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One-Stage Synthesis of Condensed Pyrimidines by Reaction of Substituted 3-(Pyrimidin-5-yl)propanoic Acids with *ortho*-Diamines: Extension of Limits

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Abstract—By condensation of 2-aryl-substituted pyrimidin-5-ylpropanoic acids with 1,2-ethanediamine and 1,2-benzenediamine in polyphosphoric acid new derivatives of heterocyclic systems were synthesized: imidazo- and benzo[4',5']imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidines. Unlike that the reaction of substituted 2-mercaptopyrimidin-5-ylpropanoic acid with 1,2-benzenediamine in polyphosphoric acid in the presence of equimolar amount of $ZnCl_2$ proceeds by a tandem mechanism with the formation of 4-methyl-5,6-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine-2-thiol and the corresponding disulfide.

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Previously we performed a one-stage synthesis of derivatives of heterocyclic systems of benzo[4',5']- and naphto[1'',2'':4,5]imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine as a result of tandem condensation of substituted 2-phenyl-3-(pyrimidin-5-yl)propanoic acids with 1,2-diamines of benzene and naphthalene and nucleophilic substitution of hydroxy group of pyrimidine ring occurring in polyphosphoric acid (PPA) [1–3].

The vital effect on the course of the discovered reaction produce evidently the *–I* and ±*M*-effects of the phenyl group [4] in the position *2* of pyrimidine decreasing the electron density in the ring and making possible the nucleophilic substitution of the hydroxy group. At the same time the other substituents in this position having +*I* (CH_3) or opposite *–I* and +*M*-effects (OH, NH_2, SH) impede the described reaction, and the CH_3 and OH groups in position *4*(*6*) of the cycle and 2-methyl group in the side chain do not affect it [2].

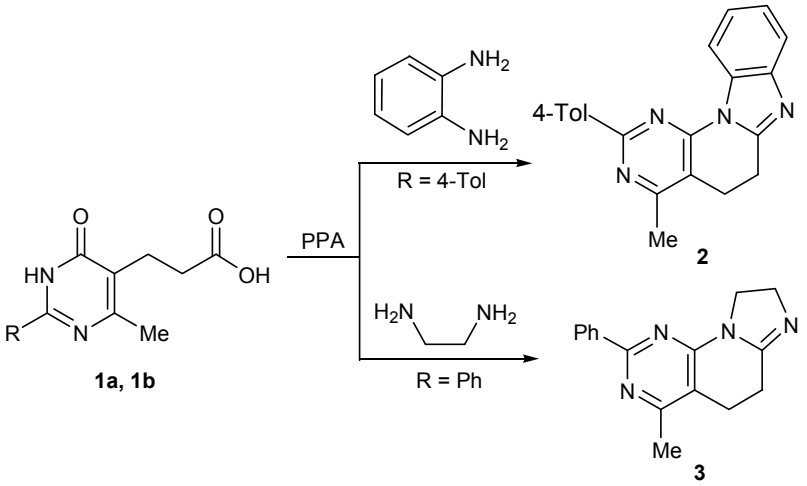
In this connection it is important to mention that substitution of the hydroxy group in the pyrimidine ring by amino and substituted amino group is usually performed indirectly through intermediate chloro- or sulfanylpyrimidines [5], while the direct substitution of OH group with nitrogen nucleophiles, extremely rare in pyrimidine, is limited to simple examples of amination of tautomeric pyrimidinediones by heating with phosphoryl- or phosphoramides at high temperature [6]; heterocyclizations by this mechanism are not known to us.

In continuation of investigations for expansion of the described method of synthesis of polyfused pyrimidines we carried out new condensations of 3-(2-substituted pyrimidin-5-yl)propanoic acids **1a–1c** with diamines in PPA.

The initial substituted pyrimidin-5-ylpropanoic acid **1a** was synthesized by reaction of diethyl 2-acetylpentadioate with 4-methylbenzamidine in the presence of sodium ethylate in anhydrous ethyl alcohol.

The reaction of acid **1a** with 1,2-benzenediamine in PPA proceeds similarly to previously described reaction of the corresponding 2-phenyl-substituted acid [1] and results in a new derivative of a tetracyclic system, benzo[4,5]imidazo-[1',2':1,6]pyrido[2,3-*d*]pyrimidine **2**. The introduction of a methyl group with +*I*-effect in the position *4* of 2-phenyl substituent of initial acid does not impede the tandem reactions of condensation and cyclization. In its turn, 2-phenylsubstituted acid **1b**

Scheme 1.

