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Synthesis of novel 6,7-dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxides

Cyrille Landreau, David Deniaud,* Alain Reliquet and Jean Claude Meslin

Laboratoire de Synthèse Organique, UMR CNRS 6513, Faculté des Sciences et des Techniques, 2, Rue de la Houssinière, BP 92 208, F-44322 Nantes Cedex 03, France

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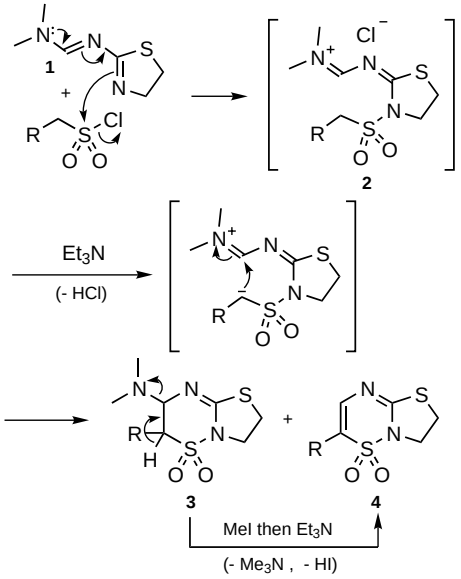
Abstract—A mild synthesis of 6,7-dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxides involving a thiazolinic diazadiene and sulfonyl chlorides is reported. Full characterisation of these novel cyclic sulfonamides is described.

Cyclic sulfonamides are a class of compounds displaying promising chemotherapeutic potentials. Among these, 1,2,4-benzothiadiazine 1,1-dioxides are known to possess diuretic and antihypertensive properties.[1] The bioisosteric replacement of the benzene ring with a pyridine nucleus,[2] principally investigated by Pirotte et al.,[3] has led to the preparation of novel potassium channel openers (PCOs), acting selectively on pancreatic endocrine tissue or vascular smooth muscle cells. Furthermore, Vega et al.[4] have described the synthesis and antiviral activity of 1,2,4-thiadiazine 1,1-dioxide derivatives fused to a thiophene nucleus. Such compounds have been successfully assessed for their antihypertensive properties as voltage-dependent calcium channel blockers.[5]



Scheme 1. Synthesis of 6,7-dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxides **4a**,**b**.

Other differently fused 1,2,4-thiadiazine 1,1-dioxides have been evaluated,[6] and on the other hand, many condensed thiazoles have been found to display significant biological activities.[7] We consequently thought that the combination of both these heterocycles might be interesting from a biological aspect.

In a previous paper,[8] we have shown that *N*′-(4,5-dihydrothiazol-2-yl)-*N*,*N*-dimethylamidines were suitable substrates for the synthesis of a wide range of imidazo[2,1-*b*]thiazole and thiazolo[3,2-*a*]pyrimidine derivatives. Following a similar synthetic strategy, we now wish to report the synthesis and characterisation of 6,7-dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxides, the first examples of compounds in this cyclic sulfonamides family.

We have recently reported that reaction between amidines such as **1** and carboxylic acid chlorides gave 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one derivatives.[8] According to these earlier experiments, we found that formamidine **1** reacted with methane or ethanesulfonyl chlorides to give the salts **2** (non-isolated), which on treatment with triethylamine underwent cyclization. In this case, how-

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* Corresponding author. Tel.: +33-2-51-12-54-57; fax: +33-2-51-12-54-02; e-mail: david.deniaud@chimie.univ-nantes.fr

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ever, a mixture of the required final product **4** together with its aminated precursor **3** was obtained (Scheme 1). Completion of the reaction was accomplished by filtration of the mixture through a short pad of silica gel followed by treatment with methyl iodide, which effected exclusively the dimethylamino group of the cycloadduct **3**. The resulting quaternary salt was thus easier deaminated in the presence of triethylamine and the corresponding 6,7-dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxides **4a**,**b** were finally isolated by a second chromatography, albeit in modest yields.[9] Moreover, attempts to improve these results by involving sulfenes, generated by dehydrohalogenation of the corresponding sulfonyl chlorides, in a [4+2] cycloaddition reaction with amidines **1** were unsuccessful.

