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A NEW ROUTE FOR THE SYNTHESIS OF 4,5-DIAMINO-6-ARYLSULFANYLPYRIMIDINE DERIVATIVES AND ALSO PURINES ON THEIR BASIS

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5-Acylamino-4-amino-6-arylsulfanylpyrimidines were formed by the reaction 3-arylsulfanyl-2-acylamino-3-chloroacrylonitriles with benzamidine. The products were converted into new derivatives of 6-arylsulfanyl-substituted purine bases by treatment with polyphosphoric acid.

Keywords: benzamidine, 4,5-diamino-6-arylsulfanylpyrimidines, purine bases, thiophenols, heterocyclization.

In the last 20 years, interest in 6-arylsulfanylpyrimidine derivatives has increased noticeably in connection with the search for effective bioregulators, especially after the discovery of preparations of the HEPT type – 6-arylsulfanylthymine based acylnucleosides with high anti-HIV activity [1–4]. In addition, many derivatives of 6-mercaptopyrimidine have a wide spectrum of biological activity. Among them are antioxidants [5], anti-inflammatories, antimicrobial preparations [6, 7], antitumor substances [8–10], insecticides, and acaricides [11].

The basic method for the synthesis of such compounds is modification of position 6 of the pyrimidine moiety [6, 8–10]. The most frequently used are 6-hydroxy derivatives of pyrimidine, which are initially converted into 6-chloro derivatives with subsequent nucleophilic substitution of the chlorine atom by sulfur-containing groups.

However, this approach is not suitable for hydroxyl groups of pyrimidines, which are containing other functional groups sensitive to the effects of chlorinating agents. In these cases, acyclic sulfur-containing reagents are used [12–19].

In the present work with the object of preparing 6-arylsulfanyl derivatives of pyrimidine containing vicinal amino functions (primary 4-amino groups and 5-acylamine radicals), 2-acylamino-3-arylsulfanyl-3-chloroacrylonitriles **2** were used, obtained from the accessible products **1** [20] (Scheme).

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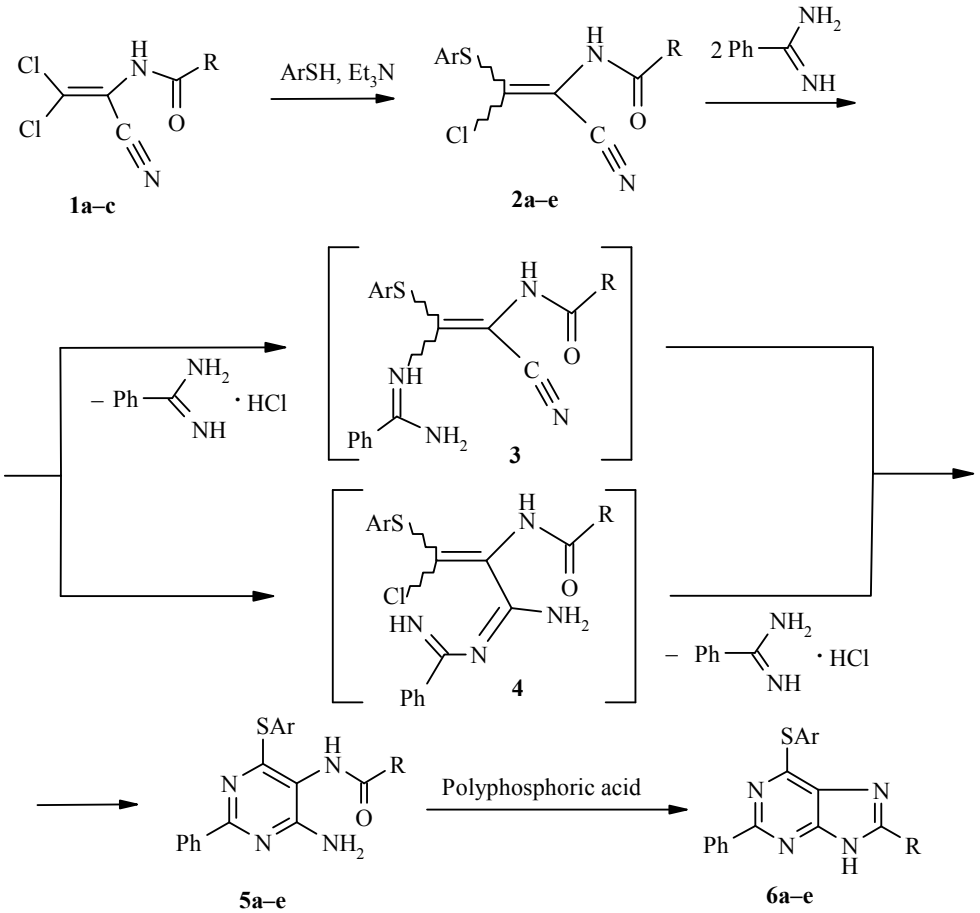