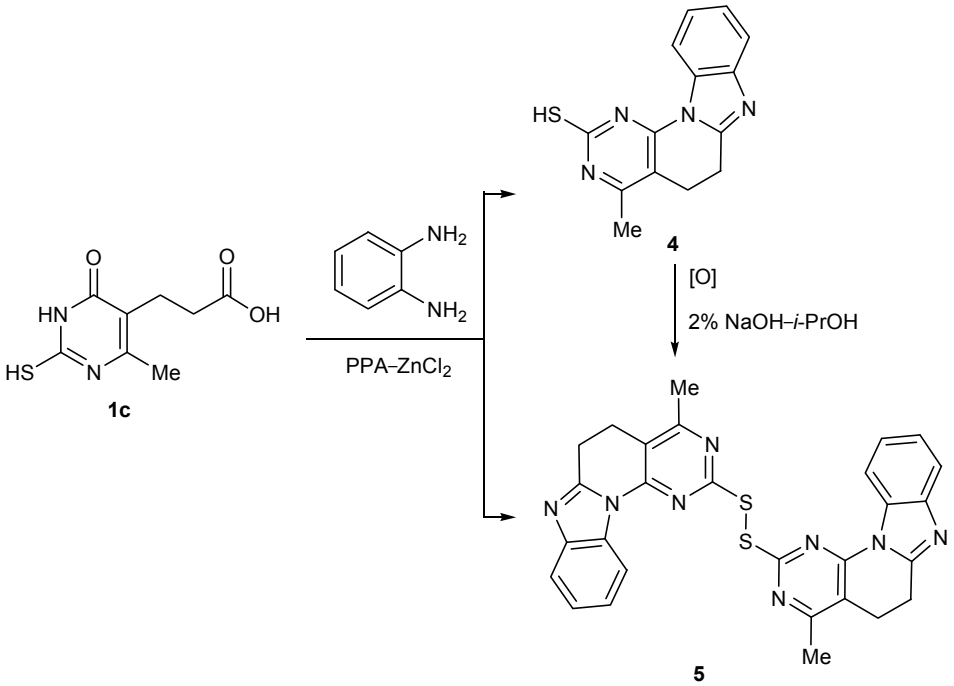


R = 4-Tol (**a**), Ph (**b**).

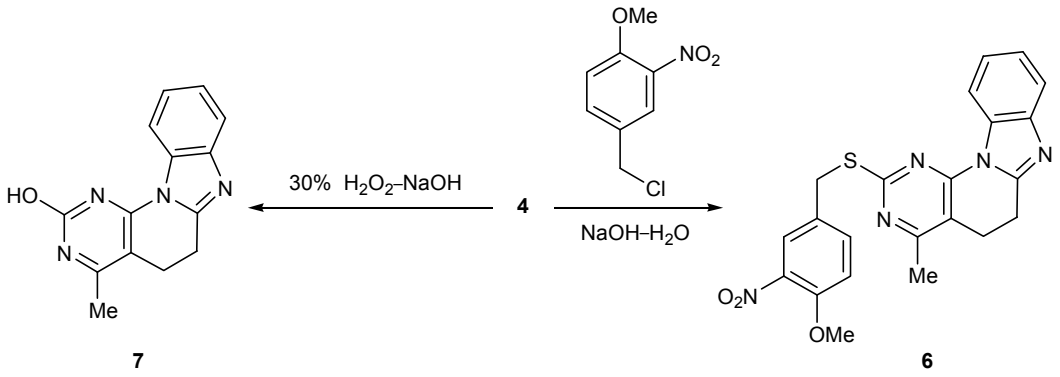
easily interacts with 1,2-diaminoethane in PPA with the formation of a derivative of tricyclic heterocyclic system, imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine **3** (Scheme 1).

We studied in more detail the condensation of 2-mercapto-substituted acid **1c** with 1,2-diaminobenzene for it had been formerly shown that in PPA the reaction proceeded only to the formation of thee corresponding benzimidazole derivative [2]. Adding to the reaction mixture of equimolar quantity of $ZnCl_2$ as a mild Lewis acid changes the reaction pathway in the direction of occurrence of the two-stage mechanism of condensation and hydroxyl group substitution in the pyrimidine ring resulting in the formation of derivatives of tetracyclic system of benzo[4,5]imidazo-[1',2':1,6]pyrido[2,3-*d*]pyrimidine, thiol **4** and disulfide **5** (Scheme 2). The latter formed as an admixture in about 15% yield directly during the condensation and

Scheme 2.



