Tetrahedron Vol. 44, No. 18, pp. 5911 to 5920, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00
Pergamon Press plc

THE REGIOCHEMISTRY AND STEREOCHEMISTRY OF 1,3-DIPOLAR CYCLOADDITION OF CYCLIC NITRONES

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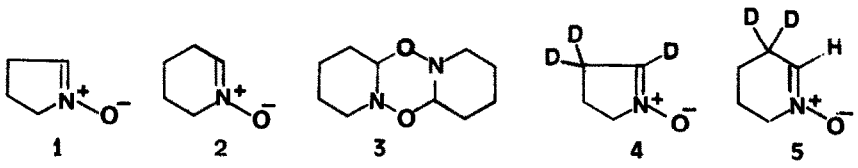
(*Received in UK* 28 *June* 1988)

Abstract: A comparative study of the regio- and stereo-chemical behaviour of the 1,3-dipolar cycloaddition of a series of alkenes with 1-pyrroline 1-oxide and 2,3,4,5-tetrahydropyridine 1-oxide has been carried out. The high degree of both regio- and stereo-chemical control observed in these reactions has been explained in terms of frontier orbital interaction, steric factors, and secondary orbital interaction in the transition state. While most common alkenes (both mono- and 1,1-di-substituted) gave 2-substituted cycloadducts, highly polarized alkene dimethyl methylenemalonate afforded mainly regioisomeric 3-substituted cycloadduct. Significant secondary orbital interaction is observed with the non-conjugated substituents, hydroxymethyl and its derivatives.

INTRODUCTION

Among a plethora of functional groups, nitrone functionality has eched an important place in organic chemistry.[1] This was possible largely owing to the brilliant efforts of Huisgen[2,3] and LeBel[4] who explored systematically the inter- and intra-molecular 1,3-dipolar cycloadditions, respectively. Even though the nitrone functionality was known in the last century, pioneering applications of the nitrone cycloaddition in the synthesis of natural product has been made only relatively recently by Tufariello.[5] Since then both inter- and intra-molecular additions involving nitrones and alkenes have culminated in the synthesis of several interesting alkaloidal and non-alkaloidal natural products.[6] Although the regiochemical aspects of nitrone cycloadditions have been explored in detail, the progress in the study of stereochemical details has been hampered in most cases because of the difficulties associated with unambiguous assignment of adduct configurations.[7-10]

Among the nitrones, 1-pyrroline 1-oxide (1) and 2,3,4,5-tetrahydropyridine 1-oxide (2) have emerged as the most important cyclic nitrones, since their addition reactions incorporate and elaborate pyrrolidine and piperidine moieties which are widespread in nature. These two cyclic nitrones behave quite differently in several aspects of their chemistry. While the nitrone 2 dimerizes on standing to give 3,[11] no such dimerization is observed for nitrone 1. The olefinic proton in the nitrone 1 is acidic enough to be exchanged with deuterium to give 4. However, similar treatment with NaOD-D_2O fails to exchange the olefinic proton in 2; deuterated nitrone 5 is obtained instead. Reactivities of these cyclic nitrones also depend on their ring size. While the cyclic nitrones, in general, react faster than their acyclic counterpart, the six membered nitrone 2 is found to undergo cycloaddition quite faster than the five membered nitrone 1.[10,12]

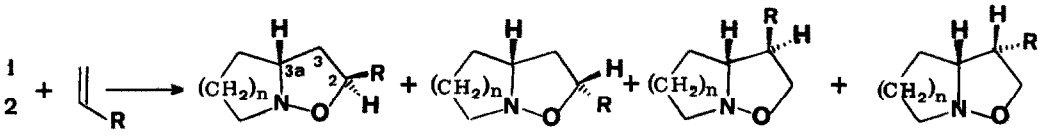


1 2 3 4 5

In light of these differences and the importance of these cyclic nitrones in synthesis of natural products we undertook a systematic study of the cycloaddition of the nitrone 1 with several alkenes and compared the results with that of the nitrone 2 cycloadditions.

RESULTS AND DISCUSSION

Initially, we chose to investigate the addition of the nitrone 1 onto several monosubstituted alkenes. The reactions were carried out under condition that would reflect kinetic rather than thermodynamic factors. The regio- and stereo-chemical details of these additions along with reaction temperature, solvent, isolated yield, and composition of isomeric cycloadducts are given in Table 1. For the purpose of comparison the corresponding results reported[9] for the cycloaddition of the nitrone 2 is also included in the Table 1.

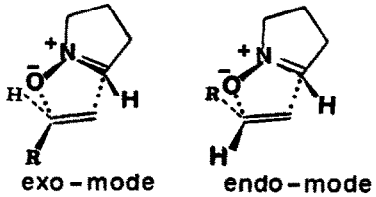


n=1; 6 7 8 9

n=2; 10 11 12 13

a; R = OEt; b; R = CH_2OH; c; R = $CH_2OSiBu^t(CH_3)_2$ d; R = CH_2OAc;

e; R = Ph; f; R = CO_2CH_3; g; R = CN; h; R = CHO.



exo-mode endo-mode

The addition of ethyl vinyl ether,[12] allyl acetate, and styrene with both the cyclic nitrones are found to be regiospecific. Only 2-substituted adducts 6 and 7 (in the addition of nitrone 1) and 10 and 11 (in the case of the nitrone 2) were obtained. While the configuration of most of the adducts 10 and 11 were unequivocally confirmed by their conversions into natural products[7,9] of known stereochemistry the configuration of the major adducts in the addition of the nitrone 1 is assumed to have the exo orientation of the C(2) substituent obtained via favourable exo- mode of attack. The compositions of the non-separable mixture of 6b, 7b, and 6d, 7d were determined by their conversions into a separable mixture of 6c and 7c (see experimental).

