Russian Journal of Organic Chemistry, Vol. 41, No. 12, 2005, pp. 1802–1805. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 12, 2005, pp. 1838–1841.

Reactions of Furoxandicarbaldehyde Dioxime with Dehydrating Agents

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Received November 11, 2004

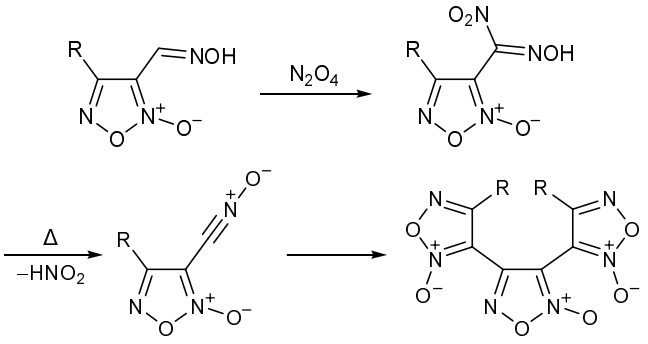
Abstract—Dehydration of furoxan-3,4-dicarbaldehyde dioxime by the action of thionyl chloride or trifluoroacetic anhydride in the presence of a base under certain conditions can be stopped at the stage of formation of 4(3)-hydroxyiminomethylfuroxan-3(4)-carbonitrile.

In the recent years, much attention is given to furoxan derivatives due to their ability to generate under physiological conditions nitrogen(II) oxide, which is the most important mediator in cardiovascular, immune, and nervous systems. Nitrogen(II) oxide donors have long been used for successful treatment of cardiovascular diseases. The scope of application of these compounds has extended considerably, and it now includes treatment of nervous, sexual, and gastrointestinal disorders, enhancement of immunity, and regulation of tumor growth [1].

According to the results of recent studies [1, 2], the most efficient nitrogen(II) oxide donors are furoxan trimers obtained by dimerization of furoxancarbonitrile oxides; the latter were generated in turn by heating products obtained by nitration of 4-substituted furoxan-3-carbaldehyde oximes with dinitrogen tetraoxide N_2O_4 (Scheme 1).

We were interested in the preparation of one more representative of this series of compounds, 4(3)-hydroxyiminomethylfuroxan-3(4)-carbonitrile, by dehydration of furoxan-3,4-dicarbaldehyde (*E*,*E*)-dioxime (**I**). It was shown previously that dehydration of dioxime **I** with excess $SOCl_2$ on slight heating leads to 4-cyanofuroxan-3-carboxamide (**III**) (Scheme 2); under these conditions, the oxime moiety in position *4* of molecule **I** is dehydrated to cyano group, while Beckmann rearrangement of the oxime moiety in position *3* gives carboxamide group. When the reaction was carried out at 70°C, the only product was furoxan-3,4-dicarbonitrile (**IV**) [3]. Presumably, chlorosulfinyl derivative **II** is formed as intermediate product. This scheme suggests that, under certain conditions, the reaction can be stopped at the stage of formation of 4(3)-hydroxyiminomethylfuroxan-3(4)-carbonitrile (**V**).

Scheme 1.



R = Ph, Me, Pr, $ClCH_2$, $HOCH_2$, EtO, PhO.

In fact, by treatment of dioxime **I** with 6 equiv of thionyl chloride at 50–55°C over a period of 5–6 min and subsequent extraction of the product into carbon tetrachloride we isolated a substance with mp 92–96°C (Scheme 3). Its ^{1}H NMR spectrum contained two signals at δ 8.32 and 7.90 ppm, which belong to the CH proton, and two signals at δ 13.02 and 12.90 ppm, which were assigned to the oxime proton; the signal intensity ratio was about 1:2. In the IR spectrum of the product we observed absorption bands at 1640, 1440, and 1020 cm^{-1}, which are typical of furoxan ring, and bands at 2280 and 3380 cm^{-1}, the latter corresponding to the oxime OH group. These findings, in combination with the data of elemental analysis, allowed us to assign the structure of 4(3)-hydroxyiminomethylfuroxan-3(4)-carbonitrile (**V**) to the isolated product. The yield was about 15%.

