

Synthesis and Fungicidal Activities of Silicon-Containing Derivatives of 2-Aryl-3-(1*H*-1,2,4-triazol-1-yl)propanenitriles

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A new series of silicon-containing derivatives of 2-aryl-3-(1*H*-1,2,4-triazol-1-yl)propanenitriles were synthesized and evaluated for fungicidal activities against rice sheath blight and powdery mildew on cucumber. These derivatives exhibited higher efficacy than reference fungicides.

Key words fungicidal activity; 1*H*-1,2,4-triazole; cyano; silicon; synthesis

In a previous paper,¹⁾ we reported synthesis and antifungal activity of triazole compounds **1** with a trimethylsilylmethyl moiety (Fig. 1). The antifungal activity of these triazoles was presumed to arise from a potential ability to inhibit the biosynthesis of ergosterol, an important constituent of the fungal membrane.²⁾ Since remarkably potent activity was observed in this series of derivatives, the trimethylsilylmethyl moiety of the common structure **1** has been identified as a key structural element for the antifungal potency. On the other hand, in azole fungicides, the hydroxy group of **3** plays a biologically isosteric role to the cyano group of **4**. For example, the cyano groups of myclobutanil³⁾ and fenbuconazole,⁴⁾ two agents successfully introduced as agricultural fungicides by Rohm and Haas Co., were interchangeable with the hydroxy groups of hexaconazole⁵⁾ and tebuconazole,⁶⁾ respectively (Fig. 2). In our research program, new derivatives **2** containing the cyano group instead of the hydroxy group were synthesized and evaluated for fungicidal activities (Fig. 1).

The preparation of the target compounds **2** involves double

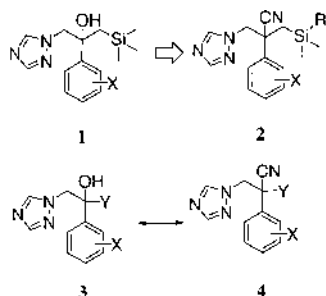


Fig. 1. Research Strategy

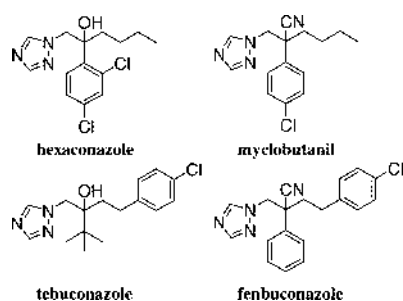


Fig. 2. Azole Fungicides

alkylations of substituted phenylacetone nitriles **5** with chloromethylsilanes **6** and chloromethyltriazole hydrochloride **8** prepared by the methods described in the literature.⁷⁾ The sequential alkylation of substituted phenylacetone nitriles **5** was achieved using sodium hydride in *N,N*-dimethylformamide to give **2** in 11–32% yield (2 steps) and another styrene **9** in 5–11% yield (2 steps). The yields, physical data, and spectroscopic data of **2** are summarized in Tables 1 and 2.

The derivatives **2** obtained above were evaluated for fungicidal activities against rice sheath blight and powdery mildew on cucumber in comparison with diclomezine,⁸⁾ a popular fungicide for rice sheath blight, and buthiobate,⁹⁾ a popular fungicide for powdery mildew on cucumber (Fig. 3). The results are shown in Table 1. Among several mono- and di-substituted phenyl derivatives, 2- or 4-halogen-substituted derivatives **2a**, **2b**, **2f**, **2h** were more active for rice sheath blight than methyl-substituted derivative **2e** and 3-halogen-substituted derivatives **2g**, **2i**. On the other hand, non-substituted derivative **2c** and 4-methoxy-substituted derivative **2d** showed fungicidal activities for both diseases. The derivatives having the dimethylphenylsilyl group instead of the trimethylsilyl group **2j**, **2k** exhibited fungicidal activity only against powdery mildew. 3-Phenoxy-substituted derivative **2l** lost fungicidal activity.

