Synthesis and Fungicidal Activity against *Rhizoctonia solani* of 2-Alkyl (Alkylthio)-5-pyrazolyl-1,3,4-oxadiazoles (Thiadiazoles)

Hansong Chen, Zhengming Li,* and Yufeng Han

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

Some series of 2-alkyl (alkythio)-5-((4-chloro)-3-ethyl-1-methyl-1H-pyrazole-5-yl)-1,3,4-oxadiazoles (thiadiazoles) were prepared as potential fungicides. Their fungicidal activity was evaluated against rice sheath blight, which is a major disease of rice in China. Structure−activity relationships for the screened compounds were evaluated and discussed. It was found that 5-(4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-yl)-1,3,4-thiadiazole-2-thione has the higher fungicidal activity.

Keywords: *Pyrazolyl-1,3,4-oxadiazole; pyrazoly1-1,3,4-thiadiazole; fungicide; rice sheath blight; Rhizoctonia solani*

1. INTRODUCTION

It is well-known that the study of pyrazole derivatives is significant in pesticide chemistry. Among the pyrazole derivatives some compounds are broadly used as insecticides, herbicides and fungicides, such as fripronil (MB46030) (Colliot et al., 1992), tebufenpyrad (Okada et al., 1988), pyrazosulfuron-ethyl (NC-311) (Nissan Chemical Industries, Ltd. 1982), and so on.

However, a survey of the literature revealed that linked biheterocyclic compounds containing pyrazole to possess biological activity are seldom reported. 1,3,4-Oxadiazole, 1,3,4-thiadiazole derivatives all being fungicidal (Ashour et al., 1994; Funatsukuri and Ueda, 1966), if they are linked to pyrazole ring respectively, the biheterocydic compounds obtained could have better fungicidal activity. As part of our program aimed at developing a new class of agrochemicals we synthesized the title compounds and studied their fungicidal activity.

2. MATERIALS AND METHODS

2.1. Synthetic procedures. All melting points were determined with Yanaco MP-300 micro melting points apparatus, and the values are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC−P200 spectrometer, using tetramethylsilane (TMS) as an internal reference and $CDCl_3$ or CD_3COCD_3 as the solvent. Elemental analyses were performed on a Yanaco CHN CORDER MT-3 instrument.

*5-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-1,3,4-oxadiazole-2-thione (**2a**).* To a solution of compound **1a** (2.35 g, 12.5 mmol) in ethanol (50 mL) at 0 °C were added carbon disulfide (3.8 g, 50 mmol) and potassium hydroxide (0.86 g, 12.5 mmol). After addition, the mixture was refluxed for 7 h. The solvent was evaporated. The residue was dissolved in water and acidified with dilute hydrochloric acid. The precipitate was filtered and recrystallized from ethanol to give 2.4 g(yield 70%) of **2a** as a white solid. Yield, 70%; mp, 199 °C (d). ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, 3H), 2.68 (q, 2H), 4.12 (s, 3H), 11.39 (s, 1H). Analysis found: C, 39.63; H, 3.78; N, 23.20. Calcd. for $C_8H_9ClN_4OS$: C, 39.26; H, 3.71; N, 22.90.

*5-(3-Ethyl-1-methyl-1H-pyrazole-5-y1)-1,3,4-oxadiazole-2-thione (**2b**).* Compound **2b** was prepared by the same method as **2a**. Yield, 76%; mp, 199−200 °C. ^{1}H NMR (CD_3COCD_3) δ: 1.69 (t, 3H), 3.09 (q, 2H), 4.53 (s, 3H), 7.19 (s, 1H), 13.80 (s, 1H). Analysis found: C, 46.03; H, 4.64; N, 26.26. Calcd. for $C_8H_{10}N_4OS$: C, 45.70; H, 4.79; N, 26.65.

