Cycloaddition reactions of 5,6-dihydro-1,3,2-oxazine 3-oxide and conformational analysis of the resultant bicyclic isoxazolidines

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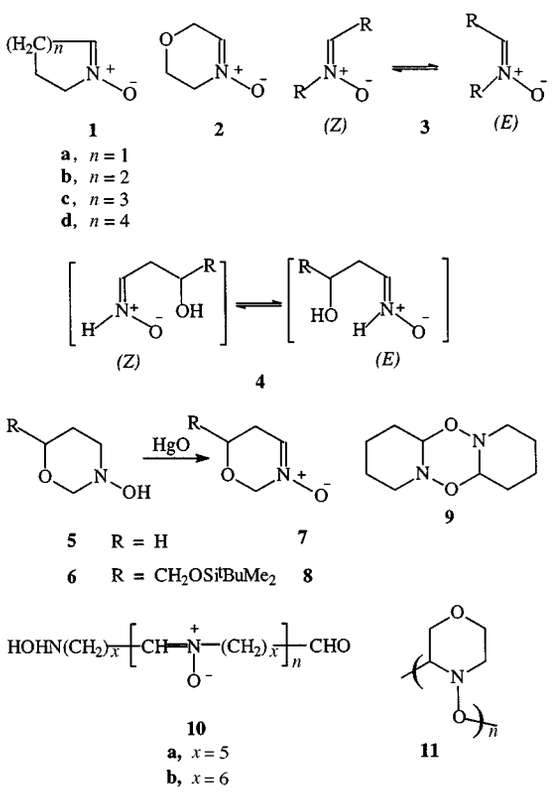
The rate constants for several addition reactions of a heterocyclic nitrone, 5,6-dihydro-1,3,2-oxazine 3-oxide (**7**), have been determined by a ^{1}H NMR technique. The heterocyclic nitrone is found to be as reactive as its carbocyclic counterparts. The nitrone underwent regio- and stereo-selective cycloaddition reaction with several alkenes to afford bicyclic isoxazolidines efficiently. The NMR studies showed that the isoxazolidines prefer the conformer with *cis* ring fusion having an equatorially oriented nitrogen lone pair capable of manifesting an *endo* anomeric effect.

Among a plethora of functional groups the nitrone functionality has etched an important place in organic synthesis.[1] Remarkable regio- and stereo-selectivity along with efficient incorporation of multiple stereocenters have made nitrone cycloaddition an attractive key step in the synthesis of a great many natural products of biological interest.[2] The 1,3-dipolar cycloadditions of the carbocyclic nitrones[3] **1** and heterocyclic nitrone **2**[4] with a variety of alkenes have been studied in some detail (Scheme 1). The cyclic nitrones, where geometric



Scheme 1

constraints do not permit $E \rightleftharpoons Z$ isomerization, undergo addition reaction with greater stereoselectivity and reactivity[5] than their acyclic counterparts **3**. Not only do these acyclic nitrones react very slowly, but the $E \rightleftharpoons Z$ isomerization often complicates the stereochemical outcome of the cycloadditions. Our synthetic plans often demand the synthetic equivalent of a hypothetical acyclic nitrone (*E*)-**4** in cyclic form (**7**, **8**) which would enjoy all the advantages associated with the cyclic nitrones. The cycloaddition products of such nitrones could be easily hydrolyzed to acyclic products thus imparting more versatility to this synthetically important nitrone functionality. Herein we describe, for the first time, the reactivity and stereochemistry of cycloaddition reactions of the heterocyclic nitrones **7** and **8**, prepared regiospecifically by mercury(II) oxide oxidation of the corresponding hydroxylamines **5** and **6** (Scheme 1). These nitrones can be considered as the synthetic equivalent of the acyclic nitrone (*E*)-**4** in cyclic form. We have also studied, using NMR spectroscopy, the influence of the anomeric effect in controlling the conformational behavior of the bicyclic addition products.

