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THE 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 3,4,5,6-TETRAHYDRO-2H-AZEPINE 1-OXIDE.

Sk. Asrof Ali*, M. I. M. Wazeer and Mazhar-Ul-Haque

Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia.

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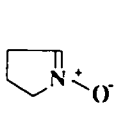
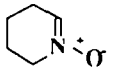
Abstract: A study of the regio- and stereo-chemical behaviour of the 1,3-dipolar cycloaddition of 3,4,5,6-tetrahydro-2H-azepine 1-oxide with a series of di- and tri-substituted alkenes has been carried out. Significant secondary orbital interactions are observed in the addition reaction of alkenes having conjugated methoxycarbonyl substituents or having oxygen at allylic or homoallylic position. Quite unexpectedly, the addition of crotonate and cinnamate esters are found to be non-unidirectional.

INTRODUCTION

The use of 1,3-dipolar cycloaddition reaction of nitrones in organic synthesis has developed quite rapidly in recent years.[1] This reaction is indeed the best chemical template for constructing isoxazolidine ring and also efficient in incorporating multiple stereocenters in a single step. Thus, among a plethora of functional groups, the nitrone functionality has secured an important place in the arsenal of synthetic chemists. The nitrone cycloadditions have culminated in the synthesis of several interesting alkaloidal and non-alkaloidal natural products[2]. The cycloadditions of cyclic nitrones 1-pyrroline 1-oxide (**1**),[3,4] 3,4,5,6-tetrahydropyridine 1-oxide (**2**),[4-6] and its 3-oxo derivative(**3**)[7] have been examined in detail. Concentrated solutions of the nitrones (**1**)-(**4**) behave differently. While the nitrones (**1**) and (**3**) are stable, the nitrone (**2**) dimerizes to (**5**) and 3,4,5,6-tetrahydro-2H-azepine 1-oxide (**4**) polymerizes[8] to (**6**) on standing. Herein, we report in detail, the regio- and stereo- chemical features associated with the 1,3-dipolar cycloaddition of 3,4,5,6-tetrahydro-2H-azepine 1-oxide (**4**) with a series of di- and tri- substituted alkenes.



(**1**)



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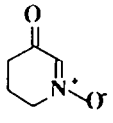
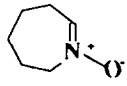
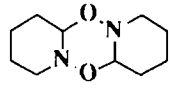


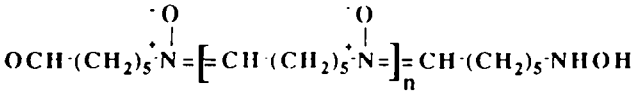
(**3**)



(**4**)



(**5**)

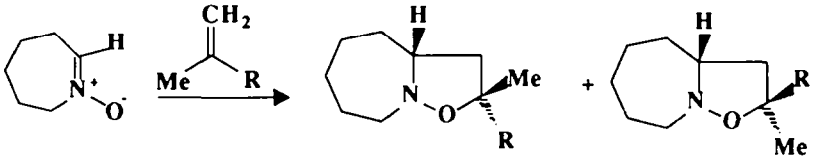


(**6**)

RESULTS AND DISCUSSION

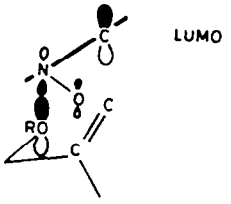
All reactions were carried out under conditions that would reflect kinetic rather than thermodynamic factors.

Addition of the nitrone (**4**) onto methyl methacrylate (**7a**) afforded a separable mixture of adducts (**8a**) and (**9a**) in a ratio of 94:6, respectively (Scheme 1).



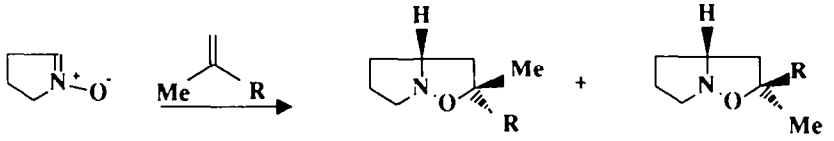
(4) (7) (8) (9)

a, R = CO_2Me	(8a)	: (9a)	94 : 6
b, R = CH_2OH	(8b)	: (9b)	93 : 7
c, R = $CH_2OSi^tBu(Me)_2$	(8c)	: (9c)	65 : 35
d, R = CH_2CH_2OH	(8d)	: (9d)	60 : 40
e, R = $CH_2CH_2OSi^tBu(Me)_2$	(8e)	: (9e)	55 : 45



Scheme 1.

The reaction of methyl allyl alcohol (**7b**) and its dimethyl-t-butylsilyl ether (**7c**) with the nitrone (**4**) gave, in each case, a mixture of isomers (**8b**),(**9b**) and (**8c**),(**9c**) in 93:7 and 65:35 ratio, respectively. The identical Stereochemistry of the major isomers (**8a**), (**8b**), and (**8c**) with *endo* oriented 'R' groups was confirmed by chemical conversions of (**8a**) and (**8c**) into (**8b**) (see Experimental). For favourable secondary orbital interactions[5], methoxycarbonyl group is assumed to have the *endo* orientation as depicted in (**8a**). This assumption gets further credence as switching the alkene from (**7a**) to (**7c**), relative proportion of the minor isomers with exo oriented 'R' group increases. Although one may be tempted to equate the overwhelming preference of the CH_2OH for the *endo* orientation to some kind of hydrogen bonding to stabilize the transition state, the rationale does not hold ground for similar preference domonstrated by $CH_2OSi^tBu(Me)_2$ group. It is more reasonable to attribute the *endo* preference of the 'R' groups to the stabilizing interaction between the orbital of the nitrogen atom of the nitrone-LUMO with the allylic oxygen lone pair.[5]



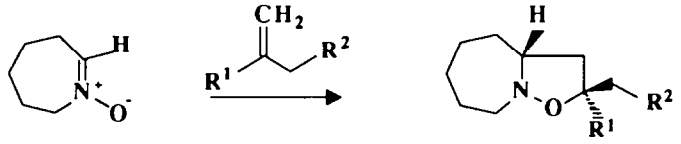
(1) (7) (10) (11)

b, R = CH_2OH	(10b)	: (11b)	85 : 15
c, R = $CH_2OSi^tBu(Me)_2$	(10c)	: (11c)	70 : 30
d, R = CH_2CH_2OH	(10d)	: (11d)	60 : 40

Scheme 2.

