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A new synthesis of a nitroimino-containing 1,2,4-triazin-5-one from 3-bromo-3-nitropropenoates

Valentina M. Berestovitskaya,*[a] Olga Yu. Ozerova,[a] Tatiana P. Efimova,[a] Vladislav V. Gurzhiy[b] and Tamara A. Novikova[a]

[a] *A. I. Herzen State Pedagogical University of Russia, 191186 St. Petersburg, Russian Federation. Fax: +7 812 571 3800; e-mail: kohrgpu@yandex.ru*
[b] *Department of Crystallography, St. Petersburg State University, 199034 St. Petersburg, Russian Federation. E-mail: vladgeo17@mail.ru*

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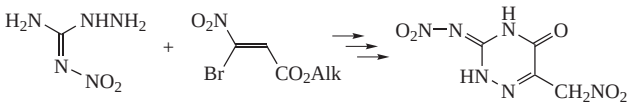
Reaction of 1-amino-2-nitroguanidine with alkyl 3-bromo-3-nitropropenoates affords 3-nitroimino-6-nitromethyl-4,5-dihydro-(2*H*)-1,2,4-triazin-5-one, whose structure was characterized by IR, UV, NMR spectroscopy and X-ray single crystal analysis.



Among nitrogen-containing heterocycles, 1,2,4-triazines are of considerable interest as they possess high biological activities such as pesticide properties (herbicides, fungicides, insecticides, plant growth stimulants and inhibitors) and pharmaceutical activities, *e.g.* neurotropic, cardiotropic, bronchodilatory, vasodilatory, antifungal and anthelminthic ones.[1,2] In particular, 1,2,4-triazin-5-one is a component of formulations with antimicrobial, anti-inflammatory and analgesic effects.[3] Substituted 1,2,4-triazin-5-one derivatives Metribuzin and Metamitron are efficient herbicides and give good results at low dosages.[2]

Analysis of literature shows that 3-substituted 1,2,4-triazin-5-ones are mainly synthesized by cyclocondensation of α-keto acids with (thio)semicarbazides, thiocarbohydrazide, mono- and diaminoguanidines.[4–6] The reactions are performed in two stages: initial formation of the corresponding α-keto acid hydrazones followed by their cyclization to give the target triazines. The synthetic potential of this method is limited because the starting α-keto acids obtained by multi-stage procedures are hardly available.

Previously, we prepared a representative nitroamino 1,2,4-triazine using a reaction of 1-amino-2-nitroguanidine with glyoxal.[7] In this study, we suggest a different approach to 1,2,4-triazin-5-one derivative by condensation of 1-amino-2-nitroguanidine[8] with alkyl 3-bromo-3-nitropropenoates (Scheme 1). The latter proved themselves as preparatively available and convenient starting reagents[9] for syntheses of nitrogen-containing heterocycles in reactions with *o*-phenylenediamine and its hetero analogues.[10,11]

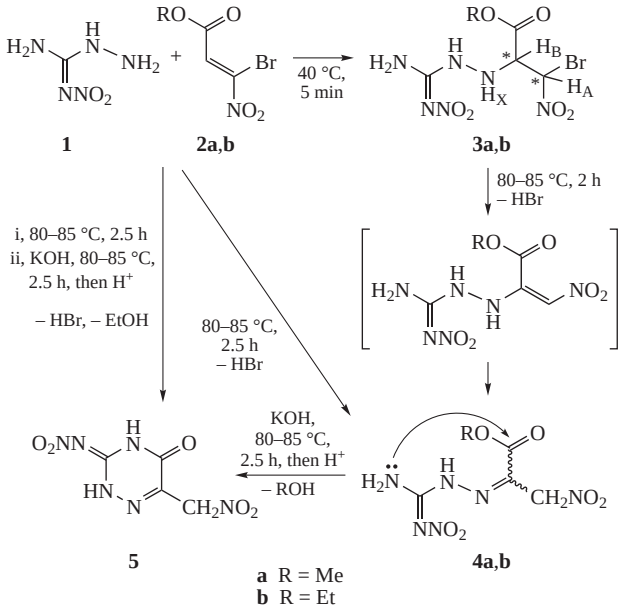
The first stage of the reaction of 1-amino-2-nitroguanidine **1** with methyl 3-bromo-3-nitropropenoate **2a** efficiently occurs in a water–ethanol medium at 40 °C to give nucleophilic addition adduct **3a**. Its heating at 85 °C is accompanied by dehydrobromination followed by isomerization of the C=C double bond to a C=N bond to afford compound **4a**. The latter can also be obtained in one pot directly from reagents **1** and **2a**. Refluxing compound **4a** under alkaline catalysis conditions in a water–methanol medium ultimately yields 3-nitroimino-6-nitromethyl-4,5-dihydro-(2*H*)-1,2,4-triazin-5-one **5**. This method also proved to be suitable for ethyl 3-bromo-3-nitropropenoate **2b** that was also subjected to multistage and one-pot processings† (see Scheme 1).

