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Isothiazoles. Part 13: Synthesis of sulfamic esters, [1,2]thiazete *S*,*S*-dioxides, benzo[*e*][1,2]thiazine *S*,*S*-dioxides or triazoles by reaction of isothiazole dioxides with sodium azide

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Abstract—The reaction of NaN_3 with 5-substituted 3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxides is presented affording [2-cyano-1-diethylamino-2-(4-methoxyphenyl)-ethylidene]-sulfamic acid derivatives, 3-diethylamino-1,1-dioxo-4-(4-methoxyphenyl)-1,2-dihydro-[1,2]thiazete-4-carbonitrile, 3-diethylamino-7-methoxy-1,1-dioxo-1,4-dihydro-benzo[*e*][1,2]thiazine-4-carbonitrile or triazole derivatives. The outcome of the reaction strongly depends on the C-5 substituent and the correct choice of the reaction conditions allows direction of the reaction towards the formation of the sulfamic esters or the [1,2]thiazete carbonitrile or the triazoles in satisfactory yield.

1. 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 as precursors both of N- and/or S-containing heterocycles and of open chain compounds through ring opening reactions.[1–6] Furthermore, previous research has been devoted to a study of the reactivity at the double bond of several nucleophiles among which the azide ion appeared to be one of the most interesting.[7]

Here we report the results of a study of the reactivity of NaN_3 with isothiazole dioxides bearing different substituents at C-5. For this study we considered as starting materials 5-bromo-3-diethylamino-4-(4-methoxyphenyl)isothiazole 1,1-dioxide **1**, an isothiazole dioxide bearing an electron withdrawing substituent at C-5 which can act as a good leaving group, 3-diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide **2** an isothiazole dioxide bearing an electronwithdrawing substituent at C-5 with a medium ability as leaving group, 3-diethylamino-5-methylsulfanyl-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide **3** bearing a bad leaving group at C-5 and 3-diethylamino-4-(4-methylphenyl)-5-phenyl-isothiazole 1,1-dioxide **4** an example of isothiazole dioxide with a group at C-5 which can not act as a leaving group. The different outcomes of the reaction strongly depend on the C-5 substituent, the appropriate choice of the starting isothiazole dioxide, and changes in the reaction conditions allows direction of the reaction towards the formation of the sulfamic esters **6** or the [1,2]thiazete carbonitrile **8** or the triazoles **10** in satisfactory yield.

2. Results and discussion

5-Bromo-3-diethylamino-4-(4-methoxyphenyl)isothiazole 1,1-dioxide **1** was allowed to react with an equimolecular amount of NaN_3 (**5**) in refluxing methanol affording **6a** in satisfactory yield (77%). The same reaction performed in ethanol, 1-propanol or 2-propanol afforded **6b–d**, demonstrating the participation of the nucleophilic solvent in the reaction (Scheme 1). Compounds **6a–d** are very stable under prolonged heating or basic treatment (ROH/RO^-; ROH/NaN_3; CH_3CN/TEA). The structure of the compounds was confirmed by analytical and spectroscopic data. ^1H NMR spectra of **6a–d** are mainly characterized by a sharp singlet at about δ 6.60 associated with H-2 whose spatial proximity with the aromatic hydrogens was apparent from NOESY experiments. ^{13}C NMR spectra show, besides the signals associated with diethylamine and the 4-methoxy-substituted aryl group, the signals at about δ 36 associated with C-2 and at about δ 120 associated with CN. Definitive

Keywords: isothiazoles; sodium azide; [1,2]thiazete; sulfamic acid derivatives; benzo[*e*][1,2]thiazine.

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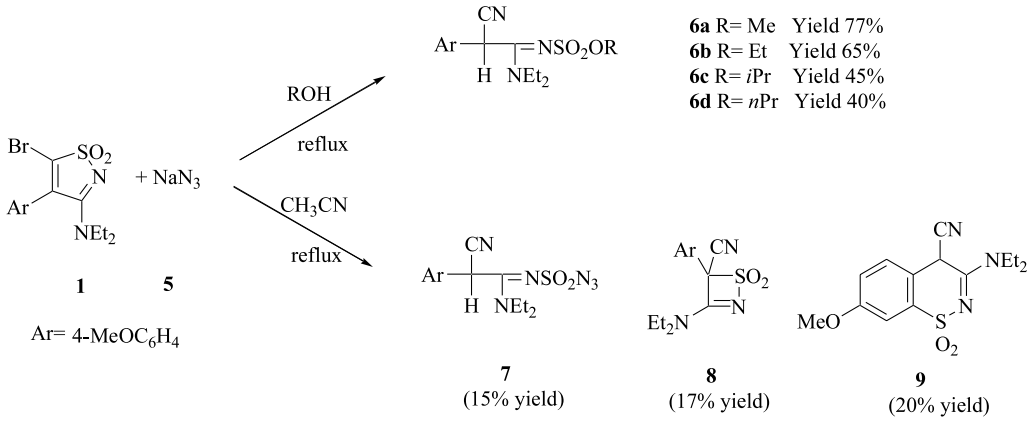


Scheme 1.

structural proof was obtained by X-ray diffraction on **6a** (Fig. 1).

