REACTIONS OF 5-(4,6-DIMETHYL-2-PYRIMIDINYL)-1,3,4-OXADIAZOLE-2(3*H*)-THIONE WITH *N*-NUCLEOPHILES

G. Mekuskiene*, J. Dodonova, M. M. Burbuliene and P. Vainilavicius
Department of Organic Chemistry, Faculty of Chemistry, Vilnius University,
Naugarduko 24, Vilnius LT-03225, Lithuania
e-mail: giedrute.mekuskiene@chf.vu.lt

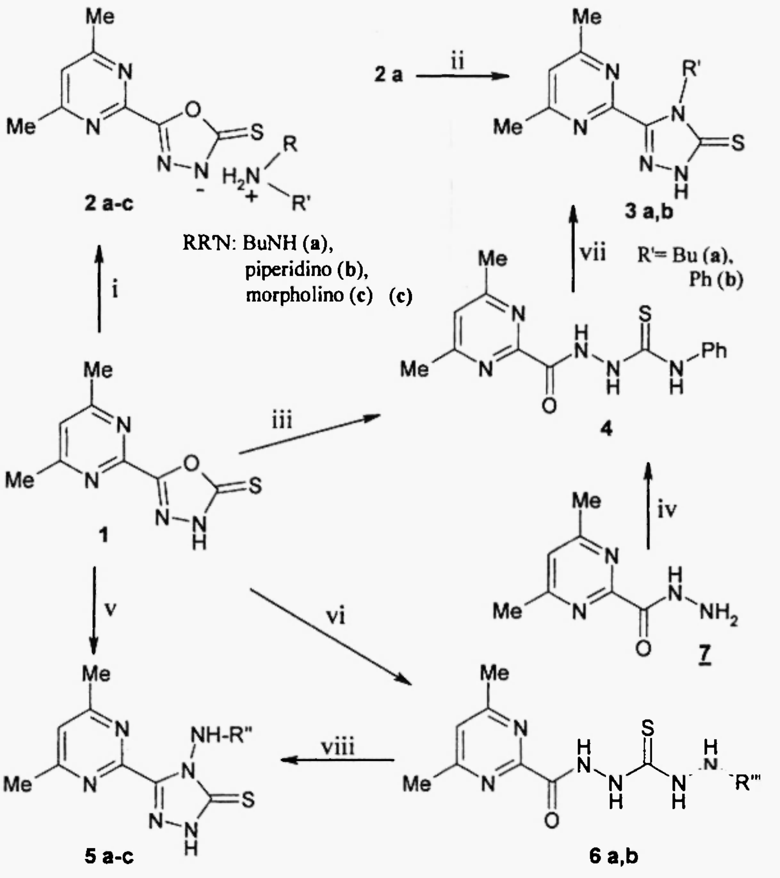
Abstract : Reactions of 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2(3*H*)-thione (**1**) with *N*-nucleophiles – butylamine, aniline, piperidine, hydrazine hydrate, ethyl-, phenyl- and acetylhydrazine was studied. Oxadiazolethione **1** formed salts **2a-c** with butylamine, piperidine and morpholine in ethanol at reflux. In chlorobenzene at reflux **2a** underwent recyclization reaction to give triazolethione **3a**. Treatment of **1** with aniline, phenyl- or acetylhydrazine gave rise to the ring opening to form phenylthiosemicarbazide **4** or thiocarbohydrazides **6a,b**, respectively. Heating **4** or **6a** in 10-20% potassium hydroxide afforded 5-(4,6-dimethyl-2-pyrimidinyl)-4-phenyl(or aminophenyl)-2,4-dihydro-1,2,4-triazole-3-thiones (**3b, 5c**). Interaction of oxadiazolethione **1** with hydrazine hydrate or ethylhydrazine led to the recyclisation reaction to form triazolethiones **5a,b**.

