Preparation of 2,2-Disubstituted 2,3-Dihydro-3-phenyl-1,3,4-thiadiazoles

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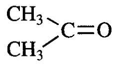
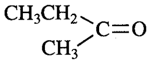
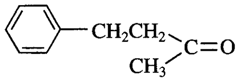
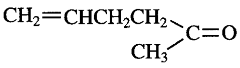
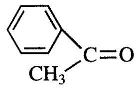
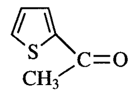
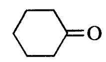
Reaction of *N'*-phenylthioformohydrazide with ketones in the presence of trimethylsilyl chloride proceeded easily to afford the corresponding 2,2-disubstituted 2,3-dihydro-3-phenyl-1,3,4-thiadiazoles in good yields.

Keywords 2,3-dihydro-3-phenyl-1,3,4-thiadiazole; trimethylsilyl chloride; ketone; cyclization

During the course of our studies on the synthesis and structure of 1,3,4-thiadiazine and 1,3,4-thiadiazole analogs, we observed that the 1,3,4-thiadiazine and 1,3,4-thiadiazole rings were stabilized by conjugation between the C = N bond and a pair of electrons on the sulfur atom.[1] In our preceding paper,[2] we described a novel method for the preparation of the 1,3,4-thiadiazole ring by the reaction of *N'*-phenylthioformohydrazide with aldehydes using trimethylsilyl chloride to give new 2-substituted 2,3-dihydro-3-phenyl-1,3,4-thiadiazoles in excellent yields. The reaction proceeded through two steps; the initial formation of an *O*-trimethylsilyl phenylhydrazonomethylmonothioacetal intermediate (**2**) by the reaction of *N'*-phenylthioformohydrazide (**1**) with carbonyl compounds in the presence of trimethylsilyl chloride, and the secondary formation of the 1,3,4-thiadiazole ring (**3**) by intramolecular cyclization. The 2,3-dihydro-3-phenyl-1,3,4-thiadiazoles are expected to have physiological activities, and may be applicable as medicines and agricultural chemicals. However, this is the first report on the chemistry of 2,3-dihydro-3-phenyl-1,3,4-thiadiazole without a functional group at the 5-position.

In this study, we have extended our investigation to the synthesis of 2,2-disubstituted 2,3-dihydro-3-phenyl-1,3,4-thiadiazoles by the treatment of *N'*-phenylthioformohydrazide with ketones, ketone analogs (carboxylic acid; acid anhydride; ester; carbonate; amide; urea; and carbamate) and epoxide in the presence of trimethylsilyl chloride. Reaction of *N'*-phenylthioformohydrazide (**1**) with ketones such as aliphatic, aromatic, and cyclic ketones proceeded smoothly to afford the corresponding 2,2-disubstituted 2,3-dihydro-3-phenyl-1,3,4-thiadiazoles (**3**) in good yields at room temperature. However, no reaction occurred with benzophenone and α,β-unsaturated ketones such as methyl vinyl ketone and 2-cyclohexen-1-one (Table I). Acetic acid, acetic anhydride, ethyl acetate, butyl carbamate, ethylene carbonate, acetamide, urea, and epichlorohydrin also failed to give the corresponding products.

TABLE I. Reaction of **1** with Ketones in the Presence of Trimethylsilyl Chloride

Ketone	1,3,4-Thiadiazole	Yield (%)	mp (°C)[a]
 $(CH_3)_2C=O$	**3a**	81	Oily
 $CH_3CH_2(CH_3)C=O$	**3b**	67	Oily
	**3c**	68	Oily
 $CH_2=CHCH_2CH_2(CH_3)C=O$	**3d**	74	Oily
	**3e**	68	90—91
	**3f**	23	55—57
	**3g**	95	77—78

a) Recrystallized from hexane.

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 spectrometer and JEOL JWA-DA 5000 mass data system. Infrared spectral data were collected on a Perkin-Elmer 1760 FT-IR spectrometer.

