SHORT PAPER

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Synthesis and biological activity of 1,3,4-oxadiazole-substituted pyridazinones†

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Novel 3-(1,3,4-oxadiazol-2-yl)-1-aryl-6-methylpyridazin-4-ones have been synthesised by two methods. A preliminary bio-activity test showed that these compounds exhibit high antifungal activity.

Keywords: 1,3,4-oxadiazoles, pyridazinones, fungicidal compounds

Pyridazinone derivatives represent a class of compounds possessing a wide spectrum of biological activity. They are widely used in pharmaceuticals and agrochemicals.[1] 1,3,4-Oxadiazole derivatives also exhibit a broad spectrum of biological activity.[2-5] These observations, coupled with our interest in 1-aryl-3-carboxy-6-methylpyridazin-4-one chemistry,[6-8] prompted us to undertake the synthesis of some as yet unreported heterocyclic compounds containing both pyridazinone and 1,3,4-oxadiazole moieties in order to obtain compounds possessing enhanced biological activity.

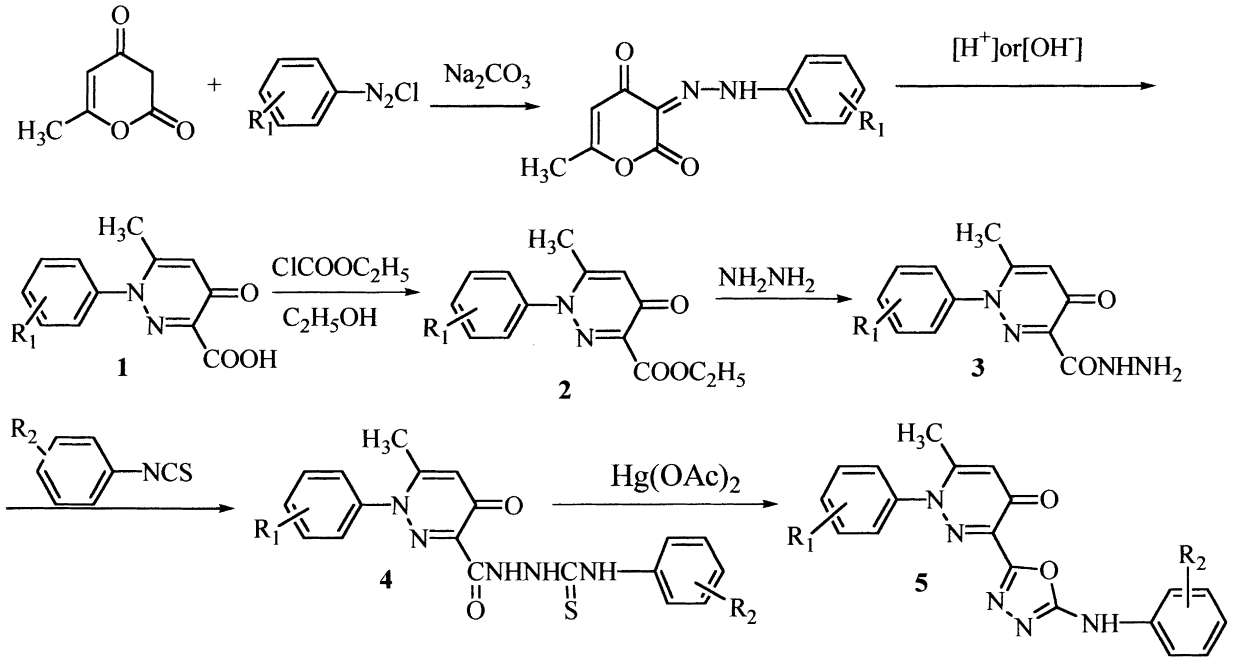
1-Aryl-1,4-dihydro-6-methyl-4-oxopyridazine-3-carboxylic acids **1**[9-11] were esterified and the ester **2** in turn was hydrazinolysed by hydrazine hydrate to give the hydrazide **3**.[7] Two different reactions were used to prepare the title compounds by using the hydrazides **3** as starting materials.

Method A: The condensation of hydrazides **3** with various arylisothiocyanates resulted in the formation of the acylthiosemicarbazides **4**. Treatment of **4** with $Hg(OAc)_2$ yielded the corresponding 1,3,4-oxadiazoles **5** (Scheme 1).

Method B: The condensation of hydrazides **3** with carbon disulfide and potassium hydroxide afforded the potassium dithiocarbazates **6**, which were cyclised under reflux to form the corresponding 1,3,4-oxadiazolethiones **7** (Scheme 2).