Product **V** showed in the ^{13}C NMR spectrum eight signals at δ_C 151.67, 136.84, 133.45, 132.66, 111.94,

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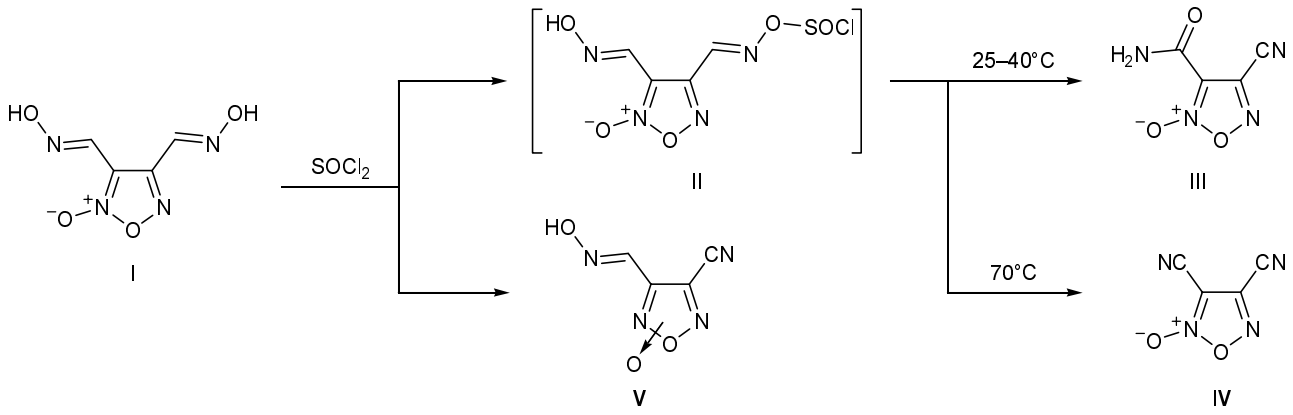
Scheme 2.



108.32, 106.87, and 95.66 ppm. By comparison with the ^{13}C NMR spectra of 4-aminofuroxan-3-carbaldehyde and 4-aminofurazan-3-carbaldehyde [4] and calculated spectra (using ABC program) we assigned the signals with δ_C 151.67, 133.45, 106.87, and 95.66 ppm to isomer **Va**, and those with δ_C 136.84, 132.66, 111.94, and 108.32 ppm, to **Vb**.

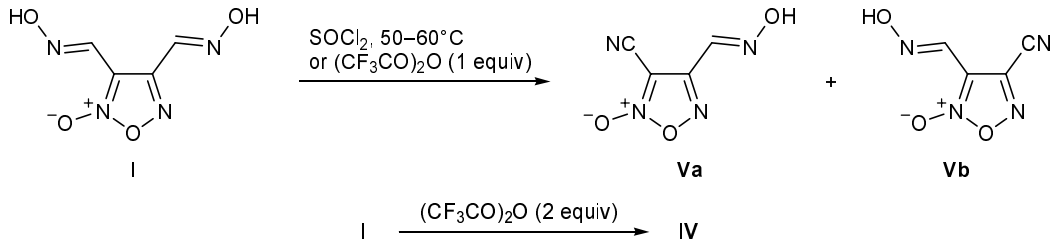
Taking into account published data on the effect of *N*-oxide moiety on the position of signals from side-chain protons [5], the signals at δ 7.80 and 12.90 ppm in the ^1H NMR spectrum were assigned to isomer **Va**, and those at δ 8.32 and 12.95 ppm, to isomer **Vb**. Thus the isolated product was a mixture of two isomers **Va** and **Vb** at a ratio of about 2:1. Unfortunately, we failed to separate the isomers or displace the equilibrium toward one of these, e.g., by heating their mixture in boiling carbon tetrachloride or toluene.

After extraction of cyanofuroxan **V** with carbon tetrachloride, the mixture contained 4-cyanofuroxan-3-carboxamide (**III**) which was identified by comparing with an authentic sample prepared independently.

