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Synthesis of 2-Substituted 5-(1-Oxido-4-pyridyl)- and 5-(1-Oxido-2-pyridyl)-1,3,4-thiadiazole Derivatives by Substitution of 2-Methylsulfonyl Group with Various Nucleophiles

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The synthesis of 2-substituted 5-(1-oxido-4-pyridyl)-(**4a**—**10a**) and 5-(1-oxido-2-pyridyl)-1,3,4-thiadiazole derivatives (**4b**—**10b**) by substitution reaction of 5-(1-oxido-4-pyridyl)- (**3a**) and 5-(1-oxido-2-pyridyl)-2-methylsulfonyl-1,3,4-thiadiazole (**3b**) is described. 5-(1-Oxido-4-pyridyl)- (**9a**) and 5-(1-oxido-2-pyridyl)-1,3,4-thiadiazole (**9b**) could be reduced with sodium dithionite to 2-(4-pyridyl)- (**11c**) and 2-(2-pyridyl)-1,3,4-thiadiazole (**11d**).

Keywords—2,3-dihydro-1,3,4-thiadiazole; oxidation; methylsulfonyl-1,3,4-thiadiazole; nucleophilic substitution; nucleophile; substituted 1,3,4-thiadiazole; hydrolysis; sodium borohydride; (1-oxidopyridyl)-1,3,4-thiadiazole; sodium dithionite

The most common procedure for the synthesis of 2,5-disubstituted 1,3,4-thiadiazoles is based on cyclization of acylated thiosemicarbazides or compounds with similar structures.¹⁾ Nucleophilic substitution reaction of 1,3,4-thiadiazole derivatives with strong electron-withdrawing substituents in the 2-position is a valuable procedure for preparing 2,5-disubstituted 1,3,4-thiadiazole derivatives which are not readily obtainable by the common procedures.

A substituent such as a halogen atom²⁾ or nitro group³⁾ in 1,3,4-thiadiazole derivatives can be readily displaced by nucleophiles, due to the low electron density at the carbon atoms in the 1,3,4-thiadiazole ring. It has also been reported that methylsulfonyl groups at carbons with low electron density in heterocyclic compounds can be displaced with nucleophiles.⁴⁾ 2-Hydrazino-5-phenyl-1,3,4-thiadiazole has been prepared by hydrazinolysis of 2-methylsulfonyl-5-phenyl-1,3,4-thiadiazole.⁵⁾

Previously, we have reported that acetylation of both pyridine-carbaldehyde methylthio(thiocarbonyl)hydrazones (**1a**,**1b**) with acetic anhydride gave the 2,3-dihydro-1,3,4-thiadiazoles (**2a**,**2b**) and oxidation of **2a**,**2b** with an excess of 30% hydrogen peroxide in acetic acid gave 2-methylsulfonyl-5-(1-oxido-pyridyl)-1,3,4-thiadiazoles (**3a**, **3b**) in good yields⁶⁾ (Chart 1).

We here report on the substitution reaction of the 2-methylsulfonyl-1,3,4-thiadiazoles

Chart 1

Chart 2

(3a,3b) with various nucleophiles. Treatment of 3a with sodium ethoxide in EtOH or with thiophenol in the presence of sodium hydride at room temperature gave 2-ethoxy- (4a) or 2-phenylthio-5-(1-oxido-4-pyridyl)-1,3,4-thiadiazole (5a) in 77% or 78% yield, respectively. Reaction of 3a with aniline at elevated temperature gave 2-anilino-5-(1-oxido-4-pyridyl)-1,3,4-thiadiazole (6a). Reaction of 3a with diethyl malonate or ethyl acetoacetate in the presence of sodium hydride afforded diethyl 5-(1-oxido-4-pyridyl)-2,3-dihydro-1,3,4-thiadiazol-2-ylidenemalonate (7a) or ethyl 1-(5-(1-oxido-4-pyridyl)-2,3-dihydro-1,3,4-thiadiazol-2-ylidene)-1-acetylacetate (8a) in 83% or 81% yield, respectively. The infrared (IR) spectra of compounds 7a and 8a showed NH absorptions at 3210 and 3230 cm^{-1} , respectively. The proton nuclear magnetic resonance (^1H -NMR) spectra of compounds 7a (δ_{H} 13.54) and 8a (δ_{H} 13.60) also indicate the presence of NH protons. These results show that 7a and 8a exist as the 2,3-dihydro-1,3,4-thiadiazole tautomers. Reaction of 3a with NaBH_4 at room temperature gave 2-(1-oxido-4-pyridyl)-1,3,4-thiadiazole (9a) by substitution of the 2-methylsulfonyl group with a hydride anion. Hydrolysis of 3a with 2N HCl under reflux gave 5-(1-oxido-4-pyridyl)-2,3-dihydro-1,3,4-thiadiazol-2-one (10a). The structures of compounds 4a—10a were supported by the analytical and spectral data (Table I).