Both compounds **4a**,**b** were unambiguously characterized by spectroscopic techniques.[10] In addition to reasonable IR absorptions at 1308 and 1156 cm^{-1} (**4a**), 1300 and 1148 cm^{-1} (**4b**) (SO_2 asym. and sym. Str.), EIMS showed the expected molecular ion peaks at *m*/*z* 190 (**4a**) and 204 (**4b**) together with the peaks at *m*/*z* 126 and 140 ascribed to the loss of sulfur dioxide. Notable features in the ^1H NMR spectra of both compounds **4a** and **4b** were the downfield shifts (approximately 0.7 ppm) observed in the resonance of NCH_2 in passing from quite similar 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines[8] to 6,7-dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxides **4**, consistent with the proximity of the sulfonamide function. Furthermore, definitive proof of the structure of compound **4b** was given by a single-crystal X-ray determination (Fig. 1).[11]

In summary, 6,7-dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxides **4a**,**b** were smoothly prepared by condensation of *N*′-(4,5-dihydrothiazol-2-yl)-*N*,*N*-dimethylformamidine with sulfonyl chlorides. To our knowledge, these heterocycles represent the first examples in this sulfonamides class. Furthermore, these compounds are expected to be employed as the starting materials for the synthesis of biologically active compounds.

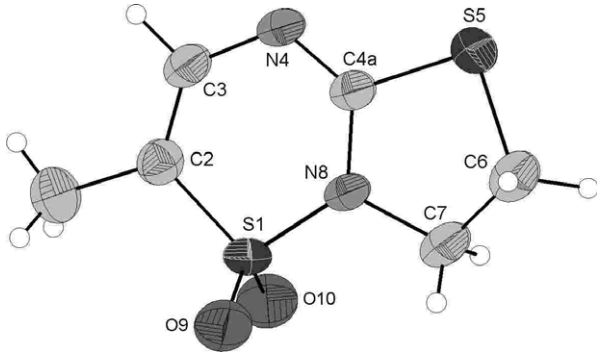

Figure 1. ORTEP view of 2-methyl-6,7-dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxide **4b**.

Acknowledgements

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9. Experimental procedure: To a solution of amidine **1** (2 mmol) in CH_2Cl_2 (10 mL) was added methane (for **4a**) or ethanesulfonyl chloride (for **4b**) (2.4 mmol), the reaction mixture was then stirred at rt for 4 h. After cooling to 0°C, Et_3N (4.8 mmol) was added and the reaction mixture was further stirred at rt for 16 h, then concentrated in vacuo. The residue was diluted with CH_2Cl_2 and filtered through a short pad of silica gel using as eluant CH_2Cl_2/EtOAc (1:1). The mixture of compounds **3** and **4** was then treated with a solution of MeI (2 mL) in THF (5 mL). After stirring at rt for 5 days, the reaction mixture was evaporated to dryness and a solution of Et_3N (1 mL) in CH_2Cl_2 (10 mL) was added to this. Stirring was continued at rt for 2 days and the solvent was removed. The resulting residue was diluted with CH_2Cl_2 and chromatographed (CH_2Cl_2/EtOAc, 5:1 for **4a**, 9:1 for **4b**). Compounds **4a** and **4b** were crystallized from Et_2O in 41 and 33% yield, respectively.

10. 6,7-Dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxide **4a**: White crystals; mp 210°C; IR (KBr): $\nu = 1576$, 1504, 1308, 1156 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.42 (t, 2H, *J* 7.3 Hz, SCH_2), 4.44 (t, 2H, *J* 7.3 Hz, NCH_2), 6.20 (d, 1H, *J* 7.9 Hz, $CHSO_2$), 7.18 (d, 1H, *J* 7.9 Hz, NCH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 26.9 (SCH_2), 48.1 (NCH_2), 106.8 ($CHSO_2$), 146.0 (NCH), 167.9 (SCN); MS (EI) m/z (%) = 190 (M^+, 100), 126 (54), 98 (9), 80 (15), 60 (45); anal. calcd for $C_5H_6N_2O_2S_2$ (190.2): C, 31.57; H, 3.18; N, 14.73. Found: C, 31.69; H, 3.34; N, 14.86%.

2-Methyl-6,7-dihydrothiazolo[32*b*]-1,2,4-thiadiazine 1,1-dioxide **4b**: Yellow crystals; mp 159°C; IR (KBr): $\nu = 1601$, 1540, 1300, 1148, 1086 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.18 (d, 3H, *J* 1.5 Hz, CH_3), 3.41 (t, 2H, *J* 7.2 Hz, SCH_2), 4.36 (t, 2H, *J* 7.2 Hz, NCH_2), 6.87 (q, 1H, *J* 1.5 Hz, NCH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.4 (CH_3), 26.8 (SCH_2), 47.0 (NCH_2), 115.7 (CSO_2), 141.2 (NCH), 164.0 (SCN). MS (EI): m/z (%) = 204 (M^+, 100), 140 (33), 112 (9), 85 (10), 60 (38); anal. calcd for $C_6H_8N_2O_2S_2$ (204.3): C, 35.28; H, 3.95; N, 13.71. Found: C, 35.34; H, 3.90; N, 13.84%.

11. Crystallographic data will be published separately.