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Stereoselective Cycloaddition of Nitrile Oxides to a Dispiroketal-protected But-3-ene-1,2-diol

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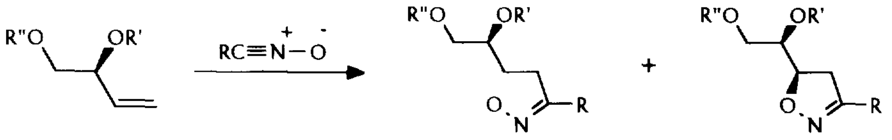
Abstract: The influence of a dispiroketal protecting group on the π-facial selectivity of nitrile oxide cycloaddition to *S*-but-3-ene-1,2-diol has been investigated. Ethoxycarbonylformonitrile oxide and benzonitrile oxide undergo regiospecific and diasteroeselective addition to alkene **7** to afford isoxazolines **11** and **12**. The major adducts (**11a** and **11b**) are formed with 44% and 50% d.e. respectively, and in each case have *S*-configuration at C-5, the new stereogenic centre.

Control of selectivity in nitrile oxide cycloaddition reactions is a key target in the development of the nitrile oxide-isoxazoline synthetic route to natural products and analogues.[1] Whereas the reaction with monosubstituted alkenes is either regiospecific or highly regioselective (>90:10) in favour of 5-substituted 2-isoxazoline (4,5-dihydroisoxazole) cycloadducts,[2] the extent of π-facial discrimination in additions to alkenes bearing an allylic stereocentre is more variable.[3-6] The ratio of products is dependent on the steric and electronic nature of both the allylic and homoallylic substitutents, and appears to be subject to subtle variations in geometry. Chiral allyl ethers yield predominantly *erythro* adducts resulting from *anti* addition, this preference being attributed to the so-called "inside alkoxy effect",[3,4,6] but for *S*-but-3-ene-1,2-diol (**1a**) and its diacetate derivative **1b** the diastereoselectivity is low with d.e. values of 22% and 6% respectively for the formation of isoxazolines **2a**/**3a** and **2b**/**3b** (Scheme 1) on reaction with benzonitrile oxide.[3] Somewhat higher levels of selectivity (55-70% d.e.) are found for the corresponding addition to 2-vinyl-1,3-dioxolanes **1c** and **1d**, the cyclic analogues in which the 1,2-diol is protected as its isopropylidene or cyclohexylidene derivatives.[3,5] Recently a new protecting group for *vicinal* diols has been developed by Ley *et al*[7] which incorporates the diol into a six-membered ring as a dispiroketal. Prompted by a report[8] that the addition of various organometallic reagents to the carbonyl group of a dispiroketal-protected D-glyceraldehyde **6** is highly



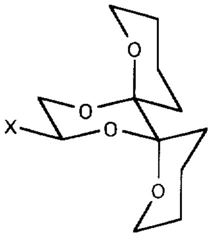
1

2 R = Ph
4 R = CO_2Et

3 R = Ph
5 R = CO_2Et

Scheme 1 [**1-5**; **a**, R' = R" = H; **b**, R' = R" = Ac; **c**, R'R" = CMe_2; **d**, R'R" = $C(CH_2)_5$]

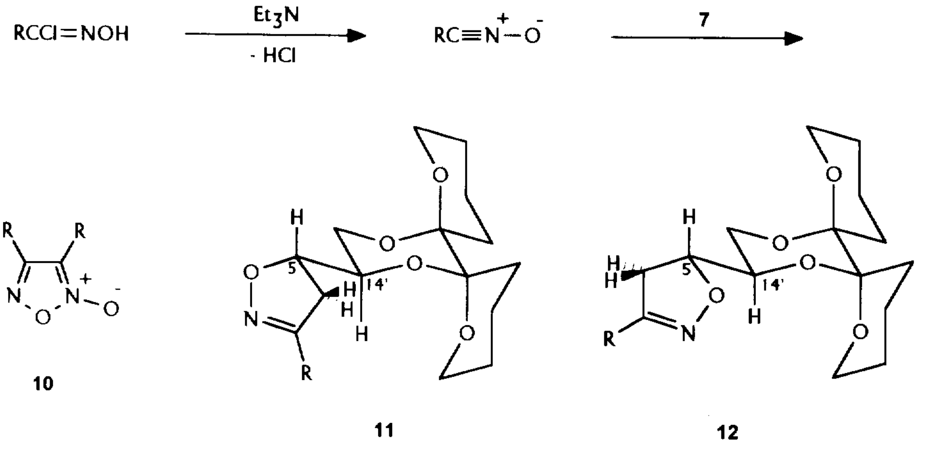
selective, an effect attributed to the rigidly-defined geometry of the dioxane ring and large steric bulk of the dispiroketal moiety, we have prepared the corresponding 2-vinyl-1,3-dioxane analogue **7** and have examined its cycloaddition reactions with nitrile oxides using benzonitrile oxide ($PhC{\equiv}N^{+}{-}O^{-}$) and ethoxycarbonylformonitrile oxide ($EtO_2CC{\equiv}N^{+}{-}O^{-}$) as representative examples.



