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Synthesis of 5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo-[3,2-*b*]pyridine-3-carboxylic acids by three-component condensation of 3-aminopyrrole derivatives

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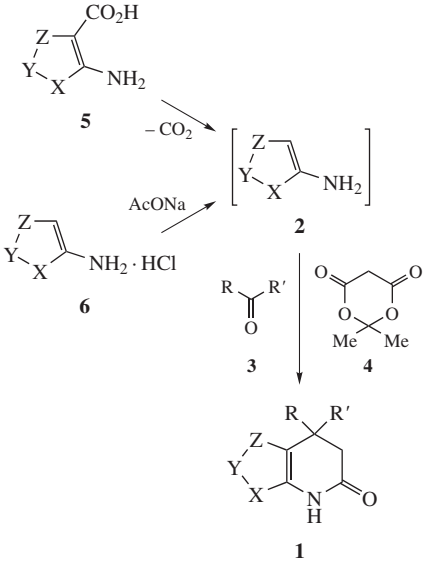
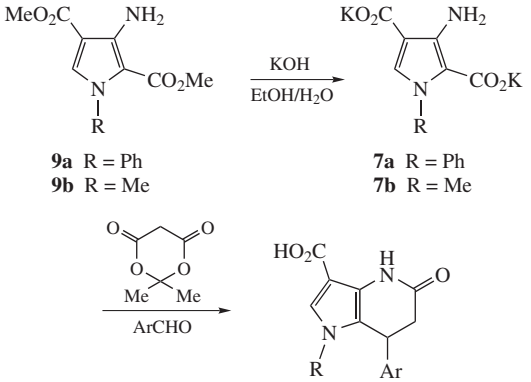
5-Oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxylic acids were prepared by three-component condensation of 3-aminopyrroles, (het)aromatic aldehydes and Meldrum's acid. The labile intermediate 3-aminopyrrole derivative was generated *in situ* by regioselective (at 2-position) decarboxylation of 3-aminopyrrole-2,4-dicarboxylic acid.

Recently,[1–6] we elaborated the general method for the synthesis of fused heterocyclic systems **1** containing dihydropyridin-2-one unit based on condensation of labile heterocyclic amines **2** with carbonyl compounds **3** and Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) **4**. The obvious advantage of this approach is the possibility to directly generate unstable amino heterocycles **2** *in situ* either from vicinal amino carboxylic acids **5** which are formed on alkaline hydrolysis of the corresponding esters or by neutralization of stable hydrochlorides **6** on treatment with sodium acetate.



Scheme 1

In the present work the condensation, outlined in Scheme 1, was performed using 3-aminopyrrole derivatives (X = Y = CH, Z = NMe or NPh). Due to the low stability of aminopyrroles[7] such a condensation is possible only for their derivatives equipped with electron withdrawing group, for example, the carboxylic one. We carried out this condensation according to our earlier protocol[2,3,5,6] in acetic acid using salts **7** as precursors of free amines. The supposed pathway of the process includes a Michael addition of the liberating *N*-R-3-aminopyrrole-4-carboxylic acid at the arylmethylidene derivatives of Meldrum's acid and subsequent intramolecular cyclization followed by CO_2 and acetone elimination (Scheme 2, for the mechanism see refs. 1–6).



8a R = Ar = Ph
8b R = Ph, Ar = 4-ClC_6H_4
8c R = Ph, Ar = 4-$MeOC_6H_4$
8d R = Ph, Ar = 3,4-$(MeO)_2C_6H_3$
8e R = Ph, Ar = thiophen-3-yl
8f R = Me, Ar = 4-ClC_6H_4
8g R = Me, Ar = 3,4-methylenedioxyphenyl

