ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 8, pp. 1200–1204. © Pleiades Publishing, Ltd., 2008.
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Cyclocondensation of *N*-Aryl-3-oxobutanethioamides with 2-Aminoimidazole and 2-Aminobenzimidazole

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Received January 9, 2008

Abstract—Cyclization of *N*-aryl-3-oxobutanethioamides with 2-aminoimidazole and 2-aminobenzimidazole gave 7-methyl-5,8-dihydroimidazo[1,2-*a*]pyrimidine-5-thione or 2-methylpyrimido[1,2-*a*]benzimidazole-4(1*H*)-thione and 4-(arylamino)-2-methylpyrimido[1,2-*a*]benzimidazoles whose ratio depends on the nature of aryl substituents in the initial butanethioamides and on the presence of a protic solvent.

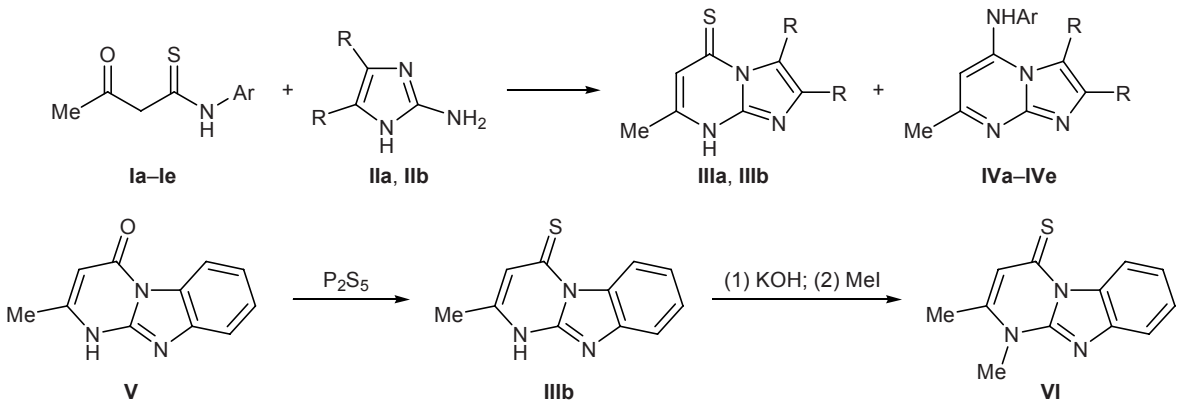
DOI: 10.1134/S1070428008080162

N-Aryl-3-oxobutanethioamides are useful reagents for the synthesis of various sulfur- and nitrogen-containing heterocycles; they can also be used as complexing agents and model structures for studying keto–enol–enethiol tautomerism [1]. Increased interest in the chemistry of *N*-aryl-3-oxobutanethioamides has stimulated development of preparative procedures for their synthesis [2, 3].

We recently published a series of studies on cyclocondensation of *N*-aryl-3-oxobutanethioamides with nitrogen-containing 1,3-binucleophiles [4–8]. As the latter we used 2-aminoazoles and 2-aminoazines with pK_a values ranging from 1.82 to 6.86. The products of these condensations were bicyclic derivatives of arylaminopyrimidines and pyrimidinethiones whose ratio depended on the nucleophile basicity, acidity of the medium, and substituent in the benzene ring of the initial thioamide [4–8].

In the present work we examined heterocyclization of *N*-aryl-3-oxobutanethioamides **Ia**–**Ie** with such strongly basic aminoazoles as 2-aminoimidazole (**IIa**) and 2-aminobenzimidazole (**IIb**) (pK_a 8.35 and 7.39, respectively [9]). We were interested in regioselectivity of the process, specifically in the effect of the nature of substituent in the benzene ring of the initial thioamide on the reaction direction in protic solvents (acetic or propionic acid) and in the absence of protic solvent. Insofar as the process follows the [3+3]-cyclocondensation pattern, it may involve three possible reaction centers in *N*-aryl-3-oxobutanethioamides **Ia**–**Ie** and

Scheme 1.



