1,3-Dipolar Cycloadditions of Cyclic Nitrones with Trisubstituted Alkenes

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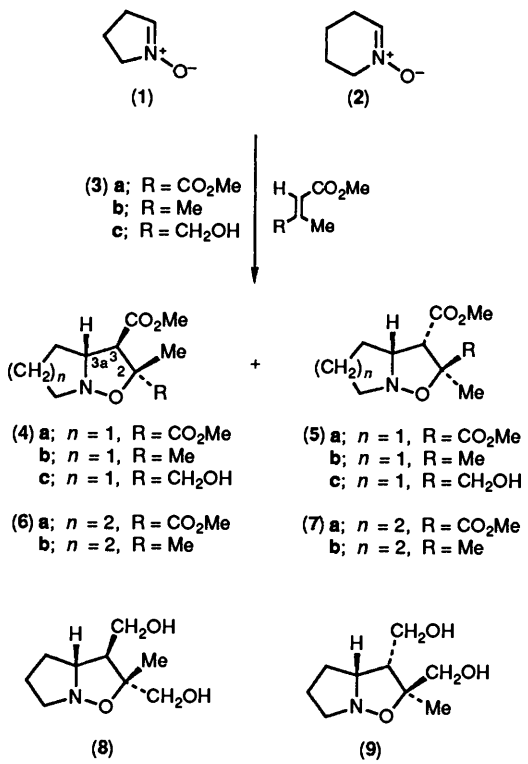
A study of the regio- and stereo-chemical behaviour of the 1,3-dipolar cycloaddition of a series of trisubstituted alkenes with the cyclic nitrones 1-pyrroline 1-oxide (**1**) and 3,4,5,6-tetrahydropyridine 1-oxide (**2**) has been carried out. Regio- and stereo-selectivity in these cycloadditions have been explained in terms of maximum overlap of frontier orbitals, steric encumbrance, and secondary orbital interactions. The activation parameters and the effect of solvent on the rate constant for the addition reaction of a highly polarized alkene indicate the concerted nature of the reaction. The nitrone (**2**) is found to be more reactive than the nitrone (**1**) in all of these additions.

1,3-Dipolar cycloadditions of cyclic nitrones to mono- and di-substituted alkenes have been studied in great detail.[1,2] Reactivity and regio- and stereo-selectivity[2,4,5] phenomena in these concerted cycloadditions can generally be rationalized by use of frontier orbital considerations.[6] 1-Pyrroline 1-oxide (**1**) and 3,4,5,6-tetrahydropyridine 1-oxide (**2**) have emerged as the most important cyclic nitrones, since their addition reactions have already had a significant impact on the synthesis of natural products containing pyrrolidine and piperidine moieties.[1]



Scheme 1.

However, the reaction of these cyclic nitrones with trisubstituted alkenes has been examined to only a limited extent.[7,8] Here, we report in detail the regio- and stereo-chemical features along with reactivity phenomena associated with the addition reactions of (**1**) and (**2**) with several trisubstituted alkenes.

Results and Discussion

All reactions were carried out under conditions that would reflect kinetic rather than thermodynamic factors. Regio- and stereo-chemical details of these additions are given in Table 1.

Table 1. Stereochemistry of cycloadditions of the nitrones (**1**) and (**2**) with trisubstituted alkenes.

Alkene	Nitrone	Composition[a] of adducts		Isolated yield (%)
(**3a**)	(**1**)	(**4a**) (100)	(**5a**) (0)	86
(**3a**)	(**2**)	(**6a**) (100)	(**7a**) (0)	93
(**3b**)	(**1**)	(**4b**) (50)	(**5b**) (50)	77
(**3b**)	(**2**)	(**6b**) (57)	(**7b**) (43)	81
(**3c**)	(**1**)	(**4c**) (60)	(**5c**) (40)	75
(**10a**)	(**1**)	(**11a**) (70)	(**12a**) (30)	74
(**10a**)	(**2**)	(**13a**) (75)	(**14a**) (25)	86
(**10b**)	(**1**)	(**11b**) (92)	(**12b**) (8)	79[b]
(**10b**)	(**2**)	(**13b**) (78)	(**14b**) (22)	84[b]
(**17**)	(**1**)	(**18**) (72)	(**19**) (28)	81
(**17**)	(**2**)	(**20**) (70)	(**21**) (30)	92