Introduction

5-Substituted 1,3,4-oxadiazole-2(3*H*)-thiones are a subject of chemical studies due to their ability to react both with electrophilic and nucleophilic reagents. In addition, 1,3,4-oxadiazole-2(3*H*)-thione derivatives are interesting for their diverse biological activity. Such compounds exhibit fungicidal[1], antibacterial[2-4], anti-inflammatory[5-7] or antimicrobial[8-10] activity. Moreover, some of them are reported as P-Glycoprotein inhibitors[11] or antivirals[10]. Earlier[5] we studied reactions of 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2(3*H*)-thione (**1**) with electrophilic reagents. In continuation of our interest in pyrimidine moiety containing 1,3,4-oxadiazole-2(3*H*)-thione chemistry, in this paper we report on the study of interaction of oxadiazolethione **1** with some *N*-nucleophiles.

Results and Discussion

In ethanol at reflux oxadiazolethione **1** reacted with primary and secondary amines (butylamine, morpholine and piperidine) like NH-acid to give salts **2a-c** (Scheme 1). The salt **2a** under heating underwent recyclisation into 1,2,4-triazole-3-thione **3a.** Under treatment with aniline the ring opening of the oxadiazolethione **1** occurred to form 1-(4,6-dimethyl-2-pyrimidinylcarbonyl)-4-phenylthiosemicarbazide (**4**). The yield of **4** is higher and the reaction is faster in butanol at reflux (15 min.) than in dioxane solution (4 h). Interaction of oxadiazolethione **1** with phenyl- or acetylhydrazine led to the ring opening reaction as well. In this case 5-phenyl(or acetyl)-1-(4,6-dimethyl-2-pyrimidinylcarbonyl)thiocarbohydrazides (**6a,b**) were obtained. Interaction of thiosemicarbazide 4 or thiocarbohydrazide **6a** with 10-20% potassium hydroxide gave rise to the cyclisation reaction to form 4-phenyl(or phenylamino)-1,2,4-triazole-3-thiones **3b**, **5c**. Oxadiazolethione **1** under treatment with hydrazine hydrate in butanol or dioxane at reflux underwent recyclization reaction to give 4-amino-5-(4,6-dimethyl-2-pyrimidinyl)-2,4-dihydro-(3*H*)-1,2,4-triazole-3-thione (**5a**). Use of butanol in this reaction is more expedient versus dioxane because the reaction time is shorter and the yield of **5a** is higher. Recyclisation reaction of **1** with ethylhydrazine to give 4-ethylamino-5-(4,6-dimethyl-2-pyrimidinyl)-2,4-dihydro(3*H*)-1,2,4-triazole-3-thione (**5b**) was performed in butanol at reflux.



Scheme-1

Reagents and conditions: i – H_2NBu (**a**), piperidine (**b**), morpholine (**c**), EtOH, Δ; ii – ClPh, Δ; iii - H_2NPh, dioxane or BuOH, Δ; iv – PhNCS, EtOH, Δ; v – $N_2H_4 \cdot H_2O$ (**a**), NH_2NHEt (**b**), BuOH, Δ; vi - NH_2NHPh (**a**), dioxane, Δ; NH_2NHAc (**b**), dioxane or BuOH, Δ; vii – 20% KOH (**b**), Δ; viii - 10% KOH (**a**), Δ;

It should be mentioned that the ring opening and recyclisation reactions of oxadiazolethione **1** proceeded with the formation of complex mixtures. Therefore the yields of isolated compounds were not high and identification of some substances was not successful.

The structure assignments of the synthesized compounds are based on their IR ^1H and ^{13}C NMR spectral data. The IR spectrum of the salt **2a** shows absorption band of $^+NH_3$ at 3022 cm^{-1}. The $^+NH_2$ group of **2b,c** absorbs in the region of 2754-2767 cm^{-1}. Furthermore, the C=S group absorption in the IR spectra of the salts **2a-c** is observed in the same range (1342-1344 cm^{-1}) as that of oxadiazolethione **1** (1347 cm^{-1})[5]. The C=S group absorption bands of triazolethiones **5a-c** are also found in the region of 1340-1345 cm^{-1}. Thiosemicarbazide **4** and thiocarbohydrazides **6a,b** show characteristic C=O group absorption in the region of 1675-1690 cm^{-1} and the absorption of C=S group is observed at 1254-1311 cm^{-1}. Along with the spectral data the structure of **4** was also confirmed by its alternate synthesis from 4,6-dimethyl-2-pyrimidinecarbohydrazide (**7**)[12] and phenylisothiocyanate. In the ^1H NMR spectra of **6a,b** two signals of NH group protons are observed in the region of 9.86-10.09 ppm (NHCSNH) and at 10.49-10.54 ppm (CONH).

