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Synthesis and fungicidal activity of new β-methoxyacrylate derivatives having thio-enol side chain

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Abstract : New β-methoxyacrylate derivatives **1~4** having thio-enol side chain were prepared and subjected to *in vivo* screening for fungicidal activity against phytopathogenic fungi and many of them showed good fungicidal activities against especially rice blast and wheat leaf rust at 100 ppm.(Received February 18, 2005; accepted June 24, 2005)

Key words : fungicide, methoxyacrylate, RCB, strobilurin, WLR.

Introduction

The strobilurins are one of the most important classes of agricultural fungicides that were developed from naturally occurring fungicidally active products (Bartlett *et al.*, 2002). The fungicidal activity of the strobilurins stems from their ability to inhibit the cytochrome bc_1 complex in the mitochondrial respiratory chain of the fungi (Xia *et al.*, 1999).

Extensive structure-activity relationship study from the literatures showed that (*E*)-methyl β-methoxyacrylate or isosteric (*E*)-methyl methoxyiminoacetate is essential structural element and the nature of *ortho*-substituted side chain with heteroatoms or unsaturation connected to the toxophore through aromatic bridge has substantial effect on the activity (Sauter *et al.*, 1999).

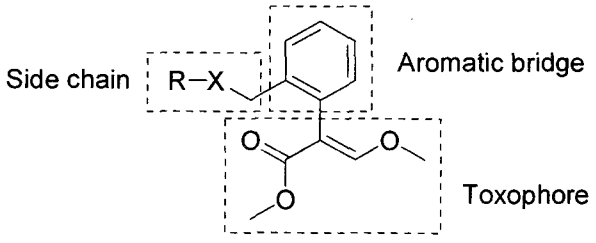

Fig. 1. Structural analysis of strobilurin fungicide.

As a consequence of wide interest in this field, six strobilurin fungicides such as azoxystrobin (Heritage®, Syngenta), kresoxim-methyl (Stroby®, BASF), trifloxystrobin (Flint®, Bayer), picoxystrobin (Syngenta), metominostrobin (Shionogi), pyraclostrobin (BASF) were introduced to commercial market by 2002.

Although there had been a lot of endeavors to develop new strobilurin fungicide having good activity, we thought that there could be still a room for variation in side chain and remaining the toxophore unchanged to enhance the fungicidal activity.

In an effort to discover highly active fungicidal candidates, we designed new strobilurins having novel side chains and subjected them to *in vivo* screening for fungicidal activity against phytopathogenic fungi.

We report herein the synthesis of new strobilurin derivatives (**1**, **2**, **3**, and **4**) having thio-enol side chain and their fungicidal activity.

Experimental

Materials

Flash column chromatography was performed on silica gel (230-400 mesh). THF and Et_2O were refluxed over sodium in the presence of benzophenone and distilled prior to use. CH_2Cl_2 was distilled from calcium hydride. DMF, benzene, CH_3CN, MeOH, toluene were dried, distilled, and stored under nitrogen. All other reagent grade chemicals obtained from commercial sources were used as received.

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General procedure for the synthesis of 3-(substitutedphenyl)-3-oxo-propanedithioic acid (**6**).

To the t-BuOK (40 mmol) in dry ether (80 ml) was added slowly a solution of 2'-bromoacetophenone (20 mmol) and CS_2 (20 mmol) in dry ether (20 ml) with good stirring at 0°C under nitrogen atmosphere. Stirring was then continued for 1 hr at room temperature. Then the mixture was poured into water, the ether layer removed, the aqueous layer acidified with conc. HCl (pH 2~3) and extracted with ether. The combined ether extracts was dried ($MgSO_4$) and evaporated and the residue recrystallized from ethyl acetate /n-Hexane or was purified by silica gel column chromatography affording 3-(2'-bromophenyl)-3-oxo-propanedithioic acid (**6a**).

Yield 75%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.5(s, 1H), 6.6(s, 1H), 7.2-7.7(m, 4H), 15.2(s, 1H).

General procedure for the synthesis of methyl 3-(substitutedphenyl)-3-oxo-propanedithioate (**7**).

