Construction of a pyrido[4,3-*d*]pyrimidine system on the basis of *N*-cyanobenzamidine and diethyl acetone-1,3-dicarboxylate

A. V. Komkov and V. A. Dorokhov★

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5328. E-mail: vador@ioc.ac.ru

Nickel acetate promoted reaction of diethyl acetone-1,3-dicarboxylate with *N*-cyanobenzamidine led to ethyl 4-amino-6-ethoxycarbonylmethyl-2-phenylpyrimidine-5-carboxylate, upon treatment of which with RNH_2, the corresponding 6-(carbamoylmethyl)pyrimidines were obtained. Cyclization of the latter upon treatment with MeONa afforded 6-R-4-amino-7-hydroxy-2-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-ones.

Key words: *N*-cyanobenzamidine, diethyl acetone-1,3-dicarboxylate, nickel acetate, ethyl 4-amino-6-ethoxycarbonylmethyl-2-phenylpyrimidine-5-carboxylate, 6-alkyl-4-amino-7-hydroxy-2-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-ones, heterocyclization.

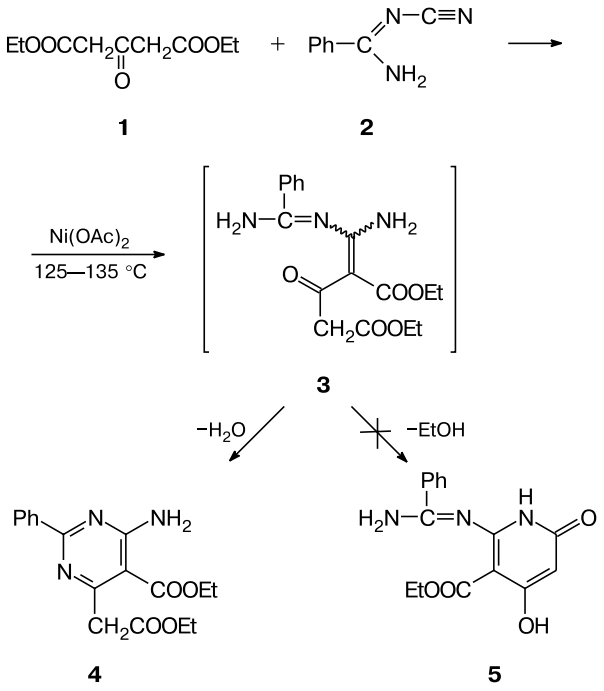
Nickel salts and complexes promote addition of the methylene-active β-dicarbonyl compounds at the C≡N bond of cyanamides.[1—4] In particular, it was found that β-diketones and β-ketoesters react with *N*-cyanoamidines in the presence of $Ni(OAc)_2$ to form 5-acyl-4-aminopyrimidines and 4-aminopyrimidine-5-carboxylic acid esters, respectively.[5—7] These pyrimidines with the vicinal functional groups were shown to be convenient starting compounds for the construction of bicyclic systems by the annulation of the second nitrogen-containing ring. Thus, for example, we proposed various versions for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives, starting from 2,6-disubstituted 5-acetyl-4-aminopyrimidines.[6—9]

Recently,[10] we also showed that the nickel acetylacetonate catalyzed addition of acetone-1,3-dicarboxylic acid esters to cyanoamide resulted in the heterocyclization, which led to 2-amino-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylic acid esters.

In the present paper, the reaction of diethyl acetone-1,3-dicarboxylate (**1**) with *N*-cyanobenzamidine (**2**) was studied. The heating of excess diester **1** with amidine **2** in the presence of equimolar (relatively to the latter) amount of $Ni(OAc)_2$ (Scheme 1) afforded ethyl 4-amino-6-ethoxycarbonylmethyl-2-phenylpyrimidine-5-carboxylate (**4**). The analytically pure pyrimidine **1** was isolated by column chromatography and recrystallization of the residue from EtOH.

Obviously, similarly to the reaction with cyanamide, the Ni salt promoted addition of ketodiester **1** at the C≡N bond of cyanoamidine **2** initially takes place to form adduct **3**. However, the intramolecular cyclization of the latter proceeds with elimination of water, rather than of ethanol, and leads to the pyrimidine ring closure (similarly to the transformations of cyanoamidines with acetoacetic and benzoylacetic acid esters[5]), rather than pyridine one (as in the reaction of ketodiester **1** with cyanamide[10]). Thus, the functionally substituted pyrimidine **4**, rather than pyridine **5**, was obtained.

