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Direction of the Reaction of 6-Methylpyrimidine-2,4(1*H*,3*H*)-dione with 2-Chloromethylthiirane: N^1- or N^3-Thietanyl Derivative?

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Abstract—The reaction of 6-methylpyrimidine-2,4(1*H*,3*H*)-dione with 2-chloromethylthiirane gave 6-methyl-*N*-(thietan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione. Its oxidation and subsequent reaction of the resulting *N*-(1,1-dioxo-λ^6-thietan-3-yl) derivative with ethyl chloroacetate afforded the corresponding ethyl pyrimidinylacetate. The structure of the latter was determined by X-ray analysis, which confirmed the formation of N^3-(thietan-3-yl) derivative rather than its N^1-substituted isomer in the title reaction. According to the results of B3LYP/6-31G++(*d*,*p*), PBE/3ζ, and MP2/6-31G++(*d*,*p*) quantum chemical calculations, the N^3-thietanyl derivative is more stable than the N^1-isomer. It was also found that the calculated barrier to internal rotation of the thietanyl group about the N–C bond in 6-methyl-3-(thietan-3-yl)-pyrimidine-2,4(1*H*,3*H*)-dione is lower than in the N^1-isomer.

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Uracil derivatives are widespread in wildlife [1]. They are successfully used for the design of new drugs [2]. It is also known that thietane derivatives are promising subjects for study due to their anti-inflammatory, sedative, and insecticidal properties [3]. One method for the introduction of a thietane ring into organic molecules is based on the thiirane–thietane rearrangement [4]. It has been successfully utilized in the synthesis of uracil derivatives containing a thietane substituent [5]. By calculating the change in the Gibbs free energy (ΔG^0_{298}) for the N^1- and N^3-thietanylation of 6-methylpyrimidine-2,4(1*H*,3*H*)-dione (**1**), it has also been concluded [5] in keeping with the Hess' law that the N^1-derivative, 6-methyl-1-(thietan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (**3**) should be formed preferentially (Scheme 1). However, no direct experimental proofs of this conclusion were given by the authors. Furthermore, the calculations were carried out for the model reaction in acidic rather than alkaline medium. Taking into account the above stated, the goal of the present work was to check the assumption made in [5] by synthesizing the corresponding derivatives of 6-methyl-*N*-(thietan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione **2** or **3** and determining their structure by X-ray analysis.

Scheme 1.

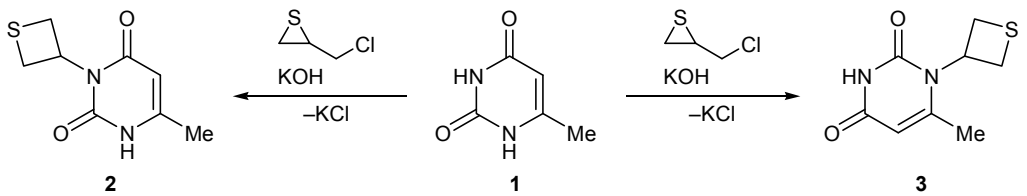


Table 1. Selected bond lengths (*d*) and bond (ω) and torsion angles (φ) in the molecule of ethyl 2-[3-(1,1-dioxo-λ^6-thietan-3-yl)-6-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl]acetate (**5**)

Bond	*d*, Å		Bond angle	ω, deg		Torsion angle	φ, deg	
	calculated	experimental		calculated	experimental		calculated	experimental
N^6–C^6	1.471	1.458(2)	$C^8S^1C^3$	79.33	82.31(8)	$N^7C^5N^6C^6$	178.95	179.49(13)
C^6–C^8	1.555	1.549(2)	$O^9S^1C^3$	110.20	114.62(10)	$C^2N^6C^6C^8$	–121.12	–115.53(17)
S^1–C^8	1.850	1.7780(19)	$C^6C^3S^1$	88.17	88.64(10)	$N^6C^6C^8S^1$	–145.65	–138.51(14)
S^1=O^{10}	1.476	1.4274(14)	$C^8C^6C^3$	98.90	98.06(14)	$C^6C^8S^1C^3$	16.08	10.66(11)
N^6–C^5	1.400	1.3907(19)	$S^2N^6C^5$	124.36	125.20(14)	$C^2N^6C^5N^7$	–2.66	–2.1(2)
C^5=O^4	1.228	1.202(2)	$N^6C^5N^7$	115.91	115.14(15)	$N^6C^5N^7C^4$	4.38	2.1(2)
C^5–N^7	1.410	1.391(2)	$N^7C^4C^{10}$	119.84	120.60(16)	$C^5N^7C^4C^{10}$	–3.74	–3.1(2)
C^4–C^{10}	1.361	1.349(2)	$C^{10}C^2N^6$	114.76	114.79(14)	$N^7C^4C^{10}C^2$	1.14	0.1(3)

