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TETRAHEDRON

Isothiazoles. Part VIII. Thermal Rearrangement to α,β-Unsaturated Nitriles of Cycloadducts from 3-Diethylamino-4-(4-methoxyphenyl)-5-vinyl-isothiazole 1,1-dioxide with Nitrile Oxides and Münchnones.

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Abstract: 3-Diethylamino-4-(4-methoxyphenyl)-5-vinyl-isothiazole 1,1-dioxide was reacted with nitrile oxides and münchnones affording the cycloadducts in good yields. The cycloaddition reaction occurred at the vinyl group exclusively. The cycloadducts undergo pyrolytic transformation into α,β-unsaturated nitriles through the isoxazole-or pyrrole-isothiazoline 1,1 -dioxide intermediates.

Keywords: Cycloaddition; Isothiazoles; Nitriles; Ring transformations.

INTRODUCTION

For some years we have been interested in the reactivity of 3-amino-isothiazole 1,1-dioxide.[1] Many works from our laboratory have dealt with the potential of this heterocycle as a versatile intermediate for interesting heterocyclic syntheses. In fact, they have been demonstrated to be effective reaction partners in 1,3-dipolar cycloaddition reactions with several dipoles such as diazoalkanes[2] oxazolones and münchnones[3] nitrile oxides[4] and azides[5] all of which occurred highly regioselectively at the C4-C5 bond. The bicyclic adducts so formed could undergo transformation reactions affording new heterocyclic compounds or opening new routes to known heterocyclic systems. In a recent paper we reported the synthesis of 3-diethylamino-4-(4-methoxyphenyl)-5-vinyl-isothiazole 1,1-dioxide (**1a**) through the palladium catalyzed cross-coupling reaction of 5-bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**2**) with vinyltributylstannane (**3**) (Scheme 1).[1] By this mild and efficient method, we made readily available compound **1a** which is expected to display an interesting reactivity pattern owing to the presence of both the vinyl group on C-5 and the C4-C5 double bond of the vinylsulfonamide group.

In this paper we describe the reaction of compound **1a** with several 1,3-dipoles such as nitrile oxides and münchnones to compare the reactivity of the two reactive double bonds and to study the thermal behaviour of the

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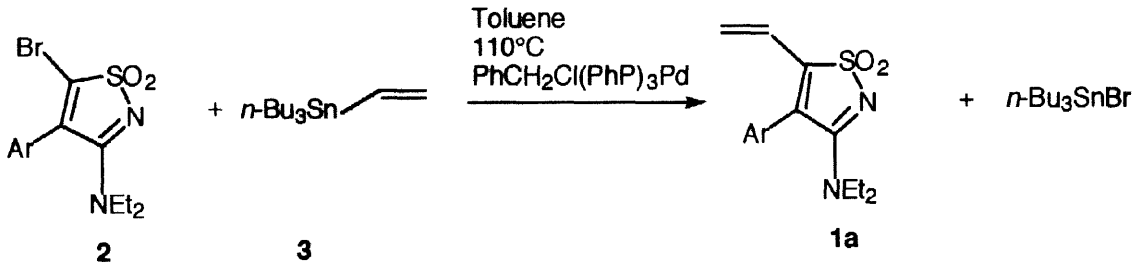
cycloadducts aiming to confirm the ability of the isothiazole dioxide to undergo useful ring transformation reactions. In this case, we observed a ring rearrangement which opens a new route to α,β-unsaturated nitriles.



2 **3** **1a**

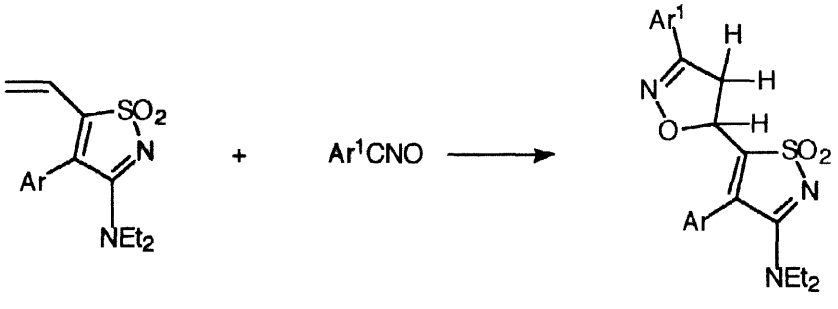
Ar = 4-OMe-Ph

Scheme 1

RESULTS AND DISCUSSION

Cycloaddition reactions of vinylisothiazole 1,1-dioxide ***1a*** *with nitrile oxides* ***4a-e***.

3-Diethylamino-4-(4-methoxyphenyl)-5-vinyl-isothiazole 1,1-dioxide (**1a**) was reacted with nitrile oxides **4a-e** in dichloromethane or in refluxing benzene according to the reactivity of the nitrile oxide (Scheme 2).



