SHORT PAPER

J. Chem. Research (S),
2002, 213–215

5-(4,6-Diphenyl-2-pyrimidinyl)-1,3,4-oxa(thia)diazoles and 1,2,4-triazoles†

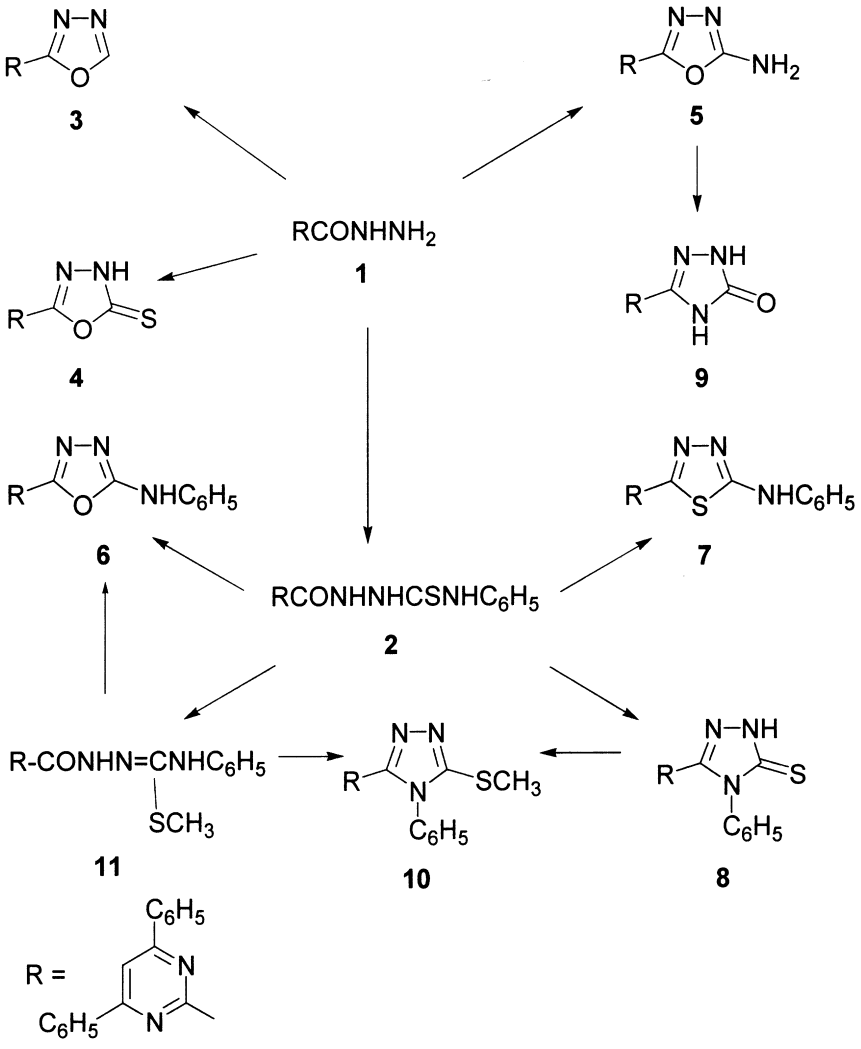
Giedrute Mekuskiene, Sigitas Tumkevicius and Povilas Vainilavicius*

Department of Organic Chemistry, Faculty of Chemistry, Vilnius University, Naugarduko 24, 2006 Vilnius, Lithuania

Synthesis of 5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-oxa(thia)diazoles and corresponding 1,2,4-triazoles from 4,6-diphenyl-2-pyrimidinecarboxylic acid hydrazide and 1-(4,6-diphenyl-2-pyrimidinylcarbonyl)-4-phenylthiosemicarbazide is described.

