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Reaction of 4-Iminothiazolidin-2-one with Acetylacetone

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Abstract—By the reaction of acetylacetone and arylazoacetylacetones with 4-iminothiazolidin-2-one thiazolo[4,5-*b*]pyridines were obtained in good yields. Optimum reaction conditions were chosen and some properties of compounds obtained were studied.

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Five-membered heterocycles fused to the pyridine ring attract constant attention since many compounds of this class possess the biologic action. Thiazolo[4,5-*b*]pyridines are among the least accessible and in turn poorly understood representatives of this class of organic substances. The information on their biological activity is also insufficient. In particular, among this type compounds substances were found possessing fungicidal action [1], antagonists of H3-histamine receptors [2], antagonists of metabotropic glutamate receptors 5 (mGluR5) [3] of high inhibitor activity with respect to the receptors of the epidermal growth factor [4] and a number of other enzymes [5, 6].

Two fundamentally different approaches exist with respect to the synthesis of the thiazolo[4,5-*b*]pyridine system. The first one is based on the fusion of the thiazole ring to the pyridine. Here 2-aminopyridines [7], thioureas[8–10], or thiocarbamates [11] are used as initial compounds. The second procedure of the pyridine ring fusion is underlain by a three-component condensation of derivatives of 4-aminothiazoles and 4-aminoselenazoles with aromatic or aliphatic aldehydes and the Meldrum's acid [12]. At the use in the reaction with 2,4-diaminothiazoles of ethyl acetoacetate and acetylacetone 2-amino-5,7-dimethylthiazolo[4,5-*b*]pyridines and 2-amino-7-methyl-4*H*-thiazolo[4,5-*b*]pyridin-5-ones were obtained respectively [13]. Examples are also known of the synthesis of 1,3-thiazolo[4,5-*b*]pyridine derivatives with the use of solid-phase carriers [14] and with the application of dominoreactions [15].

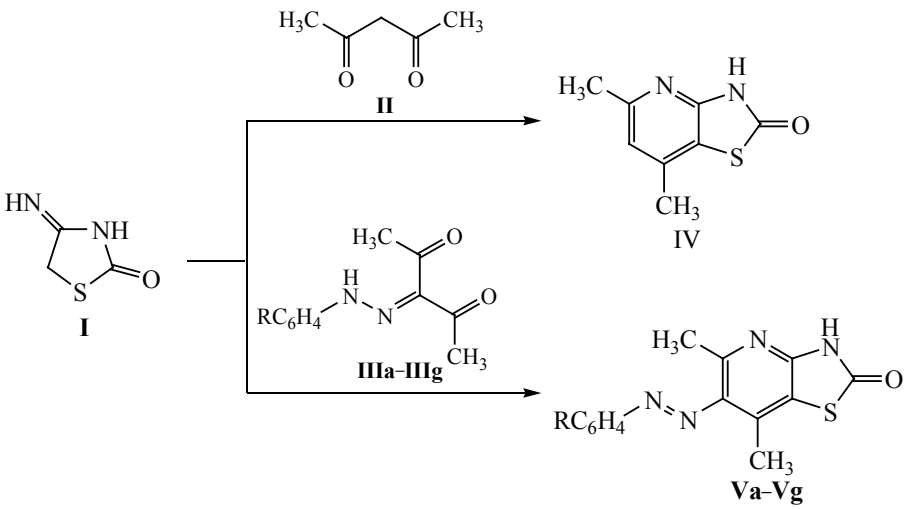
We report here on a convenient method of preparation of 3*H*-thiazolo[4,5-*b*]pyridin-2-one derivatives. We used 4-iminothiazolidin-2-one (**I**) as the initial compound[16] that was reacted with acetylacetone (**II**). We optimized the conditions of this reaction that made it possible to obtain 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]-pyridin-2-one (**IV**) in good yield. The best results were observed at keeping the reagents mixture in methanol in the presence of sodium methylate over 5 days. Similar procedure was described earlier in patent [17], but due to the low yield the method had no preparative value.

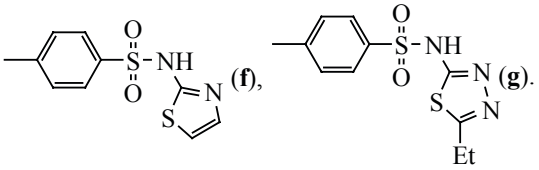
We also studied the behavior in this reaction of acetylacetone arylazo derivatives **IIIa–IIIg** (Scheme 1). Under the chosen conditions the corresponding 6-arylazo-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones **Va–Vg** formed in good yields. These substances were orange or red crystalline powders well soluble in DMF and DMSO, sparingly soluble in water and the other organic solvents.