As in the case of the nitrone 2, the addition of the nitrone 1 with methyl acrylate, acrylonitrile, and acraldehyde afforded a mixture of four possible isomers 6 - 9 in each case. The composition of methyl acrylate and acrylonitrile adducts 6f - 9f and 6g - 9g, respectively, were determined by the ^1H n.m.r. analysis of the C(2) protons, and also by chromatographic separation of the mixture of cycloadducts (see experimental). Individual treatment of the separated isomers 6g - 9g with methanolic hydrogen chloride afforded 6f - 9f, respectively. The adduct 6f, was, in turn,

converted into 6c by reduction with lithium aluminium hydride followed by silylation. For 3-substituted adducts, the major isomers were assigned the stereochemistry as depicted in 8f (in case of methyl acrylate) and 8g (in case of acrylonitrile). This is in line with the addition of nitrone 2 which affords the major adducts 12 with exo orientation of the C(3) substituents.[9] This was further supported by the stereochemistry observed in the nitrone 1 -acraldehyde reaction which afforded four possible isomers with major adducts having endo orientations of the C(2) and C(3) substituents. Because of the smaller size and favourable secondary orbital interaction, aldehyde functionality prefers to undergo addition via endo transition state.[9] Unstable nature of the acraldehyde adducts 6h-9h hampered our efforts to characterize them by n.m.r. and i.r. spectroscopy. However, immediate reduction of the adducts with sodium borohydride followed by silylation afforded a separable mixture of compounds 6c-9c the composition of which was translated into the ratio of the original acraldehyde adducts 6h-9h.

Table 1

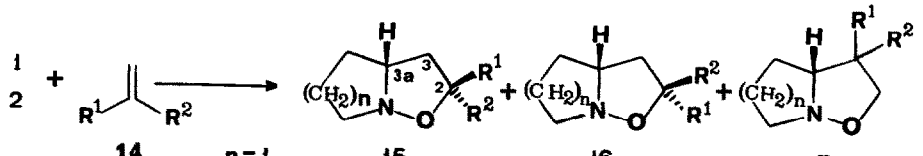
Regio- and Stereo-Chemistry of Cycloadditions of the Nitrones 1 and 2 with Monosubstituted Alkenes.

Alkene R	Nitrone 1/2	Temp °C	Reaction Time(h)	Solvent	%Composition of adduct 6/10	7/11	8/12	9/13	Isolated yield(%)
a, R = OEt	1	60	8	CH_2Cl_2	92	8			70
	2	40	12	EtOH	93	7			67
b, R = CH_2OH	1	98	2	bulk	76	24			79
	2	80	5	Toluene	83	17			84
c, R=$CH_2OSiBu^tMe_2$	1	90	1	Toluene	92	8			61
d, R = CH_2OAc	1	110	0.5	Toluene	88	12			78
e, R = Ph	1	110	5	Toluene	91	8	1		81
	2	110	5	Toluene	95	5			92
f, R = CO_2Me	1	25	2	CH_2Cl_2	43	37	11	9	89
	2	0	0.2	CH_2Cl_2	69	15	10	6	96
g, R = CN	1	25	4	CH_2Cl_2	49	24	21	6	83[a]
	2	25	0.2	CH_2Cl_2	61	20	13	6	92[a]
h, R = CHO	1	25	0.5	CH_2Cl_2	5	62	8	25	58[b]
	2	25	0.2	CH_2Cl_2	3	5	24	68	96[b]

[a] isolated yield of the corresponding carboxymethyl derivatives.
[b] isolated yield of the corresponding alcohols.

As far as the stereo- and regio-chemistry is concerned the results obtained so far indicate that both the cyclic nitrones 1 and 2 behave similarly toward addition onto mono substituted alkenes. However, notable exception was observed in the addition of acraldehyde. While the nitrone 1 afforded 2- and 3- substituted regiomers in a ratio of 2:1 respectively, reversal in the regioselection occurred in the addition of the nitrone 2 where the ratio was found to be 1:12! In the addition of methyl acrylate (or acrylonitrile) it is observed that the nitrone 1 tends to give higher proportion of 2-substituted endo isomer 7f (or 7g) in comparison to the nitrone 2. The cycloaddition products are, in principle, capable of undergoing cycloreversion[8b,c] and may thus, complicate the regio- and stereochemistry. However, when the nitrone 1 was reacted with excess methyl acrylate (or acrylonitrile) at 100°C for 4 hours in sealed tubes, cycloadducts 6f-9f (or 6g-9g) were obtained in similar composition to that observed under lower temperature and shorter reaction time (Table 1). At elevated temperatures (120°C, 12 h) the cycloadducts decomposed completely to intractable materials.

Next we pursued the cycloaddition of the nitrone 1 with several 1,1- disubstituted alkenes. The results of our regio- and stereo-chemical analysis and that of



14 n=1 15 16 17

n=2 18 19 20

a; $R^1 = CH_3$, $R^2 = CHO$; b; $R^1 = CH_3$, $R^2 = CO_2CH_3$; c; $R^1 = CH_3$, $R^2 = CH_2OH$;

d; $R^1 = CH_3$, $R^2 = CH_2OAc$ e; $R^1 = CH_3$, $R^2 = CH_2OTHP$; f; $R^1 = CH_3$, $R^2 = CH_2OSiBu^t(CH_3)_2$

g; $R^1 = CH_3$, $R^2 = Ph$; h; $R^1 = R^2 = CO_2CH_3$.

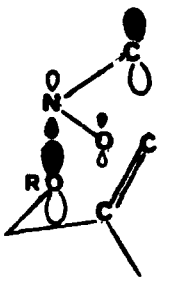
the nitrone 2 are recorded in Table 2. While alkenes 14b-g underwent regioselective addition onto the nitrone 1 and 2, varied degree of stereoselection was observed. The methacraldehyde on reaction with 1 afforded a single adduct 15a. For steric reason and favourable secondary orbital interaction the smaller aldehyde group is assumed to have the endo orientation.[10] This assumption gets further support as increasing the size of the R^2 an increasing amount of the stereoisomers 16 is obtained (Table 2). However, the alkenes 14c-14f invariably afforded the cycloadducts 15c-15f as the major isomers with endo orientation of the bulkier substituents containing the OH (or OR) group.

