

4,5-ジヒドロイソオキサゾール環を有する2-アルコキシイミノ アセトアミド誘導体の合成と殺菌活性

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Original Article

Synthesis and Fungicidal Activities of 2-Alkoxyiminoacetamides with a 4,5-Dihydroisoxazole Ring

Hiroyuki KAI, Tuneo ICHIBA, Kuniyoshi NISHIDA,
Michio MASUKO and Akira TAKASE

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

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A series of 2-alkoxyiminoacetamides with a 4,5-dihydroisoxazole ring and their related compounds were synthesized and their fungicidal activities against cucumber downy mildew were assessed. Our studies of the structure-activity relationships revealed that fungicidal activity was the strongest when the substituents on the amide nitrogen of 2-alkoxyimino-2-cyanoacetamides were 4,5-dihydroisoxazol-3-ylmethyl groups. Among the compounds examined, 2-cyano-2-methoxyimino-*N*-(5-methyl-4,5-dihydroisoxazol-3-ylmethyl) acetamide (**12**) showed a potent fungicidal activity against cucumber downy mildew.

INTRODUCTION

In our previous paper, we reported the structure-activity relationships of fungicidal 2-alkoxyimino-2-cyanoacetamide derivatives.¹⁾ Among these, 2-cyano-2-methoxyimino-*N*-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide (**A**) showed a potent activity against cucumber downy mildew.

In the course of our study, the cyano and 4,5-dihydroisoxazole ring moieties of compound **A** were modified structurally for further improvement of fungicidal activity (Fig. 1). Here, we report the synthesis and structure-activity relationships of 2-alkoxyiminoacetamides with a 4,5-dihydroisoxazole ring and their related compounds.

MATERIALS AND METHODS

1. Instrumental Analysis

Melting points were measured with a Büchi 535 melting point apparatus and are uncorrected. Refractive index were measured with an Atago Abbe-refractometer. ¹H NMR spectra were measured on a JEOL JNM-GSX 270 spectrometer at 270 MHz using tetramethylsilane (TMS) as an internal standard.

2. Synthesis of Compounds

The methods for synthesis of 2-substituted 2-alkoxyimino-*N*-(4,5-dihydroisoxazol-3-yl)acetamides (**I**) and 2-alkoxyimino-2-cyano-*N*-(4,5-dihydroisoxazol-3-ylmethyl)acetamides (**II**) are shown in Figs. 2 and 3, respectively. The typical synthetic procedures are

shown below.

2.1 2-Methoxycarbonyl-2-methoxyimino-*N*-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide: **1** (**Ia**: R¹, R², R⁴ = Me in Fig. 2)

A solution of methyl malonyl chloride (4.76 ml, 44.4 mmol) in acetonitrile (2 ml) was added dropwise to a mixture of 3-amino-5,5-dimethyl-4,5-dihydroisoxazole²⁾ (**III**: R¹, R² = Me; 4.22 g, 37 mmol), pyridine (3.51 g, 44.4 mmol) and acetonitrile (37 ml) at 0–5°C over 30 min, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into ice-water (100 ml), acidified with 5% hydrochloric acid, and extracted with dichloromethane (100 ml × 4). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 8.41 g of crude 2-methoxycarbonyl-*N*-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide (**IV**: R¹, R² = Me).

A solution of the crude 2-methoxycarbonyl-*N*-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide (**IV**: R¹, R² = Me; 8.41 g) in methanol (37 ml) was added to a solution of sodium (1.02 g, 44.4 mmol) in methanol (37 ml) in an ice bath, and the mixture was stirred at 0–5°C for 10 min. Butyl nitrite (6.50 g, 55.5 mmol) was added dropwise to the mixture at 0–5°C over 2 min, and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was poured into ice-water (100 ml), acidified with 5% hydrochloric acid, and extracted with ethyl acetate (150 ml × 3). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give crude product. The product was recrystallized from ethyl acetate to give

