Chemistry of Heterocyclic Compounds, Vol. 39, No. 10, 2003

5-(4,6-DIPHENYL-2-PYRIMIDINYL)-1,3,4-OXADIAZOLE-2-THIONE WITH SOME C-ELECTROPHILES AND N-NUCLEOPHILES

G. Mekuskiene, M. M. Burbuliene, V. Jakubkiene, E. Udrenaite, P. Gaidelis, and P. Vainilavicius

5-(4,6-Diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione reacted with haloalkanes or their derivatives containing side chain oxo group to give S-alkylated compounds. Aminomethylation and acylation of the thione yielded $N_{(3)}$*-derivatives. Treatment of the title compound with hydrazine hydrate in butanol resulted in 4-amino-5-(4,6-diphenyl-2-pyrimidinyl)-1,2,4-triazole-3-thione via a recyclization reaction. Reaction of the title compound with hydrazine hydrate or phenylhydrazine in dioxane led to formation of the corresponding thiocarbohydrazides. The latter in the presence of a base were cyclized to 4-amino-1,2,4-triazole-3-thiones.*

Keywords: 1,3,4-oxadiazole, 1,2,4-triazole-3-thione, thiocarbohydrazide, anti-inflammatory activity.

1,3,4-Oxadiazole-2-thiones have increasing importance as compounds with bactericidal [1-3], anti-inflammatory [4, 5], tuberculostatic [6], anticonvulsion [7], and fungicidal [8] activities. At the same time, they are versatile intermediates in organic synthesis as they react with electrophiles at the S or N atom [2] and with nucleophiles at the $C_{(2)}$ atom [6, 9].

Previously we have reported on some 5-(4,6-diphenyl-2-pyrimidinyl)-substituted derivatives of 1,2,4-triazole-3-thione, which were found to possess anti-inflammatory activity [10]. In continuation of our studies of 4,6-diphenyl-2-pyrimidinylazole chemistry, we report herein on the reactions of 5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (**1**) with some C-electrophiles and N-nucleophiles.

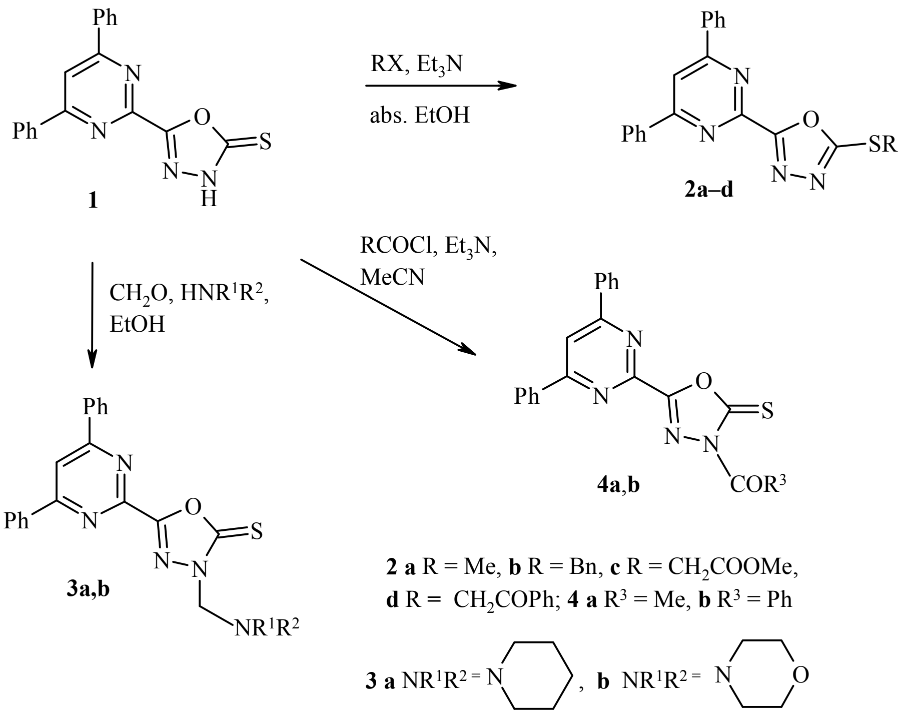
The starting compound **1** was synthesized by the reaction of 4,6-diphenyl-2-pyrimidinylcarbonylhydrazine with potassium O-ethylxanthate in ethanol on reflux [11].