Similar treatment of 3b with the nucleophiles described above also gave 2-substituted 5-(1-oxido-2-pyridyl)-1,3,4-thiadiazoles (4b—10b). The structures of compounds 4b—10b were also supported by the analytical and spectral data (Table II).

It has been reported that pteridine N-oxides could be easily reduced to pteridine by treatment with sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$).⁷⁾ In fact, reduction of 9a with 8 eq of $\text{Na}_2\text{S}_2\text{O}_4$ in 50% aqueous EtOH under reflux for 15 min gave 2-(4-pyridyl)-1,3,4-thiadiazole (11c) in 94% yield, while treatment of 9b with 30 eq of $\text{Na}_2\text{S}_2\text{O}_4$ in 50% aqueous EtOH under reflux for 1 h gave 2-(2-pyridyl)-1,3,4-thiadiazole (11d)⁸⁾ in only 56% yield.

TABLE I. 2-Substituted 5-(1-Oxido-4-pyridyl)-1,3,4-thiadiazoles (**4a**—**10a**)

Compd. No.	Yield (%)	mp (°C) (Recrystn. solvent)	IR $\nu_{\text{max}}^{\text{KBr cm}^{-1}}$			$^1\text{H-NMR}$ signals (ppm) ($J = \text{Hz}$)	Formula	Analysis (%)			MS m/z (M^+)
			NH	CO	N-O			Calcd	Found		
4a	77	159—161 (EtOH)				1260 ^{a)} 1.42 (3H, t, $J = 7$, CH_2CH_3), 4.56 (2H, q, $J = 7$, CH_2CH_3), 7.81 (2H, dd, $J = 2$, 7, PyH), 8.29 (2H, dd, $J = 2$, 7, PyH)	$\text{C}_9\text{H}_6\text{N}_3\text{O}_2\text{S}$	48.42 (48.45)	4.06 4.02	18.82 18.92	223
5a	78	141—143 (EtOH)				1285 ^{a)} 7.40—8.00 (5H, m, ArH), 7.87 (2H, dd, $J = 2$, 7, PyH), 8.30 (2H, dd, $J = 2$, 7, PyH)	$\text{C}_{13}\text{H}_6\text{N}_3\text{OS}_2$	54.34 (54.38)	3.16 3.00	14.62 14.65	287
6a	87	274—276 (EtOH)	3240			1245 ^{a)} 6.90—7.76 (5H, m, ArH), 7.85 (2H, dd, $J = 2$, 7, PyH), 8.29 (2H, dd, $J = 2$, 7, PyH), 10.99 (1H, br s, NH)	$\text{C}_{12}\text{H}_{10}\text{N}_4\text{OS}$	57.76 (57.74)	3.73 3.62	20.73 20.54	270
7a	83	185—187 (dec.) (EtOH)	3210	1640		1260 ^{b)} 1.35 (6H, t, $J = 7$, CH_2CH_3), 4.29 (4H, q, $J = 7$, CH_2CH_3), 7.67 (2H, dd, $J = 2$, 7, PyH), 8.23 (2H, dd, $J = 2$, 7, PyH), 13.54 (1H, br s, NH)	$\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_5\text{S}$	49.85 (49.49)	4.48 4.49	12.46 12.22	337
8a	81	205—207 (dec.) (EtOH)	3230	1630	1585	1240 ^{b)} 1.41 (3H, t, $J = 7$, CH_2CH_3), 2.58 (3H, s, COCH_3), 4.37 (2H, q, $J = 7$, CH_2CH_3), 7.75 (2H, dd, $J = 2$, 7, PyH), 8.26 (2H, dd, $J = 2$, 7, PyH), 13.60 (1H, br s, NH)	$\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$	50.81 (51.11)	4.26 4.27	13.67 13.37	307
9a	82	156—159 (dec.) (EtOH)				1255 ^{a)} 8.03 (2H, dd, $J = 2$, 7, PyH), 8.37 (2H, dd, $J = 2$, 7, PyH), 9.72 (1H, s, $\text{C}_5\text{-H}$)	$\text{C}_7\text{H}_5\text{N}_3\text{OS}$	46.92 (46.90)	2.81 2.64	23.45 23.19	179
10a	80	280—281 (MeOH)	3110	1660	1240 ^{c)}		$\text{C}_7\text{H}_5\text{N}_3\text{O}_2\text{S}$	43.07 (42.79)	2.58 2.47	21.53 21.51	195

