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Reactions of 1-amino-2-nitroguanidine with 3-nitroacrylates

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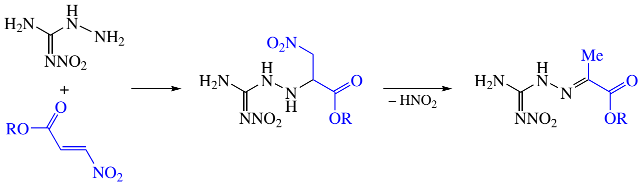
The reactions of 1-amino-2-nitroguanidine with 3-nitroacrylates afford aza-Michael adducts. The latter when refluxed in an aqueous alkaline medium undergo elimination of nitrous acid followed by shift of the resulting C=C bond into C=N position giving finally *N*-substituted alkylpyruvate hydrazones. These compounds can also be prepared in a one-pot procedure; NMR spectroscopy and X-ray diffraction analysis confirmed the existence of the obtained hydrazones as *E*-isomers.

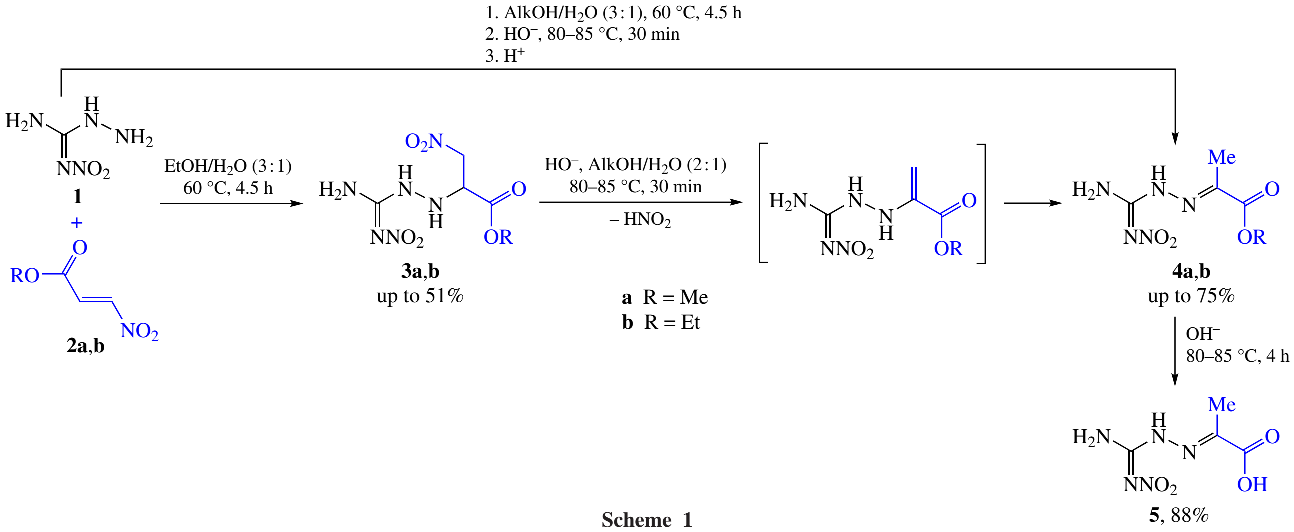


Keywords: nitroguanidine, aminonitroguanidine, nitroacrylate, hydrazone, pyruvates, nucleophilic addition, aza-Michael adduct.

Guanidine as well as semicarbazide[1] and thiosemicarbazide[2] being polynitrogen compounds are present in the structure of a number of drugs.[3–5] Aminoguanidine derivatives are potential cholinesterase inhibitors,[6] and its nitro derivatives act as promising substances for agriculture.[7] The original representative of the nitroguanidine series, 1-amino-2-nitroguanidine **1**, attracts attention as an active polynitrogen nucleophile for the production of practically significant bioactive and energetic materials. Previously studied reactions of 1-amino-2-nitroguanidine **1** with electron-deficient alkenes lead to the formation of Ad_N-E products (in the case of nitro- and *gem*-bromonitrostyrenes, *gem*-ethoxycarbonyl- and *gem*-benzoylnitroethenes), bis-hydrazones (in the case of alkyl 2,3-dibromo-3-nitroacrylates), as well as 3-nitroimino-6-nitromethyl-4,5-dihydro-2*H*-1,2,4-triazin-5-one (in the case of alkyl 3-bromo-3-nitroacrylates).

