Original Article

Synthesis and Fungicidal Activities of Phenoxyphenyl Alkoxyiminoacetamide Derivatives*

Takahiro KATAOKA,** Yoshio HAYASE, Michio MASUKO, Motomu NIIKAWA,
Mitsuhiro ICHINARI, Hideyuki TAKENAKA, Norihiko TANIMOTO,
Yoshiyuki HAYASHI*** and Reiji TAKEDA****

Aburahi Laboratories, Shionogi & Co., Ltd., 1405 Gotanda, Koka-cho, Koka-gun, Shiga 520-3423, Japan

**Bulk Chemicals Manufacturing Technical Service Dept., Shionogi & Co., Ltd.,
1-3, Terashima 2-chome, Kuise, Amagasaki 660-0813, Japan

****Technology Coordination Dept., Shionogi & Co., Ltd., 1-18, Doshomachi 3-chome,
Chuo-ku, Osaka 541-0045, Japan

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A number of alkoxyiminophenylacetamide derivatives were synthesized and their fungicidal activities were examined. Studies of structure-activity relationships revealed strongest fungicidal activity when the alkoxyimino moiety and the acetamide moiety were each substituted with a methyl group. When the 2-position of the benzene ring on the phenylacetamide moiety was substituted with a phenoxy or phenoxy-methyl group, good fungicidal activity was obtained. Introduction of other substituents on the benzene ring of the phenylacetamide moiety resulted in decrease of the fungicidal activity. However, introduction of some substituents on the benzene ring of the 2-phenoxy group increased the activity to some extent. Between the two oxime geometrical isomers, the activity of the *E*-form was much stronger than that of the *Z*-form. Consequently, (*E*)-2-methoxyimino-*N*-methyl-2-(2-phenoxyphenyl)acetamide was selected as a candidate fungicide for rice diseases.

INTRODUCTION

Musilek *et al.*^{1,2)} first discovered a second metabolite from *Oudemansiella mucida*, a species of Bacidiomycotina, which they named mucidin. Subsequently, Anke *et al.*^{3,4)} isolated strobilurins from *Strobilurus tenacellus*, also a species of Bacidiomycotina. And it was later shown that strobilurin A had the same structure as mucidin. Becker *et al.*^{5,6)} first reported the fungicidal activity of strobilurins and other natural compounds, whose mode of action was demonstrated to be an inhibition of the bc₁ segment of the respiratory chain of mitochondria. Structural modification of these lead compounds has progressed aggressively. Anke *et al.*^{7,8)} first synthesized stilbene analogues from the strobilurins, which did not show good performance under the field condition due to less persistency. In order to photostabilize the stilbene analogues, they synthesized the diphenylether analogues by replacing the styryl side chain with a phenoxy group. With this idea, the di-

phenylether type compounds were designed and synthesized by Beaument *et al.*,⁹⁾ and Clough *et al.*¹⁰⁾ On the other hand, another type of strobilurin analogues were synthesized by BASF group with phoxymethyl side chain and methoxyimino moiety.¹¹⁻¹³⁾ In 1992, ZENECA group¹⁴⁾ and BASF group¹⁵⁾ introduced β -methoxyacrylate and methoxyimino acetic acid derivatives independently, which were both derived from strobilurins, as a promising new class of broad spectrum fungicides with a new mode of action.

Shionogi & Co., Ltd., developed the antibacterial agent SINOMIN[®] for pharmaceutical use, and ISOXYL[®], an agricultural herbicide, both of which contain an isoxazole ring structure (Fig. 1). Previously, we synthesized some carbamoylisoxazole derivatives (I) by developing our isoxazole chemistry, and assessed their fungicidal activities for agricultural purposes.¹⁶⁾ These compounds were especially active against rice blast by submerged application to the water in the rice fields, despite their weak fungicidal activity *in vitro*. Furthermore, during the course of metabolic studies of ISOXYL[®], an isoxazole ring-cleaved metabolite was obtained as a soil metabolite. These observations suggested that these compounds would be activated by

* Structure and Fungicidal Activities of New Alkoxyiminoacetamide Derivatives (Part 1).

*** Present address: 15-5, Nomura 5-chome, Kusatsu, Shiga 525-0027, Japan.

cleavage of the isoxazole ring in the paddy water or soil. Accordingly, we designed new compounds by cleaving the isoxazole ring (II). In the course of screening, it had been suggested that *N*-phenyl-2-methoxyiminopropionamides (III) have good preventive and curative activities with good systemicity against rice blast and

Fig. 1 Chemical structure of SINOMIN® and ISOXYL®.

Fig. 2 Molecular design of fungicidal alkoxyiminoacetamide derivatives.

other diseases such as cucumber gray mold and powdery mildew. 2-Alkoxyimino-2-phenylacetamide derivatives (IV) showed similar fungicidal activity, and when a phenoxy group was introduced on the benzene ring of the 2-phenylacetamide moiety (V), marked improvements both in strength and spectrum of the fungicidal activity were obtained (Fig. 2). These findings and the simplicity of the structure motivated further investigation of the synthesis of methoxyiminoacetamide compounds as new fungicides. On the other hand, many of the current systemic fungicides are becoming less effective due to onset of resistance by a long-term repeated application.

This paper deals with the synthesis and biological characteristics of the new alkoxyiminoacetamide derivatives, and the relationship between structure and fungicidal activity, with special reference to the phenoxyphenylacetamide derivatives.