Results and discussion

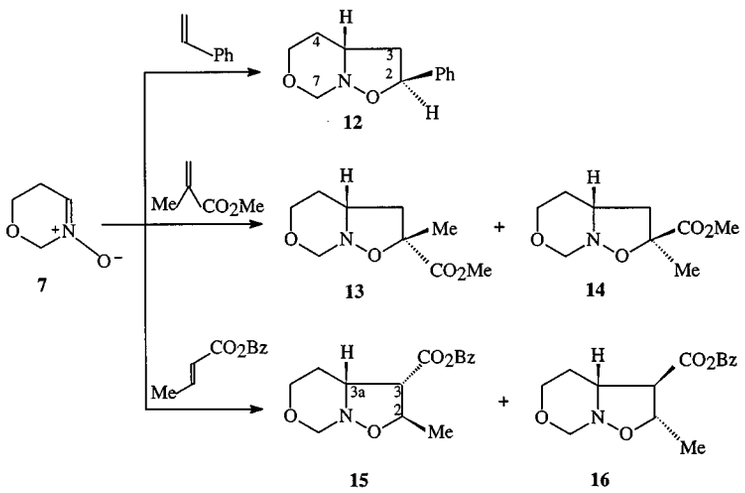
The behavior of concentrated solutions of the nitrones **1**, **2** is quite puzzling. While the nitrone **1a** is stable, the nitrone **1b** dimerizes to **9** and the nitrones **1c**, **1d** and **2** polymerize to **10a**,**b**[3c,d,6] and **11**,[4,7] respectively (Scheme 1).

Our recent work,[8] involving the regiospecific formation of the new heterocyclic nitrones **7** and **8** by mercury(II) oxide oxidation of the cyclic hydroxylamines **5** and **6**, paved the way for the present investigation. A concentrated solution (0.5 M) of the nitrone **7** in $CDCl_3$ at room temperature afforded an intractable mixture of polymeric materials displaying ^{1}H signals in the entire range of 1–8 ppm. The nitrone **7**, after stripping off the solvent, was converted to a white solid in powder form. We are unable at this stage to identify the precise nature of the polymeric material. The substituted nitrone **8**, on the other hand, remained stable either in the solution or in the absence of the solvent. A solution of the nitrone **7**, in the concentration range of 0.2–0.3 M in $CDCl_3$, can be kept in the freezer; the ^{1}H NMR spectrum remained virtually unchanged even after a week. For the efficient utilization of the cyclic nitrone **7**, it was imperative to study the kinetics of its cycloaddition reactions. In order to avoid polymerization, the kinetic runs were carried out using higher concentrations of the alkenes and keeping the molarity of the nitrone around 0.2 M.

The kinetic results obtained for the cycloaddition of the nitrone **7** with three different alkenes in $CDCl_3$ are shown in Table 1. The cycloadditions were monitored at different temperatures by the disappearance of ^{1}H NMR signals of 2-H of the nitrone and olefinic protons of the alkenes. These signals in

Table 1 Rate constants and activation parameters for cycloaddition reactions of nitrone **7** in $CDCl_3$

Alkene	Temp./°C	$k_2/10^{-5}$ dm^3 mol^{-1} s^{-1}	E_a/kJ mol^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta G^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
	16.5	36.3				
Methyl methacrylate	26.0	62.3				
	36.0	106	41.02	38.5	93.3	−177.4
	41.0	138				
Methyl acrylate	26.0	154				
Dimethyl maleate	26.0	45.2				

