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TETRAHEDRON

Peracid Induced Ring Opening of Some Isoxazolidines and Oxidation of Saturated 1,3-Oxazines to New Heterocyclic Nitrones

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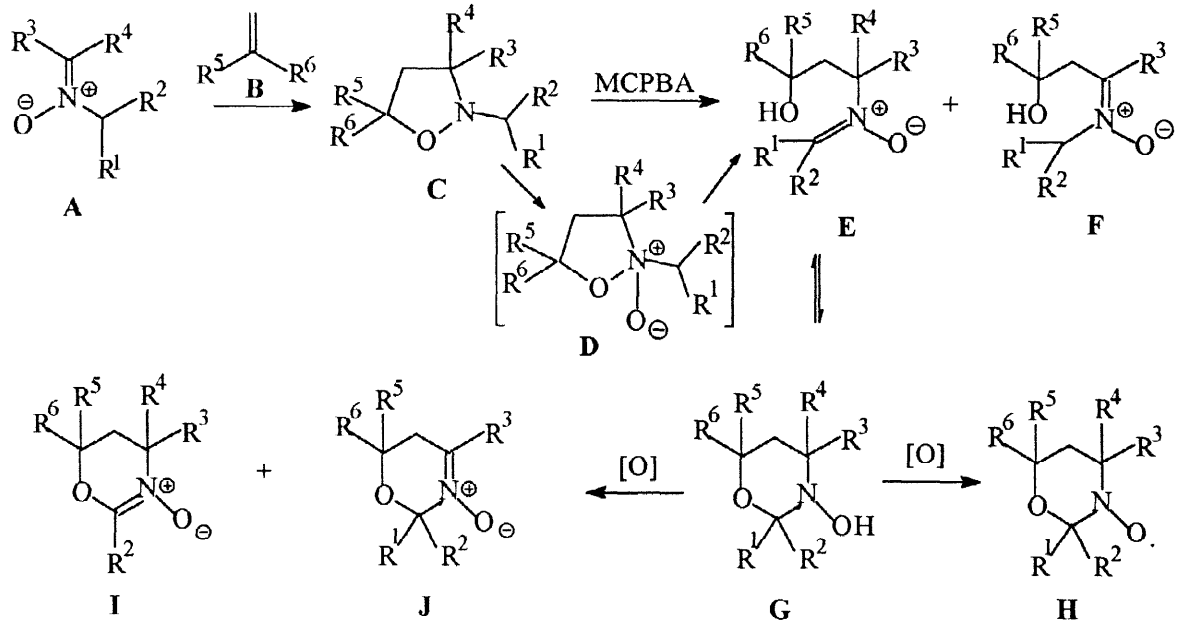
Abstract: The regiochemistry of peracid-induced ring opening of a number of isoxazolidines is investigated. The mechanism of the ring opening reaction and the effects of substituents on the regiochemical behavior have been discussed. The oxidation process gives an equilibrium mixture of nitrone and its six-membered ring hydroxylamine tautomer; the ratio of which is found to depend on the substituents. The tautomeric cyclic hydroxylamine has been converted to a new class of nitrones by oxidation with mercury (II) oxide or *p*-benzoquinone. One of the cyclic hydroxylamine lacking hydrogen at the α-carbons has been oxidized to nitroxide spin label.

INTRODUCTION

While peracid-induced ring opening of bicyclic isoxazolidines with nitrogen at the bridgehead position has been studied in some detail[1], the corresponding reaction involving monocyclic isoxazolidines **C**, derived from nitrone **(A)** - alkene **(B)** cycloaddition reaction has been examined briefly.[2] Ring opening reaction of isoxazolidine **C**



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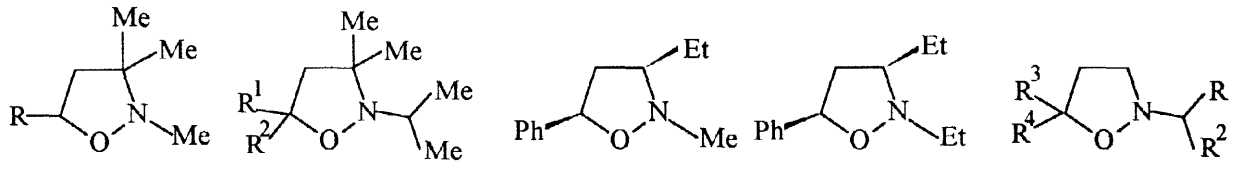
is expected to generate, *via* the intermediacy of non isolable *N*-oxide **D**, a new series of nitrones **E** and **F** which are capable of undergoing a second sequence of cycloaddition reactions. A systematic study would indeed shed light on the substituent effects on the regiochemistry as well as the mechanistic pathway associated with the oxidation process. The presence of a 3-hydroxyalkyl substituent on *N* in nitrone **E** is expected to provide an opportunity to study substituent effects on the open chain (**E**) and ring (**G**) isomerism. Subsequent oxidation of the cyclic hydroxylamine **G** would either give the nitroxide spin labels **H**, a class of compound which plays an important role in studies of biological systems,[3] or the new class of regioisomeric nitrones **I, J** depending on the absence or presence of H at the C(2) and C(4) positions, respectively.

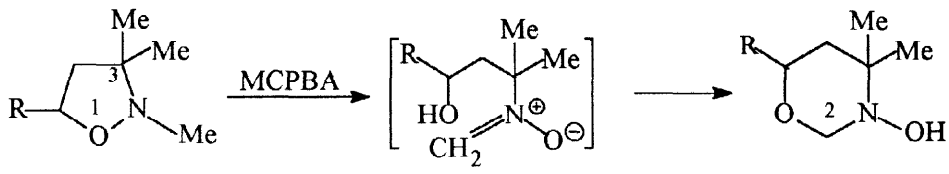
In order to achieve the objectives as outlined above we undertook a systematic study involving the peracid-induced ring opening reaction of the readily available isoxazolidines (**1**)-(**5**)[4] having a variety of substituents on the ring.



(1) (2) (3) (4) (5)

RESULTS AND DISCUSSION

Oxidation of the trisubstituted isoxazolidines (**1**) using *meta*-chloroperbenzoic acid (MCPBA) afforded the perhydro-*N*-hydroxy-1,3-oxazines (**7**) in around 90% yields. The ^{1}H nmr spectra of the reaction mixture failed to detect the presence of the intermediate nitrones **6**. Absence of C(3) H offers the oxidation process with the sole choice of abstraction of H from the *N*-methyl group (Scheme 1).



