Stereochemisty of 1,3-Dipolar Cycloadditions of Nitrones with (*E*)-1-Alkyl-2-nitroethenes

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1,3-Dipolar cycloadditions of the *C*-aryl-*N*-alkylnitrones 2a—c and the *C,N*-dialkylnitrones 2e—g with the (*E*)-1-alkyl-2-nitroethenes 1a, b afforded predominantly or exclusively the *cis*-3-substituted 4-nitroisoxazolidines 3a—d and 3f—h. Exceptions are the reactions of *C*-phenyl-*N*-isopropylnitrone (2d) and *C,N*-diisopropylnitrone (2h) with 1a which gave the 3,4-*trans* isomers 4e and 4i as the major products. These results can be rationalized in terms of secondary orbital interactions and steric effect.

Keywords 1,3-dipolar cycloaddition; stereoselectivity; nitrone; nitroalkene; 4-nitroisoxazolidine; epimerization; secondary orbital interaction; differential nuclear Overhauser effect

1,3-Dipolar cycloadditions of nitrones to alkenes provide a general access to isoxazolidines, which have been used for the synthesis of a variety of natural products.[1-10] As part of a continuing study of the synthetic applications of the cycloadditions of nitroalkenes,[11,12] we have now focused our attention on the 1,3-dipolar cycloadditions of nitroalkenes to nitrones. A survey of the literature revealed that the cycloaddition of *C*-arylnitrones to nitroalkenes gives exclusively 4-nitroisoxazolidines,[13-15] and this high regioselectivity has been interpreted by the application of frontier molecular orbital (FMO) theory.[13,14,16] However, little information is available concerning the stereochemical aspects of this cycloaddition. In this paper we report the results of our study on the stereochemistry of the 1,3-dipolar cycloadditions of (*E*)-1-alkyl-2-nitroethenes **1a, b** with the *C*-aryl-*N*-alkylnitrones **2a—d** and the *C,N*-dialkylnitrones **2e—h**.

Results

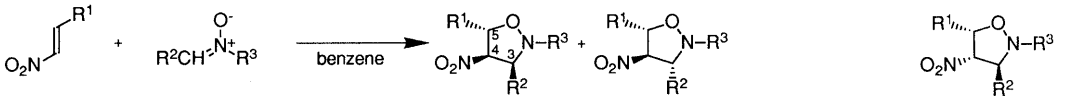
The required (*E*)-nitroalkenes **1a, b** were prepared by reported methods.[17] The nitrones **2a—h** were obtained by the condensation of the corresponding aldehydes and *N*-alkylhydroxylamines.[18]

In general, benzene solutions of (*E*)-nitroalkene (1.5 mmol) and the nitrone (1.0 mmol) were stirred at room temperature for 3 h—12 d or heated under reflux for 10 min—12 h. After evaporation of the solvent, the crude material was chromatographed on silica gel to give isoxazolidines. Thus, the reaction of the *C*-aryl-*N*-alkylnitrones **2a—c** with **1a, b** afforded the *cis*-3-aryl-4-nitroisoxazolidines **3a—d** and the *trans* isomers **4a—d**, with the former predominating (Table I). The structure and stereochemistry of these adducts were ascertained by examination of the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra and by epimerization experiments. The observed couplings ($J_{3,4}$) of 8.3 and 6.5 Hz for **3a** and **4a** are in good agreement with reported values for the $J_{3,4}$ in *cis*- and *trans*-2-methyl-4-nitro-3-phenylisoxazolidines,[4,13] suggesting C_3-H and C_4-H to be *cis* and *trans*, respectively. Further support was given by the differential nuclear Overhauser effect (NOE) experiments with **3a** and **4a** as shown in Fig. 1. Treatment of **3a** with silica gel in hexane–ethyl acetate (5:1) for 24 h induced complete epimerization at C_4[13] to give the third isomer **5a**, while **4a** was recovered unchanged under the same conditions.

TABLE I. 1,3-Dipolar Cycloaddition of (*E*)-1-Alkyl-2-nitroethenes with *C*-Aryl-*N*-alkylnitrones

Entry	Nitroalkene	Nitrone	Conditions	Total yield (%)	Adducts (ratio)
1	**1a**	**2a**	Refl., 3 h	94	**3a**+**4a** (80:20)[a]
2	**1a**	**2b**	Refl., 3.5 h	85	**3b**+**4b** (54:46)[b]
3	**1a**	**2b**	r.t., 12 d	80	**3b**+**4b** (63:37)[b]
4	**1a**	**2c**	Refl., 2 h	97	**3c**+**4c** (81:19)[a]
5	**1b**	**2c**	Refl., 3.5 h	98	**3d**+**4d** (87:13)[a]
6	**1a**	**2d**	Refl., 12 h	87	**3e**+**4e** (31:69)[a]
7[c]	**1c**	**2a**	60 °C	—	**3j**+**4j** (**3j** is major)[d]
8[e]	**1d**	**2i**	—	100	**3k**+**4k** (15:85)

a) Determined by ^{1}H-NMR spectroscopy. *b*) Determined by HPLC analysis. *c*) Ref. 13. *d*) The exact ratio is not given. *e*) Ref. 15. Refl. = reflux; r.t. = room temperature.



