Reactions of 6-aryl-5-benzoyl-4-dichloromethyl-4-hydroxyhexahydropyrimidin-2-ones with hydrazine hydrate: a new simple and efficient route to 4-aryl-5-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazin-2(1*H*)-ones

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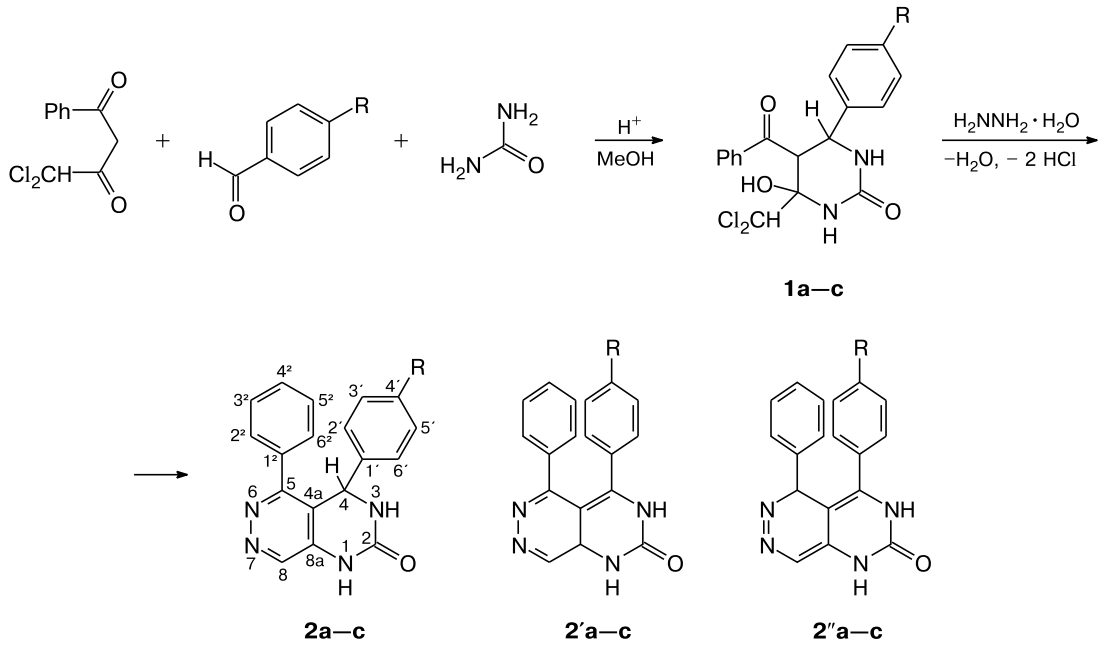
Cyclocondensation of 5-aroyl-4-dichloromethyl-4-hydroxy-6-phenylperhydropyrimidin-2-ones with 85% hydrazine hydrate in boiling toluene afforded pyrimido[4,5-*d*]pyridazines.

Key words: the Biginelli reaction, pyrimidines, cyclocondensation, pyrimido[4,5-*d*]-pyridazines, IR spectroscopy, NMR spectroscopy, X-ray diffraction analysis.

Tetraazanaphthalene derivatives play a substantial part in vital functions and are drug components. Compounds containing the pyrazino[2,3-*d*]pyrimidine (pteridine) system[1,2] are leaders in the number of natural and synthetic drugs derived therefrom. In addition, other tetraazanaphthalenes such as pyrimido[5,4-*d*]pyrimidines,[3] pyrimido[4,5-*c*]pyridazines,[4] and pyrimido[4,5-*d*]pyridazines[3,5—10] attract attention because of their cardiotonic and hypotensive effects and diuretic properties that inhibit phosphodiesterase (PDE) and its subtypes (PDE1—PDE11) responsible for erectile dysfunctions. Nevertheless, simple methods for the synthesis of such heterocyclic systems are lacking. Known routes to pyrimidopyridazines involve expensive pyrimidine[3,7,8,11] or pyridazine derivatives.[4]

