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# 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  $\alpha_{\beta}$ -unsaturated nitriles through the isoxazole-or pyrrole-isothiazoline 1,1-dioxide intermediates. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Cycloaddition; Isothiazoles; Nitriles; Ring transformations.

# INTRODUCTION

For some years we have been interested in the reactivity of 3-amino-isothiazole 1,1-dioxide.<sup>1</sup> 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<sup>2</sup> oxazolones and munchnones<sup>3</sup> nitrile oxides<sup>4</sup> and azides<sup>5</sup> 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).<sup>1</sup> 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 munchnones to compare the reactivity of the two reactive double bonds and to study the thermal behaviour of the

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  $\alpha$ ,  $\beta$ -unsaturated nitriles.



## **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).





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 <sup>1</sup>H-NMR spectra showing in the range of 3.20-3.70  $\delta$ , 4.00-4.10  $\delta$  and 5.20-5.40  $\delta$  three double doublets of an AMX system associated with the two protons of the 4-CH<sub>2</sub> and with H-5. The <sup>13</sup>C-NMR spectra showed two characteristic signals in the range of 40-45  $\delta$  and 70-75  $\delta$  associated with the CH<sub>2</sub> 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<sub>2</sub> and the *o*, *o*<sup>1</sup> 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 (<sup>1</sup>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.<sup>7</sup> 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).



**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. <sup>1</sup>H-NMR spectra of derivatives 6 showed a characteristic singlet in the range of  $6.30 - 6.60 \delta$  for *trans*-isomers and  $6.00 - 6.20 \delta$  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<sub>trans</sub> 2-3 Hz; J<sub>cis</sub> 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  $5-\alpha$ -hydroxyalkyl-isoxazoles.<sup>8</sup>

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).





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**.



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 <sup>1</sup>H- and <sup>13</sup>C-NMR spectra. <sup>1</sup>H-NMR spectra were characterized by two singlets in the range of 7.09-7.28  $\delta$  and 7.49-7.52  $\delta$  associated with the H-4 of the isoxazole ring and with the hydrogen  $\beta$  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  $\delta$  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.<sup>11</sup> 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 by <sup>1</sup>H-NMR spectra showing a characteristic singlet in the range of 5.06-5.18  $\delta$  associated with H-2 and two doublet in the range of 4.20-4.25  $\delta$  and 4.69-4.73  $\delta$  (J = 8-9 Hz) associated with H-5 and H-4 of the pyrroline ring respectively.

<sup>13</sup>C-NMR spectra show two signals in the range of 52-53  $\delta$ , 55-60  $\delta$  (C-2 and C-5 of the pyrroline ring) and a singlet in the range of 110-111  $\delta$  associated with C-4 of the pyrroline ring.

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



#### 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 munchnones **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 %.



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  $\alpha$ , $\beta$ -unsaturated nitriles substituted in the  $\beta$ -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 heterocycles.

### **EXPERIMENTAL**

<sup>1</sup>H-NMR and <sup>13</sup>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.

I doite I, cijstal data and saminary	of the may diffide bold	Aperiment for compound / a.	
crystal dimensions (mm)	0.25x0.20x0.10	scan technique	ω/2θ
empirical formula	C22H20N2O2	scan speed (deg/min)	3
formula weight	344.40	refl.s used for cell det.	32 (8°< <del>0</del> < 25°)
temperature (K)	294(2)	reflections collected	7201 (±h k ±l)
crystal system	Monoclinic	decay	1.73 %
space group	P2 <sub>1</sub> /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 <sup>2</sup>
β(deg)	104.020(10)	obs.d data (I>201)	2417
V (Å <sup>3</sup> )	1872.3(4)	no. of parameters	316
Z	4	final R(F) (on I>20I)	0.0348
F(000)	728	final wR(F) (on I>20I)	0.0959
density (calcd) (g/cm <sup>3</sup> )	1.222	final R(F) (all obs.d data)	0.0487
abs. coeff. $\mu$ (Mo K $\alpha$ ) (mm <sup>-1</sup> )	0.079	final wR(F) (all obs.d data)	0.1013
		goodness-of-fit	0.957
diffractometer	Siemens P4	largest ∆F peak (eÅ <sup>-3</sup> )	0.14
rad. wavelength (Å)	Μο Κα (0.71073)		

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

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.<sup>9</sup> Refinements were conducted with program SHELXL-93.<sup>10</sup> 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.