*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-5-methylthio-1,3,4-oxadiazole (**3a**).* A mixture of compound **2a** (0.61 g, 2.5 mmol), 1N aqueous sodium hydroxide solution (2.5 mL, 2.5 mmol), and tetrabutylammonium bromide (0.1 g) was stirred for several minutes, and then methyl iodide (0.35 g, 2.5 mmol) and toluene (20 mL) were added. After the mixture was stirred for 24 h at room temperature, the organic layer was separated and dried over magnesium sulfate. The solvent was removed in vacuo, and the residue was subjected to silica gel column chromatography to give 0.5 g of **3a** as a white powder. Yield, 77%; mp, 85−86 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H), 2.66 (q, 2H), 2.77 (s, 3H), 4.16 (s, 3H). Analysis found: C, 41.81; H, 4.32; N, 21.53. Calcd. for $C_9H_{11}ClN_4OS$: C, 45.78; H, 4.25; N, 21.65.

Compounds **3b**−**3l** were prepared in the same method as **3a** by using the corresponding alkyl halide instead of methyl iodide.

*5-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-2-propylthio-1,3,4-oxadiazole (**3b**).* Yield, 80%; mp, 37−38 °C. ^{1}H NMR ($CDCl_3$) δ: 1.05 (t, 3H), 1.24 (t, 3H), 1.86 (m, 2H), 2.64 (q, 2H), 3.27 (t, 2H), 4.15 (s, 3H). Analysis found: C, 45.99; H, 5.16; N, 19.58. Calcd. for $C_{11}H_{15}ClN_4OS$: C, 46.07; H, 5.27; N, 19.54.

*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-5-(2-methylpropylthio)-1,3,4-oxadiazole (**3c**).* Yield, 17%; an oil. ^{1}H NMR ($CDCl_3$) δ: 1.03 (t, 6H), 1.21 (t, 3H), 2.08 (m, 1H), 2.62 (q, 2H), 3.15 (d, 2H), 4.13 (s, 3H). Analysis found: C, 47.83; H, 5.54; N, 18.48. Calcd. for $C_{12}H_{17}ClN_4OS$: C, 47.91; H, 5.70; N, 18.63.

*2-Amylthio-5-(4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-1,3,4-oxadiazole (**3d**).* Yield, 79%; an oil. ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, 3H), 1.20 (t, 3H), 1.36 (m, 4H), 1.86 (m, 2H), 2.61 (q, 2H), 3.23 (t, 2H), 4.12 (s, 3H). Analysis found: C, 49.31; H, 5.92; N, 17.57. Calcd. for $C_{13}H_{19}ClN_4OS$: C, 49.60; H, 6.08; N, 17.80.

*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-5-heptylthio-1,3,4-oxadiazole (**3e**).* Yield, 73%; an oil. ^{1}H NMR ($CDCl_3$) δ: 0.84 (t, 3H), 1.08−1.46 (m, 11H), 1.81 (m, 2H), 2.63 (q, 2H), 3.25 (t, 2H), 4.14 (s, 3H). Analysis found: C, 52.68; H, 6.74; N, 16.18. Calcd. for $C_{15}H_{23}ClN_4OS$: C, 52.54; H, 6.76; N, 16.34.

*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-5-octylthio-1,3,4-oxadiazole (**3f**).* Yield, 76%; mp, <30 °C. ^{1}H NMR ($CDCl_3$) δ: 0.85 (t, 3H), 1.20−1.49 (m, 13H), 1.87 (m, 2H), 2.63 (q, 2H), 3.26 (t, 2H), 4.15 (s, 3H). Analysis found: C, 53.52; H, 6.96; N, 15.38. Calcd. for $C_{16}H_{25}ClN_4OS$: C, 53.84; H, 7.06; N, 15.70.

