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CYCLOCONDENSATION OF N-ARYL-3-OXOBUTANETHIOAMIDES WITH 5-AMINO-3-R-4-R^1-PYRAZOLES

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The cyclocondensation products of N-aryl-3-oxobutanethioamides with 5-amino-3-R-4-R^1-pyrazoles are 4-(arylamino)-2-methyl-7-R-8-R^1-pyrazolo[1,5-a]pyrimidine and pyrazolo[1,5-a]pyrimidine-4-thione derivatives, the ratio of which depends on the nucleophilicity of the starting 5-amino-3-R-4-R^1-pyrazoles and the presence of a proton donor solvent.

Keywords: 5-amino-3-R-4-R^1-pyrazoles, N-aryl-3-oxobutanethioamides, 4-(arylamino)-2-methyl-7-R-8-R^1-pyrazolo[1,5-*a*]pyrimidines, 2,7-dimethyl-1,4-dihydropyrazolo[1,5-*a*]pyrimidine-4-thione, 2-methyl-1,4-dihydropyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine-4-thione, 2-methyl-4-(phenylamino)pyrido-[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine, heterocyclization, [3+3] cyclocondensation.

We have recently shown that N-aryl-3-oxobutanethioamides react with such 2-aminoazoles (azines) as 3-amino-5-R-1,2,4-triazoles [1], 2-amino-5-R-pyridines [2], 2-amino-4-R-5-R^1-thiazoles [3], and 5-amino-tetrazole [4] *via* a [3+3] cycloaddition scheme to form two groups of compounds (pyrimidine-4-thione and 4-(arylamino)pyrimidine derivatives) the ratio of which depends on the basicity of the heterocyclic 1,3-dinucleopile and the acidity of the solvent [1-4].

The aim of this work is to continue our investigation [1-4] and study of the regioselectivity of the cyclization of the N-aryl-3-oxobutanethioamides **1a-d** with such 1,3-dinucleophiles as the 5-amino-3-R-4-R^1-pyrazoles, *viz* 5-amino-3-methylpyrazole (**2a**), 5-amino-4-cyanopyrazole (**2b**), and 3-amino-2H-pyrazolo-[3,4-*b*]pyridine (**2c**) in the absence and the presence of a proton donor solvent. Such a course should prove an addition to the general results of preceding work [1-4], in particular the observation of the effect of the nucleophilicity of the 2-aminoazole and the acidity of the solvent on the regioselectivity of the process.

Since the [3+3] cyclocondensation can occur at three reaction centers in the N-aryl-3-oxobutane-thioamides **1a-d** and at two in the 5-amino-3-R-4-R^1-pyrazoles **2a-c** the reaction products can be four groups of compounds i.e. 2(4)-methyl-7-R-8-R^1-1,4(1,2)-dihydropyrazolo[1,5-*a*]pyrimidine-4(2)-thiones and 4(2)-aryl-amino-2(4)-methyl-7-R-8-R^1-pyrazolo[1,5-*a*]pyrimidines.

It was shown that two groups of compounds are the result of the reaction, i.e. the pyrimidine thiones **3a,b** and the 4-(arylamino)pyrazolo[1,5-*a*]pyrimidines **4a-f**. The structure of the dihydropyrazolo[1,5-*a*]pyrimidine thiones **3a,b** was proved by thionation of the 2,7-dimethyl-1,4-dihydropyrazolo-[1,5-*a*]pyrimidin-4-one **5** (the structure of which had been proved using X-ray analysis [5]) to give the 2,7-dimethyl-1,4-dihydropyrazolo-[1,5-*a*]pyrimidine-4-thione (**3a**). Since the 5-amino-3-R-4-R^1-pyrazoles are isoelectronic with 3-amino-

