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# Isothiazoles. Part IX. An Efficient Synthetic Route to 5-Substituted-3-amino-4-arylisothiazole 1,1-dioxides and their 4,5-dihydro derivatives.

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**Abstract**

A simple method to introduce an heteroatom substituent at C-5 of isothiazole dioxides is reported. Through Michael addition reaction 5-substituted isothiazole and 4,5-dihydroisothiazole 1,1-dioxides were obtained allowing the preparation of a series of derivatives of special interest for biological studies. 

*Keywords:* Michael reactions; Isothiazoles; Substitution; Sulfur heterocycles.

## Introduction

The chemical reactivity of 3-amino-4-aryl-isothiazole 1,1-dioxides has been studied by us for some years and important transformations and uses of these compounds have been found, mainly as precursors of N- and/or S-containing heterocycles through 1,3-dipolar cycloaddition reactions followed by rearrangement of the cycloadducts.[1-5]

A further development has been found recently. Preliminary biological evaluations of some compounds of the isothiazole 1,1-dioxide and of the 4,5-dihydroisothiazole dioxide series have shown a promising pharmacological activity, because of their ability to inhibit the

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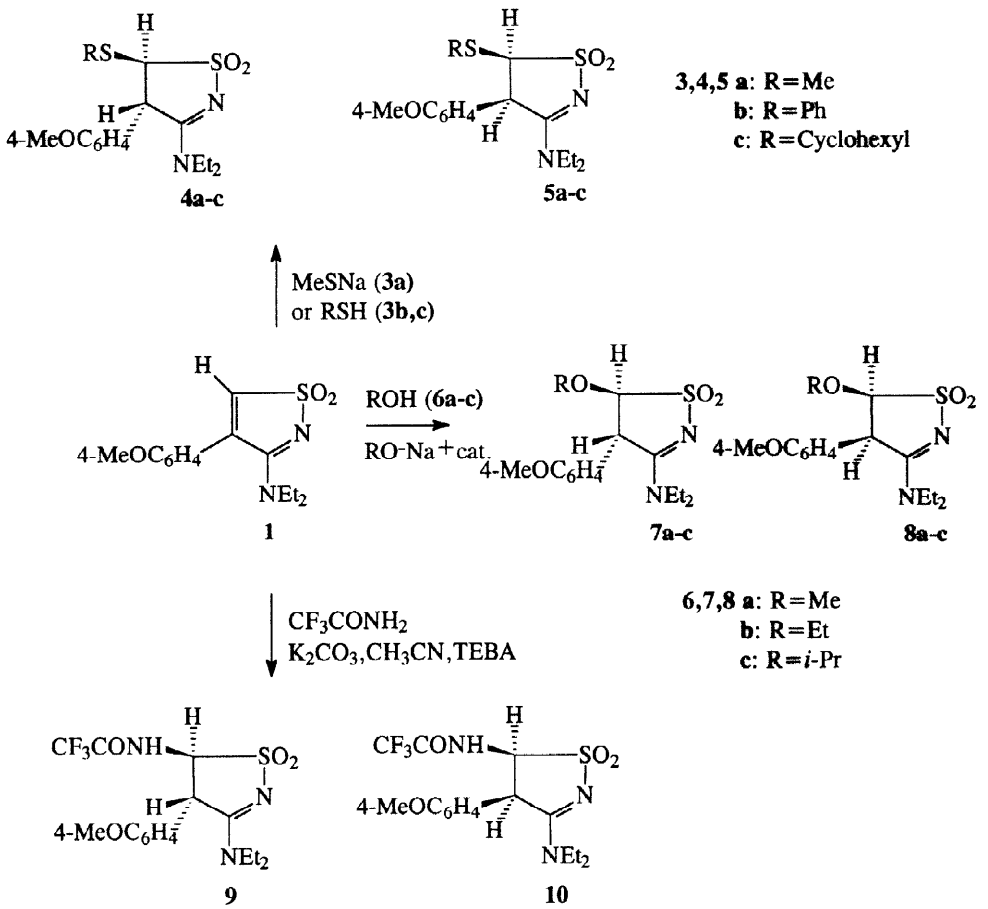
arterial smooth cells (SMC) proliferation. It is well known that in atherosclerotic plaques, SMC are the predominant cell type and their accumulation is the key prerequisite leading to vascular occlusion. Accordingly, the discovery of compounds containing the isothiazole ring potentially affecting SMC proliferation is an attractive target.[6]

Two main synthetic approaches are presently available for the synthesis of 3-amino-4-aryl-isothiazole 1,1-dioxide derivatives: (i) the base catalyzed cyclization of *N*-alkylsulfonylamidines of α-ketoacids, which affords 3-aminoisothiazole dioxides both unsubstituted and substituted at C-5 with alkyl or aryl groups, and ii) the palladium-catalyzed coupling of 5-bromoisothiazoles with organostannanes, which is a mild and efficient route to a variety of 3-amino-4-arylisothiazole 1,1-dioxides.[7,8] The latter method, which is more general, allowed the preparation of derivatives substituted at C-5 with vinyl, alkynyl, aryl and heteroaryl-groups previously not available. However, both methods are not applicable for the synthesis of 3-aminoisothiazole 1,1-dioxides and their 4,5-dihydro derivatives bearing at C-5 substituents linked through an O-, S- or N-atom. The lack of a methodology to prepare such compounds prompted us to develop an efficient synthetic route for these products.