*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-5-(1-ethoxycarbonylethylthio)-1,3,4-oxadiazole (**3g**).* Yield, 87%; an oil. ^{1}H

10.1021/jf991065s CCC: $19.00
Published on Web 10/21/2000

NMR ($CDCl_3$) δ: 1.22 (m, 6H), 1.69 (d, 3H), 2.64 (q, 2H), 4.12 (s, 3H), 4.20 (q, 2H), 4.45 (q,1H). Analysis found: C, 45.20; H, 4.78; N, 15.96. Calcd. for $C_{13}H_{17}ClNO_3S$: C, 45.28; H, 4.97; N, 16.25.

*2-(3-Ethyl-1-methyl-1H-pyrazole-5-y1)-5-methylthio-1,3,4-oxadiazole (**3h**).* Yield, 77%; mp, 68−69 °C. ^{1}H NMR ($CDCl_3$) δ: 1.21 (t, 3H), 2.62 (q, 2H), 2.72 (s, 3H), 4.16 (s, 3H), 6.55 (s, 1H). Analysis found: C, 48.30; H, 5.28; N, 24.93. Calcd. for $C_9H_{12}N_4OS$: C, 48.20; H, 5.39; N, 24.98.

*2-(3-Ethyl-1-methyl-1H-pyrazole-5-y1)-5-ethylthio-1,3,4-oxadiazole (**3i**).* Yield, 73%; mp, 34−35 °C. ^{1}H NMR ($CDCl_3$) δ: 1.21 (t, 3H), 1.47 (t, 3H), 2.63 (q, 2H), 3.26 (q, 2H), 4.16 (s, 3H), 6.55 (s, 1H). Analysis found: C, 50.35; H, 5.93; N, 23.17. Calcd. for $C_{10}H_{14}N_4OS$: C, 50.40; H, 5.92; N, 23.51.

*2-(3-Ethyl-1-methyl-1H-pyrazole-5-y1)-5-propylthio-1,3,4-oxadiazole (**3j**).* Yield, 80%; an oil. ^{1}H NMR ($CDCl_3$) δ: 1.02 (t, 3H), 1.21 (t, 3H), 1.84 (m, 2H), 2.62 (q, 2H), 3.22 (t, 2H), 4.16 (s, 3H), 6.54 (s, 1H). Analysis found: C, 52.20; H, 6.19; N, 22.47. Calcd. for $C_{11}H_{16}N_4OS$: C, 52.36; H, 6.39; N, 22.20.

*2-Amylthio-5-(3-ethyl-1-methyl-1H-pyrazole-5-y1)-1,3,4-oxadiazole (**3k**).* Yield, 71%; an oil. ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, 3H), 1.22 (t, 3H), 1.38 (m, 4H), 1.79 (m, 2H), 2.64 (q, 2H), 3.25 (t, 2H), 4.17 (s, 3H), 8.56 (s, 1H). Analysis found: C, 55.49; H, 6.96; N, 20.08. Calcd. for $C_{13}H_{20}N_4OS$: C, 55.69; H, 7.19; N, 20.08.

*2-(3-Ethyl-1-methyl-1H-pyrazole-5-y1)-5-(1-ethoxycarbonylethylthio)-1,3,4-oxadiazole (**3l**).* Yield, 84%; an oil. ^{1}H NMR ($CDCl_3$) δ: 1.16 (m, 6H), 1.64 (d, 3H), 2.5 (q, 2H), 4.16 (s, 3H), 4.19 (q, 2H), 4.38 (q, 1H), 6.52 (s, 1H). Analysis found: C, 49.96; H, 5.62; N, 17.84. Calcd. for $C_{13}H_{18}NO_3S$: C, 50.03; H, 5.84; N, 18.05.

*5-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-1,3,4-oxadiazole-2-one (**4**).* To a solution of compound **3b** (0.59 g, 2.2 mmol) in formic acid (98%, 15 mL) were added 30% hydrogen peroxide (1.0 g, 8.8 mmol, 1.1 mL) and water (1 mL). The mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo, and the solid obtained was washed with water then recrystallized from ethanol to give 0.45 g of **4** as a white solid. Yield, 75%; mp, 175−176 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H), 2.66 (q, 2H), 4.07 (s, 3H), 9.75 (s, 1H). IR: 1780 cm^{-1}. Analysis found: C, 41.70; H, 4.16; N, 24.20. Calcd. for $C_8H_9ClN_4O_2$: C, 42.03; H, 3.97; N, 24.50.