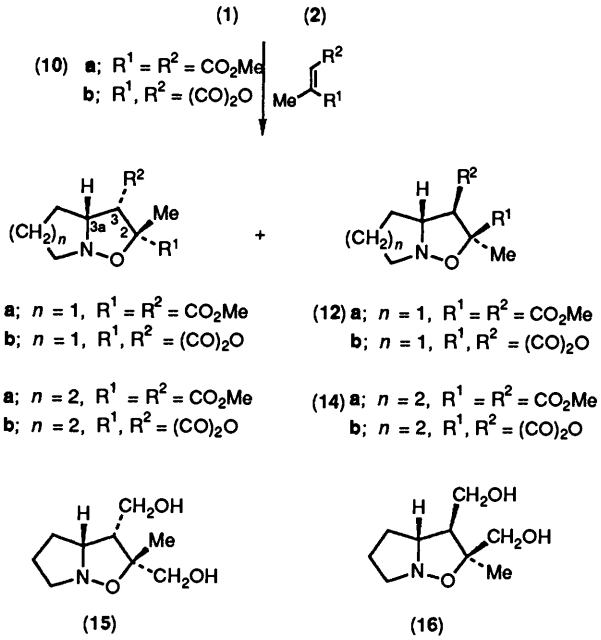
[a] Compositions are shown in parentheses. [b] Isolated yield of the corresponding carboxymethyl derivatives.

Addition of the nitrone (**1**) to dimethyl mesaconate (**3a**) gave a single adduct (**4a**) (Scheme 1). The C-3 proton of (**4a**) appeared as a doublet at δ 3.63 (*J* 7.0 Hz). The absence of the minor isomer (**5a**) was confirmed by reducing the crude reaction product (**4a**) with lithium aluminium hydride to give the diol (**8**) with known configuration (see Experimental). The nitrone (**2**) also underwent regio- and stereo-specific addition to dimethyl mesaconate (**3a**) to give the sole adduct (**6a**). Both the transition states leading to the formation of the adducts (**6a**) and (**7a**) may be stabilized due to a favourable secondary-orbital interaction[9] manifested by the *endo* oriented methoxycarbonyl (CO_2CH_3) group. However, steric encumbrance encountered in the transition state leading to (**7a**), which has two substituents in the crowded *endo* orientation, presumably precludes its formation.

The reactions of methyl 3,3-dimethylacrylate (**3b**) with the nitrones (**1**) and (**2**) were found to be regiospecific but afforded a mixture of stereoisomers in each case. A separable mixture of adducts (**4b**) and (**5b**) in 50:50 ratio and a non-separable mixture of adducts (**6b**) and (**7b**) in 57:43 ratio were obtained from the addition reactions of the nitrone (**1**) and (**2**), respectively. However, we were unable to assign the adduct configurations unambiguously. In the addition reaction of (**3a**), both steric factors and secondary orbital interactions work in favour of formation of (**4a**) as the sole adduct. However, in case of the alkene (**3b**), while the steric factors favour the formation of the adduct (**4b**), the secondary orbital interactions stabilize the transition state leading to the stereoisomer (**5b**). Thus, a mixture of isomers is obtained. Methyl *trans*-4-hydroxy-3-

methylbut-2-enoate (**3c**) appeared to undergo regiospecific addition[8] to give (**4c**) and (**5c**) in a 60:40 ratio. Due to the stabilizing interaction between the LUMO of the nitrone and the oxygen lone pair,[2,5c] the CH_2OH group in the alkene (**3c**) shows a higher preference to be in the *endo* orientation than the CH_3 group in (**3b**). On lithium aluminium hydride reduction the adducts (**4c**) and (**5c**) afforded the diols (**8**) and (**9**), respectively.

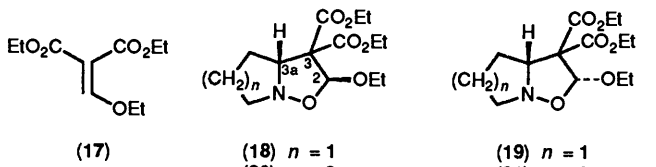
Both dimethyl citraconate (**10a**) and citraconic anhydride (**10b**) afforded mixtures of adducts and in each case the major adducts (**11**) or (**13**) had carbonyl substituents in the *endo* orientation (Scheme 2). The assignment of the configuration



Scheme 2.

