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Regiochemistry of Mercury(II) oxide Oxidation of Unsymmetrical *N,N*-Disubstituted Hydroxylamines

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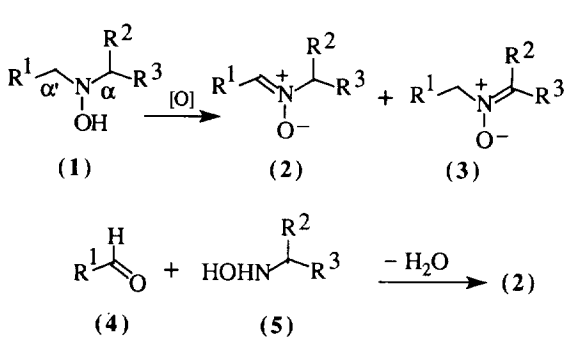
Abstract: Mercury(II) oxide oxidation of *N,N*-disubstituted hydroxylamines with the α and α' carbon atoms containing one and two hydrogen atoms, respectively, gave aldonitrones in a highly regioselective manner. Removal of the α proton is involved in the rate determining step as shown by primary kinetic isotope effect.

INTRODUCTION

Among the plethora of functional groups, nitrone functionality has etched an important place in organic synthesis[1] and in spin trapping experiments to trap and identify reactive free radicals[2] especially in biomedical fields. Generally nitrones have been prepared by oxidation of *N,N*-disubstituted hydroxylamines[1](**1**), condensation of aldehydes (**4**) or ketones with *N*-monosubstituted hydroxylamines (**5**)[1], Michael addition of oximes to electron-deficient alkenes,[3] and alkylation of oximes.[4] To overcome the difficulty associated with the nontrivial task of synthesizing the hydroxylamines, recent developments provide simpler and efficient methods for the preparation of nitrones from secondary amines by oxidation with hydrogen peroxide mediated



Scheme 1.

by selenium dioxide,[5] and ungstate catalysts.[6,7] While there are numuerous reports involving the oxidationof symmetrical amines and hydroxylamines, the study with unsymmetrical hydroxylamines (**1**) and its cyclic counterparts remains scanty[1,7, 8] apparently owing to the anticipation of regiochemical complications.

Herein we report a systematic study involving the mercury(II) oxide oxidation of several unsymmetrical cyclic and acyclic hydroxylamines with each α carbon containing at least one hydrogen atom.

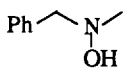
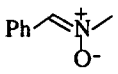
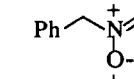
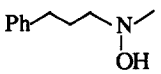
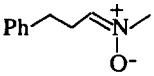
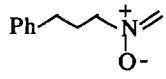
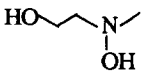
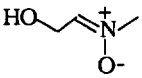
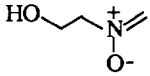
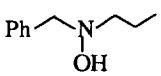
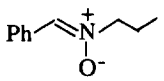
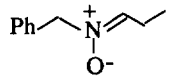
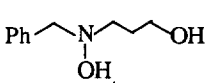
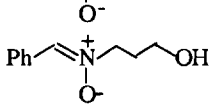
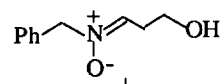
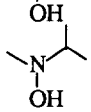
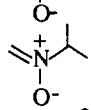
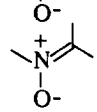
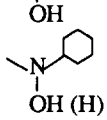
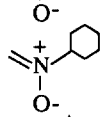
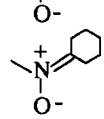
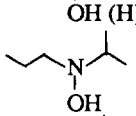
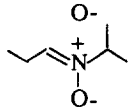
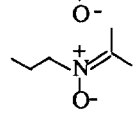
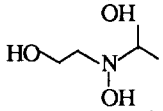
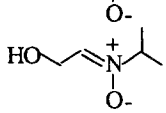
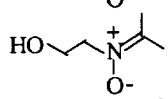
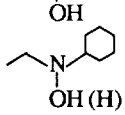
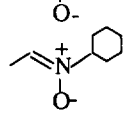
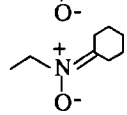
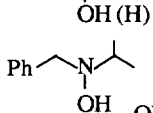
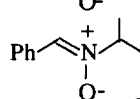
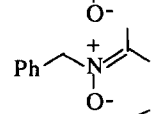
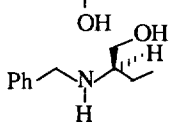
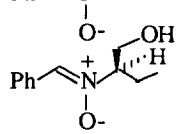
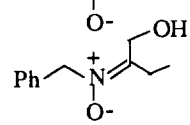
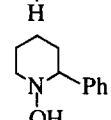
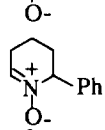
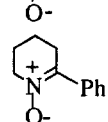
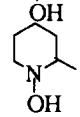
RESULTS AND DISCUSSION

The selenium dioxide mediated hydrogen peroxide oxidation of the secondary amines could conceivably provide the same information as does the HgO oxidation of the corresponding hydroxylamines on the regioselectivity of the nitrone formation, however, the presence of water in the reaction mixture sometimes leads to the hydrolysis of the resulting nitrones.[7] On the other hand, mercury(II) oxide oxidation, carried out in aprotic solvents, provides nitrones in almost quantitative yield.

