Synthesis of Pyridazinone-substituted 1,3,4-Thiadiazoles, -1,3,4-Oxadiazoles and -1,2,4-Triazoles

Xiajuan Zou and Guiyu Jin*

Institute of Elemento-Organic Chemistry, National key laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin P. R. China 300071

Received September 11, 2000

Several 1-(1-aryl-1,4-dihydro-3-carboxy-6-methylpyridazin-4-one)-4-aryl thio-semicarbazides and their corresponding oxadiazole, thiadiazole and triazole derivatives were prepared and characterized by their spectral data. The preliminary biological tests showed that some new compounds exhibit good anti-fungal activity.

J. Heterocyclic Chem., **38**, 993 (2001).

Acylthiosemicarbazides and their related heterocyclic derivatives are reported to show a broad spectrum of biological activities. Some of these compounds have been shown to exhibit bactericide, fungicide and plant growth-effecting properties [1,2,3]. These observations, and our interest in 1-aryl-1,4-dihydro-3-carboxy-6-methyl-pyridazin-4-one chemistry [4], prompted us to undertake the synthesis of an, as yet unreported series of 1-(1-aryl-1,4-dihydro-6-methylpyridazin-3-carboxy-4-one)-4-aryl thiosemicarbazides **2a-c** and their corresponding thiadiazole **3a-c**, oxadiazole **4a-c** and triazole **5a-c**, **6a-c** derivatives which are novel tri-heterocyclic compounds in order to studying their biological properties.

The starting material, hydrazide of 1-aryl-1,4-dihydro-6-methylpyridazin-3-carboxy-4-one **1** obtained according to the literature [5, 6,7], which was reacted with various arylisothiocyanates afforded the acylthiosemicarbazides **2a-c** [8,9,10]. The treatment of **2a-c** with concentrated sulfuric acid yielded the corresponding 1,3,4-thiadiazoles **3a-c**, while the treatment of **2a-c** with $Hg(OAc)_2$ resulted in the formation of 1,3,4-oxadiazoles **4a-c**. The corresponding substituted 1,2,4-triazoles **5a-c** were obtained by reacting **2a-c** with sodium carbonate. The thioethers **6a-c** were prepared by reaction of thiones **5a-c** with iodomethane in sodium hydroxide, preferably with addition some non-homogeneous catalyst, for example tetrabutylammonium ion. (Scheme 1)