By oxidation of 6-methyl-*N*-(thietan-3-yl)pyrimidin-2,4(1*H*,3*H*)-dione with hydrogen peroxide in acetic acid we obtained *N*-(1,1-dioxo-λ^6-thietan-3-yl)-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (**4**). The reaction of **4** with ethyl chloroacetate gave the corresponding ethyl pyrimidinyl acetate **5** [6] (Scheme 2). We succeeded in isolating single crystals of **5** suitable for X-ray analysis. According to the X-ray diffraction data, the ethoxycarbonylmethyl group in molecule **5** is linked to N^1, and the dioxothietanyl substituent, to N^3 of the pyrimidine ring (Fig. 1). Selected bond lengths and bond and torsion angles in molecule **5** are given in Table 1. The pyrimidine ring is almost planar, and the thietane ring has a saddle-like structure.

The conformational analysis of molecule **5** was performed in terms of the PBE/3 ζ approximation implemented in PRIRODA software package [7]. The global minimum on the potential energy surface (PES) corresponds to the conformer identical to that found in crystal (Fig. 1). The calculated bond lengths, as well as bond and torsion angles, are close to the corresponding experimental values determined by X-ray analysis (Table 1).

Thus, the reaction of 6-methylpyrimidine-2,4(1*H*,3*H*)-dione with 2-chloromethylthiirane leads to the formation of just isomer **2**. The obtained data allowed us to correctly reproduce the entire transformation sequence (Scheme 2). 6-Methyl-3-(thietan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (**2**) is the only product formed in the title reaction. Isomeric 6-methyl-1-(thietan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (**3**) either is not formed at all or is formed in a minor amount so that it could not be isolated.

The results of calculations also made it possible to answer the question which isomer, **2** or **3**, is more

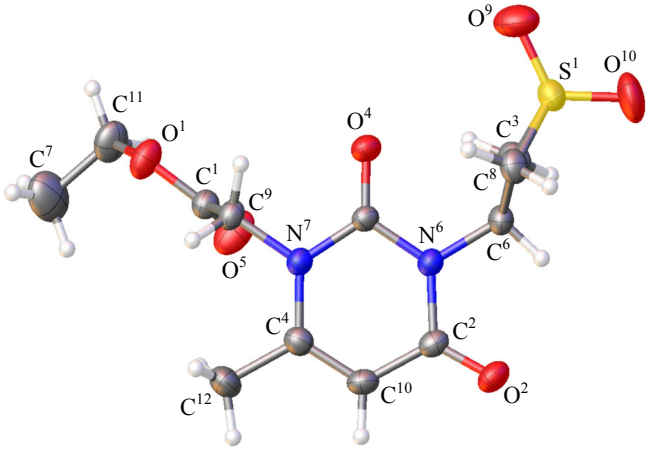


Fig. 1. Structure of the molecule of ethyl 2-[3-(1,1-dioxo-λ^6-thietan-3-yl)-6-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl]acetate (**5**) according to the X-ray diffraction data.

