Synthesis and transformations of 2-(5-amino-(mercapto)-1,3,4-thiadiazolylthio)-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines

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The reactions of 2-amino-5-mercapto-(or 2,5-dimercapto)-1,3,4-thiadiazoles with 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine to give the corresponding sulfides have been studied. The possibility of S-alkylation and addition of quinone at the free mercapto group in the 1,3.4-thiadiazole ring has been shown. The reactions at the amino group with benzoyl chloride and chloroformates have been investigated. The conditions of cyclodehydration at the amino group with ethyl acetoacetate and bromination of the pyrimidine fragment of 7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine have been found.

Key words: nucleophilic substitution, 2-amino-5-mercapto-(2,5-dimercapto)-1,3,4-thiadiazoles; 2-bromo-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine, 2-(5-amino-(mercapto)-1,3,4-thiadiazolylthio)-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine, non-symmetrically substituted bis-sulfides, amides, carbamates of 1,3,4-thiadiazole series.

Lately 5-oxo-5*H*-1,3,4-thiadiazolo[3,2-a]pyrimidines (TP) derivatives have been actively investigated. The interest in these condensed 1,3,4-thiadiazol analogs is due to the wide spectrum of pharmacological activity of their derivatives. 2-R-thio(sulfonyl)-TP have been investigated in the most detail as potential anticancer remedies.[1—4] Recently these compounds have been found to possess high fungicide activity against pathogenic fungi that damage garden cultures.[5—8] Of the 2-thio-derivatives of TP, the 1,3,4-thiadiazole derivatives have scarcely been studied, although 1,3,4-thiadiazoles themselves possess the above-mentioned types of biological activitites together with antimicrobial activity.

This work deals with the synthesis and transformations of 2-(5-mercapto-1,3,4-thiazolylthio)-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-a]pyrimidine (**1**) and 2-(5-amino-1,3,4-thiazolylthio)-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-a]pyrimidine (**2**) in order to later study their fungicide activity.

Compounds **1** and **2** were obtained by the reaction of 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (ABr)[9] with alkali solutions of 2,5-dimercapto-1,3,4-thiadiazole[11] in aqueous alcohol. Under similar conditions compounds **3—5** were obtained. Preliminary experiments showed that paraquinone adds to compound **1** readily at room temperature in an ethanol or acetic acid medium. It is convenient to control the reaction by changing the oxidizing ability of quinone in the solution (starch—iodide paper). The band in the area of 3300 cm^{-1} indicating the presence of phenol hydroxyls was observed in the IR-spectra of the product (**6**) formed in this process.

At a 1:1 molar ratio compound **2** in a glacial acetic acid medium reacts with molecular bromine to yield product **7**. In the ^1H NMR spectrum of compound **7** the signal of the pyrimidine cycle C—H proton is absent, although in the spectrum of starting compound **2** the signal with chemical shift 6.17 ppm is present. The protons of the CH groups of compounds **2** and **7** resonate at 2.17 ppm and 2.37 ppm respectively.

The reaction of amine **2** with acid chlorides readily proceeds in dioxane, THF or pyridine at room temperature. Trapping the hydrogen chloride with triethylamine or pyridine improves the yields of the target products (**8—11**). The characteristics of compounds **8—11** obtained from benzoyl chloride, ethyl, β-chloroethyl, and *n*-buthylchloroformiates are given in Table 1.

Cyclodehydration of compounds **2** and **7** with ethyl acetoacetate and diethyl malonate in polyphosphoric acid (PPA) was successful only in the case of the

