Syntheses based on 2-ethoxycarbonylmethyl-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5(5*H*)-one

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2-Ethoxycarbonylmethyl-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5(5*H*)-one containing the active methylene group reacts easily with carbon disulfide and phenyl isothiocyanate in the presence of sodium hydride. Further alkylation of the reaction product by alkyl halides results in the formation of the corresponding 1,3,4-thiadiazolo[3,2-*a*]pyrimidine derivatives containing a ketene dithioacetal fragment.

Key words: 2-ethoxycarbonylmethyl-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5(5*H*)-one, 1,3,4-thiadiazolo[3,2-*a*]pyrimidines, ethyl (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo-[3,2-*a*]pyrimidin-2-yl)methylthiothiocarbonylacetate, ethyl 2-(7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)-3,3-bis(methylthio)acrylate.

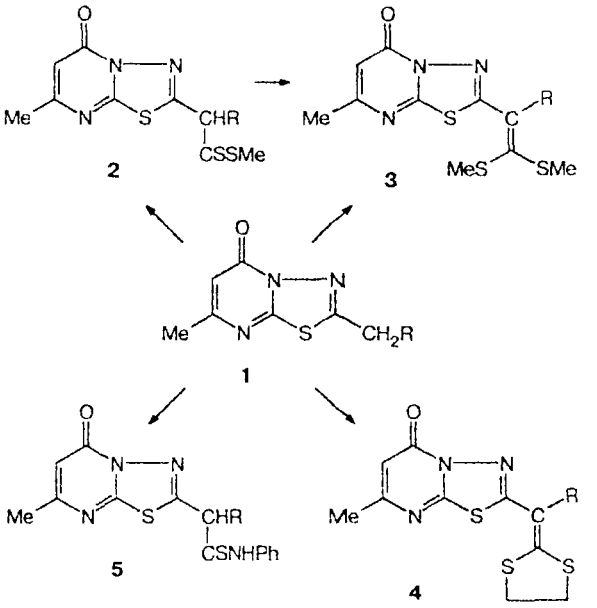
Derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine are potential biologically active substances.[1—4] The introduction of ketene dithioacetal fragments into the molecules makes it possible to synthesize heterocyclic systems with various functional groups.[5,6]

As known,[7,8] ethyl 2-(3-pyridyl)acetate enters easily into the condensation reaction with carbon disulfide, and the subsequent alkylation with alkyl halides results in the formation of the corresponding ketene dithioacetals, which serve as the starting compounds for the synthesis of physiologically active substances.

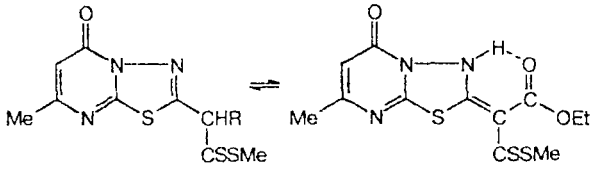
We have found that 2-ethoxycarbonylmethyl-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5(5*H*)-one (**1**) reacts readily with carbon disulfide in absolute DMF in the presence of NaH. The further alkylation by methyl iodide gives ethyl (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)methylthiothiocarbonylacetate (**2**). In the case where two equivalents of sodium hydride and methyl iodide are used, the reaction affords ethyl 2-(7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)-3,3-bis(methylthio)acrylate (**3**). When dibromoethane is used as alkyl halide, we synthesized ethyl 2-(7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)-3,3-ethylenedithioacrylate (**4**).

The reaction of compound **1** with phenyl isothiocyanate in anhydrous DMF in the presence of sodium hydride affords ethyl (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)anilinothiocarbonyl)acetate (**5**).

The compositions and structures of compounds **2**—**5** obtained were confirmed by elemental analysis and data of ^{1}H NMR and IR spectroscopy.



The IR spectrum of compound **2** contains absorption bands at 3148 cm^{-1}, which can be assigned to vibrations of the NH group, and the IR spectrum of the starting compound exhibits no absorption in this region, which indicates the presence of azinyl-ylidene tautomerism in the molecule.[9]



† Deceased.

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The spectrum also contains two absorption bands of stretching vibrations of carbonyl groups at 1760 and 1720 cm^{-1}. In the spectra of compounds **3** and **4**, absorption bands of carbonyl groups appear in the 1656—1674 cm^{-1} region. The IR spectrum of compound **5** also contains absorption bands of the NH group of the aniline fragment at 3220 cm^{-1}.

The ^1H NMR spectra of compounds **2** and **3** exhibit the signal of CH_3 of the thiomethyl group in the 2.34—2.46 ppm region and the signals of the methyl group in position 7 of the thiadiazolopyrimidine system in the 2.12—2.16 ppm region. The ^1H NMR spectrum of compound **4** contains the signals of methylene protons of the thiolane fragment at 3.44 ppm. The ^1H NMR spectrum of compound **5** is characterized by signals of protons of the phenyl ring in the 7.32—7.70 ppm region.

