PHASE TRANSFER CATALYSTS PROMOTING THE ONE-POT SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 1-(5-METHYLISOXAZOYL-4-CARBONYL)-4-ARYLTHIOSEMICARBAZIDES AND THEIR RELATED HETEROCYCLIC COMPOUNDS

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Abstract : Reaction of aryl acylhydrazine with 5-methylisoxazoyl chloride and ammonium thiocyanate under the condition of solid–liquid phase-transfer catalysis using polyethylene glycol-600 (PEG-600) as the catalyst and ultrasonic irradiation yielded 1-(5-methylisoxazoyl-4-carbonyl)-4-arylthiosemicarbazides **3a-j** in good-to-excellent yield. Furthermore a series of 1,3,4-thiadiazole derivatives **4a-j** were synthesized via reaction of the thiosemicarbazide with acetate acid. The chemical structures of all compounds were established by ^{1}H NMR, FTIR, MS, and elemental analysis, and some of these compounds were investigated for fungicidal activity. The bioassay results indicated that some of these compound exhibit moderate fungicidal activities.

Key Words : 1-(5-methylisoxazoyl-4-carbonyl)-4-arylthiosemicarbazides; 1,3,4-thidiazole derivatives; one-pot synthesis; phase transfer catalysis; fungicidal activity.

Introduction

Research on the synthesis heterocyclic compounds is an important developmental oriental in pesticide and medicine chemistry [1-4]. 5-Methylisoxazole-4-carboxylic acid is the mediate of Leflunomide which is a drug used for the treatment of rheumatoid arthritis, an illness that affects soft tissues and bones and can cause irreversible joint deformities and functional impairment [5]. Meanwhile, thiourea and its derivatives have been sisterly studied for their potential use in agriculture [6], medicine [7], and analytical chemistry [8].

Phase transfer catalysis (PTC) is a powerful technique accomplishing a variety of reactions under mild conditions and efficient way. A logical combination is when phase transfer catalyzed reactions are further promoted by ultrasound irradiation. This technique has been widely recognized as an efficient synthetic tool and attracted much attention [9-10].

In view of these facts, herein we report a one-pot facile, efficient, and high-yield method for the synthesis of 1-(5-methylisoxazoyl-4-carbonyl)-4-arylthiosemicarbazides under the

condition of liquid-liquid phase transfer catalysis using polyethylene glycol-600 (PEG-600) as the catalyst, and their biological activities were investigated.

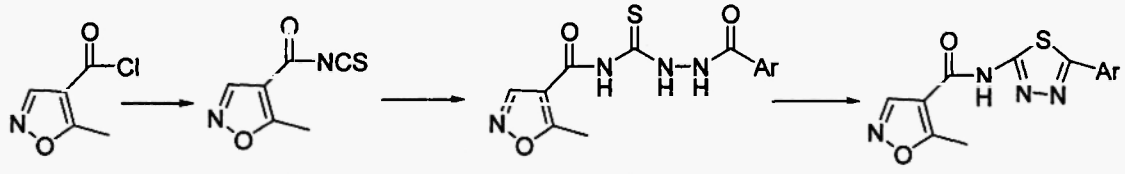
Experimental

Instruments

Melting points were determined using a X-4 apparatus and are uncorrected. Infrared spectra were recorded on a Bruker Equinox55 spectrophotometer as KBr tablet. ^{1}H NMR spectra were measured on a Bruker AC-P500 instrument (300MHz) using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analyses were performed on a Yanaco MT-3CHN elemental analyzer. Ultrasonic irradiation was carried out with KQ-218 ultrasonic cleaner 20 kHz/50 W. All starting materials are commercial products of chemical or analytic grade purity. Sulfuric chloride was distillated and ammonium thiocyanate was baked before use. Analytical TLC was performed on silica gel GF254.

Synthesis

The route shown in Scheme **1** was used for synthesizing the title compounds.



Reagents and conditions: (i) NH_4NCS, PEG-600, r.t., ultrasonic irradiation; (ii) $ArCONHNH_2$, r.t., ultrasonic irradiation; (iii) HOAc, reflux.