Keywords: pyrimidines, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 1,2,4-triazoles, thiosemicarbazides

Derivatives of 1,3,4-oxa- and –thia-diazoles and 1,2,4-triazoles bearing heterocyclic substituents in position 5 possess diverse biological activity. Among them are compounds increasing the activity of phleomycin,[1] possessing tuberculostatic,[2,3] antiinflammatory[4], anticonvulsant[5] and antidepressant[6] activity, as well as compounds exhibiting nematocidal and fungicidal[7,8] properties, have been revealed. Derivatives of 5-(4,6-diphenyl-2-pyrimidinyl)-1,2,4-triazoline-3-thione, reported by us earlier, have been found to possess antiinflammatory activity.[9a] Continuing our studies in the series of pyrimidinylazoles[9] we present herein a study on the synthesis of some derivatives of the title heterocyclic systems from the



Scheme 1

* To receive any correspondence. E-mail: povilas.vainilavicius@chf.vu.lt

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 1 Physical and analytical data for compounds **2–4**, **6–11**

Compound/ yield/%	M.p./°C (solvent)	Molecular formula	Found (required)/% C	H	N	ν_{max}/cm^{-1}	δ_H[a]
2 (67)	209.5–210 (AcOH)	$C_{24}H_{19}N_5OS$	67.65 (67.74)	4.35 (4.50)	16.74 (16.46)	3254, 3195 (NH), 1678 (C=O), 1588, 1574(C=N), (C=C), 1521 (NCS)	7.1 (1 H, t, 4-Ph-*p*-H), 7.3 (2 H, t, 4-Ph-*m*-H), 7.57 [8H, m, Ph-*m,p*-H (pyrimidine), 4-Ph-*o*-H], 8.45 [4H, m, Ph-*o*-H (pyrimidine)] 8.6 (1 H, s, CH pyrimidine)
3 (46)	209–211 (MeOH)	$C_{18}H_{12}N_4O$	71.94 (71.99)	3.98 (4.03)	18.99 (18.66)	1586, 1576, 1565 (C=N, C=C), 1066 (C-O-C)	7.57 (6 H, m, Ph-*m,p*-H), 8.4 (4 H, m, Ph-*o*-H), 8.63 (1 H, s, CH pyrimidine), 9.3 (1 H, s, CH oxadiazole)
4 (93)	274–275 (DMF+H_2O)	$C_{18}H_{12}N_4OS$	65.17 (65.04)	3.71 (3.64)	16.83 (16.86)	3116 (NH), 1602, 1587, 1577 (C=N, C=C), 1506 (NCS), 1063 (C-O-C)	7.57 (6 H, m, Ph-*m,p*-H), 8.38 (4 H, m, Ph-*o*-H), 8.58 (1 H, s, CH pyrimidine), 14.9 (1 H, br s , NH)
6 A (35) B (22)	269–270 (DMF)	$C_{24}H_{17}N_5O$	73.53 (73.64)	4.23 (4.38)	18.26 (17.89)	3370, 3180 (NH), 1660, 1584 (C=N, C=C), 1060 (C-O-C)	7.66–8.45 (15 H, m, 3 Ph-H), 8.72 (1 H, s, CH pyrimidine), 11.04 (1 H, br s, NH)
7 (55)	279–280 (BuOH)	$C_{24}H_{17}N_5S$	70.58 (70.74)	3.97 (4.20)	17.38 (17.19)	3260, 3200 (NH), 1619, 1600, 1585, 1575 (C=N, C=C)	7.00 (1 H, t, 4-CH aniline), 7.35 (2 H, t, 3-CH aniline), 7.55 (6 H, m, Ph-*m,p*-H), 7.65 (2 H, d, 2-CH aniline), 8.4 (4 H, m, Ph-*o*-H), 8.42 (1 H, s, CH pyrimidine)
8 (63)	301–301.5 (Dioxane)	$C_{24}H_{17}N_5S$	70.65 (70.74)	4.25 (4.20)	17.22 (17.19)	3166 (NH) 1585, 1576 (C=N, C=C), 1522 (NCS)	7.35–7.8 [11 H, m, Ph-*m,p*-H (pyrimidine), Ph (triazole)], 7.85–8.2 [4 H, m, Ph-*o*-H (pyrimidine)], 8.57 (1 H, s, CH pyrimidine)
9 (50)	341–342 (EtOH)	$C_{18}H_{13}N_5O$	68.20 (68.56)	4.02 (4.15)	22.01 (22.20)	3155, 3056 (NH), 1724 (C=O), 1586, 1570 (C=N, C=C)	7.5 (6 H, m, Ph-*m,p*-H), 8.43 (4 H, m, Ph-*o*-H), 8.63 (1 H, s, CH pyrimidine), 12.0 (1 H, s, NH), 12,25 (1 H, s, NH)
10 A (75) B (71) C (50)	211–211.5 (MeOH+DMF)	$C_{25}H_{19}N_5S$	71.52 (71.24)	4.47 (4.54)	16.35 (16.61)	1586, 1576 (C=N, C=C)	2.73 (3 H, s, SCH_3), 7.4 [8 H, m, Ph-*m, p*-H (pyrimidine), Ph-*o*-H (triazole)], 7.55 [3 H, m, Ph-*m,p*-H (triazole)], 8.0 [4 H, m, Ph-*o*-H (pyrimidine)], 8.4 (1 H, s, CH pyrimidine)
11 (87)	198–199	$C_{25}H_{21}N_5OS$	68.59 (68.32)	4.84 (4.82)	15.76 (15.93)	3234, 3188 (NH), 1678 (C=O), 1586, 1570 (C=N, C=C)	2.34 (3 H, s, SCH_3), 7.07–7,31 [11 H, m, Ph-*m,p*-H (pyrimidine), Ph (triazole)], 7.71 (4 H, m, Ph-*o*-H), 8.28 (1 H, s, CH pyrimidine)

