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Synthesis of Novel 2-Substituted-1,3,4-thiadiazoles

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New 2-monosubstituted and 2,2-disubstituted 2,3-dihydro-3,5-diphenyl-1,3,4-thiadiazoles (2) were synthesized by the reaction of *N*′-phenylthiobenzoylhydrazide with aliphatic, aromatic and heterocyclic aldehydes and ketones in the presence of trimethylsilyl chloride in benzene. The reaction proceeded smoothly to afford the corresponding 1,3,4-thiadiazoles (2a—2j) in excellent yields (84—96%) except for a few cases, such as the 5-methyl-2-furfural and 2-acetylthiophene systems. 2,3-Dihydro-2,2-dimethyl-3,5-diphenyl-1,3,4-thiazole (2f) showed curative activity against powdery mildew of wheat.

Key words *N*′-phenylthiobenzoylhydrazide; intramolecular cyclization; anti-mildew; 2-substituted-2,3-dihydro-3,5-diphenyl-1,3,4-thiadiazole; wheat powdery mildew

The 2-substituted 2,3-dihydro-1,3,4-thiadiazoles are expected to have physiological activities, and may be applicable as medicines and agricultural chemicals. For example, clinical investigation of dihydrothiadiazole ring-containing inhibitors of angiotensin converting enzyme has been reported by Bennion and co-workers.1) We have recently reported the synthesis of the 1,3,4-thiadiazole ring by the reaction of *N*′-phenylthioformohydrazide with carbonyl compounds (aliphatic, aromatic and heterocyclic aldehydes and ketones) using trimethylsilyl chloride at room temperature to give easily various new 2-substituted 2,3-dihydro-3-phenyl-1,3,4-thiadiazoles in excellent yield.2) Further, during the course of our synthetic and structural investigations of 1,3,4-thiadiazole analogs, we observed that the 1,3,4-thiadiazole ring is stabilized by quasi-aromatic character on the basis of spectroscopic investigation and X-ray analysis.3—5)

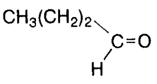
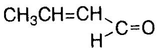
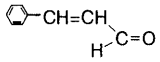
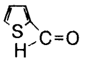
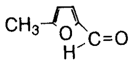
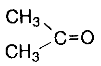
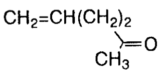
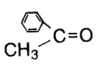
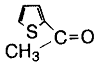
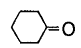
Here we describe the synthesis of new 2-monosubstituted and 2,2-disubstituted 1,3,4-thiadiazoles having a phenyl group at the 5-position by the treatment of *N*′-phenylthiobenzoylhydrazide with aldehydes and ketones in the presence of trimethylsilyl chloride. The obtained thiadiazoles (**2a**—**2j**) have been examined for biological activity.

Results and Discussion

New 2-monosubstituted and 2,2-disubstituted 2,3-dihydro-3,5-diphenyl-1,3,4-thiadiazoles (**2**) were easily synthesized by the reaction of *N*′-phenylthiobenzoylhydrazide with carbonyl compounds such as aliphatic, aromatic and heterocyclic aldehydes and ketones in the presence of trimethylsilyl chloride in benzene solution for 20 min (aldehyde system) and 1 or 2 h (ketone system) at room temperature. The reaction proceeded smoothly to afford the corresponding 1,3,4-thiadiazoles (**2a**—**2j**) in excellent yields (84—96%), except for a few cases such as the 5-methyl-2-furfural and 2-acetylthiophene systems (Table 1). The results indicate that the reaction rate of the aldehyde system is faster than that of the ketone system, and even a spiro ring is formed smoothly to give the product (**2j**) in excellent yield. This reaction appears to proceed through two steps: initial formation of the *O*-trimethylsilyl phenylhydrazonomethylmonothioacetal intermediate by the reaction of *N*′-phenylthioformohydrazide with carbonyl compounds in the presence of trimethylsilyl chloride, followed by formation of the 1,3,4-thiadiazole ring by intramolecular cyclization, as shown in Chart 1.

The obtained thiadiazoles (**2a**—**2j**) have been examined for activity against powdery mildew of wheat (Table 2). The results indicate that 2,2-disubstituted 1,3,4-thiadiazoles (**2f**—**2j**) have stronger curative activity than 2-monosubstituted 1,3,4-thiadiazoles (**2a**—**2e**). Compound **2f** (2,2-dimethyl substituent) showed the best curative activity against powdery mildew caused by *Erysiphe*

Table 1. Reaction of **1** with Carbonyl Compounds in the Presence of Trimethylsilyl Chloride[a)]

