SYNTHESIS OF OCTAHYDRO-2,5-BIS(NITROIMINO)IMIDAZO - [4,5-*d*]IMIDAZOLE

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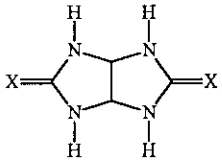
Abstract- Improved reaction conditions for the preparation of octahydro-5-imino-2-(nitroimino)imidazo[4,5-*d*]imidazole (**3**) from 4,5-dihydroxy-2-nitroimino-imidazolidine (**2**) and guanidine hydrochloride are described. Treatment of the hydrochloride salt of **3** with nitric acid at low temperature generates the nitrate salt of **3** and not octahydro-2,5-bis(nitroimino)imidazo[4,5-*d*]imidazole (**1a**) as previously reported. The bis(nitroimino) compound (**1a**) was obtained by slow addition of nitric acid to a mixture of the monohydrochloride salt of the bicyclic guanidine (**3**) and acetic anhydride.

We set out to prepare octahydro-2,5-bis(nitroimino)imidazo[4,5-*d*]imidazole (**1a**) to assess its properties as a high density energetic compound. An established synthetic route to cyclic nitroguanidines involves nitration of the imino group of cyclic guanidines using nitric acid and acetic anhydride in the presence of chloride ion [1,2] A possible precursor to **1a** in this type of approach is octahydro-2,5-bis(imino)imidazo[4,5-*d*]imidazole (**1b**), however there has been no reported synthesis of this bicyclic bisguanidine. The bisurea analogue, tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (glycoluril) (**1c**), can be prepared by the acid promoted reaction of urea with either glyoxal or 4,5-dihydroxy-2-imidazolidinone.[3,4] The reaction of guanidine hydrochloride with glyoxal gives 4,5-dihydroxy-2-iminoimidazolidine[5] or 2-imino-4-imidazolidinone[6] rather than the bicyclic bisguanidine. Boyer and co-workers[7] have condensed guanidine hydrochloride with 4,5-dihydroxy-2-nitroiminoimidazolidine (**2**) in hydrochloric acid to form octahydro-5-imino-2-nitroiminoimidazo[4,5-*d*]imidazole (**3**) which was isolated as the monohydrochloride salt. They claim to have converted this salt to the

monohydrate of the title compound (**1a**) by treatment with nitric acid (100%, -40 °C). Their analytical data are equally consistent with this product being the nitrate salt of the bicyclic guanidine (**3**). Furthermore the ^{1}H and ^{13}C nmr spectral data quoted are inconsistent with the proposed bis(nitroimino) structure (**1a**) and essentially the same as the nmr spectral data quoted by them for the nitrate salt of the bicyclic guanidine (**3**) which they obtained by treating its hydrochloride salt with silver nitrate



