Synthesis and Fungicidal Activities of 2-(α-Methoxyiminobenzyl)-1-methylimidazole Derivatives

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(Received October 23, 2000 ; Accepted January 15, 2001)

Key words: 2-(α-Methoxyiminobenzyl)-1-methylimidazole, fungicidal activity, powdery mildew, downy mildew.

INTRODUCTION

In our previous paper,1) we reported the structure-fungicidal activity relationship of (α-methoxyiminobenzyl)heterocycle derivatives, designed by replacing the isoxazole ring in known fungicidal (α-alkoxyiminobenzyl)isoxazole derivatives2,3) with other heterocycles. In these previous investigations, the strongest fungicidal activity was obtained when the heterocycle moiety was comprised of 1-methyl-2-imidazolyl and 1,3,4-oxadiazol-2-yl groups. Among the derivatives examined, (E)-2-[2-(4-chloro-2-methylphenoxymethyl)-α-methoxyiminobenzyl]-1-methylimidazole (A, in Fig. 1) exhibited potent fungicidal activity against cucumber powdery mildew and cucumber gray mold.

In the course of our study, the phenoxymethyl moiety of compound A was modified structurally for further improvement of fungicidal activity. A series of 2-(α-methoxyiminobenzyl)-1-methylimidazole derivatives (I, in Fig. 1) were synthesized and their fungicidal activities were examined with reference to the effects of substituents on the α-methoxyiminobenzyl moiety.

MATERIALS AND METHODS

1. Instrumental Analysis

Melting points were measured with a Büchi 535 melting point apparatus and are given uncorrected. Refractive indexes were measured with an Atago Abbe-refractometer. IR spectra were measured on a JASCO FT/IR-300E spectrophotometer using a potassium bromide disk. 1H NMR spectra were measured on a JEOL JNM-GSX 270 spectrometer at 270 MHz using tetramethylsilane (TMS) as an internal standard.

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2.2 2-[(α-Methoxyimino-2-(5-trifluoromethyl-2-pyridyloxy-methyl)benzyl]-1-methyl-imidazole : 2 (Method A)

Butyl lithium in hexane (2.52 M, 28.6 ml, 72 mmol) was added dropwise to a solution of 1-methylimidazole (7.88 g, 96 mmol) in tetrahydrofuran (100 ml) below -40°C under a nitrogen atmosphere, and the mixture was stirred at -40°C to room temperature for 30 min. A solution of II (13.41 g 48 mmol) in tetrahydrofuran (50 ml) was added dropwise to the above mixture below -40°C over 25 min and the mixture was stirred at -40°C to room temperature for 2 hr. The reaction mixture was poured into ice-cold water (500 ml) and extracted with ethyl ether (300 ml). The organic layer was washed brine (500 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 13.41 g (93%) of 1-methyl-2-[2-(2-tetrahydropyranyloxymethyl)benzoyl] imidazole III as a colorless oil. 1H NMR (CDCl3) δ ppm: 1.37-1.80 (6H, m), 3.40-3.47 (1H, m), 3.73-3.81 (1H, m), 4.11 (3H, s), 4.52 (1H, t, J=3.5Hz), 4.67 (1H, d, J=13.2 Hz), 4.92 (1H, d, J=13.2 Hz), 7.09 (1H, d, J= 1.0 Hz), 7.17 (1H, d, J=1.0), 7.34–7.54 (3H, m), 7.66 (1H, dd, J=7.6 & 1.3 Hz).

A mixture of III (9.04 g, 30 mmol), methoxylamine hydrochloride (7.52 g, 90 mmol), pyridine (7.83 g, 99 mmol) and methanol (60 ml) was stirred under reflux for 8 hr. The reaction mixture was poured into 5% aqueous sodium hydroxide (300 ml) and extracted with dichloromethane (100 ml×3). The combined organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/dichloromethane) to give 6.55 g (89%) of 2-(2-hydroxymethyl-α-methoxyiminobenzyl)-1-methylimidazole (IV). The product was recrystallized from ethyl acetate and hexane to give colorless prisms, mp 123–124°C. 1H NMR (CDCl3) δ ppm: 3.96 (3H, s), 4.00 (3H, s), 4.46 (2H, s), 4.85 (1H, brs), 6.94 (1H, d, J= 1.0 Hz), 7.00 (1H, d, J=1.0 Hz), 7.12 (1H, dd, J= 7.9 & 1.5 Hz), 7.33–7.47 (2H, m), 7.58 (1H, dd, J=7.9 & 1.5 Hz).