[a] ^{1}H NMR spectra of compounds **2–4, 6–10** were obtained in DMSO-D_6, **11** in CF_3COOD.

readily available hydrazide of 4,6-diphenyl-2-pyrimidinecarboxylic acid (**1**) and 1-(4,6-diphenyl-2-pyrimidinylcarbonyl)-4-phenylthiosemicarbazide (**2**) (Scheme 1).

Reaction of **1** with phenyl isothiocyanate gave the thiosemicarbazide **2**. Compound **2** appeared to be rather sensitive to heating in some solvents, and already on crystallisation from ethoxyethanol an unexpected evolution of H_2S took place with the formation of 2-anilino-1,3,4-oxadiazole **6.** In order to prove the structure unambiguously compound **6** was also synthesised by a traditional method of synthesis of 2-anilino-1,3,4-oxadiazoles[11] – by the thermal intramolecular cyclocondensation of 1-(4,6-diphenyl-2-pyrimidinylcarbonyl)-4-phenyl-*S*-methylisothiosemicarbazide (**11**). Treatment of hydrazide **1** with triethoxymethane or with potassium *O*-ethylxanthate afforded the corresponding derivatives of 1,3,4-oxadiazole **3**, **4**. A short heating of thiosemicarbazide **2** in conc. sulfuric acid gave 2-anilino-1,3,4-thiadiazole **7**, whereas reaction of **2** with 20% KOH underwent the alternative cyclisation with the formation of 4-phenyl-1,2,4-triazole-3-thione **8**. The latter compound was alkylated with iodomethane to give *S*-methyl derivative **10**. Compound **10** was also formed under the prolonged reflux of thiosemicarbazide **2** with iodomethane in the presence of sodium methoxide in methanol as well as by heating of *S*-methylisothiosemicarbazide **11** in aprotic polar solvent dimethylsulfoxide. It is known[12] that 2-amino-1,3,4-oxadiazoles under the treatment with alkali undergo recyclisation to form the 1,2,4-triazole derivatives. Using this method oxadiazole **5,** obtained from **1** and cyanogen bromide according to the procedure reported by us,[9b] was converted into the 1,2,4-triazolin-3-one **9**.