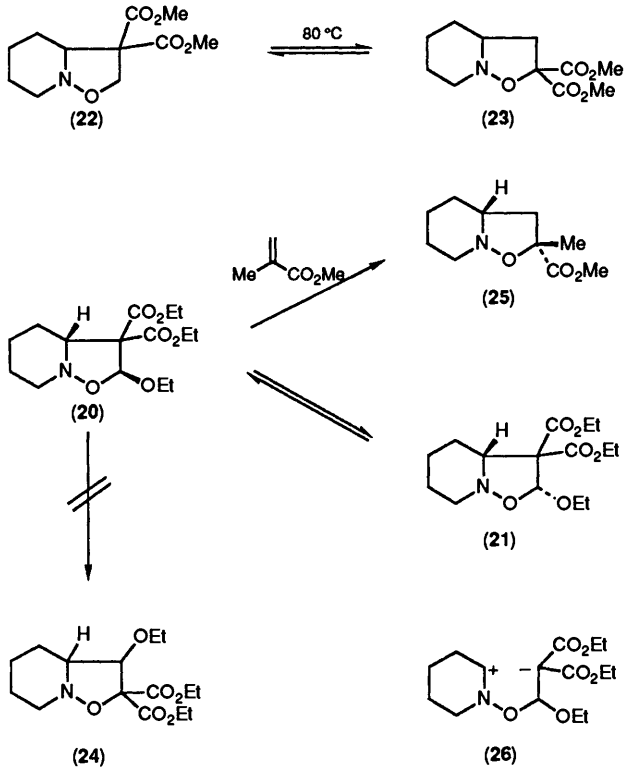
was based on two facts. The ratios of the adducts (**11**) and (**12**) which resulted from the reactions of nitrone (**1**) with dimethyl citraconate (**10a**) and citraconic anhydride (**10b**) was found to be 70:30 and 92:8, respectively. Due to the smaller size and a favourable secondary-orbital interaction, citraconic anhydride (**10b**) gave a higher amount of *endo* oriented adduct than dimethyl citraconate (**10a**). The second supportive evidence is that while the 3-H of the major isomer (**13b**) appeared at δ 3.23 as a doublet (*J* 7.2 Hz), the corresponding proton of the minor isomer (**14b**) appeared at δ 3.08 as a singlet. The near zero coupling constant for $J_{3,3a}$ leads to the fact that protons at C-3 and C-3a form a dihedral angle of *ca.* 90° in the minor isomer (**14b**). Inspection of molecular models indeed confirms this. The citraconic anhydride adducts were converted into the dimethyl citraconate adducts by treatment with methanolic HCl. For the adduct mixture (**11a**), (**12a**) and (**11b**), (**12b**) an accurate determination of adduct ratio was achieved by their conversion into the diols (**15**) and (**16**) (see the Experimental section).

Next, we pursued the cycloaddition of a highly polarized alkene, diethyl ethoxymethylenemalonate (**17**) (Scheme 3). The



Scheme 3.

results of our stereochemical analysis are recorded in Table 1. A complete reversal in the regioselection occurred to give 2,3,3-trisubstituted adducts (**18**)–(**21**). The nitrones (**1**) and (**2**) gave a mixture of (**18**), (**19**) and (**20**), (**21**) in a ratio of 72:28 and 70:30, respectively. For steric reasons, the major isomers were assigned the stereochemistry as depicted in (**18**) and (**20**). Similar electronic controlled reversal in the regioselection was observed in the addition reaction of the highly electron deficient alkene, dimethyl methylenemalonate, which afforded (**22**) as the sole adduct[5b] (Scheme 4).



Scheme 4.

The results discussed above are in general agreement with the frontier orbital treatment of the nitrone 1,3-dipolar cycloaddition.[6] The degree of regio- and stereo-selection depends on electronic and steric effects of the substituents. Secondary orbital interactions also play an important role in dictating the stereochemical outcome. In frontier orbital treatment, the preferred regioisomeric transition state will be the one in which larger terminal coefficients of the HOMO and LUMO are united. While the electron-withdrawing substituent (CO_2Me) results in a decrease in the orbital coefficient at the site of union in both the HOMO and LUMO, electron-releasing groups (OEt, Me) lower the coefficient at the point of attachment in the HOMO and raises that coefficient in the LUMO.[6] Compared with carbon, the oxygen end of the nitrone functionality has the larger orbital coefficient in the HOMO and the smaller coefficient in the LUMO. The effects of substituents on frontier orbital coefficients of the alkenes may be assumed to be an approximate sum of the individual effects of the substituents.[6] Thus the alkenes (**3a**), (**10a**), and (**10b**) should add like propylene which gives a regiospecific adduct[2] having the substituted end of the alkene attached to the oxygen terminal of the nitrone functionality. Both electronic and steric effects[7b] reinforce this regioselection. The nitrone (HOMO)–diethyl ethoxymethylenemalonate (LUMO) interaction in the transition state controls the regioselection and circumvents the steric

Table 2. Rate constants for the cycloaddition reactions at 36 °C.