In this paper we report on simple methods to introduce at C-5 of the isothiazole dioxide ring an heteroatom starting from unsubstituted or from 5-bromo-substituted isothiazoles **1** and **2**, respectively.

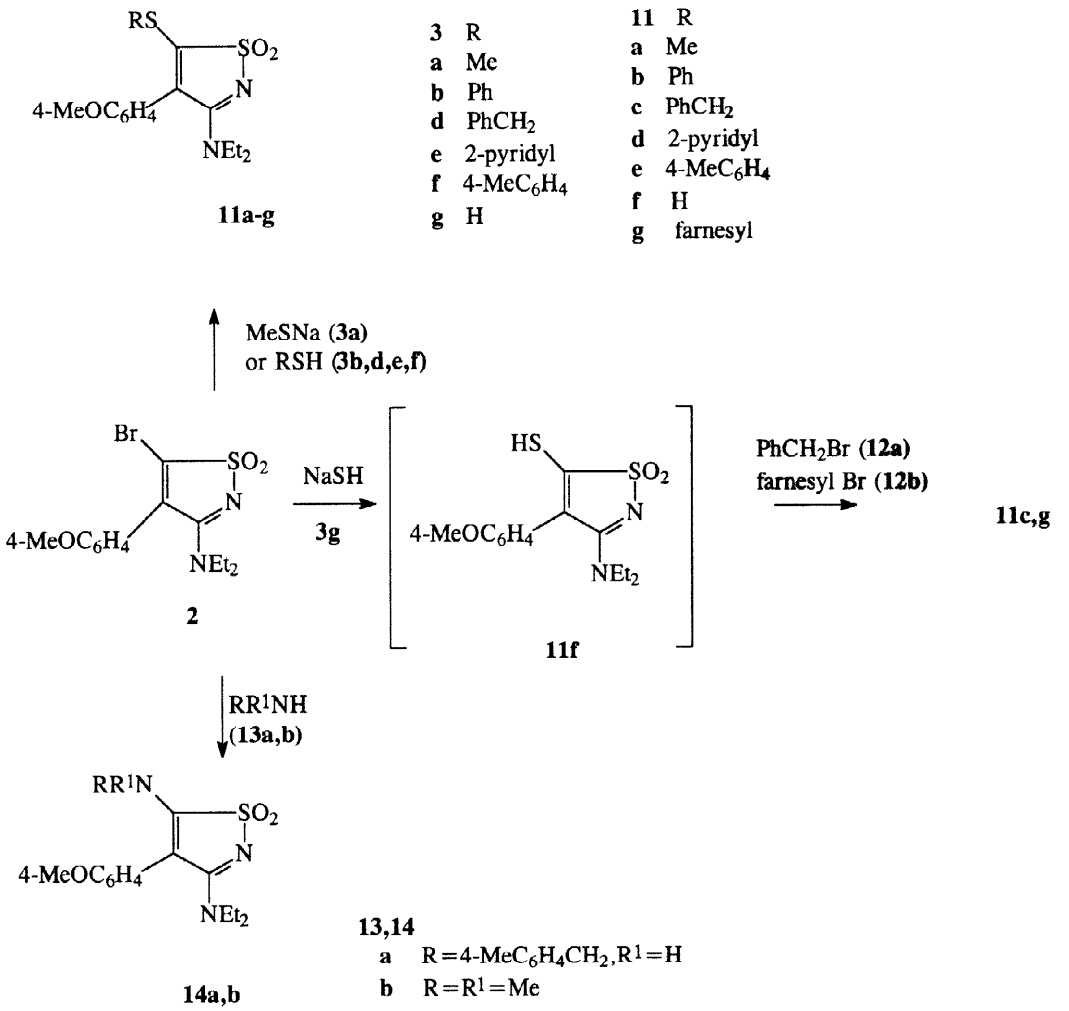
## Results and discussion

As an approach to 5-substituted 4,5-dihydroisothiazoles Michael additions to isothiazoles were considered. In previous work we demonstrated that in the 3-aminoisothiazole 1,1-dioxide ring C-5 is the more electrophilic carbon.[9] Accordingly, reactivity of **1** with nucleophiles could be expected with attack at C-5 by a Michael-type reaction and formation of 4,5-dihydro derivatives. Compound **1** was reacted with sulfur, oxygen, and nitrogen nucleophiles (Scheme 1). With methylthiolate **3a** or with mercaptans **3b,c** in acetonitrile as the solvent at room temperature compounds **4a-c** (*trans*) and **5a-c** (*cis*) were obtained in a ratio of about 2:1. By performing the reaction with aliphatic alcohols **6a-c** using a catalytic amount of the corresponding alkoxides, the two diastereoisomers **7a-c** (*trans*) and **8a-c** (*cis*) were obtained in a mixture where the *trans* isomer is the major one.




