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Synthesis of *N*-amino- and *N*-nitramino-nitroimidazoles

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ABSTRACT

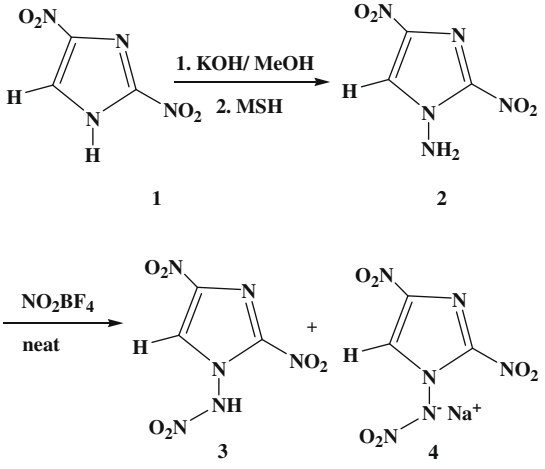
Synthesis of a new nitro-substituted 1-amino and 1-nitraminoimidazoles is described. A novel solid state nitration has been developed.

Synthesis and development of new insensitive energetic materials that contain aromatic nitrogen-containing heterocyclic core units are of intense current interest to the researchers at the Department of Defense (DoD) laboratories worldwide.[1] The primary reason for this stimulated interest is that heteroaromatic nitro compounds possess more favorable elemental composition with relatively higher energetic performance in regard to oxygen balance, density, and other thermodynamic properties when compared to their carbon-only analogous aromatic compounds. Several nitro-substituted imidazoles are reported in the literature as insensitive energetic materials.[2–6] For the past several years we have been working on the development of imidazole-based insensitive energetic materials.[5,7] It is with this background and in continuation of our program aimed at synthesis of new imidazole-based energetic materials that we have undertaken the synthesis of nitramino derivatives of nitroimidazoles. Nitramino nitroimidazoles, apart from possessing nitrogroups and *endo* cyclic nitrogen atoms, possess an *exo* cyclic energetically active unit, the nitramino group. Compounds of such type may have a wider variety of properties than those intrinsic to nitroimidazoles. Thus, for our work we have synthesized the hitherto unknown 1-nitramino-2,4-dinitroimidazole. For the first time a solid state nitration condition has been developed. In this Letter we describe the results of our synthesis of 1-nitramino derivative of dinitroimidazole.

The first step in the synthesis of nitramino nitroimidazoles was to incorporate an amino group on the nitrogen at the 1-position via an electrophilic *N*-amination reaction.

Synthesis of 1-amino mononitroimidazoles such as 1-amino-2-nitroimidazole and 1-amino-2-methyl-4-nitroimi-dazole was reported in the literature.[8] However, synthesis of 1-amino-2,4-dinitroimidazole has not been reported in the literature to the best of our knowledge.

Thus 2,4-dinitroimidazole (**1**, Scheme 1), prepared from 4-nitroimidazole in two steps using the literature procedure,[5] was first converted to the corresponding potassium salt by reacting with KOH in methanol at reflux temperature. Our attempts to aminate the resulting pale yellow potassium salt of 2,4-dinitroimidazole with readily available aminating agent hydroxylamine-*O*-sulfonic acid (HOSA) failed. Therefore, utilization of more reactive *N*-aminating reagent *O*-mesitylenesulfonylhydroxylamine (MSH)[9] was investigated. Accordingly, the potassium salt of 2,4-dinitroimidazole was then subjected to an electrophilic amination with MSH in anhydrous DMF at 0 °C followed by stirring at room temperature. Evaporation of the solvent followed by chromatographic purification of the residue afforded the hitherto unknown 1-amino-2,4-dinitroimidazole (ADNI, **2**) in 45% yield. The structure of **2** was established unambiguously via single crystal X-ray crystallography (Figs. 1 and 2).



Scheme 1.

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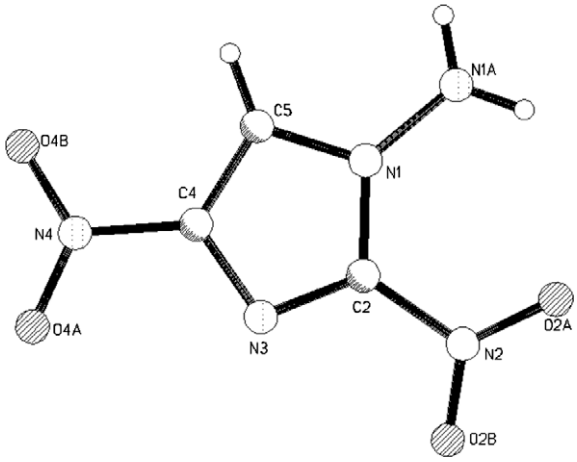

Figure 1. ORTEP view of 1-amino-2,4-dinitroimidazole (**2**).