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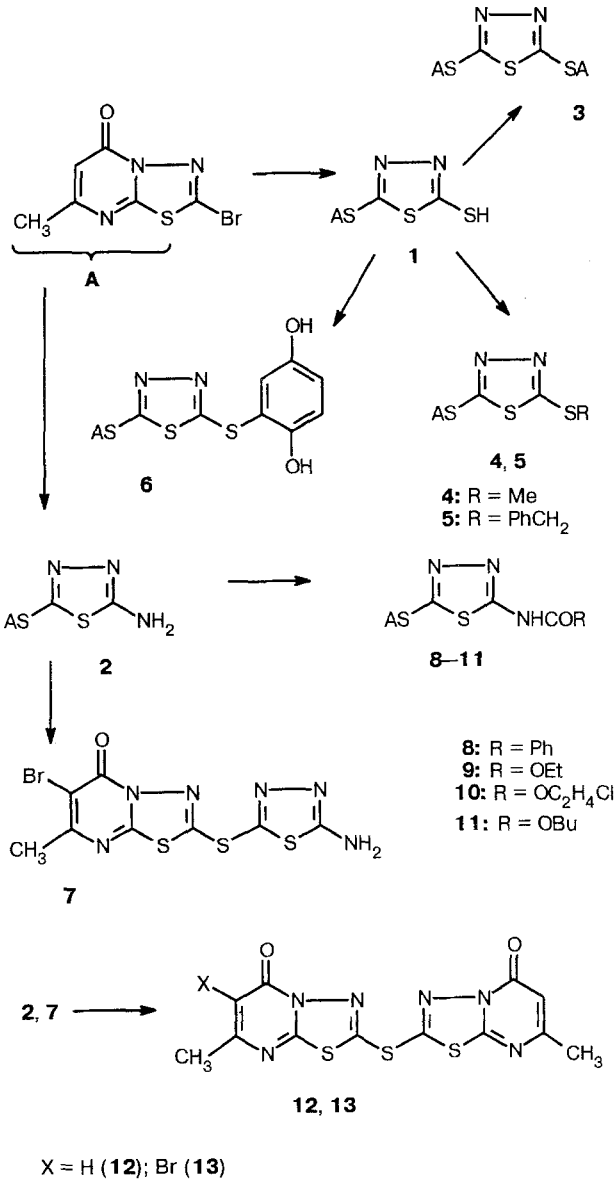
Scheme 1



ketoester. Attempts to cyclize compounds **2** and **7** with diethyl malonate in PPA at 100°C were unsuccessful regardless of the reaction time. In all cases only the initial compounds were separated. In the ^{1}H NMR spectra of compounds **12** and **13** the signals of the amino group protons at 7.87 ppm are absent, which indicates the participation of these groups in the condensation. In the IR spectra of compounds **12, 13** the characteristic carbonyl group valence vibration bands are present, *i.e.*, one band at 1690 cm^{-1} for compound **12** and two bands at 1690 and 1705 cm^{-1} for compound **13**, which verify the existence of two non-equivalent carbonyl groups in that compound. Spectral data of all the synthesized compounds are given in Table 2. In the IR spectra of compounds **1—13** an intense carbonyl group band at 1710—1690 cm^{-1} is observed. The average intensity band at 1570—1550 cm^{-1} can be assigned to the valence C=N vibrations together with CH=CH vibrations of the thiadiazolopyrimidine cycle.

Table 1. Characteristics of synthesized compounds

Compound	Yield (%)	M.p. /°C	Found (%) / Calculated C	Found (%) / Calculated H	Molecular formula
1	97	208—210	31.04 / 30.46	1.70 / 1.59	$C_8H_5N_5OS_4$
2	93	239—240	31.94 / 32.20	2.14 / 2.02	$C_8H_6N_7OS_3$
3	97	144—145	34.81 / 34.98	1.52 / 1.67	$C_{14}H_8N_8O_2S_5$
4	85	150—152	33.65 / 32.83	2.21 / 2.14	$C_9H_7N_5OS_4$
5	75	164—165	43.89 / 44.42	2.57 / 2.73	$C_{15}H_{11}N_5OS_4$
6	90	179—180	38.91 / 39.70	2.25 / 2.14	$C_{14}H_9N_5O_3S_4$
7	93	244—245	25.70 / 25.46	1.27 / 1.33	$C_8H_5BrN_6OS_3$
8	95	262—263	44.97 / 44.76	2.33 / 2.50	$C_{15}H_{10}N_6O_2S_3$
9	79	219—221	35.57 / 35.66	2.94 / 2.72	$C_{11}H_{10}N_6O_3S_3$
10	75	198—199	32.62 / 32.60	2.44 / 2.22	$C_{11}H_9ClN_6O_3S_3$
11	69	212—213	39.69 / 39.18	2.91 / 3.04	$C_{13}H_{14}N_6O_3S_3$
12	91	286—287	40.19 / 39.54	2.34 / 2.21	$C_{16}H_8N_6O_2S_3$
13	93	270—271	32.71 / 32.50	1.91 / 1.69	$C_{12}H_7BrN_6O_2S_2$

Experimental

IR spectra were recorded on a «UR-20» spectrophotometer in the 3700—400 cm^{-1} area using KBr prisms. ^{1}H NMR spectra were obtained on a «Tesla BS 487 C» spectrometer at 80 MHz in DMSO, internal standard, HMDS. Melting points were measured on a «Boetius» micro heating table.