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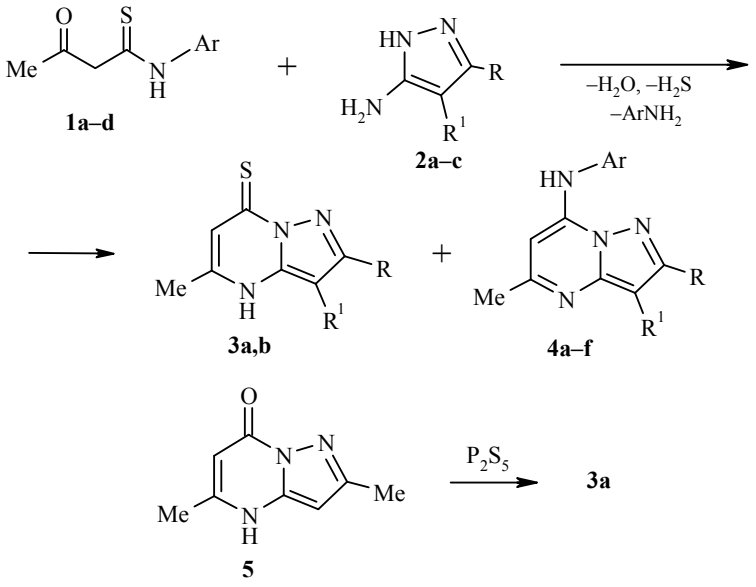
5-R-1,2,4-triazoles and characterized by approximately the same basicity (for R = R^1 = H the pK_a's are 4.11 and 4.17 respectively [6]) then, on the basis of the X-ray structural analysis the products of the reaction of the latter with N-aryl-3-oxobutanethioamides [1], it can be assumed that compounds **4a-f** are 4-arylamino-2-methyl-7-R-8-R^1-pyrazolo[1,5-*a*]pyrimidines (Tables 1-3).



1a, 4a,b,f Ar = Ph; **1b, 4c** Ar = 4-$MeOC_6H_4$; **1c, 4d** Ar = 3-$CF_3C_6H_4$; **1d, 4e** Ar = 4-$O_2NC_6H_4$;
2a–**4a** R = Me, R^1 = H; **2b, 4b–e** R = H, R^1 = CN; **2c, 3b, 4f** R + R^1 = N=CH–CH=CH

The characteristic ^{1}H NMR spectroscopic signals for the products **3a,b** and **4a-f** are the singlets for 2-CH_3, H-3, and the NH groups (2.30-2.46, 6.56-7.29, 13.06-13.10 and 2.40-2.57, 6.16-6.86, 10.16-10.84 ppm).

It follows from Table 2 that the yield and ratio of compounds **3a,b** and **4a-f** depend both on the presence of a protonating solvent and on the nucleophilicity of the 5-amino-3-R-4-R^1-pyrazoles **2a-c**. The aminopyrazoles **2a-c** show an increasing nucleophilicity of their exo- and endocyclic amino groups in the order **2a** > **2c** > **2b**.

