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Stereoselective Synthesis and Antifungal Activities of (*E*)-α-(Methoxyimino)benzeneacetate Derivatives Containing 1,3,5-Substituted Pyrazole Ring

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Thirteen novel (*E*)-α-(methoxyimino)benzeneacetate derivatives, the analogues of strobilurins, which contain two pharmacophoric substructures of the methyl (*E*)-methoxyiminoacetate moiety and 1,3,5-substituted pyrazole ring, were stereoselectively synthesized. It was found that the coupling reaction could give stereoselectively (*E*:*Z* ca. 14:1) the key intermediate material (*E*)-methyl 2-(hydroxyimino)-2-*o*-tolyl acetate (**2**). An X-ray crystallographic structure determination was carried out in a representative product. The preliminary bioassays indicated that all of the compounds **1** showed potent fungicidal activity against *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberella zeae*, *Physalospora piricola*, and *Bipolaris mayclis*.

KEYWORDS: Strobilurins; (*E*)-α-(methoxyimino)benzeneacetates; 1,3,5-substituted pyrazoles; fungicidal

INTRODUCTION

Strobilurins are a class of highly potent antifungal compounds, and they have, therefore, been applied to agricultural disinfectants in many countries (*1*, *2*). These compounds act through inhibition of mitochondrial respiration by blocking electron transfer at the ubiquinol oxidation center (Q_o site) of the cytochrome bc_1−enzyme complex (complex III) (*3*), and they have a methyl (*E*)-methoxyiminoacetate moiety as a common pharmacophoric substructure (*4*). On the other hand, substituted pyrazole ring derivatives also exhibit a broad spectrum of biological activities such as antimicrobial (*5*−*7*), herbicidal (*8*), antitumor (*9*, *10*), and antiinflammatory (*11*) activities. In view of these facts, we have developed a new and efficient method for stereoselective synthesis of the key intermediate methyl (*E*)-α-(methoxyimino)benzeneacetate and synthesized some novel analogues of strobilurins, which contain both methyl (*E*)-methoxyiminoacetate and 1,3,5-substituted pyrazole ring moieties, viz. methyl (α*E*,*E*)-α-(methoxyimino)-2-[(1,3-dimethyl-5-substituted 1*H*-pyrazol-4-yl)methyleneaminooxymethyl]-benzeneacetates (**1**), in order to obtain better fungicidal activities.

MATERIALS AND METHODS

Materials. *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberella zeae*, *Physalospora piricola*, and *Bipolaris mayclis* were provided through the courtesy of the Center for Analysis and Testing, Central China Normal University. The solvents and reagents were used as received or were dried prior to use as needed. Melting points were determined with a Tech X-6 micromelting points apparatus made in Beijing. Infrared spectra were recorded on a Perkin-Elmer PE-SPECTRUM ONE apparatus, for solid compounds in KBr-pressed disks, and the υ values were recorded in wavenumbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were obtained on a Varian Unity INOVA-600 MHz spectrometer (600 MHz, ^1H; 150 MHz, ^{13}C) in $CDCl_3$ with tetramethylsilane as the internal reference. The mass spectra were obtained on a Finnigen Trace Mass spectrometer (70 eV). Elemental analyses (C, H, and N) were performed with a Perkin-Elmer PE-2400 elemental analyzer.

X-ray Diffraction. Colorless blocks of **1g** (0.50 mm × 0.25 mm × 0.20 mm) were mounted on a quartz fiber with protection oil. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å); θ_{max} = 26.00; 24306 measured reflections; 4578 independent reflections (R_{int} = 0.0615) of which 2596 had $|F_o| > 2|F_o|$. Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.9526; T_{max} = 0.9807). The structure was solved by direct methods using SHELXS-97 (*12*); all other calculations were performed with Bruker SAINT system and Bruker SMART programs (*13*). Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0786P)^2 + 0.6674P]$ gave final values of R = 0.0586, ωR = 0.1723, and GOF(F) = 1.019 for 332 variables and 2237 contributing reflections. Maximum shift/error = 0.0000(3), max/min residual electron density = 0.292/−0.212 e $Å^{-3}$. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter. The general synthesis of target compounds is shown in **Figure 1**.

Preparation of Methyl 2-Hydroxyimino-2-*o*-tolyl Acetate (2). To 3.92 g (38 mmol) methyl 2-hydroxyiminoacetate and 17 mL of water placed in a round-bottom flask were added 0.65 g (2.6 mmol) of cupric sulfate hydrate, 0.1 g (0.79 mmol) of sodium sulfite, and a solution of

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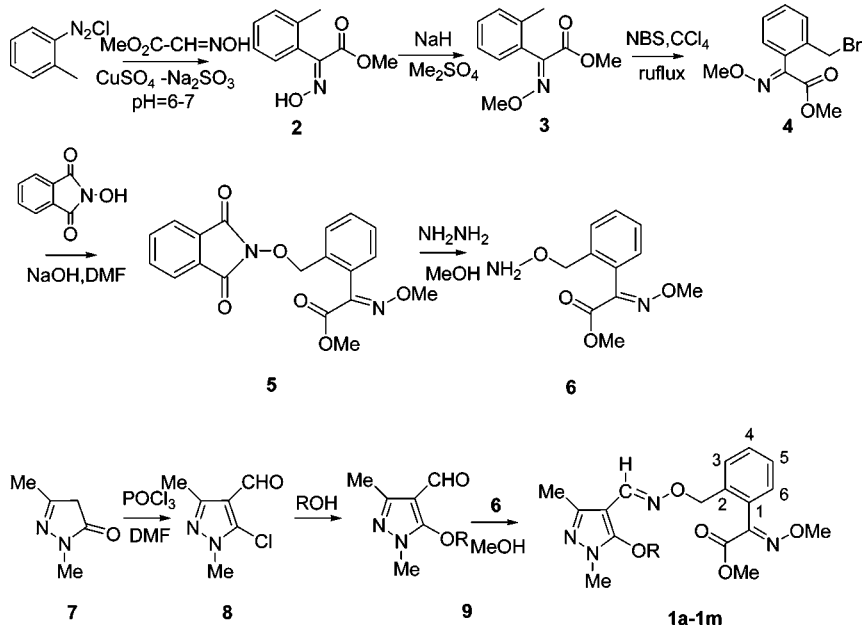

Figure 1. General synthetic route for the target compound **1**.

