4-Methyl-1,2,5-oxadiazole-3-carbonitrile in the synthesis of 1,2,5-oxadiazolyl-1,2,4-oxadiazoles

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4-Methyl-1,2,5-oxadiazole-3-carbonitrile reacts with hydroxylamine to form 4-methyl-1,2,5-oxadiazole-3-carboxamidoxime, which turned out to be the useful starting compound in the synthesis of 3-(1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazoles.

Key words: 1,2,5-oxadiazoles, 1,2,4-oxadiazoles, carboxylic anhydrides, cyclization.

Compounds of the 1,2,5-oxadiazole (furazan) series are of constant interest for researchers as biologically active substances.[1] In recent years furazans containing various heterocyclic substituents are attracting attention as modulators of tyrosine kinase activity,[2] antagonists of NK-3 receptors,[3] compounds preventing heart arrhythmia,[4] *etc*. Compounds containing the substituted amidoxime fragment seem to be especially promising as modulators of 2,3-dioxygenase indolamine.[5]

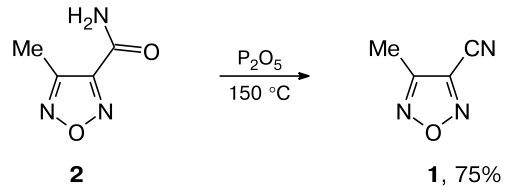
Cyanosubstituted furazans and among them 4-methyl-1,2,5-oxadiazole-3-carbonitrile (**1**) containing the chemically inert methyl group could serve as important starting compounds for the synthesis of the substances listed above. However, although some spectral characteristics and chemical transformations of compound **1** are described,[6] data on the methods for the synthesis of this nitrile are lacking. In the present work we describe the synthesis of this compound and the transformation of its nitrile group into the 1,2,4-oxadiazole cycle.

We have chosen available 4-methyl-1,2,5-oxadiazole-3-carboxamide **2** (see Ref. 7) as the starting compound for the synthesis of nitrile **1**. The transformations of furazancarboxamides, in which trifluoroacetic anhydride was used as a dehydrating agent, were described earlier.[8] The yields in these transformations reach 60—80%. We found that the application of cheaper phosphorus pentaoxide provided cyanofurazan **1** in 75% yield, which is not lower than the yields obtained when trifluoroacetic anhydride is used in the dehydration of other furazancarboxamides (Scheme 1).

4-Methyl-1,2,5-oxadiazole-3-carbonitrile (**1**) is a labile, colorless, and highly volatile liquid. Its structure was proved by the data of elemental analysis, mass spectrometry, and ^{1}H and ^{13}C NMR spectroscopy.

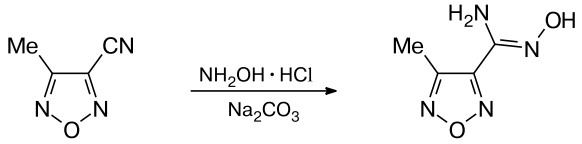
The reaction of nitrile **1** with hydroxylamine hydrochloride affords the corresponding amidoxime **3** in 80% yield (Scheme 2).

Scheme 1



2 **1**, 75%

Scheme 2



1 **3**, 80%

It is known that aromatic and heterocyclic amidoximes are the convenient starting compounds for the synthesis of 1,2,4-oxadiazoles.[9] The synthesis of oxadiazolylfurazans by the reaction of the corresponding amidoximes with acetic[10] and trichloroacetic[11] anhydrides was described. We showed that amidoxime **3** reacts on melting with cyclic succinic, glutaric, and phthalic anhydrides to form acids of the oxadiazole series **4a—c** in moderate yields (Scheme 3).

Melting of amidoxime **3** with chloroacetic anhydride turned out to be inappropriate for the synthesis of chloromethyl-substituted compound **4d**. Oxadiazole **4d** began to decompose intensely on heating of the reaction mixture to 100 °C, and we failed to isolate **4d** in significant amounts from the reaction medium. Therefore, to obtain this compound, we used the two-step synthesis with the isolation of intermediate *O*-acyloxime **5**. In the first step, the reaction of amidoxime **3** with chloroacetic anhydride (chloro-

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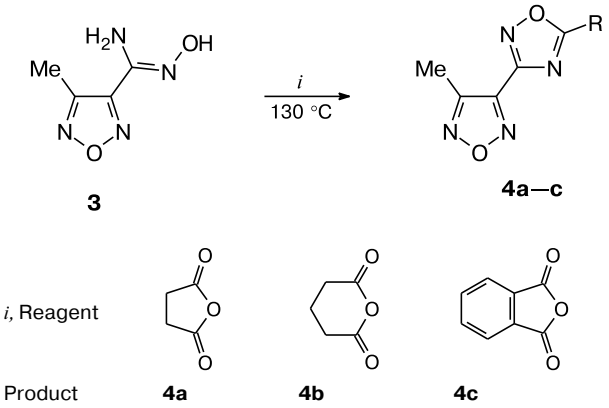
Scheme 3



R = $(CH_2)_2CO_2H$ (**4a**), $(CH_2)_3CO_2H$ (**4b**), $C_6H_4CO_2H$-*o* (**4c**)
Yield (%): 55 (**4a**), 60 (**4b**), 40 (**4c**)

acetic chloranhydride can be used instead of chloroacetic anhydride, the yield of the target *O*-acyl derivative decreases noticeably) affords *O*-acyloxime **5**, which can be isolated (60% yield) and then used in dehydration in toluene with the Dean—Stark receiver to form oxadiazole **4d**. However, it is not necessary to isolate acyloxime **5** from the reaction mixture, but the both steps can be carried out as one procedure with a slight decrease (to 48%) in the yield of the target product (Scheme 4).