Ia–Ie **IIa**, **IIb** **IIIa**, **IIIb** **IVa–IVe**

V **IIIb** **VI**

IIa, **IIIa**, R = H; **IIb**, **IIIb**, **IV**, RR = benzo; **I**, **IV**, Ar = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-MeC$_6$H$_4$ (**c**), 3-ClC$_6$H$_4$ (**d**), 3-CF$_3$C$_6$H$_4$ (**e**).

two centers in 2-aminoazoles **IIa** and **IIb**; as a result, the products may be four compounds of the imidazo-[1,2-*a*]pyrimidine series.

We found that, unlike cyclizations of ethyl acetoacetate with 2-aminoimidazole [10] and 2-aminobenzimidazole [11], the reaction under study was not selective: the products were mixtures of fused heterocyclic compounds **IIIa** or **IIIb** and **IVa**–**IVe**, whose ratio depended on the nature of the *N*-aryl substituent in the initial thioamide and on the presence of a protic solvent (Scheme 1, see table).

2-Methyl-4-(4-tolylamino)pyrimido[1,2-*a*]benzimidazole (**IVc**) was synthesized previously from 4-chloro-2-methylpyrimido[1,2-*a*]benzimidazole and 4-toluidine and was patented as antihypertensive agent [12]. Therefore, we presumed that all compounds **IVa**–**IVe** have the structure of 4-(arylamino)-2-methylpyrimido[1,2-*a*]benzimidazoles. However, the ^{1}H NMR data did not allow us to unambiguously identify products **IIIa** and **IIIb** as 2-methylimidazo[1,2-*a*]pyrimidine-4-thiones or 4-methylimidazo[1,2-*a*]pyrimidine-2-thiones. To determine their structure, we synthesized 2-methylpyrimido[1,2-*a*]benzimidazol-4(1*H*)-one (**V**) according to the procedure described in [11], and compound **V** was treated with tetraphosphorus decasulfide in pyridine to obtain 2-methylpyrimido[1,2-*a*]benzimidazole-4(1*H*)-thione (**IIIb**). The ^{1}H NMR spectra of samples of **IIIb** synthesized by reaction of thioamide **Ia** with 2-aminobenzimidazole (**IIb**) and by sulfurization of compound **V** were fully identical, and their mixture showed no depression of the melting point. Unlike 7-methyl-5,8-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-5-thiones [4], alkylation of 2-methylpyrimido-[1,2-*a*]benzimidazole-4(1*H*)-thione (**IIIb**) with methyl iodide occurred at the N^1 rather than sulfur atom to give 1,2-dimethylpyrimido[1,2-*a*]benzimidazole-4(1*H*)-thione (**VI**). Presumably, the different regioselectivity in the alkylation of **IIIb** is determined by the effect of the fused benzene ring [13], which reduces π-electron density on the azole ring and thus facilitates

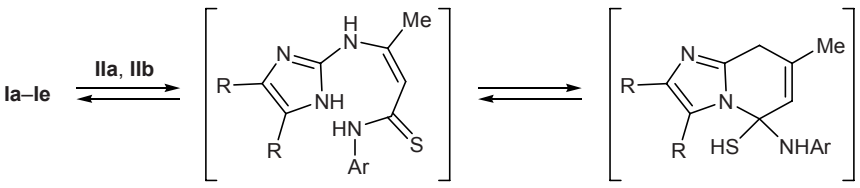
Reactions of *N*-aryl-3-oxobutanethioamides **Ia**–**Ie** with 2-aminoimidazole (**IIa**) and 2-aminobenzimidazole (**IIb**)

