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Synthesis of a 2-Hydrazinyl-1,6-dihydropyrimidine Derivative

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Abstract—Ethyl 4-methyl-6-phenyl-2-[2-(propan-2-ylidene)hydrazinyl]-1,6-dihydropyrimidine-5-carboxylate has been synthesized from ethyl 2-(ethoxymethylidene)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate.

Keywords: pyrimidine, thiazolopyrimidine, nucleophilic substitution, hydrazine derivatives, nitrosation, ethoxymethylidene derivatives.

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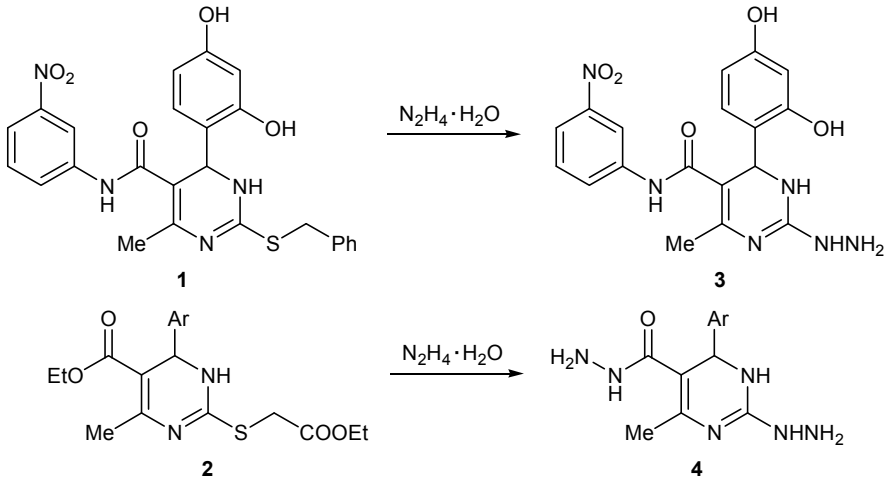
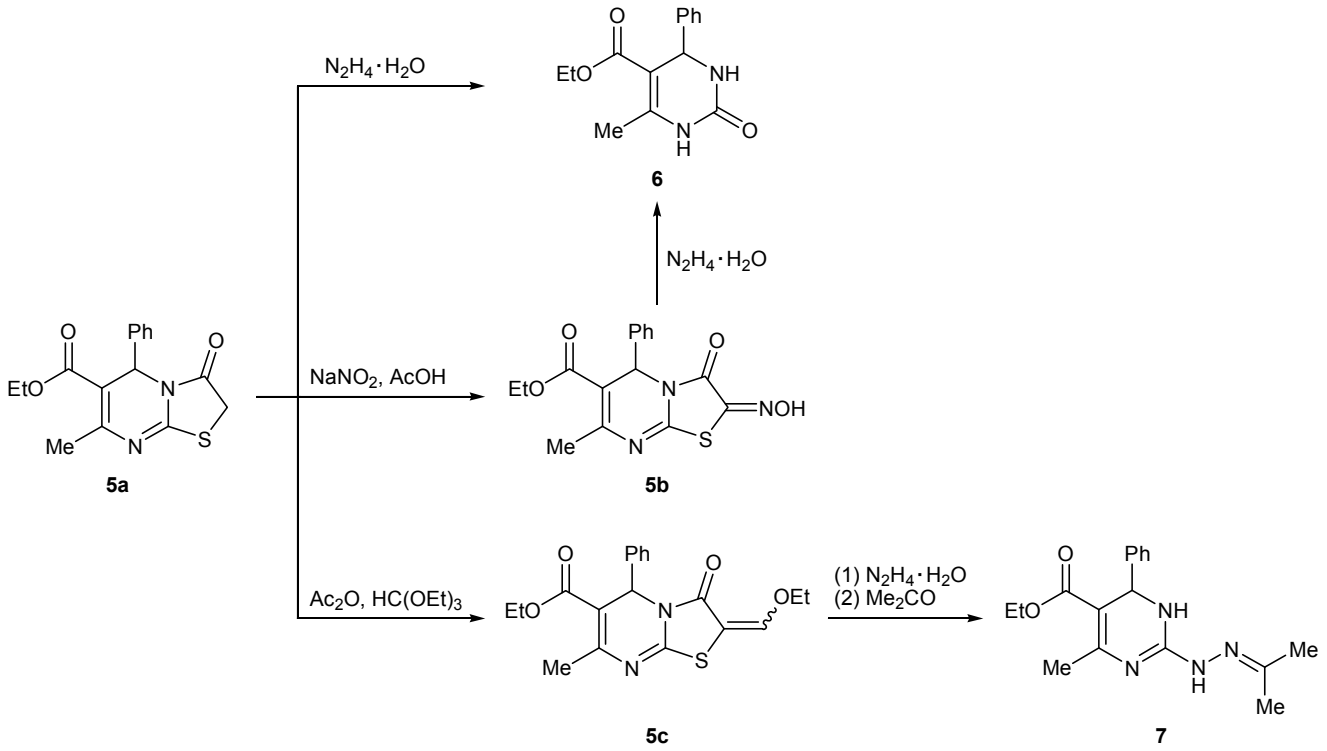
Biginelli synthesis of pyrimidines [1] is attractive due to simplicity of the experimental procedure and accessibility of initial reagents [2–6]. On the other hand, neither guanidine nor aminoguanidine can be involved in the Biginelli reaction, so that the corresponding 2-amino- and 2-hydrazinyl-1,6-dihydropyrimidines were synthesized by condensation of protected guanidine with subsequent deprotection [7] or via substitution of an appropriate nucleofugal group on C^2 of the dihydropyrimidine ring by hydrazinyl or amino group [7–10]. A series of 2-amino-1,6-dihydropyrimidines were obtained by substitution of the pyrazolyl group in N^1-Boc-2-(1*H*-pyrazol-1-yl)-1,6-dihydropyrimidines by an ammonia or primary amine residue [7, 8]. The reaction of more accessible 2-(benzylsulfanyl)-1,6-dihydropyrimidine **1** [9] or ethyl 2-(1,6-dihydropyrimidin-2-ylsulfanyl)acetates **2** [10] with hydrazine hydrate afforded 2-hydrazinyl-1,6-dihydropyrimidines **3** and **4**, respectively (Scheme 1). It should be noted that 2-hydrazinylpyrimidines **4** were converted to 2-(1*H*-pyrazol-1-yl)pyrimidines [10] which were used to synthesize 2-amino-1,6-dihydropyrimidines [7, 8].

