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5-THIAZOLYL DERIVATIVES OF 4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES

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As shown by calculations by means of the PASS software [1], the 5-(1,3-thiazol-4-yl) derivatives of 4-aryl-3,4-dihydropyrimidin-(1H)-2-ones are promising subjects in the search for physiologically active substances. Moreover, there are few publications on the synthesis of 4-aryl-3,4-dihydropyrimidin-(1H)-2-ones containing a heterocyclic fragment at position 5 [2-4], and their synthesis will make it possible to develop substantially the theories about such systems.

The most obvious way of constructing the 1,3-thiazole ring is the Hantsch reaction, the starting materials for which must be the ω-bromoacetyl derivatives of compounds produced by the Biginelli reaction.

It is known that the related 4-aryl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-ones, also produced by the Biginelli reaction, are brominated at the methyl group with the formation of 6-bromomethyl and 6,6-dibromomethyl derivatives [5-7]. We studied the bromination of the 5-acetyl derivatives of 4-aryl-3,4-dihydropyrimidin-2(1H)-ones **1** and **2** in order to determine how the presence (or absence) of the 6-methyl group in these molecules would affect the course of bromination. As found, the 6-methyl derivative **1** does not react with bromine in acetic acid at room temperature (the initial compound is recovered completely on dilution of the reaction mixture with water), while the low solubility of the compound does not permit the reaction in chloroform or alcohol. At the same time, the bromination of compound **1** in acetic acid with heat leads to resinification of the mixture.

Earlier [8, 9] we showed that by inserting a 1-alkyl substituent it is possible to eliminate the possibility of amide–imidol tautomerism in 5-acetyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones, affecting the processes involving removal of the acetyl group, and to increase their solubility significantly, and this should make it possible to realize bromination under mild conditions. This was confirmed during the bromination of the 1,6-dimethyl derivative **2**; nevertheless, a complex mixture is formed both in chloroform and in acetic acid due, probably, to crossed bromination of both the acetyl group and the 6-methyl group.

We assumed that the absence of a methyl group at position 6 of the heterocycle would make it possible to minimize the contribution from the bromination paths. Compounds **3a**,**b** corresponded fully to such a model. Our assumptions were fully confirmed; the reaction of compounds **3a**,**b** with bromine take place at a sufficiently high rate in chloroform at room temperature. Although according to ^{1}H NMR spectroscopy the bromination products represent mixtures of substances the main products among them are the ω-bromoacetyl derivatives in which we are interested, since the direct use of these mixtures in reaction with thioamides made it possible to obtain moderate yields of the corresponding thiazoles **4a-d**.

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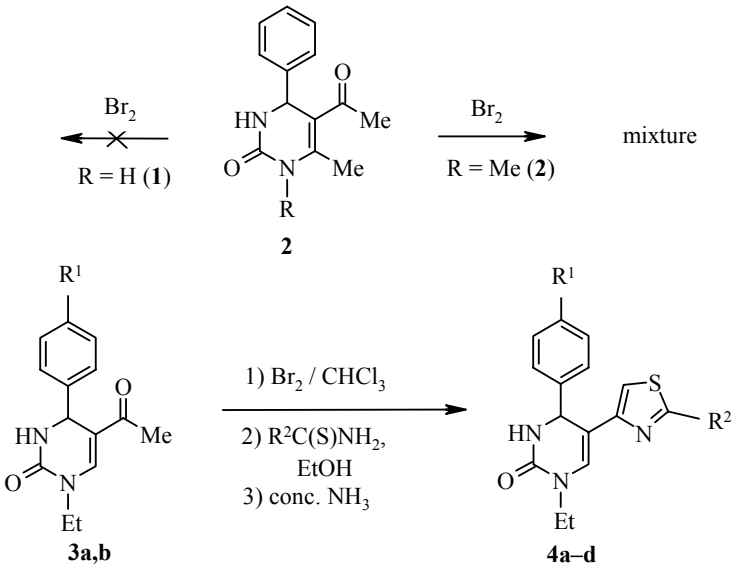
The thiazolyl derivatives **4a-d** are colorless solids moderately soluble in alcohol, ethyl acetate, and chloroform and insoluble in water. Their structure was confirmed by IR and ^{1}H NMR spectroscopy, elemental analysis, and mass spectrometry.



3 a R^1 = H; **b** R^1 = OMe; **4 a** R^1 = H, R^2 = NH_2; **b** R^1 = H, R^2 = Me;
c R^1 = OMe, R^2 = NH–N=CHPh; **d** R^1 = OMe, R^2 = NH–N=CHC_6H_4OMe-*p*

The ^{1}H NMR spectra were recorded on a Varian Mercury VX-200 spectrometer (200 MHz) in DMSO-d_6 solution with TMS as internal standard.