Upon treatment of compound **1** with haloalkanes in ethanol on reflux in the presence of triethylamine as a base, S-alkyl derivatives **2a-d** were obtained. Compound **1** underwent aminomethylation reaction in ethanol at room temperature to give $N_{(3)}$-aminomethyl derivatives **3a**,**b**. Acylation reaction of **1** with acetyl or benzoyl chloride in dry acetonitrile at room temperature in the presence of triethylamine produced $N_{(3)}$-acyl derivatives **4a**,**b** (Scheme 1).

Compound **1**, depending on the solvent used, behaved differently towards N-nucleophiles. Treatment of compound **1** with hydrazine hydrate in abs. butanol on reflux resulted in 4-amino-5-(4,6-diphenyl-2-pyrimidinyl)-1,2,4-triazole-3-thione (**6a**) formation, whereas reaction of **1** with hydrazine hydrate or phenylhydrazine in dioxane on reflux gave rise to ring opening to form thiocarbohydrazides **5a**,**b**. The latter underwent cyclization to 4-amino-1,2,4-triazolo-3-thiones **6a**,**b** under reflux in potassium hydroxide solution.

Vilnius University, Vilnius LT-2006, Lithuania; e-mail: povilas.vainilavicius@chf.vu.lt. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1548-1553, October, 2003. Original article submitted September 16, 2002.

Scheme 1

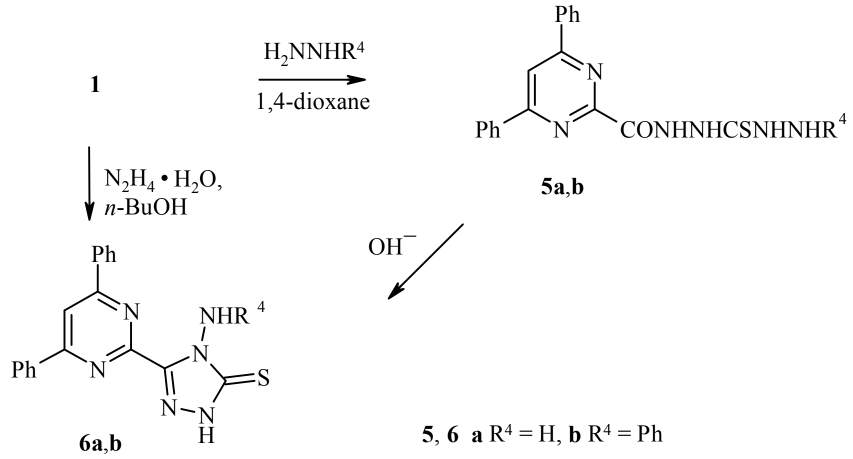


2 a R = Me, **b** R = Bn, **c** R = CH_2COOMe, **d** R = CH_2COPh; **4 a** R^3 = Me, **b** R^3 = Ph

3 a NR^1R^2 = , **b** NR^1R^2 =

The formation of the compounds mentioned was confirmed on the basis of their IR and ^1H NMR spectral data and elemental analysis. In the IR spectra of alkylated compounds **2a-d**, absorption bands characteristic of the C–O–C group of 1,3,4-oxadiazoles at 1155-1168 cm^{-1} were observed, but absorption of C=S group was absent. The following absorption was observed in aminomethyl **3a**,**b** and acyl derivatives **4a**,**b**: at 1518-1521 and 1240-1263 cm^{-1}. Furthermore, absorption of C=O group was observed for compounds **2c**,**d** and **4a**,**b** at 1739, 1680 and 1749, 1698 cm^{-1} respectively. In the ^1H NMR spectra of compounds **2b-d** the characteristic SCH_2 protons resonate at 4.39-5.27 ppm, and the chemical shifts of the N–CH_2 group characteristic of $N_{(3)}$ derivatives **3a**,**b** appear at 5.19 ppm.