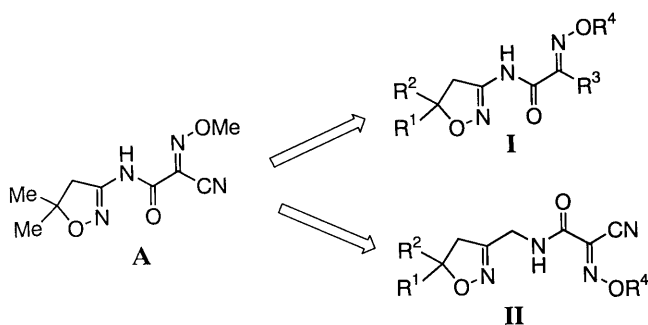
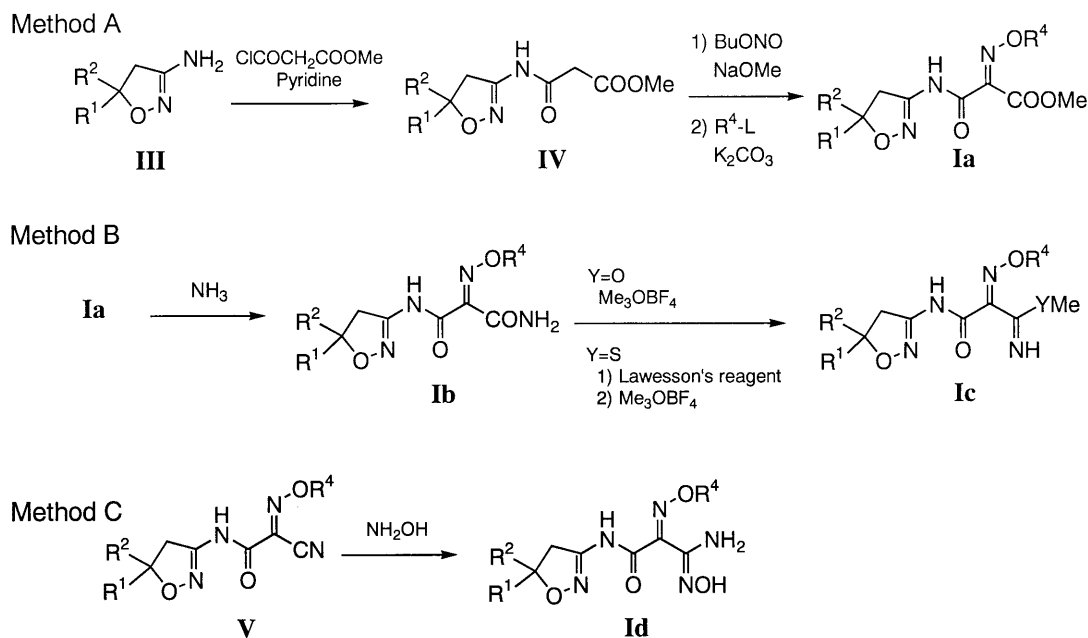
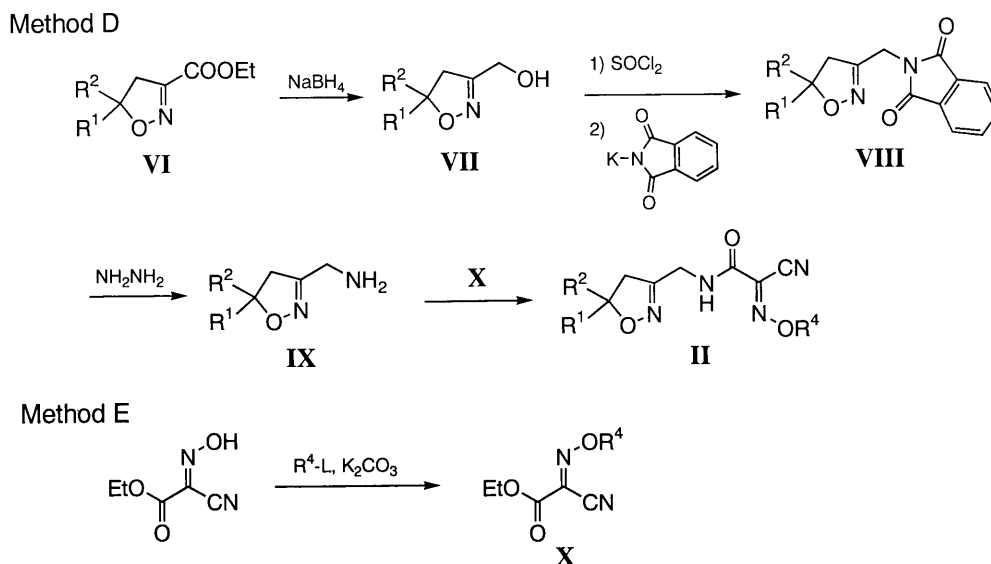