16 g of sodium acetate hydrate in 18 mL of water. The solution was maintained at 5−10 °C and stirred vigorously. Neutral 2-methylphenyl diazonium chloride (5.87 g, 38 mmol) solution was then slowly introduced into the oxime solution. After the addition of the diazonium salt solution was complete, the stirring was continued for an additional hour. Then, the mixture was stirred for 2 h at 20 °C, the mixture was extracted with 3 × 10 mL of ether. The combined ether extracts were washed with an aqueous 10% sodium bicarbonate solution and then with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was subjected to column chromatography using a mixture of *n*-hexane and ethyl acetate (4:1) as an eluent to obtain the compound (*Z*)-**2**: upper spot, R_f 0.63, as an oil; 0.22 g, 3%. IR (KBr): 3353, 1728, 1620, 1445, 1314, 1032, 930, 757, 732, 670 cm^{-1}. ^1H NMR: δ 2.36 (3H, s, Ar-CH_3), 3.88 (3H, s, −$COOCH_3$), 7.27−7.22 (3H, m, 3 × Ar-H), 7.32 (1H, d, J = 7.8 Hz, 6-ArH). Also obtained was compound (*E*)-**2**: down spot, R_f 0.50, as an oil; 3.01 g, 41%. IR (KBr): 3349, 1732, 1622, 1443, 1310, 1034, 930, 757, 730, 696 cm^{-1}. ^1H NMR: δ 2.23 (3H, s, Ar-CH_3), 3.83 (3H, s, −COOMe), 7.15 (1H, d, J = 7.8 Hz, 3-ArH), 7.25−7.28 (2H, m, 2 × Ar-H), 7.33 (1H, t, J = 7.2 Hz, 4-ArH), 10.15 (1H, s, −OH).

Preparation of Methyl (*E*)-2-Methoxyimino-2-*o*-tolyl Acetate (3). To 0.68 g (17 mmol) of 60% NaH was added 10 mL of dry dimethyl formamide (DMF) at 0 °C, and 2.9 g (15 mmol) of the compound (*E*)-**2** was added thereto. The resulting solution was stirred for 30 min at room temperature, and then, 2.52 g (20 mmol) of dimethyl sulfate was added. After 12 h at room temperature, the mixture was extracted with ethyl acetate, and the combined organic layers were washed with an aqueous 5% NaOH solution and then with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was subjected to column chromatography using a mixture of *n*-hexane and ethyl acetate (15:1) as an eluent to obtain compound (*E*)-**3** (2.82 g) in 91% yield: mp 63 °C [ref (*14*), 63−64 °C]. IR (KBr): 2949, 1726 (C═O), 1439, 1068, 1011, 755 cm^{-1}. ^1H NMR: δ 2.20 (3H, s, Ar-CH_3), 3.88 (3H, s, −COOMe), 4.06 (3H, s, N-OCH_3), 7.12 (1H, d, J = 8.4 Hz, 3-Ar-H), 7.22−7.26 (2H, m, 2 × ArH), 7.32 (1H, d, J = 7.8 Hz, 6-ArH).

Preparation of Methyl (*E*)-α-(Methoxyimino)-2-(1-bromo-methyl)benzeneacetate (4). To a mixture of 2.07 g (10 mmol) of (*E*)-**3** and 2.14 g (12 mmol) of N-bromosuccinimide in 30 mL of carbon tetrachloride was added 20 mg of 2,2′-azo-bisisobutyronitrile. The resulting solution was refluxed for 10 h, then cooled, and filtered to remove succinimide. The filtrate was evaporated under a reduced pressure, and the oily residue was subjected to column chromatography using a mixture of *n*-hexane and ethyl acetate (20:1) as an eluent to obtain (*E*)-**4** (2.32 g) in 81% yield. IR (KBr): 2942, 1728 (C═O), 1438, 1321, 1220, 1067, 1018, 958, 762 cm^{-1}. ^1H NMR: δ 3.86 (3H, s, −COOMe), 4.04 (3H, s, N-OCH_3), 4.31 (2H, s, −CH_2−), 7.13 (1H, dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 3-ArH), 7.35−7.40 (2H, m, 2 × Ar-H), 7.46 (1H, dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 6-ArH).

Preparation of Methyl (*E*)-α-(Methoxyimino)-2-(*o*-phthalimidoxymethyl)benzeneacetate (5). A dry 100 mL round-bottom flask equipped with a magnetic stirrer and nitrogen inlet was charged with 0.98 g (6 mmol) of N-hydroxyphthalimide, 0.24 g (6 mmol) of powdered sodium hydroxide, and 50 mL of DMF. The dark red solution was stirred at ambient temperature for 20 min, followed by the addition of 1.72 g (6 mmol) of (*E*)-**4** in one portion. The reaction was stirred at ambient temperature overnight, then poured into 50 mL of water, and stirred for 1 h to afford a solid, which was collected by vacuum filtration and washed with water and hexane. The tan solid was dried under vacuum at 40 °C overnight, yielding 2.01 g (91%) of **5** as a light brown solid. ^1H NMR: δ 3.84 (s, 3H, COOMe), 3.98 (s, 3H, NO-CH_3), 5.07 (s, 2H, −CH_2−), 7.18 (d, J = 7.2 Hz, 1H, 3-ArH), 7.45−7.51 (m, 2H, 3′ and 4′-ArH), 7.73−7.80 (m, 4H, 2′, 5′, 4 and 5-ArH), 7.83 (d, J = 7.2 Hz, 1H, 3-ArH).

