CYCLOADDITION OF NITRILE OXIDES TO 4-OXOBUT-2-ENOIC ACID DERIVATIVES[1]

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Abstract- The 1,3-dipolar cycloadditions of aceto-, benzo- and bromoformonitrile oxides to cyclic and open-chain 4-oxobut-2-enoic acid derivatives have been investigated. The addition to 5-methoxyfuran-2(5*H*)-one (**1**) gave regioselectively 3-substituted 6-*exo*-methoxy-3a,6a-dihydrofuro[3,4-*d*]isoxazol-4(6*H*)-ones, whereas methyl (*Z*)- and (*E*)-4,4-dimethoxybut-2-enoates (**2**) and (**3**) afforded mixtures of regioisomeric isoxazolines.

INTRODUCTION

The 1,3-dipolar cycloaddition is one of the most useful methods for the construction of five membered heterocyclic rings.[2] The cycloaddition reactions to 4-oxobut-2-enoic acid derivatives, including those of its ring-tautomer, afford functionalized heterocycles which are valuable intermediates for the synthesis of fused heterocyclic ring systems and other physiologically interesting molecules. However, there are few reports dealing with the use of these compounds as dipolarophiles, the only examples being the cycloaddition of diazomethane to 5-methoxyfuran-2(5*H*)-ones[3] and to methyl (*Z*)- or (*E*)-4,4-dimethoxybut-2-enoates,[4] described by us, the addition of arylazides to 5-alkoxyfuranones,[5] and the reactions of aryl nitrile oxides and diphenylnitrone with 5-hydroxy- or 5-alkoxyfuran-2(5*H*)-ones, reported by Fisera[6] and Feringa.[7]

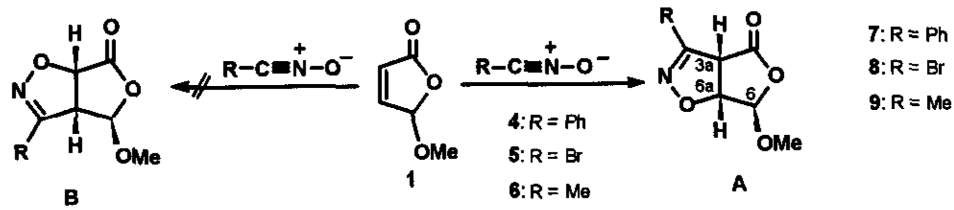
In the present paper we extend our study to the behaviour of 5-methoxyfuran-2(5*H*)-one (**1**), butenoates (**2, 3**) and their 2- and 3-bromo derivatives, towards benzo-, bromoformo-, and acetonitrile oxides (**4-6**). The reactions have been explored with cyclic and open-chain dipolarophiles to acquire information on the influence of the alkene structure upon reactivity and regioselectivity. Isoxazoles and isoxazolines, which are readily converted into polyfuctional derivatives, have received much attention as an important class of synthetic intermediates. The isoxazolines obtained by cycloaddition of nitrile oxides to 4-oxobut-2-enoic acid derivatives (**1, 2** and **3**) are appropriately functionalized and may serve as versatile synthetic intermediates for the construction of new fused heterocyclic ring systems.

RESULTS AND DISCUSSION

Benzonitrile oxide (BNO) (**4**) and bromoformonitrile oxide (**5**) were prepared by dehydrohalogenation of the corresponding hydroximic acid halides. All the cycloaddition reactions were run with excess of 1,3-dipole at room temperature under comparable conditions. The acetonitrile oxide (**6**) was generated "in situ" from nitroethane by the Mukaiyama's method,[8] and the cycloaddition reactions were carried out at room temperature and/or at 40 °C. The reactions were prolonged until disappearance of the dipolarophile was completed, the crude reaction mixtures being analyzed by ^{1}H nmr. The furoisoxazolines were isolated by column chromatography.

Cycloadditions to 5-methoxyfuran-2(5*H*)-ones

Nitrile oxides (**4-6**) reacted readily with furanone (**1**) to afford the expected adducts in moderate yields. Only one regioisomer was produced in accord with the behaviour of other furan-2(5*H*)-ones[6,7,9] and α,β-unsaturated lactones[10] towards this type of dipole. On the basis of the reported observations we have assigned the structure of type **A** (**7-9**) to the isolated furoisoxazoline derivatives, rather than the regiochemistry of type **B** (Scheme 1). The ^{1}H nmr spectra of the adducts were also consistent with the assigned structure **A**.