Fig. 1 The original lead and prepared compounds.

6.82 g (75.8%) of 2-hydroxyimino-2-methoxycarbonyl-*N*-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)-acetamide as colorless crystals.

Dimethyl sulfate (1.11 g, 8.8 mmol) was added to a mixture of 2-hydroxyimino-2-methoxycarbonyl-*N*-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide (1.95 g, 8 mmol), potassium carbonate (1.33 g, 9.6 mmol) and *N,N*-dimethylformamide (8 ml) in an ice bath, and the mixture was stirred at room temperature for 1.5 hr. The mixture was poured into water (100 ml) and extracted with ethyl acetate (100 ml \times 2). The organic layer was dried over anhydrous magnesium sulfate, and concen-

Fig. 2 Synthetic methods for 2-alkoxyimino-*N*-(4,5-dihydroisoxazol-3-yl)acetamides.Fig. 3 Synthetic methods for 2-alkoxyimino-2-cyano-*N*-(4,5-dihydroisoxazol-3-ylmethyl)acetamides.

trated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 1.03 g (50.1%) of compound **1**. The product was recrystallized from hexane and ethyl acetate to give colorless crystals, mp 149–151°C. Anal. Found: C, 46.68; H, 5.83; N, 16.16, Calcd. for C₁₀H₁₅N₃O₅: C, 46.69; H, 5.88; N, 16.33%. ¹H NMR (CDCl₃) δ ppm: 1.44 (6H, s), 3.33 (2H, s), 3.91 (3H, s), 4.09 (3H, s), 8.69 (1H, brs).

2.2 2-Carbamoyl-2-methoxyimino-N-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide: 2 (Ib: R¹, R², R⁴ = Me in Fig. 2)

A mixture of compound **1** (0.26 g, 1 mmol), 28% aqueous ammonia solution (1.2 ml) and methanol (2 ml) was stirred at room temperature for 20 hr. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate) to give 0.19 g (78.4%) of compound **2**. The product was recrystallized from hexane and ethyl acetate to give colorless crystals, mp 200–201°C. Anal. Found: C, 44.64; H, 5.78; N, 22.87, Calcd. for C₉H₁₄N₄O₄: C, 44.62; H, 5.83; N, 23.13%. ¹H NMR (CDCl₃) δ ppm: 1.44 (6H, s), 3.74 (2H, s), 4.17 (3H, s), 5.83 (1H, brs), 6.41 (1H, brs), 9.15 (1H, brs).

2.3 2-Imino(methylthio)methyl-2-methoxyimino-N-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide: 6 (Ic: R¹, R², R⁴ = Me, Y = S in Fig. 2)

A mixture of compound **2** (0.92 g, 3.8 mmol), Lawesson's reagent (0.93 g, 2.3 mmol) and toluene (8 ml) was stirred under reflux for 4 hr. The reaction mixture was poured into water (100 ml) and extracted with ethyl acetate (100 ml). The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 0.42 g (42.8%) of 2-methoxyimino-2-thiocarbamoyl-N-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide.