Bond	Value	Bond	Value
01-N1	1.408(1)	C1-C2	1.410(2)
01-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
N1-01-C3	108.50(10)	C3-C4-C5	126.63(14)
C10-O2-C13	117.7 <b>5</b> (13)	C4-C5-C6	118.80(13)
01-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)
01-C3-C2	108.79(12)	O2-C10-C9	115.64(13)
01-C3-C4	114.43(12)	O2-C10-C11	125.20(14)
C2-C3-C4	136.74(14)		

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

(b) Selected bond angles (degrees)

#### Materials.

Compounds 1a,  ${}^{1}$ 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.<sup>4</sup>

3-Methyl-2,4-bis(4'-methylphenyl)-oxazolium-5-olate (8 b) : N-methyl-C-(4-methylphenyl)-glycine hydrochloride<sup>3</sup> (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<sub>4</sub> 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<sub>2</sub>SO<sub>4</sub> 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. <sup>1</sup>H-NMR 2.35 (s, 6H, CH<sub>3</sub>); 2.80 (s, 3H, N-CH<sub>3</sub>); 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  $\mu$ L) 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<sub>2</sub>SO<sub>4</sub>, 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. <sup>a</sup>	m.p. ℃	<sup>1</sup> H-NMR (CDCl <sub>3</sub> ) δ, J (Hz)	Yi <b>ck</b> d (%)
52	209 (dec.) (Et <sub>2</sub> O)	0.99 (t, 3H, CH <sub>3</sub> , J=7.0); 1.30 (t, 3H, CH <sub>3</sub> , J=7.0); 2.29 (s, 6H, CH <sub>3</sub> ); 2.51 (s, 3H, CH <sub>3</sub> ); 2.07-3.11 (m, 2H, CH <sub>2</sub> ); 3.20 (dd, AMX system, 1H, ${}^{3}$ J=10.7, ${}^{2}$ J=17.9); 3.60 (q, 2H, CH <sub>2</sub> , J=7.0); 3.86 (s, 3H, OCH <sub>3</sub> ); 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
5 b	183.5 (dec.) (Et <sub>2</sub> O)	0.90 (t, 3H, CH <sub>3</sub> , J=6.8); 1.30 (t,3H, CH <sub>3</sub> , J=6.8); 3.08 (q, 2H, CH <sub>2</sub> , J=6.8); 3.39 (dd, AMX system, 1H, <sup>3</sup> J=11.3, <sup>2</sup> J=17.3); 3.62-3.65 (m, 2H, CH <sub>2</sub> , ); 3.87 (s, 3H, OCH <sub>3</sub> ); 4.05 (dd, AMX system, 1H, <sup>3</sup> J=11.3, <sup>2</sup> J=17.3); 5.38 (t, AMX system, 1H, <sup>3</sup> 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
5 c	145 (Et <sub>2</sub> O/ i-Pr <sub>2</sub> O)	0.88 (t, 3H, CH <sub>3</sub> , J=6.9); 1.29 (t, 3H, CH <sub>3</sub> , J=6.8); 3.08 (q, 2H, CH <sub>2</sub> , J=6.9); 3.68 (dd, AMX system, 1H, <sup>3</sup> J=11.4, <sup>2</sup> J=16.0); 3.73 (q, 2H, CH <sub>2</sub> , J=6.9); 3.83 (s, 3H, OCH <sub>3</sub> ); 3.99 (dd, AMX system, 1H, <sup>3</sup> J=8.7, <sup>2</sup> J=16.0); 5.28 (t, AMX system, 1H, <sup>3</sup> J=8.7, <sup>3</sup> 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 <sub>2</sub> O)	0.89 (t, 3H, CH <sub>3</sub> , J=7.0); 1.30 (t, 3H, CH <sub>3</sub> , J=7.0); 2.24 (s, 6H, CH <sub>3</sub> ); 2.30 (s, 3H, CH <sub>3</sub> ); 3.08 (q, 2H, CH <sub>2</sub> , J=7.0); 3.25 (dd, AMX system, 1H, $^{3}$ J=11.6, $^{2}$ J=17.8 ); 3.62 (q, 2H, CH <sub>2</sub> , J=7.0); 3.89 (s, 3H, OCH <sub>3</sub> ); 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 <sub>2</sub> O/ i-Pr <sub>2</sub> O)	0.89 (t, 3H, CH <sub>3</sub> , J=7.0); 1.28 (t, 3H, CH <sub>3</sub> , J=7.0); 3.08 (q, 2H, CH <sub>2</sub> , J=7.0); 3.47 (dd, AMX system, 1H, ${}^{3}J$ =11.5, ${}^{2}J$ =17.0); 3.61 (q, 2H, CH <sub>2</sub> , J=7.0); 3.84 (s, 3H, OCH <sub>3</sub> ); 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 <sub>2</sub> O)	0.86 (t, 3H, CH <sub>3</sub> , J=7.1); 1.30 (t, 3H, CH <sub>3</sub> , J=7.1); 1.56 (t, 3H, CH <sub>3</sub> , J=7.1); 2.11 (s, 6H, CH <sub>3</sub> ); 2.56 (s, 3H, CH <sub>3</sub> ); 3.01 (q, 2H, CH <sub>2</sub> , J=7.1); 3.28 (d, AB system, 2H, J=17.9); 3.56-3.96 (m, 4H, CH <sub>2</sub> ); 3.84 (s, 3H, OCH <sub>3</sub> ); 6.84 (s, 2H, aryl-H); 6.92-6.94 (m, 2H, aryl-H); 7.11-7.25 (m, 2H, aryl-H).	90