The structures of the synthesised compounds were proved by IR, ^{1}H NMR and elemental analysis data (Table 1). In the IR spectra of 1,3,4-oxadiazoles **3, 4** and **6** the characteristic absorption band of the C-O-C fragment was observed at 1060–1066 cm^{-1}.[13] The IR spectra of compounds **4** and **8** indicate that they exist in the thione form: there is no absorption of the SH group at 2500–2600 cm^{-1}, but bands due to NH (3116 cm^{-1} and 3166 cm^{-1}) and N-C=S groups (1506 cm^{-1}, 1522 cm^{-1}) are observed. Absorption bands of the NH group of 2-anilino-1,3,4-oxadiazole **6** and 2-anilino-1,3,4-thiadiazole **7** are observed at 3180, 3370 cm^{-1} and 3200, 3260 cm^{-1}, respectively. The IR spectrum of 1,2,4-triazolin-3-one **9** is characterised by the absorptions of C=O (1724 cm^{-1}) and NH groups (3155, 3056 cm^{-1}). In the ^{1}H NMR spectra of compounds **2–4** and **6–11** signals from protons of the pyrimidine and azole moieties as well as of the corresponding substituents are observed (Table 1).

The primary pharmacological study of the synthesised pyrimidinylazoles showed that compounds **5**, **7** and **8** possess antiinflammatory activity.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls on a Perkin-Elmer FT spectrophotometer Spectrum BX II. NMR spectra were recorded on Tesla 587A, Bruker AC-300, and AC-400 spectrometers using tetramethylsilane as internal standard. Microanalyses were performed by the Microanalyses Laboratory of the Department of Organic Chemistry of Vilnius University.

Physical, analytical and spectral data of the synthesized compounds are given in Table 1.

1-(4,6-Diphenyl-2-pyrimidinyl)-4-phenylthiosemicarbazide (**2**)[10]: To a solution of **1** (2.09 g, 7.2 mmol) in anhydrous EtOH (70 ml) phenyl isothiocyanate (1.94 g, 14.4 mmol) was added dropwise. The reaction mixture was refluxed for 2 h and cooled to room temperature. The precipitate was filtered off and recrystallised to give compound **2**.

2-(4,6-Diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole (**3**): A mixture of **1** (2 g, 6.9 mmol) and triethoxymethane (15 ml, 90 mmol) was refluxed for 24 h. After cooling to room temperature the precipitate was filtered off and recrystallised to give compound **3**.

5-(4,6-Diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (**4**): A mixture of **1** (7.58 g, 26.11 mmol), EtOH (250 ml) and potassium *O*-ethylxanthate (4.18 g, 26.11 mmol) was stirred under reflux for 13 h. Then the reaction mixture was concentrated under reduced pressure to half its volume and acidified with conc. HCl to pH ~5. The precipitate was filtered off, washed with water and recrystallized to give compound **4.**

2-Anilino-5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole (**6**): *Method A*. A mixture of **2** (0.5 g, 1.2 mmol) and ethoxyethanol (8 ml) was refluxed until the precipitate began to separate (5–10 min) The hot reaction mixture was filtered and cooled. The precipitate was filtered off and recrystallised to give compound **6**.

Method B: Compound **11** was heated at 215–220ºC for 6 min. Then the melt was cooled to room temperature and methanol (5 ml) was added. The mixture was refluxed until the solid formed. The precipitate was filtered off and recrystallised to give compound **6**.

2-Anilino-5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-thiadiazole (**7**): A mixture of **2** (1.55 g, 3.7 mmol) and conc. H_2SO_4 (7.4 ml) was heated at 90ºC for 10 min, then cooled to 10ºC and triturated with water (40 ml). Conc. ammonia was added to reach pH 8. The precipitate was filtered off and recrystallised to give compound **7**.

4-Phenyl-5-(4,6-diphenyl-2-pyrimidinyl)-1,2,4-triazole-3-thione (**8**): A mixture of **2** (2.5 g, 5.87 mmol), EtOH (50 ml) and 20% KOH (100 ml) was refluxed for 4 h. After cooling to room temperature conc. HCl was added to reach pH 4. The precipitate was filtered off and recrystallized to give compound **8**.

5-(4,6-Diphenyl-2-pyrimidinyl)-1,2,4-triazol-3-one (**9**): A mixture of **5** (0.8 g, 2.5 mmol) and 10% NaOH (25 ml) was refluxed for 6 h. After cooling to room temperature the reaction mixture was neutralised with conc. HCl. The precipitate was filtered off, washed with water and recrystallised to give compound **9**.