Table 2

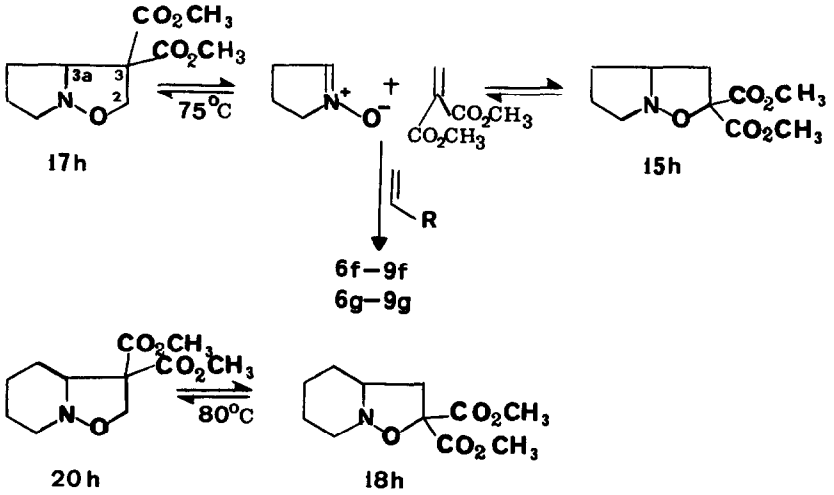
Regio- and Stereo-Chemistry of Cycloadditions of the Nitrones 1 and 2 with 1,1-disubstituted alkenes 14a-h

Alkene 14	Nitrone	Temp °C	Reaction Time(h)	Solvent	%Composition of adducts		Isolated yield(%)
					15 / 18	16 / 19	
a	1	25	4	CH_2Cl_2	100	0	95
	2	25	0.4	CH_2Cl_2	100	0	94
b	1	40	3	CH_2Cl_2	95	5	84
	2	25	1.5	CH_2Cl_2	96	4	86
c	1	115	2	bulk	85	15	70
	2	95	5	Toluene	85	15	77
d	1	110	2.5	Toluene	78	22	72
	2	95	2	Toluene	83	17	66
e	1	110	2	Toluene	70	30	50
	2	95	1.5	Toluene	67	33	58
f	1	100	2	Toluene	64	36	53
	2	95	1.5	Toluene	70	30	55
g	1	110	2	Toluene	54	46	68
	2	105	1	Toluene	58	42	71
h	1	-18	1	CH_2Cl_2	22(15)	78(17)	74
	2	0	0.2	CH_2Cl_2	0(18)	100(20)	90

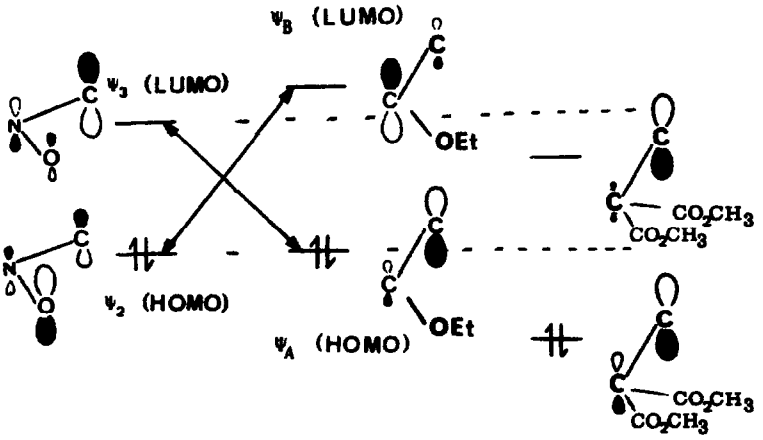
The compositions of the non-separable cycloadducts in the addition reactions of the alkenes 14a-e were determined by their conversions into a separable mixture of silylated adducts 15f and 16f (see experimental). Our accumulated data on cycloadditions involving cylic nitrones led us to believe that the endo transition state is stabilized due to the favourable interaction between the orbital of



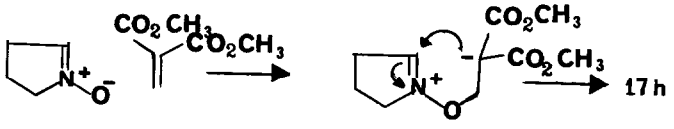
nitrogen in the nitrone LUMO with the oxygen lone pair of the alkene.[9,13] A reversal in the regioselection occurred in the addition of dimethyl methylenemalonate. While the nitrone 2 afforded a single adduct 20h regiospecifically, a mixture of cycloadducts 15h and 17h in a 22: 78 ratio was obtained from the addition of the nitrone 1. The cycloadduct 20h, during chromatographic purification, was changed into a mixture of isomers 18h and 20h. When a deuterochloroform solution of the purified isomer 17h (or 15h) was heated in a sealed n.m.r.tube at 75°C for 1.5 h, a mixture of adducts 15h and 17h in a 3:1 ratio was obtained in each case. Continued heating did not change the ratio of the regioisomers. The cycloreversion, indeed, happened via the nitrone as it was trapped quantitatively by addition onto methyl acrylate or acrylonitrile in separate experiments. The cycloadduct 18h or 20h behaved similarly. When heated both purified isomers afforded a mixture of isomers 18h and 20h in a 3:1 ratio, respectively.



The results described above are in general agreement with the frontier orbital treatment of 1,3-dipolar cycloadditions.[9,14,15] This view suggests the formation of the C(2) substituted isoxazolidines regioselectively. As the ionization potential and the electron affinity of the alkene increase (i.e. as the HOMO-LUMO levels decrease in energy) their is an increasing tendency towards the formation of a regioisomeric mixture of adducts. In this cycloaddition reaction , the carbon-carbon and carbon-oxygen bond formation in the trasition state may not happen in a synchronous manner.



Usually in the addition reaction of electron-rich alkenes, the carbon-carbon bond formation leads the carbon-oxygen bond formation. However, with very electron-deficient alkenes, the favoured transition state has the carbon-oxygen bond more developed than the carbon-carbon bond. The mechanism of nitrone cycloaddition to the highly polarized alkene, dimethyl methylenemalonate, may involve a zwitterionic intermediate or is merely nonsynchronous.[16]



In addition to the frontier orbital interactions steric factors also plays a part in regio- as well as stereo-selection. The relative stability of four isomeric transition state for the cycloaddition of nitrones 1 and 2 are different. This is evident from Table 1. The nitrone 1 affords a greater proportion of endo oriented 2-substituted adducts than the nitrone 2 in the addition of methyl acrylate, acrylonitrile, and acraldehyde. In general the cyclic nitrones 1 and 2 shows similar remarkable regio- and stereo-selectivity in their cycloaddition reactions, which would indeed be helpful in incorporating stereocenters in the synthesis of natural products.

