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Three-component condensation of 2,4-diaminothiazoles with aldehydes and Meldrum's acid: synthesis of 7-aryl(alkyl)-substituted 6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-ones

Arkady A. Dudinov, Boris V. Lichitsky, Andrey N. Komogortsev and Mikhail M. Krayushkin*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: mkray@ioc.ac.ru

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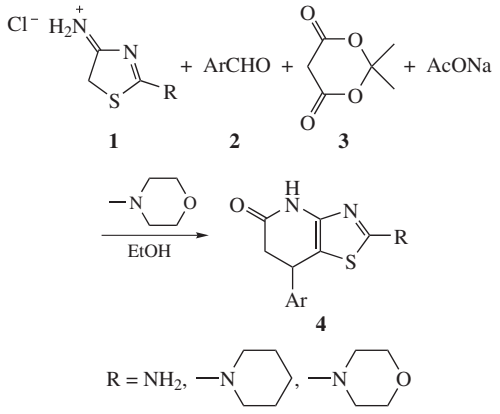
The new method of the synthesis of 6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-ones, based on decarboxylation of corresponding 2,4-diamino-5-thiazolecarboxylic acids has been elaborated; unstable derivatives of 2,4-diaminothiazole, generated *in situ* as a result of decarboxylation, react with aldehydes and Meldrum's acid forming target compounds.

It is known that derivatives of modified 2,4-diaminothiazole show specific biological activity as inhibitors of CDK.[1,2]

We have shown earlier that the hydrochlorides of 2,4-diaminothiazoles unsubstituted at the 5-position of the heterocyclic ring can enter three-component condensation with various aldehydes **2** and Meldrum's acid **3** to form substituted 6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-ones **4**[3] (Scheme 1). This method is simple and allows one to obtain, in particular, the new condensed structures from unstable 2,4-diaminothiazoles, generated *in situ* from hydrochlorides of 2-amino-4-iminothiazolidines **1**. It should be emphasized that the synthesis of starting salts was described only for substances bearing primary or tertiary amino groups in the 2-position of thiazole rings.

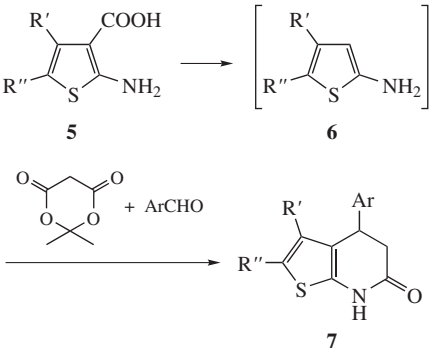


Scheme 1

We have suggested that in result of the decarboxylation of corresponding 2,4-diamino-5-thiazolecarboxylic acids bearing secondary amino groups in the 2-position, the unstable 2,4-diaminothiazoles can be obtained *in situ*. In the case of 2-aminothiophene derivatives, we have shown the possibility of decarboxylation of 2-amino-3-thiophenecarboxylic acids **5** and subsequent condensation of 2-aminothiophenes **6**, generated *in situ*, with aromatic aldehydes and Meldrum's acid, leading to 7-dihydro-5*H*-thieno[2,3-*b*]pyridin-6-ones **7**[5] (Scheme 2).

Here, we applied this approach to the synthesis of dihydrothiazolopyridinones **4a–j** (Scheme 3).†

We have elaborated the general effective method for the synthesis of compounds **4**, based on decarboxylation of readily available 2,4-diamino-5-thiazolecarboxylic acids, which were obtained by alkaline hydrolysis of corresponding esters **8**.‡ Isolated sodium salt **9**, Meldrum's acid and aromatic aldehyde



Scheme 2

entered into three-component condensation in ethanol as the solvent. Addition of acetic acid to a reaction mixture leads to

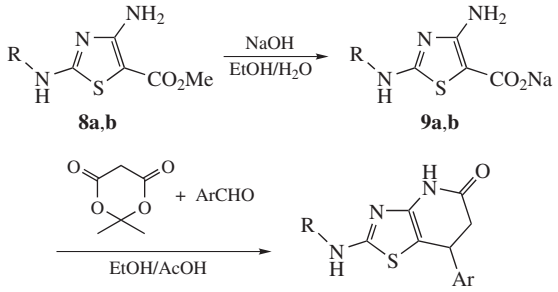
† ^{1}H NMR spectra were recorded on Bruker AM-300 (300 MHz) and Bruker WM-250 (250 MHz) instruments in [$^2H_6$]DMSO. Melting points were measured on a Boetius hot stage and not corrected. Mass spectra were determined on Finnigan MAT Incos 50 (direct injection, electron impact, 70 eV). The reaction mixtures were analyzed and the purity of the products was checked using TLC on Merck Silica gel 60 F254 plates using an AcOEt–hexane mixture (3:1) for elution.