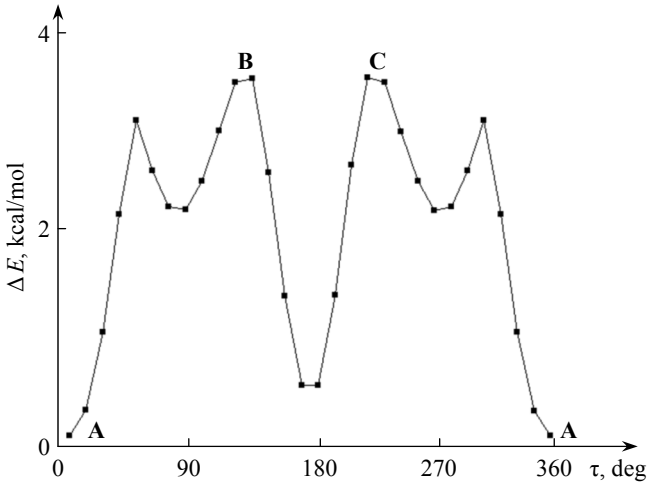
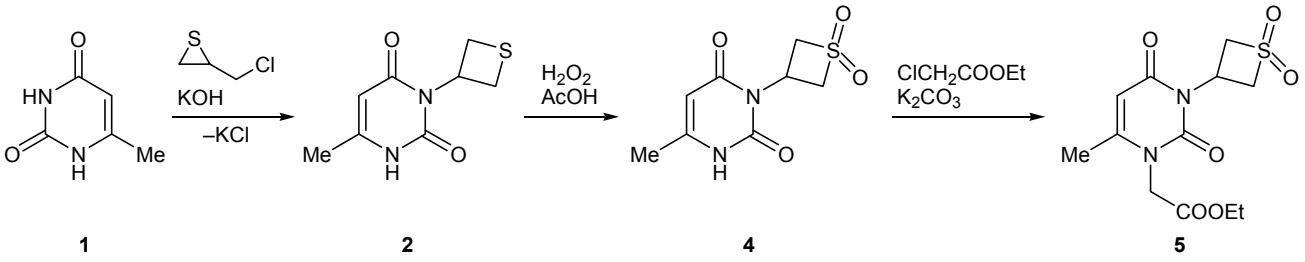


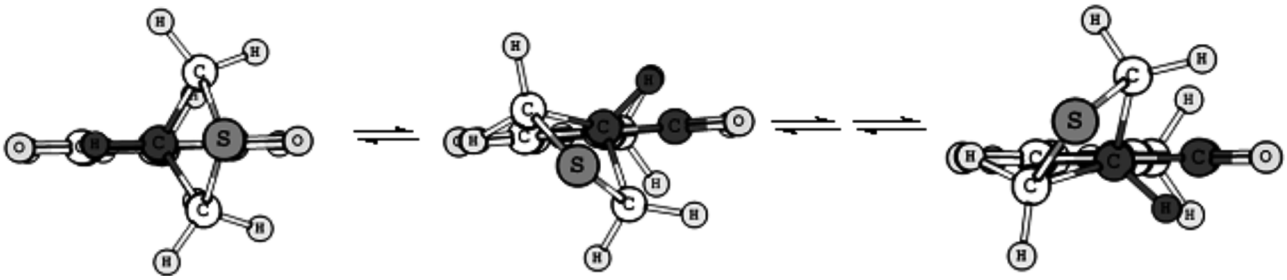
Fig. 2. Energy profile for the internal rotation of thietanyl group about the N–C bond in ethyl 2-[3-(1,1-dioxo-λ^6-thietan-3-yl)-6-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl]acetate (**5**) with respect to the torsion angle $C^4N^3C^{3'}H^{3'}$ at 0 K.

Scheme 2.



1 **2** **4** **5**

Scheme 3.



A **B** **C**

thermodynamically stable? For this purpose, thermodynamic parameters of internal rotation of the thietanyl group about the N–C bond in molecules **2** and **3** were determined by the PBE/3ζ, B3LYP/6-31G++(*d*,*p*) (ORCA [8]), and MP2/6-31G++(*d*,*p*) quantum chemical calculations (GAMESS [9]). A typical energy profile for isomer **2** (PBE/3ζ) is shown in Fig. 2. The potential curve contains several minima, among which the global minimum corresponds to structure **A**. Among several energy maxima, the highest ones correspond to energy-degenerate conformers **B** and **C** (Scheme 3).

Table 2 contains the calculated relative energies of the global minimum (**A**) and maximum (**B**) for each isomer (Δ**AB**), as well as the differences in the energies of the global minima and maxima ΔΔ**AA** and ΔΔ**BB** for isomers **2** and **3**, respectively. It seen that

Table 2. Energy parameters of internal rotation of the thietanyl group in isomers **2** and **3**