Scheme 1

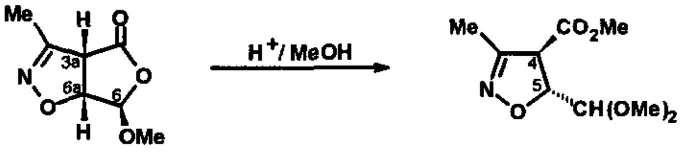
The *trans* relationship of H-6 and H-6a, and consequently the face-selectivity of the cycloadditions, was established by ^{1}H nmr (Table I). In all the isolated furoisoxazolines (**7-9**), the acetal-type proton appears as

Table I. ^{1}H nmr data of furoisoxazolines **7-9**

Compd.	R	H-3a	H-6a	H-6	OMe	Me (Ph)	$J_{3a,6a}$
7	Ph	4.73	5.26	5.53	3.56	(7.91, 7.50)	9.0
8	Br	4.27	5.17	5.44	3.53	-	9.4
9	Me	4.24	5.09	5.45	3.57	2.14	9.3

a singlet. This fact suggests that the attack of dipole occurs preferently at the face opposite to the OMe group, although this is not a very bulky group. This observation is in accord with the face-selectivity reported previously for the Diels-Alder reactions of furanone (**1**)[11] and other 5-substituted butenolides,[12] and for the 1,3-dipolar cycloaddition of nitrones to the same type of dipolarophiles.[13] It is interesting to note, however, that the addition of diazomethane to **1** leads to a mixture of *endo* and *exo* adducts.[3]

The proposed regiochemical assignment was further confirmed by conversion of **9** into **15b** (Scheme 2),[14] the structure of which was assigned as shown below.



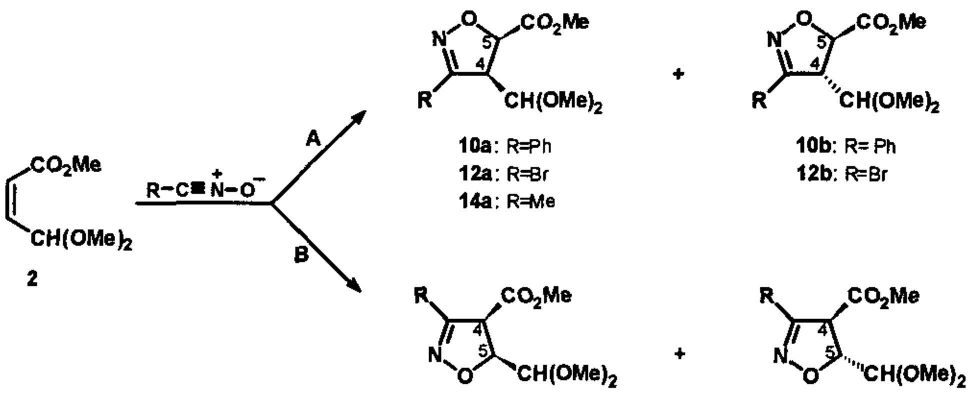
9 15b

Scheme 2

It is remarkable that 3- or 4-bromo-5-methoxyfuran-2(5*H*)-ones[15] do not react with the nitrile oxides (**4**, **5** and **6**) under the experimental conditions employed for the furanone (**1**).

Cycloadditions to methyl 4,4-dimethoxybut-2-enoates

According to literature, cycloadditions of nitrile oxides with activated 1,2-disubstituted ethylenes, such as crotonic and cinnamic esters, generally produce mixtures of regioisomers.[16] Unfortunately, the behaviour of methyl 4,4-dimethoxybut-2-enoates is not different in this regard. In fact, 1,3-dipolar cycloaddition of nitrile oxides (**4**, **5** and **6**) to the *Z*-butenoate (**2**) proceeded smoothly affording two regioisomeric adducts, each appearing as a mixture of *cis*- and *trans*-4,5-disubstituted isoxazolines. Exception was found with acetonitrile oxide (**6**) that afforded both regioisomers, although a single stereoisomer was produced in each case. The ratios of regio- and stereoisomers obtained are summarized in Table II.