*General procedure for the synthesis of 6,7-dihydro-4*H*-thiazolo[4,5-*b*]-pyridin-5-ones* **4a–j**. Mixture of ester **8a**,**b** (2 mmol) and 0.16 g of NaOH (4 mmol) in 5 ml of ethanol and 5 ml of water was refluxed for 2 h and then evaporated to dryness. To obtained residue 0.32 g (2.2 mmol) of Meldrum's acid, 2.1 mmol of a corresponding aldehyde and 0.36 g (6 mmol) of acetic acid and 4 ml of ethanol were added. This mixture was refluxed for 2 h, evaporated; the residue was crystallized from ethanol, filtered off, rinsed with ethanol and water and dried.

*2-Ethylamino-7-(4-methoxyphenyl)-6,7-dihydro-4*H*-thiazolo[4,5-*b*]-pyridin-5-one* **4a**: yield 81%, mp 198–200 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.12 (t, 3H, Me, *J* 7 Hz), 2.54 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 2.87 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 3.16 (m, 2H, CH_2), 3.72 (s, 3H, OMe), 4.16 (dd, 1H, CH, *J* 7 and 7 Hz), 6.87 (d, 2H, H_{Ar}, *J* 8 Hz), 7.11 (d, 2H, H_{Ar}, *J* 8 Hz), 7.63 (t, 1H, NH, *J* 4 Hz), 10.21 (s, 1H, NH). Found (%): C, 59.23; H, 5.71; N, 13.77; S, 10.46. Calc. for $C_{15}H_{17}N_3O_2S$ (303.39) (%): C, 59.39; H, 5.65; N, 13.85; S, 10.57.

*7-(3,4-Dimethoxyphenyl)-2-ethylamino-6,7-dihydro-4*H*-thiazolo[4,5-*b*]-pyridin-5-one* **4b**: yield 56%, mp 139–140 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.12 (t, 3H, Me, *J* 7 Hz), 2.61 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 2.82 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 3.16 (m, 2H, CH_2), 3.72 (s, 6H, 2OMe), 4.15 (dd, 1H, CH, *J* 7 and 7 Hz), 6.69 (m, 1H, H_{Ar}), 6.89 (m, 2H, H_{Ar}), 7.63 (t, 1H, NH, *J* 4 Hz), 10.21 (s, 1H, NH). Found (%): C, 57.77; H, 5.68; N, 12.69; S, 9.50. Calc. for $C_{16}H_{19}N_3O_3S$ (333.41) (%): C, 57.64; H, 5.74; N, 12.60; S, 9.62.

formation of a free acid and its decarboxylation to the corresponding unstable 2,4-diaminothiazole **10**. Formation of **4** takes place through a conjugated addition of 2,4-diaminothiazole **10** to arylmethylene derivatives **11** (formed directly in the reaction mixture) followed by imino–enamine tautomerisation and subsequent intermolecular cyclization attended with loss of acetone and carbon dioxide (Scheme 4).

