Synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives from 6-methyl-2-thiouracil and 1-acyl-2-bromoacetylenes. X-ray structural study of 3-benzoyl-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one

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3-Acyl-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones were synthesized by the reaction of 1-acyl-2-bromoacetylenes with 6-methyl-2-thiouracil, carried out with heating in DMF, dioxane, or acetonitrile in the presence of triethylamine. The structure of 3-benzoyl-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one was established by X-ray structural analysis.

Key words: 1-acyl-2-bromoacetylenes; 3-acyl-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones; intramolecular cyclization; X-ray structural analysis.

The reactions of ketones of the acetylene series with cyclic thioureas and heterocyclic compounds containing the thiourea fragment are poorly known. It is known[1] that α-oxoacetylenes and dibenzoylacetylene react with benzimidazole-2-thione in methanol or acetonitrile to form 2-(acylvinylthio)benzimidazoles in yields of 68—96%. Reactions of acylacetylenes with 1,2,4-triazole-3-thione and its 5-substituted derivatives afford substituted 2-(acylvinyl)-1,2,4-triazole-5-thione and 3-(acylvinylthio)- and 1-acylvinyl-5-(acylvinylthio)-1,2,4-triazoles.[2,3] Heating imidazolidine-2-thione with benzoylacetylene in MeOH afforded bis(2-acylvinyl) sulfides (the yields were 40—50%), whereas reactions of these compounds in MeCN at 20 °C produced 2-(benzoylvinylthio)imidazoline (the yield was 78%).[4]

We studied the reaction of 6-methyl-2-thiouracil (**1**) with an equimolar amount of 1-acyl-2-bromoacetylenes (**2a,b**) carried out in the presence of NEt_3 in DMF, MeCN, or dioxane (Scheme 1).

Apparently, intermediate acylethynyl sulfides **3a,b** or **5a,b** form at the first stage as a result of elimination of HBr. Under the conditions chosen, these intermediate compounds readily undergo intramolecular cyclization to form thiazolo[3,2-*a*]pyrimidines **4a,b** or **6a,b**. Analysis of the ^1H and ^{13}C NMR spectra makes it possible to choose between possible structures **4** and **6**; however, it was established by X-ray structural analysis that the product of the reaction of thiouracil **1** with ketone **2a** has the structure of **4a** (Fig. 1).

The bond lengths in the planar bicyclic fragment of 3-benzoyl-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**4a**) are indicative of a high degree of delocalization of the π-electron system.[5] The benzoyl group is virtually excluded from conjugation due to the rotation of this group with respect to the bicyclic fragment about the

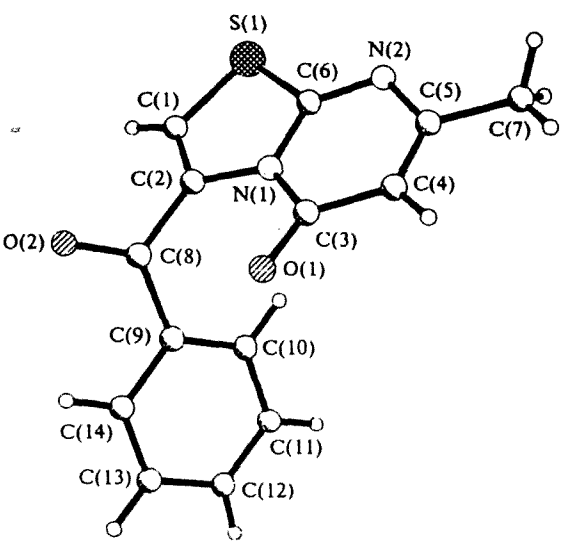

Fig. 1. Overall view of molecule **4a**.

† Deceased in 1995.

