6-ARYLAMINO-3-METHYL-7H-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZINES: NOVEL N-ARYLAMIDINE STRUCTURES

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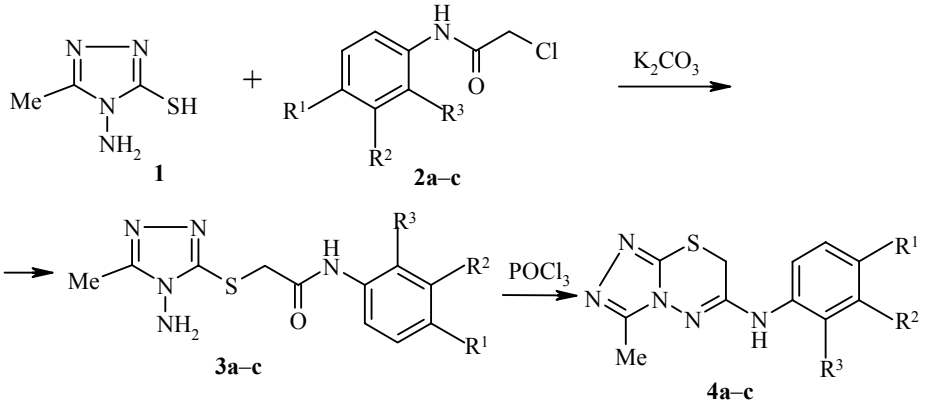
We propose a method for obtaining derivatives of 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine by alkylation of 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol by substituted α-chloroacetanilides, followed by cyclization of the intermediate by phosphorus oxychloride.

Keywords: 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol, N^1-aryl-2-(4-amino-5-methyl-4H-1,2,4-triazolyl-3-thio)acetamide, 6-arylamino-3-methyl-7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine, α-chloroacetanilide, intramolecular cyclization.

Condensed derivatives of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines have a broad spectrum of biological action, including antibacterial [1,2], antiviral, anti-inflammatory, and other types of activity [3].

Recently interest has considerably increased in heterocyclic N-arylamidines, connected with using them as the basis for obtaining the next generation of analgesics [4]. So we have attempted to obtain N-arylamidines with a 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine ring.

It was shown earlier that 4-amino-5-alkyl-4H-1,2,4-triazole-3-thiols react with such alkylating reagents as methyl iodide [1], chloroacetonitrile [2], chloroacetic acid [5], and substituted phenacyl bromides [5-8].



2–4 a R^1 = OEt, R^2 = R^3 = H; **b** R^1 = Cl, R^2 = R^3 = H; **c** R^1 = H, R^2 = R^3 = Me

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We propose a new method for obtaining derivatives of 7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine by alkylation of 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol (**1**) with substituted α-chloroacetanilides **2**, followed by cyclization of the intermediate by phosphorus oxychloride.

Reaction of thiol **1** with substituted α-chloroacetanilides in the presence of potassium carbonate occurs with formation of substituted N^1-aryl-2-(4-amino-5-methyl-4H-1,2,4-triazolyl-3-thio)acetamides **3**. When the latter are boiled with phosphorus oxychloride, intramolecular cyclization occurs and 6-arylamino-3-methyl-7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **4** are formed.

The structure of the synthesized compounds was confirmed by ^{1}H NMR spectroscopy data. Thus in the spectra of compounds **3a-c**, a three-proton singlet from the methyl group is found in the 2.28-2.34 ppm region, a two-proton singlet from the methylene group S–CH_2CONH appears in the 3.94-4.02 ppm region, and a two-proton singlet from the N-amino group resonates in the 5.71-5.89 ppm region. When the spectrum is recorded again in the presence of small amounts of D_2O, this signal disappears due to deuteron exchange. The NH-amide proton signal is observed in the range of 9.66-10.36 ppm.

A distinctive feature of the spectra of compounds **4a-c** compared with acetanilides **3a-c** is the disappearance of the two-proton singlet from the N-amino group and the signal from the acetamide proton, with the appearance of an one-proton singlet from the imino group in the position 6 of the system at 8.93-9.87 ppm.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker-300 (300 MHz) in DMSO-d_6, internal standard TMS.