Scheme 2

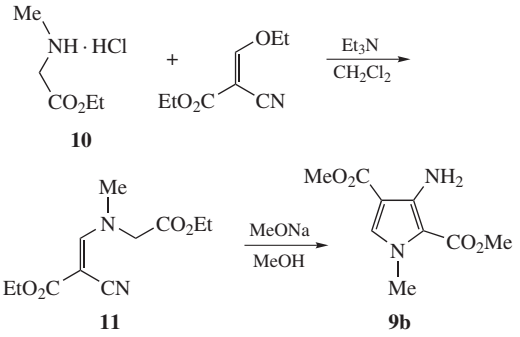
Dipotassium salts **7a**,**b** were obtained by hydrolysis of esters **9** using a 5-fold excess of potassium hydroxide in water–ethanol mixture (3:7).[8] We have shown that the optimal conditions for the synthesis of 5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]-pyridine-3-carboxylic acids **8f**,**g** comprised heating of salt **7b** with corresponding aldehydes and Meldrum's acid in acetic acid for 30 min. Prolongation of the reaction leads to the destruction of target pyrrolopyridinones. It is worth noting that decarboxylation occurs regiospecifically at the 2-positioned CO_2H group. Apparently, such a discrimination between two CO_2H groups proceeds synchronically and involves relocation of bonds with participation of amino and carboxylic groups fixed with enamine fragment of the pyrrole ring.

In the case of N-methyl substituted reactant **9b** we have observed the drastic drop in the yield of target products, probably, due to the lack of additional stabilization of pyrrole ring which occurred in aryl-substituted analogue **8a**.

Compounds **8** are stable crystalline solids. Their structure was confirmed by elemental analysis, NMR spectroscopy and mass spectrometry. The NMR spectra contained characteristic signals of proton of the dihydropyridinone system[1–6] at 4.28–

4.43 ppm for methine fragment and at 2.45–3.29 ppm for non-equivalent methylene protons. Mass spectra of compounds **8** displayed molecular ion peaks.†

The starting amino ester **9a** (R = Ph) was obtained by method described in literature.[8] The synthesis of dimethyl 3-amino-1-methylpyrrole-2,4-dicarboxylate **9b** (R = Me) according to the reported procedure[9,10] provided moderate yield of **9b** due to formation of by-products. We developed a simple and effective preparation of diester **9b** from available ethyl sarcosinate hydrochloride **10** (Scheme 3).‡ The intermediate **11** readily cyclised under the action of sodium methoxide.



Scheme 3

† ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) instrument in DMSO-d_6. Mass spectra were collected on a FINNIGAN MAT INCOS 50 (direct inlet, EI, 70 eV) mass spectrometer. Melting points were measured on a Boetius hot stage and not corrected.

*Dimethyl 3-amino-1-phenyl-1*H*-pyrrole-2,4-dicarboxylate* **9a** was obtained analogously to the published method.[7] Yield 56%, mp 120–121 °C. ^{1}H NMR, δ: 3.55 (s, 3H, OMe), 3.76 (s, 3H, OMe), 5.97 (s, 2H, NH_2), 7.31–7.52 (m, 6H, $H_{Ar, CH}$). Found (%): C, 61.57; H, 5.25; N, 10.38. Calc. for $C_{14}H_{14}N_2O_4$ (%): C, 61.31; H, 5.14; N, 10.21.

*5-Oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxcylic acids* **8a–g** *(general procedure)*. A mixture of ester **9a** (0.55 g, 2 mmol) or **9b** (0.42 g, 2 mmol), KOH (0.56 g, 10 mmol) in EtOH (1.75 ml) and water (0.75 ml) was refluxed for 0.5 h, then evaporated to dryness. Meldrum's acid (0.32 g, 2.2 mmol), the corresponding aldehyde (2.1 mmol) and acetic acid (7 ml) were added to the residue. The mixture was refluxed for 4 h, then evaporated, ethanol (3 ml) was added and the mixture was heated to boiling. After cooling, conc. HCl (1.1 g) was added and the mixture was left overnight. The precipitate was filtered off and washed with ethanol and water. Then the mixture of collected product and $NaHCO_3$ (0.5 g) in water (80 ml) was refluxed for 10 min, cooled and filtered through folded paper filter. Conc. HCl (0.6 g) was added to the filtrate, the precipitate was filtered off and washed with water.

*5-Oxo-1,7-diphenyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid* **8a**. Yield 51%, mp 231–232 °C. ^{1}H NMR, δ: 2.49 (dd, 1H, HC*H*, *J* 19 Hz, *J* 0 Hz), 3.29 (dd, 1H, *H*CH, *J* 19 Hz, *J* 8 Hz), 4.35 (dd, 1H, CH, *J* 8 Hz, *J* 0 Hz), 6.91 (d, 2H, $H_{Ar, Ar', CH}$, *J* 8 Hz), 7.15–7.46 (m, 9H, $H_{Ar, Ar', CH}$), 8.50 (s, 1H, NH), 12.59 (br. s, 1H, CO_2H). Found (%): C, 72.01; H, 4.97; N, 8.60. Calc. for $C_{20}H_{16}N_2O_3$ (%): C, 72.28; H, 4.85; N, 8.43.