This unexpected result appeared to be very interesting. To better understand the course of the reaction, compound **1** was allowed to react with **5** in several non-nucleophilic solvents (THF, dioxane, ethyl acetate, acetonitrile) and the best results were obtained in acetonitrile both at reflux or at room temperature. It has to be noted that in this case

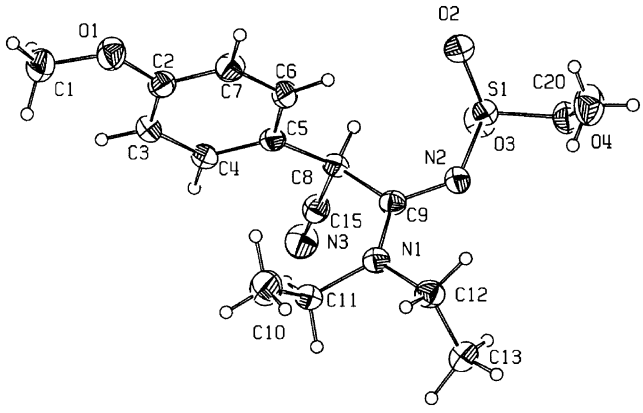


Figure 1. ORTEP plot of **6a**. Probability ellipsoids are drawn at 30% probability level. H atoms are represented by circles of arbitrary radius.

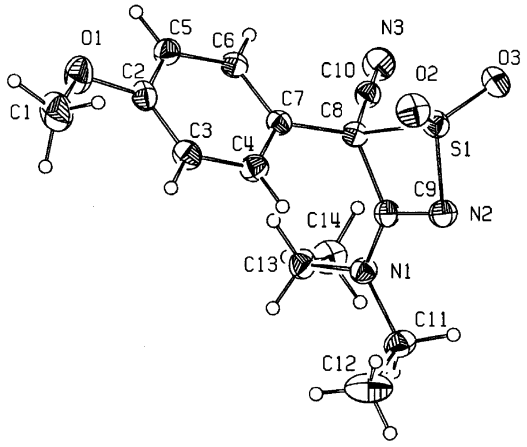


Figure 2. ORTEP plot of **8**. Probability level of ellipsoids and H atoms as in Fig. 1.

2 equiv. of **5** are required to complete the reaction. When performing the reaction in solvent at reflux, compounds **7**–**9** were obtained (Scheme 1). Compound **8** is derived from **7** as observed during the course of the reaction. Prolonged heating of the mixture resulted only in the disappearance of **7**, derivatives **8** and **9** being the sole final and thermally stable reaction products. The easy transformation of **7** into **8** was confirmed independently, by stirring pure **7** in CH_3CN at room temperature (several days) or in presence of a catalytic amount of TEA (10 min). The structures of the products were unequivocally established by analytical and spectroscopic data. The ^{1}H NMR spectrum of **7** is mainly characterized by a sharp singlet at δ 6.5 associated with H-2. The ^{13}C NMR spectrum shows, besides the signals associated with diethylamine and the 4-methoxy-substituted aryl group, the signals at δ 36 associated with C-2 and at δ 120 associated with CN. The main feature of compound **8** with respect to **7** is the absence of the singlet at δ 6.5 (^{1}H NMR) and of the signal at δ 36 (^{13}C NMR) and the presence of a signal associated with a quaternary carbon at δ 86 (^{13}C NMR). In the ^{1}H NMR spectrum of **9** only three aromatic hydrogens are evident (H-6: δ 7.05, dd, J=8.4, 2.6 Hz; H-5: δ 7.40, d, J=8.4 Hz; H-8: δ 7.6, d, J=2.6 Hz). X-Ray diffraction was performed on **8** and **9** definitively confirming their structures (Figs. 2 and 3).