Scheme 1

Phenols or the corresponding phenoxides gave no reaction under the same conditions. When aliphatic or aromatic amines were used as nucleophiles, instead of the expected Michael adducts a mixture of products derived from opening of the isothiazole ring were obtained. However, the use of trifluoroacetamide as nitrogen nucleophile in P.T.C. conditions allowed us to isolate the corresponding isomeric amides **9** (*trans*) and **10** (*cis*) in a ratio of 2:1. Structures of compounds **4-10** were confirmed by analytical and spectroscopic data. $^1$H-NMR spectra showed two doublets associated with H-4 and H-5 characterized by a small coupling ($J$ in the range 0.1-3.3 Hz ) in the *trans* isomers and a larger one ($J$ in the range 8.2-9.1 Hz) in the *cis* isomers.[10] For the preparation of the 5-substituted unsaturated isothiazole dioxides, 5-bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**2**) appeared to be a key starting material because of the possibility of elimination of bromide ion. As regards sulfur nucleophiles, two different approaches were used to synthesize thio derivatives




Scheme 2

**11**. The first made use of the bromo derivative **2** and methylthiolate **3a** or mercaptans **3b,d-f**. The reaction was performed in dichloromethane as the solvent (some drops of dimethylformamide were used in the case of **3a**) with a stoichiometric amount of triethylamine. Satisfactory results were obtained in the case of thio derivatives **11a,11d** and **11e** but poorer yields were obtained for compounds **11b,c**.

An alternative method was found with 5-mercaptoisothiazole dioxide **11f** as the key intermediate. 5-Bromo derivative **2** was transformed in good yield (67%) into compound **11f** by reaction with sodium hydrogen sulfide **3g** in methanol as the solvent. The alkylation of compound **11f** with benzyl bromide **12a** afforded compound **11c** in a satisfactory yield

(45%). An interesting improvement was achieved by performing a one pot reaction starting from the bromo derivative **2**, sodium hydrogen sulfide **3g** and appropriate bromide **12** in methanol as the solvent without isolation of the mercaptan **11f**. Using these reaction conditions **11c** was isolated in 79% yield. The validity of this method was confirmed by performing the reaction between the bromo derivative **2**, sodium hydrogen sulfide **3g** and farnesyl bromide **12b**. Compound **11g** was isolated in 47% yield.

The second method is more convenient for the preparation of 5-thioalkyl substituted isothiazole dioxides. Compound **11c** was obtained in 12% yield by the first method and in 79% yield by the second method. Furthermore, the second method is advantageous when mercaptan derivatives are not available or are difficult to synthesize (*eg.* farnesylthiol).

Good results were also obtained by reacting compound **2** with 4-methylbenzylamine **13a** and with dimethylamine **13b** in dichloromethane or ethanol as the solvent. The 5-amino substituted isothiazole dioxides **14a** and **14b** were obtained in good yields (81%, 60%, respectively). However, alcohols did not react with compound **2**, even when performing the reaction in presence of a catalytic amount of the corresponding alkoxides. The use of stoichiometric amount of alkoxide resulted in the formation of a mixture of unidentified products. These are the subject of further investigation.

The above results gave an insight into the reactivity of isothiazole dioxides **1** and **2**. Both compounds have been demonstrated to undergo Michael addition of the nucleophile affording 4,5-dihydro derivatives but, in the case of **2**, the presence of a bromine group allowed the regeneration of the 4, 5-double bond. Many attempts were made to transform the dihydro derivatives **4-10** into the corresponding isothiazole 1,1-dioxides; however, the use of the most common oxidants (*eg.* DDQ, $KMnO_4$, $NiO_2$) failed in this process. This is not surprising considering that the isothiazole dioxide ring is not aromatic. Both compounds **1** and **2** reacted easily and in mild conditions with nucleophiles. Best results were observed with powerful nucleophiles, which are in turn poorer bases. When much stronger bases are used, other products probably due to isothiazole ring opening were produced.

## Experimental

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

*Materials*

Compounds **1** and **2** have already been described.[7,8] Farnesyl bromide **12b** is commercially available (Aldrich).

*General Procedure for the Synthesis of Compounds **4a-c** and **5a-c**:*

Compound **1** (0.5 g, 1.7 mmol) was dissolved in $CH_3CN$ (5 mL) and equimolar amounts of methylthiolate (**3a**) or of the mercaptans **3b,c** were added under stirring at room temperature. When the reagent disappeared (about 1 h, T.L.C. cyclohexane/ethyl acetate 3:7) the solvent was evaporated under reduced pressure and the mixture of the two isomeric compounds **4a-c** and **5a-c** was separated by chromatography (cyclohexane/ethyl acetate 3:7) and crystallized from $CH_2Cl_2/Et_2O$.

