experiment as described above again suggested that the epoxidation process was indeed intramolecular. Having established the feasibility of the process, a range of substrates of varying alkene substitution pattern were examined (Table 1). As well as trisubstituted alkenes (**2a** and **2b**, entries 1 and 2), 1,1-disubstituted (**2c**, entry 3), and *E*- or *Z*- 1,2-disubstituted olefins (**2d-f**, entries 4-6) underwent the selective Oxone® oxidation and subsequent epoxidation. In all cases, the epoxyaldehydes **4** were obtained in moderate yields; this may be partly due to product volatility since analysis of the TLC and crude ^1H NMR spectrum did not indicate the formation of significant by-products. The low yields do not appear to be due to the presence of triflic acid (from hydrolysis of MeOTf), since addition of 2,6-di-*tert*-butylpyridine (4 eq relative to oxaziridine) to the reaction mixture did not improve yields.



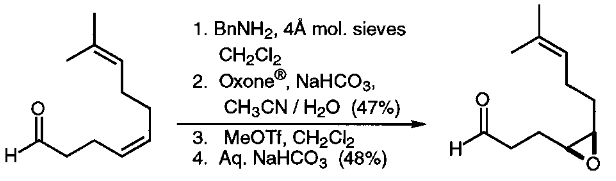
Scheme 2

Table 1. Epoxidation *via* Unsaturated Oxaziridines

Entry	Substrate	R_1	R_2	R_3	R_4	n	$1 \rightarrow 3$ (%)[a]	$3 \rightarrow 4$ (%)[a]
1	**a**	H	Me	Me	Bn	1	73	39
2	**b**	H	Me	Me	Bn	2	60	41
3	**c**	nBu	H	H	Bn	1	72	39
4	**d**	H	H	nPr	Bn	1	73	56
5	**e**	H	nBu	H	Bn	1	45	60
6	**f**	H	nBu	H	nPr	1	39	48

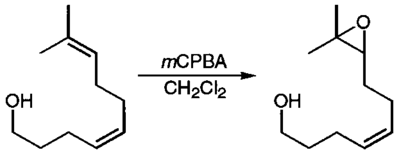
[a] See ref. 13 for typical procedure

Finally, the application of the method to the regioselective epoxidation of a polyene was investigated. We were pleased to find that treatment of unsaturated oxaziridine derived from aldehyde **6**[10] with MeOTf then aqueous $NaHCO_3$ resulted solely in epoxidation at the disubstituted olefin, leading to **7** (48%) (Scheme 3). In contrast, epoxidation of the corresponding alcohol **8** with *m*CPBA (1 eq) led to the regioisomeric epoxide **9** as the sole product (75%) *via* epoxidation of the more electron rich alkene (Scheme 4).



6 **7**

Scheme 3



8 **9**

Scheme 4

We have demonstrated that intramolecular epoxidation *via* unsaturated oxaziridinium salts is feasible, and that this method allows regioselective epoxidation of a polyene. We are currently investigating the use of the reaction sequence for acyclic stereocontrol, as well as using the unsaturated oxaziridine substrates to develop alternative methods (*e.g.* metal catalysis) to activate oxaziridines for oxygen transfer.

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References and Notes

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(13) *General procedure for preparation of unsaturated imines* **2**:
To a stirred solution of unsaturated aldehyde **1** (5.0 mmol) in CH_2Cl_2 (5 ml) under nitrogen was added benzylamine (536 mg, 5.0 mmol) followed by powdered 4Å molecular sieves (500 mg). The reaction was stirred for 15 hours, filtered and the sieves washed with CH_2Cl_2. The solvent was removed under reduced pressure to yield the crude imine **2** as a yellow oil which was carried on to the next stage without purification. In all cases, ^1H NMR showed a single imine, presumed to be the *E*-isomer.
General procedure for preparation of unsaturated oxaziridines **3**:
To a stirred solution of imine **2** (4.0 mmol) in acetonitrile (60 ml) was added deionised water (40 ml). To this homogeneous solution was added a mixture of Oxone® (1.48 g, 4.8 mmol $KHSO_5$) and $NaHCO_3$ (627 mg, 7.46 mmol). The reaction was stirred for 30 minutes, poured into water (100 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give a yellow oil. Flash column chromatography (petrol/ethyl acetate 10:1) on base-washed silica (1% Et_3N in eluent) yielded the oxaziridine as a colourless oil. In all cases, ^1H NMR indicated that a single oxaziridine diastereomer was present. All products displayed satisfactory ^1H and ^{13}C NMR, IR, MS and microanalytical or accurate mass data. Characteristic resonances for the oxaziridine were at *ca.* 3.9 ppm (t) in the ^1H NMR