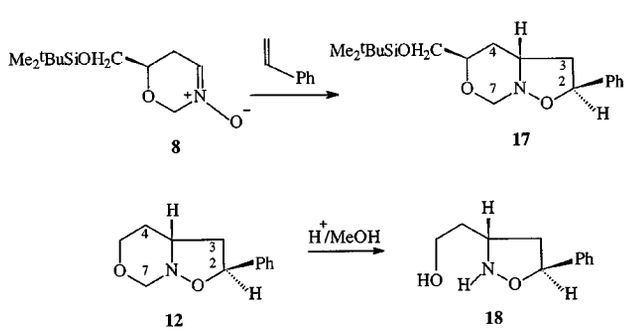


Scheme 2

the NMR spectra were free of any overlapping signals. The ratio of the concentration of the nitrone and the alkene was determined from time to time and the second order rate constants were obtained by linear regression analysis. The cycloadditions were performed under mild kinetic-controlled conditions in order to make sure that the cycloadducts did not revert to the starting materials in a manner resembling retro-Diels–Alder reactions. The cycloaddition product, nitrone and alkenes are all stable under the reaction conditions and no products other than the normal cycloadducts were obtained. The second order rate constant (k_2) for the nitrone–methyl methacrylate addition reaction in $CDCl_3$ at 36 °C was determined to be 106×10^{-5} dm^3 mol^{-1} s^{-1}; the nitrone **7** is found to be as reactive[9] as **1b** but less reactive[4] than **2** ($k_2 = 453 \times 10^5$ dm^3 mol^{-1} s^{-1}). With methyl acrylate the ratio of the rate constants for the addition reaction of the nitrone **1b** and **7** was found to be 1.22:1, respectively. In general the heterocyclic nitrone **7** is slightly less reactive than **1b** but more reactive than the five-membered nitrone **1a**.[5c] Low activation energies and large negative entropies of activation reflect the concerted nature of the multicentered cycloaddition reactions. It is evident from Table 1 that methyl acrylate is the most reactive among the three alkenes studied. Steric factors play an important role in deciding the rate of addition reactions. A crowded transition state with *cis* disposition of the methoxycarbonyl groups makes dimethyl maleate the least reactive.

Next we focused our attention on the stereo- and regiochemistry of the cycloaddition reactions. The nitrone **7** underwent stereoselective addition to styrene ($CHCl_3$, 50 °C, 3 h) *via* an *exo*-mode of approach[3a–c] of the alkene to give the adduct **12** (70%) (Scheme 2). However addition of **7** to methyl methacrylate gave cycloadducts **13** and **14** (72%) in a ratio of 95:5, respectively. The major adduct was assigned the stereochemistry depicted in **13** with an *endo*-oriented methoxycarbonyl group. There are ample literature precedents[3a,10] which describe the methoxycarbonyl group's ability to manifest favorable secondary orbital interaction in an *endo*-oriented transition state. The reaction with benzyl crotonate ($CHCl_3$, 60 °C, 2 h) afforded a mixture of the stereoisomers **15** and **16** (~70%) in a respective ratio of 85:15. It is interesting to note that the major adduct **15** has the correct relative stereochemistry (at C_2, C_3, C_{3a}) and functionality for possible conversion to thienamycin antibiotics.[11] The stereochemistry of the major adduct, depicted in **15** with an *endo*-oriented methoxycarbonyl group, is based on precedent literature[3a,10] on nitrone–crotonate addition reactions.

The addition reactions with all three alkenes were found to be regiospecific. The substituted cyclic nitrone **8** underwent addition reaction with styrene to give a single adduct **17** demonstrating the nitrone's ability to manifest face selectivity (Scheme 3). The stereochemistry as depicted is based on the

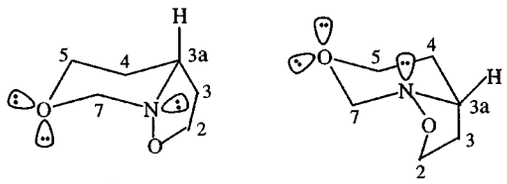


Scheme 3

reasonable assumption that the alkene would approach the nitrone from its least hindered face. Finally the cycloadduct **12** was taken as a test case and when hydrolyzed with perchloric acid[12] in methanol (55 °C, 48 h), the adduct was hydrolyzed as expected with the cleavage of the six-membered ring to the acyclic product **18**. Access to the hydrolyzed adduct **18** from **12** demonstrates the synthetic potential of this new class of nitrones in serving as the synthetic equivalent of the hypothetical nitrone (*E*)-**4**. The ring opening reactions of other cycloadducts, and possible conversion to the natural products are under study in our laboratory.

Finally we focused our attention on the conformational

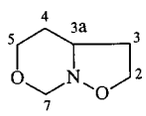
Table 2 Vicinal and geminal coupling constants (Hz) in the six-membered ring in the cycloadducts