Preparation of Methyl (*E*)-α-(Methoxyimino)-2-(aminoxymethyl)benzeneacetate (6). To a 50 mL round-bottom flask equipped with a magnetic stirrer were added 1.47 g (4 mmol) of **5**, 20 mL of anhydrous methanol, and 0.22 g (4.4 mmol) of hydrazine monohydrate. The flask was stoppered, and the reaction was stirred at ambient temperature for 2 h. The resulting solid was removed by filtration, and the filtrate was evaporated on a rotavap. The residue was slurried in 30 mL of anhydrous ether and filtered, and the filtrate was again evaporated to afford 0.85 g (89%) of **6** as a light yellow liquid. This was unstable and was used rapidly in the next step of the synthesis.

Synthesis of the Target Compounds (1). A 25 mL round-bottom flask equipped with a magnetic stirrer and nitrogen inlet was charged with **9** (2 mmol) and 0.55 g (2.3 mmol) of **6**. The mixture was dissolved in 10 mL of anhydrous methanol, and one drop of glacial acetic acid was added as a catalyst. The flask was stirred at ambient temperature overnight, then poured into 50 mL of water, and extracted with 3 × 50 mL of ethyl ether. The combined ether extracts were washed with 2 × 50 mL of water and 50 mL of brine, dried over anhydrous magnesium sulfate, and filtered, and the filtrate was evaporated to afford an oil, which was chromatographed on silica with ethyl acetate and hexane monitoring by thin-layer chromatography. The pure fractions were combined and evaporated to afford the target compounds.

Data for 1a. Yield, 65%; mp 112.2−113.7 °C. IR (KBr): 2924, 1726 (C═O), 1623, 1062, 1014 cm^{-1}. ^1H NMR: δ 2.30 (s, 3H, Ar-CH_3), 2.32 (s, 3H, C-CH_3), 3.58 (s, 3H, N-CH_3), 3.73 (s, 3H, COOMe), 3.99 (s, 3H, NO-CH_3), 4.91 (s, 2H, −CH_2−), 6.76 (d, J = 8.4 Hz, 2H,

2′ and 6′-ArH), 7.08 (d, J = 7.8 Hz, 2H, 3′ and 5′-ArH), 7.15 (d, J = 9.0 Hz, 1H, 6-ArH), 7.34−7.39 (m, 3H, 3, 4 and 5-ArH), 7.68 (s, 1H, CH═N). ^{13}C NMR: δ 15.4 (N═C−CH_3), 21.0 (ph-CH_3), 34.6 (N-CH_3), 53.3 ($COOCH_3$), 64.2 (C═NOMe), 74.7 ($NOCH_2$), 100.5 (4-HetC), 115.5, 128.1, 128.7, 129.4, 129.7, 130.3, 130.9, 133.6, 136.5, 141.3 (3-HetC), 147.3 (C═NOMe), 148.6, 150.1 (CH═N), 155.2 (5-HetC), 163.7 (COOMe). MS (70 eV): *m*/*z* (%) 450 (M^+, 100), 391 (M − $COOMe^+$, 17), 228 ([M − 222]$^+$, 65), 213 (44), 131 (33), 116 (23), 91 (5), 59 (6). Anal. calcd for $C_{24}H_{26}N_4O_5$: C, 63.99; H, 5.82; N, 12.44. Found: C, 64.11; H, 5.73; N, 12.29.

Data for 1b. Yield, 69%; mp 98.0−98.5 °C. IR (KBr): 2920, 1721 (C═O), 1622, 1060, 1017 cm^{-1}. ^{1}H NMR: δ 2.31 (s, 3H, Ar-CH_3), 2.33 (s, 3H, C-CH_3), 3.57 (s, 3H, N-CH_3), 3.73 (s, 3H, COOMe), 3.98 (s, 3H, NO-CH_3), 4.91 (s, 2H, −CH_2−), 6.66 (d, J = 7.8 Hz, 1H, 6′-ArH), 6.67 (s, 2H, 2′-ArH), 6.89 (d, J = 7.8 Hz, 1H, 4′-ArH), 7.15 (t, J = 7.8 Hz, 1H, 5′-ArH), 7.17 (d, J = 7.2 Hz, 1H, 3-ArH), 7.33−7.35 (m, 2H, 4-ArH and 5-ArH), 7.36 (d, J = 7.2 Hz, 1H, 6-ArH), 7.70 (s, 1H, CH═N). ^{13}C NMR: δ 15.4 (N═C−CH_3), 16.5 (ph-CH_3), 34.5 (N-CH_3), 53.2 ($COOCH_3$), 64.1 ($NOCH_2$), 74.6 (OCH_2), 100.3 (4-HetC), 113.8, 124.0, 126.9, 127.7, 128.1, 128.7, 129.3, 129.7, 130.3, 131.9, 136.4, 141.1 (3-HetC), 147.4 (C═NOMe), 148.6, 150.1 (CH═N), 155.4 (5-HetC), 163.7 (COOMe). MS (70 eV): *m*/*z* (%) 450 (M^+, 100), 419 (M − CH_3O^+, 12), 391 (M − $COOMe^+$, 21), 228 ([M − 222]$^+$, 99), 226 (31), 213 (43), 131 (52), 116 (32), 59 (13). Anal. calcd for $C_{24}H_{26}N_4O_5$: C, 63.99; H, 5.82; N, 12.44. Found: C, 64.13; H, 5.66; N, 12.51.