The signal of NH group proton of oxadiazolethione 1 ring appears at 14.96 ppm[5], and that of triazolethiones **3a,b** and **5a-c** is upfield shifted and is observed at 13.89-14.33 ppm. The peaks of amino group protons of **5a,b** are observed at 6.39 and 6.51 ppm respectively and the analogous NH proton of **5c** absorbs in the downfield region at 9.15 ppm. The ^{13}C NMR spectra of the synthesized compounds are in accordance with proposed structures.

Conclusions

In summary, oxadiazolethione **1** with aliphatic amines formed salts **2a-c**, with aromatic amine – aniline, phenyl- and acetylhydrazine underwent ring opening reaction to give thiosemicarbazide **4** or thiocarbohydrazides **6a,b** and with hydrazine hydrate or ethylhydrazine was recyclized to 4-amino-1,2,4-triazole-3-thione derivatives **5a,b**.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in KBr discs on a Perkin Elmer FT spectrophotometer Spectrum BX II (v, cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Inova spectrometer (300 and 75 MHz, respectively) in DMSO-d$_6$ solutions, chemical shifts are expressed in δ, ppm relative TMS. All reactions and purity of the synthesized compounds were monitored by TLC on Silica gel 60 F$_{254}$ plates (Merck), in the system methanol-ethyl acetate (1:3), visualized by UV light. Abbreviations: triazole – tr, pyrimidine – pyr, oxadiazole – ox.

5-(4,6-Dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2(3*H*)-thione 1 was synthesized according ref.[5].

5-(4,6-Dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2(3*H*)-thione ammonium salts 2a-c. ***General procedure.*** To a solution of oxadiazolethione **1** (0.5 g, 2.4 mmol) in 15 ml of ethanol at 60 °C the corresponding amine (butylamine 0.18 g, piperidine 0.20 g or morpholine 0.21 g) was added. The reaction mixture was refluxed for 1 h. Then the solvent was removed by rotary evaporator, the residue was worked up with 10 ml of ether (for **2c** – with 10 ml of dioxane). The precipitate was recrystallized from dioxane to give compounds **2a-c**.

5-(4,6-Dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2(3*H*)-thione butylammonium salt 2a: Yield 88%, m.p. 143-144 °C. IR: 3022 ($^+$NH$_3$), 1597 (C=N), 1550 (C=C), 1344 (C=S), 1175 cm^{-1} (C-O-C). ^{1}H-NMR: 0.90 (3H, t, *J* = 7.29 Hz, CH$_3$), 1.34 (2H, m, $\underline{CH_2}CH_3$). 1.52 (2H, m, $CH_2\underline{CH_2}CH_2$). 2.5 (6H, s, 2 CH$_3$), 2.79 (2H, m, NCH$_2$), 7.36 (1H, s, 5-H pyr), 7.63 ppm (3H, s, $^+$NH$_3$). ^{13}C NMR: 13.45 (CH$_3$), 19.04, 29.03, 38.6 (CH$_2$), 120.47 (C$_5$ pyr); 151.76 (C$_2$ pyr), 159.43 (C$_5$ ox), 167.35 (C$_{4,6}$ pyr), 179.93 ppm (C$_2$ ox). Anal. calcd. for $C_{12}H_{19}N_5OS$: C 51.22; H 6.80; N 24.88. Found: C 51.64; H 6.55; N 25.12.

