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THE 1,3-DIPOLAR CYCLOADDITION OF CYCLIC NITRONES WITH 1,2-DISUBSTITUTED ALKENES

Sk. Asrof Ali *, Javaid H. Khan, Mohammed I. M. Wazeer and Herman P. Perzanowski

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

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Abstract: A comparative study of the stereochemical behaviour of the 1,3-dipolar cycloaddition of a series of 1,2-disubstituted alkenes with 1-pyrroline 1-oxide (**1**) and 2,3,4,5-tetrahydropyridine 1-oxide (**2**) has been carried out. Both the nitrones exhibit very similar stereochemical properties. Rate constants for the cycloaddition of these nitrones to several disubstituted alkenes have been determined at 36°C by ^{1}H n.m.r. spectroscopy. It is found that the nitrone **1** reacts slower than **2** due to the presence of bond eclipsing strain in the transition state involving **1**.

INTRODUCTION

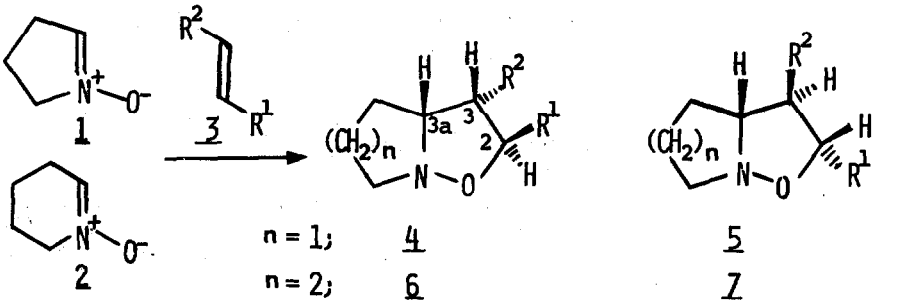
The 1,3-dipolar cycloaddition of both cyclic and acyclic nitrones with substituted alkenes shows varying degrees of regio- and stereo-selection depending on the electronic and steric effects of the substituents.[1,2] With normal and electron-rich mono- and 1,1-disubstituted alkenes the cycloadditions result in the regiospecific formation of cycloadducts having the substituted end of the alkenes attached to the oxygen terminal of the nitrone functionality. However, with electron-deficient alkenes, usually a regioisomeric mixture of adducts are obtained; and in some cases complete reversal in the regioselection is observed.[2-4] While cyclic and acyclic nitrones show remarkably similar regiochemical behavior, the cycloadditions of the former[2] are found to be more stereoselective than the latter[5]. While the frontier orbital treatment is remarkably successful in explaining the regioselectivity and reactivity phenomena,[1a,6] the secondary orbital interactions and steric factors usually dictate the stereochemical outcome of the cycloadditions.

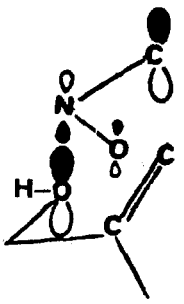
The synthetic applications of the addition of cyclic nitrones have culminated in the synthesis of several natural products.[7] The regio- and stereo-chemical integrity of these additions hold the key to the efficiency of certain total synthesis. Although the regiochemical aspects of nitrone cycloadditions are relatively easy to explore, the progress in the study of stereochemical details has been hampered in most cases because of the difficulties associated with unambiguous assignment of adduct configurations. Here, we report in detail, the stereochemical features associated with the addition reactions of cyclic nitrones 1-pyroline 1-oxide (**1**) onto several 1,2-disubstituted alkenes and compared the results with that of the additions of 2,3,4,5-tetrahydropyridine 1-oxide[2] (**2**). We also undertook a systematic kinetic study of the addition of the nitrone, **1**, onto several disubstituted alkenes using the proton n.m.r. technique which offers a convenient method for following these reactions.

RESULTS AND DISCUSSION

The results obtained for the cycloadditions of the cyclic nitrones with several 1,2-disubstituted alkenes are given in Table 1. The reactions were run under conditions that would reflect kinetic rather than thermodynamic factors.