Data for 1c. Yield, 71%; mp 104.5−104.9 °C. IR (KBr): 2921, 1723 (C═O), 1629, 1067, 1010 cm^{-1}. ^{1}H NMR: δ 2.32 (s, 3H, ArMe), 2.36 (s, 3H, N═CMe), 3.58(s, 3H, C═NMe), 3.72 (s, 3H, COOMe), 4.00 (s, 3H, N-OCH_3), 4.88 (s, 2H, −CH_2−), 6.50 (d, J = 8.4 Hz, 1H, 3′-ArH), 6.99 (t, J = 7.5 Hz, 1H, 5′-ArH), 7.06 (t, J = 7.5 Hz, 1H, 4′-ArH), 7.14 (d, J = 7.8 Hz, 1H, 6′-ArH), 7.20 (d, J = 7.8 Hz, 1H, 6 −ArH), 7.33−7.36 (m, 3H, 3, 4 and 5-ArH), 7.64 (s, 1H, −CH═N). ^{13}C NMR: δ 15.4 (N═C−CH_3), 16.5 (ph-CH_3), 34.5 (N-CH_3), 53.2 ($COOCH_3$), 64.1 ($NOCH_2$), 74.6 (OCH_2), 100.3 (4-HetC), 113.8, 124.0, 126.9, 127.7, 128.1, 128.7, 129.3, 129.7, 130.3, 131.9, 136.4, 141.1 (3-HetC), 147.4 (C═NOMe), 148.6, 150.1 (CH═N), 155.4 (5-HetC), 163.7 (COOMe). MS (70 eV): *m*/*z* (%) 451 ([M + 1]$^+$, 37), 450 (M^+, 78) , 419 (6), 391 (M − $COOMe^+$, 13), 228 ([M − 222]$^+$, 100), 213 (28), 131 (59), 116 (33), 59 (14). Anal. calcd for $C_{24}H_{26}N_4O_5$: C, 63.99; H, 5.82; N, 12.44. Found: C, 64.04; H, 5.89; N, 12.25.

Data for 1d. Yield, 67%; mp 64.8−65.5 °C. IR (KBr): 2917, 1734 (C═O), 1630, 1058, 1010 cm^{-1}. ^{1}H NMR: δ 2.34 (s, 3H, N═C−CH_3), 3.64 (s, 3H, N-CH_3), 3.76 (s, 3H, COOMe), 4.00 (s, 3H, NO-CH_3), 4.88 (s, 2H, −CH_2−), 6.81 (d, J = 8.4 Hz, 2H, 2′ and 6′-ArH), 7.15 (d, J = 9.0 Hz, 1H, 6-ArH), 7.25 (m, 3H, 3′, 5′, and 5-ArH), 7.31 (t, J = 4.2 Hz, 1H, 4-ArH), 7.36 (d, J = 4.5 Hz, 1H, 3-ArH), 7.67 (s, 1H, CH═N). ^{13}C NMR: δ 15.0 (N═C−CH_3), 34.7 (N-CH_3), 53.3 ($COOCH_3$), 64.2 ($NOCH_2$), 74.8 (OCH_2), 100.7 (4-HetC), 117.1, 128.2, 128.8, 129.3, 130.0, 130.3, 130.3, 130.4, 136.4, 140.7 (3-HetC), 147.4 (C═NOMe), 147.7, 150.1 (CH═N), 155.6 (5-HetC), 163.7 (COOMe). MS (70 eV): *m*/*z* (%) 472 ([M + 2]$^+$, 79), 470 (M^+, 100), 439 (M − CH_3O^+, 20), 411 (M − $COOMe^+$, 31), 248 ([M − 222]$^+$, 91), 233 (50), 205 (25), 131 (76), 116 (64), 59 (25). Anal. calcd for $C_{23}H_{23}ClN_4O_5$: C, 58.66; H, 4.92; N, 11.90. Found: C, 5.81; H, 4.74; N, 11.75.

Data for 1e. Yield, 78%; mp 82.7−83.7 °C. IR (KBr): 2918, 1730 (C═O), 1620, 1051, 1019 cm^{-1}. ^{1}H NMR: δ 2.29 (s, 3H, C-CH_3), 3.63 (s, 3H, N-CH_3), 3.79 (s, 3H, COOMe), 4.00 (s, 3H, NO-CH_3), 4.88 (s, 2H, −CH_2−), 6.58 (d, J = 9.6 Hz, 1H, 6′-ArH), 7.07 (d, J = 9.6 Hz, 1H, 5′-ArH), 7.15 (d, 1H, 6-ArH), 7.31 (t, J = 4.5 Hz, 1H, 5-ArH), 7.35−3.37 (m, 2H, 3 and 4-ArH), 7.43 (s, 1H, 3′-ArH), 7.68 (s, 1H, CH═N). ^{13}C NMR: δ 14.8 (N═C−CH_3), 34.7 (N-CH_3), 53.3 ($COOCH_3$), 64.2 ($NOCH_2$), 74.8 (OCH_2), 100.6 (4-HetC), 116.8, 123.9, 128.2, 128.4, 128.8, 129.2, 129.5, 129.7, 130.2, 130.9, 136.4, 140.4 (3-HetC), 147.0 (C═NOMe), 147.6, 150.1 (CH═N), 151.3 (5-HetC), 163.7 (COOMe). MS (70 eV): *m*/*z* (%) 506 ([M + 2]$^+$, 65), 504 (M^+, 100), 469 ([M − Cl]$^+$, 52), 282 ([M − 222]$^+$, 44), 233 (50), 205 (25), 131 (29), 116 (24), 59 (30). Anal. calcd for $C_{23}H_{22}Cl_2N_4O_5$: C, 54.66; H, 4.39; N, 11.09. Found: C, 54.80; H, 4.25; N, 11.21.