Scheme 1



The crystalline compound **4** is well soluble in chloroform, benzene, and acetone, moderately in alcohols, and poorly in petroleum ether. Its structure was confirmed by spectroscopy data (mass, IR, and ^1H NMR spectra). Thus,

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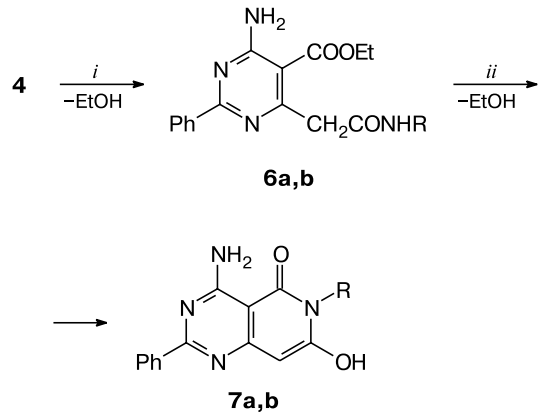
in the mass spectrum of pyrimidine **4**, there is a peak of the molecular ion, in the IR spectrum recorded in $CHCl_3$, absorption bands of the two carbonyl groups (1736 and 1688 cm^{-1}), as well as of the NH_2 group (3508 and 3376 cm^{-1}) are observed, and its ^1H NMR spectrum recorded in $CDCl_3$ is characterized by the presence of signals of the two COOEt groups (two triplets at 1.27 and 1.39 ppm; two quartets at 4.19 and 4.36 ppm), a singlet of the CH_2 group at 4.13 ppm, and a very broad signal of the NH_2 group at 5.90 ppm

The one-step synthesis of this new derivative of pyrimidine-5-carboxylic acid, presented in this work, despite of the moderate yield (32%) of the target product, is notable for the availability of the starting compounds. Moreover, the presence of the amino group and the ethoxycarbonylmethyl fragment in adjacent positions to the ethoxycarbonyl group in pyrimidine **4** allows one to consider it as the prospective reagent for the construction of bicyclic systems. To confirm this, we show a scheme for the construction of pyrido[4,3-*d*]pyrimidine system, based on compound **4**. It is known that one of the principal approaches to pyrido[4,3-*d*]pyrimidines consists in the annulation of pyridine ring to the corresponding functionally substituted pyrimidines (see, for example, Refs 11—13). We found that, when diester **4** is treated with primary amines (for example, benzylamine or butylamine), the CH_2COOEt fragment selectively participates in the reaction to yield pyrimidinylacetamides **6a,b**, treatment of which with the boiling solution of MeONa in MeOH leads to the pyridine ring closure to form 6-R-4-amino-7-hydroxy-2-phenylpyrido[4,3-*d*]pyrimidine-5(6*H*)-ones **7a,b** (Scheme 2).

Scheme 2



R = $PhCH_2$ (**a**), Bu (**b**)

i. RNH_2, 1,4-$Me_2C_6H_4$, Δ; *ii*. MeONa, MeOH, Δ.

Amides **6a,b** are white crystalline substances, poorly soluble in aromatic hydrocarbons and alcohols and well soluble in $CHCl_3$. Pyridopyrimidines **7a,b** are crystalline substances yellowish in color, poorly soluble in most organic solvents, but soluble in DMSO under heating. The structures of compounds **6a,b** and **7a,b** were confirmed by spectroscopy methods (IR, mass, and ^1H NMR spectra). In the mass spectra of these heterocycles, molecular ions are observed. In the IR spectra of amides **6a,b** in $CHCl_3$, there is no absorption in the region ~1740 cm^{-1}, characteristic of the carbonyl group of the ethoxycarbonylmethyl fragment of the starting reagent **4**. Absorption bands of the carbonyl groups of the CONH and COOEt fragments (in position 5 of pyrimidine ring) virtually coincide and are observed in the region 1680—1685 cm^{-1}. Contrary to this, in the IR spectra recorded in KBr, the two bands are observed: 1684 and 1648 cm^{-1}. In the ^1H NMR spectra of compounds **6a,b**, there is a set of signals of only one ethoxycarbonyl group. As for the IR spectra of pyridopyrimidines **7a** and **7b** in KBr or in Nujol, absorption band of the carbonyl group with frequencies of 1672 and 1676 cm^{-1}, respectively, is characteristic of them. In the ^1H NMR spectra of these bicyclic compounds in DMSO-d_6, there are no signals of protons of ethoxycarbonyl groups, rather a singlet of the H(8) proton at 5.33—5.39 ppm, two broad signals of two protons of the NH_2 group (at 8.38—8.49 and 9.33—9.42 ppm), as well as a broad signal of the OH group (at 12.05—12.18 ppm) are observed.