*5-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-3-methyl-1,3,4-oxadiazole-2-one (**5**).* To a solution of compound **4** (0.40 g, 1.7 mmol) in THF (15 mL) was added 1N aqueous sodium hydroxide (1.7 mL, 1.7 mmol). The mixture was stirred for several minutes and then methyl iodide (0.5 mL) was added. After stirring for 5 h at room temperature, the solvent was concentrated under reduced pressure. The residue was dissolved in chloroform (20 mL), washed with water two times (20 × 2), and then dried over magnesium sulfate. The solvent was removed in vacuo, and the residue was subjected to silica gel column chromatography to give 0.3 g of **5** as a white powder. Yield, 73%; mp, 114−115 °C. ^{1}H NMR ($CDCl_3$) δ: 1.22 (t, 3H), 2.61 (q, 2H), 3.50 (s, 3H), 4.01 (s, 3H). IR: 1784 cm^{-1}. Analysis found: C, 44.40; H, 4.75; N, 22.93. Calcd. for $C_9H_{11}ClN_4O_2$: C, 44.55; H, 4.57; N, 23.09.

*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-5-chloromethyl-1,3,4-oxadiazole (**6a**).* To a solution of **1a** (0.72 g, 3.5 mmol) in $POCl_3$ (7 mL) was added dry chloroacetic acid (0.33 g, 3.5 mmol). The mixture was heated under reflux for 7 h. The excess $POCl_3$ was removed under reduced pressure, and the residue was poured into ice water and allowed to stand overnight. The solid obtained was washed with dilute aqueous sodium hydroxide and water respectively, dried, and purified by silica gel column chromatography to give 0.52 g of **6a** as a white solid. Yield, 56%; mp, 100−101 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H), 2.67 (q, 2H), 4.20 (s, 3H), 4.79 (s, 2H). Analysis found: C, 41.53; H, 3.65; N, 21.44. Calcd. for $C_9H_{10}Cl_2N_4O$: C, 41.40; H, 3.86; N, 21.46.

Compounds **6b**−**6d** were prepared in the same method as **6a** using the corresponding aliphatic acid instead of chloroacetic acid.

*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-5-trifluoromethyl-1,3,4-oxadiazole (**6b**).* Yield, 71%; mp, 52−53 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H), 2.68 (q, 2H), 4.23 (s, 3H). Analysis found: C, 38.81; H, 2.68; N, 20.14. Calcd. for $C_9H_8ClF_3N_4O$: C, 38.52; H, 2.87; N, 19.96.

*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-2-ethyl-1,3,4-oxadiazole (**6c**).* Yield, 57%; mp, 62−63 °C. ^{1}H NMR ($CDCl_3$) δ: 1.24 (t, 3H), 1.42 (t, 3H), 2.65 (q, 2H), 2.96 (q, 2H), 4.17 (s, 3H). Analysis found: C, 49.94; H, 5.50; N, 23.36. Calcd. for $C_{10}H_{13}ClN_4O$: C, 49.90; H, 5.44; N, 23.28.

*2-Butyl-5-(4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-1,3,4-oxadiazole (**6d**).* Yield, 64%; mp, 43−44 °C. ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3H), 1.23 (t, 3H), 1.46 (m, 2H), 1.83 (m, 2H), 2.64 (q, 2H), 2.91 (t, 2H), 4.16 (s, 3H). Analysis found: C, 53.34; H, 6.13; N, 20.82. Calcd. for $C_{12}H_{17}ClN_4O$: C, 53.63; H, 6.38; N, 20.85.