Herein we found that the reaction of 1-amino-2-nitroguanidine **1** with alkyl 3-nitroacrylates **2a**,**b** occurred readily at 60 °C in an aqueous alcohol solution to form the corresponding aza-Michael adducts **3a**,**b** (Scheme 1). The latter would undergo elimination of nitrous acid, shift of the resulting C=C bond into the azomethine position to finally afford substituted alkyl pyruvate hydrazones **4a**,**b**. These compounds were also obtained in a one-pot procedure directly from 1-amino-2-nitroguanidine **1** and alkyl 3-nitroacrylates **2a**,**b**.

It should be noted that on prolonging the reaction time, the process is accompanied by hydrolysis of the ester function with the formation of the corresponding α-keto carboxylic acid hydrazone **5** (see Scheme 1). Previously,[6] this compound was obtained directly from 1-amino-2-nitroguanidine and methylglyoxalic acid.[6] Despite the presence of amino and carboxy groups in the molecule of compound **5** (in positions 1 and 4), the further cyclization does not occur, which is apparently due to its existence as an *E*-isomer and low nucleophilicity of the nitrogen atom of the primary amino group, the lone-pair



Scheme 1

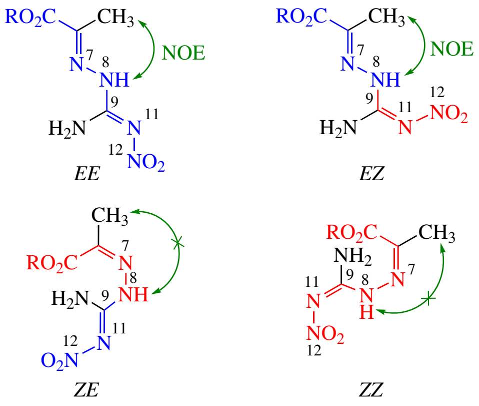


Figure 1 Possible connection configurations of **4a**,**b**.

electrons of which are involved in conjugation with the nitroimine fragment.

As we noted earlier,[8] structural analogs of compounds **4**, **5** containing an azomethine function could exist as *E*- and *Z*-geometric isomers (Figure 1), and due to free rotation along the N^7–N^8, N^8–C^9 bonds, and the N^{11}–N^{12} bond in principle could acquire conformations prone to heterocyclization.

The ^{1}H and ^{13}C NMR spectra of compounds **3**–**5** contain signals for protons and carbons of all structural fragments. According to the ^{1}H and ^{13}C NMR spectra, hydrazones **4a**,**b** are formed as configurationally homogeneous structures[9] in contrast to semicarbazones, nitropyruvates obtained as a mixture of *E*/*Z* isomers.[10] In their ^{1}H NMR spectra, a downfield shift of the signals for the protons of the secondary amino group (11.20–11.27 ppm) is observed, and in an upfield region (2.04–2.12 ppm) singlets for the protons of the methyl group are recorded, in contrast to compounds **3a**,**b**. In the IR spectra of compounds **3**–**5**, attention is drawn to the bands in the regions of 1274–1319 and 1424–1455 cm^{-1}, which should be attributed to the stretching vibrations for the NO_2 group of the nitroimine fragment. The IR spectra of compounds **3a**,**b** contain additional bands in regions of 1379–1383 and 1555–1558 cm^{-1} which belong to the stretching vibrations of the NO_2 group of the nitromethyl fragment.

According to ^{1}H–^{1}H NOESY NMR spectroscopy, in the molecule of compound **4b** the protons of the methyl and secondary amino groups demonstrate the nuclear Overhauser effect,[11,12] which indicates the existence of this compound in a solution of DMSO-d_6 in the form of *EE* or *EZ* isomers (see Figure 1), which does not exhibit a tendency to heterocyclization.

The X-ray study of compound **4a** confirms the hypothesis about its structure (Figure 2).[†] It should be noted that the crystal cell consists of two independent molecules A and B having the same planar conformation, and their geometric parameters coincide within the limits of experimental errors. Therefore, when discussing the geometry of a molecule, the parameters of one of them can be used. It is shown that the *EE* configuration of molecules (see Figure 1) is realized in the crystal when the hydrogen atoms of the methyl and secondary amino groups are close in space. This conformation is stabilized by intramolecular hydrogen bonds between the hydrogen atoms at the nitrogen atom of the primary amino group with the oxygen atom of the nitro group and the imine nitrogen atom N^7 [bond N(10)–H(10A)···O(14), and N(10)–H(10B)···N(7)], which is typical for structures containing a nitroimine fragment. Hydrogen bond parameters are given in Online Supplementary Materials.

