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Synthesis of 3-(Aminooxoethyl)-6-methyl-1-(thiethan-3-yl)-pyrimidine-2,4-(1*H*,3*H*)-diones

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Abstract—A new approach to prepare 2-chloroacetamides has been developed, based on the reaction of chloroacetyl chloride with excess of secondary amines. Alkylation of 6-methyl-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione with the synthesized 2-chloroacetamides in the presence of potassium carbonate has afforded N^3-acetamido-substituted 6-methyl-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-diones.

Keywords: *N*-(2-chloroacetyl)amine, alkylation, thiethane, pyrimidine-2,4(1*H*,3*H*)-dione

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Pyrimidine moiety is found in the molecules of many biologically active compounds. Pyrimidine-based drugs are widely used in medicine; in particular, 6-methyluracil is known for immunomodulatory activity [1].

The aim of this work was to synthesize new derivatives of 6-methyl-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione as promising biologically active substances.

One of the methods of acetamide derivatives preparation is alkylation of various nucleophiles with *N*-(2-chloroacetyl)amines. The approaches towards synthesis of *N*-(2-chloroacetyl)amines **I**–**IV** have been described in [2, 3]. Compounds **I**–**III** were obtained by refluxing equimolar amounts of chloroacetyl chloride and the secondary cyclic amines in 1,4-dioxane in the absence of any base [2] (Scheme 1).

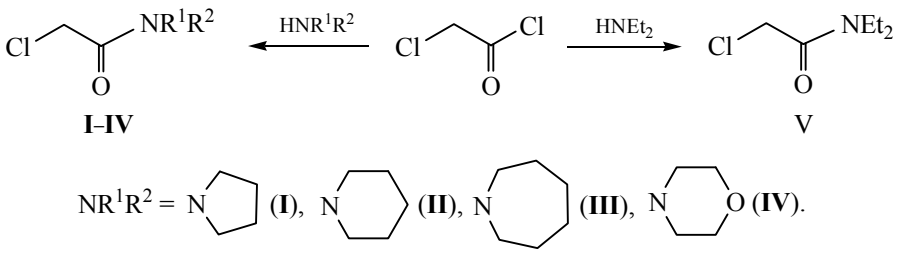
1-(Morpholin-4-yl)-2-chloroethanone **IV** was obtained via reaction of equimolar amounts of chloroacetyl chloride and morpholine in tetrahydrofuran at 0°C in the presence of 2-fold excess of potassium carbonate [3].

N-(2-Chloroacetyl)amines **I**–**V** were prepared via reaction of the secondary amines with chloroacetyl chloride in the 2 : 1 ratio in acetone at 0–5°C; the excess of the appropriate amine was used as the hydrogen chloride acceptor. This technique yielded 2-chloro-acetylamines **I**–**III** in the form of crystalline solids without need for further purification.

^{1}H NMR spectra of compounds **I**, **III,** and **V** contained signals of the protons of $CH_2C{=}O$ groups (4.00–4.07 ppm) and of amine moieties.

Alkylation of 6-methyl-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione **VI** with equimolar amount of **I**–**V** in acetonitrile in the presence of potassium carbonate resulted in N^3-(aminooxoethyl)pyrimidine derivatives **VII**–**XI** (Scheme 2).