Scheme 2



5, **6** **a** R^4 = H, **b** R^4 = Ph

TABLE 1. IR and ^{1}H NMR Data for Compounds **2-6**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm
2a	1585, 1574 (C=C, C=N), 1167 (C–O–C)	2.87 (3H, s, SCH$_3$); 7.64-8.45 (10H, m, phenyl); 8.74 (1H, s, CH-pyrimidine)
2b	1586, 1575 (C=C, C=N), 1168 (C–O–C)	4.62 (2H, s, SCH$_2$); 7.39-8.37 (15H, m, phenyl); 8.63 (1H, s, CH-pyrimidine)
2c	1739 (C=O), 1588, 1574 (C=C, C=N), 1155 (C–O–C)	3.75 (3H, s, OCH$_3$); 4.39 (2H, s, SCH$_2$); 7.63-8.40 (10H, m, phenyl); 8.69 (1H, s, CH-pyrimidine)
2d	1680 (C=O), 1577, 1566 (C=C, C=N), 1163 (C–O–C)	5.27 (2H, s, SCH$_2$); 7.61-8.37 (15H, m, phenyl); 8.73 (1H, s, CH-pyrimidine)
3a	1584, 1575 (C=C, C=N), 1521, 1258 (C=S), 1176 (C–O–C)	1.54 [6H, m, (CH$_2$)$_3$]; 2.89 [4H, m, N(CH$_2$)$_2$]; 5.19 (2H, s, NCH$_2$); 7.58-8.32 (11H, m, phenyl, CH-pyrimidine)
3b	1574 (C=C, C=N), 1519, 1248 (C=S), 1168 (C–O–C)	2.94 [4H, m, N(CH$_2$)$_2$]; 3.75 [4H, m, O(CH$_2$)$_2$]; 5.19 (2H, s, NCH$_2$); 7.58-8.21 (11H, m, phenyl, CH-pyrimidine)
4a	1749 (C=O), 1573 (C=C, C=N), 1518, 1263 (C=S)	2.79 (3H, s, CH$_3$); 7.52-7.60 (6H, m, 3,4,5-CH-phenyl); 8.21-8.29 (5H, m, 2,6-CH-phenyl, CH-pyrimidine)
4b	1698 (C=O), 1576 (C=N), 1519, 1240 (C=S)	7.56 (9H, m, 3,4,5-CH-phenyl); 7.94-8.03 (2H, m, 2,6-CH-phenyl-CO); 8.23 (5H, m, 2,6-CH-phenyl, CH-pyrimidine)
5a	3302 (NH), 3125 (NH$_2$), 1707 (C=O), 1587, 1575 (C=C, C=N), 1248 (C=S)	3.70 (2H, s, NH$_2$); 7.56-8.20 (11H, m, CH-phenyl, CH-pyrimidine); 9.21 (2H, m, CSNH); 10.14 (1H, s, CONH)
5b	3270, 3056 (NH), 1698 (C=O), 1236 (C=S)	6.80-7.22 (6H, m, CH-phenyl, NH-phenyl); 7.65-8.56 (10H, m, CH-phenyl); 8.81 (1H, s, CH-pyrimidine); 9.93 (2H, m, CSNH); 10.98 (1H, s, CONH)
6a	3256 (NH), 3116 (NH$_2$), 1586, 1573 (C=C, C=N), 1230 (C=S)	6.41 (2H, s, NH$_2$); 7.65 (6H, m, 3,4,5-CH-phenyl); 8.49 (4H, m, 2,6-CH-phenyl); 8.75 (1H, s, CH-pyrimidine); 14.31 (1H, s, NH-triazole)
6b	3429 (NH), 3059 (NH$_2$), 1587, 1575 (C=C, C=N), 1224 (C=S)	6.60-8.70 (16H, m, CH-phenyl, CH-pyrimidine); 9.36 (1H, s, NH-phenyl); 14.46 (1H, s, NH-triazole)

The IR spectra of compounds **6a**,**b** display absorption peaks of NH, NH$_2$ at 3256, 3116 cm^{-1} for **6a** and 3429, 3059 cm^{-1} for **6b**, and the absorption of the C=S group occurs at 1230 and 1224 cm^{-1} for **6a** and **6b** respectively. In the ^{1}H NMR spectra of compounds **6a**,**b** together with signals of the phenyl group and protons of position 5 of the pyrimidine ring, chemical shifts of NH$_2$ (6.41, 9.36 ppm) and NH group protons (14.31, 14.46 ppm) are observed. The IR spectra of thiocarbohydrazides **5a**,**b** display absorption bands of the C=O group at 1707 and 1698 cm^{-1} and of the NH group at 3302 and 3270, 3056 cm^{-1} respectively. The ^{1}H NMR spectra of **5a**,**b** show characteristic chemical shifts of the CSNH group at 9.21, 9.93 ppm and CONH in the downfield region at 10.14 and 10.98 ppm.