1 **6** **7**

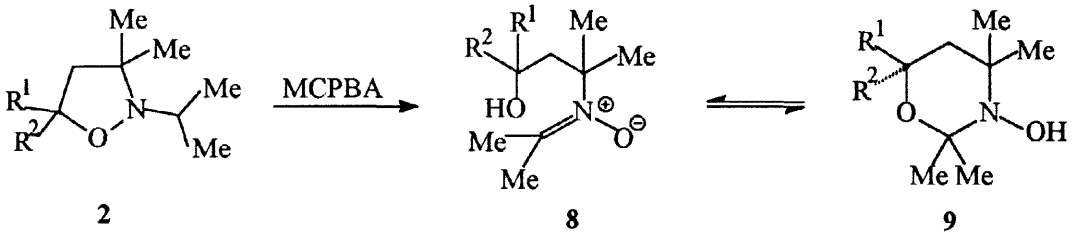
a, R = Ph; **b**, R = CH_2OH

c, R = CH_2OAc; **d**, R = CH_2CH_2OH

Scheme 1

The oxidation of the tetrasubstituted isoxazolidines (**2a**) and (**2b**) afforded an equilibrating mixture of the nitrones **8** and hydroxylamines **9** in respective ratio of ~5:95 in each case (Scheme 2). The cyclic hydroxylamines **9a** and **9b** thus remained the overwhelmingly predominant isomers. Non overlapping minor singlets at δ 2.2 ppm were attributed to the α-methyl protons of the nitrones **8**. Oxidation of the

pentasubstituted isoxazolidine **2c** afforded the isomers **8c** and **9c** in a 1:1 ratio. The ^{1}H NMR spectrum of the 50:50 mixture of the isomers **8c** and **9c** in $CDCl_3$ recorded after 3, 6, 9 and 12 h, revealed the presence of the isomers in an approximate ratio of 70:30, 84:16, 93:07 and, ~100:0, respectively.

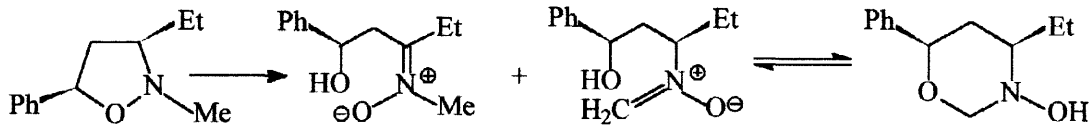


2 **8** **9**

	(8) : (9)
a, R^1 = H, R^2 = Ph	5 : 95
b, R^1 = H, R^2 = CH_2OH	3 : 97
c, R^1 = Me, R^2 = CO_2Me	100 : 0

Scheme 2

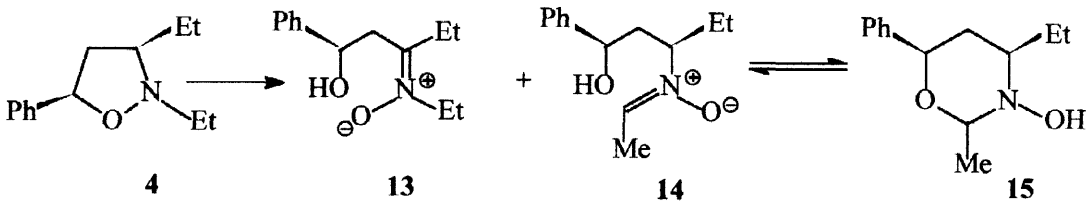
The results indicate that the tautomerization of the nitrone **8c** to the cyclic hydroxylamine is facilitated in presence of acid (one equivalent of *m*-chlorobenzoic acid is formed during oxidation). Protonation or even hydrogen bonding during aqueous work-up makes the carbon terminus of the nitrone more electrophilic towards attack by the hydroxy substituent. The additional substituent at C(6) in **9c** presumably imparts destabilizing 1,3-diaxial interactions and as such drives the equilibrium in aprotic solvent ($CDCl_3$) towards the open chain isomer **8c**.



3 **10** **11** **12**

(10) : (11) : (12)

0 : 25 : 75



4 **13** **14** **15**

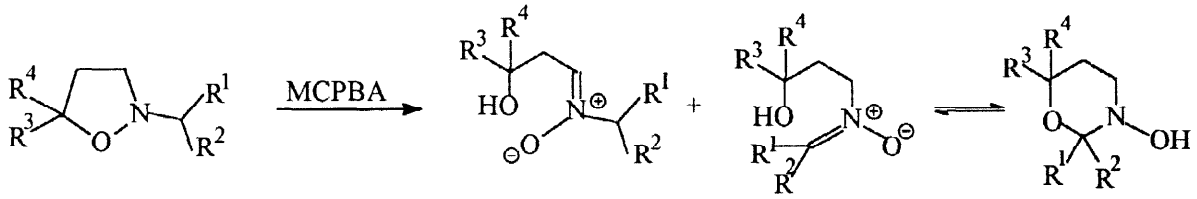
(13) : (14) : (15)

0 : 23 : 77

Scheme 3

The isoxazolidines **3** and **4**, unlike **1** and **2**, have hydrogen at both carbons attached to nitrogen and as such the oxidation process may lead to the formation of regioisomeric nitrones (Scheme 3). However absence of *N*- methyl singlets at around δ 3.7 ppm precluded the formation of the ketonitrone **10**. The less substituted nitrones **11** and **14**, formed regiospecifically, then underwent equilibration with the cyclic form **12** and **15** with an equilibrium ratio of about 1:3 in $CDCl_3$. When an ethereal solution of mixture of **14** and **15** in a respective ratio of 1:3 was slowly evaporated, the residue contained only the cyclic hydroxylamine **15** in crystalline form. The nmr spectrum revealed the absence of the nitrone **14**. While a pure sample of the hydroxylamine **15** in $CDCl_3$ at 20 ° C equilibrates very slowly to the nitrone **14**, in protic solvent (CD_3OD) the isomerization was found to be faster, with an equilibrium ratio of 83:17 in favor of the nitrone.

Regiochemistry of the oxidation of various *N,C*(5)- di- and tri-substituted isoxazolidines **(5)** and composition of the ring ⇔ chain isomers are included in Table 1 (Scheme 4). For the *N*-methylisoxazolidines **5 d-f** the aldonitrones **16 d-f** remained the minor isomers and the major methylene nitrones **17 d-f** were found to be in equilibrium with the predominant cyclic form **18 d-f** . In the oxidation of the isoxazolidines **5c,** the ketonitrone **17c** is formed as the minor isomer and does not equilibrate to the cyclic form **18c**. The oxidation process afforded the aldonitrone **16c** as the major product. The oxidation of the isoxazolidines **5 a, b** led to a mixture of aldonitrones **16** and **17** in each case in an approximate ratio of 1:1. Formation of the nitrone **17a**, stabilized by aromatic conjugation, was expected to be the overwhelming regiochemical choice, however absence of such regioselection points towards a kinetic rather than a thermodynamic phenomenon nvolving intramolecular proton transfer (*vide infra*). It is to be noted that the stabilized conjugated nitrone **17a** does not tautomerize to the cyclic hydroxylamine **18a**.