Alkene	Solvent	$k_2/10^{-5}$ dm^3 mol^{-1} s^{-1} Nitrone (**1**)	Nitrone (**2**)	$\frac{k_2(2)}{k_2(1)}$
Diethyl ethoxymethylenemalonate (**17**)[a]	$CDCl_3$	11.8	121	10.3
(**17**)	$(CD_3)_2SO$	8.61	—	
(**17**)	CD_3OD	1.86	—	
Citraconic anhydride (**10b**)	$(CD_3)_2SO$	506	4 850	9.6
Dimethyl mesaconate (**3a**)	$CDCl_3$	19.3	190	9.8
Dimethyl citraconate (**10a**)	$CDCl_3$	—	1.42	
Methyl crotonate[b]	$CDCl_3$	1.85	22.6	12.2
Methyl acrylate[c]	$CDCl_3$	62.0	340	5.48
Methyl methacrylate[b]	$CDCl_3$	23.4	105	4.49

[a] $k_2/10^{-5}$ dm^3 mol^{-1} s^{-1} values for the nitrone (**2**)–alkene (**17**) addition in $CDCl_3$ at 13.0, 26.0, and 49 °C were measured to be 17.5, 48.0, and 333, respectively; E_a/kJ mol^{-1}, $\Delta H^{\ddagger}$/kJ mol^{-1}, and $\Delta S^{\ddagger}$/J mol^{-1} K^{-1} were found to be 63.2, 60.7, and −106, respectively. [b] From ref. 5(*c*). [c] From ref. 3.

encumbrance encountered in the formation of the 2,3,3-trisubstituted adducts (**18**) or (**20**).

Finally, we measured the second order rate constants k_2 for the addition of the nitrones (**1**) and (**2**) onto several trisubstituted alkenes. The results obtained are shown in Table 2. Cycloadditions were monitored by a proton NMR technique as described before.[3,5a] The ratio of the concentrations of nitrone and alkene was determined from time to time by integrations of ^{1}H NMR signals of the 2-H of the nitrone and the alkenic proton of the alkene and the second order rate constants were obtained by linear regression analysis. The reactants and products are stable under mild, kinetically controlled reaction conditions, and the cycloadducts do not go back to the starting reactants in the manner of the retro Diels–Alder reaction. Even though the adducts (**22**) could be equilibrated to the sterically controlled, thermodynamic product (**23**) on brief heating,[5b] a solution of the adduct (**20**) in toluene, after prolonged reflux, was converted into a 2:1 mixture of (**20**) and (**21**) (Scheme 4). No trace of the regioisomer (**24**) was detected. The stereoreversion indeed happened *via* the nitrone (**2**) as it was trapped by addition to methyl methacrylate to give (**25**) in a separate experiment (toluene, 90 °C, 8 h). It was suggested by Houk[10] that the cycloaddition of a very electron-rich dipole to a very electron-deficient alkene may proceed *via* a zwitterionic intermediate. In such a two-step mechanism involving the zwitterion (**26**), the reaction rate should show an appreciable solvent effect. The second order rate constant for the addition of nitrone (**1**) to diethyl ethoxymethylenemalonate (**17**), a highly polarized alkene, in solvent of different polarity at 36 °C suggest the concerted nature of the reaction. The ratio of rate constants at 36 °C for the reactants (**2**) and (**17**) in deuteriochloroform, $(CD_3)_2SO$, and CD_3OD was found to be 6.3:4.6:1, respectively. The small solvent effect, low activation energy (63.2 kJ mol^{-1}) and large negative entropy of activation (−106 J mol^{-1} K^{-1}) certify that the 1,3-dipolar cycloaddition is a molecular reaction instead of a non-concerted one.[11] The nitrone is least reactive in methanol. The transition state is probably less polar in character than the nitrone which has appreciable dipole moment and is strongly solvated in the protic solvent methanol.

Among the four trisubstituted alkenes studied, citraconic anhydride and dimethyl citraconate were found to be the most and least reactive, respectively. The frontier-orbital treatment is successful in explaining the reactivity phenomena. A decreased HOMO (nitrone)–LUMO (citraconic anhydride) energy gap and reduced steric encumbrance provide extra stabilization to the transition state, leading to the formation of the anhydride adducts. It is of interest to note that the trisubstituted alkenes react with the six-membered ring nitrone (**2**) about 10 times faster than with the five-membered ring nitrone (**1**). Greater eclipsing strain[3] (peculiar to cyclopentane systems), introduced in the transition state where the hybridization is about to change from sp^2 to sp^3, is presumably responsible for the reduced rate observed in the addition reaction of the nitrone (**1**). For comparison purposes, second order constants for the addition of several mono- and di-substituted alkenes are included in Table 2 to demonstrate the importance of HOMO–LUMO interplay and steric factors in explaining the reactivity phenomena. Regio- and stereo-chemical analysis, along with the kinetic results presented here, would indeed be helpful for the proper utilization of these high yielding reactions in incorporating and elaborating pyrrolidine and piperidine rings.