The compounds were tested for their anti-inflammatory activity. Anti-inflammatory activity was studied by carrageenan- and bentonite-induced paw edema tests in rats. Most of the compounds were less toxic and showed higher anti-inflammatory activity than that of reference drugs – acetylsalicylic acid and ibuprofen. The most active compounds, i. e., 2-benzylthio-5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole (**2b**), decreased the rats' paw edema, induced by carrageenan and bentonite, by 51.2 and 48.6%, and 3-morpholinomethyl-5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (**3b**) – by 43.5 and 42.2%, respectively. The acute toxicity (LD$_{50}$) per os in white mice for compound **2b** is more than 1000 mg/kg and for **3b** more than 1500 mg/kg.

TABLE 2. Physical and Analytical Data of Compounds **2-6**

Compound	Empirical formula (M)	Found, % Calculated, %			mp, °C*	Yield, % (method)
		C	H	N		
2a	$C_{19}H_{14}N_4OS$ (346.41)	65.96 65.88	3.99 4.07	16.25 16.17	197-198	63
2b	$C_{25}H_{17}N_4OS$ (421.50)	71.25 71.23	4.18 4.07	13.14 13.29	145-146	60
2c	$C_{21}H_{16}N_4O_3S$ (404.45)	62.70 62.36	4.29 3.98	13.60 13.85	149-150	67
2d	$C_{26}H_{18}N_4O_2S$ (450.52)	69.59 69.36	4.26 4.03	12.56 12.44	195-196	58
3a	$C_{24}H_{23}N_5OS$ (429.55)	67.26 67.11	5.26 5.39	16.37 16.30	195.5-196.5	58
3b	$C_{23}H_{21}N_5O_2S$ (431.52)	64.29 64.02	4.91 4.90	16.30 16.23	181-182	46
4a	$C_{20}H_{14}N_4O_2S$ (374.43)	64.43 64.15	3.96 3.77	15.09 14.96	215-216.5	69
4b	$C_{25}H_{16}N_4O_2S$ (436.50)	68.88 68.79	3.52 3.69	12.98 12.84	184-185	62
5a	$C_{18}H_{16}N_6OS$ (364.43)	59.45 59.36	4.26 4.43	23.22 23.06	216-217.5	55
5b	$C_{24}H_{20}N_6OS$ (440.53)	65.58 65.44	4.42 4.58	18.89 19.08	199-200	39
6a	$C_{18}H_{14}N_6S$ (346.42)	62.48 62.41	3.98 4.07	24.13 24.28	244-245	60 (A), 64 (B)
6b	$C_{24}H_{18}N_6S$ (422.52)	68.12 68.23	4.18 4.29	19.63 19.89	216.5-217.5	73

---

* Solvents: MeCN (compounds **2a-d**, **3a**,**b** and **4a**,**b**), MeOH (compound **5a**), EtOH (compound **5b**), and DMF–H_2O (compounds **6a**,**b**).

EXPERIMENTAL

IR spectra were measured on a Spectrum BX FT-IR (Perkin-Elmer) in nujol (for compounds **5a**,**b** and **6a**,**b** in KBr pellets). The ^1H NMR spectra were recorded on a BS-587A (80 MHz, Tesla) in DMSO-d_6 (for compounds **3a**,**b** and **4a**,**b** in $CDCl_3$ with TMS as an internal standard). Chemical shifts (δ) are reported in ppm. The reactions were monitored by TLC on silica gel coated Al plates (Kavalier). All reagents were of commercial quality (Aldrich, Merck) and were used as received. Solvents (acetonitrile, ethanol, butanol, dioxane) were dried and purified using the standard technique.

5-(4,6-Diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (**1**) was synthesized as reported in [11].

2-Alkylthio-5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole (2a-d). (General Procedure). To a suspension of compound **1** (2.26 mmol, 0.75 g) in abs. C_2H_5OH (70 ml) anhydrous triethylamine (2.26 mmol, 0.23 g, 0.32 ml) and 2.26 mmol of corresponding haloalkane (MeI, $PhCH_2Cl$, $BrCH_2COOMe$, $BrCH_2COPh$) were added. The reaction mixture was stirred and refluxed for 1 h, then allowed to cool to room temperature. The solid was filtered off and recrystallized from acetonitrile.