The addition of the nitrone **1** onto trans-methyl cinnamate (**3a**) afforded a nonseparable mixture of adducts **4a** and **5a** in a 92:8 ratio as determined by integration of C-2 protons at δ 5.31 (d, J 9.0 Hz) and 5.12 (d, J 8.8 Hz). Based on precedent literature, the stereochemistry of the major adduct is depicted in **4a** having endo oriented carbomethoxy group which is known to manifest favourable secondary orbital interaction.[8] Addition of the nitrone **1** with methyl crotonate (**3b**) gave a mixture of adducts **4b** and **5b** in a 93:7 ratio respectively. Favourable secondary orbital interaction again dictated the formation of the major adduct **4b** via transition state with endo orientation of the carbomethoxy group.[9]

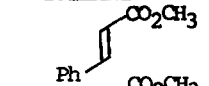
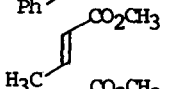
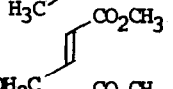
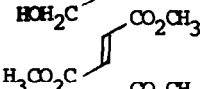
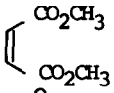
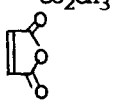




a, $R^1 = Ph$, $R^2 = CO_2CH_3$; b, $R^1 = CH_3$, $R^2 = CO_2CH_3$
c, $R^1 = CH_2OH$, $R^2 = CO_2CH_3$; d, $R^1 = R^2 = CO_2CH_3$
e, $R^1 = R^2 = CH_2OH$; f, $R^1 = R^2 = CH_2OSO_2CH_3$
g, $R^1 = R^2 = CH_3$; h, $R^1 = R^2 = CH_2OCOCH_3$
i, $R^1 = CH_3$, $R^2 = CH_2OH$; j, $R^1 = CH_3$, $R^2 = CH_2OSO_2CH_3$

Cycloadducts were obtained in excellent yields in the additions of the nitrone **1** and **2** with methyl γ-hydroxycrotonate (**3c**). While the addition reaction of methyl crotonate with nitrone **2** afforded **6b** and **7b** in a 90:10 ratio, methyl γ-hydroxycrotonate gave a separable mixture of adducts **6c** and **7c** in a 77:23 ratio. Similar trend is observed in the addition reaction of the nitrone **1**. It was anticipated that methyl γ-hydroxycrotonate having larger hydroxymethyl substituent should exhibit higher degree of stereoselection than methyl crotonate. It is interesting to note that the CH_2OH group in the alkane **3c** shows a higher preference to be in the endo orientation than the CH_3 group in methyl crotonate (**3b**). This higher preference for the endo approach could presumably be attributed to the stabilizing interaction between the nitrogen atom of the nitrone-LUMO with the oxygen lone pair. Our earlier works [2,10] on nitrone cycloadditions with methyl allyl alcohol and several of its derivatives led us to believe that hydrogen bonding alone may not be able to account for this extra stabilization of the transition state.The configurations of **6c** and **7c** were assured by their conversion into known diols[2] **6e** and **7e**, respectively. The stereochemical relationship between **4b** and **4c** was confirmed by their conversion to **4g** as described below.

TABLE 1: Stereochemistry of Cycloadditions of Nitrones 1 and 2 with Disubstituted Alkenes.

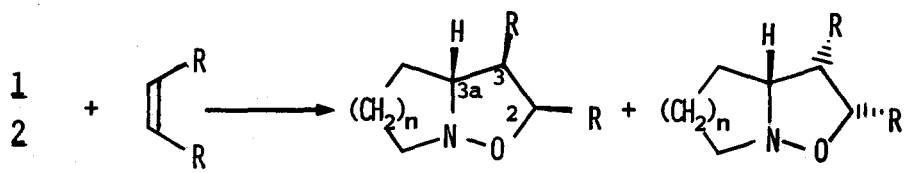
Alkene	Nitrone	Temp (°C)	Reaction time(h)	Solvent	% Composition of Adducts	Isolated Yield(%)
	1	80	4	Benzene	(4a)92 (5a)8	73
	2	55	2	Toluene	(6a)87 (7a)13	79
	1	40	2	CH_2Cl_2	(4b)93 (5b)7	72
	2	40	1	CH_2Cl_2	(6b)90 (7b)10	94
	1	25	36	CH_2Cl_2	(4c)85 (5c)15	95
	2	25	24	CH_2Cl_2	(6c)77 (7c)23	88
	1	40	1	CH_2Cl_2	(4d)45 (5d)55	79
	2	25	2	CH_2Cl_2	(6d)60 (7d)40	89
	1	50	4	$CHCl_3$	(9a)83 (10a)17	88
	2	25	2	CH_2Cl_2	(11a)84 (12a)16	93
	1	25	0.03	CH_2Cl_2	(9b)67 (10b)33	74
	2	25	0.1	CH_2Cl_2	(11b)81 (12b)19	98