EXPERIMENTAL

Elemental analyses were performed on a Carlo-Erba Elemental analyser 1106. I.r. spectra were recorded on a Nicolet 5 DXB FT.IR and are reported in wavenumbers (cm^{-1}). Most of the ^1H n.m.r. spectra were recorded on a Bruker AC 80 and a few on a XL-200 spectrometer using $CDCl_3$ with TMS as internal standard. 70 ev E. I. mass spectra were recorded on a Ribermag GC-MS system, R-10-10 with quadrupole mass filter and Riber 400 acquisition system. Silica gel chromatographic separations were performed with flash silica (Baker Chemical Co.). T.l.c. cards silica gel, aluminium backed plates (Fluka AG, layer thickness 0.2 mm) were used to determine appropriate solvent system for elution and to monitor reaction progress. All solvents were reagent grade. All the liquid alkenes, N-hydroxy-piperidine, and N-hydroxypyrrolidine were distilled and maleic anhydride and dimethyl fumarate were recrystallized before use. Cycloadditions were carried out under a positive atmosphere of nitrogen. The nitrones 1 and 2 were prepared from N-hydroxypyrrolidine and N-hydroxypiperidine, respectively, as described in the literature.[12] The formation of the nitrones was assumed to be quantitative in the percentage yield calculation for the subsequent cycloadditions. Reaction conditions, isolated yield, and composition of isomeric cycloadducts are given in Table 1 and 2. Following are the amounts (written in parantheses) of nitrone, alkene, and solvent used in cycloadditions: Nitrone 1 (5.0 mmol), ethyl vinyl ether (15 mmol), dichloromethane (2 mL); nitrone 1 (4.0 mmol), allyl alcohol (4 mL); nitrone 1 (5.0 mmol), dimethyl-t-butylsilyl allyl ether (10.0 mmol), toluene (5 mL); nitrone 1 (2.0 mmol), allyl acetate (1.0 mL), toluene (5 mL); nitrone 1 (5.0 mmol), styrene (3.0 mL), toluene (5 mL); nitrone 1 (4.0 mmol), methyl acrylate (2.0 mL), dichloromethane (12 mL); nitrone (15.0 mmol), acrylonitrile (5 mL), dichloromethane (45 mL); nitrone 1 (5.0 mmol), acraldehyde (1.0 mL), dichloromethane (15 mL); nitrone 1 (7.0 mmol), methacraldehyde (2.0 mL), dichloromethane (21 mL); nitrone 1 (4.0 mmol), methyl methacrylate (3.0 mL), dichloromethane (12 mL); nitrone 1 (3.5 mmol), methylallyl alcohol (2.0 mL); nitrone 1 (4.0 mmol), methylallyl acetate (2.0 mL), toluene (5 mL); nitrone 1 (3.0 mmol), methylallyl tetrahydropyranyl ether 14e (2.0 mL), toluene (5 mL); nitrone 1 (3.0 mmol), 14f (7.0 mmol), toluene (5 mL); nitrone 1 (4.0 mmol), α-methyl styrene 14g (2.0 mL), toluene (5 mL); nitrone 1 (7.0 mmol), dimethyl methylenemalonate 14h (7.5 mmol), dichloromethane (5 mL); and nitrone 2 (4.0 mmol), 14h (5.0 mmol), dichloromethane (10 mL). The reaction mixture, after elapsed time (Table 1 and 2), were evaporated to remove solvent and excess alkenes to give crude residues containing the cyclo-adducts which were then purified and analysed. Hydrochloride salts for a number of purified adducts were prepared. Anhydrous HCl was bubbled through a solution of the adduct in ether. The precipitated hydrochloride salt of the adduct was then crystallized from methanol-ether.

Isomers of 2-Ethoxyhexahydropyrrolo(1,2-b)isoxazole (6a) and (7a).- The isomers are prepared under conditions as described in Table 1; b.p. 60°C (0.1 mm). Careful analysis of the n.m.r. spectrum revealed the presence of two isomers 6a and 7a in a ratio of 92:8. δ_H 1.16 (3 H, t, J 7.7 Hz), 1.28 - 4.00 (11 H, m), 5.12 (1 H, dd, J 0.18 and 5.8 Hz) and a minor partially hidden dd at δ 5.09.

Isomers of 2-Hydroxymethylhexahydropyrrolo(1,2-b)isoxazole (6b) and (7b).- The crude residue on silica gel chromatography using 10% methanol in ether afforded a

non-separable mixture of adducts 6b and 7b, (colourless liquid), (Found: C, 46.57; H, 7.69; N, 7.53. $C_7H_{13}NO_2$.HCl requires C, 46.80; H, 7.29; N, 7.80%); $\nu_{max.}$ (neat) 3360, 2955, 2870, 1656, 1450, 1391, 1334, 1297, 1167, 1053, 916, and 780 cm^{-1}; δ_H 1.45 -2.65 (6 H, m), 2.80 - 3.33 (2 H, m, NCH_2), 3.38 - 3.98 (3 H, m), 4.07-4.47 (1 H, m, C(2)H), and 4.75 (1 H, bs, OH). The non-separable mixture of isomers 6b and 7b was silylated as described later to give a separable mixture of isomers 6c and 7c in a 76:24 ratio, respectively.

Isomers of 2-Dimethyl-t-butylsiloxymethylhexahydropyrrolo(1,2-b)isoxazole (6c) and(7c).-The crude residue was chromatographed over silica gel using ether as eluant. The first component isolated as a colourless liquid, was assigned structure 6c, (725 mg, 56%); $\nu_{max.}$ (neat) 2952, 2924, 2851, 1472, 1463, 1389, 1362, 1256, 1140, 1111, 1006, 924, 838, 780, and 733 cm^{-1}; δ_H 0.08 (6 H, s), 0.90 (9 H, s), 1.40 - 2.45 (6 H, m), 3.13 (2 H, m, NCH_2), 3.40 - 3.85 (3 H, m), and 4.17 (1 H, quint, J 6.0 Hz, C(2)H); m/z 257 (M^+ 19.4%). Further elution with ether afforded the minor isomer 7c, as a colourless liquid (60 mg, 4.7%); ν_{max} (neat) 2954, 2929, 2858, 1473, 1464, 1387, 1361, 1254, 1139, 1118, 1031, 1006, 912, 838 and 778 cm^{-1}; δ_H 0.08 (6 H, s), 0.90 (9 H, s), 1.60 - 2.26 (5 H, m), 2.28-2.64 (1 H, ABX, J 6.6, 8.0, and 12.0 Hz, C(3)H), 2,70 - 3.13 (1 H, m), 3.17 - 3.83 (4 H, m) and 3.85 - 4.20 (1 H,m, C(2)H).