Here we present a new simple and efficient method for the preparation of pyrimido[4,5-*d*]pyridazines from accessible starting materials. We found that 6-aryl-5-ben-

Scheme 1



R = H (**a**), Br (**b**), OMe (**c**)

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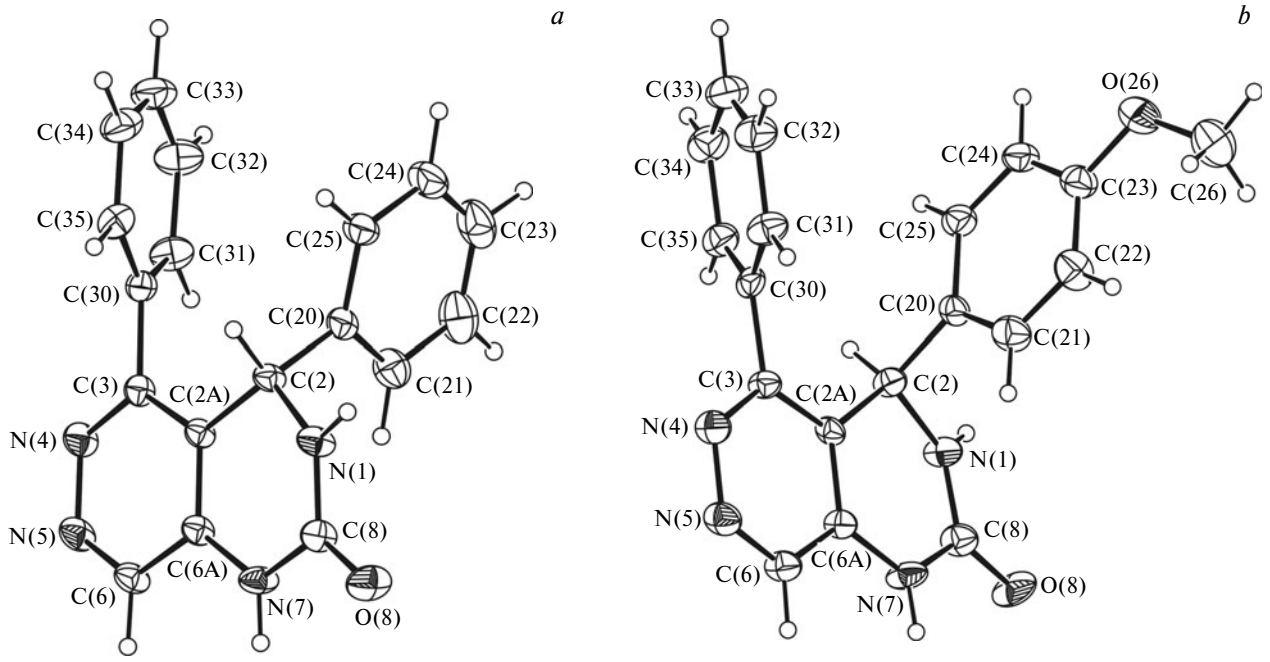

Fig. 1. Molecular geometries of compounds **2a** (*a*) and **2c** (*b*) in the crystal with atomic thermal displacement ellipsoids ($p = 50\%$) for the non-hydrogen atoms. The hydrogen atoms are depicted as circles of conventional radii.

zoyl-4-dichloromethyl-4-hydroxyhexahydropyrimidin-2-ones **1a—c** [12] (easily prepared by the Biginelli reaction from aroyl(dichloroacetyl)methane, an aromatic aldehyde, and urea) react with 85% hydrazine hydrate to give 4-aryl-5-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazin-2(1*H*)-ones **2a—c** in high (87—93%) yields (Scheme 1). It should be noted that a 20-fold excess of hydrazine hydrate is required for successful completion of the reaction; when hydrazine hydrate is used in smaller amounts, the reaction time increases and the yields of compounds **2a—c** decrease.