MATERIALS AND METHODS

1. Synthesis of Chemicals

The compounds prepared in this study are listed in Tables 1-9 along with their physical properties. The typical synthetic routes were employed for synthesizing 2-aryloxyphenylmethoxyiminoacetamide derivatives. The structures of the compounds were confirmed by ¹H-NMR spectroscopy (270 MHz with JEOL Model GSX 270 instrument) using tetramethylsilane as an internal standard and further by elemental analysis, if necessary. All melting points were uncorrected.

Scheme 1. General synthetic routes for the phenoxyphenylalkoxyiminoacetamides.

The chemicals were synthesized according to the following three routes as shown in Scheme 1.

1.1 Typical procedure of route 1

Selective lithiation with butyl lithium gave 2-lithio diphenylether, which was treated with dimethyl oxalate and then ammonia or alkylamine (R^2R^3NH) to afford α -keto amide. The α -keto amide was reacted with *O*-methylhydroxylamine hydrochloride to give 2-(2-phenoxyphenyl)-2-methoxyimino-*N*-methylacetamide. Various substituents were introduced on the benzene ring by electrophilic reaction.

Example for (*E*)-*N*-methyl-2-methoxyimino-2-[2-(4-chlorophenoxy)phenyl]acetamide (35): To a solution of butyl lithium in hexane (1.62 M, 100 ml, 0.162 mol) was added dropwise a solution of diphenyl ether (41.4 g, 0.243 mol) in tetrahydrofuran (80 ml) below 0°C over 20 min and the mixture was stirred at room temperature for 24 hr. After completion of the reaction, the reaction mixture was added dropwise to a stirring solution of dimethyl oxalate (28.7 g, 0.243 mol) in tetrahydrofuran (160 ml) below 0°C over 30 min, followed by stirring at room temperature for 24 hr. After addition of ice-water, the mixture was extracted with toluene and the extract was washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a brown oil. The resulting residue was purified by silica gel column chromatography (hexane:EtOAc=20:1) to obtain methyl 2-oxo-2-(2-phenoxyphenyl)acetate (28.5 g, yield: 68.6%) as a colorless oil. 1H NMR (in $CDCl_3$) δ ppm: 3.71 (3H, s), 6.87 (1H, dd, $J=8.8$ Hz), 7.07 (2H, d, $J=6.8$ Hz), 7.17–7.24 (2H, m), 7.35–7.52 (2H, m), 7.56 (1H, dd, $J=8.8$, 2.0 Hz), 7.97 (1H, dd, $J=7.8$, 2.0 Hz).

Methyl 2-oxo-2-(2-phenoxyphenyl)acetate (512 mg, 2.00 mmol) was dissolved in methanol (2 ml), and 40% methylamine solution (0.390 ml, 5.00 mmol) was added, which was stirred at room temperature for 1.5 hr. The reaction mixture was diluted with water and extracted with toluene. The extract was dried over sodium sulfate and evaporated to leave a crude product, which was purified by silica gel column chromatography (hexane:EtOAc=4:1) to afford *N*-methyl-2-oxo-2-(2-phenoxyphenyl)acetamide (480 mg, yield: 94.0%). 1H NMR (in $CDCl_3$) δ ppm: 2.87 (3H, d, $J=5.1$ Hz), 6.64 (1H, brs), 6.87 (1H, d, $J=8.1$ Hz), 7.08 (2H, dd, $J=7.6$, 1.2 Hz), 7.12–7.18 (2H, m), 7.33–7.36 (2H, m), 7.45 (1H, td, $J=7.8$, 1.5 Hz), 7.75 (1H, dd, $J=7.8$, 1.5 Hz).

N-Methyl-2-oxo-2-(2-phenoxyphenyl)acetamide (510 mg, 2.00 mmol) and *O*-methylhydroxylamine hydrochloride (217 mg, 2.6 mmol) in toluene (2 ml) were heated under reflux for 19 hr. Water was added to the reaction mixture, which was extracted with dichloromethane, and then the extract was dried over sodium sulfate. The resulting residue was purified by silica gel column chromatography (hexane:EtOAc=3:1) to

obtain *N*-methyl-2-methoxyimino-2-(2-phenoxyphenyl)-acetamide (440 mg, yield: 77.4%, *E/Z*=92:8 ratio). Recrystallization from ethyl acetate and hexane gave pure (*E*)-*N*-methyl-2-methoxyimino-2-(2-phenoxyphenyl)acetamide (**1a**); 1H NMR (in $CDCl_3$) δ ppm: 2.86 (3H, d, $J=5.1$ Hz), 3.90 (3H, s), 6.64 (1H, brs), 6.88 (1H, dd, $J=8.1$, 1.2 Hz), 7.00 (2H, dd, $J=8.6$, 1.2 Hz), 7.08 (1H, td, $J=8.1$, 1.2 Hz), 7.14 (1H, td, $J=8.1$, 1.2 Hz), 7.27–7.34 (3H, m), and (*Z*)-*N*-methyl-2-methoxyimino-2-(2-phenoxyphenyl)acetamide (**1b**); 1H NMR (in $CDCl_3$) δ ppm: 2.78 (3H, d, $J=4.9$ Hz), 4.00 (3H, s), 6.30 (1H, brs), 6.86 (1H, d, $J=8.3$ Hz), 6.97 (2H, dd, $J=7.7$, 1.3 Hz), 7.09 (1H, td, $J=7.7$, 1.0 Hz), 7.14 (1H, ddd, $J=8.3$, 7.7, 1.0 Hz), 7.29–7.35 (2H, m), 7.60 (1H, dd, $J=7.7$, 1.0 Hz).

