ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 1, pp. 103–107. © Pleiades Publishing, Ltd., 2007.
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Reaction of *N*-Aryl-3-oxobutanethioamides with 2-Amino-1,3-thiazole and 2-Amino-1,3-benzothiazole

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Received December 20, 2005

Abstract—*N*-Aryl-3-oxobutanethioamides react with 2-amino-1,3-thiazole (2-amino-1,3-benzothiazole) in acetic acid to give mixtures of 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-thione (2-methyl-4*H*-pyrimido-[2,1-*b*][1,3]benzothiazole-4-thione) and 5-arylimino-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines (4-aryl-imino-2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazoles), whose ratio depends on the nature of the aryl substituent in the initial butanethioamide.

DOI: 10.1134/S1070428007010137

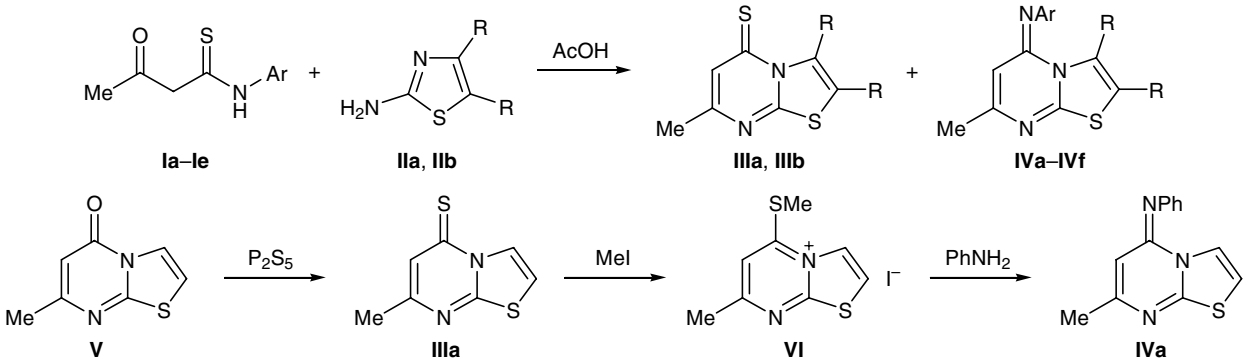
N-Aryl-3-oxobutanethioamides possess several reaction centers and are ambident substrates which can be used as starting materials in synthesis of various heterocycles [1–4]. These compounds can also act as efficient complexing agents toward heavy metal ions [5, 6], herbicides [7], and antitumor agents [8]. In addition, *N*-aryl-3-oxobutanethioamides, as well as β-dicarbonyl and β-thioxocarbonyl compounds, are capable of forming strong intramolecular hydrogen bonds, and they may exist as different tautomers, thus providing convenient models for studying prototropic tautomerism [9–11].

In continuation of our studies on heterocyclizations of *N*-aryl-3-oxobutanethioamides with difunctional 1,3-nucleophiles [12], in the present work we examined their reactions with 2-amino-1,3-thiazole and 2-amino-1,3-benzothiazole. These reactions may be considered to follow [3+3]-cyclocondensation pattern involving three possible reaction centers in *N*-aryl-3-oxobutanethioamides and two centers in 2-aminothiazole; as a result, the products may be four compounds of the thiazolo[3,2-*a*]pyrimidine series.

We found that, unlike reactions of ethyl acetoacetate and its derivatives with 2-aminothiazole and 2-aminobenzothiazole [13, 14], *N*-aryl-3-oxobutanethioamides **Ia**–**Ie** reacted with the same binucleophiles **IIa** and **IIb** in a nonselective fashion, yielding mixtures of compounds **IIIa** (**IIIb**) and **IVa**–**IVf** whose ratio depended on the nature of the aryl substituent in the initial thioamide (Scheme 1, see table).

Thiazolo[3,2-*a*]pyrimidine-5(4)-thiones **IIIa** and **IIIb** characteristically showed in the ^{1}H NMR spectra

Scheme 1.



I, Ar = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-EtOC$_6$H$_4$ (**c**), 4-ClC$_6$H$_4$ (**d**), 4-O$_2$NC$_6$H$_4$ (**e**); **II**, **III**, R = H (**a**), RR = CH=CH–CH=CH (**b**); **IV**, R = H, Ar = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-ClC$_6$H$_4$ (**c**), 4-O$_2$NC$_6$H$_4$ (**d**); RR = CH=CH–CH=CH, Ph (**e**), 4-EtOC$_6$H$_4$ (**f**).