Structure	Computational method	$-E_0$,[a] hartree	ΔE°_0, kcal/mol ($\Delta E^{\neq}_0$)[b]	ΔH°_{298}, kcal/mol ($\Delta H^{\neq}_{298}$)[b]	ΔG°_{298}, kcal/mol ($\Delta G^{\neq}_{298}$)[b]	ΔS°_{298}, cal × mol^{-1} K^{-1} ($\Delta S^{\neq}_{298}$)[b]	$\Delta\Delta E^\circ_0$, kcal/mol ($\Delta\Delta E^{\neq}_0$)[c]	$\Delta\Delta H^\circ_{298}$, kcal/mol ($\Delta\Delta H^{\neq}_{298}$)[c]	$\Delta\Delta G^\circ_{298}$, kcal/mol ($\Delta\Delta G^{\neq}_{298}$)[c]
2A	PBE/3ζ	968.264044	0	0	0	0	0	0	0
2B	PBE/3ζ	968.258164	(3.69)	(3.21)	(4.55)	(–4.49)	0	0	0
2A	B3LYP/6-31G++(*d*,*p*)	968.892443	0	0	0	0	0	0	0
2B	B3LYP/6-31G++(*d*,*p*)	968.886384	(3.80)	(3.32)	(4.61)	(–4.32)	0	0	0
2A	MP2/6-31G++(*d*,*p*)	966.680572	0	0	0	0	0	0	0
2B	MP2/6-31G++(*d*,*p*)	966.673823	(4.24)	(3.66)	(5.30)	(–5.52)	0	0	0
3A	PBE/3ζ	968.258443	0	0	0	0	3.51	3.30	3.80
3B	PBE/3ζ	968.249442	(5.65)	(5.13)	(6.57)	(–4.83)	(5.47)	(5.22)	(5.82)
3A	B3LYP/6-31G++(*d*,*p*)	968.886235	0	0	0	0	3.90	3.67	4.22
3B	B3LYP/6-31G++(*d*,*p*)	968.876641	(6.02)	(5.49)	(6.89)	(–4.67)	(6.11)	(5.84)	(6.50)
3A	MP2/6-31G++(*d*,*p*)	966.675361	0	0	0	0	3.27	3.38	2.93
3B	MP2/6-31G++(*d*,*p*)	966.665815	(5.99)	(5.45)	(6.94)	(–5.02)	(5.03)	(5.17)	(4.58)

[a] With correction for zero-point vibrational energy.
[b] Relative to the global minimum on the PES for the given isomer.
[c] Relative to the global minimum or transition state on the PES for isomer **2**.

the barrier to internal rotation ($\Delta G^{\neq}_{298}$) of the thietanyl group in molecule **2** does not exceed 5.3 kcal/mol. Conformation **A** of molecule **2** is more stable than conformer **A** of isomer **3**; the latter is also characterized by a higher barrier to internal rotation $\Delta\Delta$**BB**. Therefore, it may be presumed that the reaction **1** → **2** is thermodynamically controlled.

EXPERIMENTAL

Computer simulation of internal rotation of the thietanyl group in molecules **2** and **3** was carried out by scanning the torsion angle $C^4N^3C^{3'}H^{3'}$ in the range from 0 to 360° in terms of the PBE/3ζ, B3LYP/6-31G++(*d*,*p*), and MP2/6-31G++(*d*,*p*) approximations. The potential barriers were determined by the transition state search algorithm which localized the highest energy maximum (conformer **B**). Stationary points on the PES were identified as minima (conformer **A**) by the absence of imaginary frequencies in the corresponding Hessian matrix, and as transition state (**B**), by the presence of one imaginary frequency therein.

The X-ray diffraction data for compound **5** were obtained at 293(2) K on an XCalibur Eos automated four-circle diffractometer (Mo K_α radiation, λ 0.71073 Å, graphite monochromator, ω-scanning, $2\theta_{max}$ = 62.3°). The data were acquired and processed using CrysAlis^{Pro} (version 1.171.36.20, Oxford Diffraction). The structure was solved by the direct method and was refined by the full-matrix least-squares method in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were localized from the Fourier difference maps and were refined in isotropic approximation. The calculations were performed using SHELX97 software [10]. Crystallographic data: $C_{12}H_{16}N_2O_6S$; monoclinic crystal system, space group $P2_1/c$; unit cell parameters: a = 10.6110(5), b = 17.6870(7), c = 8.1477(4) Å; β = 111.840(6); V = 1419.39(12) Å^3; Z = 4, d_{calc} = 1.480 g/cm^3; μ = 0.258 mm^{-1}; F(000) = 664.0; θ range 4.606–62.292°; $-8 \le h \le 15$, $-11 \le k \le 25$, $-11 \le l \le 10$; 3319 reflections were used for structure refinement (R_{int} = 0.0166); 192 refined parameters; goodness of fit 1.060; final divergence factors R_1 = 0.0439, wR_2 = 0.1155 [(reflections with $I_{hkl} > 2\sigma(I)$], R_1 = 0.0544, wR_2 = 0.1240 (all independent reflections). The crystallographic data for compound **5** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1572632).