*3-Diethylamino-4,5-dihydro-4-(4-methoxyphenyl)-5-methylsulfanyl-isothiazole 1,1-dioxide:* **4a** (4S*5S*): White crystals. M.p. 143 °C; Yield 40%; Calcd. for $C_{15}H_{22}N_2O_3S_2$ (342.47): C 52.61 H 6.47 N 8.18 Found C 52.50 H 6.42 N 7.95; $^1$H-NMR ($CDCl_3$): 0.85 (t, 3H, *J* 7 Hz); 1.21 (t, 3H, *J* 7 Hz); 2.29 (s, 3H, $CH_3S$); 3.06-3.17, 3.40-3.43, 3.70-3.80 (3m, 4H, $CH_2$); 3.80 (s, 3H, $OCH_3$); 4.49 (s, 2H, H-4+H-5); 6.87 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.17 (d, AB system, 2H, *J* 9 Hz, aryl-H). **5a** (4R*5S*): oil; Yield 20%; Calcd. for $C_{15}H_{22}N_2O_3S_2$ C 52.61 H 6.47 N 8.18 Found C 52.23 H 6.12 N 7.80 ; $^1$H-NMR ($CDCl_3$): 0.82 (t, 3H, *J* 7 Hz); 1.23 (t, 3H, *J* 7 Hz); 2.38 (s, 3H, $CH_3S$); 3.03-3.29, 3.33-3.47, 3.62-3.75 (3m, 4H, $CH_2$); 3.80 (s, 3H, $OCH_3$); 4.07 (d, 1H, H-4, *J* 3 Hz); 4.11 (d, 1H, H-5, *J* 3 Hz); 6.90 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.21 (d, AB system, 2H, *J* 9 Hz, aryl-H).

*3-Diethylamino-4,5-dihydro-4-(4-methoxyphenyl)-5-phenylsulfanyl-isothiazole 1,1-dioxide:* ***4b*** (4S*5S*): White crystals. M.p. 164 °C; Yield 59%; Calcd. for $C_{20}H_{24}N_2O_3S_2$ (404.5): C 59.31 H 6.92 N 5.93 Found C 58.95 H 6.53 N 6.26; $^1$H-NMR ($CDCl_3$): 0.74 (t, 3H, *J* 7 Hz); 1.18 (t, 3H, *J* 7 Hz); 2.86-3.15, 3.28-3.48, 3.52-3.75 (3m, 4H, $CH_2$); 3.78 (s, 3H, $OCH_3$); 4.23 (d, 1H, H-4, *J* 2.6 Hz); 4.50 (d, 1H, H-5, *J* 2.6 Hz); 6.88 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.18 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.31-7.42 (m, 3H, aryl-H); 7.52-7.68 (m, 2H, aryl-

H). **5b** (4R*5S*): White crystals. M.p. 174 °C; Yield 30%; Calcd. for $C_{20}H_{24}N_2O_3S_2$ (404.5): C 59.31 H 6.92 N 5.93 Found C 58.15 H 6.77 N 6.32; $^1$H-NMR ($CDCl_3$): 0.79 (t, 3H, *J* 7 Hz); 1.17 (t, 3H, *J* 7 Hz); 2.98-3.24, 3.25-3.48, 3.55-3.76 (3m, 4H, $CH_2$); 3.79 (s, 3H, $OCH_3$); 4.61 (d, 1H, H-4, *J* 9 Hz); 4.83 (d, 1H, H-5, *J* 9 Hz); 6.90 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.18-7.61 (m, 7H, aryl-H).

*5-Cyclohexylsulfanyl-3-diethylamino-4,5-dihydro-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide:* **4c** (4S*5S*): White crystals. M.p. 132 °C; Yield 58%; Calcd. for $C_{20}H_{30}N_2O_3S_2$ (410.64): C 58.53 H 7.30 N 6.93 Found C 58.13 H 7.36 N 6.89; $^1$H-NMR ($CDCl_3$): 0.79 (t, 3H, *J* 7 Hz); 1.22 (t, 3H, *J* 7 Hz); 1.18-2.11 (m, 10H, cyclohexyl-H); 2.80-3.24, 3.25-3.45, 3.61-3.85 (3m, 5H, $CH_2$ and cyclohexyl-H); 3.81 (s, 3H, $OCH_3$); 4.06 (d, 1H, H-4, *J* 3.3 Hz); 4.23 (d, 1H, H-5, *J* 3.3 Hz); 6.89 (d, AB system, 2H, *J* 9 Hz, aryl-H)); 7.20 (d, AB system, 2H, *J* 9 Hz, aryl-H). **5c** (4R*5S*): White crystals. M.p. 181 °C; Yield 35%; Calcd. for $C_{20}H_{30}N_2O_3S_2$ (410.64): C 58.53 H 7.30 N 6.93 Found C 58.14 H 7.50 N 7.04; $^1$H-NMR ($CDCl_3$): 0.84 (t, 3H, *J* 7 Hz); 1.20 (t, 3H, *J* 7 Hz); 1.15-2.18 (m, 10H, cyclohexyl-H); 2.94-3.24, 3.30-3.52, 3.58-3.75 (3m, 5H, $CH_2$ and cyclohexyl-H); 3.79 (s, 3H, $OCH_3$); 4.42 (d, 1H, H-4, *J* 9 Hz); 4.64 (d, 1H, H-5, *J* 9 Hz); 6.86 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.15 (d, AB system, 2H, *J* 9 Hz, aryl-H).