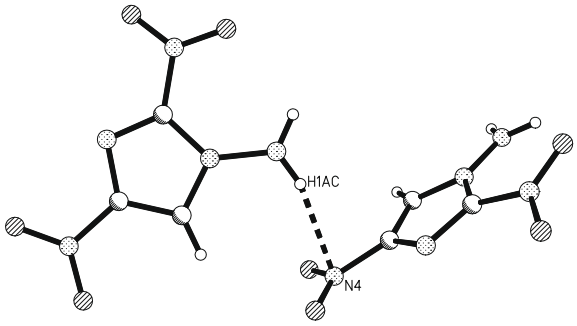

Figure 2. Crystal packing structure of 1-amino-2,4-dinitro-imidazole (**2**).

As per our synthetic scheme, the next step was the transformation of the amino group to nitramino functionality. Again, our attempts to prepare the corresponding nitramino derivative using nitric acid, acetylnitrates, mixed acids, and nitrate salts in solvents under various conditions did not result in the formation of the desired product.

Frequently, the isolated product was found to be 2,4-dinitroimidazole, thereby suggesting the highly labile nature of amino/nitramino imidazole. Our inability to synthesize the desired target compound led to the development of a solid state nitration method employing nitronium tetrafluoroborate as the nitrating agent. Thus, ADNI and nitronium tetrafluoroborate were stirred together under a nitrogen atmosphere for several days, followed by workup, resulting in isolation of the target product **3** in 25% yield as a pale yellow solid. As the proton attached to the nitramino group was highly acidic, some amount of the nitramino product transformed into the corresponding sodium salt—presumably during the workup/purification process. The sodium salt was isolated in 15% yield as a white solid. The structures of the 1-nitramino-2,4-dinitroimidazole **(3)** and its corresponding sodium salt **4** were established unambiguously via single crystal X-ray crystallographic analysis (Figs. 3 and 4). The ORTEP views of compounds **2–4** are presented in Figures 1–4.

Thus, in summary, we have successfully synthesized 1-amino-2,4-dinitroimdazole (**2**) and transformed it into its corresponding nitramino derivative **3** using a novel nitration condition. X-ray structural analysis was carried out on all compounds to establish the positions of amino and nitramino groups unambiguously.[10]

1. Experimental

All melting points were recorded by a capillary melting point apparatus and were uncorrected. The IR spectra were determined on a Perkin–Elmer FT–IR Spectrum-2000 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer with D_2O, DMSO-d_6, and acetone-d_6 solvents. The chemical shift values are reported in δ units (parts per million) relative to TMS as an internal standard. The reagent *O*-mesitylsulfonylhydroxyl-amine (MSH) was prepared using a literature reported procedure.[9c]

Caution: *O*-Mesitylsulfonylhydroxylamine (MSH) is an explosive material[9b] and should be handled with care.

1.1. Preparation of 1-amino-2,4-dinitroimidazole (2)

To a stirred solution of 2,4-dinitroimidazole (1.59 g, 9.3 mmol) in methanol (12 mL) was added ground potassium hydroxide (0.88 g) and the resulting mixture was refluxed at 75 °C for 35 min. The reaction mixture was evaporated to dryness on a rotary evaporator under reduced pressure at 40 °C. The resulting yellow solid potassium salt residue was dissolved in ice-cold DMF (35 mL) and the reaction mixture was cooled to 0 °C. To this was added drop-wise while stirring a solution of *O*-mesitylsulfonyl hydroxylamine (MSH, 2.18 g) in ice-cold DMF (25 mL). After stirring at 0 °C for 3 h, the reaction mixture was gradually allowed to reach room temperature and stirred for 20 h. The reaction mixture was evaporated to dryness on a rotary evaporator under reduced pressure at 50 °C. The residue was triturated with ethyl acetate to precipitate the mesitylene salt which was removed by filtration. The filtrate was evaporated and the crude product was purified using silica gel column chromatography (25–50% ethyl acetate-hexanes as eluent). The pure product (0.78 g, 45%) was obtained as a pale yellow solid. mp 172–173 °C ^{1}H NMR (DMSO-d_6):

