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New Synthetic Approaches to Functionally Substituted 4,5-Dihydro-1,2,3-oxadiazole 2-Oxides

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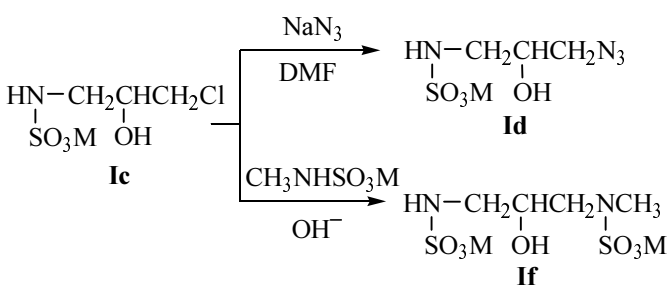
Abstract—A practical procedure has been proposed for the synthesis of functionally substituted 4,5-dihydro-1,2,3-oxadiazole 2-oxides on the basis of sulfamic acid derivatives.

Functionally substituted 4,5-dihydro-1,2,3-oxadiazole 2-oxides were synthesized for the first time by alkaline hydrolysis of the corresponding *N*-nitrosulfamides [1, 2] or functionalized *N*-nitro-2-cyanoethylalkylamines [3]. In both cases, the initial materials were difficultly accessible compounds. Taking into account recent data, such compounds attract interest as nitrogen oxide donors [4], as well as components of gas-generating compositions.

The goal of the present work was to develop a practical procedure for the preparation of both previously known and new functionally substituted 4,5-dihydro-1,2,3-oxadiazole 2-oxides. We previously studied in detail reactions of sulfamic acid salts with epoxy derivatives [5, 6] and found that this transformation can be used to obtain a wide series of the corresponding *N*-(2-hydroxyalkyl)sulfamates (compounds **Ia**–**Ic** and **Ie**) in high yields. Some compounds **I** can be subjected to further modification. For example, by nucleophilic substitution of the chlorine atom in **Ic** we obtained compounds **Id** and **If** (Scheme 1). The latter were brought into further syntheses without additional purification, for it was difficult to separate them from inorganic salts.

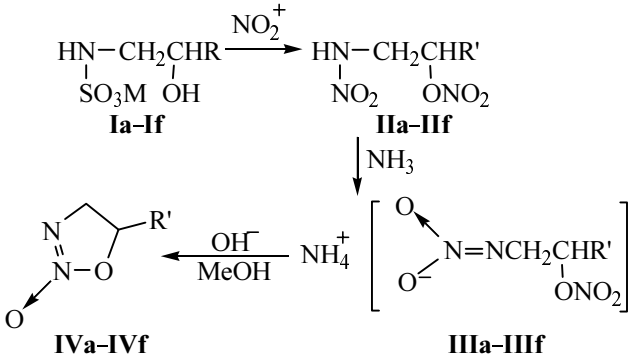
Scheme 1.



M = Na, K.

The next stage of our study was aimed at selecting optimal conditions for nitration of compounds **I**. The nitration was performed using a mixture of nitric and sulfuric acids. Only in the reaction with *N*-(3-azido-2-hydroxypropyl)sulfamate **Id** we used a mixture of nitric acid and acetic anhydride to avoid replacement of the azido group by nitrate moiety. The yields of the corresponding N-nitro amines **II** varied from 70 to 90%. Nitroamines **II** were then converted into ammonium salts **III** by saturation of their solutions in diethyl ether with gaseous ammonia. It should be emphasized that this stage was simultaneously the final stage of purification of compounds **II** from nitrolysis products. Salts **III** were subjected to cyclization in methanol in the presence of an equimolar amount of alkali or in the absence of it. As a result, we isolated a series of 4,5-dihydro-1,2,3-oxadiazole 2-oxides **IV** having functional substituents in the 5-position; the overall yield was about 50% (Scheme 2).

Scheme 2.



M = Na, K; R = R' = H (**a**), CH_2OCH_3 (**b**), CH_2Cl (**c**), CH_2N_3 (**d**); R = CH_2OH, R' = CH_2ONO_2 (**e**); R = $CH_2N(SO_3M)CH_3$, R' = $CH_2N(NO_2)CH_3$ (**f**).