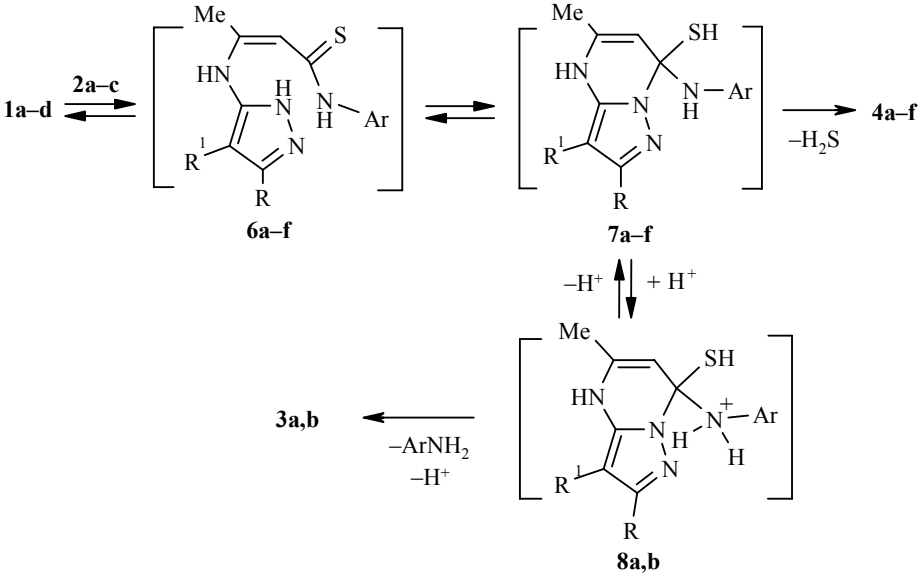
When the reaction is carried out without a protonating solvent the interaction of the starting **1a-d** with the aminopyrazoles **2a-c** occurs selectively in all cases (experiments 1-6) to give the 4-arylamino-2-methyl-7-R-8-R^1-pyrazolo[1,5-*a*]pyrimidines **4a-e** and the 2-methyl-4-(phenylamino)pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine (**4f)**.

The nucleophilicity value of the exo- and endocyclic amino groups in the aminopyrazoles **2a-c** affects the regioselectivity of the cyclocondensation in acetic acid. In the case of the 5-amino-4-cyanopyrazole (**2b)**, which is the weakest base, the regioselectivity of the process is the same both in the presence of a proton donor solvent and without it (experiments 2-5). This fact suggest that the starting aminopyrazole **2b** and the reaction intermediates are not protonated by acetic acid. For the more basic aminopyrazoles **2a,c** the regioselectivity of the process in AcOH is changed when compared with the selectivity of the reaction without it. The dihydropyrazolo[1,5-*a*]pyrimidine-4-thione **3a** is the single condensation product of the starting reagents **1a** and **2a** whereas the 2-methyl-1,4-dihydropyrido[2',3',:3,4]pyrazolo[1,5-*a*]pyrimidine-4-thione (**3b)** is the dominant product in the reaction of the starting **1a** and **2c**.

It has been proposed [7, 8] that the thioamides **1a-d** react with aminopyrazoles **2a-c**, initially to form the enamino thioamides **6a-f** which are reversibly converted to the tetrahedral intermediates **7a-f** [9].

Because cleavage of a C–S bond occurs more readily than a C–N bond (formation energies respectively 272 and 285 kJ/mol) [10] heating the intermediate **7a-f** causes elimination of hydrogen sulfide to give the 4-aryl-

It should be noted that the 2-R-1,4-dihydropyrazolo[1,5-*a*]pyrimidine-4-thiones (R = H, Ph), prepared from the corresponding 2-R-4-chloropyrazolo[1,5-*a*]pyrimidines and thiourea, show a high activity towards *Schistosoma mansoni* while the structurally similar 2-R-1,4-dihydropyrazolo[1,5-*a*]pyrimidin-4-ones do not show anthelmintic activity [11].



6a,b,f, 7a,b,f, 8a,b Ar = Ph; **6c, 7c** Ar = 4-$MeOC_6H_4$; **6d, 7d** Ar = 3-$CF_3C_6H_4$; **6e, 7e** Ar = 4-$O_2NC_6H_4$; **6a–8a** R = Me; **6b–e, 7b–e** R = H; **6a–8a** R^1 = H; **6b-e, 7b–e** R^1 =CN; **6f, 7f, 8b** R + R^1 = N=CH–CH=CH