*Potassium 3-(4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carbonyl)dithiocarbazate (**7**).* A solution of potassium hydroxide (2.06 g, 0.03mol), absolute ethanol (50 mL), and **1a** (6.10 g, 0.03 mL) was treated to the addition of carbon disulfide (3.43 g, 0.06 mol). The mixture was diluted with absolute ethanol (70 mL) and stirred for 16 h. It was then diluted with dry ether (100 mL) and vacuum-dried at 65 °C. This salt, prepared as described above, was obtained in nearly quantitative yield and was used in the next reaction without further purification.

*5-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-1,3,4-thiadiazole-2-thione (**8**).* Potassium dithiocarbazate 7 (8.5 g, 27 mmol) was added in portions to concentrated H_2SO_4 (35 mL) at 0 °C over 40 min. The mixture was stirred for 1 h at room temperature and poured over crushed ice and allowed to stand overnight. The separated solid was dissolved in dilute aqueous sodium hydroxide. The insoluble solid was filtered and the filtrate was acidified with dilute hydrochloric acid. The solid obtained was washed with water, dried, and recrystallized from ethanol to give 4.5 g of **8** as a light green solid. Yield, 64%; mp, 182−183 °C. ^{1}H NMR (CD_3COCD_3) δ: 1.20 (t, 3H), 2.59 (q, 2H), 3.21 (s, 1H), 4.06 (s, 3H). Analysis found: C, 37.00; H, 3.21; N, 21.88. Calcd. for $C_8H_9ClN_4S_2$: C, 36.85; H, 3.48; N, 21.49.

*5-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-2-methylthio-1,3,4-thiadiazole (**9a**).* A mixture of compound **8** (0.52 g, 2 mmol), 1N aqueous sodium hydroxide solution (2 mL, 2 mmol), and tetrabutylammonium bromide (0.1 g) was stirred for several minutes, and then methyl iodide (0.29 g, 2 mmol) and toluene (20 mL) were added. After stirring for 24 h at room temperature, the organic layer was separated and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was subjected to silica gel column chromatography to give 0.42 g of **9a** as a white powder. Yield, 83%; mp, 106−107 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H), 2.65 (q, 2H), 2.63 (s, 3H), 4.22 (s, 3H). Analysis found: C, 39.18; H, 4.03; N, 20.15. Calcd. for $C_9H_{11}ClN_4S_2$: C, 39.34; H, 4.04; N, 20.39.

Compounds **9b**−**9e** were prepared in the same method as **9a** by using the corresponding alkyl halide instead of methyl iodide.

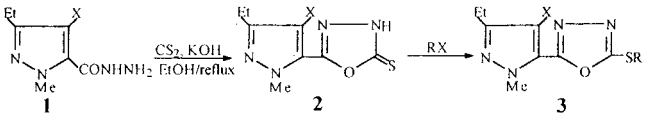
*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-5-ethylthio-1,3,4-thiadiazole (**9b**).* Yield, 85%; mp, 93−94 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H), 1.49 (t, 3H), 2.65 (q, 2H), 3.39 (q, 2H), 4.23 (s, 3H). Analysis found: C, 41.53; H, 4.52; N, 19.26. Calcd. for $C_{10}H_{13}ClN_4S_2$: C, 41.59; H, 4.54; N, 19.40.

*2-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-5-propylthio-1,3,4-thiadiazole (**9c**).* Yield, 71%; mp, 59−60 °C. ^{1}H NMR ($CDCl_3$) δ: 1.05 (t, 3H), 1.24 (t, 3H), 1.83 (m, 2H), 2.65 (q, 2H), 3.34 (t, 2H), 4.22 (s, 3H). Analysis found: C, 43.70; H, 4.91; N, 18.27. Calcd. for $C_{11}H_{15}ClN_4S_2$: C, 43.60; H, 4.99; N, 18.50.