To the solution of nBu_4NHSO_4 (20 mmol) and NaOH (40 mmol) in water (50 ml) was added **6a** (20 mmol) in $CHCl_3$ (50 ml) and stirred for 30 min. The water layer was removed and excess iodomethane (3 ml) was added. After stirring for additional hour and the solvent was distilled off under reduced pressure and the residue was extracted with ether. The ether was dried ($MgSO_4$) and stripped off, the residue was purified by silica gel column chromatography giving the methyl 3-(2'-bromophenyl)-3-oxo-propanedithioate (**7a**).

Yield 72%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.6(s, 3H), 6.6(s, 1H), 7.2-7.7(m, 4H), 15.0(s, 1H).

General procedure for the synthesis of **1**.

A mixture of methyl 3-(2'-bromophenyl)-3-oxo-propanedithioate (**7a**) (10 mmol), 2-(2-bromomethyl phenyl)-3-methoxypropenoic acid methyl ester (**8**) (10 mmol), and potassium carbonate (20 mmol) in dry DMF (10 ml)was stirred for 2-4 hours at room temperature. After addition of water, the solution was extracted with ethyl acetate (20 ml x 3). The combined organic layer was washed with brine, dried ($MgSO_4$), distilled off. The residue was purified by silica gel column chromatography (2:1/Hex:EA) affording **1a** as *E* and *Z* isomer mixture which are difficult to separate. (*E*:*Z* = 6:4 by ^{1}H-NMR)

1a: yield 82%; *E*-isomer: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.5(s, 3H), 3.65(s, 3H), 3.75(s, 3H), 4.1(s, 2H), 6.55(s, 1H), 7.1~7.6(m, 9H); *Z*-isomer: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.48(s, 3H), 3.72(s, 3H), 3.85(s, 3H), 4.2(s, 2H), 6.4(s, 1H), 7.1~7.6(m, 9H).

1b: yield 80%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.55(s, 3H), 3.65(s, 3H), 3.75(s, 3H), 4.20(s, 2H), 6.60(s, 1H), 7.15~7.60(m, 7H), 7.7(d, 1H, J=1.84).

1c: yield 69%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.45(s, 3H), 3.55(s, 3H), 3.70(s, 3H), 4.05(s, 2H), 6.55(s, 1H), 7.10~8.00(m, 12H).

1d: yield 76%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.5(s, 3H), 3.65(s, 3H), 3.75(s, 3H), 4.1(s, 2H), 6.5(s, 1H), 7.1~7.6(m, 8H).

1e: yield 34%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.50(s, 3H), 3.65(s, 3H), 3.75(s, 3H), 4.18(s, 2H), 6.65(s, 1H), 7.00~7.75(m, 9H).

1f: yield 70%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.35(s, 3H), 2.51(s, 3H), 3.61(s, 3H), 3.70(s, 3H), 4.18(s, 2H), 6.68(s, 1H), 7.20~7.60(m, 8H).

1g: yield 50%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.50(s, 3H), 3.65(s, 3H), 3.75(s, 3H), 4.18(s, 2H), 6.65(s, 1H), 7.20~7.60(m, 8H).

1h: yield 75%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.45(s, 3H), 3.65(s, 3H), 3.8(s, 3H), 4.15(s, 2H), 6.25(dd, 1H), 6.75(s, 1H), 7.0(d, 1H), 7.2~7.6(m, 5H).

1i: yield 76%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.45(s, 3H), 3.65(s, 3H), 3.8(s, 3H), 3.95(s, 3H), 4.05(s, 2H), 6.0(dd, 1H), 6.55(dd, 1H), 6.6(s, 1H), 6.7(s, 1H), 7.2~7.6(m, 4H).

1j: yield 81%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.30(s, 3H), 3.65(s, 3H), 3.75(s, 3H), 4.05(s, 2H), 6.35(s, 1H), 7.10~7.70(m, 8H).

General procedure for the synthesis of **2**.

Compound **2** was prepared from methyl 3-

(substitutedphenyl)-3-oxo-propanedithioate (**7**) and methyl (2-bromomethylphenyl)methoxyiminoacetate (**9**) by essentially the same procedure for **1**.

2a: yield 88% (*E:Z* = 1:1); *E*-isomer: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.5(s, 3H), 3.82(s, 3H), 3.98(s, 3H), 4.05(s, 2H), 6.5(s, 1H), 7.1~7.6(m, 8H); *Z*-isomer: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.48(s, 3H), 3.88(s, 3H), 4.1(s, 3H), 4.18(s, 2H), 6.4(s, 1H), 7.1~7.6(m, 8H).

