ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 10, pp. 1528–1531. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © V.N. Britsun, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 10, pp. 1550–1553.

Cyclocondensation of *N*-Aryl-3-oxobutanethioamides with 1*H*-1,2,4-Triazol-5-amine

V. N. Britsun

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 5, Kiev, 02660 Ukraine
e-mail: bvn1967@rambler.ru

Received January 25, 2008

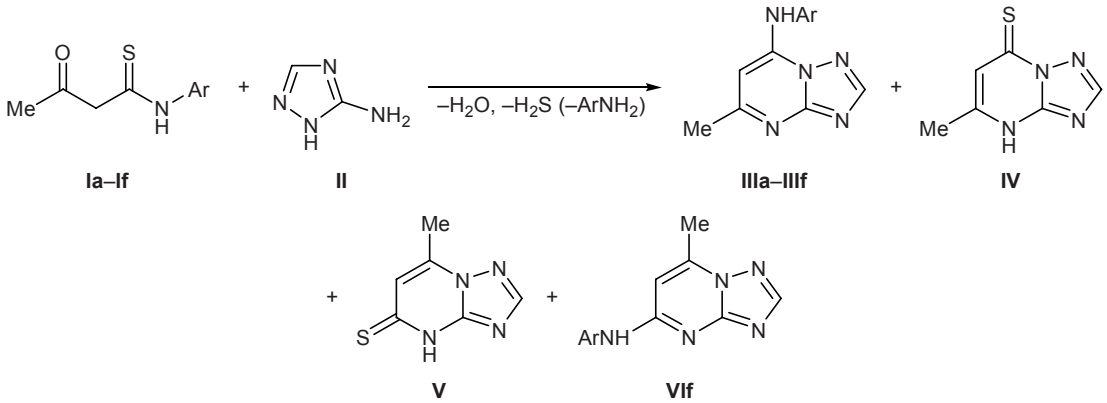
Abstract—Reactions of *N*-aryl-3-oxobutanethioamides with 1*H*-1,2,4-triazole-5-amine give mixtures of 7-arylamino-5-methyl[1,2,4]triazolo[1,5-*a*]pyrimidines, 5-methyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-thione, 7-methyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-5-thione, and 5-arylamino-7-methyl[1,2,4]triazolo[1,5-*a*]pyrimidines whose ratio depends on the substituent in the aryl group of initial *N*-aryl-3-oxobutanethioamide and solvent nature (the presence of a proton-donor solvent).

DOI: 10.1134/S1070428008100229

We recently showed [1] that *N*-phenyl-3-oxobutanethioamide reacts with 3-amino-5-R-1,2,4-triazoles (R = H, MeS) in acetic acid to give mixtures of 5-methyl-7-phenylamino-2-R-[1,2,4]triazolo[1,5-*a*]-pyrimidines, 5-methyl-2-R-4,7-dihydro[1,2,4]triazolo-[1,5-*a*]pyrimidine-7-thiones, and 7-methyl-2-R-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-5-thiones whose structure was confirmed by the ^{1}H and ^{13}C NMR spectra and X-ray diffraction data. The reaction in the absence of a proton-donor solvent was selective, and the only products were the corresponding 5-methyl-7-phenylamino-2-R-[1,2,4]triazolo[1,5-*a*]pyrimidines [2]. However, the effect of substituents in the phenyl ring of initial *N*-aryl-3-oxobutanethioamides on the reaction direction in the presence of a proton-donor solvent and in the absence of it was not studied. Therefore, in the present work we examined the regioselectivity in the cyclization of 1*H*-1,2,4-triazol-5-amine with *N*-aryl-3-oxobutanethioamides having various substituents in the benzene ring in acetic acid and under solvent-free conditions with a view to supplement and summarize our previous results [1, 2] and elucidate the mechanism of the process.

The results of the reactions of *N*-aryl-3-oxobutanethioamides **Ia**–**If** with 1*H*-1,2,4-triazol-5-amine (**II**) are collected in table (Scheme 1). The products were the corresponding 7-arylamino-5-methyl[1,2,4]triazolo-[1,5-*a*]pyrimidines **IIIa**–**IIIf**, 5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-thione (**IV**), 7-methyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-5-thione (**V**), and 5-(4-nitrophenylamino)-7-methyl [1,2,4]triazolo[1,5-*a*]pyrimidine (**VIf**).

Scheme 1.



Ia–If **II** **IIIa–IIIf** **IV** **V** **VIf**

Ar = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-MeC$_6$H$_4$ (**c**), 3-ClC$_6$H$_4$ (**d**), 3-F$_3$CC$_6$H$_4$ (**e**), 4-O$_2$NC$_6$H$_4$ (**f**).