1a—d

a: R^1=Me
b: R^1=iso-Pr
c: R^1=H
d: R^1=Ph

2a—i

a: R^2=Ph, R^3=Me
b: R^2=Ph, R^3=Bn
c: R^2=*p*-MeOC_6H_4, R^3=Me
d: R^2=Ph, R^3=iso-Pr
e: R^2=Me, R^3=Bn
f: R^2=Et, R^3=Bn
g: R^2=$(MeO)_2CHCH_2$, R^3=Bn
h: R^2=R^3=iso-Pr
i: R^2=R^3=Ph

3a—k / 4a—k

a: R^1=Me, R^2=Ph, R^3=Me
b: R^1=Me, R^2=Ph, R^3=Bn
c: R^1=Me, R^2=*p*-MeOC_6H_4, R^3=Me
d: R^1=iso-Pr, R^2=*p*-MeOC_6H_4, R^3=Me
e: R^1=Me, R^2=Ph, R^3=iso-Pr
f: R^1=Me, R^2=Me, R^3=Bn
g: R^1=Me, R^2=Et, R^3=Bn
h: R^1=Me, R^2=$(MeO)_2CHCH_2$, R^3=Bn
i: R^1=Me, R^2=R^3=iso-Pr
j: R^1=H, R^2=Ph, R^3=Me
k: R^1=R^2=R^3=Ph

5a—c

a: R^1=Me, R^2=Ph, R^3=Me
b: R^1=Me, R^2=Me, R^3=Bn
c: R^1=Me, R^2=R^3=iso-Pr

Chart 1

Interestingly, *C*-phenyl-*N*-isopropylnitrone (**2d**) and **1a** afforded the 3,4-*cis*-isomer **3e** and the *trans* isomer **4e** in a ratio of 31 : 69. The stereochemical assignment was based on a comparison of the coupling constants ($J_{3,4}$) of **3a** and **4a** with those of **3e** and **4e** in the ^{1}H-NMR spectra (see Table III).

The *C*,*N*-dialkylnitrones **2e**—**g**, on reacting with **1a**, afforded the *cis*-3-alkyl-4-nitroisoxazolidines **3f**—**h** as single stereoisomers (Table II). The stereochemistry of the adduct **3f** was assigned on the basis of the NOE experiments on **3f** and its stereoisomer **5b** obtained by epimerization of **3f** with silica gel (Fig. 1). The large coupling constants ($J_{3,4}$) of **3f**—**h** (8.1, 7.6, and 7.9 Hz, respectively) are consistent with the assigned *cis*-stereochemistry.

TABLE II. 1,3-Dipolar Cycloaddition of (*E*)-1-Alkyl-2-nitroethenes with *C*,*N*-Dialkylnitrones

Entry	Nitroalkene	Nitrone	Conditions	Yield (%)	Adduct(s) (ratio)
1	**1a**	**2e**	Refl., 10 min	94	**3f** (**3f** only)
2	**1a**	**2e**	r.t., 3 h	97	**3f** (**3f** only)
3	**1a**	**2f**	Refl., 30 min	94	**3g** (**3g** only)
4	**1a**	**2g**	Refl., 2 h	89	**3h** (**3h** only)
5	**1a**	**2h**	Refl., 4 h	72[a]	**3i**+**4i** (37 : 63)[b]

a) Obtained as an inseparable mixture. *b*) Determined by ^{1}H-NMR spectroscopy. Refl. = reflux; r.t. = room temperature.

TABLE III. The Chemical Shifts (C-3, 4, and 5 Protons) and the Vicinal Coupling Constants ($J_{3,4}$ and $J_{4,5}$) of the Products

Products	C-3	C-4	C-5	$J_{3,4}$	$J_{4,5}$
3a	3.94	5.01	4.94	8.3	5.7
4a	4.15—4.3	4.83	4.74	6.5	3.7
5a	4.39	5.19	4.61	6.1	7.0
3b	4.19	4.99	4.93	8.3	6.0
4b	4.52	4.86	4.77	6.0	3.9
3c	3.89	4.96	4.90	8.3	5.7
4c	4.12	4.80	4.71	6.7	3.8
3d	3.75—3.8	5.07	4.57	8.3	5.8
4d	4.10	4.94	4.13	7.1	3.9
3e	4.37	4.93	4.87	8.8	6.8
4e	4.81	4.79	4.6—4.7	4.9	4.9
3f	3.05—3.2	4.79	4.70	8.1	5.7
5b	3.69	4.88	4.35	5.1	6.5
3g	2.9—3.1	4.93	4.65	7.6	5.5
3h	3.25—3.35	4.90	4.53	7.7	5.8
3i	3.42	4.91	4.71	7.9	7.9
4i	3.61	4.62	4.66	2.9	7.0
5c	3.61	4.96	4.16	3.5	5.8

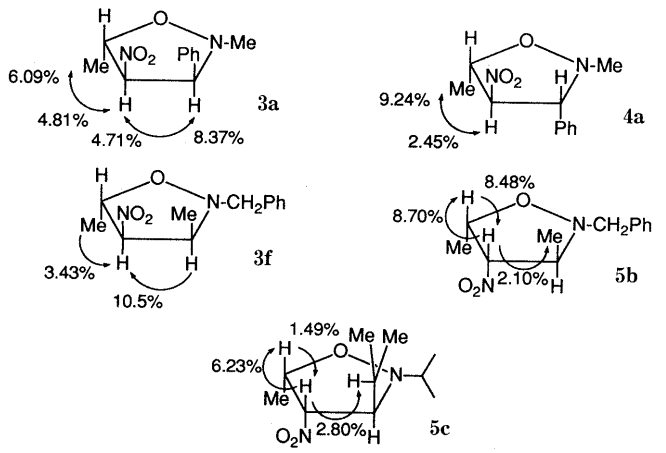


Fig. 1. The Results of NOE Experiments

The reaction of the *C*,*N*-diisopropylnitrone (**2h**) with **1a** gave an inseparable mixture of the 3,4-*cis* isomer **3i** and the *trans* isomer **4i** in a ratio of 37 : 63. When the mixture was treated with silica gel, **4i** remained unchanged but **3i** was epimerized to **5c**. Pure samples of **4i** and **5c** were obtained by preparative thin layer chromatography (TLC). The stereochemistry of these compounds were assigned on the basis of the epimerization experiment as well as an NOE experiment on **5c** (Fig. 1). It is of interest to note that the adducts **3i** and **4i** exhibited unexpectedly large *trans*-vicinal coupling constants for C_4H–C_5H (7.9 Hz for **3i** and 7.0 Hz for **4i**), while the isomer **5c** showed a small *cis*-vicinal coupling constant value ($J_{4,5}$ = 5.8 Hz). Presumably in these compounds steric repulsion between the two bulky isopropyl groups at C_3 and N_2 distorts the five-membered skeleton in such a manner as to cause the C_4H–C_5H angles to deviate from the normal values.