In summary, we have found that the biological isosterism between **3** and **4** was applicable to a series of novel silicon-containing azole derivatives that have fungicidal activities against rice sheath blight and powdery mildew. Most notably, **2c**, **2d**, **2h** were more active against both diseases than reference fungicides. Further evaluation of these derivatives as fungicides is underway.

Experimental

All melting points (mp) were taken on a Yanaco micro melting point apparatus and are uncorrected. IR was recorded on a JASCO A-102 spectrometer and ¹H-NMR spectra were recorded on a Varian Gemini 200 spectrometer using tetramethylsilane as an internal standard. MS was obtained on a JEOL JMS-D300 spectrometer and a VG Auto Spec M mass spectrometer. TLC was performed on a precoated plate of Silica gel 60 F₂₅₄ with a layer

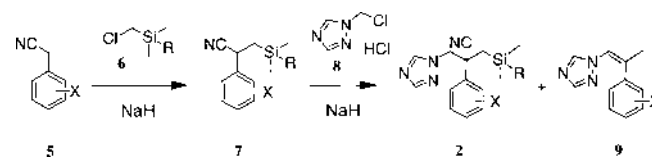


Chart 1

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Table 1. Synthesis and Fungicidal Activities of Cyano Azole Derivatives 2

Entry No.	X	R	Yield (%) ^{a)}	mp (°C)	Calcd (%) ^{b)}			Found (%) ^{b)}			S.B. ^{d)}	P.M. ^{e)}
					C	H	N	C	H	N		
2a	4-F	Me	18	128—129	59.57	6.33	18.53	59.57	6.33	18.53	2	0
2b	4-Cl	Me	32	120	56.50	6.01	17.57	56.39	5.94	17.71	2	0
2c	H	Me	23	113—114	63.34	7.09	19.70	63.12	7.01	19.70	2	2
2d	4-MeO	Me	17	120—121	61.11	7.05	17.82	60.95	6.93	17.75	2	2
2e	4-Me	Me	12	104—105	64.39	7.43	18.77	64.12	7.15	18.50	0	2
2f	2-Cl	Me	11	Oil	318.106753 ^{c)}			318.106743 ^{c)}			2	0
2g	3-Cl	Me	23	109—110	56.50	6.01	17.57	56.48	5.87	17.71	0	2
2h	2,4-Cl ₂	Me	14	62—64	50.99	5.14	15.86	51.16	5.13	15.86	2	2
2i	3,4-Cl ₂	Me	26	126	50.99	5.14	15.86	51.17	5.09	15.92	0	2
2j	4-Cl	Ph	26	Oil	380.122404 ^{c)}			380.122299 ^{c)}			0	2
2k	H	Ph	22	81	69.33	6.40	16.12	69.21	6.45	16.12	0	2
2l	3-PhO	Ph	19	Oil	438.187590 ^{c)}			438.187737 ^{c)}			0	0

a) 2 steps, b) analytical data, c) high-resolution MS spectrum data, d) sheath blight, e) powdery mildew. The activity index given in this table is based on a visual comparison of plants inoculated with the test agents and a reference fungicide. 0, disease rate was almost the same as that of an untreated plant; 1, disease rate was more severe than that of a plant treated with reference fungicide; 2, disease rate was less severe than that of a plant treated with reference fungicide.