Convincing evidence for isomers **2a—c** (rather than other plausible isomers **2′a—c** or **2″a—c**) was provided by X-ray diffraction of pyrimido[4,5-*d*]pyridazines **2a,c**. Their molecular structures are shown in Fig. 1. Both compounds form monoclinic crystals; the asymmetric parts of their unit cells contain one crystallographically independent molecule. The structures were solved in the centrosymmetric space group $P2_1/c$. Their conformations are similar, except for small differences in the angles between the phenyl substituents and the conventional plane of the pyrimido[4,5-*d*]pyridazine fragment (the angles for the planes C(20)—C(25) and C(30)—C(35) are 64.3 and 85.9° in **2a** and 61.3 and 87.8° in **2c**, respectively).

The nature of the substituent in the phenyl fragment does not affect intermolecular interactions in the crystals of these compounds. In both cases, ribbon-like supramolecular structures are stabilized by the hydrogen bonds N—H...N and N—H...O (Fig. 2, *a*). Parallel stacking of these structures along the crystallographic axis 0*c* gives rise to a bilayer crystal structure (Fig. 2, *b*).

In the ^{1}H NMR spectra of pyrimido[4,5-*d*]pyridazines **2b** and **2a,c** (the latter were identified by X-ray diffraction), the signal positions and multiplicity are identical (except for the signals of the C(4)H protons in the aryl substituent). This suggests that these compounds exist in solutions (as well as in crystals) as 4*H*-isomers **2** rather than 5*H*- or 8a*H*-isomers **2′** and **2″**, respectively. An increase in the recording temperature from 35 to 105 °C did not change the spectral pattern (*i.e.*, the 4*H*-isomer did not isomerize into other plausible structures).

Experimental

Melting points were determined on a Boetius hot-stage. IR spectra were recorded on a Vector-22 FTIR spectrometer (Bruker) in Nujol in the 400—3600 cm^{-1} range. ^{1}H NMR spectra were recorded on an Avance-600 spectrometer (Bruker) (600.13 (^{1}H) and 150.926 MHz (^{13}C)). Chemical shifts are given on the δ scale with reference to the signals for residual protons and ^{13}C atoms in DMSO-d_6 (δ_H 2.52, δ_C 40.45).

6-Aryl-5-benzoyl-4-dichloromethyl-4-hydroxyhexahydropyrimidin-2-ones 1a—c were obtained by the Biginelli reaction from benzoyl(dichloroacetyl)methane, an appropriate aromatic aldehyde, and urea as described earlier.[12]

4,5-Diphenyl-3,4-dihydropyrimido[4,5-*d*]pyridazin-2(1*H*)-one (2a). Hydrazine hydrate (85%, 1.54 g, 26.18 mmol) was added to a mixture of perhydropyrimidinone **1a** (0.50 g, 1.31 mmol) in toluene (10 mL). The reaction mixture was refluxed with a Dean—Stark trap for 20 h. After ~1 h, crystals