Discussion

In contrast to the 1,3-dipolar cycloadditions of nitrones to RCH=CH_2 (R = aryl, alkyl, OR′, COOR″, CN), which in general afford exclusively or predominantly 5-substituted isoxazolidines,[19-26] it is known that nitroalkenes give 4-nitroisoxazolidines ("reversed adducts").[13,14] These regiochemical outcomes have been rationalized by means of an FMO treatment in which the HOMO (nitrone)–LUMO (nitroethene) interactions dominate.[13,14,16] Therefore, our discussion will be concentrated on the stereochemical problems of the cycloaddition between nitrones and nitroalkenes.

The cycloaddition of the nitrones to nitroalkenes may, in principle, occur through pairs of *endo* or *exo* transition states, depending upon the stereochemistry of the nitrones, to give the *cis*- and *trans*-3-substituted 4-nitroisoxazolidines (Fig. 2).

The reaction of the *C*-aryl-*N*-alkylnitrones **2a**—**c** with **1a**, **b** and nitroethene (**1c**) with **2a** produced predominantly the 3,4-*cis* isomers **3a**—**d** and **3j**[13] (Table I). One possible explanation for the formation of the 3,4-*cis* isomers involves an assumption that the reaction proceeds *via* the (*Z*)-*exo* transition state, which would be stabilized by a

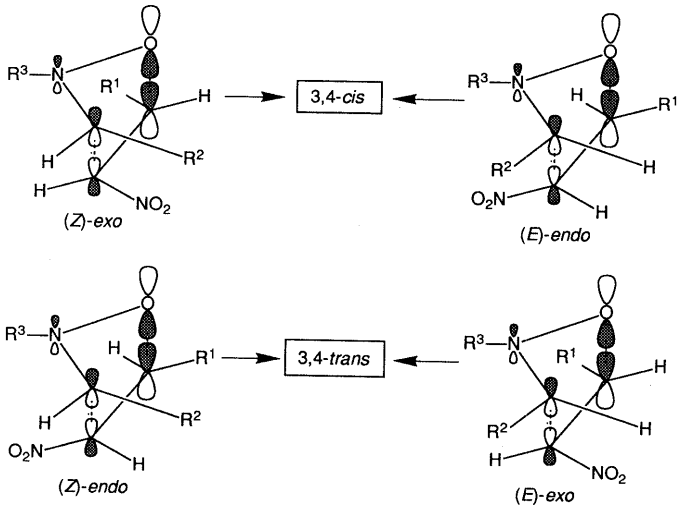


Fig. 2

favorable interaction between the orbitals of the *C*-aryl group of the nitrones and the *p*-orbital associated with the nitro group. This argument is based on the interpretation introduced by Hamelin *et al.*[27] to explain the formation of the 3,4-*cis* isomers in the reaction of **2a** with methyl crotonate. It should be noted, however, that the reaction of *C*,*N*-diphenylnitrone (**2i**) with (*E*)-β-nitrostyrene (**1d**) has been reported to give a 15:85 ratio of the 3,4-*cis* and *trans* isomers, **3k** and **4k**.[15] The latter must arise from the (*Z*)-*endo* transition state. A similar dramatic change in the proportion of the isomers has been observed in the reactions of the *N*-alkyl- and *N*-phenylnitrones with methyl crotonate, and attributed to the difference in the orbital coefficients of the nitrogen atom of the nitrones.[27] A distinctive feature of this mechanism is that the nitrones retain in the thermodynamically more stable (*Z*)-configuration throughout the reaction.

An intriguing and more likely alternative to the above mechanistic rationalization would involve prior (*E*)–(*Z*) isomerization of the nitrones **2a**—**c** followed by a cycloaddition of the more reactive (*E*)-nitrones[28,29] *via* the (*E*)-*endo* transition state, which would be doubly stabilized by the secondary orbital interactions between the *p*-orbital of the nitrogen atom of the nitrone and the *p*-orbital associated with the nitro group and by orbital interactions between the *C*-aryl group and the nitro group. Such (*Z*)–(*E*) isomerization has in fact been postulated in the reaction of **2a** with polychlorobornadiene.[29] Moreover, in the case of *C*-pentamethylphenyl-*N*-methylnitrone, both the (*E*)- and (*Z*)-isomers have been isolated.[30,31] $\Delta G^{\ddagger}$ values for the (*E*)–(*Z*) isomerization were measured (147 °C) and were found to be 33.1 [for the (*E*)-isomer] and 34.1 kcal/mol [for the (*Z*)-isomer]. These values are close to the $\Delta G^{\ddagger}$ (25.4 kcal/mol at 85°C) found for the cycloaddition of *C*-phenyl-*N*-methylnitrone to ethyl crotonate.[32] This mechanism also accounts for the higher *cis*-stereoselectivity (80:20) observed for the reaction of the *N*-methylnitrone **2a** with **1a** than that (54:46) in the case of the *N*-benzylnitrone **2b**: in the latter, the process *via* the (*E*)-*endo* transition state may compete with the one *via* the (*Z*)-*endo* transition state, perhaps because of slow (*Z*)–(*E*) isomerization. *C*-Phenyl-*N*-isopropyl-(**2d**) and *C*,*N*-diphenylnitrone (**2i**) both of which gave the 3,4-*trans* isomers as major products, may not or may only very slowly undergo such a (*Z*)–(*E*) isomerization for steric reasons, so that the cycloaddition is expected to proceed mainly *via* the (*Z*)-*endo* transition state stabilized by a secondary orbital interaction.

