ISSN 1070-4280, Russian Journal of Organic Chemistry, 2015, Vol. 51, No. 3, pp. 357–360. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © A.A. Harutyunyan, H.A. Panosyan, S.G. Chishmarityan, R.A. Tamazyan, A.G. Ayvazyan, 2015, published in Zhurnal Organicheskoi Khimii, 2015, Vol. 51, No. 3, pp. 373–376.

One-Step Synthesis of Pyrido[2,3-*d*]pyrimidines, Amides, and Benzoxazolylethylpyrimidine by Condensation of Substituted 3-(2-Phenylpyrimidin-5-yl)propanoic Acids with Aromatic Amines in Polyphosphoric Acid

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Received September 24, 2014

Abstract—Depending on the reactant structure, reactions of substituted 3-(2-phenylpyrimidin-5-yl)propanoic acids with 2-aminopyridine, *p*-toluidine, and 2-aminophenol in polyphosphoric acid afforded the corresponding *N*-(pyridin-2-yl)propanamides, 5-[2-(benzoxazol-2-yl)ethyl]pyrimidine, and pyrido[2,3-*d*]pyrimidinones.

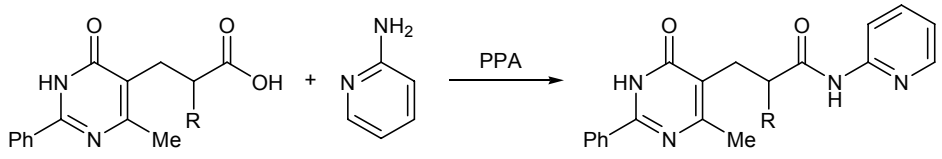
DOI: 10.1134/S1070428015030112

We previously developed procedures for the synthesis of tetra- and pentacyclic heterocyclic systems via tandem condensation and nucleophilic substitution reactions of 3-(4-methyl-6-oxo-2-phenyl-1,6-dihydropyrimidin-5-yl)propanoic acids **1a** and **1b** with *o*-phenylenediamine and 1,2-diaminonaphthalene in polyphosphoric acid (PPA) [1–3]. With the goal of extending the scope of this heterocyclization involving direct nucleophilic substitution of the tautomeric 6-hydroxy group in 2-phenylpyrimidine ring by nitrogen-centered nucleophiles we examined the condensation of propanoic acids **1a** and **1b** with aromatic amines, 2-aminopyridine, *p*-toluidine, and 2-aminophenol, in PPA at 230–240°C.

The condensation of acids **1a** and **1b** with 2-aminopyridine gave the corresponding *N*-(pyridin-2-yl) amides **2a** and **2b**, while no subsequent heterocyclization was observed (Scheme 1). A probable reason is relatively weak basicity of pyridin-2-amine (pK_a 6.86) and delocalization of the lone electron pair on the amide nitrogen atom over the endocyclic nitrogen atom in the pyridine ring. The nucleophilicity of the amide nitrogen atom in **2a** and **2b** is reduced even more strongly due to protonation of the pyridine nitrogen atom by PPA.

Under analogous conditions, acids **1a** and **1b** reacted with *p*-toluidine (pK_a 8.83) in different ways. From acid **1a** having no methyl group in the α-position we obtained *N*-(*p*-tolyl) amide **3**, whereas the reaction of 2-methylpropanoic acid **1b** with *p*-toluidine afforded 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one **4** (Scheme 2). Presumably, the corresponding amide

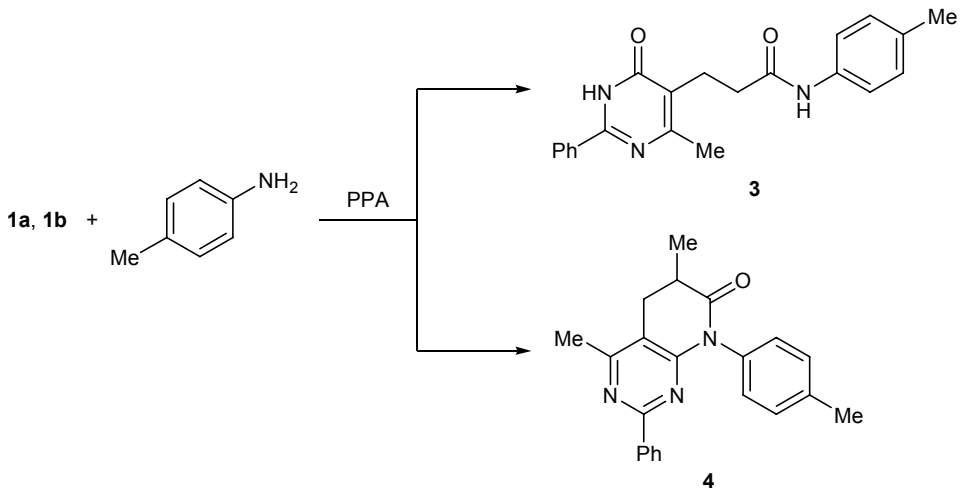
Scheme 1.