The regiochemical details of the oxidation of various unsymmetrical hydroxylamines and amines by HgO and H_2O_2/SeO_2, respectively, are included in the table. While a mixture of nitrones is expected in entries 2 and 3, the formation of the nitrones **B** in significant amount by abstraction of the nonbenzylic hydrogen (entries 1, 4, 5) is quite surprising. Conjugated nitrones **A** should have been the sole or overwhelmingly predominant products. Contrary to the common understanding, the regiochemistry of the nitrone formation is thus not governed significantly by the different acidities of the α protons. Entries 6-12 describes the oxidation of hydroxylamines in which one of the α carbon contains a hydrogen atom. Even though the ketonitrones (**B**) are expected to be more stable, aldonitrones (**A**) are the ones formed in a highly regioselective manner. This could be attributed to the kinetic preference for the abstraction of the less hindered α hydrogen. It was reported[9,10] that while mercury(II) oxide oxidation of 2-phenyl-N-hydroxypiperidine (entry 13) gave the nonconjugated nitrone **A** as the sole product, the five-membered counterpart in entry 15 provided the conjugated nitrone **B** exclusively. Reexamination of the oxidation of these two hydroxylamines, however, revealed the formation of two isomeric nitrones with the predominance of the conjugated isomer **B** in both the cases (table).

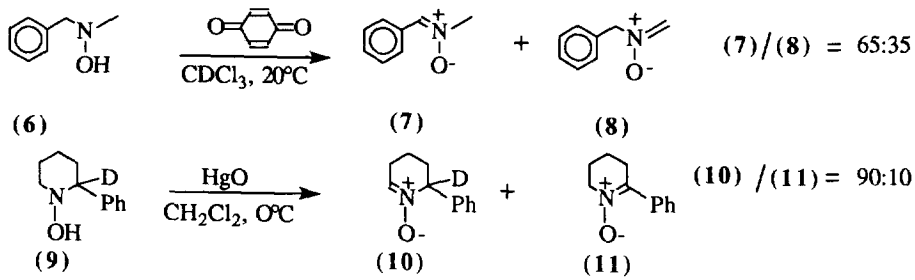
In contrast to the acyclic hydroxylamines, the cyclic counterparts behave differently in their regioselection. (Compare, for instance, the oxidation of acyclic hydroxylamine and its cyclic counterpart in entries 8 and 14). The higher acidity of the benzylic hydrogen, however, does not control the regioselection (compare entries 13, 14). Quite interesting is the observation: how differently the cyclic hydroxylamine (entry 16) and its acyclic counterpart (entry 4) behave in their regioselection! While the former gave the conjugated nitrone as exclusive product, the latter afforded the conjugated and non-conjugated nitrones in almost 1:1 ratio. We are at this stage unable to offer a convincing rationale for the difference in the regioselection of the cyclic and acyclic cases.The selenium dioxide mediated hydrogen peroxide oxidation of *N*-methylcyclohexylamine (entry 7) and *N*-ethylcyclohexylamine (entry 10) in acetone and methanol, respectively, afforded the aldonitrones in a highly regioselective manner. Regiochemical behaviour of the hydrogen peroxide and mercury(II) oxide

Table. Oxidation of Secondary Hydroxylamines with Mercury(II) oxide in CH_2Cl_2 .

Entry	Hydroxylamines	Nitrones (A)	(B)	Composition (A) : (B)
1				62:38
2				63:37
3				58:42
4				55:45
5				55:45
6				90:10
7				85:15 (93:07)[a]
8				90:10
9				92:08
10				90:10 (~100:0)[a]
11				94:06
12				~100:0
13				30:70
14				25:75
15				17:83
16				~100:0

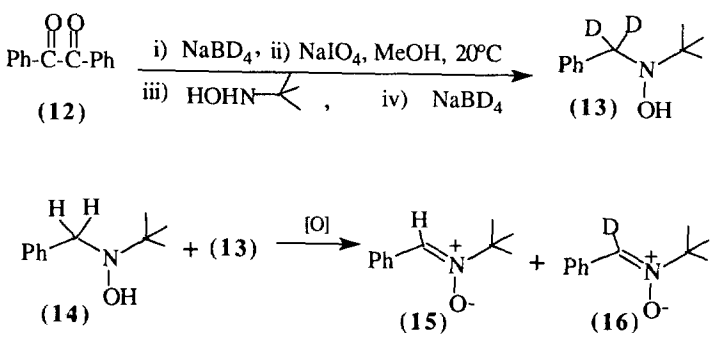
[a] Oxidation of the amine by H_2O_2/SeO_2.

processes are thus found to be similar. Efficient and regioselective formation of the chiral nitrone (A) (entry 12) from the corresponding amine (prepared from *(R)*-2-amino-1-butanol) paves the way to study asymmetric induction and the effects of hydroxyl group in nitrone cycloaddition reactions.

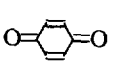


Scheme 2.

Even though there are numerous reports on the oxidation process leading to the nitrones, to the best of our knowledge, the mechanistic pathway this reaction traverses is not investigated to any meaningful extent. The oxidation of *N*-methyl-*N*-benzylhydroxylamine **(6)** (entry 1) with one equivalent of p-benzoquinone in CDCl3 afforded a mixture of nitrones **(7)** and **(8)** in a similar ratio as in the case of mercury(II) oxidation, indicating that both the oxidation processes may be traversing similar mechanistic pathways (Scheme 2). The oxidation of the C(2) deuteriated hydroxylamine **(9)** showed a dramatic reversal in the regioselection of the products **(10)** and **(11)** in comparison to its C(2)H counterpart (entry 13).



