New Dihydro-1,2,4-Triazolo[1,5-*a*]pyrimidines Based on Arylidene Derivatives of 5-Acetylbarbituric and Dehydroacetic Acids

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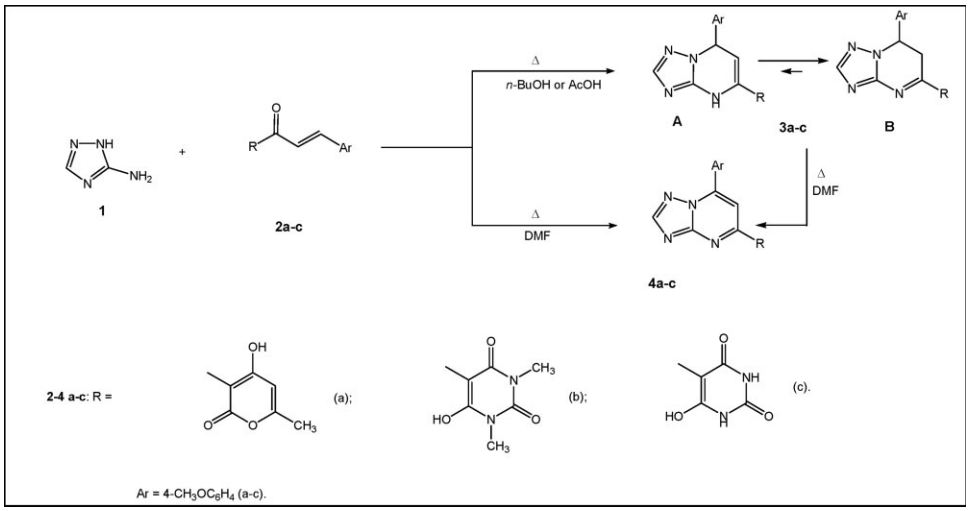

The reaction of 3-amino-1,2,4-triazole (**1**) with arylidene-5-acetyl barbituric acid (**2b,c**) or dehydroacetic acid (**2a**) by refluxing in butanol leads to the formation of dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines **3a–c**.

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INTRODUCTION

Azolopyrimidines are analogs of many naturally occurring compounds, such as purines, and therefore they have been excellent objects for the search of new physiologically active compounds for quite a long time [1–3]. The entrance of a pharmacofore into the molecule of azolopyrimidine can lead to compounds with interesting biological properties.

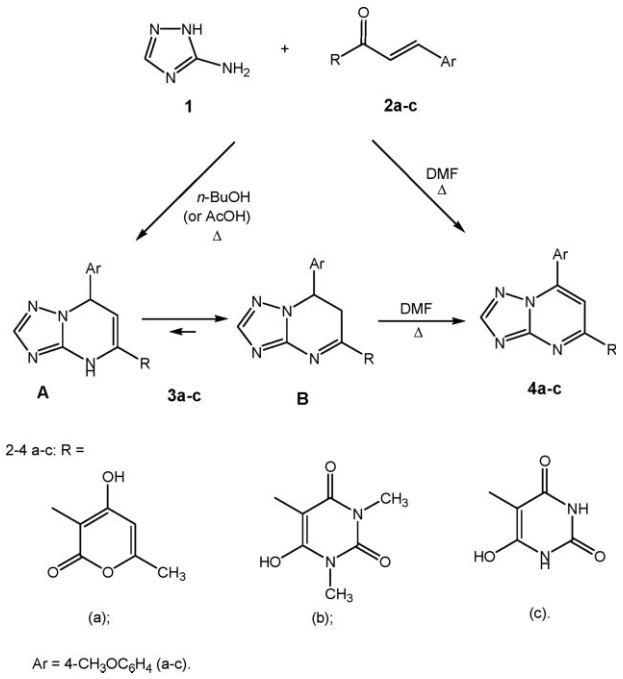
From the other side, it was shown [4] that partially hydrogenated azoloazines with a nodal nitrogen are useful for studying a wide set of theoretical problems, for example, imine-enamine tautomerization. Therefore, the important aim of this work was a continuation of our previous research about tautomerization processes in dihydroazolopyrimidines [5,6], especially synthesis of dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines with a proton-acceptor substituent which could lead to the intramolecular hydrogen bond between a substituent and the NH group of pyrimidine ring, and investigation of the tautomeric equilibrium in such compounds. In our opinion, one of the possible solutions for both problems would be synthesis of dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines that contained 6-hydroxypyrimidine-2,4-dion-5-yl or 4-hydroxy-6-methylpyran-2-on-3-yl substituents.