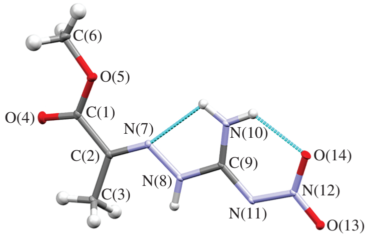


Figure 2 Geometry of molecule **4a** in crystal with intramolecular hydrogen bonds indicated.

The crystal structure of a compound is primarily determined by the hydrogen bonds within it. The H atoms at the nitrogen atoms N^8 and N^{10} form intermolecular hydrogen bonds with neighboring molecules, due to which endless hydrogen bonds are formed from alternating independent molecules A and B (see Online Supplementary Materials). The crystal packing of compound **4a** can be represented as parallel layers of flat ribbons formed by molecules of the compound connected by hydrogen bonds (see Online Supplementary Materials).

To conclude, the reactions of 1-amino-2-nitroguanidine **1** with alkyl 3-nitroacrylates **2a**,**b** when heated (60 °C) in the absence of catalysts lead to the corresponding aza-Michael adducts, alkyl 3-nitro-2-[2-(*N*′-nitrocarbamidoyl)hydrazinyl]-propanoates, which under alkaline conditions are finally converted into substituted hydrazones, alkyl 2-[2-(*N*′-nitro-carbamidoyl)hydrazinylidene]propanoates whose ester group can be easily hydrolyzed. X-ray diffraction and NMR spectroscopy (^{1}H–^{1}H NOESY) confirmed the existence of hydrazone **4a** in the form of an *EE* isomer which is not capable of further heterocyclization under the conditions studied.

This study was performed as part of a state assignment with financial support from the Ministry of Education of the Russian Federation (grant no. VRFY-2023-0003). The X-ray diffraction study was performed at the Department of X-ray Diffraction Research of the Multiple-Access Center on the basis of the Laboratory of Diffraction Research Methods of the A. E. Arbuzov Institute of Organic and Physical Chemistry, the Kazan Scientific Center of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.033.

[†] *Crystal data for* **4a**. $C_5H_9N_5O_4$, $M = 203.17$, triclinic, space group $P\bar{1}$, at 100(2) K, $a = 7.2127(4)$, $b = 9.2346(5)$ and $c = 14.8660(8)$ Å, $\alpha = 96.229(2)$, $\beta = 96.708(2)$ and $\gamma = 111.099(2)°$, $V = 905.27(9)$ Å^3, $Z = 4$ (two independent molecules), $d_{\text{calc}} = 1.491$ g cm^{-3}, μ(MoKα) 0.129 mm^{-1}, $F(000) = 424$. A total of 49771 reflections were collected [6273 independent reflections, $R_{\text{int}} = 0.068$, 4831 observed with $I \geqslant 2\sigma(I)$], GOOF 1.014, final *R* indexes (observed reflections): $R_1 = 0.0434$, $wR_2 = 0.1209$, all data $R_1 = 0.0613$, $wR_2 = 0.1313$, 257 refined parameters.

X-ray diffraction analysis was performed on a Bruker D8 QUEST automatic three-circle diffractometer with a PHOTON III two-dimensional detector and an IµS DIAMOND microfocus X-ray tube (λ [MoKα] = 0.71073 Å) under cooling conditions (100 K). Data collection and processing of diffraction data were performed using an APEX3 software package. All of the structures were solved by the direct method using the SHELXT program[13] and refined by the full-matrix least squares method over F^2 using the SHELXL program.[14] All of the calculations were performed in the WinGX software package,[14] the calculation of the geometry of the molecules and the intermolecular interactions in the crystals was carried out using the PLATON program[15] and the drawings of the molecules were performed using the MERCURY[16] programs. The non-hydrogen atoms were refined in the anisotropic approximation. The hydrogen atoms were placed in geometrically calculated positions and included in the refinement in the ‘riding’ model.

CCDC 2301778 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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