Aminomethylation of 6-Methyl-1-(thietan-3-yl)pyrimidine-2,4(1H,3H)-dione

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Abstract—Mannich reactions of 6-methyl-1-(thietan-3-yl)pyrimidine-2,4(1H,3H)-dione with formaldehyde and morpholine, piperidine, N-methylpiperazine, and diethylamine gave the corresponding 5-aminomethyl-substituted pyrimidine derivatives. The title compound reacted with excess piperazine to form 3,5-bis-(piperazin-1-yl) derivative, while its reaction with an equimolar amount of piperazine afforded 5,5′-(piperazin-1,4-diylbismethylene)bis[6-methyl-1-(thietan-3-yl)pyrimidine-2,4(1H,3H)-dione].

Scheme 1.

Aminomethylation of pyrimidine-2,4(1H,3H)-diones having no substituents on the nitrogen atoms was reported in [1–5]. The direction of this reaction is largely determined by the presence of a substituent on C5 in the pyrimidine ring. 5-Unsubstituted pyrimidine-2,4(1H,3H)-dione undergoes aminomethylation at the C5 atom [1, 2], while with excess reagent both C5 and N3 are involved [2] to give N,C-bis(aminomethyl) derivatives. If the 5-position is occupied, the reaction occurs at the nitrogen atom. According to the data of [3], aminomethylation of thymine and 5-fluorouracil leads to the formation of 1,3-bis(aminomethyl) derivatives, and the Mannich reaction of 5-nitro- and 5-hydroxyuracils involves the nitrogen atom in position 3 [2, 5]. The synthesis of 1-aminomethyl-5-fluorouracils was described in [3, 4]. Aminomethylation of 3-[2-(isobutylsulfanyl)ethyl]-6-methyluracil gave 5-mono- and 1,5-bis(aminomethyl) derivatives [5]. Aminomethylation of 1-substituted pyrimidine-2,4(1H,3H)-diones according to Mannich was not reported.

With a view to explore the reactivity of 6-methyl-1-(thietan-3-yl)pyrimidine-2,4(1H,3H)-dione (I), it was brought into reaction with formaldehyde and secondary amines. The reaction direction depended on the conditions and reactant ratio. By heating compound I with equimolar amounts of formaldehyde and secondary cyclic amines IIa–IIc for 5 h in boiling ethanol at pH 6–7 we obtained the corresponding 5-aminomethylpyrimidine-2,4(1H,3H)-diones IIIa–IIIc in no more than 40% yield, whereas the yield increased to 65% at pH 1–2, the reaction time being the same (Scheme 1). Replacement of ethanol as solvent by acetone (pH 6–7) ensured 65% yield in a shorter time (3 h). Raising the amount of secondary amines to 3–5 equiv and of formaldehyde to 10-equiv improved the yield to 72–77%, and compounds IIIa–IIIc were obtained as the only products. According to the TLC data, the reaction mixtures contained no 3,5-bis(aminomethyl) derivatives.

Compound I failed to react with secondary aliphatic amines (dimethyl- and diethylamine) under analogous conditions. 5-(Diethylaminomethyl)-6-methyl-1-(thietan-3-yl)pyrimidine-2,4(1H,3H)-dione (IIId) was obtained in 57% yield by heating equimolar amounts of the reactants in boiling acetic acid (Scheme 1).

The reaction of pyrimidine I with equimolar amounts of piperazine and formaldehyde in boiling acetonitrile was complete in 1 h with formation of 62% of...
5,5′-(piperazine-1,4-diylbismethylene)bis[6-methyl-1-(thietan-3-yl)pyrimidine-2,4(1H,3H)-dione] (IV) (Scheme 2). When the amount of piperazine was reduced by half, the yield of IV decreased to 50%. In the presence of excess piperazine and formaldehyde we isolated 3,5-bis(piperazin-1-ylmethyl) derivative V.