*2-Allylthio-5-(4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-1,3,4-thiadiazole (**9d**).* Yield, 83%; mp, 66−67 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H), 2.67 (q, 2H), 3.99 (d, 2H), 4.23 (s, 3H), 5.28 (s × 4, 2H), 5.99 (m, 1H). Analysis found: C, 43.77; H, 4.23; N, 18.41. Calcd. for $C_{11}H_{13}ClN_4S_2$: C, 43.92; H, 4.36; N, 18.62.

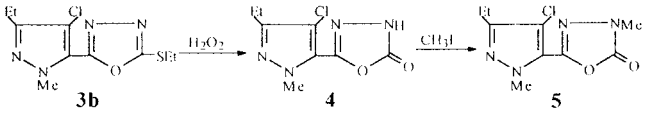
*2-Amylthio-5-(4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-y1)-1,3,4-thiadiazole (**9e**).* Yield, 83%; mp, 54−55 °C. ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, 3H), 1.25 (t, 3H), 1.38 (m, 4H), 1.82 (m, 2H), 2.65 (q, 2H), 3.34 (t, 2H), 4.22 (s, 3H). Analysis found:

Scheme 1



1a-b X=Cl, H; **2a-b** X=Cl, H; **3a-g** X=Cl, R=CH_3, n-C_3H_7, $CH_2CH(CH_3)_2$, n-C_5H_{11}, n-C_7H_{11}, n-C_8H_{17}, $CH(CH_3)CO_2C_2H_5$; **3h-l** X=H, R=CH_3, C_2H_5, n-C_3H_7, n-C_5H_{11}, $CH(CH_3)CO_2C_2H_5$

Scheme 2



Scheme 3

6a-d R_1=CH_2Cl, CF_3, C_2H_5, n-C_4H_9

C, 47.47; H, 5.72; N, 16.82. Calcd. for $C_{13}H_{19}ClN_4S_2$: C, 47.19; H, 5.79; N, 16.93.

2.2 Biological assay. Most of compounds were tested for control of rice sheath blight pathogen, *Rhizoctonia solani*, on rice seedlings at the fifth-leaf stage. The compounds were formulated in water and DMF (5 + 1 by volume) (containing 2.5 g liter^{-1} Tween 80) to 500- and 100-mg-liter^{-1} solutions which were applied to the rice seedlings as foliar sprays using a hand-held spray gun. The next day the seedlings were inoculated with the chaff medium within *Rhizoctonia solani* (the causal fungus of the rice sheath blight). Then the plants were immediately placed in a temperature- and humidity-controlled chamber at 28 °C for 4 days. After treatment, percentage of disease control in the treated seedlings was compared to that of seedlings with a treatment in the absence of the experimental compounds, and fungicidal activity was estimated. Four replicates were included in the evaluation. For comparative purposes, the commercial fungicide Carbendazim was tested under the same conditions as the title compounds.

3. RESULTS AND DISCUSSION

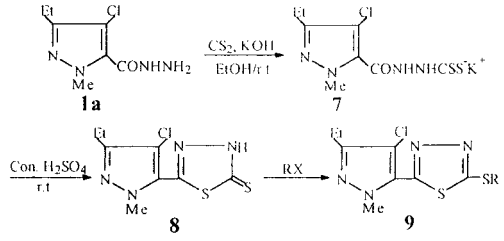
3.1 Synthesis. In our previous paper, we reported the synthesis of 5-pyrazole formic acid hydrazide (**1**) (Li et al., 1997). 5-pyrazolyl-1,3,4-oxadiazole-2-thione compounds (**2**) were obtained via compounds **1** reacted with carbon disulfide and potassium hydroxide in refluxing ethanol; then alkylation of **2** afforded 2-alkylthio-5-pyrazolyl-1,3,4-oxadiazoles (**3**) (Scheme 1).

Oxidation of 2-ethylthio-5-pyrazolyl-1,3,4-oxadiazole by hydrogen peroxide in formic acid afforded 5-pyrazolyl-1,3,4-oxadiazole-2-one (**4**), which was alkylated by methyl iodide to give 3-methyl-5-pyrazolyl-1,3,4-oxadiazole (**5**) (Scheme 2).