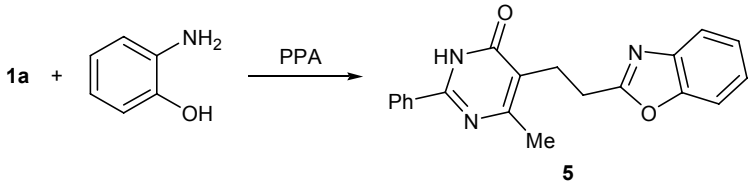
1a, **1b** **2a**, **2b**

R = H (**a**), Me (**b**).

Scheme 2.



Scheme 3.



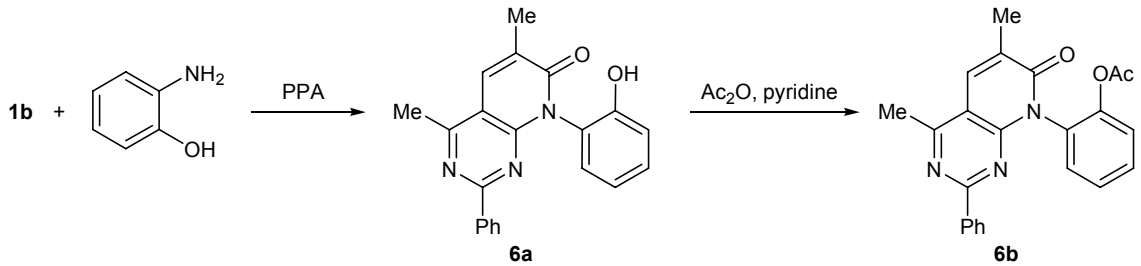
formed in the first step underwent intramolecular cyclization via nucleophilic substitution of the hydroxy group in the pyrimidine ring.

The condensation of acid **1a** with 2-aminophenol (pK_a 9.7) led to the formation of expected benzoxazole derivative **5** (Scheme 3). Analogous reaction with 2-methylpropanoic acid **1b** involved the condensation, cyclization, and dehydrogenation steps and finally produced substituted 7,8-dihydropyrido[2,3-*d*]pyrimidin-7-one **6a** whose structure was determined on the basis of the ^{1}H and ^{13}C NMR spectra (including NOESY experiment) and X-ray diffraction data. Compound **6a** was also converted into *O*-acetyl derivative **6b** (Scheme 4). The aromatic region of the ^{1}H NMR spectrum of **6a** contained a quartet with a coupling constant *J* of 1.2 Hz, which was assigned to 5-H. The NOESY spectrum of **6a** displayed correlation between 5-H and protons of both methyl groups, which indicated their spatial proximity and hence cyclic structure of **6a**.

Compound **6a** crystallized in monoclinic crystal system as twinned crystals where the components are related to each other through a second-order symmetry axis perpendicular to the (1 0 0) plane or through a mirror reflection with respect to the same plane (Fig. 1). Such crystal twinning implies that only 0*kl* reflexes are superpositions of reflexes from both components and that the other reflexes are specific for one or another component. The volume ratio of the twin components was estimated at 1:4 as a result of structure refinement.