It is known [4] that the most convenient preparative method for synthesis of dihydroazolopyrimidines with nodal nitrogen atom is the reaction of aromatic α,β-unsaturated ketones or their synthetic precursors with aminoazoles which contain an amidine fragment. This synthetic way allowed obtaining a large number of dihydroazolopyrimidine derivatives that have different electronic properties of azole ring and contain various alkyl or aryl substituents in pyrimidine ring causing a wide set of electronic and solvation properties.

RESULTS AND DISCUSSION

We established that 3-amino-1,2,4-triazole (**1**) can react with arylidene derivatives of dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one**, 2a**), 5-acetyl-1,3-dimethylbarbituric (**2b**) and 5-acetylbarbituric (**2a**) acids by heating their equimolar amounts in

Scheme 1



n-buthanol or acetic acid, which leads to 6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines (**3a–c**) that contain a 4-hydroxy-6-methyl-2*H*-pyrane-2-one-3-yl (**3a**), 6-hydroxy-1,3-dimethylpyrimidine-2,4-dione-5-yl (**3b**), and 6-hydroxy-1*H*-pyrimidine-2,4-dione-5-yl (**3c**), respectively, on the C-5 of triazolopyrimidine system.

Performing the reaction between amine **1** and compounds **2a–c** by heating in dimethylformamide led to the formation of heteroaromatic azolopyrimidines (**4a–c**). The same compounds were obtained by heating **3a–c** in DMF.

The structure of **3a–c** was established by their NMR data. ^{1}H NMR spectra of **3a–c** (in DMSO-d_6) contained signals corresponding to an AMX system, multiplet of aromatic ring, singlet of triazole proton, and signals of heterocyclic substituent. Thus, the NMR data showed the existence of **3a–c** in the tautomeric 6,7-dihydro form exclusively (*i.e.*, ''**B**'' form on the Scheme 1). Additionally, ^{13}C NMR spectra of **3a** and **3c** confirmed their structure. The mass spectra of **3a–c** showed molecular ion peaks.

Concerning the tautomerism of considered dihydroazolopyrimidines, it is necessary to mention that, according to our previous research, 4,7-diphenyldihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine (**5**) exists exclusively in the 1,4-dihydro form (*i.e.*, ''**A**'' form on the Scheme 2) in the solid state and in solutions [6], whereas 2-hydroxyaryl derivative (**6**) is a mixture of two tautomeric forms ''**A**'' and ''**B**'' in DMSO-d_6 with relative ratio of ''**A**'' form 75–85% [5].

Further, it was shown [7] that the ''**B**'' form can be partially stabilized by entrance of electron-donating aryl, *e.g., p*-dimethylaminophenyl, on C-5 of the corresponding dihydroazolopyrimidine (according to [7] azolopyrimidine **7** leads to mixture of imine and enamine forms in ratio ~55:45).

The relative stabilization of the ''**B**'' form in **3a–c** should be explained, in our opinion, by the influence of two effects, especially electron-donating properties of substituent on C-5 on the one hand and hydrogen bond formation on the other hand.

