# Synthesis of 3-methoxy-5-oxo-6-phenyl-5,6-dihydro-4*H*-isothiazolo[5,4-*b*]-1,4-thiazine 7,7-dioxide, the first representative of a new heterocyclic system

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When treated with an excess of MeONa in DMF, 5-benzylsulfonyl-3-chloro-4-methoxycarbonylaminoisothiazole undergoes cyclization into 3-methoxy-5-oxo-6-phenyl-5,6-dihydro-4*H*-isothiazolo[5,4-*b*]-1,4-thiazine 7,7-dioxide, the first representative of a new heterocyclic system. The starting 5-benzylsulfonyl-3-chloro-4-methoxycarbonylaminoisothiazole was prepared by the reaction of 5-benzylsulfonyl-4-carbamoyl-3-chloroisothiazole with $PhI(OAc)_2$ in methanol.

**Key words:** 2,3-dihydro-1,4-thiazin-3-ones, isothiazolo[5,4-*b*]-1,4-thiazin-5-ones, intramolecular cyclization, phenyl iodosoacetate.

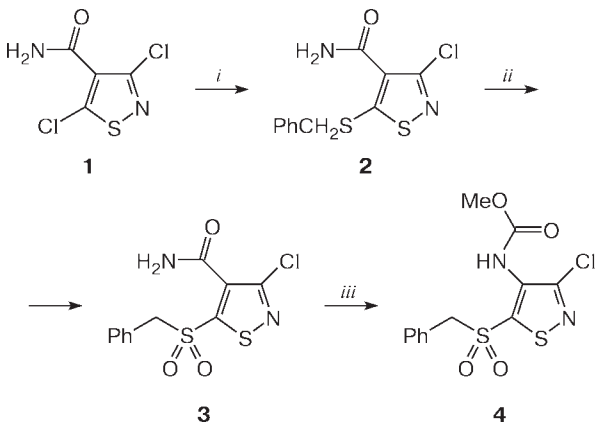
Derivatives of annelated 2,3-dihydro-1,4-thiazin-3-ones attract attention because of a broad spectrum of their biological activity.[1—5]

Recently, we have developed a method for the synthesis of 2,3-dihydrobenzothiazin-3-one derivatives. The key stage in this method is a base-induced intramolecular cyclization of *N*-(methoxycarbonyl)anilines containing *ortho*-sulfide or sulfonyl groups with an active methylene fragment adjacent to the S atom.[6] This reaction underlies a new strategy of the synthesis of annelated 2,3-dihydrothiazin-3-ones with the formation of a C(2)—C(3) bond of the thiazine ring at the stage of cyclization.

We demonstrated that the cyclization of this type is of general character and can be used to obtain 2,3-dihydrothiazin-3-ones annelated with heterocycles, particularly with the isothiazole ring.

An isothiazole derivative required for cyclization was prepared from available 4-carbamoyl-3,5-dichloroisothiazole[7,8] (**1**) in several steps. First, the chlorine atom in position 5 was replaced by a benzylthio group to give 5-benzylthio-4-carbamoyl-3-chloroisothiazole (**2**). Compound **2** was oxidized into 5-benzylsulfonyl-4-carbamoyl-3-chloroisothiazole (**3**), which was converted to 5-benzylsulfonyl-3-chloro-4-methoxycarbonylaminoisothiazole (**4**) under the action of $PhI(OAc)_2$ in methanol (Scheme 1).

**Scheme 1**

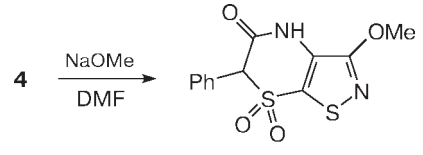



**1** **2** **3** **4**

**Reagents and conditions:** *i*. $PhCH_2SH$, $K_2CO_3$, DMF, yield 46%. *ii*. $H_2O_2$, AcOH, yield 90%. *iii*. $PhI(OAc)_2$, MeOH, yield 81%.

It turned out that the reaction of compound **4** with an excess of MeONa in DMF gives 3-methoxy-5-oxo-6-phenyl-5,6-dihydro-4*H*-isothiazolo[5,4-*b*]-1,4-thiazine 7,7-dioxide (**5**) in 81% yield. The heterocyclization is accompanied by the nucleophilic replacement of the Cl atom with a methoxy group in position 3 of the heterocycle (Scheme 2).

**Scheme 2**




**5** (81%)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 175—177, January, 2002.

1066-5285/02/5101-187 $27.00 

The structure of compound **5** was determined from $^1$H and $^{13}$C NMR spectra and mass spectra and confirmed by elemental analysis data.

Thus, compound **5** was synthesized, which is, as far as we know, the first representative of the isothiazolo[5,4-*b*]-1,4-thiazine heterocyclic system.

## Experimental

Solvents were purified according to the standard procedures.[9] $^1$H and $^{13}$C NMR spectra were recorded on Bruker AM-250 and Bruker AM-300 spectrometers (250 and 300 MHz, respectively) in DMSO-$d_6$. Mass spectra (EI, 70 eV) were recorded on a Kratos MS-30 instrument. TLC was performed on Silufol UV-254 silica gel with benzene—acetone as an eluent.