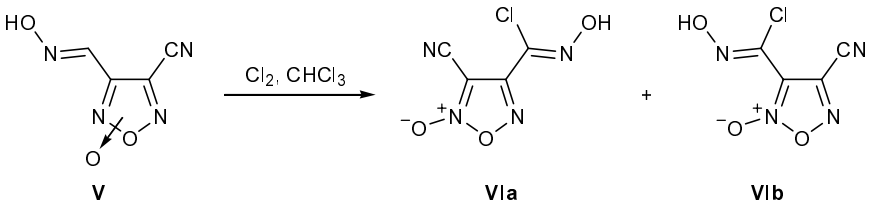
It is known that (*E*)-aldehyde oximes are successfully converted into the corresponding nitriles by the action of trifluoroacetic anhydride in the presence of pyridine [6]. This system turned out to be suitable for dehydration of dioxime **I** as well. Depending on the **I**–$(CF_3CO)_2O$ ratio, the reaction stops at the stage of formation of 4(3)-hydroxyminomethylfuroxan-3(4)-carbonitrile (**V**) or gives furoxan-3,4-dicarbonitrile. As previously, furoxan **V** was also isolated as a mixture of isomers; the yield and isomer ratio depended on the temperature: at 0–5°C, the yield was ~ 40%, and isomer **Vb** prevailed (according to the ^1H NMR data). Raising the temperature did not increase the yield, but increased the fraction of isomer **Va**. In addition, an appreciable amount of furoxan-3,4-dicarbonitrile was detected in the reaction mixture by TLC.

Chlorination of cyanofuroxan **V** (a mixture of isomers at a ratio of 3:2) with gaseous chlorine in chloroform afforded a mixture of isomeric 4(3)-chloro(hydroxymino)methylfuroxan-3(4)-carbonitriles **VIa** and **VIb** in an overall yield of 90% (Scheme 4). During the process, a solid material separated from the reaction mixture. Recrystallization of this product from $CHCl_3$–CCl_4 (1:1) gave a substance with mp 162–163°C. According to the ^1H and ^{13}C NMR data, 3-chloro(hydroxymino)methylfuroxan-4-carbonitrile (**VIb**) prevailed among the isomeric products. The ^1H NMR spectrum contained a strong signal at δ 13.95 ppm and a weak signal at δ 13.70 ppm, corresponding to the NOH proton of **VIb** and **VIa**, respectively. In the ^{13}C NMR spectrum, four signals at δ_C 151.30, 125.32, 107.54, and 98.28 ppm were present. After separation of the solid product, the solution contained a mixture

Scheme 3.



Scheme 4.



of isomers **VIa** and **VIb**, the former prevailing: the intensity ratio of the signals at δ 13.95 and 13.70 ppm (NOH) in the ^{1}H NMR spectrum was 2:3.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu FTIR 8400 spectrometer in KBr. The ^{1}H NMR spectra were obtained on a Perkin–Elmer R-12 instrument (60 MHz) from solutions in acetone-d_6 or DMSO-d_6; the chemical shifts were measured relative to hexamethyldisiloxane as internal reference. The elemental compositions were determined on a Hewlett–Packard 185B CHN analyzer. Thin-layer chromatography was performed on Silufol UV-254 plates; spots were visualized under UV light.

Furoxan-3,4-dicarbaldehyde dioxime (I). Nitromethane, 108 ml (2.0 mol), was slowly added (over a period of 1.5 h) to a solution of 120 g (3.00 mol) of sodium hydroxide in 240 ml of water, heated to 50–55°C. The mixture was heated to 60°C, kept for 1 h at that temperature, cooled to 0°C, and acidified to pH ~1 by adding concentrated hydrochloric acid (about 270 ml) at such a rate that the temperature did not exceed 10°C. The mixture was cooled to 0°C, and the precipitate was filtered off, thoroughly squeezed, and added in small portions under vigorous stirring at 10–15°C to 420 ml of concentrated sulfuric acid. The mixture was kept for 30 min, poured onto ice, and left overnight in a refrigerator. The colorless crystals were filtered off and dried at 50°C. Yield 31.6 g (18%), mp 157°C. Recrystallization from 260 ml of dichloroethane–dioxane (1:1) gave 21.5 g (12%) of compound **I** with mp 168°C. IR spectrum, ν, cm^{-1}: 3298, 1627, 1601, 1559, 1499, 1420, 1399, 1319, 1261, 1054, 996, 920, 904, 853, 731, 703, 658. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 12.4 and 12.35 (NOH), 8.2 and 8.5 (CH). Found, %: C 27.91; H 2.71; N 32.77. $C_4H_4N_4O_4$. Calculated, %: C 27.92; H 2.34; N 32.55.