2

10a: R=Ph
12a: R=Br
14a: R=Me

10b: R= Ph
12b: R=Br

11a: R=Ph
13a: R=Br

11b: R= Ph
13b: R=Br
15b: R=Me

Scheme 3

Table II. Cycloadditions to methyl (*Z*)- and (*E*)-4,4-dimethoxybut-2-enoates

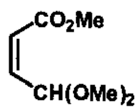
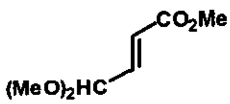
Dipolarophile	Dipole	Isoxazolines (Ratio)	Ratio A/B	Yield %
	$Ph-C\equiv N^{+}-O^{-}$ (4)	**10a, 10b, 11a, 11b** (16:10:60:14)	26 : 74	48
	$Br-C\equiv N^{+}-O^{-}$ (5)	**12a, 12b, 13a, 13b** (44:18:13:25)	62 : 38	55
2 (*Z*)	$Me-C\equiv N^{+}-O^{-}$ (6)	**14a, 15b** (65:35)	65 : 35	50
	$Ph-C\equiv N^{+}-O^{-}$ (4)	**10b, 11b** (46 : 54)	46 : 54	55
	$Br-C\equiv N^{+}-O^{-}$ (5)	**12b, 13b** (70:30)	70 : 30	60
3 (*E*)	$Me-C\equiv N^{+}-O^{-}$ (6)	**14b, 15b** (60:40)	60 : 40	55

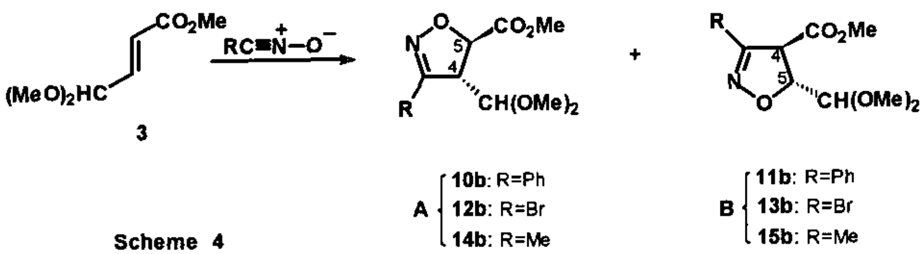
Table III. ^{1}H Nmr data of isoxazolines (**10-15**)

Comp.	R	H-4	H-5	C$\underline{H}$(OMe)$_2$	CO_2Me	OMe	R	$J_{4,5}$	$J_{C\underline{H},4}$	$J_{C\underline{H},5}$
10a	Ph	4.13	5.09	4.58	3.84	3.30, 3.11	7.7-7.4	9.3	7.4	
10b	Ph	4.31	5.32	4.57	3.79	3.38, 3.32	7.7-7.4	4.2	4.1	
11a	Ph	4.54	4.88	4.70	3.72	3.55, 3.37	7.7-7.4	11.1		7.3
11b	Ph	4.42	5.00	4.59	3.68	3.47, 3.45	7.7-7.4	4.4		5.5
12a	Br	3.87	5.11	4.69	3.81	3.45, 3.35	-	10.7	6.9	
12b	Br	3.94	5.17	4.59	3.83	3.49, 3.48	-	6.0	4.0	
13a	Br	4.28	4.86	4.64	3.81	3.51, 3.33	-	11.3		7.2
13b	Br	4.26	5.02	4.46	3.83	3.48, 3.45	-	6.8		4.0
14a	Me	3.69	4.97	4.65	3.78	3.39, 3.35	2.05	10.8	6.7	
14b	Me	3.73	4.94	4.46	3.80	3.43, 3.40	2.05	5.2	6.5	
15b	Me	4.06	4.95	4.30	3.79	3.46, 3.45	2.05	6.7		4.3

The structure of the regioisomeric isoxazolines was established on the basis of the chemical shift of the proton coupled with the acetal proton (Table III). In 5-methoxycarbonylisoxazolines (**10**, **12**, and **14**) H-4 appears as a double doublet at higher field than in the corresponding 4-methoxycarbonylisoxazolines (**11**, **13**, and **15**). The *cis* or *trans* relationship between protons H-4 and H-5 can directly be deduced from the magnitude of the coupling constant $J_{4,5}$; in fact, smaller values were observed (compounds **10b-15b**) when these protons are *trans* to each other, while larger values were present in the *cis* isomers (**10a-14a**).