The reaction of the *C*,*N*-dialkylnitrones **2e**—**g** with **1a** resulted in the exclusive formation of the 3,4-*cis* adducts **3f**—**h**. These products must arise from either the (*Z*)-*exo* or (*E*)-*endo* transition state. Considering that the former transition state suffers from severe steric repulsion due to eclipsing of the alkyl group and the nitro group, the latter transition state stabilized by a secondary orbital effect should be favored. A similar process has been postulated in the reaction of *C*,*N*-dialkylnitrones with methyl crotonate.[33] The situation is reversed in the case of *C*,*N*-diisopropylnitrone **2h**, which reacts with **1a** to give the 3,4-*trans* adduct **4i** as the major product *via* the (*Z*)-*endo* transition state. These arguments are based on the assumption that the nitrones **2e**—**g** react in the (*E*)-form,[34,35] while **2h** prefers the (*Z*)-form due to a steric effect.

In conclusion, our studies have revealed that the 1,3-dipolar cycloadditions of *C*-aryl-*N*-alkylnitrones and *C*,*N*-dialkylnitrones with (*E*)-1-alkyl-2-nitroethenes give predominantly or exclusively the *cis*-3-substituted 4-nitroisoxazolidines, unless a bulky substituent is placed on the nitrogen of the nitrones. With these results in hand, we are now applying this reaction to the synthesis of natural products.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-1 spectrophotometer. ^{1}H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer using deuteriochloroform as a solvent unless otherwise noted and tetramethylsilane as an internal standard. High resolution mass spectra (MS) were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was carried out on Silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure. E. Merck precoated TLC plates, Silica gel F_{254}, were used for preparative TLC. High-performance liquid chromatography (HPLC) was performed on a JASCO analytical chromatograph equipped with an 880-PU solvent delivery system, a Model 7125 injector, and an 875-UV detector. A 4.6 mm × 150 mm column packed with COSMOSIL (Nacalai Tesque, Inc.) was employed. Chromatograms were recorded on an SIC Chromatocorder 12. (*E*)-Nitroalkenes **1a**, **b** were prepared according to the reported procedures.[17]

General Procedure for the Preparation of Nitrones 2a—h Nitrones **2a**—**h** were prepared by condensation of the corresponding aldehydes and *N*-alkylhydroxylamines.[18] The *N*-alkylhydroxylamine (15 mmol) [or *N*-methylhydroxylamine hydrochloride (15 mmol) and triethylamine (15 mmol)] was added to a stirred suspension of the aldehyde (10 mmol) and sodium sulfate (3 g) in methylene chloride (10 ml) at room temperature and the mixture was stirred overnight. The mixture was partitioned between methylene chloride (30 ml) and 5% hydrochloric acid solution (30 ml), and the aqueous layer was extracted with methylene chloride (20 ml × 3). The combined extracts were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt) to give **2a**—**h**.

C-Phenyl-*N*-methylnitrone (**2a**), 50% yield from *N*-methylhydroxylamine hydrochloride, triethylamine, and benzaldehyde, mp 82—82.5 °C (hexane) (lit. 84—86 °C,[25] 82—84 °C[28]). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1595, 1440, 1410, 1390. ^{1}H-NMR (60 MHz) δ: 3.85 (3H, s, Me), 7.2—7.5 (4H, m, CH= and ArH), 8.1—8.5 (2H, m, ArH). *N*-Benzyl-*C*-phenylnitrone (**2b**), 85% yield from *N*-benzylhydroxylamine and benzaldehyde, mp 75—75.5 °C (hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1580, 1490, 1445, 1320. ^{1}H-NMR (60 MHz) δ: 4.99 (2H, s, CH_2Ph), 7.2—7.6 (9H, m, CH= and ArH), 8.0—8.3 (2H, m, ArH). *Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.62; H, 6.16; N, 6.64. Found: C, 79.64; H, 6.24; N, 6.78. *C*-(*p*-Methoxyphenyl)-*N*-methylnitrone (**2c**), 75% yield from *N*-methylhydroxylamine hydrochloride and *p*-methoxybenzaldehyde, mp 71—71.5 °C (hexane–AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1560, 1500, 1455, 1405. ^{1}H-NMR (60 MHz) δ: 3.80 (6H, s, OMe and Me), 6.89 (2H, d, J=9.0 Hz, ArH), 7.26 (1H, s, CH=), 8.17 (2H, d, J=9.0 Hz, ArH). *Anal.* Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.67; N, 8.48. Found: C, 65.33; H, 6.74; N, 8.52. *N*-Isopropyl-*C*-phenylnitrone (**2d**), 47% yield from *N*-isopropylhydroxylamine and benzaldehyde, mp 25—26 °C (hexane–AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1580, 1560, 1445, 1375, 1360, 1305. ^{1}H-NMR (60 MHz) δ: 1.48 (6H, d, J=7.0 Hz, Me × 2), 4.18 (1H, heptet, J=7.0 Hz, CH<), 7.2—7.5 (4H, m, CH= and ArH), 8.0—8.3 (2H, m, ArH). *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.64; H, 7.94; N, 8.89. *N*-Benzyl-*C*-methylnitrone (**2e**), 55% yield from *N*-benzylhydroxylamine and acetaldehyde, mp 77—77.5 °C (hexane–AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1605, 1495, 1435, 1350, 1300. ^{1}H-NMR (60 MHz) δ: 2.00 (3H, d, J=6.0 Hz, Me), 4.88 (2H, s, CH_2Ph), 6.73 (1H, q, J=6.0 Hz, CH=), 7.38 (5H, s, ArH). ^{1}H-NMR (300 MHz in C_6D_6) δ: 1.65 (3H, d, J=5.8 Hz, Me), 4.42 (2H, s, CH_2Ph), 5.94 (1H, q, J=5.8 Hz, CH=), 7.0—7.3 (5H, m, ArH). *Anal.* Calcd for $C_9H_{11}NO$: C, 72.48; H, 7.38; N, 9.40. Found: C, 72.21; H, 7.34; N, 9.19. *N*-Benzyl-*C*-ethylnitrone (**2f**), 49% yield from *N*-benzylhydroxylamine and propionaldehyde, mp