The IR spectra of compounds **5a–l** and **7a–c** show C=C/C=N absorption bands between 1590 and 1410 cm^{-1}. The absorption bands due to the C=O group were observed in the range of 1660–1615 cm^{-1}. The compounds **5a–l** exhibited N-H stretching absorption bands in the region between 3210 and 3285 cm^{-1}. The compounds **7a–c** which are potentially tautomeric exhibited C=S absorption bands in the region 1285–1360 cm^{-1}, which showed that compounds **7a–c** exist mainly as the thione forms. In the nuclear magnetic resonance spectra, compounds **5a–l** and **7b** exhibited broad singlets between 9.76 and 11.08 ppm due to the N–H protons. These peaks disappear upon addition of deuterium oxide.

Biological activity: The antifungal activity was tested *in vivo* on the wheat leaf rust *Puccinia recondita* at 0.001M. The screening results show inhibition of mortality levels between 20 and ~ 90% and are given in Table 1. A further study of their biological activity is under way.



Scheme 1

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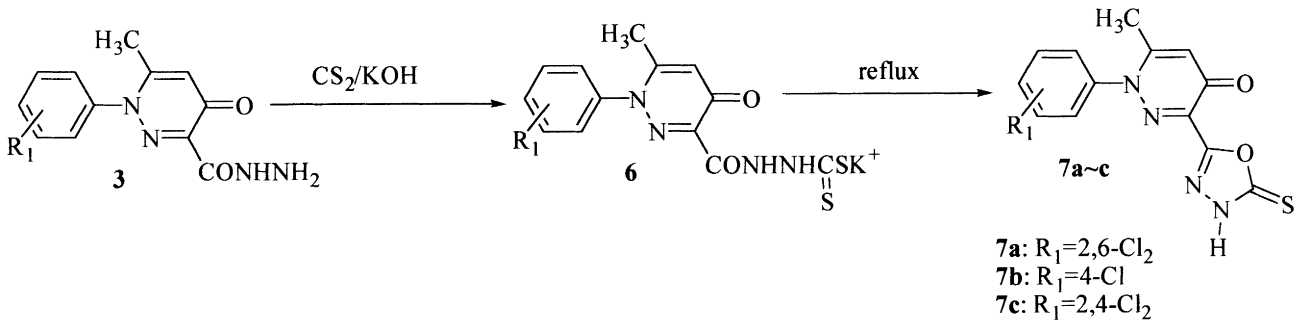
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2

Table 1 Inhibition by compounds **5a–l** and **7a** of mortality of wheat seedlings caused by rust fungus

Compd.	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	7a
R_1	*o*-Cl	*o*-Cl	*o*-Cl	H	H	2,6-Cl_2	*p*-Cl	*p*-Cl	2,4,5-Cl_3	2,4-Me_2	2,4-Me_2	*p*-Cl	2,6-Cl_2
R_2	*m*-CF_3	*o*-F	H	*o*-F	*m*-CF_3	*o*-F	*m*-CF_3	*o*-F	*o*-F	*m*-CF_3	*o*-F	*p*-OMe	–
Inhibition (%)	90	80	10	90	80	80	90	70	90	70	80	80	70

Experimental

Melting points were determined on a Yanaco micro melting point apparatus. The IR spectra (potassium bromide) were recorded with a Shimadzu IR-435 and ^{1}H NMR spectra on JEOL FX-90Q spectrometer with TMS as internal standard (chemical shifts are in δ values). Elemental (C, H, and N) analyses were carried out on a MT-3 analyzer.

1-(1-Aryl-1,4-dihydro-4-oxo-6-methylpyridazine-3-carbonyl)-4-arylthiosemicarbazides (**4**):[12] Equimolar quantities of 1-aryl-1,4-dihydro-4-oxo-6-methylpyridazinecarbohydrazide **3** and the appropriate arylisothiocyanate (1 mmol) were refluxed in 30 ml of absolute ethanol for 3 h. The excess of solvent was removed under reduced pressure. The solid mass thus obtained was washed with ethanol, dried and recrystallised from ethanol.

5-[1-(2-Chlorophenyl)-1,4-dihydro-4-oxo-6-methylpyridazin-3-yl]-2-[3-(trifluoromethyl)phenylamino]-1,3,4-oxadiazole (**5a**): To a solution of the appropriate compound **4** (0.5mmol) in ethanol (20ml) was added 0.5mmol $Hg(OAc)_2$. The reaction mixture was refluxed for 3 h and concentrated under reduced pressure. The solid was dissolved in hot *N,N*-dimethylformamide and filtered. The filtrate was concentrated under reduced pressure and recrystallised from ethanol/DMF. **5a** (R_1 = *o*-Cl, R_2 = *m*-CF_3): m.p. 142–144 °C; yield 90%; ν_{max}/ cm^{-1}: 1627, 1590, 1495, 1334, 755, 695; ^{1}H NMR: δ 2.04 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone-H), 7.20–8.00 (m, 8H, Ar–H), 11.08 (bs, N–H). Anal. Calc. for $C_{20}H_{13}ClF_3N_5O_2$: C, 53.62; H, 2.90; N, 15.70. Found: C, 53.56; H, 2.85; N, 15.62.