6 X = CH=O
7 X = $CH{=}CH_2$
8 X = CH_2CH_2OH
9 X = CH_2CH_2OTs

Results and Discussion

The required 2-vinyl-1,4-dioxane dispiroketal dipolarophile **7** was prepared from β-hydroxyethyl compound **8**, as previously described,[8] by conversion to the tosyl derivative **9** followed by treatment with potassium *tert*-butoxide. The first nitrile oxide to be examined was ethoxycarbonylformonitrile oxide, which was generated *in situ* by dehydrochlorination of ethyl chloro(hydroxyimino)acetate.[9] The competing dimerisation to 3,4-ethoxycarbonylfurazan *N*-oxide (**10a**)[10] was minimised by slow addition (over 36 hours) of triethylamine to a solution of the hydroximoyl chloride and a slight excess of alkene **7** (1:1.5) in diethyl ether at 0 °C. From the reaction mixture were isolated by chromatography unreacted **7** (53% recovered), furazan *N*-oxide **10a** (6%) and a mixture of two isoxazoline cycloadducts **11a** and **12a** in a combined yield of 53% (Scheme 2). The individual adducts were separated by chromatography and the major product purified by crystallisation.



Scheme 2 [**10**-**12**; **a**, R = CO_2Et; **b**, R = Ph]

The isomers were readily identified from their NMR spectra (Table 1). The isoxazoline ring protons give rise to a characteristic ABX system with 5-H, which is adjacent to the ring oxygen, at highest chemical shift. The ^3J values of 8-11 Hz for 4ab-H/5-H, and the geminal coupling of *ca* 18 Hz for 4a-H/4b-H are also typical of 3,5-disubstituted isoxazolines.[1f,11-13] It is noteworthy that the coupling of 7.0 Hz between protons 5-H and 14'-H in the major isomer is significantly greater than that for the minor product (4.8 Hz), suggesting that the two compounds adopt different conformations in solution. The isomer ratio (72:28) was measured from the ^{1}H NMR spectrum of the product mixture by comparison of the 5-H signals, which are well separated ($\Delta\delta_H = 0.12$ ppm); HPLC analysis gave a similar value (71:29).

Table 1 Selected NMR data (δ_X/ppm, $J_{x,y}$ Hz) for isoxazolines[a]