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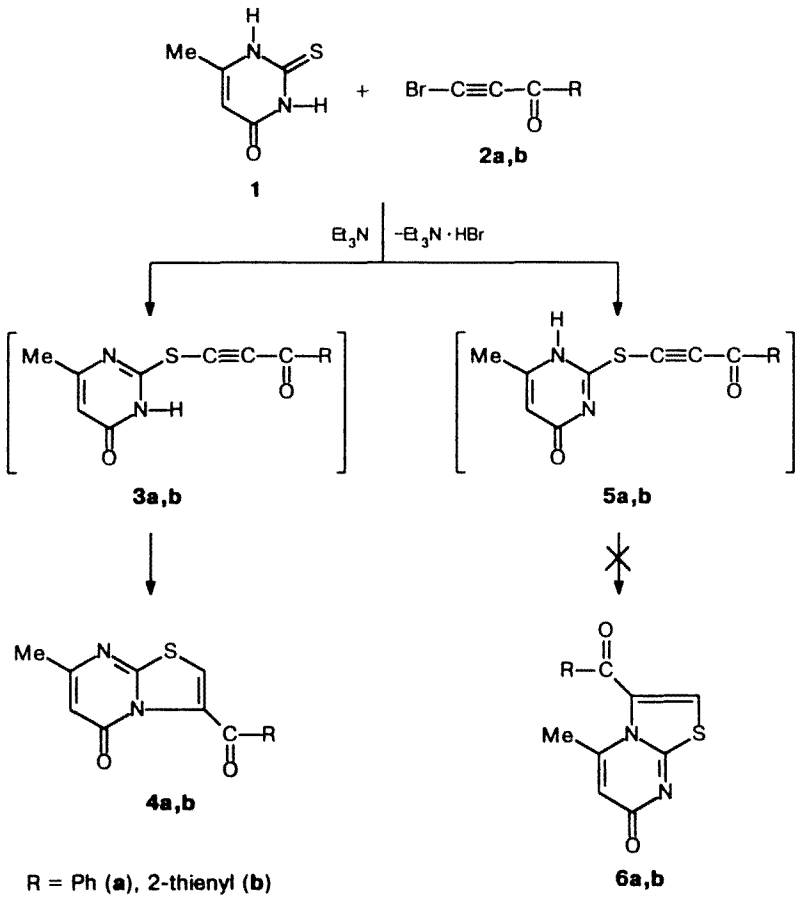
Scheme 1



C(2)—C(8) bond by 58.1(3)° (the C(1)—C(2)—C(8)—O(2) torsion angle); the carbonyl group is slightly bent away from the plane of the benzene ring (the O(2)—C(8)—C(9)—C(14) torsion angle is 9.7(3)°).

The molecular packing in the crystal is determined by the normal van der Waals contacts[6] and has no special features.

The reaction of compounds **1** with **2b** in the absence of NEt_3 yielded thiazolo[3,2-*a*]pyrimidin-5-one hydrobromide (**4b**).

Experimental

The ^1H NMR spectra (in DMSO-d_6) were recorded on a BS-487C spectrometer (80 MHz) with HMDS as the internal standard. The ^{13}C NMR spectra were measured on an FX-90Q spectrometer (22.49 MHz) in $CDCl_3$ with HMDS as the internal standard.

3-Benzoyl-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (4a). Two drops of NEt_3 were added to a solution of thiouracil **1** (1.41 g, 0.01 mol) in DMF (10 mL), and then a solution of ketone **2a** (2.09 g, 0.01 mol) in DMF (10 mL) was added slowly to the reaction mixture (the reaction mixture warmed up). The mixture was stirred at 60—70 °C for 5 h and then kept at ~20 °C for 8 h. The precipitate that formed was filtered off and recrystallized from EtOH. Thiazolo[3,2-*a*]pyrimidine **4a** was obtained in a yield of 2.02 g (75%), m.p. 176—179 °C. When the reaction was performed in dioxane at 85—90 °C, the yield was 63%; when the reaction was carried out in MeCN at 80 °C, the yield was 38%. Found (%): C, 62.0; H, 3.7; N, 10.3; S, 11.6. $C_{14}H_{10}N_2O_2S$. Calculated (%): C, 62.2; H, 3.7; N, 10.4; S, 11.9. ^1H NMR, δ: 2.35 (s, 3 H, CH_3); 6.05 (s, 1 H, C(6)H); 7.08 (s, 1 H, C(2)H); 7.36—7.90 (m, 5 H, H arom.). ^{13}C NMR, δ: 23.88 (C(7)); 104.84 (C(4)); 112.64 (C(1)); 128.67, 128.99, 133.70, 136.48 (Ph); 134.65 (C(5)); 158.14 (C(2)); 162.05 (C(6)); 164.30 (C(8)); 184.23 (C(3)).

