Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(6):22-27

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of 5-methyl-4-thio-6-(1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidines and their antimicrobial activity study

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ABSTRACT

Interaction of 5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid with benzohydrazide promoted by 1,1'-carbonyldiimidazole leads to N'-benzoyl-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbohydrazide. The cyclization of the hydrazide with phosphorous oxychloride resulted in the unstable 4-chloro-5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-d]pyrimidine, which formed 5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-d]pyrimidine-4(3H)-thione after reaction with thiourea in dimethylformamide. All of the compounds tested showed moderate unspecific antimicrobial activity against the strains of bacteria and fungi similar to Synthomycine an higher then Streptomycin against Proteus vulgaris and Pseudomonas aeruginosa.

Keywords: thiophene, pyrimidine, cyclization, oxadiazole, alkylation.

INTRODUCTION

The derivatives of 5-methylthieno[2,3-*d*]pyrimidine-4(3*H*)-one are of the great interest as the compounds with antifungal activity [1] or as the drugs to cure and prevent cerebral ischemia [2]. Some of the thieno[2,3-d]pyrimidines are calcium channels blockers [3], while the other ones are inhibitors of Mnk1 or Mnk2 kinase and may be applied to cure diabetes and cancer [4].

Moreover the derivatives of 4-thiothieno[2,3-*d*]pyrimidines are also known as biologically active compounds, for example as tumor necrosis α-factor inhibitors [5]. Evaluation of the inhibitors on seven protein kinases revealed considerable selectivity towards of some of substituted (thieno[2,3-*d*]pyrimidin-4-ylthio)carboxylic acids CK2 [6]. 4-Thiothieno[2,3-*d*]pyrimidine-6-carboxylic acids are patented as PDE9 inhibitors [7]; some of the relative compounds with alkoxy group in position 2 are antimicrobial agents useful for protect agricultural plants from pathogenic bacteria and fungi [8]. The compounds from thieno[2,3-*d*]pyrimidine range are also known to be active against *E.Coli* [9].

But the only one publication devoted to 6-oxadiazolyl-5-methylthieno[2,3-*d*]pyrimidine-2,4-diones, which were reported as A2A adenosine receptor antagonists was published [10]. In view of that we focused our efforts on the synthesis 5-methyl-4-thio-6-(1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidines, as the novel and potentially biologically active heterocycles.

EXPERIMENTAL SECTION

Melting points (°C) were measured with a with a Koeffler melting point apparatus and were not corrected. Elemental analysis were within ±0.4% of the theoretical value. IR spectra were recorded on FT-IR Bruker tensor-27 spectrometers in KBr. ^{1}H and ^{13}C NMR spectral data were recordered at 200 and 75 MHz respectively on Varian Mercycry-200 and Varian Geminy-300 spectrometers using TMS as an internal standard. Mass-spectral analyses were obtained on a PE SCIEX API 150EX device equipped with mass spectrometer.

5-Methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylate 1, 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbohydrazide 2, and 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid 3 were obtained according to the known methods [11,12].

Procedure for preparation of *N*'-benzoyl-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbohydrazide 4.

Method A: to the mixture of 2 mmole of 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbohydrazide **3** and 2 mmole of dried potassium carbonate in 10 ml of 1,4-dioxane 2.1 mmole of benzoyl chloride was added. The mixture was stirred at 50-70°C for 5 hours. Then it was quenched with water 40 ml. The resulted precipitate was filtered off and dried.

Method B: to the suspension 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid **1** (0.0095 mole) in DMF 10 ml 1,1-carbonyldiimdazole (0.01 mole) was added. The mixture was heated at 100°C for 20 minutes and then cooled. Then 0.0095 mol of benzohydrazide was added and the mixture was stirred at 50-70°C for 3-5 hours. After the reaction mixture was cooled and 40 ml of water was added; the precipitate formed was filtered off, washed with plenty of water and dried.