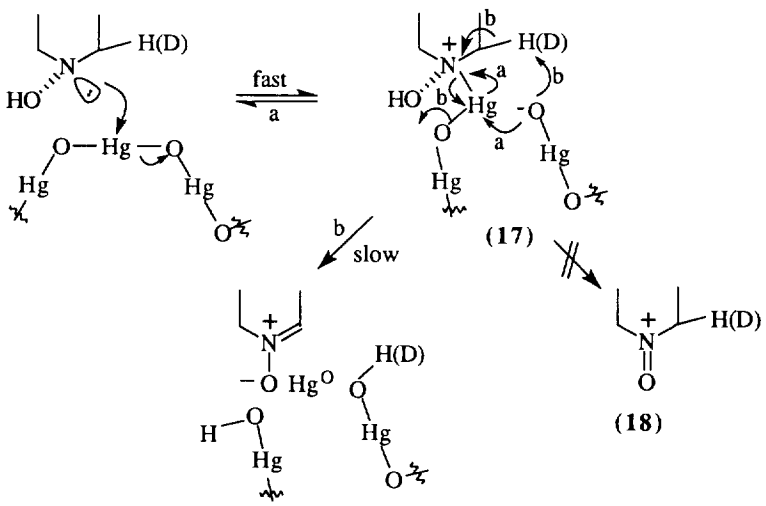
[O], HgO k_H / k_D = 7.0

[O],  k_H / k_D = 7.5

Scheme 3.

Finally, the dideuteriated hydroxylamine **(13)** was prepared by the synthetic route shown in the scheme 3. Reduction of benzil with $NaBD_4$ afforded hydrobenzoin-d_2 which on periodate oxidation gave benzaldehyde-d_1. The nitrone **16** was prepared by condensation of PhCDO with *t*-butylhydroxylamine and the reduction of the nitrone **16** with $NaBD_4$ provided the dideuteriated hydroxylamine **13**. The hydroxylamine **(14)** was prepared by $NaBH_4$ reduction of the nitrone **(15)**.[6] When a mixture of the hydroxylamine **(14)** (0.474 mmol) and **(13)** (0.915 mmol) in $CDCl_3$ (5 cm^3) was treated with HgO (0.60 mmol) at 0 °C, ^1H nmr spectrum revealed the presence of 0.106 mmol of unreacted **(14)**, 0.738 mmol of unreacted **(13)** along with the presence of the product nitrones **(15)** and **(16)** (0.545 mmol). Using the rate equation of Ingold and Shaw[11] the k_H/k_D was found to be 7.0. The corresponding k_H/k_D for the oxidation using *p*-benzoquinone in $CDCl_3$ was determined to be 7.5.

In order to account for the primary isotope effect the reversible formation of the metal complex **(17)** is envisaged (scheme 4). The complex **(17)** may either reverse to the starting reactants (pathway "a") or go to the nitrone upon removal of the proton (or deuteron) (pathway "b") in the rate determining step. Formation of the nitrosonium ion **(18)** is excluded since its irreversible presence in the mechanistic pathway would be unable to manifest deuterium effect in the present experimental set up (scheme 3).



Scheme 4.

EXPERIMENTAL

All m.p.s are uncorrected. Elemental analysis were performed on a carlo - Erba elemental analyzer 1106. IR spectra were recorded on a nicolet 5DXB FT IR and are reported in wave numbers (cm^{-1}). ^1H nmr spectra were recorded on a XL 200 using deuteriated chloroform with Me_4Si as internal standard. 70 e.v. EI. Mass spectra were recorded on a Ribermag GC-MS system, R-10-10 with Quadrupole mass filter and Riber 400

acquisation system. Silica gel chromatographic separations were performed with flash silica (Baker Chemical Co.). HPLC grade dichloromethane was used. Hydroxylamines in entries (3, 4, 8, 9, 11)[12] and (13, 15)[9,10] prepared as described. Oxidation of hydroxylamines in entry 14 is described in our earlier work.[8d] *R*-(-)2-amino -1- butanol (~ 90% pure, $[\alpha]^{25}{}_{D}$ = -8.5 (*c* 2, ethanol) from fluka was used as received.

Preparation and mercury(II) oxide oxidation of the hydroxylamines (General Procedure) : To a solution of the hydroxylamine (2.0 mmol) in CH_2Cl_2 (10 cm^3) at 0°C was added yellow HgO (3.0 mmol) in three portions (*ca.* 20 min) and stirred for 1 h. The resulting greyish mixture was filtered through a small bed of $MgSO_4$. Evaporation of the solvent gave the nitrones in almost quantitative yield. The composition of the nitrones was determined by integration of several proton signals.

Entry 1: *N*-Methyl-*N*-Benzylhydroxylamine was prepared using procedure as described[13] (m.p. 40-41°C ; lit. 40 - 41°C). On HgO oxidation the hydroxylamine afforded a mixture of the nitrones **A** and **B** in a respective ratio of 62 : 38 as determined by integration of several proton signals. The ^1H n.m.r. data for the major nitrone **A** matched with those described in the literature.[13] The spectral data for the isomers was deduced from the ^1H n.m.r. spectrum of the mixture of nitrones. Nitrone **A**: δ_H 3.93 (3 H, s) 7.50 (4 H, m), 8.30 (2 H, m). Nitrone **B** : δ_H 4.98 (2 H, s), 6.32 (1 H, d, *J* 7.0 Hz), 6.64 (1 H, d, *J* 7.0), 7.50 (5 H, m).