Yields of compounds **III** and **IV** in the reactions of *N*-aryl-3-oxobutanethioamides **Ia**–**Ie** with 2-amino-1,3-thiazole (**IIa**) and 2-amino-1,3-benzothiazole (**IIb**)

Initial reactants	Yield, %	
	III	**IV**
Ia + **IIa**	30	35
Ib + **IIa**	52	20
Id + **IIa**	15	69
Ie + **IIa**	–	70
Ia + **IIb**	16	62
Ic + **IIb**	31	33

singlets from protons in the 7(2)-Me group and 6(3)-H at δ 2.32–2.35 and 7.23–7.32 ppm, respectively. The spectra of 5(4)-aryliminothiazolopyrimidines **IVa**–**IVf** contained signals from the 7(2)-Me group and 6(3)-H at δ 2.08–2.17 and 5.90–6.10 ppm. In the IR spectra of **IIIa** and **IIIb** we observed absorption bands belonging to stretching vibrations of the C=N and =C–H bonds at 1570–1580 and 3100 cm^{-1}, respectively, while the corresponding absorption bands in the spectra of **IVa**–**IVf** were located at 1590–1610, 1630–1650, and 2900–3100 cm^{-1}. However, the IR and ^1H NMR data did not allow us to distinguish between 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-thiones and 5-arylimino-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines, on the one hand, and isomeric 5-methyl-7*H*-[1,3]thiazolo[3,2-*a*]-pyrimidine-7-thiones and 7-arylimino-5-methyl-7*H*-[1,3]thiazolo[3,2-*a*]pyrimidines. Therefore, we performed a series of chemical transformations to determine the structure of compounds **III** and **IV**.

By reaction of 2-amino-1,3-thiazole with ethyl acetoacetate according to the procedure described in [13] we synthesized 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]-pyrimidin-5-one (**V**), and treatment of the latter with P_2S_5 in pyridine gave thiazolo[3,2-*a*]pyrimidine **IIIa**. The ^1H NMR spectra of samples of **IIIa** prepared from thioamide **Ia** and 2-amino-1,3-thiazole (**IIa**) and by sulfurization of known thiazolopyrimidinone **V** [13] were fully identical, and their mixture showed no depression of the melting point.

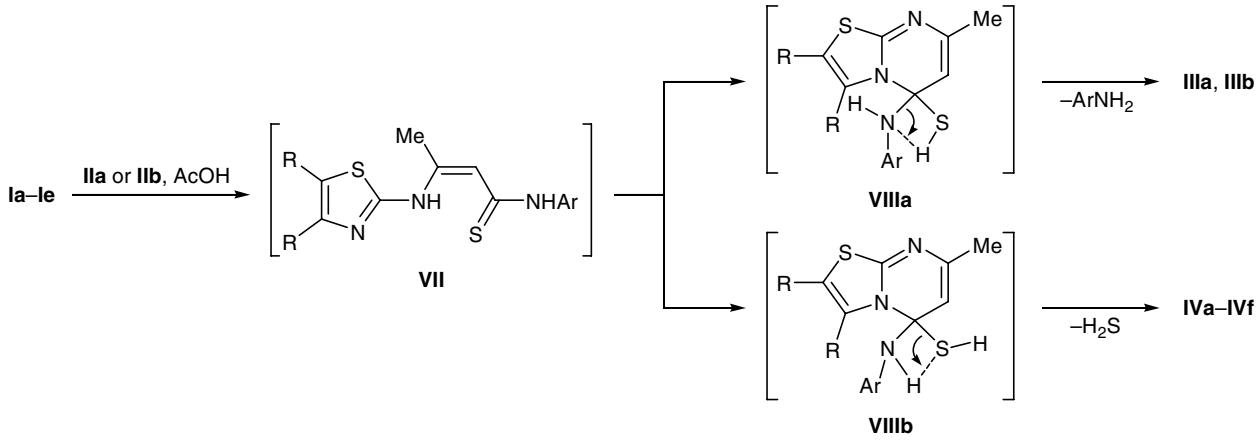
The structure of aryliminothiazolo[3,2-*a*]pyrimidines **IVa**–**IVf** was confirmed as follows. Alkylation of **IIIa** with methyl iodide gave 7-methyl-5-methylsulfanyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium iodide (**VI**). Unlike initial compound **IIIa**, all signals in the ^1H NMR spectrum of **VI** were displaced downfield by 0.35–0.76 ppm (except for the 3-H proton which is also strongly deshielded in the initial compound), indicating reduced electron density in the thiazolopyrimidine ring system of **VI**. Heating of a solution of iodide **VI** in aniline at 150°C resulted in nucleophilic replacement of the methylsulfanyl group by phenylimino with liberation of methanethiol and formation of thiazolo-[3,2-*a*]pyrimidine **IVa** (Scheme 1). The ^1H NMR spectra of samples of **IVa** obtained by aminolysis of iodide **VI** and by reaction of thioamide **Ia** with aminothiazole **IIa** were identical, and their mixture showed no depression of the melting point. Thus the structure of compounds **IIIa**, **IIIb**, and **IVa**–**IVf** was unambiguously proved by independent syntheses.