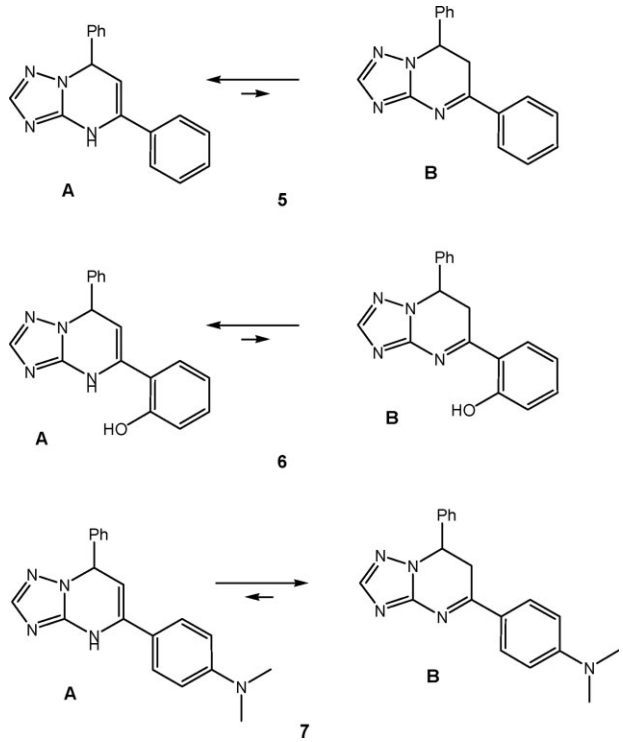
The ^{1}H NMR spectra of **4a–c** contained multiplets of 4-methoxyphenyl substituent in the aromatic area, singlets of pyrimidine and triazole ring in the low-field area, signals corresponding to the substituents at C-5 of triazolopyrimidine, and a broad singlet corresponding to the hydroxy group at 16–18 ppm, which is totally consistent with proposed structure of **4a–c**.

EXPERIMENTAL

Starting 3-amino-1,2,4-triazole, dehydroacetic acid, 5-acetylbarbituric, and 5-acetyl-1,3-dimethylbarbituric acid are commercially available. The compounds **2a,c** were prepared according to [8] (**2a**), [9] (**2c**). Compound **2b** was prepared similar to **2c** [9].

Each reaction was monitored by TLC on Silufol UV-254 plates with ethyl acetate/chloroform (1:1). Melting points were

Scheme 2



determined with a Kofler apparatus. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 200 MHz (50 MHz for ^{13}C) on a Varian Mercury VX-200 spectrometer and analyzed with ADVASP™ Analyzer program (Umatek International Inc.). Chemical shifts are reported in ppm (δ−scale), coupling constants (*J*) in Hz, internal standard was $Si(CH_3)_4$. The EI mass spectra were obtained on Varian 1200L with electron energy 70 eV.

6-Hydroxy-5-[3-(4-methoxyphenyl)-propenon-1-yl]-1,3-dimethyl-pyrimidine-2,4-dione (2b). The mixture of 3.96 g (0.02 mol) 5-acetyl-1,3-dimethylbarbituric acid, 2.72 g (0.02 mol) of 4-methoxybenzaldehyde and 0.8 g (0.02 mol) of sodium hydroxide in 20 mL of methanol was refluxed for 12 h. The reaction mixture was cooled to room temperature and neutralized with concentrated HCl. The precipitate formed was filtered off. Yield 4.0 g (63%), mp 190–191°C (from methanol); ^{1}H NMR: δ 3.19 (s, 6H, 2*CH_3); 3.81 (s, 3H, CH_3O); 7.03 (m, 2H, *m*-ArH); 7.68 (m, 2H, *o*-ArH); 7.94 (d, 1H, J = 15.8 Hz (α-H)); 8.34 (d, 1H, (β-H)); 17.0 (br. s, 1H, (OH)). Anal. Calcd. for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found C, 60.45; H, 4.95; N, 8.77.

5-(4-Hydroxy-6-methylpyran-2-on-3-yl)-7-(4-methoxy-phenyl)-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (3a). ***Method A.*** The mixture of 3-(4-hydroxy-6-methyl-2-oxo-2*H*-3-pyranyl)-1-(4-methoxyphenyl)-2-propen-1-one (**2a** [8], 2.86 g, 0.01 mol) and 3-amino-1,2,4-triazole (**1,** 0.92 g, 0.011 mol) in 15 mL of *n*-buthanol was refluxed for 1 h. The reaction mixture was cooled to room temperature, the precipitate that formed was filtered off. The yield was 2.53 g (72%), mp 181–183°C (from ethanol).

Method B. The 2.86 g (0.01 mol) of **2a** and 0.92 g (0.011 mol) of **1** in 5 mL glacial acetic acid were refluxed for 2 h. The mixture was cooled and diluted with 10 mL of acetone. The precipitate that formed was filtered off. Yield was 1.96 g (56%), mp 181–183°C (from ethanol).