To evaluate the real importance of the substituent on C-5 for the course of the reaction, we performed the reaction on **2**–**4** in acetonitrile as the solvent (Schemes 2 and 3). It has to be

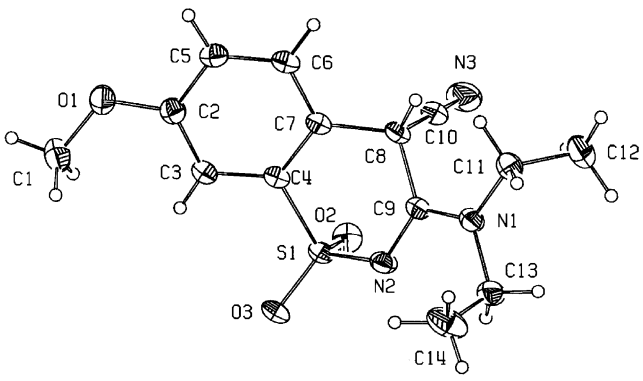
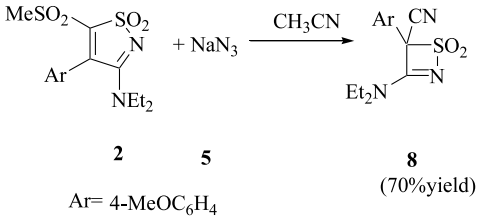
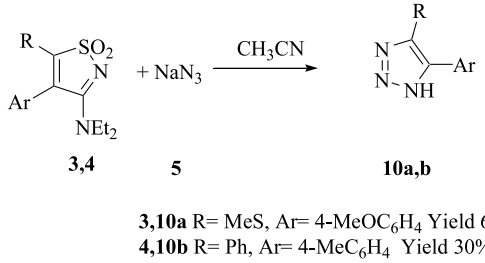


Figure 3. ORTEP plot of **9**. Probability level of ellipsoids and H atoms as in Fig. 1.



Scheme 2.

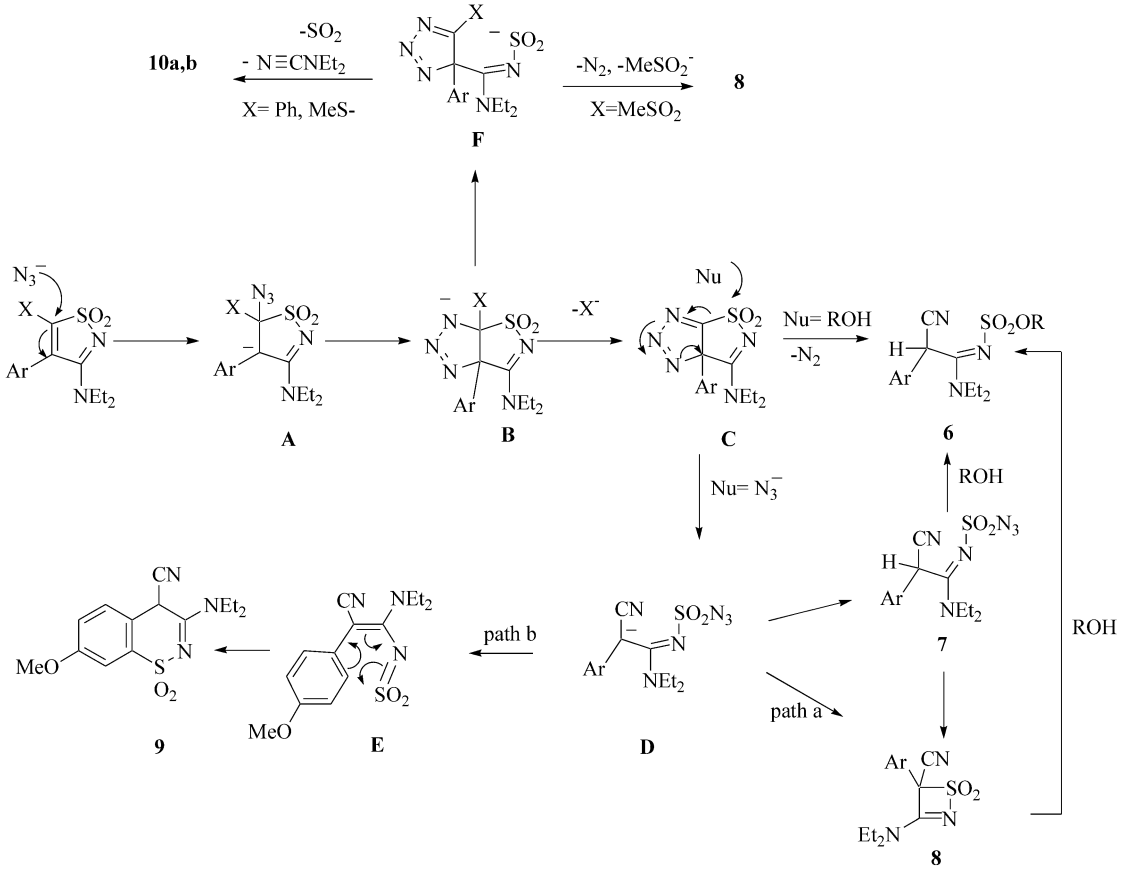


Scheme 3.

noted that in the former case, the reaction proceeded very quickly even at room temperature (15 min) and with 1 equiv. of NaN_3 affording as the sole stable reaction product compound **8** in a very good yield (70%), derivatives **7** and **9** being not detectable. In the case of compounds **3** and **4**, a different outcome was observed, compounds **10a** and **10b** being obtained as the main reaction products (60 and 30%, yield, respectively).