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, and all the liquid alkenes were distilled prior to use. Depending on the reaction conditions as described in the literature, citraconic anhydride (**10b**) was converted into citraconic acid[12a] and mesaconic acid[12b] which on treatment with diazomethane afforded dimethyl citraconate (**10a**) and dimethyl mesaconate (**3a**), respectively. 3,3-Dimethylacrylic acid was esterified with diazomethane to give methyl 3,3-dimethylacrylate (**3b**). Methyl *trans*-4-hydroxy-3-methylbut-2-enoate (**3c**) was prepared as described.[13] 1-Pyrroline 1-oxide (**1**) and 3,4,5,6-tetrahydropyridine 1-oxide (**2**) were prepared as before.[3]

^{1}H NMR spectra for the kinetic runs were recorded on a Varian XL 200 NMR spectrometer operating at a proton frequency of 200 MHz and in the pulse Fourier transform mode. A flip angle of 20°, digital resolution of 0.15 Hz, and four transients were employed in all measurements. The absolute intensity mode was used to measure integrals of interested peaks, which were well separated without any overlap. Spectra at different times for the kinetic runs were obtained by arraying the pre-acquisition delay times. The temperature in the probe was controlled by standard Varian equipment and was accurate to ±0.5 °C. The temperature was calibrated by standard chemical shifts of methanol. Deuteriated chloroform (99.95% isotope purity) with Me_4Si as an internal standard was used. For analysis of the cycloadducts, the proton NMR spectra were recorded on a Bruker AC 80 spectrometer, operating at a proton frequency of 80 MHz. Cycloaddition reactions were carried out under nitrogen.

The kinetics of the cycloaddition reaction were studied in sealed NMR tubes as described in our earlier work.[3] The ratio

of the concentrations of the reactants was determined from time to time by integration of signals due to 2-H of the nitrone and the alkenic proton of the alkene. The second-order rate constant was determined by linear-regression analysis of the data and it was reproducible to within 5–10%. The additions were followed up to 40–80% chemical conversion.

trans-*Dimethyl 2-Methylhexahydropyrrolo*[1,2-b]*isoxazole-2,3-dicarboxylate* (**4a**).—A solution of the nitrone (**1**) (4.5 mmol) and dimethyl mesaconate (**3a**) (474 mg, 4.0 mmol) in chloroform (10 cm^3) was refluxed for 2 h. ^1H NMR spectroscopy failed to detect the presence of the minor isomer (**5a**). The crude adduct was purified by chromatography with ether as the eluant to yield (**4a**) as a colourless oil (840 mg, 86%) (Found: C, 54.1; H, 6.85; N, 5.7; $C_{11}H_{17}NO_5$ requires C, 54.3; H, 7.0; N, 5.8%); ν_{max}(neat) 2 918, 1 735, 1 431, 1 375, 1 205, 1 120, 1 028, 980, and 915 cm^{-1}; δ_H 1.47 (3 H, s), 1.62–2.22 (4 H, m), 2.93–3.40 (2 H, m), 3.63 (1 H, d, *J* 7.0 Hz), 3.73 (3 H, s), 3.81 (3 H, s), and 4.17 (1 H, m).

trans-*Dimethyl 2-Methylhexahydro-2H-isoxazolo*[2,3-a]*pyridine-2,3-dicarboxylate* (**6a**).—A solution of the nitrone (**2**) (3.0 mmol) and dimethyl mesaconate (**3a**) (522 mg, 3.3 mmol) in dichloromethane (10 cm^3) was stirred at 20 °C for 24 h. The ^1H NMR spectrum of the crude reaction mixture revealed the presence of a single isomer (**6a**). The reaction mixture was chromatographed using ether as eluant to give (**6a**) (93%). An analytical sample of (**6a**) was obtained after crystallization (ether–hexane) as white crystals, m.p. 58–59 °C (Found: C, 56.2; H, 7.4; N, 5.3. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.4; N, 5.45%); ν_{max}(KBr) 2 925, 2 905, 2 823, 2 808, 1 745, 1 723, 1 434, 1 395, 1 362, 1 328, 1 258, 1 232, 1 205, 1 160, 1 127, 1 073, 1 027, 993, and 968 cm^{-1}; δ_H 1.20–2.10 (6 H, m), 1.40 (3 H, s), 2.30–2.90 (2 H, m), 3.30–3.68 (2 H, m), 3.75 (3 H, s), and 3.80 (3 H, s).

Isomers of Methyl 2,2-Dimethylhexahydropyrrolo[1,2-b]*isoxazole-3-carboxylate* (**4b**) *and* (**5b**).—A solution of the nitrone (**1**) (4.0 mmol) and methyl 3,3-dimethylacrylate (**3b**) (342 mg, 3.0 mmol) in toluene (5 cm^3) was heated to 80 °C for 6 h. The ^1H NMR spectrum of the crude reaction mixture revealed the presence of the isomers in 50:50 ratio, as indicated by the integration of the C-2 methyl protons. Chromatography of the crude adducts using ether as eluant afforded the first component (**4b**) [or (**5b**)] as a colourless oil (Found: C, 60.6; H, 8.5; N, 6.95. $C_{10}H_{17}NO_3$ requires C, 60.3; H, 8.6; N, 7.0%); ν_{max}(neat) 2 944, 2 920, 1 736, 1 440, 1 386, 1 368, 1 238, 1 206, 1 174, 1 132, 1 089, 1 066, and 1 038 cm^{-1}; δ_H 1.27 (3 H, s), 1.42 (3 H, s), 1.50–2.30 (4 H, m), 2.70 (1 H, d, *J* 7.6 Hz), 2.80–3.50 (2 H, m), 3.73 (3 H, s), and 4.25 (1 H, m).