1a **4a-e** **5a-e**

Ar = 4-methoxyphenyl

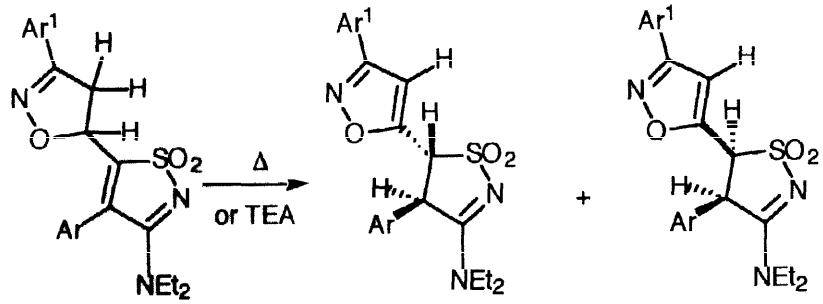
4a, **5a** Ar^1 = 3,5-dichloro-2,4,6-trimethylphenyl
4b, **5b** Ar^1 = 2,6-dichlorophenyl
4c, **5c** Ar^1 = 4-chlorophenyl
4d, **5d** Ar^1 = 2,4,6-trimethylphenyl
4e, **5e** Ar^1 = 4-nitrophenyl

Scheme 2

As usual **4c**, **d** were generated *in situ* by treatment of the corresponding hydroximoyl chloride with triethylamine (TEA) according to a well established procedure.[6]

In the case of **4a, b, e** the nitrile oxides were isolated and used as pure compounds. The structures of compounds **5a-e** were confirmed by ^{1}H-NMR spectra showing in the range of 3.20-3.70 δ, 4.00-4.10 δ and 5.20-5.40 δ three double doublets of an AMX system associated with the two protons of the 4-CH_2 and with H-5. The ^{13}C-NMR spectra showed two characteristic signals in the range of 40-45 δ and 70-75 δ associated with the CH_2 and CH of the isoxazoline ring as confirmed by an heterocorrelation experiment. In the case of **5a**, a NOESY experiment showing a clear relationship between 4-CH_2 and the *o,o'* methyl groups of the aryl substituent linked to C-3, clearly supported the assigned regiochemistry. The structures of the other cycloadducts were assigned by analogy and this conclusion was confirmed by unambiguous determination of the structure of their transformation products (see later). The reaction always afforded a single cycloadduct **5** at least at the detection limits (^{1}H-NMR, TLC of the crude reaction mixture) showing high regioselectivity. The 1,3-dipolar addition of a nitrile oxide to a double bond is a well-known and throughly studied process and our results are in good agreement with general trend displayed by nitrile oxides in cycloaddition reactions involving electron-deficient alkenes.[7] It has to be noted that, under the conditions adopted, the reaction was very chemoselective, only the vinyl group being involved in the cycloaddition.

Heating of compounds **5a,b,d** in a high boiling solvent (anisole, dimethylsulfoxide) produced complete transformation of the starting materials in compounds **6a,b,d** as a mixture of the *trans*- and *cis* - diastereoisomers in a ratio of about 1:1 (Scheme 3).



5a,b,d ***trans* 6a,b,d** ***cis* 6a,b,d**

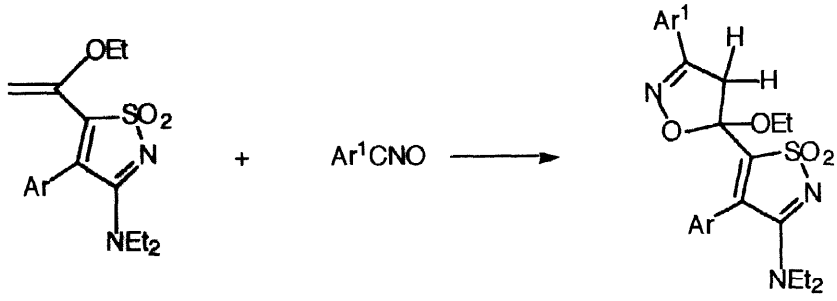
5a, 6a Ar^1= 3,5-dichloro-2,4,6-trimethylphenyl
5b, 6b Ar^1= 2,6-dichlorophenyl
5d, 6d Ar^1= 2,4,6-trimethylphenyl

Scheme 3

The structure of compounds **6** was confirmed by analytical and spectroscopic data. ^{1}H-NMR spectra of derivatives **6** showed a characteristic singlet in the range of 6.30 - 6.60 δ for *trans*-isomers and 6.00 - 6.20 δ for *cis*-isomers associated with H-4 of the isoxazole ring and an AB system associated with the two protons on C-4 and C-5 of the isothiazoline ring (J_{trans} 2-3 Hz; J_{cis} 9-9.5 Hz). The internal redox reaction was observed also during an attempt to reduce the isoxazoline ring of compounds **6** with Raney-nickel or by treament with TEA.

These results suggested that two base catalyzed 1,3-H-shifts (TEA, traces of bases in Raney-nickel, autocatalysis by diethylamine) could be responsible of the observed reaction. This process is clearly favoured by the acidity given to H-5 of the isoxazoline ring by the EWG-effect of the unsaturated isothiazole substituent. An analogy can be found in the reported internal redox reaction of 5-acylisoxazolines which are isomerized by bases to 5-α-hydroxyalkyl-isoxazoles .[8]

All this is confirmed by the stability under similar conditions of the cycloadduct **5f** deriving from cycloaddition of nitrile oxide **4d** and compound **1b** (Scheme 4).

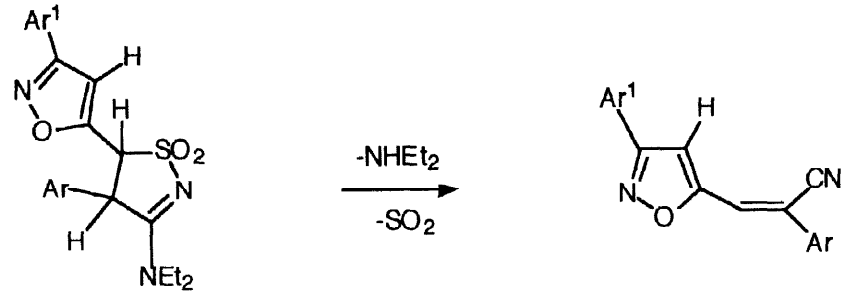


1b **4d** **5f**

Ar = 4-methoxyphenyl **4d**; **5f** Ar^1= 2,4,6-trimethylphenyl

Scheme 4

Heating of compounds **6a,b,d** at their melting point or a few degrees above until complete tranformation of the starting materials, produced compounds **7a,b,d** (Scheme 5). When the *cis* and *trans*-isomers were separately heated, rapid equilibration was observed. Prolonging the heating both *cis* - and *trans* -isomers afforded compound **7**.