The structure of compounds obtained was proved by NMR spectra. For instance, the proton signals of the methyl groups of the pyridine ring are observed at 2.42–2.46 and 2.49–2.87 ppm respectively, and of NH groups, in a relatively wide range of 9.78–14.29 ppm.

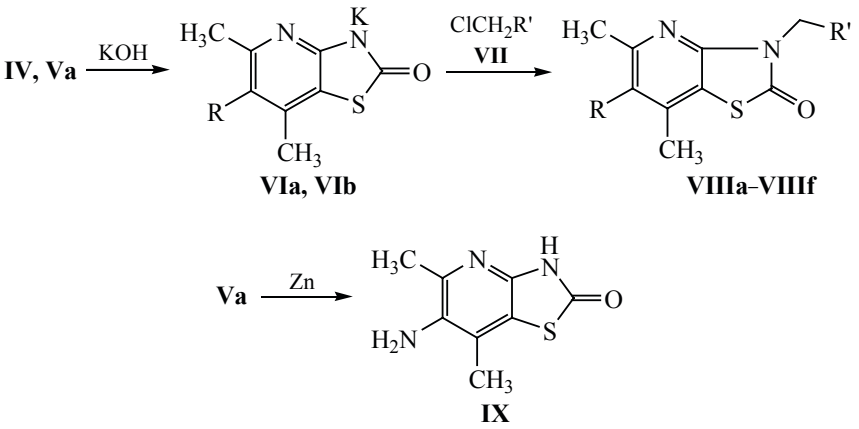
Some properties of compounds obtained were investigated. The proton in the position *3* retained the acid properties, and the reaction with potassium hydroxide afforded the corresponding salts **VIa, VIb**. The obtained salts exhibited nucleophilic properties and under mild conditions reacted with electrophilic reagents to give N-alkylated products (Scheme 2).

Scheme 1.



III, V, R = H (**a**), 2-CH_3 (**b**), 4-CH_3 (**c**), NO_2 (**d**), COOH (**e**),  (**f**), (**g**).

Scheme 2.



VI, R = H (**a**), $C_6H_5N{=}N$ (**b**); **VIII**, R = H, R' = 4-$NO_2C_6H_4$ (**a**), 4-$CH_3C_6H_4NHC(O)$ (**b**), 2-$C_2H_5C_6H_4NHC(O)$ (**c**), 2-$ClC_6H_4NHC(O)$ (**d**); R = $C_6H_5N{=}N$, R' = 4-$CH_3C_6H_4NHC(O)$ (**e**), 4-$C_2H_5C_6H_4NHC(O)$ (**f**).

In reaction with reducers compound **Va** was readily converted into 6-amino-5,7-dimethyl-3*H*-thiazolo[4,5-*b*] pyridin-2-one (**IX**). Optimum yield of compound **IX** was obtained in the process carried out in the mixture acetic acid–pyridine using zinc powder as reducer.

Thus a convenient method was developed for the preparation of 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one derivatives in high yields from available initial reagents. The possibilities of their synthetic application were demonstrated.

EXPERIMENTAL

^{1}H NMR spectra of compounds in DMSO-d_6 solution were registered on a spectrometer Varian Mercury VX-400 (400 MHz), internal reference TMS.

5,7-Dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one (IV). In 125 ml of anhydrous methanol 2.5 g (109 mmol) of sodium was dissolved, and to the solution obtained at 20°C was added 6.8 g (50 mmol) of 4-iminothiazolidin-2-one (**I**) and 8 ml of acetylacetone. The mixture was left standing for 5 days with the intermittent stirring, then it was acidified with acetic acid to pH ~5, five-fold diluted with water, the precipitate was filtered off, washed with water, and dried. Yield 6.7 g (74%), mp 277°C (ethanol). White crystalline powder, well soluble in DMF, DMSO, solutions of alkali and mineral acids, sparingly soluble in the other organic solvents. ^{1}H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 2.40 s (3H, CH_3), 6.91 s (1H, Py), 12.44 s (1H, NH). Found, %: C 53.31; H 4.47; N 15.54. $C_8H_8N_2OS$. Calculated, %: C 53.02; H 4.49; N 15.44.