^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3); 3.76 (s, 3H, CH_3O); 3.98 (dd, 1H, ^3J = 7.1, ^2J = 18.7 H_a-6); 4.41 (dd, 1H, ^3J = 5.6, H_b-6); 5.58 (dd, 1H, H-7); 5.82 (s, 1H, H-5'); 6.85 (m, 2H, *m*-ArH); 7.02 (m, 2H, *o*-ArH); 7.82 (s, 1H, H-2); 16.4 (br. s, 1H, OH); ^{13}C NMR: δ 19.9 (CH_3); 34.7 (C-6); 55.4 (CH_3O); 55.6 (C-7); 97.4 (C-5'); 114.8 (*m*-C_{Ar}), 128.5 (*o*-C_{Ar}), 130.2 (*i*-C_{Ar}), 159.9 (*p*-C_{Ar}); 151.0 (C-2); 106.8, 146.5, 161.9, 166.2, 169.8, 185.4 (C-3*a* + C-4*a* + C_{HetAr}); MS (EI, *m*/*z* (rel. %)): 352 (96) [M^+], 325 (46), 309 (12), 267 (22), 245 (100), 227 (12), 161 (14). Anal. Calcd. for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found C, 61.28; H, 4.57; N, 15.88.

5-[6-Hydroxy-1,3-dimethylpyrimidine-2,4-dion-5-yl]-7-(4-methoxyphenyl)-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (3b). Compound **3b** was prepared similar to **3a** from 0.01 mol of **1** and 5-acetyl-1,3-dimethylbarbituric acid **2b**. Yield 2.48 g (65%); mp 192–194°C (from ethanol). ^{1}H NMR: 3.12 (s, 3H, CH_3); 3.20 (s, 3H, CH_3); 3.71 (s, 3H, CH_3O); 4.17 (dd, 1H, ^3J = 6.8, ^2J = 18.2, H_a-6); 4.51 (dd, 1H, ^3J = 5.6 H_b-6); 5.76 (dd, 1H, H-7), 6.90 (m, 2H, *m*-ArH); 7.09 (m, 2H, *o*-ArH); 7.93 (s, 1H, H-2); 14.3 (s, 1H, OH); ^{13}C NMR: δ 28.3, 28.4 (CH_3); 33.8 (C-6); 55.2 (CH_3O); 55.7 (C-7); 130.4 (*i*-C_{Ar}); 114.8 (*m*-C_{Ar}), 128.2 (*o*-C_{Ar}), 159.8 (*p*-C_{Ar}); 150.8 (C-2), 93.4 (C-5'), 146.5, 150.6, 162.1, 165.6, 166.4 (C-3*a* + C-4*a* + C_{HetAr}); MS (EI, *m*/*z* (rel. %)): 382 (100) [M^+], 355 (14), 275 (83), 266 (16). Anal. Calcd. for $C_{18}H_{18}N_6O_4$: C, 56.54; H, 4.74; N, 21.98. Found C, 56.50; H, 4.75; N, 21.93.

5-[6-Hydroxy-1H-pyrimidine-2,4-dion-5-yl]-7-(4-methoxyphenyl)-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (3c). Compound **3c** was prepared similar to **3a** from **1** and 5-acetylbarbituric acid **2c**. Yield 2.3 g (65%); mp > 300°C (from ethanol). ^{1}H NMR: δ 3.71 (s, 3H, CH_3O); 4.17 (dd, 1H, ^3J = 6.6, J = 17.9, H_a-6); 4.41 (dd, 1H, ^3J = 6.0, H_b-6); 5.71 (dd, 1H, H-7), 6.91 (m, 2H, *m*-ArH); 7.11 (m, 2H, *o*-ArH); 7.90 (s, 1H, H-2); 11.0 (br.s. 1H, NH); 11.4 (br.s. 1H, NH); 14.2 (s, 1H, OH); ^{13}C NMR: δ 33.3 (C-6); 55.2 (CH_3O); 55.6 (C-7); 150.6 (C-2); 114.8 (*m*-C_{Ar}), 128.3 (*o*-C_{Ar}), 130.3 (*i*-C_{Ar}), 159.8 (*p*-C_{Ar}); 93.0 (C-5'), 146.5, 149.6, 163.9, 165.4, 168.6 (C-3*a* + C-4*a* + C_{HetAr}); MS (EI, *m*/*z* (rel. %)): 354 (100) [M^+], 336 (14), 325 (24), 286 (18), 266 (14), 256 (14), 247 (19), 225 (17), 121 (34), 115 (19). Anal. Calcd. for $C_{16}H_{14}N_6O_4$: C, 54.24; H, 3.98; N, 23.72. Found C, 54.30; H, 3.99; N, 23.75.