The results of our study show that, unlike 5-substituted 3-amino-1,2,4-triazoles [12], the exocyclic amino group in aminothiazoles **IIa** and **IIb** is more reactive than the endocyclic imino group N^3H (in the 2-imino tautomer) toward *N*-aryl-3-oxobutanethioamides **Ia**–**Ie**. The carbonyl group in *N*-aryl-3-oxobutanethioamides **Ia**–**Ie** is more reactive than the C=S group in reactions with 2-aminothiazoles **IIa** and **IIb**, as in reactions with arylamines [15].

It is known that thioamide **Ia** reacts with aniline and other aromatic amines in acetic acid to give enaminothioamides [15]. Therefore, we expected initial formation of enaminothioamides **VII** by reaction of thioamides **Ia**–**Ie** with aminothiazoles **IIa** and **IIb** (Scheme 2). As follows from the data in table, the mode of cyclization of enaminothioamides **VII** depends on the nature of the substituent in the benzene ring of *N*-aryl-3-oxobutanethioamide **Ia**–**Ie**. Electron-donor substituents favor formation of the corresponding thiazolo[3,2-*a*]pyrimidine-5-thione **III**. For example, in going from thioamide **Ia** (Ar = Ph) to **Ib** (Ar = 4-$MeOC_6H_4$), the yield of compound **IIIa** increases from 30 to 52%, while the yield of alternative product **IV** decreases from 35 (**IVa**) to 20% (**IVb**). By contrast, in the reaction with *p*-nitrophenyl derivative **Ie**, the yield of **IVd** reached 70%, while thazolopyrimidinethione **IIIa** was not formed at all.

Taking into account that nucleophilic substitution at a carbon atom linked to oxygen or sulfur by a double bond involves formation of a tetrahedral intermediate [16], there are reasons to believe that intramolecular cyclization of enaminothioamides **VII** follows two concurrent pathways: (1) through intermediate **VIIIa** with elimination of substituted aniline and formation of thiazolo[3,2-*a*]pyrimidine-5(4)-thione **IIIa** or **IIIb** and (2) through intermediate **VIIIb** which loses hydrogen sulfide molecule to give 5(4)-aryliminothiazolo-[3,2-*a*]pyrimidines **IVa**–**IVf**. Presumably, interme-

Scheme 2.



diates **VIIIa** and **VIIIb** are transformed via four-membered cyclic transition states in which a weak hydrogen bond (coordination) exists between the SH proton (NH proton of the *N*-arylamino group) and nitrogen atom of *N*-arylamino group (sulfur atom), depending on the basicity of the *N*-aryl group. The proposed scheme is consistent with the data given in table, which illustrate the effect of the substituent nature in initial thioamides **Ia**–**Ie** on the ratio of products **III** and **IV**.

Thus 2-amino-1,3-thiazole and 2-amino-1,3-benzothiazole react with *N*-aryl-3-oxobutanethioamides to give mixtures of 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-thione (2-methyl-4*H*-pyrimido[2,1-*b*][1,3]-benzothiazole-4-thione) and 5-arylimino-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines (4-arylimino-2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazoles), whose ratio depends on the nature of the aryl substituent in the initial butanethioamide.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded from solutions in DMSO-d_6 on a Varian-300 spectrometer (300 MHz) using tetramethylsilane as internal reference. The IR spectra were recorded in KBr on a UR-20 instrument. 7-Methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (**V**) was synthesized by the procedure reported in [13].