Isomers of 2-Acetoxymethylhexahydropyrrolo(1,2-b)isoxazole (6d) and (7d).-The crude residue was passed through a short silica gel column using ether as eluant to give the cycloadducts as a colourless liquid (288 mg, 78%); $\nu_{max.}$ (neat) 2940, 1740, 1448, 1386, 1235, 1046, 923, and 733 cm^{-1}; δ_H 1.40 - 2.45 (6 H, m), 2.08 (3 H, s), 2.83 - 3.45 (2 H, m, NCH_2), 3.70 (1 H, m, C(3a)H), and 3.86 - 4.53 (3 H, m); m/z 185 (M^+ 15.3%).The ^1H n.m.r. of the cycloadducts fails to determine the isomer ratio. The mixture containing the acetates was reduced with lithium aluminium hydride to give alcohols 6b and 7b, (85%), which on silylation followed by chromatographic separation as described later afforded 6c and 7c, in a 88:12 ratio, respectively.

Isomers of 2-Phenylhexahydropyrrolo(1,2-b)isoxazole (6e) - (8e).- Compounds are prepared as described in the literature.[17] The crude adducts were separated by silica gel chromatography using ether as eluant to give 8e, 6e, and finally 7e as colourless liquids. Compound 6e: δ_H (200 MHz) 1.60 - 2.22 (4 H, m), 2.30 - 2.62 (2 H, m), 3.28 (2 H, t, J 7.0 Hz, NCH_2), 3.92 (1 H, m, C(3a)H), 5.09 (1 H, dd, J 6.5, 8.5 Hz, C(2)H), and 7.25 - 7.64 (5 H, m). Compound 7e: δ_H (200 MHz) 1.60 - 2.26 (5 H, m), 2.80 - 3.10 (2 H, m), 3.36 (1 H, m), 3.90 (1 H, m, C(3a)H), 4.97 (1 H, dd J 6.5, 9.5 Hz, C(2)H) and 7.28 - 7.56 (5 H, m). Compound 8e: δ_H (200 MHz) 1.64 - 2.16 (4 H, m), 3.00 - 3.20 (1 H, m), 3.24 - 3.48 (2 H, m), 3.64 - 3.80 (1 H, m, C(3a)H), 3.82 (1 H, t, J 7.5 Hz, $C(2)H_A$), 4.28 (1 H, t, J 7.5 Hz, $C(2)H_B$), 7.24 - 7.52 (5 H, m).

Isomers of Methyl hexahydropyrrolo(1,2-b)isoxazole-2- and -3-carboxylate (6f).-(9f).- Cycloaddition products were separated by chromatography over silica gel using ether as eluant. The first component, isolated as a colourless liquid, was assigned the structure 9f, (8.0%); (Found: C, 46.43; H, 6.55; N, 6.54. $C_8H_{13}NO_3$.HCl requires C, 46.27; H, 6.79; N, 6.74%); ν_{max} (neat) 2989, 2894, 1739, 1438, 1377, 1317, 1267, 1203, 1115, 1050, 1019, 920, and 732 cm^{-1}; δ_H 1.65 - 2.30 (4 H, m), 2.95 - 3.43 (3 H, m), 3.74 (3 H, s), 4.06 (1 H, t, J 8.4 Hz, $C(2)H_A$), 4.22 (1 H, t J 8.4 Hz, $C(2)H_B$), and 3.95 - 4.20 (1 H, m underneath, C(3a)H). On further elution with ether the second component was obtained as a colourless liquid and was assigned the structure 8f (9.8%). (Found: C, 45.99; H, 6.64; N, 6.53. $C_8H_{13}NO_3$.HCl requires C, 46.27; H, 6.79; N, 6.74%); ν_{max} (neat) 2950, 2878, 1739, 1438, 1372, 1307, 1262, 1203, 1179, 1058, 1012, and 958 cm^{-1}; δ_H 1.50 - 2.30 (4 H, m), 3.04 - 3.23 (2 H,m), 3.50 - 4.30 (4 H, m), and 3.72 (3 H, s). Continued elution with ether afforded the third fraction which contained non-separable mixture of 6f and 7f (71.0%), in a ratio of 54:46, respectively, as determined by n.m.r. analysis of C(2) protons. The isolated yield of the cycloaddition products was, thus, 89% and the adducts 6f-9f were found to be a 43:37:11:9 mixture.

Isomers of Hexahydropyrrolo(1,2-b)isoxzole-2- and -3-carbonitrile (6g) - (9g).-Chromatography of the crude reaction products using ether as eluant afforded the first component 6g as a colourless liquid (847 mg, 41%). ν_{max} (neat) 2986, 2884, 2249, 1456, 1442, 1328, 1295, 1058, 1034, 1000, 914, and 770 cm^{-1}. δ_H 1.40 - 2.56 (5 H, m), 2.62 - 3.60 (3 H, m), 3.65 - 4.03 (1 H, m, C(3a)H), and 4.83 (1 H, dd, J 3.2, 8.0 Hz, C(2)H). The second component 9g was obtained also as a colourless liquid (103 mg, 5.0%). ν_{max} (neat) 2971, 2893, 2245, 1485, 1460, 1448, 1217, 1188, 1072, 1052, 1011, 953, 919, 772, and 733 cm^{-1}; δ_H 1.50 - 2.38 (4 H, m), 2.90 - 3.54 (3 H, m), 3.97 (1 H, dd, J 7.0, 8.5 Hz, $C(2)H_A$ and another H underneath C(3a)H), and 4.26 (1 H, t, J 8.5 Hz, $C(2)H_B$). Continued elution with ether gave the third component 7g as a colourless liquid. ν_{max} (neat) 2966, 2878, 2268, 1455, 1349, 1208, 1110, 1055, 1022, 961, 917, 810, and 733 cm^{-1}. δ_H 1.52 - 2.60 (5 H, m), 2.70 - 4.03 (4 H, m) and 4.68 (1 H, dd, J 5.0, 8.6 Hz, C(2)H). Further elution with ether afforded a mixture of the 7g and the fourth component 8g and finally, the fourth component 8g. A total of 776 mg (37.5%) of 7g and 8g was isolated. Compound 8g (colourless liquid); ν_{max} (neat) 2960, 2882, 2248, 1450, 1291, 1241, 1211, 1055, 1037, 1016, 952, 920, 776 and 747 cm^{-1}; δ_H 1.64 - 2.30 (4 H, m), 3.20 (2 H, m), 3.40 - 4.00 (2 H, m) and 4.10 (2 H, apparent d, J 6.6 Hz, $C(2)H_2$). The ratio of 7g and 8g was found to be 53:47, respectively as determined by ^1H n.m.r. analysis of the C(2) protons of the mixture and the known amounts of 7g and 8g in pure form. The cycloaddition products were thus obtained in 83.4% yield. Both ^1H n.m.r. of the crude adducts and the chromatographic separation revealed the presence of 6g-9g, in

an approximate ratio of 49:24:21:6, respectively.