Data for 1f. Yield, 81%; mp 135.3−135.8 °C. IR (KBr): 2914, 1727 (C═O), 1615, 1335, 1046, 1018 cm^{-1}. ^{1}H NMR: δ 2.33 (s, 3H, C-CH_3), 3.65 (s, 3H, N-CH_3), 3.79 (s, 3H, COOMe), 3.99 (s, 3H, NO-CH_3), 4.80 (s, 2H, −CH_2−), 7.12 (d, J = 7.2 Hz, 1H, 6′-ArH), 7.19−7.22 (m, 2H, 6 and 5-ArH), 7.31−7.33 (m, 2H, 3 and 4-ArH), 7.44 (t, J = 8.4 Hz, 1H, 5′-ArH), 7.69 (s, 1H, 2′-ArH), 7.72 (s, 1H, CH═N), 7.92 (d, J = 7.8 Hz, 1H, 4′-ArH). ^{13}C NMR: δ 14.8 (N═C−CH_3), 34.7 (N-CH_3), 53.2 ($COOCH_3$), 64.1 ($NOCH_2$), 74.7 (OCH_2), 100.6 (4-HetC), 111.1, 111.5, 119.0, 119.8, 122.0, 128.0, 128.8, 129.6, 130.0, 131.0, 131.4, 136.4, 140.4 (3-HetC), 147.9 (C═NOMe), 149.6, 150.0 (CH═N), 151.0 (5-HetC), 163.7 (COOMe). MS (70 eV): *m*/*z* (%) 483 ([M + 2]$^+$, 4) , 481 (M^+, 5), 450 (M − CH_3O^+, 14), 259 ([M − 222]$^+$, 55), 131 (100), 116 (53), 70 (36), 59 (30). Anal. calcd for $C_{23}H_{23}N_5O_7$: C, 57.38; H, 4.82; N, 14.55. Found: C, 57.50; H, 4.73; N, 14.52.

Data for 1g. Yield, 69%; mp 118.9−119.3 °C. IR (KBr): 2927, 1708 (C═O), 1615, 1058, 1018 cm^{-1}. ^{1}H NMR: δ 2.30 (s, 3H, C-CH_3), 3.64 (s, 3H, N-CH_3), 3.77 (s, 3H, COOMe), 4.00 (s, 3H, NO-CH_3), 4.87 (s, 2H, −CH_2−), 6.75 (t, J = 7.8 Hz, 1H, 4′-ArH), 7.01 (t, 1H, 5′-ArH), 7.05 (d, 1H, 6′-ArH), 7.15−7.18 (m, 2H, 6 and 3′-ArH), 7.34−7.36 (m, 3H, 3, 4 and 5-ArH), 7.70 (s, 1H, CH═N). ^{13}C NMR: δ 15.1 (N═C−CH_3), 34.7 (N-CH_3), 53.3 ($COOCH_3$), 64.2 ($NOCH_2$), 74.7 (OCH_2), 100.3 (4-HetC), 117.2, 117.5, 117.7, 125.0, 125.1, 128.1, 128.8, 129.3, 130.3, 136.4, 140.8 (3-HetC), 147.5 (C═NOMe), 147.5, 150.1 (CH═N), 151.5, 153.2 (5-HetC), 163.7 (COOMe). MS (70 eV): *m*/*z* (%) 454 (M^+, 100), 423 (M − CH_3O^+, 43), 395 (M − $COOMe^+$, 54), 232 ([M − 222]$^+$, 65), 217 (36), 131 (30), 116 (25), 59 (17). Anal. calcd for $C_{23}H_{23}FN_4O_5$: C, 60.79; H, 5.10; N, 12.33. Found: C, 60.91; H, 5.19; N, 12.46. Crystal data, colorless block, ($C_{23}H_{23}FN_4O_5$), M_r = 454.45; μ = 0.098 mm^{-1}, d_x = 1.294 g/cm^3, P 2$_1$/c, Z = 8, a = 14.2781-(10), b = 16.1865(12), c = 20.1828(15) Å, α = 90°, β = 90°, γ = 90°, V = 4664.5(6) Å^3.

Data for 1h. Yield, 67%; mp 83.5−84.6 °C. IR (KBr): 2929, 1718 (C═O), 1610, 1053, 1019 cm^{-1}. ^{1}H NMR: δ 2.31 (s, 3H, C-CH_3), 3.60 (s, 3H, N-CH_3), 3.74 (s, 3H, COOMe), 3.99 (s, 3H, NO-CH_3), 4.89 (s, 2H, −CH_2−), 6.83 (t, J = 8.4 Hz, 2H, 2′ and 4′-ArH), 6.97 (d, J = 9.0 Hz, 2H, 3′ and 5′-ArH), 7.15 (d, J = 7.8 Hz, 1H, 6-ArH), 7.33−7.37 (m, 3H, 3, 4 and 5-ArH), 7.69 (s, 1H, CH═N). ^{13}C NMR: δ 15.07 (N═C−CH_3), 34.6 (N-CH_3), 53.3 ($COOCH_3$), 64.2 ($NOCH_2$), 74.7 (OCH_2), 100.5 (4-HetC), 116.9, 117.0, 128.1, 128.8, 129.2, 129.7, 130.2, 136.4, 140.4 (3-HetC), 147.5 (C═NOMe), 148.2, 150.1 (CH═N), 153.0 (5-HetC), 160.0, 163.7 (COOMe). MS (70 eV): *m*/*z* (%) 454 (M^+, 100), 423 (M − CH_3O^+, 22), 395 (M − $COOMe^+$, 30), 232 ([M − 222]$^+$, 11), 217 (35), 146 (15), 131 (21), 116 (27), 59 (21). Anal. calcd for $C_{23}H_{23}FN_4O_5$: C, 60.79; H, 5.10; N, 12.33. Found: C, 60.90; H, 5.05; N, 12.41.