The nonseparable mixture of **4c, 5c** was reduced with lithium aluminium hydride to diols **4e, 5e** which were then methanesulfonylated to give a nonseparable mixture of **4f** and **5f**. The dimethanesulfonates **4f** and **5f** was then converted into a nonseparable mixture of **4g** and **5g** by Super-Hydride induced S_N2 displacement of the methylsulfonate function by hydride ion.[11] The approximate ratio of **4g** and **5g**, hence that of the original adducts **4c** and **5c**, was determined by integration of methyl protons at C-3 of **4g** and **5g** which appeared at δ 1.00 (d, J 7.0 Hz) and 1.08 (d, J 6.6 Hz) respectively. The ^1H n.m.r. spectrum of the nonseparable acetylated mixture of **4h** and **5h** also supported the ratio as obtained above (see experimental). In a similar fashion methyl crotonate adduct mixture **4b** and **5b** was converted into **4g** and **5g** via the methanesulfonates **4j** and **5j**. The methyl protons at C-2 and C-3 of **4g** appeared at δ 1.20 (d, J 6.0 Hz) and 1.00 (d, J 7.0 Hz), respectively. However, the proton n.m.r. spectrum did not reveal the small percentage of the compound **5g**.

The addition of nitrone **1** onto dimethyl fumarate afforded a separable mixture of **4d** and **5d** in a ratio of 45:55, respectively. The stereochemistry of the major adduct as depicted in **5d** was assured by its conversion to **5g** via **5e** and **5f** as described previously. The methyl protons at C-2 and C-3 of **5g** appeared at δ 1.20 (d, J 6.2 Hz) and 1.08 (d, J 6.6 Hz) respectively.

The reaction of the nitrone **1** with dimethyl maleate (**8a**) afforded a nonseparable mixture of adducts **9a** and **10a**. The ^1H n.m.r. spectrum exhibited a major doublet at δ 4.86 (J 7.5 Hz) and a minor doublet at δ 4.70 (J 7.0 Hz) in a ratio of 83:17, respectively. The major adduct **9a** would originate from sterically favoured exo-transition state. The assignment of the stereochemistry was based on the information obtained from the addition reaction of maleic anhydride, which afforded a mixture of adducts **9b** and **10b**. The ^1H n.m.r. spectrum displayed the

presence of a pair of doublets at δ 5.15 (J 7.2 Hz) and 3.99 (J 7.2 Hz) assigned respectively, to the C-2 and C-3 protons of the major adduct **9b**.



8 n = 1 **9** **10**

n = 2 **11** **12**

a, R = CO_2CH_3; **b**, R , R = $(CO)_2O$

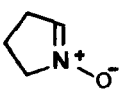
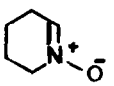
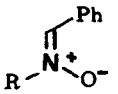
Inspection of molecular models revealed the protons at C-3 and C-3a form a dihedral angle of ca. 90° in adduct **9b**. This is indeed demonstrated in the n.m.r. spectrum which shows the C-3 proton as doublet instead of a triplet or a doublet of doublets as expected. The near zero coupling constant for $J_{3,3a}$ thus confirms the stereochemistry of the major adduct **9b**. Irradiation of the doublet at δ 5.15 caused the doublet at δ 3.99 to collapse into a singlet thus assuring the correct assignment of the C-3 proton. A minor doublet (J 8.0 Hz) at δ 5.04 indicated the presence of the minor isomer **10b** (70:30 ratio). The ratio of the maleic anhydride adduct **9b, 10b** was also determined by their conversion to **9a, 10a** by treatment with methanolic-HCl (5:3 w/w) and was found to be 67:33 respectively. Thus in contrast to many Diels-Alder reactions, the steric factor prevails over the favourable secondary orbital interaction in the addition reaction of maleic anhydride with cyclic nitrones.

Measurement of rate constants for the addition of the nitrone **1** onto several disubstituted alkenes was achieved using ^{1}H n.m.r. technique.[12a] Kinetic results obtained for the cycloaddition in $CDCl_3$ are shown in Table 2. For the purpose of comparison the corresponding results reported for some other cyclic [12a,b] and acyclic nitrones are also included in the Table 2.[12c] The ^{1}H n.m.r. signals of C(2) H of the nitrone **1** and olefinic protons of alkenes and in some cases C(2) H of cycloadducts were free of overlapping signals. Thus the ratio of concentration of the nitrone and alkene was determined and second order rate constants were obtained by linear regression analysis.