5-(4,6-Dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2(3*H*)-thione piperidinium salt 2b: Yield 86%, m.p. 142-143 °C. IR: 2754 ($^+$NH$_2$), 1593 (C=N), 1555 (C=C), 1342 (C=S), 1105 cm^{-1} (C-O-C). ^{1}H NMR: 1.57-1.67 [6H, m, (CH$_2$)$_3$], 2.49 (6H, s, 2 CH$_3$), 3.05 [4H, t, *J* = 5.4, N(CH$_2$)$_2$], 7.30 (1H, s, 5-H pyr), 8.34 ppm (2H, br. s, H$_2$N$^+$). ^{13}C NMR: 22.35 (CH$_3$), 22.93, 24.13, 39.42, 44.49 (CH$_2$), 120.49 (C$_5$ pyr), 153.05 (C$_2$ pyr), 160.80 (C$_5$ ox), 167.85 (C$_{4,6}$ pyr), 181.91 ppm (C$_2$ ox). Anal. calcd. for $C_{13}H_{19}N_5OS$: C 53.22; H 6.53; N 23.87. Found: C 53.42; H 6.32; N 23.27.

5-(4,6-Dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2(3*H*)-thione morpholinium salt 2c: Yield 67%, m.p. 161-162 °C. IR: 2767 ($^+NH_2$), 1591 (C=N), 1559 (C=C), 1344 (C=S), 1104 cm^{-1} (C-O-C). ^{1}H NMR: 2.48 (6H, s, 2 CH_3), 3.14 [4H, m, $N(CH_2)_2$], 3.78 [4H, m, $O(CH_2)_2$], 7.29 (1H, s, 5-H pyr), 8.74 ppm (2H, br. s, H_2N^+). ^{13}C NMR: 24.14 (CH_3), 39.40, 43.65, 64.07 (CH_2), 120.39 (C_5 pyr), 153.13 (C_2 pyr), 160.95 (C_5 ox), 167.83 ($C_{4,6}$ pyr), 182.17 ppm (C_2 ox). Anal. calcd. for $C_{12}H_{17}N_5O_2S$: C 48.80; H 5.80; N 23.71. Found: C 48.79; H 5.61; N 23.90.

4-Butyl-5-(4,6-dimethyl-2-pyrimidinyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (3a). The salt **2a** (0.25 g, 0.89 mmol) was refluxed for 8 min. in 1 ml of chlorobenzene, then the mixture was rotary evaporated to dryness. The oily residue was worked with 2 ml of ethanol-water (1:2). The powder formed was filtered off, dried and recrystallized to give 0.03 g (13%) of **3a**, m.p. 220-221 °C [from ethanol-water (1:2)]. Ref.[13]: m.p. 220-221 °C (from benzene). IR: 3221 (NH), 1594 (C=C, C=N), 1353 cm^{-1} (C=S). ^{1}H NMR: 0.89 (3H, t, *J*= 7.27 Hz, CH_3), 1.31 (2H, m, $\underline{CH_2}CH_3$). 1.68 (2H, m, $\underline{CH_2}CH_2CH_3$). 2.51 (6H, s, 2 CH_3), 4.57 (2H, t, *J*= 6.2 Hz, NCH_2), 7.45 (1H, s, 5-H pyr), 14.16 ppm (1H, s, NH).

5-(4,6-Dimethyl-2-pyrimidinyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (3b). The mixture of phenylthiosemicarbazide **4** (0.25 g, 0.829 mmol) and 5 ml of 20% potassium hydroxide solution was refluxed under stirring for 5 h. After cooling to room temperature the reaction mixture was filtered off and acidified with conc. HCl to pH 5. The precipitate was filtered off and dried to give 0.06 g (39%) of **3b**, m.p. 275 °C. IR: 3222 (NH), 1598 (C=N), 1593 (C=C), 1498, 1342 cm^{-1} (C=S). ^{1}H NMR: 2.26 (6H, s, 2 CH_3), 7.28-7.48 (6H, m, Ph, 5-H pyr), 14.33 ppm (1H, s, NH tr). ^{13}C NMR: 23.87 (CH_3), 121.07 (C_5 pyr), 129. 07, 129.25, 129.38, 136.28 (C Ph), 149.13 (C_5 tr), 153.99 (C_2 pyr), 167.56 ($C_{4,6}$ pyr), 169.83 ppm (C_3 tr). Anal. calcd. for $C_{14}H_{13}N_5S$: C 59.34; H 4.62; N 24.72. Found: C 59.42; H 4.58; N 24.69.