A solution of (*E*)-*N*-methyl-2-methoxyimino-2-(2-phenoxyphenyl)acetamide (500 mg, 1.76 mmol) in dichloromethane was cooled to 0°C, and sulfuryl chloride (285 mg, 2.11 mmol) was added dropwise. The mixture was stirred at the same temperature for 2 hr, diluted with water and extracted with diethyl ether. The organic layer was dried and evaporated to leave a residue, which was subjected to HPLC (hexane:EtOAc=2:1) to give (*E*)-*N*-methyl-2-methoxyimino-2-[2-(4-chlorophenoxy)phenyl]acetamide (**35**) (382 mg, yield: 67.7%). 1H NMR (in $CDCl_3$) δ ppm: 2.87 (3H, d, $J=4.9$ Hz), 3.90 (3H, s), 6.67 (1H, brs), 6.89 (1H, d, $J=8.5$ Hz), 6.95 (2H, d, $J=9.0$ Hz), 7.17 (1H, td, $J=8.5$, 1.2 Hz), 7.26 (2H, d, $J=9.0$ Hz), 7.30–7.38 (2H, m).

1.2 Typical procedure of route 2

The compounds containing oxygen functional group on the phenoxy ring were synthesized by a procedure similar to route 1 from 2-bromodiphenyl ether, which was obtained by condensation of 2-chloronitrobenzene and alkoxy phenol, reduction of the nitro group and then Sandmeyer reaction.

Example for (*E*)-*N*-methyl-2-[2-(4-methoxyphenoxy)phenyl]-2-methoxyiminoacetamide (41): To a solution of 4-methoxyphenol (1.50 g, 12.1 mmol) and 2-chloronitrobenzene (1.91 g, 12.1 mmol) in dimethylformamide (10 ml) was added anhydrous potassium carbonate (3.34 g, 24.2 mmol). The reaction mixture was stirred at 120°C for 12 hr and cooled to room temperature, diluted with water and extracted with diethyl ether. The solvent was evaporated to give 4-methoxy-2'-nitrodiphenyl ether (2.61 g, yield: 88.0%). 1H NMR (in $CDCl_3$) δ ppm: 3.82 (3H, s), 6.91 (2H, d, $J=9.1$ Hz), 7.02 (2H, d, $J=9.1$ Hz), 7.12 (1H, t, $J=8.0$ Hz), 7.45 (1H, ddd, $J=9.1$, 8.0, 1.7 Hz), 7.92 (1H, dd, $J=8.0$, 1.7 Hz).

To a solution of 4-methoxy-2'-nitrodiphenyl ether (2.61 g, 10.7 mmol) in the mixed solvent of water (30 ml) and toluene (30 ml) was added ammonium chloride (5.11 g, 95.3 mmol) and iron powder (1.79 g, 32.0 mmol). The resulting mixture was heated under reflux and vigorously stirred for 4 hr. The reaction mixture was cooled

to room temperature, followed by removal of insoluble materials by filtration. The filtrate was extracted with diethyl ether and the ether solution was dried and evaporated to give 2-(4-methoxyphenoxy)aniline (2.31 g, yield: quantitative). ^1H NMR (in CDCl_3) δ ppm: 3.78 (3H, s), 3.80 (2H, brs), 6.65–6.95 (8H, m).

2-(4-Methoxyphenoxy)aniline (2.31 g, 10.7 mmol) was dissolved in acetic acid (3 ml), followed by addition of conc. hydrobromic acid (3 ml). The resulting mixture was cooled to 0°C and an aqueous solution (1 ml) of sodium nitrite (741 mg, 10.7 mmol) was further added to make a diazonium salt, which was added dropwise to a solution of copper(I) bromide (918 mg, 6.42 mmol) in conc. hydrobromic acid (2 ml) in another flask. The mixture was stirred at 100°C for 2 hr, cooled to room temperature and diluted with water, followed by extraction with diethyl ether. The extract was washed with a saturated aqueous sodium hydrogencarbonate solution, dried and evaporated to leave a residue, which was purified by silica gel column chromatography (hexane:EtOAc=20:1) to give 4-methoxy-2'-bromodiphenyl ether (1.89 g, yield: 63.3%). ^1H NMR (in CDCl_3) δ ppm: 3.80 (3H, s), 6.81–6.98 (6H, m), 7.21 (1H, t, $J=7.3$ Hz), 7.60 (1H, dd, $J=7.9$, 1.6 Hz).

To a solution of 4-methoxy-2'-bromodiphenyl ether (1.19 g, 4.27 mmol) in tetrahydrofuran (20 ml) was added a solution of butyl lithium (3.2 ml, 5.12 mmol) at -78°C . The resulting solution was stirred at the same temperature for 1 hr, followed by addition of dimethyl oxalate (1.01 g, 8.54 mmol) in tetrahydrofuran (2 ml). The mixture was further stirred at room temperature for 2 hr. The reaction mixture was diluted with a saturated ammonium chloride solution and extracted with diethyl ether. The organic layer was dried and evaporated, and the residue was purified by silica gel column chromatography (hexane:EtOAc=12:1) to give methyl 2-[2-(4-methoxyphenoxy)phenyl]-2-oxoacetate (723 mg, yield: 59.2%). ^1H NMR (in CDCl_3) δ ppm: 3.75 (3H, s), 3.82 (3H, s), 6.80 (1H, d, $J=8.3$ Hz), 6.91 (2H, d, $J=9.0$ Hz), 7.02 (2H, d, $J=9.0$ Hz), 7.16 (1H, t, $J=7.8$ Hz), 7.50 (1H, ddd, $J=8.3$, 7.8, 1.7 Hz), 7.94 (1H, dd, $J=7.8$, 1.7 Hz).