A mixture of 2-methoxyimino-2-thiocarbamoyl-N-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide (0.42 g, 1.6 mmol), trimethyloxonium tetrafluoroborate (0.24 g, 1.6 mmol) and dichloromethane (6 ml) was stirred at room temperature for 3 hr. The reaction mixture was poured into water (100 ml) and extracted with dichloromethane (50 ml × 2). The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 0.12 g (27.5%) of compound **6**. The product was recrystallized from hexane and ethyl acetate to give pale yellow crystals, mp 107–108°C. Anal. Found: C, 44.00; H, 5.82; N, 20.41, Calcd. for C₁₀H₁₆N₄O₃S: C, 44.10; H, 5.92; N, 20.57%. ¹H NMR (CDCl₃) δ ppm: 1.44 (6H, s), 2.45 (3H, s), 3.34 (2H, s), 4.10 (3H, s), 8.82 (1H, brs).

2.4 2-Amino(hydroxyimino)methyl-2-methoxyimino-N-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide: 7 (Id: R¹, R², R⁴ = Me in Fig. 2)

2-Cyano-2-methoxyimino-N-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamide¹⁾ (**V**: R¹, R², R⁴ = Me; 0.34 g, 1.5 mmol) was added to a mixture of hydroxylamine hydrochloride (0.23 g, 3.3 mmol), sodium methoxide (0.16 g, 3 mmol) and methanol (4 ml) in an ice bath, and the mixture was stirred under reflux for 1 hr. The mixture was poured into water (100 ml) and extracted with dichloromethane (80 ml × 2). The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 0.24 g (62.2%) of compound **7**. The product was recrystallized from hexane and ethyl acetate to give colorless crystals, mp 148–150°C(dec.). Anal. Found: C, 41.95; H, 5.76; N, 27.10, Calcd. for C₉H₁₅N₅O₄: C, 42.01; H, 5.89; N, 27.23%. ¹H NMR (CDCl₃) δ ppm: 1.44 (6H, s), 3.35 (2H, s), 3.60 (1H, brs), 4.14 (3H, s), 5.16 (2H, brs), 9.22 (1H, brs).

2.5 3-Aminomethyl-5-tert-butyl-4,5-dihydroisoxazole (IX: R¹ = tert-Bu, R² = H in Fig. 3)

Sodium borohydride (29.51 g, 0.78 mol) was added to a solution of ethyl 5-tert-butyl-4,5-dihydro-3-isoxazole-carboxylate³⁾ (**VI**: R¹ = tert-Bu, R² = H; 25.90 g, 0.13 mol) in methanol (260 ml) at 0–5°C over 15 min, and the mixture was stirred under reflux for 1 hr. The reaction mixture was poured into water (1000 ml) and extracted with dichloromethane (1000 ml × 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 19.5 g of crude 5-tert-butyl-3-hydroxymethyl-4,5-dihydroisoxazole (**VII**: R¹ = tert-Bu, R² = H).

A mixture of crude **VII** (R¹ = tert-Bu, R² = H; 19.5 g, 0.124 mol), thionyl chloride (19.04 g, 0.16 mol) and benzene (200 ml) was stirred under reflux for 1 hr. The reaction mixture was concentrated under reduced pressure to give crude 5-tert-butyl-3-chloromethyl-4,5-dihydroisoxazole. The crude 5-tert-butyl-3-chloromethyl-4,5-dihydroisoxazole in *N,N*-dimethylformamide (200 ml) and potassium phthalimide (29.91 g, 0.16 mol) was stirred at room temperature for 19 hr. The reaction mixture was poured into water (700 ml) and extracted with ether (700 ml). The organic layer was washed with brine (700 ml), dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 20.00 g (56.3%) of *N*-(5-tert-butyl-4,5-dihydroisoxazol-3-ylmethyl)phthalimide (**VIII**: R¹ = tert-Bu, R² = H) as a pale yellow powder. ¹H NMR (CDCl₃) δ ppm: 0.88 (9H, s), 2.71 (1H, dd, *J* = 17.6 & 9.8 Hz), 2.86 (1H, dd, *J* = 17.6 & 10.7 Hz), 4.33 (1H, dd, *J* = 10.7 & 8.8 Hz), 4.57 (2H, s), 7.71–7.90 (4H, m).