2b: yield 71%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.5(s, 3H), 3.8(s, 3H), 4.0(s, 3H), 4.1(s, 2H), 6.4(s, 1H), 7.1~7.6(m, 8H).

2c: yield 83%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.45(s, 3H), 3.85(s, 3H), 4.04(s, 3H), 4.1(s, 2H), 6.45(dd, 1H), 6.75(s, 1H), 7.0(d, 1H), 7.2~7.6(m, 5H).

2d: yield 68%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.45(s, 3H), 3.85(s, 3H), 4.01(s, 3H), 4.02(s, 2H), 6.05(dd, 1H), 6.55(dd, 1H), 6.65(s, 1H), 7.2~7.6(m, 4H).

2e: yield 52%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.50(s, 3H), 3.80(s, 3H), 4.00(s, 3H), 4.18(s, 2H), 6.64(s, 1H), 7.10~7.80(m, 8H).

2f: yield 85%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.50(s, 3H), 3.80(s, 3H), 3.95(s, 3H), 4.00(s, 2H), 6.30(s, 1H), 7.10~7.70(m, 8H).

2g: yield 89%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.50(s, 3H), 3.80(s, 3H), 3.81(s, 3H), 4.00(s, 3H), 4.10(s, 2H), 6.30(s, 1H), 6.75~7.90(m, 8H).

2h: yield 80%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.55(s, 3H), 3.85(s, 3H), 4.00(s, 3H), 4.18(s, 2H), 6.60(s, 1H), 7.10~7.60(m, 7H), 7.7(d, 1H, J=2.03).

2i: yield 56%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.55(s, 3H), 3.80(s, 3H), 3.98(s, 3H), 4.15(s, 2H), 6.62(s, 1H), 7.10~7.95(m, 8H).

2j: yield 72%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.59(s, 3H), 3.85(s, 3H), 4.05(s, 3H), 4.09(s, 2H), 6.79~7.95(m, 8H).

General procedure for the synthesis of methyl 3-(substitutedphenyl)-3-oxo-propanethioamide (**11**).

To a solution of 4'-fluoroacetopheone (10 mmol) and methyl isothiocyanate (10 mmoll) in DMF (10 ml) was added slowly sodium hydride (25 mmol) with good stirring at 0°C and stirred for additional 1-4 hours under nitrogen atmosphere. Then the reaction mixture was poured into water and acidified with dilute HCl (pH 2~3) and extracted with ethyl acetate (10 ml x 3). The combined organic layers was dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography affording methyl 3-(4'-fluorophenyl)-3-oxo-propanethioamide (**11a**).

Yield 72%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.2(d, 3H), 4.45(s, 2H), 7.0~7.2(m, 2H), 8.1~8.2(m, 2H), 9.2(bs, 1H).

General procedure for the synthesis of **3**.

Compound **3** was prepared from methyl 3-(substitutedphenyl)-3-oxo-propanethioamide (**11**) and 2-(2-bromomethylphenyl)-3-methoxypropenoic acid methyl ester (**8**) by essentially the same procedure for **1**.

3a: yield 63%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.05(d, 3H, *J*=5.0Hz), 3.68(s, 3H), 3.77(s, 3H), 4.10(s, 2H), 5.59(s, 1H), 6.98~7.06(m, 2H), 7.16~7.21(m, 1H), 7.27~7.36(m, 2H), 7.51~7.56(m, 1H), 7.61(s, 1H), 7.66~7.74(m, 2H).

3b: yield 93%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.02(d, 3H, *J*=5.0Hz), 3.63(s, 3H),3.72(s, 3H), 3.98(s, 2H), 5.21(s, 1H), 7.11~7.15(m, 1H), 7.41~7.38(m, 3H), 7.57(s, 1H), 7.62~7.67(m, 1H).

3c: yield 76%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.05(d, 3H, *J*=5.0Hz), 3.68(s, 3H), 3.76(s, 3H), 4.10(s, 2H), 5.59(s, 1H), 7.16~7.21(m, 1H), 7.26~7.36(m, 4H), 7.51~7.56(m, 2H), 7.61~7.65(m, 3H).

3d: yield 77%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.07(d, 3H, *J*=5.0Hz), 3.67(s, 3H), 3.75(s, 3H), 4.12(s, 2H), 5.62(s, 1H), 7.18~7.22(m, 1H), 7.33~7.37(m, 2H), 7.52~7.62(m, 4H), 7.75~7.79(m, 2H).