The ^{1}H NMR spectrum was recorded on a Bruker AM-500 spectrometer using tetramethylsilane as internal standard. The IR spectrum was measured in the frequency range 700–3500 cm^{-1} on a Bruker Vertex 70V spectrometer from a sample prepared as thin film. The purity of compound **5** was checked by TLC on Silufix plates using ethyl acetate or chloroform–ethyl acetate as eluent. Spots were visualized under UV light and by treatment with iodine vapor.

6-Methyl-3-(thietan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (2) was described in detail in [5], where it was erroneously assigned isomeric structure **3**.

3-(1,1-Dioxo-λ^6-thietan-3-yl)-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (4) was described in [6], where it was erroneously assigned the structure of 1-(1,1-dioxo-λ^6-thietan-3-yl)-6-methylpyrimidine-2,4(1*H*,3*H*)-dione.

Ethyl 2-[3-(1,1-dioxo-λ^6-thietan-3-yl)-6-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl]acetate (5). A suspension of 4.6 g (20 mmol) of compound **3** and 4.14 g (30 mmol) of finely ground calcined potassium carbonate in 125 mL of acetonitrile was refluxed for 30 min. Ethyl chloroacetate, 2.45 g (20 mmol), was added, the mixture was refluxed for 2 h, an additional 1.23 g (10 mmol) of ethyl chloroacetate was added, and the mixture was refluxed for 5 h more. The mixture was cooled, and the precipitate was filtered off and washed with acetonitrile. The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol. Yield 79%, mp 153–154°C, R_f 0.41 (EtOAc), 0.72 ($CHCl_3$–EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 1742 s (C=O), 1711 s (C^2=O), 1653 m, 1626 s (C^4=O, C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.22 t (3H, $OCH_2C\mathbf{H}_3$, ^3J = 7.1 Hz), 2.19 s (3H, 6-CH_3), 4.18 q (2H, $OC\mathbf{H}_2CH_3$, ^3J = 7.1 Hz), 4.30–4.38 m [2H, $S(CH)_2$], 4.67 s (2H, 1-CH_2), 4.82–4.90 m [2H, $S(CH)_2$], 5.59–5.71 m (1H, 3-CH), 5.78 s (1H, 5-H).

The structural studies of acetate **5** were performed at the *Agidel* Joint Center (Institute of Petrochemistry and Catalysis, Russian Academy of Sciences). This study was performed under financial support by the Ministry of Education and Science of the Russian Federation (project no. 16.1969.2017/4.6).

REFERENCES

1. Belikov, V.G., *Farmatsevticheskaya khimiya* (Pharmaceutical Chemistry), Moscow: MEDpress-inform, 2008, 2nd ed.
2. Rakhimov, A.I., Kameneva, I.Yu., Navrotskii, M.B., Titova, E.S., and Kudashev, S.V., *Russ. J. Gen. Chem.*, 2008, vol. 78, p. 971.

3. Block, E., *Comprehensive Heterocyclic Chemistry*, Katritzky, A.R. and Rees, C.W., Eds., Oxford: Pergamon, 1984, vol. 7, p. 403.
4. Fokin, A.V. and Kolomiets, A.F., *Khimiya tiiranov* (Chemistry of Thiiranes), Moscow: Nauka, 1978, p. 130.
5. Kataev, V.A., Meshcheryakova, S.A., Lazarev, V.V., and Kuznetsov, V.V., *Russ. J. Org. Chem*., 2013, vol. 49, p. 743.
6. Meshcheryakova, S.A., Kataev, V.A., Munasipova, D.A., and Fattakhova, I.Ya., *Russ. J. Gen. Chem*., 2014, vol. 84, p. 865.
7. Laikov, D.N. and Ustynyuk, Yu.A., *Russ. Chem. Bull., Int. Ed*., 2005, vol. 54, p. 820.
8. ORCA version 2.9. http//www.thch.uni-bonn.de
9. Schmidt, M.W., Baldridge, K.K., Boatz, J.A., Elbert, S.T., Gordon, M.S., Jensen, J.H., Koseki, S., Matsunaga, N., Nguyen, K.A., Su, S., Windus, T.L., Dupuis, M., and Montgomery, J.A., *J. Comput. Chem*., 1993, vol. 14, p. 1347.
10. Sheldrick, G.M., *Acta Crystallogr., Sect. A*, 2008, vol. 64, p. 112.