If we admit a concerted mechanism, the formation of isoxazolines (**10b-15b**) with the methoxycarbonyl and dimethoxymethyl groups in a *trans* arrangement, which was not present in the starting dipolarophile (**2**), may be ascribed to a subsequent isomerization of the primary adduct. A similar isomerization has been observed in related cycloadducts.[16b]

The 1,3-dipolar cycloaddition of nitrile oxides (**4**, **5**, **6**) to the *E*-dipolarophile (**3**) was carried out under experimental conditions similar to those used for the *Z*-dipolarophile (**2**). The reactions proceeded at a rate somewhat faster than those of the *Z*-ester, affording two regioisomeric adducts with complete retention of stereochemistry (Scheme 4).



Scheme 4

The low regioselectivity observed in the cycloadditions of nitrile oxides (**4**, **5** and **6**) to the open-chain dipolarophiles (**2**) and (**3**) (Table II) is in accord with the general fact reported for the additions of nitrile oxides to other 1,2-unsymmetrically substituted alkenes.[2,17-19] The reactions of benzonitrile oxide (**4**) with *Z*- and *E*-butenoates (**2**) and (**3**) afford the 4-methoxycarbonylisoxazolines (**11a,b**) as the major regioisomers (A/B < 1, Table II) in agreement with the regiochemistry reported for the additions to crotonic and cinnamic esters.[16] In contrast, the addition of acetonitrile oxide (**6**) to **2** and **3** gives the 5-methoxycarbonylisoxazoline (**14**) as the major regioisomer (A/B > 1); this fact does not agree with the regiochemistry previously reported[16a,c,d] for cycloadditions of dipole (**6**) to crotonic and cinnamic esters. It is noteworthy that the regioselectivity is significantly affected by the stereochemistry of the dipolarophile (A/B = 0.35 and 0.85 for *Z* and *E* dipolarophile, respectively), whereas the regioselectivity of acetonitrile oxide additions is barely influenced by the *Z* or *E* geometry of the dipolarophile. The results obtained for the cycloadditions of bromoformonitrile oxide (**5**) to the butenoates (**2**) and (**3**) parallel those obtained with the acetonitrile oxide (**6**).

As indicated above for the cyclic dipolarophile (**1**), a bromine atom linked to the double bond of the esters (**2**) or (**3**) practically inhibits the cycloaddition of the nitrile oxides (**4-6**) under the experimental conditions employed.

In summary, cycloadditions to the cyclic dipolarophile (**1**) occur with high face- and regioselectivity and proceed faster than those to the open-chain dipolarophiles (**2** and **3**).

EXPERIMENTAL

Mps are uncorrected. Ir spectra were recorded on a Phillips model P.V-9716 spectrophotometer (ν_{max}, cm^{-1}). ^{1}H and ^{13}C nmr spectra were obtained on a Bruker WP 200SY spectrometer for $CDCl_3$ solutions, using TMS (δ=0 ppm) as internal reference. Mass spectra were determined on a Hewlett-Packard model 5985. Silica gel Merck 230-400 mesh and DC-Alufolien 60 were used for flash and analytical thin layer chromatography, respectively.

The dipolarophiles (**1**),[20](**2**),[21d](**3**)[21d] and their halo derivatives[15a,b] were prepared according to the previously reported procedures.

6-*exo*-Methoxy-3-phenyl-3a,6a-dihydrofuro[3,4-*d*]isoxazol-4(6*H*)-one (7)[6]

To a stirred mixture of 10% sodium hydroxide solution (20 ml) and ether (20 ml) was added portionwise during 10 min at 0 °C the benzaldehyde chloroxime (1.55 g, 10 mmol). The ethereal layer was separated, quickly dried over magnesium sulfate and added to a solution of the 5-methoxyfuran-2(5*H*)-one (1) (1.03 g, 9 mmol) in dry ether (10 ml). After stirring for 12 h at room temperature, a second addition of dipole (10 mmol) was made and the mixture allowed to stand at room temerature for 24 h. The adduct was isolated by filtration, mp 108-110 °C. Lit.[6] 109-111 °C. A second crop of **7** was obtained from the ethereal solution. Yield 60% (1.26 g). Ir (nujol): 1805, 1780, 1565. ^{13}C Nmr: 169.6 (C-4), 152.4 (C-3), 130.7 (Ar), 128.6 (Ar),127.7 (Ar), 126.5 (Ar), 107.7 (C-6), 86.7 (C-6a), 57.2 (C-3a), 53.7 (OMe). Ms, m/z (%): 233 (49), 174 (10), 144 (100), 115 (28), 104 (40), 77(60).