This compound was obtained in 78% (**method A**) and 85 % (**method B**) yield as a white solid, mp > 300˚C ; IR (cm^{-1}): 3290, 3061, 2937, 2869, 1906, 1688, 1643, 1602, 1579, 1525, 1486, 1379, 1320, 1294, 1255, 1155, 1093, 1027, 1002, 987, 929, 899, 872, 798, 787, 758, 716, 693, 676, 590, 553, 520, 461; ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.57 (3H, s, CH_3); 7.20 (3H, m, 3-H+4-H+5-H); 7.57 (2H, m, 2-H+6-H); 7.76 (1H, s, CH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.24, 123.56, 125.12, 127.51, 128.59, 131.98, 132.45, 137.76, 147.58, 158.38, 161.77, 164.54, 165.76; lcms: m/z (MH^+) 329. Anal. calcd. for $C_{15}H_{12}N_4O_3S$: H, 3.68; C, 54.87; N, 17.06; S, 9.77. Found: H, 3.42; C, 54.99; N, 17.15; S, 9.85.

Procedure for preparation of 5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidine-4(3*H*)-thione 6.

To 4 g of *N*'-benzoyl-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbohydrazide **4** 25 ml of phosphorous oxychloride was added. The reaction mixture was boiled for 2-3 hours until formation of the clear solution. Then the excess of $POCl_3$ was distilled off and crashed ice was added to the cold residue. The precipitate formed was filtered off and used as the crude product for further transformations. The dried at 40˚C crude solid of **5** (3 g) to the mixture of thiourea (0.8 g) and DMF 10 ml was added. The reaction mixture was heated at 130˚C for 2 hours and then cooled. The reaction was quenched with water (60 ml) and the precipitated formed was filtered off and dried.

This compound was obtained in 77% as a yellow solid, mp >300˚C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.11 (3H, s, CH_3); 7.52 (3H, m, 3H+4H+5H); 7.97 (2H, m, 2H+6H); 8.19 (1H, s, CH); 13.95 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 17.53, 116.62, 122.95, 126.76, 129.53, 131.88, 132.27, 140.01, 146.19, 160.26, 163.69, 163.82, 179.87; lcms: m/z (MH^+) 326. Anal. calcd. for $C_{15}H_{10}N_4OS_2$: H, 3.09; C, 55.20; N, 17.17; S, 19.65. Found: H, 3.18; C, 55.07; N, 17.42; S, 19.83.

General procedure for preparation of 5-methyl-4-(alkylthio)-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*] pyrimidines 7 a-e.

To the suspension of 5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidine-4(3*H*)-thione **6** (1 mmole) in 5 ml of DMF 1.1 mmole of triethylamine and 1 mmol of corresponding alkylating agent were added. The mixture was stirred at 90°C for 3-5 hours. Then the reaction mixture as quenched with water and precipitate formed was filtered off.

Physical and spectral data of the products 7

5-Methyl-4-(methylthio)-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidine 7a.

This compound was obtained in 56% yield as a beige solid, mp 210-212˚C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.64 (3 H, s, SCH_3), 3.03 (3 H, s, CH_3), 7.51 (3 H, m, H-3+ H-4+H-5), 8.08 (2 H, m, H-2+H-6), 8.87 (1 H, s, CH); lcms: m/z (MH^+) 341. Anal. calcd. for $C_{16}H_{12}N_4OS_2$: H, 3.55; C, 56.45; N, 16.46; S, 18.84. Found: H, 3.67; C, 56.38; N, 16.78; S, 19.02.

4-(Benzylthio)-5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidine 7b.

This compound was obtained in 79% yield as a yellowish solid, mp 215-217˚C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.04 (3 H, s, CH_3), 4.67 (2 H, s, CH_2), 7.28 (3 H, m, H-3'+ H-4'+H-5'), 7.47 (2 H, m, H-2'+H-6'), 7.62 (3 H, m, H-3+ H-4+H-5), 8.07 (2 H, m, H-2+H-6), 8.89 (1 H, s, CH); ^{13}C NMR (75 MHz, DMSO-d_6): 16.61, 33.52, 123.09, 126.92, 127.39, 128.56, 129.21, 129.48, 132.29, 134.90, 136.79, 153.33; lcms: m/z (MH^+) 416. Anal. calcd. for $C_{22}H_{16}N_4OS_2$: H, 3.87; C, 63.44; N, 13.45; S, 15.40. Found: H, 3.98; C, 63.12; N, 13.62; S, 15.67.