		11a	**12a**	**11b**	**12b**	**4d**	**5d**	**4a**	**5a**
δ_H	4a-H	3.18	3.18	3.40	3.31	3.26	3.24	3.17	3.28
	4b-H	3.25	3.18	3.40	3.31	3.26	3.14	3.29	3.20
	5-H	4.64	4.76	4.63	4.73	4.70	4.83	4.86	4.91
	6-H					3.85	4.25	3.82	3.81
	7a-H					4.10	4.05	[3.54-	[3.60-
	7b-H					4.06	3.84	-3.63]	-3.64]
$J_{x,y}$	4a,4b	17.8	[b]	[b]	[b]	[b]	17.8	17.6	17.4
	4a,5	10.9	10.2	8.8	9.8	8.9	11.4	11.4	11.3
	4b,5	8.1	10.2	8.8	9.8	8.9	8.5	8.5	9.0
	5,14'	7.0	4.8	7.7	5.3				
	5,6					7.0	4.2	4.5	3.1
	6,7a					6.3	6.8	~5	[b]
	6,7b					4.0	6.3	~5	[b]
	7a,7b					[b]	8.7	[b]	[b]
δ_C	C-3	151.4	151.1	156.2	156.1	151.6	151.4	151.9	151.9
	C-4	35.4	34.5	37.2	35.9	36.3	35.6	33.8	35.3
	C-5	82.4	82.1	80.2	79.9	83.7	82.5	84.2	83.8
	C-14'	66.7	67.1	67.0	67.2				
	C-6					75.1	75.6	71.8	73.1
	C-7					66.4	64.6	63.1	63.0
	C=O	160.5	160.5			160.3	160.4	160.7	160.8
	O*C*H$_2$CH$_3$	[b]	[b]			62.0	62.0	61.4	61.4
	OCH$_2$*C*H$_3$	13.9	13.9			14.0	14.0	13.7	13.7
	Ph*C*			129.2	129.3				
	Ph*C*H			126.6	126.6				
				128.5	128.6				
				130.0	129.3				

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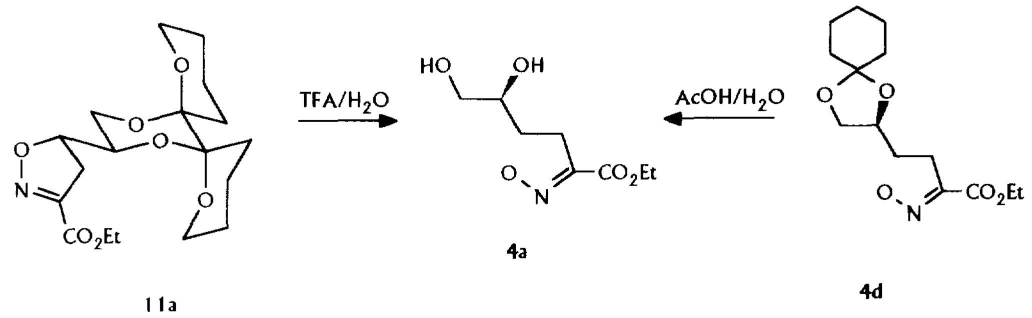
[a] Recorded in CDCl$_3$ at 360 MHz (^{1}H) and 90 MHz (^{13}C); [b] not determined

In order to identify the individual isomers the major adduct was deprotected by treatment with aqueous trifluoroacetic acid to afford the corresponding 5-(1,2-dihydroxyethyl)isoxazoline, which was then compared with authentic samples of the two possible products **4a** and **5a** (Scheme 1). These were prepared in two steps from cyclohexylidene-protected *S*-but-3-ene-1,2-diol **1d**. Cycloaddition of ethoxycarbonylformonitrile oxide to alkene **1d** afforded a readily separable mixture of *erythro* isoxazoline **4d** (52%) and its *threo* isomer **5d** (16%), the structures of which are firmly established.[14] Subsequent deprotection of the individual adducts **4d** and **5d** with aqueous acetic acid yielded 1,2-dihydroxyethyl-isoxazolines **4a** and **5a** respectively. Compound **4a** proved to be identical to the product resulting from deprotection of the major adduct derived from the dispiroketal-protected alkene (Scheme 3). This adduct is therefore assigned structure **11a** in which the newly created stereogenic centre (C-5) has *S*-configuration and there is an *erythro* relationship between this carbon and the adjacent stereogenic centre (C-14') of the dispiroketal 1,3-dioxane unit. The minor isomer therefore has *threo* structure **12a**.