1-(4,6-Dimethyl-2-pyrimidinylcarbonyl)-4-phenylthiosemicarbazide (4). ***Method A***. Aniline (0.34 g, 3.6 mmol) was added to a stirred solution of oxadiazolethione **1** (0.5 g, 2.4 mmol) in 15 ml of dry dioxane and the reaction mixture was refluxed for 4 h. After cooling the precipitate was filtered off. The filtrate was evaporated to dryness and worked up with ether to form an additional amount of compound. The precipitates were combined, dried and recrystallized to give 0.22 g (35%) of **4**, m.p. 210 °C (from dioxane).

Method B. Aniline (0.34 g, 3.6 mmol) was added to a stirred solution of oxadiazolethione **1** (0.5 g, 2.4 mmol) in **4** ml of dry butanol and the reaction mixture was refluxed for 15 min. The precipitate was filtered off, washed with ether and dried to give 0.46 g (64%) of **4**, m.p. 210°C (from dioxane).

Method C. Phenylisothiocyanate (0.6 g, 4.44 mmol) was added to a solution of hydrazide **7** (0.5 g, 3.0 mmol) in 15 ml of ethanol. The reaction mixture was refluxed under stirring for 6 h. The precipitate was filtered off, washed with ethanol, dried and recrystallized to give 0.6 g (66%) of **4**, m.p. 210 °C (from dioxane). IR: 3273, 3194 (NH), 1675 (C=O), 1596 (C=N), 1556 (C=C), 1299 cm^{-1} (C=S). ^{1}H NMR: 2.54 (6H, s, 2 CH_3), 7.17 (1H, t, *J* = 7.5 Hz, 4-H Ph), 7.35 (2H, t, *J* = 7.5 Hz, 3, 5-H Ph), 7.48 (3H, m, 5-H pyr, 2, 6-H Ph), 9.8 (2H, s, 2 NH), 10.75 ppm (1H, s, NH). ^{13}C NMR: 24.08 (CH_3), 122.46 (C_5 pyr), 125.59, 126.27, 128.73, 139.94 (C Ph), 157.29 (C_2 pyr), 163.07 (C=O), 167.67 ($C_{4,6}$ pyr), 181.25 ppm (C=S). Anal. calcd. for $C_{14}H_{15}N_5OS$: C 55.79; H 5.02; N 23.24. Found: C 55.94; H 5.23; N 23.17.

4-Amino-5-(4,6-dimethyl-2-pyrimidinyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (5a). ***Method A***. To a solution of oxadiazolethione **1** (0.52 g, 2.5 mmol) in 4 ml of abs. butanol 64% hydrazine hydrate (0.22 g, 2.75 mmol) was added and the reaction mixture was refluxed under stirring for 2 h. Then the mixture was filtered off to give 0.13 g of unidentified substance. The filtrate was evaporated to dryness under reduced pressure. The residue was washed with ether, dried and recrystallized to give 0.2 g (36%) of **5a**, m.p. 239-240 °C (from methanol).

Method B. To a solution of oxadiazolethione **1** (1.04 g, 5 mmol) in 20 ml of dry dioxane 64% hydrazine hydrate (0.43 g, 5.5 mmol) was added and the reaction mixture was refluxed for 3 h. After cooling to room temperature the mixture was filtered off to give 0.1 g of unidentified substance. The filtrate was evaporated to dryness in vacuum. The oily residue was worked up with 4 ml of methanol, the precipitate was filtered off and recrystallized to give 0.3 g (27%) of **5a**, m.p. 239-240 °C (from methanol). IR: 3414, 3208 (NH),1596 (C=C, C=N), 1345 cm^{-1} (C=S). ^1H NMR: 2.54 (6H, s, 2 CH_3), 6.39 (2H, s, NH_2), 7.46 (1H, s, 5-H pyr), 13.89 (1H, br. s, NH). ^{13}C NMR: 24.14 (CH_3), 121.49 (C_5 pyr), 146.26 (C_5 tr), 154.37 (C_2 pyr), 164.56 (C_3 tr), 168.03 ppm ($C_{4,6}$ pyr). Anal. calcd. for $C_8H_{10}N_6S$: C 43.23; H 4.53; N 37.81. Found: C 43.53; H 4.31; N 37.94.