Cycloaddition of the nitrone (**4**) with 3-methyl-3-buten-1-ol (**7d**) and its dimethyl-t-butylsilyl ether (**7e**) afforded in each case, a mixture of adducts (**8d**),(**9d**) and (**8e**),(**9e**) in 60:40 and 55:45 ratios, respectively (Scheme 1). The stereochemistry of these adducts were confirmed by lengthy interconversions as described later. It is indeed

puzzling to note that the 'R' groups prefer *endo* orientation over methyl group even though the former would impart more severe steric constraints. The transition state is, presumably, stabilized by the favourable interaction of the orbital of the nitrogen atom in the nitrone-LUMO and the homoallylic oxygen lone pair of electrons. Similar trend is observed in the addition reaction of the nitrone (**1**) with alkenes (**7b,c**)[4b] and (**7d**). The 'R' groups containing allylic[4b] and homoallylic oxygen prefer *endo* orientations (Scheme 2).



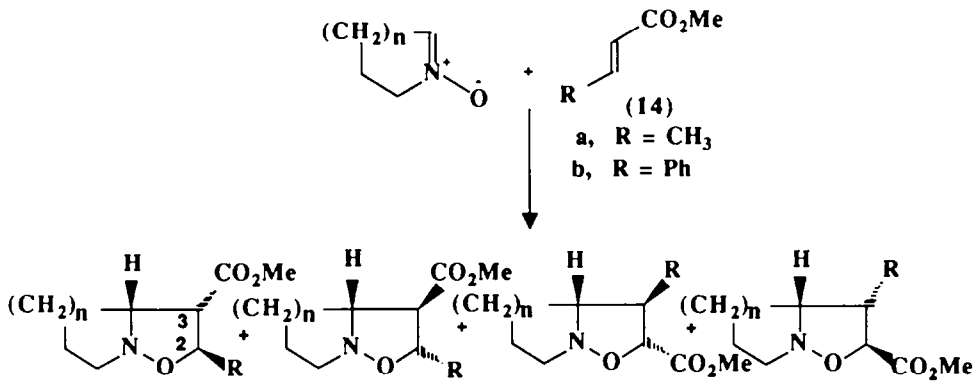
(**4**) (**12**) (**13**)

a, $R^1 = R^2 = CO_2Me$
b, $R^1 = R^2 = (CO)_2O$
c, $R^1 = R^2 = CH_2OH$
d, $R^1 = CH_2OH$, $R^2 = CH_2OSi^tBu(Me)_2$
e, $R^1 = CH_2OSi^tBu(Me)$, $R^2 = CH_2OH$;
f, $R^1 = R^2 = CH_2OSi^tBu(Me)_2$
g, $R^1 = CH_2OSO_2CH_3$, $R^2 = CH_2OSi^tBu(Me)_2$

Scheme 3.

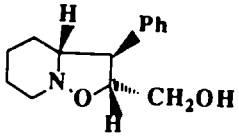
The significant tendency of conjugated carbonyl group to manifest secondary orbital interaction is demonstrated in the addition reaction of dimethyl itaconate(**12a**) and itaconic anhydride (**12b**) with the nitrone (**4**) affording sole adducts (**13a**) and (**13b**), respectively (Scheme 3). The stereochemistry as depicted in (**13**) is presumed to have the 'R^1' group in the *endo* orientation. The 'R^2' group being the more bulkier and unable to manifest secondary orbital interactions is forced to accept the *exo* position. The stereochemistry of the adduct (**13b**) was confirmed by its conversion into (**13a**) on treatment with methanolic-HCl. The cycloadduct (**13a**) was converted into (**9d**) by several steps as described below. The diol (**13c**), obtained by lithium aluminium hydride reduction of the adduct (**13a**), was silylated to give (**13d**) as the major product. Minor amounts of silylated (**13e**) and disilylated (**13f**) ethers were also obtained. The compound (**13d**), on methanesulphonation, afforded (**13g**) which on treatment with Super-hydride gave (**9e**) by S_N2 displacement of the methanesulphonate function by hydride ion.[9] The compound (**9e**) on disilylation afforded (**9d**) cleanly.

Next, we pursued the cycloaddition of cinnamate and crotonate esters onto cyclic nitrones (Scheme 4). Both alkenes (**14a, b**) demonstrated overwhelming preference to approach the cyclic nitrones (**1**), (**2**), and (**4**) with the methoxycarbonyl group in the *endo* orientation to give (**15**), (**19**), and (**23**), respectively. The stereochemistry of the major adduct (**19b**) was determined by X-ray diffraction study and was found to have the 'ee' conformation in the solid state[10](Vide Infra). However, in solution a mixture of three isomers can exist by slow nitrogen inversion.[6] Formation of the major adducts (**15b**), (**19b**), and (**23b**) certifies the methoxycarbonyl group's superiority over phenyl ring in manifestation of secondary orbital interactions. The addition reactions of the nitrones (**1**) and (**2**) onto methyl-crotonate and - cinnamate were found to be highly regioselective[4c,5], if not regiospecific.



n = 1,	(15)	(16)	(17)	(18)
n = 2,	(19)	(20)	(21)	(22)
n = 3,	(23)	(24)	(25)	(26)

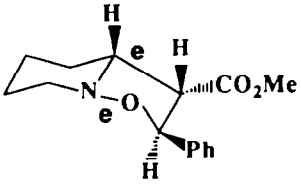
(15a) (93)	**(16a)** (7)	**(17a)** (~0)	**(18a)** (~0)
(15b) (87)	**(16b)** (8)	**(17b)** (5)	**(18b)** (~0)
(19a) (90)	**(20a)** (10)	**(21a)** (~0)	**(22a)** (~0)
(19b) (83)	**(20b)** (12)	**(21b)** (5)	**(22b)** (~0)
(23a) (80)	**(24a)** (12)	**(25a)** (7)	**(26a)** (1)
(23b) (50)	**(24b)** (13)	**(25b)** (31)	**(26b)** (6)



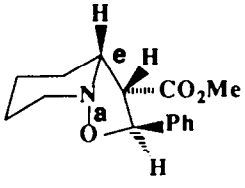
(25c)

Scheme 4.

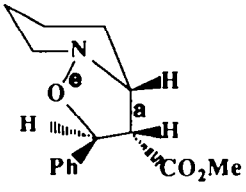
However, regioisomers with methoxycarbonyl group attached to C-2 were formed in appreciable quantities in the corresponding addition reaction of the nitrone **(4)**. The nitrone **(4)** - methyl crotonate **(14a)** addition reaction afforded a mixture of four isomers **(23a)**-**(26a)** in a ratio of 80:12:7:1 respectively (See Experimental).