As we showed previously on the basis of the X-ray diffraction data [1, 3, 4], 1,2,4-triazole derivatives react with electrophiles exclusively at the N^2 atom. Therefore, compound **VIf** was assigned the structure of [1,2,4]triazolo[1,5-*a*]pyrimidine rather than isomeric [1,2,4]triazolo[4,3-*a*]pyrimidine. Taking into account that our experiments were performed with structurally related initial compounds, the corresponding substituent constants σ are given in table to estimate the substituent effect. It is seen that the reactions carried out in the absence of a proton-donor solvent were generally selective: the major products were 7-arylamino-5-methyl[1,2,4]triazolo[1,5-*a*]pyrimidines **IIIa**–**IIId** (run nos. 1–4, see table). In going to strong electron-withdrawing substituents (such as trifluoromethyl and nitro groups; Hammett constants σ +0.43 and +0.778, respectively), the reaction becomes nonselective (run nos. 5 and 6). The condensations in acetic acid were not selective, and the products were mixtures of compounds **IIIa**–**IIIe**, **IV**, **V**, and **VIf**. Obviously, the regioselectivity of the process is controlled by both substituent nature in the initial thioamide and proton-donor solvent.

The cyclocondensation of 1*H*-1,2,4-triazole-5-amine (**II**) with *N*-aryl-3-oxobutanethioamides **Ia**–**If** could involve attack by the exocyclic amino group in **II** at both carbonyl and thiocarbonyl groups in substrate **Ia**–**If**, followed by ring closure. Both in acetic acid and without a solvent, the main reaction pathways are those leading to [1,2,4]triazolo[1,5-*a*]pyrimidines **IIIa**–**IIIf** and **IV**: their overall yield ranges from 41 to 75%. [1,2,4]Triazolo[1,5-*a*]pyrimidine derivatives **V** and **VIf** are formed as minor products (overall yield 8–30%). Thus the cyclization involving attack by the amino group of aminotriazole **II** at the ketone carbonyl group of *N*-aryl-3-oxobutanethioamide **Ia**–**If** is the preferred reaction path.

Reaction of *N*-aryl-3-oxobutanethioamides **Ia**–**If** with 1*H*-1,2,4-triazol-5-amine (**II**)

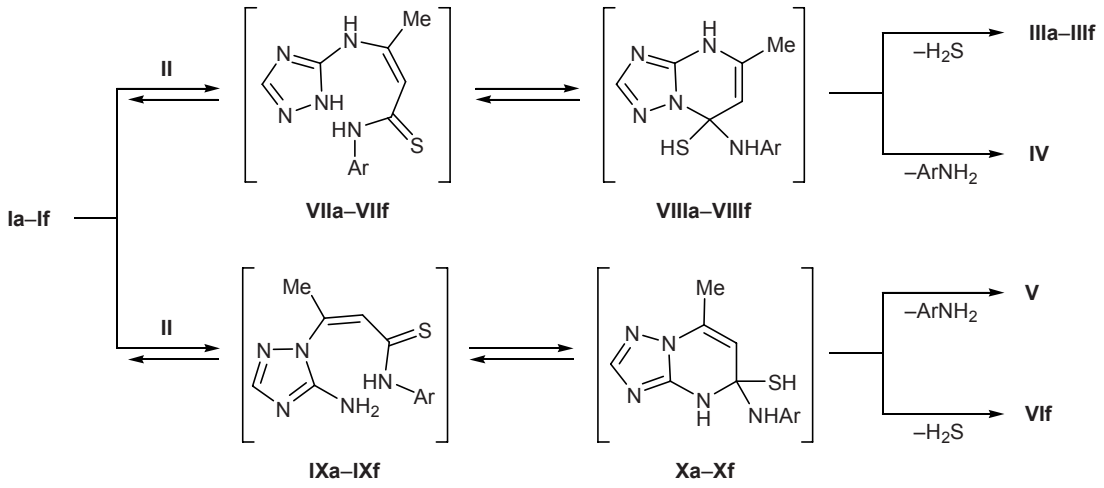
Run no.	Initial compound no.	Yields of **III**, **IV**, and **V**, %		Hammett constant σ
		AcOH	no solvent	
1[a]	**Ia**	18, 44, 15	62, 0, 0	0.000
2	**Ib**	0, 41, 30	50, 0, 0	–0.268
3	**Ic**	31, 32, 16	70, 0, 0	–0.170
4	**Id**	43, 26, 11	68, 0, 0	+0.373
5	**Ie**	33, 22, 8	64, 11, 0	+0.430
6	**If**	41, 0, 0[b]	40, 5, 0[c]	+0.778

[a] Data of [1, 2].
[b] Compound **VIf** was also formed (yield 19%).
[c] Compound **VIf** was also formed (yield 24%).