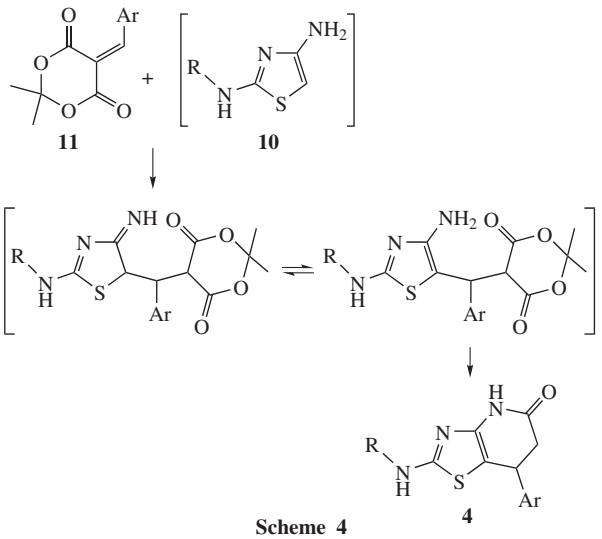


8, **9**: **a** R = Et
b R = Ph

4a R = Et, Ar = 4-$MeOC_6H_4$
4b R = Et, Ar = 3,4-$(MeO)_2C_6H_3$
4c R = Et, Ar = 3-MeO-4-HOC_6H_3
4d R = Et, Ar = thiophen-3-yl
4e R = Et, Ar = 4-ClC_6H_4
4f R = Ar = Ph
4g R = Ph, Ar = pyridin-3-yl
4h R = Ph, Ar = 2,4-$(MeO)_2C_6H_3$
4i R = Ph, Ar = 4-ClC_6H_4
4j R = Ph, Ar = Bu^i

Scheme 3

Compounds **4a–j** are stable crystalline solids, their structures were confirmed by elemental analysis, NMR spectroscopy and mass spectrometry. ^{1}H NMR spectra exhibit characteristic signals of protons of the dihydropyridinone system[3,5] in the field of 3.02–4.40 ppm for methine fragment and in the field of 2.30–2.70 ppm for nonequivalent protons of methylene.[3,5] In mass spectra of compounds **4**, peaks of corresponding molecular ions are found.



Scheme 4

*2-Ethylamino-7-(4-hydroxy-3-methoxyphenyl)-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-one* **4c**: yield 40%, mp 214–216 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.12 (t, 3H, Me, *J* 7 Hz), 2.55 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 2.81 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 3.16 (m, 2H, CH_2), 3.72 (s, 6H, 2OMe), 4.09 (dd, 1H, CH, *J* 7 and 7 Hz), 6.55 (m, 1H, H_{Ar}), 6.70 (m, 1H, H_{Ar}), 6.80 (m, 1H, H_{Ar}), 7.63 (t, 1H, NH, *J* 4 Hz), 8.90 (br. s, 1H, OH), 10.20 (s, 1H, NH). Found (%): C, 56.56; H, 5.45; N, 13.27; S, 10.18. Calc. for $C_{15}H_{17}N_3O_3S$ (319.39) (%): C, 56.41; H, 5.37; N, 13.16; S, 10.04.

*2-Ethylamino-7-thiophen-3-yl-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-one* **4d**: yield 42%, mp 205–206 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.12 (t, 3H, Me, *J* 7 Hz), 2.65 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 2.87 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 3.16 (m, 2H, CH_2), 4.29 (dd, 1H, CH, *J* 7 and 7 Hz), 7.00 (m, 1H, H_{Thi}), 7.18 (s, 1H, H_{Thi}), 7.49 (m, 1H, H_{Thi}), 7.63 (t, 1H, NH, *J* 4 Hz), 10.22 (s, 1H, NH). Found (%): C, 51.73; H, 4.75; N, 15.15; S, 23.09. Calc. for $C_{12}H_{13}N_3O_3S_2$ (279.38) (%): C, 51.59; H, 4.69; N, 15.04; S, 22.95.

*7-(4-Chlorophenyl)-2-ethylamino-6,7-dihydro-4*H*-thiazolo[4,5-b]pyridin-5-one* **4e**: yield 65%, mp 228–229 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.12 (t, 3H, Me, *J* 7 Hz), 2.55 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 2.93 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 3.16 (m, 2H, CH_2), 4.23 (dd, 1H, CH, *J* 7 and 7 Hz), 7.21 (d, 2H, H_{Ar}, *J* 8 Hz), 7.39 (d, 2H, H_{Ar}, *J* 8 Hz), 7.63 (t, 1H, NH, *J* 4 Hz), 10.30 (s, 1H, NH). Found (%): C, 54.76; H, 4.51; N, 13.77; S, 10.56; Cl, 11.64. Calc. for $C_{14}H_{14}ClN_3OS$ (307.80) (%): C, 54.63; H, 4.58; N, 13.65; S, 10.42; Cl, 11.52.