Nitrone cycloaddition is a type II process [13], where both HOMO-LUMO interactions contribute to the stabilization of the transition state. As can be seen from Table 2, the nitrone **1** reacts faster with dimethyl fumarate than with the other alkenes. This is because of the extra stablization of the transition state by the decreased HOMO (nitrone)-LUMO(alkene) energy gap[1a]. However, frontier orbital interaction relates to an early point on the reaction coordinate and accounts for a fraction of activation energy. Some strain (or its relief) present in the reactants and products must be considered to envisage a better model of the transition state. The five membered nitrone **1** reacts slower than the six membered nitrone **2**. This could be attributed to greater eclipsing strain (peculiar to cyclopentane system) introduced in the transition state (for the addition of the nitrone **1**) where the hybridization is about to change from sp^2 to sp^3. It is also evident from the Table 2 that cyclic nitrones, which can exist only in E-

form (because of structural constraints), react much faster than their acyclic counterparts which exist in more stable Z-configuration.[14] It is of interest to note that 1,2-disubstituted alkenes react with the nitrone **2** about 12 to 19 times faster than with the nitrone **1** whereas the rate ratio is approximately 5 for mono- and 1,1-disubstituted alkenes. This probably demonstrates that substituent in the alkene approaching the C-terminus of the nitrone functionality experiences more steric hindrance in **1** than in the case of the nitrone **2**. However, this effect is less pronounced when the substitutent approaches the O-terminus of the nitrones.

Table 2: Rate constants (k_2) for the cycloaddition reactions at 36°C in deuterochloroform.

	$k_2 \times 10^5$ l mol^{-1}s^{-1}			
				
Alkene	1	2		$\frac{k_2(2)}{k_2(1)}$
Dimethyl fumarate	178	3370	72.5[a,c]	18.9
Dimethyl maleate	13.8	209	24.7[b,c]	15.1
Methyl crotonate	1.85	22.6	55.4[b,c]	12.2
Methyl methacrylate	23.4	105	-	4.49
Methyl acrylate[d]	62.0	340	-	5.48

[a]R=CH_3, 85°C, Toluene; [b]R=Ph, 100°C, Toluene; [c]Ref.12(c); [d]Ref.12(a)

Since the nitrone **1** is less reactive than the nitrone **2** we decided to examine their relative rate of formation from the corresponding N-hydroxy compounds. Eclipsing strain present in the starting N-hydroxypyrrolidine is greater than the angular strain introduced in nitrone **1**. As expected the nitrone **1** is formed at a faster rate than the nitrone **2**, due to lower energy of activation for the former process. When a $CDCl_3$ solution (1.5 mL) containing N-hydroxypyrrolidine (1.0 mmol) and N-hydroxypiperidine (1.0 mmol) was treated with yellow mercuric oxide (1.0 mmol), 0.27 mmol of the nitrone **1** and 0.13 mmol of the nitrone **2** were formed. ^{1}H n.m.r. also revealed the presence of unreacted N-hydroxypyrrolidine (0.69 mmol) and N-hydroxypiperidine (0.90 mmol). The ratio of nitrones **1** and **2** was thus found to be 2:1, respectively.

Alkaloids containing pyrrolidine and piperidine rings are widespread in nature. Stereochemical analysis and the kinetic results presented here would indeed be useful for the proper utilization of these high yielding reactions in incorporating and elaborating pyrrolidine and piperidine rings.

EXPERIMENTAL

Elemental analysis were preformed on a Carlo-Erba elemental analyser 1106. I.r. spectra were recorded on a Nicolet 5 DBX FT IR and are reported in wave numbers (cm^{-1}). ^{1}H n.m.r. spectra were recorded on a Bruker AC-80 and Varian XL-200 n.m.r. spectrometers using deuterochloroform as solvent and TMS as internal

standard. Silica gel chromatographic separations were performed with flash silica gel(Baker Chemical Co.). All solvents were reagent grade. All the liquids alkenes, N-hydroxypyrrolidine, N-hydroxypiperidine were distilled and maleic anhydride and dimethyl fumarate were recrystallized prior to use. Cycloadditions were conducted under a positive pressure of nitrogen. The nitrone 1 and 2 were prepared according to reported procedures.[12a] Kinetic runs were studied at 36 ± 0.5°C in $CDCl_3$ by ^1H n.m.r. technique as described before.[12a,b] The ratio of the concentrations of the nitrone and alkene was determined from time to time by integration of signals due to 2-H of the nitrone and the olefinic protons. The second order rate constant was determined by linear regression analysis of the data and was reproducible within 5-10%. In one set of experiments, the initial concentrations of the nitrone 1-dimethyl fumarate, nitrone 1-demethyl maleate, nitrone 1-methyl crotonate, nitrone-1-methyl methacrylate were kept between 0.268-0.416 M, 0.482-1.45 M, 0.495-1.49 M, and 0.350-1.11 M, respectively. The additions were followd up to 40-80% chemical conversion.