**5-Benzylthio-4-carbamoyl-3-chloroisothiazole (2).** Benzylthiol (0.70 mL, 5.86 mmol) and $Na_2CO_3$ (0.62 g, 5.86 mmol) were successively added with stirring to a solution of 4-carbamoyl-3,5-dichloroisothiazole (**1**) (1.10 g, 5.33 mmol) in 6 mL of DMF. The reaction mixture was kept at 40 °C for 120 h (monitoring by TLC) and mixed with water (45 mL). The precipitate that formed was filtered off and washed with water (3×15 mL). The product obtained was recrystallized from Pr$^i$OH—acetone to give isothiazole **2** (0.69 g, 46%), m.p. 181.5—183 °C, $R_f$ 0.58 (benzene—acetone, 5 : 1). $^1$H NMR (DMSO-$d_6$), δ: 4.38 (s, 2 H, $CH_2$); 7.28—7.48 (m, 5 H, Ph); 7.77 (br.s, 2 H, $NH_2$).

**5-Benzylsulfonyl-4-carbamoyl-3-chloroisothiazole (3).** A 50% solution of $H_2O_2$ (0.48 mL, 11.3 mmol) was added dropwise to a solution of isothiazole **2** (0.30 g, 1.05 mmol) in 4 mL of glacial AcOH. The reaction mixture was heated at 90 °C for 6 h (monitoring by TLC), cooled, and mixed with water (30 mL). The precipitate that formed was filtered off, washed with water (2×5 mL), and dried in air to give isothiazole **3** (0.30 g, 90%), m.p. 176—178 °C, $R_f$ 0.51 (benzene—acetone, 4 : 1). $^1$H NMR (DMSO-$d_6$), δ: 5.01 (s, 2 H, $CH_2$); 7.22—7.44 (m, 5 H, Ph); 8.31, 8.47 (both br.s, each 1 H, NH). Found (%): C, 42.23; H, 3.03; Cl, 10.78; N, 8.59; S, 19.49. $C_{11}H_9ClN_2O_3S_2$. Calculated (%): C, 41.71; H, 2.86; Cl, 11.19; N, 8.84; S, 20.24.

**5-Benzylsulfonyl-3-chloro-4-methoxycarbonylaminoisothiazole (4).** $PhI(OAc)_2$ (0.36 g, 1.11 mmol) was added to a suspension of isothiazole **3** (0.30 g, 0.95 mmol) in 4 mL of MeOH. The reaction mixture was stirred at 15 °C for 12 h (monitoring by TLC) and poured into water (30 mL). The crystalline product that formed was filtered off and washed with water (2×5 mL) and hexane (7 mL), and dried in air to give isothiazole **4** (0.30 g, 91%), m.p. 116—119.5 °C, $R_f$ 0.73 (benzene—acetone, 4 : 1). $^1$H NMR (DMSO-$d_6$), δ: 3.82 (s, 3 H, Me); 4.91 (s, 2 H, $CH_2$); 7.32—7.45 (m, 5 H, Ph); 8.69 (br.s, 1 H, NH). Found (%): C, 41.46; H, 3.11; Cl, 9.98; N, 8.03; S, 18.05. $C_{12}H_{11}ClN_2O_4S_2$. Calculated (%): C, 41.56; H, 3.20; Cl, 10.22; N, 8.08; S, 18.49.

**3-Methoxy-5-oxo-6-phenyl-5,6-dihydro-4*H*-isothiazolo[5,4-*b*]-1,4-thiazine 7,7-dioxide (5).** Isothiazole **4** (0.15 g, 0.43 mmol) was added to a suspension of MeONa (0.05 g, 0.91 mmol) in 2 mL of anhydrous DMF. The reaction mixture was stirred at ~20 °C for 1 h (monitoring by TLC) and poured into 10 mL of 2 *M* HCl. The precipitate that formed was filtered off, washed with water (2×5 mL), and dried in air to give *S*,*S*-dioxide **5** (0.11 g, 81%), m.p. 115—117.5 °C, $R_f$ 0.61 (benzene—acetone, 4 : 1). $^1$H NMR (DMSO-$d_6$), δ: 3.77 (s, 3 H, Me); 7.08 (s, 1 H, CH); 7.51—7.76 (m, 5 H, Ph); 9.22 (br.s, 1 H, NH). $^{13}$C NMR (DMSO-$d_6$), δ: 53.7 (OMe); 85.5 (CH); 105.5; 112.8; 129.5; 129.9; 130.0; 131.1; 131.8, 154.4 (C=O). Found (%): C, 46.70; H, 3.19; N, 8.75; S, 20.19. $C_{12}H_{10}N_2O_4S_2$. Calculated (%): C, 46.44; H, 3.25; N, 9.03; S, 20.66. MS, $m/z$ ($I_{rel}$ (%)): 310 $[M]^+$ (0.6), 278 $[M - S]^+$ (0.5), 246 $[M - SO_2]^+$ (1.3), 214 $[M - SO_2MeOH]^+$ (4.9), 156 (10.3), 128 (3.3), 106 $[PhCOH]^+$ (91.4), 105 $[PhCO]^+$ (95.7), 91 $[PhCH_2]^+$ (16.7), 78 $[PhH]^+$ (66), 77 $[Ph]^+$ (100.0), 64 $[SO_2]^+$ (69.9).

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*Received July 18, 2001;*
*in revised form October 29, 2001*