Initial compounds	Products	Yield, %; ratio **III**:**IV**		Hammett constant σ
		EtCOOH	no solvent	
Ia + **IIa**	**IIIa**	42	–	0.000
Ia + **IIb**	**IIIb**, **IVa**	20:28	28:26	0.000
Ib + **IIb**	**IIIb**, **IVb**	31:10	0:49	–0.268
Ic + **IIb**	**IIIb**, **IVc**	36:17	22:33	–0.170
Id + **IIb**	**IIIb**, **IVd**	15:28	31:25	+0.373
Ie + **IIb**	**IIIb**, **IVe**	10:38	27:20	+0.430

generation of the corresponding anion by the action of bases. The negative charge in that anion is delocalized over the thiolic sulfur atom and N^1 atom in the pyrimidine ring. In addition, the formation of carbon–nitrogen bond is more favorable than the formation of carbon–sulfur bond for energy reasons (the energies of formation of the C–N and C–S bonds are 285 and 272 kJ/mol, respectively) [14]. Thus, S- and N-alkylation are, respectively, the kinetically and thermodynamically controlled processes.

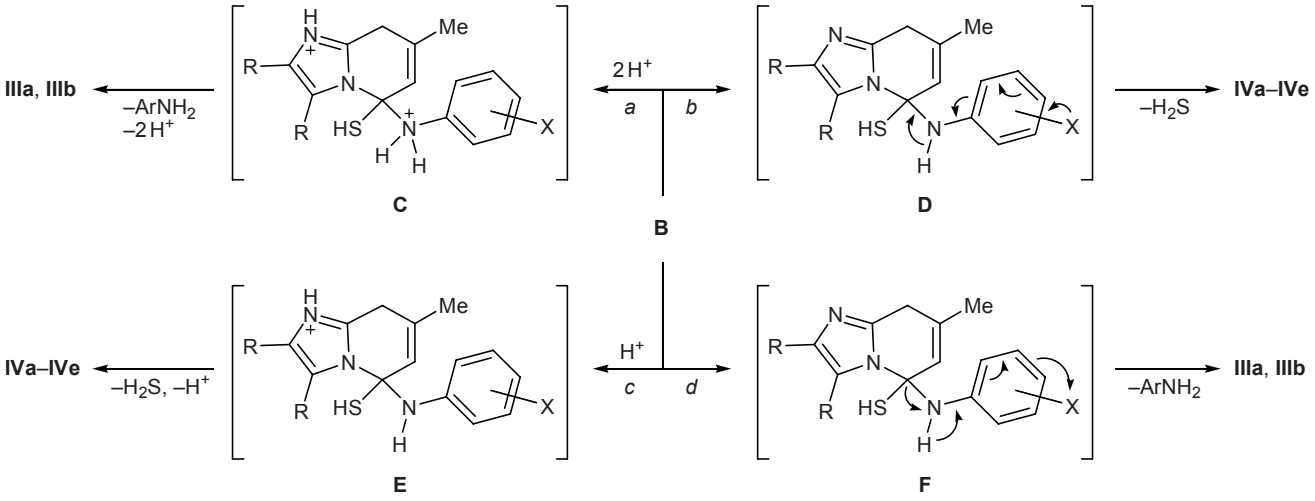
In the ^{1}H NMR spectra of imidazo[1,2-*a*]pyrimidinethiones **IIIa**, **IIIb**, and **VI** characteristic are singlets from the 2(7)-CH_3, 3-H, and 6-H protons (δ 2.33–2.36, 6.95–7.02, and 9.72–9.76 ppm, respectively), while 4-(arylamino)pyrimido[1,2-*a*]benzimidazole-4(1*H*)-thiones **IVa**–**IVe** displayed singlets from the 2-CH_3, 3-H, and 6-H protons at δ 2.15–2.18, 5.52–5.55, and 8.58–8.62 ppm, respectively. It is seen that the chemical shifts of protons in the imidazole and pyrimidine rings of compounds **IVa**–**IVe** are lower by 1.10–1.47 ppm than the corresponding values for compounds **IIIa**, **IIIb**, and **VI**; presumably, increased shielding of the above protons in **IVa**–**IVe** is related to conjugation between the lone electron pair on the nitrogen atom in the arylamino group and bicyclic pyrimido[1,2-*a*]benzimidazole system.

Scheme 2.



X = H, 4-MeO, 4-Me, 3-Cl, 3-F_3C; R = H; RR = benzo.

