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Reaction of *N*-Aryl-3-oxobutanethioamides with Bis(guanidinium) Carbonate

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Abstract—Reactions of *N*-aryl-3-oxobutanethioamides with bis(guanidinium) carbonate lead to the formation of *N*-aryl-3-guanidinobut-2-enethioamides, 4-arylamino-6-methylpyrimidin-2-amines, guanidinium acetate, and arylamines, depending on the temperature conditions.

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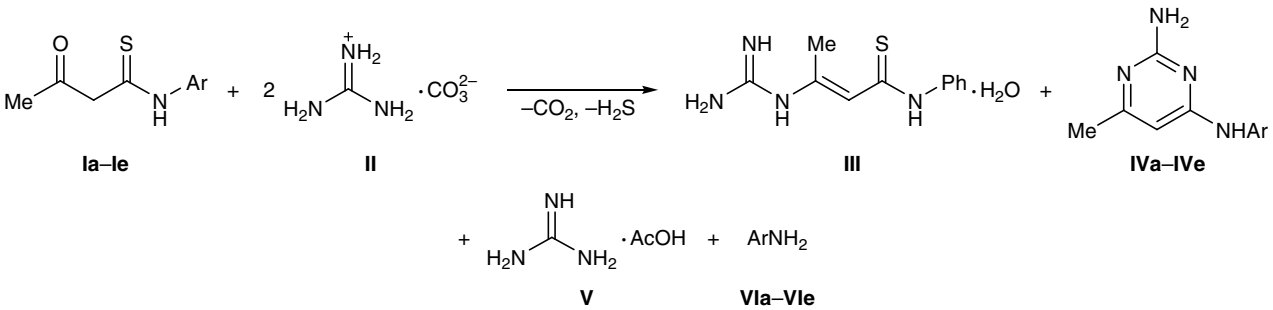
N-Aryl-3-oxobutanethioamides are polyfunctional compounds that can be used as starting materials in the synthesis of various heterocycles, such as 4*H*-1,3-thiazin-4-ones, 4*H*-thiopiran-4-ones [1], 1,2,5-oxadiazoles [2], pyrazoles [3], 1,3-thiazolidine-4,5-diones, and thiophene-2,3-diones [4]. We have recently found that *N*-aryl-3-oxobutanethioamides react with 5-substituted 3-amino-1,2,4-triazoles [5], 5-substituted 2-aminopyridines [6], and 2-aminothiazoles [7] in acetic acid to give fused heterocycles containing a pyrimidine ring. In continuation of our studies on heterocyclizations of *N*-aryl-3-oxobutanethioamides with 1,3-binucleophiles, in the present work we examined reactions of these compounds with guanidinium salts. These reactions can occur at three reaction centers of *N*-aryl-3-oxobutanethioamides with elimination of hydrogen sulfide and arylamines; as a result, 2-amino-4-(arylamino)-6-methylpyrimidines and 2-amino-4-methylpyrimidine-6(1*H*)-thione can be obtained, respectively.

Unlike our previous results, no heterocyclic products were isolated in reactions of *N*-aryl-3-oxobutanethioamides **Ia**–**Ie** with guanidinium acetate in acetic acid. Therefore, we applied more severe conditions: compounds **Ia**–**Ie** were fused with bis(guanidinium) carbonate (**II**). In this case, the reaction was not selective, and the products were compounds **III**, **IVa**–**IVe**, **V**, and **VIa**–**VIe**, whose ratio depended on the temperature and substituent nature in the aryl fragment of initial thioamide **Ia**–**Ie** (Scheme 1). The yields of products **III**–**VI** are given in table.

By heating 3-oxo-*N*-phenylbutanethioamide (**Ia**) with guanidinium salt **II** at 100°C over a period of 1 h we obtained 32% of 3-guanidino-*N*-phenylbut-2-enethioamide (**III**). The latter was also synthesized in 61% yield by reaction of thioamide **Ia** with guanidinium acetate on heating in acetic acid for 2 h. We can conclude that the carbonyl group in 3-oxo-*N*-phenylbutanethioamide (**Ia**) is more reactive than the thiocar-

Scheme 1.



I, **IV**, **VI**, Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-MeC_6H_4 (**c**), 3-$F_3CC_6H_4$ (**d**), 3-ClC_6H_4 (**e**).

