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Isothiazoles. Part V. [1]Cycloaddition Reaction of Nitrile Oxides to 3-Diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-Dioxide: an Entry to 5-Acyl- and 5-Cyano-isothiazole 1,1-Dioxide Derivatives.

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Abstract: Nitrile oxides **2** reacted with 3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**1**) affording through a highly regioselective 1,3-dipolar cycloaddition reaction isothiazolo[5,4-*d*]isoxazoline 4,4-dioxides **3**. Reduction of **3** afforded a mixture of the *E* and *Z* forms of the corresponding 5-(amino-aryl-methylene]-dihydro-isothiazole 1,1-dioxides **4**/**5** which were transformed into 5-acyl-dihydro-isothiazole 1,1-dioxides **6** and the corresponding dehydrated products **7**. Compound **3f** was easily transformed into 5-cyano-isothiazole 1,1-dioxide **11**.

Previous work in our laboratory dealt with the reactivity of 3-amino-isothiazole 1,1-dioxides as reactive dipolarophiles in 1,3-dipolar cycloaddition reactions. Several dipoles such as diazoalkanes, oxazolones and münchnones afforded with high regioselectivity the corresponding cycloadducts. One of the most interesting synthetic applications of these reactions has to be seen in the easy transformations of these cycloadducts by simple heating and/or basic treatments. Both rings of the bicyclic system are susceptible to cleavage and which ring is cleaved easier depends on several factors such as the substitution pattern.[1,2]

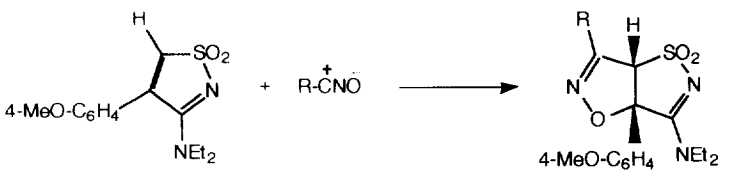
These useful results prompted us to investigate another class of 1,3-dipole, *viz.* the nitrile oxides. This paper describes the reactions of 3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**1**) with several nitrile oxides **2a-f** and a new route to 5-functionalized isothiazole 1,1-dioxides as a consequence of transformation reactions of the cycloadducts.

RESULTS AND DISCUSSION

Cycloaddition reactions of isothiazole 1,1-dioxide 1 with nitrile oxides 2a-f. The cycloaddition reaction was usually performed in refluxing dichloromethane or benzene according to the reactivity of the nitrile oxides **2** except in the case of **2f** which required a low temperature (THF, 0°C) to avoid dimerization. As usual, **2a-c,f** were generated *in situ* by treatment of the corresponding hydroximoyl chloride with triethylamine (TEA) according to a well established procedure.[3,4] In the case of **2d,e** the nitrile oxides were isolated and used as pure compounds. The structure of compounds **3** was confirmed by ^{1}H-NMR spectra showing in the range of δ 4.5-5.2 a singlet clearly associated with H-3*a*. These shift values are in good agreement with literature data of other condensed dihydroisothiazole dioxides. [5] In the case of **3e**, NOESY experiments showing a clear relationship between H-3*a* and the *o,o'* methyl groups of the aryl substituent linked to C-3, clearly supported the assigned regiochemistry. Performing the same experiments, analogous conclusions about the spatial proximity of H-3*a* and the COOEt group were possible in the case of **3f**. The structures of the other

cycloadducts **3a-d** was 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 **3** at least at the detection limits (^{1}H-NMR, TLC on the crude reaction mixture) showing high regioselectivity (Scheme 1).

Scheme 1



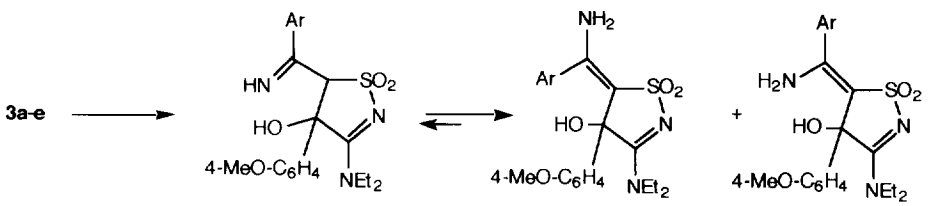
1 **2a-f** **3a-f**

2, 3	R
a	4-NO_2-C_6H_4
b	4-OMe-C_6H_4
c	4-Cl-C_6H_4
d	2,6-Cl_2-C_6H_3
e	2,4,6-Cl_3-3,5-Me_2-C_6
f	COOEt

The 1,3-dipolar addition of a nitrile oxide to a double bond is a well known and thoroughly studied process.[6] Several papers have appeared in the literature describing the reactions of nitrile oxides with cyclic and acyclic sulfones.[7,8] When arenecarbonitrile oxides were made to react with phenyl-vinyl sulfone or with methyl-vinyl sulfone, the 5-sulfonyl isomer was obtained as the sole or dominant product; β-alkyl and β-phenyl substituents cause a reversal of regiochemistry. A similar behaviour was observed with cyclic sulfones: thiete *S,S*-dioxides, thiophene *S,S*-dioxides, benzothiophene *S,S*-dioxides, 2,3-dihydro-benzothiophene *S,S*-dioxides all react with these nitrile oxides affording the 4-sulfonyl isomer. Also in our case the orientation is that which places the sulfonyl group in the 4-position of the resulting heterocyclic system. This corresponds to bond formation between the carbon of the 1,3 dipole and the carbon α to the SO_2 group of the isothiazole dioxide: this carbon has been demonstrated to be the more electrophilic centre in the isothiazole 1,1-dioxide.[9] Accordingly, a charge-controlled reaction would produce a regiochemistry opposite to that observed. It has to be noted that a parallel behaviour is displayed by isothiazol-3(2*H*)-one 1,1-dioxides where the charge distribution is self evident.[10] Apparently, in our case the main interactions have to be seen in the steric effects of the bulky substituents on the dipolarophile and on the dipole which determine an unfavourable approach in the transition state.