***trans* + *cis* 6a,b,d** **7a,b,d**

6a, 7a Ar^1= 3,5-dichloro-2,4,6-trimethylphenyl
6b, 7b Ar^1= 2,6-dichlorophenyl
6d, 7d Ar^1= 2,4,6-trimethylphenyl

Scheme 5

As expected, prolonged heating of compound **5f** neat or in high boiling solvent did not produce any transformation.

The structures of these compounds were established by ^{1}H- and ^{13}C-NMR spectra. ^{1}H-NMR spectra were characterized by two singlets in the range of 7.09-7.28 δ and 7.49-7.52 δ associated with the H-4 of the isoxazole ring and with the hydrogen β to the nitrile group, respectively. In the case of **7d**, n. O. e. experiments confirmed these assignments showing clear spatial relationships between the signal at 7.49 δ and *o,o'*-hydrogens of the 4-methoxyphenyl substituent. The structures of the other compounds were assigned by analogy.

For **7d**, x-ray analysis was also performed showing that the CN group lies on the same side of the isoxazolyl substituent thus confirming the stereochemistry (Fig. 1).

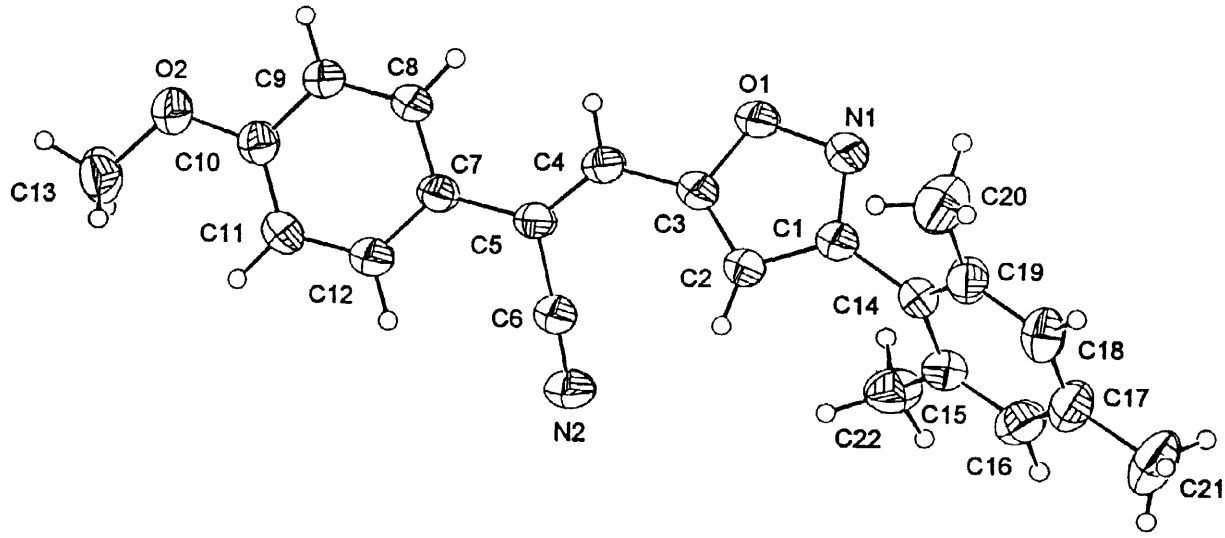


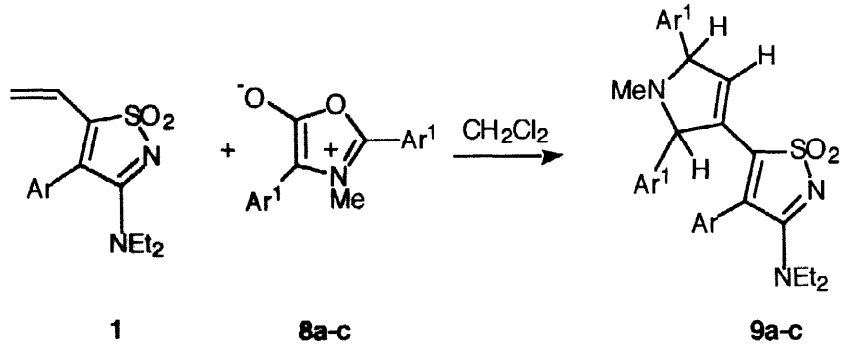
Figure 1. ORTEP plot of **7d**. Probability ellipsoids are drawn at 40% probability level. H atoms are represented by circles of arbitrary radius.

Cycloaddition reactions of vinylisothiazole 1,1-dioxide 1a with münchnones 8a-c.

Vinyl derivative **1a** reacted with münchnones **8a-c**. The cycloaddition reaction was performed by generating the reactant **8** *in situ* by heating the appropriate *N*-aroyl-*C*-arylglycines with acetic anhydride in dichloromethane at room temperature according to a well established procedure.[11] Comparable results were obtained also when münchnones **8a-c** were isolated and used as pure compounds. To a solution of compounds **8a-c** the vinylisothiazole **1a** was added and the reaction continued until completion. In all cases a complex mixture of the isomeric cycloadducts was obtained in which **9a-c** were isolated as the main products (Scheme 6). The structure of compounds **9a-c** was confirmed by ^{1}H-NMR spectra showing a characteristic singlet in the range of 5.06-5.18 δ associated with H-2 and two doublet in the range of 4.20-4.25 δ and 4.69-4.73 δ (J = 8-9 Hz) associated with H-5 and H-4 of the pyrroline ring respectively.