1 a R = Ph, **b** R = 4-MeC_6H_4, **c** R = 4-ClC_6H_4; **2, 5, 6 a** R = Ph, Ar = 4-MeC_6H_4, **b** R = Ph, Ar = 4-ClC_6H_4, **c** R = 4-MeC_6H_4, Ar = 4-ClC_6H_4, **d** R = 4-ClC_6H_4, Ar = 4-MeC_6H_4, **e** R = Ar = 4-ClC_6H_4

Cyclocondensation products **5** (trifunctionalized pyrimidines) were formed by reaction of reagents **2** with benzamidine, which is in agreement with cyanovinylation and subsequent cyclization **2** → **3** → **5**. However, one cannot exclude the alternative route **2** → **4** → **5** which involves initial addition of the amine to the nitrile group, although the electrophilicity of the latter in the acrylonitrile unit of compound **2** is decreased in consequence of the electron donor influence of the sulfur atom in the conjugated system $ArS-C=C-C\equiv N$ (cf, the interaction of $H-C=C-C\equiv N$ with benzamidine [21] which leads to the synthesis of imidazole derivatives).

New derivatives of purine **6** are formed in reasonable yield (Table 1) on heating compounds **5** with polyphosphoric acid. The structures of compounds **5** and **6** were confirmed by complex spectroscopic studies. Thus, in the IR spectra of compounds **5** bands $\nu_{C=O}$ of the acylamine residues were observed (1637–1639 cm^{-1}), bands of the nitrile groups at ν 2215–2225 cm^{-1} were absent, and in the ^1H NMR spectra there were signals of the primary amino groups (δ_{NH2} 6.92–7.06 ppm). Formation of the imidazole ring during the conversion **5**→**6** is in agreement with the IR, ^1H NMR, and mass spectrometric data (Table 2).

We note in conclusion that data on the synthesis of derivatives of 2-aryl-6-arylsulfanyl-7(9)H-purine of type **6** and 2-aryl-6-arylsulfanylpyrimidine **5** are absent from the literature.

Our proposed route to the synthesis of purine bases permits the regioselective introduction of aryl substituents in positions 2 and 8, and also arylsulfanyl groups into position 6 of the purine bases, which makes possible the synthesis of a large series of compounds for the development of new biologically active substances (see [22–24]).

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %					mp, °C*	Yield, %
		C	H	Cl	N	S		
2d	$C_{17}H_{12}Cl_2N_2OS$	56.51 / 56.21	3.45 / 3.33	19.75 / 19.52	7.92 / 7.71	8.56 / 8.83	197–199	75
2e	$C_{16}H_9Cl_3N_2OS$	50.29 / 50.09	2.16 / 2.36	27.93 / 27.72	7.44 / 7.30	8.31 / 8.36	222–224	81
5a	$C_{24}H_{20}N_4OS$	69.05 / 69.88	4.58 / 4.89	–	13.24 / 13.58	7.61 / 7.77	239–241	56
5b	$C_{23}H_{17}ClN_4OS$	63.48 / 63.81	3.73 / 3.96	8.05 / 8.19	12.81 / 12.94	7.35 / 7.41	245–247	61
5c	$C_{24}H_{19}ClN_4OS$	64.19 / 64.49	4.03 / 4.28	7.98 / 7.93	12.94 / 12.54	7.32 / 7.17	246–248	60
5d	$C_{24}H_{19}ClN_4OS$	64.25 / 64.49	4.09 / 4.28	7.88 / 7.93	12.88 / 12.54	7.44 / 7.17	234–236	66
5e	$C_{23}H_{16}Cl_2N_4OS$	59.03 / 59.11	3.12 / 3.45	15.09 / 15.17	12.19 / 11.99	6.74 / 6.86	249–251	71
6a	$C_{24}H_{18}N_4S$	73.25 / 73.07	4.43 / 4.60	–	14.44 / 14.20	8.31 / 8.13	221–223	57
6b	$C_{23}H_{15}ClN_4S$	66.37 / 66.58	3.23 / 3.64	8.72 / 8.54	13.88 / 13.50	7.33 / 7.72	262–264	59
6c	$C_{24}H_{17}ClN_4S$	67.13 / 67.20	3.65 / 3.99	8.13 / 8.27	13.85 / 13.06	7.66 / 7.48	253–255	54
6d	$C_{24}H_{17}ClN_4S$	67.01 / 67.20	3.54 / 3.99	8.21 / 8.27	12.81 / 13.06	7.82 / 7.48	261–263	58
6e	$C_{23}H_{14}Cl_2N_4S$	61.33 / 61.48	3.43 / 3.14	15.09 / 15.78	12.82 / 12.47	7.05 / 7.14	268–270	61

* Solvents for recrystallization: ethanol (compounds **2–5**), acetonitrile (compounds **6**).