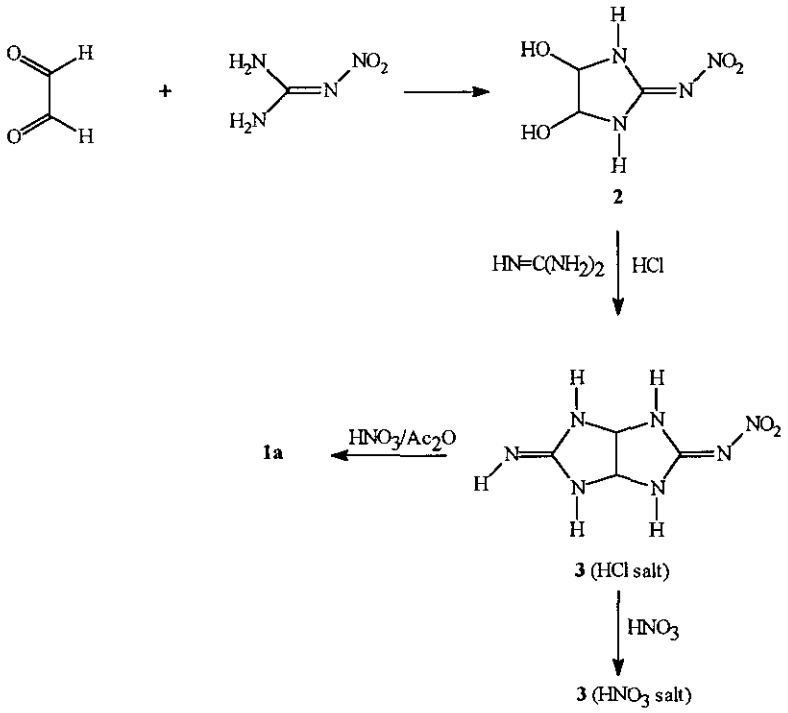
1a X = NNO_2
1b X = NH
1c X = O

This paper describes a reinvestigation of the reported synthetic route to compound (**1a**), improved reaction conditions for the preparation of the bicyclic guanidine (**3**), full characterisation of the product obtained when the hydrochloride salt of compound (**3**) is treated with nitric acid, and the first method for preparing the title compound (**1a**) (see Scheme 1).

The yield for the cyclocondensation reaction of guanidine hydrochloride with the dihydroxy compound (**2**) in hydrochloric acid was increased from 36% to 50% by using an acid strength of 40% w/w, reducing the reaction temperature (from 25 °C to 15 °C) and an increase in the reaction time (from 17 h to 4 days). The bicyclic guanidine (**3**) was isolated as the analytically pure monohydrochloride salt, after crystallization from chilled concentrated hydrochloric acid It has been reported that treatment of the monohydrochloride of the bicyclic guanidine (**3**) with nitric acid produces the bis(nitroimino) compound (**1a**).[7] We found that the reaction conditions described actually produce the nitrate salt of **3** This revised structural assignment is supported by analytical data, the presence of a strong peak for the protonated molecular ion of **3** in the electrospray mass spectrum, and the ir spectrum which shows a guanidine C=N stretch at 1705 cm^{-1} A comparison of the spectral data (^{1}H and ^{13}C nmr) and the melting points reported by Boyer and co-workers for both their product from this reaction and that of the nitrate salt of **3**, which they prepared by treating the hydrochloride salt of **3** with $AgNO_3$,[7] clearly indicates that these are the same compound The imino group in this cyclic guanidine is

strongly basic and nitration does not occur in nitric acid because under these conditions amines of this type exist exclusively in the unreactive protonated form.[8]

Scheme 1



The monohydrochloride salt of the bicyclic guanidine (**3**) was converted to the bis(nitroimino) compound (**1a**) using nitric acid in acetic anhydride. In nitrations of this type it has been established that the nitric acid oxidises the chloride ion to generate chlorine acetate (ClOAc), and this reacts with the basic amine to form the less basic chloramine which is converted to the nitramine.[9] Methods previously reported for the nitration of cyclic guanidines involve adding the hydrochloride salt,[2] (or the nitrate salt and ammonium chloride[1]) to ten equivalents of nitric acid in acetic anhydride then heating the mixture to 32 °C to effect the nitration. We found that under these conditions the monohydrochloride salt of **3** was converted to its corresponding nitrate salt. Nitration to form the nitrimine was effected by slow addition of nitric acid (approximately three equivalents) to a mixture of the monohydrochloride salt of **3** in excess acetic anhydride maintained at 20-30 °C. Presumably

under these conditions sufficient of the unprotonated substrate is present to allow the reaction with chlorine acetate to proceed. The nitration was less efficient, and the nitrate salt of **3** was also formed, when the concentration of unreacted nitric acid in the reaction mixture became too high as a result of either too rapid addition of the acid or performing the reaction at lower temperature where the rate of nitration was slower. The reaction was carried out in a closed vessel (vented through a bubbler), rather than under a stream of nitrogen gas, to reduce the loss of the electropositive chlorine from the reaction system [10] Compound (**1a**) was purified by crystallization from dilute nitric acid heated to 70 °C. Heating above this temperature caused hydrolysis of the product, a behaviour that has been previously observed with other substituted nitroguanidines.[11] The structure of compound (**1a**) is supported by analytical data, a strong absorption in the ir spectrum at 1590 cm^{-1} assigned to the C=N vibration of the nitroguanidine groups,[12,13] a peak for the protonated molecular ion of **1a** in the FAB mass spectrum, and consistent nmr spectral data.