*General Procedure for the Synthesis of Compounds 7a-c and 8a-c:*

Compound **1** (0.5 g, 1.7 mmol) was dissolved in the appropriate alcohol **6a-c** (30 mL) and a catalytic amount of the corresponding alcoholate was added under stirring at room temperature. In a few minutes the reagent disappeared (about 20-30 min, T.L.C. cyclohexane/ethyl acetate 2:3) affording **7a-c** and **8a-c** in mixture. The solvent was evaporated under reduced pressure and the isomeric mixture was separated by chromatography ($CH_2Cl_2$/$Et_2O$ 1:1) and crystallized from $CH_2Cl_2$/$Et_2O$.

*3-Diethylamino-4,5-dihydro-5-methoxy-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide:*

**7a** (4S*5S*): White crystals. M.p. 108 °C; Yield 65%; Calcd. for $C_{15}H_{22}N_2O_4S$ (326.42): C 55.20 H 6.74 N 8.58 Found C 54.93 H 6.55 N 8.49; $^1$H-NMR ($CDCl_3$): 0.86 (t, 3H, *J* 7 Hz); 1.22 (t, 3H, *J* 7 Hz); 2.96-3.15, 3.31-3.41, 3.63-3.77 (3m, 4H, $CH_2$); 3.72, 3.80 (2s, 6H, $OCH_3$); 4.20 (d, 1H, H-4, *J* 0.1 Hz); 4.39 (d, 1H, H-5, *J* 0.1 Hz); 6.90 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.19 (d, AB system, 2H, *J* 9 Hz, aryl-H). **8a** (4R*5S*): White crystals. M.p. 154-156 °C ; Yield 5%; Calcd. for $C_{15}H_{22}N_2O_4S$ (326.42): C 55.20 H 6.74 N 8.58 Found C

54.86 H 6.62 N 8.33; $^1$H-NMR ($CDCl_3$): 0.86 (t, 3H, *J* 7 Hz); 1.22 (t, 3H, *J* 7 Hz); 2.96-3.15, 3.25-3.41, 3.58-3.75 (3m, 4H, $CH_2$); 3.72, 3.80 (2s, 6H, $OCH_3$); 4.45 (d, 1H, H-4, *J* 8.4 Hz); 4.86 (d, 1H, H-5, *J* 8.4 Hz); 6.88 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.13 (d, AB system, 2H, *J* 9 Hz, aryl-H).

*3-Diethylamino-4,5-dihydro-5-ethoxy-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide:* **7b** (4S*5S*) : White crystals. M.p. 90 °C; Yield 75%; Calcd. for $C_{16}H_{24}N_2O_4S$ (340.44): C 56.47 H 7.06 N 8.23 Found C 56.11 H 7.02 N 8.46; $^1$H-NMR ($CDCl_3$): 0.84 (t, 3H, *J* 7 Hz); 1.22, 1.27 (2t, 6H, *J* 7 Hz); 3.00-3.29, 3.33-3.43, 3.58-3.78 (3m, 6H, $CH_2N$ and $CH_2O$); 3.79 (s, 3H, $OCH_3$); 4.20 (d, 1H, H-4, *J* 0.2 Hz); 4.48 (d, 1H, H-5, *J* 0.2 Hz); 6.90 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.19 (d, AB system, 2H, *J* 9 Hz, aryl-H). **8b** (4R*5S*): White crystals. M.p. 125-127 °C; Yield 10%; Calcd. for $C_{16}H_{24}N_2O_4S$ (340.44): C 56.47 H 7.06 N 8.23 Found C 56.10 H 7.01 N 8.58; $^1$H-NMR ($CDCl_3$): 1.09-1.90 (m, 9H); 2.98-3.18, 3.30-3.41, 3.62-3.79 (3m, 4H, $CH_2$); 3.80 (s, 3H, $OCH_3$); 3.92-4.04 (m, 2H, $OCH_2$); 4.43 (d, 1H, H-4, *J* 8.2 Hz); 4.95 (d, 1H, H-5, *J* 8.2 Hz); 6.89 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.12 (d, AB system, 2H, *J* 9 Hz, aryl-H).

*3-Diethylamino-4,5-dihydro-5-isopropoxy-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide:* **7c** (4S*5S*): White crystals. M.p. 121-123 °C; Yield 55%; Calcd. for $C_{17}H_{26}N_2O_4S$ (354.47): C 57.61 H 7.34 N 7.90 Found C 57.35 H 7.50 N 8.25; $^1$H-NMR ($CDCl_3$): 0.84 (t, 3H, *J* 7 Hz); 1.17 (t, 3H, *J* 7 Hz); 1.28 (d, 6H, *J* 6 Hz); 2.94-3.28; 3.22-3.49; 3.64-3.84 (3m, 4H, $CH_2$); 3.78 (s, 3H, $OCH_3$); 4.13 (sext, 1H, *J* 6 Hz); 4.14 (d, 1H, H-4, *J* 0.1 Hz); 4.57 (d, 1H, H-5, *J* 0.1 Hz); 6.88 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.15 (d, AB system, 2H, *J* 9 Hz, aryl-H). **8c** (4R*5S*): White crystals. M.p. 126 °C; Yield 3%; Calcd. for $C_{17}H_{26}N_2O_4S$ (354.47): C 57.61 H 7.34 N 7.90 Found C 56.89 H 7.41 N 8.18; $^1$H-NMR ($CDCl_3$): 0.86 (t, 3H, *J* 7 Hz); 1.02-1.61 (m, 9H); 2.98-3.24, 3.27-3.49, 3.59-3.82 (3m, 4H, $CH_2$); 3.79 (s, 3H, $OCH_3$); 4.00 (sext, 1H, *J* 6.5 Hz); 4.38 (d, 1H, H-4, *J* 8.4 Hz); 5.04 (d, 1H, H-5, *J* 8.4 Hz); 6.86 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.10 (d, AB system, 2H, *J* 9 Hz, aryl-H).