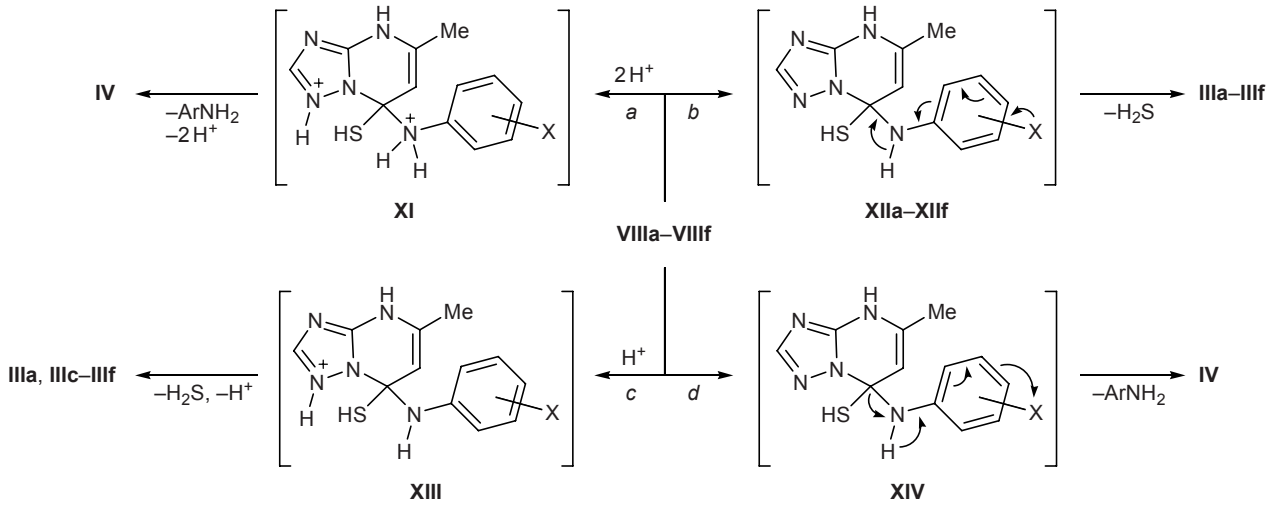
There are reasons to believe [5, 6] that thioamides **Ia**–**If** react with aminotriazole **II** to form initially enamino thioamides **VIIa**–**VIIf** and **IXa**–**IXf** and that the latter are converted into tetrahedral intermediates **VIIIa**–**VIIIf** and **Xa**–**Xf**, respectively [7]. These processes are reversible (Scheme 2). The direction of further transformations of intermediates **VIIIa**–**VIIIf** and **Xa**–**Xf** depends on the nature of substituent in the benzene ring and proton-donor power of the solvent (AcOH; Scheme 3).

Since the energy of C–S bond is lower than that of the C–N bond (272 and 285 kJ/mol, respectively [8]), high selectivity of the process in the absence of proton-donor solvent for Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, and 3-ClC_6H_4 may be rationalized assuming that intermediate **VIIIa**–**VIIId** is transformed only through

Scheme 2.



Scheme 3.



transition state **XIIa**–**XIId** (path *b*). Fairly high electron density on the N–C^5 bond therein makes that bond strong, which favors dissociation of the C–S bond with elimination of hydrogen sulfide and formation of [1,2,4]triazolo[1,5-*a*]pyrimidine **IIIa**–**IIId**. Electron-withdrawing substituents (X = CF_3, NO_2) reduce the electron density on the N–C^5 bond, thus favoring its cleavage with elimination of arylamine and formation of [1,2,4]triazolo[1,5-*a*]pyrimidine-5-thione (**IV**) (path *d*, transition state **XIV**).

In going to acid medium, the effect of substituent in the benzene ring of *N*-aryl-3-oxobutanethioamides **Ia**–**If** changes to the opposite. Depending on the substituent nature, protonation of intermediate **VIII** in acetic acid can occur either at both nitrogen atoms (N^3 and exocyclic, intermediate **XI**) or only at N^3 (intermediate **XIII**). If the X substituent is electron-donating (the most pronounced effect is observed for X = MeO), protonation of the exocyclic nitrogen atom facilitates elimination of aromatic amine with formation of thione **IV** (path *a*). If X is an electron-withdrawing group, elimination of hydrogen sulfide is likely to follow path *c* through intermediate **XIII**. Presumably, the formation of triazolo[1,5-*a*]pyrimidines **IIIa** and **IIIc**–**IIIf** is also favored to some extent by protonation of intermediate **XIII** at the sulfur atom.