B **C**

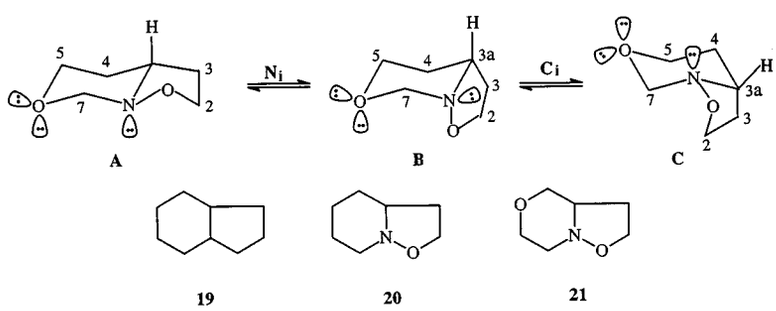
Compound	$3a_{ax}$ 4a	$3a_{ax}$ 4e	$3a_{eq}$ 4a	$3a_{eq}$ 4e	4a 4e	4a 5a	4a 5e	4e 5a	4e 5e	5a 5e	7a 7e
12	11.9	4.7	—	—	13.6	12.5	4.7	2.3	2.3	11.6	12.5
13	11.0	4.5		—	12.3	11.6	4.5	1.5	3.4	11.3	12.4
15	11.6	4.3	—	—	13.5	11.8	4.9	2.2	4.6	11.6	12.5
17	—	—	3.9	2.9	14.3	10.0	—	3.8	—	—	9.9

Table 3 ^{13}C NMR chemical shifts[a] of the cycloadducts in $CDCl_3$ at 23 °C



Compound	C-2	C-3	C-3a	C-4	C-5	C-7	Others[b]
12	77.40	44.64	56.43	25.56	65.30	80.35	^{i}143.91, ^{o}127.23, ^{m}125.60, ^{p}128.45
13	81.63	46.34	56.38	26.19	65.29	80.15	Me 25.81, Me 52.73, CO 173.59
15	73.50	59.13	58.24	22.59	66.82	80.27	Me 21.63, CH_2 64.97, CO 169.32, ^{i}135.31, ^{o}128.53, ^{m}128.41, ^{p}128.64
17	79.17	40.25	56.54	26.03	71.15	80.15	$SiMe_2$ −5.38, CH_2 65.27, SiC 18.48, 3-Me 25.85, ^{i}141.35, ^{o}127.81, ^{m}126.26, ^{p}128.50

[a] In ppm relative to internal TMS. [b] *i*, *o*, *p* and *m* refer to *ipso*, *ortho*, *para* and *meta* carbons of the phenyl group respectively.



A **B** **C**

19 **20** **21**

Scheme 4

analysis of the cycloadducts. The bicyclic isoxazolidines, *i.e.*, the cycloaddition products, can in principle exist in three different conformations as depicted in Scheme 4: the *trans* conformer **A** and the *cis* pair **B** and **C**. While the *cis* pair is in rapid equilibrium by chair inversion ($\mathbf{C_i}$), one of the *cis* conformers, **B**, is converted into the *trans* conformer **A** by a relatively slow nitrogen inversion process ($\mathbf{N_i}$). For the carbocyclic counterpart **19** (hydrindane), the ΔG value of around 1.06 kJ mol^{-1} at 25 °C favors the *trans* isomer.[13] For the bicyclic systems **20** and **21**, the stereochemistry of the preferred conformer was shown to have *trans* (type **A**) and *cis* (type **B**) ring junctions, respectively. For the compounds **20** and **21** the ratio of the *trans* and *cis* invertomers[14] was found to be 76:24 and 14:86, respectively, at −50 °C. Unlike the isoxazolidines **20** and **21**, the cycloadducts in the present study gave sharp spectral lines in the ^1H and ^{13}C NMR spectra recorded at ambient temperatures. On lowering the temperature to −95 °C (CD_2Cl_2) the NMR spectra remained virtually identical, indicating the presence of one conformer only. In order to identify the exclusive conformer, several decoupling experiments were performed to obtain ^2J and ^3J values and are given in Table 2. ^{13}C NMR chemical shifts (Table 3) were assigned on the basis of general chemical shifts arguments and consideration of substituent effects. The chemical shifts were also confirmed by COSY and Heterocorrelated ^1H–^{13}C 2D NMR spectroscopy. Typical reversal of chemical shifts of protons at C5 (the equatorial proton resonates at higher field than the axial proton) of tetrahydro-1,3-oxazines[15] is also observed for the compounds under discussion (the numbering system makes this C4 in the present bicyclic isoxazolidines). A large coupling constant of 11–11.9 Hz (J_{3a-4a}) indicates the axial nature of the bridgehead proton. Inspection of molecular models revealed that the C3a–H and C3–H_α form a dihedral angle of *ca*. 90° in the conformer **B** and the observed coupling constant of 1.6 Hz for these protons (in compound **13**) strongly suggests the absence of the isomers **A** and **C** in the conformational equilibria. In a series of tetrahydro-1,3-oxazine derivatives it has been established[15] that the conformer with a large geminal coupling constant of around 11 Hz for the O–CH_2–N protons has an equatorial lone pair on nitrogen and the axial proton resonates at lower field than the equatorial proton. A coupling constant value of ~7.5 Hz for the geminal protons indicates the opposite orientation of the lone pair. The geminal coupling constant, J_{7a7e}, of 12.5 Hz, observed in our study, confirms the presence of the isomer **B** with axially oriented substituent on nitrogen. The NMR spectra of the compounds **20** and **21** show the presence of two invertomers even at ambient temperature; an electronegative oxygen directly attached to nitrogen is known to raise the nitrogen inversion barrier.[16] As