Continued elution with ether gave a mixture of (**4b**) and (**5b**) and finally the second component (**5b**) [or (**4b**)]. A total of 460 mg (77%) of (**4b**) and (**5b**) was isolated. Adduct (**5b**) (colourless liquid); ν_{max}(neat) 2 926, 2 846, 1 734, 1 440, 1 386, 1 371, 1 276, 1 205, 1 163, and 1 038 cm^{-1}; δ_H 1.27 (3 H, s), 1.47 (3 H, s), 1.60–2.36 (4 H, m), 2.70–3.40 (2 H, m), 3.48 (1 H, d, *J* 7.0 Hz), and 3.69 (3 H, s and an overlapping 1 H, m).

Isomers of Methyl 2,2-Dimethylhexahydro-2H-isoxazolo[2,3-a]*pyridine-3-carboxylate* (**6b**) *and* (**7b**).—A solution of the nitrone (**2**) (3.0 mmol) and methyl 3,3-dimethylacrylate (**3b**) (685 mg, 6.0 mmol) in toluene (10 cm^3) was heated to 80 °C for 5 h. The non-separable mixture of adducts was purified by chromatography using 5:1 dichloromethane-ether mixture as the eluant to give (**6b**) and (**7b**) as a colourless oil (518 mg, 81%) (Found: C, 61.6; H, 8.9; N, 6.4. $C_{11}H_{19}NO_3$ requires C, 61.9; H, 9.0; N, 6.6); ν_{max}(neat) 2 908, 2 831, 1 738, 1 440, 1 389, 1 370, 1 268, 1 203, 1 172, 1 145, and 1 035 cm^{-1}. The ^1H NMR spectrum revealed the presence of (**6b**) and (**7b**) in an approximate ratio of 57:43, respectively, as determined by the integration of the methyl protons. The C-2 methyls and CO_2CH_3 protons of the major isomer (**6b**) appeared as singlets at δ 1.15, 1.50, and 3.70 and the corresponding methyl protons of the minor isomer (**7b**) appeared as singlets at δ 1.33, 1.40, and 3.66.

Conversion of the Cycloadducts (**4a**), (**4c**), *and* (**5c**) *into Isomers of* trans-2,3-*Bis(hydroxymethyl)-2-methylhexahydropyrrolo*[1,2-b]*isoxazole* (**8**) *and* (**9**).—Lithium aluminium hydride reduction of the (**4a**) adduct as described before[2] gave the diol (**8**) as a colourless oil (95% yield). The ^1H NMR spectrum revealed the presence of a single isomer, ν_{max}(neat) 3 300br, 2 920, 1 453, 1 388, 1 139, 1 059, 923, 816, and 745 cm^{-1}; δ_H 1.28 (3 H, s), 1.60–2.10 (4 H, m), 2.25 (1 H, dt, *J* 6.5, 8.5 Hz), 2.70–3.83 (7 H, m), and 3.95 (2 H, br s).

The lithium aluminium hydride reduction of the adduct[8] (**4c**) also afforded the diol (**8**) (85% yield) identical in every respect with that obtained from the reduction of the adduct (**4a**). When the adducts (**4c**) and (**5c**) in a ratio of 1:3, respectively, were reduced, a non-separable mixture of diols (**8**) and (**9**) in the same ratio was obtained. The C-2 methyl protons of the diol (**9**) appeared as singlet at δ 1.19.

Isomers of cis-*Dimethyl 2-Methylhexahydropyrrolo*[1,2-b]*isoxazole-2,3-dicarboxylate* (**11a**) *and* (**12a**).—A solution of the nitrone (**1**) (5.0 mmol) and dimethyl citraconate (**10a**) (950 mg, 6.0 mmol) in toluene (7 cm^3) was stirred at 85 °C for 6 h. The ^1H NMR spectrum displayed the presence of two isomers (**11a**) and (**12a**). The non-separable mixture of adducts was purified by chromatography with ether as the eluant to give the isomers as an oil (900 mg, 74%). The ^1H NMR spectrum was more or less identical with that of the adducts obtained from the esterification of the citraconic anhydride adducts. The lithium aluminium hydride reduction of the adducts afforded a non-separable mixture of the diols (**15**) and (**16**) in a 70:30 ratio, respectively, as determined by the C-2 methyl protons at δ 1.42 and 1.26.