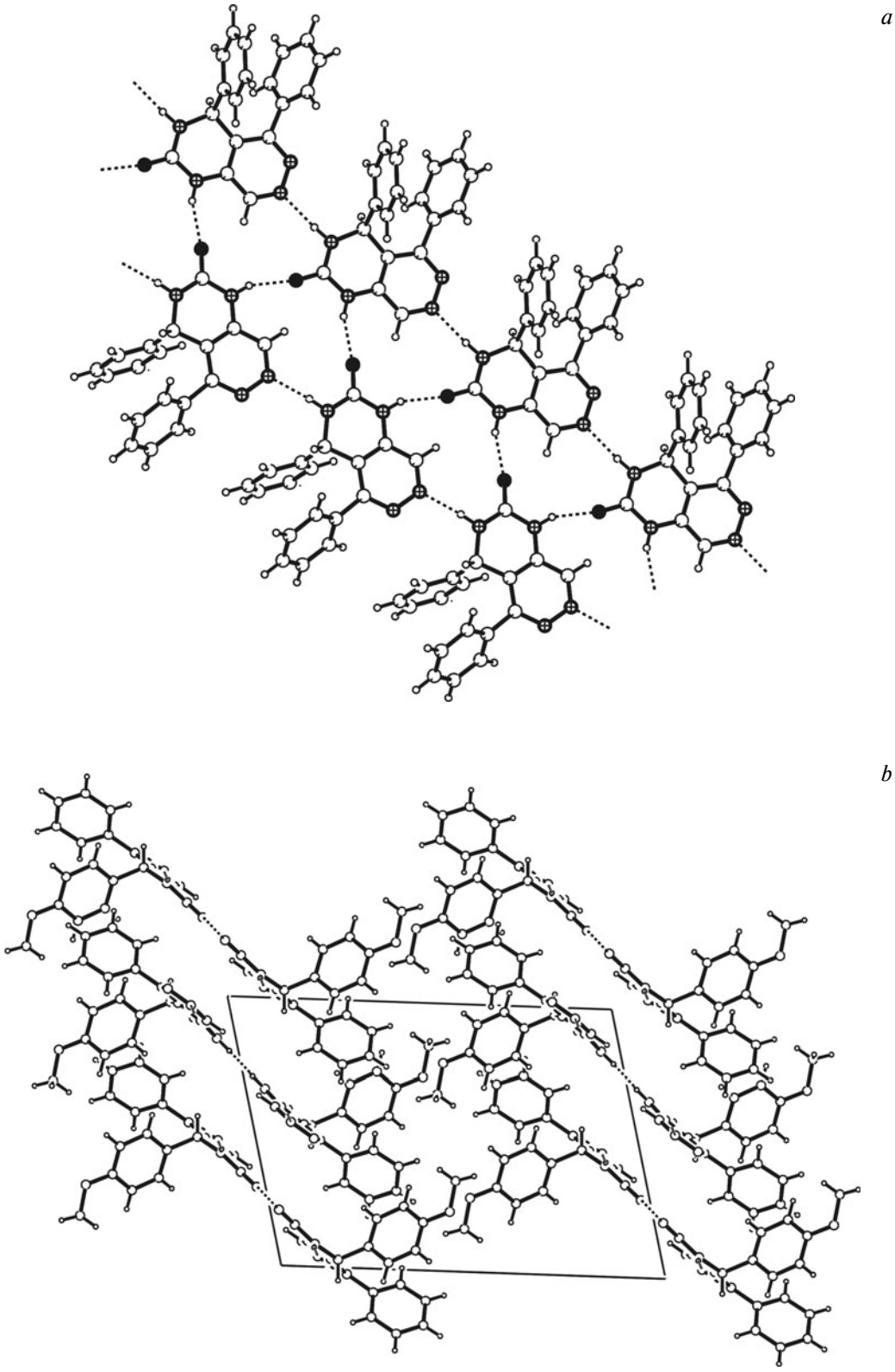

Fig. 2. *a*. Formation of ribbon-like supramolecular structures in the crystal of compound **2a** by means of the N—H...N and N—H...O hydrogen bonds (indicated with dashed lines). The view along the crystallographic axis 0*c* is shown. *b*. Molecular packing in the crystal structure **2c**. The view along the crystallographic axis 0*b* is shown. Hydrogen bonds are indicated with dashed lines.