It is known that some substituted 4-aminopyrido[4,3-*d*]pyrimidines inhibit tyrosinekinase[14] and derivatives of pyrido[4,3-*d*]pyrimidine-5(6*H*)-one have antihypertensive[15] and antiallergic properties.[16] The synthesized by us compounds of the type **7**, apparently, can be modified by transformations at the unsubstituted amino group, which seems significant for further quest of biologically active compounds in pyrido[4,3-*d*]pyrimidine series.

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 spectrometer, IR spectra were recorded on a Specord-M80 spectrometer, mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV; the ionizing chamber temperature, 250 °C; direct inlet of a substance).

Ethyl 4-amino-6-ethoxycarbonylmethyl-2-phenylpyrimidine-5-carboxylate (4). A mixture of cyanoamidine **2** (0.2 g, 1.38 mmol) and $Ni(OAc)_2$ (0.24 g, 1.38 mmol) in diethyl acetone-1,3-dicarboxylate (**1**) (1 mL, 5.50 mmol) was heated for 5 h at 125—135 °C, cooled to ~20 °C, benzene (2 mL) was added to this, and the residue was subjected to column chromatography on SiO_2 (eluent: benzene). The solvent was evaporated *in vacuo*, light petroleum (5 mL) was added to the residue, crystals formed were filtered off and recrystallized from EtOH (3 mL) to obtain compound **4** (0.217 g, 32%) as white crystals, m.p. 133—134°C. Found (%): C, 61.88; H, 5.95; N, 12.58. $C_{17}H_{19}N_3O_4$. Calculated (%): C, 61.99; H, 5.81; N, 12.76. MS, *m/z* (I_{rel} (%)): 329 $[M]^+$ (15), 284 $[M - OEt]^+$ (10), 257 $[M - C_2H_4 - CO_2]^+$ (33), 185 $[M - 2C_2H_4 - 2CO_2]^+$ (100), 104 $[PhC{=}NH]^+$ (56). IR ($CHCl_3$), ν/cm^{-1}: 3508, 3376 (NH_2);

1736 (CO); 1688 (CO); 1596, 1552. ^{1}H NMR ($CDCl_3$), δ: 1.27 (t, 3 H, $\underline{Me}CH_2$, J = 6.8 Hz); 1.39 (t, 3 H, $\underline{Me}CH_2$, J = 6.8 Hz); 4.13 (s, 2 H, CH_2); 4.19 (q, 2 H, $\underline{CH_2}Me$, J = 6.8 Hz); 4.36 (q, 2 H, $\underline{CH_2}Me$, J = 6.8 Hz); 5.90 (br.s, NH_2); 7.46 (m, 3 H, Ph); 8.40 (m, 2 H, Ph).

Ethyl 4-amino-6-benzylcarbamoylmethyl-2-phenylpyrimidine-5-carboxylate (6a). A mixture of diester **4** (0.33 g, 1 mmol) and benzylamine (0.87 mL, 8 mmol) in *p*-xylene (7 mL) was refluxed for 5 h and kept for 12 h at 20 °C. The precipitate formed was filtered off and washed with light petroleum to obtain compound **6a** (0.13 g, 34%), m.p. 192—193 °C. Found (%): C, 67.65; H, 5.98; N, 14.00. $C_{22}H_{22}N_4O_3$. Calculated (%): C, 67.68; H, 5.68; N, 14.35. MS, m/z (I_{rel} (%)): 390 $[M]^+$ (31), 257 $[M - PhCH_2NCO]^+$ (56), 185 $[M - PhCH_2NCO - C_2H_4 - CO_2]^+$ (100), 104 $[PhC{=}NH]^+$ (44). IR ($CHCl_3$), ν/cm^{-1}: 3508, 3376 (NH_2); 1680 (CO); 1596, 1552, 1524. IR (Nujol), ν/cm^{-1}: 3420, 3400, 3288, 3188, 1684 (CO); 1648 (CO); 1632, 1548, 1536. ^{1}H NMR ($CDCl_3$), δ: 1.42 (t, 3 H, $\underline{Me}CH_2$, J = 6.8 Hz); 4.11 (s, 2 H, CH_2); 4.41 (q, 2 H, $\underline{CH_2}Me$, J = 6.8 Hz); 4.48 (d, 2 H, $\underline{CH_2}Ph$, J = 5.0 Hz); 7.02 (br.s, 1 H, NH); 7.27 (s, 5 H, $\underline{Ph}CH_2$); 7.45 (m, 3 H, Ph); 8.30 (m, 2 H, Ph).