5,7-Dimethyl-6-arylazo-3*H*-thiazolo[4,5-*b*]pyridin-2-ones **Va–Vg** were obtained similarly from compound **I** and appropriate α-arylazoacetylacetones **IIIa–IIIg** [18].

5,7-Dimethyl-6-phenylazo-3*H*-thiazolo[4,5-*b*]-pyridin-2-one (Va). Yield 86%, mp 258–259°C (toluene). ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 2.61 s (3H, CH_3), 7.60 m (3H, C_6H_5), 7.80 d (2H, C_6H_5, *J* 8.0 Hz), 12.78 s (1H, NH) Found, %: C 58.81; H 4.32; N 19.79. $C_{14}H_{12}N_4OS$. Calculated, %: C 59.14; H 4.25; N 19.70.

5,7-Dimethyl-6-*o*-tolylazo-3*H*-thiazolo[4,5-*b*]-pyridin-2-one (Vb). Yield 85%, mp 259–260°C (decomp.) (toluene). ^{1}H NMR spectrum, δ, ppm: 2.47 s (3H, CH_3), 2.65 s (3H, CH_3), 2.67 s (3H, CH_3), 7.33–7.37 m (1H, C_6H_4), 7.46 d (2H, C_6H_4, *J* 3.9 Hz), 7.59 d (1H, C_6H_4, *J* 8.0 Hz), 12.75 (1H, NH). Found, %: C 60.30; H 4.63; N 18.75. $C_{15}H_{14}N_4OS$. Calculated, %: C 60.38; H 4.73; N 18.78.

5,7-Dimethyl-6-*p*-tolylazo-3*H*-thiazolo[4,5-*b*]-pyridine-2-one (Vc). Yield 75%, mp 252°C (decomp.) (toluene). ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, $CH_3C_6H_4$), 2.42 s (3H, CH_3), 2.60 s (3H, CH_3), 7.41 d (2H, C_6H_4, *J* 7.6 Hz), 7.78 d (2H, C_6H_4, *J* 7.6 Hz), 12.74 s (1H, NH). Found, %: C 60.30; H 4.63; N 18.75. $C_{15}H_{14}N_4OS$. Calculated, %: C 60.38; H 4.73; N 18.78.

5,7-Dimethyl-6-(4-nitrophenylazo)-3*H*-thiazolo-[4,5-*b*]pyridine-2-one (Vd). Yield 81%, mp 194°C. (toluene). ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 2.49 s (3H, CH_3), 7.74 d (2H, C_6H_4, *J* 9.1 Hz), 8.28 d (2H, C_6H_4, *J* 9.1 Hz), 13.30 s (1H, NH). Found, %: C 51.18; H 3.47; N 21.00. $C_{14}H_{11}N_4O_3S$. Calculated, %: C 51.06; H 3.37; N 21.26.

4-(5,7-Dimethyl-2-oxo-2,3-dihydrothiazolo[4,5-*b*]-pyridin-6-ylazo)benzoic acid (Ve). Yield 74%, mp 350°C (decomp.) (2-propanol). ^{1}H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3), 2.49 s (3H, CH_3), 7.65 d (2H, C_6H_4, *J* 8.6 Hz), 7.98 d (2H, C_6H_4, *J* 8.6 Hz), 13.68 s (1H, NH), 14.08 s (1H, COOH). Found, %: C 54.99; H 3.60; N 17.86. $C_{15}H_{12}N_4O_3S$. Calculated, %: C 54.87; H 3.68; N 17.06.

4-(5,7-Dimethyl-2-oxo-2,3-dihydrothiazolo[4,5-*b*]-pyridin-6-ylazo)-*N*-thiazol-2-ylbenzenesulfonamide (Vf). Yield 76%, mp 264–265°C (decomp.) (benzene). ^{1}H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3), 2.65 s (3H, CH_3), 6.88 d (1H, thiazole, *J* 4.0 Hz), 6.89 d (1H, thiazole, *J* 4.0 Hz), 7.97–8.02 m (4H, C_6H_4), 12.85 s (1H, NH). Found, %: C 45.93; H 3.23; N 18.92. $C_{17}H_{14}N_6O_3S_3$. Calculated, %: C 45.73; H 3.16; N 18.82.