Reactions of *N*-aryl-3-oxobutanethioamides Ia–Ie with 2-amino-1,3-thiazole (IIa) and 2-amino-1,3-benzothiazole (IIb) (*general procedure*). A solution of 10 mmol of *N*-aryl-3-oxobutanethioamide **Ia**–**Ie** and 10 mmol of 2-amino-1,3-thiazole (**IIa**) or 2-amino-1,3-benzothiazole (**IIb**) in 8 ml of acetic acid was heated for 4 h at 100°C. The mixture was cooled, and the precipitate of compound **IIIa** or **IIIb** was filtered off. The filtrate was treated with 50 ml of 25% aqueous Na_2CO_3, the mixture was left to stand for 12 h, and the precipitate of 5-arylimino-7-methyl-5*H*-[1,3]thiazolo-[3,2-*a*]pyrimidine **IVa**–**IVd** or 4-arylimino-2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole **IVe** or **IVf** was filtered off. The yields of compounds **IIIa**, **IIIb**, and **IVa**–**IVf** are given in table.

7-Methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-thione (IIIa). mp 142–143°C (from ethanol). IR spectrum, ν, cm^{-1}: 1210, 1310, 1370, 1460, 1580, 3100. ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, 7-CH_3), 7.23 s (1H, 6-H), 7.84 d (1H, 2-H, J = 4.8 Hz), 8.66 d (1H, 3-H, J = 4.8 Hz). Found, %: C 45.86; H 3.03; N 15.18; S 35.30. $C_7H_6N_2S_2$. Calculated, %: C 46.13; H 3.32; N 15.37; S 35.18.

2-Methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-4-thione (IIIb). mp 181–183°C (from nitromethane). IR spectrum, ν, cm^{-1}: 1320, 1360, 1450, 1530, 1570, 3100. ^{1}H NMR spectrum, δ, ppm: 2.32 s (3H, 2-CH_3), 7.32 s (1H, 3-H), 7.52–7.69 m (2H, H_{arom}), 8.11 d (1H, 9-H, J = 7.8 Hz), 10.45 d (1H, 6-H, J = 8.7 Hz). Found, %: C 57.02; H 3.70; N 11.79. $C_{11}H_8N_2S_2$. Calculated, %: C 56.87; H 3.47; N 12.06.

***N*-(7-Methyl[1,3]thiazolo[3,2-*a*]pyrimidin-5-ylidene)aniline (IVa).** mp 150–153°C (from nitromethane). IR spectrum, ν, cm^{-1}: 1350, 1370, 1400, 1490, 1510, 1580, 1600, 1650, 3100. ^{1}H NMR spectrum, δ, ppm: 2.10 s (3H, 7-CH_3), 5.91 s (1H, 6-H), 6.87 m (2H, H_{arom}), 7.00 m (1H, H_{arom}), 7.31 m (2H, H_{arom}), 7.42 d (1H, 2-H, J = 4.5 Hz), 8.12 d (1H, 3-H, J = 4.5 Hz). Found, %: C 64.89; H 4.32; N 17.19. $C_{13}H_{11}N_3S$. Calculated, %: C 64.71; H 4.59; N 17.41.

4-Methoxy-*N*-(7-methyl[1,3]thiazolo[3,2-*a*]pyrimidin-5-ylidene)aniline (IVb). mp 146–148°C (from

ethanol). IR spectrum, ν, cm^{-1}: 1350, 1370, 1400, 1440, 1510, 1560, 1610, 1630, 2900–3100. ^1H NMR spectrum, δ, ppm: 2.08 s (3H, 7-CH_3), 3.73 s (3H, CH_3O), 5.90 s (1H, 6-H), 6.78 d (2H, H_{arom}, J = 8.6 Hz), 6.85 d (2H, H_{arom}, J = 8.6 Hz), 7.37 d (1H, 2-H, J = 4.3 Hz), 8.08 d (1H, 3-H, J = 4.3 Hz). Found, %: C 61.75; H 5.02; N 15.21. $C_{14}H_{13}N_3OS$. Calculated, %: C 61.97; H 4.83; N 15.49.

4-Chloro-*N*-(7-methyl[1,3]thiazolo[3,2-*a*]pyrimidin-5-ylidene)aniline (IVc). mp 183–185°C (from nitromethane). IR spectrum, ν, cm^{-1}: 1340, 1370, 1410, 1505, 1570, 1590, 1640, 3000–3100. ^1H NMR spectrum, δ, ppm: 2.12 s (3H, 7-CH_3), 5.91 s (1H, 6-H), 6.79–6.87 m (2H, H_{arom}), 7.03 m (1H, H_{arom}), 7.31 m (1H, H_{arom}), 7.43 d (1H, 2-H, J = 4.6 Hz), 8.08 d (1H, 3-H, J = 4.6 Hz). Found, %: C 56.45; H 3.37; N 15.49. $C_{13}H_{10}ClN_3S$. Calculated, %: C 56.62; H 3.66; N 15.24.