4-[(4-Chlorobenzyl)thio]-5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidine 7c.
This compound was obtained in 84% yield as a beige solid, mp 204-206˚C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.03 (3 H, s, CH_3), 4.66 (2 H, s, CH_2), 7.38 (2 H, d, J = 8.5 Hz, H-3'+ H-5'), 7.53 (2 H, d, J = 8.5 Hz, H-2'+H-6'), 7.68 (3 H, m, H-3+ H-4+H-5), 8.07 (2 H, m, H-2+H-6), 8.94 (1 H, s, CH); ^{13}C NMR (75 MHz, DMSO-d_6): 16.56, 32.68, 118.13, 123.07, 126.90, 128.17, 128.48, 129.45, 131.00, 132.28, 134.77, 136.10, 153.27, 160.30, 164.12, 166.04. lcms: m/z (MH^+) 451. Anal. calcd. for $C_{22}H_{15}ClN_4OS_2$: H, 3.35; C, 58.59; N, 12.42; S, 14.22. Found: H, 3.18; C, 58.44; N, 12.75; S, 14.34.

4-[(4-Fluorobenzyl)thio]-5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidine 7d.
This compound was obtained in 81% yield as a beige solid, mp 198-200 ˚C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.99 (3 H, s, CH_3), 4.68 (2 H, s, CH_2), 7.15 (2 H, t, J = 8.8 Hz, H-2'+ H-6'), 7.62 (5 H, m, H-2'+H-6'+H-3+ H-4+H-5), 8.04 (2 H, m, H-2+H-6), 8.89 (1 H, s, CH); ^{13}C NMR (75 MHz, DMSO-d_6): 16.55, 32.69, 115.13, 115.41, 118.08, 123.05, 126.88, 128.12, 129.44, 131.23, 132.26, 133.11, 134.82, 153.27, 160.29, 163.26, 164.11, 166.20; lcms: m/z (MH^+) 435. Anal. calcd. for $C_{22}H_{15}FN_4OS_2$: H, 3.48; C, 60.81; N, 12.89; S, 14.76. Found: H, 3.57; C, 61.07; N, 12.85; S, 14.82.

***N*-(2,4-Difluorophenyl)-2-{[5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]thio}acetamide 8e.** This compound was obtained in 92% yield as a beige solid, mp 246-248 ˚C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.08 (3 H, s, CH_3), 4.38 (2 H, s, CH_2), 7.02 (2 H, t, J = 9.1 Hz, H-5'), 7.30 (2 H, m, H-3'), 7.61 (3 H, m, H-3+ H-4+H-5), 7.78 (2 H, m, H-2'), 8.06 (2 H, m, H-2+H-6), 8.84 (1 H, s, CH); ^{13}C NMR (75 MHz, DMSO-d_6): 16.55, 34.07, 104.39, 111.20, 118.29, 123.08, 126.94, 128.34, 129.47, 132.30, 134.76, 153.17, 160.31, 164.17, 165.88, 166.20; lcms: m/z (MH^+) 496. Anal. calcd. for $C_{23}H_{15}F_2N_5O_2S_2$: H, 3.05; C, 55.75; N, 14.13; S, 12.94. Found: H, 3.15; C, 55.61; N, 14.24; S, 13.12.

Antimicrobial activity study
According to the WHO recommendations [13-18] the following microorganisms test-strains have been used *Staphylococcus aureus* ATCC 25923, *Esherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* ATCC 4636, *Bacillis subtilis* ATCC 6633, *Candida albicans* ATCC653/885. Bacterial concentration was 10^7 CFU/ml (determined by McFarland standard). Overnight cultures kept for 18-24 h at 36ºC ± 1ºC were used. The bacterial suspension was inoculated onto the entire surface of a Mueller-Hinton agar (Dagestan Scientific research institute of nutrient media). The compounds were introduced to the wells in the form of DMSO solution in concentrations 100 μg/ml; the open wells were filled with 0.3 ml of the solution.

For evaluation of antimicrobial activity the following criteria were used: in the case of inhibition zone absence or its diameter less then 10 mm either the bacteria strains were considered to be resistant or the concentration of the tested compound rather low for inhibition effect; the diameter of inhibition zone 10-15 mm — low sensitivity of the bacteria strain to the compound in the given concentration; the diameter of inhibition zone 15-25 mm was considered as the sign of the substance activity against the microorganism strain; the diameter of inhibition zone 25 mm or more was considered as the evidence of the high antimicrobial activity of the compound tested.