Scheme I

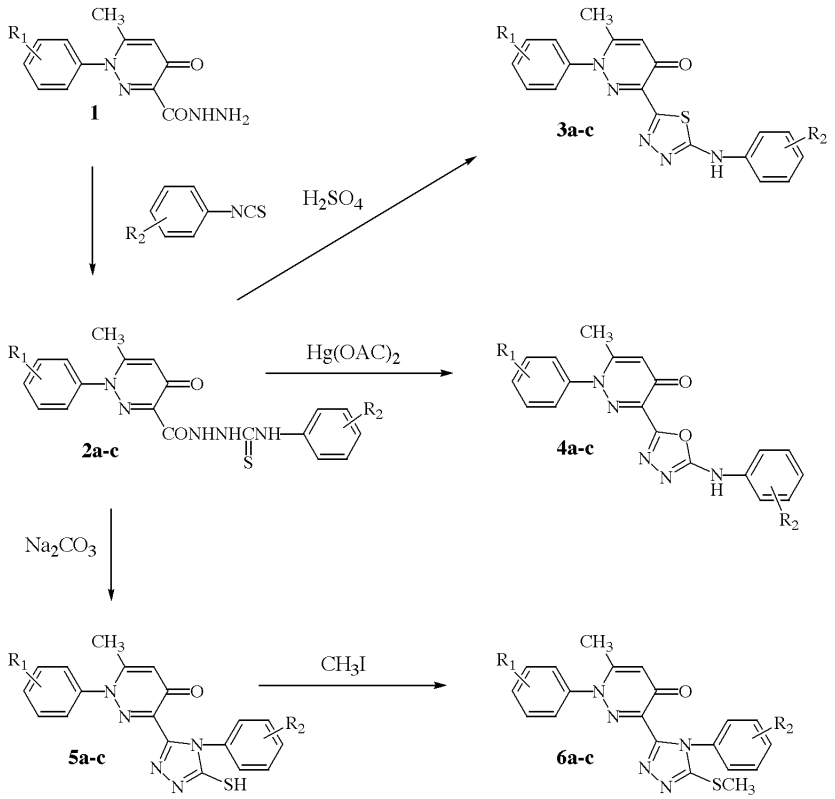


Table 1

Physical Data of New Compounds

No.	R_1	R_2	M.p (°C)	Yield (%)	Formula	Analysis % Calcd./Found C	H	N
2a	*p*-Cl	*o*-F	231-2	94	$C_{19}H_{15}ClFN_5O_2S$	52.84/52.94	3.48/3.60	16.22/16.36
2b	*p*-Cl	*m*-CF_3	234-5	95	$C_{20}H_{15}ClF_3N_5O_2S$	49.84/49.61	3.16/3.13	14.54/14.40
2c	*o*-Cl	*m*-CF_3	227-8	94	$C_{20}H_{15}ClF_3N_5O_2S$	49.84/49.75	3.16/3.11	14.54/14.49
3a	*p*-Cl	*o*-F	298-30	95	$C_{19}H_{13}ClFN_5OS$	55.10/55.37	3.16/3.11	16.98/16.98
3b	*p*-Cl	*m*-CF_3	>300	95	$C_{20}H_{13}ClF_3N_5OS$	51.77/51.55	2.80/2.81	15.16/15.25
3c	*o*-Cl	*m*-CF_3	>300	90	$C_{20}H_{13}ClF_3N_5OS$	51.77/51.60	2.80/2.84	15.16/15.15
4a	*p*-Cl	*o*-F	257-8	86.3	$C_{19}H_{13}ClFN_5O_2$	57.33/57.12	3.27/3.47	17.28/17.49
4b	*p*-Cl	*m*-CF_3	278-80	85.6	$C_{20}H_{13}ClF_3N_5O_2$	53.62/53.52	2.90/3.25	15.70/15.78
4c	*o*-Cl	*m*-CF_3	142-4	88	$C_{20}H_{13}ClF_3N_5O_2$	53.62/53.56	2.90/2.85	15.70/15.62
5a	*p*-Cl	*o*-F	>250	89.7	$C_{19}H_{13}ClFN_5OS$	55.10/54.99	3.16/3.11	16.93/16.70
5b	*p*-Cl	*m*-CF_3	>250	96	$C_{20}H_{13}ClF_3N_5OS$	51.77/51.79	2.80/3.00	15.16/15.15
5c	*o*-Cl	*m*-CF_3	>240	95	$C_{20}H_{13}ClF_3N_5OS$	51.77/51.69	2.80/2.80	15.16/15.15
6a	*p*-Cl	*o*-F	110-2	85	$C_{20}H_{15}ClFN_5OS$	56.12/56.07	3.50/3.44	16.44/16.45
6b	*p*-Cl	*m*-CF_3	171-3	84	$C_{21}H_{15}ClF_3N_5OS$	52.72/52.42	3.14/3.11	14.72/14.83
6c	*o*-Cl	*m*-CF_3	198-20	88	$C_{21}H_{15}ClF_3N_5OS$	52.72/52.55	3.14/3.12	14.72/14.72