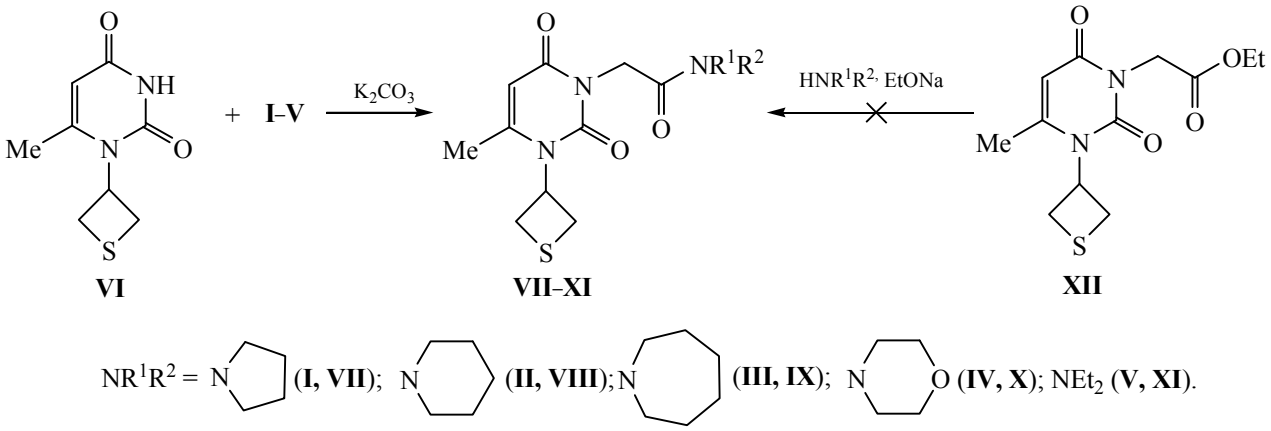
Scheme 1.



I–**IV** V

NR^1R^2 = N (**I**), N (**II**), N (**III**), N O (**IV**).

Scheme 2.



Broad singlet around 10.30 ppm, characteristic of N^3-unsubstituted 1-(thiethan-3-yl)pyrimidine **VI** [4], was not found in ^{1}H NMR spectra of compounds **VIII**–**X**. Signals of the protons of $CH_2C{=}O$ groups manifested in the range of 4.65–4.78 ppm. In addition, the spectra contained signals of the protons of the secondary cyclic amines. Two pseudo triplets and one multiplet in the ranges of 3.07–3.14 [$S(CH)_2$], 4.14–4.21 [$S(CH)_2$], and 6.00–6.12 ppm (NCH) were identified in the spectra of **VIII** and **X** recorded in DMSO-d_6. Those signals were shifted downfield by 0.7, 0.6, and 0.18 ppm, respectively, in the spectrum of **IX** recorded in $CDCl_3$, indicating retention of the thietane ring in the *N*-alkylation reactions [4, 5].

IR spectra of compounds **VII**–**XI** contained strong absorption band of the carbonyl groups stretching (1717–1638 cm^{-1}), indicating the existence of thietanepyrimidine in the diketone form. The strong absorption maxima at 1467–1430 cm^{-1} were assigned to the "amide II" band. The absence of N–H stretching at 3098 cm^{-1}, characteristic of N^3-unsubstituted 1-thietanylpyrimidine **VI** [6], further confirmed the formation of N^3-(aminooxoethyl)-substituted pyrimidines.

Acetamide derivatives can be prepared via the corresponding esters aminolysis [7]. However, boiling a mixture of ethyl 2-[6-methyl-2,4-dioxo-1-(thietan-3-yl)-1,2,3,4-tetrahydropyrimidin-3-yl]acetate **XII** with 5-fold molar excess of the secondary cyclic amine in DMF containing 15% of methanol (or in an amine medium) in the presence of catalytic amounts of sodium ethoxide (10 mol %) afforded only the starting ester (TLC and IR spectroscopy). That fact led to conclusion that **XII** was inert with respect to the secondary amines.

In summary, acetyl derivatives of the secondary amines, containing 1-(thiethan-3-yl)-2,4-dioxotetrahydropypyrimidin-3-yl fragment, can be obtained via direct *N*-alkylation of 6-methyl-1-(thiethan-3-yl)-pyrimidine-2,4(1*H*,3*H*)-dione with *N*-(2-chloroacetyl)-amine.

EXPERIMENTAL

^{1}H NMR spectra were recorded with the Bruker AMX-300 spectrometer (300 MHz) relative to the signal of residual solvent protons (DMSO-d_6 or $CDCl_3$). IR spectra (KBr) were registered with the Infralum FT-02 instrument. TLC analysis was performed using Silufix plates, eluting with the 1 : 1 acetonitrile–acetone mixture and developing with UV light or iodine vapor.

6-Methyl-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione **VI** was prepared as described in [4]. Ethyl 2-[6-methyl-2,4-dioxo-1-(thietan-3-yl)-1,2,3,4-tetrahydropyrimidin-3-yl]acetate **XII** was synthesized according to the procedure in [8].