*7-Phenyl-2-phenylamino-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-one* **4f**: yield 67%, mp 260–261 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.65 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 2.99 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 4.31 (dd, 1H, CH, *J* 7 and 7 Hz), 6.90–7.60 (m, 10H, H_{Ar}), 10.20 (s, 1H, NH), 10.49 (s, 1H, NH_{Ar}). Found (%): C, 67.41; H, 4.76; N, 13.19; S, 10.12. Calc. for $C_{18}H_{15}N_3OS$ (321.40) (%): C, 67.27; H, 4.70; N, 13.07; S, 9.98.

*2-Phenylamino-7-pyridin-3-yl-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-one* **4g**: yield 56%, mp 249–250 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.70 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 3.01 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 4.40 (dd, 1H, CH, *J* 7 and 7 Hz), 6.95 (m, 1H, H_{Ar}), 7.29 (m, 2H, H_{Ar}), 7.35 (m, 1H, H_{Py}), 7.59 (m, 2H, H_{Ar}), 7.62 (m, 1H, H_{Py}), 8.49 (s, 2H, H_{Py}), 10.24 (s, 1H, NH), 10.52 (s, 1H, NH_{Ar}). Found (%): C, 63.49; H, 4.43; N, 17.24; S, 10.10. Calc. for $C_{17}H_{14}N_4OS$ (322.39) (%): C, 63.34; H, 4.38; N, 17.38; S, 9.95.

*7-(2,4-Dimethoxyphenyl)-2-phenylamino-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-one* **4h**: yield 57%, mp 254–255 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.53 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 2.99 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 3.61 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.40 (dd, 1H, CH, *J* 7 and 7 Hz), 6.41–7.65 (m, 8H, H_{Ar}), 10.19 (s, 1H, NH), 10.40 (s, 1H, NH_{Ar}). Found (%): C, 63.11; H, 4.95; N, 11.13; S, 8.53. Calc. for $C_{20}H_{19}N_3O_3S$ (381.46) (%): C, 62.98; H, 5.02; N, 11.02; S, 8.41.

*7-(4-Chlorophenyl)-2-phenylamino-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-one* **4i**: yield 68%, mp 279–280 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.61 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 3.00 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 4.35 (dd, 1H, CH, *J* 7 and 7 Hz), 6.95 (m, 1H, H_{Ar}), 7.29 (m, 4H, H_{Ar}), 7.40 (d, 2H, H_{Ar}, *J* 8 Hz), 7.58 (d, 2H, H_{Ar}, *J* 8 Hz), 10.25 (s, 1H, NH), 10.51 (s, 1H, NH_{Ar}). Found (%): C, 60.90; H, 4.06; N, 11.92; S, 9.14; Cl, 10.08. Calc. for $C_{18}H_{14}ClN_3OS$ (355.85) (%): C, 60.76; H, 3.97; N, 11.81; S, 9.01; Cl, 9.96.

*7-Isobutyl-2-phenylamino-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-one* **4j**: yield 45%, mp 236–237 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.89 (m, 6H, 2Me), 1.35 (m, 2H, CH_2), 2.30 (dd, 1H, HC*H*, *J* 7 and 17 Hz), 2.69 (m, 1H, CH), 2.70 (dd, 1H, *H*CH, *J* 7 and 17 Hz), 3.02 (dd, 1H, CH, *J* 7 and 7 Hz), 6.94 (m, 1H, H_{Ar}), 7.30 (m, 2H, H_{Ar}), 7.58 (m, 2H, H_{Ar}), 10.25 (s, 1H, NH), 10.30 (s, 1H, NH_{Ar}). Found (%): C, 70.13; H, 6.21; N, 11.20; S, 8.62. Calc. for $C_{22}H_{23}N_3OS$ (301.41) (%): C, 70.00; H, 6.14; N, 11.13; S, 8.49.

‡ Ester **8b** was obtained by the described method.[6]

Methyl 4-amino-2-ethylaminothiazole-5-carboxylate **8a** was obtained analogously to ester **8b**. Yield 69%, mp 149–150 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.16 (t, 3H, Me), 3.21 (m, 2H, CH_2), 3.60 (s, 3H, OMe), 7.75 (s, 2H, NH_2), 8.29 (s, 1H, NH). Found (%): C, 41.61; H, 5.60; N, 20.75; S, 16.04. Calc. for $C_7H_{11}N_3O_2S$ (201.25) (%): C, 41.78; H, 5.51; N, 20.88; S, 15.93.

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