Scheme 3.



There are reasons to believe [7, 15] that the reaction of thioamides **Ia**–**Ie** with aminoimidazoles **IIa** and **IIb** involves initial formation of enaminothioamide **A** which is converted into tetrahedral intermediate **B** and that these processes are reversible (Scheme 2). The data given in table show that the direction of the subsequent decomposition of intermediate **B** depends on both substituent nature in the benzene ring and the presence of protic solvent (AcOH, EtCOOH). In most cases, the reaction in the absence of acid is not selective, and the products are mixtures of imidazo[1,2-*a*]-pyrimidines **IIIb** and **IVa** and **IVc**–**IVe**. Only the condensation of *N*-(4-methoxyphenyl)-3-oxobutanethioamide (**Ib**) selectively gives pyrimidobenzimidazole **IVb** (see table). On the whole, the ratio of compounds **IIIb** and **IVa**–**IVe** changes in parallel with the Hammett constants σ of the corresponding substituents: the stronger the electron-donating power of the substituent, the lesser the fraction of imidazo[1,2-*a*]pyrimidine-4-thione (**III**) and vise versa (the stronger the electron-withdrawing power of the substituent, the larger the ratio **III**:**IV**).

These results may be interpreted as shown in Scheme 3. If the X substituent is an electron-donating group (path *b*, intermediate **D**), the electron density on the N–C^4 bond increases (the N–C^4 bond becomes stronger), and hydrogen sulfide is released. If the X substituent is an electron-withdrawing group (path *d*, intermediate **F**), the electron density on the N–C^4 bond decreases, so that its dissociation with elimination of aromatic amine is favored.

The reactions in acetic or propionic acid were generally nonselective; only the cyclization of 2-aminoimidazole (**IIa**) with *N*-phenyl-3-oxobutanethioamide (**Ia**) gave 7-methyl-5,8-dihydroimidazo[1,2-*a*]pyrimidine-5(8*H*)-thione (**IIIa**) as the only product. Presumably, the reason is high basicity of initial 2-aminoimidazole (imidazole), pK_a 8.35 (6.99) [9], and easy formation and subsequent decomposition of intermediate **C** (path *a*). In going to acid medium, the substituent effect changes to the opposite. Electron-donating substituent X favors protonation of the exocyclic nitrogen atom (intermediate **C**), which facilitates elimination of aromatic amine and formation of thiones **IIIa** and **IIIb** (path *a*).

Elimination of hydrogen sulfide from intermediate **B** having electron-withdrawing substituent X is likely to involve formation of structure **E** protonated at the N^8 atom (path *c*). Since the energy of the S–C bond is higher than the energy of the C–N bond, rise in temperature favors the transformation of intermediate **E** into compounds **IVa**–**IVe**. This assumption is supported by the fact that thioamides **Id** and **Ie** react with 2-aminobenzimidazole (**IIb**) only in propionic acid at 135–140°C, while no reaction occurs in acetic acid at 100–110°C. It is known that less basic 2-amino-4-R-5-R′-thiazoles (pK_a 4.51–5.39) react with *N*-(4-nitrophenyl)-3-oxobutanethioamide in acetic acid at 100–110°C [6]. Probably, protonation of intermediate **E** at the sulfur atom favors formation of arylaminopyrimidine derivatives **IVa**–**IVe**.

Thus the cyclocondensation of *N*-aryl-3-oxobutanethioamides with 2-aminoimidazoles is generally nonselective, and it gives mixtures of two different products. On the other hand, the reaction direction may be controlled by using protic solvent, as well as by selecting appropriate 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 Unity 300 spectrometer (300 MHz); the chemical shifts were measured relative to tetramethylsilane as internal reference. 2-Methylpyrimido[1,2-*a*]benzimidazol-4(1*H*)-one (**V**) was synthesized according to the procedure reported in [11].