Oxidation using p-benzoquinone was carried out as follows. The p- benzoquinone (54 mg, 0.50 mmol) was added to a solution of the hydroxylamine (69 mg, 0.50 mmol) in $CDCl_3$ (1 cm^3) at 20°C. The solution turned blue within few minutes and become colorless again (10 min) . The precipitate of hydroquinone was filtered and the nmr of the filtrate revealed the formation of nitrones **A** and **B** in a respective ratio of 65:35.

Entry 2 : *N*-Methyl-*N*-(3-phenylpropyl)hydroxylamine was prepared by $NaBH_4$ reduction of the nitrone **A**. To a solution of *N*- methylhydroxylamine hydrochloride (251 mg , 3.0 mmol) in ethanol (2 cm^3) was added in succession sodium acetate (3.5 mmol) and hydrocinnamaldehyde (3.3 mmol). The resulting mixture was stirred at 20°C for 1 h and was taken up in CH_2Cl_2 (30 cm^3). The organic layer was washed with 20 % K_2CO_3 solution (10 cm^3) , dried (Na_2SO_4) and purified by chromatography using 10 : 1 ether - methanol mixture as the eluent to give the nitrone **A** as colorless flakes (383 mg, 78.3 %), m.p. 41-42°C (hexane-ether) (Found : C, 73.3 ; H, 7.9 ; N, 8.4. $C_{10}H_{13}NO$ requires C, 73.59 ; H, 8.03 ; N 8.58 %); $\nu_{max.}$ (KBr) 3022, 2912, 1493, 1406, 1148, 1019, 752, 706 cm^{-1}; δ_H 2.85 (4 H, m), 3.65 (3 H, s) , 6.70 (1 H, br t, *J* 6.0 Hz), 7.30 (5 H, m).

To a solution of the nitrone **A** (277 mg, 1.70 mmol) in ethanol (3 cm^3) was added excess sodium borohydride (10 mmol) in five portions over a period of 5 h. The resulting mixture after stirring overnight was diluted with water (15 cm^3) and extracted with dichloromethane (3x20 cm^3). (In cases of water soluble hydroxylamine the aqueous layer was saturated with K_2CO_3). The organic layer was dried (Na_2SO_4) and purified by chromatography using 1:1 ether - hexane mixture as the eluent to give the hydroxylamine as a colorless liquid (230 mg, 82.4 %) (Found : C, 72.8: H, 9.0; N, 8.3. $C_{10}H_{15}NO$ requires C, 72.69; H, 9.15; N, 8.48%); $\nu_{max.}$ (neat) 3230, 3025, 2950, 2863, 1606, 1499, 1455, 1034, 796, 754, and 703 cm^{-1} ;

δ_H 1.93 (2 H, quint, *J* 7.0 Hz), 2.62 (3 H, s), 2.66 (4 H, m), 7.30 (5 H, m), 7.58 (1 H, br, OH). Mass spectrum : m/z 165 (M^+ 35), 117 (15), 91 (75), 77 (25), 60 (100).

Entry 3: The hydroxylamine prepared as described[12], on HgO oxidation afforded a mixture of nitrones **A** and **B** as a pale yellow liquid, $\nu_{max.}$ (neat) 3320, 2940, 2857, 1664, 1625, 1593, 1429, 1410, 1295, 1166, 1061, 987, 941 cm^{-1}. The nmr signals of the nitrones **A** and **B** were deduced from the spectrum of the mixture.

Nitrone **A** : δ_H 3.95 (3 H, s), 4.43 (2 H, m), 5.00 (1 H, br, OH), 7.02 (1 H, t, *J* 4.0 Hz).

Nitrone **B** : δ_H 3.70 (4 H, br, s), 5.00 (1 H, br, OH), 6.36 (1 H, d, *J* 8.0 Hz), 6.54 (1 H, d, *J* 8.0 Hz).

The nitrones were found to be quite unstable and darkens to brown colour after 2 days at room temperature.

Entry 4 : The nitrone **B** and *N*-propyl-*N*-benzylhydroxylamine were prepared as described.[12] Thus, the *N*-benzylhydroxylamine (733 mg, 5.96 mmol) was reacted with propanal (380 mg, 6.55 mmol) in ethanol (5 cm^3) at 20°C for 1 h. The resulting nitrone **B** was obtained as colorless needles (90%), m.p. 84-85°C (ether) (Found : C, 73.7 ; H, 7.9 ; N, 8.45. $C_{10}H_{13}NO$ requires C, 73.59 ; H, 8.03 ; N, 8.58 %); $\nu_{max.}$ (KBr) 3050, 2980, 1595, 1491, 1463, 1426, 1287, 1206, 1166, 1111, 930, 907, 743, 700 cm^{-1}; δ_H 1.08 (3 H, t, *J* 7.0Hz), 2.50 (2 H, quint, *J* 7.0 Hz), 4.94 (2 H, s), 6.70 (1 H, t, *J* 6.5 Hz), 7.45 (5 H, m).

The hydroxylamine[12], obtained by $NaBH_4$ reduction of the nitrone **B**, on oxidation afforded a mixture of the nitrones **A** and **B** in a respective ratio of 55 : 45 as determined by integration of several proton signals. The ^1H nmr signal of the major nitrone was deduced from the spectrum of the mixture : δ_H 1.00 (3 H, t, *J* 7.0 Hz) , 2.03 (2 H, hex, *J* 7.0 Hz), 3.93 (2 H, t, *J* 6.5 Hz), 7.50 (4 H, m), 8.32 (2 H, m).