Sodium hydride (60% oil dispersion ; 0.06 g, 1.5 mmol) was added to a mixture of IV (0.25 g, 1.0 mmol), 2-chloro-5-trifluoromethylpyridine (0.27 g, 1.5 mmol) and tetrahydrofuran (3 ml) in an ice bath, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ethyl ether (100 ml) and washed with brine (50 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 0.32 g (82%) of compound 2. The product was recrystallized from ethyl acetate and hexane.

Fig. 1 Chemical structures of 2-(α-methoxyiminobenzyl)-1-methylimidazoles.

Fig. 2 Methods for synthesis of 2-(α-methoxyiminobenzyl)-1-methylimidazoles.
to give colorless prisms, mp 82.5-83.5°C. Anal. Found: C, 58.39; H, 4.31; N, 14.32; F, 14.33. Calcd. for C_{28}H_{29}F_{3}N_{5}O_{2}: C, 58.46; H, 4.39; N, 14.35; F, 14.60%. 1H NMR (CDCl_3) δ ppm: 3.87 (3H, s), 3.93 (3H, s), 5.31 (2H, s), 6.63 (1H, d, J = 8.6 Hz), 6.90 (1H, d, J = 1.3 Hz), 7.04 (1H, d, J = 1.3 Hz), 7.28-7.31 (1H, m), 7.39-7.45 (2H, m), 7.56-7.59 (1H, m), 7.69 (1H, d, J = 8.6 & 2.3 Hz), 8.32-8.33 (1H, m). IR (KBr) cm⁻¹: 3440, 2940, 2820, 1920, 1620, 1440, 1320, 1270, 1160, 1060, 1040, 990.

2.4 2-[(4-(3,4-Dichlorophenyl)-2,3-diaza-1,3-pentadienyl]-α-methoxybenzyl]-1-methylimidazole: 6 (Method B)

A solution of dimethyl sulfoxide (0.64 ml, 9.0 mmol) in dichloromethane (2 ml) was added dropwise to a mixture of V (0.12 g, 0.5 mmol) and methanol (2 ml) below -55°C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 hr. The resulting solid was collected by filtration, washed with anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 0.16 g (82%) of compound 8 as colorless oil. Anal. Found: C, 58.39; H, 4.96; N, 13.02; F, 13.24. 1H NMR (CDCl_3) δ ppm: 3.94 (3H, s), 3.98 (3H, s), 6.95 (1H, d, J = 1.0 Hz), 7.02 (1H, d, J = 1.0 Hz), 7.38-7.41 (1H, m), 7.54-7.70 (2H, m), 7.98 (1H, dd, J = 7.8 & 1.5 Hz), 9.88 (1H, s).

3. Biological Tests

3.1 Plant materials

Cucumber (Cucumis sativus L. cv. Sagamihanpaku) seedlings were used for the assay of disease controlling activity by foliar application. The seedlings were prepared as described previously.²

3.2 Methods for fungicidal activity assay

Disease controlling activities of the test compounds by foliar application on cucumber powdery mildew (St: Sphaerotheca fuliginea), cucumber gray mold (Bc: Botrytis cinerea), and cucumber downy mildew (Pc: Pseudoperonospora cubensis) were assessed as described previously.²

The fungicidal activity by preventive application was expressed as an index of 5, 4, 3, 2, 1 or 0, each corresponding to approximately 90% (cucumber powder mildew) or 50% (cucumber gray mold and cucumber downy mildew) control at 2 hr, 7.8, 31.3, 125, 500 ppm or less than 90% (cucumber powdery mildew) or 50% (cucumber gray mold and cucumber downy mildew) control at 500 ppm, respectively.

RESULTS AND DISCUSSION

Table 1 shows the effects of substituent (R) on the benzyl moiety of 2-(α-methoxyiminobenzyl)-1-methylimidazoles on the activities against cucumber powdery mildew, cucumber gray mold and cucumber downy mildew. Against both powdery mildew and downy mildew, (α-methylenzyl)oxyiminomethyl derivatives (7-9) exhibited excellent activ-
Table 1: 2-(2-Substituted $\alpha$-methoxyiminobenzyl)-1-methylimidazoles and their fungicidal activities.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>mp(°C) or $n_D$ (°C)</th>
<th>Sf</th>
<th>Bc</th>
<th>Pc</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>OMe</td>
<td>87.5 - 88.5</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>OMe</td>
<td>84 - 86</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>CF$_3$O</td>
<td>82.5 - 83.5</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>ClO</td>
<td>56 - 58</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>ClO(Me)NN=CH$-\cdot$</td>
<td>1.6520 (24)</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>CF$_3$O(Me)NN=CH$-\cdot$</td>
<td>110 - 112</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>ClO(Me)NN=CH$-\cdot$</td>
<td>143 - 145</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>ClO(Me)NN=CH$-\cdot$</td>
<td>1.6056 (23)</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>ClO(Me)NN=CH$-\cdot$</td>
<td>1.5665 (23)</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>ClO(Me)NN=CH$-\cdot$</td>
<td>1.6129 (23)</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Sf: cucumber powdery mildew, Bc: cucumber gray mold, Pc: cucumber downy mildew. Fungicidal activities are expressed as an index of 5, 4, 3, 2, 1 or 0, corresponding to approximately 90% (Sf) or 50% (Bc and Pc) control at 2.0, 7.8, 31.3, 125, 500 ppm or less than 90% (Sf) or 50% (Bc and Pc) control at 500 ppm, respectively.