Scheme 3

Benzonitrile oxide, which was generated by triethylamine-induced dehydrochlorination of benzohydroximoyl chloride, reacted similarly yielding 3,4-diphenylfurazan *N*-oxide (**10b**, 8%) and a mixture of two isoxazolines **11b** and **12b** in a combined yield of 40% with an isomer ratio of 75:25. The products were separated by chromatography and the structures of the individual isomers were assigned by comparison of their physical and spectroscopic properties with those of the ethoxycarbonyl analogues **11a** and **12a** described above. The NMR data for the isoxazoline portion of these adducts are distinctive (see Table 1). In particular, for the major adducts the proton 5-H absorbs at significantly lower frequency ($\Delta\delta_H$ -0.12 ppm for **11a**/**12a**, -0.10 ppm for **11b**/**12b**) and 4b-H at higher frequency ($\Delta\delta_H$ +0.07 ppm for **11a**/**12a**, +0.09 ppm for **11b**/**12b**) than the corresponding peaks for the minor product. The major adduct again has the larger $J_{7,14'}$ value (7.7 *cf* 5.3 Hz). In the ^{13}C NMR spectra C-4 resonates at higher frequency for the major isomer ($\Delta\delta_C$ +0.9 ppm for **11a**/**12a**, +1.3 ppm for **11b**/**12b**). Furthermore, the major isomer in each case has the more positive/less negative specific rotation(**11a** +14.9 , **12a** -206.5 ; **11b** -3.4 , **12b** -175.5), and is faster eluting on TLC (silica, ether/hexane). Similar correlations have been observed previously for diastereoisomeric pairs of isoxazolines resulting from nitrile oxide cycloadditions to carbohydrate alkenes.[12,13] On this basis the major adduct derived from benzonitrile oxide and alkene **7** was assigned structure **11b** which, like **11a**, has the *S*-configuration at the newly-created stereogenic centre C-5 and an *erythro* relationship between this carbon and the adjacent carbon (C-14') of the dioxane ring. The minor slower eluting isomer therefore has structure **12b**.

Table 2 π–Facial selectivity for the cycloaddition of ethoxycarbonylformonitrile oxide and benzonitrile oxide to *S*-but-3-en-1,2-diol and derivatives

Alkene	R'	R"	Nitrile oxide	Isoxazolines(%) *erythro*	*threo*	Reference
7	dispiroketal[a]		EtO_2CCNO	75	25	[b]
			PhCNO	72	28	[b]
1a	H	H	PhCNO	61	39	3
1b	Ac	Ac	PhCNO	53	47	3
1c	$-CMe_2-$		EtO_2CCNO	80	20	5
				77	23	15
			PhCNO	85	15	3, 13
				83	17	5
				79	21	15
1d	$-C(CH_2)_5-$		EtO_2CCNO	77	23	[b]
			PhCNO	81	19	3, 13
				79	21	15

[a] see Scheme 2; [b] present work.

The ratios of products resulting from the cycloaddition of benzonitrile oxide and ethoxycarbonylformonitrile oxide to alkene **7** are given in Table 2, from which it is evident that incorporating the allylic and homoallylic hydroxyls into the six-membered 1,3-dioxane ring of the dispiroketal results in enhanced selectivity compared with the open-chain compounds **1a** and **1b**,[3] and at a level comparable with those observed for 2-vinyl-1,3-dioxolanes.[3,5,13,15] The predominance of *erythro* adducts can be rationalised in terms of the "inside alkoxy effect" proposed by Houk *et al*[3,4,6] to account for nitrile oxide cycloadditions to chiral allyl ethers; the preferred transition state has the largest substituent *anti*, the smallest (H) "outside", and the alkoxy in the "inside" position. For the 2-vinyl-1,3-dioxane and 2-vinyl-1,3-dioxolanes the *anti* substituent is linked *via* the six- or five-membered ring to the inside alkoxy as illustrated in Figure 1. The increased selectivity in these cases compared with the acyclic analogues may be associated with a through-space interaction of a lone pair of the homoallylic oxygen with the alkene π-bond[16] and the conformational restraints imposed by the ring.

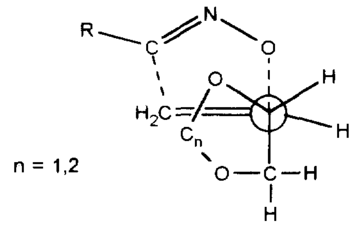


Figure 1

Experimental

The analytical methods and instrumentation were as previously described.[11,12] Benzohydroximoyl chloride was prepared by chlorination of benzaldoxime in chloroform,[17] and ethyl chloro(hydroxyimino)acetate was obtained by the literature procedure[9] from glycine ethyl ester by treatment with $NaNO_2$/HCl. Dispiroketal-protected alkene **7** (6*R*, 7*R*, 14*S*-14-vinyl-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane) was synthesised from β-hydroxyethyl compound **8** *via* its tosylate derivative **9** in 35% overall yield as previously described.[8] 1,2-Dideoxy-3,4-*O*-cyclohexylidene-D-*glycero*-but-1-enitol (**1d**)[13] was prepared from 2,3-*O*-cyclohexylidene-D-glyceraldehyde and methylenetriphenylphosphorane (generated from $MePh_3P^+I^-$ and $KOBu^t$ in THF).