Methyl 2-[2-(4-methoxyphenoxy)phenyl]-2-oxoacetate was treated in the same manner as route 1 to give (*E*)-*N*-methyl-2-[2-(4-methoxyphenoxy)phenyl]-2-methoxyimino acetamide (**41**). ^1H NMR (in CDCl_3) δ ppm: 2.88 (3H, d, $J=4.9$ Hz), 3.79 (3H, s), 3.95 (3H, s), 6.70 (1H, brs), 6.79 (1H, d, $J=8.6$ Hz), 6.84 (2H, d, $J=9.0$ Hz), 6.98 (2H, d, $J=9.0$ Hz), 7.11–7.35 (3H, m).

1.3 Typical procedure of route 3

Reaction of substituted diphenylether in the same manner as shown in route 1 provided two isomers of 2-methoxyimino acetamides. Each isomer was separated by column chromatography.

To a solution of 3-phenoxytoluene (2.00 g, 10.9 mmol)

in diethyl ether (30 ml), was added a solution of butyl lithium (8.15 ml, 13.0 mmol) at 0°C . The resulting solution was stirred at room temperature for 12 hr, followed by addition of dimethyl oxalate (2.57 g, 21.8 mmol) in diethyl ether (30 ml) at 0°C . The mixture was further stirred for 5 hr and neutralized with 1 *N* hydrochloric acid followed by extraction with diethyl ether. The organic layer was dried and evaporated, and the residue was purified by silica gel column chromatography (hexane:EtOAc=20:1) to give methyl 2-[2-(3-tolyloxy)phenyl]-2-oxoacetate (965 mg, yield: 32.7%), ^1H NMR (in CDCl_3) δ ppm: 2.35 (3H, s), 3.72 (3H, s), 6.86 (1H, d, $J=7.8$ Hz), 6.88 (1H, s), 7.00 (1H, d, $J=7.8$ Hz), 7.17–7.28 (3H, m), 7.51 (1H, td, $J=7.8$, 2.0 Hz), and methyl 2-(4-methyl-2-phenoxy)phenyl-2-oxoacetate (260 mg, yield: 8.8%) ^1H NMR (in CDCl_3) δ ppm: 2.32 (3H, s), 3.69 (3H, s), 6.65 (1H, s), 7.03–7.11 (2H, m), 7.14–7.19 (2H, m), 7.34–7.38 (2H, m), 7.88 (1H, d, $J=7.8$ Hz).

In the same manner as route 1, (*E*)-*N*-methyl-2-[2-(3-tolyloxy)phenyl]-2-methoxyiminoacetamide (**30**) and (*E*)-*N*-methyl-2-(4-methyl-2-phenoxy)phenyl-2-methoxyiminoacetamide (**22**) were prepared from methyl 2-[2-(3-tolyloxy)phenyl]-2-oxoacetate and methyl 2-(4-methyl-2-phenoxy)phenyl-2-oxoacetate, respectively. (**30**) ^1H NMR (in CDCl_3) δ ppm: 2.31 (3H, s), 2.87 (3H, d, $J=4.9$ Hz), 3.91 (3H, s), 6.62 (1H, brs), 6.80–6.91 (4H, m), 7.10–7.21 (2H, m), 7.29–7.35 (2H, m). (**22**) ^1H NMR (in CDCl_3) δ ppm: 2.31 (3H, s), 2.86 (3H, d, $J=4.9$ Hz), 3.90 (3H, s), 6.61 (1H, brs), 6.70 (1H, s), 6.83–7.33 (7H, m).

Oxime formation gave the *E*-isomer as the major product along with the *Z*-isomer. These isomers were easily separated by silica gel column chromatography and/or recrystallization. Isomerization from *Z* to *E* was carried out under acidic conditions. Each of the isomers was sufficiently stable to survive at least during the process of separation and purification.

The α -keto amide as a key intermediate was also prepared by hydrolysis of benzoyl cyanide, or condensation of benzoyl chloride with methyl isocyanide. 2-Methoxyiminoacetamide was alternatively obtained by nitrosation of phenoxylbenzyl cyanide, followed by methylation and hydrolysis (Fig. 3).

2. Plant Materials

Cucumber (*Cucumis sativus* L. cv. Tsukuba-shiroibo) seedlings and rice (*Oryza sativa* L. cv. Aichi-asahi) seedlings were used to assay disease controlling activity *in vivo*. The seeds were sown in plastic cups containing sterilized soil and grown in the greenhouse. Two weeks after sowing, the cucumber seedlings were used for fungicidal activity against gray mold, powdery mildew and downy mildew. Two weeks after sowing, the rice seedlings were transplanted and grown for further two weeks and used for fungicidal activity tests against rice blast

Fig. 3 Synthetic route of 2-methoxyiminoacetamide derivatives.

and rice sheath blight.

3. Assay Methods for Fungicidal Activity

3.1 *In vitro* tests

Mycelial growth inhibition tests were carried out by the agar dilution method. Each test compound dissolved and diluted in acetone was added to potato sucrose agar (PSA) medium (kept at 50°C after autoclaving) to the appropriate concentration. The final concentration of acetone of each medium was 1%. Three mycelial disks (4 mm in diameter) of each test organism, precultured on potato dextrose agar (PDA) medium, were placed on the PSA medium containing the given concentrations of the test compound. The diameter of the mycelial mat of each organism was measured when the diameter of each corresponding untreated control reached about 20–30 mm. Effective concentration for 50% inhibition (EC_{50} , ppm) of mycelial growth was calculated by the linear regression formula obtained from the logarithm of concentration and the inhibition rate at each concentration against untreated control.

