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A Simple Approach to the Synthesis of 2-(2-Amino-4-arylthiazol-5-yl)pyrimidines

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Abstract—The synthesis of 2-(2-amino-4-arylthiazol-5-yl)pyrimidin-4(3*H*)-ones from the available 2-(2-oxo-2-arylethylidene)-2,3-dihydropyrimidin-4(1*H*)- ones was developed.

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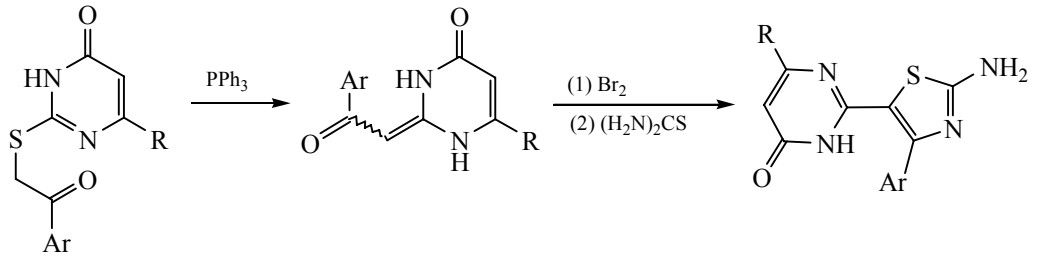
The synthesis of heterocyclic systems containing pyrimidine and thiazole rings connected by the C–C bond are developed to a lesser extent compared to their fused analogs [1–4], except for 5-(2-amino-4-arylthiazol-5-yl)-6-hydroxypyrimidine-2,4-diones obtained via the reaction of 5-(2-oxo-2-arylethylidene)pyrimidine-2,4,6-triones with thiourea [5].

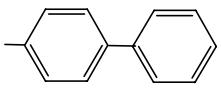
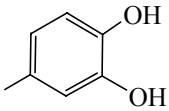
We developed the synthesis of 2-amino-4-arylthiazolyl-substituted pyrimidines pyrimidines starting from 2-(2-oxo-2-arylethylidene)-2,3-dihydropyrimidin-4(1*H*)-ones **Ia**–**Ig**.

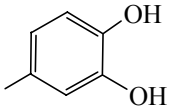
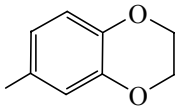
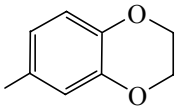
Several methods of the synthesis of the 2-oxo-2-arylethylidene-containing pyrimidines [3, 6] are known. The simplest of these methods [3], which consists in the desulfurization of 2-(2-oxoarylethylsulfanyl)pyrimidines **IIa**–**IIc** in diphenyl ether at a temperature above 200°C, we used with slight modification to obtain the starting pyrimidines **Ia**–**Ig** by boiling compounds **IIa**–**IIg** in DMF with an equimolar amount of triphenylphosphine. This reduces significantly the temperature of the sulfur elimination.

According to the ^{1}H NMR data (see table), pyrimidines **Ia**–**Ig**, as well as similar compounds [6], have the enaminoketone structure. In the case of 6-methyl-substituted pyrimidines **Ib**, **Ic**, **Ie**, **Ig** the *cis*- and *trans*-isomers form in an equal ratio. For compounds **Ia**, **Id**,



IIa–IIg **Ia–Ig** **IIIa–IIIg**

R = H, Ar = Ph (**a**); R = CH_3, Ar = Ph (**b**); R = CH_3, Ar  (**c**); R = H, Ar =  (**d**);

R = CH_3, Ar =  (**e**); R = H, Ar =  (**f**); R = CH_3, Ar =  (**g**).

