Preparation of 3-Methyl-4-vinyl-1,2,5-oxadiazole and 3-Methyl-4-vinyl-1,2,5-thiadiazole

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Short and high yielding preparations of 3-Methyl-4-vinyl-1,2,5-oxadiazole (**6a**) and 3-Methyl-4-vinyl-1,2,5-thiadiazole (**6b**) are described.

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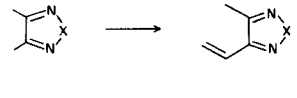


1a X = O
1b X = S

6a X = O
6b X = S

In the course of on going synthetic studies in our laboratories we have had the occasion to investigate the chemistry of the 1,2,5-oxadiazole (furazan) and 1,2,5-thiadiazole (piazthiole) nuclei (1,2). As a result of our initial studies we would like to disclose simple preparations of 3-methyl-4-vinyl-1,2,5-oxadiazole (**6a**) and 3-methyl-4-vinyl-1,2,5-thiadiazole (**6b**).

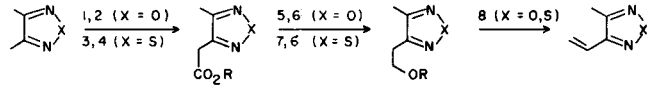
Initial efforts to prepare **6a,b** using the standard, short processes that have been employed for the preparation of other vinyl heterocycles have met with little success (3). For instance, treatment of 3,4-dimethyl-1,2,5-oxadiazole with formaldehyde (formalin, paraformaldehyde) under a wide variety of conditions in both protic and non-protic solvents failed to produce **6a** (4). In contrast, the routes illustrated in Scheme I and detailed below provide effective means of procuring **6a,b** in pure form and in high yield.

Metallation (3e) of 3,4-dimethyl-1,2,5-oxadiazole [3,4-dimethylfurazan **1a** (5)] employing *n*-butyllithium followed by carboxylation of **Ia** with carbon dioxide afforded the known acid **2a** (3e). Fisher esterification followed by lithium aluminum hydride reduction yielded the primary alcohol **4a**. While all direct attempts to eliminate the β-hydroxy group in **4a** failed to give the desired vinyl oxadiazole **6a** cleanly (6), the formation of mesylate **5a** (7) followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded 3-methyl-4-vinyl-1,2,5-oxadiazole (**6a**) in 90% overall yield from **4a**.

Ia X = O
Ib X = S

Although the extension of this same process for use in the preparation of 3-methyl-4-vinyl-1,2,5-thiadiazole appears straightforward, recent studies demonstrated a potential shortcoming. While 3-lithiomethyl-4-methyl-1,2,5-oxadiazole (**Ia**) can be quantitatively generated using *n*-butyllithium a similar treatment of 3,4-dimethyl-1,2,5-thiadiazole (**1b**) (8) results in cleavage of the heterocyclic nucleus (3e). Though this decomposition process has not been thoroughly investigated, it has been postulated that the problems arise not from decomposition of the desired anion, 3-lithiomethyl-4-methyl-1,2,5-thiadiazole **Ib**, but from nucleophilic attack of the alkyllithium reagent at the sulfur atom of the 1,2,5-thiadiazole ring system (3e). Based on this premise, metallation of 3,4-dimethyl-1,2,5-thiadiazole (**1b**) using a non-nucleophilic base, lithium diisopropylamide, was investigated and found satisfactory. Thus, treatment of **1b** with lithium diisopropylamide followed by carboxylation of **Ib** with carbon dioxide afforded the acid **2b** and subsequent treatment with diazomethane gave the ester **3b**. Diisobutylaluminum hydride reduction of ester **3b**, mesylation (7) of the crude alcohol **4b** and subsequent treatment with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) afforded 3-methyl-4-vinyl-1,2,5-thiadiazole **6b** cleanly. Interestingly, agents commonly employed to effect the reduction of an ester group failed to produce the desired alcohol **4b** from **3b** in satisfactory yield (9).

Scheme I



1a X = O
1b X = S

2a X = O, R = H
3a X = O, R = CH_3

4a X = O, R = H
5a X = O, R = SO_2CH_3

6a X = O

2b X = S, R = H
3b X = S, R = CH_3

4b X = S, R = H
5b X = S, R = SO_2CH_3

6b X = S

(1) *n*-BuLi, THF, −78°, 30 minutes; CO_2, −78°, 60 minutes, 84%; (2) MeOH, H^+, 88%; (3) LDA, THF-Et_2O, −110°C, 15 minutes; CO_2, −110° to 25°, 2 hours, 82%; (4) CH_2N_2, Et_2O, 90-100%; (5) $LiAlH_4$, THF, 20°, 2.5 hours, 84%; (6) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°, 30-120 minutes, 90-100%; (7) Dibal-H, toluene-THF, −78° to 20°, 30 minutes, 43%; (8) DBU, THF, 25°, 24 hours, 95%.