Scheme-1

Aryl acylhydrazine and 5-methyl-isoxazolecarboxylic acid

All the aryl acylhydrazine and 5-methyl-isoxazolecarboxylic acid were prepared according reference [11, 5]. The physical data are according with the reference.

1-(5-Methylisoxazoyl-4-carbonyl)-4-arylthiosemicarbazides

Powdered ammonium thiocyanate (1.14 g, 15 mmol), 5-methylisoxazole-4-carbonyl chloride (1.41 g, 10 mmol), PEG-600 (0.18 g, 3% with respect to ammonium thiocyanate) and methylene dichloride (25 ml) were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred under ultrasonic irradiation at room temperature for 0.5 h. Then substituted aryl acylhydrazine (4.5 mmol) in methylene dichloride (10 ml) were dropwised over 0.5 h, and the mixture was stirred for 0.5 h under ultrasonic irradiation. The corresponding 1-(5-methylisoxazoyl-4-carbonyl)-4-arylthiosemicarbazides precipitated

immediately. The product was filtered, washed with water to remove inorganic salts, dried, The products **3a-3j** were recrystallized from DMF-EtOH-H_2O, dried on the infrared lamp.

1-(5-Methylisoxazoyl-4-carbonyl)-4-phenylthiosemicarbazide (**3a**)

Yield: 82.5 %; m.p.: 195-196 □; ^{1}H NMR: 12.30 (s, 1H, NH), 11.78 (s, 1H, NH), 11.19 (s, 1H, NH), 9.25 (s, 1H, H-isoxazole), 7.44-7.95 (m, 5H, C_6H_5), 2.73 (s, 3H, CH_3); IR (KBr) 240 : 1188 (C=S), 1687 (C=O), 3161 (N-H) ; ESI-MS: 302 (M-1) ; Anal. calcd. For $C_{13}H_{12}N_4O_3S$: C 51.31, H 3.97, N 18.41; found: C 51.45, H 3.99, N 18.43.

1-(5-Methylisoxazoyl-4-carbonyl)-4-(2-cholrophenyl)thiosemicarbazide (**3b**)

Yield: 78.1 %; m.p.: 175-176 □; ^{1}H NMR: 12.33 (s, 1H, NH), 11.74 (s, 1H, NH), 11.23 (s, 1H, NH), 9.23 (s, 1H, H-isoxazole), 7.33-7.85 (m, 4H, C_6H_4), 2.72 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1195 (C=S), 1687 (C=O), 3169 (N-H) ; ESI-MS: 337 (M-1) ; Anal. calcd. For $C_{13}H_{11}ClN_4O_3S$: C 46.09, H 3.27, N 16.54; found: C 45.96, H 3.29, N 16.45.

1-(5-Methylisoxazoyl-4-carbonyl)-4-(2-methylphenyl)thiosemicarbazide (**3c**)

Yield: 83.5 %; m.p.: 146-148 □; ^{1}H NMR: 12.28 (s, 1H, NH), 11.74 (s, 1H, NH), 11.25 (s, 1H, NH), 9.26 (s, 1H, H-isoxazole), 7.41-7.92 (m, 4H, C_6H_4), 3.36 (s, 3H, CH_3), 2.59 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1195 (C=S), 1687 (C=O), 3169 (N-H) ; ESI-MS: 317 (M-1) ; Anal. calcd. For $C_{14}H_{14}N_4O_3S$: C 52.82, H 4.43, N 17.60; found: C 53.01, H 4.41, N 17.65.

1-(5-Methylisoxazoyl-4-carbonyl)-4-(3-methylphenyl)thiosemicarbazide (**3d**)

Yield: 83.5 %; m.p.: 165-167 □; ^{1}H NMR: 12.09 (s, 1H, NH), 10.40 (s, 1H, NH), 10.19 (s, 1H, NH), 8.97 (s, 1H, H-isoxazole), 7.11-7.37 (m, 4H, C_6H_4), 2.71 (s, 3H, CH_3), 2.38 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1195 (C=S), 1680 (C=O), 3161 (N-H) ; ESI-MS: 317 (M-1) ; Anal. calcd. For $C_{14}H_{14}N_4O_3S$: C 52.82, H 4.43, N 17.60; found: C 52.99, H 4.51, N 17.77.