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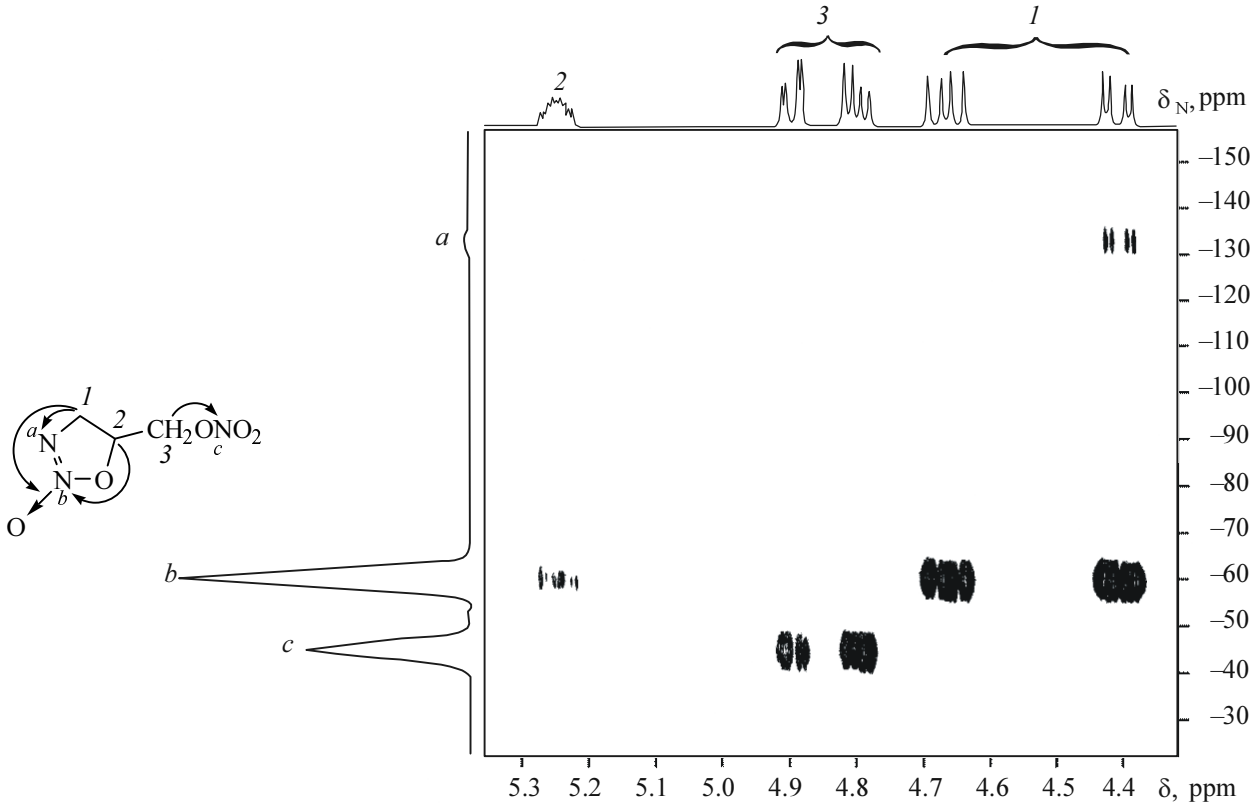

Two-dimensional $^{1}H–^{15}N$ correlation NMR spectrum of 5-nitroxymethyl-4,5-dihydro-1,2,3-oxadiazole 2-oxide (**IVe**) (Bruker DRX-500).

It is notable that the formation of compound **IVe** from ammonium salt **IIIe** was accompanied by replacement of the nitrate moiety exclusively in position *2*. The structure of **IVe** was determined on the basis of the ^{1}H NMR and two-dimensional $^{1}H–^{15}N$ correlation data (see figure). We observed cross peaks between the $O^{15}NO_2$ group and protons in the $CHC\mathbf{H}_2ONO_2$ fragment, between $–N=^{15}N(O)–O–$ and $CH_2C\mathbf{H}O$ protons, and also between protons of the $NC\mathbf{H}_2CHO$ fragment and $–^{15}N=N(O)–O–$ and $–N=^{15}N(O)–O–$.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker WM-250 (250.13 MHz) and Bruker AC-300 (300.13 MHz) instruments from solutions in acetone-d_6 using HMDS as internal reference. The ^{15}N NMR spectrum and the two-dimensional correlation spectrum were obtained on a Bruker DRX-500 spectrometer.