101—101.5 °C (hexane–AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1490, 1450, 1400, 1290. ^{1}H-NMR (60 MHz) δ: 1.07 (3H, t, J=7.0 Hz, Me), 2.2—2.8 (2H, m, CH_2), 4.86 (2H, s, CH_2Ph), 6.57 (1H, t, J=6.0 Hz, CH=), 7.33 (5H, s, ArH). *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.62; H, 7.98; N, 8.59. Found: C, 73.64; H, 8.15; N, 8.52. *N*-Benzyl-*C*-(2,2-dimethoxyethyl)nitrone (**2g**), 30% yield from *N*-benzylhydroxylamine and 3,3-dimethoxypropionaldehyde, an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1605, 1495, 1450, 1400, 1355. ^{1}H-NMR (60 MHz) δ: 2.79 (2H, t, J=6.0 Hz, CH_2), 3.30 (6H, s, OMe×2), 4.57 (1H, t, J=6.0 Hz, CH≺), 4.85 (2H, s, CH_2Ph), 6.73 (1H, t, J=6.0 Hz, CH=), 7.32 (5H, s, ArH). Exact MS *m/z*: Calcd for $C_{12}H_{17}NO_3$: 223.1207. Found: 223.1187. *C*,*N*-Diisopropylnitrone (**2h**), 47% yield from *N*-isopropylhydroxylamine and isobutyraldehyde, an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1590, 1460, 1380, 1360, 1300. ^{1}H-NMR (60 MHz) δ: 1.10 (3H, d, J=6.0 Hz, Me), 1.40 (3H, d, J=6.0 Hz, Me), 3.16 (1H, octet, J=6.0 Hz, CH), 3.97 (1H, heptet, J=6.0 Hz, CH), 6.53 (1H, d, J=6.0 Hz, CH=). Exact MS *m/z*: Calcd for $C_7H_{15}NO$: 129.1153. Found: 129.1170.

General Procedure for the Cycloaddition of (*E*)-1-Alkyl-2-nitroethenes with Nitrones A nitrone **2** (1 mmol) was added to a solution of **1** (1.5 mmol) in benzene (2 ml) and the mixture was stirred at room temperature for 3 h—12 d or heated under reflux for 10 min—12 h (Tables I and II). After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 5 : 1—30 : 1) to give **3** and **4**.

3,4-*cis*-4,5-*trans*- (3a) and 3,4-*trans*-4,5-*trans*-2,5-Dimethyl-4-nitro-3-phenylisoxazolidine (4a) Compounds **3a** (130 mg, 73%) and **4a** (37 mg, 21%) were obtained from **1a** (88 mg, 1.01 mmol) and **2a** (108 mg, 0.8 mmol). **3a**: Colorless needles, mp 67.5—68.5 °C (hexane–AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1545, 1450, 1360, 1300. ^{1}H-NMR (300 MHz) δ: 1.47 (3H, d, J=6.2 Hz, C_5-Me), 2.64 (3H, s, NMe), 3.94 (1H, d, J=8.3 Hz, C_3-H), 4.94 (1H, quintet, J=6.1 Hz, C_5-H), 5.01 (1H, dd, J=8.3, 5.7 Hz, C_4-H), 7.3—7.4 (5H, m, ArH). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.46; H, 6.31; N, 12.61. Found: C, 59.22; H, 6.37; N, 12.57. **4a**: A colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1450, 1365. ^{1}H-NMR (300 MHz) δ: 1.59 (3H, d, J=6.5 Hz, C_5-Me), 2.67 (3H, s, NMe), 4.15—4.3 (1H, br, C_3-H), 4.74 (1H, qd, J=6.5, 3.7 Hz, C_5-H), 4.83 (1H, dd, J=6.5, 3.7 Hz, C_4-H), 7.33 (5H, s, ArH). Exact MS *m/z*: Calcd for $C_{11}H_{14}N_2O_3$: 222.1002. Found: 222.0992.

3,4-*cis*-4,5-*trans*- (3b) and 3,4-*trans*-4,5-*trans*-2-Benzyl-5-methyl-4-nitro-3-phenylisoxazolidine (4b) Under reflux conditions, compounds **3b** (140 mg, 47%) and **4b** (112 mg, 38%) were obtained from **1a** (131 mg, 1.5 mmol) and **2b** (211 mg, 1 mmol). **3b**: Colorless plates, mp 108—109 °C (hexane–AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1545, 1490, 1455, 1365, 1300. ^{1}H-NMR (300 MHz) δ: 1.41 (3H, d, J=6.1 Hz, C_5-Me), 3.67 and 4.06 (1H each, ABq, J=14.6 Hz, CH_2Ph), 4.19 (1H, d, J=8.3 Hz, C_3-H), 4.93 (1H, quintet, J=6.1 Hz, C_5-H), 4.99 (1H, dd, J=8.3, 6.0 Hz, C_4-H), 7.25—7.5 (10H, m, ArH). *Anal.* Calcd for $C_{17}H_{18}N_2O_3$: C, 68.46; H, 6.04; N, 9.40. Found: C, 68.75; H, 6.00; N, 9.13. **4b**: A colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1545, 1490, 1450, 1365. ^{1}H-NMR (300 MHz) δ: 1.57 (3H, d, J=6.4 Hz, C_5-Me), 3.93 and 4.06 (1H each, ABq, J=14.2 Hz, CH_2Ph), 4.52 (1H, d, J=5.9 Hz, C_3-H), 4.77 (1H, qd, J=6.4, 3.9 Hz, C_5-H), 4.86 (1H, dd, J=6.0, 3.9 Hz, C_4-H), 7.2—7.5 (10H, m, ArH). Exact MS *m/z*: Calcd for $C_{17}H_{18}N_2O_3$: 298.1317. Found: 298.1324. At room temperature, compounds **3b** (326 mg, 55%) and **4b** (151 mg, 25%) were obtained from **1a** (261 mg, 3 mmol) and **2b** (422 mg, 2 mmol).