The IR spectra were obtained on a Specord IR-75 spectrometer in tablets with KBr. The mass spectra were obtained on an Agillent 1100 LC-MS instrument.

Compounds **1-3** were obtained according to the procedures described in [8, 10].

4-Aryl-1-ethyl-5-(1,3-thiazol-4-yl)- 3,4-dihydropyrimidin-2(1H)-ones 2a-d (General Method). A solution of bromine (0.163 ml, 3.15 mmol) in chloroform (6 ml) was added to a solution of the respective compound **1** (3 mmol) in chloroform (6 ml) over 10 min with stirring and cooling in iced water. The stirring was continued for 30 min, after which the solvent was distilled at reduced pressure, 5 ml of ethanol was added, and the solvent was again distilled. The product was washed three times with ethanol in order to remove the chloroform completely, ethanol (15 ml) and respective thioamide (2.7 mmol) were added, and the mixture was boiled for 5-10 min. It was then cooled, and the precipitate was filtered off and washed with ethanol. After drying it was stirred with concentrated aqueous solution of ammonia (20 ml), and the thiazole **2** was filtered off, washed with water, and dried in air.

5-(2-Amino-1,3-thiazol-4-yl)-1-ethyl-4-(4-phenyl) -3,4-dihydropyrimidin-2(1H)-one (4a). The yield was 54%; mp 141-143°C (ethanol). IR spectrum, ν, cm^{-1}: 1642, 3070 (CH), 3223 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.9 (H, br. s, NH_2); 8.0 (H, br. s, NH_2); 7.48 (H, br. d, *J* = 2.8, NH); 7.20-7.36 (5H, m, C_6H_5); 7.0 (H, s, CH); 6.20 (H, s, CH); 5.16 (H, d, *J* = 2.8, H-4); 3.3-3.7 (2H, m, CH_2); 1.15 (3H, t, *J* = 7.2, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 301 $[M+1]^+$ (100). Found, %: N 18.61. $C_{15}H_{16}N_4OS$. Calculated, %: N 18.65.

1-Ethyl-5-(2-methyl-1,3-thiazol-4-yl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4b). The yield was 63%; mp 125-127°C (ethanol). IR spectrum, ν, cm^{-1}: 1669, 3083 (CH), 3223 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.55 (1H, br. d, *J* = 3.0, NH); 7.1-7.4 (6H, m, C_6H_5 + CH); 6.93 (1H, s, CH); 5.17 (1H, d, *J* = 3.0, H-4); 3.3-3.8 (2H, m, CH_2); 2.16 (3H, s, CH_3 (thiazolyl)); 1.15 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$). Found, %: N 13.90. $C_{16}H_{17}N_3OS$. Calculated, %: N 14.04.

5-[2-(2-Benzylidenehydrazin-1-yl)-1,3-thiazol-4-yl]-1-ethyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4c). The yield was 40%; mp 147-149°C (decomp., ethanol). IR spectrum, ν, cm^{-1}: 1562, 1609, 1655, 3403 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.0 (H, br. s, N–NH); 7.96 (H, br. d, *J* = 2.8, N(3)H); 7.59 (2H, d, *J* = 8.0, ArH); 7.44 (H, s, CH); 7.38 (2H, d, *J* = 8.0, ArH); 7.26 (2H, d, *J* = 8.0, ArH); 7.03 (1H, s, CH); 6.86 (2H, d, *J* = 8.0, ArH); 6.34 (1H, s, CH); 5.18 (H, d, *J* = 2.8, H-4); 3.69 (3H, s, CH_3O); 3.3-3.8 (2H, m, CH_2); 1.12 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$). Found, %: N 16.01. $C_{23}H_{23}N_5O_2S$. Calculated, %: N 16.15.

1-Ethyl-5-{2-[2-(4-methoxybenzylidene)hydrazine-1-yl]-1,3-thiazol-4-yl}-3,4-dihydropyrimidin-2(1H)-one (4d). The yield was 50%; mp 145-147°C (ethanol). IR spectrum, ν, cm^{-1}: 1602, 1662, 2936 (CH), 3410 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.9 (H, br. s, N–NH); 7.9 (H, br. d, *J* = 2.8, N(3)H); 7.53 (2H, d, *J* = 8.8, ArH); 7.44 (1H, s, CH); 7.26 (2H, d, *J* = 8.8, ArH); 7.02 (1H, s, CH); 6.95 (2H, d, *J* = 8.8, ArH); 6.86 (2H, d, *J* = 8.8, ArH); 6.30 (H, s, CH); 5.15 (H, d, *J* = 2.8, H-4); 3.4-3.8 (2H, m, CH_2); 3.76 (3H, s, CH_3O); 3.69 (3H, s, CH_3O); 1.12 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$). Found, %: N 14.98. $C_{24}H_{25}N_5O_3S$. Calculated, %: N 15.11.

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