4-Ethylamino-5-(4,6-dimethyl-2-pyrimidinyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (5b). To a solution of oxadiazolethione **1** (1.04 g, 5 mmol) in 4 ml of abs. butanol ethylhydrazine (0.22 g, 3.6 mmol) was added and the reaction mixture was refluxed under stirring for 1 h. Then the reaction mixture was rotary evaporated to dryness and the residue was crystallized to give 0.15 g (25%) of **5b**, m.p. 125 °C [from ethanol-water (1:4)]. IR: 3436, 3282, 3211 (NH), 1595 (C=C, C=N), 1340 cm^{-1} (C=S). ^1H NMR: 1.36 (3H, t, J = 7.2 Hz, $CH_2\underline{CH_3}$), 2.55 (6H, s, 2 CH_3), 4.27 (2H, k, J = 7.5 Hz, $\underline{CH_2}CH_3$). 6.51 (1H, s, NH), 7.48 (1H, s, 5-H pyr), 14.09 ppm (1H, s, NH tr). ^{13}C NMR: 13.89 ($CH_2\underline{CH_3}$). 24.14 (CH_3), 44.93 ($\underline{CH_2}CH_3$). 121.57 (C_5 pyr), 144.96 (C_5 tr), 154.18 (C_2 pyr), 163.43 (C_3 tr), 168.08 ppm ($C_{4,6}$ pyr). Anal. calcd. for $C_{10}H_{14}N_6S$: C 47.98; H 5.64; N 33.57. Found: C 48.02; H 5.62; N 33.48.

4-Phenylamino-5-(4,6-dimethyl-2-pyrimidinyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (5c). A mixture of **6a** (0.5 g, 1.58 mmol), 10% KOH (12 ml) and methanol (5 ml) was refluxed for 1 h. After cooling to room temperature the mixture was acidified with diluted HCl (1:1) to pH 5-6. The precipitate was filtered off, washed with water, dried and recrystallized to give 0.29 g (62%) of **5c**, m.p. 216-217 °C (from ethyl acetate). IR: 3451, 3253, 3034 (NH), 1595 (C=N), 1532 (C=C), 1345 cm^{-1} (C=S). ^1H NMR: 2.51 (6H, s, 2 CH_3), 6.08 (1H, t, J= 8.4 Hz, 4H Ph), 6.63 (2H, d, J = 9.6 Hz, 2,6-H Ph), 7.17 (2H, t, J = 8.4 Hz, 3,5-H Ph), 7.35 (1H, s, 5-H pyr), 9.15 (1H, s, NHPh), 14.30 ppm (1H, s, NH tr). Anal. calcd. for $C_{14}H_{14}N_6S$: C 56.36; H 4.73; N 28.17. Found: C 56.63; H 4.58; N 28.41.

1-(4,6-Dimethyl-2-pyrimidinylcarbonyl)-5-phenylthiocarbohydrazide (6a). To a solution of oxadiazolethione **1** (0.5 g, 2.4 mmol) in 20 ml of dry dioxane phenylhydrazine (0.35 g, 3.6 mmol) was added and the reaction mixture was refluxed for 4 h. After cooling to room temperature the mixture was filtered off, the filtrate was evaporated to dryness in vacuum. The oily residue was worked up with 4 ml of methanol, the precipitate was filtered off and recrystallized to give 0.31 g (41%) of **6a**, m.p. 201-202 °C (from methanol). IR: 3258, 3187 (NH), 1690 (C=O), 1597 (C=N), 1563 (C=C), 1497, 1312 cm^{-1} (C=S). ^{1}H NMR: 2.53 (6H, s, 2 CH_3), 6.81 (3H, m, Ph), 7.21 (2H, m, Ph), 8.02 (1H, s, NHPh), 9.86-10.09 (2H, m, NHCSNH), 10.49 ppm (1H, s, CONH). ^{13}C NMR: 24.10 (CH_3), 113.90, 120.42 (Ph), 122.50 (C_5 pyr), 129.38, 148.74 (C Ph), 157.32 (C_2 pyr), 161.58 (C=O), 167.74 ($C_{4,6}$ pyr), 183.95 ppm (C=S). Anal. calcd. for $C_{14}H_{16}N_6OS$: C 53.15; H 5.10; N 26.56. Found: C 53.07; H 5.10; N 26.81.