Reaction of the Nitrone 1 with Acraldehyde and the Conversion of the Adducts 6h - 9h into Silylethers 6c - 9c.- The crude residue was dissolved in ethanol (3 mL) and immediately reduced with sodium borohydride (200 mg) at room temperature for 1 h. To the reaction mixture was added saturated potassium carbonate solution (10 mL) and the mixture was extracted with dichloromethane (5 x 15 mL). The organic layer was dried with magnesium sulphate and removal of the organic solvent afforded a yellow oil which was purified by chromatography over silica gel using 10% methanol-dichloromethane mixture to give the non-separable mixture of alcohols 6b - 9b (418 mg, 58.4% overall). To the mixture of alcohols (2.92 mmol) in 1 mL DMF was added a solution of imidazole (544 mg, 8.0 mmol) and dimethyl-t-butyl chlorosilane (600 mg, 4,0 mmol) in 3 mL DMF. Usual work up followed by chromatographic separation yielded the silylated compounds 6c - 9c. The first fraction contained the mixture of 6c and 9c and second and third fractions contained, respectively 8c and 7c. The isomers 6c - 9c, were found to be in a ratio of 5:62:8:25. Compound 8c: (colourless liquid), ν_{max} (neat) 2957, 2929, 2855, 1472, 1463, 1389, 1361, 1256, 1095, 1005, 939, 837, and 777 cm^{-1}; δ_H 0.07 (6 H, s), 0.90 (9 H, s), 1.55 - 2.05 (4 H, m), 2.84 - 3.22 (3 H, m) and 3.45 - 4.06 (5 H, m); m/z 257 (M^+ 38.8%). The ^1H n.m.r. spectrum of 9c containing minor amount of 6c has the following n.m.r. signals at δ_H 0.07 (6 H, s), 0.90 (9 H, s), 1.53 - 2.67 (5 H, m), 2.95 - 3.75 (6 H, m) and 4.00 (1 H, dd, J 6.5, 8.5 Hz, C(2)H).

Conversion of the Acrylonitrile Adducts 6g - 9g into the Methyl acrylate Adducts 6f - 9f.- A methanol-HCl mixture (30:18 w/w) at -10°C was added to the adduct 6g (179 mg). The mixture was allowed to stand 15 min at 0°C and 1.5 h at room temperature. After removal of the methanol the residual liquid was transferred into a separatory funnel containing 10 mL saturated potassium carbonate solution and ether (15 mL). The aqueous layer was extracted with ether (2 x 15 mL). The combined organic layer was dried (magnesium sulphate) and evaporated to give a yellow oil which was purified by passing through a short silica gel column using ether as eluant to give 6f, as a colourless liquid (132 mg, 62.7%); (Found: C,46.30 H,6.61; N,6.55. $C_8H_{13}NO_3.HCl$ requires C,46.27; H,6.79; N,6.74%); ν_{max} (neat) 2954, 2876, 1737, 1438, 1292, 1258, 1217, 1069, 1024, 732 cm^{-1}; δ_H 1.40 - 2.53 (5 H, m), 2.62 - 3.90 (4 H, m), 3.77 (3 H, s), 4.60 (1 H, dd, J 5.2, 8.3 Hz, C(2)H). Likewise 7g, 8g, and 9g were converted into 7f (60.0%), 8f (65.3%), and 9f (58.5%), respectively. Compound 7f:(colourless liquid), ν_{max} (neat) 2968, 2877, 1742, 1453, 1439, 1278, 1212, 1119, 1074, 1028, 811, and 734 cm^{-1}; δ_H 1.60 - 2.45 (5 H, m), 2.65 - 4.00 (4 H, m), 3.77 (3 H, s), and 4,58 (1 H, t, J 8.0 Hz, C(2)H); m/z 171 (M^+ 30%). The ester adduct 6f was converted into silyl ether 6c, by lithium aluminium hydride reduction followed by silylation as described earlier.

Thermal Study on the Acrylonitrile Adducts 6g - 9g, and Methyl acrylate Adducts 6f - 9f.- A mixture of 6g - 9g (50 mg) and acrylonitrile (0.5 mL) was heated to 100°C for 5 h in a sealed tube. However, the n.m.r. spectrum was virtually unchanged with respect to that of the original mixture. The ratio of adducts 6f - 9f, in a similar experimental condition, in the presence of methyl acrylate failed to alter the ratio of the original mixture. When the above two experiments were repeated at 120°C for 12 h only decomposed materials were obtained. ^1H n.m.r. spectra failed to reveal the presence of any starting materials.

Isomer of 2-Methylhexahydropyrrolo(1,2-b)isoxazole-2-carbaldehyde (15a).- Chromatography of the crude adduct over silica gel using ether as eluant gave an analytical sample of 15a as a colourless liquid; ν_{max} (neat) 2978, 2878, 2741, 1733, 1447, 1376, 1255, 1121, 1074, 974, 913, 795, and 733 cm^{-1}; δ_H 1.35 (3 H, s), 1.45 - 2.22 (4 H, m), 2.33 (2 H, d, J 6.0 Hz, C(3)H_2), 3.18 (2 H, m, NCH_2), 3.78 (1 H, m, C(3a)H), and 9.60 (1 H, s). The major part of the product 15a, was used without purification for the subsequent reactions. Crude adduct (748 mg, 4.8 mmol) was reduced with sodium borohydride to give 15c , a portion of which was purified by chromatography over silica gel using 5% methanol in ether as eluant to give 15c as a colourless liquid (77.5%); ν_{max} (neat) 3267, 2970, 2920, 2867, 1451, 1374, 1063, 897, and 753 cm^{-1}; δ_H 1.25 (3 H, s), 1.42 - 2.35 (6 H, m), and 2.65 - 3.98 (6 H, m, including a 2H, AB, J 11.0 Hz centered at δ 3.50, C(2)CH_2O-); m/z 157 (M^+ 26.7%). Another portion of the crude alcohol was silylated as described before to give 15f (82.8%). ^1H n.m.r. spectrum and careful t.l.c. analysis failed to reveal the presence of the minor isomer 16f.