General Procedure for the Reaction of *N'*-Phenylthioformohydrazide with Ketones in the Presence of Trimethylsilyl Chloride A typical procedure is described for the reaction of *N'*-phenylthioformohydrazide with acetone in the presence of trimethylsilyl chloride. Acetone (5 mmol) was added dropwise to a benzene solution (10 ml) of *N'*-phenylthioformohydrazide (1 mmol) and trimethylsilyl chloride (1.5 mmol). After the addition was completed, the mixture was stirred for 15 h at room temperature. As judged by TLC analysis, the starting material was completely consumed. Aqueous sodium hydrogen carbonate was added,

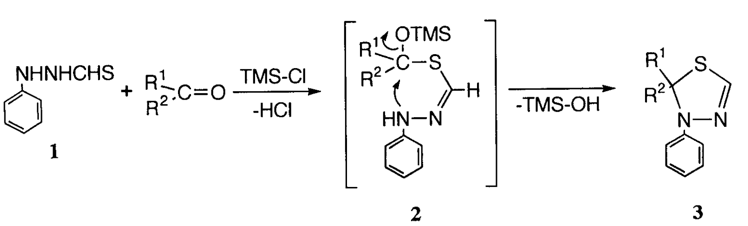


Chart 1

then the aqueous layer was extracted with benzene, and the organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel) with benzene to give 1,3,4-thiadiazole, **3a**, in 81% isolated yield. The results of elemental analysis, and ^{1}H- and ^{13}C-NMR spectral data for **3a** confirmed the formation of 2,3-dihydro-2,2-dimethyl-3-phenyl-1,3,4-thiadiazole.

2,3-Dihydro-2,2-dimethyl-3-phenyl-1,3,4-thiadiazole (**3a**): ^{1}H-NMR ($CDCl_3$) δ: 1.69 (6H, s, CH_3), 7.10—7.32 (5H, m, aromatic), 7.21 (1H, s, CH). ^{13}C-NMR ($CDCl_3$) δ: 28.3 (CH_3), 81.9 (C), 131.4 (CH, $J_{CH}=210$ Hz), 122.9, 124.6, 128.6, 143.3 (each aromatic). IR (neat): 2973, 2925, 1597, 1543, 1490, 1275, 1246, 1163, 819, 764, 698 cm^{-1}. HR-MS *m/z*: Calcd for $C_{10}H_{12}N_2S$: 192.0720. Found: 192.0691. *Anal.* Calcd for $C_{10}H_{12}N_2S$: C, 62.47; H, 6.29; N, 14.57. Found: C, 62.39; H, 6.34; N, 14.53.

2-Ethyl-2,3-dihydro-2-methyl-3-phenyl-1,3,4-thiadiazole (**3b**): ^{1}H-NMR ($CDCl_3$) δ: 1.64 (3H, s, CH_3), 1.09 (3H, t, CH_3), 1.83 (1H, m, CH_2), 2.19 (1H, m, CH_2), 7.04—7.33 (5H, m, aromatic), 7.11 (1H, s, CH). ^{13}C-NMR ($CDCl_3$) δ: 10.1 (CH_3), 33.9 (CH_2), 27.4 (CH_3), 86.4 (C), 130.1 (CH, $J_{CH}=210$ Hz), 121.3, 123.7, 128.6, 143.5 (each aromatic). IR (neat): 2971, 2933, 1597, 1490, 1315, 1288, 762, 696 cm^{-1}. HR-MS *m/z*: Calcd for $C_{11}H_{14}N_2S$: 206.0880. Found: 206.0879. *Anal.* Calcd for Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.60. Found: C, 64.01; H, 6.91; N, 13.58.

2,3-Dihydro-2-methyl-2-phenethyl-3-phenyl-1,3,4-thiadiazole (**3c**): ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, CH_3), 2.11 (1H, m, CH_2), 2.44 (1H, m, CH_2), 2.87 (2H, m, CH_2), 7.06—7.31 (10H, m, aromatic), 7.24 (1H, s, CH). ^{13}C-NMR ($CDCl_3$) δ: 32.1 (CH_2), 43.2 (CH_2), 28.2 (CH_3), 85.0 (C), 130.1 (CH, $J_{CH}=210$ Hz), 121.3, 123.9, 126.0, 128.4, 128.5, 128.8, 141.2, 143.5 (each aromatic). IR (neat): 3026, 2926, 1597, 1490, 1455, 1319, 1272, 823, 752, 699 cm^{-1}. HR-MS *m/z*: Calcd for $C_{17}H_{18}N_2S$: 282.1190. Found: 282.1212. *Anal.* Calcd for $C_{17}H_{18}N_2S$: C, 72.30; H, 6.42; N, 9.92. Found: C, 72.22; H, 6.51; N, 9.87.