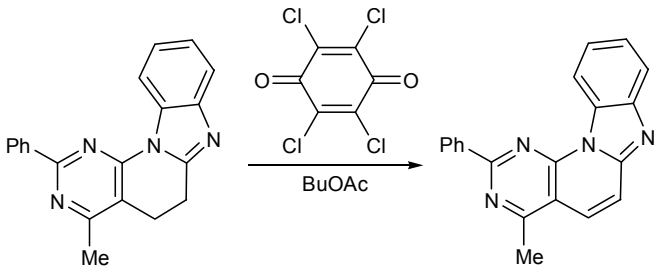
Scheme 3.



also by the oxidation the 2-thioxo derivative **4** with air oxygen in 2-propanol in the presence of NaOH.

The alkylation of thiol **4** with 4-methoxy-3-nitrobenzyl chloride afforded compound **6**, and treating the alkaline solution of thiol with H_2O_2 provided 2-hydroxy derivative **7** (Scheme 3).

Therefore the condensation of 2-mercapto-substituted acid **1c** with 1,2-diaminobenzene in the system PPA–$ZnCl_2$ provides new synthetic possibilities for the preparation of derivatives of poorly studied tetracyclic system of benzo[4',5']imidazo[1',2':1,6]pyrido[2,3-*d*]-pyrimidine considering the versatile chemical transformations inherent to the tautomeric thioxo group.



In conclusion we carried out the oxidative aromatization of 5,6-dihydro derivative **8** that we had described before [2]. The reaction was performed using chloranil in boiling butyl acetate to obtain heteroaromatic compound **9** with 16π-electron contour.

EXPERIMENTAL

IR spectra were recorded on a Nicolet Avatar 330 spectrophotometer from mulls in mineral oil, ^1H and ^{13}C NMR spectra were registered on a Varian Mercury-300 VX spectrometer, operating frequency 300.8 and 75.46 MHz correspondingly, internal reference TMS. TLC was carried out on Silufol UV-254 plates in a system ethanol–dichloroethane, 1 : 10, development with iodine vapor. Compounds **1a** and **2–7** were recrystallized from 60% CH_3COOH.

3-[4-Methyl-2-(4-methylphenyl)-6-oxo-1,6-dihydropyrimidine-5-yl]propanoic acid (1a). To a solution of 4.6 g (0.2 mol) of sodium in 150 mL of anhydrous EtOH was added 17.01 g (0.1 mol) of 4-methylbenzamidine hydrochloride, the mixture was stirred for 10 min, to the suspension 23.0 g (0.1 mol) of diethyl ether 2-acetylpentanedioate was added, the reaction mixture was boiled for 6 h and then 2/3 of ethanol was distilled off. To the residue 5.0 g (0.125 mol) of NaOH was added, the mixture was boiled for 4 h, acidified with HCl to pH 6 and left overnight in the cold. The precipitate was filtered off and dried. Yield 19.6 g (72%), mp 239–241°C, R_f 0.46. IR spectrum, ν, cm^{-1}: 1698 (CO), 1627 (C=C–C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.32 s (3H, CH_3), 2.33 s (3H, CH_3), 2.38–2.44 m (2H, CH_2), 2.64–2.71 m (2H, CH_2), 7.27–7.33 m (2H) and 7.95–8.01 m (2H, C_6H_4), 12.31 br.s (2H, COOH, NH). Found, %: N 9.98. $C_{15}H_{16}N_2O_3$. Calculated, %: N 10.29.

4-Methyl-2-(4-methylphenyl)-5,6-dihydrobenzo-[4',5']imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine (2). A mixture of 1.08 g (0.01 mol) of *o*-phenylendiamine and 2.72 g (0.01 mol) of acid **1a** in 10 g of PPA was heated for 3 h at 210–220°C, cooled, treated with excess of NH_4OH, the precipitate was filtered off and dried. Yield 2.5 g (77%), mp 227–229°C, R_f 0.68. IR spectrum, ν, cm^{-1}: 1620 (C=C–C=N). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ, ppm: 2.40 s (3H, CH_3), 2.56 s (2H, CH_3), 3.06–3.13 m (2H, CH_2), 3.25–3.30 m (2H, CH_2), 7.34 d.d.d (1H, C_6H_4, *J* 7.8, 7.7, 1.4 Hz),

7.35–7.40 m (2H, Tol), 7.43 d.d.d (1H, C_6H_4, *J* 7.8, 7.5, 1.2 Hz), 7.69 br.d (1H, C_6H_4, *J* 7.8 Hz), 8.31–8.36 m (2H, Tol), 8.59 br.d (1H, C_6H_4, *J* 7.8 Hz). ^{13}C NMR spectrum, δ, ppm: 20.0 (CH_2), 21.0 (CH_3), 21.9 (CH_3), 22.4 (CH_2), 114.5 (CH), 114.6, 119.0 (CH), 123.5 (CH), 123.7 (CH), 127.5 (2 CH), 129.3 (2 CH), 131.4, 134.2, 140.6, 143.4, 152.5, 154.4, 160.8, 165.1. Found, %: N 17.51. $C_{21}H_{18}N_4$. Calculated, %: N 17.17.