61	ь	0.93 (t, 3H, CH3, J=7.1); 0.94 (t, 3H, CH3, J=7.3); 1.27 (t, 3H, CH3, J=7.1); 1.29 (t, 3H, CH3,	<b>5</b> 0
trans+cis		J=7.3); 1.83 (s, 6H, CH3); 2.18 (s, 6H, CH3); 2.52 (s, 3H, CH3); 2.56 (s, 3H, CH3); 3.13-	
		3.72 (m, 8H, CH <sub>2</sub> ); 3.76 (s, 3H, OCH <sub>3</sub> , (Z)-isomer); 3.83 (s, 3H, OCH <sub>3</sub> , (E)-isomer); 4.74 (d,	
		AB system, 1H, Jtrans=2.8); 4.86 (d, AB system, 1H, Jcis=9.1); 4.98 (d, AB system, 1H,	
		J <sub>trans</sub> =2.8); 5.16 (d, AB system, 1H, J <sub>cis</sub> =9.1); 6.08 (s, 1H, H4, (Z)-isomer); 6.36 (s, 1H, H4,	
		(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).	
б Ь	c	0.95 (m, 3H, CH3); 1.29 (m, 3H, CH3); 3.10-3.50 (m, 4H, CH2); 3.75 (s, 3H, OCH3); 4.85 (d,	65 <sup>d</sup>
cis		AB system, 1H, J <sub>cis</sub> =9.2); 5.18 (d, AB system, 1H, J <sub>cis</sub> =9.2); 6.20 (s, 1H, H4); 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)	
<b>6</b> b	195-196	0.91 (t, 3H, CH <sub>3</sub> , J=7.1); 1.29 (t, 3H, CH <sub>3</sub> , J=7.1); 3.12-3.50 (m, 4H, CH <sub>2</sub> ); 3.82 (s, 3H,	65 <sup>d</sup>
trans	(Et2O)	OCH3); 4.76 (d, AB system, 1H, Jtrans=2.6); 4.97 (d, AB system, 1H, Jtrans=2.6); 6.56 (s, 1H,	
		H4); 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).	
6d	221	0.93 (t, 3H, CH3, J=7.1); 1.26 (t, 3H, CH3, J=7.1); 1.82 (s, 6H, CH3); 2.26 (s, 3H, CH3); 3.00-	35
cis	CH2Cl2	3.30; 3.40-3.55 (2m, 4H, CH <sub>2</sub> ); 3.73 (s, 3H, OCH <sub>3</sub> ); 4.85 (d, AB system, 1H, J <sub>cis</sub> =9.2); 5.15 (d,	
	/Et2O	AB system, 1H, J <sub>cis</sub> =9.2); 6.04 (s, 1H, H4); 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).	
6d	170.5	0.91 (t, 3H, CH3, J=7.0); 1.27 (t, 3H, CH3, J=7.1); 2.15 (s, 6H, CH3); 2.32 (s, 3H, CH3); 3.13-	30
trans	CH2Cl2	3.28; 3.38-3.48; 3.73-3.78 (3m, 4H, CH <sub>2</sub> ); 3.82 (s, 3H, OCH <sub>3</sub> ); 4.73 (d, AB system, 1H,	
	/Et <sub>2</sub> O	J <sub>cis</sub> =2.6); 4.99 (d, AB system, 1H, J <sub>cis</sub> =2.6); 6.36 (s, 1H, H4); 6.90-7.00 (m, 5H, aryl-H); 7.22-	
		7.35 (m, 2H, aryl-H).	
7 <b>a</b>	139.5	1.56 (s, 6H, CH3); 2.21 (s, 3H, CH3); 3.89 (s, 3H, OCH3); 7.01 (d, AB system, 2H, aryl-H,	33
	(EtOH)	J=8.9); 7.09 (s, 1H); 7.50 (s, 1H); 7.68 (d, AB system, 2H, aryl-H, J=8.9).	