Reaction of the Nitrone 1 with Methyl Cinnamate (3a). A solution containing the nitrone 1 (4.0 mmol) and methyl cinnamate (7.0 mmol) in benzene (10 ml) was refluxed under N_2 for 4 h. The ^1H n.m.r. spectrum of the crude reaction mixture revealed the presence of **4a** and **5a** in a 92:8 ratio, respectively, as determined by the integration of their C-2 protons at δ 5.31 and 5.12 (d, J 8.8 Hz). The adduct mixture was purified by chromatography, using ether as an eluant to give a mixture of **4a** and **5a** and finally pure adduct **4a,** (721 mg, 73%) as a colourless oil; (Found: C, 67.69; H, 6.73; N, 5.81. $C_{14}H_{17}NO_3$ requires C, 67.99; H, 6.93; N, 5.67%); $\nu_{max.}$ (neat) 3049, 2961, 2882, 1737, 1492, 1453, 1434, 1347, 1245, 1196, 1173, 1002, 759, and 700 cm^{-1} ; δ_H 1.50-2.25 (4 H, m), 3.13-3.46 (2 H, m), 3.70 (3H, s) and an overlapping (1H, m), 3.90-4.27 (1 H, m), 5.31 (1 H, d, J 9.0 Hz), and 7.18-7.58 (5 H, m).

Reaction of the Nitrone 1 with Methyl Crotonate and Conversion of Cycloadducts 4b, 5b into 4i, 5i. A dichloromethane solution (9 ml) containing the nitrone 1 (3.0 mmol) and methyl crotonate (2.0 ml) was refluxed under N_2 for 2 h. After removal of solvent and excess alkene a minor portion of the yellowish residue was chromatographed using ether as eluant to give **4b, 5b,** as a colourless oil (72%); $\nu_{max.}$ (neat) 2979, 2936, 2893, 1736, 1438 and 1202 cm^{-1} ; δ_H 1.32 (3 H d J 6.0 Hz), 1.46-2.12 (4 H, m), 3.04-3.35 (3 H, m), 3.72 (3 H, s), 3.98 (1 H, m) and 4.18-4.53 (1 H, dq, J 6.0, 9.5 Hz). The presence of a minor singlet at δ 3.78 due to CO_2CH_3 indicates the presence of the minor isomer **5b.** Integration revealed the presence of cycloadducts in 93:7 ratio.

The major portion of the crude cycloaddition products **4b, 5b** was reduced with lithium aluminium hydride to give **4i, 5i** as a yellow liquid which was purified by chromatography using 10% methanol in ether as eluant to give **4i** and **5i** as a colourless liquid (66% overall); $\nu_{max.}$ (neat) 3460-3200, 2973, 2930, 2874, 1449, 1384, 1077, 1053, and 1026 cm^{-1} δ_H (200 MHz) 1.28 (3 H, d, J 6.0 Hz), 1.50-2.15 (4 H, m), 2.59 (1 H, quint, J 8.0 Hz), 3.21 (2 H, m), and 3.55-4.00 (4 H, m), and 4.88 (1 H, bs). Methanesulfonylation (CH_3SO_2Cl, Pyridine, 0°C 24 h) of the alcohol **4i, 5i** afforded **4j, 5j** (85%); (Found : C, 46.24; H, 7.17; N, 5.83. $C_9H_{17}NO_4S$ requires C, 45.94; H, 7.28; N, 5.95%); δ_H (200 MHz) 1.30 (3 H, d, J 6.0 Hz), 1.40-2.10 (4 H, m), 2.30 (1 H, m), 2.80-3.50 (2 H, m), 3.05 (3 H, s), and 3.60-4.85 (4 H, m). The methanesulfonates were converted to **4g** by treatment with Super-Hydride as described later. ^1H n.m.r could not detect the presence of minor isomer **5g.**

Reaction of the Nitrone 1 with Methyl γ− Hydroxycrotonate and Conversion of Adducts 4c, 5c into 4g, 5g.- A solution of the nitrone 1 (6 mmol) and methyl γ− hydroxycrotonate[15] (348 mg, 3 mmol) in dichloromethane (2 ml) was stirred at room temperature for 36 h. After removal of the solvent the yellow residue was chromatographed using 5% methanol in ether to give the nonseparable mixture of adducts **4c, 5c** (570 mg, 95%). The analytical data of this mixture of adducts is already reported in the literature[15b]. ^1H spectrum failed to determine the adduct ratio.

The mixture of adducts **4c, 5c** on acetylation (acetic anhydride, rt, 1 h) afforded a mixture of adducts **4h, 5h.** We again failed to separate the isomers. However, the ^1H n.m.r. spectrum revealed the presence of major and minor isomers in a ratio of 85:15 (δ_H (200 MHz) 3.96-4.65 (4 H, m), 3.76 (3 H, s), 2.94-3.64 (3 H, m), 1.45-2.24 (7 H, m including a 3 H,S at 2.11) and minor methyl singlets appeared at δ3.82 and 2.06. The acetylated compounds are not analyzed further.