The above results allow the formation of a mechanistic model as depicted in Scheme 4.

Nucleophilic addition of the azide ion to C-5 followed by ring closure affords the triazoline anion **B**. In the case of compound **1**, bearing a good leaving group at C-5, the formation of the triazole-isothiazole ring **C** through intermediate **B** could be hypothized through elimination of bromide. Opening of the bicyclic system through nucleophilic attack of the azide ion to the electrophilic sulfur atom and loss of nitrogen from the triazole moiety afford **D** which could be easily protonated to **7** or directly cyclized intramolecularly (pathway a) to **8**. The formation of **9** could be explained through pathway (b) in which the reactive intermediate **E**, obtained by N_3^- elimination, was transformed into **9** by electrocyclic ring closure. Since electrocyclic reactions are thermally favored, in order to confirm our hypothesis the same reaction was performed in acetonitrile at room temperature (72 h).[8] As expected, adopting these conditions compound **9** apparently was not formed in detectable amount (TLC, ^1H NMR). The same mechanistic picture could be invoked for the formation of **6a–d**. The ring opening of **C** is effected by the nucleophilic solvent (methanol, ethanol, etc.) with formation of the sulfamic esters. It has to be noted that treatment of **7** or **8** with methanol and a basic catalyst (sodium methoxide or NaN_3 or TEA) resulted quantitatively in the formation of **6a**. This picture is in accordance with previously observed transformation reactions of bicyclic isothiazole dioxide system whose thermal instability has already been described.[5]



Scheme 4.

In the case of compound **2**, we could hypothesize that the common intermediate **B** undergoes ring opening by cleavage of the isothiazole ring affording an unstable 4*H*-triazole **F** from which, through intramolecular cyclization and loss of nitrogen and SO_2Me group, compound **8** could be formed. From this picture, the role of the substituent on C-5 in directing the reaction is apparent. In fact, the presence of a group characterized by a poorer leaving ability than bromide favors the opening of the isothiazole ring. For **3** and **4** we could hypothize a similar pathway affording the same intermediate **F** from which elimination of SO_2 and diethylcyanamide affords **10a**,**b**. In this case the more stable triazole intermediate **F** is less prone to cleavage taking into account the presence on C-4 of the phenyl group which can not act as a leaving group. Furthermore the more drastic conditions adopted (long time, reflux) make easier the elimination of SO_2 and diethylcyanamide as already noted in previously published papers.[3]

3. Structures

Crystalline samples of compounds **6a**, **8** and **9** were selected for the X-ray diffraction experiments at room temperature. To our knowledge, **8** is the second thiazete *S*,*S* dioxide whose geometry has been determined by X-ray diffraction (the first having been published in 1996, by Clerici et al.[5]), while **9** is the first benzo[*e*][1,2]thiazine *S*,*S* dioxide characterized by X-ray diffraction.

(**6a**): Fig. 1 shows the ORTEP[9] plot of the molecule with the numbering scheme. The $-SO_2OMe$ group has *cis* (*Z*) geometry across the N=C bond with respect to the 1-cyano-1-(4-methoxyphenyl)methyl substituent. The C9=N2 distance, 1.307(3) Å, compares very well with the value of 1.302(21) Å reported in the literature[10] for this kind of bond, while the C9–N1 one is significantly shorter (1.337(3) vs 1.355(14) Å from the literature[10]). This fact could suggest the existence of some conjugation in the amidine moiety: support for this hypothesis also comes from the marked planarity observed around the nitrogen atom of the diethylamino substituent (the sum of bond angles around N1 amounts to 359.9°) and from the values of torsion angles N2–C9–N1–C12, t=2.7(2)°, and C12–N1–C9–C8, t=−3.3(1)°.

Two O···H and two N···H intermolecular contacts shorter than the sum of the van der Waals radii are present in the crystal, all involving atoms of symmetry related molecules. The O···H distances are in the range 2.50(2)–2.63(2) Å, while both the N···H intermolecular contacts amount to 2.77(2) Å.

(**8**): The ORTEP[9] plot of **8** is shown in Fig. 2. In the present case, the asymmetric unit contains only one independent molecule (instead of two in Ref. 5) and no evidence of disorder in the molecule has been detected. S–O distances compare well both with the values reported in Ref. 5 (1.431(3) and 1.433(3) Å) and with an average value of 1.430(9) for the same bond in several sulfonamides found in the literature.[11]

As in **6a**, marked planarity is observed around the nitrogen atom of the diethylamino group (sum of bond angles at N1 amounts to 360.0°); the exocyclic C9–N1 bond is remarkably short (1.317(2) Å), if compared with an average value of 1.355(14) Å for this kind of CN bond in the literature[10]; besides, torsion angles close to zero are observed for N2–C9–N1–C11, t=2.4(2)°, and N2–C9–N1–C13, t=−2.4(2)°. These findings again give evidence of significant conjugation in the amidine moiety and are in perfect agreement with the findings in Ref. 5.