3e: yield 95%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.04(d, 3H, *J*=4.8Hz), 3.68(s, 3H), 3.76(s, 3H), 4.11(s, 2H), 5.68(s, 1H), 7.16~7.20(m, 1H), 7.31~7.38(m, 5H), 77.51~7.55(m,

1H), 7.60(s, 1H), 7.70~7.74(m, 2H).

3f: yield 52%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.03(s, 3H), 3.65(s, 3H), 3.68(s, 3H), 4.16(s, 2H), 5.80(s, 1H), 7.20~7.24(m, 1H), 7.34~7.39(m, 2H), 7.46~7.50(m, 2H), 7.51~7.60(m, 2H), 7.61~7.88(m, 4H), 8.11(s, 1H), 11.74(br, 1H).

3g: yield 64%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.38(s, 3H), 3.03(s, 3H), 3.68(s, 3H), 3.76(s, 3H), 4.01(s, 2H), 5.67(s, 1H), 7.14~7.19(m, 3H), 7.28~7.35(m, 2H), 7.50~7.54(m, 1H), 7.60~7.66(m, 3H), 11.64(br, 1H).

3h: yield 82%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.11(s, 9H), 2.95(d, 3H, *J*=4.2Hz), 3.72(s, 3H), 3.85(s, 3H), 4.00(s, 2H), 5.19(s, 1H), 7.16~7.19(m, 1H), 7.29~7.3(m, 4H), 7.41~7.46(m, 1H), 7.62(s, 1H).

3i: yield 88%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.04(d, 3H, *J*=3.8Hz), 3.66(s, 3H), 3.70(s, 3H), 3.75(s, 3H), 4.03(s, 2H), 5.33(s, 1H), 7.13~7.28(m, 2H), 7.30(s, 1H), 7.32~7.38(m, 3H), 7.46~7.50(m, 1H), 7.59(s, 1H).

3j: yield 96%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.04(d, 3H, *J*=4.8Hz), 3.65(s, 3H), 3.74(s, 3H), 4.03(s, 2H), 5.3(s, 1H), 7.13~7.17(m, 2H), 7.20~7.37(m, 4H), 7.47~7.58(m, 3H), 11.50(br, 1H).

General procedure for the synthesis of **4**.

Compound **4** was prepared from methyl 3-(substitutedphenyl)-3-oxo-propanethioamide (**11**) and methyl (2-bromomethylphenyl)methoxyiminoacetate (**9**) by essentially the same procedure for **1**.

4a: yield 74%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.05(d, 3H, *J*=5.2Hz), 3.86(s, 3H), 4.01(s, 3H), 4.02(s, 2H), 5.57(s, 1H), 6.98~7.07(m, 2H), 7.18~7.21(m, 1H), 7.35~7.41(m, 2H), 7.42~7.47(m, 1H), 7.54~7.58(m, 1H), 7.66~7.74(m, 2H), 11.62(br, 1H).

4b: yield 81%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.03(d, 3H, *J*=4.4Hz), 3.38(s, 3H), 3.85(s, 3H), 4.03(s, 3H), 4.06(s, 2H), 5.62(s, 1H), 6.84 ~ 6.88(m, 2H), 7.17~7.21(m, 1H), 7.38~7.43(m, 2H), 7.54~7.58(m, 1H), 7.67~7.72(m, 2H).

4c: yield 54%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.08(d, 3H, *J*=5.2Hz), 3.83(s, 3H), 3.98(s, 3H), 4.13(s, 2H), 5.78(s, 1H), 7.21~7.24(m, 1H), 7.39~7.54(m, 3H), 7.60~7.64(m, 1H), 7.81~7.87(m, 5H), 8.12(s, 1H), 11.72(br, 1H).

4d: yield 82%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.30(s, 3H), 2.33(s, 3H), 3.03(d, 3H, *J*=5.0Hz), 3.82(s, 3H), 3.94(s, 3H), 3.95(s, 2H), 5.24(s, 1H), 6.92 ~ 6.97(m, 2H), 7.14~7.18(m, 2H), 7.34~7.46(m, 2H), 7.51~7.55(m, 1H).