*7-(4-Chlorophenyl)-5-oxo-1-phenyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid* **8b**. Yield 64%, mp > 300 °C. ^{1}H NMR, δ: 2.49 (dd, 1H, HC*H*, *J* 16 Hz, *J* 0 Hz), 3.25 (dd, 1H, *H*CH, *J* 16 Hz, *J* 7 Hz), 4.38 (dd, 1H, CH, *J* 7 Hz, *J* 0 Hz), 6.93 (d, 2H, $H_{Ar, Ar', CH}$, *J* 8 Hz), 7.28–7.47 (m, 8H, $H_{Ar, Ar', CH}$), 8.53 (s, 1H, NH), 12.51 (br. s, 1H, CO_2H). Found (%): C, 65.73; H, 4.00; N, 7.79. Calc. for $C_{20}H_{15}ClN_2O_3$ (%): C, 65.49; H, 4.12; N, 7.64.

*7-(4-Methoxyphenyl)-5-oxo-1-phenyl-4,5,6,7-tetrahydro-1*H*-pyrrolo-[3,2-*b*]pyridine-3-carboxylic acid* **8c**. Yield 45%, mp 221–222 °C. ^{1}H NMR, δ: 2.48 (dd, 1H, HC*H*, *J* 16 Hz, *J* 0 Hz), 3.20 (dd, 1H, *H*CH, *J* 16 Hz, *J* 7 Hz), 3.71 (s, 3H, OMe), 4.28 (dd, 1H, CH, *J* 7 Hz, *J* 0 Hz), 6.73–6.91 (m, 4H, $H_{Ar, Ar', CH}$), 7.21–7.53 (m, 6H, $H_{Ar, Ar', CH}$), 8.47 (s, 1H, NH), 12.49 (br. s, 1H, CO_2H). Found (%): C, 69.83; H, 5.13; N, 7.90. Calc. for $C_{21}H_{18}N_2O_4$ (%): C, 69.60; H, 5.01; N, 7.73.

*7-(3,4-Dimethoxyphenyl)-5-oxo-1-phenyl-4,5,6,7-tetrahydro-1*H*-pyrrolo-[3,2-*b*]pyridine-3-carboxylic acid* **8d**. Yield 68%, mp 238–239 °C. ^{1}H NMR, δ: 2.52 (dd, 1H, HC*H*, *J* 16 Hz, *J* 0 Hz), 3.20 (dd, 1H, *H*CH, *J* 16 Hz, *J* 7 Hz), 3.60 (s, 3H, OMe), 3.68 (s, 3H, OMe), 4.27 (dd, 1H, CH, *J* 7 Hz, *J* 0 Hz), 6.38 (d, 1H, H_{Ar}, *J* 8 Hz), 6.50 (s, 1H, H_{Ar}), 6.79 (d, 1H, H_{Ar}, *J* 8 Hz), 7.28–7.42 (m, 6H, $H_{Ar, Ar', CH}$), 8.48 (s, 1H, NH), 12.48 (br. s, 1H, CO_2H), Found (%): C, 67.13; H, 5.02; N, 7.30. Calc. for $C_{22}H_{20}N_2O_5$ (%): C, 67.34; H, 5.14; N, 7.14.

*5-Oxo-1-phenyl-7-(thiophen-3-yl)-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid* **8e**. Yield 48%, mp 235–237 °C. ^{1}H NMR, δ: 2.51 (dd, 1H, HC*H*, *J* 16 Hz, *J* 0 Hz), 3.16 (dd, 1H, *H*CH, *J* 16 Hz, *J* 7 Hz), 4.39 (dd, 1H, CH, *J* 7 Hz, *J* 0 Hz), 6.61 (m, 1H, $H_{Ar, Ar', CH}$), 6.80 (m, 1H, $H_{Ar, Ar', CH}$), 7.31–7.51 (m, 7H, $H_{Ar, Ar', CH}$), 8.45 (s, 1H, NH), 12.47 (br. s, 1H, CO_2H). Found (%): C, 64.10; H, 4.29; N, 8.05. Calc. for $C_{18}H_{14}N_2O_3S$ (%): C, 63.89; H, 4.17; N, 8.28.