Table 2. ¹H-NMR, IR and MS Spectrum Data on 2

Entry No.	¹ H-NMR (200 MHz), δ (ppm) in CDCl ₃	IR (cm ⁻¹)	MS (<i>m/z</i>)
2a	−0.24 (9H, s), 1.32 (1H, d, <i>J</i> =14.9 Hz), 1.42 (1H, d, <i>J</i> =14.9 Hz), 4.38 (1H, d, <i>J</i> =14.1 Hz), 4.54 (1H, d, <i>J</i> =14.1 Hz), 6.95 (2H, t, <i>J</i> =8.9 Hz), 7.23 (2H, dd, <i>J</i> =5.0, 8.9 Hz), 7.72 (1H, s), 7.78 (1H, s)	2958, 2249, 1510, 1274, 1240, 1137	302 (M ⁺), 287, 220
2b	−0.09 (9H, s), 1.45 (1H, d, <i>J</i> =14.6 Hz), 1.50 (1H, d, <i>J</i> =14.6 Hz), 4.47 (1H, d, <i>J</i> =14.1 Hz), 4.61 (1H, d, <i>J</i> =14.1 Hz), 7.30 (2H, d, <i>J</i> =8.9 Hz), 7.39 (2H, d, <i>J</i> =8.9 Hz), 7.88 (1H, s), 7.90 (1H, s)	3107, 2956, 2248, 1506, 1426, 1274, 1248, 1137, 1099	318 (M ⁺), 303, 236
2c	−0.12 (9H, s), 1.44 (1H, d, <i>J</i> =14.4 Hz), 1.55 (1H, d, <i>J</i> =14.4 Hz), 4.50 (1H, d, <i>J</i> =13.9 Hz), 4.65 (1H, d, <i>J</i> =13.9 Hz), 7.39 (5H, s), 7.81 (1H, s), 7.89 (1H, s)	3108, 2951, 2249, 1507, 1449, 1274, 1249, 1140	284 (M ⁺), 269, 202
2d	−0.19 (9H, s), 1.31 (1H, d, <i>J</i> =14.7 Hz), 1.43 (1H, d, <i>J</i> =14.7 Hz), 3.72 (3H, s), 4.37 (1H, d, <i>J</i> =14.1 Hz), 4.53 (1H, d, <i>J</i> =14.1 Hz), 6.81 (2H, d, <i>J</i> =9.0 Hz), 7.21 (2H, d, <i>J</i> =9.0 Hz), 7.71 (1H, s), 7.79 (1H, s)	2964, 2248, 1618, 1515, 1274, 1251, 1194, 1139	314 (M ⁺), 299, 232
2e	−0.12 (9H, s), 1.38 (1H, d, <i>J</i> =15.1 Hz), 1.51 (1H, d, <i>J</i> =15.1 Hz), 2.36 (3H, s), 4.46 (1H, d, <i>J</i> =14.0 Hz), 4.61 (1H, d, <i>J</i> =14.0 Hz), 7.21—7.32 (4H, m), 7.79 (1H, s), 7.97 (1H, s)	3106, 2956, 2247, 1508, 1438, 1273, 1248, 1140	298 (M ⁺), 283, 216
2f	−0.13 (9H, s), 1.38 (1H, d, <i>J</i> =14.9 Hz), 2.29 (1H, d, <i>J</i> =14.9 Hz), 4.82 (1H, d, <i>J</i> =14.3 Hz), 5.22 (1H, d, <i>J</i> =14.3 Hz), 7.21—7.61 (4H, m), 7.79 (1H, s), 7.97 (1H, s)	3122, 2955, 2897, 2239, 1505, 1475, 1434, 1274, 1251, 1138	318 (M ⁺), 283, 236