4e: yield 68%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.10(s, 9H), 2.94(d, 3H, *J*=5.2Hz), 3.89(s, 3H), 3.96(s, 2H), 4.07(s, 3H), 5.17(s, 1H), 7.15~7.20(m, 1H), 7.36~7.42(m, 2H), 7.44~7.51(m, 1H).

4f: yield 79%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.02(s, 3H), 3.84(s, 3H), 3.88(s, 3H), 4.02(s, 3H), 4.06(s, 2H), 5.54(s, 1H), 6.86~6.94(m, 1H), 7.16~7.21(m, 1H), 7.34~7.57(m, 5H).

4g: yield 74%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.03(d, 3H, *J*=5.2Hz), 3.86(s, 3H), 3.98(s, 2H), 4.02(s, 3H), 5.28(s, 1H), 6.85~6.93(m, 2H), 7.14~7.22(m, 2H), 7.29~7.43(m, 2H), 7.45~7.53(m, 1H).

4h: yield 60%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.03(d, 3H, *J*=5.2Hz), 3.88(s, 3H), 4.09(s, 3H), 4.17(s, 2H), 6.63(s, 1H), 7.15~7.20(m, 1H), 7.29~7.45(m, 3H), 7.53~7.58(m, 1H), 7.75~7.83(m, 1H), 8.08~8.12(m, 1H), 8.57~8.61(m, 1H), 11.77(br, 1H).

4i: yield 89%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.03(d, 3H, *J*=4.8Hz), 3.86(s, 3H), 4.03(s, 3H), 4.05(s, 2H), 5.49(s, 1H), 7.17~7.23(m, 2H), 7.32~7.46(m, 3H), 7.54~7.59(m, 1H), 7.69~7.70(m, 1H).

4j: yield 79%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.70(d, 3H, *J*=5.2Hz), 3.85(s, 3H), 4.00(s, 3H), 4.08(s, 2H), 5.60(s, 1H), 7.18~7.23(m, 1H), 7.41~7.45(m, 2H), 7.55~7.62(m, 3H), 7.75~7.79(m, 2H).

Evaluation of fungicidal activity against phyto-pathogenic fungi.

The fungicidal activities of compounds **1~4** were tested

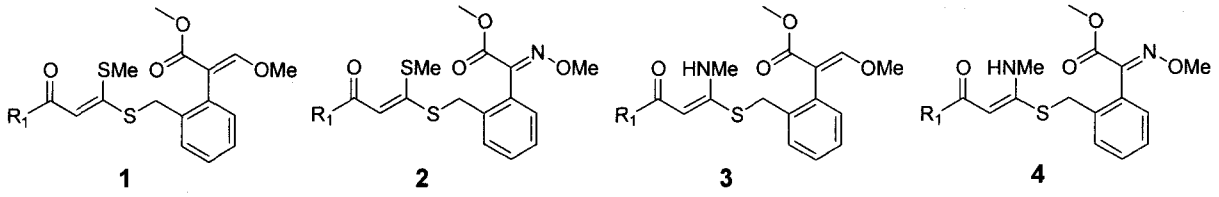


Fig. 2. New β-methoxyacrylate derivatives having thio-enol side chain.

as follow, wherein the test material was dissolved in 10% acetone to a concentration of 100 ppm and Tween 20 was added thereto a concentration of 250 ppm. 50 ml of the resulting solution was sprayed on leaves or stems of a host plant. The plant was kept at room temperature for 24 hours to let the solvent evaporate, and then a pathogenic fungus was inoculated thereon. After the plant was held in a humidity chamber for 24 hours, it was transferred to a plant growth room kept 20~27°C and a relative humidity of 60~80% and was kept to induce disease. Subsequently the lesion area (L.A.) attacked by pathogenic fungus was measured. This procedure was repeated twice for each test. 10% Acetone solution containing 250 ppm Tween 20 was used as a control.

The fungicidal activity of the compound is represented by a control value (C.V., % inhibition) calculated as ;

C.V.(%) = [(L.A. of control - L.A. of test)/(L.A. of control)] x 100

Test 1. Fungicidal activity against rice blast (RCB).