Molecule **6a** consists of three cyclic fragments: phenyl ring, hydroxyphenyl ring, and pyrido[2,3-*d*]-pyrimidine system. All cyclic fragments are planar, and

Scheme 4.



the maximum deviations of atoms from the corresponding mean-square planes do not exceed 0.0104(2) Å for the phenyl ring, 0.0034(2) Å for the hydroxyphenyl ring, and 0.0528(3) Å for pyrido-[2,3-*d*]pyrimidine. Molecules **6a** in crystal are linked by classical intermolecular hydrogen bonds O^{26}–$H^{26}\cdots O^{11}$ [D–H 1.05(5), H···A 1.67(5), D···A 2.720(3) Å; ∠DHA 172(3)°] to form infinite chains along the [0 0 1] direction (Fig. 2).

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Avatar 330 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Mercury-300 instrument at 300 MHz from solutions in DMSO-d_6–CCl_4 (1 : 3) using tetramethylsilane as internal reference. Analytical TLC was performed on Silufol UV-254 plates using ethanol–chloroform (1 : 10) as eluent; spots were detected by treatment with iodine vapor.

The X-ray diffraction data for a single crystal of **6a** were obtained at room temperature on an Enraf–Nonius CAD-4 automated diffractometer (MoK_α radiation, graphite monochromator, θ/2θ scanning). The unit cell parameters were determined and refined from 24 reflections in the range $13.7 < \theta < 14.8$: a = 7.8581(16), b = 22.537(5), c = 10.314(2) Å; β = 108.15(3)°; V = 1735.7(7) Å^3; Z = 4; space group $P2_1/c$. Intensities of 5368 reflections were measured in the ranges $0 \le h \le 11$, $0 \le k \le 31$, $-14 \le l \le 13$; θ_{max} = 30°. Averaging of symmetry-equivalent reflections left 5043 independent reflections (R_{int} = 0.015), including 2249 reflections with $I > 3\sigma(I)$. The structure was solved by the Superflip method [4] using JANA2006 software package [5]. The coordinates of hydrogen atoms were determined from the Fourier difference syntheses. Hydrogen atoms in the methyl groups were localized by geometry calculations, and their positions were refined according to the riding model assuming C–H 0.96 Å, U_{iso}(H) = 1.5U_{eq}(C). The structure was refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms and isotropic approximation for hydrogens. Final divergence factor R = 0.048, goodness of fit S = 1.05. All calculations were performed using JANA2006 [5]. The crystallographic data for compound **6a** were deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 1010232).

Compounds 2–6a (*general procedure*). A mixture of 0.01 mol of acid **1a** or **1b**, 0.012 mol of the corresponding amine, and 15 g of PPA was heated for 4 h at 230–240°C on a metal bath. The melt was cooled and neutralized with dilute (1 : 1) aqueous ammonia, and the precipitate was filtered off, dried, and recrystallized.

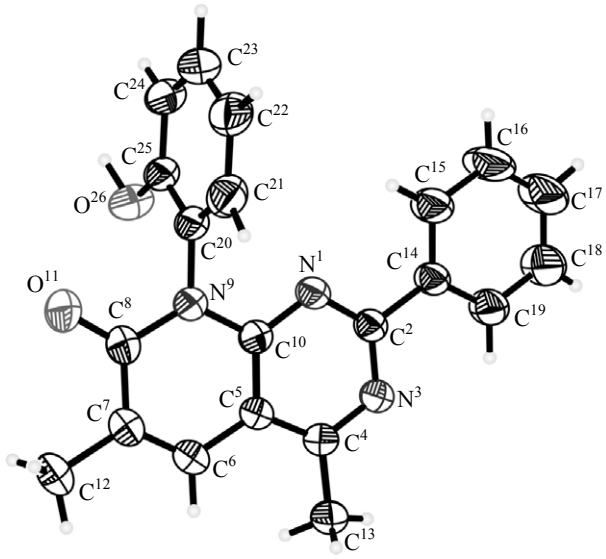


Fig. 1. Structure of the molecule of 8-(2-hydroxyphenyl)-4,6-dimethyl-2-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6a**) according to the X-ray diffraction data (arbitrary atom numbering); non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