(19b) ee



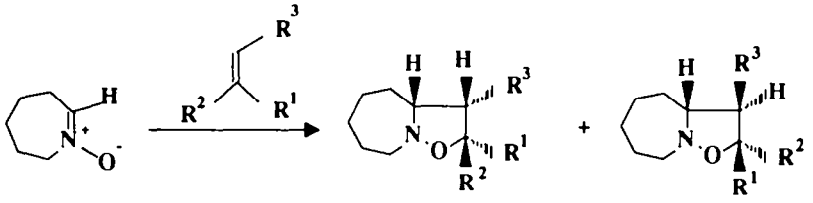
(19b) ea



(19b) ae

The nitrone **(4)** - phenyl cinnamate **(14b)** addition reaction also afforded a mixture of regiomers. The ratio of

the adducts (**23b**)-(**26b**) at 20°C and in refluxing ethanol was found to be 50:13:31:6 and 36:28:31:5, respectively. The C-2 protons of (**23b**)-(**26b**) appeared as doublets at δ5.44 (J 7.5 Hz), 5.30 (J 7.2 Hz), 4.54 (J 6.5 Hz) and 4.64 (3.5 Hz), respectively. It is a reasonable assumption to assign *endo* stereochemistry of the methoxycarbonyl at C-2 in (**25b**). Transition state leading to its formation will have relatively less steric crowding as well as favourable secondary orbital interactions than the transition state leading to (**26b**). (The C-3 carbon has more crowded environment than C-2, thus, making the former more reluctant to accept an *endo* substituent). The attachment of the methoxycarbonyl group at C-2 as depicted in (**25b**) was confirmed by its reduction to the corresponding alcohol (**25c**) by lithium aluminium hydride. The appearance of C-2 proton at δ4.17 as an X of an ABMX (J 2.8, 4.3, 6.2 Hz) instead of a doublet precludes the attachment of phenyl ring at C-2 in (**25c**) or (**25b**). Contrary to precedent literature[11], the addition of crotonate and cinnamate esters are thus found to be non-unidirectional. The frontier orbital interactions[12] inherent in the addition of these cyclic nitrones (**1**), (**2**) and (**4**) onto methyl cinnamate (or methyl crotonate) are probably similar. However, the difference in the regioisomeric distributions is presumably dictated by the difference in the steric factors in the regioisomeric transition states.



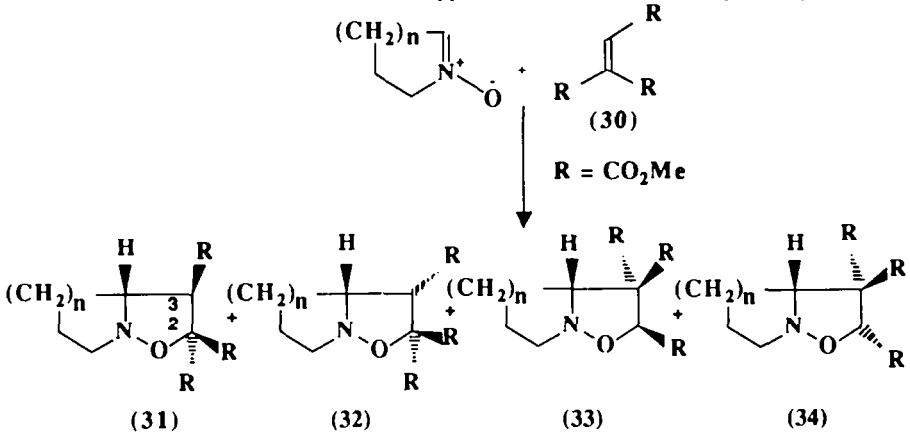
(4) (27) (28) (29)

a, $R^1 = R^3 = CO_2Me$, $R^2 = Me$,	(**28a**) : (**29a**)	75:25
b, $R^1, R^3 = (CO)_2O$, $R^2 = Me$,	(**28b**) : (**29b**)	92 :8
c, $R^1 = Me$, $R^2 = R^3 = CO_2Me$	(**28c**) : (**29c**)	~0:100

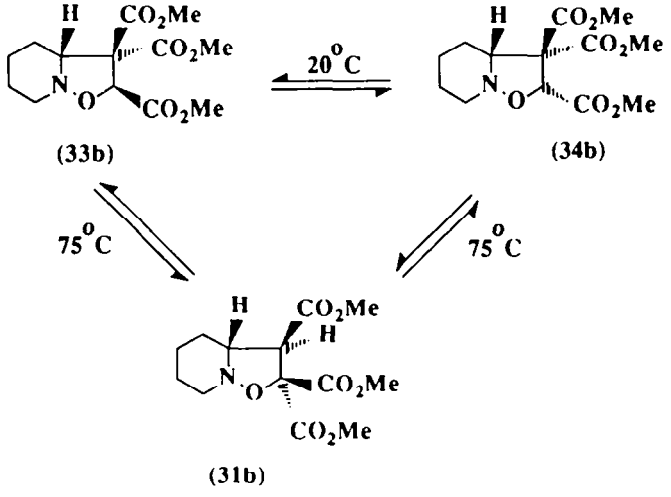
Scheme 5.

Finally, we focussed our attention to the addition reactions of some trisubstituted alkenes (**27a-c**) and (**30**) (Scheme 5 and 6). While the addition of the nitrone (**4**) onto dimethyl citraconate (**27a**) afforded (**28a**) and (**29a**) in a ratio of 75:25, the cycloaddition of citraconic anhydride (**27b**) was found to be more stereoselective to give (**28b**) and (**29b**) in 92:8 ratio, respectively (Scheme 5). All these additions demonstrate the ability of the conjugated carbonyl group to stabilize the transition state by secondary orbital interaction and circumvent the severe steric hindrance encountered in the formation of the major adducts (**28a,b**). The assignment of the configuration of the major adducts (**28a**) and (**28b**) is based on the reasonable assumption that citraconic anhydride (**27b**), due to its smaller size should give a higher proportion of *endo* oriented carbonyl groups than dimethyl citraconate (**27a**). The adducts (**28a**) and (**28b**) have similar configuration as the later was converted to the former on treatment with methanolic-HCl. In the addition reaction of dimethyl mesaconate (**27c**) both the steric factors and secondary orbital interactions work in favour of formation of (**29c**) as the sole adduct.

The regiochemical outcome observed for the addition of 1,1-di- and tri-substituted alkenes are in general agreement with the frontier orbital treatment[12] of the 1,3-dipolar cycloaddition. However, electronic controlled reversal in the regioselection was observed[4b,11b,13] in the addition reaction of highly electron deficient mono-,di-, or tri-substituted alkenes. In our study, the addition of trimethyl ethylenetricarboxylate (**30**) onto cyclic nitrones gave a mixture of isomers (**33**) and (**34**) in an approximate ratio of 64:36, respectively (Scheme 6).



a, n = 1;	**(31a)** (-o)	**(32a)** (-o)	**(33a)** (66)	**(34a)** (34)
b, n = 2;	**(31b)** (-o)	**(32b)** (-o)	**(33b)** (64)	**(34b)** (36)
c, n = 3;	**(31c)** (-o)	**(32c)** (-o)	**(33c)** (64)	**(34c)** (36)



Scheme 6.