Ethyl 4-amino-6-butylcarbamoylmethyl-2-phenylpyrimidine-5-carboxylate (6b). A mixture of diester **4** (0.165 g, 0.5 mmol) and butylamine (0.90 mL, 9.0 mmol) in *p*-xylene (4 mL) was refluxed for 12 h and kept for 12 h at 20 °C. The precipitate formed was filtered off and washed with petroleum ether to obtain compound **6b** (0.075 g, 42%), m.p. 166—167 °C. Found (%): C, 63.92; H, 7.01; N, 15.34. $C_{19}H_{24}N_4O_3$. Calculated (%): C, 64.03; H, 6.79; N, 15.72. MS, m/z (I_{rel} (%)): 356 $[M]^+$ (8), 284 $[M - C_4H_9NH]^+$ (35), 257 $[M - C_4H_9NCO]^+$ (27), 238 $[M - C_4H_9NH - C_2H_5OH]^+$ (33), 211 $[M - C_4H_9NCO - C_2H_5OH]^+$ (27), 185 $[M - C_4H_9NCO - C_2H_4 - CO_2]^+$ (100). IR ($CHCl_3$), ν/cm^{-1}: 3508, 3372 (NH_2); 1684 (CO); 1596, 1552. IR (KBr), ν/cm^{-1}: 3408, 3292, 3184, 1684 (CO); 1648 (CO); 1624, 1552, 1528. ^{1}H NMR (DMSO-d_6), δ: 0.83 (t, 3 H, $\underline{Me}CH_2$, J = 6.8 Hz); 1.30 (t, 3 H, $\underline{Me}CH_2O$, J = 6.8 Hz); 1.20—1.48 (m, 4 H, 2 CH_2); 3.10 (m, 2 H, CH_2N); 3.90 (s, 2 H, CH_2CO); 4.18 (q, 2 H, CH_2O, J = 6.8 Hz); 7.40—7.58 (m, 5 H, 3 H—Ph and NH_2); 7.78 (br.s, 1 H, NH); 8.32 (m, 2 H, Ph).

4-Amino-6-benzyl-7-hydroxy-2-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (7a). A mixture of amide **6a** (0.13 g, 0.33 mmol) and MeONa (0.66 mmol) in MeOH (10 mL) was refluxed until complete dissolution (10 min), cooled to 20 °C, and acidified with AcOH. The precipitate formed was filtered off and washed with MeOH (15 mL) to obtain pyridopyrimidine **7a** (0.10 g, 87%), m.p. >360 °C. Found (%): C, 69.60; H, 4.87; N, 15.90. $C_{20}H_{16}N_4O_2$. Calculated (%): C, 69.75; H, 4.68; N, 16.27. MS, m/z (I_{rel} (%)): 344 $[M]^+$ (50), 316 $[M - CO]^+$ (15), 315 $[M - CO - H]^+$ (20), 211 $[M - PhCH_2NCO]^+$ (23), 185 $[M - PhCH_2NCO - C_2H_2]^+$ (100). IR (Nujol), ν/cm^{-1}: 3300 (NH); 3200—3000 (NH, OH, CH); 1676 (CO); 1616, 1592, 1580, 1568, 1508. ^{1}H NMR (DMSO-d_6), δ: 5.08 (s, 2 H, CH_2); 5.39 (s, 1 H, H(8)); 7.24 (m, 5 H, $\underline{Ph}CH_2$); 7.62 (m, 3 H, Ph); 8.09 (m, 2 H, Ph); 8.49, 9.33 (both br.s, 1 H each, NH_2); 12.18 (br.s, 1 H, OH).

4-Amino-6-butyl-7-hydroxy-2-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (7b). The product was synthesized similarly to compound **7a** from amide **6b** and MeONa in MeOH. The yield was 92%, m.p. >360 °C. Found (%): C, 65.58; H, 5.97; N, 17.76. $C_{17}H_{18}N_4O_2$. Calculated (%): C, 65.79; H, 5.85; N, 18.05. MS, m/z (I_{rel} (%)): 310 $[M]^+$ (27), 254 $[M - C_4H_8]^+$ (100), 238 $[M - C_4H_9NH]^+$ (68), 211 $[M - C_4H_9NCO]^+$ (92), 185 $[M - C_4H_9NCO - C_2H_2]^+$ (10), 104 $[PhC{=}NH]^+$ (91). IR (KBr), ν/cm^{-1}: 3296 (NH); 3160, 3128, 3060, 2952, 2872, 1672 (CO); 1616, 1580, 1560, 1508. ^{1}H NMR (DMSO-d_6), δ: 0.90 (t, 3 H, Me, J = 6.8 Hz); 1.30 (m, 2 H, CH_2); 1.52 (m, 2 H, CH_2); 3.89 (t, 2 H, CH_2N, J = 6.8 Hz); 5.33 (s, 1 H, H(8)); 7.62 (m, 3 H, Ph); 8.09 (m, 2 H, Ph); 8.38, 9.42 (both br.s, 1 H each, NH_2); 12.05 (br.s, 1 H, OH).

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