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*
		C	H	N	
3a	$C_8H_9N_3S$	53.47 / 53.61	5.29 / 5.06	23.31 / 23.44	304-306
3b	$C_{10}H_8N_4S$	55.79 / 55.54	3.55 / 3.73	26.07 / 25.91	341-345
4a	$C_{14}H_{14}N_4$	70.42 / 70.57	6.06 / 5.92	23.72 / 23.51	145-147
4b	$C_{14}H_{11}N_5$	67.39 / 67.46	4.38 / 4.45	27.93 / 28.09	180-182
4c	$C_{15}H_{13}N_5O$	64.42 / 64.51	4.76 / 4.69	24.82 / 25.07	161-163
4d	$C_{15}H_{10}F_3N_5$	56.86 / 56.79	2.89 / 3.18	21.90 / 22.07	157-159
4e	$C_{14}H_{10}N_6O_2$	56.96 / 57.14	3.27 / 3.43	28.81 / 28.56	315-317
4f	$C_{16}H_{13}N_5$	69.53 / 69.80	4.55 / 4.76	25.30 / 25.44	207-210

Compounds **3a,b, 4e** were recrystallized from DMSO, **4a,c,d** from ethanol, and **4b,f** from nitromethane.

TABLE 2. Yields of the Reaction Products of the N-Aryl-3-oxobutane-thioamides **1a-d** with 5-Amino-3-R-4-R[1]-pyrazoles **2a-c**

Experiment number	Starting reagents	Reaction products	Yield of compounds **4a–f (3a,b)**, %	
			AcOH	Without solvent
1	**1a**, **2a**	**4a (3a)**	0 (66)	62
2	**1a**, **2b**	**4b**	61	59
3	**1b**, **2b**	**4c**	49	47
4	**1c**, **2b**	**4d**	54	58
5	**1d**, **2b**	**4e**	55	51
6	**1a**, **2c**	**4f (3b)**	13 (47)	63

TABLE 3. ^{1}H NMR Spectra of Compounds **3a,b** and **4a-f**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
3a	2.30 (3H, s, 7-CH_3); 2.35 (3H, s, 2-CH_3); 6.11 (1H, s, H-8); 6.56 (1H, s, H-3); 13.06 (1H, br. s, H-1)
3b	2.46 (3H, s, 2-CH_3); 7.29 (2H, m, H-3,9); 8.78 (1H, d, *J* = 5.4, H-10); 8.88 (1H, d, *J* = 8.1, H-8); 13.10 (1H, br. s, H-1)
4a	2.33 (3H, s, 7-CH_3); 2.44 (3H, s, 2-CH_3); 6.12 (1H, s, H-8); 6.14 (1H, s, H-3); 7.24 (1H, m, C_6H_5); 7.43 (4H, m, C_6H_5); 9.64 (1H, s, NH)
4b	2.43 (3H, s, 2-CH_3); 6.37 (1H, s, H-3); 7.31 (1H, m, C_6H_5); 7.46 (4H, m, C_6H_5); 8.64 (1H, s, H-7), 10.35 (1H, s, NH)
4c	2.40 (3H, s, 2-CH_3); 3.80 (3H, s, CH_3O); 6.16 (1H, s, H-3); 7.03 (1H, d, *J* = 9.0, 4-C_6H_4); 7.32 (1H, d, *J* = 9.0, 4-C_6H_4); 8.62 (1H, s, H-7), 10.16 (1H, s, NH)
4d	2.46 (3H, s, 2-CH_3); 6.49 (1H, s, H-3); 7.62 (1H, m, 3-$CF_3C_6H_4$); 7.71 (1H, m, 3-$CF_3C_6H_4$); 7.79 (2H, m, 3-$CF_3C_6H_4$); 8.67 (1H, s, H-7); 10.54 (1H, s, NH)
4e	2.50 (3H, s, 2-CH_3); 6.86 (1H, s, H-3); 7.75 (1H, d, *J* = 8.9, 4-C_6H_4); 8.31 (1H, d, *J* = 8.9, 4-C_6H_4); 8.76 (1H, s, H-7); 10.84 (1H, s, NH)
4f	2.57 (3H, s, 2-CH_3); 6.77 (1H, s, H-3); 7.22 (1H, m, H-9); 7.32 (1H, m, C_6H_5); 7.53 (4H, m, C_6H_5); 8.64 (1H, d, *J* = 8.1, H-10); 8.82 (1H, d, *J* = 4.9, H-8); 10.41 (1H, s, NH)

The cyclocondensation of the thioamide **1a** with aminopyrazole **2c** occurs nonselectively in acid medium, likely as a result of the realization of two reaction paths one of which (conversion of **7f** *via* **8b** and **3b**) dominates.