3-Bromo-6-*exo*-methoxy-3a,6a-dihydrofuro[3,4-*d*]isoxazol-4(6*H*)-one (8)

To a vigorously stirred mixture of 5-methoxyfuran-2(5*H*)-one (1)(513 mg, 4,5 mmol), ethyl acetate (23 ml), sodium bicarbonate (773 mg, 9.2 mmol), and water (1.5 ml), was added solid dibromoformaldoxime (913 mg, 4.5 mmol) in small portions. Stirring was maintained during 30 h at room temperature. The precipitated salt was filtered off, the filtrate was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue analyzed by ^{1}H nmr, contained the adduct (**8**) as the main component and traces of methyl 3-bromo-5-formylisoxazole-4-carboxylate. The crude product was chromatographed on silica gel (ethyl acetate-hexane 1:3) to afford the pure furoisoxazoline (**8**) in 45 % yield (478 mg). Recrystallized from carbon tetrachloride mp

105-108 °C. Anal. Calcd for $C_6H_6NO_4Br$: C, 30.51; H, 2.54; N, 5.93; Br, 33.90. Found: C, 30.60; H, 2.64; N, 5.91, Br, 33.98. Ir (nujol): 1810, 1780, 1565. ^{13}C Nmr: 167.3 (C-4), 132.7 (C-3), 108.2 (C-6), 86.8 (C-6a), 58.1 (C-3a), 57.6 (OMe). Ms, m/z(%): 237-235 (2), 206-204 (4), 149-147 (53), 112 (53), 84 (100).

6-*exo*-Methoxy-3-methyl-3a,6a-dihydrofuro[3,4-*d*]isoxazol-4(6*H*)-one (9)

To a solution of 5-methoxy-2(5*H*)-furanone (1) (2.85 g, 25 mmol) and triethylamine (1 ml) in toluene (70 ml) was added phenyl isocyanate (5.95 g, 50 mmol), and nitroethane (2.24 g, 30 mmol) in four portions over a period of 1 h. Stirring was maintained during 4 h at room temperature. The precipitated *N,N*-diphenylurea was filtered off. Evaporation of solvent gave a residue, that was purified by column chromatography (ethyl acetate-hexane 1:3). Yield 70 % (2.99 g). Recrystallized from cyclohexane mp 70-73 °C. Anal. Calcd for $C_7H_9NO_4$: C, 49.12; H, 5.26; N, 8.19. Found: C,49.23; H, 5.45; N, 8.24. Ir (nujol): 1800, 1780. ^{13}C Nmr: 169.7 (C-4), 150.7 (C-3), 108.9 (C-6), 85.2 (C-6a), 57.3 (C-3a), 57.2 (OMe), 10.9 (Me). Ms, m/z(%): 171 (3), 140 (3), 93 (76), 83 (56), 69 (100).

Cycloaddition of Benzonitrile Oxide (4) to Methyl 4,4-Dimethoxybut-2-enoates

a) To an ice cooled solution of methyl (*Z*)-4,4-dimethoxybut-2-enoate **(2)** (800 mg, 5 mmol) in methylene chloride (25 ml) was added with stirring triethylamine (2.1 ml, 15 mmol). To the stirred solution was added benzaldehyde chloroxime (800 mg, 5.5 mmol) in small portions. After 3 days at room temperature, a new portion of benzaldehyde chloroxime (5.5 mmol) was added and the mixture allowed to stand for 6 days. The solvent was removed under reduced pressure, after addition of hexane, the precipitate was filtered off and the solution washed several times with water. The organic layer was dried ($MgSO_4$), and after removing of solvent afforded a brown oil, that analyzed by ^{1}H nmr contains the isomeric isoxazolines **(10a, 10b, 11a** and **11b)** in a 16:10:60:14 ratio. The products were separated by column chromatography (hexane-ethyl acetate, 3:1). Total yield 48% (670 mg).

b) Following the procedure outlined above, the *E* butenoate **(3)** and benzaldehyde chloroxime at room temperature (2 days after the first addition and 4 days after the second addition), gave a mixture which contained the regioisomeric isoxazolines **(10b** and **11b)** in 46:54 ratio, determinated by ^{1}H nmr. The products were separated by column chromatography (hexane-ethyl acetate, 3:1). Total yield 55% (767 mg).