5-(4,6-Diphenyl-2-pyrimidinyl)-3-methylthio-1,2,4-triazole (**10**): *Method A*. To a mixture of **8** (0.7 g, 1.7 mmol) and sodium methoxide in MeOH, prepared from sodium (0.039 g, 1.7 mmol) and MeOH (10 ml), iodomethane (0.24 g, 1.7 mmol) was added dropwise. The reaction mixture was refluxed for 1 h and cooled to room temperature. The precipitate was filtered off and recrystallised to give compound **10**.

Method B: To a mixture of **2** (1 g, 2.35 mmol) and sodium methoxide in MeOH, prepared from sodium (0.054 g, 2.35 mmol) and MeOH (10 ml), iodomethane (0.98 g, 7 mmol) was added dropwise. The reaction mixture was refluxed for 13 h and cooled to room temperature. The precipitate was filtered off and recrystallised to give compound **10**.

Method C: Compound **11** (0.44 g, 1 mmol) was dissolved in boiling DMSO (2 ml) and the mixture was cooled to room temperature. The precipitate was filtered off, washed with methanol and recrystallised to give compound **10**.

1-(4,6-Diphenyl-2-pyrimidinylcarbonyl)-4-phenyl-S-methylisothiosemicarbazide (**11**): To a boiling mixture of **2** (1 g, 2.35 mmol), iodomethane (0.98 g, 7 mmol) and anhydrous MeOH (10 ml) a solution of sodium methoxide in MeOH, prepared from sodium (0.054 g, 2.35 mmol) and anhydrous MeOH (10 ml), was added dropwise under stirring. The reaction mixture was refluxed for 15 min. The precipitate was filtered off and dried to give compound **11**.

Received 9 July 2001; accepted 6 November 2001
Paper 01/983

References

1 D.J. Brown and W.B. Cowden, *Austral. J. Chem.,* 1983, **36**, 1469.
2 D. Pancechowska-Ksepko, H. Foks, E. Landowska, M. Janowiec and Z. Zwolska-Kwiek, *Acta Pol. Pharm.,* 1986, **43**, 116.
3 D. Pancechowska-Ksepko, H. Foks, M. Janowiec and Z. Zwolska-Kwiek, *Acta Pol. Pharm.,* 1993, **50**, 259.
4 T.R. Belliotti, D.T. Konnor and C.R. Costlan, WOP 9213844 (*Chem. Abstr.,* 1993, **118**, 6990).
5 J.M. Kane, B.M. Baron, M.W. Dudley, S.M. Sorensen, M.A. Staeger and F.P. Miller, *J. Med. Chem.,* 1990, **33**, 2772.
6 J.M. Kane and F.P. Miller, USP 4912095 (*Chem. Abstr.,* 1990, **113**, 211 991).
7 W. Eckhardt, E. Beriger and H. Zondler, EP 371925 (*Chem. Abstr.,* 1990, **113**, 191 385).
8 W. Eckhardt and E. Beriger, EP 389426 (*Chem. Abstr.,* 1991, **114**, 102 006).
9 (a) G. Mekuškienė, P. Gaidelis and P. Vainilavičius, *Pharmazie,* 1998, **53**, 94; (b) A. Hetzheim, G. Müller, P. Vainilavičius and D. Girdžiūnaitė, *Pharmazie,* 1985, **40**, 17; (c) G. Mekuškienė, P. Vainilavičius, A. Hetzheim and R. Šematovič, *Khim. Geterotsikl. Soedin.,* 1993, N5, 710; A. Hetzheim, G. Müller, P. Vainilavičius and G. Mekuškienė, *Pharmazie,* 1985, **40**, 197.
10 G. Mekuškienė, P. Vainilavičius and L. Jasinskas, *Liet. TSR Aukst. Mokyklu Mokslo Darb., Chem. Chem. Technol.,* 1975, **17**, 179 (*Chem. Abstr.,* 1976, **85**, 63 027).
11 E. Hoggart, *J. Chem. Soc.,* 1949, 1918.
12 G. Blankenstein and K. Möckel, *Z. Chem.,* 1962, **2**, 69.
13 D.A. Charistos, G.V. Vagenas, L.C. Tzavellas, C.A. Tsoleridis and N.A. Rodios, *J. Heterocycl. Chem.,* 1994, **31**, 1593.