7-Methylimidazo[1,2-*a*]pyrimidine-5(8*H*)-thione (IIIa). A solution of 0.386 g (2 mmol) of 3-oxo-*N*-phenylbutanethioamide (**Ia**), 0.264 g (1 mmol) of 2-aminoimidazole (**IIa**) sulfate, and 0.164 g of sodium acetate in 3 ml of acetic acid was heated for 8 h at 110°C. The mixture was cooled, and the precipitate was filtered off. Yield 0.139 g (42%), mp 330–333°C. ^{1}H NMR spectrum, δ, ppm: 2.33 s (3H, CH_3), 6.95 s (1H, 6-H), 7.80 d (1H, 2-H, J = 2.7 Hz), 8.04 d (1H, 3-H, J = 2.7 Hz), 13.40 br.s (1H, NH). Found, %: C 51.12; H 3.99; N 25.40. $C_7H_7N_3S$. Calculated, %: C 50.89; H 4.27; N 25.43.

4-Arylamino-2-methylpyrimido[1,2-*a*]benzimidazoles IVa–IVe (*general procedure*). *a*. A solution of 2 mmol of *N*-aryl-3-oxobutanethioamide **Ia**–**Ie** and 2 mmol of 2-aminobenzimidazole (**IIb**) in 5 ml of propionic acid was heated for 7 h at 135°C. The mixture was cooled, and the precipitate of 2-methylpyrimido-[1,2-*a*]benzimidazole-4(1*H*)-thione (**IIIb**) was filtered off. The yields of **IIIb** are given in table. mp 340–343°C. ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 6.99 s (1H, 3-H), 7.35 m (1H, 8-H), 7.58 m (2H, 7-H, 9-H), 9.72 d (1H, 6-H, J = 7.8 Hz), 13.30 br.s (1H, NH). Found, %: C 61.15; H 3.94; N 19.61. $C_{11}H_9N_3S$. Calculated, %: C 61.37; H 4.21; N 19.52.

The filtrate was evaporated, the residue was ground with diethyl ether, and the precipitate of compound **IVa**–**IVe** was filtered off. The yields of **IVa**–**IVe** are given in table.

b. A mixture of finely powdered *N*-aryl-3-oxobutanethioamide **Ia**–**Ie**, 2 mmol, and 2-aminobenzimidazole (**IIb**), 2 mmol, was heated for 0.5 h at 130–140°C. The mixture was cooled to 70°C, treated with 3 ml of boiling isopropyl alcohol, and cooled to 5°C, and the precipitate (a mixture of compounds **IIIb** and **IVa**–**IVe**) was filtered off. The ratio **IIIb**:**IV** was determined by ^{1}H NMR spectroscopy. The product mixture was treated with a 10% aqueous solution of potassium hydroxide, the undissolved material (compound **IVa**–**IVe**) was filtered off, the filtrate was acidified with acetic acid, and the precipitate of **IIIb** was filtered off.

2-Methyl-*N*-phenylpyrimido[1,2-*a*]benzimidazol-4-amine (IVa). mp 311–313°C. ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, CH_3), 5.53 s (1H, 3-H), 6.98 m (2H, H_{arom}), 7.03 m (1H, 8-H), 7.37 m (4H, H_{arom}, NH), 7.55 m (2H, H_{arom}), 8.60 d (1H, 6-H, J = 7.5 Hz). Found, %: C 74.66; H 5.24; N 20.57. $C_{17}H_{14}N_4$. Calculated, %: C 74.43; H 5.14; N 20.42.

***N*-(4-Methoxyphenyl)-2-methylpyrimido[1,2-*a*]-benzimidazol-4-amine (IVb).** mp 303–305°C. ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 3.76 s (3H, CH_3O), 5.55 s (1H, 3-H), 6.88 d (2H, C_6H_4, J = 8.5 Hz), 6.94 d (2H, C_6H_4, J = 8.5 Hz), 7.21 m (1H, 8-H), 7.34 m (1H, 7-H), 7.52 d (1H, 9-H, J = 5.7 Hz), 7.57 br.s (1H, NH), 8.61 d (1H, 6-H, J = 7.8 Hz). Found, %: C 70.78; H 5.42; N 18.64. $C_{18}H_{16}N_4O$. Calculated, %: C 71.04; H 5.30; N 18.41.