Cycloaddition Reactions.– General procedure. A solution of triethylamine (1.1 mmol) in dry diethyl ether was added over 32-45 h using a motorised syringe to an ice-cooled stirred solution of the alkene (1.5 mmol) and hydroximoyl chloride (1.0 mmol) in diethyl ether. After stirring for a further 8 h the mixture was filtered to separate precipitated triethylamine hydrochloride, and the solvent removed *in vacuo*. Chromatography of the residue (silica, gradient elution with hexane/diethyl ether) afforded in order of elution unreacted alkene, furazan *N*-oxide **10** (identified by TLC compared with an authentic sample), and the diastereoisomeric isoxazolines **11**/**12** or **4d**/**5d**.

Addition of ethoxycarbonylformonitrile oxide to alkene 7. Using the procedure described above ethyl chloro(hydroxyimino)acetate and alkene **7** afforded in order of elution unreacted alkene (53%), 3,4-diethoxycarbonylfurazan *N*-oxide **10a** (6%), 5S-3-*ethoxycarbonyl*-5-(6R,7R,14R-1,8,13,16-*tetraoxadispiro*[5.0.5.4]*hexadecan*-14-*yl*)-4,5-*dihydroisoxazole* **11a** (42%) [white needles (from hexane/diethyl ether), m.p. 110-111 °C (Found: C, 58.7; H, 7.2; N, 3.3. $C_{18}H_{27}NO_7$ requires C, 58.5; H, 7.3; N, 3.8%); $[\alpha]_D^{24}$ +14.9 (*c* 0.33 in $CHCl_3$); *m/z* (FAB, thioglycerol) 370.1866 (M + 1), $C_{18}H_{28}NO_7$ requires 370.18656], and 5R-3-*ethoxycarbonyl*-5-(6R,7R,14R-1,8,13,16-*tetraoxadispiro*[5.0.5.4]*hexadecan*-14-*yl*)-4,5-*dihydroisoxazole* **12a** (17%) [$[\alpha]_D^{24}$ -206.5 (*c* 0.68 in $CHCl_3$); *m/z* (FAB, thioglycerol) 370.1866 (M+1), $C_{18}H_{28}NO_7$ requires 370.18656]. NMR data for isoxazolines **11a** and **12a** are given in Table 1. The isomer ratio (**11a**:**12a** = 72:28) was measured from the ^1H NMR spectrum of the mixture of adducts by comparison of the isoxazoline 5-H signals at 4.64 and 4.76 ppm; HPLC analysis (ODS silica, MeOH/H_2O) gave a ratio **11a**:**12a** = 71:29.

Addition of benzonitrile oxide to alkene 7. Using the procedure described above benzohydroximoyl chloride and alkene **7** afforded in order of elution unreacted alkene (54%), 3,4-diphenylfurazan *N*-oxide **10b** (8%), 5S-3-*phenyl*-5-(6R,7R,14R-1,8,13,16-*tetraoxadispiro*[5.0.5.4]*hexadecan*-14-*yl*)-4,5-*dihydroisoxazole* **11b** (30%) [white needles (from hexane/diethyl ether), m.p. 189.2-190.3 °C (Found: C, 67.8; H, 7.3; N, 3.7. $C_{21}H_{28}NO_5$ requires C, 67.6; H, 7.2; N, 3.7%); $[\alpha]_D^{24}$ -3.4 (*c* 0.56 in $CHCl_3$); *m/z* (FAB, thioglycerol) 374