1-(5-Methylisoxazoyl-4-carbonyl)-4-(4-methylphenyl)thiosemicarbazide (**3e**)

Yield: 83.5 %; m.p.: 183-185 □; ^{1}H NMR: 12.28 (s, 1H, NH), 11.76 (s, 1H, NH), 11.21 (s, 1H, NH), 9.26 (s, 1H, H-isoxazole), 7.39-7.89 (m, 4H, C_6H_4), 2.71 (s, 3H, CH_3), 2.36 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1166 (C=S), 1680 (C=O), 3161 (N-H) ; ESI-MS: 317 (M-1) ; Anal. calcd. For $C_{14}H_{14}N_4O_3S$: C 52.82, H 4.43, N 17.60; found: C 53.05, H 4.28, N 17.61.

1-(5-Methylisoxazoyl-4-carbonyl)-4-(4-chlorophenyl)thiosemicarbazide (**3f**)

Yield: 80.1 %; m.p.: 160-161 □; ^{1}H NMR: 12.21 (s, 1H, NH), 11.74 (s, 1H, NH), 11.24 (s, 1H, NH), 9.23 (s, 1H, H-isoxazole), 7.11-7.91 (m, 4H, C_6H_4), 2.68 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1162 (C=S), 1677 (C=O), 3144 (N-H) ; ESI-MS: 337 (M-1) ; Anal. calcd. For $C_{13}H_{11}ClN_4O_3S$: C 46.09, H 3.27, N 16.54; found: C 46.13, H 3.23, N 16.55.

1-(5-Methylisoxazoyl-4-carbonyl)-4-(2-fluorophenyl)thiosemicarbazide (**3g**)

Yield: 78.9 %; m.p.: 178-179 □; ^{1}H NMR: 12.27 (s, 1H, NH), 11.35 (s, 1H, NH), 10.56 (s, 1H, NH), 9.21 (s, 1H, H-isoxazole), 6.93-7.60 (m, 4H, C_6H_4), 2.67 (s, 3H, CH_3); IR (KBr) νcm^{-1}: 1188 (C=S), 1687 (C=O), 3161 (N-H) ; ESI-MS: 321 (M-1) ; Anal. calcd. For $C_{13}H_{11}FN_4O_3S$: C 48.44, H 3.44, N 17.38; found: C 48.51, H 3.60, N 17.54.

1-(5-Methylisoxazoyl-4-carbonyl)-4-(2-nicotinoyl)thiosemicarbazide (**3h**)

Yield: 83.2 %; m.p.: 148-149 □; ^{1}H NMR: 12.20 (s, 1H, NH), 11.76 (s, 1H, NH), 11.37 (s, 1H, NH), 9.24 (s, 1H, H-isoxazole), 7.00-8.77 (m, 4H, C_5H_4N), 2.68 (s, 3H, CH_3); IR 241 νcm^{-1}: 1166 (C=S), 1680 (C=O), 3169 (N-H) ; ESI-MS: 304 (M-1) ; Anal. calcd. For $C_{12}H_{11}N_5O_3S$: C 47.21, H 3.63, N 22.94; found: C 47.11, H 3.60, N 22.89.

1-(5-Methylisoxazoyl-4-carbonyl)-4-(4-fluorophenyl)thiosemicarbazide (**3i**)

Yield: 79.2 %; m.p.: 155-156 □; ^{1}H NMR: 12.25 (s, 1H, NH), 11.75 (s, 1H, NH), 11.23 (s, 1H, NH), 9.25 (s, 1H, H-isoxazole), 7.26-7.94 (m, 4H, C_6H_4), 2.69 (s, 3H, CH_3); IR (KBr) νcm^{-1}: 1296 (C=S), 1680 (C=O), 3161 (N-H) ; ESI-MS: 321 (M-1) ; Anal. calcd. For $C_{13}H_{11}FN_4O_3S$: C 48.44, H 3.44, N 17.38; found: C 48.38, H 3.22, N 17.44.