General procedure for the synthesis of sulfides 1—5: 2-(5-mercapto-1,3,4-thiadiazolylthio)- (**1**), 2-(5-amino-1,3,4-thiadiazolylthio)- (**2**), 2-(5-methylthio-1,3,4-thiadiazolylthio)- (**4**) and 2-(5-benzylthio-1,3,4-thiadiazolylthio)-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (**5**), 2,5-bis-(7-methyl-5-ozo-5*H*-1,3,4-thiadiazolyl[3,2-*a*]pyrimidyl-2-thio)-1,3,4-thiadiazole (**3**).

Table 2. Spectral characteristics of compounds **1—13**

Compound	IR, ν/ cm^{-1}	^1H NMR, δ
1	1691 (C=O); 1568 (C=N); 3309 (NH)	6.19(s, 1 H, CH); 2.33(s, 3 H, CH_3)
2	1680 (C=O); 1565 (C=N); 3280 (NH)	7.87(s,2 H, NH_2); 6.17(s, 1 H, CH); 2.17(s, 3 H, CH_3)
3	1680 (C=O); 1568 (C=N)	6.23(s, 1 H, CH); 2.20(s, 3 H, CH_3)
4	1690 (C=O); 1570 (C=N)	6.20(s, 1 H, CH); 2.72(s, 3 H, CH_3); 2.21(s, 3 H, CH_3)
5	1685 (C=O); 1570 (C=N)	7.3 (m, 5 H, Ar); 6.2(s, 1 H, CH); 4.55(s, 2 H, CH); 2.30(s, 3 H, CH_3)
6	1683 (C=O); 1572 (C=N); 3300 (OH)	7.1(m, 2 H, Ar); 6.82(s, 1 H, Ar)
		6.21(s, 1 H, CH); 2.22(s, 3 H, CH_3)
7	1680 (C=O); 1550 (C=N); 3370 (NH); 760 (C—Br)	7.87(s, 2 H, NH_2); 2.37(s, 3 H, CH_3)
8	1680 (C=O); 1660 (C=O); 1550 (C=N); 3340 (NH)	7.62(m, 2 H, Ar); 7.21(m, 3 H, Ar); 6.22(s, H, CH); 2.21(s, 3 H, CH_3)
9	1715 (C=O); 1695 (C=O); 1570 (C=N); 3430 (NH)	6.22(s, 1 H, CH); 4.22(q, 2 H, CH_2); 2.2(s, 3 H, CH_3); 1.1(t, 3 H, CH_3)
10	1683 (C=O); 1725 (C=O); 1568 (C=N); 3400 (NH)	6.2(s, 1 H, CH); 4.42(t, 2 H, CH_2); 3.82(t, 2 H, CH_2); 2.37(s, 3 H, CH_3)
11	1690 (C=O); 1680 (C=O); 1570 (C=N); 3275 (NH)	7.9(s, 1 H, NH); 6.22(s, 1 H, CH); 4.2(t, 2 H, CH_2); 2.17(s, 3 H, CH_3)
		1.45(m, 4 H, CH_2); 0.8(t, 3 H, CH_3)
12	1690 (C=O); 1570 (C=N)	6.25(s, 1 H, CH); 2.21(s, 3 H, CH_3)
13	1703 (C=O); 1690 (C=O); 1570 (C=N); 780 (C—Br)	6.1(s, 1 H, CH); 2.72(s, 3 H, CH_3); 2.2(s, 3 H, CH_3)

0.01 mol of sodium hydroxide in 5 ml of water, and then, over 15 min, 0.01 mol of the respective alkyl halide were added to a solution or suspension of 0.01 mol of mercapto-1,3,4-thiadiazole in 15 ml of alcohol at ~20°C with stirring. The reaction mixture was stirred at 40—50°C for 40—60 min. The solution was cooled and diluted with an equal volume of water, and the precipitate was filtered off, washed with water (20 ml) and dried. The target products were crystallized from aqueous dioxane (1:3). In the syntheses of compounds **1—3** 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,4-*a*]pyrimidine was used, while methyl iodide and benzyl chloride were used for preparations of **4** and **5** respectively.