Table 1. Bond lengths (*d*) in molecule **4a**

Bond	*d*/Å	Bond	*d*/Å
S(1)—C(1)	1.724(3)	C(3)—C(4)	1.422(3)
S(1)—C(6)	1.734(2)	C(4)—C(5)	1.359(4)
N(1)—C(2)	1.409(3)	C(5)—C(7)	1.494(4)
N(1)—C(3)	1.416(3)	C(8)—C(9)	1.485(3)
N(1)—C(6)	1.374(3)	C(9)—C(10)	1.381(3)
N(2)—C(5)	1.367(3)	C(9)—C(14)	1.394(3)
N(2)—C(6)	1.304(3)	C(10)—C(11)	1.391(4)
O(1)—C(3)	1.226(3)	C(11)—C(12)	1.369(4)
O(2)—C(8)	1.217(3)	C(12)—C(13)	1.372(4)
C(1)—C(2)	1.334(3)	C(13)—C(14)	1.376(4)
C(2)—C(8)	1.503(3)		

Table 2. Bond angles (ω) in molecule **4a**

Angle	ω/deg	Angle	ω/deg
C(1)—S(1)—C(6)	90.1(1)	C(4)—C(5)—C(7)	121.9(2)
C(2)—N(1)—C(3)	124.8(2)	S(1)—C(6)—N(1)	110.7(2)
C(2)—N(1)—C(6)	113.6(2)	S(1)—C(6)—N(2)	123.9(2)
C(3)—N(1)—C(6)	121.3(2)	N(1)—C(6)—N(2)	125.4(2)
C(5)—N(2)—C(6)	114.9(2)	O(2)—C(8)—C(2)	117.7(2)
S(1)—C(1)—C(2)	114.0(2)	O(2)—C(8)—C(9)	122.5(2)
N(1)—C(2)—C(1)	111.5(2)	C(2)—C(8)—C(9)	119.3(2)
N(1)—C(2)—C(8)	124.8(2)	C(8)—C(9)—C(10)	122.2(2)
C(1)—C(2)—C(8)	123.5(2)	C(8)—C(9)—C(14)	118.2(2)
N(1)—C(3)—O(1)	119.3(2)	C(10)—C(9)—C(14)	119.6(2)
N(1)—C(3)—C(4)	111.7(2)	C(9)—C(10)—C(11)	119.6(2)
O(1)—C(3)—C(4)	129.0(2)	C(10)—C(11)—C(12)	120.3(3)
C(3)—C(4)—C(5)	122.3(2)	C(11)—C(12)—C(13)	120.2(3)
N(2)—C(5)—C(4)	123.5(2)	C(12)—C(13)—C(14)	120.5(3)
N(2)—C(5)—C(7)	114.6(2)	C(9)—C(14)—C(13)	119.8(2)

Table 3. Coordinates of nonhydrogen atoms (×10⁴) and hydrogen atoms (×10³) in the structure of **4a**