Experimental

^{1}H NMR spectra (in $CDCl_3$) were obtained on Bruker WM-250 and Bruker AM-300 instruments with working frequencies of 250 and 300 MHz, respectively. Chemical shifts in the NMR spectra are given in the δ scale relative to $SiMe_4$. Melting points were determined on a Kofler heating stage and were not corrected. Mass spectra (EI) were measured on a Finnigan MAT INCOS 50 instrument with an ionization energy of 70 eV. IR spectra were recorded for KBr pellets on a Specord M-80 instrument.

4-Methyl-1,2,5-oxadiazole-3-carboxamide (**2**) was synthesized by a described procedure.[7]

4-Methyl-1,2,5-oxadiazole-3-carbonitrile (1). A finely triturated mixture of amide **2** (0.76 g, 6 mmol) and P_2O_5 (3 g, 20 mmol) was placed in a Claisen flask with an air condenser. The contents of the flask was heated in an oily bath to 150 °C at 20 Torr, and the receiver was cooled with hard CO_2. Nitrile **1** was obtained as a colorless liquid in a yield of 0.45 g (75%), n_D^{20} 1.4342, d_4^{20} 1.149; b.p. 158 °C. Found (%): C, 44.10; H, 2.80; N, 38.52. $C_4H_3N_3O$. Calculated (%): C, 44.04; H, 2.77; N, 38.62. ^{1}H NMR ($CDCl_3$), δ: 2.50 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 8.07 (CH_3); 107.5, 133.8, 152.5 (3 quaternary C atoms). MS, *m/z* (I_{rel} (%)): 109 $[M]^+$ (64), 97 (16), 79 (100), 68 (57), 57 (95), 44 (54). IR, ν/cm^{-1}: 3000 (C—H); 2250 (CN); 1430 (C=N).

4-Methyl-1,2,5-oxadiazole-3-carboxamidoxime (3). Sodium carbonate (0.21 g, 2 mmol) was added with stirring to a solution of nitrile **1** (0.33 g, 3 mmol) and hydroxylamine hydrochloride (0.21 g, 3 mmol) in a mixture of water (10 mL) and isopropyl alcohol (3 mL). The reaction mixture was kept at room temperature for 1 h, and the precipitate was filtered off, washed with water, dried in air, and recrystallized from methanol. The yield was 0.34 g (80%), colorless crystals with m.p. 170—171 °C. Found (%): C, 33.86; H, 4.30; N, 39.68. $C_4H_6N_4O_2$. Calculated (%): C, 33.80; H, 4.26; N, 39.43. ^{1}H NMR (DMSO-d_6), δ: 2.52 (s, 3 H, CH_3); 6.15 (s, 2 H, NH_2); 10.50 (s, 1 H, OH). MS, *m/z* (I_{rel} (%)): 142 $[M]^+$ (100), 125 (50), 110 (35), 86 (85), 69 (45), 55 (100). IR, ν/cm^{-1}: 3400—3200 (C—H); 1630 (C=N).

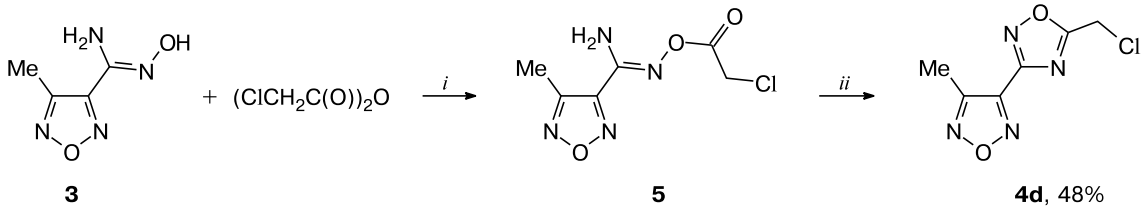
Reactions of amidoxime 3 with acid anhydrides (general procedure). A thoroughly triturated mixture of amidoxime **3** (2.84 g, 20 mmol) and an acid anhydride (20 mmol) was heated in an oily bath to 130 °C and kept at this temperature for 40 min. The reaction mixture was cooled to room temperature, and the product was recrystallized from an appropriate solvent.