5-Chloromethyl-4,5-dihydro-1,2,3-oxadiazole 2-oxide (IVc). Potassium *N*-(3-chloro-2-hydroxypropyl)-sulfamate (**Ic**), 8.7 g (38 mmol), was added to a mixture of 14 ml of sulfuric acid (d^{20} = 1.820 g/cm^3), 21 ml of 98% nitric acid, and 7 ml of chloroform, cooled to –25 to –30°C. The mixture was stirred for 50 min at that temperature, poured into 130 ml of an ice–water mixture, and extracted with ethyl acetate (3 × 25 ml). The extract was washed with water (3 × 25 ml) and evaporated under reduced pressure. The residue was dissolved in 140 ml of anhydrous diethyl ether, and the solution was saturated with gaseous ammonia until crystalline ammonium salt **IIIc** separated. The precipitate was filtered off and dried on a filter. Yield 6.04 g (28 mmol, ~74%). Salt **IIIc** was dissolved in a mixture of 70 ml of methanol and 1.83 g (33 mmol) of sodium hydroxide. The mixture was left to stand for 6 h at 45–48°C and evaporated under reduced pressure. The residue was treated with diethyl ether (3 × 20 ml), and the extract was washed with 20 ml of water and evaporated under reduced pressure. Yield of **IVc** 2.95 g (56%), n_D^{20} = 1.5013 [3]. ^{1}H NMR spectrum, δ, ppm: 3.84 d.d (2H, CH_2Cl, J = –9.7, 5.3 Hz), 4.43 d.d (1H, $NC\mathbf{H}_2CH$, J = –13.3, 5.3 Hz), 4.63 d.d (1H, $NC\mathbf{H}_2CH$, J = –17.7, 9.7 Hz), 5.18 m (1H, CHO).

Compounds **IVa**, **IVb**, and **IVe** were synthesized in a similar way.

4,5-Dihydro-1,2,3-oxadiazole 2-oxide (IVa). Yield 44%, n_D^{20} = 1.4808 [1, 2]. ^{1}H NMR spectrum, δ, ppm: 4.3–4.7 m (4H, NCH_2CH_2O).

5-Methoxymethyl-4,5-dihydro-1,2,3-oxadiazole 2-oxide (IVb) was purified by vacuum distillation, bp 83–84°C (0.7–1.0 mm). Yield 44%. ^{1}H NMR spectrum, δ, ppm: 3.35 s (3H, OCH_3), 3.58 d.d (2H, C**H**$_2$OCH$_3$, *J* = –9.4, 5.1 Hz), 4.23 d.d (1H, NC**H**$_2$CH, *J* = –17.0, 6.8 Hz), 4.50 d.d (1H, NC**H**$_2$CH, *J* = –17.0, 9.3 Hz), 4.96 m (1H, CHO). Found, %: C 36.47; H 6.11; N 21.28. $C_4H_8N_2O_3$. Calculated, %: C 36.36; H 6.10; N 21.20.

5-Nitroxymethyl-4,5-dihydro-1,2,3-oxadiazole 2-oxide (IVe) was isolated by recrystallization from ethanol. Yield 51%, mp 73–74°C, d^{20} = 1.73–1.74 g/cm^3. ^{1}H NMR spectrum, δ, ppm: 4.41 d.d (1H, NC**H**$_2$CH, *J* = –20.1, 5.6), 4.66 d.d (1H, NC**H**$_2$CH, *J* = –20.1, 10.0 Hz), 4.80 d.d (1H, CH_2ONO_2, *J* = –12.4, 6.3 Hz), 4.90 d.d (1H, CH_2ONO_2, *J* = –12.9, 2.6 Hz), 5.24 m (1H, CHO). ^{15}N NMR spectrum, δ_N, ppm: –44.6 s (O–$^{14}NO_2$), –59.7 s [–N=^{14}N(O)–O–], –131.7 s [–^{14}N=N(O)–O–]. Found, %: C 22.23; H 3.54; N 25.85. $C_3H_5N_3O_5$. Calculated, %: C 22.09; H 3.09; N 25.77.