began to form in the boiling homogeneous mixture. The amount of trapped water was 0.23 mL. The solvent and the excess hydrazine hydrate were removed in a water aspirator vacuum. The resulting semicrystalline substance was diluted with ethanol (10 mL). The crystals that formed were filtered off, dried in air, recrystallized from DMSO, washed with Pr^iOH (2×10 mL), and dried again in air. The yield was 0.36 g (91.0%), white crystals, m.p. 301—302 °C. Found (%): C, 71.70; H, 4.81; N, 18.52. $C_{18}H_{14}N_4O$. Calculated (%): C, 71.51; H, 4.67; N, 18.53. IR, ν/cm^{-1}: 3252, 3142, 1701, 1678, 1606, 1570, 1498, 1271, 1255, 1123, 1096, 969, 514, 477. ^{1}H NMR (DMSO-d_6), δ: 5.57 (d, 1 H, 1 H(4), J = 2.7 Hz); 6.74 (d, 2 H, H(2′) + H(6′), J = 6.4 Hz); 7.19 (m, 3 H, H(3′) + H(5′) + H(4′)); 7.29 (d, 2 H, H(2″) + H(6″), J = 7.3 Hz); 7.43 (dd, 2 H, H(3″) + H(5″), J = 7.3 Hz, J = 7.1 Hz); 7.48 (dd, 1 H, H(4″), J = 7.1 Hz, J = 7.1 Hz); 7.98 (br.s, 1 H, N(3)H); 8.90 (s, 1 H, H(8)); 10.17 (br.s, 1 H, N(1)H).

4-(4-Bromophenyl)-5-phenyl-3,4-dihydropyrimido[4,5-*d*]-pyridazin-2(1*H*)-one (2b) was obtained in a similar way from perhydropyrimidinone **1b** (0.50 g, 1.09 mmol) and hydrazine hydrate (1.28 g, 21.8 mmol). Yield 0.36 g (87.0%), white crystals, m.p. 310—311 °C. Found (%): C, 56.67; H, 3.49; Br, 21.12; N, 14.73. $C_{18}H_{13}BrN_4O$. Calculated (%): C, 56.71; H, 3.44; Br, 20.96; N, 14.70. IR, ν/cm^{-1}: 3284, 3058, 1704, 1679, 1267, 1125, 775, 705, 480, 411. ^{1}H NMR (DMSO-d_6), δ: 5.59 (d, 1 H, H(4), J = 2.9 Hz); 6.68 (d, 2 H, H(3′) + H(5′), J = 8.2 Hz); 7.31 (d, 2 H, H(2″) + H(6″), J = 7.1 Hz); 7.38 (d, 2 H, H(2′) + H(6′), J = 8.2 Hz); 7.44 (dd, 2 H, H(3″) + H(5″), J = 7.1 Hz, J = 7.6 Hz); 7.48 (dd, 1 H, H(4″), J = 7.6 Hz, J = 7.6 Hz); 7.95 (br.s, 1 H, N(3)H); 8.86 (s, 1 H, H(8)); 10.15 (br.s, 1 H, N(1)H). ^{13}C NMR (DMSO-d_6), δ: 116.45 (br.s, C(8a)); 122.03 (dd, C(4a), J = 10.8 Hz, J = 10.8 Hz); 129.33 (dd, C(2′) + C(6′) + C(2″) + C(6″), J = 164.3 Hz, J = 6.3 Hz); 129.52 (ddd, C(3″) + C(5″), J = 162.8 Hz, J = 6.3 Hz, J = 6.3 Hz); 129.96 (ddd, C(4″), J = 161.6 Hz, J = 7.2 Hz, J = 7.2 Hz); 132.46 (dd, C(3′) + C(5′), J = 167.6 Hz, J = 5.4 Hz); 136.96 (dd, C(1′), J = 7.5 Hz, J = 7.5 Hz); 137.94 (br.s, C(4′)); 140.10 (d, C(8), J = 185.0 Hz); 142.50 (ddd, C(1″), J = 6.4 Hz, J = 6.0 Hz, J = 4.8 Hz); 152.58 (d, C(5), J = 5.4 Hz); 158.83 (s, C(2)).