5-Acetyl-1-(4,6-dimethyl-2-pyrimidinylcarbonyl)thiocarbohydrazide (**6b**). ***Method A***. To a solution of oxadiazolethione **1** (0.15 g, 0.72 mmol) in 4.5 ml of dry dioxane acetylhydrazine (0.062 g, 0.83 mmol) was added and the mixture was refluxed under stirring for 1 h. The precipitate was filtered off, washed with ether and recrystallized to give 0.08 g (40%) of **6b**, m.p. 181 °C (from ethanol).

Method B. To a solution of oxadiazolethione **1** (0.5 g, 2.4 mmol) in 4 ml of dry butanol acetylhydrazine (0.21 g, 2.88 mmol) was added and the mixture was refluxed under stirring for 0.5 h. The precipitate was filtered off, washed with ether and recrystallized to give 0.07 g (10%) of **6b**, m.p. 181 °C (from ethanol). IR: 3443, 3206 (NH), 1688 (C=O), 1598 (C=C, C=N), 1254 cm^{-1} (C=S). ^{1}H NMR: 1.88 (3H, s, CH_3), 2.54 (6H, s, 2 CH_3), 7.48 (1H, s, 5-H pyr), 9.89 (2H, s, NHCSNH), 10.54 ppm (2H, s, 2 CONH). ^{13}C NMR: 21.52 ($COCH_3$), 24.08 (CH_3), 122.50 (C_5 pyr), 157.32 (C_2 pyr), 161.95 (C=O pyr), 167.72 ($C_{4,6}$ pyr), 175.07 (C=O), 183.40 ppm (C=S). Anal. calcd. for $C_{10}H_{14}N_6O_2S$: C 42.54; H 5.00; N 29.77. Found: C 42.49; H 5.12; N 29.58.

References

1 H. Chen, Zh. Li, Y. Han, *J. Agric. Food Chem.* **48**, 5312 (2000).
2 M. Mashaly, M. N. Khodeir, M. Hanna, H. El-Shafei, *Bull. Chim. Farm.* **134**, 28 (1995).
3 M. G. Mamolo, D. Zampieri, L. Vio, M. Fermeglia, M. Ferrone, S. Pricl, G. Scialino, E. Banfi, *Bioorg. Med. Chem.* **13**, 3797 (2005).
4 F. Macaev, G. Rusu, S. Pogrebnoi, A. Gudima, E. Stingaci, L. Vlad, N. Shvets, F. Kandemirli, A. Dimoglo, R. Reynolds, *Bioorg. Med. Chem.* **13**, 4842 (2005).
5 G. Myakushkene, P. Vainilavichyus, A. Getchaim, R. Shematovich, *Chem. Heterocycl. Comp. (Russ.).* 700 (1993).
6 V. Jakubkiene, M. M. Burbuliene, G. Mekuškiene, E. Udrenaite, P. Gaidelis, P. Vainilavicius, *Il Farmaco* **58**, 323 (2003).
7 M. M. Burbuliene, V. Jakubkiene, G. Mekuškiene, E. Udrenaite, R. Smicius, P. Vainilavičius, *Il Farmaco* **59**, 767 (2004).
8 A. H. El-masry, H. H. Fahmy, S. H. A. Abdelwahed, *Molecules* **5**, 1429 (2000).
9 G. Sahin, E. Palaska, M. Ekizoglu, M. Ozalp, *Il Farmaco* **57**, 539 (2002).
10 A. A. El-Emam, O. A. Al-Deeb, M. Al-Omar, J. Lehmann, *Bioorg. Med. Chem.* **12**, 5107 (2004).
11 C. Loetchutinat, F. Chau, S. Mankhetkorn, *Chem. Pharm. Bull.* **51**, 728 (2003).
12 P. Vainilavicius, G. Mekuskiene, L. Jasinskas, *Zh. Vses. Khim. O-va* **21**, 348 (1976); C. A., **85**, 123853t (1976).

Received on March 17, 2007