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Note

A highly chemoselective reduction of isosorbide-2,5-dinitrate mediated by tetrathiomolybdate

Debjani Bhar & Srinivasan Chandrasekaran*
Department of Organic Chemistry,
Indian Institute of Science,
Bangalore 560 012, India

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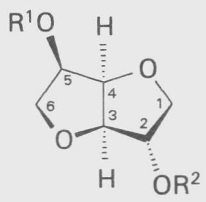
In an interesting reaction mediated by benzyltriethylammonium tetrathiomolybdate, $[(PhCH_2NEt_3)_2MoS_4]$ isosorbide-2,5-dinitrate undergoes selective reduction to isosorbide- 5-mono-nitrate in good yield.

1,4:3,6-Dianhydro-D-glucitol-2,5-dinitrate[1] **2** (isosorbide- 2,5-dinitrate) is a well established compound used in the treatment of coronary diseases. It is rapidly metabolized in the organism and 1,4:3,6-dianhydro-D -glucitol-2-nitrate **3a** (isosorbide-2-nitrate) and 1, 4 :3 , 6 -dianhydro-D-glucitol-5- nitrate **3b** (isosorbide-5-nitrate) occur as metabolities[2]. The mononitrates **3a** and **3b** act as nonspecific smooth muscle relaxant and as blood vessel dilators[3]. Compared to the dinitrate **2**, the mononitrates **3a** and **3b** are advantageously distinguished by various therapeutically important parameters such as resorption behaviour, half life, toxicity and oral applicability[4]. Because of this fundamental difference in the pharmaceutical application of the two compounds it is necessary to device methods so as to obtain isomerically pure mononitrates. A number of methods have been developed over the years for the synthesis of isosorbide mononitrates with varying degree of success. One of the approaches to the synthesis of 1,4:3,6-dianhydro-D-glucitol 5-mononitrate **3b** involves selective esterification of 1,4:3,6-dianhydro-D-glucitol **4** with carboxylic acids[5-7], followed by nitration and hydrolysis[7,8].

In addition to these two methods, selective reductions of 1,4:3,6-dianhydro- D-glucitol 2,5-dinitrate to the 2- or 5- mononitrate using reagents like hydrazine hydrate[3,9], ferrous sulfate[10,11], cupric chloride[11], powdered zinc[10,12], Pd/C in the presence of nickel chloride[12] and titanium (III) tetrahydroborates[13] have also been described.



	R^1	R^2
2	NO_2	NO_2
3a	H	NO_2
3b	NO_2	H
4	H	H

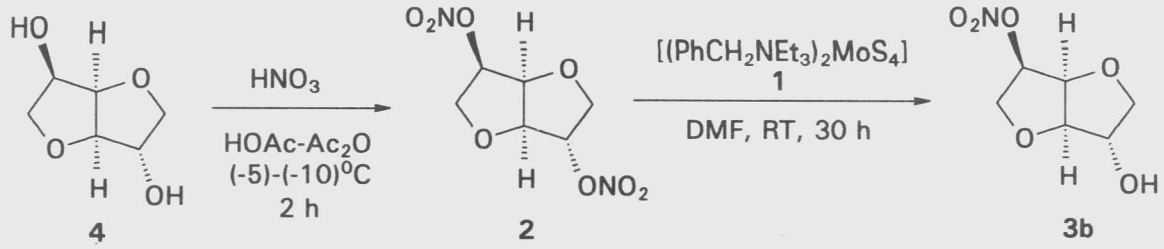
Of all the methods available for the synthesis of 2- or 5- mononitrate, the one reported by Modena involving chemoselective reduction of isosorbide-2,5-dinitrate with Zn/acetic acid or ferrous sulphate is the most attractive[10].

Previously we have shown from our laboratory that benzyltriethylammonium tetrathiomolybdate, $(PhCH_2NEt_3)_2MoS_4$(**1**) effects the reduction of a number of azides and isocyanides to the corresponding amines with evolution of nitrogen, a reaction reminiscent of nitrogenase enzyme[14].