4-Methyl-2-phenyl-5,6,8,9-tetrahydroimidazo-[1',2':1,6]pyrido[2,3-*d*]pyrimidine (3). A mixture of 0.66 g (0.011 mol) of ethanediamine, 2.58 g (0.01 mol) of acid **1b** [7], and 5.0 g of PPA was heated for 3 h at 210–220°C in a flask with a reflux condenser, cooled, treated with excess of NH_4OH, the precipitate was filtered off and dried. Yield 2.3 g (87%), mp 178–180°C, R_f 0.41. IR spectrum, ν, cm^{-1}: 1645 (C=C–C=N). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ, ppm: 2.51 s (3H, CH_3), 2.71 t (2H, C^5H_2, *J* 7.6 Hz), 2.93 t (2H, C^9H_2, *J* 6.5 Hz), 2.96 t (2H, C^6H_2, *J* 7.6 Hz), 4.23 t (2H, C^8H_2, *J* 6.5 Hz), 7.37–7.47 m (3H, Ph), 8.35–8.41 m (2H, Ph). Found, %: N 20.96. $C_{16}H_{16}N_4$. Calculated, %: N 21.20.

Compounds 4 and 5. A mixture of 5.16 g (0.02 mol) of acid **1b**, 2.38 g (0.022 mol) of 1,2-diaminobenzene, 2.74 g (0.02 mol) of just fused $ZnCl_2$ in 25 g of PPA was heated on Wood's alloy bath for 5 h at 220–230°C. After cooling the precipitate was neutralized with diluted NH_4OH (1 : 1), filtered off, and dried. We obtained 4.5 g of grey-brown mixture of compounds **4** and **5**; 1 g of the mixture was dissolved in 30 mL of 2% solution of NaOH at heating to 70–80°C; after cooling to room temperature brown disulfide **5** insoluble in alkali solution of NaOH was filtered off. Mother liquor was acidified with AcOH to pH 6, precipitated yellow thiol **4** was filtered off and dried.

4-Methyl-5,6-dihydrobenzo[4',5']imidazo[1',2':1,6]-pyrido[2,3-*d*]pyrimidine-2-thiol (4). Yield 0.75 g (63%), mp 302–304°C, R_f 0.64. IR spectrum, ν, cm^{-1}: 1606 (C=C–C=N). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ, ppm: 2.41 s (3H, CH_3), 2.93 t (2H, CH_2, *J* 7.3 Hz), 3.23 t (2H, CH_2, *J* 7.0 Hz), 7.25–7.37 m (2H, Ar), 7.58 d.d (1H, $H^{9,10}$, *J* 7.7 Hz), 8.62 d.d (1H, $H^{9,10}$, *J* 7.7 Hz), 13.35 br.s (1H, SH). Found, %: N 20.63. $C_{14}H_{12}N_4S$. Calculated, %: N 20.88.

1,2-Bis(4-methyl-5,6-dihydrobenzo[4',5']imida-zo-[1',2':1,6]pyrido[2,3-*d*]pyrimidin-2-yl) disulfide (5). Yield 0.15 g (13%), mp 265–266°C, R_f 0.78. IR spectrum, ν, cm^{-1}: 1617 (C=C–C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.55 s (6H, CH_3), 2.98–3.05 m (4H, CH_2), 3.14–3.20 m (4H, CH_2), 7.10 d.d.d (2H, Ar, *J* 8.0, 7.4, 1.1 Hz), 7.24 d.d.d (2H, Ar, *J* 8.0, 7.4, 1.1 Hz), 7.58 d.t (2H, Ar, *J* 8.0, 1.1 Hz), 8.32 d.t (2H, Ar, *J* 8.0, 1.1 Hz). Found, %: N 21.05. $C_{28}H_{22}N_8S_2$. Calculated, %: N 20.96.

