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Synthesis and Heterocyclization of 2-{[2-(4-Bromophenyl)-2-oxoethyl]sulfanyl}pyrimidin-4(3*H*)-ones

T. V. Frolova, D. G. Kim, V. V. Sharutin, and E. N. Shal'kova

South Ural State University, pr. Lenina 76, Chelyabinsk, 454071 Russia
e-mail: chemitash@gmail.com

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Abstract—Alkylation of sodium 4(5)-alkyl-6-oxo-1,6-dihydropyrimidine-2-thiolates with 2-bromo-1-(4-bromophenyl)ethan-1-one afforded 2-{[2-(4-bromophenyl)-2-oxoethyl]sulfanyl}pyrimidin-4(3*H*)-ones. Analogous reaction with sodium 4-trifluoromethyl-6-oxo-1,6-dihydropyrimidine-2-thiolate gave a mixture of 2-{[2-(4-bromophenyl)-2-oxoethyl]sulfanyl}-4-(trifluoromethyl)pyrimidin-4(3*H*)-one and its intramolecular cyclization product, 3-(4-bromophenyl)-3-hydroxy-7-trifluoromethyl-2,3-dihydro[1,3]thiazolo[3,2-*a*]-pyrimidin-5-one.

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Compounds containing a pyrimidine ring, in particular thiouracil derivatives, exhibit a broad spectrum of biological activity [1, 2]. Among pyrimidine derivatives, fused pyrimidines are of considerably greater interest than monocyclic compounds from the viewpoint of biological activity. A particular place is occupied by thiazolopyrimidines which were shown to possess fungicidal [3], anticonvulsant, antidiabetic, anti-inflammatory, and analgesic properties [4], as well as to act as efficient calcium channel blockers [5].

A convenient procedure for the preparation of thiazolopyrimidinones is based on intramolecular cyclization of 2-[(2-oxoethyl)sulfanyl]pyrimidin-4(3*H*)-ones by the action of sulfuric acid [6]. The authors [6] presumed that the heterocyclization involved the N^3 rather than N^1 atom on the basis of only ^{1}H NMR data.

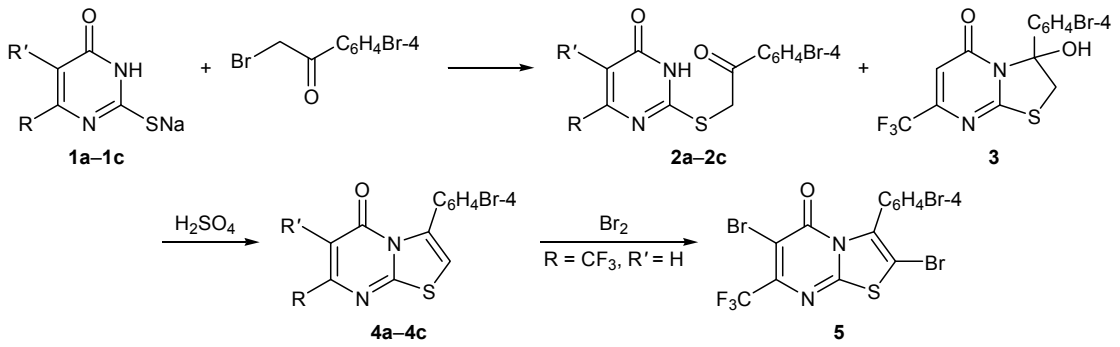
In this work we studied the reaction of 2-bromo-1-(4-bromophenyl)ethan-1-one with sodium 6-oxo-1,6-dihydropyrimidine-2-thiolates **1a**–**1c** prepared by condensation of thiourea with 1,3-dicarbonyl compounds [7]. The alkylation of **1a** and **1b** gave 2-{[2-(4-bromophenyl)-2-oxoethyl]sulfanyl}pyrimidin-4(3*H*)-ones **2a** and **2b** (Scheme 1). The product structure was confirmed by their ^{1}H NMR spectra which contained a singlet at δ 4.71 (**2a**) and 4.66 ppm (**2b**) due to the SCH_2 protons and aromatic proton signals in the region δ 7.75–8.00 ppm. In the IR spectra of **2a** and **2b** we observed absorption bands in the region 1658–1695 cm^{-1}, corresponding to stretching vibrations of two carbonyl groups.