Similarly **5b–5l** are synthesised and their characterisation data are given below:

5b (R_1 = *o*-Cl, R_2 = *o*-F): m.p. 252–253 °C; yield 83 %; ν_{max}/ cm^{-1}: 3206, 1620, 1583, 1478, 1257, 875, 736; ^{1}H NMR: δ 2.04 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone-H), 6.88–8.20 (m, 8H, Ar–H), 10.20 (bs, N–H). Anal. Calc. for $C_{19}H_{13}ClFN_5O_2$, C, 57.41; H, 3.27; N, 17.70. Found: C, 57.30; H, 3.15; N, 17.51.

5c (R_1 = *o*-Cl, R_2 = H): m.p. 266–269 °C; yield 84 %; ν_{max}/ cm^{-1}: 3242, 1634, 1578, 1480, 1315, 1205, 863, 759; ^{1}H NMR: δ 2.04 (s, 3H, CH_3), 6.64 (s, 1H, pyridazinone-H), 6.96–7.84 (m, 9H, Ar–H), 10.20 (bs, N–H). Anal. Calc. for $C_{19}H_{14}ClN_5O_2$: C, 60.05; H, 3.68; N, 18.51. Found: C, 59.80; H, 3.75; N, 18.51.

5d (R_1 = H, R_2 = *o*-F), m.p. 245–246 °C; yield 80 %; ν_{max}/ cm^{-1}: 3285, 1645, 1591, 1502, 1468, 1323, 1202, 758, 696; ^{1}H NMR: δ 2.00 (s, 3H, CH_3), 6.36 (s, 1H, pyridazinone-H), 6.80–8.00 (m, 9H, Ar–H), 10.80 (bs, N–H). Anal. Calc. for $C_{19}H_{14}FN_5O_2$: C, 62.77; H, 3.85; N, 19.35. Found: C, 62.57; H, 3.95; N, 19.32.

5e (R_1 = H, R_2= *m*-CF_3): m.p. 254–256 °C; yield 83 %; ν_{max}/ cm^{-1}: 3242, 1629, 1589, 1550, 1461, 1338, 1297, 796, 699; ^{1}H NMR: δ 2.20 (s, 3H, CH_3), 6.68 (s, 1H, pyridazinone-H), 7.20–8.00 (m, 9H, Ar–H). Anal. Calc. for $C_{20}H_{14}F_3N_5O_2$: C, 58.08; H, 3.38; N, 17.01. Found: C, 57.80; H, 3.15; N, 16.90.

5f (R_1 = 2,6-Cl_2, R_2 = *o*-F): m. p. 262–263 °C; yield 95 %; ν_{max}/ cm^{-1}: 3198, 1619, 1581, 1459, 1256, 875, 794; ^{1}H NMR: δ 2.04 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone-H), 6.88–8.20 (m, 7H, Ar–H), 10.10 (bs, N–H). Anal. Calc. for $C_{19}H_{12}Cl_2FN_5O_2$: C, 52.77; H, 2.77; N, 16.27. Found: C, 52.43; H, 2.74; N, 16.47.

5g (R_1 = *p*-Cl, R_2 = *m*-CF_3): m.p. 278–280 °C; yield 90 %; ν_{max}/ cm^{-1}: 3151, 1655, 1592, 1490, 1297, 841, 670; ^{1}H NMR: δ 2.20 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone-H), 7.20–8.04 (m, 8H, Ar–H), 11.08 (bs, N–H). Anal. Calc. for $C_{20}H_{13}ClF_3N_5O_2$: C, 53.62; H, 2.90; N, 15.70. Found: C, 53.52; H, 3.25; N, 15.78.

5h (R_1 = *o*-Cl, R_2 = *o*-F): m.p. 257–258 °C; yield 90 %; ν_{max}/ cm^{-1}: 1631, 1586, 1504, 1454, 1281, 1222, 961, 786; ^{1}H NMR: δ 2.20 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone-H), 6.88–8.20 (m, 8H, Ar–H), 10.64 (bs, N–H). Anal. Calc. for $C_{19}H_{13}ClFN_5O_2$: C, 57.33; H, 3.27; N, 17.68. Found: C, 57.12; H, 3.47; N, 17.49.