The regiochemical outcome is in line with the prediction based on the dominant nitrone (HOMO) - alkene (LUMO) interaction in the transition state.[12] The major isomer is assumed to have the stereochemistry as depicted in (**33**) on the assumption that the transition state leading to its formation would be less crowded with *exo* oriented methoxycarbonyl group at C-2. The adduct (**33**) is indeed more stable than (**34**) as demonstrated by an

experiment where a solution of the pure isomer (**33b**) in chloroform at 20°C was equilibrated to a mixture of (**33b**) and (**34b**) in a ratio of 70:30, respectively. However, at 75°C the adducts (**33b**) and (**34b**) were converted into thermodynamically controlled adduct (**31b**) almost completely (Scheme 6). We were unable to detect the presence of the isomer (**32b**) in the equilibrium mixture. The most stable adduct was assigned the least crowded stereochemistry as depicted in (**31**) with *exo* methoxycarbonyl group at C-3.

EXPERIMENTAL

All m.p.s. are uncorrected. Elemental analyses were performed on a Carlo-Erba Elemental analyser 1106. IR spectra were recorded on a Perkin-Elmer instrument Model 237B, and are reported in cm^{-1}. Silica gel chromatographic separations were performed with flash silica (Baker Chemical Co.). All solvents were reagent grade. The N-hydroxypyrrolidine, N-hydroxypiperidine, N-hydroxyhexahydroazepine[14] and all the liquid alkenes were distilled prior use. Depending on the reaction conditions as described in the literature, citraconic anhydride (**27b**) was converted into citraconic acid[16a] and mesaconic acid[16b] which on treatment with diazomethane afforded dimethyl citraconate (**27a**) and dimethyl mesaconate (**27c**), respectively. Trimethyl ethylenetricarboxylate (**30**) was prepared by literature procedure.[15] 1-Pyrroline 1-oxide (**1**), 3,4,5,6-tetrahydropyridine 1-oxide (**2**), and 3,4,5,6-tetrahydro-2H-azepine 1-oxide (**4**) were made as described before.[3] The solution of the nitrone (**2**) and (**4**) were kept in the freezer in order to avoid dimer- and polymer-ization, respectively. ^1H NMR spectra were recorded on a Bruker AC 80 spectrometer, operating at a proton frequency of 80 MHz. Some of the spectra were recorded on a Varian XL 200 NMR Spectrometer operating at a proton frequency of 200 MHz and in the pulse Fourier Transform mode. Deuteriated chloroform with Me_4Si as an internal standard was used. Cycloaddition reactions were carried out under nitrogen.

Reaction of the Nitrone (4) with Methyl methacrylate (7a).- A solution of the nitrone (**4**) (5.0 mmol) and methyl methacrylate (5.0 mL) in dichloromethane (20 mL) was stirred at 20°C for 24 h. After removal of the solvent and excess alkene the residual liquid was chromatographed using dichloromethane - ether mixture (60:40) as eluant to give (**8a**) as a colourless liquid (862 mg, 81%). On further elution the minor adduct (**9a**) was obtained as a colourless liquid (55 mg, 5.2%). Adduct (**8a**): (Found: C, 52.72; H, 8.11; N, 5.24. $C_{11}H_{19}NO_3$.HCl requires C, 52.90; H, 8.07; N, 5.61 %); υ_{max}(neat) 2916, 2840, 1734, 1454, 1301, 1194, 1174, 1130, and 964 cm^{-1}; δ_H (200 MHz)1.49 (3 H, s), 1.46-2.14 (8 H, m), 2.28 (1 H, dd, J 7.0, 12.0 Hz), 2.59 (1 H, dd, J 9.0, 12.0 Hz), 2.68 (1 H, m), 2.97 (1 H, m), 3.56 (1 H, m), and 3.80 (3 H, s). A portion of the adduct (**8a**) was reduced with lithium aluminium hydride to afford (**8b**) as a colourless liquid (90%), the IR and NMR spectra of which virtually matched with that of the 2-methyl-2-propen-1-ol adducts. Adduct (**9a**): υ_{max}(neat) 2928, 2848, 1734,1448, 1298, 1198, 1173, and 913 cm^{-1}; δ_H (200 MHz) 1.53 (3 H, s), 1.40-2.12 (6 H, m), 2.00 (1 H, dd, J 10.5,12.0 Hz), 2.20-2.60 (2 H, m), 2.86 (1 H, dd, J 7.0, 12.0 Hz), 2.92 (1 H, m), 3.14 (1 H, m), 3.50 (1 H, m), and 3.80 (3 H, s).

Reaction of the Nitrone (4) with 2-methyl-2-propen-1-ol (7b).- A solution of the nitrone (**4**) (5.0 mmol) and the alkene (**7b**) (5.0 mL) in dichloromethane (30 ml) was stirred at 20°C for 24 h. The reaction mixture was then reduced to a volume of 10 mL by blowing a gentle stream of nitrogen and stirring was continued for a further 24 h. After removal of the solvent and excess alkene the residual liquid was chromatographed using a mixture of ether - methanol (95:5) as eluant to afford a non-separable mixture of isomers (**8b**) and (**9b**) as a colourless oil (77%) in a ratio of 93:7 as determined by the integration of the methyl singlets; (Found: C, 54.37; H, 9.29; N, 6.37. $C_{10}H_{19}NO_2$.HCl requires C, 54.17; H, 9.09; N, 6.32%); υ_{max}(neat) 3400, 2908, 2845, 1660, 1453, 1404, 1304, 1160, 1054 and 960 cm^{-1}; δ_H (200 MHz) 1.22 (3 H,s) and a minor singlet at δ1.31, 1.40-2.00 (8 H, m), 2.18 (2 H, d, J 6.0 Hz), 2.56(1 H, m), 2.90 (1 H, m), 3.46 (2 H, m) and 3.60 (2 H, AB, J 10.0 Hz).

