Synthesis of nitroxyalkylammonium nitrates

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A method for *O*-nitration of amino alcohols with a non-detonating mixture of nitric acid with dichloromethane has been proposed. The target crystalline products were precipitated from the reaction mixture by acetic anhydride.

Key words: nitroxyalkylammonium nitrates; amino alcohols; *O*-nitration; concentration limits of detonation; explosion-proof process.

2-Nitroxyethylammonium nitrate (**1**), which is known as a rather powerful explosive,[1] was prepared as early as 1929 by treating monoethanolamine with an excess of concentrated nitric acid.[2] However, the procedure used to isolate this compound[2] is dangerous and not very suitable even for laboratory practice, not only because this compound is explosive, but, most of all, because nitric acid forms explosive mixtures with organic compounds.

Nevertheless, this method was later used[3] for preparing a number of nitroxyalkyl- and nitroxyarylammonium nitrates and, after mild neutralization with sodium carbonate, for preparing the corresponding nitrates of amino alcohols. More recently, compound **1** has attracted attention, since it can be used for the synthesis of *N*-(2-nitroxyethyl)nicotinamide (nicorandyl),[4—6] a new highly efficient medicine, which is finding increasing application for treating stenocardia and heart incompetence.[7,8] In this connection we developed a safer general method for preparing nitroxyalkylammonium nitrates.

These salts are poorly soluble in halogen-containing organic solvents, which allowed us to use these solvents for the nitration of amino alcohols with nitric acid and for direct isolation of the target products from the reaction mixture.

To prepare nitrating mixtures we chose low-boiling and relatively non-toxic dichloromethane, which dissolves HNO_3 with practically no heat evolution. Previously we developed a method for determining the concentration thresholds of detonation of liquid homogeneous mixtures of explosives.[9] We used this method to choose a non-detonating mixture: solutions of nitric acid (d_4^{20} = 1.510) in dichloromethane that contain more than 87 % CH_2Cl_2 cannot detonate under normal conditions. On the other hand, these solutions possess relatively high nitrating ability with respect to aliphatic amino alcohols. When monoethanolamine, 3-amino-1-propanol, 1,3-diamino-2-propanol, or tris(hydroxymethyl)aminomethane is added at 0—5 °C to a 10 % solution of HNO_3 in CH_2Cl_2, and the resulting mixture is stirred for 15 min, the target nitroxyalkyl nitrates are separated from the reaction mixture as oils that contain water formed during *O*-nitration, in addition to the major compound. When acetic anhydride in an amount sufficient to bind the water is added to the reaction mixture, the target products precipitate as crystalline solids and can be separated by ordinary filtration.

Experimental

^1H NMR spectra were recorded on an NMR spectrometer with a superconducting magnet (294 MHz) designed and produced at the Institute of Chemical Physics in Chernogolovka of the RAS.

2-Nitroxyethylammonium nitrate (1). A solution of monoethanolamine (1.2 g) in CH_2Cl_2 (5 mL) was added dropwise over a period of 20 min to a cooled mixture of HNO_3 (3.8 g) and CH_2Cl_2 (25 mL). The temperature of the bath was maintained in the range 0—5 °C. Then the reaction mixture was stirred at this temperature for 15 min, acetic anhydride (3 mL) was added dropwise, and the mixture was stirred for an additional 15 min. The precipitate was separated and dried in a vacuum desiccator over P_2O_5 to give 3.1 g (91.2 %) of compound **1**, m.p. 100—102 °C. After recrystallization from EtOH, the yield of compound **1** was 69—72 %, m.p. 102—103 °C (*cf.* Refs. 1—3: m.p. 102—103 °C), d_4^{20} = 1.62. ^1H NMR (CD_3CD_2OD, TMS), δ: 3.4 (t, 2 H, CH_2, ^3J = 5 Hz); 4.8 (t, 2 H, CH_2, ^3J = 5 Hz); 5.3 (br.s, NH_2).

3-Nitroxypropylammonium nitrate (2) was prepared from 3-amino-1-propanol (3 g) and HNO_3 (7.56 g) by the procedure described above for the preparation of compound **1**. Yield 5.54 g (75.7 %), m.p. 62—63 °C, d_4^{20} = 1.51. Found (%): C, 19.51; H, 4.87; N, 23.10. $C_3H_9N_3O_6$. Calculated (%): C, 19.67; H, 4.95; N, 22.94. ^1H NMR (CD_3CD_2OD, TMS), δ: 2.15 (q, 2 H, CH_2, ^3J = 6.8 Hz); 3.13 (t, 2 H, CH_2, ^3J = 6.8 Hz); 4.62 (t, 2 H, CH_2, ^3J = 6.5 Hz); 5.24 (br.s, NH_2).

2-Nitroxytrimethylenediammonium dinitrate (3). At 0—5 °C, 1,3-diamino-2-propanol (2.7 g) was slowly added to

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a solution of HNO_3 (8.5 g) in CH_2Cl_2 (57.8 mL). The mixture was stirred at this temperature for 15 min, acetic anhydride (3 mL) was added, and the mixture was stirred for an additional 15 min. The precipitate was separated, dried in a vacuum desiccator over P_2O_5, and recrystallized from EtOH to give 3.9 g (50 %) of compound **3**, m.p. 122—123 °C, d_4^{20} = 1.60. Found (%): C, 13.67; H, 4.31; N, 26.38. $C_3H_{11}N_5O_9$. Calculated (%): C, 13.79; H, 4.25; N, 26.81. ^1H NMR (CD_3OD, TMS), δ: 3.1 (4 H, CH_2, AB-pattern, $\Delta\nu$ = 54.4 Hz, $^2J_{gem}$ = −13 Hz, $^3J_1$ = 3 Hz, $^3J_2$ = 8 Hz); 4.13 (m, H, CH, $^3J_1$ = 3 Hz, $^3J_2$ = 8 Hz); ~4.9 (br.s, NH_2).

Tris(nitroxymethyl)methylammonium nitrate (4) was prepared from tris(hydroxymethyl)aminomethane (2.42 g) and HNO_3 (7.56 g) by the procedure described for the preparation of compound **3**. Yield 4.76 g (74.6 %), m.p. 110—111 °C, d_4^{20} = 1.72. Found (%): C, 14.98; H, 2.76; N, 21.90. $C_4H_9N_5O_{12}$. Calculated (%): C, 15.05; H, 2.84; N, 21.94. ^1H NMR (CD_3OD, TMS), δ: 4.85 (s, 6 H, CH_2); ~5.0 (br.s, NH_2).

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