Unlike compounds **1a** and **1b**, the reaction of 4-trifluoromethyl-substituted derivative **1c** with 2-bromo-1-(4-bromophenyl)ethan-1-one was accompanied by intramolecular cyclization of the alkylation product, 2-{[2-(4-bromophenyl)-2-oxoethyl]sulfanyl}-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (**2c**), with formation of 3-(4-bromophenyl)-3-hydroxy-7-trifluoromethyl-2,3-dihydro[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (**3**). According to the ^{1}H NMR data, the ratio **2c**:**3** was 0.4:1. The observed difference in the reaction directions may be rationalized by strong electron-withdrawing effect of the trifluoromethyl group, which enhances the NH acidity of **2c** and facilitates its cyclization. Compound **3** displayed in the ^{1}H NMR spectrum signals from aromatic protons, a singlet at δ 5.78 ppm from the OH proton, and two one-proton doublets at δ 3.45–3.93 ppm from the SCH_2 group.

Treatment of mixture **2c**/**3** with concentrated sulfuric acid afforded 90% of 3-(4-bromophenyl)-7-trifluoromethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (**4c**). Proton in position *2* of **4c** (thiazole ring) resonated in the ^{1}H NMR spectrum as a singlet at δ 7.57 ppm. The regioselectivity of the cyclization of **2c**, which involved exclusively the N^3 atom, was confirmed by X-ray analysis of thiazolopyrimidinone **4c** (Fig. 1).

The thiazolopyrimidine system in molecule **4c** is planar, and the bromophenyl group is turned through a dihedral angle of 50° with respect to that plane. Packing of molecules **4c** in crystal involves three short contacts, two of which are formed between the sulfur

Scheme 1.



R = Me, R′ = H (**a**), Et (**b**); R = CF_3, R′ = H (**c**).

and fluorine atoms (S···F 3.174 Å), and the third contact is formed between aromatic hydrogen atoms of different benzene rings (3.709 Å). Short contacts between the fluorine atoms of different molecules (2.669 Å) arrange stacks of molecular layers along the *c* crystallographic axis (Fig. 2).

Treatment of sulfides **2a** and **2b** with sulfuric acid gave 3-(4-bromophenyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-ones **4a** and **4b**. Unlike initial sulfides **2a** and **2b**, compounds **4a** and **4b** showed in the IR spectra only one carbonyl stretching band at 1686 and 1692 cm^{-1}, respectively.

Insofar as compound **4c** may be regarded as an aromatic system with free positions *2* and *6*, it was interesting to find out which position is more reactive toward electrophiles. For this purpose, compound **4c** was subjected to bromination with bromine in chloroform on cooling. According to the ^1H NMR data, the product was 2,6-dibromo-3-(4-bromophenyl)-7-trifluoromethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (**5**) (Scheme 1).

EXPERIMENTAL

The IR spectra were recorded on a Varian 800 FT-IR Scimitar Series spectrometer. The ^1H NMR spectra were measured from solutions in DMSO-d_6 on a Bruker DRX-400 spectrometer (400 MHz) using tetramethylsilane as internal standard. The elemental analyses were obtained on a Carlo Erba CHNS-O EA 1108 analyzer.

The X-ray diffraction data for compound **4c** were acquired with a Bruker D8 QUEST automated four-circle diffractometer (Mo K_α radiation, λ 0.71073 Å, graphite monochromator). The data were collected and edited, the unit cell parameters were refined, and a correction for absorption was applied using SMART [8] and SAINT-Plus [9]. The structure was solved by the direct method and refined by the least-squares procedure in anisotropic approximation for non-hydrogen atoms using SHELXL/PC [10]. The complete tables of atom coordinates, bond lengths, and bond angles were deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 1013415).