Transformation Reactions of 3a-e. Synthetically useful transformations of the cycloadducts **3a-e** occurred by reduction. In the case of **3a-e**, among the several reducing reagents considered (H_2-Pd/C; Raney Ni; $LiAlH_4$; $NaBH_4$; $NaBH_4$-$CoCl_2$; BH_3-Me_2S), the best results were obtained with Raney Ni or $NaBH_4$-$CoCl_2$.[11] Under these conditions compounds **3a-e** afforded a mixture of stereoisomeric enamines **4** and **5** (Scheme 2):

Scheme 2

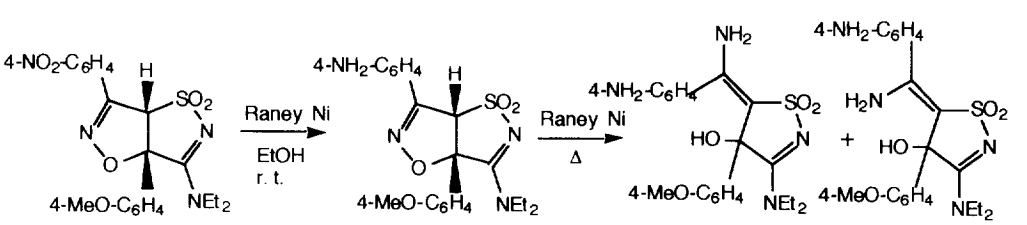


A **4a-e** **5a-e**

4, 5	Ar
a	4-NH_2-C_6H_4
b	4-OMe-C_6H_4
c	4-Cl-C_6H_4
d	2,6-Cl_2-C_6H_3
e	2,4,6-Cl_3-3,5-Me_2-C_6

The imines A are formed as primary products through reductive cleavage of the N-O bond. Tautomerization of the intermediate A afforded the more stable enamines **4** and **5** in an *E/Z* ratio of ca. 9:1. It may be noted that when **3a** was treated with Raney nickel it was possible to isolate in good yields the intermediate **3g** obtained by reduction of the NO_2 group. This latter was afterwards transformed into the enamines **4/5a** by prolonged heating with the same reagent (Scheme 3).

Scheme 3

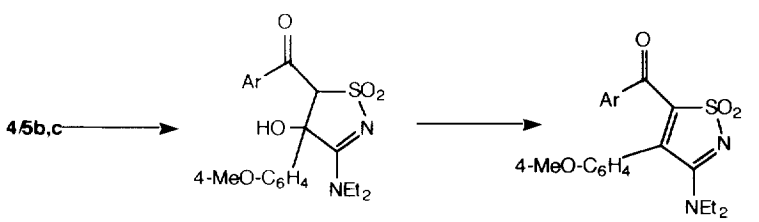


3a **3g** **4a** **5a**

On the other hand treatment of **3a** with $NaBH_4$-$CoCl_2$ directly afforded **4/5a** with better yields through reduction of both the NO_2 group and the isoxazoline ring. The structure of compounds **4** and **5** was confirmed by ^{1}H-NMR data. The broad signal associated with the OH group is clearly deshielded in compounds **5** due to the possibility of a hydrogen bond with the NH_2 group. The ^{1}H-NMR spectra of **4** showed signals associated with the aromatic hydrogens of the 4-methoxy substituted phenyl group upfield of the same hydrogens in compounds **5**: this must be ascribed to the shielding effect exerted by the other aromatic ring as evidenced by molecular models.

Compounds **4/5b,c** were easily hydrolyzed to the ketones **6a,b** which were dehydrated to the 5-aroyl-3-amino-isothiazoles **7a,b**. Compounds **4/5d,e** required more forcing conditions and longer reaction times probably due to the steric effects exerted by the substituents on the aryl group linked to the enamine carbon, which resulted in a difficult approach of the nucleophile (Scheme 4).

Scheme 4



4,5	Ar
b	4-OMe-C_6H_4
c	4-Cl-C_6H_4

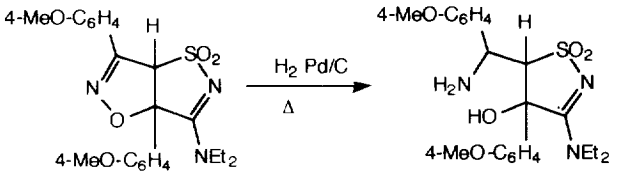
6,7	Ar
a	4-OMe-C_6H_4
b	4-Cl-C_6H_4

Another attempt at reduction was performed on **3b** with H_2 Pd/C in THF at reflux. The amine compound **8** was obtained as a mixture of two diastereoisomers. The structure was confirmed by ^{1}H-NMR spectrum showing four singlets (δ 3.74, 3.77, 3.79, 3.84) associated to the OCH_3 group of the two diastereoisomers and two couples of doublets (δ 3.58, 4.38 J=2.2 Hz and δ 3.63, 5.08 J=2.9 Hz) associated to H-5 and to the hydrogen α to the NH_2 group (Scheme 5).