Methyl *trans*-4-dimethoxymethyl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (10b)[16d]

Ir (film): 1730, 1595, 1565. ^{13}C Nmr: 170.7 (C=O), 156.1 (C-3), 130.2 (Ar), 128.7 (Ar), 128.5 (Ar), 127.4 (Ar), 103.0 (C_{Ac}H), 79.8 (C-5), 56.0 (OMe), 55.6 (OMe), 55.5 (OMe), 52.7 (C-4). Ms, m/z(%): 143 (5), 129 (15), 77 (5), 75 (7), 57 (100).

Methyl *cis*-5-dimethoxymethyl-3-phenyl-4,5-dihydroisoxazole-4-carboxylate (11a)

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.09; N, 5.02. Found: C, 60.53; H, 5.85; N, 5.31. Ir (film): 1740, 1595, 1565. ^{13}C Nmr: 168.5 (C=O), 155.1 (C-3), 130.5 (Ar), 128.9 (Ar), 126.6 (Ar), 102.6 ($C_{Ac}H$), 83.8 (C-5), 55.4 (OMe), 54.8 (C-4), 54.5 (OMe). Ms, m/z(%): 248 (1), 144 (9), 77 (7), 75 (100).

Methyl *trans*-5-dimethoxymethyl-3-phenyl-4,5-dihydroisoxazole-4-carboxylate (11b)[16d]

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.09; N, 5.02. Found: C, 60.03; H, 6.41; N, 5.38. Ir (film): 1740, 1600, 1570. ^{13}C Nmr: 169.5 (C=O), 154.1 (C-3), 130.1 (Ar), 128.5 (Ar), 128.0 (Ar), 126.8 (Ar), 103.4 ($C_{Ac}H$), 85.2 (C-5), 56.3 (OMe), 55.3 (OMe), 54.0 (C-4), 52.7 (OMe). Ms, m/z(%): 219 (18), 120 (47), 77 (91), 75 (100).

Cycloaddition of Bromoformonitrile Oxide (5) to Methyl 4,4-Dimethoxybut-2-enoates

a) To a vigorously stirred mixture of methyl (*Z*)-4,4-dimethoxybut-2-enoate (**2**) (800 mg, 5 mmol), ethyl acetate (25 ml), potassium bicarbonate (1.1 g, 11 mmol) and water (1.7 ml), was added solid dibromoformaldoxime (1.16 g, 5.5 mmol) in small portions. After 24 h and 48 h the same amounts of reagents were added to generate new portions of dipole (**5**). The reaction mixture was allowed to stand at room temperature for 4 days. The precipitate was filtered off, the solution was dried ($MgSO_4$) and the solvent removed. ^1H Nmr analysis showed the presence of **12a**, **12b**, **13a**, and **13b** in a 44:18:13:25 ratio. The products were separated by column chromatography (hexane-ethyl acetate, 3:1). Total yield 55% (776 mg).

b) Starting from methyl (*E*)-4,4-dimethoxybut-2-enoate (**3**) (5 mmol) and dibromoformaldoxime (5.5 mmol), following the above procedure, after 24 h at room temperature was obtained a mixture which contained the regioisomeric isoxazolines (**12b** and **13b**) in a 70:30 ratio. Total yield 60% (846 mg).

Methyl *cis*-3-bromo-4-dimethoxymethyl-4,5-dihydroisoxazole-5-carboxylate (12a)

Anal. Calcd for $C_8H_{12}NO_5Br$: C, 34,16; H, 4,27; N, 4.98; Br, 28.11. Found: C, 33,86; H, 4,26; N, 5.18; Br, 28.26. Ir (film): 1750, 1610, 1580. ^{13}C Nmr: 167.6 (C=O), 138.1 (C-3), 101.3 ($C_{Ac}H$), 80.1 (C-5), 56.8 (C-4), 55.0 (OMe), 54.5 (OMe), 52.4 (OMe). Ms, m/z(%): 252-250 (7), 192-190 (1), 178-176 (2), 75 (100).