3.2 Disease controlling tests by foliar application

3.2.1 Rice blast

Test compounds were dissolved in a small amount of *N,N*-dimethylformamide (DMF) and diluted to 500 to 2.0 ppm with distilled water containing sticker. The test solutions or suspensions were sprayed onto the host plant 24 hr before (preventive) or after (curative) inoculation. Inoculation was carried out by spraying a conidial suspension of *Pyricularia oryzae* (teleomorph: *Magnaporthe grisea*) precultured on oatmeal agar medium onto the rice seedlings. After five days of incubation in a humid chamber (100% R.H., at $27 \pm 2^\circ\text{C}$), percent of infected leaf area was assessed and percent of control was calculated.

3.2.2 Rice sheath blight

The test compounds were applied as described above for rice blast. Inoculation was carried out by putting the mycelia of *Thanatephorus cucumeris* (anamorph: *Rhizoctonia solani* AG-1) precultured on rice bran medium with the rice bran at the feet of the rice seedlings, and the inoculated plants were kept in a humid chamber (98% R.H., at $26 \pm 2^\circ\text{C}$). Assessment of activity performed five days after inoculation by measuring the height of mycelia along the sheath of the rice seedlings, and percent of control was calculated.

3.2.3 Cucumber powdery mildew

Test compounds were applied as described above for rice blast except the curative application which was performed 48 hr after inoculation. Inoculation was carried out by spraying the conidial suspension of *Sphaerotheca fuliginea* onto the adaxial (upper) surface of the cucumber leaf where the compound was applied. After ten days incubation in the greenhouse at $23 \pm 2^\circ\text{C}$, percent of infected leaf area was assessed and percent of control was calculated.

3.2.4 Cucumber gray mold

Test compounds were applied as described above for rice blast. Inoculation was carried out by putting the mycelial disks (4 mm in diameter) of *Botrytis cinerea* precultured on PSA medium onto the adaxial (treated) surface of the cucumber leaf. After three days incubation in the humid chamber (98% R.H., at $22 \pm 2^\circ\text{C}$), the diameter of the lesion around the inoculum was measured and percent of control was calculated.

3.2.5 Cucumber downy mildew

Test compounds were applied as described for cucumber powdery mildew. Inoculation was carried out by spotting a droplet of 10 ml of zoosporangial suspension of *Pseudoperonospora cubensis* onto the adaxial (treated)

surface of the cucumber leaf. After ten days incubation in the humid chamber (98% R.H., at $22 \pm 2^\circ\text{C}$), assessment was performed by scoring the degree of infection around the inoculum.

3.3 Disease controlling tests by submerged application for rice blast

Rice seeds were sown in plastic cups containing sterilized sand. Two weeks after sowing, the solution of test compound dissolved in acetone was poured into the paddy water in the plastic cup to the appropriate concentration. The final concentration of acetone in the paddy water did not exceed 1%. Seven days after application, inoculation and assessment were carried out as described above for foliar application.

Percent of control was calculated by comparing the difference of the infected leaf area, height of mycelia, diameter of the lesion or degree of infection, between the untreated control and the treated plots by those of the untreated control. The fungicidal activity by foliar

application was expressed as an index of 4, 3, 2, 1 and 0, each corresponding to approximately 70% control at 2.0, 7.8, 31.3, 125 ppm and less than 70% control at 125 ppm, respectively. The controlling activity against rice blast by submerged application was expressed as an index of 4, 3, 2, 1 and 0, each corresponding to approximately 50% control at 0.16, 0.63, 2.5, 10 ppm and less than 50% control at 10 ppm, respectively.

RESULTS AND DISCUSSION

1. Physical and Chemical Properties of *N*-Methyl-2-methoxyimino-2-(2-phenoxyphenyl)acetamide

Geometric configurations of the oximes were confirmed by comparing the proton NMR chemical shifts of both 6-position protons, where *Z*-isomers (*trans* to benzene ring) generally show a shift in a lower magnetic field relative to related *E*-isomers (*cis* to benzene ring) as shown in Table 1. In addition, as a general rule, *E*-isomers tended to be eluted forward with hexane/

Table 1 ^1H NMR chemical shifts of (*E*)- and (*Z*)-2-methoxyimino-*N*-methyl-2-(2-phenoxyphenyl)acetamides.

Compounds				mp ($^\circ\text{C}$)	$\text{C}_6\text{-H}$ NMR (ppm)
No.	R^4	R^5	$\text{Is}^{\text{a)}$		
1a	H	H	<i>E</i>	86–87	6.70–7.47 ^{b)}
1b	H	H	<i>Z</i>	108.5	7.60
21a	4-Me	H	<i>E</i>	oil	6.83–7.33 ^{b)}
21b	4-Me	H	<i>Z</i>	98–100	7.49
23a	5-OMe	H	<i>E</i>	oil	7.23–7.29 ^{b)}
23b	5-OMe	H	<i>Z</i>	oil	7.36
25a	5-SiMe ₃	H	<i>E</i>	86–88	7.42–7.46 ^{b)}
25b	5-SiMe ₃	H	<i>Z</i>	80–82	7.68
30a	H	3-Me	<i>E</i>	oil	7.29–7.35 ^{b)}
30b	H	3-Me	<i>Z</i>	oil	7.58
34a	H	4-SiMe ₃	<i>E</i>	oil	7.44
34b	H	4-SiMe ₃	<i>Z</i>	103–105	7.60

^{a)} Geometrical configuration (*E/Z*).

^{b)} Contained together with aromatic protons.

Table 2 Fungicidal activities of two geometrical isomers of *N*-methyl-2-methoxyimino-2-(2-phenoxyphenyl)acetamide *in vitro*.