2-Methyl-*N*-(4-methylphenyl)pyrimido[1,2-*a*]-benzimidazol-4-amine (IVc). mp 310–312°C; published data [12]: mp 312–313°C. ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, 2-CH_3), 2.31 s (3H, C**H**$_3$C$_6$H$_4$), 5.52 s (1H, 3-H), 6.83 d (2H, C_6H_4, J = 7.9 Hz), 7.16 m (3H, C_6H_4, 8-H), 7.35 m (1H, 7-H), 7.56 d (1H, 9-H, J = 6.3 Hz), 7.63 br.s (1H, NH), 8.60 d (1H, 6-H, J = 7.5 Hz). Found, %: C 75.14; H 5.73; N 19.62. $C_{18}H_{16}N_4$. Calculated, %: C 74.98; H 5.59; N 19.43.

***N*-(3-Chlorophenyl)-2-methylpyrimido[1,2-*a*]-benzimidazol-4-amine (IVd).** mp 323–325°C. ^{1}H NMR spectrum, δ, ppm: 2.18 s (3H, CH_3), 5.54 s (1H, 3-H), 6.89 d (1H, 4′-H, J = 7.2 Hz), 6.95 s (1H, 2′-H), 7.07 m (1H, H_{arom}), 7.20 m (1H, H_{arom}), 7.35 m (2H, H_{arom}), 7.52 d (1H, 9-H, J = 6.6 Hz), 7.56 br.s (1H, NH), 8.58 d (1H, 6-H, J = 7.9 Hz). Found, %: C 66.29; H 4.03; N 18.35. $C_{17}H_{13}ClN_4$. Calculated, %: C 66.13; H 4.24; N 18.15.

2-Methyl-*N*-(3-trifluoromethylphenyl)pyrimido-[1,2-*a*]benzimidazol-4-amine (IVe). mp 293–295°C. ^{1}H NMR spectrum, δ, ppm: 2.18 s (3H, CH_3), 5.53 s (1H, 3-H), 7.21 m (3H, H_{arom}), 7.37 m (2H, H_{arom}), 7.56 m (3H, H_{arom}, NH), 8.62 d (1H, 6-H, J = 7.1 Hz). Found, %: C 63.01; H 4.05; N 16.11. $C_{18}H_{13}F_3N_4$. Calculated, %: C 63.16; H 3.83; N 16.37.

Sulfurization of 2-methylpyrimido[1,2-*a*]benzimidazole-4(1*H*)-thione (V). A solution of 1.99 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 magnesium sulfate and evaporated, and the residue was recrystallized from DMSO. Yield of thione **IIIb** 0.667 g (31%). The product was identical in the melting point and ^{1}H NMR data to

a sample of **IIIb** prepared from *N*-phenyl-3-oxobutanethioamide (**Ia**) and 2-aminobenzimidazole (**IIb**).

1,2-Dimethylpyrimido[1,2-*a*]benzimidazole-4(1*H*)-thione (VI). A solution of 0.056 g (1 mmol) of potassium hydroxide, 0.215 g (1 mmol) of thione **IIIb**, and 0.213 g (1.5 mmol) of methyl iodide in 5 ml of ethanol was heated for 4 h under reflux. The mixture was cooled, and the precipitate was filtered off. Yield 0.142 g (62%), mp 269–271°C. ^{1}H NMR spectrum, δ, ppm: 2.36 s (3H, 2-CH_3), 3.83 s (3H, 1-CH_3), 7.02 s (1H, 3-H), 7.40 m (1H, 8-H), 7.65 m (1H, 7-H), 7.78 d (1H, 9-H, J = 5.4 Hz), 9.76 d (1H, 6-H, J = 7.5 Hz). Found, %: C 63.02; H 5.05; N 18.47. $C_{12}H_{11}N_3S$. Calculated, %: C 62.86; H 4.84; N 18.33.

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