Carbonyl compound	1,3,4-Thiadiazole	Time	Yield (%)	mp (°C)
 $CH_3(CH_2)_2CHO$	**2a**	20 min	92	Oily
 $CH_3CH=CHCHO$	**2b**	20 min	84	Oily
	**2c**	20 min	96	Oily
	**2d**	20 min	96	Oily
	**2e**	20 min	60	Oily
 $(CH_3)_2C=O$	**2f**	1 h	90	43—44[b)]
 $CH_2=CH(CH_2)_2C(=O)CH_3$	**2g**	1 h	93	Oily
	**2h**	2 h	88	Oily
	**2i**	23 h	42	Oily
	**2j**	2 h	84	96—97[b)]

a) Compound **1** (1 mmol), an aldehyde (1 mmol) or a ketone (5 mmol), and trimethylsilyl chloride (1.5 mmol) in benzene (10 ml) at room temperature. *b*) Recrystallized from hexane.

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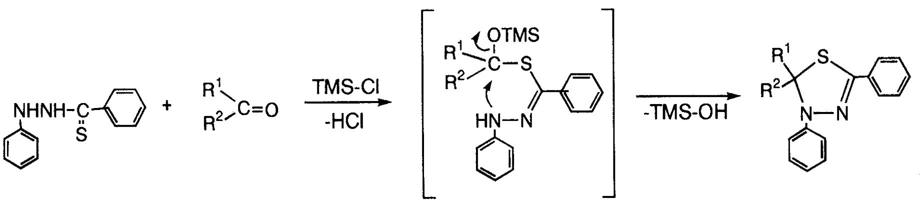

1a-j

2a-2j

Chart 1

Table 2. Curative Activity of 2-Monosubstituted and 2,2-Disubstituted 2,3-Dihydro-3,5-diphenyl-1,3,4-thiadiazoles against Powdery Mildew of Wheat

Activity	Compound									
	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j
EGR[a)]	0	1	0	0	0	4	3	3	3	2

a) Powdery mildew of wheat was caused by *Erysiphe graminis* and the activity was expressed on a scale of 0 to 5 : 5, 100% controlled *vs.* untreated controls; 4, <100%; 3, <90%; 2, <75%; 1, <50%; 0, <25%.

graminis at the concentration of 500 ppm (w/v), where infection of the leaf area is less than 10%.

Experimental

General Data Melting points were obtained on a Yanaco hot-stage apparatus without correction. ^{1}H-NMR spectra (270 Hz, $CDCl_3$) and ^{13}C-NMR spectra (67.5 Hz, $CDCl_3$) were recorded on a JEOL GSX 270 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a JEOL JMS-HX 100 mass spectrometer and a JEOL JWA-DA 5000 mass data system apparatus. Infrared (IR) spectral data were collected on a Perkin-Elmer 1760 FT-IR spectrometer.

General Procedure for the Reaction of *N'*-Phenylthiobenzoylhydrazide with Aldehydes and Ketones in the Presence of Trimethylsilyl Chloride A typical procedure is described for the reaction of *N'*-phenylthiobenzohydrazide with acetone in the presence of trimethylsilyl chloride. Acetone (5 mmol) was added dropwise to a benzene solution (10 ml) of *N'*-phenylthiobenzohydrazide (1 mmol) and trimethylsilyl chloride (1.5 mmol). After the addition was completed, the mixture was stirred for 1 h at room temperature. As judged by TLC analysis, the starting material was completely consumed, and then aqueous sodium hydrogen carbonate was added. The aqueous solution was extracted with benzene, the organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel) with benzene to give 2,3-dihydro-2,2-dimethyl-3,5-diphenyl-1,3,4-thiadiazole (**2f**) in 90% isolated yield.

2,3-Dihydro-3,5-diphenyl-2-propyl-1,3,4-thiadiazole (**2a**): Oil, ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, CH_3), 1.46 (2H, m, CH_2), 1.86 (2H, m, CH_2), 5.93 (1H, q, CH), 6.87—7.78 (10H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 13.5 (CH_3), 17.6 (CH_2), 37.5 (CH_2), 71.7 (CH, $J_{CH}=153$ Hz), 131.5 (C=N), 114.0, 120.0, 126.7, 128.4, 129.2, 129.3, 143.2, 143.9 (each aromatic). IR (neat): 1597, 1491, 1331, 759, 689 cm^{-1}. HR-MS *m/z*: Calcd for $C_{17}H_{18}N_2S$: 282.1190. Found: 282.1183. *Anal.* Calcd for $C_{17}H_{18}N_2S$: C, 72.30; H, 6.42; N, 9.92. Found: C, 72.33; H, 6.47; N, 9.98.