1-(5-Methylisoxazoyl-4-carbonyl)-4-(2,4-dichlorophenyl)thiosemicarbazide (**3j**)

Yield: 83.5 %; m.p.: 153-155 □; ^{1}H NMR: 12.23 (s, 1H, NH), 11.77 (s, 1H, NH), 11.31 (s, 1H, NH), 9.23 (s, 1H, H-isoxazole), 7.09-7.89 (m, 3H, C_6H_3), 2.66 (s, 3H, CH_3); IR (KBr) νcm^{-1}: 1195 (C=S), 1680 (C=O), 3154 (N-H) ; ESI-MS: 372 (M-1) ; Anal. calcd. For $C_{13}H_{10}Cl_2N_4O_3S$: C 41.84, H 2.70, N 15.01; found: C 41.68, H 2.81, N 14.97.

N-(5-(substitute-phenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazole-4-carboxamide

1-(5-methylisoxazoyl-4-carbonyl)-4-arylthiosemicarbazides (2.5 mmol) and 5 mL acetate acid were heated to the boil, then dropwised acetate acid, until 1-(5-methylisoxazoyl-4-carbonyl)-4-arylthiosemicarbazides were resolved, then continuing refluxing 2 h.

5-Methyl-N-(5-phenyl-1,3,4-thiadiazol-2-yl)isoxazole-4-carboxamide (**4a**)

Yield: 60.1 %; m.p.: 243-245 □; ^{1}H NMR: 12.42 (s, 1H, NH), 9.21 (s, 1H, H-isoxazole), 7.72-7.89 (m, 4H, C_6H_4), 2.66 (s, 3H, CH_3); IR (KBr) νcm^{-1}: 1296 (C=S), 1680 (C=O), 3161 (N-H) ; ESI-MS: 285 (M-1) ; Anal. calcd. For $C_{13}H_{10}N_4O_2S$: C 41.84, H 2.70, N 15.01; found: C 41.68, H 2.81, N 14.97.

N-(5-(2-chlorophenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazole-4-carboxamide (**4b**)

Yield: 62.9 %; m.p.: 224-225 □; ^{1}H NMR: 12.12 (s, 1H, NH), 9.19 (s, 1H, H-isoxazole), 7.60-8.01 (m, 4H, C_6H_4), 2.78 (s, 3H, CH_3); IR (KBr) νcm^{-1}: 1680 (C=O), 3154 (N-H) ; ESI-

MS: 319 (M-1) ; Anal. calcd. For $C_{13}H_9ClN_4O_2S$: C 48.68, H 2.83, N 17.47; found: C 48.66, H 2.71, N 17.66.

N-(5-(2-Methylphenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazole-4-carboxamide (**4c**)

Yield: 65.3 %; m.p.: 242-243 □; ^{1}H NMR: 9.24 (s, 1H, H-isoxazole), 7.17-7.42 (m, 4H, C_6H_4), 2.72 (s, 3H, CH_3) , 1.87 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1687 (C=O), 3255 (N-H) ; ESI-MS: 299 (M-1) ; Anal. calcd. For $C_{14}H_{12}N_4O_2S$: C 55.99, H 4.03, N 18.65; found: C 56.03, H 4.10, N 18.66.

N-(5-(3-Methylphenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazole-4-carboxamide (**4d**)

Yield: 65.3 %; m.p.: 210-211 □; ^{1}H NMR: 8.94 (s, 1H, H-isoxazole), 7.47-7.91 (m, 4H, 242), 2.82 (s, 3H, CH_3) , 2.76 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1689 (C=O), 3148 (N-H) ; ESI-MS: 299 (M-1) ; Anal. calcd. For $C_{14}H_{12}N_4O_2S$: C 55.99, H 4.03, N 18.65; found: C 56.03, H 4.10, N 18.66.

N-(5-(4-Methylphenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazole-4-carboxamide (**4e**)

Yield: 73.2 %; m.p.: 251-252 □; ^{1}H NMR: 8.97 (s, 1H, H-isoxazole), 7.39-7.99 (m, 4H, C_6H_4), 2.79 (s, 3H, CH_3) 2.76 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1682 (C=O), 3155 (N-H) ; ESI-MS: 299 (M-1) ; Anal. calcd. For $C_{14}H_{12}N_4O_2S$: C 55.99, H 4.03, N 18.65; found: C 56.03, H 4.33, N 18.56.