Magnaporthe grisea KJ-201 was inoculated on rice bran agar medium (rice bran 20 g, dextrose 10 g, agar 15 g and distilled water 1 L) and cultured at 26°C for 1 week. The surface of the medium was scratched using a rubber polishman to remove aerial mycelia, and cultured under a fluorescent light for 48 hours to form a spore. Spores were suspended in sterilized water at a concentration of 1 x 10^6 spores/ml. The spore suspension was sprayed enough to soak the leaves of a Nakdong rice plant having 3 or 4 leaves. The rice plant was held in a humidified dark room for 24 hours, transferred to an incubator kept at 24 to 28°C and a relative humidity of more than 80% and was kept for 5 days to induce RCB. L.A. on a fully grown leaf appearing underneath of an uppermost leaf was measured to calculate a C.V..

Test 2. Fungicidal activity against wheat leaf rust (WLR).

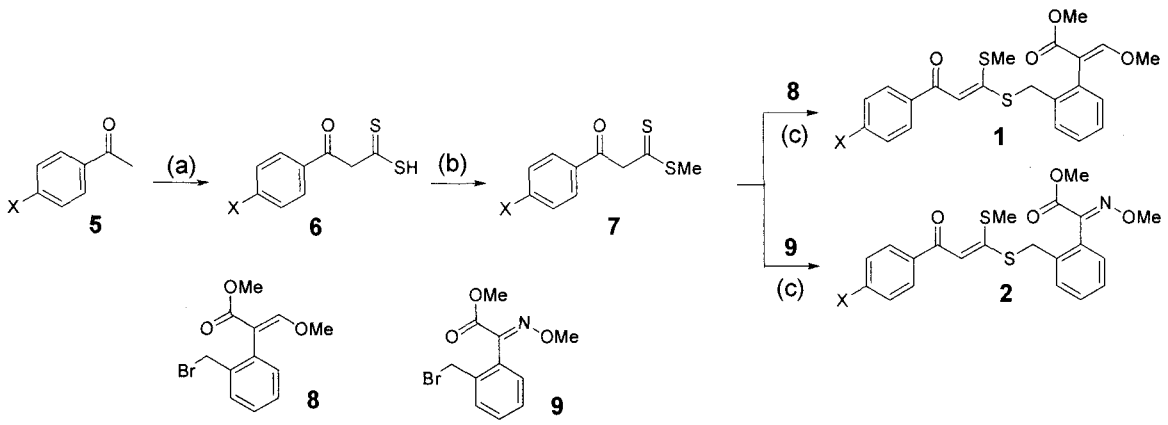
Puccinia recondita was subcultured on a wheat plant in a laboratory. 15 g of wheat seed was sowed in a pot (diameter 6.5 cm) and cultured in a greenhouse for 7 days to obtain a wheat plant having only a primary leaf. The treated wheat plant was inoculated by spraying a spore suspension (0.67 g spores/ml) of the fungus. The inoculated wheat plant was held in a humidified room at 20°C for 24 hours, transferred to an incubator maintained at a temperature of 20°C and a relative humidity of 70% and cultured for 10 days to induce WLR. L.A. on the primary leaf was measured to calculate a C.V..

Results and Discussion

Preparation of **1**, **2**, **3**, and **4** from substituted acetophenone were summarized in schemes 1 and 2.

Treatment of substituted acetophenones **5** with CS_2 in the presence of t-BuOK produced 3-(substitutedphenyl)-3-oxo-propanedithioic acid (**6**). As the side chain moiety of **1** and **2**, methyl 3-(substitutedphenyl)-3-oxo-propanedithioate (**7**) was prepared from the reaction of **6** and iodomethane in the presence of base (NaOH) and nBu_4NHSO_4 using so called the ion-pair extraction technique, (Larsson and Lawesson, 1972) that is the ion-pair of mono anion of **6** and Bu_4N cation was extractioned with $CHCl_3$ and then treated with excess iodomethane affording only mono-methylated **7**. Finally coupling reaction of the **7** and 2-(2-bromomethylphenyl)-3-methoxypropenoic acid methyl ester (**8**) (Pak *et al.*, 2002) afforded the desired strobilurin derivative **1** as *E* and *Z* mixture. (Table 1)

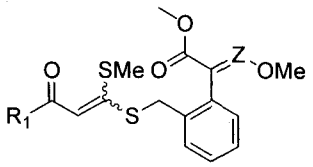
For the side chain of **3** and **4**, methyl 3-(substitutedphenyl)-3-oxo-propanethioamide (**11**) was conveniently prepared from the reaction of substituted acetophenone **5** and methyl isothiocyanate (**10**). Treatment of **11** with **8** smoothly afforded the desired strobilurin derivative **3** only *E*-isomer which is stabilized by



Reagents and conditions (a) CS_2, t-BuOK, THF, 0°C~rt, 1hr, then HCl: (b) $CHCl_3$-H_2O/NaOH, Bu_4NHSO_4, then separation of $CHCl_3$, CH_3I; (c) K_2CO_3, DMF, rt

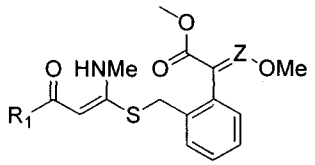
Scheme 1. Synthesis of strobilurin derivative **1** and **2**.