Transformation reactions of **3f**. A different behaviour was found in the case of **3f**. Many reducing agents such as H_2 Pd/C, H_2 PtO_2, Zn/AcOH, $NaBH_4$, $NaBH_4$-$CoCl_2$ were tried without any useful results. Either cycloadduct **3f** was unaffected to the treatment or intractable mixtures of products were obtained when reaction

conditions were more vigorous.

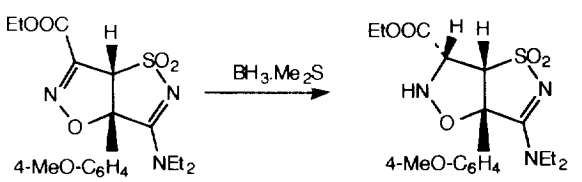
Scheme 5



3b **8**

Using $NaBH_4$ only reduction of COOEt group to CH_2OH was observed without participation of the isoxazoline ring. An successful result was obtained with $BH_3.Me_2S$ which afforded the isoxazolidine derivative **9**. The structure of compound **9** was confirmed by ^1H-NMR spectra which showed an AMX system clearly associated with H-3*a*; H-3; NH (δ 4.19, 4.53, 6.40, respectively). The coupling constant of 7.2 Hz (H-3*a*, H-3) supported the *cis* configuration (Scheme 6).[5]

Scheme 6



3f **9**

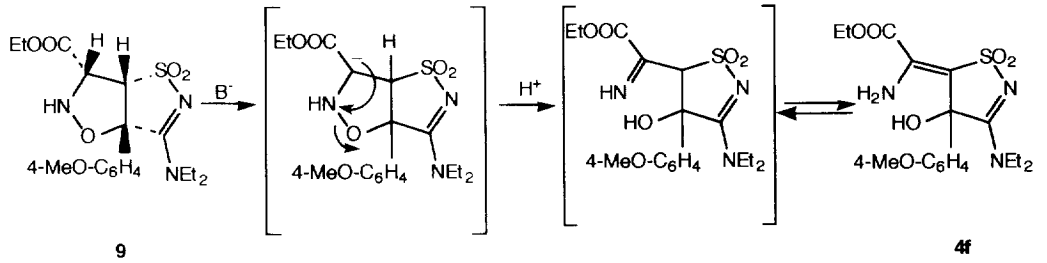
Cycloadduct **3f** was hydrolyzed with 10% NaOH to the corresponding carboxylic acid **10**. This latter was heated without solvent at a temperature 5-10°C above its melting point and evolution of carbon dioxide was apparent. The crude reaction mixture was chromatographed on silica gel to give 3-diethylamino-4-(4-methoxyphenyl)-isothiazole-5-carbonitrile 1,1-dioxide (**11**). Decarboxylative ring opening took place as shown in Scheme 7 according to a mechanism already observed in other cases[12], through the β-hydroxynitrile B which spontaneously eliminates water affording **11**.

This result appeared to be very interesting because of the possibility to introduce a CN group easily and in high yield into the isothiazole 1,1-dioxide ring, which represents a good starting point for the synthesis of other derivatives.

These results with nitrile oxides confirmed the good reactivity of **1** as dipolarophile in 1,3-dipolar cycloaddition reactions. The isothiazole ring in the dihydro-isothiazolo[5,4-*d*]isoxazole system is stable allowing transformations of the isoxazoline ring which result in functionalized isothiazole 1,1-dioxides not available by the known synthetic route, i. e., base-catalyzed cyclization of N-alkylsulfonylamidines of α-ketoacids, which severely limitate the substitution on C(4) and C(5) owing to the scarce availability of the

necessary starting materials.[13]

Scheme 7



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EXPERIMENTAL

Melting points were determined using a Büchi 510 (capillary) or a Electrothermal 9100 apparatus. ^{1}H-NMR spectra (ppm, tetramethylsilane as internal standard, $CDCl_3$ as solvent except when indicated) were obtained with a Bruker AC 200, Bruker AC 300 and a Varian Gemini 200 instruments. Chemical shifts (δ) are given in ppm and the coupling constants (J) are given in Hz. TLC: ready-to-use silica gel plates. Column chromatography: silica gel [Kieselgel 60-70 230 ASTM (Merck)] with the eluant indicated. 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).

Materials. **1**[13], **2d-e**[14-17] have already been described. Nitrile oxides **2a-c,f** were synthesized *in situ* from the corresponding hydroximoyl chlorides according to published procedure.[3,4,6]

General Procedure for the Cycloaddition Reaction of Isothiazole 1,1-Dioxide **1** *with* **2d-e.** Equimolecular amounts of **1** (0.5 g, 1.7 mmol) and **2d-e** (1.7 mmol) were dissolved in dichloromethane (20 mL) and stirred at room temperature for about 2-12 h until disappearance of the reactants (T.L.C. cyclohexane/ethyl acetate 3/2). The solvent was evaporated under reduced pressure and the residue crystallized from dichloromethane/ diisopropyl ether affording **3d-e**.