2-[5[(2,5-Dihydroxyphenylthio)-1,3,4-thiadiazolylthio]-7-methyl-5-oxo-5*H*-1,3,4-thidiazolo[3,2-*a*]pyrimidine (6). 0.01 mol of compound **1** was suspended in 15 ml of ethanol and 0.01 mol of *para*-quinone was added. The reaction mixture was stirred for 2.5 h. The precipitated residue was filtered off, washed with water (2× 10 ml), dried in the air, and recrystallized from aqueous dioxane (1:4).

2-(5-Amino-1,3,4-thiadiazolylthio)-6-bromo-7-methyl-5-oxo-5*H*-1,3,4-thidiazolo[3,2-*a*]pyrimidine (7).

To a suspension of 0.01 mol of compound **2** in 10 ml of glacial acetic acid was added 0.01 mol of bromine in 5 ml of acetic acid. The reaction mixture was stirred for 2 h and then stored for 5—8 h. Then a solution of 0.01 mol of sodium acetate in 30 ml of water was added to the reaction mixture. The precipitate was filtered off, washed with water (20 ml), and dried in the air. The target product was recrystallized from aqueous dioxane (1:2).

General procedure for the synthesis of 2-(5-R′-1,3,4-thiadiazolylthio)-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines 8 — 11: 2-(5-benzoylamino- (**8**), 2-(5-ethoxycarbonylamino- (**9**), 2-(5-β-chloroethoxycarbonylamino- (**10**) and 2-(5-butoxycarbonylamino-1,3,4-thiadiazolylthio)-7-methyl-5-oxo-5*H*-1,3,4-thidiazolo[3,2-*a*]pyrimidine (**11**).

To 15 ml of pyridine at 0—5°C was added 0.01 mol of amine **2**. The reaction mixture was stored for 30 min, and then 0.01 mol of benzoyl chloride (compound **8**) or the respective chloroformate (compounds **9—11**) was added dropwise over a period of 20 min. The reaction mixture was stirred for 2—3 h, then stored for 8—10 h at ~20°C and diluted with 50 ml of water. The precipitate was filtered off, washed with water (3 × 10 ml), dried in the air, and recrystallized from a water—dioxane mixture (1:4).

Synthesis of the bis-(7-methyl-5-oxo-5*H*-1,3,4-thidiazolo[3,2-*a*]pyrimidyl-2)sulfide (12) and 6-bromo-bis-(7-

methyl-5-oxo-5*H*-1,3,4-thidiazolo[3,2-*a*]pyrimidyl-2)sulfide (13). 0.01 mol of **6** or **7** was dissolved in 10—15 g of PPA with mild heating, and with vigorous stirring 0.011 mole of ethyl acetate was added dropwise. The reaction mixture was heated for 3 h at 100°C over a boiling water bath. After cooling, the reaction mixture was diluted with 30—50 ml of water. The precipitate was filtered off and recrystallized from aqueous dioxane (1:3).

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Interaction of 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine with methylene-active compounds and acid hydrolysis of its products

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Reactions of 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine with sodium derivatives of pentane-2,4-dione, malonodinitrile, Meldrum acid, acetoacetic, cyanoacetic and malonic esters have been shown to give the respective substituted derivatives. Azinyl-ylidene tautomerism has been found to be characteristic of these compounds, the latter existing mainly in the ylidene form. The acid hydrolysis of pentane-2,5-dione and cyanoacetic and malonic esters derivatives has been investigated.

Key words: nucleophilic substitution reaction, 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine, methylene active compounds (pentane-2,5-dione, malonodinitrile, Meldrum acid, acetoacetic, cyanoacetic, malonic esters), azinyl-ylidene tautomerism, ketonic and acidic cleavage.

In a continuation of our investigations of the reactivity of the bromine atom in 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (BTP) under conditions of nucleophilic substitution,[1—3] the interactions of BTP with methylene-active compounds (MC) have been examined. The latter, when converted to sodium derivatives with the use of sodium ethylate in absolute EtOH, participate in the reaction to yield new 1,3,4-thiadiazolo[3,2-*a*]pyrimidine (TP) derivatives (Scheme 1).

We used such MC as pentane-2,5-dione, Meldrum acid (isopropylidenemalonate, 2,2-dimethyl-1,3-dioxane-4,6-dione), malonodinitrile, and acetoacetic, cyanoacetic, and malonic esters. The reaction of MC with BTP proceeds at room temperature. Mild heating or reflux of the reaction mixture accelerates completion of the reac-

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