Entry 5 : 3-Amino-1-propanol (7 equiv) was reacted with benzylbromide (1 equiv) at 20°C for 24 h. The resulting mixture was taken up in CH_2Cl_2 and washed with water. The organic layer was dried, concentrated and distilled to give 3-(*N*-benzylamino)-1-propanol (b.p.3mmHg 108 °C). Using procedure as described[5] the amine on SeO_2 mediated oxidation using H_2O_2 in acetone afforded a mixture of the nitrones **A** and **B** in a ratio of 65 : 45, respectively. The above mixture of the nitrones on $NaBH_4$ reduction afforded 3-(*N*-benzylhydroxylamino)-1-propanol which was purified by chromatography using 2 : 1 hexane- ether mixture as the eluent (two steps 65% yield), white crystals, mp 51-52 °C (ether) (Found : C, 66.4, H, 8.2 ; N, 7.70 $C_{10}H_{15}NO_2$ requires C, 66.27 ; H, 8.34 , N, 7.73%); $\nu_{max.}$ (KBr) 3320, 3034, 2962, 2847, 1457, 1346, 1074, 1033, 1001, 918, 826, 757, and 697 cm^{-1}; δ_H 1.73 (2 H, m), 2.88 (2 H, t , *J* 6.0 Hz), 3.57 (2 H, t, *J* 6.0 Hz) 3.79 (2 H, s) 7.30 (5 H, m); hydroxyl proton signals were too broad to be seen. The hydroxylamine on HgO oxidation afforded a mixture of the nitrones **A** and **B** in a respective ratio of 55 : 45 as determined by integration of several proton signals. The ^1H nmr signal of the major nitrone **A** matches with those reported.[14] The following signals were deduced from the spectrum of the mixture of the nitrones: **(A)** : δ_H 2.14 (2 H, q, *J* 6 .0 Hz) , 3.75 (2 H, t, *J* 6.0 Hz), 4.10 (2 H, t, J 6.0 Hz), 5.2 (1 H, br OH), 7.20- 7.55 (4 H, m) , 8.20 (2 H, m). **(B)** 2.70 (2 H, q, *J* 6. 0 Hz) , 3.78 (2 H, t, *J* 6.0 Hz), 4.90 (2 H, s), 5.2 (1 H, br OH), 6.92 (1 H, t, *J* 6.0 Hz), 7.30 (5 H, m).

Entry 6 : A mixture of *N*- isopropylhydroxylamine (750 mg, 10.0 mmol) and formaldehyde (350 mg, 12.0 mmole) in ethanol was heated at 70°C in a closed flask for 20 min. The mixture was then cooled to 20°C and the crude nitrone **A** was reduced with $NaBH_4$. The reaction mixture was acidified with 20% HCl solution (10 cm^3) and the volume of the solution was reduced to half by blowing a gentle stream of nitrogen at 50°C. The solution was then satutated with K_2CO_3 and extracted with ether (3x15 cm^3). The organic layer was dried (Na_2SO_4) and HCl gas was passed through the solution to obtain *N*-Methyl-*N*-isopropylhydroxylamine hydrochloride as a colorless liquid (1.08 g, 86%) (Found : C, 38.0; H, 9.4; N, 10.9. $C_4H_{11}NO.HCl$ requires, C, 38.25; H 9.63; N 11.15 %).

Treatment of the aqueous solution of the hydrochloride salt with K_2CO_3 and extraction with ether, followed by careful removal of ether afforded the free hydroxylamine as a colorless volatile liquid, $\nu_{max.}$ (neat) 3207, 2976, 2857, 1461, 1341, 1318, 1208, 1143, 1051, 932, 858, 747 cm^{-1}; δ_H (45 °C) 1.09 (6 H, d, *J* 6.5 Hz), 2.59 (3 H, s), 2.80 (1 H, hept, *J* 6.5 Hz), 8.00 (1H ,br). The proton signals at ambient temperature were broad due to slow nitrogen inversion.

HgO oxidation of the hydroxylamine afforded a mixture of the nitrones **A** and **B** as a colorless liquid, $\nu_{max.}$ (neat) 2976, 1572, 1457, 1365, 1295, 1213, and 1065 cm^{-1}; δ_H 1.46 (6 H, d, *J* 6.5 Hz), 4.18 (1 H, hept, *J* 6.5 Hz), 6.48 (2 H, s). The presence of the minor isomer **B** was indicated by the presence of signals at δ_H 2.15 (3 H, s), 2.18 (3 H, s), 3.87 (3 H, s).

Entry 7 : Oxidation with SeO_2, H_2O_2 of *N*-methylcyclohexylamine in acetone using the procedure as described[5] afforded a mixture of the nitrones **A** and **B** in a respective ratio of 93 : 07, respectively. The crude mixture of nitrones on $NaBH_4$ reduction in ethanol gave *N*-cyclohexyl-*N*-methylhydroxylamine which was purified by chromatography using ether as eluent. The overall yield of the reactions was 75%; colorless needles, mp 61-62°C (hexane) (Found : C, 64.95, H, 11.6 ; N, 10.8. $C_7H_{15}NO$ requires C, 65.07; H, 11.70 ; N, 10.84 %); $\nu_{max.}$ (KBr) 3150, 2925, 2850, 1443, 1374, 1350, 1204, 1061, 1028, 945, 900, 829, 778, 638 and 623 cm^{-1}; δ_H 1.00 - 2.24 (10 H, m), 2.48 (1 H, m), 2.66 (3 H, s), 7.30 (1 H, br OH).