3,4-*cis*-4,5-*trans*- (3c) and 3,4-*trans*-4,5-*trans*-2,5-Dimethyl-3-(*p*-methoxyphenyl)-4-nitroisoxazolidine (4c) Compounds **3c** (104 mg, 83%) and **4c** (18 mg, 14%) were obtained from **1a** (65 mg, 0.75 mmol) and **2c** (83 mg, 0.5 mmol). **3c**: Colorless prisms, mp 74—75 °C (hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615, 1550, 1510, 1455, 1365, 1300. ^{1}H-NMR (300 MHz) δ: 1.45 (3H, d, J=6.2 Hz, C_5-Me), 2.62 (3H, s, NMe), 3.78 (3H, s, OMe), 3.89 (1H, d, J=8.3 Hz, C_3-H), 4.90 (1H, quintet, J=5.9 Hz, C_5-H), 4.96 (1H, dd, J=8.3, 5.7 Hz, C_4-H), 6.86 (2H, d, J=8.9 Hz, ArH), 7.24 (2H, d, J=8.9 Hz, ArH). *Anal.* Calcd for $C_{12}H_{16}N_2O_4$: C, 57.14; H, 6.35; N, 11.11. Found: C, 57.07; H, 6.45; N, 11.03. **4c**: A colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615, 1550, 1510, 1455, 1365, 1300. ^{1}H-NMR (300 MHz) δ: 1.59 (3H, d, J=6.4 Hz, C_5-Me), 2.64 (3H, s, NMe), 3.81 (3H, s, OMe), 4.12 (1H, br, C_3-H), 4.71 (1H, qd, J=6.4, 3.8 Hz, C_5-H), 4.80 (1H, dd, J=6.7, 3.8 Hz, C_4-H), 6.91 (2H, d, J=8.8 Hz, ArH), 7.30 (2H, d, J=8.6 Hz, ArH). Exact MS *m/z*: Calcd for $C_{12}H_{16}N_2O_4$: 252.1108. Found: 252.1085.

3,4-*cis*-4,5-*trans*- (3d) and 3,4-*trans*-4,5-*trans*-5-Isopropyl-3-(*p*-methoxyphenyl)-2-methyl-4-nitroisoxazolidine (4d) Compounds **3d** (124 mg, 89%) and **4d** (12 mg, 9%) were obtained from **1b** (86 mg, 0.75 mmol) and **2c** (83 mg, 0.5 mmol). **3d**: A colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1550, 1510, 1460, 1365, 1300. ^{1}H-NMR (300 MHz) δ: 0.98 (3H, d, J=6.8 Hz, Me), 1.05 (3H, d, J=6.8 Hz, Me), 1.96 (1H, m, CH), 2.61 (3H, s, NMe), 3.78 (3H, s, OMe), 3.75—3.8 (1H, m, C_3-H), 4.57 (1H, dd, J=7.5, 5.8 Hz, C_5-H), 5.07 (1H, dd, J=8.3, 5.8 Hz, C_4-H), 6.86 (2H, d, J=8.9 Hz, ArH), 7.24 (2H, d, J=8.5 Hz, ArH). Exact MS *m/z*: Calcd for $C_{14}H_{20}N_2O_4$: 280.1421. Found: 280.1406. **4d**: Colorless prisms, mp 61—61.5 °C (petroleum ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615, 1545, 1510, 1460, 1365, 1300. ^{1}H-NMR (300 MHz) δ: 1.00 (3H, d, J=6.8 Hz, Me), 1.09 (3H, d, J=6.8 Hz, Me), 2.1—2.2 (1H, m, CH), 2.63 (3H, s, NMe), 3.81 (3H, s, OMe), 4.10 (1H, br s, C_3-H), 4.13 (1H, dd, J=9.2, 3.9 Hz, C_5-H), 4.94 (1H, dd, J=7.1, 3.9 Hz, C_4-H), 6.91 (2H, d, J=8.8 Hz, ArH), 7.27 (2H, d, J=8.6 Hz, ArH). *Anal.* Calcd for $C_{14}H_{20}N_2O_4$: C, 60.00; H, 7.14; N, 10.00. Found: C, 60.21; H, 7.12; N, 10.30.