spectrum (*H*C(O)N), and at 81-83 ppm in the ^{13}C NMR (oxaziridine ring carbon).

Data for **3a**: colourless oil, ν_{max} (film) 2916, 1640, 1496, 1453, 737, 697 cm^{-1}; δ_H (270 MHz, CDCl$_3$) 7.37-7.29 (5H, m, Ar-*H*), 5.11-5.05 (1H, m, *H*C=C(CH$_3$)$_2$), 3.90 (1H, t, 5.0 Hz, *H*CN(O)), 3.83 (2H, s, PhC*H*$_2$N), 2.14-2.06 (2H, m, CH$_2$), 1.74-1.67 (2H, m, CH$_2$), 1.67 (3H, s, CH$_3$), 1.58 (3H, s, CH$_3$); δ_C (68 MHz, CDCl$_3$) 135.5 (s), 132.7 (s), 128.8 (d), 128.6 (d), 127.8 (d), 122.7 (d), 81.8 (d), 65.6 (t), 32.3 (t), 25.6 (q), 22.7 (t), 17.6 (q); m/z (CI) 218 (M+H, 100%), 200, 146, 132, 126, 106, 91. (Observed MH$^+$ 218.1544. $C_{14}H_{20}NO$ requires 218.1545).

General procedure for methylation of oxaziridines ***3*** *and hydrolysis to epoxy aldehydes* ***4:*** To a stirred solution of oxaziridine **3** (0.25 mmol) in freshly distilled CH$_2$Cl$_2$ (6 ml) under nitrogen was added methyltrifluoromethanesulfonate (0.056 ml, 0.5 mmol) dropwise. The reaction was followed by TLC with a further amount of methyltrifluoromethanesulfonate (0.5 mmol) added every 90 minutes until reaction was complete. Saturated aqueous NaHCO$_3$ (3 ml) was added and the reaction stirred vigorously for 20 minutes before separation and extraction of the aqueous layer with CH$_2$Cl$_2$ (3 x 5 ml). The combined organic extracts were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure to yield a yellow oil. Flash column chromatography (petrol/ethyl acetate 5:1) yielded the epoxy aldehyde as a colourless oil. All products displayed satisfactory ^{1}H and ^{13}C NMR, IR, MS and microanalytical or accurate mass data.

Data for **4a**: colourless oil, ν_{max} (film) 2965, 2728, 1724, 1458, 1380, 1252, 1124, 916 cm^{-1}; δ_H (270 MHz, CDCl$_3$) 9.83 (1H, t, 1.5 Hz, *H*C=O), 2.77 (1H, dd, 7.5, 5.0 Hz, *H*C(O)C(CH$_3$)$_3$), 2.69-2.63 (2H, m, C*H*$_2$C(H)=O), 2.03-1.90 (1H, m, C*H*HCH(O)), 1.80-1.67 (1H, m, CH*H*CH(O)), 1.32 (3H, s, CH$_3$), 1.30 (3H, s, CH$_3$); δ_C (68 MHz, CDCl$_3$) 201.6 (d), 63.4 (d), 59.2 (s), 41.1 (t), 25.0 (q), 21.8 (t), 19.0 (q); m/z (EI) 129 (M+H, 100%), 111, 95, 85, 71. (Observed MH$^+$ 129.0911. $C_7H_{13}O_2$ requires 129.0915).

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