Reaction of the Nitrone (4) with t-Butyl-dimethylsilyl ether (7c). - A solution of the nitrone (**4**) (2.0 mmol) and the alkene (**7c**) (1.0 g, 5.4 mmol) in ethanol (10 mL) was refluxed under N_2 for 24 h. The crude mixture of adducts was separated by chromatography using hexane - ethyl acetate (90:10) as eluant to give (**8c**) as a colourless liquid (210 mg, 35%); $\upsilon_{max.}$ (neat) 2907, 2828, 1462, 1385, 1363, 1257, 1108, and 845 cm^{-1}; δ_H 0.06 (6 H, s), 0.90 (9 H, s), 1.24 (3 H, s), 1.35-2.25 (10 H, m), 2.40-3.20 (2 H, m), 3.40 (1 H, m), and 3.55 (2 H, AB, J 10.0 Hz). Continued elution afforded (**9c**) as a colourless liquid (112 mg, 19%); $\upsilon_{max.}$(neat) 2906,

2833, 1463, 1387, 1366, 1261, 1111, and, 849 cm^{-1}; δ_H 0.06 (6 H, s), 0.90 (9 H, s), 1.30 (3 H, s), 1.43-2.05 (9 H, m), 2.28-3.10 (3 H, m, including an 1H, dd (J 6.5, 12.0 Hz at δ2.48), 3.40 (2 H, AB, J 10.0 Hz) and an overlapping m for 1 H). The separated isomers (**8c**) and (**9c**) was thus formed in a ratio of 65:35, respectively. The integration of the C(2) methyl singlets of the crude reaction mixture also revealed the similar ratio (62:38). Desilylation of the major adduct with aqueous HCl afforded the isomer (**8b**) in almost quantitative yield.

Reaction of the Nitrone (4) with 3-Methyl-3-buten-1-ol (7d). - A solution of the nitrone (**4**) (4.0 mmol) and the alkene (**7d**) (4 mL) in ethanol (10 mL) was refluxed under N_2 for 24 h. After removal of the solvent and excess alkene, the non-separable mixture of adducts was purified by chromatography using hexane-ethyl acetate mixture (70:30) as eluant to give (**8d**), (**9d**) as a colourless liquid (560 mg, 70%). The ^1H NMR spectrum revealed the presence of two isomers. Integration of the C(2) methyl singlets at δ 1.31 and 1.38 revealed the presence of the adducts (**8d**) and (**9d**) in a ratio of 60:40, respectively. (Found: C, 66.05; H, 10.45; N, 6.95. $C_{11}H_{21}NO_2$ requires C, 66.29; H, 10.62; N, 7.03%). The NMR and IR spectra of the adduct (**9d**) prepared by a different route are described later. The adduct mixture was silylated (dimethyl formamide, imidazole, t-butyl-dimethylchlorosilane) to give a separable mixture of compounds (**8e**) and (**9e**) in an approximate ratio of 60:40 respectively.

Reaction of the Nitrone (4) with t-Butyl-dimethylsilyl ether (7e).- A solution of the nitrone (**4**) (2.0 mmol) and the alkene (**7e**) (1.2 g, 6.0 mmol) in ethanol (10 mL) was refluxed under N_2 for 24 h. After removal of the solvent the residual mixture was chromatographed using hexane-ethyl acetate mixture as eluant to give (**8e**), followed by a major portion of the mixture (**8e**) and (**9e**) and finally the pure adduct (**9e**). A total of 320 mg (51%) of the adducts was isolated. Careful analysis of the NMR spectra of the crude reaction mixture and different eluted fractions revealed the presence of the isomers (**8e**) and (**9e**) in a ratio of 55:45, respectively. The ratio was determined by the integration of the C-2 methyl protons. Compound (**8e**): Colourless liquid, $\upsilon_{max.}$(neat) 2904, 2832, 1462, 1386, 1260, 1097, 920 and 845 cm^{-1}; δ_H 0.06 (6 H, s), 0.90 (9 H, s), 1.24 (3 H, s), 1.40-2.26 (12 H, m), 2.40-3.20 (2 H, m), 3.40 (1 H, m), and 3.70 (2 H, t, J 7.0 Hz). Compound (**9e**): Colourless liquid, $\upsilon_{max.}$(neat) 2900, 2830, 1465, 1391, 1263, 1099, and 848 cm^{-1}; δ_H 0.06 (6 H, s), 0.90 (9 H, s), 1.33 (3 H, s), 1.20 - 2.00 (11 H, m), 2.27 - 3.05 (3 H, m including an 1 H, dd (J 7.0, 12.0 Hz) at δ 2.44), 3.42 (1 H, m) , and 3.72 (2 H, t, J 7.0 Hz).

Reaction of the Nitrone (1) with 3-Methyl-3-buten-1-ol (7d). - A solution of the nitrone (**1**) (3.0 mmol) and the alkene (**7d**) (3 mL) was heated at 90° for 10 h. Chromatographic purification using ether-methanol (10:1) as the eluant afforded a non-separable mixture of isomers (**10d**) and (**11d**) in a ratio of 60:40, respectively as a colourless liquid (450 mg, 88%); $\upsilon_{max.}$(neat) 3220, 2930, 2852, 1447, 1377, 1296, 1120, 1052, and 912 cm^{-1}; δ_H 1.32 (0.45x3 H, s), 1.37 (0.55 x 3 H, s), 1.48-2.73 (8 H, m), 2.80-3.60 (4 H, m), and 3.78 (2 H, two overlapping triplets).

Reaction of the Nitrone (4) with Dimethyl Itaconate (12a).- A solution of the nitrone (**4**) (9.0 mmol) and dimethyl itaconate (1.71g, 15 mmol) in dichloromethane (40 mL) was stirred at 20°C for 5 h. After removal of the solvent the residual liquid was purified by chromatography using dichloromethane-ethyl acetate mixture (90:10) as eluant to give the adduct (**13a**) as a colourless liquid (2.03 g, 83%). (Found: C, 50.35; H, 7.24; N, 4.46. $C_{13}H_{21}NO_5$.HCl requires C, 50.73; H, 7.20; N, 4.45 %); $\upsilon_{max.}$(neat) 2910, 2833, 1736, 1440, 1360, 1314, 1194, 1023 and 930 cm^{-1}; δ_H 1.33-2.20 (8 H, m), 2.40-3.20 (6 H, m, including a 2 H, s at δ 2.90), 3.45 (1 H, m), 3.66 (3 H, s), and 3.78 (3 H, s).

Reaction of the nitrone (4) with Itaconic anhydride (12b) and conversion of the Adduct (13b) into (13a). - To a solution of the nitrone (**4**) (2.7 mmol) in dichloromethane (12 mL) was added itaconic anhydride (320 mg, 2.86 mmol) and the reaction mixture was stirred at 20°C for 5 h. The reaction mixture containing (**13b**), after removal of the solvent, was treated with methanolic-HCl (5 mL, 5:3 w/w) and kept at 20°C for 12 h. The acid solution was taken up in H_2O (15 mL) and washed with ether (3x10 mL). The aqueous layer was then basified and saturated with K_2CO_3. Extraction of the aqueous layer with ether (3x15 mL) followed by drying ($MgSO_4$) and evaporation of the organic layer afforded the adduct (**13a**) (500 mg) as a yellow liquid. Overall yield of the reaction was found to be 79%.