Oxidation (HgO) of the hydroxylamine afforded a mixture of the nitrones **A** and **B** from which the the nitrone **A** was separated by crystallization as colorless flakes, m.p. 56-58°C (ether) (Found: C, 65.9; H, 10.4; N, 10.9. $C_7H_{13}NO$ requires C, 66.10; H, 10.30; N, 11.02%); $\nu_{max.}$ (KBr) 2940, 2857, 1563, 1457, 1369, 1295, 1143, 1074, 899, 849 cm^{-1} ; δ_H 1.08 - 2.00 (10 H, m), 3.74 (1 H, m), 6.36 (1 H, d, *J* 8.0 Hz), 6.49 (1 H, d, *J* 8.0 Hz). The presence of minor isomer **B** was revealed by the the overlapping singlet at 3.73 ($N-CH_3$). The ratio of **A** and **B** was estimated to be 93 : 07.

Entry 8 : The nitrone **A** and *N*-propyl-*N*-isopropylhydroxylamine were prepared as described.[12] Thus a solution of *N*-isopropylhydroxylamine (700 mg , 9.3 mmol) in ethanol (5 cm^3) was treated with propanal (596 mg, 10.3 mmol) at 20°C for 30 min. Removal of the solvent and excess aldehyde afforded the nitrone **A** in quantitative yield as colorless liquid. An analytical sample was prepared by washing the nitrone with cold hexane ether mixture (Found : C, 62.4 ; H, 11.5 ; N, 12.0. $C_6H_{13}NO$ requires C, 62.57; H, 11.38; N, 12.16 %); $\nu_{max.}$ (neat) 2965, 2925, 1590, 1452, 1373, 1287, 1176, 1078, and 920 cm^{-1}; δ_H

1.12 (3 H, t , *J* 7.0 Hz) , 1.42 (6 H, d, *J* 7.0 Hz) , 2.52 (2 H, quint, *J* 7.0 Hz) , 4.07 (1 H, hept, *J* 7.0 Hz), 6.79 (1 H, t, *J* 6.5 Hz).

The hydroxylamine on oxidation gave a mixture of the nitrones **A** and **B** in a respective ratio 90 : 10 as determined by integration of several proton signals. The signals of the minor nitrone **B** was deduced from the spectrum of the mixture; δ_H 0.98 (3 H, t, *J* 7.0 Hz), 1.90 (2 H, hex, *J* 7.0), 2.15 (3 H, s), 2.18 (3 H, s), 3.86 (2 H, t, *J* 6.5 Hz).

Entry 9 : The hydroxylamine, prepared as described[12], on HgO oxidation afforded a mixture of nitrones **A** and **B**. The protons signals for the major and minor isomers was deduced from the spectrum of the mixture of isomers. The major isomer **A** was crystallized from CH_2Cl_2 - hexane - ether mixture, colorless needles, m.p. 66 - 68°C (Found : C, 51.1; H, 9.4; N, 12.0. $C_5H_{11}NO_2$ requires C, 51.26; H, 9.47; N, 11.96%). $\nu_{max.}$ (KBr) 3225, 2986, 2949, 2892, 1609, 1452, 1295, 1157, 1088, 978, 927, and 849 cm^{-1}; δ_H 1.43 (6 H, d, *J* 6.5 Hz), 4.08 (1 H, hept, *J* 6.5 Hz), 4.47 (2 H, d, *J*, 4.3 Hz), 4.95 (1 H, s), 7.12 (1 H, t, *J*, 4.5 Hz). Nitrone **B:** δ_H 2.21 (6 H, s), 4.08, (4 H accendental degeneracy of the *N*- alkyl proton signals). Mass spectrum : m/z 117 (M^+ 12), 116 (23), 88 (30), 74 (100).

Entry 10 : Oxidation of *N*-ethylcyclohexylamine with SeO_2, H_2O_2 in methanol using literature procedure[5] gave the only nitrone **A** which without purification was reduced with $NaBH_4$ in ethanol to give *N*-ethyl-*N*- cyclohexylhydroxylamine. The product was purified by chromatography using ether as eluent. The overall yield was found to be 83%, colorless liquid; hydrochloride salt, colorless needles (ether- methanol), mp 125-126°C, (Found : C, 53.6; H, 10.2; N, 8.0. $C_8H_{17}NO.HCl$ requires C, 53.47; H, 10.10; N, 7.80%). $\nu_{max.}$ (neat) 3250, 2920, 2890, 1446, 1366, 1342, 1163, 1103, 1042, and 890 cm^{-1}; δ_H 1.14 (3 H, t, *J* 7.0 Hz), 1.26 (5 H , m), 1.52-2.08 (5 H, m), 2.60 (1 H, m), 2.81 (2 H, q, *J* 7.0 Hz) , 7.32 (1 H, br OH).