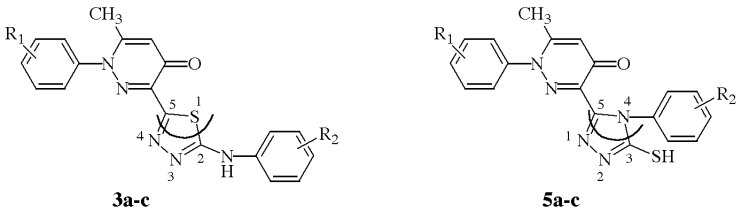
Table 2

Spectral Analyses of New Compounds

No	IR(ν/cm^{-1})	^{1}H-NMR(Solvent/δ)
2a	3266.5 (NH), 1670.0, 1639.5 (C=O), 1347 (C=S).	($DMSOd_6$): 2.20 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone), 7.20-7.84 (m, 8H, $2C_6H_4$), 9.76(bs), 12.20 (bs).
2b	3263.5 (NH), 1670.5, 1622. 0 (C=O), 1349.4 (C=S)	($DMSOd_6$): 2.20 (s, 3H, CH_3), 6.96 (s, 1H, pyridazinone), 7.44-8.24 (m, 8H, $2C_6H_4$), 10.28 (bs), 12.20 (bs).
2c	3232.0 (NH), 1700.7, 1626.0 (C=O),1329.2 (C=S)	($DMSOd_6$): 2.20 (s, 3H, CH_3), 7.12 (s, 1H, pyridazinone), 7.44-8.32 (m, 8H, $2C_6H_4$), 10.40 (bs).
3a	3235.5 (NH), 1619.1 (C=O)	($DMSOd_6$): 2.20 (s, 3H, CH_3), 6.64 (s, 1H, pyridazinone), 7.15-8.44 (m, 8H, $2C_6H_4$).
3b	3255.0 (NH), 1605.1 (C=O)	($DMSOd_6$): 2.20 (s, 3H, CH_3), 6.88 (s, 1H, pyridazinone), 7.36-8.32 (m, 8H, $2C_6H_4$), 10.96 (bs).
3c	3261.0 (NH), 1604.7 (C=O)	($DMSOd_6$): 2.20 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone), 7.36-8.40 (m, 8H, $2C_6H_4$), 11.04 (bs).
4a	1631.1 (C=O).	($DMSOd_6$): 2.20 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone), 7.12-8.32 (m, 8H, $2C_6H_4$), 10.64 (bs).
4b	3151.0 (NH), 1655.6 (C=O)	($DMSOd_6$): 2.20 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone), 7.36-8.08 (m, m, $2C_6H_4$), 11.28 (bs).
4c	3250.0 (NH), 1627.1 (C=O)	($DMSOd_6$): 2.00 (s, 3H, CH_3), 6.80 (s, 1H, pyridazinone), 7.28-8.00 (m, 8H, $2C_6H_4$), 11.12 (bs).
5a	2709.5, 1619.1 (C=O)	($DMSOd_6$): 2.10 (s, 3H, CH_3), 6.60 (s, 1H, pyridazinone), 7.20-7.80 (m, 9H, $2C_6H_4$,triazole-H).
5b	2730.0, 1618.2 (C=O)	($DMSOd_6$): 2.10 (s, 3H, CH_3), 6.41 (s, 1H, pyridazinone), 7.10-7.64 (m, 8H, $2C_6H_4$), 8.18 (s, 1H).
5c	2726.5, 1615.8 (C=O)	($DMSOd_6$): 2.00 (s, 3H, CH_3), 6.41 (s, 1H, pyridazinone), 7.44-7.80 (m, 9H, $2C_6H_4$,triazole-H).
6a	1631.1 (C=O)	($CDCl_3$): 2.20 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 6.60 (s, 1H, pyridazinone), 7.20-7.70 (m, 8H, $2C_6H_4$).
6b	1632.1(C=O)	($CDCl_3$+$DMSOd_6$): 2.20 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 6.40 (s, 1H, pyridazinone), 7.00-7.80 (m, 8H, $2C_6H_4$).
6c	1635.6 (C=O)	($CDCl_3$): 2.20 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 6.60 (s, 1H, pyridazinone), 7.32-7.90 (m, 8H, $2C_6H_4$).