2,3-Dihydro-3,5-diphenyl-2-(1-propenyl)-1,3,4-thiadiazole (**2b**): Oil, ^{1}H-NMR ($CDCl_3$) δ: 1.69 (3H, d, CH_3), 5.62 (1H, q, vinylic), 5.78 (1H, m, vinylic), 6.27 (1H, d, CH), 5.87—7.74 (10H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 17.4 (CH_3), 72.0 (CH, $J_{CH}=151$ Hz), 120.2 (vinylic), 128.5 (vinylic), 131.5 (CH), 114.4, 126.7, 128.5, 129.0, 129.0, 129.4, 142.8, 144.3 (each aromatic). IR (neat): 1598, 1498, 1446, 1364, 1259, 1125, 689 cm^{-1}. HR-MS *m/z*: Calcd for $C_{17}H_{16}N_2S$: 280.1030. Found: 280.1041. *Anal.* Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99. Found: C, 78.86; H, 5.81; N, 10.04.

2,3-Dihydro-3,5-diphenyl-2-styryl-1,3,4-thiadiazole (**2c**): Oil, ^{1}H-NMR ($CDCl_3$) δ: 6.30 (1H, q, vinylic), 6.47 (1H, d, vinylic), 6.61 (1H, d, CH), 6.86—7.76 (15H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 72.5 (CH, $J_{CH}=151$ Hz), 131.4 (C=N), 114.4, 120.4, 126.6, 126.8, 126.9, 128.3, 128.5, 128.6, 129.1, 129.5, 135.5, 143.0, 144.3 (vinylic, each aromatic). IR (neat): 1596, 1496, 1121, 688 cm^{-1}. HR-MS *m/z*: Calcd for $C_{22}H_{18}N_2S$: 342.1190. Found 342.1202. *Anal.* Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 77.20; H, 5.37; N, 8.24

2,3-Dihydro-3,5-diphenyl-2-thienyl-1,3,4-thiadiazole (**2d**): Oil, ^{1}H-NMR ($CDCl_3$) δ: 6.88—7.90 (13H, m, aromatic, thiophenic), 7.07 (1H, s, CH). ^{13}C-NMR ($CDCl_3$) δ: 69.2 (CH, $J_{CH}=156$ Hz), 131.2 (C=N), 114.7, 120.8, 124.8, 125.0, 126.5, 126.8, 128.6, 129.1, 129.6, 142.8, 144.2, 145.2 (each aromatic, thiophenic). IR (neat): 1599, 1497, 1259, 760, 689 cm^{-1}. HR-MS *m/z*: Calcd for $C_{18}H_{14}N_2S_2$: 322.0600. Found: 322.0596. *Anal.* Calcd for $C_{18}H_{14}N_2S_2$: C, 67.05; H, 4.38; N, 8.69. Found: C, 67.11; H, 4.42; N, 8.75.

2,3-Dihydro-2-(5-methyl-2-furyl)-3,5-diphenyl-1,3,4-thiadiazole (**2e**): Oil, ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s, CH_3), 5.87 (1H, d, furanic), 6.19 (1H, d, furanic), 6.81 (1H, s, CH), 6.88—7.77 (10H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 13.6 (CH_3), 66.6 (CH, $J_{CH}=156$ Hz), 131.3 (C=N), 106.8, 109.0, 114.3, 120.5, 126.8, 128.5, 129.0, 129.5, 142.8, 144.3, 149.9, 153.0 (each aromatic, furanic). IR (neat): 1597, 1497, 1355, 1258, 733, 690 cm^{-1}. HR-MS *m/z*: Calcd for $C_{19}H_{16}ON_2S$: 320.0980. Found: 320.0971. *Anal.* Calcd for $C_{19}H_{16}ON_2S$: C, 71.23; H, 5.03; N, 8.74. Found: C, 71.26; H, 5.10; N, 8.81.

2,3-Dihydro-2,2-dimethyl-3,5-diphenyl-1,3,4-thiadiazole (**2f**): mp 43—44 °C, ^{1}H-NMR ($CDCl_3$) δ: 1.78 (6H, s, CH_3), 7.10—7.71 (10H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 28.5 (CH_3), 83.3 (C), 132.0 (C=N), 122.8, 124.5, 126.5, 128.4, 128.6, 129.2, 143.3, 143.5 (each aromatic). IR (neat): 1596, 1489, 1330, 1313, 1253, 1166, 762, 691, 679 cm^{-1}. HR-MS *m/z*: Calcd for $C_{16}H_{16}N_2S$: 268.1030. Found: 268.1005. *Anal.* Calcd for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44. Found: C, 71.67; H, 6.07; N, 10.51.

