Synthesis of 3-methyl-4-(5-R-1*H*-1,2,4-triazol-3-yl)-1,2,5-oxadiazoles

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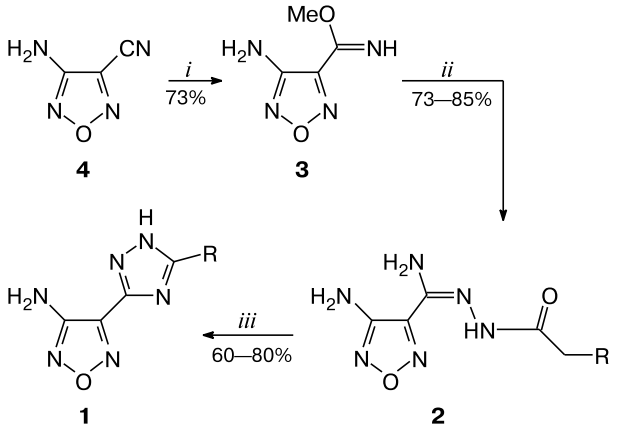
A number of 3-methyl-4-(5-R-1*H*-1,2,4-triazol-3-yl)-1,2,5-oxadiazoles were obtained in high yields by thermal dehydration of acylated 4-methyl-1,2,5-oxadiazole-3-carboxamide hydrazones.

Key words: synthesis, 1,2,5-oxadiazoles, 1,2,4-triazoles, amidrazones, dehydration, cyclization.

1,2,5-Oxadiazole (furazan) derivatives are of permanent interest for synthetic chemists as biologically active compounds.[1] Recently, furazans containing various heterocyclic substituents have attracted attention as AKT kinase inhibitors,[2] antagonists of neurokinin-3 receptors (NK-3),[3] antiarrhythmic agents,[4] *etc*. Earlier, we have published data on the synthesis of 1,2,5-oxadiazole (furazan) derivatives with 1,2,4-oxadiazole[5] and tetrazole substituents[6] at the C(4) atom of the furazan ring. In our continued investigations of the synthesis of hetarylfurazans, we tried to obtain 1,2,4-triazolylfurazans.

Several examples of such structures with an amino group in position 3 of the furazan ring have been documented. Common routes to compounds **1** involve thermal dehydration of acylamidrazones **2** (see Ref. 7) obtained from aliphatic acid hydrazides containing various functional substituents and methyl 3-aminofurazan-4-carboximidate (**3**), which is prepared from 3-amino-1,2,5-oxadiazole-4-carbonitrile (**4**) (Scheme 1).[8]

Scheme 1



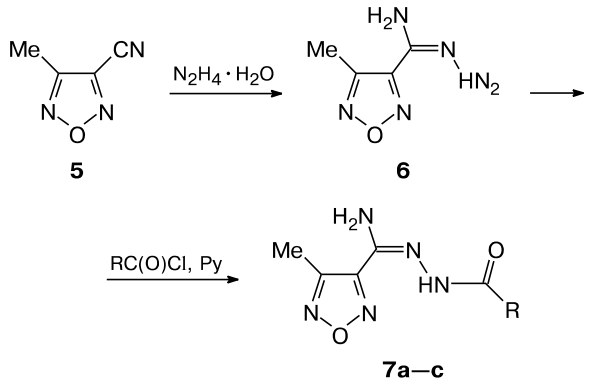
4 **3** **1** **2**

i. MeONa, MeOH; *ii*. $H_2NNC(O)CH_2R$; *iii*. Heating.

This very advantageous synthetic approach has, however, a drawback: aliphatic acid hydrazides are often not commercially available and should be prepared from appropriate acid chlorides, which increases the number of steps in this process.

We developed, with 4-methyl-1,2,5-oxadiazole-3-carbonitrile (**5**) as an example, an alternative approach to the synthesis of triazolyloxadiazoles. Previously,[6] we demonstrated that treatment of nitrile **5** with hydrazine hydrate in isopropyl alcohol affords the corresponding amidrazone **6** in 78% yield. A room-temperature reaction of amidrazone **6** with commercial aliphatic acid chlorides and benzoyl chloride in chloroform in the presence of pyridine gave acylamidrazones **7** in high yields (Scheme 2).