4-(4-Methoxyphenyl)-5-phenyl-3,4-dihydropyrimido[4,5-*d*]-pyridazin-2(1*H*)-one (2c) was obtained in a similar way from perhydropyrimidinone **1c** (0.50 g, 1.22 mmol) and hydrazine hydrate (1.43 g, 24.4 mmol). Yield 0.38 g (93.0%), white crystals, m.p. 316—317 °C (from DMSO). Found (%): C, 68.69; H, 4.74; N, 16.52. $C_{19}H_{16}N_4O_2$. Calculated (%): C, 68.66; H, 4.85; N, 16.86. IR, ν/cm^{-1}: 3253, 3146, 3035, 2953, 1702, 1680, 1608, 1581, 1502, 1270, 1249, 1124, 1098, 970, 776, 514. ^{1}H NMR (DMSO-d_6), δ: 3.68 (s, 3 H, CH_3O); 5.51 (d, 1 H, H(4), J = 2.9 Hz); 6.67 (d, 2 H, H(3′) + H(5′), J = 8.6 Hz); 6.75 (d, 2 H, H(2′) + H(6′), J = 8.6 Hz); 7.31 (d, 2 H, H(2″) + H(6″), J = 7.1 Hz); 7.45 (dd, 2 H, H(3″) + H(5″), J = 7.1 Hz, J = 7.1 Hz); 7.49 (dd, 1 H, H(4″), J = 7.1 Hz, J = 7.1 Hz); 7.90 (br.s, 1 H, N(3)H); 8.87 (s, 1 H, H(8)); 10.12 (br.s, 1 H, N(1)H).

Single-crystal X-ray diffraction analysis of compounds **2a,c** was performed at the X-ray Diffraction Division of the Collective Use Center of the Spectroanalytical Center based on the Diffraction Investigations Laboratory of the A. E. Arbuzov Institute of Organic and Physical Chemistry (Kazan Research Center, Russian Academy of Sciences). Crystallographic parameters and the data collection and refinement statistics for structures **2a,c** are given in Table 1. Experiments were carried out at 20 °C on a Bruker AXS SMART APEX II automatic three-circle diffractometer fitted with a CCD area detector (graphite monochromator, Mo-Kα radiation). The structures were solved by the direct methods and refined first isotropically and then anisotropically (for all non-hydrogen atoms) with the SHELXTL[13] and WinGX programs.[14] The coordinates of the hydrogen atoms of the amino groups were determined from difference electron-density maps (the other H atoms were located from stereochemical considerations) and refined using appropriate riding models. Experimental data were collected and edited, and the unit cell parameters were refined, with the APEX2 program.[15] Intermolecular interactions were analyzed, and the molecular structures were drawn, with the PLATON program.[16]

Table 1. Crystallographic parameters and the data collection statistics for compounds **2a,c**

Parameter	**2a**	**2c**
Crystal color	Colorless	
Crystal shape	Prisms	
Molecular formula	$C_{18}H_{14}N_4O$	$C_{19}H_{16}N_4O_2$
Molecular weight	302.33	332.36
Crystal system	Monoclinic	
Space group	$P2_1/c$	$P2_1/c$
a/Å	16.384(1)	17.311(3)
b/Å	7.7381(7)	7.736(1)
c/Å	12.341(1)	12.353(2)
β/deg	110.307(1)	103.323(2)
V/Å^3	1467.4(2)	1609.6(4)
Z	4	4
d_{calc}/g cm^{-3}	1.369	1.371
μ/cm^{-1}	0.89	0.92
Absorption correction	Multi-scan	
Radiation, λ/Å	Mo-Kα, 0.71073	
F(000)	632	696
Number of measured reflections	13042	19019
R_{int}	0.0250	0.1615
Number of independent reflections with $I > 2\sigma(I)$	2640	1064
Final residuals	R = 0.0424, R_w = 0.1082	R = 0.0391, R_w = 0.0578
GOOF	1.039	0.652
Number of refined parameters	264	227

The atomic coordinates in structures **2a,c** and their thermal parameters have been deposited with the Cambridge Crystallographic Data Center (http://www.ccdc.cam.ac.uk; CCDC Nos 687 136 and 687 137, respectively).

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