In most cases, the transformation of intermediate **Xa**–**Xe** in acid medium leads to formation of thione **V** via elimination of arylamine, which may also be explained by protonation of the exocyclic nitrogen atom. If the basicity of the latter is reduced (e.g., due to electron-withdrawing effect of the nitro group), intermediate **Xf** is stabilized through a transition state analogous to **XIII**.

Thus we have shown that cyclocondensation of *N*-aryl-3-oxobutanethioamides with 1*H*-1,2,4-triazol-5-amine could give rise to four different products whose ratio and yield may be controlled by varying the solvent nature (using proton-donor solvents) and substituent in the benzene ring of the initial thioamide.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded from solutions in DMSO-d_6 on a Varian-300 instrument (300 MHz) using tetramethylsilane as internal reference.

General procedure for the reaction of *N*-aryl-3-oxobutanethioamides Ia–If with 1*H*-1,2,4-triazol-5-amine (II). *a*. A solution of 10 mmol of *N*-aryl-3-oxobutanethioamide **Ia**–**If** and 0.84 g (10 mmol) of aminotriazole **II** in 5 ml of acetic acid was heated for 5 h at 100°C. The mixture was cooled, and the precipitate (a mixture of compounds **IV** and **V** or **IIIf** and **VIf**) was filtered off, washed on a filter with diethyl ether (2×3 ml), and dried. The ratio of regioisomers **IV** and **V** was determined from the ^{1}H NMR spectra by comparing intensities of the 2-H and 6-H signals [1], and the isomers were separated according to the procedure described in [1]. The filtrate was evaporated in air to isolate triazolo[1,5-*a*]pyrimidines **IIIa**–**IIIe**. Compounds **IIIf** and **VIf** were separated by fractional crystallization from benzonitrile. The yields of compounds **IIIa**–**IIIf**, **IV**, **V**, and **VIf** are given in table.

b. A mixture of finely powdered *N*-aryl-3-oxobutanethioamide **Ia**–**If**, 10 mmol, and 1*H*-1,2,4-triazol-5-amine (**II**), 0.84 g (1 mmol), was thoroughly ground and heated for 0.5 h at 130°C. The mixture was cooled and treated with 4 ml of diethyl ether, and the precip-

itate was filtered off. The products were separated and identified as described above in *a*.

5-Methyl-*N*-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (IIIa). mp 182–184°C (from propan-2-ol); published data [1]: mp 183–185°C. The ^{1}H NMR spectrum of **IIIa** coincided with that given in [1]. Found, %: C 64.15; H 5.19; N 30.80. $C_{12}H_{11}N_5$. Calculated, %: C 63.99; H 4.92; N 31.09.

***N*-(4-Methoxyphenyl)-5-methyl[1,2,4]triazolo-[1,5-*a*]pyrimidin-7-amine (IIIb).** mp 188–190°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 3.80 s (3H, CH_3O), 6.16 s (1H, 6-H), 7.06 d (2H, 2′-H, 6′-H, J = 8.4 Hz), 7.32 d (2H, 3′-H, 5′-H, J = 8.4 Hz), 8.43 s (1H, 2-H), 10.05 s (1H, NH). Found, %: C 60.96; H 4.87; N 27.62. $C_{13}H_{13}N_5O$. Calculated, %: C 61.17; H 5.13; N 27.43.

5-Methyl-*N*-(4-methylphenyl)[1,2,4]triazolo-[1,5-*a*]pyrimidin-7-amine (IIIc). mp 197–199°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, 4′-CH_3), 2.40 s (3H, 5-CH_3), 6.28 s (1H, 6-H), 7.27 d (2H, 3′-H, 5′-H, J = 8.1 Hz), 7.31 d (2H, 2′-H, 6′-H, J = 8.1 Hz), 8.44 s (1H, 2-H), 10.10 s (1H, NH). Found, %: C 64.99; H 5.71; N 29.12. $C_{13}H_{13}N_5$. Calculated, %: C 65.26; H 5.48; N 29.27.