EXPERIMENTAL

Melting points were determined on a Hoover uni-melt. Infrared spectra were recorded as thin films or in chloroform on a Beckman IR-33 spectrometer. Proton magnetic resonance (pmr) spectra were recorded in deuteriochloroform with tetramethylsilane as the internal standard on a Varian FT-80A spectrometer; chemical shifts are reported in parts per million (ppm) from tetramethylsilane. Mass spectra were recorded by Mr.

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Robert Drake, University of Kansas, using a Varian CH-5B, and microanalysis were performed by Mr. T. N. Ngvyen, University of Kansas, microanalytical services.

3-Methyl-1,2,5-oxadiazol-4-acetic Acid (**2a**).

The acid was prepared as described (3e) in 84% yield; nmr: δ 2.15 (s, 3H), 3.6 (s, 2H), 8.52 ppm (s, 1H).

3-Methyl-1,2,5-oxadiazol-4-acetic Acid Methyl Ester (**3a**).

A solution of the acid (**2a**, 1.438 g, 10.13 mmoles) in 15 ml of absolute methanol containing 4 drops of concentrated sulfuric acid was stirred for 44 hours before the reaction mixture was quenched with potassium carbonate, filtered and concentrated *in vacuo*. The resulting oil was taken up in methylene chloride, dried (sodium sulfate) and the solvent removed *in vacuo* affording 1.391 g of the ester **3a** (88%); ir (film): 2980, 1740, 1475, 1420, 1320, 1190, 1170, 1020, 950, 750, 690, 630 cm^{-1}; nmr: δ 2.35 (s, 3H), 3.65 (s, 3H, $-CO_2CH_3$), 3.81 (s, 2H); ms (relative intensity): 156 (M^+, 0.5), 155 (4), 141 (0.1), 140 (0.3), 139 (7), 127 (8), 126 (19), 125 (8), 124 (2), 100 (6), 98 (2), 97 (22), 94 (11), 84 (2), 83 (14), 59 (50), 32 (base).

Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.49; H, 5.2; N, 18.3.

3-(β-Hydroxyethyl)-4-methyl-1,2,5-oxadiazole (**4a**).

The ester (**3a**, 1.39 g, 8.9 mmoles) in 20 ml of dry tetrahydrofuran was added dropwise over 15 minutes to a stirred suspension of lithium aluminum hydride (0.342 g, 9.0 mmoles) in 20 ml of tetrahydrofuran under nitrogen at room temperature. The reaction mixture was stirred for an additional 2.5 hours before the cautious, sequential addition of water (0.336 ml), 10% aqueous sodium hydroxide (0.67 ml), and water (1.0 ml). After the suspension had turned white, the solution was filtered through Celite (ether wash), dried (magnesium sulfate) and concentrated *in vacuo* affording 0.956 g of alcohol **4a** (84%); ir (film): 3040 (broad), 2950, 2890, 1600, 1450, 1400, 1375, 1175, 1040, 950 cm^{-1}; nmr: δ 2.35 (s, $-CH_3$, 3H), 2.53 (s, -OH, 1H), 2.83 (t, J = 6 Hz), 3.90 (t, J = 6 Hz); ms: (relative intensity) 110 ($-H_2O$, 0.07), 99 (0.2), 98 (-CHO, 0.2), 97 (6), 84 (0.1), 80 (0.3), 69 (0.2), 58 (3), 57 (0.8), 53 (7), 52 (0.8), 42 (2), 41 (5), 40 (2.8), 31 (base).

Anal. Calcd. for $C_5H_8N_2O_2$: C, 46.87; N, 21.87; H, 6.29. Found: C, 46.78; N, 21.90; H, 6.10.

3-(β-Hydroxyethyl)-4-methyl-1,2,5-oxadiazole Methanesulfonate (**5a**).

The alcohol (**4a**, 0.956 g, 7.47 mmoles) in 40 ml of dry methylene chloride under nitrogen cooled to 0-5° was treated sequentially with triethylamine (11.2 mmoles, 1.5 equivalents, 1.56 ml), methanesulfonyl chloride (8.96 mmoles, 1.2 equivalents, 0.694 ml) and the mixture was stirred at 0° for an additional 2 hours before being poured onto water. The organic phase was washed with 5% hydrochloric acid, 5% sodium bicarbonate, dried (sodium sulfate) and concentrated *in vacuo* affording 1.302 g (84%, generally 90-100%) of mesylate **5a**; ir (film): 2950, 1440, 1275, 1160, 950, 900, 790 cm^{-1}; nmr: δ 2.25 (s, 3H), 2.95 (s, 3H), 3.1 (t, J = 7 Hz), 4.4 (t, J = 7 Hz); ms: (relative intensity) 206 (M^+, 5), 176 (18), 150 (11), 146 (18), 127 (11), 120 (8), 111 (5), 110 (-MsOH, 61), 109 (34), 98 (11), 97 (24), 81 (5), 80 (9), 79 (base), 71 (4), 70 (30), 69 (30), 68 (8), 67 (5), 63 (5), 57 (9), 56 (20), 54 (26), 42 (11), 41 (11), 39 (13), 30 (11).