5 **16** **17** **18**

a, $R^1 = R^4 = H$, $R^2 = Ph$, $R^3 = CH_2OSi^tBuMe_2$

b, $R^1 = R^4 = H$, $R^2 = Me$, $R^3 = Ph$

c, $R^1 = R^2 = Me$, $R^3 = CH_2OSi^tBuMe_2$, $R^4 = H$

d, $R^1 = R^2 = R^4 = H$, $R^3 = CH_2CH_2OH$

e, $R^1 = R^2 = R^3 = R^4 = H$

f, $R^1 = R^2 = R^4 = H$, $R^3 = CH_2OSi^tBuMe_2$

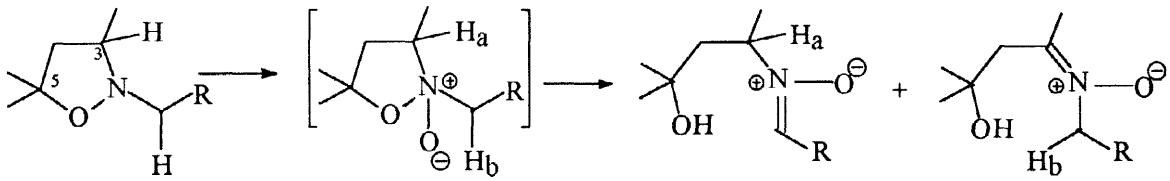
g, $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = CH_2OH$

Scheme 4

Table 1. Regiochemistry of peracid-induced ring opening of the isoxazolidines **(5)** in dichloromethane

Isoxazolidine	Composition of the products		
5	**16**	**17**	**18**
a	45	55	0
b	45	32	33
c	80	20	0
d	32	10	58
e	22	22	56
f	20	8	72
g	55	10	35

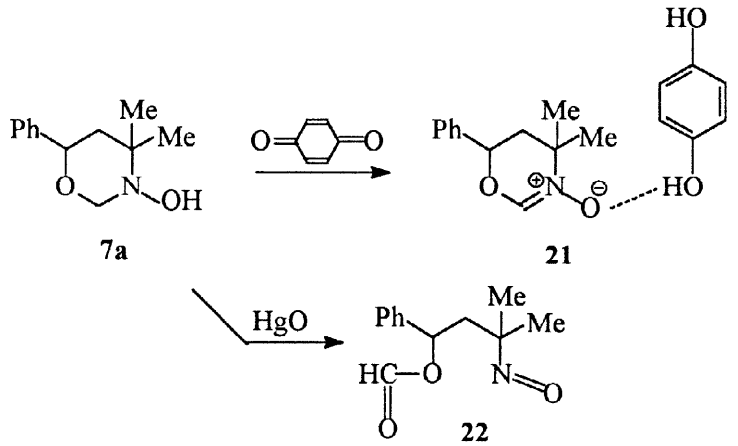
Regioselection in the nitrone formation involves competition for hydrogen abstraction from C(3) and *N*-alkyl substituent of the isoxazolidines. Initial formation of the unstable *N*-oxide **19** followed by ring opening would lead to the methylene-(R=H) or aldo-nitrones **20a** by abstraction of proton H_b. Abstraction of the proton H_a, on the other hand, would give the ketonitrone **20b**. Preferred regiochemistry involves kinetically controlled transfer of the less crowded H thus leading to the less substituted nitrones as the major products Wherever there is a choice, our experimental results indicate the rate of formation of the nitrones as : ketonitrone < aldonitrone < methylene nitrone. In line with the alkene stability, the ketonitrone is expected to be more stable than methylene nitrones. Experimental results thus indicate that a kinetic factor, rather than a thermodynamic one, controls the regioselection. While the isoxazolidines **3** and **4** failed to afford any of the ketonitrones (**10** and **13**), the isoxazolidine **5c** gave the ketonitrone **17c** (20%) as a minor regiomer.



19 **20a** **20b**

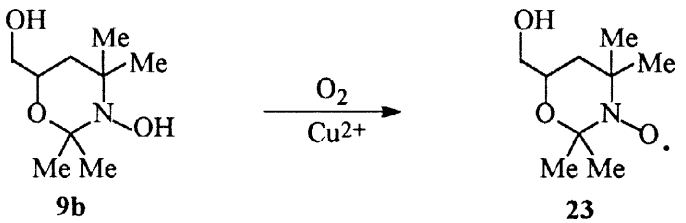
Peracid induced ring opening led to a variety of *N*-hydroxy perhydro-1,3-oxazines which enabled us to study the oxidation of this cyclic hydroxylamines to generate spin labels and a variety of nitrones. Thus the hydroxylamine **7a** upon oxidation with *p*-benzoquinone afforded the nitrone-hydroquinol pair **21** (Scheme 5). The oxidation using mercury(II) oxide however led to a blue coloured compound (derived from hydrolysis of the nitrone **21** by one equivalent of water generated during the oxidation process) which was assigned the

structure as depicted in **22** based on ^1H spectral analysis. The nitrone **21** represents the first example of a cyclic aldonitrone with oxygen at 3 position of the ring. The cycloaddition reaction of this important class of nitrone is recently communicated.[5]