Only one N···H intermolecular contact shorter than the sum of the Van der Waals radii is present in the crystal: it involves atom N2 in x, y, z and atom H3 in $1/2-x$, $1/2+y$, $1/2-z$ and amounts to 2.74(2) Å. No short O···H intermolecular contacts are observed.

(**9**): The ORTEP[9] plot of the molecule with the numbering scheme is shown in Fig. 3. As in **6a** and **8**, some conjugation in the amidine moiety is observed: considerable planarity is indeed found around the nitrogen atom of the diethylamino group (sum of bond angles at N1 amounts to 359.6°), together with very similar values for the exocyclic C9–N1 bond (1.323(3) Å) and the C9=N2 bond, 1.313(2) Å, and with torsion angles around the exocyclic C9–N1 bond close to zero (N2–C9–N1–C13, t=1.6(2)°, and C8–C9–N1–C13, t=−1.7(2)°). The fused system is not completely planar: the heterocycle in compound **9** is in an enevelope conformation with atoms N2 and C9 at 0.918(2) and 0.904(2) Å, respectively, from the least-squares plane through atoms C2, C3, C4, C5, C6, C7, C8 and S1.

Two O···H intermolecular contacts shorter than the sum of the van der Waals radii are present in the crystal, involving atoms of symmetry related molecules and with O···H distances in the range 2.46(2)–2.62(2) Å.

4. Conclusions

In conclusion, the isothiazole dioxide moiety has been confirmed to be a very reactive species and a suitable starting material for the synthesis of various heterocycles and/or open chain compounds. In particular, by choosing the appropriate reaction conditions (solvent, amount of NaN_3) and the reagent (**1**, **2**, **3** or **4**) satisfactory yields of [2-cyano-1-diethylamino-2-(4-methoxyphenyl)-ethylidene]-sulfamic acid esters **6a**–**d** or 3-diethylamino-1,1-dioxo-4-(4-methoxyphenyl)-1,2-dihydro-[1,2]thiazete-4-carbonitrile **8** or 4-substituted 5-aryltriazoles **10a**,**b** could be obtained.

5. Experimental

^1H NMR spectra were obtained in $CDCl_3$ as the solvents with Bruker AC 200, Bruker Avance 300 and Varian Gemini 200 instruments. Melting points were determined using a Büchi 510 (capillary) or an Electrothermal 9100 apparatus. IR spectra were recorded on a Jasco IR report 100 spectrophotometer. Mass spectra were obtained by electron impact ionisation at 70 eV from a Finnigan INCOS 50 instrument using the direct exposure probe (DEP).

5.1. X-Ray data

For compound (**6a**), the only crystalline sample suitable for the data collection was very small, bigger samples always presented some degree of gemination. For this reason, the X-ray experiment on (**6a**) was performed on a diffractometer equipped with an area-detector (CCDC, see Table 1), which allows collection of a great amount of data in a very short time. For each compound, the intensities of three standard reflections were periodically re-measured, revealing no significant decay in the course of data collections. Intensities were corrected for Lorentz and polarization, but not for decay nor absorption. The structures were solved by direct methods, employing program SHELXL86.[12] Refinements were conducted with program SHELXL93.[13] All the independent reflections were fitted. Positional parameters were varied for all the nuclei: non-H atoms were refined anisotropically, hydrogen atoms isotropically. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 179040–179042. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.

Compounds **1**,[14] **3**,[15] **4**,[2] **10a**[16] are known.

5.1.1. Diethyl-[5-methanesulfonyl-4-(4-methoxyphenyl)-1,1-dioxo-isothiazol-3-yl-]amine 2. 3-Diethylamino-4-(4-methoxyphenyl)-5-methylsulfanyl-isothiazole 1,1-dioxide[15] (440 mg, 1.29 mmol) was dissolved in dichloromethane (10 mL) and *m*-chloroperbenzoic acid (490 mg, 2.84 mmol) was added in one portion. The mixture was stirred at room temperature for 12 h. The benzoic acid precipitated was filtered off and the filtrate washed with $NaHCO_3$ (20%, 3 mL) and then twice with water (3 mL each). The organic layer was separated, dried with Na_2SO_4 and evaporated to dryness affording **2**.