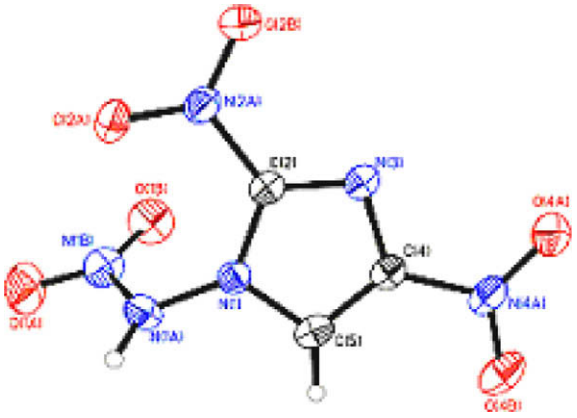

Figure 3. ORTEP view of 1-nitramino-2,4-dinitroimidazole (**3**).

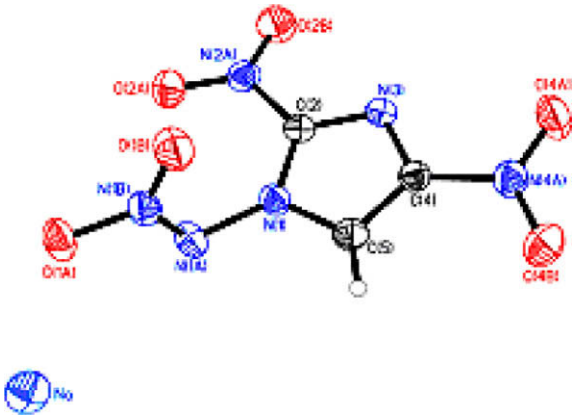

Figure 4. ORTEP view of sodium salt of 1-nitramino-2,4-dinitroimidazole (**4**).

6.87 (br s, 2H, $-NH_2$, D_2O exchangeable), and 8.43 (s, 1H, aromatic). ^{13}C NMR (DMSO-d_6): 124.0, 145.1, 145.5. Structure of this product was established unambiguously via single crystal X-ray crystallography. Selected X-ray data: crystal system, orthorhombic; space group, $Pca2_1$; volume, 657.16 (A^3); Z, 4; density, 1.75 mg/m^3.

1.2. 1-Nitramino-2,4-dinitroimidazole (3) and sodium salt (4)

To a round-bottomed (10 mL) flask containing a magnetic stirring bar and ADNI (174 mg, 1.0 mmol) was added nitronium tetrafluoroborate (132 mg, 1.0 mmol) in one portion at room temperature and the resulting solid mixture was stirred at room temperature for 9 days under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (10 mL) and stirred at room temperature for 5 min. A two-phase solution was formed. This solution was transferred into a separatory funnel and the lower layer was removed and the remaining ethyl acetate layer was sequentially washed with water (1×5 mL), brine (1×3 mL), then dried (Na_2SO_4), and filtered. The filtrate was then evaporated to yield a crude product as an off-white sticky mass. This sticky residue was stirred with ether (5 ml) and the separated white solid was removed via filtration. The yield of this solid **4** was 15% (36 mg). A small sample of this product was crystallized from EtOAc–hexanes for X-ray structural analysis. Mp 202–204 °C (decomposes). ^1H NMR (acetone-d_6): 8.14 (s, 1H). ^{13}C NMR (acetone-d_6): 123.0 and 141.4. Selected X-ray data: crystal system, orthorhombic; space group, *Pbcn*; volume, 1718.60 (A^3); Z, 8; density, 1.856 mg/m^3.

The filtrate was evaporated to dryness and the residue was subjected to column chromatography (silica gel, 25% ethyl acetate–hexanes). The pure nitramino product **3** was obtained as a pale yellow solid in 25% (56 mg) yield. A small sample was re-crystallized from ethyl acetate-hexanes for X-ray analysis. Mp 237–239 °C. ^1H NMR (acetone-d_6): 6.34 (br s, 1H) and 8.86 (s, 1H). ^{13}C NMR (acetone-d_6): 126.7, 139.4 and 142.4. Selected X-ray data: crystal system, orthorhombic; space group, $P2_12_12_1$; volume, 802.9 (A^3); Z, 4; density, 1.804 mg/m^3.

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10. Complete crystallographic information files for compounds **2**, **3**, and **4** have been deposited with the Cambridge Crystallographic Data Center as supplementary publications CCDC 751370, 751371, and 751372, respectively. Copies of this data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (UK); Tel.: (+44) 1223-336-408, Fax: (+44) 1223-336-033, or E-mail: deposit@ccdc.cam.ac.uk.