***N*-(3-Chlorophenyl)-5-methyl[1,2,4]triazolo-[1,5-*a*]pyrimidin-7-amine (IIId).** mp 238–240°C (from DMSO). ^{1}H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3), 6.48 s (1H, 6-H), 7.31 m (1H, 5′-H), 7.43–7.49 m (3H, 2′-H, 4′-H, 6′-H), 8.47 s (1H, 2-H), 10.31 s (1H, NH). Found, %: C 55.25; H 3.70; N 27.19. $C_{12}H_{10}ClN_5$. Calculated, %: C 55.50; H 3.88; N 26.97.

5-Methyl-*N*-[3-(trifluoromethyl)phenyl][1,2,4]-triazolo[1,5-*a*]pyrimidin-7-amine (IIIe). mp 185–187°C (from nitromethane). ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 6.49 s (1H, 6-H), 7.59 m (1H, 6′-H), 7.70 m (1H, 5′-H), 7.77–7.83 m (2H, 2′-H, 4′-H), 8.49 s (1H, 2-H), 10.41 s (1H, NH). Found, %: C 53.02; H 3.62; N 24.12. $C_{13}H_{10}F_3N_5$. Calculated, %: C 53.25; H 3.44; N 23.88.

5-Methyl-*N*-(4-nitrophenyl)[1,2,4]triazolo[1,5-*a*]-pyrimidin-7-amine (IIIf). mp 320–325°C (from DMSO). ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 6.81 s (1H, 6-H), 7.70 d (2H, 2′-H, 6′-H, J = 9.0 Hz), 8.29 d (2H, 3′-H, 5′-H, J = 9.0 Hz), 8.53 s (1H, 2-H), 10.70 br.s (1H, NH). Found, %: C 53.58; H 3.70; N 30.93. $C_{12}H_{10}N_6O_2$. Calculated, %: C 53.33; H 3.73; N 31.10.

5-Methyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-thione (IV). mp 296–298°C; published data: mp 295–297°C [1], 310°C [9]. The ^{1}H NMR spectrum of **IV** coincided with that reported in [1]. Found, %: C 43.52; H 3.42; N 33.95. $C_6H_6N_4S$. Calculated, %: C 43.36; H 3.64; N 33.71.

7-Methyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-5-thione (V). mp 321–324°C; published data [1]: mp 323–325°C. The ^{1}H NMR spectrum of **V** coincided with that reported in [1]. Found, %: C 43.10; H 3.39; N 33.45. $C_6H_6N_4S$. Calculated, %: C 43.36; H 3.64; N 33.71.

7-Methyl-*N*-(4-nitrophenyl)[1,2,4]triazolo[1,5-*a*]-pyrimidin-5-amine (VIf). mp 350–355°C (from PhCN). ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 5.76 s (1H, 6-H), 7.20 d (2H, 2′-H, 6′-H, J = 9.0 Hz), 8.20 d (2H, 3′-H, 5′-H, J = 9.0 Hz), 9.00 s (1H, 2-H), 10.76 br.s (1H, NH). Found, %: C 53.07; H 4.02; N 31.16. $C_{12}H_{10}N_6O_2$. Calculated, %: C 53.33; H 3.73; N 31.10.

REFERENCES

1. Britsun, V.N., Borisevich, A.N., Samoilenko, L.S., Chernega, A.N., and Lozinskii, M.O., *Russ. J. Org. Chem*., 2006, vol. 42, p. 1516.
2. Britsun, V.N., Borisevich, A.N., and Lozinskii, M.O., *Russ. J. Org. Chem*., 2007, vol. 43, p. 1548.
3. Britsun, V.N., Esipenko, A.N., Chernega, A.N., and Lozinskii, M.O., *Russ. J. Org. Chem*., 2005, vol. 41, p. 108.
4. Britsun, V.N., Esipenko, A.N., Chernega, A.N., Rusanov, E.B., and Lozinskii, M.O., *Khim. Geterotsikl. Soedin*., 2007, p. 1660.
5. Borisevich, A.N. and Pel'kis, P.S., *Zh. Org. Khim*., 1967, vol. 3, p. 1339.
6. Britsun, V.N., Borisevich, A.N., and Lozinskii, M.O., *Russ. J. Org. Chem*., 2007, vol. 43, p. 907.
7. March, J., *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, New York: Wiley, 1985. Translated under the title *Organicheskaya khimiya*, Moscow: Mir, 1987, vol. 2, p. 55.
8. Gauptman, Z., Grefe, Yu., and Remane, Kh., *Organicheskaya khimiya*, Moscow: Khimiya, 1979, p. 52.
9. Allen, C.F., Beilfuss, H.R., Burness, D.M., and Reynolds, G.A., *J. Org. Chem*., 1959, vol. 24, p. 787.