2: Yield 71%. Mp 159–161°C (white powder from diethyl ether). ^{1}H NMR (δ) 0.90 (t, 3H, J=6.9 Hz, CH_3), 1.30 (t, 3H, J=6.9 Hz, CH_3), 3.10 (q, 2H, J=6.9 Hz, CH_2), 3.18 (s, 3H, SO_2CH_3), 3.70 (q, 2H, J=6.9 Hz, CH_2), 3.88 (s, 3H, Ar-OCH_3), 7.00 (AB syst., J_{AB}=8.8 Hz, 2H, aryl-H), 7.33 (AB syst., J_{AB}=8.8 Hz, 2H, aryl-H); ^{13}C NMR 11.7, 14.2, 44.1, 44.2, 47.9, 55.4, 109.8, 114.7, 120.0, 129.2, 142.3, 158.5, 161.4. Calcd for $C_{15}H_{20}N_2O_5S_2$ (372.46) C 48.38, H 5.41, N 7.52; found C 48.22, H 5.45, N 7.35. *m/z* 372 (M+).

5.1.2. [2-Cyano-1-diethylamino-2-(4-methoxyphenyl)-ethylidene]-sulfamic acid esters 6a–d. Compound **1** (373 mg, 1 mmol) was suspended under stirring in the appropriate alcohol (5 mL) and NaN_3 (**5**) (65 mg, 1 mmol) was added in one portion. The reaction proceeded quickly in refluxing solvent (about 2–4 h), but could also be performed at room temperature (e.g. with ethanol at 25°C, 72 h, TLC: AcOEt/cyclohexane, 1:1). At the end of the reaction the solvent was evaporated under reduced pressure and the residue was taken up with dichloromethane (20 mL) and washed twice with water (10 mL each). The organic layer, separated and dried under Na_2SO_4, was evaporated and the residue crystallized with diethyl ether affording pure **6a–d**.

6a: Yield 77%. Mp 95°C (white powder from diethyl ether). IR (nujol) cm^{-1} 2300–2350 (feeble, CN), 1580; ^{1}H NMR (δ) 0.90 (t, 3H, J=6.9 Hz, CH_3), 1.25 (t, 3H, J=6.9 Hz, CH_3), 3.30–3.40; 3.50–3.60 (2m, 4H, CH_2), 3.84 (s, 3H, Ar-OCH_3), 3.98 (s, 3H, SO_2OCH_3), 6.59 (s, 1H, H-2), 7.00 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H), 7.37 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H); ^{13}C NMR 11.7, 12.6, 37.1, 44.5, 44.8, 55.8, 57.2, 115.5, 115.6, 121.8, 127.9, 159.2, 160.4. Calcd for $C_{15}H_{21}N_3O_4S$ (339.41) C 53.08, H 6.24, N 12.38; found C 53.08, H 6.26, N 12.30. *m/z* 339 (M+).

6b: Yield 65%. Mp 89–90°C (white powder from diisopropyl ether). IR (nujol) cm^{-1} 2350 (feeble, CN), 1570; ^{1}H NMR (δ) 0.90 (t, 3H, J=6.9 Hz, CH_3), 1.25 (t, 3H, J=6.9 Hz, CH_3), 1.44 (t, 3H, J=6.9 Hz, OCH_2CH_3), 3.30–3.43; 3.47–3.62 (2m, 4H, CH_2), 3.84 (s, 3H, Ar-OCH_3), 4.40 (q, 2H, J=6.9 Hz, OCH_2CH_3), 6.60 (s, 1H, H-2), 7.00 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H), 7.37 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H); ^{13}C NMR 11.3, 12.2, 14.9, 36.7, 44.1, 44.3, 55.5, 67.3, 115.1, 115.3, 121.4, 127.5, 158.7, 159.9. Calcd for $C_{16}H_{23}N_3O_4S$ (353.44) C 54.37, H 6.56, N 11.89; found C 54.16, H 6.50, N 11.60. *m/z* 353 (M+).

6c: Yield 45%. Mp 76–77°C (white powder from dichloromethane/hexane). IR (nujol) cm^{-1} 2300–2350 (feeble, CN), 1578; ^{1}H NMR (δ) 0.87 (t, 3H, J=7.0 Hz, CH_3), 1.23 (t, 3H, J=7.0 Hz, CH_3), 1.46 (d, 6H, J=6.5 Hz, CH_3), 3.32–3.37; 3.45–3.57 (2m, 4H, CH_2), 3.84 (s, 3H, Ar-OCH_3), 4.94 (sept, 1H, J=6.5 Hz, CH), 6.59 (s, 1H, H-2), 6.96 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H), 7.38 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H); ^{13}C NMR 11.3, 12.2, 22.8, 22.9, 36.7, 43.9, 44.3, 55.5, 77.4, 115.1, 115.4, 121.6, 127.6, 158.7, 159.9. Calcd for $C_{17}H_{25}N_3O_4S$ (367.46) C 55.57, H 6.86, N 11.44; found C 55.87, H 7.02, N 11.15. *m/z* 367 (M+).