ities, followed by 4-phenyl-2,3-diaza-1,3-pentadienyl derivatives (4-6). Pyridyloxymethyl derivatives (1-3) showed decreased activity against downy mildew. However, all of the compounds except original lead compound A were less active or inactive against gray mold. When the substituent (R) was a phenoxy or 6-(2-cyanophenoxy)-4-pyrimidinyloxy, each structurally equivalent to the side chain part of the known strobilurin-derived fungicide, metominostrobin or azoxystrobin, their fungicidal activities were weak (data were not shown).

Table 2 shows the effects of substituents (X) on the $\alpha$-methylenbenzylxylo moiety of 2-[$\alpha$-methoxyimino-2-($\alpha$-methylenbenzylxyominobenzyl)-1-methylimidazoles on the fungicidal activities against cucumber powdery mildew and cucumber downy mildew. Among three kinds of mono-substituted regio isomers at the benzene ring (Cl, Me, CF$_3$ : 7, 8, 11-17), substitution with a chloro or a trifluoromethyl group at position-4 (7 and 8) resulted in most favorable fungicidal activities, whereas substitution at position-2 (11, 13 and 16) gave weak or no activity. Then, the 4-substituted derivatives were synthesized and their structure-activity relationship were examined. Among compounds with other substituent at position-4 (18-20), trifluoromethoxy (20) and bromo (18) derivatives showed potent activities against both diseases. Methyl (15) and methoxy (19) derivatives showed inferior activities against both diseases as compared with trifluoromethyl (8) and trifluoromethoxy (20) derivatives. These findings suggested that the presence of an electron-withdrawing group as well as the hydrophobic effect of the substituent at position-4 on the phenyl moiety were responsible for increasing fungicidal activities. Between di-substituted derivatives (9 and 21), the 3,4-dichloro derivative (9) showed stronger activity. The fungicidal activity of 2,4-dichloro derivative (21) was markedly weaker than that of 4-chloro derivative (9). Further, introduction of a substituent at position-2 (11, 13 and 16) did not increase the activity of unsubstituted derivative (10). These results suggested that introduction of a substituent at position-2 was not favorable for the activity. A plausible explanation for the former finding is that the benzene ring may not take a suitable conformation for exhibiting activity due to restricted rotation by the substituent at position-2.

Table 3 shows the effects of substituents (Y) at position-$\alpha$-
of the 4-chlorobenzyloxy moiety of 2-[2-(4-chlorobenzyloxyiminomethyl)-\(\alpha\)-methoxyiminobenzyl]-1-methylimidazoles and the fungicidal activities.

Among the compounds (7, 22 and 23), methyl (7) derivative was most active, followed by ethyl (23) derivative. Unsubstituted derivative (22) was inactive against downy mildew. One possible explanation for this is that the favorable conformation of the benzyloxyiminomethyl moiety for the activity was transformed by the steric influence of the methyl group at position-\(\alpha\). Among the 23 compounds examined, 2-[\(\alpha\)-methoxyimino-2-(4-trifluoromethyl-\(\alpha\)-methylbenzyl)oxyiminomethyl]benzyl]-1-methylimidazole (8) and 2-[\(\alpha\)-methoxyimino-2-(4-trifluoromethoxy-\(\alpha\)-methylbenzyl)oxyiminomethyl]benzyl]-1-methylimidazole (20) showed potent activities against cucumber powdery mildew and cucumber downy mildew.

In conclusion, the present study indicated that 2-[\(\alpha\)-methoxyimino-2-(\(\alpha\)-methylbenzoyloxyiminomethyl)benzyl]-1-methylimidazole derivatives may be useful as a new group of fungicides highly effective against cucumber powdery mildew and cucumber downy mildew.

ACKNOWLEDGMENTS

We wish to express our thanks to Dr. Masafumi Fujimoto, Director of Aburahi Laboratories, Shionogi & Co., Ltd., for encouragement and permission to publish this work. We also wish to thank Drs. Koichi Morita, Toshikazu Ohtsuka and Michio Masuko for invaluable discussions and encouragement.

REFERENCES