^{13}C-NMR spectra show two signals in the range of 52-53 δ, 55-60 δ (C-2 and C-5 of the pyrroline ring) and a singlet in the range of 110-111 δ associated with C-4 of the pyrroline ring.

To study the reactivity of the cycloadducts deriving from the reaction of **1a** and münchnones, compounds **9a-c** were heated resulting in the formation of the nitriles **10a-c**. Checking the reactions by TLC and ^{1}H-NMR, a diastereoisomeric mixture of the intermediate isothiazoline (*cis+trans*) **11a-c** could be detected.



1 **8a-c** **9a-c**

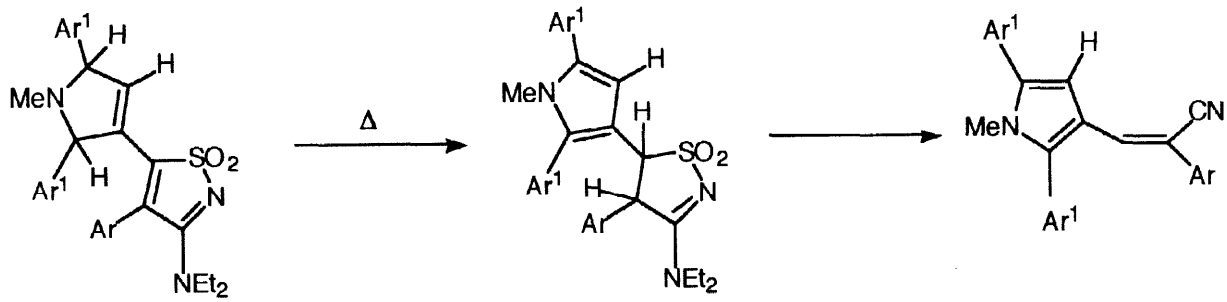
Ar= 4-methoxyphenyl

8a,9a Ar^1= phenyl
8b, 9b Ar^1= 4-methylphenyl
8c, 9c Ar^1= 4-methoxyphenyl

Scheme 6

In the case of **9a**, stopping the reactions before completion (*cis +trans*) **11a** could be isolated (Scheme 7).

The synthesis of compounds **10** could be also performed as a "one pot" reaction with some improvements in the yields. **1a** was stirred at room temperature in dichloromethane as the solvent with an equimolar amount of the isolated münchnones **8a-c** until reactants disappeared. The solvent was evaporated under reduced pressure and the mixture was heated in an oil bath (200-230°C) until complete transformation was observed. Chromatographic purification afforded compounds **10a-c** in a 30-40 yield %.



9a-c **11a-c** **10a,b,c**

Scheme 7

CONCLUSIONS

These results demonstrated the good reactivity of 5-vinylisothiazole as dipolarophile in 1,3-dipolar cycloadditions and that in most instances the vinyl group is more reactive than the C4-C5 double bond in the isothiazole ring. The thermal behaviour of the cycloadducts have been investigated and ring transformation reactions were observed affording new α,β-unsaturated nitriles substituted in the β-position with various heterocycles. We have confirmed that isothiazole 1,1-dioxide are very reactive species and suitable starting materials for the synthesis of substituted heterocyles.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were obtained with Brucker AC 200, Brucker AC 300 and Varian Gemini 200 instruments. Melting points were deteremined using a Büchi 510 (capillary) or a Electrothermal 9100 apparatus. Mass spectra were obtained by an electron impact ionization technique at 70 eV from a Finningan INCOS 50 instrument using the direct exposure probe (DEP).

X-Ray Data.

A crystalline specimen of compound **7d** was analysed by X-ray diffraction at room temperature. Its dimensions, together with details about the data collection, processing and refinement are reported in Table 1.

Table 1. Crystal data and summary of the X-ray diffraction experiment for compound **7d**.

crystal dimensions (mm)	0.25x0.20x0.10	scan technique	ω/2θ
empirical formula	$C_{22}H_{20}N_2O_2$	scan speed (deg/min)	3
formula weight	344.40	refl.s used for cell det.	32 (8°<θ< 25°)
temperature (K)	294(2)	reflections collected	7201 (±h k ±l)
crystal system	Monoclinic	decay	1.73 %
space group	$P2_1/c$ (#14)	$2\theta_{max}$ (deg)	50
a (Å)	20.252(2)	no. of independent refls.	3305
b (Å)	6.8810(10)		
c (Å)	13.8480(10)	refinement method	full matrix l.s. on F^2
β (deg)	104.020(10)	obs.d data (I>2σI)	2417
V (Å^3)	1872.3(4)	no. of parameters	316
Z	4	final R(F) (on I>2σI)	0.0348
F(000)	728	final wR(F) (on I>2σI)	0.0959
density (calcd) (g/cm^3)	1.222	final R(F) (all obs.d data)	0.0487
abs. coeff. μ (Mo Kα) (mm^{-1})	0.079	final wR(F) (all obs.d data)	0.1013
		goodness-of-fit	0.957
diffractometer	Siemens P4	largest ΔF peak (eÅ^{-3})	0.14
rad. wavelength (Å)	Mo Kα (0.71073)		

The intensities of three standard reflections were periodically re-measured: they showed a slight decay (1.73 %) in the course of data collection. Intensities were so corrected for Lorentz, polarization and decay, but not for

absorption. The structure was solved by direct methods, employing program SHELXS-86.[9] Refinements were conducted with program SHELXL-93.[10] All the independent reflections were fitted. Positional parameters were varied for all the nuclei: non-H atoms were refined anisotropically, hydrogen atoms isotropically. Selected bond distances and angles are listed in Table 2, while tables of coordinates and displacement parameters, together with those containing all the bond lengths, bond angles and torsion angles have been deposited as supplementary material.