far as the NMR detection limit is concerned, the NMR spectra (^{1}H and ^{13}C) revealed the absence of the *trans* isomer **A** in the temperature range of +25 to −90 °C for the isoxazolidines **12**, **13** and **15**. Such a strong preference for the conformer **B** can be attributed to anomeric[17] stabilization owing to the antiperiplanar n–σ* interaction involving the equatorial nitrogen lone pair with the antibonding orbital of the C(7)–O bond. In all three conformers the antiperiplanar arrangement of the equatorially disposed lone pair on the oxygen and the C–N bond can also manifest an anomeric effect, but this effect is weak since the C–N bond is a weaker acceptor and oxygen a weaker donor.

Inspection of various coupling constants in Table 2 clearly indicates that the bicyclic isoxazolidines **12**, **13** and **15** remain in the stable form **B** exclusively. However the situation is changed in the adduct **17** where there is a substituent at C(5). Analysis of the coupling constant values reveals the equatorial nature of the bridgehead proton C(3a)–H and C(5) hydrogen. The decreased value of the geminal coupling constant of 9.9 Hz for the C(7) protons also indicate the axial nature of the nitrogen lone pair. These coupling constants are somewhat larger than the suggested value of ~7.5 Hz for the axially oriented nitrogen lone pair. The axial nature of C5–H is indicated by a large coupling constant value of 10.0 Hz ($J_{4a,5a}$) (Table 2). Thus for the compound **17** the conformer **C** becomes the preferred isomer, even though it may be in rapid equilibrium with the minor form **B** by chair inversion. However we were unable to detect the presence of any minor conformer **B** even at −95 °C where the chair inversion is expected to be slowed down enough on the NMR time scale for its detection. The upfield chemical shift of C(3) of **17** by about 4.4 ppm compared to that of the compound **12** also suggests its crowded axial orientation (Table 3). The preference for the conformer **C** is attributed to the energetically favorable equatorial orientation of the C(5) substituent which must occupy the axial position in conformer **B**. The NOESY and the NOE spectra substantiated the findings of the conformational analysis based on observed coupling constants. The ^{1}H NMR spectrum of the adduct **17** revealed a doublet of doublets at δ 5.41 which was assigned to the C2–H. The C7–H_{ax} and C7–H_{eq} appeared at chemical shifts of δ 4.46 and 4.78, respectively. The ^{1}H-2D NOESY spectrum displayed a cross peak between the signals of the C2–H and C7–H_{ax}. When the C2–H was irradiated, NOE was observed at C7–H_{ax} indicating the proximity of these two protons; this proximity is only possible in the conformation **C**. We did not observe any cross peak or NOE between the C2–H and C7–H of the adducts **12**, **13** and **15**, thereby substantiating the presence of the conformer **B** for these adducts. Inspection of molecular models revealed the closeness of the C2–H and C4–H_{ax} in the conformer **B**. This is indeed demonstrated by the irradiation of the C2–H signal of the adduct **12**; the NOE, observed at the C4–H_{ax}, substantiates the absence of the conformer **A**.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Nicolet 5 DBX FT IR instrument and are reported in wave numbers (cm^{-1}). The kinetic study was done using a Varian XL-200 instrument. The ^{1}H and ^{13}C spectra were recorded on Jeol Lambda 500 NMR spectrometers, using deuterochloroform as solvent and TMS as internal standard. Chemical shifts are given in ppm and *J* values in Hz. Mass spectra at 70 eV E.I. were recorded on a Ribermag GC–MS system, R-10-10, with a quadrupole mass filter and a Riber 400 acquisition system. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analyzer. Cycloaddition 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.