Anal. Calcd. for $C_6H_{10}N_2O_4S$: C, 34.94; H, 4.89; N, 13.59. Found: C, 35.26; H, 4.80; N, 13.98.

3-Methyl-4-vinyl-1,2,5-oxadiazole (**6a**).

The mesylate (**5a**, 2 mmoles, 412 mg) in 14 ml of dry tetrahydrofuran cooled to 0° was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 mmoles, 0.3 ml) and stirring was continued at 25° for 23 hours before the reaction mixture was poured into water. The organic phase was washed with 1% hydrochloric acid, 5% sodium bicarbonate, brine, dried (magnesium sulfate), and concentrated under reduced pressure (11). Passage of the crude product through a plug of silica gel (50:50 ether:pentane eluant) afforded 213 mg (97%) of vinyl oxadiazole **6a**; ir (film): 1460, 1432, 1380, 1180, 1010, 960, 920, 875 cm^{-1}; nmr: δ 2.38 (3H, s, $-CH_3$), 5.55 (1H, dd, J = 2, 11 Hz), 5.82 (1H, dd, J = 2, 17 Hz), 6.55 (1H, dd, J = 11, 17 Hz); ms: (relative intensity) 110 (M^+, 55), 86 (11), 84 (17), 80 (4), 70 (4), 69 (base), 57 (9), 54 (18), 53 (11), 52 (12), 51 (6), 41 (13), 39 (55), 38 (7), 31 (79); C-13 nmr: δ 151.7, 150.0, 123.7, 121.8, 9.2 uv λ max (heptane): 232 nm (ε = 4340).

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.80; H, 5.58; N, 25.80.

3-Methyl-1,2,5-thiadiazol-4-acetic Acid (**2b**).

3,4-Dimethyl-1,2,5-thiadiazole (**1b**, 1.824 g, 16 mmoles) (8) in 8 ml of 1:1 ether:tetrahydrofuran was added dropwise over 20 minutes to a solution of freshly generated lithium diisopropylamide (16 mmoles) in 40 ml of 1:1 ether:tetrahydrofuran under argon at −110°. The resulting reaction mixture was stirred at −110° for an additional 15 minutes, quenched with excess dry ice and allowed to warm to 25° before being poured into water containing a few drops of 10% sodium hydroxide. The organic phase was washed twice with aqueous sodium hydroxide and the combined aqueous phase was acidified to a *p*H of 1 with 10% aqueous hydrochloric acid and extracted three times with ether. The combined ethereal layer was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* affording 1.69 g (67%, generally 67-82%) of acid **2b** as a white solid, mp 77-78°; ir (chloroform): 3020 (broad), 1715, 1425, 1225, 810 cm^{-1}; nmr: δ 2.52 (s, 3H), 3.95 (s, 2H), 10.9 (s, 1H); ms: (relative intensity) 158 (M^+, 68), 140 (57), 114 (45), 111 (23), 110 (base), 89 (8), 75 (8), 74 (12), 73 (69), 72 (73), 71 (7), 69 (7), 57 (11).

Anal. Calcd. for $C_5H_6N_2O_2S$: C, 37.96; H, 3.82; N, 17.71. Found: C, 38.18; H, 3.89; N, 17.50.

3-Methyl-1,2,5-thiadiazol-4-acetic Acid Methyl Ester (**3b**).

Diazomethane esterification of acid **2b** (1.69 g, 10.6 mmoles) and passage of the crude product through silica gel afforded 1.62 g (92%) of ester **3b**; ir (film): 2970, 1740, 1430, 1330, 1250, 1200, 1150, 1000, 805, 770 cm^{-1}; nmr: δ 2.5 (s, 3H), 3.67 (s, 3H), 3.90 (s, 2H); ms: (relative intensity) 172 (M^+, base), 153 (11), 143 (9), 140 (62), 127 (9), 114 (5), 113 (7), 74 (8), 73 (13), 72 (11), 59 (8).

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68; N, 16.27. Found: C, 41.52; H, 4.70; N, 16.65.