A mixture of **VIII** ($R^1 = \text{tert-Bu}$, $R^2 = \text{H}$; 10.31 g, 36 mmol), 80% hydrazine hydrate (2.74 g, 43.2 mmol) and methanol (72 ml) was stirred at 60°C for 15 hr. The reaction mixture was poured into 4% aqueous sodium hydroxide (200 ml) and extracted with dichloromethane (200 ml \times 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 4.53 g (80.5%) of **IX** ($R^1 = \text{tert-Bu}$, $R^2 = \text{H}$) as a brown oil. $^1\text{H NMR}$ (CDCl_3) δ ppm: 0.92 (9H, s), 1.55 (2H, brs), 2.75 (1H, dd, $J = 17.6$ & 8.8 Hz), 2.88 (1H, dd, $J = 17.6$ & 10.7 Hz), 3.57 (2H, s), 4.32 (1H, dd, $J = 10.8$ & 8.8 Hz).

2.6 2-Cyano-2-methoxyimino-*N*-(5-*tert*-butyl-4,5-dihydroisoxazol-3-ylmethyl)acetamide: **14** (**II**: $R^1 = \text{tert-Bu}$, $R^2 = \text{H}$, $R^4 = \text{Me}$ in Fig. 3)

Dimethyl sulfate (6.94 g, 55 mmol) was added dropwise to a mixture of ethyl 2-cyano-2-hydroxyiminoacetate (7.11 g, 50 mmol), potassium carbonate (8.29 g, 60 mmol) and *N,N*-dimethylformamide (100 ml) at 0–5°C over 10 min, and the mixture was stirred at room temperature for 5 hr. The mixture was poured into water (500 ml) and extracted with ether (500 ml). The organic layer was washed with brine (500 ml), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 4.53 g (58.0%) of crude ethyl 2-cyano-2-methoxyiminoacetate (**X**: $R^4 = \text{Me}$) as a brown oil. $^1\text{H NMR}$ (CDCl_3) δ ppm: 1.40 (3H, t, $J = 6.8$ Hz), 4.33 (3H, s), 4.42 (2H, q, $J = 6.8$ Hz).

A mixture of **IX** ($R^1 = \text{tert-Bu}$, $R^2 = \text{H}$; 0.31 g, 2 mmol), **X** ($R^4 = \text{Me}$; 0.34 g 2.2 mmol) and methanol (4 ml) was stirred at room temperature for 6 hr. The reaction mixture was poured into ice-water (80 ml), acidified with 5% hydrochloric acid, and extracted with ether (100 ml). The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure and the residue was purified on silica gel column chromatography (ethyl acetate/hexane) to give 0.33 g (62.0%) of compound **14** as a pale yellow oil. Anal. Found: C, 53.84; H, 6.85; N, 20.42, Calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}_3$: C, 54.11; H, 6.83; N, 21.04%. $^1\text{H NMR}$ (CDCl_3) δ ppm: 0.91 (9H, s), 2.74 (1H, dd, $J = 17.6$ & 9.6 Hz), 2.89 (1H, dd, $J = 17.6$ & 10.7 Hz), 4.24–4.40 (3H, m), 4.26 (3H, s), 7.06 (1H, brs).