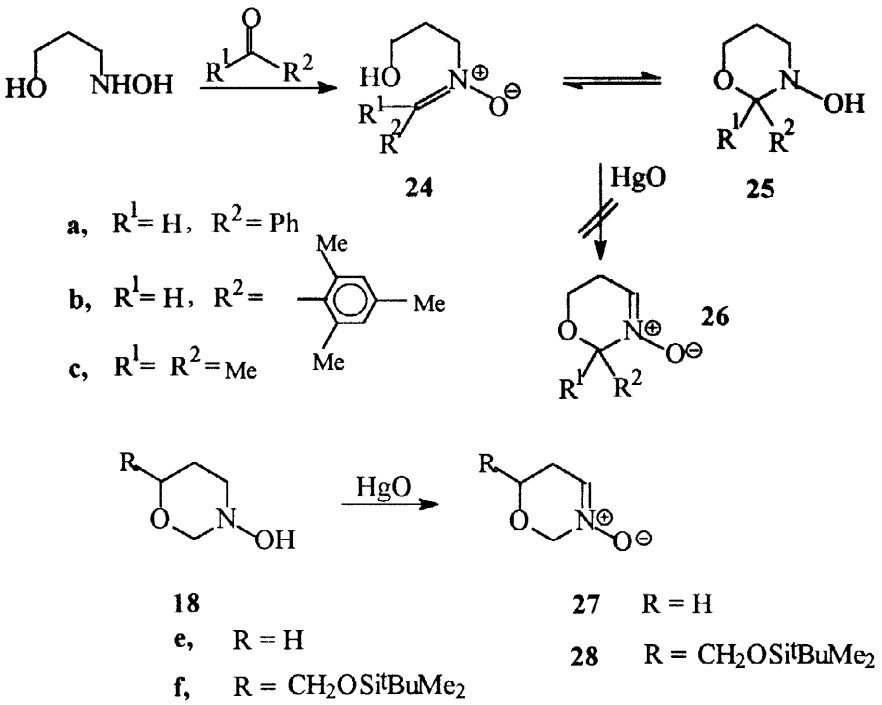
Scheme 5

The oxidation of the cyclic hydroxylamine **9b** using $Cu(OAc)_2.H_2O$[6] (methanol, 20 °C, 30 min) in air afforded the nitroxide **23** (M^+ 188) (Scheme 6). Its solution in ethyl acetate (10^{-4} M) showed the typical three-line[7] nitroxide ESR spectrum.



Scheme 6

Several nitrones **24** were prepared and subjected to mercury(II) oxide oxidation in the hope that the presence of even a minor amount of the tautomeric hydroxylamine **25** would generate the nitrone **26** and continually shift the equilibrium towards the hydroxylamine **25**. However ^1H nmr spectra of **24** revealed the absence of cyclic tautomers **25** and we were unable to obtain the expected nitrone **26** from mercury(II)oxidation. However the cyclic hydroxylamine **18 e,f** upon mercury(II) oxide oxidation, to our delight, afforded the cyclic nitrones **27** and **28** regiospecifically (Scheme 7). The regioisomeric nitrones upon removal of the hydrogen from C-2 position is not detected by proton nmr spectra. The cycloadditions of this synthetically important new class of nitrones are currently under investigation.



Scheme 7

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Nicolet 5 DBX FT IR and are reported in wave numbers (cm^{-1}). The ^1H spectra were recorded on a Varian XL-200 and Jeol Lambda 500 NMR spectrometers, using deuterochloroform as solvent and TMS as internal standard. Mass spectra at 70 ev E.I. were recorded on a Ribermag GC-MS system, R-10-10 with quadrupole mass filter and Riber 400 acquisition system. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analyser. Ring opening reactions were carried out under a positive atmosphere of nitrogen. Silica gel chromatographic separations were performed with flash silica (Baker Chemical Co.). All solvents were reagent grade. Dichloromethane was alumina dried, and MCPBA of 99% purity was prepared by washing 85% pure material with a phosphate buffer of pH 7.5 and drying the residue under vacuum.

General procedure for the MCPBA oxidation of the isoxazolidines - To a solution of the isoxazolidine (10.0 mmol) in dichloromethane (10 cm^3) at -15 °C was added dropwise a solution of MCPBA (11.0 mmol) in dichloromethane (100 cm^3) over a period of 0.5 h. The reaction mixture was then stirred at 0 °C for 0.5 h and for another 0.5 h at 20 ° C. The organic layer was washed with 5% sodium bicarbonate solution (3x35 cm^3). The combined aqueous layers was reextracted with dichloromethane three times (3x25 cm^3). The combined organic layers was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography, crystallization or used as it is. The isolated yields were in the range of 85-95%. However for

very water-soluble hydroxylamines a different work up procedure was adapted. To the reaction mixture was added a saturated aqueous solution of K_2CO_3 (15-20 cm^3) and was stirred for 10 min. The mixture was filtered and the residue was washed with liberal excess of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 until the tlc experiment (silica, ether) revealed the absence of the cyclic hydroxylamine and or nitrone in the organic layer. The combined organic layers was dried (Na_2SO_4) and purified as discussed above.

3-Hydroxy-4,4-dimethyl-6-phenyltetrahydro-1,3-oxazine (7a) - MCPBA oxidation of the isoxazolidine **1a** afforded the hydroxylamine **7a** which was purified by crystallization and obtained as colourless needles (1.70 g, 82 %), m. p. 84 - 85 ° C (hexane-ether) (Found: C, 69.5; H, 8.15; N, 6.7. $C_{12}H_{17}NO_2$ requires C, 69.53; H, 8.27; N, 6.76%); $\nu_{max.}$ (KBr) 3237, 3055, 2988, 2975, 2861, 2817, 1487, 1472, 1447, 1340, 1161, 826, 754, and 701 cm^{-1}; δ_H ($CDCl_3$, + 45 °C) 1.29 (3 H, s), 1.36 (3 H, s), 1.52 (1 H, d, *J* 12.5 Hz), 2.12 (1 H, t, *J* 12.5 Hz), 4.75 (1 H, dd, *J* 12.0, 2.4 Hz), 4.84 (2 H, s), 5.85 (1 H, br, OH), 7.46 (5 H, m); Mass spectrum: *m/z* 207 (M^+ 20 %).

3-Hydroxy-4,4-dimethyl-6-hydroxymethyltetrahydro-1,3-oxazine (7b) - MCPBA oxidation of the isoxazolidine **1b,** using work up procedure adapted for water-soluble hydroxylamines, followed by chromatographic purification using 95:5 CH_2Cl_2-methanol mixture as the eluant afforded the hydroxylamine **7b** as a colourless liquid (1.45 g, 90%) (Found; C, 52.0; H, 9.3; N, 8.7. $C_7H_{15}NO_3$ requires C, 52.15; H, 9.40; N; 8.69%); $\nu_{max.}$ (neat) 3368, 2920, 1448, 1385, 1367, 1263, 1228, 1185, 1169, 1066, 1042, 888 and 816 cm^{-1}; δ_H ($CDCl_3$,+ 45 °C) 1.15 (1 H, d, *J*, 13.0 Hz), 1.25 (6 H, s), 1.92 (1 H, t, *J* 13.0 Hz), 3.59 (2 H, m), 3.82 (1 H, m), 4.68 (2 H, br, s), hydroxyl protons signals were not observed. Mass spectrum: *m/z* 161 (M^+ 9.0 %).

3-Hydroxy-4,4-dimethyl-6-acetoxymethyltetrahydro-1,3-oxazine (7c) - MCPBA oxidation of the isoxazolidine **1c** followed by chromatographic purification using 1:1 mixture of CH_2Cl_2-Et_2O as the eluant afforded the hydroxylamine **7c** as a colourless liquid (1.89 g, 93%) (Found: C, 53.0; H, 8.3; N, 6.7. $C_9H_{17}NO_4$ requires C, 53.18; H, 8.43; N, 6.89%); $\nu_{max.}$ (neat) 3151, 3023, 2988, 2968, 2955, 2938, 2886, 1723, 1482, 1455, 1448, 1385, 1373, 1300, 1280, 1253, 1225, 1208, 1173, 1071, 1021, 917, 899, 831, 787,and 710 cm^{-1}; δ_H ($CDCl_3$, + 45 °C) 1.12 (1 H, d, *J* 12.0 Hz), 1.16 (3 H, s), 1.18 (3 H, s), 1.88 (1 H, t, *J* 12.0 Hz), 2.08 (3 H, s), 3.68 - 4.16 (3 H, m), 4.69 (2 H, br, s), hydroxyl proton signal was not observed. Mass spectrum: *m/z* 203 (M^+ 6.3 %).