***N*-(7-Methyl[1,3]thiazolo[3,2-*a*]pyrimidin-5-ylidene)-4-nitroaniline (IVd).** mp 215–217°C (from DMSO). IR spectrum, ν, cm^{-1}: 1250, 1320, 1410, 1500, 1560, 1590, 1640, 3100. ^1H NMR spectrum, δ, ppm: 2.17 s (3H, 7-CH_3), 6.10 s (1H, 6-H), 7.08 d (2H, H_{arom}, J = 8.4 Hz), 7.52 d (1H, 2-H, J = 4.0 Hz), 8.16–8.19 m (3H, H_{arom}, 3-H). Found, %: C 54.35; H 3.31; N 19.69. $C_{13}H_{10}N_4O_2S$. Calculated, %: C 54.54; H 3.52; N 19.57.

***N*-(2-Methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-ylidene)aniline (IVe).** mp 198–199°C (from DMSO). IR spectrum, ν, cm^{-1}: 1360, 1390, 1460, 1490, 1540, 1590, 1645, 3100. ^1H NMR spectrum, δ, ppm: 2.09 s (3H, 2-CH_3), 5.99 s (1H, 3-H), 6.89 m (2H, H_{arom}), 7.06 m (1H, H_{arom}), 7.35 m (2H, H_{arom}), 7.49 (2H, H_{arom}), 7.96 m (1H, H_{arom}), 9.37 m (1H, H_{arom}). Found, %: C 69.82; H 4.71; N 14.29. $C_{17}H_{13}N_3S$. Calculated, %: C 70.08; H 4.50; N 14.42.

4-Ethoxy-*N*-(2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-ylidene)aniline (IVf). mp 178–181°C (from DMSO). IR spectrum, ν, cm^{-1}: 1290, 1360, 1390, 1520, 1590, 1640, 3000. ^1H NMR spectrum, δ, ppm: 1.36 t (3H, C**H**$_3$CH$_2$O, J = 6.9 Hz); 2.09 s (3H, 2-CH_3); 3.99 q (2H, CH_2O, J = 6.9 Hz); 6.03 s (1H, 3-H); 6.80 d (2H, C_6H_4, J = 8.1 Hz); 6.91 d (2H, C_6H_4, J = 8.1 Hz); 7.48 m (2H), 7.93 (1H), and 9.36 m (1H) (6-H–9-H). Found, %: C 67.81; H 5.32; N 12.72. $C_{19}H_{17}N_3OS$. Calculated, %: C 68.04; H 5.11; N 12.53.

Sulfurization of 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (V). A solution of 1.66 g (10 mmol) of compound **V** and 2.22 g (10 mmol) of P_2S_5 in 10 ml of pyridine was heated for 10 h under reflux. The mixture was cooled, diluted with 30 ml of water, and extracted with chloroform (2×10 ml). The extract was dried over $MgSO_4$ and evaporated under reduced pressure (water-jet pump), and the residue was recrystallized from ethanol. Yield of compound **IIIa** 0.783 g (43%), mp 142–143°C.

7-Methyl-5-methylsulfanyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium iodide (VI). A solution of 0.91 g (5 mmol) of compound **IIIa** and 1.14 g (8 mmol) of methyl iodide in 10 ml of benzene was heated for 8 h at 50°C. The mixture was cooled, and the precipitate was filtered off. Yield 1.085 g (67%), mp 215–216°C. IR spectrum, ν, cm^{-1}: 1310, 1340, 1370, 1430, 1490, 1560, 1585, 2900–3100. ^1H NMR spectrum, δ, ppm: 2.77 s (3H, 7-CH_3), 2.97 s (3H, SCH_3), 7.99 s (1H, 6-H), 8.46 d (1H, 2-H, J = 4.0 Hz), 8.65 d (1H, 3-H, J = 4.0 Hz). Found, %: C 29.92; H 2.52; N 8.47. $C_8H_9IN_2S_2$. Calculated, %: C 29.64; H 2.80; N 8.64.

A solution of 0.81 g (2.5 mmol) of iodide **VI** in 3 ml of aniline was heated for 0.5 h at 150°C. The mixture was cooled, and the precipitate was filtered off, washed in succession with diethyl ether (2×5 ml), 20% aqueous Na_2CO_3 (2×10 ml), and water, and dried. Yield of thiazolopyrimidine **IVa** 0.374 g (62%), mp 150–153°C (from nitromethane).

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