3-[3-(4-Methyl-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazol-5-yl]propionic acid (4a). The yield was 2.46 g (55%), colorless crystals, m.p. 105 °C (from benzene). Found (%): C, 42.91; H, 3.65, N, 25.03. $C_8H_8N_4O_4$. Calculated (%): C, 42.86; H, 3.60, N, 24.99. ^{1}H NMR (DMSO-d_6), δ: 2.63 (s, 3 H, CH_3); 2.87 (t, 2 H, CH_2, J = 6.7 Hz); 3.29 (t, 2 H, CH_2, J = 6.7 Hz). MS, *m/z* (I_{rel} (%)): 224 $[M]^+$ (5), 179 (100), 109 (67), 83 (61), 78 (79). IR, ν/cm^{-1}: 3450 (OH); 2900—2600 (CH); 1720 (C=O); 1600 (C=N).

4-[3-(4-Methyl-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazol-5-yl]butyric acid (4b). The yield was 2.86 g (60%), colorless crystals, m.p. 95 °C (from a benzene—hexane (1 : 1) mixture). Found (%): C, 45.60; H, 4.01; N, 23.77. $C_9H_{10}N_4O_4$. Calculated (%): C, 45.38; H, 4.23; N, 23.52. ^{1}H NMR (DMSO-d_6), δ: 2.02 (q, 2 H, CH_2, J = 7.3 Hz); 2.40 (t, 2 H, CH_2, J = 7.3 Hz); 2.63 (s, 3 H, CH_3); 3.13 (t, 2 H, CH_2, J = 7.3 Hz); 12.20 (s, H, OH). MS, *m/z* (I_{rel} (%)): 238 $[M]^+$ (2), 220 (71), 192 (18), 179 (91), 166 (15), 122 (23), 84 (50), 45(100). IR, ν/cm^{-1}: 3100 (OH); 2900 (CH); 1700 (C=O); 1580 (C=N).

2-[3-(4-Methyl-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazol-5-yl]benzoic acid (4c). The yield was 2.18 g (40%), colorless crystals, m.p. 100 °C (from benzene). Found (%): C, 53.15; H, 2.72; N, 20.70. $C_{12}H_8N_4O_4$. Calculated (%): C, 52.94; H, 2.96;

Scheme 4



i. ~20 °C, 24 h; *ii*. Δ, toluene.

N, 20.58. ^{1}H NMR (DMSO-d_6), δ: 2.70 (s, 3 H, CH_3); 7.82 (m, 2 H, Ar); 7.95 (m, 1 H, Ar); 8.05 (m, 1 H, Ar); 13.50 (s, H, OH). MS, m/z (I_{rel} (%)): 272 $[M]^+$ (4), 255 (12), 228 (13), 147 (7), 104 (48), 76 (67), 50 (100). IR, ν/cm^{-1}: 3200 (OH); 2900 (CH); 1700 (C=O); 1560 (C=N).

***O*-Chloroacetyl-4-methyl-1,2,5-oxadiazole-3-carboxamidoxime (5).** Chloroacetic anhydride (6.84 g, 0.04 mol) was added to a solution of amidoxime **3** (5.68 g, 0.04 mol) in toluene (50 mL). The reaction mixture was left for 16 h at room temperature. The precipitate was filtered off, washed with water, and dried in air. The yield was 2.46 g (55%), colorless crystals, m.p. 100 °C (from toluene). Found (%): C, 33.01; H, 3.50, Cl, 16.28; N, 25.90. $C_6H_7ClN_4O_3$. Calculated (%): C, 32.96; H, 3.22; Cl, 16.22; N, 25.63. ^{1}H NMR (DMSO-d_6), δ: 2.56 (s, 3 H, CH_3); 4.62 (s, 2 H, CH_2); 6.84 (s, 2 H, NH_2). IR, ν/cm^{-1}: 3440 (NH_2); 2960 (CH); 1700 (C=O); 1660 (C=N); 800 (C—Cl).

5-Chloromethyl-3-(4-methyl-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazole (4d). The reaction mixture obtained as described in the previous experiment after addition of chloroacetic anhydride (6.84 g, 0.04 mol) to a solution of amidoxime **3** (5.68 g, 0.04 mol) in toluene (50 mL) was left for 16 h. The contents of the flask was refluxed with the Dean—Stark receiver until water stopped to form (3 h). The organic layer was washed with a saturated solution of soda and water and dried with $MgSO_4$. The solvent was distilled off *in vacuo*, and the residue was recrystallized from CCl_4. The yield of compound **4d** was 3.84 g (48%), colorless crystals, m.p. 35 °C (from CCl_4). Found (%): C, 36.01; H, 2.71; Cl, 17.59; N, 27.88. $C_6H_5ClN_4O_2$. Calculated (%): C, 35.92; H, 2.51; Cl, 17.67; N, 27.93. ^{1}H NMR (DMSO-d_6), δ: 2.65 (s, 3 H, CH_3); 5.30 (s, 2 H, CH_2). MS, m/z (I_{rel} (%)): 200 $[M]^+$ (15), 170 (20), 159 (59), 125 (84), 93 (62), 83 (100), 76 (82). IR, ν/cm^{-1}: 3050, 2950 (CH); 1550 (C=N); 800 (C—Cl).

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