3-Hydroxy-4,4-dimethyl-6-(2-hydroxyethyl)tetrahydro-1,3-oxazine (7d) - MCPBA oxidation of the isoxazolidine **1d,** using work up procedure adapted for water-soluble hydroxylamines, followed by chromatographic purification using 97:3 CH_2Cl_2-MeOH mixture as the eluant afforded the hydroxylamine **7d** as a colourless liquid (1.59 g, 91%) (Found : C, 54.9; H, 9.6; N, 7.9. $C_8H_{17}NO_3$ requires (C, 54.84 : H, 9.77 ; N, 8.01%); $\nu_{max.}$(KBr): 3205, 2974, 2878, 2841, 2819, 1488, 1447, 1385, 1232, 1192, 1158, 1141, 1054, 898, 887, 711 cm^{-1}; δ_H ($CDCl_3$, + 45 °C) 1.27 (6 H, s and 1 H underneath), 1.54 - 1.92 (2 H, m), 1.98 (1 H, t,

J 12.0 Hz), 3.75 (2 H, m), 3.79 (1 H, m), 4.75 (2 H, br, s), hydroxyl protons signals were not observed. Mass spectrum: *m/z* 175 (M^+ 5.7 %).

3-Hydroxy-2,2,4,4-tetramethyl-6-phenyltetrahydro-1,3-oxazine (9a) - MCPBA oxidation of the isoxazolidine **2a** followed by chromatographic purification using 2 : 1 hexane-ether as the eluant afforded the hydroxylamine **9a** as a colourless liquid (1.99 g, 85%) (Found C, 71.2; H, 8.9; N, 5.9. $C_{14}H_{21}NO_2$ requires C, 71.45; H, 9.00; N, 5.95%); $\nu_{max.}$(neat): 3387, 3028, 2979, 2943, 1495, 1489, 1452, 1422, 1382, 1242, 1214, 1088, 1045, 990, 753, 699, cm^{-1}; δ_H ($CDCl_3$, 25 °C): 1.26 (3 H, s), 1.38 (3 H, s), 1.54 (6 H, s), 1.66-2.10 (2 H, m), 4.93 (1 H, d, *J* 6.0 Hz), 7.40 (5 H, m); m/z 236 $(M+1)^+$ 26.6 %.

Non overlapping peaks for the minor nitrone **8a** were present at δ 2.20 (3 H, s), 2.27 (3 H, s). The ratio of **9a** and **8a** was determined to be 95 : 5, respectively, by integration.

3-Hydroxy-2,2,4,4-tetramethyl-6-hydroxymethyltetrahydro-1,3-oxazine (9b) - MCPBA oxidation of the isoxazolidine **2b** followed by crystallization using ether-hexane at 0 °C afforded the hydroxylamine **9b** as white crystals (1.75 g, 93%); m.p. 85-86 °C (ether) (Found : C, 57.2 ; H, 10.2; N, 7.3. $C_9H_{19}NO_3$ requires C, 57.11; H, 10.12 ; N, 7.40%); $\nu_{max.}$ (KBr): 3295, 3019, 2981, 2972, 2843, 2875, 1474, 1379, 1242, 1218, 1204, 1177, 1102, 1054, 1021, 975, 714 cm^{-1}; δ_H ($CDCl_3$ 25 °C): 1.18 (6 H, s), 1.38 (6 H, s), 1.48-1.72 (2 H, m, overlapping), 3.06 (1 H, br, OH), 3.53 (2 H, m), 3.94 (1 H, m), δ 5.26 (1 H, br, OH). *m/z* 190 $(M+1)^+$, 32.6 %. Non overlapping peaks for minor isomer **8b** were present at 2.14 (3 H, s), 2.28 (3 H, s). The ratio of **9b** and **8b** was determined to be 97 : 3, respectively, by integration.

3-Hydroxy-2,2,4,4,6-pentamethyl-6-carbomethoxytetrahydro-1,3-oxazine (9c) and its isomeric nitrone 8c - MCPBA oxidation was carried out using 2 mmol (0.430 g) of the isoxazolidine **2c** The ^1H nmr spectrum of the crude reaction mixture indicated the presence of **8c** and **9c**. The reaction mixture was quickly passed through alumina using ether as eluant to give a mixture of **8c** and **9c** in an almost 1 : 1 ratio as a colourless liquid (0.300 g, 63%). However nmr spectrum recorded after 12 h indicated the presence of only nitrone **8c**. (Found: C, 57.0; H, 9.2; N, 6.1. $C_{11}H_{21}NO_4$ requires C, 57.12; H, 9.15; N, 6.06%); $\nu_{max.}$ (neat): 3340, 2995, 1732, 1689, 1455, 1370, 1315, 1165, 1104, 1084, 995 cm^{-1}; *m/z*: 232 $(M+1)^+$ 100 %. The ^1H nmr signals of **8c** and **9c** were deduced as follows: **8c** δ_H ($CDCl_3$, +25 °C) 1.47 (3 H, s), 1.61 (6 H, s), 2.17 (3 H, s), 2.32 (3 H, s), 2.37 (1 H, d, *J* 12.0 Hz, overlapping), 2.84 (1 H, d, *J* 12.0 Hz), 3.77 (3 H, s), 3.91 (1 H, br, OH, overlapping). **9c**: δ_H ($CDCl_3$, + 25 °C): 1.16 (3 H, s), 1.22 (3 H, s), 1.37 (3 H, s), 1.41 (3 H, s), 1.43 (3 H, s),1.82 (1 H, d, *J* 12.0 Hz), 2.52 (1 H, d, *J* 12.0 Hz), 3.74 (3 H, s), 5.04 (1 H, br, OH).

Peracid oxidation of the isoxazolidine 3 - Peracid oxidation of the isoxazolidine **3** afforded a mixture of **11** and **12** in the ratio of 1:3, respectively. Absence of *N*-Me singlet signal around δ 3.7 ppm precluded the formation of **10**. The presence of the nitrone **11** was revealed by the presence of signal at δ6.56 (2 H, AB, *J* 8.0 Hz), 4.12 (1 H, m) and 0.98 (3 H, t, *J* 6.5 Hz). The non overlapping ^1H signals for the compound **12** appeared at δ0.97 (3 H, t, *J* 7.0 Hz), 3.15 (1 H, m), and overlapping signal at 4.75 (3 H, m).