2-(3-Butenyl)-2,3-dihydro-2-methyl-3,5-diphenyl-1,3,4-thiadiazole (**2g**): Oil, ^{1}H-NMR ($CDCl_3$) δ: 1.75 (3H, s, CH_3), 1.98 (1H, m, CH_2), 2.32 (1H, m, CH_2), 2.38 (2H, m, CH_2), 4.97 (1H, q, vinylic), 5.04 (1H, q, vinylic), 5.83 (1H, m, vinylic), 6.96—7.70 (10H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 28.1 (CH_3), 30.0 (CH_2), 40.4 (CH_2), 86.8 (C), 115.1 (vinylic), 137.4 (vinylic), 131.8 (C=N), 121.4, 123.7, 126.4, 128.4, 128.8, 129.1, 142.0, 143.6 (each aromatic). IR (neat): 1597, 1490, 1319, 1252, 983, 913, 760, 690 cm^{-1}. HR-MS *m/z*: Calcd for $C_{19}H_{20}N_2S$: 308.1350. Found: 308.1317. *Anal.* Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 74.02; H, 6.60; N, 9.13.

2,3-Dihydro-2-methyl-2,3,5-triphenyl-1,3,4-thiadiazole (**2h**): Oil, ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s, CH_3), 6.82—7.77 (15H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 25.6 (CH_3), 84.8 (C), 131.6 (C=N), 117.5, 121.2, 126.4, 126.5, 128.2, 128.5, 128.6, 128.8, 129.3, 140.7, 142.9, 143.2 (each aromatic). IR (neat): 1598, 1493, 1331, 1255, 983, 909, 733, 691 cm^{-1}. HR-MS *m/z*: Calcd for $C_{21}H_{18}N_2S$: 330.1190. Found: 330.1160. *Anal.* Calcd for $C_{21}H_{18}N_2S$: C, 76.33; H, 5.94; N, 8.48. Found: C, 76.38; H, 5.99; N, 8.52.

2,3-Dihydro-2-methyl-3,5-phenyl-2-thienyl-1,3,4-thiadiazole (**2i**): Oil, ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s, CH_3), 6.94—7.72 (13H, m, aromatic, thiophenic). ^{13}C-NMR ($CDCl_3$) δ: 26.5 (CH_3), 83.2 (C), 131.5 (C=N), 119.1, 122.6, 125.7, 126.5, 126.6, 127.8, 128.5, 128.6, 129.5, 141.9, 143.4, 148.7 (each aromatic, thiophenic). IR (neat): 1597, 1490, 1252, 1237, 1128, 982, 760, 707, 690 cm^{-1}. HR-MS *m/z*: Calcd for $C_{19}H_{16}N_2S_2$: 336.0760. Found: 336.0783. *Anal.* Calcd for $C_{19}H_{16}N_2S_2$: C, 67.83; H, 4.79; N, 8.33. Found: C, 67.89; H, 4.86; N, 8.40.

Cyclohexanespiro-2'-(2,3-dihydro-3,5-diphenyl-1,3,4-thiadiazole) (**2j**): Oil, ^{1}H-NMR ($CDCl_3$) δ: 0.96—2.36 (10H, m, CH_2, spirocyclohexane), 7.15—7.74 (10H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 25.0, 25.4, 37.1 (CH_2, spirocyclohexane), 91.4 (C), 132.0 (C=N), 125.0, 125.2, 126.5, 128.4, 128.5, 129.1, 143.3, 143.7 (each aromatic). IR (KBr): 2947, 2934, 1594, 1489, 1448, 773, 762, 697 cm^{-1}. HR-MS *m/z*: Calcd for $C_{19}H_{20}N_2S$: 308.1350. Found: 308.1317. *Anal.* Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 74.05; H, 6.61; N, 9.12.

Biological Test Methods Curative activity against powdery mildew on wheat (foliar application); Wheat seedlings at the first-leaf stage grown in plastic pots were inoculated with the conidia of *Erysiphe graminis* and kept in a room at 15 °C under fluorescent lamps. After two days, the seedlings were sprayed with aqueous solutions or dispersions of test compounds at a designated concentration. The plants were kept in the room for 10 days. The curative activity was evaluated by measuring the degree of fungal infection, and the percentage of disease control was calculated as compared with the untreated, inoculated control plants. The activity was expressed as a score of 0 to 5 (5, 100% controlled *vs.* untreated controls; 4, <100%; 3, <90%; 2, <75%; 1, <50%; 0, <25%).

The curative activity of 2,2-disubstituted 1,3,4-thiadiazoles (**2f**—**2j**) was stronger than that of 2-monosubstituted 1,3,4-thiadiazoles (**2a**—**2e**). Compound **2f** (2,2-dimethyl substituent) showed the best curative activity compared with other thiadiazoles against powdery mildew caused by *Erysiphe graminis* at the concentration of 500 ppm (w/v), where infection of the leaf area was less than 10%.

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