3-(2,6-Dichlorophenyl)-6-diethylamino-3a,6a-dihydro-6a-(4-methoxyphenyl)-isothiazolo[5,4-d]isoxazole 4,4-Dioxide (3d): Yield: 65%. M.p.: 191-192°C. Calcd.: C 52.28% H 4.35% N 8.71% Found: C 51.84% H 4.44% N 8.54%. ^{1}H-NMR: 0.95 (t, 3H, J=7 Hz, CH_3), 1.29 (t, 3H, J=7 Hz, CH_3), 3.20-3.40, 3.50-3.70 (2m, 4H, CH_2), 3.84 (s, 3H, OCH_3), 5.36 (s, 1H, H-3*a*), 7.02 (AB system, J=8.8 Hz, 2H, Aryl-H), 7.20-7.45 (m, 5H, Aryl-H).

*3-(3,5-Dichloro-2,4,6-trimethylphenyl)-6-diethylamino-3a,6a-dihydro-6a-(4-methoxyphenyl)-isothiazolo[5,4-d]isoxazole 4,4-Dioxide (**3e**):* Yield: 85%. M.p.: 221°C. Calcd.: C 54.96% H 5.19% N 8.01% Found: C 54.89% H 5.08% N 7.98%. ^{1}H-NMR: 0.93 (t, 3H, J=7 Hz, CH_3), 1.30 (t, 3H, J=7.2 Hz, CH_3), 2.26 (s, 6H, CH_3), 2.53 (s, 3H, CH_3), 3.20-3.40, 3.45-3.75 (2m, 4H, CH_2), 3.85 (s, 3H, OCH_3), 4.88 (s, 1H, H-3*a*), 7.00 (AB system, J=8.9 Hz, 2H, Aryl-H), 7.40 (AB system, J=8.9 Hz, 2H, Aryl-H).

*General Procedure for the Cycloaddition Reaction of Isothiazole 1,1-Dioxide **1** with **2a-c**.* A benzene solution of the hydroximoyl chloride (6.8 mmol) was dropped into a stirred solution of triethylamine (0.95 mL, 6.8 mmol) in the same solvent at 0°C. After a few minutes the mixure was run to room temperature and a solution of **1** (2 g, 6.8 mmol) in benzene (40 mL) was added dropwise. At the end of addition the mixture was refluxed until reactants disappeared (TLC cyclohexane/ethyl acetate 3/2, 1-24 h). The solvent was evaporated under reduced pressure, the residue was neutralized with a 10% HCl solution and 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 **3a-c** were crystallized from dichloromethane/ diisopropyl ether.

*6-Diethylamino-3a,6a-dihydro-6a-(4-methoxyphenyl)-3-(4-nitrophenyl)-isothiazolo[5,4-d]isoxazole 4,4-Dioxide (**3a**):* Yield: 79%. M.p.: 265-266°C. Calcd.: C 55.02% H 4.80% N 12.22% Found: C 54.52% H 4.90% N 12.06%. ^{1}H-NMR: 0.89 (t, 3H, J=7 Hz, CH_3), 1.29 (t, 3H, J=7.1 Hz, CH_3), 3.20-3.52, 3.60-3.80 (2m, 4H, CH_2), 3.84 (s, 3H, OCH_3), 5.11 (s, 1H, H-3*a*), 7.00 (AB system, J=8.9 Hz, 2H, Aryl-H), 7.38 (AB system, J=8.9 Hz, 2H, Aryl-H), 7.95 (AB system, J=9 Hz, 2H, Aryl-H), 8.29 (AB system, J=9 Hz, 2H, Aryl-H).

*6-Diethylamino-3a,6a-dihydro-3a,6a-di-(4-methoxyphenyl)-isothiazolo[5,4-d]isoxazole 4,4-Dioxide (**3b**):* Yield: 72%. M.p.: 169-170°C. Calcd.: C 59.59% H 5.64% N 9.48% Found: C 59.57% H 5.72% N 9.45%. ^{1}H-NMR: 0.85 (t, 3H, J=7 Hz, CH_3), 1.27 (t, 3H, J=7.1 Hz, CH_3), 3.20-3.50, 3.62-3.80 (2m, 4H, CH_2), 3.82 (s, 6H, OCH_3), 5.08 (s, 1H, H-3*a*), 6.94 (m, 4H, Aryl-H), 7.36, 7.73 (2 AB system, J=8.8 Hz, 4H, Aryl-H).

*3-(4-Chlorophenyl)-6-diethylamino-3a,6a-dihydro-6a-(4-methoxyphenyl)-isothiazolo[5,4-d]isoxazole 4,4-Dioxide (**3c**):* Yield: 65%. M.p.: 179-180°C. Calcd.: C 56.31% H 4.91% N 9.38% Found: C 56.41% H 4.91% N 9.40%. ^{1}H-NMR: 0.87 (t, 3H, J=7.1 Hz, CH_3), 1.27 (t, 3H, J=7.1 Hz, CH_3), 3.18-3.50, 3.60-3.80 (2m, 4H, CH_2), 3.83 (s, 3H, OCH_3), 5.06 (s, 1H, H-3*a*), 6.98 (AB system, J=8.8 Hz, 2H, Aryl-H), 7.42 (AB system, J=8.8 Hz, 2H, Aryl-H), 7.52 (AB system, J=8.8 Hz, 2H, Aryl-H), 7.72 (AB system, J=8.8 Hz, 2H, Aryl-H).

