Some transformations of 2-chloromethyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one

S. Sh. Shukurov,[a] M. A. Kukaniev,[a] M. I. Nasyrov,[a] K. S. Zakharov,[a] and R. A. Karakhanov[b]*

[a]V. I. Nikitin Institute of Chemistry, Academy of Sciences of Republic Tadzhikistan, 734063 Dushanbe, Tadzhikistan
[b]I. M. Gubkin State Academy of Petroleum and Gas, 65 Leninsky prosp., 117917 Moscow, Russian Federation. Fax: +7 (095) 135 8895

The reactions of 2-chloromethyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one with *tert*-butyl hypochlorite and molecular bromine and the replacement of the chlorine atom in the chloromethyl group through the action of piperidine and morpholine were investigated.

Key words: electrophilic and nucleophilic substitution; 2-chloromethyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one; *tert*-butyl hypochlorite; molecular bromine; piperidine; morpholine.

Chloromethyl substituted 5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones (TP) attract attention of researchers owing to their high reactivity. Methods for the preparation of 7-chloromethyl-2-methylthio-TP[1] and 2-chloromethyl-7-methyl-TP[2] (**1**) have been reported. Derivatives of **1** have not been investigated due to its multistep synthesis. Recently we have developed a relatively simple (one-pot) method for preparing compound **1** in 63 % yield by the following reaction:

$$NH_2NHCSNH_2 + ClCH_2COOH + CH_3COCH_2COOC_2H_5 \rightarrow \mathbf{1}$$

The synthesis of TP **1** will be described in more detail in a separate communication. In the present work we report some tentative results of the study of chemical transformations of compound **1** (Scheme 1). In particular, we have found a relatively simple way to introduce a Cl atom into the pyrimidine ring using *tert*-butyl hypochlorite. The reaction of **1** with an equimolar amount of a chlorinating agent in *tert*-butyl alcohol occurs over 2 h and gives chloride **2** in a quantitative yield. The existing methods for the synthesis of 6-chloro-TP, in which chloroketoethers are used for building the pyrimidine ring of TP, seem to be more complex.

The bromo substituted derivative **3** is formed through the action of molecular bromine on TP **1** in glacial acetic acid. The ^1H NMR spectra of compounds **2** and

Scheme 1

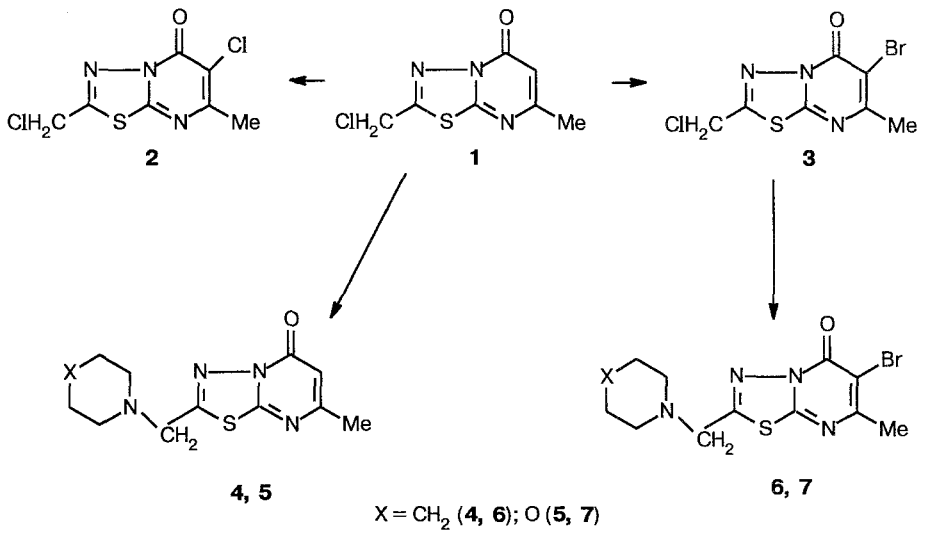

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Table 1. Characteristics of compounds **1**—**7** synthesized

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
2-Chloromethyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**1**)	63	182—183	38.58 38.98	2.68 2.80	19.33 19.48	$C_7H_6ClN_3OS$
6-Chloro-2-chloromethyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**2**)	90	154—156	34.03 33.61	1.80 2.01	16.65 16.80	$C_7H_5Cl_2N_3OS$
6-Bromo-2-chloromethyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**3**)	96	158—161	28.14 28.54	1.93 1.71	14.06 14.26	$C_7H_5ClBrN_3OS$
7-Methyl-2-(piperidinomethyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**4**)	60	149—150	54.04 54.52	5.85 6.10	21.05 21.19	$C_{12}H_{16}N_4OS$
7-Methyl-2-(morpholinomethyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**5**)	65	166—167	52.36 52.78	5.31 5.64	22.17 22.38	$C_{11}H_{14}N_4O_2S$
6-Bromo-7-methyl-2-(piperidinomethyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**6**)	70	109—114	42.32 41.99	4.10 4.40	16.24 16.32	$C_{12}H_{15}BrN_4OS$
6-Bromo-7-methyl-2-(morpholinomethyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**7**)	64	141—143	39.71 40.13	4.12 3.98	16.76 17.02	$C_{11}H_{13}BrN_4O_2S$

3 exhibit no signals in the 6.2 ppm region corresponding to a proton in position 6 and exhibit signals at 2.52 ppm (compound **2**) or 2.57 ppm (compound **3**) associated with the methyl-group protons. Singlets at 4.87 ppm confirm that both compounds contain a chloromethyl group.