Abbreviations: br s, broad singlet; dd, doublet of doublets; m, multiplet; q, quartet; s, singlet; t, triplet. ^{a)} In DMSO- d_6 . ^{b)} In CDCl_3 . ^{c)} Not soluble in DMSO- d_6 or in CDCl_3 .

TABLE II. 2-Substituted 5-(1-Oxido-2-pyridyl)-1,3,4-thiadiazoles (**4b**—**10b**)

Compd. No.	Yield (%)	mp (°C) (Recrystn. solvent)	IR $\nu_{\max}^{\text{KBr cm}^{-1}}$			$^1\text{H-NMR}$ signals (ppm) ($J=\text{Hz}$)	Formula	Analysis (%)			MS m/z (M^+)
			NH	CO	N-O			Calcd	Found	N	
4b	98	183—184 (EtOH)			1245	a 1.50 (3H, t, $J=7$, CH_2CH_3), 4.55 (2H, q, $J=7$, CH_2CH_3), 7.56—7.74 (2H, m, PyH), 8.38—8.60 (2H, m, PyH)	$\text{C}_9\text{H}_9\text{N}_3\text{O}_2\text{S}$	48.42 (48.62)	4.06 3.96	18.82 18.99)	223
5b	97	172—174 (EtOH)			1250	a 7.40—7.90 (7H, m, ArH), 8.40—8.65 (2H, m, PyH)	$\text{C}_{13}\text{H}_9\text{N}_3\text{O}_2\text{S}_2$	54.34 (54.39)	3.16 2.90	14.62 14.71)	287
6b	82	275—278 (dec.) (EtOH)	3250		1250	a 6.92—7.80 (7H, m, ArH), 8.40—8.58 (2H, m, PyH), 10.85 (1H, brs, NH)	$\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_2\text{S}$	57.76 (57.82)	3.73 3.59	20.73 20.78)	270
7b	74	182—184 (dec.) (EtOH)	3190	1640 1620	1240	b 1.36 (6H, t, $J=7$, CH_2CH_3), 4.28 (4H, q, $J=7$, CH_2CH_3), 7.30—7.56 (2H, m, PyH), 8.20—8.50 (2H, m, PyH), 14.01 (1H, brs, NH)	$\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$	49.85 (49.75)	4.48 4.61	12.46 12.16)	337
8b	64	217—220 (dec.) (EtOH)	3190	1635 1585	1250	b 1.41 (3H, t, $J=7$, CH_2CH_3), 2.59 (3H, s, COCH_3), 4.36 (2H, q, $J=7$, CH_2CH_3), 7.34—7.56 (2H, m, PyH), 8.26—8.56 (2H, m, PyH), 12.00—14.50 (1H, br, NH)	$\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$	50.81 (50.51)	4.26 3.96	13.67 13.56)	307
9b	76	192—193 (EtOH)			1255	a 7.59—7.78 (2H, m, PyH), 8.54—8.73 (2H, m, PyH), 9.75 (1H, s, $\text{C}_2\text{-H}$)	$\text{C}_7\text{H}_5\text{N}_3\text{O}_2\text{S}$	46.92 (46.83)	2.81 2.63	23.45 23.40)	179
10b	95	270—272 (dec.) (Benzene-MeOH)	3080		1240	a 7.50—7.64 (2H, m, PyH), 8.06—8.50 (2H, m, PyH), 13.75 (1H, brs, NH)	$\text{C}_7\text{H}_5\text{N}_3\text{O}_2\text{S}$	43.07 (43.04)	2.58 2.37	21.53 21.29)	195

Abbreviations: br, broad; brs, broad singlet; m, multiplet; q, quartet; s, singlet; t, triplet. a) In DMSO- d_6 . b) In CDCl_3 .