The mixture of adducts **4c, 5c** (390 mg, 1.94 mmol) was reduced with lithium aluminium hydride to give the diols **4e, 5e** as colourless liquid (300 mg, 89%); $\nu_{max.}$ 3300 (br), 2908, 2847, 1449, 1388, 1096, 1046 and 918 cm^{-1} ; δ_H (200 MHz) 2.80-4.10 (10 H, m), 1.46-2.30 (5 H, m).

The crude mixture of diols, **4e, 5e** was then dimethanesulfonylated (CH_3SO_2Cl, pyridine, 0°C) to give a mixture of **4f, 5f** (δ_H 1.30-2.25 (5 H, m), 2.90-3.85 (3 H, m), 3.08 (3 H, s), 3.13 (3 H, s), and 4.00-4.75 (5 H, m)), which on treatment with Super-Hydride afforded **4g, 5g** as an oil; δ_H (200 MHz) 1.00 (3 H, d, J 7.0 Hz), 1.20 (3 H, d, J 6.0 Hz), 1.48-2.08 (4 H, m), 2.30 (1 H, m), 2.92-3.42 (2 H, m), 3.48-3.84 (2 H, m), and a minor doublet at δ 1.08

indicate the presence of minor isomer **5g**. The ratio of the isomers was approximately 85:15.

Reaction of the Nitrone 2 with Methyl γ− Hydroxycrotonate.- A solution of the nitrone **2** (5.0 mmol) and methyl γ− hydroxycrotonate[15] (348 mg, 3 mmol) in dichloromethane (10 ml) was stirred at room temperature for 24 h. After removal of the solvent the faint yellow residue was chromatographed using ether as eluant to give the minor isomer **7c** as a colourless liquid (129 mg, 20%); $\nu_{max.}$ 3380 (br), 2927, 2842, 1742, 1449, 1282, 1211, 1183, 1031, 933 and 989 cm^{-1} ; δ_H (200 MHz) 4.38 (1 H, m), 3.60-4.00 (5 H, m including a 3 H, s at δ 3.74), 3.46 (1 H, m), 3.26 (1 H, bs), 3.08 (1 H, dd, J 5.8, 10.0 Hz), 2.50 (2 H, m), 2.13 (1 H, m) and 1.08-1.92 (5 H, m). Continued elution with ether afforded the major isomer **6c** as a colourless liquid (440 mg, 68%); (Found: C, 55.45; H, 7.71; N, 6.62. $C_{10}H_{17}NO_4$ requires C, 55.80; H,7.96; N,6.51); $\nu_{max.}$ 3380 (br), 2917, 2834, 1735, 1442, 1388, 1267, 1175, 1090, 1053, 1020 and 915 cm^{-1} ; ^1H (200 MHz) 4.56 (1 H, m), 3.46-3.98 (6 H, m, including a 3 H, s at δ 3.74), 3.30 (1 H, dd, J 5.0, 8.0 Hz), 2.57 (1 H, bs), 2.43 (2 H, m), 1.98 (1 H, m), and 1.08-1.88 (5 H, m). Thus the isomers **6c** and **7c** were obtained in a ratio of 77:23, respectively. The major isomer **6c** (142 mg. 0.66 mmol) on reduction with lithium aluminium hydride afforded the known diol[2] **6e** (100 mg, 81%). Similar reduction of the isomer **7c** (43 mg, 0.20 mmol) gave the known diol[2] **7e** (30 mg, 80%).

Reaction of the Nitrone 1 with Dimethyl Fumarate.- A solution of the nitrone 1 (4.0 mmol) and dimethyl fumarate (5.5 mmol) in dichloromethane (12 ml) was refluxed for 1 h. ^1H n.m.r. spectrom of the crude reaction mixture revealed the presence of **4d, 5d** in a 45:55 ratio as determined by the integration of C-2 protons. The adducts were purified by chromatography with ether as eluant. The first component, isolated as colourless oil, was the major isomer **5d,** $\nu_{max.}$ (neat) 2978, 1745, 1439, 1279, 1212, and 1023 cm^{-1} ; δ_H (200MHz) 1.68-2.24 (4 H, m), 3.06 (1 H, m), 3.40 (2 H, m, including an 1 H, dd, J 5.2, 7.5 Hz), 3.78 (3 H, s), 3.81 (3 H, s), 3.92 (1 H, m), and 4.86 (1 H, d, J 7.5 Hz) Continued elution with ether afforded a mixture of **4d** and **5d** and finally the pure isomer **4d** as white crystals, m.p. 57-58°C (ether) (Found : C,52.11; H,6.37; N,6.35. $C_{10}H_{15}NO_5$ requires C,52.40; H,6.60; N,6.11%); $\nu_{max.}$ 2963, 1742, 1436, 1371-1176, 1077, and 1017 cm^{-1} ; δ_H (200 MHz) 1.50-2.28 (4 H, m), 3.08 (1 H, m), 3.56(1 H, m), 3.77 (3 H, s) 3.80 (3 H, s), 3.90 (1 H, m), 4.12 (1 H, dd, J 5.4, 8.0 Hz), and 4.99 (1 H, d, J 5.4 Hz). The total amount of adducts isolated was 726 mg (79%).