Reaction of the Nitrone (**1**) *with Citraconic Anhydride* (**10b**) *and Conversion of the Cycloadducts* (**11b**) *and* (**12b**) *into Diesters* (**11a**) *and* (**12a**).—A solution of the nitrone (**1**) (1.0 mmol) and citraconic anhydride (**10b**) (168 mg, 1.5 mmol) in dichloromethane (5 cm^3) was stirred at 20 °C for 8 h. A crystalline precipitate of (**11b**) was formed, m.p. 155–157 °C (decomp.); δ_H[$(CD_3)_2SO$] 1.58 (3 H, s), 1.56–2.16 (4 H, m), 2.84–3.24 (2 H, m), and 4.08 (2 H, m). The adduct was found to be very hygroscopic and unstable. We were unable to determine the presence of minor isomer (**12b**) at this stage.

In another experiment a mixture of the nitrone (**1**) (3.0 mmol) and citraconic anhydride (**10b**) (500 mg, 4.5 mmol) in dichloromethane (8 cm^3) was stirred at 20 °C for 8 h. After removal of the solvent the crude adducts were esterified with methanol–HCl (5:3 w/w). Usual work-up followed by chromatography using ether as eluant gave a non-separable mixture of adducts (**11a**) and (**12a**) as a colourless oil (580 mg, 79%) (Found: C, 54.5; H, 7.2; N, 6.0. $C_{11}H_{17}NO_5$ requires C, 54.3; H, 7.0; N, 5.8%); ν_{max}(neat) 2 934, 1 740, 1 441, 1 376, 1 272, 1 204, 1 134, 1 082, 1 040, and 994 cm^{-1}; δ_H 1.69 (3 H, s), 1.60–2.25 (4 H, m), 2.70–4.10 (4 H, m), 3.70 (3 H, s), and 3.74 (3 H, s). A pair of singlets which appeared around δ 3.76 was attributed to the CO_2CH_3 protons of the minor isomer (**12a**). Due to the proximity of the methoxycarbonyl signals and the degeneracy of the C-2 methyl signals, an accurate determination of the adduct ratio was not possible.

A portion of the above adducts was reduced with lithium aluminium hydride as described before.[2] However, after aqueous work up the inorganic salts were repeatedly washed with hot CH_2Cl_2. The organic solution was then dried ($MgSO_4$)

and concentrated to give a colourless oil (90% yield) containing a non-separable mixture of the diols (**15**) and (**16**) in a ratio of 92:8, respectively, as determined by the integration of their C-2 methyl protons, ν_{max}(neat) 3 300br, 2 900, 1 449, 1 374, 1 055, 898, and 831 cm^{-1}; δ_H 1.42 (3 H, s), 1.50–2.25 (4 H, m), and 2.75–4.15 (10 H, m). The minor singlet due to C-2 CH_3 of the diol (**16**) appeared at δ 1.26.

Isomers of cis-*Dimethyl* 2-*Methylhexahydro*-2H-*isoxazolo*-[2,3-a]*pyridine*-2,3-*dicarboxylate* (**13a**) *and* (**14a**).—A mixture containing the nitrone (**2**) (3.5 mmol) and dimethyl citraconate (**10a**) (791 mg, 5.0 mmol) in toluene (8 cm^3) was stirred at 65 °C for 2 h. The adducts were purified by chromatography with ether as the eluant to yield two fractions. The first component, isolated as a colourless oil, was the minor isomer (**14a**) (195 mg, 21.6%); ν_{max}(neat) 2 933, 2 840, 1 740, 1 441, 1 375, 1 293, 1 267, 1 240, 1 205, 1 138, 1 033, and 928 cm^{-1}; δ_H 1.00–2.30 (6 H, m), 1.70 (3 H, s), 2.40–3.12 (3 H, m), 3.24–3.56 (1 H, m), 3.70 (3 H, s), and 3.73 (3 H, s). The second component, the major isomer, was isolated as white crystals, and assigned structure (**13a**) (583 mg, 64.7%); m.p. 59–60 °C (ether–hexane) (Found: C, 55.8; H, 7.25; N, 5.6. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.4; N, 5.45%); ν_{max}(KBr) 2 930, 2 905, 2 810, 2 784, 1 758, 1 740, 1 718, 1 444, 1 386, 1 261, 1 203, 1 176, 1 140, 994, and 930 cm^{-1}; δ_H 1.60 (3 H, s), 1.30–2.05 (6 H, m), 2.25–2.84 (2 H, m), 3.33 (1 H, d, *J* 6.8 Hz), 3.57 (1 H, m), 3.70 (3 H, s), and 3.76 (3 H, s).