2g	−0.10 (9H, s), 1.42 (1H, d, <i>J</i> =14.2 Hz), 1.51 (1H, d, <i>J</i> =14.2 Hz), 4.47 (1H, d, <i>J</i> =14.2 Hz), 4.61 (1H, d, <i>J</i> =14.2 Hz), 7.26—7.38 (4H, m), 7.89 (1H, s), 7.90 (1H, s)	3222, 3122, 2944, 1511, 1244, 1133, 1022	305 (M ⁺), 290, 274, 133
2h	−0.10 (9H, s), 1.40 (1H, d, <i>J</i> =14.9 Hz), 2.24 (1H, d, <i>J</i> =14.9 Hz), 4.77 (1H, d, <i>J</i> =14.3 Hz), 5.20 (1H, d, <i>J</i> =14.3 Hz), 7.20 (1H, dd, <i>J</i> =2.2, 8.5 Hz), 7.44 (1H, d, <i>J</i> =2.2 Hz), 7.79 (1H, d, <i>J</i> =8.5 Hz), 7.79 (1H, s), 8.03 (1H, s)	3104, 2953, 2245, 1514, 1476, 1275, 1248, 1150	354 (M ⁺ +2), 352 (M ⁺), 337
2i	−0.06 (9H, s), 1.44 (1H, d, <i>J</i> =14.2 Hz), 1.50 (1H, d, <i>J</i> =14.2 Hz), 4.47 (1H, d, <i>J</i> =14.2 Hz), 4.60 (1H, d, <i>J</i> =14.2 Hz), 7.20 (1H, dd, <i>J</i> =2.3, 8.4 Hz), 7.48 (1H, d, <i>J</i> =2.3 Hz), 7.48 (1H, d, <i>J</i> =8.4 Hz), 7.89 (1H, s), 7.97 (1H, s)	3106, 2956, 2248, 1508, 1475, 1280, 1250, 1139	354 (M ⁺ +2), 352 (M ⁺), 337
2j	0.16 (3H, s), 0.33 (3H, s), 1.63 (1H, d, <i>J</i> =14.9 Hz), 1.72 (1H, d, <i>J</i> =14.9 Hz), 4.41 (1H, d, <i>J</i> =14.2 Hz), 4.56 (1H, d, <i>J</i> =14.2 Hz), 7.15 (2H, d, <i>J</i> =9.1 Hz), 7.22 (2H, d, <i>J</i> =9.1 Hz), 7.26—7.35 (5H, m), 7.85 (1H, s), 7.86 (1H, s)	3070, 2956, 2240, 1504, 1428, 1274, 1208, 1137, 1113	380 (M ⁺), 365, 298
2k	0.03 (3H, s), 0.31 (3H, s), 1.63 (1H, d, <i>J</i> =14.9 Hz), 1.75 (1H, d, <i>J</i> =14.9 Hz), 4.42 (1H, d, <i>J</i> =14.2 Hz), 4.58 (1H, d, <i>J</i> =14.2 Hz), 7.25—7.35 (10H, m), 7.74 (1H, s), 7.84 (1H, s)	3097, 2960, 2244, 1509, 1449, 1279, 1252, 1138	346 (M ⁺), 331, 264
2l	0.12 (3H, s), 0.35 (3H, s), 1.61 (1H, d, <i>J</i> =14.9 Hz), 1.71 (1H, d, <i>J</i> =14.9 Hz), 4.41 (1H, d, <i>J</i> =14.1 Hz), 4.56 (1H, d, <i>J</i> =14.1 Hz), 6.88—7.40 (14H, m), 7.82 (1H, m), 7.87 (1H, s)	3069, 2956, 2240, 1583, 1487, 1428, 1273, 1231, 1138	438 (M ⁺), 423, 356