Spectral characteristics of compounds **I** and **III**

Comp. no.	*m*/*z* (I_{rel}, %)	^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)
Ia	214 (43), 186 (26), 137 (30), 105 (100), 77 (75), 70 (21)	13.84 s (0.3H, NH), 13.72 s (0.7H, NH), 11.75 s (0.7H, NH), 11.68 (0.3H, NH), 7.81–7.46 m (5H, CH_{arom}), 7.70–7.68 m (1H, C^5H), 5.78–5.71 m (2H, CH)
Ib	228 (39), 200 (18), 151 (37), 105 (100), 84 (32), 77 (90)	14.40 s (0.5H, NH), 13.70 s (0.5H, NH), 11.74 s (0.5H, NH), 11.54 s (0.5H, NH), 7.65–7.47 m (5H, CH_{arom}), 5.80 s (0.5H, CH), 5.72 s (0.5H, CH), 5.66 s (0.5H, CH), 5.57 s (0.5H, CH), 2.23 s (1.5H, CH_3), 2.15 s (1.5H, CH_3)
Ic	304 (51), 276 (17), 181 (100), 152 (34), 84 (22)	14.44 s (0.5H, NH), 13.76 s (0.5H, NH), 11.83 s (0.5H, NH), 11.60 s (0.5H, NH), 7.90–7.40 m (9H, CH_{arom}), 5.86 s (0.5H, CH), 5.78 s (0.5H, CH), 5.68 s (0.5H, CH), 5.60 s (0.5H, CH), 2.25 s (1.5H, CH_3), 2.17 s (1.5H, CH_3)
Id	246 (57), 218 (7) 137 (100), 109 (22)	13.79 s (1H, NH), 11.55 s (1H, NH), 9.47 s (1H, OH), 9.20 s (1H, OH), 7.62 m (1H, C^6H), 7.25 m (3H, CH_{arom}), 5.62 m (2H, CH)
Ie	260 (80), 232 (6), 151 (23), 137 (100), 124 (34), 109 (19), 84 (21)	14.46 s (0.5H, NH), 13.67 s (0.5H, NH), 11.56 s (0.5H, NH), 11.31 s (0.5H, NH), 9.46 s (1H, OH), 9.18 s (1H, OH), 7.26–6.77 m (3H, CH_{arom}), 5.66 s (0.5H, CH), 5.60 s (0.5H, CH), 5.58 s (0.5H, CH), 5.48 s (0.5H, CH), 2.20 s (1.5H, CH_3), 2.12 s (1.5H, CH_3)
If	272 (27), 244 (13), 163 (100)	13.74 s (0.3H, NH), 13.64 s (0.7H, NH), 11.62 s (1H, NH), 7.67 d (1H, C^6H, *J* 6.0), 6.28–6.19 m (3H, CH_{arom}), 5.67 m (2H, CH_2), 4.28 s (4H, CH_2)
Ig	286 (35), 258 (7), 163 (100), 151 (10), 135 (12), 107 (11), 84 (9)	14.33 s (0.5H, NH), 13.63 s (0.5H, NH), 11.60 s (0.5H, NH), 11.35 s (0.5H, NH), 7.26–6.91 m (3H, CH_{arom}) 5.67 s (0.5H, CH), 5.66 s (0.5H, CH), 5.58 s (0.5H, CH), 5.57 s (0.5H, CH), 4.28 s (4H, CH_2), 2.18 s (1.5H, CH_3), 2.14 s (1.5H, CH_3)
IIIa	270 (30), 269 (100), 200 (7)	11.57 s (1H, NH), 7.92 br.s (1H, C^6H), 7.63 s (2H, NH_2), 7.49–7.38 m (5H, CH_{arom}), 6.16 br.s (1H, C^5H, *J* 4.8)
IIIb	284 (78), 283 (100), 200 (18)	11.28 s (1H, NH), 7.53 s (2H, NH_2), 7.51–7.38 m (5H, CH_{arom}), 5.99 s (1H, C^5H), 2.16 s (3H, CH_3)
IIIc	360 (27), 359 (100), 276 (10)	11.78 s (1H, NH), 7.73–7.37 m (9H, CH_{arom}), 7.67 s (2H, NH_2), 6.07 s (1H, C^5H), 2.19 s (3H, CH_3)
IIId	302 (76), 301 (100,) 232 (7)	11.00 s (1H, NH), 9.26 s (1H, OH), 9.14 s (1H, OH), 7.87 d (1H, C^6H, *J* 6.0), 7.63 s (2H, NH_2), 6.93 s (1H, CH_{arom}), 6.74 s (2H, CH_{arom}), 6.10 d (1H, C^5H, *J* 6.0)
IIIe	316 (100), 315 (10), 232 (10)	10.83 s (1H, NH), 9.24 s (1H, OH), 9.15 s (1H, OH), 7.59 s (2H, NH_2), 6.93 s (1H, CH_{arom}), 6.74 s (2H, CH_{arom}), 5.96 s (1H, C^5H), 2,15 s (3H, CH_3)
IIIf	328 (54), 327 (100), 258 (1)	11.57 s (1H, NH), 7.93 d (1H, C^6H, *J* 6.0), 7.60 s (2H, NH_2), 6.98–6.83 m (3H, CH_{arom}), 6.17 d (1H, C^5H, *J* 6.0), 4.26 s (4H, CH_2)
IIIg	342 (100), 341 (57), 258 (6)	11.50 s (1H, NH), 7.61 s (2H, NH_2),7.00–6.84 m (3H, CH_{arom}), 6.03 s (1H, C^5H),4.27 s (4H, $2CH_2$), 2.17 s (3H, CH_3)

If, there is the predominance of one of the isomers (see the table). The mass spectra of pyrimidines **Ia**–**Ig** contain the peaks of the molecular ions of medium intensity, whose primary fragmentation consists in a concurrent cleavage of the aryl moiety and the carbonyl group. In addition, there are intensive peaks of $ArCO^+$ cations.