*Cycloaddition Reaction of **1** with **2f**: Synthesis of 6-Diethylamino-3a,6a-dihydro-6a-(4-methoxyphenyl)-isothiazolo[5,4-d]isoxazole-3-carboxylic Acid Ethyl ester 4,4-Dioxide (**3f**):* A solution of **1** (2.94 g, 10 mmol) in anhydrous THF (7 mL) was dropped into a vigorously stirred solution of ethyl chlorooximidoacetate (10 mmol) and triethylamine (1.5 mL) in the same solvent (15 mL) at 0°C. Stirring was continued until TLC

analysis revealed the absence of reactants (TLC cyclohexane/ethyl acetate 3/2, 1-5 h). The solvent was evaporated under reduced pressure and 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. The crude product was chromatographed on silica gel with cyclohexane/ethyl acetate 3/2 as eluant. Pure **3f** was crystallized from dichloromethane/diethyl ether. Yield: 70%. M.p.: 129°C. ^{1}H-NMR: 0.88 (t, 3H, J=7.0 Hz, CH_3), 1.26 (t, 3H, J=7.0 Hz, CH_3), 1.39 (t, 3H, J=7.0 Hz, CH_3), 3.18-3.35, 3.35-3.45, 3.61-3.71 (3m, 4H, CH_2), 3.83 (s, 3H, OCH_3), 4.42 (q, 2H, J=7.0 Hz, CH_2), 4.96 (s, 1H, H-3*a*), 6.97 (AB system, J=8.7 Hz, 2H, Aryl-H), 7.28 (AB system, J=8.7 Hz, 2H, Aryl-H). *m/z* 410 (M^++1).

*3-(4-Aminophenyl)-6-diethylamino-3a,6a-dihydro-6a-(4-methoxyphenyl)-isothiazolo[5,4-d]isoxazole 4,4-Dioxide (**3g**):* Raney nickel catalyst (1 g) was suspended in ethanol (under nitrogen) at room temperature. **3a** (0.5 g, 1.1 mmol) was added in one portion and the reaction mixture was stirred until the reactant has been consumed (TLC cyclohexane/ethyl acetate 3/2, 1-2 h). The nickel catalyst was filtered off and washed twice with ethanol. The filtrate was evaporated under reduced pressure and the crude product was crystallized from dichloromethane/ diisopropyl ether. Yield: 74% M.p.: 184-185°C. ^{1}H-NMR: 0.84 (t, 3H, J=7.1 Hz, CH_3), 1.26 (t, 3H, J=7.1 Hz, CH_3), 3.20-3.50, 3.60-3.80 (2m, 4H, CH_2), 3.82 (s, 3H, OCH_3), 3.90-4.10 (bs, 2H, NH_2), 5.05 (s, 1H, H-3*a*), 6.65 (AB system, J=8.8 Hz, 2H, Aryl-H), 6.95 (AB system, J=8.8 Hz, 2H, Aryl-H), 7.35 (AB system, J=8.8 Hz, 2H, Aryl-H), 7.56 (AB system, J=8.8 Hz, 2H, Aryl-H). *m/z* 428 (M^+).

*General Procedure for the Hydrogenation Reaction of **3a-d**. Method A (reduction with Raney nickel catalyst):* Raney nickel catalyst (1g) was suspended in ethanol (under nitrogen) at room temperature. Compounds **3** (1.1 mmol) were added in one portion and the reaction mixture was stirred at 40°-50°C until the reactant has been consumed (TLC cyclohexane/ethyl acetate 3/2, 1-2 h). The nickel catalyst was filtered off and washed twice with ethanol. The combined filtrates was evaporated under reduced pressure and the crude product was crystallized from dichloromethane/diisopropyl ether affording the isomer **5** as pure compound. The mother liquor was evaporated and chromatographed on silica gel affording generally further amount of pure **5**. The isomer **4** was always obtained in mixture with **5** and any attemp to purify it failed except in the case of **4d**. In the case of **4b,d** characteristic signals in the ^{1}H-NMR spectra of the mixture of the two diastereoisomeric enamines are reported. *Method B (reduction with $NaBH_4$-$CoCl_2$):* $NaBH_4$ (0.1 g, 2.8 mmol) was added portionwise under nitrogen atmosphere to a stirred solution of compounds **3** (1.1 mmol) and $CoCl_2.6H_20$ (0.45 g, 2.2 mmol) in methanol (20 mL) and the mixture stirred for 4-8 h. The methanol was removed under reduced pressure and 25% aqueous NH_3 solution (15 mL per mmol of **3**) and CH_2Cl_2 (an equal volume) were added to the residue; the mixture was then stirred exposed to the air until the organic layer was yellow-brown (one night). The mixture was separated and the aqueous layer extracted with CH_2Cl_2. After drying over Na_2SO_4 the organic phase was evaporated under reduced pressure to give the crude reaction product which was cromatographed on silica gel affording **5** as pure compound. Compound **4** was always obtained in mixture with **5** except in the case of **4d** as said above.