Reactions of *N*-aryl-3-oxobutanethioamides **Ia**–**Ie** with bis(guanidinium) carbonate (**II**)

Initial compound no.	Yield, %			
	III	**IV**	**V**	**VI**
Ia[a]	32	–	–	–
Ia[b]	–	28	35	33
Ib[b]	–	22	34	29
Ic[b]	–	24	32	30
Id[b]	–	40	28	26
Ie[b]	–	30	33	31

[a] Reaction time 1 h, temperature 100°C.
[b] Reaction time 3 h, temperature 140°C.

bonyl group toward guanidinium salts at 100°C (as in reactions with arylamines [8]).

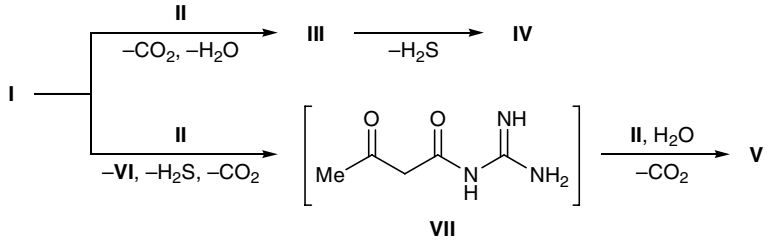
Fusion of *N*-aryl-3-oxobutanethioamides **Ia**–**Ie** with bis(guanidinium) carbonate (**II**) at elevated temperature (140°C, 3 h) led to the formation of 2-amino-4-(arylamino)-6-methylpyrimidines **IVa**–**VIe**, arylamines **VIa**–**VIe**, and guanidinium acetate (**V**). Pyrimidine **IVa** was also obtained in 41% yield by heating but-2-enethioamide **III** for 3 h at 140°C. In the reactions of salt **II** with thioamides **Id** and **Ie** having electron-withdrawing substituents in the benzene ring (CF_3, Cl), the yields of pyrimidines **IVd** and **IVe** were greater (30–40%) than in reactions with thioamides **Ia**–**Ic** possessing electron-donor groups (MeO, Me; yield 22–24%). Presumably, electron-withdrawing groups reduce the electron density on the thiocarbonyl carbon atom, so that the rate of nucleophilic attack by the amino group of guanidine increases. However, the reactions of thioamides **Ia**–**Ie** with guanidinium carbonate at 140°C are generally nonselective.

Enethioamide **III** is a light yellow crystalline substance, which is very readily soluble in water and polar organic solvents. Pyrimidines **IVa**–**IVe** are colorless substances; they are sparingly soluble in water and readily soluble in polar organic solvents. Compound **III** showed in the ^{1}H NMR spectrum singlets from the methyl protons, 2-H, and NH + NH_2 + H_2O and NH protons (δ 1.67, 5.18, 6.94, and 14.12 ppm, respectively. Its IR spectrum contained absorption bands at 1560–1600 (C=C), 1650 (C=N), and 3200 cm^{-1} (NH). In the ^{1}H NMR spectra of aminopyrimidines **IVa**–**IVe** we observed singlets at δ 2.06–2.12 (CH_3), 5.77–5.91 (5-H), 5.92–6.18 (NH_2), and 8.69–9.32 ppm (NH). It is seen that the chemical shifts vary within a narrow range (Δδ = 0.26 ppm), except for the NH protons (Δδ = 0.63 ppm). The reason is that the NH protons suffer from shielding by the neighboring phenyl ring (π-electron ring current), whose magnitude depends on the substituent in the ring. The IR spectra of **IVa**–**IVe** contain characteristic absorption bands belonging to stretching vibrations of the C=C, C=N, and N–H bonds (1580–1610, 1640–1650, and 3300–3500 cm^{-1}, respectively). The structure of guanidinium acetate **V** and arylamines **VIa**–**VIe** was confirmed by the spectral data and elemental analyses.

Our results led us to presume that the examined reaction involves two concurrent pathways (Scheme 2). According to the first of these, initial nucleophilic attack by the amino group of guanidine on the carbonyl carbon atom of thioamide **I** gives enethioamide **III** which undergoes thermal intramolecular cyclization to pyrimidine **IV**. The presence of an electron-withdrawing group in the benzene ring of *N*-aryl-3-oxobutanethioamide favors this pathway. The second pathway includes transamination and hydrolysis of thioamide **I** by the action of guanidine and water. Here, a probable intermediate is *N*-[amino(imino)methyl]-3-oxobutanamide (**VII**), and arylamine **VI** is liberated during the process. Like other acetoacetamides [9], butanamide **VII** readily undergoes hydrolysis at the C^2–C^3 bond on heating with water in the presence of guanidinium carbonate; as a result, guanidinium acetate (**V**) is formed.