EXPERIMENTAL

IR spectra of KBr disks were recorded on a Vertex 70 spectrometer, ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were measured on a Bruker Avance DRX-500 (500 MHz) instrument. Mass spectra were recorded on an Agilent 1100/DAD/MSD VL G1965 instrument. Melting points were measured with a Fisher-Johns apparatus.

2-Acylamino-3-arylsulfanyl-3-chloroacrylonitriles 2a–c were prepared by a known method [20], the previously unknown compounds **2d,e** were prepared analogously.

6-Amino-5-arylamino-4-arylsulfanyl-2-phenylpyrimidines 5a–e. Benzamidine (2.64 g, 22 mmol) was added to a solution of one of the compounds **2a–d** (10 mmol) in tetrahydrofuran (50 ml). The mixture was stirred for 20 h at 40°C, the residue was filtered off, washed with water, added to the product obtained after evaporation of the solvent, and compounds **5a–e** were purified by recrystallization.

8-Aryl-6-arylsulfanyl-2-phenyl-7(9)H-purines 6a–e. A mixture of one of the compounds **5a–e** (5 mmol) and polyphosphoric acid (10 g) was heated on an oil bath for 6 h at 160°C, the viscous mass formed was cooled, cold water (50 ml) was added, stirred, the precipitate was filtered off, washed with 25% aqueous ammonia, and purified by recrystallization.

TABLE 2, IR, ^{1}H NMR, and Mass Spectra of the Compounds Synthesized

Compound	IR spectra, ν, cm^{-1}	^{1}H NMR spectra, δ, ppm	Mass spectra, *m/z* $[M]^+$
2d	1662 (NC=O), 2215 (C≡N), 3268 (NH as.)	2.36 (3H, s, CH_3); 7.46–7.97 (8H, m, H arom.); 10.68 (1H, s, NH)	364
2e	1666 (NC=O), 2220 (C≡N), 3267 (NH as.)	7.59–7.96 (8H, m, H arom.); 10.76 (1H, s, NH)	385
5a	1637* (NC=O), 3283 (NH as.), 3422, 3473 (NH_2)	2.39 (3H, s, CH_3); 6.92 (2H, s, NH_2); 7.31–8.07 (14H, m, H arom.); 9.78 (1H, s, NH)	413
5b	1637* (NC=O), 3286 (NH as.), 3404, 3475 (NH_2)	7.00 (2H, s, NH_2); 7.39–8.13 (14H, m, H arom.); 9.80 (1H, s, NH)	433
5c	1639* (NC=O), 3229 (NH as.), 3410, 3469 (NH_2)	2.41 (3H, s, CH_3); 6.97 (2H, s, NH_2); 7.34–8.02 (13H, m, H arom.); 9.73 (1H, s, NH)	447
5d	1638* (NC=O), 3287 (NH as.), 3405, 3472 (NH_2)	2.39 (3H, s, CH_3); 6.97 (2H, s, NH_2); 7.29–8.08 (13H, m, H arom.); 9.86 (1H, s, NH)	447
5e	1637* (NC=O), 3268 (NH as.), 3421, 3479 (NH_2)	7.06 (2H, s, NH_2); 7.39–8.10 (13H, m, H arom.); 9.90 (1H, s, NH)	467
6a	3058 (NH as.)*[2]	2.46 (3H, s, CH_3); 7.41–8.28 (14H, m, H arom.)*[3]	395
6b	3054 (NH as.)*[2]	7.44–8.26 (14H, m, H arom.)*[3]	415
6c	3052 (NH as.)*[2]	2.42 (3H, s, CH_3); 7.43–8.14 (13H, m, H arom.)*[3]	429
6d	3054 (NH as.)*[2]	2.45 (3H, s, CH_3); 7.40–8.26 (13H, m, H arom.)*[3]	429
6e	3101 (NH as.)*[2]	7.43–8.23 (13H, m, H arom.)*[3]	449

* Band with a shoulder.

*[2] No band in the 1600–1700 cm^{-1} region.

*[3] N–H in exchange.

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