Isomers of Methyl 2-methylhexahydropyrrolo(1,2-b)isoxazole-2-carboxylate (15b) and (16b).- Chromatography over silica gel using ether as eluant gave a non-separable mixture of 15b and 16b as a colourless liquid (622 mg, 84%), (Found: C, 48.31; H, 7.53; N, 6.19. $C_9H_{15}NO_3.HCl$ requires C, 48.76; H, 7.28; N, 6.32%); ν_{max} (neat) 2956, 2881, 1736, 1452, 1369, 1299, 1246, 1207, 1122, 1050, and 968 cm^{-1}; δ_H 1.50 (3 H, s and an overlapping minor s at 1.46), 1.53 - 2.18 (4 H, m), 2.48 (2 H, ABX, J 4.8, 7.2, and 12.8 Hz, C(3)H_2), 2,75 - 3.90 (3 H, m) and 3.74 (3 H, s); m/z 185 (M^+ 63.5%). Isomer ratio of methyl methacrylate adducts 15b and 16b was determined after their conversion into corresponding alcohols 15c and 16c by lithium aluminium hydride reduction (quantitative) followed by silylation as described earlier. The silyl ether 15f and 16f, thus obtained was found to be in 95:5 ratio.

Isomers of 2-Hydroxymethyl-2-methylhexahydropyrrolo(1,2-b)isoxazole (15c) and (16c).- The non-separable mixture of crude adducts, 15c and 16c was silylated as described before to give 15f and 16f in a 85:15 ratio as determined by the integration of methyl singlets at δ1.24 and 1.28, respectively.

Isomers of 2-Acetoxymethyl-2-methylhexahydropyrrolo(1,2-b)isoxazole (15d) and 16d).- The cycloadducts were purified by flushing through silica gel using ether as

eluant to give a colourless liquid (572 mg, 71.7%); ν_{max} (neat) 2970, 2892, 1743, 1452, 1385, 1371, 1237, 1043, and 909 cm^{-1}; δ_H 1.32 (3 H, s), 1.47 - 2.60 (6 H, m), 2.08 (3 H, s), 2.70 - 3.93 (3 H, m), and 4.05 (2 H, AB, J 12.0 Hz, C(2)CH_2O-); m/z 199. The adduct mixture containing 15d and 16d (140 mg, 0.70 mmol) was reduced with lithium aluminium hydride to give the mixture of alcohols, 15c and 16c, in quantitative yield. The alcohols were then silylated as described before to give the mixture of isomers 15f and 16f in a 78:22 ratio as determined by the integration of methyl singlets at δ1.24 and 1.28, respectively.

Isomers of 2-Hydroxymethyl-2-methylhexahydropyrrolo(1,2-b)isoxazol-2-yl tetrahydropyranyl ether (15e) and (16e).- A portion of the brown residue was chromatographed using dichloromethane as eluant to give the adducts as a colourless liquids (50.0%); ν_{max} (neat) 2942, 2867, 1458, 1199, 1124, 1069, 1035, 970, 897, 864, and 815 cm^{-1}; δ_H 1.29 (1.5 H, s), 1.35 (1.5 H, s), 1.05 -2.65 (12 H, m), 2.70-4.05 (7 H, m), and 4.65 (1 H, bs); m/z 241 (M^+ 5.4%). Another portion of the crude adducts on hydrolysis (5% HCl solution) followed by silylation gave a mixture of adducts 15f and 16f in a 70:30 ratio as determined by the integration of the methyl singlets at δ1.24 and 1.28, respectively.

Isomers of 2-Dimethyl-t-butylsiloxymethyl-2-methylhexahydropyrrolo(1,2-b)isoxazole (15f) and (16f).- The reaction mixture was chromatographed over silica using ether as eluant. The first component, isolated as a colourless liquid, was assigned the structure 16f; ν_{max} (neat) 2964, 2933, 2841, 1473, 1462, 1364, 1253, 1100, 1007, 854, 837, 777, and 671 cm^{-1}; δ_H 0.05 (6 H, s), 0.90 (9 H, s), 1.28 (3 H, s), 1.44-2.32 (5 H, m), 2.56 (1 H, dd, J 8.0, 12.0 Hz, C(3)H_A), and 2.75 - 3.85 (5 H, m); m/z 271 (M^+ 14.7%). Continued elution with ether afforded the major isomer 15f as a colourless liquid (268 mg, 32.9%); ν_{max} (neat) 2956, 2920, 2848, 1472, 1463, 1417, 1385, 1358, 1253, 1106, 999, 892, 832, 778, and 666 cm^{-1}; δ_H 0.05 (6 H, s), 0.90 (9 H, s), 1.24 (3 H, s), 1.40 - 2.30 (6 H, m), and 2.67 - 3.95 (5 H, m); m/z 271 (M^+ 51.3%). The major and minor isomers 15f and 16f was, thus, obtained in a 62:38 ratio, respectively. ^{1}H n.m.r. analysis of the crude adducts also revealed a similar ratio (64:36) as determined by the methyl signals at δ1.24 and 1.28, respectively.

Isomers of 2-Methyl-2-phenylhexahydropyrrolo(1,2-b)isoxazole (15g) and (16g).- The brown residue was chromatographed over silica gel using 50:50 dichloromethane-ether mixture as eluant to give the first component, 16g (255 mg, 31.4%); ν_{max}2973, 2879, 1496, 1446, 1368, 1269, 1092, 1070, 1046, 1029, 764, and 701 cm^{-1}; δ_H 1.61 (3H, s), 1.45 - 2.33 (5 H, m), 2.54 - 4.10 (4 H, m), and 7.10 - 7.55 (5 H, m); m/z 203 (M^+ 53.7%). Further elution afforded the second component 15g (300 mg, 36.9%); ν_{max} (neat) 2974, 2893, 1493, 1446, 1377, 1276, 1125, 1070, 1027, 915, 765 and 701 cm^{-1}; δ_H 1.52 (3 H, s), 1.35 - 2.35 (5 H, m), 2.70 - 3.74 (4 H, m) and 7.03 - 7.68 (5 H, m); m/z 203 (M^+ 99.6%).