Conversion of 5d into 5g.- Lithium aluminium hydride reduction of **5d** (340 mg, 1.48 mmol) afforded the diol **5e** as a thick oil in almost quantitative yield; $\nu_{max.}$ (neat) 3300, 2897, 2843, 1445, 1097, 1055 and 925 cm^{-1} ; δ_H (200 MHz); 1.60-2.36 (5 H, m), 2.78-3.00 (1 H, m), 3.26-3.54 (2 H, m), 3.62-4.00 (5 H, m), and 4.18 (2 H, bs). The diol **5e** (220 mg, 1.27 mmol) was methanesulfonated using methanesulfonyl chloride and pyridine at 0°C to give dimethanesulfonated derivative **5f** which was purified by chromatography with 10% methanol in ether as eluant to afford **5f** as a faint yellow liquid (280 mg, 68%); $\nu_{max.}$ (neat) 2913, 1453, 1353, 1175, 1050, and 963 cm^{-1} ; δ_H (200 MHz); 1.67-2.24 (4 H, m), 2.56-2.72 (1 H, m), 2.84-3.07 (1 H, m), 3.10 (6 H, two closely spaced singlets), 3.38-3.57 (2 H, m), 4.10 (1 H, m) and 4.28-4.55 (4 H, m). The dimethanesulfonate **5f** (220 mg, 0.61 mmol) was treated with a solution of super-Hydride ($LiEt_3BH$) in THF (4 mL, 4 mmol) at 50°C for 1 h. Usual work up[2] afforded **5g** as a faint yellow liquid; $\nu_{max.}$ (neat) 2939, 2905, 2849, 1462, 1389, and 927 cm^{-1} ; δ_H 1.08 (3 H, d, J 6.6 Hz), 1.20 (3 H, d, J 6.2 Hz), 1.40-2.06 (5 H, m), 2.87 (1 H, m), 3.36 (2 H, m), and 3.56 (1 H, m).

Reaction of the Nitrone 1 with Dimethyl Maleate.- A solution containing the nitrone 1 (360 mg, 2.5 mmol) in chloroform (2 ml) was heated to 50°C for 4 h. The nonseparable adducts **9a, 10a** were purified by chromatography using ether as eluant and obtained as a colourless oil (401 mg, 88%). (Found: C, 52.03; H, 6.47; N, 5.89. $C_{10}H_{15}NO_5$ requires C, 52.40; H, 6.60; and N, 6.11%); $\nu_{max.}$ 2938, 2860, 1742, 1442, 1376, 1214, and 1075 cm^{-1} ; δ_H (200 MHz)1.68-2.26 (4 H, m), 3.07 (1 H, M), 3.36 (2 H, m, including 1 H dd, J 6.0, 7.5 Hz), 3.76 (3 H, s), 3.80 (3 H, s), 4.19 (1 H, m), 4.86 (1 H, d 7.5 Hz), and a minor doublet at δ 4.70 (J 8.0 Hz). The ratio of **9a** and **10a** was found to be 83:17 respectively.

Reaction of the Nitrone 1 with Maleic Anhydride.- The reaction of maleic anhydride with the nitrone 1 afforded adducts which were gradually converted into unknown insoluble material. The approximate ^1H spectrum of the major adduct **9b** was obtained when the reaction was run in DMSO-d_6 in an n.m.r. tube; δ_H (200 MHz) 1.56 - 2.20 (4 H, m), 2.96 (1 H, m), 3.37 (1 H, m), 3.76 (1 H, t, J 8.3 Hz, C(3a)H), 3.99 (1 H, d, J 7.2, C(3)H) and 5.15 (1 H, d, J 7.2 Hz, C(2)H). Irradiation of the doublet at δ5.15 caused the doublet at δ3.99 to collapse into a singlet. The n.m.r. spectrum also revealed the presence of minor isomer **10b** of which the C(2)H and C(3)H appeared at δ5.04 (d, J 8.0 Hz) and 4.31 (dd, J 8.0, 9.5 Hz), respectively. The ratio of the adducts was found to be 70:30. The DMSO-d_6 solution containing the adducts gradually darkened on standing at room temperature. Attempts to isolate the adducts in pure form were unsuccessful.