Reaction of the Nitrone (**2**) *with Citraconic Anhydride* (**10b**) *and the Conversions of the Cycloadducts* (**13b**) *and* (**14b**) *into Diesters* (**13a**) *and* (**14a**).—A solution of the nitrone (**2**) (1.0 mol) and citraconic anhydride (**10b**) (146 mg, 1.3 mmol) in dichloromethane (5 cm^3) was stirred at 20 °C for 6 h. The ^1H NMR spectrum of the crude reaction mixture revealed the presence of two isomers (**13b**) and (**14b**) in an approximate ratio of 75:25, respectively, as determined by the integration of the C-2 methyl singlets at δ 1.67 and 1.70. The crude adducts, after crystallization from dichloromethane–ether, afforded a mixture of adducts. On concentration, the mother liquor gave an analytical sample of the adduct (**13a**) as white plates, m.p. 127–131 °C (Found: C, 56.6; H, 6.0; N, 6.65. $C_{10}H_{13}NO_4$ requires C, 56.9; H, 6.2; N, 6.6); ν_{max}(KBr) 2 929, 2 910, 2 819, 1 857, 1 775, 1 448, 1 389, 1 330, 1 267, 1 248, 1 222, 1 192, 1 130, 1 080, 1 017, 972, 950, and 917 cm^{-1}; δ_H 1.00–2.25 (6 H, m), 1.67 (3 H, s), 2.30–2.80 (2 H, m), 3.23 (1 H, d, *J* 7.2 Hz), and 3.37–3.70 (1 H, m).

In a separate experiment, a mixture of the nitrone (**2**) (3.0 mmol) and citraconic anhydride (**10b**) (640 mg, 5.7 mmol) in dichloromethane (20 cm^3) was stirred at 20 °C for 4 h. Using a gentle stream of N_2 the solvent was removed and to the residual reaction mixture methanol–HCl (8 cm^3, 5:3 w/w) was added immediately and stirred at 20 °C overnight. The reaction mixture was taken up in water (20 cm^3) and washed with ether (3 × 15 cm^3). The aqueous layer, after saturation with anhydrous K_2CO_3, was extracted with ether (3 × 15 cm^3). The ether layer was evaporated and the residual mixture was separated as before to give the major (**13a**) (480 mg, 62.2%) and minor isomer (**14a**) (133 mg, 21.7%) in a ratio of 78:22, respectively.

Isomers of Diethyl 2-*Ethoxyhexahydropyrrolo*[1,2-b]*isoxazole*-3,3-*dicarboxylate* (**18**) *and* (**19**).—A mixture containing the nitrone (**1**) (5.0 mmol) and diethyl ethoxymethylenemalonate (**17**) (1.51 g, 7.0 mmol) in dichloromethane (5 cm^3) was stirred at 20 °C for 48 h. The ^1H NMR spectrum of the crude reaction mixture revealed the presence of the adducts (**18**) and (**19**) in a ratio of 72:28, respectively, as indicated by the integration of C-2 protons. The non-separable mixture of adducts was purified by chromatography using ether as the eluant to give (**18**) and (**19**) as a colourless oil (1.22 g, 81%); ν_{max}(neat) 2 950, 1 736, 1 469, 1 449, 1 374, 1 266, 1 215, 1 090, and 1 029 cm^{-1}; δ_H 0.90–2.40 (13 H, m), 2.90–4.70 (9 H, m), 5.56 (0.28 H, s), and 5.62 (0.72 H, m).

Isomers of Diethyl 2-*Ethoxyhexahydro*-2H-*isoxazolo*[2,3-a]-*pyridine*-3,3-*dicarboxylate* (**20**) *and* (**21**).—A solution of the nitrone (**2**) (6.0 mmol) and diethyl ethoxymethylenemalonate (**17**) (1.51 g, 7.0 mmol) in dichloromethane (30 cm^3) was stirred at 20 °C for 24 h. The NMR spectrum of the crude reaction mixture revealed the presence of the adducts (**20**) and (**21**) in a ratio of 70:30, respectively, as determined by the integration of the C-2 protons. The non-separable mixture of adducts was purified by chromatography with ether as eluant to yield (**20**) and (**21**) (1.74 g, 92%). An analytical sample of (**20**) was obtained after crystallization from hexane-ether as white crystals, m.p. 51–52 °C (Found: C, 56.9; H, 8.0; N, 4.3. $C_{15}H_{25}NO_6$ requires C, 57.1; H, 8.0; N, 4.4%); ν_{max} 2 952, 2 908, 2 832, 1 735, 1 470, 1 442, 1 375, 1 340, 1 274, 1 210, 1 100, 1 028, 995, and 948 cm^{-1}; δ_H 1.05–2.87 (16 H, m), 3.15 (1 H, m), 3.37–3.98 (3 H, m), 4.05–4.47 (4 H, m), and 5.58 (1 H, s). The 2-H of the minor isomer appeared at δ 5.68 as a singlet.

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