3. Biological Tests

3.1 Plant materials

Cucumber (*Cucumis sativus* L. cv. Tsukuba-shiroibo) seedlings were used for the assay disease controlling activity by foliar application. The seedlings were prepared as described previously.¹⁾

3.2 Assay methods for fungicidal activity against cucumber downy mildew

Preventive and curative activities of the test compounds on cucumber downy mildew were assessed by foliar application. The details of the fungicidal assay

were described previously.¹⁾

The fungicidal activity by preventive application was expressed as an index of 4, 3, 2, 1 and 0, each corresponding to approximately 70% control at less than 7.8, 31.3, 125, 500 ppm and less than 70% control at 500 ppm, respectively.

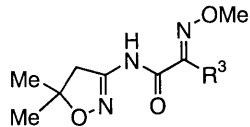
RESULTS AND DISCUSSION

1. Fungicidal Activities of 2-Substituted 2-Alkoxyimino-*N*-(4,5-dihydroisoxazol-3-yl)acetamides (**I**)

The effects of R^3 on the fungicidal activity were examined with various kinds of derivatives in which R^1 , R^2 and R^4 of **I** were fixed as methyl (Table 1). Among these, amino(hydroxyimino)methyl derivative (**7**) was the most active, whereas methoxycarbonyl (**1**), carbamoyl (**2–4**) and imino(methoxy)methyl (**5**) derivatives were inactive. Imino(methylthio)methyl derivative (**6**) had a lower activity.

Table 2 shows the effects of substituents (R^2) on the

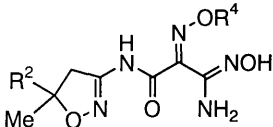
Table 1 2-Substituted 2-methoxyimino-*N*-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)acetamides and their fungicidal activities against cucumber downy mildew.



Compound No.	R^3	mp(°C)	Fungicidal activity
1	COOMe	140.5–142	0
2	CONH ₂	200–201	0
3	CONHMe	154.5–155.5	0
4	CON(Me) ₂	135–136	0
5^{a)}	C(=NH)OMe	105–106	0
6	C(=NH)SMe	107–108	2
7	C(=NOH)NH ₂	148–150(d)	3
A^{b)}	CN	167.5–168.5	4

^{a)} 5-Methyl-4,5-dihydroisoxazole derivative. ^{b)} Data were taken from our previous paper.¹⁾

Table 2 2-Alkoxyimino-2-amino(hydroxyimino)methyl-*N*-(4,5-dihydroisoxazol-3-yl)acetamides and their fungicidal activities against cucumber downy mildew.



Compound No.	R^2	R^4	mp(°C)	Fungicidal activity
7	Me	Me	148–150(d)	3
8	H	Me	144–145(d)	3
9	Et	Me	143–144(d)	3
10	Me	Et	151–153(d)	3
11	Me	Benzyl	135–139	0

4,5-dihydroisoxazole ring and oxime ether moiety (R^4) of 2-alkoxyimino-2-amino(hydroxyimino)methyl-*N*-(4,5-dihydroisoxazol-3-yl)acetamides. When the methyl group at position-5 (R^2) on the 4,5-dihydroisoxazole ring of compound **7** was removed or changed to an ethyl group, the fungicidal activity was not affected (**8** and **9**). Regarding to the oxime ether moiety, methyl and ethyl derivatives (**7–10**) were active, whereas benzyl derivative (**11**) was inactive. A series of amino(hydroxyimino)-methyl derivatives seemed to be inferior to the original lead compound **A**.

From these results, it might be concluded that the cyano group of the bioactive compound could possibly be replaced with amino(hydroxyimino)methyl group.

2. Fungicidal Activities of 2-Alkoxyimino-2-cyano-*N*-(4,5-dihydroisoxazol-3-ylmethyl)acetamides (**II**)

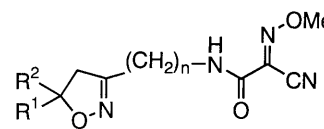
The fungicidal activities of 4,5-dihydroisoxazol-3-ylmethyl derivatives (**II**, $n=1$) and 4,5-dihydroisoxazol-3-yl derivatives (**V**, $n=0$) are compared in Tables 3 and 4.