N-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazole-4-carboxamide (**4f**)

Yield: 68.9 %; m.p.: 207-208 □; ^{1}H NMR: 9.27 (s, 1H, H-isoxazole), 7.18-7.97 (m, 4H, C_6H_4), 2.72 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1680 (C=O), 3161 (N-H) ; ESI-MS: 319 (M-1) ; Anal. calcd. For $C_{13}H_9ClN_4O_2S$: C 48.68, H 2.83, N 17.47; found: C 48.56, H 2.68, N 17.56.

N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazole-4-carboxamide (**4g**)

Yield: 72.1 %; m.p.: 243-244 □; ^{1}H NMR: 9.23 (s, 1H, H-isoxazole), 7.21-7.48 (m, 4H, C_6H_4), 2.76 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1687 (C=O), 3161 (N-H) ; ESI-MS: 303 (M-1) ; Anal. calcd. For $C_{13}H_9FN_4O_2S$: C 51.31, H 2.98, N 18.41; found: C 51.23, H 3.05, N 18.58.

5-Methyl-N-(5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl)isoxazole-4-carboxamide (**4h**)

Yield: 72.1 %; m.p.: 214-215 □; ^{1}H NMR: 9.27 (s, 1H, H-isoxazole), 7.11-7.73 (m, 4H, C_5H_4N), 2.71 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1694 (C=O), 3161 (N-H) ; ESI-MS: 315 (M-1) ; Anal. calcd. For $C_{12}H_9N_5O_2S$: C 53.16, H 3.82, N 17.71; found: C 53.05, H 3.75, N 17.88.

N-(5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazole-4-carboxamide (**4i**)

Yield: 60.1 %; m.p.: 219-221 □; ^{1}H NMR: 12.91 (s, 1H, NH), 8.99 (s, 1H, H-isoxazole), 7.42-7.99 (m, 4H, C_6H_4), 2.80 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1627 (C=O), 3049 (N-H) ; ESI-

MS: 303 (M-1) ; Anal. calcd. For $C_{13}H_9FN_4O_2S$: C 51.31, H 2.98, N 18.41; found: C 51.35, H 2.95, N 18.43.

N-(5-(2,4-dichlorophenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazole-4-carboxamide (**4j**)

Yield: 65.4 %; m.p.: 224-226 □; ^{1}H NMR: 9.79 (s, 1H, NH), 8.18 (s, 1H, H-isoxazole), 7.20-7.89 (m, 3H, C_6H_3), 2.72 (s, 3H, CH_3); IR (KBr) vcm^{-1}: 1685 (C=O), 3124 (N-H) ; ESI-MS: 354 (M-1) ; Anal. calcd. For $C_{13}H_8Cl_2N_4O_2S$: C 43.96, H 2.27, N 15.77; found: C 53.89, H 2.43, N 15.66.

Bioassay of Fungicidal Activities

The method for testing the primary biological activities was performed in an isolated culture. Under a sterile condition, 1 mL of sample was added to the culture plates, followed by the addition of 9 mL of culture medium. The final mass concentration was 50 μg/mL. The 243 assay was performed with 1 mL of sterile water. Circle mycelium with a diameter of 4 mm was cut using a drill. The culture plates were cultivated at (24±1)□. The extended diameters of the circle mycelium were measured after 72 h. The relative inhibition rate of the circle mycelium compared to blank assay was calculated via the following equation:

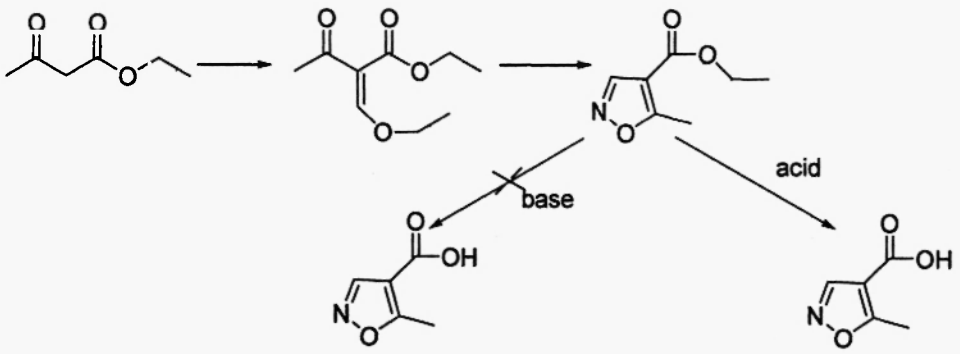
$$\text{Relative inhibition rate (\%)} = \frac{d_{ex} - d_{ex}'}{d_{ex}} \times 100\%$$