*3-Diethylamino-4,5-dihydro-4-(4-methoxyphenyl)-5-trifluoroacetylamino-isothiazole 1,1-dioxides **9** and **10**.*

Compound **1** (0.5 g, 1.7 mmol) was dissolved in $CH_3CN$ (5 mL). $CF_3CONH_2$ (0.38 g, 3.4 mmol), TEBA (0.041 g, 0.17 mmol), and anhydrous $K_2CO_3$ (0.47 g, 3.4 mmol) were added under stirring and the mixture was refluxed under nitrogen atmosphere. The reaction was

completed in 1 h (T.L.C. ethyl acetate/cyclohexane 3:7). The solvent was evaporated under reduced pressure and the mixture was taken up with water and neutralized with dilute HCl. Extraction with $CH_2Cl_2$ of the mixture afforded the two isomeric amides **9** and **10** which were separated by chromatography (ethyl acetate/cyclohexane 1:2). **9** (4S*5S*): Amorphous solid. M.p. 176-177 °C; Yield 65%; Calcd. for $C_{16}H_{20}F_3N_3O_4S$ (407.41): C 47.16 H 4.94 N 10.31 Found C 47.52 H 4.67 N 10.68; $^1$H-NMR ($CDCl_3$): 0.86 (t, 3H, *J* 7 Hz); 1.25 (t, 3H, *J* 7 Hz); 3.00-3.20, 3.20-3.48, 3.64-3.81 (3m, 4H, $CH_2$); 3.81 (s, 3H, $OCH_3$); 4.44 (d, 1H, H-4, *J* 0.2 Hz); 4.81 (dd, 1H, H-5, *J* 0.2, 5 Hz); 6.93 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.30 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.48 (d, 1H, NH, *J* 5 Hz). $^{19}$F-NMR ($CDCl_3$): –75.9. **10** (4R*5S*): Amorphous solid. M.p. 161 °C; Yield 27%; Calcd. for $C_{16}H_{20}F_3N_3O_4S$ (407.41): C 47.16 H 4.94 N 10.31 Found C 47.36 H 4.65 N 10.37; $^1$H-NMR ($CDCl_3$): 0.93 (t, 3H, *J* 7 Hz); 1.25 (t, 3H, *J* 7 Hz); 3.02-3.27, 3.36-3.50, 3.67-3.85 (3m, 4H, $CH_2$); 3.80 (s, 3H, $OCH_3$); 4.72 (d, 1H, H-4, *J* 9 Hz); 5.45 (dd, 1H, H-5, *J* 9 Hz, *J* 8 Hz); 6.33 (d, 1H, NH, *J* 8 Hz); 6.70 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.03 (d, AB system, 2H, *J* 9 Hz, aryl-H).$^{19}$F- NMR ($CDCl_3$): –73.6.

*General Procedure for the Synthesis of Mercapto-derivatives **11a, b, d, e.***

Compound **2** (50 mg, 0.13 mmol) was dissolved in $CH_2Cl_2$ (1 mL, some DMF was necessary in the case of sodium hydrogen sulfide) and the mercaptan **3a, b, e, f** (0.13 mmol) and equimolar amount of TEA (0.13 mmol, except in the case of sodium hydrogen sulfide) were added under stirring at room temperature. Stirring was continued until disappearance of the reactants (about 2-4 h, T.L.C. ethyl acetate/cyclohexane 2:3). The mixture was neutralized with dilute HCl and extracted with $CH_2Cl_2$. The organic layer was separated, dried over $Na_2SO_4$, filtered and the solvent was evaporated under reduced pressure. Chromatographic purification (ethyl acetate/cyclohexane 0:100⟶ 100:0) afforded compounds **11a, b, d, e** which were crystallized from $CH_2Cl_2$/diisopropyl ether (**11 b, d, e**) or $Et_2O$ (**11a**).

*3-Diethylamino-4-(4-methoxyphenyl)-5-methylsulfanyl-isothiazole 1,1-dioxide (**11a**):* White crystals. M.p. 174 °C; Yield 68%; Calcd. for $C_{15}H_{20}N_2O_3S_2$ (308.12): C 58.42 H 6.54 N 9.09 Found C 58.65 H 6.40 N 8.95; $^1$H-NMR ($CDCl_3$): 0.85 (t, 3H, *J* 7 Hz); 1.28 (t, 3H, *J* 7 Hz); 2.78 (s, 3H, $CH_3S$); 3.07-3.11, 3.58-3.61 (2m, 4H, $CH_2$); 3.85 (s, 3H, $OCH_3$); 6.98-7.27 (m, 4H, aryl-H).