3,4-*cis*-4,5-*trans*- (3e) and 3,4-*trans*-4,5-*trans*-2-Isopropyl-5-methyl-4-nitro-3-phenylisoxazolidine (4e) Compounds **3e** (33 mg, 26%) and **4e** (76 mg, 61%) were obtained from **1a** (65 mg, 0.75 mmol) and **2d** (82 mg, 0.5 mmol). **3e**: Colorless prisms, mp 49.5—50 °C (petroleum ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1545, 1485, 1375, 1360. ^{1}H-NMR (300 MHz) δ: 1.04 (3H, d, J=6.7 Hz, one of N-CH(C$\underline{H}_3$)$_2$), 1.08 (3H, d, J=6.3 Hz, one of N-CH(C$\underline{H}_3$)$_2$), 1.43 (3H, d, J=6.1 Hz, C_5-Me), 2.96 (1H, heptet, J=6.5 Hz, N-CH≺), 4.37 (1H, d, J=8.8 Hz, C_3-H), 4.87 (1H, quintet, J=6.8 Hz, C_5-H), 4.93 (1H, dd, J=8.8, 6.8 Hz, C_4-H), 7.3—7.4 (5H, m, ArH). Exact MS *m/z*: Calcd for $C_{13}H_{18}N_2O_3$: 250.1316. Found: 250.1329. **4e**: A colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1545, 1485, 1445, 1370, 1360. ^{1}H-NMR (300 MHz) δ: 1.06 (3H, d, J=6.4 Hz, one of N-CH(C$\underline{H}_3$)$_2$), 1.15 (3H, d, J=6.2 Hz, one of N-CH(C$\underline{H}_3$)$_2$), 1.52 (3H, d, J=6.2 Hz, C_5-Me), 3.17 (1H, heptet, J=6.3 Hz, N-CH≺), 4.6—4.7 (1H, m, C_5-H), 4.79 (1H, t, J=4.9 Hz, C_4-H), 4.81 (1H, d, J=4.9 Hz, C_3-H), 7.3—7.5 (5H, m, ArH). Exact MS *m/z*: Calcd for $C_{13}H_{18}N_2O_3$: 250.1317. Found: 250.1319.

3,4-*cis*-4,5-*trans*-2-Benzyl-3,5-dimethyl-4-nitroisoxazolidine (3f) Under reflux conditions, compound **3f** (446 mg, 94%) was obtained from **1a** (261 mg, 3 mmol) and **2e** (298 mg, 2 mmol) as colorless needles, mp 50—50.5 °C (petroleum ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1450, 1380, 1320. ^{1}H-NMR (300 MHz) δ: 1.16 (3H, d, J=6.6 Hz, C_3-Me), 1.35 (3H, d, J=6.2 Hz, C_5-Me), 3.05—3.2 (1H, br, C_3-H), 3.76 and 4.11 (1H each, ABq, J=14.4 Hz, CH_2Ph), 4.70 (1H, quintet, J=6.1 Hz, C_5-H), 4.79 (1H, dd, J=8.1, 5.7 Hz, C_4-H), 7.25—7.45 (5H, m, ArH). *Anal.* Calcd for $C_{12}H_{16}N_2O_3$: C, 61.02; H, 6.78; N, 11.86. Found: C, 60.70; H, 6.91; N, 11.80. At room temperature, compound **3f** (307 mg, 97%) was obtained from **1a** (175 mg, 2 mmol) and **2e** (200 mg, 1.34 mmol).

3,4-*cis*-4,5-*trans*-2-Benzyl-3-ethyl-5-methyl-4-nitroisoxazolidine (3g) Compound **3g** (223 mg, 94%) was obtained from **1a** (123 mg, 1.4 mmol) and **2f** (154 mg, 0.95 mmol) as colorless prisms, mp 45—46 °C (petroleum ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1450, 1380, 1325. ^{1}H-NMR (300 MHz) δ: 0.99 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.37 (3H, d, J=6.4 Hz, C_5-Me), 1.45—1.7 (2H, m, $C\underline{H}_2CH_3$), 2.9—3.1 (1H, br, C_3-H), 3.79 and 4.18 (1H each, ABq, J=14.3 Hz, CH_2Ph), 4.65 (1H, br quintet, J=6.0 Hz, C_5-H), 4.93 (1H, dd, J=7.6, 5.5 Hz, C_4-H), 7.25—7.4 (5H, m, ArH). *Anal.* Calcd for $C_{13}H_{18}N_2O_3$: C, 62.40; H, 7.20; N, 11.20. Found: C, 62.10; H, 7.31; N, 11.21.

3,4-*cis*-4,5-*trans*-2-Benzyl-3-(2,2-dimethoxyethyl)-5-methyl-4-nitroisoxazolidine (3h) Compound **3h** (94 mg, 89%) was obtained from **1a** (44 mg, 0.51 mmol) and **2g** (92 mg, 0.34 mmol) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1440, 1380, 1320. ^{1}H-NMR (300 MHz) δ: 1.39 (3H, d, J=6.3 Hz, C_5-Me), 1.80—2.05 (2H, m, $C\underline{H}_2CH$≺), 3.25—3.35 (1H, br, C_3-H), 3.30 (3H, s, OMe), 3.31 (3H, s, OMe), 3.78 and 4.16 (1H each, ABq, J=14.4 Hz, CH_2Ph), 4.42 (1H, t, J=5.1 Hz, $CH_2C\underline{H}$≺), 4.53 (1H, br quintet, J=6.0 Hz, C_5-H), 4.90 (1H, dd, J=7.7, 5.8 Hz, C_4-H), 7.25—7.4 (5H, m, ArH). Exact MS *m/z*: Calcd for $C_{15}H_{22}N_2O_5$: 310.1528. Found: 310.1544.