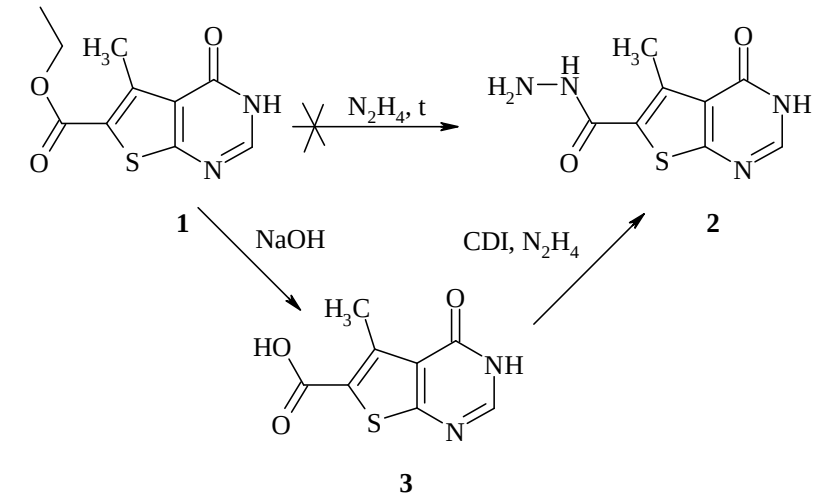
RESULTS AND DISCUSSION

The most common way for 1,3,4-oxadiazole preparation is cyclization of diacyl hydrazides [19-23]. The authors of patent [10] described the synthesis of 5-methylthieno[2,3-*d*]pyrimidine-2,4-dione-6-carboxyxlic acid hydrazide preparation by reaction of the corresponding ester with hydrazine hydrate at 120°C (1-6 hours). We similarly tried to obtain 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid hydrazide **2** by hydrazinolysis of ester **1**, but the only products of molecule destruction were isolated. Therefore, we used the other synthetic route based on milder reaction of easily available 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid **3** [11] with hydrazine hydrate, promoted by 1,1-carbonyldiimidazole (scheme 1). Unfortunately isolation of hydrazide **2**, because of its high solubility, required DMF distillation, which was inconvenient [12]. The other disadvantages of this method were low yield and purity of the hydrazide **2** in some cases.

The further investigations showed that the better way to product **4** was a direct interaction of generated *in situ* 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid imidazolide with benzohydrazide (scheme 2). This method allowed us to obtain compound **4** in high yield and purity right from the acid **3** in one step.

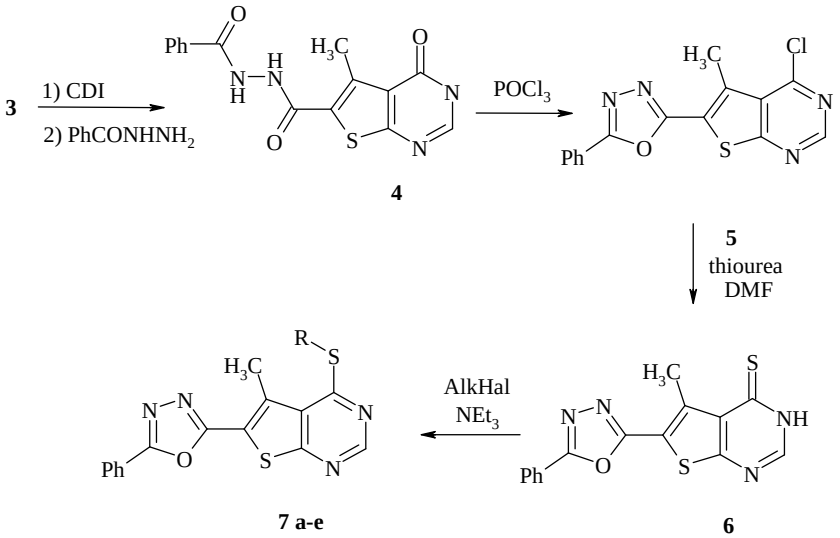
Cyclyzation of **4** has been carried out by reflux in phosphorous oxychlode at stirring. The product **5** formed crystals after distillation of $POCl_3$ and addition of ice. However the spectrum of **5** in DMSO-d_6 showed the mixture of two compounds with one singlet of CH at 8.20 ppm and the other at 8.98 ppm. Probably destruction of compound **5** was caused by its partial hydrolysis with the traces of water. It appeared to be impossible to identify compound **5** as