(M + 1)], and 5R-3-*phenyl*-5-(6R,7R,14R-1,8,13,16-*tetraoxadispiro*[5.0.5.4]*hexadecan*-14-*yl*)-4,5-*dihydroisoxazole* **12b** (10%) [$[\alpha]_D^{24}$ -175.7 (*c* 0.33 in $CHCl_3$); *m/z* (FAB, thioglycerol) 374.1967 (M + 1), $C_{21}H_{28}NO_5$ requires 374.19673]. NMR data for isoxazolines **11b** and **12b** are given in Table 1. The isomer ratio (**11b**:**12b** = 75:25) was measured from the ^1H NMR spectrum of the mixture of adducts by comparison of the isoxazoline 5-H signals at 4.64 and 4.76 ppm.

Addition of ethoxycarbonylformonitrile oxide to alkene **1d**. Using the procedure described above ethyl chloro(hydroxyimino)acetate and alkene **1d** afforded in order of elution unreacted alkene (19%), 3,4-diethoxycarbonylfurazan *N*-oxide **10a** (16%), 5S-5-(1,2-O-*cyclohexylidene*-D-glycero-*diitol*-1-*yl*)-3-*ethoxycarbonyl*-4,5-*dihydroisoxazole* **4d** (52%) [white needles (from Et_2O), m.p. 40.8-41.9 °C (Found: C, 59.7; H, 7.7; N, 5.0. $C_{14}H_{21}NO_5$ requires C, 59.4; H, 7.4; N, 5.0%); $[\alpha]_D^{24}$ +58.1 (*c* 0.31 in $CHCl_3$); *m/z* (FAB, thioglycerol) 284 (M + 1), and 5R-5-(1,2-O-*cyclohexylidene*D-glycero-*diitol*-1-*yl*)-3-*ethoxycarbonyl*-4,5-*dihydroisoxazole* **5d** (16%) [white needles (from Et_2O/hexane), m.p. 47-49 °C (Found: C, 59.4; H, 7.7; N, 4.6. $C_{14}H_{21}NO_5$ requires C, 59.4; H, 7.4; N, 5.0%); $[\alpha]_D^{24}$ -153.8 (*c* 0.10 in $CHCl_3$); *m/z* (FAB, thioglycerol) 284 (M + 1)]; NMR data for isoxazolines **4d** and **5d** are given in Table 1.

Deprotection of Isoxazoline **4d**.– Isoxazoline **4d** (80 mg, 0.28 mmol) was heated at 80 °C with a mixture of glacial acetic acid and water (3:2) for 2 h. Concentration of the mixture *in vacuo*, repeated addition and removal (4 x 10 ml) of 1:1 toluene-heptane, followed by preparative TLC (silica, Et_2O) afforded 5S-5-(D-glycero-*diitol*-1-*yl*)-3-*ethoxycarbonyl*-4,5-*dihydroisoxazole* (**4a**) (77%) as a pale yellow oil; $[\alpha]_D^{26}$ +109.9 (*c* 0.78 in CH_3OH); *m/z* (FAB, thioglycerol) 204.0872 (M+1), $C_8H_{14}NO_5$ requires 204.08719; NMR data for isoxazoline **4a** are given in Table 1.

Deprotection of Isoxazoline **5d**.– Similar treatment to that described above for compound **4d** afforded 5R-5-(D-glycero-*diitol*-1-*yl*)-3-*ethoxycarbonyl*-4,5-*dihydroisoxazole* (**5a**) (80%) as a pale yellow oil $[\alpha]_D^{26}$ +124.9 (*c* 0.56 in CH_3OH); *m/z* (FAB, thioglycerol) 204.0872 (M+1), $C_8H_{14}NO_5$ requires 204.08719; NMR data for isoxazoline **5a** are given in Table 1.

Deprotection of Isoxazoline **11a**.– Isoxazoline **11a** (30 mg, 81 mmol) was treated with a mixture of trifluoroacetic acid (1.0 ml) and water (0.1 ml) for 1 h. Concentration of the mixture *in vacuo*, repeated addition and removal (4 x 10 ml) of 1:1 toluene-heptane, followed by preparative TLC (silica, Et_2O) afforded a material (91%) which was shown by TLC and NMR spectroscopy to be identical to compound **4a**.

Acknowledgements

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