Scheme 2



5 **6** **7a—c**

7	R	Yield (%)
a	Me	68
b	CH_2Cl	81
c	Ph	60

According to ^{1}H NMR data, acyl derivatives **7a—c** are mixtures of two isomers with identical sets of signals for the protons, as shown for other acylamidrazones of the furazan series.[7]

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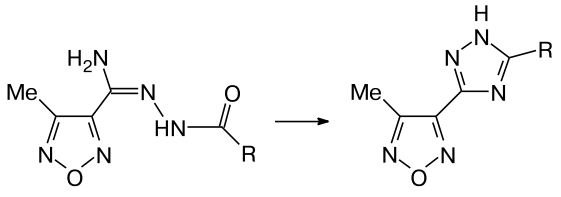
We attempted to dehydrate acylamidrazones **7** by refluxing their solutions in toluene using a Dean—Stark trap for removal of the resulting water. However, the reaction proceeded slowly: even upon 20-h reflux, a great deal of the starting compound remained intact. That is why, we heated acylamidrazones at temperatures above their melting points by 2—3 °C.[7] In this case, the reaction was completed in 5—7 min, giving triazoles **8** in good yields (Scheme 3).

Scheme 3



7 **8**

8	R	Yield (%)
a	Me	72
b	CH_2Cl	84
c	Ph	64

Experimental

^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker AM-300 instruments (250 and 300 MHz, respectively) in DMSO-d_6. Chemical shifts are expressed in terms of the δ scale and referenced to $SiMe_4$. Melting points were determined on a Kofler hot stage and are given uncorrected. Mass spectra were measured on a Finnigan MAT INCOS 50 instrument (EI, 70 eV). IR spectra were recorded on a Specord M80 instrument (KBr pellets).

4-Methyl-1,2,5-oxadiazole-3-carboxamide hydrazone **6** was prepared as described earlier.[6] Commercial acetyl, chloroacetyl, and benzoyl chlorides were employed.

Synthesis of furazanylamidrazones 7 (general procedure). Pyridine (79 mg, 1 mmol) was added to a solution of amidrazone **6** (140 mg, 1 mmol) in dry chloroform (20 mL). Then a solution of an appropriate acid chloride (1 mmol) in chloroform (10 mL) was added with vigorous stirring. The reaction mixture was stirred at room temperature for 2 h and left for 16 h. The precipitate that formed was filtered off, washed with water, and dried in air.

***N′*-Acetyl-4-methyl-1,2,5-oxadiazole-3-carboxamide hydrazone (7a).** Yield 124 mg (68%), colorless crystals, m.p. 150 °C (from Pr^iOH). Found (%): C, 39.68; H, 5.00; N, 38.39. $C_6H_9N_5O_2$. Calculated (%): C, 39.34; H, 4.95; N, 38.24. ^{1}H NMR, δ: 2.27 and 2.29 (both s, 3 H, CH_3), 2.55 and 2.56 (both s, 3 H, CH_3), 6.70 and 6.95 (both s, 2 H, NH_2), 10.35 and 10.50 (both s, H, NH). MS, *m*/*z* (I_{rel} (%)): 183 [M^+] (30), 168 (100), 125 (60), 83 (40). IR, ν/cm^{-1}: 3030 and 2900 (C—H and N—H), 1700 (C=O), 1630 (C=N).

***N′*-Chloroacetyl-4-methyl-1,2,5-oxadiazole-3-carboxamide hydrazone (7b).** Yield 176 mg (81%), colorless crystals, m.p. 190 °C (from ethanol). Found (%): C, 33.35; H, 3.82; N, 32.21, Cl, 16.38. $C_6H_8ClN_5O_2$. Calculated (%): C, 33.11; H, 3.70; N, 32.18, Cl, 16.29. ^{1}H NMR, δ: 2.55 and 2.56 (both s, 3 H, CH_3), 4.13 and 4.62 (both s, 2 H, CH_2), 6.73 and 6.90 (both s, 2 H, NH_2), 10.40 and 10.55 (both s, H, NH). MS, *m*/*z* (I_{rel} (%)): 217 [M^+] (30), 200 (5), 168 (100), 141 (20), 110 (20). IR, ν/cm^{-1}: 3040 and 2960 (NH, NH_2), 1700 (C=O), 1240, 800.