Oxidation of hydrosulfide (4) into disulfide (5). In a two-neck conic flask of 300 mL capacity equipped with reflux condenser was placed transparent mother liquor of 0.75 g of hydrosulfide **4** in 30 mL of 2% NaOH, obtained after separating insoluble compound **5** (see above the synthesis of compounds **4** and **5**), 3 mL of *i*-PrOH was added, and air was bubbled through the solution at 60–70°C. The evaporation of solvents was intermittently replenished to maintain the approximate volume and ratio of solvents. The reaction proceeded with some inductive period, after 3–4 h the solution dimmed, and after 10 h the reaction was practically complete. Yellow precipitate was filtered off, dried, and recrystallized. Yield of disulfide **5** 0.65 g (87%), mp 265–266°C.

4-Methyl-2-[(4-methoxy-3-nitrobenzyl)sulfanyl]-5,6-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido-[2,3-*d*]pyrimidine (6). To solution of 2.68 g (0.01 mol) of hydrosulfide **4** and 0.44 g (0.011 mol) of NaOH in 50 mL of water and 2 mL of 2-propanol was added 2.2 g (0.011 mol) of 4-methoxy-3-nitrobenzyl chloride and the suspension was stirred for 1 day at room temperature, then heated on a water bath for 2 h and filtered. Yield 83%, mp 200–202°C, R_f 0.68. IR spectrum, ν, cm^{-1}: 1698 (NO_2), 1621 (C=C–C=N). ^{1}H NMR spectrum, (DMSO-d_6–CCl_4, 1 : 3), δ, ppm: 2.55 s (6H, CH_3), 3.03–3.10 m (2H, CH_2), 3.21–3.29 m (2H, CH_2), 3.93 s (3H, OCH_3), 4.45 s (2H, SCH_2), 7.19 d (1H, H^5, C_6H_3, *J* 8.7 Hz), 7.22–7.28 m (2H, C_6H_4), 7.55–7.61 m (1H, C_6H_4), 7.70 d.d (1H, H^6, C_6H_3, ^1J 8.7, ^2J 2.3 Hz), 7.98 d (1H, H^2, C_6H_3, *J* 2.3 Hz), 8.27–8.33 m (1H, C_6H_4). Found, %: N 16.38. $C_{22}H_{19}N_5O_3S$. Calculated, %: N 16.16.

4-Methyl-5,6-dihydrobenzo[4',5']imidazo[1',2':1,6]-pyrido[2,3-*d*]pyrimidin-2-ol (7). To solution of 1.34 g (5 mmol) of thiol **4** and 0.4 g (11 mmol) of NaOH in 20 mL of water at room temperature was added dropwise 1 mL of 30% H_2O_2 during 15 min, after that the solution was heated on a water bath for 15 min more, cooled, and acidified with AcOH to pH 6. After being left overnight in the cold the precipitate was filtered off and dried. Yield 71%, mp > 360°C, R_f 0.39. IR spectrum, ν, cm^{-1}: 3376, 3330 (OH), 1652 (C=C–C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.29 s

(3H, CH_3), 2.80–2.86 m (2H, CH_2), 3.13–3.20 m (2H, CH_2), 7.28–7.38 m (2H, C_6H_4), 7.62–7.66 m (1H, C_6H_4), 8.43–8.48 m (1H, C_6H_4), 11.75 br.s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 16.3, 18.7, 22.9, 100.3, 115.6 (CH), 118.9 (CH), 123.7 (CH), 123.9 (CH), 131.4, 143.2, 153.1, 154.8, 155.8, 159.0. Found, %: N 21.93. $C_{14}H_{12}N_4O$. Calculated, %: N 22.21.

4-Methyl-2-phenylbenzo[4',5']imidazo[1',2':1,6]-pyrido[2,3-*d*]pyrimidine (9). To solution of 3.12 g (0.01 mol) of reactant **8** in 100 mL of butyl acetate was added 2.7 g (0.011 mol) of 2,3,5,6-tetrachloro-1,4-quinone and the mixture was boiled for 8 h at reflux, left in the cold for a night, the precipitated crystals were filtered off, washed with cold butyl acetate, and dried. Yield 2.5 g (80%), mp 237–239°C (DMF), R_f 0.70. IR spectrum, ν, cm^{-1}: 1625 (C=C–C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.93 s (3H, CH_3), 7.55–7.66 m (5H, $H^{9,10}$, C_6H_4, $H^{3,4,5}$, C_6H_5), 7.69 d (1H, H^5, *J* 8.7 Hz), 7.89–7.95 m (1H, H^{11}, C_6H_4), 8.10 d (1H, H^6, *J* 9.7 Hz), 8.56–8.62 m (2H, $H^{2,6}$, C_6H_5), 9.07–9.13 m (1H, H^8, C_6H_4). Found, %: N 18.31. $C_{20}H_{14}N_4$. Calculated, %: N 18.05.

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