5-(4-Hydroxy-6-methyl-pyran-2-on-3-yl)-7-(4-methoxy-phenyl)-1,2,4-triazolo-[1,5-*a*]pyrimidine (4a). The mixture of 3-(4-hydroxy-6-methyl-2-oxo-2a-3-pyranyl)-1-(4-methoxy-phenyl)-2-propene-1-one (**2a**, 0.286 g, 0.001 mol) and **1** (0.092 g 0.0011 mol) in dimethylformamide (0.5 mL) was refluxed for 30 min and after cooling to room temperature diluted with benzene (10 mL). The precipitate formed was filtered off and dried. Yield 0.15 g (44%), mp 252–254°C (from ethanol). ^{1}H NMR: δ 2.28 (s, 3H, CH_3), 3.88 (s, 3H, CH_3O), 6.33 (s, 1H, H-5'), 7.20 (m, 2H, *m*-ArH); 8.14 (m, 2H, *o*-ArH); 8.63 (s, 1H, C_2-H), 8.67 (s, 1H, C_6-H), 17.5 (br. s, 1H, OH). MS (EI, *m*/*z* (rel. %)): 350 (100) [M^+], 335 (17), 307 (21), 265 (62), 251 (15). Anal. Calcd for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.03; N, 15.99. Found C, 61.75; H, 4.05; N, 15.95.

5-(6-Hydroxy-1,3-dimethylpyrimidine-2,4-dion-5-yl)-7-(4-methoxyphenyl)-1,2,4-triazole[1,5-*a*]pyrimidine (4b). Compound **4b** was prepared similar to **4a** from 1 and 5-acetyl-1,3-dimethylbarbituric acid **2b**. Yield 0.18 g (47%), mp > 270°C (from ethanol). ^{1}H NMR: δ 3.23 (s, 6H, 2*CH_3), 3.88 (s, 3H, CH_3O), 7.21 (m, 2H, *m*-ArH); 8.10 (m, 2H, *o*-ArH); 8.53 (s, 1H, C_2-H), 8.87 (br. s, 1H, C_6-H), 16.6 (br. s, 1H, OH). MS (EI, *m*/*z* (rel. %)): 380 (100) [M^+], 353 (15), 275 (73). Anal. Calcd. for $C_{18}H_{16}N_6O_4$: C, 56.84; H, 4.24; N, 22.10. Found C, 56.90; H, 4.22; N, 22.07.

5-(6-Hydroxy-1*H*-pyrimidine-2,4-dion-5-yl)-7-(4-methoxyphenyl)-1,2,4-triazole[1,5-*a*]pyrimidine (4c). Compound **4c** was prepared similar to **4a** from **1** and 5-acetylbarbituric acid **2c** and **1**. Yield 0.17 g (48%), mp > 300°C (from ethanol). ^{1}H NMR: δ 3.87 (s, 3H, CH_3O), 7.19 (m, 2H, *m*-ArH); 8.07 (m, 2H, *o*-ArH); 8.51 (s, 1H, C_2-H), 8.78 (br. s, 1H, C_6-H), 16.5 (br. s, 1H, OH). MS (EI, *m*/*z* (rel. %)): 352 (100) [M^+], 321 (29), 245 (82), 225 (15). Anal. Calcd for $C_{16}H_{12}N_6O_4$: C, 54.55; H, 3.43; N, 23.85. Found C, 54.45; H, 3.44; N, 23.81.

Transformation of 6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines 3a–c into 1,2,4-triazolo[1,5-*a*]pyrimidines (4a-c). The 0.001 mol (0.35 g) of **3a** in 1 mL DMF was heated for 30 min and diluted with 20 mL benzene after cooling. 0.28 g (79%) of **4a** was isolated.

In analogous way, **4b** and **4c** were isolated with yields 75 and 84%, correspondingly.

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