5-Azidomethyl-4,5-dihydro-1,2,3-oxadiazole 2-oxide (IVd). Potassium *N*-(3-chloro-2-hydroxypropyl)-sulfamate (**Ic**), 20 g (88 mmol), was added to a solution of 11 g (170 mmol) of sodium azide in 90 ml of DMF, and the mixture was heated for 2.5 h at 100–105°C under stirring. The mixture was then evaporated, the residue was dissolved in 40 ml of boiling methanol, the solution was cooled, and 70 ml of diethyl ether was added. The precipitate was filtered off and dried on a filter. The isolated material, 29.5 g, was a mixture of *N*-(3-azido-2-hydroxypropyl)sulfamate **Id** and inorganic salts. It was dissolved in a mixture of 24 ml of 98% nitric acid and 75 ml of acetic anhydride, cooled to –15 to –20°C. The mixture was stirred for 1 h at that temperature, poured into 180 ml of an ice–water mixture, and extracted with ethyl acetate (1 × 90 ml and 2 × 45 ml). The extract was evaporated under reduced pressure, the residue was dissolved in 180 ml of anhydrous diethyl ether, and gaseous ammonia was passed through the solution until solid material no longer separated. The precipitate was filtered off, dried on a filter, and dissolved in 180 ml of methanol. The solution was heated for 6 h at 45–48°C and evaporated under reduced pressure. The residue was extracted with diethyl ether (3 × 45 ml), and the extract was washed with water (45 ml) and evaporated under reduced pressure. Yield of compound **IVd** 5.65 g (45%, calculated on the initial compound **Ic**), n_D^{20} = 1.4938 [3]. ^{1}H NMR spectrum, δ, ppm: 3.62 d.d (2H, CH_2N_3, *J* = –17.2, 8.0 Hz), 4.17 d.d (1H, NC**H**$_2$CH, *J* = –20.6, 7.5 Hz), 4.48 d.d (1H, C**H**$_2$CH, *J* –20.0, 9.7 Hz), 4.98 m (1H, CHO).

5-(Methylnitramino)methyl-4,5-dihydro-1,2,3-oxadiazole 2-oxide (IVf). Sulfamate **Ic**, 6 g (26.4 mmol), and potassium methylsulfamate, 4.32 g (29 mmol), were dissolved in 16 ml of water heated to 40°C, and 1.48 g (26.4 mmol) of potassium hydroxide was added. The mixture was stirred for 40 min, adjusted to pH 8–10 by adding hydrochloric acid or potassium hydroxide, heated to 50°C, kept for 70 h at that temperature, and evaporated. The residue, 11.32 g, was dissolved in a mixture of 12 ml of sulfuric acid (d^{20} = 1.820 g/cm^3) and 28 ml of 98% nitric acid, cooled to –25 to –30°C, and the mixture was vigorously stirred for 40 min, poured into 160 ml of an ice–water mixture, and extracted with ethyl acetate (3 × 30 ml). The extract was washed with water (6 × 30 ml) and evaporated, the residue was dissolved in 150 ml of anhydrous diethyl ether, and gaseous ammonia was passed through the solution until solid material no longer separated. The precipitate of ammonium salt **IIIf** was filtered off and dried on a filter. The product, 4.5 g, was dissolved in 70 ml of methanol, 0.97 g of sodium hydroxide was added, and the mixture was kept for 6 h at 48–50°C and evaporated under reduced pressure. The residue was extracted with ethyl acetate (2 × 25 ml), and the extract was washed with water (2 × 20 ml) and evaporated under reduced pressure to isolate 2.76 g of crude compound **IVf**. Recrystallization from 30 ml of ethanol afforded 1.67 g (36%, calculated on the initial compound **Ic**) of oxadiazole **IVf** with mp 79.5–80.5°C, d^{20} = 1.56–1.57 g/cm^3. ^{1}H NMR spectrum, δ, ppm: 3.47 s (3H, NCH_3), 4.16 d.d (1H, C**H**$_2$NCH$_3$, *J* = –14.3, 8.8 Hz), 4.30 m (2H, NC**H**$_2$CH, C**H**$_2$NCH$_3$), 4.65 d.d (1H, NC**H**$_2$CH, *J* = –16.6, 9.4 Hz), 4.24 m (1H, CHO). Found, %: C 27.34; H 4.62; N 31.84. $C_4H_8N_4O_4$. Calculated, %: C 27.28; H 4.58; N 31.81.

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