*3-Diethylamino-4-(4-methoxyphenyl)-5-phenylsulfanyl-isothiazole 1,1-dioxide (**11b**)*: Yellow crystals. M.p. 128-130 °C; Yield 31%; Calcd. for $C_{20}H_{22}N_2O_3S_2$ (402.11): C 59.69 H 5.51 N 6.96 Found C 59.50 H 5.75 N 6.60; $^1$H-NMR ($CDCl_3$): 0.86 (t, 3H, *J* 7 Hz); 1.25 (t, 3H, *J* 7 Hz); 3.06-3.09; 3.55-3.59 (2m, 4H, $CH_2$); 3.86 (s, 3H, $OCH_3$); 7.00, 7.20 (2d, AB system, 4H, *J* 8.8 Hz, aryl-H); 7.30-7.40, 7.60-7.70 (2m, 5H, aryl-H).

*3-Diethylamino-4-(4-methoxyphenyl)-5-(pyridin-2-ylsulfanyl)-isothiazole 1,1-dioxide (**11d**)*: White crystals. M.p. 154 °C; Yield 73%; Calcd. for $C_{19}H_{21}N_3O_3S_2$ (403.10): C 56.56 H 5.25 N 10.42 Found C 56.40 H 5.14 N 10.22; $^1$H-NMR ($CDCl_3$): 0.90 (t, 3H, *J* 7 Hz); 1.28 (t, 3H, *J* 7 Hz); 3.12, 3.59 (2q, 4H, $CH_2$, *J* 7 Hz); 3.84 (s, 3H, $OCH_3$); 6.90 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.20-7.30 (m, 3H, aryl-H); 7.60-7.70 (m, 2H, aryl-H); 8.50-8.60 (m, 1H, aryl-H).

*3-Diethylamino-4-(4-methoxyphenyl)-5-(4-methylphenylsulfanyl)-isothiazole 1,1-dioxide (**11e**)* : White crystals. M.p. 121 °C; Yield 88%; Calcd. for $C_{21}H_{24}N_2O_3S_2$ (416.12): C 60.56 H 5.81 N 6.73 Found C 60.15 H 5.90 N 6.60; $^1$H-NMR ($CDCl_3$): 0.88 (t, 3H, *J* 6.6 Hz); 1.25 (t, 3H, *J* 6.6 Hz); 2.34 (s, 3H, $CH_3$); 2.90-3.20, 3.45-3.62 (2m, 4H, $CH_2$); 3.88 (s, 3H, $OCH_3$); 7.00 (d, AB system, 2H, *J* 8.7 Hz, aryl-H); 7.12 (d, AB system, 2H, *J* 8.3 Hz, aryl-H); 7.19 (d, AB system, 2H, *J* 8.7 Hz, aryl-H); 7.50 (d, AB system, 2H, *J* 8.3 Hz, aryl-H).

*3-Diethylamino-4-(4-methoxyphenyl)-5-thio-isothiazole 1,1-dioxide* (**11f**).

Compound **2** (186 mg, 0.5 mmol) was suspended in methanol (5 mL). Sodium hydrogen sulfide (74 mg, 1 mmol) in fine powder was added under stirring. The solution turned yellow and compound **2** disappeared (about 10 min, T.L.C. cyclohexane/ethyl acetate 1:1). Methanol was evaporated under reduced pressure and the mixture was taken up with ethyl acetate. After filtration of the precipitated salts and evaporation of the ethyl acetate, the crude mixture was crystallized from $CH_2Cl_2$ affording pure **11f**. Amorphous solid. M.p. 167 °C; Yield 67%; Calcd. for $C_{14}H_{18}N_2O_3S_2$ (326.07): C 51.52 H 5.56 N 8.59 Found C 51.75 H 5.41 N 8.20; $^1$H-NMR ($CDCl_3$): 0.98 (m, 6H, $CH_3$); 2.52 (q, 4H, $CH_2$); 3.77 (s, 3H, $OCH_3$); 6.95 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.10 (d, AB system, 2H, *J* 9 Hz, aryl-H). IR (nujol): 3450 $cm^{-1}$ (SH).

*5-Benzylsulfanyl-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide(**11c**).*

*Method A*: Compound **2** (50 mg, 0.13 mmol) was dissolved in $CH_2Cl_2$ (3 mL). Benzylmercaptan (0.024 mL, 0.2 mmol) and TEA (18 μL, 0.13 mmol) were added with stirring and the mixture was then refluxed. After 24 h the mixture was washed with dilute

HCl and then with a saturated solution of $NaHCO_3$. The organic layer was separated, dried over $Na_2SO_4$ and the solvent evaporated under reduced pressure, affording compound **11c** in a 12% yield.

*Method B*: Compound **11f** (109 mg, 0.31 mmol) was suspended in anhydrous $CH_3CN$ (3 mL) with stirring at room temperature. Benzyl bromide (56 mg, 0.33 mmol) was added and a white precipitate was immediately observed. After 30 min the precipitate was collected by filtration and thoroughly dried. Compound **11c** was obtained in 45% yield.