Table 1. Yields and isomeric ratios of strobilurin derivative **1** and **2**

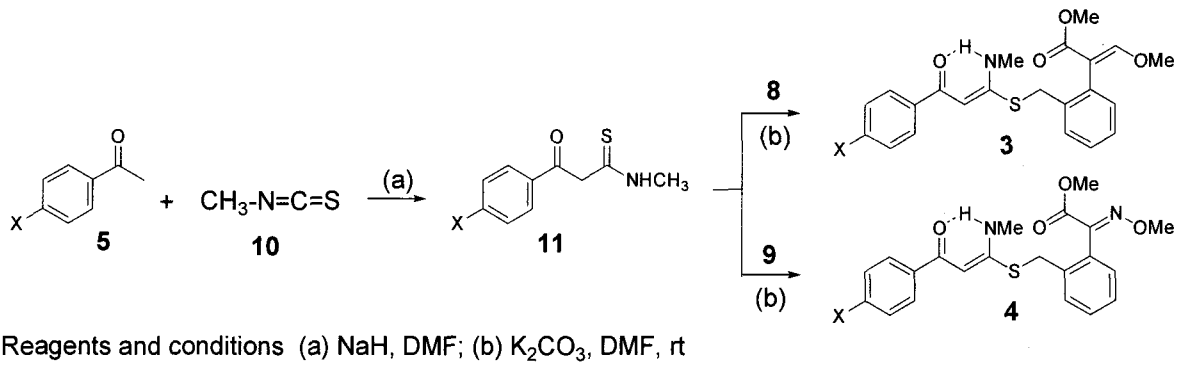


Entry	R_1	Z	Yield(%)	*E:Z*
1a	2-Br-Phenyl	CH	82	6:4
1b	3,4-Cl_2-Phenyl	CH	80	1:1
1c	1-Naphthyl	CH	69	7:3
1d	2,5-Cl_2-Phenyl	CH	76	1:0
1e	4-F-Phenyl	CH	34	3:1
1f	3-CH_3-Phenyl	CH	70	1:0
1g	4-Br-Phenyl	CH	50	12:1
1h	2-Furanyl	CH	75	1:0
1i	1'-CH_3-2-Pyrrolyl	CH	76	1:0
1j	2-CF_3-Phenyl	CH	81	1:0
2a	2-Br-Phenyl	N	88	1:1
2b	2,5-Cl_2-Phenyl	N	71	1:0
2c	2-Furanyl	N	83	1:0
2d	1'-CH_3-2-Pyrrolyl	N	68	1:0
2e	4-Br-Phenyl	N	52	9:1
2f	2-CF_3-Phenyl	N	85	1:0
2g	4-CH_3O-Phenyl	N	89	2:1
2h	3,4-Cl_2-Phenyl	N	80	1:1
2i	4-CN-Phenyl	N	56	1:0
2j	2,4-F_2-Phenyl	N	72	1:0

Table 2. Yields and isomeric ratios of strobilurin derivative **3** and **4**



Entry	R_1	Z	Yield(%)	*E:Z*
3a	4-F-Phenyl	CH	63	1:0
3b	2-CF_3-Phenyl	CH	93	1:0
3c	4-Cl-Phenyl	CH	76	1:0
3d	4-CF_3-Phenyl	CH	77	1:0
3e	Phenyl	CH	95	1:0
3f	2-Naphthyl	CH	52	1:0
3g	4-CH_3-Phenyl	CH	64	1:0
3h	t-Butyl	CH	82	1:0
3i	2,4-Cl_2-Phenyl	CH	88	1:0
3j	2-Br-Phenyl	CH	96	1:0
4a	4-F-Phenyl	N	74	1:0
4b	4-CH_3O-Phenyl	N	81	1:0
4c	2-Naphthyl	N	54	1:0
4d	2,4-$(CH_3)_2$-Phenyl	N	82	1:0
4e	t-Butyl	N	68	1:0
4f	3-F-4-CH_3O-Phenyl	N	79	1:0
4g	2,6-F_2-Phenyl	N	74	1:0
4h	2-Pyridyl	N	60	1:0
4i	3-Thiopheneyl	N	89	1:0
4j	4-CF_3-Phenyl	N	79	1:0



Scheme 2. Synthesis of strobilurin derivative **3** and **4**.

intramolecular H-bonding between carbonyl oxygen and amido proton as shown in scheme 2.