N^1-(4-Ethoxyphenyl)-2-(4-amino-5-methyl-4H-1,2,4-triazolyl-3-thio)acetamide (3a). Solution of 4-ethoxyanilide of chloroacetic acid (2.13 g, 10 mmol) in ethanol (20 ml) was added to solution of compound **1** (1.3 g, 10 mmol) in aqueous ethanol (40 ml) containing K_2CO_3 (1.38 g, 10 mmol). The reaction mixture was boiled for 30 min and cooled down, then water (50-60 ml) was added. The colorless precipitate was filtered off, washed with water, and dried. Yield 2.85 g (93%); mp 226°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 1.30 (3H, t, $OCH_2\underline{CH_3}$); 2.28 (3H, s, CH_3); 3.96 (2H, q, $O\underline{CH_2}CH_3$); 4.02 (2H, s, CH_2CO); 5.89 (2H, s, NH_2); 6.85 and 7.43 (4H, dd, C_6H_4); 10.16 (1H, s, NH). Found, %: N 23.0. $C_{13}H_{17}N_5O_2S$. Calculated, %: N 22.8.

N^1-(4-Chlorophenyl)-2-(4-amino-5-methyl-4H-1,2,4-triazolyl-3-thio)acetamide (3b) was obtained similarly to compound **3a**, from equimolar (10 mmol each) amounts of compound **1** and 4-ethoxyanilide of chloroacetic acid. Yield 2.71 g (91%); mp 211°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 2.31 (3H, s, CH_3); 4.02 (2H, s, CH_2CO); 5.83 (2H, s, NH_2); 7.31 and 7.58 (4H, dd, C_6H_4); 10.36 (1H, s, NH). Found, %: N 23.2. $C_{11}H_{12}ClN_5OS$. Calculated, %: N 23.5.

N^1-(2,3-Dimethylphenyl)-2-(4-amino-5-methyl-4H-1,2,4-triazolyl-3-thio)acetamide (3c) was obtained similarly to compound **3a**, from equimolar (10 mmol each) amounts of compound **1** and 2,3-dimethyl-α-chloroacetanilide. Yield 2.45 g (84%); mp 173°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 2.11 (3H, s, CH_3); 2.28 (3H, s, CH_3); 2.34 (3H, s, CH_3); 3.94 (2H, s, CH_2CO); 5.71 (2H, s, NH_2); 6.92-7.31 (3H, m, C_6H_3); 9.66 (1H, s, NH). Found, %: N 24.2. $C_{13}H_{17}N_5OS$. Calculated, %: N 24.0.

6-(4-Ethoxyphenylamino)-3-methyl-7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine Hydrochloride (4a). Acetamide **3a** (2 g, 6.5 mmol) in phosphorus oxychloride (30 ml) was boiled for 2-3 h; the excess oxychloride was evaporated under vacuum to dryness. The oily residue was triturated with ether. The crystallized precipitate was filtered off, washed with water, and dried. Yield 1.75 g (83%); mp >250°C (ethanol–DMF). ^{1}H NMR spectrum, δ, ppm: 1.31 (3H, t, $OCH_2\underline{CH_3}$); 2.46 (3H, s, CH_3); 3.98 (2H, q, $O\underline{CH_2}CH_3$); 4.01 (2H, s, SCH_2); 6.95 and 7.63 (4H, dd, C_6H_4); 9.87 (1H, s, NH). Found, %: N 21.3. $C_{13}H_{15}N_5OS{\cdot}HCl$. Calculated, %: N 21.5.

6-(4-Chlorophenylamino)-3-methyl-7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine Hydrochloride (4b) was obtained similarly to compound **4a**, from acetamide **3b** (2 g, 6.7 mmol). Yield 1.97 g (93%); mp >250°C (ethanol–DMF). ^{1}H NMR spectrum, δ, ppm: 2.46 (3H, s, CH_3); 3.88 (2H, s, SCH_2); 7.27 and 7.71 (4H, dd, C_6H_4); 9.75 (1H, s, NH). Found, %: N 22.4. $C_{11}H_{10}ClN_5S{\cdot}HCl$. Calculated, %: N 22.1.

6-(2,3-Dimethylphenylamino)-3-methyl-7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (4c). Acetamide **3c** (2 g, 6.9 mmol) in phosphorus oxychloride (30 ml) was boiled for 2-3 h; the excess oxychloride was evaporated under vacuum to dryness and the oily residue was triturated with 10% NaOH solution (50 ml). The crystallized precipitate was filtered off, washed with water, and dried. Yield 1.38 g (74%); mp >250°C (ethanol–DMF). ^{1}H NMR spectrum, δ, ppm: 2.14 (3H, s, CH_3); 2.19 (3H, s, CH_3); 2.26 (3H, s, CH_3); 3.92 (2H, s, SCH_2); 7.05-7.27 (3H, m, C_6H_3); 8.93 (1H, s, NH). Found, %: N 25.5. $C_{13}H_{15}N_5S$. Calculated, %: N 25.6.

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