Experimental

Melting points were determined by the capillary method and are uncorrected. IR spectra were recorded on a Hitachi 215 spectrometer. $^1\text{H-NMR}$ spectra were recorded on a JEOL PS-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a JEOL D-300 instrument. For column chromatography, Silica gel 60 (230—400 mesh, Nakarai Chemicals, Ltd.) was employed. Yields, melting points, analytical and spectral data for **4a**—**10a** and **4b**—**10b** are given in Tables I and II, respectively.

2-Ethoxy-5-(1-oxido-4-pyridyl)- (4a) and 2-Ethoxy-5-(1-oxido-2-pyridyl)-1,3,4-thiadiazole (4b)—General Procedure: A suspension of **3a** or **3b** (150 mg, 0.58 mmol) in EtOH (5 ml) was added dropwise to a stirred solution of EtONa (1.74 mmol) in EtOH (4 ml) at room temperature. After 1 h, the mixture was neutralized with HCl/EtOH solution and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (CHCl_3 -MeOH, 20:1, v/v). Evaporation of the eluates gave a solid, which was crystallized from EtOH to give **4a** or **4b**.

2-Phenylthio-5-(1-oxido-4-pyridyl)- (5a) and 5-(1-Oxido-2-pyridyl)-1,3,4-thiadiazole (5b)—General Procedure: A suspension of sodium hydride (105 mg, 2.62 mmol, 60% dispersion in oil, washed twice with ether) in dry tetrahydrofuran (THF 4 ml) was added dropwise to a stirred solution of thiophenol (285 mg, 2.59 mmol) in dry THF (4 ml) at room temperature. After 1 h, a suspension of **3a** or **3b** (300 mg, 1.17 mmol) in dry THF (7 ml) was added dropwise to the solution of the sodium salt of thiophenol at room temperature. After being stirred for 15 min, the mixture was neutralized with aqueous acetic acid, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (CHCl_3 -acetone, 20:1, v/v). Evaporation of the eluates gave a solid, which was crystallized from EtOH to give **5a** or **5b**.

2-Anilino-5-(1-oxido-4-pyridyl)- (6a) and 2-Anilino-5-(1-oxido-2-pyridyl)-1,3,4-thiadiazole (6b)—General Procedure: A mixture of **3a** or **3b** (150 mg, 0.58 mmol) and aniline (1 ml) was stirred at 110—130 °C for 5 h. The mixture was chromatographed on a silica gel column (CHCl_3 -MeOH, 20:1, v/v). Evaporation of the eluates gave a solid, which was crystallized from EtOH to give **6a** or **6b**.

Diethyl 5-(1-Oxido-4-pyridyl)- (7a) and Diethyl 5-(1-Oxido-2-pyridyl)-2,3-dihydro-1,3,4-thiadiazol-2-ylidene-malonate (7b)—General Procedure: A suspension of sodium hydride (117 mg, 2.93 mmol, 60% dispersion in oil, washed twice with ether) in dry THF (4 ml) was added dropwise to a stirred solution of diethyl malonate (470 mg, 2.93 mmol) in dry THF (4 ml) at room temperature. After 1 h, a suspension of **3a** or **3b** (150 mg, 0.58 mmol) in dry THF (7 ml) was added dropwise to the solution of the sodium salt of diethyl malonate at room temperature. After being stirred for 3 h, the mixture was neutralized with aqueous acetic acid, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (CHCl_3 -MeOH, 20:1, v/v). Evaporation of the eluates gave a solid, which was crystallized from EtOH to give **7a** or **7b**.

