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A Novel Method for the Preparation of 2,2′-Substituted-2,3-dihydro-3-phenyl-1,3,4-thiadiazoles Using Trimethylsilyl Chloride

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Reaction of *N*′-phenylthioformohydrazide with carbonyl compounds, such as aliphatic, aromatic and heterocyclic aldehydes and a ketone, in the presence of trimethylsilyl chloride proceeded easily to afford the corresponding 2,2′-substituted-2,3-dihydro-3-phenyl-1,3,4-thiadiazoles in good yields under mild conditions.

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

In our preceding paper,[1)] we reported the synthesis of new 5-oxo-5,6-dihydro-4-phenyl-4*H*-1,3,4-thiadiazines and 3-phenyl-1,3,4-thiadiazol-2(3*H*)-one by the reaction of *N*′-phenylthioformohydrazide with chloroacetic acid or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ). In order to extend the chemistry of 1,3,4-thiadiazole, we wished to employ this reaction to obtain 2,2′-substituted-2,3-dihydro-3-phenyl-1,3,4-thiadiazoles without a functional group at the 5-position. Huisgen and co-workers,[2)] and Wolkoff and Hammerum[3)] reported that the reactions of benzohydrazonyl halides with *N*,*N*-dialkylthiobenzamides led to 2-dialkylamino-2,3,5-triaryl-1,3,4-thiadiazoles, and Heindel and co-workers[4)] reported that the reaction of aromatic thiohydrazide with dimethylacetylenedicarboxylate or methyl propiolate led to carbomethoxymethyl-1,3,4-thiadiazoles. However, no report has appeared on the chemistry of 2,3-dihydro-3-phenyl-1,3,4-thiadiazole without a functional group at the 5-position. On the other hand, thiosilane compounds are becoming of interest as synthetic reagents,[5)] *e.g.* in the monothioacetalization of organosulfur compounds with carbonyl compounds, using methylthiotrimethylsilane.[6)] Further, Mukaiyama and co-workers reported the synthesis of sulfides *via* monothioacetals as intermediates by the reaction of aldehydes and α,β-unsaturated ketones with trimethylsilyl sulfides and trimethylsilylchloride.[7)]

Thus, we have developed a novel method for the preparation of 2,2′-substituted-2,3-dihydro-3-phenyl-1,3,4-thiadiazoles using *O*-trimethylsilyl phenylhydrazonomethylmonothioacetal intermediates by the treatment of *N*′-phenylthioformohydrazide with carbonyl compounds (aliphatic, aromatic and heterocyclic aldehydes and a ketone) in the presence of trimethylsilyl chloride. The results are summarized in Table I. The reactions proceeded smoothly to afford the corresponding 2,2′-substituted-2,3-dihydro-3-phenyl-1,3,4-thiadiazoles in good yields under mild conditions.

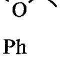
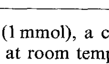
However, no reaction occurred in the absence of trimethylsilyl chloride while in the presence of Lewis acids such as zinc (IV) chloride ($ZnCl_4$), tin (IV) chloride ($SnCl_4$) and titanium (IV) chloride ($TiCl_4$) in place of trimethylsilyl chloride, the 2,3-dihydro-3-phenyl-1,3,4-thiadiazoles were obtained in quite low yields (1—8%). The reaction solution exhibited a red color, which has an absorption peak at 490 nm. This suggests resonance interaction between the electron-donating of sulfur atom on *N*′-phenylthioformohydrazide and the electron-accepting of silyloxonium carbon. Consequently, the formation of the 1,3,4-thiadiazole ring may proceed through two steps; initial formation of an *O*-trimethylsilyl phenylhydrazonomethylmonothioacetal (**2′**) intermediate by the reaction of *N*′-phenylthioformohydrazide with a carbonyl compound in the presence of trimethylsilyl chloride, followed by formation of the 1,3,4-thiadiazole ring by intramolecular condensation.