4-(5,7-Dimethyl-2-oxo-2,3-dihydrothiazolo[4,5-*b*]-pyridin-6-ylazo)-*N*-[1,3,4]thiadiazol-2-ylbenzenesulfonamide (Vg). Yield 85%, mp 280–281°C (decomp.) (toluene). ^{1}H NMR spectrum, δ, ppm: 1.24 t (3H, CH_3, *J* 7.5 Hz), 2.66 s (3H, CH_3), 2.87 q (2H, CH_2, *J* 7.5 Hz), 8.00 s (4H, C_6H_4), 12.86 s (1H, NH), 14.10 s (1H, NH). Found, %: C 43.10; H 2.25; N 21.99. $C_{16}H_{13}N_7O_3S_3$. Calculated, %: C 42.94; H 2.93; N 21.91.

5,7-Dimethyl-3*H*-thiazolo[4,5-*b*]-pyridin-2-one potassium salt (VIa). To 20 ml of water and 0.56 g (10 mmol) of potassium hydroxide was added 1.8 g (10 mmol) of compound **IV**, and the mixture was heated to complete dissolution. The solution obtained was evaporated to dryness. The residue was dried at 100°C. Yield quantitative, mp >300°C (water). Lightly colored crystalline powder soluble in water and alcohols, sparingly soluble in organic solvents. ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 2.44 s (3H, CH_3), 6.44 s (1H, Py). Found, %: C 44.22; H 3.53; N 12.80. $C_8H_7KN_2OS$. Calculated, %: C 44.03; H 3.23; N 12.84.

5,7-Dimethyl-6-phenylazo-3*H*-thiazolo[4,5-*b*]pyridin-2-one potassium salt (VIb) was obtained similarly. Yield quantitative, mp >300°C (water). Red crystalline powder soluble in water and alcohols, sparingly soluble in organic solvents. ^{1}H NMR spectrum, δ, ppm: 2.48 s (3H, CH_3), 2.64 s (3H, CH_3), 7.43 d (1H, C_6H_5, *J* 6.8 Hz), 7.53 t (2H, C_6H_5, *J* 7.6 Hz), 7.75 d (2H, C_6H_5, *J* 7.6 Hz). Found, %: C 52.34; H 3.32; N 17.41. $C_{14}H_{11}KN_4OS$. Calculated, %: C 52.15; H 3.44; N 17.38.

General alkylation procedure. To a solution obtained by heating 9 mmol of potassium salt **VIa** or **VIb** in 12 ml of DMF was added 9 mmol of an appropriate alkylating agent. The mixture was boiled for 20 min, a bulky white

precipitate separated. The hot mixture was filtered, the precipitate was washed on the filter with hot DMF. To the filtrate cooled to ~50°C was added at stirring 100 ml of water, and the mixture was cooled to 12–15°C. The separated precipitate was filtered off, washed with water, and dried.

5,7-Dimethyl-3-(4-nitrobenzyl)-3*H*-thiazolo-[4,5-*b*] pyridin-2-one (VIIIa). Yield 72%, mp 180°C (DMF). ^{1}H NMR spectrum, δ, ppm: 2.33 s (3H, CH_3), 2.44 s (3H, CH_3), 5.29 s (2H, CH_2), 7.04 s (1H, Py) 7.56 d (2H, C_6H_4, *J* 10.5 Hz), 8.20 d (2H, C_6H_4, *J* 10.5 Hz). Found, %: C 57.25; H 4.05; N 13.40. $C_{15}H_{13}N_3O_3S$. Calculated, %: C 57.13; H 4.16; N 13.33.

2-(5,7-Dimethyl-2-oxothiazolo[4,5-*b*]pyridin-3-yl)-*N*-*p*-tolylacetamide (VIIIb). Yield 90%, mp 202°C (DMF–ethanol, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 2.34 s (3H, CH_3), 2.43 s (3H, CH_3), 4.78 s (2H, CH_2), 7.02 s (1H, Py), 7.12 d (2H, C_6H_4, *J* 8.1 Hz), 7.45 d (2H, C_6H_4, *J* 8.1 Hz), 10.30 s (1H, NH). Found, %: C 62.20; H 5.33; N 12.53. $C_{17}H_{17}N_3O_2S$. Calculated, %: C 62.37; H 5.23; N 12.83.