The $^1$H NMR spectra of compounds IIIa, IIIb, and IIIId contained a broadened singlet from the N$^3$H proton, a singlet from protons in the methylene group on C$^5$, and signals from the secondary amine residue, which indicated formation of 5-aminomethyl derivatives. In the $^{13}$C NMR spectra of IIIa–IIIc we observed signals from the 6-methyl-1-thietanylpyrimidine fragment, 5-CH$_2$ signal, and signals typical of secondary amine residue.

In the $^1$H NMR spectrum of IV signals from protons in the 6-methyl-1-(thietan-3-yl)pyrimidine fragments and 5-CH$_2$ group had double intensity as compared to the piperazine signal which appeared at $\delta$ 2.36 ppm (8H). The $^1$H NMR spectrum of V was characterized by double intensity of the signals from methylene protons and piperazine residues ($\delta$ 2.31–2.42 ppm, 16H). The lack of signals assignable to 5-H ($\delta$ 4.60 ppm) and N$^3$H ($\delta$ 10.30 ppm) in the pyrimidine ring [6] confirmed the formation of 3,5-bis(piperazin-1-ylmethyl) derivative V.

EXPERIMENTAL

The $^1$H and $^{13}$C NMR spectra were recorded on Bruker AMX-300 (300 MHz for $^1$H) and Bruker Avence III 500 spectrometers (500 MHz for $^1$H). The chemical shifts were determined relative to the residual proton and carbon signals of the deuterated solvents. Analytical thin-layer chromatography was performed using Silufix plates which were eluted with butan-1-ol–acetic acid–water (4:1:2); spots were detected under UV light or by treatment with iodine vapor.

6-Methyl-1-(thietan-3-yl)pyrimidine-2,4(1H,3H)-dione (I) was synthesized according to the procedure described in [6].

6-Methyl-5-(piperidin-1-ylmethyl)-1-(thietan-3-yl)pyrimidine-2,4(1H,3H)-dione (IIIa). a. Compound I, 0.79 g (4 mmol), was dissolved in 25 mL of ethanol, 0.4 mL (4.4 mmol) of 33.7% formaldehyde solution, 0.37 g (4.4 mmol) of piperidine, and 0.44 mL of 1 M aqueous HCl were added under stirring, and the mixture was heated for 5 h under reflux. The solvent was distilled off under reduced pressure, and the precipitate was washed with water and dried. Yield 65%.

b. Compound I, 0.6 g (3 mmol), was dispersed in 20 mL of acetone, 2.7 mL (30 mmol) of 33.7% formaldehyde solution and 0.77 g (9 mmol) of piperidine were added, and the mixture was heated for 3 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with water, and dried. Yield 72%, mp 181–183°C (from benzene–hexane, 1:2).

$^1$H NMR spectrum (500 MHz, CDCl$_3$), $\delta$, ppm: 1.41 m (2H, CH$_2$), 1.51–1.56 m (4H, CH$_2$), 2.31 s (3H, CH$_3$), 2.38 m [4H, N(CH$_2$)$_2$], 3.17–3.21 m (2H, SCH$_2$), 3.21 s (2H, 5-CH$_2$), 4.33–4.37 m (2H, SCH$_2$), 6.23–6.30 m (1H, NCH), 10.33 br.s (1H, 3-H). $^{13}$C NMR spectrum (500 MHz, CDCl$_3$), $\delta$, ppm: 17.04 (6-CH$_3$), 24.40 (C$^4$), 26.07 (C$^3$, C$^5$), 32.04 (SCH$_2$), 47.54 (1-CH), 52.76 (5-CH$_2$), 54.53 (C$^2$, C$^6$), 108.15 (C$^5$), 149.73 (C$^6$), 152.87 (C$^2$), 163.57 (C$^4$). Found, %: C 56.42; H 7.91; N 14.23. C$_{14}$H$_{21}$N$_3$O$_2$S. Calculated, %: C 56.54; H 7.80; N 14.13.