Experimental

General Data Melting points were obtained on a Yanaco hot-stage apparatus and are uncorrected. ^1H-NMR spectra (270 MHz, $CDCl_3$) 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 apparatus. Infrared (IR) spectral data were collected on a Perkin-Elmer 1760 FT-IR spectrometer.

General Procedure for the Synthesis of 2,2′-Substituted-2,3-dihydro-3-phenyl-1,3,4-thiadiazoles (2a—2h) A typical procedure is described for the reaction of *N*′-phenylthioformohydrazide with benzaldehyde in the presence of trimethylsilyl chloride. Benzaldehyde (1 mmol) was added dropwise to an anhydrous benzene solution (10 ml) of *N*′-phenylthioformohydrazide (**1**) (1 mmol) and trimethylsilyl chloride (1.5 mmol) under an argon atmosphere at room temperature. The reaction mixture acquired a red color. After the addition was completed, the mixture was stirred at room temperature. As judged by TLC analysis, the starting materials were completely consumed within 20 min, and then aqueous sodium hydrogencarbonate was added. The red color of the resulting

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

	R_1	R_2	Time (min)	Yield (%)	mp (°C)	Color
2a	H	Ph	20	96	107	Pale yellow
2b	H	CH_3	20	87	Oily	Pale yellow
2c	H	$CH_3CH_2CH_2$	20	88	Oily	Pale yellow
2d	H	CH_3CHCH	20	40	Oily	Pale yellow
2e	H	PhCHCH	20	92	102—103	Orange
2f	H		20	96	71—73	Pale yellow
2g	H		20	76	71—73	Pale yellow
2h	CH_3	Ph	1 d	43	89—90	Pale yellow

a) Compound **1** (1 mmol), a carbonyl compound (1 mmol), and trimethylsilyl chloride (1.5 mmol) at room temperature.

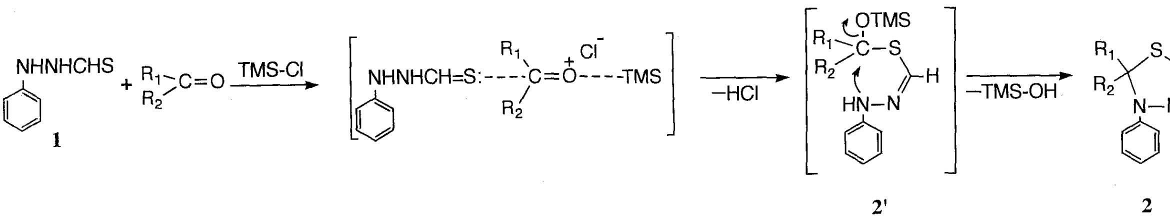


Chart 1

reaction mixture disappeared. The aqueous layer was extracted with benzene, and the organic layer was dried and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel) with benzene and/or recrystallization from hexane, to give 1,3,4-thiadiazole, **2a**, in 96% isolated yield. The results of elemental analysis, and ^{1}H- and ^{13}C-NMR spectroscopies for **2a** confirmed the formation of 2-phenyl-2,3-dihydro-3-phenyl-1,3,4-thiadiazole.

2,3-Dihydro-2,3-diphenyl-1,3,4-thiadiazole (**2a**): ^{1}H-NMR (CDCl$_3$) δ: 6.66 (1H, s, CH), 6.82—7.39 (10H, m, aromatic), 7.20 (1H, s, CH). ^{13}C-NMR (CDCl$_3$) δ: 71.4 (CH, $J_{CH}=154$ Hz), 129.9 (CH, $J_{CH}=215$ Hz), 114.0, 120.4, 125.6, 128.7, 129.1, 129.2, 141.4, 144.4 (each aromatic). IR (KBr): 3027, 1595, 1498, 1324, 743 cm^{-1}. HR-MS *m/z*: Calcd for $C_{14}H_{12}N_2S$: 240.0720. Found: 240.0701. *Anal.* Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66. Found: C, 69.84; H, 5.08; N, 11.62.