Compounds 2a–2c and 3 (*general procedure*). Compound **1a**–**1c**, 0.01 mol, was dissolved in 10 mL of DMF, 2.78 g (0.01 mol) of *p*-bromophenacyl bromide was added, and the mixture was stirred for

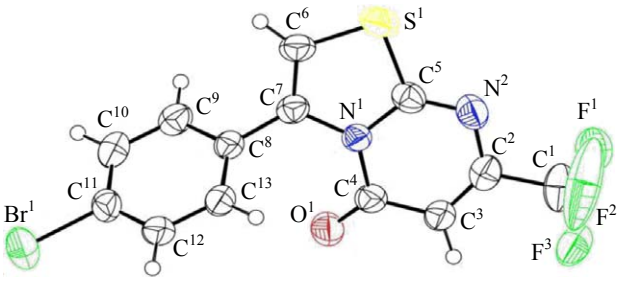


Fig. 1. Structure of the molecule of 3-(4-bromophenyl)-7-trifluoromethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (**4c**) according to the X-ray diffraction data.

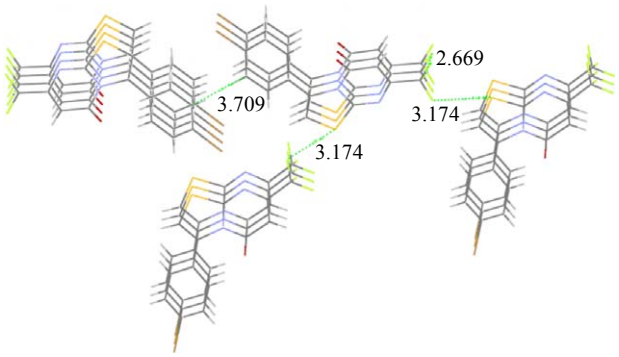


Fig. 2. Crystal packing of 3-(4-bromophenyl)-7-trifluoromethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (**4c**) according to the X-ray diffraction data.

2 h. The mixture was then diluted with 35 mL of water, and the precipitate was filtered off.

2-{[2-(4-Bromophenyl)-2-oxoethyl]sulfanyl}-6-methylpyrimidin-4(3*H*)-one (2a). Yield 2.27 g (67%), mp 160°C. IR spectrum, ν, cm^{-1}: 1695, 1661 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.95 s (3H, CH_3), 4.71 s (2H, SCH_2), 5.96 s (1H, 5-H), 7.79 d (2H, H_{arom}, J = 8.34 Hz), 7.98 d (2H, H_{arom}, J = 8.35 Hz). Found, %: C 46.16; H 3.12; N 8.31. $C_{13}H_{11}BrN_2O_2S$. Calculated, %: C 46.01; H 3.24; N 8.25.

2-{[2-(4-Bromophenyl)-2-oxoethyl]sulfanyl}-5-ethyl-6-methylpyrimidin-4(3*H*)-one (2b). Yield 2.27 g (62%), mp 184°C. IR spectrum, ν, cm^{-1}: 1684, 1638 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.93 t (3H, C**H**$_3$CH$_2$, J = 7.30 Hz), 1.93 s (3H, CH_3), 2.29 q (2H, C**H**$_2$CH$_3$, J = 7.02 Hz), 4.66 s (2H, SCH_2), 7.79 d (2H, H_{arom}, J = 8.47 Hz), 7.97 d (2H, H_{arom}, J = 8.42 Hz). Found, %: C 48.99; H 4.15; N 7.63. $C_{15}H_{15}BrN_2O_2S$. Calculated, %: C 49.04; H 4.08; N 7.62.