***N*-(2-Chloroacetyl)amine (I–V).** A solution of 5.65 g (0.05 mol) of chloroacetyl chloride in 10 mL of acetone was added dropwise to a solution of 0.1 mol of the appropriate amine in 30 mL acetone cooled to 0°C. The reaction mixture was stirred during 1 h at 0–5°C and during 1 h at 20–25°C. The formed precipitate was filtered off, and the solvent was distilled off in vacuum. The oily residue was dissolved in 30 mL of ethyl acetate, and 10 mL of water acidified with HCl to pH ~ 2 was added. The organic layer was separated, washed portionwise (10 mL) with water until neutral reaction and dried over anhydrous sodium sulfate during 1 day. Next, the solvent was removed in vacuum. The residue was purified by chromatography to yield *N*-(2-chloroacetyl)amines as pale-yellow

viscous liquids, crystallizing after 1 day in the cases of **I–III**.

1-(Pyrrolidin-1-yl)-2-chloroethanone (I). Yield 60%, colorless crystals, mp 42–43°C, R_f 0.50. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.84–1.93 m (2H, CH_2), 1.96–2.05 m (2H, CH_2), 3.48–3.54 m [4H, $N(CH_2)_2$], 4.00 s (2H, CH_2CO). Found, %: C 49.02; H 6.75; N 9.76. $C_6H_{10}ClNO$. Calculated, %: C 48.82; H 6.83; N 9.49.

1-(Piperidin-1-yl)-2-chloroethanone (II). Yield 68%, colorless needle-shaped crystals, mp 213–215°C, R_f 0.72. Found, %: C 51.97; H 7.63; N 8.95. $C_7H_{12}ClNO$. Calculated, %: C 52.02; H 7.48; N 8.67.

1-(Azepan-1-yl)-2-chloroethanone (III). Yield 79%, colorless crystals, mp 193–194°C, R_f 0.63. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.56–1.59 m [4H, $(CH_2)_2$], 1.72–1.78 m [4H, $(CH_2)_2$], 3.47–3.54 m [4H, $N(CH_2)_2$], 4.07 s (2H, CH_2CO). Found, %: C 54.77; H 7.86; N 8.04. $C_8H_{14}ClNO$. Calculated, %: C 54.70; H 8.03; N 7.97.

1-(Morpholin-4-yl)-2-chloroethanone (IV). Yield 63%, yellow oil, bp 177°C (360 mmHg), R_f 0.75, n_D^{20} 1.4878. Found, %: C 43.84; H 5.87; N 8.66. $C_6H_{10}ClNO_2$. Calculated, %: C 44.05; H 6.16; N 8.56.

***N*,*N*-Diethyl-2-chloroacetamide (V).** Yield 57%, yellow oil, bp 159°C (360 mmHg), R_f 0.53, n_D^{20} 1.4691. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.13 t (3H, CH_3, J 7.2 Hz), 1.22 t (3H, CH_3, J 7.2 Hz), 3.32–3.42 m [4H, $N(CH_2)_2$], 4.05 s (2H, CH_2CO). Found, %: C 48.02; H 8.21; N 9.42. $C_6H_{12}ClNO$. Calculated, %: C 48.17; H 8.08; N 9.36.

6-Methyl-3-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (VII). A suspension of 0.5 g (2.5 mmol) of **VI** and 0.52 g (3.75 mmol) of calcined and milled potassium carbonate in 12 mL acetonitrile was refluxed during 30 min. Then a solution of 0.44 g (3 mmol) of **I** in 3 mL of acetonitrile was added to the reaction mixture, and refluxing was continued during another 7 h. The hot reaction mixture was filtered, and the solvent was removed in vacuum. The residue was recrystallized from isopropanol. Yield 96%, mp 169–170°C, R_f 0.45. IR spectrum, ν, cm^{-1}: 2961, 2878 m (C–H), 1717 s (C^2=O), 1655, 1638 s (C^4=O, C=O, C=C), 1459, 1430 s (C–N), 1361, 1336 m (C–N). Found, %: C 54.56; H 6.04; N 13.63. $C_{14}H_{19}N_3O_3S$. Calculated, %: C 54.35; H 6.19; N 13.58.