The Cl atom of the chloromethyl group may be readily replaced through the action of various nucleophiles. We studied the reactions of compounds **1** and **3** with piperidine and morpholine occurring at room temperature in ethanol to afford amines **4** and **5** and the corresponding bromoamines **6** and **7** in moderate yields. The properties of the compounds synthesized are listed in Table 1.

It should be noted that even an excess of amine and boiling the reaction mixture do not result in the replacement of the bromine atom in the pyrimidine ring of TP.

Though we did not study the conversion of compounds **4** and **5** into bromides **6** and **7**, one may say with confidence that this transformation is possible. This conclusion is based on the detailed study of bromination of 2-amino-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one and the corresponding TP with *N*-substituents in the pyrimidine ring.[3] Oxidative bromination only occurs in the case of 2-hydrazino substituted TP.[4]

The ^{1}H NMR spectra of compounds **4** and **6** (Table 2) exhibit multiplet signals for methylene protons in the 1.55—1.50 and 2.57—2.27 ppm regions corresponding to the piperidine ring. The singlets at 3.80 and 3.88 ppm are due to the presence of a bridging CH_2 group.

The ^{1}H NMR spectra of compounds **5** and **7** (see Table 2) exhibit signals corresponding to the four meth-

Table 2. Spectroscopic parameters of compounds **1**—**7**

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ
1	1710 (S=O); 1575 (C=N)	6.27 (s, H, CH); 4.85 (s, 2 H, CH_2); 2.35 (s, 3 H, CH_3)
2	1680 (S=O); 1560 (S=N)	4.87 (s, 2 H, CH_2); 2.52 (s, 3 H, CH_3)
3	1681 (S=O); 1565 (S=N)	4.87 (s, 2 H, CH_2); 2.57 (s, 3 H, CH_3)
4	1692 (S=O); 1555 (S=N)	6.22 (s, H, CH); 3.80 (s, 2 H, CH_2); 2.57 (m, 4 H, CH_2); 2.35 (s, 3 H, CH_3); 2.27 (m, 4 H, CH_2); 1.55 (m, 2 H, CH_2)
5	1685 (S=O); 1570 (S=N)	6.20 (s, H, CH); 3.85 (s, 2 H, CH_2); 3.60 (t, 4 H, CH_2—O); 2.70 (t, 4 H, CH_2—N); 2.35 (s, 3 H, CH_3)
6	1693 (S=O); 1572 (S=N)	3.88 (s, 2 H, CH_2); 2.58 (s, 3 H, CH_3); 2.55 (m, 8 H, CH_2); 1.50 (m, 2 H, CH_2)
7	1692 (S=O); 1560 (S=N)	3.85 (s, 2 H, CH_2); 3.60 (t, 4 H, CH_2—O); 2.70 (t, 4 H, CH_2—N); 2.57 (s, 3 H, CH_3)

ylene protons of the $-CH_2OCH_2-$ group in the 3.60 ppm region, four protons of the $-CH_2NCH_2-$ group (~2.70 ppm), and two protons of the CH_2 group at the thiadiazole ring (3.85 ppm).

From the analysis of the ^1H NMR spectra of compounds **1—3** and **4—7** it follows that the signals for the protons of the CH_2 group directly bound to the thiadiazole ring shift upfield from the 4.85—4.87 ppm region typical of chloromethyl derivatives, due to the lower electronegativity of the amino group.

The IR spectra of compounds **1—7** (see Table 2) display an intense band in the 1680—1710 cm^{-1} region associated with the stretching vibrations of the carbonyl group. The bands at 1550—1580 cm^{-1} may be assigned to vibrations of the C=N and C=C bonds of the TP ring.

Experimental

IR spectra were recorded on a UR-20 instrument in the region from 3700 cm^{-1} to 400 cm^{-1} in thin films using KBr prisms. ^1H NMR spectra were run on a Tesla BS 487 C spectrometer (80 MHz) in DMSO, and HMDS was used as the internal standard. Melting points were determined on a Boetius hot-stage apparatus.

6-Chloro-2-chloromethyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (2). Compound **1** (0.01 mol) and 15 mL of *tert*-butanol were placed in a flask equipped with a reflux condenser, and *tert*-butyl hypochlorite (0.0105 mol) was added with boiling. The reaction mixture was refluxed for an additional 2 h. Evaporation of the solvent gave 2.25 g of compound **2**. The product was recrystallized from dioxane.

6-Bromo-2-chloromethyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3). Compound **1** (0.04 mol) and 20 mL of glacial acetic acid were placed in a flask equipped with a mechanical stirrer. A solution of bromine (0.04 mol) in 10 mL of glacial acetic acid was added portionwise over a period of 10—15 min. The mixture was stirred for 2 h at ~20 °C and 1 h at 50 °C and diluted with a solution of NaOAc (0.04 mol) in 100 mL of water. The precipitate was filtered off and dried to give 11.2 g of compound **3**. The product was recrystallized from aqueous dioxane (1 : 1).

6-Bromo-7-methyl-2-morpholino(piperidino)methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones (4—7). Piperidine or morpholine (0.02 mol) was added with stirring to compound **1** or **3** (0.01 mol) in 15 mL of aqueous ethanol (1:1). The reaction mixture was stirred for 12 h, allowed to stand for 24 h, and diluted with 20 mL of water. The precipitate was filtered off and dried in air. Compounds **4—7** were crystallized from a chloroform—hexane mixture (1:1).

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