Chromatographic separation to isolate **11** and **12** was not possible since they were equilibrating mixture. The compounds were not analyzed further.

Peracid oxidation of the isoxazolidine 4 - The crude reaction mixture from the oxidation of the isoxazolidine **4** (0.410 g, 2.0 mmol) contained a mixture of **14** and **15** (almost quantitative) in an approximate ratio of 40:60, respectively. The nmr spectrum of the crude reaction mixture revealed the presence of **14** by showing signals at δ 0.88 (3 H, t, *J* 7.0 Hz), 2.06 (3 H, d, *J* 6.5 Hz), 3.69 (1 H, m), 4.73 (1 H, dd, *J* 4.0, 9.0 Hz), 6.85 (1 H, q, *J* 6.5 Hz). The compound **14** in the mixture was tautomerized to *4-ethyl-3-hydroxy-2-methyl-6-phenyltetrahydro-1,3-oxazine* (**15**) completely upon crystallization from ether. m.p: 95-96 °C (ether) (Found : C, 70.2; H, 8.3; N, 6.3. $C_{13}H_{19}NO_2$ requires C, 70.55; H, 8.65; N, 6.33%); $\nu_{max.}$(KBr) 3208, 3055, 2994, 2988, 2944, 2813, 2878, 1448, 1356, 1166, 1153, 1093, 993, 748, 699 cm^{-1}; δ_H ($CDCl_3$, +22 °C) 1.00 (3 H, t, *J* 7.0 Hz), 1.30-2.20 (4 H, m), 1.49 (3 H, d, *J* 5.0 Hz), 2.50-3.18 (1 H, m) 4.00-5.04 (3 H, m including OH), 7.40 (5 H, m); *m/z* 204 (M^+ - OH 39.4%).

A sample of the crystallized **15** in $CDCl_3$ revealed the absence of tautomeric nitrone **14**. However when the above sample was heated at 50 °C in nmr probe for 10 min, the spectrum revealed the presence of **14** and **15** in a ratio of 23 : 77 respectively. Same tube heated at 55 °C (30 min) the ratio was changed to 31: 69 respectively (equilibrium value). When the above nmr sample was taken in ether and evaporated in refrigerator, the crystalline sample revealed the absence of the nitrone **14**.

While the hydroxylamine **15** in $CDCl_3$ at 20 °C equilibrates very slowly (after 3 h, *ca.* 10% nitrone **14**), however in CD_3OD (20 °C) it equilibrated to a mixture of **14** and **15** within 5 min to an approximate ratio 60 : 40, respectively. After 2.5 h the equilibrium ratio was 83 : 17. The spectra of the mixture revealed the following non overlapping signals for the nitrone **14**. δ_H (CD_3OD): 0.82 (3 H, t, *J* 7.0 Hz), 1.95 (3 H, d, *J* 6.5 Hz), 2.37 (1 H, m), 3.70 (1 H, m), 7.05 (1 H, q, *J* 6.5 Hz).

Peracid oxidation of the isoxazolidine 5a - Oxidation of the isoxazolidine **5a** (0.614 g, 2.0 mmol) afforded a non separable mixture of **16a** and **17a** (90%) in a respective ratio of 45:55 as a colourless liquid (after purification by chromatography using 90:10 ether-methanol mixture as the eluant). (Found: C, 62.9; H, 9.1; N, 4.2. $C_{17}H_{29}NO_3Si$ requires C, 63.11; H, 9.04; N, 4.33%). The proton signals for the individual nitrones were deduced from the spectrum of the mixture and are as follows: **Nitrone (16)**: δ_H ($CDCl_3$,+22 °C) 0.06 (6 H, s), 0.88 (9 H, s), 2.70 (2 H, m), 3.46-4.40 (4 H, m), 4.94 (2 H, s), 7.00 (1 H, t, *J* 7.0 Hz), 7.45, (m, 5 H). **Nitrone (17)**: δ_H ($CDCl_3$,+22 °C) 0.04 (6 H, s), 0.86 (9 H s), 1.90 (1 H, m), 2.32 (1 H, m), 3.46-4.40 (6 H, m), 7.45, (m, 3 H), 7.56 (1 H, s), 8.31 (2 H, m). *m/z* 324 $(M+1)^+$ 63%, $(M - OH)^+$ 29%.

Peracid oxidation of the isoxazolidine 5b - Oxidation of the isoxazolidine **5b** (0.354 g, 2.0 mmol) afforded a mixture of **16b-18b** (quantitative) as a colourless liquid. Using integration of several signals the approximate ratio of **16b-18b** was determined to be 45:32:23, respectively. The mixture was not analyzed further. The nonoverlapping proton signals ($CDCl_3$) for **16b-18b** are deduced from the spectrum of their

mixture and are as follows: (**16b**): δ_H : 1.40 (3 H, t, *J* 7.0 Hz), 3.75 (2 H, q, *J* 7.0 Hz), 5.04 (1 H, t, *J* 6.0 Hz), 6.85 (1 H, t, *J* 5.5 Hz). (**17b**): δ_H : 2.04 (3 H, d, *J* 6.0 Hz), 3.96 (2 H, m), 4.88 (1 H, dd, *J* 4.0, 9.0 Hz), 6.92 (1 H, q, *J* 6.0 Hz). (**18b**): δ_H : overlapping doublets at δ 1.40 and at 4.60 (m). *m/z* 194 $(M+1)^+$, 100 %.

Peracid oxidation of the isoxazolidine 5c - Oxidation of the isoxazolidine **5c** (0.519 g, 2.0 mmol) afforded a mixture of **16c** and **17c** (quantitative) as a colourless liquid. The major isomer **16c** has the following signals: δ_H ($CDCl_3$ +22 °C) 0.06 (6 H, s), 0.87 (9 H, s), 1.40 (6 H, d, *J* 6.0 Hz), 2.67 (2 H, m), 3.53 (2 H, *app.* d, *J* 6.0 Hz), 3.76-4.40 (3 H, m), 6.90 (1 H, t, *J* 6.0 Hz); *m/z* 276 $(M+1)^+$, 62%. The presence of the minor nitrone **17c** was revealed by the signal at δ 2.15 (br, s) assigned to the six methyl protons.