individual one. The reaction between 4-chlorothieno[2,3-*d*]pyrimidines and thiourea is a good way to thieno[2,3-d]pyrimidine-4-thiones [7,9,24,25]. Therefore we treated compound **5** with thiourea at heating in DMF. This experiment resulted the compound with NH proton signal at 13.97 ppm, while its LC/MS showed quasi-molecular ion peak at 326, which confirmed formation of 5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidine-4(3*H*)-thione **6**.



1 **2** **3**

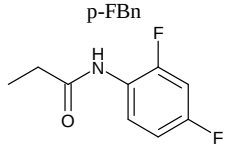
Scheme 1. 5-Methylthieno[2,3-*d*]pyrimidine-2,4-dione-6-carboxyxlic acid hydrazide preparation



3 **4** **6** **7 a-e**

Scheme 2. Synthesis and transformations of 5-methyl-4-thio-6-(1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidines

Table 1. 5-Methyl-4-(alkylthio)-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-d]pyrimidines 7 a-e

Compnd. №	R	Yield, %*	lcms, m/z (MH^+)
7a	Me	56	341
7b	Bn	79	417
7c	p-ClBn	84	451
7d	p-FBn	81	435
7e		92	496

** Yield in alkylation step is given*

The alkylation of compound **6** with different halides in DMF-trethylamine system resulted in the compounds **7a-e** (table 1). All the ^{1}H NMR spectra of compounds **7** contain the signals of alkyl radicals CH_3 at 4.67 ppm for **7a**, and CH_2 in the range 4.38-4.68 ppm for **7b**-**7e** (Table 1).

The screening of antimicrobial activity for the compounds **6** and **7a- e** was performed by agar well diffusion method; the data is presented in table 2. Most of the compounds tested showed moderate antimicrobial activity, but it could be seen that S-alkylation increases the activity, especially for compound with the halogen in benzyl fragment (Table 2).

Table 2. Antimicrobial activity of 5-methyl-4-thio-6-(1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidines 6, 7a- e (concentration 100 µg/ml) *

Compnd. №	*Staphylococcus aureus ATCC 25923*	*Esherichia coli ATCC 25922*	*Pseudomonas aeruginosa ATCC 27853*	*Proteus vulgaris ATCC 4636*	*Bacillis subtilis ATCC 6633*	*Candida albicans ATCC 653/885*
6	++	++	-	++	++	+
7a	++	++	++	++	++	++
7b	++	++	++	+	+	+
7c	+	++	++	++	++	++
7d	+	++	++	++	++	++
7e	+	++	+	++	++	++
Str.**	++	++	-	-	++	-
Synt. **	+	++	++	++	++	-

** – - diameter of growth inhibition zone less than 10 mm; + - diameter of growth inhibition zone 10-15 mm; ++ - diameter of growth inhibition zone 15-25 mm; +++ - diameter of growth inhibition zone more than 25 mm.*

*** concentration of antibiotics 30 µg/ml; **Str**. — streptomycine (H_2O solution); **Synt. —** synthomycine (H_2O solution);*

CONCLUSION

A convenient and effective method for synthesis of 5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-d]pyrimidine-4(3H)-thione has been developed. By the alkylation of the corresponding thione in dimethylformamide with alkylating agents the series of 5-methyl-4-alkylthio-6-(1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidines was obtained. All of the compounds tested showed moderate unspecific antimicrobial activity against the strains of bacteria and fungi similar to Synthomycine an higher than Streptomycin against *Proteus vulgaris* and *Pseudomonas aeruginosa*.

Acknowledgement
Authors gratefully acknowledge Tatyana P. Osolodchenko the Head of microorganism biochemistry and nutrient media laboratory of Institute microbiology and immunology n.I.I.Mechnikov NAMS of Ukraine for the microbiological experiment.

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