*5-[Amino-(4-aminophenyl)-methylene]-3-diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-4,5-dihydro-isothiazol-4-ol (**4a,5a**):* Total yield: 74%. **5a**: M.p.: 187°C. ^{1}H-NMR (DMSO): 0.57 (t, 3H, J=7.1 Hz, CH_3), 1.06 (t, 3H, J=7.0 Hz, CH_3), 2.90-3.35 (m, 4H, CH_2), 3.75 (s, 3H, OCH_3), 5.30-5.50 (bs, 2H, NH_2), 5.60-5.80

(bs, 2H, NH_2), 6.48 (AB system, J=8.1 Hz, 2H, Aryl-H), 6.96 (AB system, J=8.5 Hz, 2H, Aryl-H), 7.29 (AB system, J=8.1 Hz, 2H, Aryl-H), 7.54 (AB system, J=8.5 Hz, 2H, Aryl-H), 7.63 (s,1H, OH). *m/z* 412 (M- H_2O).

*5-[Amino-(4-methoxyphenyl)-methylene]-3-diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-4,5-dihydro-isothiazol-4-ol (**4b**,**5b**):* Total yield: 57%. **5b**: M.p.: 168°-170°C. ^{1}H-NMR : 0.53 (t, 3H, J=7.0 Hz, CH_3), 1.16 (t, 3H, J=7.1 Hz, CH_3), 3.10-3.75 (3m, 4H, CH_2), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.56-4.61 (bm, 3H, NH_2 and OH), 6.90 (AB system, J=8.9 Hz, 2H, Aryl-H), 6.95 (AB system, J=8.9 Hz, 2H, Aryl-H), 7.60 (AB system, J=8.9 Hz, 2H, Aryl-H), 7.63 (AB system, J=8.9 Hz, 2H, Aryl-H). *m/z* 445 (M^+). In the ^{1}H-NMR spectrum of the diastereoisomeric mixture some significative signals associable to **4b** are: 0.48 (t, 3H, J=7.0 Hz, CH_3), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.65-4.75 (bm, 2H, NH_2), 5.00-5.10 (bm, 1H, OH), 6.55, 6.65 (2 AB system, J=8.8 Hz, 4H, Aryl-H).

*5-[Amino-(4-chlorophenyl)-methylene]-3-diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-4,5-dihydro-isothiazol-4-ol (**4c**,**5c**):* Total yield: 50%. **5c**: M.p.: 194°-195°C. Calcd.: C 56.06% H 5.33% N 9.34% Found: C 55.95% H 5.34% N 9.27%. ^{1}H-NMR : 0.52 (t, 3H, J=7.0 Hz, CH_3), 1.18 (t, 3H, J=7.0 Hz, CH_3), 3.10-3.50 (m, 3H, CH_2), 3.60-3.78 (m, 1H, CH_2), 3.83 (s, 3H, OCH_3), 4.54 (bm, 3H, NH_2 and OH), 6.94 (AB system, J=8.9 Hz, 2H, Aryl-H), 7.37 (AB system, J=8.5 Hz, 2H, Aryl-H), 7.58 (AB system, J=8.9 Hz, 2H, Aryl-H), 7.63 (AB system, J=8.5 Hz, 2H, Aryl-H).

*5-[Amino-(2,6-dichlorophenyl)-methylene]-3-diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-4,5-dihydro-isothiazol-4-ol (**4d**,**5d**):* Total yield: 70%. **5d**: Yield: 40%. M.p.: 228°C. ^{1}H-NMR : 0.60 (t, 3H, J=7.0 Hz, CH_3), 1.15 (t, 3H, J=7.1 Hz, CH_3), 3.19-3.70 (m, 4H, CH_2), 3.83 (s, 3H, OCH_3), 3.95 (s, 1H, OH), 4.25-4.35 (bs, 2H, NH_2), 6.95 (AB system, J=8.8 Hz, 2H, Aryl-H), 7.26-7.40 (m, 3H, Aryl-H), 7.65 (AB system, J=8.8 Hz, 2H, Aryl-H). *m/z* 484 (M^+). **4d:** Yield: 30%. M.p.: 226°C. ^{1}H-NMR : 0.58 (t, 3H, J= 6.9 Hz, CH_3), 1.19 (t, 3H, J=7.1 Hz, CH_3), 3.02-3.40 (m, 3H, CH_2), 3.45-3.60 (m, 1H, CH_2), 3.52 (s, 1H, OH), 3.77 (s, 3H, OCH_3), 4.92 (s, 2H, NH_2), 6.62 (AB system, J=8.9 Hz, 2H, Aryl-H), 6.82 (AB system, J=8.9 Hz, 2H, Aryl-H), 6.96 (dd, J_{orto}=8.0 Hz, J_{meta}=0.92 Hz, 1H, Aryl-H), 7.22 (t, J=8.0 Hz, 1H, Aryl-H); 7.40 (dd, J_{orto}=8.0 Hz, J_{meta}=0.92 Hz, 1H, Aryl-H). *m/z* 484 (M^+).

*5-[Amino-(3,5-dichloro-2,4,6-trimethylphenyl)-methylene]-3-diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-4,5-dihydro-isothiazol-4-ol (**4e**,**5e**):* Total yield: 46%. **5e**: M.p.: 222°C. ^{1}H-NMR: 0.51-1.60 (m, 6H, CH_3), 2.43, 2.52 (2s, 9H, CH_3), 3.05-3.45 (m, 3H, CH_2), 3.50-3.70 (m, 1H, CH_2), 3.70 (s, 1H, OH), 3.78 (s, 3H, OCH_3), 4.86-4.96 (bs, 2H, NH_2), 6.62 (AB system, J=9.0 Hz, 2H, Aryl-H), 6.75 (AB system, J=9.0 Hz, 2H, Aryl-H).