Thus, unlike 2-aminoazoles [5, 7] and 5-substituted 2-aminopyridines [6], *N*-aryl-3-oxobutanethioamides react with bis(guanidinium) carbonate under more severe conditions, and the reaction leads to the forma-

Scheme 2.



tion of both heterocyclic products, 4-arylamino-6-methylpyrimidin-2-amines, and acyclic compounds, arylamines and guanidinium acetate.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian-300 spectrometer (300 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The IR spectra were measured in KBr on a UR-20 instrument.

3-Guanidino-*N*-phenylbut-2-enethioamide (III). A mixture of 10 mmol of *N*-aryl-3-oxobutanethioamide **Ia**–**Ie** and 10 mmol of finely ground bis(guanidinium) carbonate (**II**) was heated for 1 h at 100°C. The mixture was cooled, treated with 10 ml of isopropyl alcohol, and filtered from undissolved material, the filtrate was evaporated, and the residue was treated with 10 ml of diethyl ether. The undissolved material was filtered off, dried, and recrystallized from isopropyl alcohol. Yield 32%, mp 149–151°C. IR spectrum, ν, cm^{-1}: 1290, 1370, 1430, 1480, 1500, 1560, 1600, 1650, 3000–3200. ^{1}H NMR spectrum, δ, ppm: 1.67 s (3H, CH_3), 5.18 s (1H, 2-H), 6.93 m (1H, C_6H_5), 6.94 s (6H, NH, NH_2, H_2O), 7.17 m (2H, C_6H_5), 7.84 m (2H, C_6H_5), 14.12 s (1H, NH). Found, %: C 52.13; H 6.09; N 22.48. $C_{11}H_{16}N_4OS$. Calculated, %: C 52.36; H 6.39; N 22.20.

Reaction of *N*-aryl-3-oxobutanethioamides Ia–Ie with bis(guanidinium) carbonate. A mixture of 10 mmol of *N*-aryl-3-oxobutanethioamide **Ia**–**Ie** and 10 mmol of finely ground salt **II** was heated for 3 h at 140°C. The mixture was cooled and treated with 10 ml of isopropyl alcohol. The mixture was filtered from initial guanidinium carbonate, the filtrate was evaporated, and the residue was treated with 10 ml of diethyl ether. The undissolved material (a mixture of compounds **IV** and **V**) was filtered off, dried, and treated with 5 ml of water. The aqueous phase containing guanidinium acetate **V** was separated from crystals of **IVa**–**IVe** and evaporated, and salt **V** was recrystallized from isopropyl alcohol. The ether solution was evaporated to isolate arylamines **VIa**–**VIe**.

6-Methyl-4-phenylaminopyrimidin-2-amine (IVa). mp 170–172°C. IR spectrum, ν, cm^{-1}: 1365, 1410, 1470, 1500, 1580, 1610, 1650, 2900–3200, 3300, 3500. ^{1}H NMR spectrum, δ, ppm: 2.08 s (3H, 6-CH_3), 5.88 s (1H, 5-H), 6.18 s (2H, NH_2), 6.92 m (1H, C_6H_5), 7.25 m (2H, C_6H_5), 7.68 m (2H, C_6H_5), 8.99 s (1H, NH). Found, %: C 66.19; H 5.88; N 28.18. $C_{11}H_{12}N_4$. Calculated, %: C 65.98; H 6.04; N 27.98.

4-(4-Methoxyphenylamino)-6-methylpyrimidin-2-amine (IVb). mp 220–222°C. IR spectrum, ν, cm^{-1}: 1370, 1410, 1460, 1510, 1580, 1610, 1640, 2940, 3100, 3320, 3480. ^{1}H NMR spectrum, δ, ppm: 2.06 s (3H, 6-CH_3), 3.72 (3H, CH_3O) 5.77 s (1H, 5-H), 5.92 s (2H, NH_2), 6.81 d (2H, C_6H_4, J = 8.7 Hz), 7.49 d (2H, C_6H_4, J = 8.7 Hz), 8.69 s (1H, NH). Found, %: C 62.82; H 6.01; N 24.55. $C_{12}H_{14}N_4O$. Calculated, %: C 62.59; H 6.13; N 24.33.