Data for 1i. Yield, 54%; mp 85.6−86.9 °C. IR (KBr): 2918, 1709 (C═O), 1620, 1048, 1017 cm^{-1}. ^{1}H NMR: δ 2.32 (s, 3H, C-CH_3), 3.61 (s, 3H, N-CH_3), 3.75 (s, 3H, COOMe), 3.98 (s, 3H, NO-CH_3), 4.84 (s, 2H, −CH_2−), 7.00 (t, J = 8.4 Hz, 1H, 6′-ArH), 7.14 (d, J = 8.4 Hz, 1H, 6-ArH), 7.17 (s, 1H, 2′-ArH), 7.30 (d, 1H, J = 9.0 Hz, 4′-ArH), 7.33−7.37 (m, 3H, 4, 5 and 5′-ArH), 7.40 (d, J = 8.4 Hz, 1H, 3-ArH), 7.70 (s, 1H, CH═N). ^{13}C NMR: δ 14.9 (N═C−CH_3), 34.7 (N-CH_3), 53.2 ($COOCH_3$), 64.2 ($NOCH_2$), 74.8 (OCH_2), 100.8 (4-HetC), 118.8, 120.9, 128.1, 128.8, 129.2, 129.7, 130.3, 131.1, 136.3, 140.6 (3-HetC), 147.1 (C═NOMe), 147.7, 150.1 (CH═N), 151.2, 157.1 (5-HetC), 163.7 (COOMe). MS (70 eV): *m*/*z* (%) 504 (M^+, 12), 473 (M − CH_3O^+, 27), 445 (M − $COOMe^+$, 24), 282 ([M − 222]$^+$, 78), 245 (M − $OphCF_3^+$, 100), 186 (63), 161 (CF_3phO^+, 16), 145 (CF_3-ph$^+$, 48), 131 (61), 116 (64), 59 (28). Anal. calcd for $C_{24}H_{23}F_3N_4O_5$: C, 57.14; H, 4.60; N, 11.11. Found: C, 57.03; H, 4.55; N, 11.24.

Data for 1j. Yield, 71%; mp 102.6−103.1 °C. IR (KBr): 2916, 1707 (C═O), 1615, 1041, 1010 cm^{-1}. ^{1}H NMR: δ 2.25 (s, 3H, ═C−CH_3), 3.60 (s, 3H, N-Me), 3.83 (s, 3H, COOMe), 3.90 (s, 3H, OMe), 4.02 (s, 3H, N-OCH_3), 5.02 (s, 2H, −CH_2−), 7.18 (d, J = 7.2 Hz, 1H, 6-ArH), 7.36 (t, J = 7.2 Hz, 1H, 5-ArH), 7.41 (t, J = 7.2 Hz, 1H, 4-ArH), 7.47 (d, J = 7.8 Hz, 1H, 3-ArH), 7.95 (s, 1H, CH═N). ^{13}C NMR: δ 14.3 (3-HetCH_3), 34.1 (1-HetCH_3), 53.3 ($COOCH_3$), 62.0 (5- HetOCH_3), 64.2 ($NOCH_3$), 74.7 (OCH_2), 97.6 (4-HetC), 128.1 (5-C), 128.9 (6-C), 129.2 (3-C), 129.8(4-C), 130.3 (1-C), 137.0 (2-C), 142.0 (3-HetC), 147.3 (C═NOMe), 150.2 (CH═N), 153.4 (5-HetC), 163.8 (COOMe). MS (70 eV): *m*/*z* (%) 504 (M^+, 12), 473 (M − CH_3O^+, 27), 445 (M − $COOMe^+$, 24), 282 ([M − 222]$^+$, 78), 245 (M

Table 1. Fungicidal Activities of (*E*)-α-(Methoxyimino)benzeneacetate Derivatives **1** (50 μg/mL, Relative Inhibitory Rate %)[a]

compds		inhibitory rate %				
		R. solani	*B. cinereapers*	*G. zeae*	*P. piricola*	*B. mayclis*
1a	4-methylphenyl	90.2	80.8	50.0	88.2	72.7
1b	2-methylphenyl	83.7	80.8	53.1	76.5	72.7
1c	3-methylphenyl	88.0	80.8	96.9	100	81.8
1d	4-chlorophenyl	100	100	80.0	92.6	92.9
1e	2,4-dichlorophenyl	99.0	100	88.6	96.3	92.9
1f	3-nitrophenyl	91.6	98.8	62.9	77.8	64.3
1g	2-fluorophenyl	83.7	84.6	50.0	88.2	68.2
1h	4-fluorophenyl	90.2	88.5	59.4	100	86.4
1i	3-trifluoromethyl-phenyl	83.7	92.3	68.8	88.2	68.2
1j	methyl	82.7	85.4	79.4	100	86.7
1k	ethyl	92.5	96.8	90.5	100	92.6
1l	*n*-propyl	87.8	87.1	78.4	93.8	85.0
1m	2,2,2-trifluoroethyl	91.8	100.0	80.0	95.5	90.9
	kresoxim-methyl	66.1	97.2	96.8	98.5	90.6

[a] Growth inhibition expressed as a percentage of the control (mean ± SD, $n = 3$).

$- \mathrm{OphCF_3^+}$, 100), 186 (63), 161 ($\mathrm{CF_3phO^+}$, 16), 145 ($\mathrm{CF_3ph^+}$, 48), 131 (61), 116 (64), 59 (28). Anal. calcd for $\mathrm{C_{18}H_{22}N_4O_5}$: C, 57.75; H, 5.92; N, 14.96. Found: C, 57.71; H, 5.86; N, 14.73.