3,4-*cis*-4,5-*trans*- (3i) and 3,4-*trans*-4,5-*trans*-2,3-Diisopropyl-5-methyl-4-nitroisoxazolidine (4i) Compounds **3i** and **4i** (78 mg, 72%) were obtained from **1a** (65 mg, 0.75 mmol) and **2h** (65 mg, 0.5 mmol) as an inseparable mixture of **3i** and **4i** in a ratio of 37 : 63. A mixture of **3i** and **4i**: a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1465, 1380, 1365, 1350. ^{1}H-NMR (300 MHz, only the signals of **3i** are recorded; for the data of **4i**, *vide infra*) δ: 0.92 (3H, d, J=6.8 Hz, one of C_3-CH(C$\underline{H}_3$)$_2$), 1.02 (3H, d, J=6.6 Hz, one of C_3-CH(C$\underline{H}_3$)$_2$), 1.12 (3H, d, J=6.2 Hz, one of N-CH(C$\underline{H}_3$)$_2$), 1.15 (3H, d, J=6.4 Hz, one of N-CH(C$\underline{H}_3$)$_2$), 1.40 (3H, d, J=6.2 Hz, C_5-Me), 1.90 (1H, d heptet, J=6.7 and 4.8 Hz, C_3-CH≺), 2.99 (1H, heptet, J=6.3 Hz, N-CH≺), 3.42 (1H, dd, J=7.9, 4.8 Hz, C_3-H), 4.71 (1H, dq, J=7.9, 6.2 Hz, C_5-H), 4.91 (1H, t, J=7.9 Hz, C_4-H). Exact MS *m/z*: Calcd for $C_{10}H_{20}N_2O_3$: 216.1472. Found: 216.1488.

General Procedure for the Epimerization of *cis*-3-Substituted 4-Nitro-

isoxazolidines 3b, e Dry silica gel (Silica gel PF_{254}) (20 g) was added to a solution of **3b, e** in hexane–AcOEt (5 : 1). The resulting mixture was stirred at room temperature for 24 h and filtered through Celite. The solvent was evaporated off to give **5a, b** in quantitative yield.

3,4-*trans*-4,5-*cis*-2,5-Dimethyl-4-nitro-3-phenylisoxazolidine (**5a**): A colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1545, 1450, 1365, 1320. ^{1}H-NMR (300 MHz) δ: 1.31 (3H, d, J=6.4 Hz, C_5-Me), 2.72 (3H, s, NMe), 4.39 (1H, d, J=6.1 Hz, C_3-H), 4.61 (1H, qd, J=6.4, 7.0 Hz, C_5-H), 5.19 (1H, dd, J=7.0, 6.1 Hz, C_4-H), 7.37 (5H, s, ArH). Exact MS m/z: Calcd for $C_{11}H_{14}N_2O_3$: 222.1004. Found: 222.1013.

3,4-*trans*-4,5-*cis*-2-Benzyl-3,5-dimethyl-4-nitroisoxazolidine (**5b**): Colorless needles, mp 88.5—89 °C (hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1450, 1380, 1320. ^{1}H-NMR (300 MHz) δ: 1.22 (3H, d, J=6.5 Hz, C_5-Me), 1.26 (3H, d, J=6.5 Hz, C_3-Me), 3.69 (1H, qd, J=6.5, 5.1 Hz, C_3-H), 4.06 (2H, s, CH_2Ph), 4.35 (1H, quintet, J=6.5 Hz, C_5-H), 4.88 (1H, dd, J=6.5, 5.1 Hz, C_4-H), 7.25—7.4 (5H, m, ArH). *Anal.* Calcd for $C_{12}H_{16}N_2O_3$: C, 61.02; H, 6.78; N, 11.86. Found: C, 60.72; H, 6.87; N, 11.64.

3,4-*trans*-4,5-*trans*- (4i) and 3,4-*trans*-4,5-*cis*-2,3-Diisopropyl-5-methyl-4-nitroisoxazolidine (5c) Using a similar procedure to that described for the epimerization of **3b, e**, a mixture of **3i** and **4i** was treated with silica gel to give a mixture of **4i** and **5c** which was separated by prepative TLC (hexane : AcOEt = 5 : 1). **4i**: A colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1460, 1380, 1365, 1350. ^{1}H-NMR (300 MHz) δ: 1.00 (3H, d, J=6.6 Hz, one of C_3-CH($C\underline{H}_3$)$_2$), 1.01 (3H, d, J=6.6 Hz, one of C_3-CH($C\underline{H}_3$)$_2$), 1.06 (3H, d, J=6.1 Hz, one of N-CH($C\underline{H}_3$)$_2$), 1.16 (3H, d, J=6.1 Hz, one of N-CH($C\underline{H}_3$)$_2$), 1.46 (3H, d, J=5.9 Hz, C_5-Me), 1.83 (1H, d heptet, J=7.9, 6.6 Hz, C_3-C$\underline{H}$<), 3.33 (1H, heptet, J=6.1 Hz, N-C$\underline{H}$<), 3.61 (1H, dd, J=7.9, 2.9 Hz, C_3-H), 4.62 (1H, dd, J=7.0, 2.9 Hz, C_4-H), 4.66 (1H, dd, J=7.0, 5.9 Hz, C_5-H). Exact MS m/z: Calcd for $C_{10}H_{20}N_2O_3$: 216.1473. Found: 216.1495. **5c**: A colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1460, 1380, 1360, 1325. ^{1}H-NMR (300 MHz) δ: 0.96 (3H, d, J=6.9 Hz, one of C_3-CH($C\underline{H}_3$)$_2$), 0.97 (3H, d, J=6.9 Hz, one of C_3-CH($C\underline{H}_3$)$_2$), 1.20 (3H, d, J=6.5 Hz, one of N-CH($C\underline{H}_3$)$_2$), 1.22 (3H, d, J=6.5 Hz, one of N-CH($C\underline{H}_3$)$_2$), 1.24 (3H, d, J=6.2 Hz, C_5-Me), 1.84 (1H, d heptet, J=6.9, 4.3 Hz, C_3-C$\underline{H}$<), 3.16 (1H, heptet, J=6.5 Hz, N-C$\underline{H}$<), 3.61 (1H, dd, J=4.3, 3.5 Hz, C_3-H), 4.16 (1H, quintet J=6.1 Hz, C_5-H), 4.96 (1H, dd, J=5.8, 3.5 Hz, C_4-H). Exact MS m/z: Calcd for $C_{10}H_{20}N_2O_3$: 216.1473. Found: 216.1499.

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