*Reduction of **3f** with $BH_3.Me_2S$:* Cycloadduct **3f** (0.491g, 1.2 mmol) was dissolved in anhydrous THF (10 mL) under nitrogen and $BH_3.Me_2S$ (0.61 mL of a 2M solution in THF) was dropped into the solution. Stirring was continued until disappearance of the reactant (TLC diethyl acetate/cyclohexane 1/1, 12 h). The solvent was evaporated at reduced pressure and extracted in dichloromethane. The organic layer, washed twice with water, was dried (Na_2SO_4), filtered and the solvent was evaporated. The crude mixture was

chromatographed on silica gel (eluent: ethyl acetate/cyclohexane 3/7) affording pure **9**. Yield: 50%. ^{1}H-NMR: 0.78 (t, 3H, J=7.0 Hz, CH_3), 1.25 (t, 3H, J=7.0 Hz, CH_3), 1.32 (t, 3H, J=7.0 Hz, CH_3), 3.07-3.19, 3.32-3.45, 3.60-3.77 (3m, 4H, CH_2), 3.83 (s, 3H, OCH_3), 4.19 (d, 1H, J_{AM}=7.2 Hz, H-3a), 4.31 (q, 2H, J=7.0 Hz, CH_2), 4.53 (dd, 1H, J_{AM}=7.2 Hz, J_{MX}=14.0 Hz, H-3), 6.40 (d, 1H, J_{MX}=14.0 Hz, NH), 6.94 (AB system, J=8.8 Hz, 2H, Aryl-H), 7.36 (AB system, J=8.8 Hz, 2H, Aryl-H). *m/z* 411 (M^+).

*3-[Diethylamino-4-hydroxy-4-(4-methoxyphenyl)-1,1-dioxo-4,5-dihydro-isothiazol-5-yl]-(4-methoxyphenyl)-methanone (**6a**):* A mixture of **4b** and **5b** (0.3 g, 0.67 mmol) dissolved in CH_2Cl_2 (10 mL) was vigorously stirred with a solution of NH_4Cl (20 mL) until disappearance of the reactants (TLC cyclohexane/ethyl acetate 3/2, 8-24 h). The organic layer was separated, dried over Na_2SO_4, filtered and the solvent was evaporated at reduced pressure yielding **6a**. Yield: 95%. M.p.: 157°C. ^{1}H-NMR: 0.90 (t, 3H, J=7.0 Hz, CH_3), 1.26 (t, 3H, J=7.1 Hz, CH_3), 3.10-3.60 (m, 3H, CH_2), 3.65-3.78 (m, 1H, CH_2), 3.81 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.17 (s, 1H, H-5), 6.90-7.00 (m, 4H, Aryl-H), 7.45 (AB system, J=8.8 Hz, 2H, Aryl-H), 7.47 (s, 1H, OH), 8.00 (AB system, J=8.8 Hz, 2H, Aryl-H). *m/z* 447 (M^++1).

*3-[Diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-isothiazol-5-yl]-(4-methoxyphenyl)-methanone (**7a**):* A benzene solution (5 mL) of **6a** (0.48 g, 0.89 mmol), containing a few drops of conc. H_2SO_4 was refluxed until disappearance of the reactant (TLC cyclohexane/ethyl acetate 3/2, 24-30 h). The solvent was evaporated under reduced pressure, extracted with dichloromethane and washed with water. The organic layer was separated, dried over Na_2SO_4, filtered and the solvent was concentrated under reduced pressure. The residue was crystallized with dichloromethane/diethyl ether affording **7a**. Yield: 52%. M. p.: 168°-170°C. ^{1}H-NMR: 0.93 (t, 3H, J=7.2 Hz, CH_3); 1.34 (t, 3H, J=6.8 Hz, CH_3); 3.13 (q, 2H, J=6.8 Hz, CH_2); 3.68 (q, 2H, J=7.2 Hz, CH_2); 3.75 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 6.83 (AB system, J=8.8 Hz, 2H, Aryl-H); 6.89 (AB system, J=8.8 Hz, 2H, Aryl-H); 7.19 (AB system, J=8.8 Hz, 2H, Aryl-H); 7.90 (AB system, J=8.8 Hz, 2H, Aryl-H). *m/z* 428 (M^+).

*3-[Diethylamino-4-hydroxy-4-(4-chlorophenyl)-1,1-dioxo-4,5-dihydro-isothiazol-5-yl]-(4-methoxyphenyl)-methanone (**6b**):* A mixture of **4c** and **5c** (0.1 g, 0.22 mmol) dissolved in dioxane (10 mL) was vigorously stirred with a 10% HCl (2 mL) solution until disappearance of the reactants (TLC cyclohexane/ethyl acetate 3/2, 8-24 h). The solvent was evaporated and the residue extracted with dichloromethane and washed twice with water. The organic layer was separated, dried over Na_2SO_4, filtered and the solvent was evaporated at reduced pressure yielding pure **6b**. Yield: 80%. M.p.: 125°-126°C. ^{1}H-NMR: 0.93 (t, 3H, J=7.0 Hz, CH_3), 1.27 (t, 3H, J=7.0 Hz, CH_3), 3.10-3.50 (m, 3H, CH_2), 3.60-3.78 (m, 1H, CH_2), 3.82 (s, 3H, OCH_3), 5.18 (s, 1H, H-5), 6.95 (AB system, J=8.9 Hz, 2H, Aryl-H), 7.06 (s, 1H, OH), 7.45 (AB system, J=8.9 Hz, 2H, Aryl-H), 7.48 (AB system, J=8.7 Hz, 2H, Aryl-H), 7.97 (AB system, J=8.7 Hz, 2H, Aryl-H). *m/z* 432 (M^+-H_2O).