5-(4,6-Diphenyl-2-pyrimidinyl)-3-piperidinomethyl-1,3,4-oxadiazole-2-thione (3a) and 5-(4,6-Diphenyl-2-pyrimidinyl)-3-morpholinomethyl-1,3,4-oxadiazole-2-thione (3b). To a suspension of compound **1** (2.26 mmol, 0.75 g) in ethanol (70 ml) 35% formalin (3.3 mmol, 0.29 g, 0.26 ml) and piperidine (2.26 mmol, 0.19 g, 0.22 ml) or morpholine (2.26 mmol, 0.19 g, 0.2 ml) was added. The reaction mixture was stirred at room temperature for 3 h, then the solid was filtered off and recrystallized from acetonitrile.

3-Acetyl-5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (4a) and 3-Benzoyl-5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (4b). To a stirred solution of compound **1** (2.26 mmol, 0.75 g) and triethylamine (2.26 mmol, 0.23 g, 0.32 ml) in dry acetonitrile (70 ml) freshly distilled acetyl chloride (2.26 mmol, 0.18 g, 0.16 ml) (for **4b** benzoyl chloride, 2.26 mmol, 0.32 g, 0.26 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, then the solid was filtered off and recrystallized from acetonitrile.

1-(4,6-Diphenyl-2-pyrimidinylcarbonyl)thiocarbohydrazide (5a) and 1-(4,6-Diphenyl-2-pyrimidinylcarbonyl)-5-phenylthiocarbohydrazide (5b). Compound **1** (3 mmol, 1.0 g) was dissolved in abs. dioxane (50 ml) on reflux and then 85% hydrazine hydrate (3.15 mmol, 0.23 g, 0.19 ml), in the case of **5b** phenylhydrazine (3.15 mmol, 0.34 g, 0.21 ml), was added. The reaction mixture was refluxed for 6-8 h and cooled. The solid was filtered off and recrystallized.

4-Amino-5-(4,6-diphenyl-2-pyrimidinyl)-1,2,4-triazole-3-thione (6a). A. To a stirred solution of compound **1** (3 mmol, 1.0 g) in boiling abs. butanol (170 ml) 85% hydrazine hydrate (3.15 mmol, 0.23 g, 0.19 ml) was added dropwise. The reaction mixture was refluxed for 4 h, then concentrated to 50 ml volume and cooled. The solid was filtered off and recrystallized from a mixture of DMF–H_2O.

B. A. solution of compound **5a** (1.37 mmol, 0.5 g **)** in 10% potassium hydroxide (12 ml) was refluxed for 1.5 h and allowed to cool to room temperature. Then under cooling with ice-water it was neutralized with 15% HCl. The solid was filtered off, washed with H_2O, and recrystallized from DMF–H_2O.

4-Phenylamino-5-(4,6-diphenyl-2-pyrimidinyl)-1,2,4-triazole-3-thione (6b) was synthesized as described for **6a** by the method B.

REFERENCES

1. M. A. Salama, F. M. A. Moti, A. G. Ghattas, and A. Abdullah, *Egypt. J. Chem*., **24**, 47 (1981); *Chem. Abstr*., **99**, 53674 (1983).
2. A. G. Ghattas, H. A. El-sherief, A. E. Abdelrahman, and A. M. Mahmoud, *Pharmazie*, **37**, 410 (1982).
3. G. Mazonne and F. Bonina, *Farmaco Ed. Sci*, **34**, 390 (1979).
4. D. H. Boschelli, D. T. Connor, D. A. Bornemeier, R. D. Dyer, J. A. Kennedy, P. J. Kuipers, G. C. Okonkwo, D. J. Schrier, and C. D. Wright, *J. Med. Chem.*, **36**, 1802 (1993).
5. T. R. Bellioti, D. T. Connor, and C. R. Kostlan, WO Pat. 9213844; *Chem. Abstr*., **118**, 6990 (1993).
6. D. Pancechowska-Ksepko, H. Foks, H. Janowiec, and Z. Zvolska-Kwiek, *Acta Pol. Pharm*., **50**, 259 (1993).
7. Ram Vishnu Ji and H. N. Pandey, *J. Indian Chem. Soc*., **51**, 634 (1974).
8. W. Eckhardt, E. Beriger, and H. Zondler, EP Pat. 371925; *Chem. Abstr*., **113**, 191385 (1990).
9. J. R. Reid and N. D. Heindel, *J. Heterocycl. Chem.*, **13**, 925 (1976).
10. G. Mekuskiene, P. Gaidelis, and P. Vainilavicius, *Pharmazie*, **53**, 94 (1998).
11. G. Mekuskiene, S. Tumkevicius, and P. Vainilavicius, *J. Chem. Res*. (*S*), 213 (2002).