Compounds		EC ₅₀ (ppm)									
No.	Is ^{a)}	P.a.	S.s.	G.c.	C.r.	B.c.	A.m.	F.o.	P.o.	C.l.	C.h. ^{b)}
1a	<i>E</i>	2.8	2.0	7.2	2.5	1.1	20.8	6.2	5.6	4.7	4.5
1b	<i>Z</i>	28.1	11.9	16.2	41.1	11.7	>64.0	58.1	49.1	61.8	41.8

^{a)} Geometrical configuration (*E/Z*).

^{b)} The abbreviation for the plant pathogenic fungi are as follows: P.a.: *Pythium aphanidermatum*, S.s.: *Sclerotinia sclerotiorum*, G.c.: *Glomerella cingulata*, C.r.: *Corticium rolfsii*, B.c.: *Botrytis cinerea*, A.m.: *Alternaria alternata* apple pathotype, F.o.: *Fusarium oxysporum*, P.o.: *Pyricularia oryzae*, C.l.: *Colletotrichum lagenarium*, C.h.: *Cladosporium herbarum*.

ethylacetate mixture on silica gel column chromatography, and show higher *R_f* values when developed with the same solvent system on silica gel thin layer chromatography (TLC). These generalizations were verified by X-ray diffraction analysis of both isomeric compounds

Fig. 4 X ray crystallographic structures of *E* and *Z*-isomer.

(**1a**, **1b**) as shown in Fig. 4.

2. Fungicidal Activities of Two Geometrical Isomers

Fungicidal activities of both *E* and *Z*-isomers of *N*-methyl-2-methoxyimino-2-(2-phenoxyphenyl)acetamide (**1a**, **1b**) were tested against ten species of plant pathogenic fungi *in vitro*, as well as against five diseases *in vivo* by foliar application. The results are summarized in Tables 2 and 3. The *in vitro* test indicated that the *E*-isomer possessed about five- (*S. sclerotiorum*) to 20-fold (*C. rolsii*) higher activity than the *Z*-isomer. Disease controlling activity of the *E*-isomer by foliar application was also stronger against all of the five diseases than that of the *Z*-isomer. The results suggested that **1a** exhibits good fungicidal activity against a wide range of plant pathogenic fungi. It was also suggested that the *E*-form is a favorable configuration for fungicidal activity.

3. Effects of *O*-Substituents (*R*¹) of the (*E*)-Alkoxyimino Moiety

The physical properties and the disease controlling activities of the *O*-substituent (*R*¹) of 2-alkoxyimino-*N*-methylacetamide derivatives were shown in Table 4.

Table 3 Controlling activities^{a)} of two geometrical isomers of *N*-methyl-2-methoxyimino-2-(2-phenoxyphenyl)-acetamide on rice and cucumber diseases by foliar application.

Compounds		Rice									Cucumber					
		Blast			Sheath blight			Powdery mildew			Glax mold			Downy mildew		
No.	Is ^{b)}	125 ^{c)}	31.3	7.8	500	125	31.3	125	31.3	7.8	125	31.3	7.8	125	31.3	7.8
1a	<i>E</i>	97	90	30	70	70	50	100	100	70	95	92	73	100	100	30
1b	<i>Z</i>	50	30	0	50	0	0	100	100	40	44	36	18	70	0	0

^{a)} Percent of control by preventive application, ^{b)} geometrical configuration, ^{c)} concentration of active ingredient (ppm).

Table 4 Effects of oxime substituent *R*¹ on fungicidal activities^{a)} by preventive application.

Compounds				Rice					Cucumber		
				Blast	Sheath blight	Powdery mildew	Gray mold	Downy mildew			
No.	<i>R</i> ¹	Md. ^{b)}	mp (°C)								
1a	Me	1	86–87	4	3	3	4	3			
2	Et	1	oil	1	0	1	1	0			
3	i-Pr	1	oil	1	0	0	0	0			
4	H	1	184–185	0	0	0	1	0			

^{a)} Fungicidal activities are expressed as an index of 4, 3, 2, 1 or 0, each corresponding to approximately 70% control at 2.0, 7.8, 31.3, 125 ppm or less than 70% control at 125 ppm, respectively.

^{b)} General synthetic route described in Scheme 1.

Ethoxyimino (**2**) and isopropoxyimino (**3**) derivatives, as well as hydroxyimino compound (**4**) exhibited weak activities against all diseases tested, while only methoxyimino derivative (**1a**) showed excellent activity against all five diseases.

4. Effects of *N*-Substituents (R^2 , R^3) of the Amide Moiety

The effects of the *N*-substituents (R^2 , R^3) of the acetamide group on the disease controlling activities and physical properties are shown in Table 5. The dimethylamide derivative (**6**) and the ethylamide derivative (**7**) as well as the unsubstituted amide derivative (**5**) exhibited rather weak activities against all five diseases compared to the monomethylamide derivative (**1a**). These results suggest that the bulkiness of the amide group is not necessary for the activity, and steric hindrance in the vicinity of the methoxyimino group is unfavorable for the activity.

5. Positional Effects of the Phenoxy Moiety

The positional effects of the phenoxy group attached to the benzene ring of the phenylacetamide moiety on fungicidal activity were examined (Table 6). *Meta*- (**8**) and *para*- (**9**) phenoxyphenyl derivatives exhibited poor activity against all five diseases, while *ortho*-phenoxyphenyl derivative (**1a**) showed excellent control against these diseases. These results indicate that the phenoxy group at the 2-position on the benzene ring of the 2-phenylacetamide moiety plays a very important role in the fungicidal activity of this series of compounds. These results coincided with the case of β -methoxyacrylates.⁹⁾

6. Effects of Bridge Part between the Two Benzene Rings

The positional effects on the benzene ring of the 2-phenylacetamide moiety were examined with a phenoxy group as described above. Substitution at the *ortho* position was essential for fungicidal activity. Then the effects of the bridge part between the two benzene rings

Table 5 Effects of substituents R^2 and R^3 on amide moiety on fungicidal activities^{a)} by preventive application.