2,3-Dihydro-2-methyl-3-phenyl-1,3,4-thiadiazole (**2b**): ^{1}H-NMR (CDCl$_3$) δ: 1.47 (3H, d, CH$_3$), 5.85 (1H, q, CH, $J=6$ Hz), 5.97—7.32 (5H, m, aromatic), 7.15 (1H, s, CH). ^{13}C-NMR (CDCl$_3$) δ: 22.7 (CH$_3$), 65.0 (CH, $J_{CH}=159$ Hz), 130.9 (CH, $J_{CH}=216$ Hz), 114.3, 120.3, 129.3, 143.9 (each aromatic). IR (neat): 3085, 2921, 1687, 1602, 1496, 1343, 747 cm^{-1}. HR-MS *m/z*: Calcd for $C_9H_{10}N_2S$: 178.0560. Found: 178.0550. *Anal.* Calcd for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.72. Found: C, 60.41; H, 5.73; N, 15.68.

2,3-Dihydro-3-phenyl-2-propyl-1,3,4-thiadiazole (**2c**): ^{1}H-NMR (CDCl$_3$) δ: 0.86 (3H, d, CH$_3$), 1.33 (2H, m, CH$_2$), 1.70 (2H, m, CH$_2$) 5.69 (1H, q, CH, $J=4$ Hz), 6.79—7.25 (5H, m, aromatic), 7.09 (1H, s, CH). ^{13}C-NMR (CDCl$_3$) δ: 13.5 (CH$_3$), 17.7 (CH$_2$), 37.7 (CH$_2$), 70.1 (CH, $J_{CH}=157$ Hz), 131.3 (CH, $J_{CH}=206$ Hz), 114.0, 120.2, 129.3, 144.3 (each aromatic). IR (neat): 3070, 2943, 1687, 1602, 1496, 1347, 1198, 751 cm^{-1}. HR-MS *m/z*: Calcd for $C_{11}H_{14}N_2S$: 206.0880. Found: 206.0850. *Anal.* Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 64.01; H, 6.89; N, 13.59.

2,3-Dihydro-3-phenyl-2-(1-propenyl)-1,3,4-thiadiazole (**2d**): ^{1}H-NMR (CDCl$_3$) δ: 1.78 (3H, d, CH$_3$), 5.56 (1H, q, vinylic), 5.57 (1H, m, vinylic), 6.25 (1H, d, $J=7$ Hz, CH), 6.86—7.30 (5H, m, aromatic), 7.15 (1H, s, CH). ^{13}C-NMR (CDCl$_3$) δ: 17.4 (CH$_3$), 70.3 (CH, $J_{CH}=156$ Hz), 120.3 (vinylic), 128.4 (vinylic), 130.6 (CH, $J_{CH}=211$ Hz), 114.3, 129.0, 129.0, 144.6 (each aromatic). IR (neat): 2928, 1680, 1602, 1496, 1347, 1262, 751 cm^{-1}. HR-MS *m/z*: Calcd for $C_{11}H_{12}N_2S$: 204.0720. Found: 204.0716. *Anal.* Calcd for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.71; H, 5.99; N, 13.83.

2,3-Dihydro-3-phenyl-2-styryl-1,3,4-thiadiazole (**2e**): ^{1}H-NMR (CDCl$_3$) δ: 6.20 (1H, d, vinylic), 6.29 (1H, q, vinylic), 6.57 (1H, d, $J=15$ Hz, CH), 6.86—7.37 (10H, m, aromatic), 7.19 (1H, s, CH). ^{13}C-NMR (CDCl$_3$) δ: 70.7 (CH, $J_{CH}=152$ Hz), 130.8 (CH, $J_{CH}=216$ Hz), 128.4 (vinylic), 131.3 (vinylic), 114.3, 120.6, 126.4, 135.4, 126.9, 128.6, 129.1, 144.6 (each aromatic). IR (KBr): 3021, 1687, 1595, 1496, 1340, 751 cm^{-1}. HR-MS *m/z*: Calcd for $C_{16}H_{14}N_2S$: 266.0880. Found: 266.0847. *Anal.* Calcd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30; N, 10.52. Found: C, 71.95; H, 5.33; N, 10.45.