Where dex is the extended diameter of the circle mycelium during the blank assay; and d_{ex}', is the extended diameter of the circle mycelium during testing.

Results And Discussion

Synthesis

Synthesis of the starting isoxazole derivative was attempted as shown in Scheme 2. The condensation of ethyl ethoxymethyleneacetoacetate, formed in the known reaction of triethyl orthoformate, acetic anhydride, and ethyl acetoacetate with hydroxylamine, produced ethyl 5-methylisoazol-4-ylcarboxylate. The acid obtained by hydrolysis of the ester was converted into the acid chloride with thionyl chloride. The isoxazole derivatives are sensitive to base.



Scheme-2 : The synthesis route of 5-methylisoxazole-4-carboxylic acid

The same reaction under ultrasound required only 0.5 h to complete with excellent yields (Table-1). Ultrasonic irradiation was carried out with KQ-218 ultrasonic cleaner 20 kHz/50W. Compared with the conventional method, a shorter time, cleaner reaction accompained with higher yields were observed (from 73–78% to 78-83% compared with conventional method at r.t.). Generally, the reaction proceeded quickly with excellent yield as shown in Table-1.

Table-1 : Effect of different reaction conditions

Compounds	Reaction Time		Yield (%)	
	r.t.	Ultrasonic	r.t.	Ultrasonic
3a	3 h	0.5 h	78.1	82.5
3b	3 h	0.5 h	75.3	78.1
3e	3 h	0.5 h	73.5	83.5

We have conducted our reaction using PEG-600 as liquid-liquid phase transfer catalyst, this is a facile and convenient method for the synthesis of 1-(5-methylisoxazoyl-4-carbonyl)-4-arylthiosemicarbazides (**Scheme-1**), PEG-600 as a phase transfer catalyst is indispensable for these reactions. It can easily react with NH_4SCN to form complex [PEG-600-NH_4^+]SCN^-, which makes it possible for SCN^- to readily react with 5-methylisoxazoyl chloride. In addition, the ultrasonic irradiation method distinctly improves the efficiency of the synthetic process and shorten there action time. The catalyst PEG-600 is inexpensive, relatively nontoxic, highly stable and easily available.

Biological Activities

Fungicidal activities of compounds **3a, 3c, 3e, 4a, 4c,** 4e against *G. zeae* Petch, *Phytophthora infestans* (Mont.) de Bary, *Botryosphaeria berengeriana* f. sp. *piricola* (Nose) koganezawa et Sakuma, *Fusarium oxysporum* f.sp. *cucumerinum*, and *Cercospora arachidicola.* The

fungicidal activities of **3a, 3c, 3e, 4a, 4c, 4e** were determined. The results were shown in Table-2. It was also found that some of these compounds displayed moderate fungicidal activity.

Table-2 : The Fungicidal Activity of tested Compounds at 50 ppm

No	R	*G. zeae* Petch	*Phytophthora infestans* (Mont.) de Bary	*Botryosphaeria berengeriana* f. sp. *piricola* (Nose) koganezawa et Sakuma	*Fusarium oxysporum* f.sp. *cucumerinum*	*Cercospora arachidicola*
3a	C_6H_5	10	23	7	26	0
3c	o-$CH_3C_6H_4$	5	40	21	45	7
3e	p-$CH_3C_6H_4$	28	0	49	38	0
4a	C_6H_5	51	21	8	62	15
4c	o-$CH_3C_6H_4$	0	35	41	55	8
4e	p-$CH_3C_6H_4$	5	18	28	25	3

Acknowledgements

This work was supported financially by Department of Science and Technology of Zhejiang Province(2006C22066)

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Received on March 10, 2007.