Figure 1 shows the ORTEP plot of compound **7d**: it may be seen that the CN group lies on the same side of the isoxazolyl substituent, and that they are arranged in a nearly planar configuration, the torsion angle C3-C4=C5-C6 amounting to -3.7(2)°. One O . . . H and two N . . . H intermolecular contacts shorter than the sum of the Van der Waals radii are present in the crystal: the O . . . H interaction involves atom O1 of the molecule in the unit cell and atom H22C of the molecule in x, 1+y, z, and amounts to 2.69(2) Å, while the N . . . H contacts (N2 . . . H4[1] and N2 . . . H8[1] with [1] = x, -1+y, z) are in the range 2.58(1) Å - 2.67(1) Å.

Table 2. Selected bond lengths and bond angles in compound **7d**, with esd's in parentheses.

Bond	Value	Bond	Value
O1-N1	1.408(1)	C1-C2	1.410(2)
O1-C3	1.357(1)	C2-C3	1.344(2)
O2-C10	1.365(1)	C3-C4	1.446(2)
O2-C13	1.423(2)	C4-C5	1.346(2)
N1-C1	1.307(2)	C5-C6	1.444(2)
N2-C6	1.139(2)	C5-C7	1.477(2)

(a) Selected bond lengths (Å)

Angle	Value	Angle	Value
N1-O1-C3	108.50(10)	C3-C4-C5	126.63(14)
C10-O2-C13	117.75(13)	C4-C5-C6	118.80(13)
O1-N1-C1	106.02(12)	C4-C5-C7	125.39(13)
N1-C1-C2	110.76(13)	C6-C5-C7	115.79(12)
N1-C1-C14	119.95(13)	N2-C6-C5	177.94(15)
C2-C1-C14	129.27(13)	C5-C7-C8	121.63(12)
C1-C2-C3	105.91(13)	C5-C7-C12	121.08(12)
O1-C3-C2	108.79(12)	O2-C10-C9	115.64(13)
O1-C3-C4	114.43(12)	O2-C10-C11	125.20(14)
C2-C3-C4	136.74(14)		

(b) Selected bond angles (degrees)

Materials.

Compounds **1a**, **1b**,[1] **2**,[1] **4a,b**,[4] **8a,c**[12] have already been described. **4c-d** were synthesized *in situ* from the corresponding hydroximoyl chloride according to known procedures.[4]

3-Methyl-2,4-bis(4'-methylphenyl)-oxazolium-5-olate (8b) : *N*-methyl-*C*-(4-methylphenyl)-glycine hydrochloride[3] (4.64 g, 0.025 mol) was suspended in 10% NaOH (70 ml). The solution of 4-methylbenzoyl chloride (3.99 g, 0.025 mol) in CCl_4 was added under vigorous stirring at room temperature. Stirring was

continued for 3 hours and the reaction mixture was acidified to pH 3 with 10% HCl. The oily phase was separated, diluted with ethyl acetate and dried over Na_2SO_4 and evaporated. The residue was crystallized from dichloromethane/diisopropyl ether affording pure *N*-methyl-*N*-(4-methylbenzoyl)-*C*-(4-methylphenyl)-glycine. M.p. 154-155°C. ^{1}H-NMR 2.35 (s, 6H, CH_3); 2.80 (s, 3H, N-CH_3); 6.35 (s, 1H, CH); 7.10-7.45 (m, 8H, Aryl-H); 9.50 (bs, 1H, COOH).

The *N*-methyl-*N*-(4-methylbenzoyl)-*C*-(4-methylphenyl)-glycine (1.2 g, 4 mmol) was suspended in acetic anhydride (5 mL) and stirred at 50°C for 20 min. under nitrogen atmosphere. The solvent was evaporated under reduced pressure and pure **8b** (m. p. 150°C) was precipitated with anhydrous diethyl ether.

General Procedure for Cycloaddition Reaction of 5-Vinyl-isothiazole 1,1-Dioxides ***1a-b*** *and* ***4a,b,d.*** Equimolecular amounts of **1** (0.156 mmol) and **4** (0.156 mmol) were dissolved in dichloromethane (2 mL) and stirred at room temperature for about 3-5 h until disappearance of the reactants (T.L.C. 3:2 v/v cyclohexane/ethyl acetate). The solvent was evaporated under reduced pressure and the residue crystallized from diethyl ether affording **5a,b,d,f**. See Table 3 for data.

General Procedure for Cycloaddition Reaction of 5-Vinyl-isothiazole 1,1-Dioxide ***1a*** *and* ***4c,e.*** A benzene solution of the hydroximoyl chloride (0.372 mmol) was dropped into a stirred solution of triethylamine (0.372 mmol, 27.44 μL) in the same solvent at 0°C. After a few minutes the mixture was allowed to warm to room temperature and a solution of **1** (120 mg, 0.372 mmol) in benzene (4 mL) was added dropwise. At the end of addition the mixture was mantained at 45-50°C until disappearance of the reactants (T.L.C. 3:2 v/v cyclohexane/ethyl acetate). The solvent was evaporated under reduced pressure, the residue was neutralized with 10% HCl solution, extracted into dichloromethane and washed twice with water. The organic layer was separated, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Pure **5c,e** were crystallized from diethyl ether/diisopropyl ether. See Table 3 for data.