6d: Yield 40%. Mp 75–77°C (white powder from diisopropyl ether). IR (nujol) cm^{-1} 2356 (feeble, CN), 1575; ^{1}H NMR (δ) 0.88 (t, 3H, J=7.0 Hz, CH_3), 1.03 (t, 3H, J=7.3 Hz, CH_3), 1.24 (t, 3H, J=7.0 Hz, CH_3), 1.75–1.85 (m, 2H, CH_2), 3.30–3.65 (2m, 4H, CH_2), 3.83 (s, 3H, Ar-OCH_3), 4.25 (t, 2H, J=7.3 Hz, OCH_2), 6.60 (s, 1H, H-2), 6.98 (AB syst., J_{AB}=8.7 Hz, 2H, aryl-H), 7.40 (AB syst., J_{AB}=8.7 Hz, 2H, aryl-H); ^{13}C NMR 10.2, 11.3, 12.2, 22.5, 36.7, 44.1, 44.3, 55.5, 72.7, 115.1, 115.3, 121.4, 127.5, 158.7, 159.9. Calcd for $C_{17}H_{25}N_3O_4S$ (367.46) C 55.57, H 6.86, N 11.44; found C 55.30, H 7.00, N 11.55. *m/z* 367 (M+).

5.2. Reaction of 1 and 5 in CH_3CN

Compounds **1** (373 mg, 1 mmol) and **5** (130 mg, 2 mmol) were suspended in CH_3CN (5 mL) and heated to reflux. The reaction was checked by TLC (50 min; TLC: AcOEt/cyclohexane, 3:2). The solvent was evaporated i.v., the residue taken up with dichloromethane (20 mL), washed twice with water (10 mL each) and the two layers were separated. The organic layer was dried over Na_2SO_4, and the solvent evaporated to dryness affording a mixture of **7** and **8** which could be separated by column chromatography on silica gel (cyclohexane/AcOEt, 100:0–0:100). The aqueous layer was acidified with HCl (2 mL, 10%, Congo red) and extracted with dichloromethane. The organic layer was

dried over Na_2SO_4, and the solvent evaporated to dryness affording pure **9**.

5.3. Reaction of 2 and 5 in CH_3CN

Compounds **2** (100 mg, 0.27 mmol) and **5** (17.4 mg, 0.27 mmol) were suspended in CH_3CN (5 mL) and stirred at room temperature. The reaction was checked by TLC (about 2 h; TLC: AcOEt/cyclohexane, 3:2). The solvent was evaporated i.v., the residue taken up with dichloromethane (20 mL), washed twice with water (10 mL each). The organic layer was dried over Na_2SO_4 and the solvent evaporated to dryness affording **8** (70% yield) which could be crystallized from dichloromethane/diethyl ether.

5.3.1. Compound 7. Yield: 15%. Mp 83°C (crystallizes very slowly as white powder from diethyl ether). IR (nujol) cm^{-1} 2060–2100; ^1H NMR (δ) 0.90 (t, 3H, J=7.0 Hz, CH_3), 1.30 (t, 3H, J=7.0 Hz, CH_3), 3.30–3.50; 3.55–3.75 (2m, 4H, CH_2), 3.85 (s, 3H, OCH_3), 6.50 (s, 1H, H-2), 7.00 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H), 7.35 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H); ^{13}C NMR 11.3, 12.0, 36.6, 44.9, 55.5, 114.9, 115.4, 121.9, 127.5, 159.5, 160.2. Calcd for $C_{14}H_{18}N_6O_3S$ (350.40) C 47.99, H 5.18, N 23.98; found C 47.80, H 5.25, N 23.77. *m/z* 351 (M+1); 322 (M−28), 308 (M−42).

5.3.2. Compound 8. Yield 17%. Mp 121°C (white powder from diethyl ether). IR (nujol) cm^{-1} 2246 (CN); ^1H NMR (δ) 1.13 (t, 3H, J=7.2 Hz, CH_3), 1.35 (t, 3H, J=7.2 Hz, CH_3), 3.11–3.24; 3.28–3.48; 3.48–3.75 (3m, 4H, CH_2), 3.89 (s, 3H, OCH_3), 7.06 (AB syst., J_{AB}=8.9 Hz, 2H, aryl-H), 7.47 (AB syst., J_{AB}=8.9 Hz, 2H, aryl-H); ^{13}C NMR 11.6, 12.9, 42.4, 45.5, 55.6, 86.6, 111.4, 115.4, 116.9, 128.7, 161.1, 162.0. Calcd for $C_{14}H_{17}N_3O_3S$ (307.37) C 54.71, H 5.57, N 13.67; found C 54.82, H 5.62, N 13.54. *m/z* 307 (M+); 243 (M−64).