In another trial maleic anhydride (196 mg, 2.0 mmol) was added to a solution of the nitrone 1 (1.5 mmol) in dichloromethane (1 ml). The reaction mixture was stirred at room teperature under N_2 for 2 min. After removal of the solvent, 5 ml of a mixture of MeOH-HCl (5:3 w/w) at 0°C was added to the residue and stirred at room temperature for 2 h. The mixture was taken up in saturated K_2CO_3 solution (10 ml) and extracted with CH_2Cl_2 (3x15 ml). The organic layer was dried ($MgSO_4$) and rotovaped to give a light yellow liquid, the ^1H n.m.r. spectrum of which revealed the presence of isomers **9a** and **10a** in a 67:33 ratio, respectively. The crude adducts were purified by chromatography using CH_2Cl_2 ether mixture as an eluant to give **9a** and **10a** as a colourless liquid (254 mg, 74%). The maleic anhydride adducts **9b, 10b** were thus also formed in 67:33 ratio. The acidic medium ($CH_3OH-HCl$) does not change the stereochemistry of the epimerizable centers C(2) and C(3). Thus adducts **4d, 5d** and dimethyl maleate adduct **9a, 10a** on treatment with CH_3OH:HCl (30:18 w/w) for 2 h remained unchanged.

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REFERENCES:

1. a) Huisgen. R. J. Org. Chem, **1976,** 41, 403-419. b) Tufariello. J. J. In '1,3-Dipolar Cycloaddition Chemistry', ed. A. Padwa, Wiley-Interscience, New York, 1984, Vol. 2, Ch.9.

2. Ali.Sk.A.; M. I. M. Wazeer, J. Chem. Soc., Perkin Trans.I **1988,** 597-605.

3. Ali.Sk. A.; Seneratne. P.A.; Illig.C. R.; Meckler. H.; Tufariello. J. J. Tetrahedron Lett. **1979,** 4167-4170.

4. (a) Hauk. K. N.; Sims.J. J. Am. Chem. Soc., **1973,** 95, 5798-5800. (b) Padwa. A.; Fisera. L.; Koehler. K. F.; Rodriguez. A; Wong. G. S. K., J. org. Chem., **1984,** 49 276-281.

5. (a) Huisgen. R.; Grashey.R.;Hauck. H.; Seidl. H. Chem. Ber., **1968,** 101, 2548. (b) Dicken. C. M.; Deshong. P. J. Org. Chem., **1982,** 47, 2047-2051.

6. (a) Houk. K. N.; Sims. J.; Duke. R. E.; Strozier. R. W.; George. J. K. J. Am. Chem. Soc., **1973,95,** 95, 7287-7301. (b) Houk. K. N.; Sims. J.; Watts. C. R.; Luskus. L. J. J. Am. Chem. Soc., **1973,** 95, 7301-7315.

7. (a) Tufariello. J. J. Acc. Chem. Res., **1979,** 12, 396-403. (b) Ida. H.; Kibayashi. C. Yuki Gosei Kagaku Kyokaishi, **1983,** 41, 652-664.

8. Joucla. M.; Tonnard. F.; Gree. D.; Hamelin. J. J. Chem. Res., (s) **1978,** 240-241; (M) **1978,** 2901-2912.

9. Tufariello. J. J.; Lee. G. E.; Senaratne. P. A.; Al-Nuri. M. Tetrahedron Lett., **1979,** 4359.

10. Ali. Sk. A.; Khan. J. H.; Wazeer. M. I. M. Tetrahedron, **1988,** 44, 5911-5920.

11. Krishnamurthy. S.; Brown. H. C. J. Org. Chem., **1976,** 41, 3064-3066.

12. (a) Ali. Sk. A.; Wazeer. M. I. M. J. Chem. Soc., Perkin Trans.2, **1986,** 1789-1792. (b) Ali. Sk. A.; Wazeer. M. I. M. Tetrahedron, **1988,** 44, 187-193. (c) Huisgen. R.; Seidl. H.; Bruning. I. Chem. Ber., **1969,** 102, 1102-1116.

13. Sustmann. R. Pure Appl. Chem., **1974,** 40, 569-595.

14. Boyle. L. W.; Peagram. M. J.; Whitham. G. H. J. Chem. Soc. B, **1971,** 1728-1733.

15. (a) Rambaud. R. R. Bull. Soc. Chim. Fr., **1934,** 1317. (b) Tufariello. J. J.; Tette.J.P. J. Org. Chem., **1975,** 40, 3866-3869.