3-Diethylamino-5-(3-aryl-4-isoxazolyl)-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide ***6a,b,d:*** Compounds **5a,b,d** (0.1 mmol) were boiled under reflux in anisole (3 mL) until complete transformation (T.L.C. 3:2 v/v cyclohexane/ethyl acetate, about 6h). After evaporation of the solvent at reduced pressure the mixture was purified by column chromatography yielding *cis* - **6a,b,d** and *trans* -- **6a,b,d**. See Table 3 for data.

*Pyrolysis of cis -****6a,b,d*** *and trans -****6a,b,d:*** Compounds **6** (0.1 mmol) were heated at their melting points or slightly above and the reaction checked by T.L.C. (3:2 v/v cyclohexane/ethyl acetate). Nitriles **7a,b,d** were purified by column chromatography. See Table 3 for data.

General Procedure for Cycloaddition Reactions of 5-Vinyl-isothiazole 1,1-Dioxide ***1a*** *and* ***8a,b,c.***

Method A: In a typical experiment the *N*-aroyl-*N*-methyl-*C*-arylglycine (0.78 mmol) was suspended under nitrogen in anhydrous dichloromethane (2 mL) and acetic anhydride (0.1 mL) was added slowly. When the mixture turned yellow, solid **1a** (0.125 g, 0.7 mmol) was added in one portion. The reaction mixture was stirred at room temperature until the reactants disappeared (T.L.C. 3:2 v/v cyclohexane/ethyl acetate, 2-6 h). The solvent was evaporated under reduced pressure and the mixture purified by column chromatography yielding **9a,b,c**. See Table 3 for data.

Method B: Compounds **8** (0.9 mmol) were suspended in anhydrous dichloromethane (4 mL), solid **1a** (0.9 mmol) was added in one portion. The reaction mixture was stirred at room temperature until the reactants disappeared (T.L.C. 3:2 v/v cyclohexane/ethyl acetate, 2-6 h). The solvent was evaporated under reduced pressure and the mixture purified by column chromatography yielding **9a,b,c.** See Table 3 for data.

Pyrolysis of ***9a,b,c***. Compounds **9** (0.1 mmol) were heated at their melting points or slightly above and the reaction checked by T.L.C. (3:2 v/v cyclohexane/ethyl acetate). Chromatographic purification of the mixture afforded nitriles **10a,b,c**. See Table 3 for data.

One pot reaction: Compounds **8** (0.9 mmol) were suspended in anhydrous dichloromethane (5 mL), solid **1a** (0.9 mmol) was added in one portion. The reaction mixture was stirred at room temperature until the reactants disappeared (T.L.C. 3:2 v/v cyclohexane /ethyl acetate, 2-6 h). The solvent was evaporated under reduced pressure and the mixture melted (200-250°C) checking by T.L.C. (3:2 v/v cyclohexane/ethyl acetate). Chromatographic purification of the mixture afforded nitriles **10a,b,c**.

Table 3. Analytical and Spectroscopic Data.

Comp.[a]	m.p. °C	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	Yield (%)
5a	209 (dec.) (Et_2O)	0.99 (t, 3H, CH_3, J=7.0); 1.30 (t, 3H, CH_3, J=7.0); 2.29 (s, 6H, CH_3); 2.51 (s, 3H, CH_3); 2.07-3.11 (m, 2H, CH_2); 3.20 (dd, AMX system, 1H, ^{3}J=10.7, ^{2}J=17.9); 3.60 (q, 2H, CH_2, J=7.0); 3.86 (s, 3H, OCH_3); 3.98 (dd, AMX system, 1H, ^{3}J=10.7, ^{2}J=17.9); 5.26 (t, AMX system, 1H, ^{3}J=10.7); 6.95-7.03 (m, 2H, aryl-H); 7.10-7.20 (m, 2H, aryl-H); 7.30-7.40 (m, 2H, aryl-H).	77
5b	183.5 (dec.) (Et_2O)	0.90 (t, 3H, CH_3, J=6.8); 1.30 (t,3H, CH_3, J=6.8); 3.08 (q, 2H, CH_2, J=6.8); 3.39 (dd, AMX system, 1H, ^{3}J=11.3, ^{2}J=17.3); 3.62-3.65 (m, 2H, CH_2,); 3.87 (s, 3H, OCH_3); 4.05 (dd, AMX system, 1H, ^{3}J=11.3, ^{2}J=17.3); 5.38 (t, AMX system, 1H, ^{3}J=11.3); 7.01 (d, AB system, 2H, aryl-H, J=8); 7.10-7.20 (m, 2H, aryl-H); 7.23-7.38 (m, 5H, aryl-H).	78
5c	145 (Et_2O/ i-Pr_2O)	0.88 (t, 3H, CH_3, J=6.9); 1.29 (t, 3H, CH_3, J=6.8); 3.08 (q, 2H, CH_2, J=6.9); 3.68 (dd, AMX system, 1H, ^{3}J=11.4, ^{2}J=16.0); 3.73 (q, 2H, CH_2, J=6.9); 3.83 (s, 3H, OCH_3); 3.99 (dd, AMX system, 1H, ^{3}J=8.7, ^{2}J=16.0); 5.28 (t, AMX system, 1H, ^{3}J=8.7, ^{3}J=11.4); 6.96-7.00 (m, 2H, aryl-H); 7.15-7.25 (m, 2H, aryl-H); 7.35 (d, AB system, 2H, aryl-H, J=8.5); 7.54 (d, AB system, 2H, aryl-H, J=8.5).	59
5d	169-170 (Et_2O)	0.89 (t, 3H, CH_3, J=7.0); 1.30 (t, 3H, CH_3, J=7.0); 2.24 (s, 6H, CH_3); 2.30 (s, 3H, CH_3); 3.08 (q, 2H, CH_2, J=7.0); 3.25 (dd, AMX system, 1H, ^{3}J=11.6, ^{2}J=17.8); 3.62 (q, 2H, CH_2, J=7.0); 3.89 (s, 3H, OCH_3); 4.00 (dd, AMX system, 1H, ^{3}J=10.6, ^{2}J=17.8); 5.20 (t, AMX system, 1H, ^{3}J=10.6, ^{3}J=11.6); 6.86 (s, 2H, aryl-H, J=7.7); 6.95-7.10; 7.10-7.21; 7.30-7.40 (3m, 4H, aryl-H).	89
5e	190 (Et_2O/ i-Pr_2O)	0.89 (t, 3H, CH_3, J=7.0); 1.28 (t, 3H, CH_3, J=7.0); 3.08 (q, 2H, CH_2, J=7.0); 3.47 (dd, AMX system, 1H, ^{3}J=11.5, ^{2}J=17.0); 3.61 (q, 2H, CH_2, J=7.0); 3.84 (s, 3H, OCH_3); 4.07 (dd, AMX system, 1H, ^{3}J=8.2, ^{2}J=17.0); 5.33 (dd, AMX system, 1H, ^{3}J=8.2, ^{3}J=11.5); 6.99 (d, AB system, 2H, aryl-H, J=7.7); 7.01-7.31 (m, 2H, aryl-H); 7.78 (d, AB system, 2H, aryl-H, J=8.9); 8.24 (d, AB system, 2H, aryl-H, J=8.9).	37
5f	152-154 (Et_2O)	0.86 (t, 3H, CH_3, J=7.1); 1.30 (t, 3H, CH_3, J=7.1); 1.56 (t, 3H, CH_3, J=7.1); 2.11 (s, 6H, CH_3); 2.56 (s, 3H, CH_3); 3.01 (q, 2H, CH_2, J=7.1); 3.28 (d, AB system, 2H, J=17.9); 3.56-3.96 (m, 4H, CH_2); 3.84 (s, 3H, OCH_3); 6.84 (s, 2H, aryl-H); 6.92-6.94 (m, 2H, aryl-H); 7.11-7.25 (m, 2H, aryl-H).	90