5.3.3. Compound 9. Yield 20%. Mp 173°C (white powder from diethyl ether). IR (nujol) cm^{-1} 2300 (feeble CN), 1602, 1578; ^1H NMR (δ) 1.20–1.45 (m, 6H, CH_3), 3.40–3.65 (2m, 4H, CH_2), 3.90 (s, 3H, OCH_3), 5.05 (s, 1H), 7.05 (dd, 1H, J=8.4 Hz, J=2.6 Hz, aryl-H), 7.40 (d, 1H, J=8.4 Hz, aryl-H), 7.60 (d, 1H, J=2.6 Hz, aryl-H). ^{13}C NMR 12.7, 43.3, 45.0, 54.3, 104.3, 117.1, 122.4, 122.6, 126.7, 130.0, 153.8, 161.2. Calcd for $C_{14}H_{17}N_3O_3S$ (307.37) C 54.71, H 5.57, N 13.67; found C 54.62, H 5.75, N 13.45. *m/z* 307 (M+); 292 (M−15).

5.4. Reaction of 3, 4 and 5 in CH_3CN

Compounds **3** or **4** (0.3 mmol) and **5** (40 mg, 0.6 mmol) were suspended in CH_3CN (5 mL) and brought to reflux. The reaction was checked by TLC until disappearance of the starting material. The solvent was evaporated i.v., the residue taken up with dichloromethane (20 mL), washed twice with water (10 mL each). The organic layer was dried over Na_2SO_4, and the solvent evaporated to dryness affording **10a**, **b** which could be purified by column chromatography on silica gel (cyclohexane/AcOEt, 100:0–0:100).

5.4.1. Compound 10a. Yield 60%. Oil. IR (nujol) cm^{-1} 3000–3200 (NH); ^1H NMR (δ) 2.59 (s, 3H, CH_3), 3.86 (s, 3H, Ar-OCH_3), 7.00 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H), 7.84 (AB syst., J_{AB}=8.6 Hz, 2H, aryl-H), 13.5 (bs, 1H, NH); ^{13}C NMR 16.6, 55.4, 114.3, 122.1, 128.6, 139.4, 143.8, 160.0. Calcd for $C_{10}H_{11}N_3OS$ (221.28) C 54.28, H 5.01, N 18.99; found C 54.01, H 5.22, N 18.78. *m/z* 221 (M+).

5.4.2. Compound 10b. Yield 30%. Mp 126°C (lit.[16] 128–130°C). ^1H NMR (δ) 2.40 (s, 3H, CH_3), 7.19 (AB syst., J_{AB}=7.8 Hz, 2H, aryl-H), 7.37–7.40 (m, 3H, aryl-H), 7.46 (AB syst., J_{AB}=7.8 Hz, 2H, aryl-H), 7.57–7.61 (m, 3H, aryl-H), 8.2 (bs, 1H, NH).

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References

1. Clerici, F.; Gelmi, M. L.; Soave, R.; Valle, M. *Tetrahedron* **1998**, *54*, 11285–11296.
2. Clerici, F.; Ferrario, T.; Gelmi, M. L.; Marelli, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2533–2536.
3. Baggi, P.; Clerici, F.; Gelmi, M. L.; Mottadelli, S. *Tetrahedron* **1995**, *51*, 2455–2466.
4. Clerici, F.; Ferraris, F.; Gelmi, M. L. *Tetrahedron* **1995**, *51*, 12351–12362.
5. Clerici, F.; Galletti, F.; Pocar, D.; Roversi, P. *Tetrahedron* **1996**, *52*, 7183–7200.
6. Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 14975–14984.
7. Carugo, O.; Clerici, F.; Pocar, D. *Tetrahedron* **1993**, *49*, 9117–9126.
8. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976 pp 86–181.
9. Johnson, C. K.; Burnett, M. N. ORTEPIII Version 1.0.2, 1996, ORNL-6895.
10. Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.
11. Wilson, A. J. C., Ed.; *International Tables for X-ray Crystallography*, Kluwer Academic: Dordrecht, 1995; Vol. C, p. 701.
12. Sheldrick, G. M. *SHELXS-86*: *Program for the Solution of Crystal Structures*; University of Göttingen: Germany, 1985.
13. Sheldrick, G. M. *SHELXL-93*: *Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1993.
14. Clerici, F.; Erba, E.; Gelmi, M. L.; Valle, M. *Tetrahedron* **1997**, *53*, 15859–15866.
15. Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 2001–2012.
16. Suzuki, H.; Nakaya, C.; Matano, Y. *Tetrahedron Lett.* **1993**, *34*, 1055–1056.