Conversion of the Dimethyl itaconate adduct (13a) into (9d). - The adduct (**13a**) (900 mg, 3.3 mmol) was reduced with lithum aluminium hydride as before.[5] Extensive wash of the inorganic salt with ether,

dichloromethane, and finally methanol afforded the diol which on chromatographic purification with 95:5 ethyl acetate-methanol as eluant afforded the diol (**13c**) (650 mg, 91%) as a colourless liquid, υ_{max}(neat) 3300, 2902, 2834, 1454, 1291, 1062, and 922 cm^{-1}; δ_H 1.30-2.45 (12 H, m), 2.50-3.12 (2 H, m), 3.45 (3 H, m), 3.60 (2 H, s), and 3.75 (2 H, m). To a solution of the diol (**13c**) (430 mg, 2.0 mmol) in dimethyl formamide (3 mL) was added imidazole (272 mg, 4 mmol) and t-butyl-dimethylsilylchloride (226 mg, 1.5 mmol). The reaction mixture after keeping at 20°C for 4 h was taken up in ether (20 mL) and washed with saturated $NaHCO_3$ solution (15 mL) and water (3x15 mL). The organic layer after concentration was chromatographed using 4:1 hexane-ethyl acetate as eluant to give disilyl ether (**13f**) (120 mg, 14%) as a colourless liquid, υ_{max}(neat) 2918, 2887, 2822, 1469, 1460, 1387, 1259, 1097, and 833 cm^{-1}; δ_H 0.06 (12 H, s), 0.90 (18 H, s), 1.20-2.95 (14 H, m), and 3.25-4.02 (5 H, m). Continued elution afforded probably (**13e**) in minor quantity (20 mg, 3%) which was not further analyzed. Further elution gave the anticipated compound (**13d**) as a colourless liquid (230 mg, 35%), υ_{max}(neat) 3360, 2900, 2830, 1461, 1388, 1260, 1096, 920, and 848 cm^{-1}; δ_H 0.07 (6 H, s), 0.90 (9 H, s), 1.30-3.00 (15 H, m), 3.45 (1 H, m), 3.62 (2 H, s), and 3.75 (2 H, t, J 6.3 Hz).

To a solution of the compound (**13d**) (220 mg, 0.67 mmol) in pyridine (1 mL) was added methanesulfonyl chloride (1.2 mmol) at -15°C. The mixture was kept at 0°C for 12 h, then added onto ice-H_2O and extracted with chloroform (3 x 10 mL). The organic layer was washed with saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated to give the methanesulfonate (**13g**) as a faint yellow liquid (242 mg, 89%), υ_{max}(neat) 2926, 2900, 2827, 1461, 1362, 1260, 1183, 1098, and 970 cm^{-1}; δ_H 0.06 (6 H, s), 0.89 (9 H, s), 1.30-2.04 (11 H, m, including an overlapping 2H, t, J 6.0 Hz at δ 1.88), 2.20 - 2.85 (3 H, m), 3.06 (3 H, s), 3.49 (1 H, m), 3.78 (2 H, t, J 6.0 Hz), 4.10 (1 H, d, J 10.8 Hz, part of an AB) and 4.50 (1 H, d, J 10.8 Hz, part of an AB). To the methanesulfonate (**13g**) (150 mg, 0.37 mmol) was added a solution of super-hydride in THF (2 mL, 2 mmol) and the closed system was heated to 75°C for 4 h. TLC experiment using ether indicated the completion of the reaction. Aqueous work up and extraction with ether afforded a crude mixture of products which were separated by chromatography using 4:1 Hexane-ethyl acetate as eluant to give the desired compound (**9e**) (17 mg, 15%) and finally the adduct (**13d**) (68 mg, 56%) through O-S bond fission.

To the compound (**9e**) (17 mg, .054 mmol) in a vial was added 10% aqueous HCl and the mixture was shaken. After washing the acidic solution with ether (3x2 mL) the aqueous layer was basified (K_2CO_3) and extracted with ether (3x2 mL). The organic layer was dried (Na_2SO_4) and concentrated to give (**9d**) (8 mg, 74%); $\upsilon_{max.}$ 3350, 2907, 2822, 1452, 1390, 1287, 1062, and 952 cm^{-1}; δ_H 1.38 (3 H, s), 1.45-2.03 (11 H, m), 2.15-3.60 (5 H, m including a dd (1 H, J 7.5 Hz) at δ 2.45 ppm), and 3.80 (2 H, apparent t, J 6.0 Hz).

Reaction of the Nitrone (4) with Methyl Crotonate (14a).- A solution of the nitrone (**4**) (5.0 mmol) and methyl crotonate (5 mL) in dichloromethane (20 mL) was stirred at 20°C for 24 h. After reducing the volume of the reaction mixture to 10 mL it was stirred at 20°C for a further 24 h. The reaction mixture, after removal of the solvent and excess alkene, was purified by chromatography using ether as eluant to give a non-separable mixture of adducts (**23a**) and (**24a**) as a colourless liquid. (Found C, 61.78; H, 9.07; N, 6.38. $C_{11}H_{19}NO_3$ requires C, 61.94; H, 8.98; N, 6.57%); $\upsilon_{max.}$(neat) 2914, 2844, 1734, 1439, 1384, 1199, 1134, 1041 and 954 cm^{-1}; δ_H (200 MHz) 1.31 (3 H, d, J 6.0 Hz), 1.40 - 2.00 (8 H, m), 2.68 (1 H, m), 3.00 (1 H, dd, J 8.0, 10.0 Hz), 3.22 (1 H, m), 3.56 (1 H, m), 3.75 (3 H, s) and 4.51 (1 H, quint, J 6.0 Hz). There was a minor at δ1.35 (J 6.0 Hz) and a minor quintet at δ4.38 (J 6.0 Hz). Continued elution afforded a mixture of (**25a**) and (**26a**) and finally the pure isomer (**25a**). Adduct (**25a**) : colourless liquid; δ_H 1.24 (3 H, d, J 6.0 Hz), 1.36-2.10 (8 H, m), 2.48 (2 H, m), 2.76 (1 H, m), 3.60 (1 H, m), 3.80 (3 H, s), and 4.15 (1 H, d, J 8.0 Hz). The NMR spectrum of the mixture of isomers displayed an 1 H, d, J 5.0 Hz and 3 H, d, J 6.0 at δ 4.17 and 1.19, respectively, assigned to the C-2 H and C-3 methyl of the minor isomer (**26a**). Careful analysis of the NMR spectra of crude reaction mixture and different eluted fraction revealed the presence of the isomers (**23a**)-(**26a**) in a ratio of 80:12:7:1, respectively. A total of 840 mg (79%) of adducts was isolated.