The chemical literature records several synthetic routes leading to the formation of 3,5-disubstituted-1,3,4-oxadiazole (Yang and Hua, 1996). In this paper, 2-alkyl-5-pyrazolyl-1,3,4-oxadiazoles were synthesized from compound **1a** and aliphatic acid via a one-pot synthetic method in the presence of phosphorus oxychloride (Scheme 3).

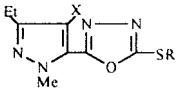
The synthesis of 2-alkylthio-5-pyrazolyl-1,3,4-thiadiazoles (**9**) is outlined in Scheme 4. 5-pyrazole hydrazide (**1a**) reacted with carbon disulfide in ethanolic potassium hydroxide at room temperature to yield the potassium 1-(4-chloro-3-ethyl-1-ethyl-1H-pyrazole-5-carbonyl) dithiocarbazates (**7**), which were cyclized in

Scheme 4



9a-b R=CH_3, C_2H_5, n-C_3H_7, $CH_2CH{=}CH_2$, n-C_5H_{11}

Table 1. Fungicidal Screening Results of Compounds 2, 3, 4, and 5



compd.	X	R	inhibition of rice sheath blight[a] 500 ppm	100 ppm
2a	Cl	H	1	0
2b	H	H	2	1
3a	Cl	CH_3	4	3
3b	Cl	*n*-C_3H_7	4	2
3d	Cl	*n*-C_5H_{11}	3	1
3e	Cl	*n*-C_7H_{15}	2	2
3f	Cl	*n*-C_8H_{17}	2	2
3g	Cl	$CH(CH_3)CO_2Et$	0	0
3h	H	CH_3	4	2
3i	H	C_2H_5	4	2
3j	H	*n*-C_3H_7	3	1
3k	H	*n*-C_5H_{11}	2	0
3l	H	$CH(CH_3)CO_2Et$	1	0
4			0	0
5			1	0
carbendazim			5	5

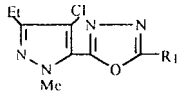
[a] On a scale of 0−5, where 0 = 0−24% control; 1 = 25−49% control; 2 = 50−69% control; 3 = 70−89% control; 4 = 90−99% control, and 5 = complete control.

concentrated sulfuric acid to afford 5-pyrazolyl-1,3,4-thiadiazole-2-thiones (**8**), which, when followed by alkylation, gave compounds **9**.

Oxidation of **3b** by hydrogen peroxide gave **4** instead of the corresponding compound 2-ethysulfonyl-5-pyrazolyl-1,3,4-oxadiazole. A strong oxidant is the cause of the result. Compound **4** exists in "one" form, which was confirmed by its infrared spectra. A strong absorption was observed in the region of 1780 cm^{-1}, which is indicative of a carbonyl group.

Alkylation of **4** by methyl iodide yielded **5**, and infrared spectra confirmed its structure as well. A methyl group is linked to the N atom at the 3-position of the 1,3,4-oxadiazole ring instead of the O-atom of the 2-position. This result is different from the methylation of compound **2**. The theory of hard soft acid base can explain this phenomenon. The S atom of **2** is a soft base, the N atom is a medium base, and the C atom of **4** is a hard acid. Methyl iodide as soft acid preferred to S rather than N when it reacted with **2**. But when it reacted with **4**, it preferred N to O.

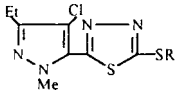
Table 2. Fungicidal Screening Results of Compounds 6



compd.	R_1	inhibition of rice sheath blight[a] 500 ppm	100 ppm
6a	CH_2Cl	4	2
6b	CF_3	3	1
6c	C_2H_5	3	1
6d	n-C_4H_9	3	1

[a] On a scale of 0−5, where 0 = 0−24% control; 1 = 25−49% control; 2 = 50−69% control; 3 = 70−89% control; 4 = 90−99% control, and 5 = complete control.