*7-(4-Chlorophenyl)-1-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid* **8f**. Yield 0.13 g (21%), mp 255–256 °C. ^{1}H NMR, δ: 2.49 (dd, 1H, HC*H*, *J* 16 Hz, *J* 0 Hz), 3.19 (dd, 1H, *H*CH, *J* 16 Hz, *J* 8 Hz), 3.31 (s, 3H, Me), 4.43 (dd, 1H, CH, *J* 8 Hz, *J* 0 Hz), 7.08 (d, 2H, C_6H_4, *J* 8 Hz), 7.21 (s, 1H, $CH_{pyrrole}$), 7.39 (d, 2H, C_6H_4, *J* 8 Hz), 8.32 (s, 1H, NH), 2.18 (br. s, 1H, CO_2H). Found (%): C, 59.34; H, 4.42; N, 9.35. Calc. for $C_{15}H_{13}ClN_2O_3$ (%): C, 59.12; H, 4.30; N, 9.19.

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*7-(Benzo[1,3]dioxol-5-yl)-1-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo-[3,2-*b*]pyridine-3-carboxylic acid* **8g**. Yield 0.12 g (20%), mp 249–250 °C. ^{1}H NMR, δ: 2.45 (dd, 1H, HC*H*, *J* 16 Hz, *J* 0 Hz), 3.17 (dd, 1H, *H*CH, *J* 16 Hz, *J* 8 Hz), 3.31 (s, 3H, Me) 4.35 (dd, 1H, CH, *J* 8 Hz, *J* 0 Hz), 6.01 (s, 2H, OCH_2O), 6.49 (d, 1H, C_6H_3, *J* 8 Hz), 6.61 (s, 1H, C_6H_3), 6.83 (d, 1H, C_6H_3, *J* 8 Hz), 7.21 (s, 1H, $CH_{pyrrole}$), 8.32 (s, 1H, NH), 2.18 (br. s, 1H, CO_2H). Found (%): C, 60.90; H, 4.60; N, 9.07. Calc. for $C_{16}H_{14}N_2O_5$ (%): C, 61.14; H, 4.49; N, 8.91.

‡ *Diethyl 2-cyano-4-methyl-4-azahex-2-enedioate* **11** *(mixture of* E- *and* Z-*isomers)*. Triethylamine (6.36 g) was added to a solution of ethyl sarcosinate hydrochloride (9.68 g, 63 mmol) and ethyl (ethoxymethylidene)cyanoacetate (8.94 g, 53 mmol) in CH_2Cl_2 (400 ml). The solution was stirred at room temperature for 3 h, then evaporated, and water (100 ml) was added to the residue. The separated oil was left to crystallization at 4 °C. The crystallized product was filtered off and washed with water. Yield 7.05 g (48%), mp 77–78 °C. ^{1}H NMR, δ: 1.21–1.42 (m, 6H, 2Me), 3.25, 3.42 (s, 3H, Me), 4.05, 4.41 (s, 2H, CH_2), 4.18–4.38 (m, 4H, $2CH_2$), 7.67, 7.80 (s, 1H, CH). Found (%): C, 55.22; H, 6.82; N, 11.82. Calc. for $C_{11}H_{16}N_2O_4$ (%): C, 54.99; H, 6.71; N, 11.66.

*Dimethyl 3-amino-1-methyl-1*H*-pyrrole-2,4-dicarboxylate* **9b**. Sodium metal (1.38 g, 60 mmol) was dissolved in absolute methanol (60 ml), and ester **11** (9.61 g, 40 mmol) was added to the solution. The solution was refluxed for 1 h, cooled, the product was filtered off and washed with methanol and water. Yield 7.12 g (84%), mp 130–131 °C. ^{1}H NMR, δ: 3.62–3.80 (m, 9H, 3Me), 5.80 (s, 2H, NH_2), 7.48 (s, 1H, $CH_{pyrrole}$). Found (%): C, 51.16; H, 5.82; N, 13.37. Calc. for $C_{11}H_{16}N_2O_4$ (%): C, 50.94; H, 5.70; N, 13.20.