General procedure for the formation of cyclic nitrones

To a solution of the cyclic hydroxylamine (**5** or **6**) (15 mmol) in alumina-dried chloroform (100 cm^3) was added HgO (50 mmol) at 0 °C. The reaction mixture was then stirred at 0 °C for 1 h, and at 25 °C for 2–3 h until a TLC (silica, 1:1 methanol–ether) experiment indicated complete formation of the nitrone (**7** or **8**). The reaction mixture was then filtered through a bed of $MgSO_4$ and washed with a liberal excess of chloroform. The formation of the nitrone was assumed quantitative in the subsequent yield calculation of the cycloaddition reactions. For the kinetic runs, the nitrone **7** was prepared by HgO (6.0 mmol) oxidation of the hydroxylamine **5** (2.0 mmol) in $CDCl_3$ (10 cm^3). δ_H ($CDCl_3$ + 25 °C) 2.65 (2 H, m), 4.00 (2 H, t, *J* 5.8), 4.98 (2 H, A_2 with fine allylic splitting), 7.30 (1 H, m).

The concentration of the nitrone's stock solution was around 0.2 M in $CDCl_3$. It was kept in the refrigerator whenever not in use. Unlike the nitrone **7**, the NMR spectrum of a 0.2 M solution of the nitrone **8** revealed that the nitrone remained stable and did not polymerize with time.

Kinetics of cycloaddition reaction

Kinetic runs in $CDCl_3$ were studied by NMR as described previously.[9] The ratio of the concentration of the reactants was determined from time to time by integration of the signals due to 2-H of the nitrone and the olefinic proton of the alkene. The second order rate constant was determined by linear regression analysis of the data and was reproducible within 2–5%. The additions were followed up to 60–80% of the chemical conversion. The initial concentrations, written in parentheses, of the nitrone **7** and alkenes for the kinetic runs were as follows: nitrone (0.200 M)–methyl acrylate (0.510 M); nitrone (0.194 M)–methyl methacrylate (0.602 M); nitrone (0.208 M)–dimethyl maleate (0.502 M).

Cycloaddition reaction of the nitrone 7 with styrene

A solution of the nitrone **7** (1.0 mmol) and styrene (1.5 cm^3) in chloroform (15 cm^3) was stirred at 50 °C for 3 h or until a TLC (silica, ether–methanol, 2:1) experiment indicated the absence of the nitrone. After removal of the solvent and excess alkene the residual liquid was purified by chromatography using 3:1 hexane–ether as the eluant to give the cycloadduct *2-phenylperhydro-1,2-oxazolo[2,3-c][1,3]oxazine* (**12**) as a colorless liquid (144 mg, 70%). The NMR spectrum did not reveal the presence of any other isomeric adduct (Found: C, 70.2; H, 7.2; N, 6.8. $C_{12}H_{15}NO_2$ requires: C, 70.22; H, 7.37; N, 6.83%); ν_{max} (neat) 3062, 3026, 2954, 1724, 1604, 1494, 1450, 1430, 1386, 1360, 1282, 1260, 1224, 1104, 1090, 1074, 1044, 996, 968, 930, 878, 758 and 760 cm^{-1}; δ_H 1.45 (1 H, d, *J* 13.6 and each signal is split into a triplet of doublets, *J* 2.3, 4.6, C4–H_{eq}), 2.06 (1 H, dq, *J* 4.7, 12.6, C4–H_{ax}), 2.48 (2 H, m, C3–H_2), 3.60 (1 H, m, C3a–H_{ax}), 3.63 (1 H, dt, *J* 2.3, 11.9, C5–H_{ax}), 4.06 (1 H, dd, *J* 4.4, 11.6, C5–H_{eq}), 4.56 (1 H, d, *J* 12.5, C7–H_{eq}), 5.01 (1 H, d, *J* 12.5, C7–H_{ax}), 5.27 (1 H, t, *J* 7.5, C2–H), 7.24 (1 H, t, *J* 7.4), 7.33 (1 H, t, *J* 8.0), 7.39 (1 H, d, *J* 7.6); *m/z* 205 (M^+ 77.6%). At −35 and −50 °C the spectra remain virtually identical.