We previously found that ethyl 2-(1,6-dihydropyrimidin-2-ylsulfanyl)acetates **2** as free bases are unstable in solution and that they readily undergo intramolecular cyclization to [1,3]thiazolo[3,2-*a*]pyrimidin-3(2*H*)-ones [11]. The latter were expected to give rise to 2-hydrazinyl-1,6-dihydropyrimidines in reaction with hydrazine hydrate. However, the reaction of

Scheme 1.



Scheme 2.



thiazolopyrimidine **5a** with hydrazine hydrate led to the formation of known 1,2,3,4-tetrahydropyrimidine-2-one **6** (Scheme 2) which was also synthesized by reaction of hydrazine hydrate with 2-hydroxyimino derivative **5b** prepared by nitrosation of **5a** [12]. In order to obtain 2-substituted 1,6-dihydropyrimidines, we have synthesized 2-(ethoxymethylidene)[1,3]thiazolo[3,2-*a*]pyrimidine **5c** by treatment of **5a** with triethyl orthoformate in acetic anhydride. The reaction of **5c** with hydrazine hydrate afforded 2-hydrazinyl-1,6-dihydropyrimidine which was isolated as acetone hydrazone **7**. The ethoxy group in 5-(ethoxymethylidene)-2-sulfanylidene-1,3-thiazolidin-4-one can be replaced by hydrazine residue [13], while the thiazolidine ring in [1,3]thiazolo[3,2-*a*]pyrimidine is readily opened by the action of, e.g., piperidine [14]. Hydrazine is a binucleophile which is likely to replace the ethoxy group in **5c** in the initial stage and thus favors further transformations leading to 2-hydrazinyl-1,6-dihydropyrimidine derivative. The described reaction opens a new synthetic route to 2-hydrazinyl-1,6-dihydropyrimidines.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR Affinity-1 spectrometer equipped with an ATR accessory. The ^{1}H and ^{13}C NMR spectra were measured on a Jeol JNM ECX spectrometer at 400 and 100 MHz, respectively, using $CDCl_3$ as solvent and reference. The elemental analyses were obtained on a EuroVector EA 3000 automated CHNS analyzer. The melting points were measured in capillaries on an OptiMelt SRS MPA100 apparatus. Thin-layer chromatography was performed on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor. [1,3]Thiazolo[3,2-*a*]pyrimidines **5a** and **5b** were synthesized according to the procedures described in [12, 15].

Ethyl 2-(ethoxymethylidene)-7-methyl-5-phenyl-3,5-dihydro-2*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (5c). A mixture of 1.00 g (3.16 mmol) of thiazolopyrimidine **5a**, 1.65 mL (9.91 mmol) of triethyl orthoformate, and 10 mL of acetic anhydride was refluxed for 5 h. Excess acetic anhydride and liberated acetic acid were distilled off on an oil bath under reduced pressure (water-jet pump), and the residue was recrystallized from ethanol. Yield 0.40 g (34%), claret red crystals, mp 154–155°C. IR spectrum, ν, cm^{-1}: 3032 w (C–H$_{arom}$), 2978 w and 2928 w (C–H$_{aliph}$), 1703 s (C=O), 1632 s (C=N), 1607 s (C=C), 1533 s (C=C$_{arom}$), 1304 s (C–N), 1217 s (C–O), 1123 s (C–O), 1070 s (C–O), 1013 s (C–O), 733 s (δC–H$_{arom}$), 694 s (δC–H$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 1.17 t (3H,