Data for 1k. Yield, 68%; mp 75.9−76.7 °C. IR (KBr): 2911, 1717 (C═O), 1625, 1035, 1019 $\mathrm{cm^{-1}}$. ^{1}H NMR: δ 1.25 (t, $J = 7.2$ Hz, 3H, $-\mathrm{CH_2}\mathit{CH_3}$), 2.22 (s, 3H, $=\mathrm{C}-\mathrm{CH_3}$), 3.59 (s, 3H, N-Me), 3.83 (s, 3H, COOMe), 4.03 (s, 3H, N-$\mathrm{OCH_3}$), 4.08 (m, $J = 7.2$ Hz, 2H, $-\mathrm{O}\mathit{CH_2}$-$\mathrm{CH_3}$), 5.02 (s, 2H, $-\mathrm{CH_2}-$), 7.18 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.36 (t, $J = 7.2$ Hz, 1H, 5-ArH), 7.41 (t, $J = 7.2$ Hz, 1H, 4-ArH), 7.47 (d, $J = 7.8$ Hz, 1H, 3-ArH), 7.92 (s, 1H, CH═N). ^{13}C NMR: δ 14.3 (3-Het$\mathrm{CH_3}$), 15.8 ($-\mathrm{CH_2}\mathit{CH_3}$), 34.1 (1-HetCH3), 53.3 ($\mathrm{COOCH_3}$), 64.2 (5-Het$\mathrm{OCH_2}$), 71.0 ($\mathrm{NOCH_3}$), 74.7 ($\mathrm{OCH_2}$), 98.1 (4-Het), 128.0 (5-C), 128.9 (6-C), 129.1 (3-C), 129.7 (4-C), 130.2 (1-C), 137.0 (2-C), 142.0 (3-HetC), 147.3 (C═NOMe), 150.2 (CH═N), 153.4 (5-HetC), 163.8 (COOMe). MS (70 eV): *m*/*z* (%) 388 ($\mathrm{M^+}$, 97), 357 ($\mathrm{M - CH_3O^+}$, 31), 329 ($\mathrm{M - COOMe^+}$, 57), 206 (86), 166 ($[\mathrm{M - 222}]^+$, 99), 151 (100), 137 (99), 116 (99), 89 (70), 66 (99), 59 (95). Anal. calcd for $\mathrm{C_{19}H_{24}N_4O_5}$: C, 58.75; H, 6.23; N, 14.42. Found: C, 58.81; H, 6.14; N, 14.50.

Data for 1l. Yield, 66%; mp 95.6−96.4 °C. IR (KBr): 2921, 1724 (C═O), 1634, 1026, 1011 $\mathrm{cm^{-1}}$. ^{1}H NMR: δ 0.95 (t, $J = 7.5$ Hz, 3H, $-\mathrm{CH_3}$), 1.67 (m, 2H, $-\mathrm{CH_2}-$), 2.22 (s, 3H, $=\mathrm{C}-\mathrm{CH_3}$), 3.60 (s, 3H, N-Me), 3.83 (s, 3H, COOMe), 3.97 (t, $J = 7.5$ Hz, 2H, $-\mathrm{CH_2}-$), 4.02 (s, 3H, N-$\mathrm{OCH_3}$), 5.01 (s, 2H, $-\mathrm{CH_2}-$), 7.18 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.36 (t, $J = 7.2$ Hz, 1H, 5-ArH), 7.40 (t, $J = 7.2$ Hz, 1H, 4-ArH), 7.47 (d, $J = 7.2$ Hz, 1H, 3-ArH), 7.93 (s, 1H, CH═N). ^{13}C NMR: δ 10.6 ($-\mathrm{CH_2}\mathit{CH_3}$), 14.4 (3-Het$\mathrm{CH_3}$), 23.5 ($-\mathit{C}\mathrm{H_2CH_3}$), 34.1 (N-$\mathrm{CH_3}$), 53.3 ($\mathrm{COOCH_3}$), 64.2 ($\mathrm{NOCH_3}$), 74.7 ($\mathrm{NOCH_2}-$), 76.8 (5-Het$\mathrm{OCH_2}-$), 98.0 (4-HetC), 128.1 (5-C), 129.0 (6-C), 129.1 (3-C), 129.7 (4-C), 130.3 (1-C), 137.0 (2-C), 142.1 (3-HetC), 147.3(*C*═NOMe), 150.3 (CH═N), 152.8 (5-HetC), 163.8 (*C*OOMe). MS (70 eV): *m*/*z* (%) 402 ($\mathrm{M^+}$, 97), 371 ($\mathrm{M - CH_3O^+}$, 31), 343 ($\mathrm{M - COOMe^+}$, 55), 222 (37), 206 (97), 180 (Het-CH═$\mathrm{NO^+}$, 90), 165 (90), 147 (86),131 (97), 116 (100), 99 (97), 59 (98). Anal. calcd for $\mathrm{C_{20}H_{26}N_4O_5}$: C, 59.69; H, 6.51; N, 13.92. Found: C, 59.51; H, 6.39; N, 13.87.

Data for 1m. As an oil, yield, 59%. IR (KBr): 2910, 1711 (C═O), 1626, 1037, 1025 $\mathrm{cm^{-1}}$. ^{1}H NMR: δ 2.20 (s, 3H, $=\mathrm{C}-\mathrm{CH_3}$), 3.60 (s, 3H, N-Me), 3.82 (s, 3H, COOMe), 4.00 (s, 3H, N-$\mathrm{OCH_3}$), 4.09 (s, 2H, $-\mathrm{OCH_2CF_3}$), 5.02 (s, 2H, $-\mathrm{CH_2}-$), 7.18 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.35 (t, $J = 7.2$ Hz, 1H, 5-ArH), 7.40 (t, $J = 7.2$ Hz, 1H, 4-ArH), 7.42 (d, $J = 7.8$ Hz, 1H, 3-ArH), 7.85 (s, 1H, CH═N). ^{13}C NMR: δ 13.3 (3-Het$\mathrm{CH_3}$), 34.3 (1-Het$\mathrm{CH_3}$), 53.3 ($\mathrm{COO}\mathit{CH_3}$), 64.2 ($\mathrm{NOCH_3}$), 69.9 ($\mathrm{OCH_2}$), 74.9 (5-Het$\mathrm{OCH_2}$), 97.6 (4-HetC), 128.2 (5-C), 129.0 (6-C and $\mathrm{CF_3}$), 129.3 (3-C), 129.7 (4-C), 130.2 (1-C), 137.4 (2-C), 141.6 (3-HetC), 147.5 (C═NOMe), 150.2 (CH═N), 150.7 (5-HetC), 163.7 (COOMe). MS (70 eV): *m*/*z* (%): 444 ($[\mathrm{M} + 2]^+$, 12), 442 ($\mathrm{M^+}$, 71), 411 ($\mathrm{M - CH_3O^+}$, 80), 338 ($\mathrm{M - COOMe^+}$, 71), 222 (76), 220 (77), 206 (45), 190 (67), 137 (86), 131 (45), 116 (100), 59 (38). Anal. calcd for $\mathrm{C_{19}H_{21}F_3N_4O_5}$: C, 51.58; H, 4.78; N, 12.66. Found: C, 51.47; H, 4.69; N, 12.73.