6-Methyl-4-(4-methylphenylamino)pyrimidin-2-amine (IVc). mp 225–227°C. IR spectrum, ν, cm^{-1}: 1370, 1410, 1460, 1510, 1580, 1650, 3000, 3100, 3200, 3300, 3480. ^{1}H NMR spectrum, δ, ppm: 2.07 s (3H, 6-CH_3), 2.25 s (3H, CH_3), 5.82 s (1H, 5-H), 5.97 s (2H, NH_2), 7.03 d (2H, C_6H_4, J = 8.1 Hz), 7.50 d (2H, C_6H_4, J = 8.1 Hz), 8.79 s (1H, NH). Found, %: C 66.98; H 6.31; N 25.95. $C_{12}H_{14}N_4$. Calculated, %: C 67.27; H 6.59; N 26.15.

6-Methyl-4-[3-(trifluoromethyl)phenylamino]-pyrimidin-2-amine (IVd). mp 95–97°C. IR spectrum, ν, cm^{-1}: 1330, 1420, 1470, 1590, 1600, 1640, 3100, 3300, 3450. ^{1}H NMR spectrum, δ, ppm: 2.12 s (3H, 6-CH_3), 5.91 s (1H, 5-H), 6.18 s (2H, NH_2), 7.19 d (1H, C_6H_4, J = 8.1 Hz), 7.45 m (1H, C_6H_4), 7.95 s (1H, C_6H_4), 8.13 d (1H, C_6H_4, J = 8.4 Hz), 9.32 s (1H, NH). Found, %: C 54.01; H 3.85; N 21.05. $C_{12}H_{11}F_3N_4$. Calculated, %: C 53.73; H 4.13; N 20.89.

4-(3-Chlorophenylamino)-6-methylpyrimidin-2-amine (IVe). mp 117–119°C. IR spectrum, ν, cm^{-1}: 1410, 1460, 1580, 1640, 3100, 3300, 3450. ^{1}H NMR spectrum, δ, ppm: 2.10 s (3H, 6-CH_3), 5.87 s (1H, 5-H), 6.13 s (2H, NH_2), 6.91 d (1H, C_6H_4, J = 8.3 Hz), 7.19 m (1H, C_6H_4), 7.59 d (1H, C_6H_4, J = 8.5 Hz), 7.87 s (1H, C_6H_4), 9.16 s (1H, NH). Found, %: C 56.52; H 5.00; N 24.11. $C_{11}H_{11}ClN_4$. Calculated, %: C 56.30; H 4.72; N 23.87.

Guanidinium acetate (V). mp 225–227°C; published data [10]: mp 227–229°C. ^{1}H NMR spectrum, δ, ppm: 1.65 s (3H, CH_3), 7.73 s (6H, NH_2). Found, %: C 30.39; H 7.41; N 34.98. $C_3H_9N_3O_2$. Calculated, %: C 30.25; H 7.61; N 35.27.

Aniline (VIa). bp 179–182°C; published data [11]: bp 183–183.7°C. Found, %: C 77.22; H 7.84; N 14.79. C_6H_7N. Calculated, %: C 77.38; H 7.58; N 15.04.

4-Methoxyaniline (VIb). mp 54–57°C; published data [12]: mp 57.2°C. Found, %: C 67.98; H 7.62; N 11.51. C_7H_9NO. Calculated, %: C 68.27; H 7.37; N 11.37.

4-Methylaniline (VIc). mp 40–42°C; published data [13]: mp 42.5–43°C. Found, %: C 78.22; H 8.25;

N 12.82. C_7H_9N. Calculated, %: C 78.46; H 8.47; N 13.07.

3-(Trifluoromethyl)aniline (VId). bp 182–185°C; published data [14]: bp 187.5°C. Found, %: C 51.93; H 4.03; N 8.88. $C_7H_6F_3N$. Calculated, %: C 52.18; H 3.75; N 8.69.

3-Chloroaniline (VIe). bp 231–234°C; published data [15]: bp 236.5°C. Found, %: C 56.61; H 5.02; N 11.14. C_6H_6ClN. Calculated, %: C 56.49; H 4.74; N 10.98.

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