Peracid oxidation of the isoxazolidine 5d - MCPBA oxidation of the isoxazolidine **5d** (0.262 g, 2.0 mmol), using work up procedure adapted for water-soluble hydroxylamines, afforded a mixture of **16d, 17d** and, **18d** (quantitative) as a colourless liquid, in an approximate ratio of 32:10:58 , respectively, as determined by integration of several proton signals. The reaction mixture was chromatographed over silica using ether as eluant to obtained the cyclic hydroxylamine, 3-hydroxy-6-(2-hydroxyethyl)tetrahydro-1,3-oxazine (**18d**) (177 mg, 60%) as a colourless liquid . (Found: C, 48.8; H, 8.9; N, 9.6. $C_6H_{13}NO_3$ requires C, 48.96; H, 8.90; N, 9.52%); $\nu_{max.}$ (neat) 3362, 2924, 1654, 1598, 1436, 1168, 1054, 912, 868 and 776 cm^{-1}; δ_H (+20 ° C) :1.30 (1 H, m), 1.56-1.59 (2 H, m), 2.20 (1 H, m), 3.18 (1 H, m), 3.38 (1 H, m), 3.80 (2 H, t, *J* 6.0 Hz and overlapping 1 H, m), 4.46 (1 H, d, *J* 11.0 Hz), 4.74 (1 H, d, *J* 11.0 Hz). The broader doublet at δ 4.46 indicate its equatorial disposition experiencing W coupling. *m/z* 147 (M^+ 22%).

Continued elution with 90:10 ether-methanol mixture as eluant afforded a mixture of **16d** and **17d** as a pale yellow liquid. The total isolated yield was 86%. The nmr spectrum of the mixture of **16d** and **17d** revealed signals at δ 3.74 (3 H, s), 7.02 (1 H, t, *J* 5.5 Hz) attributed to **16d** and at δ 6.48 (2 H, AB, *J* 8.0 Hz) attributed to **17d**.

Peracid oxidation of the isoxazolidine 5e - MCPBA oxidation of the isoxazolidine **5e** (0.174 g, 2.0 mmol), using work up procedure adapted for water-soluble hydroxylamines, afforded a mixture of **16e-18e** as a colourless liquid in the approximate ratio of 22:22:56, respectively, as determined by integration of several proton signals. During the work up $CHCl_3$ was used instead of CH_2Cl_2 for the extraction purposes. The nmr spectrum revealed the presence of **16e** by showing signals at δ 3.72 (3 H, s), and 7.03 (1 H, t, *J* 6.0 Hz), and of **17e** by presence of (2 H, AB , *J* 8.0 Hz) at δ 6.58.

The reaction mixture was chromatographed over silica using ether as eluant to give a mixture of **17e** and **18e** in ratio of 10:90 as colourless liquid (125 mg, 61%). (Found: C, 46.7; H, 8.7; N, 13.5. $C_4H_9NO_2$ requires C, 46.58; H, 8.80; N, 13.59%); *m/z* 104 $(M+1)^+$, 100%. (**17e**): δ_H : (+20 ° C): 2.29 (2 H, quint, *J* 6.0 Hz), 3.59-4.15 (4 H, m, overlapping), 6.49 (1 H, d, *J* 8.0 Hz), 6.62 (1 H, d, *J* 8.0 Hz), 7.01 (1 H, br, OH). (**18e**): δ_H : (+20 °C): 1.42 (1 H, m), 2.29 (1 H, m), 3.19 (2 H, m), 3.72 (2 H, m, overlapping), 4.49 (2 H, AB, *J* 11.0 Hz), 6.99 (1 H, br, OH).

Peracid oxidation of the isoxazolidine 5f - Oxidation of the isoxazolidine **5f** (2.31 g, 10.0 mmol) afforded a mixture of **16f-18f** as a colourless liquid in an approximate ratio of 20:10:70, respectively. The nmr spectrum revealed the presence of **16f** by showing signal at δ 7.01 (1 H, t, *J* 7.0 Hz), and 3.75 (3 H, s), and of **17f** by presence of (2 H, AB, *J* 6.0 Hz) at δ 6.49. The crude reaction mixture was chromatographed over silica using hexane-ether (1:1) as eluant to give compound *3-Hydroxy-6-tert-butyldimethylsilyloxymethyl-tetrahydro-1,3-oxazine* (**18f**) (55%) as colourless crystals, m.p. 65-66 °C (hexane-ether) (Found: C, 53.3; H, 10.2; N, 5.6. $C_{11}H_{25}NO_3Si$ requires C, 53.40; H, 10.19; N, 5.67%); $\nu_{max.}$ (KBr): 3242, 2958, 2929, 2857, 1472, 1460, 1438, 1384, 1359, 1255, 1181, 1099, 1074, 874, 818, 757, cm^{-1}; δ_H (+23 ° C): 0.07 (6 H, s), 0.90 (9 H, s), 1.37 (1 H, m), 2.03 (1 H, m), 3.15 (1 H, m), 3.37 (1 H, m), 3.47-3.87 (4 H, m, including OH), 4.45 (1 H, d, *J* 12.0 Hz), 4.77 (1 H, d, *J* 12.0 Hz). *m/z* 248 $(M+1)^+$ 8.5% The nmr spectrum did not reveal the presence of the acyclic tautomeric nitrone **17f** indicating the overwhelming thermodynamic preference for the cyclic form.

Peracid oxidation of the isoxazolidine 5g - MCPBA oxidation of the isoxazolidine **5g** (0.263 g, 2.0 mmol), using work up procedure adapted for water-soluble hydroxylamines, afforded a mixture of **16g-18g** in the approximate ratio of 55:10:35. The crude reaction mixture when chromatographed over silica using CH_2Cl_2-MeOH (5:1) as eluant, first fraction contained only **18g.** (Found: C, 48.8; H, 8.9; N, 9.5. $C_6H_{13}NO_3$ requires C, 48.96; H, 8.90; N, 9.52); $\nu_{max.}$ (neat): 3361, 2974, 2937, 2872, 1657, 1564, 1541, 1460, 1421, 1374, 1302, 1269, 1139, 1049 and 929 cm^{-1}; δ_H (50 ° C) 0.96 (1 H, m), 1.22 (3 H, s), 2.06 (1 H, m), 2.68 (1 H, m), 3.36 (1 H, m overlapping), 3.50 (2 H, AB, *J* 12.0 Hz overlapping), 4.62 (2H, AB, *J* 12.0 Hz), 5.19 (1 H, br OH), 8.46 (1 H, br, OH). *m/z* 148 $(M+1)^+$, 47 %. Further elution with CH_2Cl_2-MeOH (5:1) as eluant, gave a mixture of **16g** and **17g.** From the nmr spectrum of the mixture following signals were assigned to **16g** and **17g.** δ_H **16g:** 1.23 (3 H, s), 2.72 (2 H, d, *J*, 6.0 Hz), 3.39 (2 H, s), 3.74 (3 H, s), 4.80 (2 H, br, OH), 7.14 (1 H, t, *J* 6.0 Hz). δ_H **17g:** 1.16 (3 H, s), 2.02 (1 H, m), 2.34 (1 H, m), 3.46 (2 H, s), 4.07 (2 H, t, *J* 6.5 Hz), 6.69 (2 H AB *J* Hz).

