Chemistry of Heterocyclic Compounds, Vol. 39, No. 4, 2003

NEW SYNTHESIS OF DERIVATIVES OF 6-ARYL-3-METHYL-6,7-DIHYDRO-5H-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZINE-7-CARBOXYLIC ACID

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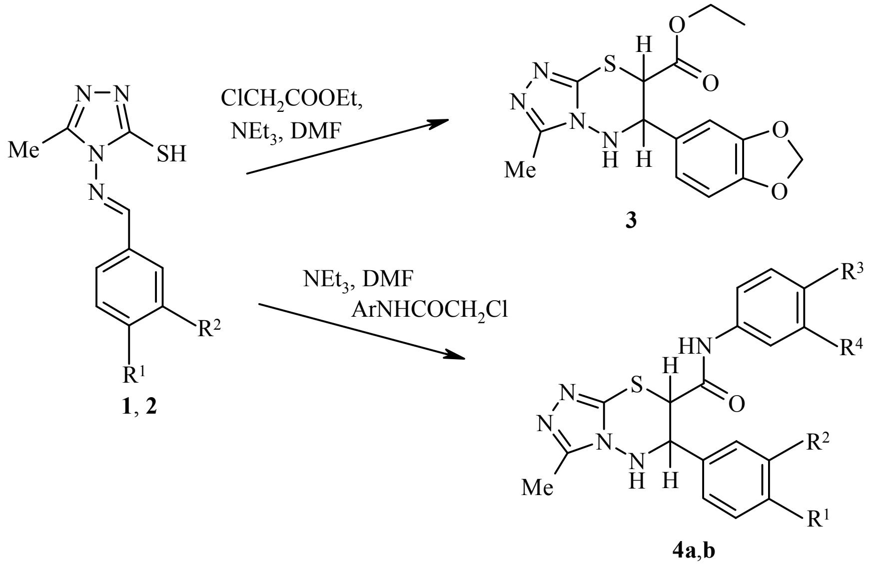
Keywords: 6-aryl-3-methyl-7-(4-R-benzoyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines, asymmetric carbon atoms, α-chloroacetanilide, ethyl chloroacetate.

Compounds with the 7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine system display antibacterial, fungicide, and anti-inflammatory activity [1, 2]. Thus, the study of new modifications of this system holds considerable interest.

However, there have been only a few reports on the synthesis of analogs with a hydrogenated thiadiazine ring. The preparation of 3-alkyl-6-aryl-7-(4-R-benzoyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazines has been carried out by reduction of 7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine ring or by alkylation of 5-R-4-(1-arylmethylideneamino-4H-1,2,4-triazole-3-thiones using either phenacyl bromides or ethyl chloroacetate in the presence of a two-fold excess of triethylamine [4, 5]. In the preparation of this system by the latter method, the formation of one or two diastereomers is possible due to the existence of two asymmetric carbon atoms [4, 5].



1 R^1R^2 = $-OCH_2O-$; **2** R^1 = Cl, R^2 = H; **4 a** R^1 = R^3 = Cl, R^2 = R^4 = H; **b** R^1 = Cl, R^2 = R^3 = H, R^4 = CF_3

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We have found that only one isomer is formed in the alkylation of Schiff bases **1** using ethyl chloroacetate or substituted α-chloroacetanilides, as indicated by the lack of doubling of the signals in the ^{1}H NMR spectra of the products. The proposed cyclization mechanism [5] would lead us to predict *trans* arrangement of the groups at $C_{(6)}$ and $C_{(7)}$ atoms.

The structures of all synthesized products were confirmed by their ^{1}H NMR spectral data.

Ethyl 6-(1,3-Benzodioxol-5-yl)-3-methyl-6,7-dihydro-5H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate (3). Solution of compound **1** (2.6 g, 10 mmol), ethyl chloroacetate (1.23 g, 10 mmol), and triethylamine (2 ml) in DMF (10 ml) was heated at reflux for 5 min and then cooled. The reaction mixture was poured into water (100 ml). The crystalline precipitate was filtered off, washed with water, and dried to give 2.54 g (73%) of compound **3**; mp 176-177°C (ethanol). ^{1}H NMR spectrum (500 MHz, DMSO-d$_6$, TMS as the internal standard), δ, ppm, (*J*, Hz): 1.09 (3H, t, *J* = 6.9, $OCH_2OC\underline{H}_3$); 2.28 (3H, s, CH_3); 4.07 (2H, q, *J* = 6.9, $OC\underline{H}_2CH_3$); 4.66 (1H, d, *J* = 6.9, SCH); 4.69 (1H, dd, J_1 = 7.2, J_2 = 6.9, $NHC\underline{H}$); 6.01 (2H, s, OCH_2O); 6.88-7.02 (3H, m, C_6H_3); 6.93 (1H, d, *J* = 7.2, $N\underline{H}CH$). Found, %: N 16.3. $C_{15}H_{16}N_4O_4S$. Calculated, %: N 16.1.

6-(4-Chlorophenyl)-3-methyl-6,7-dihydro-5H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carbox(4-chloranilide) (4a) was obtained analogously to compound **3** from compound **2** (10 mmol) and 4-chloro-α-chloroacetanilide (10 mmol). The yield of compound **4a** was 2.98 g (71%); mp 220°C (ethanol–DMF). ^{1}H NMR spectrum (500 MHz, DMSO-d$_6$, TMS as the internal standard), δ, ppm, (*J*, Hz): 2.36 (3H, s, CH_3); 4.57 (1H, d, *J* = 3.9, SCH); 4.79 (1H, dd, J_1 = 5.7, J_2 = 3.9, $NHC\underline{H}$); 6.96 (1H, d, *J* = 5.7, $N\underline{H}CH$); 7.23-7.54 (8H, m, Ar); 10.28 (1H, s, NH). Found, %: N 16.4. $C_{18}H_{15}Cl_2N_5OS$. Calculated, %: N 16.7.

6-(4-Chlorophenyl)-3-methyl-6,7-dihydro-5H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carbox(3-trifluoromethylanilide) (4b) was obtained analogously to compound **3** from compound **2** (10 mmol) and 3-trifluoromethyl-α-chloroacetanilide (10 mmol). The yield of compound **4b** was 2.86 g (63%); mp 182-183°C (ethanol–DMF). ^{1}H NMR spectrum (500 MHz, DMSO-d$_6$, with TMS as the internal standard), δ, ppm, (*J*, Hz): 2.37 (3H, s, CH_3); 4.59 (1H, d, *J* = 4.2, SCH); 4.82 (1H, dd, J_1 = 5.7, J_2 = 4.2, $NHC\underline{H}$); 6.97 (1H, d, *J* = 5.7, $N\underline{H}CH$); 7.32-7.96 (8H, m, Ar); 10.48 (1H, s, NH). Found, %: N 15.2. $C_{19}H_{15}ClF_3N_5OS$. Calculated, %: N 15.4.

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