2,3-Dihydro-3-phenyl-2-thienyl-1,3,4-thiadiazole (**2f**): ^{1}H-NMR (CDCl$_3$) δ: 6.86—7.27 (8H, m, aromatic and thiophenic), 7.26 (1H, s, CH), 6.98 (1H, s, CH). ^{13}C-NMR (CDCl$_3$) δ: 114.6, 67.4 (CH, $J_{CH}=156$ Hz), 130.4 (CH, $J_{CH}=210$ Hz), 120.9, 124.8, 126.6, 126.9, 129.1, 144.3, 145.3 (each aromatic and thiophenic). IR (KBr): 3070, 1599, 1492, 1322, 1173, 712 cm^{-1}. HR-MS *m/z*: Calcd for $C_{12}H_{10}N_2S_2$: 246.0290. Found: 246.0314. *Anal.* Calcd for $C_{12}H_{10}N_2S_2$: C, 58.51; H, 4.09; N, 11.37. Found: C, 58.41; H, 4.11; N, 11.33.

2,3-Dihydro-2-(5-methyl-2-furyl)-3-phenyl-1,3,4-thiadiazole (**2g**): ^{1}H-NMR (CDCl$_3$) δ: 2.26 (3H, s, CH$_3$), 5.87 (1H, d, furanic), 6.15 (1H, d, furanic), 6.65 (1H, s, CH), 6.86—7.27 (5H, m, aromatic), 7.26 (1H, s, CH). ^{13}C-NMR (CDCl$_3$) δ: 13.6 (CH$_3$), 64.8 (CH, $J_{CH}=156$ Hz), 130.5 (CH, $J_{CH}=208$ Hz), 106.8, 153.1, 109.0, 114.3, 120.6, 129.0, 144.5, 149.9 (each aromatic and furanic). IR (KBr): 3056, 2928, 1595, 1496, 1333, 1021, 857, 744 cm^{-1}. HR-MS *m/z*: Calcd for $C_{13}H_{12}N_2OS$: 246.0670. Found: 244.0661. *Anal.* Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.82; H, 5.02; N, 11.41.

2,3-Dihydro-2-methyl-2,3-diphenyl-1,3,4-thiadiazole (**2h**): ^{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.

References

1) Y. Matsubara, M. Yoshihara, T. Nakamura, S. Yamada, T. Maeshima, *Phosphorus and Sulfur*, **16**, 89 (1983); Y. Matsubara, S. Yamada, M. Yoshihara, T. Maeshima, *Chem. Pharm. Bull.*, **32**, 1590 (1984); Y. Matsubara, K. Kitano, Y. Sasaki, A. Tsutsumi, M. Yoshihara, T. Maeshima, *Nippon Kagaku Kaishi*, **1991**, 1502.
2) R. Huisgen, R. Grashey, M. Seidel, H. Knupfer, R. Schmidt, *Justus Liebigs Ann. Chem.*, **658**, 168 (1962).
3) P. Wolkoff, S. Hammerum, *Acta Chem. Scand., Ser. B.* **30**, 837 (1976).
4) N. D. Heindel, G. Friedrich, M. C. Tsai, *J. Heterocycl. Chem.*, **17**, 191 (1980).
5) J. R. Hwu, S.-C. Tsay, *J. Org. Chem.*, **55**, 5987 (1990).
6) D. A. Evans, K. G. Grimm, L. K. Truesdale, *J. Am. Chem. Soc.*, **97**, 3229 (1975).
7) T. Soga, T. Takenoshita, M. Yamada, J. S. Han, T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **64**, 1108 (1991); T. Mukaiyama, T. Ohno, T. Nishiyama, J. S. Han, S. Kobayashi, *ibid.*, **64**, 2524 (1991).