Strobilurin derivatives **2** and **4** were also obtained from the reaction of **7** and **11** with methyl (2-bromomethyl phenyl)methoxyiminoacetate (**9**) (Pak *et al.*, 2002) under essentially the same reaction condition for **1** and **3** respectively. (Table 1 and 2)

The strobilurin derivatives **1**, **2**, **3**, and **4** having thio-enol side chain were subjected to *in vivo* screening for fungicidal activity against phytopathogenic fungi and the results are summarized in table 3. As shown in table 3, a number of the strobilurin derivatives **1**, **2**, **3**, and **4** exhibited good to excellent fungicidal activities against rice blast (*Magnaporthe grisea*) and wheat leaf rust (*Puccinia recondita*) at a 100 ppm concentration. Within our experiments, the strobilurin derivative series **1** showed the most prominent activity against rice blast and wheat leaf rust. Especially, **1b**, **1c**, **1g** showed perfect control

Table 3. Fungicidal activities of new strobilurin derivatives **1~4** against rice blast and wheat leaf rust at 100 ppm (*in vivo*)

Entry	% inhibition at 100 ppm		Entry	% inhibition at 100 ppm	
	RCB[a]	WLR[b]		RCB[a]	WLR[b]
1a	90	96	**3a**	75	33
1b	100	100	**3b**	0	83
1c	100	100	**3c**	13	60
1d	99	100	**3d**	5	53
1e	96	100	**3e**	16	66
1f	95	100	**3f**	10	86
1g	100	100	**3g**	0	83
1h	0	60	**3h**	16	93
1i	16	100	**3i**	25	93
1j	80	60	**3j**	8	83
2a	92	100	**4a**	8	20
2b	98	93	**4b**	0	66
2c	0	0	**4c**	16	73
2d	0	73	**4d**	0	20
2e	0	90	**4e**	0	73
2f	50	0	**4f**	17	10
2g	75	0	**4g**	0	10
2h	97	93	**4h**	0	53
2i	0	0	**4i**	0	53
2j	0	0	**4j**	0	20

[a] RCB(rice blast): *Magnaporthe grisea.*

[b] WLR(wheat leaf rust): *Puccinia recondita.*

against both of rice blast and wheat leaf rust at 100 ppm.

In summary, we prepared new strobilurin derivatives having thio-enol side chain **1~4** and many of them showed good fungicidal activities against phytopathogenic fungi especially rice blast and wheat leaf rust at 100 ppm.

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티오엔올 곁가지를 가진 메톡시아크릴레이트 화합물의 합성 및 살균활성 연구

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요약 : 천연 살균활성 물질인 strobilurin으로부터 유래된 β-methoxyacrylate 계열 화합물들은 천연물 자체보다 높은 살균활성 및 안정성을 보이는 것으로 알려졌으며 실제로 다수의 화합물이 우수한 농업용 살균제로 개발 시판되어 지고 있다. 본 연구에서는 보다 나은 살균제를 개발하기 위한 일환으로 티오엔올 곁가지를 가진 새로운 β-methoxyacrylate 계열 화합물을 고안하고 합성하였으며 이들의 살균활성을 6가지 균주에 대하여 *in vivo* 활성검색을 수행하였다. 새로이 합성된 화합물들은 선택적으로 벼도열병균 및 밀녹병균에 대하여 우수한 살균활성을 보였으며 특히 **1b, 1c, 1g** 화합물은 100 ppm 농도에서 벼도열병균과 밀녹병균에 대하여 100% 살균효과를 보였다. (2005년 2월 18일 접수, 2005년 6월 24일 수리)

색인어 : 메톡시아클리레이트, 밀녹병균, 벼도열병균, 살균제, 스트로비루린.

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