Cycloaddition reaction of the nitrone 7 with methyl methacrylate

A solution of the nitrone **7** (1.0 mmol) and methyl methacrylate (0.5 cm^3) in chloroform (15 cm^3) was stirred at 20 °C for 2 h or until a TLC (silica, ether–methanol, 2:1) experiment indicated consumption of the nitrone. After removal of the solvent and excess alkene the residual liquid was purified by chromatography using 3:1 hexane–ether to afford the cycloadduct *methyl 2-methylperhydro-1,2-oxazolo[2,3-c][1,3]oxazine-2-carboxylate* **13** and **14** as a colorless liquid (145 mg, 72%). The NMR spectrum revealed the presence of minor isomer **14** to the extent of 5%. An analytical sample of the adduct was obtained upon crystallization as colorless needles, mp 39–40 °C (ether–

hexane) (Found: C, 53.7; H, 7.4; N, 6.8. $C_9H_{15}NO_4$ requires: C, 53.72; H, 7.51; N, 6.96%); ν_{max} (neat) 2958, 2846, 1732, 1434, 1388, 1366, 1308, 1256, 1228, 1206, 1144, 1088, 1074, 1034, 970 and 880 cm^{-1}; δ_H ($CDCl_3$ + 25 °C) 1.34 (1 H, br d, *J* 12.8, C4–H_{eq}; at −30 °C it appeared as tdd, *J* 2.4, 4.5, 13.7), 1.56 (3 H, s), 2.02 (1 H, dq, *J* 4.5, 11.6, C4–H_{ax}), 2.35 (1 H, dd, *J* 7.1, 12.6, C3–H_β), 2.50 (1 H, dd, *J* 1.6, 12.6, C3–H_α), 3.51 (1 H, app quint, *J* 5.5, C3a–H), 3.58 (1 H, dt, *J* 1.5, 11.6, C5–H_{ax}), 3.80 (3 H, s), 3.99 (1 H, dd, *J* 3.4, 11.3, C5–H_{eq}), 4.52 (1 H, d, *J* 12.4, C7–H_{eq}), 4.92 (1 H, d, *J* 12.4, C7–H_{ax}). A non-overlapping peak for the minor isomer was present at δ 1.70 (3 H, s); *m/z* 201 (M^+, 69%).

Cycloaddition reaction of the nitrone 7 with benzyl crotonate

A solution of the nitrone **7** (10.0 mmol) and benzyl crotonate (40.0 mmol) in chloroform (150 cm^3) was stirred at 60 °C for 24 h or until a TLC (silica, ether–methanol, 2:1) experiment indicated the absence of the nitrone. Removal of the solvent followed by purification of the residual liquid by chromatography using 2:1 hexane–ether as the eluant afforded a non-separable mixture of the cycloadducts *benzyl 2-methylperhydro-1,2-oxazolo[2,3-c][1,3]oxazine-3-carboxylate* **15** and **16** as a colorless liquid (1.90 g, 68.5%) in a respective ratio of 85:15 as determined by the integration of the proton NMR signals (Found: C, 64.9; H, 6.8; N, 5.0. $C_{15}H_{19}NO_4$ requires: C, 64.96; H, 6.91; N, 5.05%); ν_{max} (neat) 3064, 3032, 2968, 2828, 2890, 2844, 2760, 1736, 1586, 1498, 1456, 1386, 1342, 1260, 1186, 1086, 1062, 1030, 978, 922, 800, 750 and 700 cm^{-1}; Major isomer **15**: δ_H 1.18 (1 H, br d, *J* 13.5, C4–H_{eq}), 1.36 (3 H, d, *J* 6.1), 1.96 (1 H, dq, *J* 4.9, 12.5, C4–H_{ax}), 3.29 (1 H, t, *J* 6.8, C3–H_β), 3.52 (1 H, dt, *J* 2.2, 12.4, C5–H_{ax}), 3.71 (1 H, app td, *J* 5.5, 11.3, C3a–H_{ax}), 3.99 (1 H, dd, *J* 4.6, 11.6, C5–H_{eq}), 4.47 (1 H, d, *J* 12.5, C7–H_{eq}), 4.68 (1 H, quint, *J* 6.4, C2–H_α), 4.83 (1 H, d, *J* 12.5, C7–H_{ax}), 5.13 (1 H, d, *J* 12.2, CH-Ph), 5.17 (1 H, d, *J* 12.2, CH-Ph), 7.35 (5 H, m). Minor isomer **16**: δ_H 1.28 (1 H, m), 1.48 (3 H, d, *J* 6.1), 2.20 (1 H, m), 3.66 (1 H, m), 3.86 (1 H, m), 4.25 (1 H, m), 4.40 (1 H, d, *J* 12.8), 4.93 (1 H, d, *J* 12.8); *m/z* 277 (M^+ 9.1%).