Table 3 shows the effects of substituents at position-5 on the 4,5-dihydroisoxazole ring. Among the 4,5-dihydroisoxazol-3-ylmethyl derivatives (**12–15**), methyl (**12**) and dimethyl (**13**) derivatives showed higher activities than those with larger substituents (*tert*-butyl, **14**; phenyl, **15**). Regarding to the bridge part between 4,5-dihydroisoxazole ring and acetamide moiety, 4,5-dihydroisoxazol-3-ylmethyl derivatives ($n=1$) exhibited stronger activity than 4,5-dihydroisoxazol-3-yl derivatives ($n=0$) except when the substituents at position-5 on the 4,5-dihydroisoxazole ring were dimethyl groups.

Table 4 shows the effects of substituents (R^4) on the oxime ether. Among the 5-methyl-4,5-dihydroisoxazol-3-ylmethyl derivatives (**12, 19–21**), methyl derivative (**12**) was the most active, whereas substituents larger than the methyl group (ethyl, **19**; isopropyl, **20**; benzyl, **21**), reduced the activity. The 4,5-dihydroisoxazol-3-ylmethyl derivatives ($n=1$: **12, 19** and **21**) were more active than the corresponding 4,5-dihydroisoxazol-3-yl derivatives ($n=0$: **16, 22** and **24**), although the isopropyl derivatives (**20** and **23**) showed the same activity.

In conclusion, the 4,5-dihydroisoxazol-3-ylmethyl derivatives (**II**), as induced by inserting $-\text{CH}_2-$ between the 4,5-dihydroisoxazole ring and amide moiety of the 4,5-dihydroisoxazol-3-yl derivatives (**V**), had an increased fungicidal activity.⁴⁾ The effect was presumed to be due to an increased structural flexibility of the 4,5-dihydroisoxazole ring, and due to a reduced steric factor influence of substituents at position-5 on the 4,5-dihydroisoxazole ring and substituents (R^4) on the oxime moiety of the derivatives **II**. The 4,5-dihydroisoxazole ring and the oxime moiety fit to the better position of a target site. To know yet more detailed mode of action, it will be necessary to search for

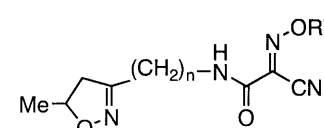
Table 3 *N*-Substituted 2-cyano-2-methoxyiminoacetamides and their fungicidal activities against cucumber downy mildew.



Compound No.	R^1	R^2	n	mp(°C) or n_D (°C)	Fungicidal activity
12	Me	H	1	102–103	4
13	Me	Me	1	95–97	4
14	<i>t</i> -Bu	H	1	1.4992(23.5)	3
15	Ph	H	1	1.5599(24)	2
16 ^{a)}	Me	H	0	154–155	3
A ^{a)}	Me	Me	0	167.5–168.5	4
17 ^{a)}	<i>t</i> -Bu	H	0	92.5–93.5	2
18 ^{a)}	Ph	H	0	149.5–150	0

^{a)} Data were taken from our previous paper.¹⁾

Table 4 2-Alkoxyimino-2-cyanoacetamides and their fungicidal activities against cucumber downy mildew.



Compound No.	R^4	n	mp(°C) or n_D (°C)	Fungicidal activity
12	Me	1	102–103	4
19	Et	1	1.5009(23.5)	3
20	<i>i</i> -Pr	1	1.4979(24)	2
21	Benzyl	1	62–64	3
16 ^{a)}	Me	0	154–155	3
22	Et	0	123–124	2
23	<i>i</i> -Pr	0	126.5–127.5	2
24	Benzyl	0	144–145	0

^{a)} Data were taken from our previous paper¹⁾

a receptor binding mechanism.