The infrared spectra of **3a-c**, **4a-c**, **5a-c** and **6a-c** show C=C/C=N absorption bands between 1593.6-1400.0 cm^{-1} and show a broad band at 1314.5-1398.9 cm^{-1}. The compounds **3a-c** and **4a-c** exhibited N-H stretching absorption bands in the region between 3151.0-3261.0 cm^{-1}. The absorption bands due to the C=O group were observed in the range of 1604.7-1655.6 cm^{-1}. In the nuclear magnetic resonance spectra, compounds **3a-c** and

Scheme II



3a-c **5a-c**

Table 3

Mass Spectra of some New Compounds

No.	m/e (Relative Intensity)
3a	413(41), 394(52), 354(3), 263(3), 246(21), 229(12), 201(18), 193(34), 178(78), 168(61), 164(45), 152(89), 136(21), 111(100), 95(19), 75(95), 51(18).
3c	463(43), 444(2), 274(12), 263(1), 246(34), 218(63), 203(24), 193(43), 178(83), 152(100), 145(40), 125(18), 111(52), 95(12), 75(53).
5a	413(54), 394(16), 380(1), 340(11), 302(8), 246(10), 219(10), 201(38), 193(30), 178(71), 164(49), 152(62), 150(45), 123(22), 111(100), 95(49), 75(91).
5c	463(85), 444(4), 430(3), 404(2), 341(8), 298(7), 269(31), 246(29), 218(18), 203(3), 193(36), 178(94), 152(100), 145(46), 130(15), 111(59), 95(9), 75(48).

4a-c exhibited broad singlet between 10.64-11.28 ppm due to the phenylamino N-H protons. These peaks disappear upon addition of deuterium oxide.

The 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-4-aryl-1,2,4-triazole-3-thiol **5a-c** exhibited a characteristic band between 2709.5-2726.5 cm^{-1} due to the S-H group because there are large *ortho*-space block. These absorption bands disappear after compounds **5a-c** were reacted with iodomethane in sodium hydroxide to produce thioether **6a-c**. The previous reference mentioned that substituted 1,2,4-triazole thiols exist in a tautomeric form [2,11]. We found that compound **5a-c** exist mainly as the thiol form. Addition of silver nitrate solution dropwise to the solution of compounds **5a-c** in DMF, causes a white solid to appear immediately. The absorption bands due to the C=O group were observed in the ranged of 1615.0-1619.1 cm^{-1}. In the nuclear magnetic resonance spectra of **5a-c**, the S-H protons showed a singlet between 7.53-8.18 ppm. These peaks disappear upon addition of deuterium oxide.

The mass spectra of **3a**, **3c**, **5a** and **5c** were studied (scheme II). The molecular ion peak was found to be present in all the compounds. The intensity of the peaks varied from 1-100%. The cleavage of S-C2 and N4-C5 bonds gave ion with m/e 263 in 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-thiadiazoles **3a** and **3c**. The cleavage of N1-C5 and N4-C3 in 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-4-aryl-1,2,4-triazole-3-thiols **5a** and **5c** yield ion of m/e 390 and 340, respectively. In triazole **5a** and **5c**, the molecular ion lost HS• to give ions of m/e 380 and 430. This observation is accordant with our inference.

The preliminary biological tests showed that new compounds **2** exhibit antiviral activity against TMV. Compounds **3a-c** and **4c** gave mortality levels of 100% against *Puccinia recondita* and compound **5c** gave mortality levels of 80% at 500 ppm *in vivo*. A further study of their biological activity is underway.

EXPERIMENTAL

Melting points were measured on a Yanaco melting point apparatus and are uncorrected. Infrared spectra (ir) (potassium bromide) were recorded in a Shimadzu IR-435. ^1H NMR spectra on a JEOL FX-90Q spectrometer were used TMS as internal standard (chemical shift are in δ values). A HP 5988 A spectrometer operating at 70 ev was used to obtain the mass spectra. Elemental (C, H, and N) analyses were carried out on MT-3 analyzer.

(1-Aryl-1,4-dihydro-3-carboxy-6-methylpyridazin-4-one)-4-aryl Thiosemicarbazides (**2a-c**).

Equimolar quantities of hydrazide of 1-aryl-1,4-dihydro-3-carboxy-6-methylpyridazin-4-one **1** and appropriate arylisothiocyanates (1 mmol) were refluxed in 30 mL of absolute ethanol for 3 hours. The excess of solvent was removed under reduced pressure. The solid mass thus obtained was washed with ethanol, dried and recrystallized from ethanol. The physical constants and spectral analyses of these substituted thiosemicarbazides are recorded in Table 1 and Table 2.

5-[1-Aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-thiadiazole (**3a-c**).