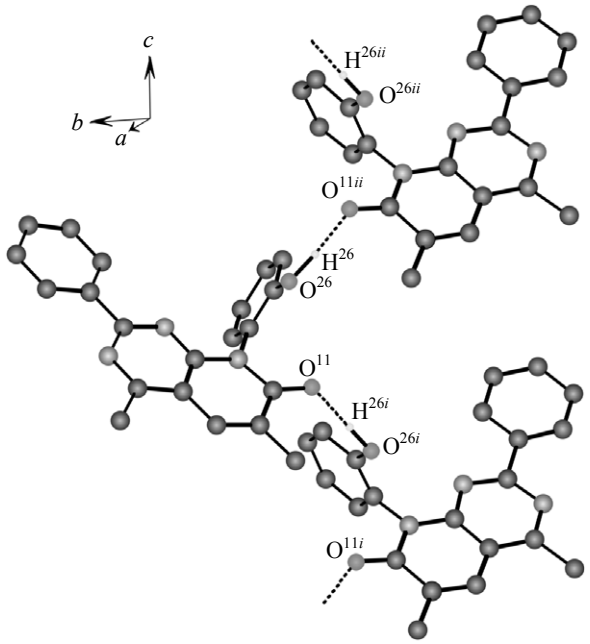


Fig. 2. Infinite chain formed by molecules of 8-(2-hydroxyphenyl)-4,6-dimethyl-2-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6a**) in crystal along the [0 0 1] plane; symmetry operations: *i* = *x*, 0.5 – *y*, –0.5 + *z*; *ii* = *x*, 0.5 – *y*, 0.5 + *z*.

3-(4-Methyl-6-oxo-2-phenyl-1,6-dihydropyrimidin-5-yl)-*N*-(pyridin-2-yl)propanamide (2a) was synthesized from acid **1a** [6]. Yield 79%, mp 244–246°C (from EtOH), R_f 0.40. IR spectrum, ν, cm^{-1}: 3293 (N–H), 1715 (C=O). ^1H NMR spectrum, δ, ppm: 2.55 s (3H, CH_3), 2.59 t (2H, CH_2, J = 7.1 Hz), 3.02 t (2H, CH_2, J = 7.1 Hz), 6.95 d.d.d (1H, 5-H, J = 7.2, 4.8, 1.0 Hz), 7.38–7.45 m (3H, H_{arom}), 7.74 d.d.d (1H, 4-H, J = 8.5, 7.2, 2.0 Hz), 8.26 d.d.d (1H, 6-H, J = 4.8, 1.8, 1.0 Hz), 8.31–8.40 m (3H, H_{arom}), 9.02 br.s (1H, N**H**Py), 12.20 br.s (1H, NH). Found, %: N 16.47. $C_{19}H_{18}N_4O_2$. Calculated, %: N 16.76.

2-Methyl-3-(4-methyl-6-oxo-2-phenyl-1,6-dihydropyrimidin-5-yl)-*N*-(pyridin-2-yl)propanamide (2b) was synthesized from acid **1b** [1]. Yield 83%, mp 237–239°C (from EtOH), R_f 0.57. IR spectrum, ν, cm^{-1}: 3270 (N–H), 1663 (C=O). ^1H NMR spectrum, δ, ppm: 1.20 d (3H, C**H**$_3$CH, J = 6.9 Hz), 2.36 s (3H, 4′-CH_3), 2.62 d.d and 2.80 d.d (1H each, CH_2, J = 13.3, 6.9 Hz), 3.00 sext [1H, C**H**(CH_3)], 6.92–6.97 m (1H, 5-H), 7.38–7.48 m (3H, H_{arom}), 7.61–7.67 m (1H, H_{arom}), 8.12–8.21 m (4H, H_{arom}), 10.10 s (1H, N**H**Py), 12.45 br.s (1H, NH). Found, %: N 16.22. $C_{20}H_{20}N_4O_2$. Calculated, %: N 16.08.

3-(4-Methyl-6-oxo-2-phenyl-1,6-dihydropyrimidin-5-yl)-*N*-(4-methylphenyl)propanamide (3). Yield 68%, mp 296–298°C (from DMF), R_f 0.73. IR spectrum, ν, cm^{-1}: 3285 (N–H), 1644 (C=O). ^1H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3), 2.39 s (3H, CH_3), 2.50 t (2H, CH_2, J = 7.5 Hz), 2.81 t (2H, CH_2, J = 7.5 Hz), 6.97–7.03 m (2H, C_6H_4), 7.39–7.49 m (5H, C_6H_5), 8.12–8.19 m (2H, C_6H_4), 9.56 s (1H, N**H**C_6H_4), 12.45 br.s (1H, NH). Found, %: N 12.22. $C_{21}H_{21}N_3O_2$. Calculated, %: N 12.10.