Compounds **VIII–XI** were prepared similarly starting from the appropriate *N*-(2-chloroacetylmethyl)-amines **II–V**.

6-Methyl-3-[2-oxo-2-(piperidin-1-yl)ethyl]-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (VIII). Yield 66%, mp 229–231°C (EtOH), R_f 0.58. IR spectrum, ν, cm^{-1}: 2929 m (C–H), 1714 s (C^2=O), 1699, 1646 s (C^4=O, C=O, C=C), 1461, 1437 s (C–N), 1346, 1255 m (C–N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.41–1.47 m (2H, CH_2), 1.55–1.63 m [4H, $(CH_2)_2$], 2.08 s (3H, 6-CH_3), 3.08–3.14 m [2H, $S(CH)_2$], 3.39–3.46 m [4H, $N(CH_2)_2$], 4.14–4.21 m [2H, $S(CH)_2$], 4.77 s (2H, 3-CH_2CO), 5.65 s (1H, H^5), 6.00–6.12 m (1H, NCH). Found, %: C 55.89; H 6.66; N 13.04. $C_{15}H_{21}N_3O_3S$. Calculated, %: C 55.71; H 6.55; N 12.99.

3-[2-(Azepan-1-yl)-2-oxoethyl]-6-methyl-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (IX). Yield 75%, mp 173–175°C (PrOH), R_f 0.43. IR spectrum, ν, cm^{-1}: 2931 m (C–H), 1713 s (C^2=O), 1698, 1659, 1643 s (C^4=O, C=O, C=C), 1454, 1437 s (C–N), 1361, 1281 m (C–N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.59–1.62 m [4H, $(CH_2)_2$], 1.72–1.76 m (2H, CH_2), 1.82–1.86 m (2H, CH_2), 2.14 s (3H, 6-CH_3), 3.14–3.19 m [2H, $S(CH)_2$], 3.48–3.58 m [4H, $N(CH_2)_2$], 4.30–4.36 m [2H, $S(CH)_2$], 4.65 s (2H, 3-CH_2CO), 5.59 s (1H, H^5), 6.18–6.30 m (1H, NCH). Found, %: C 56.39; H 6.78; N 12.84. $C_{16}H_{23}N_3O_3S$. Calculated, %: C 56.95; H 6.87; N 12.45.

6-Methyl-3-[2-(morpholin-4-yl)-2-oxoethyl)]-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (X). Yield 95%, mp 200–202°C (PrOH), R_f 0.65. IR spectrum, ν, cm^{-1}: 2953, 2842 m (C–H); 1716 s (C^2=O), 1641 s (C^4=O, C=O, C=C); 1458, 1435 s (C–N); 1353, 1243 m (C–N); 1112, 1070 m (C–O–C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.09 s (3H, 6-CH_3), 3.07–3.13 m [2H, $S(CH)_2$], 3.45–3.64 m [8H, $N(CH_2)_2$, $O(CH_2)_2$], 4.14–4.19 m [2H, $S(CH)_2$], 4.78 s (2H, 3-CH_2CO), 5.66 s (1H, H^5), 6.00–6.12 m (1H, NCH). Found, %: C 51.82; H 5.86; N 12.73. $C_{14}H_{19}N_3O_4S$. Calculated, %: C 51.68; H 5.89; N 12.91.

***N*,*N*-Diethyl-2-[6-methyl-2,4-dioxo-1-(thiethan-3-yl)-1,2,3,4-tetrahydro-3-yl]acetamide (XI).** Yield 96%, mp 122–124°C (*i*-PrOH–H_2O, 1 : 1), R_f 0.55. IR spectrum, ν, cm^{-1}: 2962 m (C–H), 1715 s (C^2=O); 1691, 1666, 1642 s (C^4=O, C=O, C=C); 1467, 1437 s (C–N); 1368, 1266 m (C–N). Found, %: C 54.19; H 6.67; N 13.66. $C_{14}H_{21}N_3O_3S$. Calculated, %: C 54.00; H 6.80; N 13.49.

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