3-(β-Hydroxyethyl)-4-methyl-1,2,5-thiadiazole (**4b**).

The ester (**3b**, 172 mg, 1 mmole) in 4 ml of tetrahydrofuran was added dropwise to a solution of diisobutylaluminum hydride (4.17 ml of 0.48 *M* in toluene, 2 mmoles) cooled to −78° under argon and the resulting reaction mixture was allowed to warm to room temperature before being quenched with water (0.1 ml) and 10% aqueous sodium hydroxide (0.1 ml). After filtration through Celite (ether and methylene chloride wash) the filtrate was dried (magnesium sulfate) and concentrated *in vacuo*. Chromatography (silica gel, 90:10 ether-hexane eluant) afforded 62 mg of alcohol **3b** (43%); ir (film): 3440, 2940, 2890, 1410, 1130, 1040, 810 cm^{-1}; nmr: δ 2.5 (s, 3H), 3.0 (t, J = 6 Hz, 2H), 4.0 (q, J = 6 Hz, 2H); ms: (relative intensity) 144 (M^+, 32), 127 (22), 126 (24), 114 (base), 97 (16), 85 (25), 74 (23), 73 (57), 72 (28), 57 (31).

Anal. Calcd. for $C_5H_8N_2OS$: C, 41.65; H, 5.59; N, 19.43. Found: C, 42.03; H, 5.50; N, 19.30.

3-(β-Hydroxyethyl)-4-methyl-1,2,5-thiadiazole Methanesulfonate (**5b**).

The mesylate **5b** was prepared as described above for **5a** in 84% yield; ir (film): 3030, 2950, 1420, 1340, 1165, 960, 900, 810, 785 cm^{-1}; nmr: δ 2.50 (3H, s), 2.95 (3H, s), 3.28 (2H, J = 7 Hz, t), 4.6 (2H, J = 7 Hz, t); ms: (relative intensity) 222 (M^+, 12), 175 (4), 172 (2), 152 (4), 143 (16), 127 (18), 126 (base), 120 (7), 113 (13), 91 (14), 79 (18), 73 (44), 72 (38), 51 (10).

Anal. Calcd. for $C_6H_{10}N_2O_3S$: C, 32.42; H, 4.54; N, 12.60. Found: C, 32.60; H, 4.50; N, 12.60.

3-Methyl-4-vinyl-1,2,5-thiadiazole (**6b**).

Vinyl thiadiazole **6b** was prepared in 95% yield as described above for **6a** (10); ir (film): 2940, 1840 (weak), 1625 (weak), 1425, 1375, 1355, 1305, 1285, 1170, 1130, 970, 925, 815, 770 cm^{-1}; nmr: δ 2.6 (s, 3H), 6.8 (1H, dd, J = 11, 17 Hz), 6.15 (1H, dd, J = 17, 2 Hz), 5.55 (1H, dd, J = 11, 2 Hz);

ms: (relative intensity) 126 (M^+, base), 113 (26), 111 (12), 85 (31), 79 (34), 73 (33), 72 (34), 57 (51); C-13 nmr: δ 157.3, 157.2, 126.5, 121.2, 15.7; uv λ max (methanol): 285 nm (ε = 9070), 219 nm (ε = 6500).

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(4) In each case 3,4-dimethyl-1,2,5-oxadiazole was recovered unchanged.

(5) 3,4-Dimethyl-1,2,5-oxadiazole is commercially available from ICN Pharmaceuticals, K and K laboratories; for its preparation see: L. C. Behr and J. T. Brent, *Org. Synth.*, Col. Vol. IV, 342 (1963).

(6) Under all conditions tested, alcohol **4a** was recovered unchanged or converted to a number of products including the vinyl-1,2,5-oxadiazole **6a**. For example, treatment of **4a** with potassium *t*-butoxide under protic or aprotic conditions resulted in mixtures of **4a**, **6a**, and 3-[β-*t*-butoxyethyl]-4-methyl-1,2,5-oxadiazole.

(7) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

(8) L. M. Weinstock, P. Davis, B. Handelsman and R. Tull, *ibid.*, **32**, 2823 (1967). We have found that the following precautions and change ensure a simple and convenient preparation of 3,4-dimethyl-1,2,5-thiadiazole: (i) slow, portionwise addition of dimethylglyoxime; (ii) slow, dropwise addition of water; (iii) extraction with pentane substitutes nicely in place of the steam distillation.

(9) Lithium aluminum hydride and sodium bis(2-methoxyethoxy)-aluminum hydride (Red-al) reduction failed to produce the alcohol **4b** in high or reproducible yields.

(10) Vinyl oxadiazole **6a** and vinyl thiadiazole **6b** are volatile.