Substituted thiosemicarbazides **2a-c** 0.5 mmol was added in portion to concentrated sulfuric acid (5 mL) at 0 °C and stirred for 1 hour maintaining the temperature at 0 °C. The reaction

mixture was then allowed to stand for 20 hours at room temperature, poured over crushed ice with stirring and the separated solid was washed with water and recrystallized from ethanol/DMF. The physical constants and spectral analyses of these substituted 1,3,4-thiadiazoles are recorded in Table 1, Table 2 and Table 3.

5-[1-Aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-aryl-amino-1,3,4-oxadiazole (**4a-c**).

To a solution of compound **2a-c** 0.5 mmol in ethanol (20 mL) was added 0.5 mmol $Hg(OAc)_2$. The reaction mixture was refluxed for 3 hours and concentrated under reduced pressure. The solid was dissolved in hot *N*,*N*-dimethylformamide and filtered. The filtrate was concentrated under reduced pressure and recrystallized from ethanol/DMF. The physical constants and spectral analyses of these substituted 1,2,4-oxadiazoles are recorded in Table 1 and Table 2.

5-[1-Aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-4-aryl-1,2,4-triazole-3-thiol (**5a-c**).

Compound **2a-c** (1 mmol) was refluxed in 30 mL of 5% aqueous sodium carbonate solution for 5 hours. The reaction mixture was filtered, cooled and acidified to pH 2 with 2 *N* hydrochloric acid. The precipitate of the crude product was filtered, washed several times with cold water, dried and purified by silica gel column chromatography, eluted with ethyl acetate. The physical constants and spectral analyses of these substituted 1,2,4-triazole-3-thiols are recorded in Table 1, Table 2 and Table 3.

5-[1-Aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-4-aryl-1,2,4-triazole-3-methylthio (**6a-c**).

A mixture of compound **5a-c** (0.5 mmol) and 0.1ml of 20% sodium hydroxide and 2.5 X 10^{-3} mmol tetrabutylammonium in 15 mL dichloromethane was stirred for 10 minutes, then iodomethane (0.5 mmol) was added at 5 °C .The suspension formed was stirred at room temperature for 2 days and 4 mL of water was added. The mixture was stirred at room temperature for 1 hour. The dichloromethane was isolated and concentrated under pressure. The residue was purified by silica gel column chromatography, eluted with ethyl acetate/acetone. The physical constants and spectral analyses of these substituted 1,2,4-triazole-3-methylthioes are recorded in Table 1 and Table 2.

Acknowledgements.

Financial support of this work by the National Nature Science Foundation of China (projects number 29832050) is gratefully acknowledged.

REFERENCES AND NOTES

[1] H. V. Patel and P. S. Fernandes, *J. Indian Chem. Soc.*, **67**, 401 (1990).

[2] P. J. Kothari, M. A. Mehlhoff, S. P. Singh, S. S. Parmar, and V. I. Stenberg, *J. Heterocyclic Chem.*, **17**, 1369 (1980).

[3] P. F. Juby and T. W. Hudyma, *J. Med. Chem*., **12**, 396 (1969).

[4] Z. M. Li, X. J. Zou , E. Y. Yao and S. H. Wang, *Chinese Journal Apply Chemistry*, **10(6)**, 86-88. (1993)

[5] T. T. Fujimoto, US 4,345,934; *Chem. Abstr*., **97**, p194594 (1982).

[6] T. T. Fujimoto, Ger Offen. 2,808,795; *Chem. Abstr*., **90**, p1691 (1978).

[7] E. Haddock, W. J. Hopwood, EP 0037133; *Chem. Abstr*., **96**, p69011 (1981).

[8] B. Rigo, *J. Heterocyclic chem*.., **26**, 1723 (1989).

[9] B. K. Paul and U. P. Basu, *J. Indian Chem. Soc*., **46**, 1121 (1969).

[10] Z. Y. Zhang and. H. Yang, *Chinese Journal of Organic Chemistry*, **3**, 184 (1986).

[11] A. K. S. Gupta and H. K. Misra, *J. Indian Chem. Soc*., Vol. **LVIII**, 508 (1981).