Dimethyl hexahydropyrrolo(1,2-b)isoxazole-2,2- and -3,3- dicarboxylate (15h) and (17h).- The ^{1}H n.m.r. of the crude residual liquid revealed the presence of 15h and 17h in a ratio of 22:78, respectively. The mixture of isomers were separated by silica gel chromatography using ether as eluant to give the major isomer 17h as a thick colourless oil (842 mg, 52.5%); (Found: C, 52.51; H, 6.65; N, 6.37. $C_{10}H_{15}NO_5$ requires C, 52.39; H, 6.59; N, 6.11%); ν_{max} (neat) 2973, 2909, 1743, 1437, 1281, 1267, 1213, 1101, 1067, 1001, 918, and 733 cm^{-1}; δ_H 1.30 - 2.22 (4 H, m), 3.22 (2 H, m, NCH_2), 3.77 (3 H, s), 3.80 (3 H, s), 4.10 (1 H, d, J 9.0 Hz, C(2)H_A), 4.34 (1 H, m, C(3a)H), and 4.50 (1 H, d, J 9.0 Hz, C(2H_B)). Continued elution with ether afforded the minor isomer 15h as a thick colourless oil (344 mg, 21.4%); (Found: C, 44.67; H, 5.97; N, 5.53. $C_{10}H_{15}NO_5$.HCl requires C, 45.20; H, 6.07; N, 5.27%); ν_{max} (neat) 2967, 2887, 1747, 1438, 1285, 1207, 1171, 1134, 1101, 1062, 1032, 973, 906, 833, and 811 cm^{-1}; δ_H 1.50 - 2.36 (4 H, m), 2.60 (1 H, dd, J4.0, 13.0 Hz, C(3)H_A), 2.85 - 3.97 (3 H, m), 3.24 (1 H, dd, J 7.4, 13.0 Hz, C(3)H_B, 3.80 (3 H, s), and 3.83 (3 H, s) . It was noted that the ratio of adducts 15h and 17h obtained by chromatographic separation was different from the ratio determined by the ^{1}H n.m.r. analysis of the crude reaction mixture. This indicates the possible isomerization of 17h to 15h. When purified adduct 17h was subjected to rechromatography over silica gel using ether as eluant, a mixture of adducts 15h and 17h was obtained.

Dimethyl hexahydro-2H-isoxazolo(2,3-a)pyridine-2,2- and -3,3- dicarboxylate (18h) and (20h).- The n.m.r. spectrum of the residue revealed the presence of single adduct 20h. The crude reaction mixture was converted into a mixture of 18h and 20h, during chromatographic separation. The total isomer yield after chromatographic purification was 96%. The isomers were separated by performing flash silica gel chromatography using ether as eluant to give pure 20h, a mixture of 18h, 20h, and finally the isomer 18h. Compound 20h: (colourless liquid); (Found: C, 46.98; H, 6.13; N, 4.88. $C_{11}H_{17}NO_5$.HCl requires C, 47.22; H, 6.49; N, 5.01%); ν_{max} (neat) 2929, 2830, 1743, 1440, 1260, 1235, 1203, 1140, 1095, and 1043 cm^{-1}; δ_H 1.05 - 3.00 (8 H, m), 3.77 (6 H, s and an overlapping 1 H,m C(3a)H), 4.26 (1 H, d, J 9.0 Hz, C(2)H_A), and 4.52 (1 H, d, J 9.0 Hz, C(2)H_B). Second isomer: 18h, colourless liquid; ν_{max} (neat) 2944, 2845, 1746, 1435, 1279, 1256, 1233, 1203, 1138, 1104, 1041, 918, and 736 cm^{-1}; δ_H 1.10 - 2.12 (6 H, m), 2.23 - 3.10 (4 H, m), 3.80 (3 H, s), 3.83 (3 H, s) and an overlapping (1 H, m, C(3a)H) at δ3.8.

Thermal study of Cycloadducts 17h and 20h, and their regiomers.- A solution of the adduct 15h (50.0 mg, 0.22 mmol) in deuterochloroform(0.6 mL) in a sealed n.m.r. tube was heated to 75°C. After 45 min at 75°C the ratio of 15h and 17h was found to be 80:20, respectively. After continued heating for another 45 min the ratio was changed to 75:25 and remained at that ratio for further heating at 75°C for 4 h.

The ratio was determined by integration of the C(2) and C(3) protons of 17h and 15h. Starting with 50 mg of the pure isomer 17h in deuterochloroform(0.6 mL) the similar ratio of 15h and 17h was achieved after heating at 75°C for 1 h. The n.m.r. spectra in both experiments failed to reveal the presence of the nitrone and alkene. In one experiment 50 mg of 17h, was heated with methyl acrylate (0.5 mL) at 75°C for 1.5 h under nitrogen. After removal of the excess methyl acrylate, it was found that the n.m.r. spectrum was virtually identical to that of the adducts obtained from the cycloaddition of the nitrone 1 with methyl acrylate. In another experiment 17h (35 mg) and acrylonitrile (0.5 mL) was heated at 83°C for 1.5 h. A mixture of adducts 6q - 9q was obtained in similar ratio as found in the addition of nitrone 1 with acrylonitrile. The n.m.r. spectrum failed to reveal the presence of 15h and 17h.

Thermal Equilibration of 18h and 20h.- The adduct 18h or 20h (40 mg) in deuterochloroform (0.6 mL) was heated at 80°C in a sealed n.m.r. tube. In both the experiments a mixture of 18h and 20h was obtained in a 77:23 ratio, respectively, as determined by the ^{1}H n.m.r. analysis of the carbomethoxy singlets.

ACKNOWLEDGEMENTS: Facilities provided by the King Fahd University of Petroleum and Minerals, Dhahran, is gratefully acknowledged. We thank Mr. M. Saleem for recording mass spectra, Mr. M. Dawson for elemental analyses and Mr. F. S. Sikander for recording i.r. spectra.

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