Table 3. *continued*

6a *trans+cis*	b	0.93 (t, 3H, CH_3, J=7.1); 0.94 (t, 3H, CH_3, J=7.3); 1.27 (t, 3H, CH_3, J=7.1); 1.29 (t, 3H, CH_3, J=7.3); 1.83 (s, 6H, CH_3); 2.18 (s, 6H, CH_3); 2.52 (s, 3H, CH_3); 2.56 (s, 3H, CH_3); 3.13-3.72 (m, 8H, CH_2); 3.76 (s, 3H, OCH_3, (Z)-isomer); 3.83 (s, 3H, OCH_3, (E)-isomer); 4.74 (d, AB system, 1H, J_{trans}=2.8); 4.86 (d, AB system, 1H, J_{cis}=9.1); 4.98 (d, AB system, 1H, J_{trans}=2.8); 5.16 (d, AB system, 1H, J_{cis}=9.1); 6.08 (s, 1H, H_4, (Z)-isomer); 6.36 (s, 1H, H_4, (E)-isomer); 6.78 (d, AB system, 2H, aryl-H, J=8.7); 6.84 (d, AB system, 2H, aryl-H, J=8.8); 7.06 (d, AB system, 2H, aryl-H, J=8.7); 7.23 (d, AB system, 2H, aryl-H, J=8.8).	50
6b *cis*	c	0.95 (m, 3H, CH_3); 1.29 (m, 3H, CH_3); 3.10-3.50 (m, 4H, CH_2); 3.75 (s, 3H, OCH_3); 4.85 (d, AB system, 1H, J_{cis}=9.2); 5.18 (d, AB system, 1H, J_{cis}=9.2); 6.20 (s, 1H, H_4); 6.77 (d, AB system, 2H, aryl-H, J=8.3); 7.04 (d, AB system, 2H, aryl-H, J=8.3); 7.20-7.40 (m, 3H, aryl-H)	65[d]
6b *trans*	195-196 (Et_2O)	0.91 (t, 3H, CH_3, J=7.1); 1.29 (t, 3H, CH_3, J=7.1); 3.12-3.50 (m, 4H, CH_2); 3.82 (s, 3H, OCH_3); 4.76 (d, AB system, 1H, J_{trans}=2.6); 4.97 (d, AB system, 1H, J_{trans}=2.6); 6.56 (s, 1H, H_4); 6.94 (d, AB system, 2H, aryl-H, J=8.4); 7.30 (d, AB system, 2H, aryl-H, J=8.4); 7.30-7.46 (m, 3H, aryl-H).	65[d]
6d *cis*	221 CH_2Cl_2 /Et_2O	0.93 (t, 3H, CH_3, J=7.1); 1.26 (t, 3H, CH_3, J=7.1); 1.82 (s, 6H, CH_3); 2.26 (s, 3H, CH_3); 3.00-3.30; 3.40-3.55 (2m, 4H, CH_2); 3.73 (s, 3H, OCH_3); 4.85 (d, AB system, 1H, J_{cis}=9.2); 5.15 (d, AB system, 1H, J_{cis}=9.2); 6.04 (s, 1H, H_4); 6.75 (d, AB system, 2H, aryl-H, J=8.9); 6.83 (s, 2H, aryl-H); 7.05 (d, AB system, 2H, aryl-H, J=8.9).	35
6d *trans*	170.5 CH_2Cl_2 /Et_2O	0.91 (t, 3H, CH_3, J=7.0); 1.27 (t, 3H, CH_3, J=7.1); 2.15 (s, 6H, CH_3); 2.32 (s, 3H, CH_3); 3.13-3.28; 3.38-3.48; 3.73-3.78 (3m, 4H, CH_2); 3.82 (s, 3H, OCH_3); 4.73 (d, AB system, 1H, J_{cis}=2.6); 4.99 (d, AB system, 1H, J_{cis}=2.6); 6.36 (s, 1H, H_4); 6.90-7.00 (m, 5H, aryl-H); 7.22-7.35 (m, 2H, aryl-H).	30
7a	139.5 (EtOH)	1.56 (s, 6H, CH_3); 2.21 (s, 3H, CH_3); 3.89 (s, 3H, OCH_3); 7.01 (d, AB system, 2H, aryl-H, J=8.9); 7.09 (s, 1H); 7.50 (s, 1H); 7.68 (d, AB system, 2H, aryl-H, J=8.9).	33
7b	139-141 (Et_2O)	3.88 (s, 3H, OCH_3); 7.00 (d, AB system, 2H, aryl-H, J=9.0); 7.28 (s, 1H); 7.34-7.49 (m, 3H, aryl-H); 7.52 (s, 1H); 7.69 (d, AB system, 2H, aryl-H, J=9.0).	50