Preparation of the alkoxy nitrone (21) - To a solution of the hydroxylamine **7a** (2.0 mmol) in anhydrous benzene (35 cm^3) was added under N_2 *p*-benzoquinone (2.3 mmol) at 25 °C. The reaction mixture turned blue within 15 min (presumably a radical-cation-radical-anion pair by SET mechanism[8]) which on heating at 50-60 °C (10 min) resulted in precipitation of a white solid of the nitrone-hydroquinone pair **21** (mp 151-152°C, closed capillary) as charge transfer complex, short H-bonded specie or an acid-base salt. While the free nitrone **21** is expected to be soluble in $CDCl_3$, the pair remained almost insoluble in $CDCl_3$ but readily dissolves in rigorously dried DMSO-d_6 (δ_H 1.49 (3 H, s), 1.59 (3 H, s), 2.41 (2 H, m), 5.54 (1 H, dd, *J* 5.0, 9.5 Hz), 6.70 (4 H, s, hydroquinone), 7.56 (5 H, m), 8.11 (1 H, s, CH=N), 9.10 (2 H, s, hydroxyls). Alkoxy-nitrones are known[9] to be unstable, but the pair **21** remained stable under anhydrous conditions at room temperature and when used after two months it afforded cycloadducts with the same ease. When the

oxidation of hydroxylamine was carried out with mercury (II) oxide in anhydrous dichloromethane, it resulted in the formation of a blue colour compound which was assigned the structure **22** based on ^{1}H spectral analysis. δ_H ($CDCl_3$) 1.14 (3 H, s), 1.17 (3 H, 3), 2.48 (1H, dd, *J* 4.0, 15.0 Hz), 2.08 (1 H, dd, *J* 10.0, 15.0 Hz), 5.90 (1 H, dd, *J* 4.0, 10.0 Hz), 7.38 (5 H, m), 7.92 (1 H, s).

Preparation of the nitrone 24a - The nitrone **24a** is prepared as described in the literature.[10a]

***C*-(2,4,6-Trimethylphenyl)-*N*-(3-hydroxypropyl)nitrone (24b)** - To a solution of 3-hydroxylamino-1-propanol[10] (91 mg, 1 mmol) in methanol (1 cm^3) was added mesitylaldehyde (148 mg, 1 mmol) and was heated to 60 °C (closed vessel) for 4 h. After removal of the solvent the residual solid was crystallised in ether to give the nitrone **24b** as colourless needles (166 mg, 75%), m.p. 101-102 °C (ether) . (Found: C, 70.5; H, 8.5; N, 6.3. $C_{13}H_{19}NO_2$ requires C, 70.55; H, 8.65; N, 6.33%); $\nu_{max.}$ (neat): 3418, 3218, 3010, 2960, 1688, 1612, 1598, 1440, 1386, 1278, 1168, 1148, 1088, 1042, 954, 920, 858 and 761 cm^{-1}; δ_H ($CDCl_3$) 2.17 (2 H, quint, *J* 5.8 Hz), 2.27 (6 H, s), 2.29 (3 H, s), 3.83 (2 H, q, *J* 5.8 Hz), 4.01 (1 H, t, *J* 5.8 Hz, OH exchanged with D_2O, the signal at δ 3.83 becomes a triplet), 4.18 (2 H, t, *J* 5,8 Hz), 6.89 (2 H, s), 7.67 (1 H, s); *m/z* 221 (M^+13.4%).

***C,C*-dimethyl-*N*-(3-hydroxypropyl)nitrone (24c)** - To 3-hydroxylamino-1-propanol (91 mg, 1 mmol) was added acetone (1 cm^3) and kept overnight at 30 °C. After removal of the solvent and passing the residue through a short silica column using 90:10 ether-methanol mixture as eluant afforded the nitrone **24c** as a colourless liquid (104 mg, 80%); (Found: C, 54.8; H, 9.8; N, 10.6; N, 9.5. $C_6H_{13}NO_2$ requires C, 54.94; H, 9.99; N, 10.68); $\nu_{max.}$ (neat): 3296, 2958, 2869, 2300, 2196, 1600, 1620, 1504, 1442, 1378, 1306, 1238, 1214, 1150, 1064, 992, 918 and 870 cm^{-1}; δ_H ($CDCl_3$) 2.03 (2 H, quint, *J* 6.0 Hz), 2.18 (6 H, s), 3.75 (2 H, t, *J* 6.0 Hz), 4.05 (2 H, t, *J* 6.0 Hz), 4.85 (1 H, br OH); *m/z* 131 (M^+16.4%).

General procedure for the preparation of cyclic nitrones (27 and 28):

To a solution of cyclic hydroxylamine (15 mmol) in alumina dried chloroform (100 ml) was added at 0 °C HgO (50 mmol.) The reaction mixture was then stirred at 0 °C for 1 h, and at 25 °C for 2-3 h until TLC experiment, (silica, 1:1 methanol-ether) indicated complete formation of the nitrone. The reaction mixture was then filtered through a bed of celite and $MgSO_4$ and washed with a liberal excess of chloroform. On stripping off the solvent the nitrone **27** (obtained from oxidation of the hydroxylamine **18e**) polymerized to an intractable mixture (containing several tlc spots). However a $CHCl_3$ solution of the nitrone (~ 0.2 M) kept in the freezer remained stable.

For recording the nmr spectrum, nitrone **27** was prepared by HgO oxidation of hydroxylamine **18e** in $CDCl_3$. $\nu_{max.}$ ($CHCl_3$) 3230, 2980, 2958, 1618, 1364, 1140, 1052, 1016, 908, and 882 cm^{-1}; δ_H ($CDCl_3$ + 25 °C) 2.65 (2 H, m), 4.00 (2 H, t, *J* 5.8, Hz), 4.98 (2 H, A_2 with fine allylic splitting), 7.30 (1 H, m).

Unlike the nitrone **27**, the nmr of 0.2 M solution of nitrone **28** (obtained *via* oxidation of the hydroxylamine **18f**) was found to be stable and did not polymerize with time. After stripping of the solvent

the nitrone was obtained as colourless liquid. The nmr spectrum remained unchanged when taken again. The strong absorption at 3230 indicate the hygroscopic nature of the nitrone. $\nu_{max.}$ (neat) 3230, 2940, 2856, 2358, 1628, 1464, 1372, 1254, 1114, 842, and 780, cm^{-1}; δ_H ($CDCl_3$ +25 °C) 0.12 (9 H, s), 0.96 (6 H, s), 2.53 (2 H, m), 3.80 (3 H, m), 5.03 (2 H, s), 7.22 (1 H, m).

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