*3-[Diethylamino-4-(4-chlorophenyl)-1,1-dioxo-isothiazol-5-yl]-(4-methoxyphenyl)-methanone (**7b**):* A solution of **6b** (0.1 g, 0.22 mmol) in benzene (5mL) containing a few drops of conc. H_2SO_4 was refluxed until disappearance of the reactant (TLC cyclohexane/ethyl acetate 3/2, 24-30 h).The solvent was evaporated under reduced pressure, extracted with dichloromethane and washed with water. The organic layer was separated,

dried over Na_2SO_4, filtered and the solvent was concentrated under reduced pressure. The residue was crystallized with dichloromethane/diethyl ether affording **7b**.Yield: 47%. M.p.: 185°-186°C dec. ^{1}H-NMR: 0.93 (t, 3H, J=6.9 Hz, CH_3), 1.35 (t, 3H, J=7.0 Hz, CH_3), 3.15 (q, 2H, J=6.9 Hz, CH_2), 3.68 (q, 2H, J=7.0 Hz, CH_2), 3.75 (s, 3H, OCH_3), 6.80 (AB system, J=8.6 Hz, 2H, Aryl-H), 7.13 (AB system, J=8.6 Hz, 2H, Aryl-H), 7.38 (AB system, J=8.6 Hz, 2H, Aryl-H), 7.84 (AB system, J=8.6 Hz, 2H, Aryl-H). *m/z* 432 (M^+).

Reduction of 3b with H_2 Pd/C: **3b** (0.5 g, 1.1 mmol) was dissolved in THF (30 mL) and hydrogenated at reflux with 10% Pd/ C as the catalyst (0.5 g, 0.43 mmol). Heating was continued until reactant disappeared (TLC: ethyl acetate/cyclohexane 1/1). The catalyst was filtered off and the solvent was evaporated under reduced pressure. The crude mixture was chromatographed on silica gel (ethyl acetate/cyclohexane 1/1) affording **8** as a diastereoisomeric mixture. Yield: 50%. ^{1}H-NMR: 0.66-0.74 (m, 6H, CH_3), 1.18-1.25 (m, 6H, CH_3), 3.10-3.50 (m, 8H, CH_2), 3.58 (d, 1H, J=2.2 Hz, CH), 3.63 (d, 1H, J=2.9 Hz, CH), 3.74, 3.77, 3.79, 3.84 (4s, 12H, 4 OCH_3), 4.38 (d, 1H, J=2.2 Hz, CH), 5.08 (d, 1H, J=2.9 Hz, CH), 6.70 (AB system, J=8.9 Hz, 2H, Aryl-H), 6.80-6.90 (m, 4H, Aryl-H), 6.90-7.11 (m, 4H, Aryl-H), 7.20-7.32 (m, 4H, Aryl-H), 7.42-7.46 (m, 2H, Aryl-H). *m/z* 447 (M^+).

6-Diethylamino-3a,6a-dihydro-4,4-dioxide-6a-(4-methoxyphenyl)-isothiazolo[5,4-d]isoxazole-3-carboxylic Acid (10): The cycloadduct **3f** (0.9 g, 2.2 mmol) in sodium hydroxide (5 mL of a 10% solution) was stirred until TLC confirmed the absence of starting material (TLC methanol/dichloromethane 5/1, 1 h). The reaction mixture was acidified to a pH of 3 with HCl (10%), and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated to give **10** of a purity satisfactory for the decarboxylation step. Yield: 90%. ^{1}H-NMR: 0.85 (t, 3H, J=7.0 Hz, CH_3), 1.24 (t, 3H, J=7.0 Hz, CH_3), 3.18-3.59, 3.63-3.69 (2m, 4H, CH_2), 3.81 (s, 3H, OCH_3), 4.98 (s, 1H, H-3*a*), 6.96 (AB system, J=8.4 Hz, 2H, Aryl-H), 7.24 (AB system, J=8.4 Hz, 2H, Aryl-H), 8.30 (s, 1H, COOH). *m/z* 382 (M^++1).

Thermal Decomposition of 10: Synthesis of 3-Diethylamino-1,1-dioxide-4-(4-methoxyphenyl)-isothiazole-5-carbonitrile (11): Acid **10** (0.2 g, 0.52 mmol) was heated without solvent at a temperature of about 170°C until the evolution of carbon dioxide ceased. The crude product was chromatographed on silica gel (diethyl acetate/cyclohexane 2/3) yielding the nitrile **11** wich crystallized with dichloromethane/diethyl ether. Yield: 55%. ^{1}H-NMR: 0.97 (t, 3H, J=6.9 Hz, CH_3), 1.32 (t, 3H, J=6.9 Hz, CH_3), 3.18 (q, 2H, J=6.9 Hz, CH_2), 3.66 (q, 2H, J=6.9 Hz, CH_2), 3.88 (s, 3H, OCH_3), 7.08 (AB system, J=8.7 Hz, 2H, Aryl-H), 7.32 (AB system, J=8.7 Hz, 2H, Aryl-H). *m/z* 320 (M^++1).

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