2-(3-Butenyl)-2,3-dihydro-2-methyl-3-phenyl-1,3,4-thiadiazole (**3d**): ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, s, CH_3), 1.91 (1H, m, CH_2), 2.22 (1H, m, CH_2), 2.23 (2H, m, CH_2), 4.98 (1H, m, vinylic), 5.04 (1H, m, vinylic), 5.83 (1H, m, vinylic), 7.05—7.33 (5H, m, aromatic), 7.12 (1H, s, CH). ^{13}C-NMR ($CDCl_3$) δ: 27.7 (CH_3), 85.2 (C), 115.1 (vinylic), 137.3 (vinylic), 130.2 (CH, $J_{CH}=210$ Hz), 121.6, 123.9, 128.7, 143.4 (each aromatic). IR (neat): 1598, 1490, 1319, 1272, 913, 824, 762, 697 cm^{-1}. HR-MS *m/z*: Calcd for $C_{13}H_{16}N_2S$: 232.1030. Found: 232.1005. *Anal.* Calcd for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06. Found: C, 67.15; H, 7.01; N, 11.99.

2,3-Dihydro-2-methyl-2,3-diphenyl-1,3,4-thiadiazole (**3e**): ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, CH_3), 6.81—7.72 (10H, m, aromatic), 7.19 (1H, s, CH). ^{13}C-NMR ($CDCl_3$) δ: 25.2 (CH_3), 82.9 (C), 128.8 (CH, $J_{CH}=211$ Hz), 117.5, 121.4, 126.6, 128.2, 128.6, 128.7, 143.2, 143.2 (each aromatic). IR (KBr): 3063, 3062, 2981, 1598, 1494, 1317, 819, 775, 695 cm^{-1}. HR-MS *m/z*: Calcd for $C_{15}H_{14}N_2S$: 255.0960. Found: 255.0931. *Anal.* Calcd for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01. Found: C, 70.77; H, 5.61; N, 11.08.

2,3-Dihydro-2-methyl-3-phenyl-2-(2-thienyl)-1,3,4-thiadiazole (**3f**): ^{1}H-NMR ($CDCl_3$) δ: 2.02 (3H, s, CH_3), 6.90—7.42 (8H, m, aromatic and thiophenic), 7.27 (1H, s, CH). ^{13}C-NMR ($CDCl_3$) δ: 26.1 (CH_3), 81.6 (C), 129.8 (CH, $J_{CH}=212$ Hz), 119.1, 122.7, 125.7, 126.6, 127.7, 128.5, 143.2, 149.0 (each aromatic and thiophenic). IR (neat): 1596, 1547, 1494, 1292, 1250, 1239, 823, 786, 752, 713 cm^{-1}. HR-MS *m/z*: Calcd for $C_{13}H_{12}N_2S_2$: 260.0440. Found: 260.0443. *Anal.* Calcd for $C_{13}H_{12}N_2S_2$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.93; H, 4.70; N, 10.70.

Cyclohexanespiro-2′-(2,3-dihydro-3-phenyl-1,3,4-thiadiazole) (**3g**): ^{1}H-NMR ($CDCl_3$) δ: 0.91—1.82 (10H, m, CH_2, spirocyclohexane), 7.14—7.36 (5H, m, aromatic), 7.17 (1H, s, CH). ^{13}C-NMR ($CDCl_3$) δ: 24.9, 25.2, 36.9 (CH_2, spirocyclohexane), 90.0 (C), 131.5 (CH, $J_{CH}=209$ Hz), 124.9, 125.3, 128.5, 143.6 (each aromatic). IR (KBr): 2929, 2854, 1538, 1490, 1447, 837, 811, 786, 777, 704 cm^{-1}. HR-MS *m/z*: Calcd for $C_{13}H_{16}N_2S$: 232.1030. Found: 232.1004. *Anal.* Calcd for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06. Found: C, 67.15; H, 7.02; N, 12.01.

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