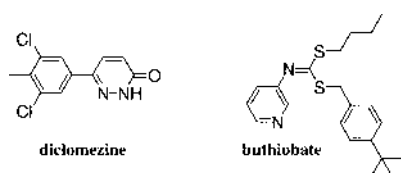


Fig. 3. Reference Fungicides

thickness of 0.25 mm (E. Merck), and spots were made visible by ultraviolet (UV) irradiation. Silica gel (350—250 mesh, Yamamura Chemical Laboratories Co., Ltd.) was used for column chromatography and preparative TLC was carried out on plates of Silica gel 60 F₂₅₄ with a layer thickness of 2 mm (E. Merck). The following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; br, broad.

2-(4-Fluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-trimethylsilylmethylpropanenitrile (2a) Sodium hydride (60% mineral oil dispersion, 500 mg, 12.5 mmol) was added to a solution of 2-(4-fluorophenyl)acetonitrile **5a**

(1.35 g, 10.0 mmol) in *N,N*-dimethylformamide (40 ml) and stirred for 30 min at 0 °C. Chloromethyltrimethylsilane **6** (2.45 g, 20.0 mmol) was added to the mixture and stirred for 2 h at room temperature. The reaction mixture was poured into ice water, quenched with an aqueous solution of ammonium chloride, and extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated to give a solid, which was chromatographed on silica gel (ethyl acetate–hexane, 9 : 1, v/v) to afford 2-(4-fluorophenyl)-3-trimethylsilylpropanenitrile (**7a**) (1.2 g, 54%). **7a**: ¹H-NMR (200 MHz, CDCl₃) δ: 0.03 (9H, s), 1.19 (1H, dd, *J*=9.0, 14.7 Hz), 1.39 (1H, dd, *J*=9.0, 14.7 Hz), 3.50 (1H, dd, *J*=7.1, 9.0 Hz), 7.06 (2H, t, *J*=8.7 Hz), 7.32 (2H, dd, *J*=5.1, 8.7 Hz). MS *m/z*: 221 (M⁺), 206, 122.

The product **7a** (440 mg, 2.0 mmol) was added to a suspension of sodium hydride (60% mineral oil dispersion, 220 mg, 5.5 mmol) in *N,N*-dimethylformamide (10 ml) at 0 °C and stirred for 30 min. 1-Chloromethyl-1*H*-1,2,4-triazole hydrochloride **8** (320 mg, 2.1 mmol) was added to the mixture at room temperature and stirred for 1 h. The reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with a saturated solution of ammonium chloride and dried over magnesium sulfate. The solid remaining after evaporation of the solvent was purified by thin layer chromatography (ethyl acetate–hexane, 1 : 1, v/v) to afford **2a** (300 mg, 50%) as colorless crystals (recrystallized from diisopropyl ether) from more polar fractions and 1-[2-(4-fluorophenyl)-1-propenyl]-1*H*-1,2,4-triazole (**9a**) (30 mg, 20%) as colorless crystals (recrystallized from diisopropyl ether) from less polar fractions. **9a**: mp 42–44 °C. ¹H-NMR (200 MHz, CDCl₃) δ: 2.27 (3H, d, *J*=1.5 Hz), 7.05 (1H, m), 7.09 (2H, t, *J*=8.9 Hz), 7.44 (2H, dd, *J*=5.3, 8.9 Hz), 8.06 (1H, s), 8.25 (1H, s). MS *m/z*: 203 (M⁺), 175, 148, 122.

The other silicon-containing azole derivatives (**2b–1**) were obtained in a similar way to that described for the preparation of **2a**. The yields, physical data, spectroscopic data, and elementary analysis data on these derivatives **2** are given in Tables 1 and 2.

Preventive Activity against Rice Sheath Blight Rice seedlings (variety Sachikaze) at the 3–4 leaf stage grown in pots were sprayed with an aqueous suspension of the test compound at a concentration of 300 ppm. After the seedlings had been kept in a greenhouse for 2 d, they were inoculated

with a previously cultured strain of *Rhizoctonia solani* and kept in a moist chamber (relative humidity: 100%) for 4 d at 25–27 °C. The results are shown in Table 1.

Preventive Activity against Powdery Mildew on Cucumber Cucumber seedlings (variety Sagamihanpaku) at the first leaf stage grown in pots were sprayed with an aqueous suspension of the test compound at a concentration of 300 ppm. After the seedlings had been kept in a greenhouse for 2 d, they were inoculated with a previously cultured strain of *Sphaerotheca fuliginea* and kept in a moist chamber (relative humidity: 100%) for 4 d at 25–27 °C. The results are shown in Table 1.

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