Table 3. Fungicidal Screening Results of Compounds 8 and 9



compd.	R	inhibition of rice sheath blight[a] 500 ppm	100 ppm
8	H	5	4
9a	CH_3	4	4
9b	C_2H_5	4	4
9c	n-C_3H_7	3	3
9d	$CH_2CH{=}CH_2$	2	1
9e	n-C_5H_{11}	3	1

[a] On a scale of 0−5, where 0 = 0−24% control; 1 = 25−49% control; 2 = 50−69% control; 3 = 70−89% control; 4 = 90−99% control, and 5 = complete control.

3.2. Structure−Activity Relationship (SAR). Tables 1−3 summarize the fungicidal screening results of the study compounds. The results indicated that compounds **3** had significant potency against *Rhizoctonia solani*, and compounds **2** had hardly any inhibition against *R.solani*, that is to say, the activity of compounds that were substituted by alkylthio at the 2-position of the 1,3,4-oxadiazole ring was higher than the activity of those compounds that were substituted by mercapto. The activity was found to fall off with increasing size of the alkyl group (*R*). The preferred substituent for *R* was found to be methyl. Loss of biological activity was observed if the chloride atom at the 4-position of the pyrazole ring was substituted by hydrogen. Oxidation of the sulfide group of compound **3** to 2-one analogue **5** almost eliminated the activity.

Removal of the sulfur atom, by replacement of the alkylthio group with an alkyl group, resulted in some decrease in activity. A sulfur atom at the 2-position of 1,3,4-oxadiazole is necessary for fungicidal activity to occur.

The idea of bioisosterism is one of the most successful techniques of bioactive compound design (Lipinski, 1986). The substitution of oxygen for sulfur in the heterocyclic ring represents an example of an approach that is commonly known as bioisosterim. The 1,3,4-thiadiazole ring is a bioisosteric analogue of the 1,3,4-oxadiazole. The bioassay indicated that replacing O for S appears to retain fungicidal activity. As with compounds **3**, the activity of compounds **9** was found to increase with decreasing size of the alkyl group *R* at the 3-position of the 1,3,4-thiadiazole. Compound **8** has the same activity as compounds **9**, which is different from compounds **2** and **3**.

LITERATURE CITED

Ashour F. A.; El-Hawash S. A. M.; Mahran, M. A.; et al. Synthesis, antibacterial and antifungal activity of some new 1,3,4-oxadiazoles and 2-substituted amino-1,3,4-oxadizole derivatives containing benzimidazole moiety. *Bull. Pharm. Sci., Assiut Univ.* **1994**, *17*(1), 17.

Colliot F.; Kukorowski K. A.; Hawkins D. W., et al. Fipronil: a new soil and foliar broad spectrum insecticide. Proceedings of *Brighton Crop Prot. Conf. — Pests & Disease* **1992**, *1*, 29.

Funatsukuri, G.; Ueda, M. 5-Amino-1,3,4-thiadiazoles. Japanese Patent 20,944.

Lipinski, C. A. Bioisosterism in drug design. *Annu. Rep. Med. Chem.* **1986**, *21*, 283.

Li, Z.; Chen, H,; Zhao, W., et al. Synthesis and biological activity of pyrazole derivatives. *Chem. J. Chin. Univ.* **1997**, *18* (11), 1794.

Nissan chemical industries, Ltd. Pyrazolesulfonylurea derivatives. Japanese Patent 122,488.

Okada I.; Okui S.; Tsakahshi Y. *et al.* Preparation and testing of pyrazolecarboxamides as insecticides and acaricides. European Patent 289,879.

Yang, J.; Hua, W.. Review: Synthesis of 2,5-substituted-1,3,4-oxadizole derivatives. *Chemistry* **1996**, *9*, 18.

Received for review September 27, 1999. Revised manuscript received May 7, 2000. Accepted May 7, 2000. This project was supported by the National Natural Science Foundation of China (project no. 29832050).

JF991065S