7d	134.5 (Et_2O)	2.18 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 3.88 (s, 3H, OCH_3); 6.92-7.02 (m, 4H, aryl-H); 7.11 (s, 1H, H_4); 7.49 (s, 1H); 7.67 (d, AB system, 2H, aryl-H, J=8.4).	26
9a	232 (Et_2O/ i-Pr_2O)	0.88 (t, 3H, CH_3, J=7.2); 1.24 (t, 3H, CH_3; J=7.1); 2.95-3.22; 3.31-3.50; 3.71-3.81 (3m, 4H, CH_2); 3.37 (s, 3H, CH_3); 3.78 (s, 3H, OCH_3); 4.24 (d, AB system, 1H, J=8.7); 4.73 (d, AB system, 1H, J=8.7); 5.18 (s, 1H); 6.85 (d, AB system, 2H, aryl-H, J=8.9); 7.00-7.30; 7.35-7.60 (2m, 12H, aryl-H).	35
9b	244 (dec.) (Et_2O/ i-Pr_2O)	0.87 (t, 3H, CH_3, J=7.1); 1.23 (t, 3H, CH_3; J=7.1); 2.33; 2.42 (2s, 6H, CH_3); 2.98-3.17; 3.41-3.53 (2m, 4H, CH_2); 3.34 (s, 3H, CH_3); 4.22 (d, AB system, 1H, J=8.7); 4.69 (d, AB system, 1H, J=8.7); 5.13 (s, 1H); 6.80 (d, AB system, 2H, aryl-H, J=8.9); 7.01-7.10; 7.20-7.42 (2m, 10H, aryl-H).	10
9c	246-247 (Et_2O/ i-Pr_2O)	0.87 (t, 3H, CH_3, J=7.1); 1.21 (m, 3H, CH_3; J=7.1); 2.95-3.22; 3.31-3.50; 3.71-3.81 (3m, 4H, CH_2); 3.37 (s, 3H, CH_3); 3.78; 3.80; 3.86 (3s, 9H, OCH_3); 4.20 (d, AB system, 1H, J=8.7); 4.70 (d, AB system, 1H, J=8.7); 5.06 (s, 1H); 6.80-6.99; 7.03-7.09; 7.35-7.52 (3m, 12H, aryl-H).	23

Table 3. *continued*

10a	142 (Et_2O)	3.50 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 6.87 (d, AB system, 2H, aryl-H, J=8.9); 7.17 (s, 1H); 7.37-7.56 (m, 13H, aryl-H).	30
10b	203 (Et_2O)	2.41 (s, 3H, CH_3); 2.46 (s, 3H, CH_3); 3.49 (s, 3H, CH_3); 3.81 (s, 3H, OCH_3); 6.87 (d, AB system, 2H, aryl-H, J=8.9); 7.18 (s, 1H); 7.24-7.49 (m, 11H, aryl-H).	35
10c	143 (Et_2O)	3.46 (s, 3H, CH_3); 3.81; 3.87; 3.89 (3s, 9H, OCH_3); 6.87 (d, AB system, 2H, aryl-H, J=8.9); 6.99 (d, AB system, 2H, aryl-H, J=8.9); 7.03 (d, AB system, 2H, aryl-H, J=8.7); 7.16 (s, 1H); 7.30 (s, 1H); 7.33-7.46 (m, 6H, aryl-H).	45
11a	123 (Et_2O)	0.82 (t, 3H, J=7); 1.26 (t, 3H, J=7); 2.95-3.20; 3.31-3.50; 3.60-3.80 (3m, 4H, CH_2); 3.42 (s, 3H, CH_3); 3.77 (s, 3H, OCH_3); 4.31, 4.46 (2d, AB system, 2H, J=3.0); 6.2 (s, 1H, $H_{pyrrol.}$); 6.80 (d, AB system, 2H, aryl-H, J=9.0); 7.1 (d, AB system, 2H, aryl-H, J=9.0); 7.30-7.60 (m, 10H, aryl-H).	<5

a) Satisfactory elemental anlyses obtained: C, H, N ± 0.4

b) They were obtained always in mixture.

c) *cis* isomer was not obtained sufficiently pure for an accurate melting point.

d) Total yield of the diastereoisomeric mixture

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