Ethyl 1-(5-(1-Oxido-4-pyridyl)- (8a) and Ethyl 1-(5-(1-Oxido-2-pyridyl)-2,3-dihydro-1,3,4-thiadiazol-2-ylidene)-1-acetylacetate (8b)—General Procedure: A suspension of sodium hydride (117 mg, 2.93 mmol, 60% dispersion in oil, washed twice with ether) in dry THF (4 ml) was added dropwise to a stirred solution of ethyl acetoacetate (380 mg, 2.92 mmol) in dry THF (4 ml) at room temperature. After 1 h, a suspension of **3a** or **3b** (150 mg, 0.58 mmol) in dry THF (7 ml) was added dropwise to the solution of the sodium salt of ethyl acetoacetate at room temperature. After being stirred at 70 °C for 1 h, the mixture was neutralized with aqueous acetic acid, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (CHCl_3 -MeOH, 20:1, v/v). Evaporation of the eluates gave a solid, which was crystallized from EtOH to give **8a** or **8b**.

2-(1-Oxido-4-pyridyl)- (9a) and 2-(1-Oxido-2-pyridyl)-1,3,4-thiadiazole (9b)—General Procedure: NaBH_4 (for **3a**, 56 mg, 1.48 mmol; for **3b**, 90 mg, 2.38 mmol) was added portionwise to a stirred suspension of **3a** or **3b** (150 mg, 0.58 mmol) in EtOH (4 ml) at 0 °C. After being stirred at room temperature for 1 h, the mixture was neutralized with acetic acid, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (CHCl_3 -MeOH, 20:1, v/v). Evaporation of the eluates gave a solid, which was crystallized from EtOH to give **9a** or **9b**.

5-(1-Oxido-4-pyridyl)- (10a) and 5-(1-Oxido-2-pyridyl)-2,3-dihydro-1,3,4-thiadiazol-2-one (10b)—General Procedure: A mixture of **3a** or **3b** (150 mg, 0.58 mmol) and 2N HCl (7 ml) was refluxed for 3 h. The mixture was neutralized with saturated K_2CO_3 aqueous solution. i) For **3a**: The resulting solid was collected by filtration and washed with hot MeOH to give **10a**. ii) For **3b**: The mixture was concentrated under reduced pressure. The residue was chromatographed on a silica gel column (CHCl_3 -MeOH, 20:1, v/v). Evaporation of the eluates gave a solid, which was crystallized from benzene-MeOH to give **10b**.

2-(4-Pyridyl)-1,3,4-thiadiazole (11c)—A mixture of **9a** (100 mg, 0.56 mmol) and $\text{Na}_2\text{S}_2\text{O}_4$ (780 mg, 4.48 mmol) in 50% aqueous EtOH (8 ml) was refluxed for 15 min. The mixture was extracted with CHCl_3 (3 $\times$ 50 ml). The combined extract was washed with brine, and dried over Na_2SO_4 . After removal of the solvent by evaporation, the residue was crystallized from ether to give **11c** (86 mg, 94%) as colorless crystals, mp 112—114 °C. IR(KBr): 1600 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 7.98 (2H, dd, ArH), 8.80 (2H, dd, ArH), 9.82 (1H, s, C₂-H). *Anal.* Calcd for $\text{C}_7\text{H}_5\text{N}_3\text{S}$: C, 51.52; H, 3.09; N, 25.75. Found: C, 51.57; H, 2.96; N, 25.72.

2-(2-Pyridyl)-1,3,4-thiadiazole (11d)—A mixture of **9b** (100 mg, 0.56 mmol) and $\text{Na}_2\text{S}_2\text{O}_4$ (2.918 g, 16.76 mmol) in 50% aqueous EtOH (15 ml) was refluxed for 1 h. The mixture was extracted with CHCl_3 (3 $\times$ 80 ml). The combined

extract was washed with brine, and dried over Na_2SO_4 . After removal of the solvent by evaporation, the residue was chromatographed on a silica gel column (CHCl_3 -MeOH, 50:1, v/v). Evaporation of the eluates gave a solid, which was crystallized from petroleum ether to give **11d** (51 mg, 56%), mp 80–82 °C (lit.⁸⁾ 83–84 °C).

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