Atom	*x*	*y*	*z*
S(1)	3524(1)	2783(1)	100(1)
N(1)	206(4)	3174(2)	822(1)
N(2)	2502(4)	5180(2)	563(1)
O(1)	−3362(3)	3228(2)	1353(1)
O(2)	−2937(4)	−38(2)	783(1)
C(1)	1778(5)	1422(3)	345(1)
C(2)	133(5)	1760(2)	721(1)
C(3)	−1547(5)	3867(2)	1154(1)
C(4)	−859(5)	5272(2)	1206(1)
C(5)	1103(5)	5860(2)	929(1)
C(6)	1996(5)	3874(2)	529(1)
C(7)	1894(8)	7324(3)	1003(1)
C(8)	−1392(5)	731(2)	1027(1)
C(9)	−703(5)	568(2)	1596(1)
C(10)	1418(5)	1269(3)	1850(1)
C(11)	2052(6)	1027(3)	2379(1)
C(12)	594(6)	94(3)	2646(1)
C(13)	−1502(6)	−611(3)	2394(1)
C(14)	−2188(6)	−373(3)	1873(1)
H(1)	219(6)	55(3)	23(1)
H(4)	−177(6)	579(3)	143(1)
H(7a)	166(6)	788(3)	70(1)
H(7b)	105(6)	771(3)	122(1)
H(7c)	395(7)	744(3)	105(1)
H(10)	256(6)	193(3)	166(1)
H(11)	356(6)	149(3)	255(1)
H(12)	103(6)	−16(3)	299(1)
H(13)	−262(6)	−124(3)	258(1)
H(14)	−371(6)	−82(3)	168(1)

7-Methyl-3-thienyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (4b) was prepared analogously to compound **4a** from ketone **2b** and thiouracil **1**. The yield of **4b** was 53%, m.p. 148—149 °C (from the 1 : 1 EtOH—H_2O mixture). Found (%): C, 52.1; H, 2.8; N, 9.8; S, 23.3. $C_{12}H_8N_2O_2S_2$. Calculated (%): C, 52.2; H, 2.9; N, 10.1; S, 23.2. ^{1}H NMR, δ: 2.32 (s, 3 H, CH_3); 6.11 (s, 1 H, C(6)H); 7.05 (s, 1 H, C(2)H); 7.35—8.03 (m, 3 H, thienyl).

Hydrobromide of compound 4b. A mixture of thiouracil **1** (0.35 g, 2.5 mmol) and ketone **2b** (0.54 g, 2.5 mmol) in dioxane (25 mL) was warmed at 85—90 °C for 4 h and then cooled. The yellow precipitate that formed was filtered off, washed on a filter with cold ether, and dried. Hydrobromide **4b** was obtained in a yield of 0.47 g (52%), m.p. 254—255 °C (in MeCN, the yield was 32%). Found (%): C, 40.3; H, 2.3; Br, 22.3; N, 7.9; S, 17.7. $C_{12}H_9BrN_2O_2S_2$. Calculated (%): C, 40.3; H, 2.5; Br, 22.4; N, 7.8; S, 17.9. ^{1}H NMR, δ: 2.36 (s, 3 H, CH_3); 6.19 (s, 1 H, C(6)H); 6.89 (s, 1 H, C(2)H); 7.30—8.11 (m, 3 H, thienyl).

X-ray structural study of compound 4a. Crystals of compound **4a** are monoclinic, at 20 °C: a = 4.926(2) Å, b = 9.791(3) Å, c = 25.576(5) Å, β = 93.27(2)°, V = 1232(2) Å^3, d_{calc} = 1.458 g cm^{-3}, space group $P2_1/n$, Z = 4. The unit cell parameters and intensities of 1855 reflections with $F > 6\sigma(F)$ were measured on an automated Enraf-Nonius CAD-4 diffractometer (Mo-Kα radiation, graphite monochromator, θ/2θ-scanning technique, $2\theta_{max}$ = 60°).

The structure was solved by the direct method with the use of the SHELXTL PLUS program package.[7] The positions of the hydrogen atoms were located from the difference electron density synthesis and refined isotropically. Full-matrix least-squares refinement with anisotropic thermal parameters for nonhydrogen atoms converged to R = 0.039 (R_w = 0.039, S = 1.39). The bond lengths and bond angles are given in Tables 1 and 2, respectively. Atomic coordinates for the structure of **4a** are listed in Table 3.

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