Methyl *trans*-3-bromo-4-dimethoxymethyl-4,5-dihydroisoxazole-5-carboxylate (12b)

Anal. Calcd for $C_8H_{12}NO_5Br$: C, 34,16; H, 4,27; N, 4.98; Br, 28.11. Found: C, 33,97; H, 4,31; N, 5.10; Br, 28.43. Ir (film): 1750, 1605, 1585. ^{13}C Nmr: 169.3 (C=O), 136.6 (C-3), 101.9 ($C_{Ac}H$), 79.2 (C-5), 59.4 (C-4), 56.2 (OMe), 55.5 (OMe), 53.0 (OMe). Ms, m/z(%): 252-250 (1), 192-190 (5), 112 (12), 75 (100).

Methyl *cis*-3-bromo-5-dimethoxymethyl-4,5-dihydroisoxazole-4-carboxylate (13a)

Ir (film): 1745, 1605, 1570. ^{13}C Nmr: 167.7 (C=O), 134.7 (C-3), 103.1 ($C_{Ac}H$), 84.9 (C-5), 58.5 (C-4), 57.0 (OMe), 55.6 (OMe), 53.3 (OMe).

Methyl *trans*-3-bromo-5-dimethoxymethyl-4,5-dihydroisoxazole-4-carboxylate (13b)

Ir (film): 1750, 1610, 1580. ^{13}C Nmr: 167.3 (C=O), 134.3 (C-3), 103.0 ($C_{Ac}H$), 84.8 (C-5), 58.4 (C-4), 56.8 (OMe), 55,4 (OMe), 53.2 (OMe).

Cycloaddition of Acetonitrile Oxide (6) to Methyl 4,4-Dimethoxybut-2-enoates

To a solution of methyl (*Z*)-4,4-dimethoxybut-2-enoate (**2**) (1.28 g, 8 mmol), triethylamine (0.4 ml), and phenyl isocyanate (2.14 g, 20 mmol) in toluene (36 ml), was added nitroethane (950 mg, 12 mmol) in four portions over a period of 4 h. Stirring was maintained during 24 h at 40 °C. The precipitated *N,N*-diphenylurea was filtered off. Evaporation of solvent gave a residue, whose ^{1}H nmr analysis showed the presence of **14a** and **15b** in a 65:35 ratio. The products were separated by column chromatography (hexane-ethyl acetate, 3:1). Total yield 50% (868 mg).

b) Following the procedure outlined above, the *E* butenoate (**3**) after 18 h gave a mixture which contained the regioisomeric isoxazolines (**14b** and **15b**) in a 60:40 ratio, determinated by ^{1}H nmr. The products were separated by column chromatography (hexane-ethyl acetate, 3:1). Total yield 55% (955 mg).

Methyl *cis*-4-dimethoxymethyl-4,5-dihydroisoxazole-5-carboxylate (14a)

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.91; N, 6.45. Found: C, 49.84; H, 7.10; N, 6.38. Ir (film): 1750, 1630, 1600. ^{13}C Nmr: 169.1 (C=O), 155.3 (C-3), 101.4 (C_{Ac}H), 78.6 (C-5), 55.9 (C-4), 54.4 (OMe), 53.9 (OMe), 51.9 (OMe), 12.6 (Me). Ms, m/z(%): 186 (4), 101 (3), 75 (100).

Methyl *trans*-5-dimethoxymethyl-4,5-dihydroisoxazole-4-carboxylate (15b)

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.91; N, 6.45. Found: C, 50.10; H, 7.20; N, 6.30. Ir (film): 1740, 1630, 1600. ^{13}C Nmr: 168.3 (C=O), 151.9 (C-3), 103.2 (C_{Ac}H), 82.6 (C-5), 56.5 (C-4), 55.8 (OMe), 54.8 (OMe), 52.4 (OMe), 11.7 (Me).

Methyl *trans*-4-dimethoxymethyl-4,5-dihydroisoxazole-5-carboxylate (14b)

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.91; N, 6.45. Found: C, 50.00; H, 7.14; N, 6.69. Ir (film): 1745, 1630, 1600. ^{13}C Nmr: 170.6 (C=O), 155.0 (C-3), 102.9 (C_{Ac}H), 79.1 (C-5), 58.0 (C-4), 54.9 (OMe), 53.5 (OMe), 52.6 (OMe), 12.5 (Me). Ms, m/z(%): 186 (5), 126 (16), 101 (3), 75 (100).

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