4,5-Disubstituted 2-aminothiazoles **IIIa**–**IIIg** were synthesized by the Hantzsch–Traumann reaction [7, 8] of pyrimidines **Ia**–**Ig** with an equimolar amount of bromine, followed by heating with an excess of thiourea in ethanol. The structure of the reaction products was proved by the mass spectrometry and ^{1}H NMR spectroscopy (see the table). The mass spectra of thiazoles **IIIa**–**IIIg** contain the intensive peaks of the molecular ions. The main direction of their fragmentation is due to the loss of the hydrogen atom and the pyrimidine ring decay to eliminate the RC_2HCONH fragment. In the ^{1}H NMR spectra of compounds **IIIa**–**IIIg** there are the signals of amide proton at 11.78–10.83 ppm, two amino protons at 7.67–7.53 ppm, the $H^{5,6}$ proton of pyrimidine ring

(**IIIa**, **IIId**, **IIIf**) at 7.93–7.87 and 6.17–5.96 ppm, respectively, the three methyl protons (**IIIb**, **IIIc**, **IIIe**, **IIIg**) at 2.19–2.15 ppm, and of the protons of aryl fragments and their substituents.

EXPERIMENTAL

Compounds **IIa**–**IIg** were obtained as in [1]. Triphenylphosphine (Acros) was used without further purification. The used solvents were purified by the standard procedures [9]. TLC was carried out using Silufol UV-254-VIS plates eluting with a chloroform–acetonitrile mixture (5:1, 1:1). The ^{1}H NMR spectra were taken on a Varian WXP-300 instrument (299.9 MHz). The mass spectra were obtained on a MX 1321 mass spectrometer (70 eV, temperature of the ion source 220°C).

(*E*,*Z*)-2-(2-Oxo-2-phenylethylidene)-2,3-dihydropyrimidin-4(1*H*)-one (Ia). To a solution of 0.5 g of compound **IIa** in 25 ml of DMF was added 0.5 g of PPh_3. The reaction mixture was boiled for 6 h and then poured into 100 ml of water. The resulting precipitate was filtered off, dried in air, and washed with hot benzene. The residue was crystallized from ethanol. Yield 0.26 g (67%), mp 242°C. Found, %: C 67.25; H 4.75; N 13.00. $C_{12}H_{10}N_2O_2$. Calculated, %: C 67.28; H 4.71; N 13.08.

(*E*,*Z*)-6-Methyl-2-(2-oxo-2-phenylethylidene)-2,3-dihydropyrimidin-4(1*H*)-one (Ib) was prepared similarly from compound **IIb**. Yield 0.34 g (86%), mp 250–252°C. Found, %: C 68.48, H 5.36; N 12.21. $C_{13}H_{12}N_2O_2$. Calculated, %: C 68.41, H 5.30; N 12.27.

(*E*,*Z*)-2-[2-(Biphenyl-4-yl)-2-oxoethylidene]-6-methyl-2,3-dihydropyrimidin-4(1*H*)-one (Ic) was prepared similarly from compound **IIc**. Yield 50%, mp 265°C. (dec.). Found, %: C 74.93; H 5.30; N 9.18. $C_{19}H_{16}N_2O_2$. Calculated, %: C 74.98; H 5.30; N 9.20.

(*E*,*Z*)-2-(3,4-Dihydroxyphenyl)-2-oxoethylidene)-2,3-dihydropyrimidin-4(1*H*)-one (Id) was prepared similarly from compound **IId**. Yiled 28%, mp 299°C. Found, %: C 58.52; H 4.12; N 11.35. $C_{12}H_{10}N_2O_4$. Calculated, %: C 58.54; H 4.09; N 11.38.