4,6-Dimethyl-8-(4-methylphenyl)-2-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (4). Yield 75%, mp 219–221°C, R_f 0.57. IR spectrum: ν 1700 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 1.35 d (3H, CHC**H**$_3$, J = 6.5 Hz), 2.49 s (3H, CH_3), 2,56 s (3H, CH_3), 2.72–2.92 m (1H, CH_2, ^2J = 15.0, ^3J = 11.7 Hz), 2.82–2.95 m (1H, CH), 3.17 d.d (1H, CH_2, ^2J = 15.0, ^3J = 5.4 Hz); 7.03–7.08 m (2H), 7.25–7.35 m (5H), 7.99–8.04 m (2H) (H_{arom}). Found, %: N 12.17. $C_{22}H_{21}N_3O$. Calculated, %: N 12.24.

5-[2-(1,3-Benzoxazol-2-yl)ethyl]-4-methyl-2-phenylpyrimidin-4(3*H*)-one (5). Yield 89%, mp 237–239°C (from DMF), R_f 0.72. IR spectrum: ν 1645 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3), 3.00 t (2H, CH_2, J = 7.4 Hz), 3.15 t (2H, CH_2, J = 7.4 Hz), 7.30–7.38 m (2H, C_6H_4), 7.46–7.59 m (3H, C_6H_5), 7.64–7.70 m (2H, C_6H_4), 8.04–8.12 m (2H, C_6H_5), 12.65 m (1H, NH). Found, %: N 12.52. $C_{20}H_{17}N_3O_2$. Calculated, %: N 12.68.

8-(2-Hydroxyphenyl)-4,6-dimethyl-2-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (6a). Yield 77%, mp 312–314°C (from DMF), R_f 0.71. IR spectrum: ν 1661 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 2.22 d (3H, 6-CH_3, J = 1.2 Hz), 2.82 s (3H, 4-CH_3), 6.97 d.d.d (1H, 5′-H, J = 7.8, 7.3, 1.3 Hz), 7.04 d.d (1H, 3′-H, J = 8.1, 1.3 Hz), 7.17 d.d (1H, 6′-H, J = 7.8, 1.7 Hz), 7.34 d.d.d (1H, 4′-H, J = 8.1, 7.3, 1.7 Hz), 7.38–7.48 m (3H, *m*-H, *p*-H), 8.05–8.10 m (2H, *o*-H), 8.17 q (1H, 5-H, J = 1.2 Hz), 9.52 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 17.0 (CH_3), 21.0 (CH_3), 109.7, 116.2 (=CH), 118.9 (=CH); 123.9, 127.6, 128.3 (C_{arom}); 129.3 (=CH), 129.9 (=CH), 130.8 (=CH), 131.0, 131.1 (=CH), 136.7, 153.0, 154.5, 160.4, 162.4, 164.5. Found, %: N 12.41. $C_{21}H_{17}N_3O_2$. Calculated, %: N 12.24.

2-(4,6-Dimethyl-7-oxo-2-phenyl-7,8-dihydropyrido[2,3-*d*]pyrimidin-8-yl)phenyl acetate (6b). A mixture of 1.0 g (3 mmol) of compound **6a**, 4 mL of pyridine, and 6 mL of acetic anhydride was stirred for 3 h at 80°C. The mixture was poured into 20 mL of water and kept for 2 h at 5°C, and the precipitate was filtered off and dried. Yield 89%, mp 202–204°C (from DMF), R_f 0.67. IR spectrum, ν, cm^{-1}: 1767, 1660 (C=O). ^1H NMR spectrum, δ, ppm: 1.84 s (3H, COC**H**$_3$), 2.23 d (3H, 6-CH_3, J = 1.2 Hz), 2.83 s (3H, 4-CH_3), 7.36–7.50 m (6H, H_{arom}), 7.60 d.d.d (1H, C_6H_4, J = 8.0, 5.9, 2.8 Hz), 8.05–8.09 m (2H, *o*-H), 8.22 q (1H, 5-H, J = 1.2 Hz). Found, %: N 10.78. $C_{23}H_{19}N_3O_3$. Calculated, %: N 10.90.

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