7Ъ	139-141	3.88 (s, 3H, OCH3); 7.00 (d, AB system, 2H, aryl-H, J=9.0); 7.28 (s, 1H); 7.34-7.49 (m, 3H,	<b>5</b> 0
	(Et2O)	aryl-H); 7.52 (s, 1H); 7.69 (d, AB system, 2H, aryl-H, J=9.0).	
7d	134.5	2.18 (s, 3H, CH3); 2.34 (s, 3H, CH3); 3.88 (s, 3H, OCH3); 6.92-7.02 (m, 4H, aryl-H); 7.11 (s,	26
	(Et2O)	1H, H4); 7.49 (s, 1H); 7.67 (d, AB system, 2H, aryl-H, J=8.4).	
9a	232	0.88 (t, 3H, CH <sub>3</sub> , J=7.2); 1.24 (t, 3H, CH <sub>3</sub> ; J=7.1); 2.95-3.22; 3.31-3.50; 3.71-3.81 (3m, 4H,	35
	(Et2O/	CH2); 3.37 (s, 3H, CH3); 3.78 (s, 3H, OCH3); 4.24 (d, AB system, 1H, J=8.7); 4.73 (d, AB	
	i-Pr2O)	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).	
9b	244	0.87 (t, 3H, CH3, J=7.1); 1.23 (t, 3H, CH3; J=7.1); 2.33; 2.42 (28, 6H, CH3); 2.98-3.17; 3.41-	10
	(dec.)	3.53 (2m, 4H, CH2); 3.34 (s, 3H, CH3); 4.22 (d, AB system, 1H, J=8.7); 4.69 (d, AB system,	
	(Et2O/	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,	
	i-Pr2O)	10H, aryl-H).	
9c	246-247	0.87 (t, 3H, CH3, J=7.1); 1.21 (m, 3H, CH3; J=7.1); 2.95-3.22; 3.31-3.50; 3.71-3.81 (3m, 4H,	23
	(Et2O/	CH <sub>2</sub> ); 3.37 (s, 3H, CH <sub>3</sub> ); 3.78; 3.80; 3.86 (3s, 9H, OCH <sub>3</sub> ); 4.20 (d, AB system, 1H, J=8./);	
	i-P <b>r2</b> O)	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-	
		HD.	

1 <b>0a</b>	142	3.50 (s, 3H, CH3); 3.80 (s, 3H, OCH3); 6.87 (d, AB system, 2H, aryl-H, J=8.9); 7.17 (s, 1H);	30
	(Et2O)	7.37-7.56 (m, 13H, aryl-H).	
10b	203	2.41 (s, 3H, CH3); 2.46 (s, 3H, CH3); 3.49 (s, 3H, CH3); 3.81 (s, 3H, OCH3); 6.87 (d, AB	35
	(Et2O)	system, 2H, aryl-H, J=8.9); 7.18 (s, 1H); 7.24-7.49 (m, 11H, aryl-H).	
10c	143	3.46 (s, 3H, CH3); 3.81; 3.87; 3.89 (3s, 9H, OCH3); 6.87 (d, AB system, 2H, aryl-H, J=8.9);	45
	(Et2O)	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).	
11 <b>a</b>	123	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 <sub>2</sub> ); 3.42 (s,	<5
	(Et2O)	3H, CH3); 3.77 (s, 3H, OCH3); 4.31, 4.46 (2d, AB system, 2H, J=3.0); 6.2 (s, 1H, Hpyrrol.);	
		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).	

Table 3. continued

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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