2-(5,7-Dimethyl-2-oxothiazolo[4,5-*b*]pyridin-3-yl)-*N*-(2-ethylphenyl)acetamide (VIIIc). Yield 86%, mp 190–191°C (DMF–ethanol, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 1.15 t (3H, CH_3CH_2, *J* 7.3 Hz), 2.34 s (3H, CH_3), 2.45 s (3H, CH_3), 2.63 q (2H, CH_2CH_3, *J* 7.3 Hz), 4.81 s (2H, CH_2), 7.17 s (1H, Py), 7.25–7.30 m (4H, C_6H_4), 10.78 s (1H, NH). Found, %: C 63.24; H 5.72; N 12.50. $C_{18}H_{19}N_3O_2S$. Calculated, %: C 63.32; H 5.61; N 12.31.

2-(5,7-Dimethyl-2-oxothiazolo[4,5-*b*]pyridin-3-yl)-*N*-(2-chlorophenyl)acetamide (VIIId). Yield 74%, mp 174°C (DMF–ethanol, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 2.45 s (3H, CH_3), 4.88 s (2H, CH_2), 7.02 s (1H, Py), 7.21 d.t (1H, C_6H_4, ^4J 1.2, ^3J 8.0 Hz), 7.33 d.t (1H, C_6H_4, ^4J 1.2, ^3J 8.0 Hz), 7.52 d.d (1H, C_6H_4, ^4J 1.2, ^3J 7.8 Hz), 7.70 d.d (1H, C_6H_4, ^3J 1.2, *J* 7.8 Hz), 10.08 s (1H, NH). Found, %: C 55.18; H 4.17; N 12.08. $C_{16}H_{14}ClN_3O_2S$. Calculated, %: C 55.25; H 4.06; N 12.08.

2-(5,7-Dimethyl-2-oxo-6-phenylazothiazolo[4,5-*b*]-pyridin-3-yl)-*N*-*p*-tolylacetamide (VIIIe). Yield 74%, mp 250°C (DMF–ethanol, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, $C_6H_4CH_3$), 2.37 s (3H, CH_3), 2.64 s (3H, CH_3), 4.86 s (2H, CH_2) 7.13 d (2H, $C_6H_4CH_3$, *J* 7.6 Hz), 7.46 d (2H, $C_6H_4CH_3$, *J* 7.6 Hz), 7.62 m (3H, C_6H_5), 7.90 d (2H, C_6H_5, *J* 7.20 Hz), 10.38 s (1H, NH). Found, %: C 64.22; H 4.92; N 16.43. $C_{23}H_{21}N_5O_2S$. Calculated, %: C 64.02; H 4.91; N 16.23.

2-(5,7-Dimethyl-2-oxo-6-phenylazothiazolo[4,5-*b*]-pyridin-3-yl)-*N*-(4-ethylphenyl)acetamide (VIIIf). Yield 79%, mp 200–201°C (DMF–ethanol, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 1.17 t (3H, CH_2CH_3, *J* 7.3 Hz), 2.51 s (3H, CH_3), 2.64 s (3H, CH_3), 3.29 q (2H, CH_2CH_3), 4.85 s (2H, CH_2), 7.16 d (2H, $C_6H_4C_2H_5$, *J* 7.8 Hz), 7.48 d (2H, $C_6H_4C_2H_5$, *J* 7.8 Hz), 7.62 m (3H, Ar), 7.89 d (2H, Ar, *J* 6.8 Hz), 10.38 s (1H, NH). Found, %: C 64.84; H 5.02; N 15.78. $C_{24}H_{23}N_5O_2S$. Calculated, %: C 64.70; H 5.20; N 15.72.

6-Amino-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one (IX). To a solution of 20 ml of pyridine and 15 ml of acetic acid was added 1.42 g (5 mmol) of compound **Va**. The mixture was heated to boiling, compound **Va** completely dissolved. To the solution obtained was added at heating in several portions within 1 h 2.3 g (35 mmol) of activated zinc powder, the solution decolorized, it was filtered, the filtrate cooled to room temperature was diluted with 50 ml of water and left standing for 4 h. The separated precipitate was filtered off, washed with water, and dried. Yield 0.6 g (62%), mp 280°C (decomp.) (acetic acid). White crystalline powder, well soluble in DMF, DMSO, solutions of alkali and mineral acids, insoluble in water. ^{1}H NMR spectrum, δ, ppm: 2.11 s (3H, CH_3), 2.83 s (3H, CH_3), 4.67 s (2H, NH_2), 11.89 s (1H, NH). Found, %: C 49.25; H 4.73; N 21.57. $C_8H_9N_3OS$. Calculated, %: C 49.21; H 4.65; N 21.52.

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