No.	Compounds		Md. ^{b)}	mp (°C)	Rice		Cucumber		
	R^2	R^3			Blast	Sheath blight	Powdery mildew	Gray mold	Downy mildew
1a	Me	H	1	86-87	4	3	3	4	3
5	H	H	1	93-99	1	0	1	2	0
6	Me	Me	1	63-64	1	1	1	1	0
7	Et	H	1	oil	2	1	1	2	0

^{a)} Fungicidal activities are expressed as in Table 4.

^{b)} General synthetic route described in Scheme 1.

Table 6 Positional effects of phenoxy group attached to the benzene ring on fungicidal activities^{a)} by preventive application.

Compounds No.	Position of phenoxy	mp (°C)	Rice		Cucumber		
			Blast	Sheath blight	Powdery mildew	Gray mold	Downy mildew
1a	2	86-87	4	3	3	4	3
8	3	59-60	2	1	1	2	0
9	4	95-97	1	0	1	1	0

^{a)} Fungicidal activities are expressed as in Table 4.

were examined and the results are shown in Table 7. The fungicidal activity was excellent when the two benzene rings were connected with oxygen (**1a**). An oxymethylene group between the two benzene rings (**11**) also showed some activity. However, the fungicidal activities of the other compounds (**10**, **12-19**) were markedly inferior to the above two compounds.

7. Effects of the Substituents R^4 on the Benzene Ring of the Phenylacetamide Moiety

The effects of substituents (R^4) other than the 2-phenoxy group on the benzene ring of the phenylacetamide moiety were examined. The results are shown in Table 8. With introduction of 5-fluoro, 4-methyl, 5-methyl or 5-methoxy (**20-23**), the fungicidal

Table 7 Effects of the bridge part between two benzene rings on fungicidal activities^{a)} by preventive application.

No.	Compounds -X-	mp (°C)	Rice		Cucumber		
			Blast	Sheath blight	Powdery mildew	Gray mold	Downy mildew
1a	-O-	86-87	4	3	3	4	3
10	-CH ₂ O-	123-126	0	0	1	1	0
11	-OCH ₂ -	119-120	3	2	2	3	3
12	-S-	105-107	2	1	3	2	1
13	-SCH ₂ -	oil	1	1	2	3	1
14	-CH=CH- (<i>cis</i>)	94-95	3	1	2	3	1
15	-CH=CH- (<i>trans</i>)	165-166	1	0	3	3	2
16	-CH ₂ CH ₂ -	130-131	1	0	1	2	0
17	-COO-	170	0	0	1	1	0
18	-CO-	oil	1	0	0	1	0
19	-NHCH ₂ -	115-118	0	0	0	1	0

^{a)} Fungicidal activities are expressed as in Table 4.

Table 8 Effects of the substituent R^4 on the benzene ring on fungicidal activities^{a)} by preventive application.

No.	Compounds		mp (°C)	Rice		Cucumber		
	R^4	Md. ^{b)}		Blast	Sheath blight	Powdery mildew	Gray mold	Downy mildew
1a	H	1	86-87	4	3	3	4	3
20	5-F	3	oil	3	2	2	3	1
21	4-Me	3	98-100	2	2	3	3	2
22	5-Me	3	oil	2	1	3	3	1
23	5-OMe	3	oil	2	1	1	2	1
24	5-CF ₃	3	oil	0	0	0	0	0
25	5-SiMe ₃	3	86-88	0	0	0	0	0
26	3-NO ₂	1	oil	0	0	0	0	0
27	5-NO ₂	1	oil	0	0	0	1	0
28	6-OMe ₃	3	106-108	1	0	0	2	0

^{a)} Fungicidal activities are expressed as in Table 4.

^{b)} General synthetic route described in Scheme 1.

Table 9 Effects of the substituents R⁵ of the phenoxy group on the fungicidal activities.^{a)}

No.	Compounds	R ⁵	Md. ^{b)}	mp (°C)	Rice				Cucumber			
					Blast		Sheath blight	Powdery mildew	Gray mold		Downy mildew	
					Fol. ^{c)}	Sub. ^{d)}			Pre.	Cur.		
1a	H		1	86-87	4	4	3	3	3	4	3	2
29	2-Me		3	oil	2	2	0	2	2	2	0	NT ^{e)}
30	3-Me		3	oil	3	4	2	2	3	3	2	1
31	4-Me		3	113-115	4	4	1	3	3	4	0	NT
32	4-i-Pr		1	oil	2	1	1	3	2	3	1	NT
33	4-t-Bu		1	oil	1	2	1	2	2	3	0	0
34	4-SiMe ₃		3	oil	0	0	0	1	1	0	0	NT
35	4-Cl		1	108-109	2	4	1	3	3	4	2	1
36	4-Br		1	99-101	2	4	1	3	2	4	0	0
37	4-I		1	96	1	3	1	3	3	4	1	1
38	4-NO ₂		1	110-112	1	NT	0	1	2	3	0	0
39	2-NO ₂		1	oil	0	NT	0	0	0	0	0	0
40	3-OMe		2	49-50	3	4	2	3	3	4	1	0
41	4-OMe		2	118	2	4	2	3	3	4	1	1
42	3-OH		2	157-159	1	NT	1	0	1	NT	0	NT
43	3-OPh		2	oil	4	2	2	3	3	4	2	1
44	4-OPh		2	oil	1	1	1	2	1	NT	0	NT
45	3-OCH ₂ C≡CH		2	80-81	4	4	1	1	3	3	2	0
46	3-OCH ₂ CN		2	oil	0	0	0	1	1	NT	0	NT
47	3-Me-4-Cl		1	oil	0	3	1	3	3	3	3	1
48	3,4-Cl ₂		3	80-81	3	1	1	3	3	4	2	1
49	3-OCH ₂ CH=CH ₂		2	oil	3	2	2	3	3	4	4	1
50	3-OCH ₂ Ph		2	oil	1	0	1	2	2	2	1	NT
51	4-OCH ₂ Ph		2	130-131	0	NT	0	0	0	NT	0	NT
52	2,4-i-Pr ₂		1	92-95	1	NT	1	1	1	NT	0	NT