Oxidation (HgO) of the hydroxylamine afforded a mixture of nitrones **A** and **B** in a respective ratio of 90 : 10. which on crystallization gave the nitrone **A**. Colourless needles (hexane-ether), m.p. 80-81°C(Found : C, 67.9; H, 10.9; N, 9.8. $C_8H_{15}NO$ requires C, 68.04; H, 10.71; N, 9.92%); ν_{max} (KBr) 2920, 2840, 1598, 1442, 1348, 1298, 1180, 1143, 1095, 1042, 893, 875, and 784 cm^{-1}; δ_H 1.08- 1.52 (3 H, m), 2.02 (3 H, d, *J* 7.0 Hz) 1.56-2.16 (7 H, m), 3.72 (1 H, m) 6.94 (1 H, q, *J* 7.0 Hz). The presence of minor nitrone **B** in the original mixture was revealed by the presence of the signal at δ 3.98 (2 H, q, *J* 7.0 Hz, *N*-CH_2-), 2.76 (2 H, m, allylic axial hydrogens) and 2.52 (2 H m, allylic equatorial hydrogens). The original mixture of the nitrones on treatment with methanol (2 h, 20°C) failed to reveal the presence of the ketonitrone **B**, thus indicating its hydrolysis under this condition. This could be the reason for the absence of minor nitrone **B** in the SeO_2/ H_2O_2 oxidation in methanol.

Entry 11 : *N*- benzyl-*N*- isopropylhydroxyl amine was prepared from the nitrone **A** as described[12] (using $NaBH_4$ reduction). The oxidation of the hydroxylamine afforded a mixture of the nitrones **A** and **B** in a respective ratio of 94 : 06 as determined by the integration of several proton signals. The mixture of nitrones

was crystallized (hexane-ether) in the freezer to give the nitrone **A**, colorless liquid (solidifies in the freezer), (Found : C, 73.4 ; H, 7.8 ; N, 8.6. $C_{10}H_{13}NO$ requires C, 73.59 ; H, 8.03 ; N, 8.58); $\nu_{max.}$ (neat) 3055, 2970, 2925, 1575, 1556, 1446, 1374, 1360, 1305, 1172, 1144, 1086, 925, 803, 750 and 690 cm^{-1}; δ_H 1.51 (6 H, d, *J* 7.0 Hz), 4.23 (1 H, hept, *J* 7.0 Hz) 7.45 (3 H, m), 7.50 (1 H, s), 8.28 (2 H, m) . The ^1H nmr spectrum of the minor isomer **A** was deduced from the nmr spectrum of the mixture; δ_H 2.14 (3 H, s) , 2.19 (3 H, s), 5.09 (2 H, s), 7.45 (5 H, m).

Entry 12 : *(R)*-2- amino -1-butanol (7 equiv) was reacted with benzylbromide (1 equiv) using procedure as described in entry 5 to give (R)-2-(*N*-benzylamino)-1-butanol as colorless needles, (needless to say this is not the efficient method to prepare the amine. The amine could be prepared *via* the benzamide derivative with $LiAlH_4$ reduction), b.p. 0.1 mmHg 107°C ; m.p. 72-73°C (Found C, 73.6 ; H, 9.6 ; N, 7.8. $C_{11}H_{17}NO$ requires C, 73.70 ; H, 9.56 ; N, 7.82%); $\nu_{max.}$ (KBr) 3300, 3090, 3057, 2958, 2850, 1461, 1380, 1350, 1139, 1082, 1064, 978, 939, 864, 835, 748, and 700 cm^{-1}; δ_H 0.90 (3 H, t, *J* 7.0 Hz), 1.40 (2 H, q, *J* 7.0 Hz), 2.24 (2 H, br s), 2.57 (1 H, m), 3.44 (2 H, m), 3.77 (2 H, s), 7.30 (5 H, m). Mass spectrum : m/z 179 (M^+ 1), 148 (31), 91 (100).

The amine was oxidised as described[5] using H_2O_2/SeO_2 in methanol to give the only nitrone **A** (63%) as colorless needles, m.p. 109-110 °C (ether) (Found : C, 68.2; H, 7.7 ; N, 7.2. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25 %); $\nu_{max.}$ (KBr) 3275, 3057, 2950, 2912, 1598, 1464, 1347, 1154, 1085, 906, 867, 793, 763, 750, and 697 cm^{-1};
δ_H 0.96 (3 H, t, *J* 7.0 Hz), 1.73 (1 H, m), 2.07 (1 H, m), 3.55 (1 H, br OH), 3.87 (1 H, m and 1 H, dd, *J* 3.0 , 11.5 Hz), 4.01 (1 H, dd, *J* 7.5, 11.5 Hz), 7.47 (4 H, m), 8.28 (2 H, m). Mass spectrum : m/z 193 (M^+ 24), 162 (76), 122 (100), 91 (38), 77 (66).$[\alpha]^{25}{}^{\circ}D$ = -24.0° (*c* 0.05, ethanol)

Entry 13 : Oxidation (HgO) of 2-phenyl-*N*-hydroxypiperidine was reexamined.[9,10a] The earlier report[10a] indicated the formation of the nonconjugated nitrone **A** as the exclusive product. However we found a mixture of the nitrones **A** and **B** in a ratio of 30 : 70, respectively, as determined by the ^1H nmr integration. The following ^1H nmr signals for the major nitrone **B** was deduced from the spectrum of the mixture. δ_H 1.32 - 2.16 (4 H, m), 2.66 (2 H , m), 3.89 (2 H , t, *J* 6.0 Hz), 7.28 (3 H, m), 7.96 (2 H, m). The broad triplet at δ 4.91 (*J* 6.0 Hz) was assigned to the benzylic proton of the minor nitrone **A**. The above nonseparable mixture of the nitrones (2.0 mmol) in CH_2Cl_2 (1 cm^3) was treated with methyl acrylate (0.8 mmol) at 20°C for 2 h. Under this condition the minor nitrone **A** reacted completly to give a mixture of cycloadducts which was seperated easily by chromatography (ether) . The polar nitrone **B** (colourless liquid 60%) was eluted with 2 : 1 ethyl acetate - methanol mixture .