Hence the products of the reaction of the N-aryl-3-oxobutanethioamides **1a-d** with the 5-amino-3-R-4-R[1]-pyrazoles **2a-c** without proton donor solvent are only the 4-arylamino-2-methyl-7-R-8-R[1]-pyrazolo-[1,5-*a*]pyrimidines **4a-f** while carrying out the cyclocondensation reaction of **1a** with pyrazoles **2a,c** in AcOH preferably gives the 1,4-dihydropyrazolo[1,5-*a*]pyrimidine-4-thiones **3a,b**.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian-300 instrument (300 MHz) using DMSO-d_6 and with TMS as internal standard. 2,7-Dimethyl-1,4-dihydropyrazolo[1,5-*a*]pyrimidin-4-one **5** was prepared by method [5].

Reaction of N-aryl-3-oxobutanethioamides 1a-d with 5-Amino-3-R-4-R[1]-pyrazoles 2a-c. A. A solution of N-aryl-3-oxobutane thioamide **1a-d** (2 mmol) and 5-amino-3-R-4-R[1]-pyrazole **2a-c** (2 mmol) was heated in AcOH (5 ml) for 6 h at 100-110°C, cooled, and the 2,7-dimethyl-1,4-dihydropyrazolo[1,5-*a*]pyrimidine-4-thione **3a** (2-methyl-1,4-dihydropyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine-4-thione **3b**) were filtered off.

The filtrate was evaporated, triturated with diethyl ether (3ml), and 4-(arylamino)-2-methyl-7-R-8-R^1-pyrazolo[1,5-*a*]pyrimidine **4a-e** (2-methyl-4-phenylaminopyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine **4f**) were filtered off.

B. A mixture of finely powdered N-aryl-3-oxobutanethioamide **1a-d** (2 mmol) and 5-amino-3-R-4-R^1-pyrazole **2a-c** (2 mmol) was heated for 0.5 h at 100-110°C, cooled, and treated with refluxing 2-propanol (3 ml). The suspension was cooled and the precipitated compound **4a-e** (mixture of compounds **3b** and **4f**) filtered off. The ratio of the **3b** and **4f** products was measured using ^{1}H NMR spectroscopy. Compounds **3b** and **4f** were separated by treatment of the mixture with a 10% aqueous solution of KOH., The insoluble pyrazolo-[1,5-*a*]pyrimidine **4f** was filtered off and the basic solution was acidified with AcOH and the thione **3b** was filtered off.

Thionation of 2,7-Dimethyl-1,4-dihydropyrazolo[1,5-*a*]pyrimidin-4-one (5). A solution of the pyrazolo[1,5-*a*]pyrimidin-4-one **5** (1.63 g, 10 mmol) and P_2S_5 (2.22 g, 10 mmol) in pyridine (8 ml) was refluxed for 10 h, cooled, diluted with water (30 ml), and extracted with chloroform (2×15 ml). The chloroform solution was dried over $MgSO_4$, evaporated *in vacuo* on a water pump, and compound **3a** was recrystallized from DMSO. The yield of thione **3a** was 0.63 g (35%). The melting point and ^{1}H NMR spectra of compound **3a** prepared by reaction of the N-phenyl-3-oxobutane thioamide **1a** with 5-amino-3-methylpyrazole **2a** and by sulfurization of the pyrazolo[1,5-*a*]pyrimidin-4-one **5** were identical.

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