CH_3, J = 7.1 Hz), 1.34 t (3H, CH_3, J = 7.4 Hz), 2.46 s (3H, CH_3), 4.06–4.14 m (4H, CH_2O), 6.1 s (1H, CH), 7.25–7.35 m (6H, Ph, OCH=). ^{13}C NMR spectrum, δ_C, ppm: 14.2 (CH_3), 15.4 (CH_3), 22.9 (CH_3), 55.1 (CH), 60.4 (CH_2O), 72.2 (CH_2O), 101.4 (C^2), 108 (C^6); 127.9 (CH), 128.5 (CH), 128.6 (CH), 140.7 (Ph); 153.0 (C^7), 153.3 (**C**HOEt), 157.5 (C^{8a}) 165.3 (C^3), 165.7 (6-C=O). Found, %: C 61.38; H 5.49; N 7.40; S 8.53. $C_{19}H_{20}N_2O_4S$. Calculated, %: C 61.27; H 5.41; N 7.52; S 8.61.

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6). Hydrazine hydrate, 0.4 mL (8 mmol), was added with stirring to a solution of 190 mg (0.6 mmol) of thiazolopyrimidine **5a** or 210 mg (0.6 mmol) of **5b** in 5 mL of ethanol. The mixture was refluxed for 3 h and cooled, and the precipitate was filtered off and washed with ethanol. Yield 110 mg (70%) from **5a** or 96 mg (61%) from **5b**, white crystals, mp 201–202°C; published data [16]: mp 202–204°C. IR spectrum, ν, cm^{-1}: 3246 s (N–H), 3117 s (N–H), 2980 m (C–H), 2930 m (C–H), 1726 s (C=O), 1701 s (C=O), 1649 s (C=C), 1223 s (C–O), 1092 s (C–O), 758 m (δC–H_{arom}), 698 m (δC–H_{arom}). ^1H NMR spectrum, δ, ppm: 1.15 t (3H, CH_3, J = 7.1 Hz), 2.34 s (3H, CH_3), 4.01–4.11 m (2H, CH_2O), 5.40 s (1H, CH), 5.61 s (1H, NH), 7.20–7.35 m (5H, Ph), 7.83 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 12.8 (CH_3), 17.4 (CH_3), 54.4 (CH), 58.7 (CH_2O), 100.1 (C^5); 125.2 (CH), 126.6 (CH), 127.4 (CH), 142.3 (Ph); 144.8 (C^6), 151.7 (C^2), 164.2 (5-C=O). Found, %: C 64.72; H 6.09; N 10.90. Calculated, %: C 64.60; H 6.20; N 10.76. $C_{14}H_{16}N_2O_3$.

Ethyl 4-methyl-6-phenyl-2-[2-(propan-2-ylidene)hydrazinyl]-1,6-dihydropyrimidine-5-carboxylate (7). A mixture of 180 mg (0.48 mmol) of thiazolopyrimidine **5c**, 4 mL of propan-2-ol, and 0.3 mL (6.0 mmol) of hydrazine hydrate was stirred for 3 h at room temperature. The mixture was diluted with 20 mL of water and extracted with ethyl acetate (3×10 mL), the combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure, and the oily residue was crystallized from benzene–petroleum ether–acetone (30:10:1). Yield 68 mg (44%), pale pink crystals, mp 147–148°C. IR spectrum, ν, cm^{-1}: 3030 m (NH), 2908 w (C–H_{aliph}), 1681 s (C=O), 1660 m (C=N), 1591 s (C=C_{arom}), 1223 s (C–O), 1083 s (C–O), 694 s (δC–H_{arom}). ^1H NMR spectrum, δ, ppm: 1.15 t (3H, CH_3, J = 7.1 Hz), 1.96 s (3H, CH_3), 2.11 s (3H, CH_3), 2.47 s (3H, CH_3), 4.00–4.16 m (2H, CH_2O), 5.55 s (1H, CH), 7.20–7.40 m (5H, Ph), 11.53 br.s (1H, NH), 12.05 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.1 (CH_3), 18.6 (CH_3), 19.4 (CH_3), 25.2 (CH_3), 54.1 (CH), 60.9 (CH_2O), 103.8 (C^5); 127.0 (CH), 129.1 (CH), 129.2 (CH), 141.5 (Ph); 142.9 (Me_2**C**=), 149.1 (C^6), 159.7 (C^2), 164.6 (5-C=O). Found, %: C 64.91; H 7.17; N 17.78. $C_{17}H_{22}N_4O_2$. Calculated, %: C 64.95; H 7.05; N 17.82.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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