EXPERIMENTAL SECTION

CAUTION: Compound (**1a**) is a sensitive explosive and should be handled with the appropriate precautions

Nmr spectra were recorded on a Bruker AM 300 spectrometer. Chemical shifts are reported in ppm and are relative to internal tetramethylsilane. Melting points were determined with an Electrothermal IA 9200 melting point apparatus and are corrected Fast atom bombardment mass spectra (FABms) were recorded on a ZAB 2HF instrument by dissolving the compounds in DMSO and using glycerol as the matrix. Electrospray mass spectra (ESms) were recorded using a VG Bio Q (VG Instruments) spectrometer; an approximately 0.2 mM solution of the sample was injected directly into the source using a 3 μl/min continuous flow of methanol/water (1 1) containing 1% acetic acid. Elemental analyses were performed by the National Analytical Laboratories, Pty Ltd., Victoria, Australia. All samples were dried at 50 °C (0.001 mm) for 24 h over silica gel prior to elemental analysis

4,5-Dihydroxy-2-nitroiminoimidazolidine (2).

Compound (**2**) was prepared by the following modification of a literature method [14] A mixture of glyoxal (40% w/w, 1.4 g, 24 mmol), nitroguanidine (1.0 g, 9 6 mmol), sodium bicarbonate (0.025 g, 0.30 mmol) and water (0.75 ml) was stirred at 20 °C for 16 h. A white solid was collected, washed with chilled water and dried to give the product (1.0 g, 64%), mp 165 °C (decomp.) [lit.,[14] 169 °C (decomp)]

Octahydro-5-imino-2-nitroiminoimidazo[4,5-*d*]imidazole (3).

Compound (**3**) was prepared by modifying the method of Boyer and co-workers.[7] Finely ground **2** (2 8 g, 17 3 mmol) was added in portions over 20 min to a stirred solution of guanidine hydrochloride (4 0 g, 41 9 mmol) in hydrochloric acid (40% w/w, 7 2 ml) at 15 °C. The reaction mixture was then stirred at 15 °C for 4 days and the collected solid washed with tetrahydrofuran (10 ml). The solid (2 2 g) was dissolved in hydrochloric acid (36% w/w, 22 ml) at 20 °C and crystallized on cooling to -40 °C The recovered monohydrochloride salt of **3** (1.9 g, 50%) was obtained as white needles, mp 274-276 °C (decomp.) [lit.,[7] mp 268-270 °C (decomp.)].

The monohydrochloride salt of **3** (1.5 g, 6 8 mmol) was added in portions over 30 min to a stirred solution of nitric acid (100%, 15 ml) at -38 °C under nitrogen. The solution was maintained at -38 °C for a further 1 h then slowly added to ice (200 g) The collected solid was washed with chilled water and recrystallized from dilute nitric acid (0.5% w/w) to give the mononitrate salt of **3** (1.0 g, 64%) as white needles, mp 251 °C (explosive decomp.) [lit.,[7] 245-246 °C (explosive decomp.)].

Octahydro-2,5-bis(nitroimino)imidazo[4,5-*d*]imidazole (1a).

Nitric acid (100%, 1 9 g, 30 2 mmol) was slowly added over a 6 h period to a stirred mixture of the monohydrochloride of **3** (2 0 g, 9 0 mmol) and acetic anhydride (9.5 g, 93.0 mmol) maintained at 25-30 °C in a closed vessel vented to a bubbler. After the addition was completed the reaction mixture was stirred at 25 °C for 16 h, chilled then slowly added to ice (20 g). A white solid was isolated, washed with chilled water (6 ml) and tetrahydrofuran (20 ml) then dried to give the crude product (1.9 g). The collected solid was crystallized by taking a filtered solution of the compound in nitric acid (100%, 12 ml) and adding it to dilute nitric acid (1% w/w, 550 ml) at 70 °C The product (1 2 g, 58%) separated on cooling as fine white needles, mp 326 °C (explosive decomp). Ir (KBr) ν_{max} 1590 (C=N), 1575 (NO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ 5.84 (s, 2H, CH), 9 47 (s, 4H); ^{13}C nmr (DMSO-d_6) δ 68 94 (CH), 161 29 (C=N), FABms *m/z* (rel intensity) 231 (MH^+, 4) Anal. Calcd for $C_4H_6N_8O_4$. C, 20 87, H, 2.63, N, 48.69 Found C, 20.84, H, 2.62, N, 48.44.

ACKNOWLEDGMENTS

The authors wish to thank Dr Robert Spear for helpful discussions The mass spectra were recorded by Dr. R Colton (La Trobe University), Mr. T. Blumenthal (University of Adelaide) and Ms V Borrett The contributions of all these people are gratefully acknowledged.

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Received, 15th October, 1993