2-{[2-(4-Bromophenyl)-2-oxoethyl]sulfanyl}-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (2c). ^{1}H NMR spectrum, δ, ppm: 4.64 s (2H, SCH_2), 6.53 s (1H, 5-H), 7.66 d (2H, H_{arom}, J = 8.73 Hz), 7.88 d (2H, H_{arom}, J = 8.69 Hz).

3-(4-Bromophenyl)-3-hydroxy-7-trifluoromethyl-2,3-dihydro[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (3). ^{1}H NMR spectrum, δ, ppm: 3.45 d and 3.93 d (1H each, SCH_2, J = 11.73 Hz), 5.78 s (1H, OH), 6.54 s (1H, 5-H), 7.24 d (2H, H_{arom}, J = 8.78 Hz), 7.56 d (2H, H_{arom}, J = 8.80 Hz).

Compounds 4a–4c (*general procedure*). A mixture of 1 mmol of compound **2a**–**2c** and 10 mL of sulfuric acid was left to stand for 24 h at room temperature. The mixture was poured into cold water and neutralized with aqueous sodium hydroxide, and the precipitate was filtered off, washed with water, and dried.

3-(4-Bromophenyl)-7-methyl-5*H*-[1,3]thiazolo-[3,2-*a*]pyrimidin-5-one (4a). Yield 0.176 g (57%), mp 110°C. IR spectrum: ν 1686 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3), 6.06 s (1H, 6-H), 7.65 d (2H, H_{arom}, J = 8.66 Hz), 7.69 s (1H, 2-H), 7.75 d (2H, H_{arom}, J = 8.49 Hz). Found, %: C 48.54; H 2.86; N 8.65. $C_{13}H_9BrN_2OS$. Calculated, %: C 48.59; H 2.80; N 8.72.

3-(4-Bromophenyl)-6-ethyl-7-methyl-5*H*-[1,3]-thiazolo[3,2-*a*]pyrimidin-5-one (4b). Yield 0.235 g (70%), mp 120°C. IR spectrum: ν 1692 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 0.93 t (3H, CH_2C**H**$_3$, J = 7.40 Hz), 2.32 s (3H, CH_3), 2.41 q (2H, C**H**$_2$CH$_3$, J = 7.22 Hz), 7.32 s (1H, 2-H), 7.34 d (2H, H_{arom}, J = 8.47 Hz), 7.56 d (2H, H_{arom}, J = 8.46 Hz). Found, %: C 51.51; H 3.78; N 8.12. $C_{15}H_{13}BrN_2OS$. Calculated, %: C 51.57; H 3.72; N 8.02.

3-(4-Bromophenyl)-7-trifluoromethyl-5*H*-[1,3]-thiazolo[3,2-*a*]pyrimidin-5-one (4c). Yield 0.337 g (90%), mp 140°C. IR spectrum: ν 1692 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 6.67 s (1H, 6-H), 7.41 d (2H, H_{arom}, J = 8.46 Hz), 7.57 s (1H, 2-H), 7.61 d (2H, H_{arom}, J = 8.47 Hz). Found, %: C 41.57; H 1.58; N 7.51. $C_{13}H_6BrF_3N_2OS$. Calculated, %: C 41.60; H 1.61; N 7.46.

2,6-Dibromo-3-(4-bromophenyl)-7-trifluoromethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (5). A solution of 0.1 mL (0.001 mol) of bromine in 5 mL of $CHCl_3$ was added on cooling to 0.271 g (0.001 mol) of compound **4c** in 10 mL of $CHCl_3$. After 24 h, the mixture was evaporated, and the residue was washed with 5 mL of ethanol. Yield 0.265 g (51%), mp 178°C. ^{1}H NMR spectrum, δ, ppm: 7.41 d (2H, H_{arom}, J = 8.47 Hz), 7.64 d (2H, H_{arom}, J = 8.52 Hz). Found, %: C 29.32; H 0.65; N 5.29. $C_{13}H_4Br_3F_3N_2OS$. Calculated, %: C 29.26; H 0.75; N 5.25.

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