Reaction of the Nitrones (1), (2) and (4) with trans-Methyl Cinnamate (14b).- A solution of the nitrone (**4**) (4.0 mmol) and methyl cinnamate (1.62 g, 10 mmol) in ethanol (10 mL) was refluxed under N_2 for 20 h. After removal of the solvent the residue was chromatographed using hexane-ethyl acetate (93:7) as eluant to give a non-separable mixture of isomers (**23b**) and (**24b**) (520 mg, 47%). Crystalization from dichloromethane-

ether afforded **(23b)** as colourless needles, m.p. 79-80°C (Found: C, 69.75; H, 7.63; N, 4.91. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09%); $\upsilon_{max.}$(KBr) 2995, 2960, 2904, 2815, 1725, 1456, 1442, 1385, 1360, 1239, 1196, 1176, 1065, and 1032 cm^{-1}; δ_H 1.35-2.20 (8 H, m), 2.65-3.05 (1 H, m), 3.25-3.70 (3 H, m), 3.74 (3 H, s), 5.44 (1 H, d, J 7.5 Hz), and 7.35 (5 H, m). After repeated crystallization, the mother liquor was stripped of the major isomer **(23b)** and concentration of the mother liquor afforded the adduct **(24b)** as a colourless liquid; (Found: C, 70.01; H, 7.52; N, 4.86. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09%); $\upsilon_{max.}$(neat) δ_H 1.35-2.25 (8 H, m), 2.65-3.65 (3 H, m), 3.15 (1 H, dd, J 7.2, 9.3 Hz), 3.74 (3 H, s), 5.30 (1 H, d, J 7.2 Hz), and 7.20-7.60 (5 H, m). Continued elution afforded a mixture of (23b), (24b), (26b) (200 mg, 18%) and finally the pure adduct **(25b)** was obtained as a colourless liquid (200 mg, 18%) ; $\upsilon_{max.}$(neat) 2995, 2902, 2830, 1744, 1456, 1439, 1260, 1206, 1088, 1024, 800, 775, and 715 cm^{-1}; δ_H 1.28-2.12 (8 H, m), 2.60-3.20 (2 H, m), 3.60 (1 H, dd, J 6.5, 9.5 Hz and another 1 H, m underneath), 3.75 (3 H, s), 4.54 (1 H, d, J 6.5 Hz) and 7.32 (5 H, s). The ^1H NMR spectrum of the crude reaction mixture indicated the presence of **(23b)**, **(24b)**, **(25b)** and **(26b)** in a ratio of 36:28:31:5, respectively, as determined by the integration of the C-2 protons. The C-2 H of the isomer **(26b)** appeared at δ 4.64 as a doublet (J 3.5 Hz). However, when a solution of the nitrone **(4)** (1.5 mmol) and methyl cinnamate (486 mg, 3.0 mmol) in dichloromethane (10 mL) was stirred at 20°C for 72 h, NMR spectra of the crude reaction mixture and purified adducts (51%) revealed the presence of all four isomers **(23b)**, **(24b)**, **(25b)**, and **(26b)** in a ratio of 50:13:31:6, respectively, as determined by the integration of the C-2 protons.

Addition reactions of the nitrones **(1)** and **(2)** with phenyl cinnamate, already reported[4c,5] as regiospecific, are repeated in refluxing ethanol for 4 h. Detailed analysis of the NMR spectrum of the crude reaction mixture displayed minor doublets at δ4.53 (J 7.8 Hz) and 4.50 (J 6.0 Hz) assigned to the C-2 H of **(17b)** and **(21b)**, respectively (see Scheme 4).

Conversion of the Cycloadduct (25b) into (25c).- The adduct **(25b)** (70 mg, 0.25 mmol) on reduction with lithium aluminium hydride afforded the alcohol **(25c)** as a colourless liquid (60 mg, 97%); υ_{max}(neat) 3340, 2900, 2830, 1490, 1448, 1380, 1070, 1043, 884, 786, and 756 cm^{-1}; δ_H 1.20-2.20 (8 H, m), 2.50-3.85 (7 H, m including an 1H (dd, Z 6.2, 8.8 Hz) at δ3.27 and a 2 H (ABX, J 2.8, 4.3, 11.6 Hz at δ3.70), 4.17 (1 H, ABMX, J 2.8, 4.3, 6.2 Hz), and 7.26 (5 H, m).

Reaction of the Nitrone (4) with Dimethyl citraconate (27a). - A solution of the nitrone **(4)** (2.0 mmol) and dimethyl citraconate (3.0 mmol) in dichloromethane (20 mL) was refluxed for 12 h. After removal of the solvent the residual liquid was chromatographed using dichloromethane - ethyl acetate (85:15) mixture as eluant to give a mixture of **(28a)**, **(29a)** and finally the pure isomer **(28a)**. A total of 397 mg (73%) was recovered. The major isomer **(28a)** was isolated as a colourless liquid; (Found: C, 50.46; H, 7.10; N, 4.27. $C_{13}H_{21}NO_5$. HCl requires C, 50.73; H, 7.21; N, 4.55 %); υ_{max}(neat) 2918, 2840, 1736, 1440, 1375, 1252, 1202, 1171, 1130, 1051, 966, and 920 cm^{-1}; δ_H 1.10-2.10 (8 H, m), 1.59 (3 H, s), 2.44-2.90 (1 H, m), 3.16 (1 H, m), 3.40 (1 H, d, J 7.0 Hz), 3.65 (1 H, m), 3.70 (3 H, s) and 3.76 (3 H, s). The ^1H nmr spectrum of the mixture of isomers displayed the following identifiable signals for the minor isomer **(29a)**: δ 1.65 (3 H, s), 3.02 (1 H, d, J 10.0 Hz), and two closely spaced singlets at δ 3.73 due to CO_2CH_3 signals. Nmr analysis of the crude reaction mixture and the purified adducts revealed the presence of the isomer **(28a)**, **(29a)** in a 75:25 ratio, respectively.

Reaction of the Nitrone (4) with Citraconic Anhydride (27b).- To a solution of the nitrone **(4)** (2.0 mmol) in dichloromethane (10 mL) containing citraconic anhydride (2.0 mmol) was stirred at 20°C for 4 h. After removal of the solvent, the residual solid is crystallized from dichloromethane-ether mixture to give **(28b)** as colourless plates, m.p. 71-72°C (dichloromethane - ether) (Found: C, 58.81; H, 6.64; N, 6.32. $C_{11}H_{15}NO_4$ requires C, 58.65; H, 6.71; N, 6.22%);

υ_{max}(KBr) 2914, 2830, 1852, 1775, 1470, 1450, 1384, 1243, 1195, 1072, 1048, 990 and 930 cm^{-1}; δ_H 1.26-2.00 (7 H, m), 1.62 (3 H, s), 2.16 (1 H, m), 2.64 (1 H, m), 3.04 (1 H, m), 3.25 (1 H, d, J 8.0 Hz) and 3.56 (1 H, m). The above experiment was repeated and the residual solid was treated with 5 mL methanol - HCl (5:3 w/w). The mixture was stirred overnight and usual work up afforded the esterified adducts **(28a)** and **(29a)**, (410 mg, 76%) as a faint yellow liquid. The NMR analysis revealed the presence of the above isomers in a 93:7 ratio.