Bioassays of Fungicidal Activities. The fungistatic activity measurement method was adapted from the method described by Molina Torres et al. (*15*). The synthesized target compounds were dissolved in 0.5−1.0 mL of DMF to the concentration of 500 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) under 50 °C. The mixtures were poured into Petri dishes. After the dishes were cooled, the solidified plates were incubated with 4 mm mycelium disk, inverted, and incubated at 28 °C for 48 h. Water was used as the blank control. Three replicates of each test were carried out. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibition rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, I is the growth inhibition rate (%), C is the control settlement radius (mm), and T is the treatment group fungi settlement radius (mm). The results are given in **Table 1**.

RESULTS AND DISCUSSION

Based on previous literature (*16*, *17*), we found that the coupling reaction between the aryldiazonium salt derived from 2-methylaniline and the methyl 2-(hydroxyimino)acetate gave stereoselectively the oxime **2** in 44% yield. The *E*/*Z* ratio in the crude mixture was determined by ^{1}H NMR spectroscopy as ca. 14:1. After further column chromatography purification, the purity of *E*-**2** obtained in 41% yield exceeded 99%. The compound *E*-**2** was methylated by sodium hydride-dimethyl sulfate in 91% yield and successively brominated with NBS to afford the oxime ether **4** in 81% yield.

The aldehyde 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (**8**) was obtained by heating of 1,3-dimethyl-1-*H*-pyrazol-5(4*H*)one with phosphoryl trichloride in DMF. Reaction of aldehyde **8** with substituted phenols or alcohols yielded the 5-substituted-1,3-dimethyl-1*H*-pyrazole-4-carbaldehydes (**9**). For the detailed reaction conditions used to prepare compounds **7**−**9**, refer to the literature (*18*, *19*).

Initially, we employed some oximes, derived from corresponding 5-substituded-1,3-dimethyl-1*H*-pyrazole-4-carbaldehydes (**9**) and hydroxylamine hydrochloride, to react with **4** using MeONa as a base. However, the products were mixtures of stereoisomers and the yields were low. However, the synthetic route depicted in **Figure 1** gave good results. Thus, oxime ether **4** was reacted with N-hydroxyphthalimide to give methyl (*E*)-α-(methoxyimino)-2-(*o*-phthalimidoxymethyl)benzeneacetate (**5**), which was then treated with hydrazine monohydrate to obtain methyl (*E*)-α-(methoxyimino)-2-(aminoxymethyl)benzeneacetate (**6**). The reaction of carbaldehydes **9** with **6** proceeded smoothly, and stereospecificity afforded the (*E*)-configurated

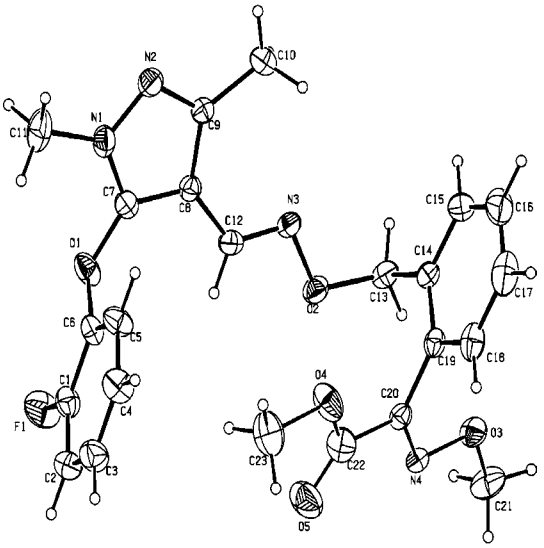

Figure 2. Molecular structure of **1g**.

target compounds in satisfactory yields. The structures of **1a**−**m** were confirmed by elemental analyses, IR, ^{1}H NMR, ^{13}C NMR, and EI-MS spectral data. The (α*E*,*E*)-configurations of compounds **1** were assigned on the basis of their ^{1}H two-dimensional (2D) NOESY spectra. The 2D-NOESY experiments all showed the presence of a cross-peak between the resonance of the $NOCH_3$ protons and that of 6-ArH and the other cross-peak between the resonance of the CH═NO proton and that of $ArCH_2$. In addition, the *E*-configuration of compounds **1g** was proven on the basis of single-crystal structure (**Figure 2**). The bond angles of C(22)−C(20)−N(4)−O(3) and C(8)−C(12)−N(3)−O(2) are 177.4(2) and 179.0(2)°, respectively, which indicates that both of the C═N double bonds are *E*-configurations.

The five fungi used, *R. solani*, *B. cinereapers*, *G. zeae*, *P. piricola*, and *B. mayclis*, belong to the group of field fungi and were isolated from corresponding crops. The results of preliminary bioassays were compared with that of a commercial agricultural fungicide, kresoxim-methyl. As indicated in **Table 1**, all of the compounds **1a**−**m** showed potent fungicidal activities against all of the fungi tested and had more potent fungicidal activities against *R. solani* than kresoxim-methyl. These results also demonstrated that the introduction of 1,3,5-substituted pyrazole rings to the strobilurin fungicides might improve their fungicidal activities. On the other hand, the chlorinated compounds such as **1d** and **1e** showed higher activity among 5-phenoxy-substituted compounds while the 5-ethoxyl-substituted compounds such as **1k** and **1m** had more significant potency among 5-alkoxyl-substituted ones.

Supporting Information Available: Tables of crystal data and structure refinement, equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, torsion angles, and hydrogen bonds. This material is available free of charge via the Internet at http://pubs.acs.org.

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