The nitrone **B** was reduced with $NaBD_4$ in ethanol to give the C (2) Deuterohydroxylamine (**9**) in 85% yield. Oxidation of the hydroxylamine afforded a mixture of the nitrone (**10**) and (**11**) in a ratio of 90 : 10, respectively, as determined by the integration of the ortho aromatic protons at δ7.96 ppm and C (6) protons at δ3.89 ppm of (**11**) and the total integration for the aromatic and CH=N protons.

Entry 15 : A reexamination[9] of the oxidation of 2-phenyl-*N*- hydroxypyrrolidine revealed the formation of a mixture of the nitrones **A** and **B** in a respective ratio of 17 : 83. The following signals were assigned to the major nitrone **B** : δ_H 2.22 (2 H, app. quint, *J* 7.0 Hz), 3.18 (2 H, app. t, *J* 7.0 Hz), 4.25 (2 H, app. t, *J* 7.0 Hz), 7.50 (3 H, m), 8.40 (2 H, m) .
The minor signals at δ2.28 (2 H, overlapping, m), 2.79 (2 H, m), 5.08 (1 H, br t,*J* 6.0 Hz), 7.12 (1 H, m), 7.40 (5 H, m) were assigned to the minor isomer **A.**

Entry 16 : The hydroxylamine, prepared as described[10b] from its corresponding amine, on oxidation afforded the conjugated nitrone **A** as the sole product. The structure of **A** was identified by comparison of its spectroscopic data with those described in the literature.[15] The nmr spectrum failed to detect the minor isomer **B.**

Preparation and oxidation of *N*-benzyl-*N*-*t*-butylhydroxylamine (14) and *N*-dideuteriobenzyl-*N*-*t*-butylhydroxylamine (13).

Condensation of *t*-butylhydroxylamine (0.890 g , 10.0 mmol) and benzaldehyde (1.06 g , 10.0 mmol) in ethanol (5 cm^3) at 80°C for 5 h afforded the nitrone **15** in 90 % yield. The spectroscopic data (δ_H 1.58 (9 H , s), 7.42 (3 H, m) , 7.49 (1 H, s) , 8.34 (2 H , m)) and m.p. (74-75°C; lit. 74-75°C) for the nitrone matched with those reported in the literature. [6,16] The above nitrone was reduced as usual with the excess $NaBH_4$ in ethanol (20°C, 12 h and 60°C, 4 h). The resulting product was purified by chromatography using 10 : 1 hexane-ether as eluent to give the hydroxylamine **14** (77% yield) as colorless needles , mp. 70-71 °C (hexane) (Found C, 7.38; H, 9.4 ; N, 7.8 . $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56 ; N, 7.82 %); ν_{max}. (KBr) 3400, 3162, 3125, 2976, 2924, 1496, 1455, 1437, 1365, 1234, 1210, 1070, 1031, 927, 826, 727 and 697 cm^{-1}; δ_H 1.17 (9 H , s) , 3.70 (2 H, s) , 4.50 (1 H , br, OH) , 7.25 (5 H, m)

Deuteriobenzaldehyde (PhCDO) was prepared by usual reduction of benzil (**12**) with $NaBD_4$ followed by treatment of the resulting diol, hydrobenzoin, with $NaIO_4$ in ethanol at 20 °C. The overall yield of the two steps was 80%. As described above the condensation of the PhCDO with *t*-butylhydroxylamine afforded the nitrone (**16**) as colorless needles , m.p. 73 - 74 °C (Found : C , 74.1; H, 9.0 ; N, 7.7. $C_{11}H_{14}DNO$ requires C, 74.12 ; H, 9.04 ; N, 7.86 %); ν_{max}.(KBr) 3060, 2975, 2925, 2294, 1553, 1481, 1446, 1323, 1308, 1237, 1195, 1154, 957, 891, 778, and 703 cm^{-1}; δ_H 1.58 (9 H, s), 7.42 (3 H, m), 8.34 (2 H, m). Mass spectrum : m/z 178 (M^+ 57), 122 (31), 90 (38), 77 (31), 57 (100)
The nitrone (**16**) on reduction with $NaBD_4$ gave the dideuteriohydroxylamine (**13**) as colorless needles, m.p. 69 - 70 °C (hexane) (Found : C, 72.6; H, 10.5; N 7.7. $C_{11}H_{15}D_2NO$ requires C, 72.88 ; H, 10.56 ; N 7.73); ν_{max} . (KBr) 3400, 3075, 2976, 2225 (W) 1452, 1370, 1359, 1288, 1213, 1076, 1025, 724, and 697 cm^{-1}; δ_H 1.17 (9 H, s) 4.55 (1 H, br OH), 7.25 (5 H, m). Mass spectrum : m/z 181 (M^+ 21), 97 (100), 57 (100).

To a solution of the hydroxylamines (**14**) (85.0 mg, 0.474 mmol) and (**13**) (164 mg, 0.915 mmol) in $CDCl_3$ (5 cm^3) at 0°C was added yellow HgO (0.60 mmol) in five portions over a period of 50 min. The reaction mixture was stirred for an additional period of 30 min. The proton nmr spectrum revealed the

presence of starting material and the nitrones. Using integration of several proton signals the amounts of various compounds were quantified as described in the results and discussion.

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