(*E*,*Z*)-2-(3,4-Dihydroxyphenyl)-2-oxoethylidene)-6-methyl-2,3-dihydropyrimidin-4(1*H*)-one (Ie) was prepared similarly from compound **IIe**. Yield 35%, mp 310°C. Found, %: C 59.98; H 4.67; N 10.74. $C_{13}H_{12}N_2O_4$. Calculated, %: C 60.00; H 4.65; N 10.76.

(*E*,*Z*)-2-(2,3-Dihydrobenzo[*b*]-1,4-dioxin-6-yl)-2-oxoethylidene)-2,3-dihydropyrimidin-4(1*H*)-one (If) was prepared similarly from compound **IIf**. Yield 26%, mp 272–274°C (acetonitrile). Found, %: C 61.80; H 4.49; N 10.25 $C_{14}H_{12}N_2O_4$. Calculated, %: C 61.76; H 4.44; N 10.29.

(*E*,*Z*)-2-(2,3-Dihydrobenzo[*b*]-1,4-dioxin-6-yl)-2-oxoethylidene)-6-methyl-2,3-dihydropyrimidin-4(1*H*)-one (Ig) was prepared similarly from compound **IIg**. Yield 32%, mp 239–240°C. Found, %: C 62.90; H 4.98; N 9.76 $C_{15}H_{14}N_2O_4$. Calculated, %: C 62.93; H 4.93; N 9.78.

2-(2-Amino-4-phenylthiazol-5-yl)pyrimidin-4(3*H*)-one (IIIa). To a solution of 0.24 g of compound **Ia** in 3270 ml of ethanol was added 0.22 g of bromine. After stirring for 1 min, to the mixture was added 0.52 g of thiourea, and the mixture was refluxed for 6 h. The solvent was removed in a vacuum. The residue was filtered off, washed with 1% $NaHCO_3$ aqueous solution and then with water, dried in air and crystallized from ethanol. Yield 0.18 g (59%), mp 298°C (dec.). Found, %: C 57.80; H 3.77; N 20.70. $C_{13}H_{10}N_4OS$. Calculated, %: C 57.76; H 3.73; N 20.73.

2-(2-Amino-4-phenylthiazol-5-yl)-6-methylpyrimidin-4(3*H*)-one (IIIb) was prepared similarly from compound **Ib**. Yield 69%, mp 265°C (dec.). Found, %: C 59.12; H 4.27; N 19.68. $C_{14}H_{12}N_4OS$. Calculated, %: C 59.14; H 4.25; N 19.70.

2-[2-Amino-4-(biphenyl-4-yl)thiazol-5-yl]-6-methylpyrimidin-4(3*H*)-one (IIIc) was prepared similarly from compound **Ic**. Yield 52%, mp 299°C (dec.). Found, %: C 66.70; H 4.50; N 15.50. $C_{20}H_{16}N_4OS$. Calculated, %: C 66.65; H 4.47; N 15.54.

2-[2-Amino-4-(3,4-dihydroxyphenyl)thiazol-5-yl]-pyrimidin-4(3*H*)-one (IIId) was prepared similarly from compound **Id**. Yield 47%, mp 310°C (dec.). Found, %: C 51.70; H 3.41; N 18.50. $C_{13}H_{10}N_4O_3S$. Calculated, %: C 51.65; H 3.33; N 18.53.

2-[2-Amino-4-(3,4-dihydroxyphenyl)thiazol-5-yl]-6-methylpyrimidin-4(3*H*)-one (IIIe) was prepared similarly from compound **Ie**. Yield 45%, mp 330°C (dec.). Found, %: C 53.10; H 3.77; N 17.65. $C_{14}H_{12}N_4O_3S$. Calculated, %: C 53.16; H 3.82; N 17.71.

2-[2-Amino-4-(2,3-dihydrobenzo[*b*]-1,4-dioxin-6-yl]thiazol-5-yl)pyrimidin-4(3*H*)-one (IIIf) was prepared similarly from compound **If**. Yield 41%, mp 268–269°C (acetonitrile). Found, %: C 54.84; H 3.70; N 17.05. $C_{13}H_{10}N_4OS$. Calculated, %: C 54.87; H 3.68; N 17.06.

2-[2-Amino-4-(2,3-dihydrobenzo[b]-1,4-dioxin-6-yl)thiazol-5-yl]-6-methyl-pyrimidin-4(3*H*)-one (IIIg) was prepared similarly from compound **Ig**. Yield 76%, mp 308°C (dec.). Found, %: C 56.10; H 4.14; N 16.33. $C_{16}H_{14}N_4O_3S$. Calculated, %: C 56.13; H 4.12; N 16.36.

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