Dehydration of furoxan-3,4-dicarbaldehyde dioxime (I) with thionyl chloroide. Compound **I**, 16.5 g (10 mmol), was added to 42 ml (60 mmol) of thionyl chloride under vigorous stirring at room temperature. The resulting suspension was heated to 60°C over a period of 10 min, kept for 5–8 min at that temperature, cooled, and left to stand on exposure to air until volatile compounds escaped completely. The reddish–yellow solid residue was treated with 50 ml of carbon tetrachloride. Removal of the solvent left 2.15 g (14%) of 4(3)-hydroxyiminomethylfuroxan-3(4)-carbonitrile (**V**), mp 92–96°C. IR spectrum, ν, cm^{-1}: 3368, 2259, 1624, 1472, 1425, 1317, 1260, 1138, 1036, 1003, 918, 806, 775, 692. ^{1}H NMR spectrum, δ, ppm: 12.95 and 12.90 (NOH), 8.32 and 7.8 (CH). Found, %: C 30.7; H 1.1; N 35.7. $C_4H_2N_4O_3$. Calculated, %: C 31.2; H 1.3; N 36.4.

The solid residue remaining after treatment with carbon tetrachloride was recrystallized from water to isolate 2.8 g (19%) of 4-cyanofuroxan-3-carboxamide (**III**), mp 186°C [3]. IR spectrum, ν, cm^{-1}: 3396, 3229, 2257, 1717, 1622, 1504, 1489, 1382, 1286, 1069, 1032, 839, 791, 754. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.55 and 8.35 (NH_2). Found, %: C 32.04; H 1.55; N 36.19. $C_4H_2N_4O_3$. Calculated, %: C 31.18; H 1.31; N 36.36.

Dehydration of furoxan-3,4-dicarbaldehyde dioxime (I) with trifluoroacetic anhydride in the presence of pyridine. *a. At 0–5°C.* Trifluoroacetic anhydride, 17 ml (100 mmol), was added dropwise over a period of 1.5 h under stirring at 0–5°C to a solution of 15 g (9 mmol) of furoxan **I** in a mixture of 60 ml of dioxane and 29 ml (36 mmol) of anhydrous pyridine. The mixture was stirred for 2–2.5 h at that temperature and poured into cold water, the precipitate was filtered off and dissolved in 25–30 ml of diethyl ether, and the solution was washed first with 1–2% hydrochloric acid and then with water. After removal of the solvent, the solid residue was recrystallized from carbon tetrachloride to obtain 5.5 g (40%) of 4(3)-hydroxyiminomethylfuroxan-3(4)-carbonitrile (**V**), mp 102–104°C. IR spectrum, ν, cm^{-1}: 3368, 2259, 1624, 1472, 1425, 1317, 1260, 1138, 1036, 1003, 918, 806, 775, 692. ^{1}H NMR spectrum, δ, ppm: 12.95 and 12.90 (NOH), 8.32 and 7.8 (CH). Found, %: C 31.03; H 1.02; N 36.67. $C_4H_2N_4O_3$. Calculated, %: C 31.18; H 1.31; N 36.36.

b. At 18–20°C. The reaction was carried out as described above in *a*, but the reaction mixture was then allowed to warm up to room temperature and was kept for 20 h. Yield of compound **V** 40%, mp 104–105°C. ^{1}H NMR spectrum, δ, ppm: 13.02 and 12.90 (NOH), 8.32 and 7.90 (CH). Found, %: C 30.93; H 0.97; N 36.63. $C_4H_2N_4O_3$. Calculated, %: C 31.18; H 1.31; N 36.36.

3(4)-Chloro(hydroxymino)methylfuroxan-4(3)-carbonitrile (VI). Furoxan **V**, 2 g (13 mmol), was dissolved in 70 ml of chloroform, the solution was cooled to 5°C, and gaseous chlorine was passed through a solution over a period of 2 h (until the initial compound disappeared according to the TLC data). The precipitate was filtered off, washed with water, dried, and recrystallized from $CHCl_3$–CCl_4 (1:1). Yield 0.4 g (16%), mp 162–163°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 13.95 (NOH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 151.30, 125.32, 107.54, 98.28. Found, %: C 25.26; H 0.90; Cl 18.52; N 29.38. $C_4HClN_4O_3$. Calculated, %: C 25.48; H 0.53; Cl 18.81; N 29.72.

Removal of the solvent from the filtrate gave 1.85 g (75%) of a substance with mp 120–125°C. IR spectrum, ν, cm^{-1}: 3298, 2360, 2264, 2042, 1628, 1515, 1475, 1417, 1319, 1171, 1145, 1115, 1086, 1049, 1022, 939, 912, 829, 813, 754. ^{1}H NMR spectrum, δ, ppm: 13.95 and 12.90. Found, %: C 25.69; H 0.53; Cl 18.48; N 29.55. $C_4HClN_4O_3$. Calculated, %: C 25.48; H 0.53; Cl 18.81; N 29.72.

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