5i (R_1 = 2, 4, 5-Cl_3, R_2 = *o*-F): m.p. 268–269 °C; yield 90 %; ν_{max}/ cm^{-1}: 3260, 1641, 1590, 1502, 1464, 1353, 1255, 892, 766; ^{1}H NMR: δ 2.20 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone-H), 6.88–8.40 (m, 6H, Ar–H), 10.96 (bs, N–H). Anal. Calc. for $C_{19}H_{11}Cl_3FN_5O_2$: C, 48.87; H, 2.36; N, 15.07. Found: C, 48.85; H, 2.40; N, 15.25.

5j (R_1 = 2, 4-$(CH_3)_2$, R_2 = *m*-CF_3): m.p. 251–252 °C; yield 83 %; ν_{max}/ cm^{-1}: 3267, 1630, 1587, 1560, 1500, 1458, 1298, 800, 697; ^{1}H NMR: δ 2.04 (s, 6H, $2CH_3$), 2.40 (s, 3H, CH_3), 6.68 (s, 1H, pyridazinone-H), 7.12–8.00 (m, 7H, Ar–H). Anal. Calc. for $C_{22}H_{18}F_3N_5O_2$: C, 59.84; H, 4.08; N, 15.93. Found: C, 59.60; H, 3.98; N, 15.97.

5k (R_1 = 2, 4-$(CH_3)_2$, R_2 = *o*-F), m.p. 195–196 °C; yield 77%; ^{1}H NMR: δ 2.04 (s, 6H, $2CH_3$), 2.20 (s, 3H, CH_3), 6.68 (s, 1H, pyridazinone-H), 7.04–8.40 (m, 7H, Ar–H) . Anal. Calc. for $C_{21}H_{18}FN_5O_2$: C, 64.41; H, 4.60; N, 17.97. Found: C, 64.26; H, 4.93; N, 17.78.

5l (R_1 = *p*-Cl, R_2 = *p*-OCH_3): m.p. 268–270 °C; yield 78 %; ^{1}H NMR: δ 2.20 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 6.68 (s, 1H, pyridazinone-H), 6.80–7.68 (m, 8H, Ar–H), 10.40 (bs, N–H). Anal. Calc. for $C_{20}H_{16}ClN_5O_3$: C, 58.58; H, 3.90; N, 17.16. Found: C, 58.70; H, 3.83; N, 16.82.

5-[1-(2,6-Dichlorophenyl)-1,4-dihydro-4-oxo-6-methylpyridazin-3-yl]-1,3,4-oxadiazole-2(3H)-thione (**7a**): To a solution of compound **3** (1mmol) in ethanol (20ml) was added carbon disulfide (2 mmol) and potassium hydroxide (1.1mmol) on a water-bath. The reaction mixture was refluxed for 8 h. The separated solid was filtered, dissolved in water and acidified with 5N hydrochloric acid. The precipitate was filtered, washed with water, dried and recrystallised from DMF. **7a** (R_1 = 2,6-Cl_2): m.p. > 245 °C, yield 80 %; ν_{max}/ cm^{-1}: 3175, 3064, 1650, 1572, 1460, 1380, 1283; ^{1}H NMR: δ 2.04 (s, 3H, CH_3), 6.65 (s, 1H, pyridazinone-H), 7.68–7.99 (m, 3H, Ar-H). Anal. Calc. for $C_{13}H_8Cl_2N_4O_2S$: C, 43.94; H, 2.25; N, 15.84. Found: C, 43.48; H, 2.58; N, 15.71.

Similarly, **7b, 7c** are synthesised and their characterisation data are given below:

7b (R_1 = *p*-Cl): m.p. 234–236 °C; yield 80 %; ν_{max}/ cm^{-1}: 1661, 1619, 1583, 1489, 1291; ^{1}H NMR: δ 2.20 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone-H), 7.20–8.56 (m, 4H, Ar–H), 9.76(bs, N–H). Anal. Calc. for $C_{13}H_9Cl_3N_4O_2S$: C, 48.66; H, 2.80; N, 17.54. Found: C, 48.31; H, 2.38; N, 17.89.

7c (R_1 = 2,4-Cl_2): m.p. 266–269 °C; yield 84 %; ν_{max}/ cm^{-1}: 1614, 1537, 1479, 1406, 1365; ^{1}H NMR δ 2.06 (s, 3H, CH_3), 6.68 (s, 1H, pyridazinone-H), 7.71–8.56 (m, 3H, Ar–H). Anal. $C_{13}H_8Cl_2N_4O_2S$, Calcd: C, 43.94; H, 2.25; N, 15.84. Found: C, 43.65; H, 2.54; N, 16.05.

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