^{a)} Fungicidal activities are expressed as in Table 4, ^{b)} general synthetic route described in Scheme 1, ^{c)} foliar application, ^{d)} submerged application, ^{e)} preventive activity, ^{f)} curative activity, ^{g)} not tested.

activities were reduced compared to **1a**. Introduction of other substituents (**24–28**) also depressed the activities against all diseases markedly. These results indicate that the benzene ring of the phenylacetamide moiety should not be substituted besides the 2-phenoxy group to obtain best fungicidal activity.

8. Effects of Substituents R^5 on the Phenoxy Moiety

Table 9 lists the physical properties and fungicidal activities in relation to substituents R^5 of the phenoxy moiety. These compounds can be divided into six groups. Group 1 consisted of alkyl substituents (**29–33**, **52**), group 2 of halogen substituents (**35–37**, **48**), group 3 of nitro substituents (**38**, **39**), group 4 of alkoxy or phenoxy substituents (**40**, **41**, **43–46**, **49–51**), group 5 of alkyl and halogen di-substituents (**47**) and group 6 of other substituents (**34**, **42**).

The fungicidal activities of group 1 with alkyl substituents varied depending on the position of the substituents. The activity of 2-methyl derivative (**29**) was inferior to those of 3-methyl (**30**) or 4-methyl (**31**) derivatives. At the 4-position, halogen substituents (compounds of group 2, **35**, **36**, **37**) seemed to have the same activity as 4-methyl derivative (**31**). However, introduction of branched alkyl (**32**, **52**) or bulky substituents such as *t*-butyl (**33**), trimethylsilyl group (**34**), phenoxy group (**44**), and benzyloxy group (**50**) depressed the fungicidal activity. Furthermore, introduction of substituents which increase the overall hydrophilicity of the molecule such as nitro group (**38**, **39**) or hydroxyl group (**42**) at any position caused decrease in activity.

On the other hand, 3-propargyloxy (**45**) or 3-allyloxy (**49**) derivatives as well as 3-phenoxy derivative (**43**), showed almost the same activity as unsubstituted compound (**1a**) against all diseases tested. The activities of 3-propargyloxy (**45**) and 3-phenoxy derivative (**43**) against rice blast by foliar application was excellent, while that of 3-phenoxy derivative (**43**) by submerged application was extremely weak. In contrast, the activities of 4-chloro- (**35**), 4-bromo- (**36**), 4-iodo- (**37**), 4-methoxy (**41**) and 3-methyl-4-chloro (**47**) derivatives against rice blast by submerged application were stronger than those by foliar application. The differences in activity by application method might be due to the water solubility or log *P* of the compounds. It is worth noting that 3-propargyloxy (**45**) and 3-allyloxy (**49**) derivatives showed strong activity against rice blast and cucumber gray mold, whereas, incorporation of cyanomethyloxy group (**46**) at the 3-position, which can be regarded as equivalent with a propargyloxy group resulted in a marked decrease in activity. Structure-activity relationship studies on phenoxyphenylmethoxyiminoacetamide derivatives suggested that the phenoxy group at the 2-position of phenylacetamide moiety and overall hydrophilicity may play important roles in fungicidal activity.

Consequently, the unsubstituted compound (**1a**), (*E*)-2-methoxyimino-*N*-methyl-2-(2-phenoxyphenyl)acetamide, exhibited the best fungicidal activity among the derivatives examined.

Based on the results of the present study, compound **1a** was selected as a candidate fungicide, SSF-126, from the viewpoint of activity, productivity and weakness of toxicity in mammals, fish and plants.

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要 約

フェノキシフェニルアルコキシミノアセトアミド誘導体の合成と殺菌活性

片岡隆博, 早瀬善男, 益子道生, 新川 求, 市成光広
竹中秀行, 谷本憲彦, 林 幸之, 武田禮二
種々のアルコキシミノフェニル酢酸アミド誘導体を合成し, それらの殺菌活性における構造と活性相関について

調べた。その結果, アルコキシミノ部はメトキシミノ体で, 酢酸アミド部はモノメチルアミド体の活性が最も高く, フェニル酢酸アミド部のベンゼン環は *ortho* 位に無置換のフェノキシ基が導入された化合物が最も活性が高かった。メトキシミノ部の幾何異性体間では *E*-体の方が *Z*-体より活性が高かった。以上の結果より, (*E*)-2-メトキシミノ-*N*-メチル-2-(2-フェノキシフェニル)アセトアミドを開発候補剤として選抜した。本化合物は抗菌スペクトラムが広く, 浸透移行性に優れ予防効果も治療効果も認められる。イネいもち病に対しては茎葉散布および水面施用で有効である。