*Method C*: Compound **2** (74.6 mg, 0.2 mmol) was suspended in methanol (3 mL) and sodium hydrogen sulfide (74 mg, 1 mmol) was added. Complete dissolution of the reagents was observed. When compound **2** disappeared (T.L.C. cyclohexane/ethyl acetate 1:1) benzyl bromide was added (24 μL, 0.2 mmol). The reaction was complete in about 20 min. The precipitate so formed was collected and crystallized from $Et_2O$ affording **11c** in 79% yield.

**11c**: White crystals. M.p. 164 °C (dec.); Calcd. for $C_{21}H_{24}N_2O_3S_2$ (416.12): C 60.56 H 5.81 N 6.73 Found C 60.92 H 5.46 N 6.53; $^1$H-NMR ($CDCl_3$): 0.86 (t, 3H, *J* 7 Hz); 1.29 (t, 3H, *J* 7 Hz); 3.09, 3.63 (2q, 4H, *J* 7 Hz, $CH_2$); 3.81 (s, 3H, $OCH_3$); 4.71 (s, 2H, $CH_2Ar$); 6.95-7.32 (m, 9H, aryl-H).

*3-Diethylamino-4-(4-methoxyphenyl)-(2,6,10-trimethyl-undeca-1,5,9-trienylsulfanyl)-isothiazole 1,1-dioxide (**11g**)*: With method C, **11g** was obtained after chromatographic purification (ethyl acetate/cyclohexane) as an oil. Calcd. for $C_{28}H_{40}N_2O_3S_2$ (516.25): C 65.08 H 7.81 N 5.42 Found C 65.19 H 8.15 N 5.00; $^1$H-NMR ($CDCl_3$): 0.84 (m, 3H, $CH_3$); 1.25 (m, 3H, $CH_3$); 1.51-1.61 (m, 14H); 1.89-2.00 (m, 10H); 3.08, 3.58 (2q, 4H, $CH_2$); 3.81 (s, 3H, $OCH_3$); 4.14 (d, 2H, $CH_2S$); 5.19 (m, 2H); 5.23 (m, 1H); 6.97 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.16 (d, AB system, 2H, *J* 9 Hz, aryl-H).

*3-Diethylamino-4-(4-methoxyphenyl)-5-(4-methylbenzylamino)-isothiazole 1,1-dioxide (**14a**)*: Compound **2** (166 mg, 0.4 mmol) was dissolved in $CH_2Cl_2$ (7 mL) and 4-methyl-benzylamine (55 mg, 0.44 mmol) was added with stirring at room temperature. Stirring was continued until disappearance of the reactants (about 36 h, T.L.C. ethyl acetate/cyclohexane 7:3). The mixture was washed with dilute HCl and extracted with $CH_2Cl_2$. The organic layer was separated, dried over $Na_2SO_4$, filtered and the solvent was evaporated under reduced pressure. Compound **14a** was crystallized from ethanol. Amorphous solid. M.p. 139 °C; Yield 81%; Calcd. for $C_{22}H_{27}N_3O_3S$ (413.53): C 63.90 H 6.58 N 10.56 Found C 63.79 H 6.55

N 10.30; $^1$H-NMR ($CDCl_3$): 0.82-0.84 (m, 3H, $CH_3$); 1.25-1.28 (m, 3H, $CH_3$); 2.32 (s, 3H, $CH_3$); 3.02-3.06, 3.57-3.60 (2m, 4H, $CH_2$); 3.81 (s, 3H, $OCH_3$); 4.50-4.53 (bt, 1H, NH); 4.62-4.65 (m, 2H, $CH_2$); 6.69-7.26 (m, 8H, aryl-H).

*3-Diethylamino-5-dimethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**14b**)*:

Compound **2** (373 mg, 1 mmol) was dissolved in $CH_3OH$ (7 mL) and refluxed. Dimethylamine (146 mg, 2 mmol, 33% in ethanol) was added dropwise with stirring. Stirring at reflux was continued until disappearance of the reactants (about 2 h, T.L.C. ethyl acetate/cyclohexane 1:1). Solvent was evaporated and the crude mixture taken up with $CH_2Cl_2$, washed with dilute HCl and then with water. The organic layer was separated, dried over $Na_2SO_4$, filtered and the solvent was evaporated under reduced pressure. Compound **14b** was crystallized with $Et_2O$. White crystals. M.p. 150 °C (dec.); Yield 60%; Calcd. for $C_{16}H_{23}N_3O_3S$ (337.44): C 56.95 H 6.87 N 12.45 Found C 56.79 H 6.75 N 12.20; $^1$H-NMR (DMSO-$d_6$): 0.85-1.01 (m, 6H, $CH_3$); 2.82 (s, 6H, $NCH_3$); 3.00-3.53 (m, 4H, $CH_2$); 3.84 (s, 3H, $OCH_3$); 7.00 (d, AB system, 2H, *J* 9 Hz, aryl-H); 7.35 (d, AB system, 2H, *J* 9 Hz, aryl-H).

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