Cycloaddition reaction of the nitrone 8 with styrene

A solution of the nitrone **8** (1.0 mmol) and styrene (1.5 cm^3) in chloroform (15 cm^3) was stirred at 50 °C for 3 h or until a TLC (silica, ether–methanol, 2:1) experiment indicated the absence of the nitrone. Removal of the solvent and excess alkene followed by purification by chromatography using 3:1 hexane–ether as the eluant afforded the cycloadduct *5-tert-butyldimethylsiloxymethyl-2-phenylperhydro-1,2-oxazolo[2,3-c]-[1,3]oxazine* **17** as a colorless liquid (247 mg, 70%). The NMR spectrum did not reveal the presence of any other isomeric adduct (Found: C, 65.3; H, 8.9; N, 3.9. $C_{19}H_{31}NO_3Si$ requires: C, 65.29; H, 8.94; N, 4.00%); ν_{max} (neat) 3018, 2950, 2856, 2360, 1460, 1350, 1254, 1188, 1096, 964, 844, 744 and 704 cm^{-1}. δ_H 0.08 (6 H, s), 0.90 (9 H, s), 1.90 (1 H, td, *J* 4.0, 14.3, C4–H_{eq}), 2.06 (1 H, ddd, *J*, 5.1, 10.0, 14.3, C4–H_{ax}), 2.30 (1 H, ddd, *J* 5.8, 8.0, 12.5, C3–H), 2.75 (1 H, ddd, (app td) *J* 7.6, 8.5, 12.5, C3–H), 3.72 (2 H, ABX, J_{AB} 10.7, J_{AX} 5.2, J_{BX} 5.2, CH_2OSi), 3.90 (1 H, app hex, *J* 4.9, C5–H_{ax}), 4.00 (1 H, m, C3a–H_{eq}), 4.46 (1 H, d, *J* 9.9, C7–H_{ax}), 4.78 (1 H, d, *J* 9.9, C7–H_{eq}), 5.41 (1 H, dd, *J* 5.8, 8.5, C2–H), 7.35 (5 H, m); *m/z* 349 (M^+ 5.3%).

Ring opening reaction of cycloadduct 12 with perchloric acid

To a solution of the cycloadduct **12** (75 mg, 0.37 mmol) in methanol (3 cm^3) was added $HClO_4$ (52.7 mg, 0.53 mmol) and the mixture was heated at 50–55 °C for 48 h. Workup was done by adding saturated K_2CO_3 solution (15 cm^3). The product was extracted from the aqueous layer with CH_2Cl_2 (3 × 10 cm^3). The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography using CH_2Cl_2–MeOH (4:1) as the eluant to give **18** as a colorless liquid (55 mg, 77%) (Found: C, 68.3; H, 7.8; N, 7.1. $C_{11}H_{15}NO_2$ requires: C, 68.36; H, 7.82; N, 7.25%); ν_{max} (neat) 3293, 3063, 3026, 2934, 2869, 1956, 1886, 1814, 1710, 1604, 1494, 1450, 1366, 1056, 876, 758 and 702 cm^{-1}; *m/z* 193 (M^+ 19.6%); δ_H 1.84 (2 H, m, C3–CH_2), 2.37 (1 H, ddd, *J* 5.6, 8.4, 12.6, C4–H), 2.44 (1 H, ddd, *J* 5.6, 7.5, 12.6, C4–H), 3.70 (1 H, m, C3–H), 3.80 (2 H, m, CH_2O), 5.17 (1 H, dd, *J* 5.7, 8.2, C5–H), 7.35 (5 H, m, Ph).

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