Reaction of the Nitrone (4) with Dimethyl mesaconate (27c). - A solution of the nitrone (**4**) (1.0 mmol) and dimethyl mesaconate (175 mg, 1.1 mmol) in dichloromethane (10 mL) was stirred at 20°C for 12 h. Removal of the solvent and chromatographic purification using dichloromethane-ether mixture afforded (**28d**) as the sole adduct (240 mg, 88%) as colourless needles, m.p. 59-60°C (dichloromethane-ether) (Found: C, 57.53; H, 7.76; N, 4.98. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.80; N, 5.16 %); $\upsilon_{max.}$(KBr) 2912, 2817, 1726, 1440, 1383, 1357, 1282, 1245, 1213, 1125, 994, 963 and 860 cm^{-1}; δ_H 1.38 (3 H, s), 1.45-2.25 (8 H, m), 2.52-2.90 (1 H, m), 3.10-3.67 (2 H, m), 3.76 (1 H, d, J 8.3 Hz), 3.73 (3H, s) and 3.80 (3 H, s).

Reaction of the Nitrone (1) with Trimethyl ethylenetricarboxylate (30).- To a solution of the nitrone (**1**) (1.0 mmol) in dichloromethane (5 mL) at -15°C (salt-ice) was added the alkene (**30**) (1.0 mmol) and the mixture was stirred at -15°C for 30 min. After removal of the solvent the NMR spectrum of the crude adducts revealed the presence of isomers (**33a**), (**34a**) in a ratio of 66:34, respectively, as determined by the integration of C-2 protons. Attempt to purify and separate the isomers by flash silica gel chromatography using cold (-10°C) dichloromethane - ether (4:1) as eluant was unsuccessful as extensive decomposition to starting materials happened. The NMR spectrum of the crude reaction mixture revealed the following identifiable peaks: three methyl singlets at δ 3.72, 3.74, 3.79 and a C-2 H singlet at δ5.22 was attributed to the major isomer (**33a**); the corresponding peaks for the minor isomer (**34a**) appeared at δ 3.70, 3.77, 3.83 and 4.90, respectively. We were unable to detect the presence of regioisomers (**31a**) or (**32a**). The IR spectrum has a strong absorption at 1747 cm^{-1}. When a solution of the above mixture of adducts (**33a**) and (**34b**) (50 mg) in $CDCl_3$ was heated at 75°C in a sealed NMR tube for 90 min., a new adduct (**31a**) was formed. Methyl singlets for the regiomer appeared at δ 3.71, 3.80, and 3.85. The ratio of the isomers (**31a**), (**33a**), and (**34a**) after equilibration was found to be approximately 80:15:6, respectively, as determined by the detailed analysis of the NMR spectrum. We were unable to detect the presence of the isomer (**32a**).

Reaction of the Nitrone (2) with Trimethyl ethylenetricarboxylate (30).- To a solution of the nitrone (**2**) (4.0 mmol) in dichloromethane at -15°C was added the alkene (**30**) (606 mg, 3.0 mmol) and stirred for 30 min. After removal of the solvent the crude adduct mixture was chromatographed using a cold (-10°C) mixture of dichloromethane-ether (9:1) as the eluant. Extensive decomposition occurred during chromatography. However, we were able to obtain an analytically pure sample of the adduct (**33b**) (228 mg, 25%). Most of the other eluted fraction contained a mixture of adducts (**33b**) and (**34b**) along with the alkene (**30**). Adduct (**33b**): colourless crystals, m.p. 71-73 °C (ether-hexane) (Found: C, 51.94; H, 6.19; N, 4.45. $C_{13}H_{19}NO_7$ requires C, 51.82; H, 6.36; N, 4.65%); $\upsilon_{max.}$(KBr) 2937, 2917, 2816, 1760, 1729, 1438, 1322, 1282, 1218, 1148, 1084, 1068, 1030, 974, and 925 cm^{-1}; δ_H 1.05-2.35 (6 H, m), 2.65 (1 H, m), 3.12 (1 H, m), 3.55 (1 H, m), 3.70 (3 H, s), 3.73 (3 H, s), 3.80 (3 H, s), and 5.25 (1 H, s). ^1H NMR spectrum of a fraction rich in the isomer (**34b**), displayed the signals due to the three methyls and C(2) proton at δ3.72, 3.76, 3.87, and 4.98, respectively. The NMR spectrum of the crude adducts revealed the presence of the isomers (**33b**) and (**34b**) in a ratio of 64:36, respectively as determined by the integration of the C-2 protons. Cycloreversion of these adducts happens so readily that when a solution of the adduct (**33b**) (50 mg) in $CDCl_3$ (0.7 mL) was kept at 20°C for 24 h, it was converted into a mixture of (**33b**) and (**34b**) in a ratio of 70:30, respectively. When the adduct mixture was heated to 72°C for 20 h in a sealed NMR tube it was converted into the regioisomeric adduct (**31b**); δ_H 1.05-2.05 (6 H, m), 2.35-3.00 (3 H, m), 3.50 (1 H, m), 3.70 (3 H, s), 3.77 (3 H, s), and 3.84 (3 H, s). The NMR spectra revealed the presence of the isomers (**33b**), (**34b**) in a minor quantity (approximately 8% of the total adducts).

Reaction of the Nitrone (4) and trimethyl ethylenetricarboxylate (30).- The cycloaddition of the nitrone (**4**) with alkene (**30**) at -15°C afforded a mixture of adducts (**33c**) and (**34c**) in a ratio of 64:36, respectively, as determined by the integration of C-2 protons. As in the case of the nitrone (**1**) adducts, chromatographic purification of the adduct mixture was unsuccessful even when the cold (-10°C) eluant dichloromethane-ether (95:5) was used for the flash silica gel chromatography. Decomposition of the adducts to starting materials was more complete in this case as the eluted materials contained mostly the starting alkene. The NMR spectrum of the crude adducts displayed the following identifiable signals: three carboxmethoxy methyls and the C-2 proton of the major isomer (**33c**) appeared at δ 3.73, 3.76, 3.83 and 5.17, respectively. The corresponding signals for the minor isomer (**34c**) appeared at δ 3.76 (two of the three methyls), 3.86, and 5.05, respectively.

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10. Results of the X-ray structure determination and substituent effects on the nitrogen inversions will be published elsewhere.

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