Experimental

^1H NMR spectra were recorded on a Tesla BS-58773 C spectrometer (100 MHz, DMSO-d_6 as the solvent, HMDS as the internal standard). IR spectra were obtained on an UR-20 spectrometer in pellets with KBr. Melting points were determined on a Boetius microheating table. The starting ester **1** was obtained by the known method.[10]

Ethyl (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)methylthiothiocarbonylacetate (2). NaH (0.12 g, 0.005 mol) and CS_2 (0.57 g, 0.0075 mol) were added to a solution of ester **1** (1.27 g, 0.005 mol) in anhydrous DMF (10 mL). The mixture was stirred at ~20 °C for 4 h, MeI (0.71 g, 0.005 mol) was added, and the resulting mixture was stirred for 8 h. The reaction mixture was diluted with water (30 mL) and let to stand for 2 days until the mass solidified. The residue was filtered off, washed with water, and dried in air. The reaction product was recrystallized from EtOH. Product **2** (0.7 g, 40.8%) with m.p. 220—221 °C was obtained. Found (%): C, 41.50; H, 3.39. $C_{12}H_{13}N_3O_3S_3$. Calculated (%): C, 41.97; H, 3.82. IR, ν/cm^{-1}: 3148 (NH); 1720 (C=O); 1714 (C=O); 1654 (C=N). ^1H NMR, δ: 6.12 (s, 1 H, CH); 4.16 (q, 2 H, CH_2, J = 6.7); 2.39 (s, 3 H, CH_3); 2.12 (s, 3 H, CH_3); 1.02 (t, 3 H, CH_3, J = 6.7).

Ethyl 2-(7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)-3,3-bis(methylthio)acrylate (3). NaH (0.24 g, 0.01 mol) and CS_2 (0.57 g, 0.0075 mol) were added to a solution of ester **1** (1.27 g, 0.005 mol) in anhydrous DMF (10 mL). The mixture was stirred for 4 h, MeI (1.42 g, 0.01 mol) was added, and the resulting mixture was treated as in the previous experiment. Ester **3** (1.3 g, 72.7%) with m.p. 125—127 °C was obtained. Found (%): C, 43.17; H, 4.01. $C_{13}H_{15}N_3O_3S_3$. Calculated (%): C, 43.68; H, 4.23. IR, ν/cm^{-1}: 1714 (C=O); 1660 (C=O); 1656 (C=N). ^1H NMR, δ: 6.16 (s, 1 H, CH); 4.26 (q, 2 H, CH_2); 2.46 (s, 3 H, CH_3); 2.16 (s, 3 H, CH_3); 1.14 (t, 3 H, CH_3).

Ethyl 2-(7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)-3,3-ethylenedithioacrylate (4) was obtained similarly to compound **3** from ester **1** (1.27 g, 0.005 mol), NaH (0.24 g, 0.01 mol), CS_2 (0.57 g, 0.0075 mol), and dibromoethane (0.94 g, 0.005 mol). The reaction product was recrystallized from dioxane to obtain compound **4** (1.04 g, 58.5%) with m.p. 214—216 °C. Found (%): C, 43.29; H, 3.71. $C_{13}H_{13}N_3O_3S_3$. Calculated (%): C, 43.93; H, 3.69. IR, ν/cm^{-1}: 1768 (C=O); 1674 (C=O); 1660 (C=N). ^1H NMR, δ: 6.12 (s, 1 H, CH); 4.26 (q, 2 H, CH_2, J = 7.1); 3.44 (s, 4 H, 2 CH_2); 2.14 (s, 3 H, CH_3); 1.22 (t, 3 H, CH_3, J = 7.1).

Ethyl (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-2-yl)anilinothiocarbonyl)acetate (5). Phenyl isothiocyanate (0.67 g, 0.005 mol) and NaH (0.12 g, 0.005 mol) were added to a solution of ester **1** (1.27 g, 0.005 mol) in anhydrous DMF (10 mL). The mixture was stirred for 5 h and then treated as in the previous experiments to obtain ester **5** (1.25 g, 64.4%) with m.p. 162—164 °C. Found (%): C, 52.30; H, 3.98. $C_{17}H_{16}N_3O_3S_2$. Calculated (%): C, 52.56; H, 4.15. IR, ν/cm^{-1}: 3220 (NH); 1780 (C=O); 1700 (C=O); 1630 (C=N). ^1H NMR, δ: 7.32—7.70 (m, 5 H, Ph); 6.12 (s, 1 H, CH); 4.12 (q, 2 H, CH_2, J = 7.2); 2.22 (s, 3 H, CH_3); 1.04 (t, 3 H, CH_3, J = 7.2).

References

1. Pat. 2712932, Germany, *RZhKhim.*, 1980, 9.0.171P (Russ. Transl.).
2. Pat. 4742063 USA, *RZhKhim.*, 1989, 1.0.401P (in Russian).
3. Pat. 4866064 USA, *RZhKhim.*, 1991, 7.0384P (in Russian).
4. M. Suiko and K. Maekawa, *Agric. Biol. Chem.*, 1977, **41**, 2042.
5. Y. Tominaga, *J. Heterocycl. Chem.*, 1989, **26**, 1167.
6. H. Junjappa, H. Ila, and C. V. Asokan, *Tetrahedron*, 1990, **46**, 5423.
7. Pat. 5061716 USA, *RZhKhim.*, 1993, 21.0218P (Russ. Transl.).
8. Pat. 211568, Japan, *RZhKhim.*, 1992, 15.0.62P (Russ. Transl.).
9. S. Sh. Shukurov, M. A. Kukaniev, I. M. Nasyrov, K. S. Zakharov, and R. A. Karakhanov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1962 [*Russ. Chem. Bull.*, 1993, **42**, 1879 (Engl. Transl.)].
10. S. Sh. Shukurov, M. A. Kukaniev, I. M. Nasyrov, and R. A. Karakhanov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 1187 [*Bull. Russ. Acad. Sci.*, 1992, **41**, 936 (Engl. Transl.)].

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