***N′*-Benzoyl-4-methyl-1,2,5-oxadiazole-3-carboxamide hydrazone (7c).** Yield 147 mg (60%), colorless crystals, m.p. 170 °C (from ethanol). Found (%): C, 54.01; H, 4.63; N, 28.72. $C_{11}H_{11}N_5O_2$. Calculated (%): C, 53.87; H, 4.52; N, 28.56. ^{1}H NMR, δ: 2.55 and 2.56 (both s, 3 H, CH_3), 7.33 and 7.53 (both s, 2 H, NH_2); 7.47—7.77 (m, 3 H, Ph); 7.63—7.90 (m, 2 H, Ph); 10.53 and 11.02 (both s, H, NH). MS, *m*/*z* (I_{rel} (%)): 245 [M^+] (50), 168 (90), 125 (50), 83 (80). IR, ν/cm^{-1}: 3040 and 2935 (C—H and N—H), 1700 (C=O), 1560 (C=N).

Synthesis of triazolylfurazans 8 (general procedure). Acylamidrazone **7** (2 mmol) was heated on an oil bath for 5—7 min at a temperature above its melting point by 2—3 °C. On cooling to room temperature, the residue was recrystallized from acetonitrile.

3-Methyl-4-(5-methyl-1*H*-1,2,4-triazol-3-yl)-1,2,5-oxadiazole (8a). Yield 72%, colorless crystals, m.p. 260 °C (from acetonitrile). Found (%): C, 43.87; H, 4.39; N, 42.63. $C_6H_7N_5O$. Calculated (%): C, 43.63; H, 4.27; N, 42.41. ^{1}H NMR, δ: 2.45 (s, 3 H, CH_3), 2.69 (s, 3 H, CH_3), 14.30 (br.s, 1 H, NH). MS, *m*/*z* (I_{rel} (%)): 165 [M^+] (41), 148 (29), 124 (19), 109 (100), 56 (19). IR, ν/cm^{-1}: 3100 (N—H), 2960 (C—H), 1460 (C=N), 1180, 990, 750.

4-(5-Chloromethyl-1*H*-1,2,4-triazol-3-yl)-3-methyl-1,2,5-oxadiazole (8b). Yield 84%, colorless crystals, m.p. 200 °C (from acetonitrile). Found (%): C, 36.23; H, 3.07; N, 35.19, Cl, 17.95. $C_6H_6ClN_5O$. Calculated (%): C, 36.10; H, 3.03; N, 35.39, Cl, 17.76. ^{1}H NMR, δ: 2.62 (s, 3 H, CH_3), 5.00 (s, 2 H, CH_2), 15.30 (br.s, 1 H, NH). MS, *m*/*z* (I_{rel} (%)): 199 [M^+] (30), 182 (26), 143 (100), 123 (34), 69 (36), 55 (58). IR, ν/cm^{-1}: 3110 (N—H), 2930 (C—H), 1420 (C=N), 1040, 890.

3-Methyl-4-(5-phenyl-1*H*-1,2,4-triazol-3-yl)-1,2,5-oxadiazole (8c). Yield 64%, colorless crystals, m.p. 240 °C (from acetonitrile). Found (%): C, 58.14; H, 4.07; N, 31.13. $C_{11}H_9N_5O$. Calculated (%): C, 58.14; H, 3.99; N, 30.82. ^{1}H NMR, δ: 2.70 (s, 3 H, CH_3), 7.55 (m, 3 H, Ph), 8.08 (d, 2 H, Ph, J = 8.1 Hz), 15.15 (br.s, 1 H, NH). MS, *m*/*z* (I_{rel} (%)): 227 [M]$^+$ (56), 186 (53), 170 (45), 118 (69), 105 (80), 77 (100). IR, ν/cm^{-1}: 3000 (N—H), 2920 (C—H), 1490 (C=N), 1430, 1180, 980, 900, 700.

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