It has already been established that *Neurospora nitrate reductase*, an enzyme which catalyses the reduction of nitrates, is a metallo flavoprotein with flavine adenine dinucleotide (FAD) as the prosthetic group and molybdenum as the metal component[15]. As part of our continuing interest in the chemistry and reactivity of tetrathiomolybdate **1** it was of interest to find out whether tetrathiomolybdate **1** would induce reduction of nitrate esters and if so whether it can be utilized for the selective reduction of isosorbide 2,5-dinitrate **2**. Accordingly an exploratory reaction was carried out with **2.**

Treatment of the dinitrate **2** with benzyltriethylammonium tetrathiomolybdate **1** in DMF (RT, 30 hr) effected a smooth and highly chemoselective reduction of the 2-*exo*-nitrate group to afford the mononitrate **3b** (Scheme I) as the only product in 70% yield.

Isosorbide dinitrate **2** possesses two different nitrate groups[16-18], the sterically less hindered and more easily accessible 2- *exo*-nitrate and the more hindered 5-*endo*- nitrate[16,17]. Regioselectivity in reduction in this particular substrate probably arises from the attack of the sterically more demanding



Scheme I

tetrathiomolybdate **1** on the more easily accessible 2- *exo*-nitrate.

This has proved to be an efficient method for the synthesis of isomerically pure isosorbide mononitrate **3b** from the readily available isosorbide dinitrate **2.** This simple procedure offers a practical route to selective monofunctionalization of isosorbide.

Experimental Section

General. Melting points were determined with a uni-melt capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded on a Jeol 90 FXQ 90 MHz instrumental using tetramethylsilane as internal reference. Mass spectra were recorded on a Jeol DX-303 spectrometer. TLC was performed on 0.25 mm E. Merck precoated silica (60 F-254) plates. Product was purified by column chromatography over silica gel.

Isosorbide-2,5-dinitrate 2. Fuming HNO_3 (sp. gr. 1.57, 40 mL, 1 mole) was slowly added to acetic acid - acetic anhydride (1:1, 120 mL) maintained at -5 to -10 °C. The mixture was added dropwise with stirring, to isosorbide **4** (14.6g, 0.1 mmol) in acetic acid-acetic anhydride (2:1, 120 mL) maintained at -5 to -10 °C. After standing for 2 hr at 5 to 10 °C, the mixture was poured onto ice (600 g). The solid that separated was filtered, dried and recrystallised from pet. ether (60-80°) (21.6 g, 92%), m.p. 51-52° (lit.m.p., 50.5-51.5°); $[\alpha]_D^{22}$ +139.71° (*c* 2.1, EtOH, lit.1 + 141°); IR (thin film): 2930, 1650, 1290, 1120, 860 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ3.90 (2H, dd, J = 7.5, 11.3 Hz), 4.05-4.20 (2H, m), 4.55 (1H, d, J = 6.0 Hz), 5.00 (1H, t, J = 6.0 Hz), 5.35 (2H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 69.3, 71.5, 80.7, 81.4, 84.7, 85.2; MS: m/z 237 (M^++1,2), 190 (1), 144 (36), 127 (50), 85 (53), 69 (89), 57 (85), 46 (100), 43 (98).

Reaction of dinitrate 2 with tetrathimolybdate 1. To a solution of **2** (0.21 g, 0.89 mmol) in DMF (6 mL) was added tetrathiomolybdate **1** (2.2 g, 3.6 mmoles). The reaction mixture was allowed to stir at RT for 30 hr. Once the reaction was over, DMF was removed under reduced pressure and the residue extracted with CH_2Cl_2 (5 x 2mL), ether (5 x 10 mL), and EtOH (5 x 10 mL), and filtered through a pad of Celite. The solvent was evaporated and the crude material purified by column chromatography on silica gel. The mononitrate **3b** (0.12g, 70%) was obtained as a white solid using 25% EtOAc in pet. ether as eluent, m.p. 89.5- 91° (lit.19, m.p. 92°); $[\alpha]_D^{22}$ + 171.2° (*c* 1.4, (EtOH, lit.19 + 173.5°; IR (thin film): 3400, 2920, 1640, 1290, 1100, 860 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): d 3.8-4.1 (5 H, m), 4.35 (1H, d, J = 3.7 Hz), 4.38 (1H, d, J = 6.0 Hz), 4.98 (1H, t, J = 6.0 Hz), 5.35 (1H, td, J = 3.8, 6.0 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$): d 69.1, 75.5, 75.6, 81.1, 81.3, 88.7; MS: m/z 192 (M^+ + 1,0.5), 146 (2.5), 127 (47), 85 (45), 69 (54), 57 (46), 43 (100).

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