3. Fungicidal Activities of 2-Cyano-2-methoxyimino-*N*-(substituted methyl)acetamides

Since 2-methoxyimino-2-cyanoacetamides with 4,5-dihydroisoxazol-3-ylmethyl group on the amide nitrogen were found to be favorable for the fungicidal activity, 4,5-dihydroisoxazole moieties of compound **12** were modified structurally. Compounds **25–31** were prepared by the reaction of substituted methylamines with ethyl 2-cyano-2-methoxyiminoacetate.

Table 5 shows the effects of *Z* on the fungicidal activities examined with various kinds of derivatives. Among these, the 4,5-dihydroisoxazole derivative (**12**) was most active, followed by isoxazole (**25**) and pyridine (**27**) derivatives. Cyano derivative (**28**) exhibited a lower activity, while thiophene derivative (**26**), ethynyl

Table 5 2-Cyano-2-methoxyimino-*N*-(substituted methyl)-acetamides and their fungicidal activities against cucumber downy mildew.

Compound No.	Z	mp(°C) or n_D (°C)	Fungicidal activity
12		102-103	4
25		124-125	3
26		1.5568(23)	0
27		139-140	3
28	N≡C—	84-85	2
29	HC≡C—	97-98	0
30	H ₂ C=CH—	47.5-48.5	0
31	ClCH ₂ —	65-67	0

(29), vinyl (30) and chloromethyl (31) derivatives exhibited an extremely weak activity. These results revealed that the 4,5-dihydroisoxazol-3-ylmethyl group on the amide nitrogen atom of 2-alkoxyimino-2-cyanoacetamides was presumed to be of serious role by the occurrence of a potent fungicidal activity. The 4,5-dihydroisoxazole ring can form a hydrogen bond and have a suitable bulkiness.

4. Fungicidal Activities of Selected Compounds

Based on the above results, compounds **12** and **13** were chosen for the second step of evaluation (Table 6). Compound **12** showed the most potent activity among this series of derivatives. It showed an excellent control at the application rate of 7.8 ppm by both preventive and curative application, being more active than the original lead compound **A**, 2-cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide (cymoxanil) and *N*-(2,6-dimethylphenyl)-*N*-(phenylacetyl)alanine methyl ester (benalaxyl).

Our studies indicated that these 2-(alkoxyimino)-2-cyano-*N*-(substituted 4,5-dihydroisoxazol-3-ylmethyl)acetamide derivatives, a new class of fungicides, are highly effective against cucumber downy mildew.

Table 6 Disease control activities of selected compounds against cucumber downy mildew.

Compound	Application	Control(%)	
		31.3	7.8
12	Preventive	100	85
	Curative	75	75
13	Preventive	100	75
	Curative	75	30
A	Preventive	75	70
	Curative	70	50
Cymoxanil	Preventive	70	5
	Curative	55	35
Benalaxyl	Preventive	75	55
	Curative	70	40

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要 約

4,5-ジヒドロイソキサゾール環を有する 2-アルコキシイミノアセトアミド誘導体の合成と殺菌活性

甲斐浩幸, 市場常男, 西田邦好, 益子道生, 高瀬 晃
我々は先に, 2-シアノ-2-メトキシイミノ-*N*-(5,5-ジメチル-4,5-ジヒドロイソキサゾール-3-イル)アセトアミドがキュウリのべと病に対して高い活性を有することを報告した. 本研究では, さらに高い抗べと病活性を有する化合物の探索を目的として, 4,5-ジヒドロイソキサゾール環を有する 2-アルコキシイミノアセトアミド誘導体と関連化合物を合成し, キュウリのべと病に対する殺菌活性を評価した. その結果, アセトアミドの窒素原子に 4,5-ジヒドロイソキサゾール-3-イルメチル基を有する化合物が高い活性を示した. 中でも, 2-シアノ-2-メトキシイミノ-*N*-(5-メチル-4,5-ジヒドロイソキサゾール-3-イルメチル)アセトアミドは, 最も高い抗べと病活性を示した.