The structures of hitherto unknown compounds **3a**,**b**, **4a**,**b** and **5** were studied by IR, UV, ^{1}H and ^{13}C{^{1}H} NMR spectro-

† ^{1}H, ^{13}C-{^{1}H}, ^{1}H-^{13}C NMR, HMQC and HMBC spectra were recorded using a Jeol ECX400A spectrometer [399.78 (^{1}H) and 100.52 (^{13}C) MHz] in DMSO-d_6. The residual signal of non-deuterated solvent was used as the internal standard. IR spectra were obtained in KBr pellets on a Shimadzu IRPrestige-21 Fourier spectrometer. Electronic spectra were recorded in quartz cells (l = 0.1 cm, c ~ 0.3 mmol dm^{-3}) on a Shimadzu UV-2401 PC spectrophotometer, using ethanol as the solvent. Elemental analyses were performed using a EuroVector EA 3000 analyzer (CHN Dual mode).

*Methyl 3-bromo-3-nitro-2-[2-(*N′*-nitrocarbamimidoyl)hydrazinyl]-propanoate* **3a**. A solution of methyl 3-bromo-3-nitropropenoate **2a**[9] (0.3 g, 1.4 mmol) in ethanol (5 ml) was added dropwise at 40 °C to a suspension of 1-amino-2-nitroguanidine **1**[8] (0.16 g, 1.4 mmol) in water (10 ml). The mixture was stirred for 5 min and then cooled to 18–20 °C. The resulting crystalline precipitate was filtered, washed with water, ethanol and diethyl ether on the filter, and dried in air to give compound **3a** (0.36 g, 78%) as a mixture of diastereomers (2 : 1), mp 135–138 °C. IR (ν/cm^{-1}): 1331, 1424 (NNO_2), 1355, 1576 (CH_2NO_2), 1641 (C=N), 1751 (C=O), 3199, 3294, 3376 (NH). ^{1}H NMR, δ: **3a**′ 3.69 (s, 3H, Me), 4.70 (dd, 1H, CH_B, $^3J_{H_AH_B}$ 4.27 Hz, $^3J_{H_BH_X}$ 6.41 Hz), 6.21 (d, 1H, NH_X, $^3J_{H_BH_X}$ 6.41 Hz), 7.06 (d, 1H, CH_A, $^3J_{H_AH_B}$ 4.27 Hz), 7.26 (s, 1H, NH_2), 8.48 (s, 1H, NH_2), 9.57 (s, 1H, NH); **3a**″ 3.72 (s, 3H, Me), 4.76 (dd, 1H, CH_B, $^3J_{H_AH_B}$ 4.58 Hz, $^3J_{H_BH_X}$ 6.41 Hz), 6.25 (d, 1H, NH_X, $^3J_{H_BH_X}$ 6.41 Hz), 7.08 (d, 1H, CH_A, $^3J_{H_AH_B}$ 4.58 Hz), 6.97 (s, 1H, NH_2), 8.48 (s, 1H, NH_2), 9.50 (s, 1H, NH). ^{13}C NMR, δ: **3a**′ 53.45 (MeO), 66.24 (CH_B), 80.70 (CH_A), 161.61 (C=NNO_2), 167.98 (C=O); **3a**″ 53.71 (MeO), 65.63 (CH_B), 80.28 (CH_A), 161.51 (C=NNO_2), 168.32 (C=O).

*Ethyl 3-bromo-3-nitro-2-[2-(*N′*-nitrocarbamimidoyl)hydrazinyl]-propanoate* **3b** was obtained (0.17 g, 38%) from 1-amino-2-nitroguanidine **1**[8] (0.15 g, 1.2 mmol) in water (10 ml) and ethyl 3-bromo-3-nitropropenoate **2b**[9] (0.28 g, 1.2 mmol) in ethanol (5 ml) using a procedure similar to the synthesis of compound **3a** and isolated as a mixture of diastereomers (2 : 1), mp 112–116 °C. IR (ν/cm^{-1}): 1318, 1417 (NNO_2), 1371, 1560 (CH_2NO_2) 1644 (C=N), 1706 (C=O), 3141, 3158, 3332 (NH). ^{1}H NMR, δ: **3b**′ 1.21 (m, 3H, *Me*CH_2O) 4.17 (m, 2H, Me*C*H_2O), 4.72 (dd, 1H, CH_B, $^3J_{H_AH_B}$ 3.97 Hz, $^3J_{H_BH_X}$ 6.10 Hz), 6.20 (d, 1H, NH_X,



1 **2a**,**b** **3a**,**b** **5** **4a**,**b**

a R = Me
b R = Et

Scheme 1

scopy, along with ^{1}H-^{13}C HMQC and HMBC experiments. In addition, X-ray single-crystal analysis was performed for heterocycle **5**.

The ^{1}H and ^{13}C NMR spectra of compounds **3a**,**b** contain a double set of signals from protons and carbon atoms due to their diastereomerism in DMSO-d_6 solution. According to ^{1}H and ^{13}C NMR data, compound **4a** was isolated as a mixture of *Z*- and *E*-isomers (6 : 1) with respect to the C=N bond,[12] whereas compound **4b** was stereo-uniform.

X-ray single-crystal analysis of heterocycle **5** has shown that the nitroimine moiety, the triazine ring and the carbonyl group in its structure are arranged in the same plane (Figure 1). In the nitroimine moiety, like in nitroimines of other compounds,[13]

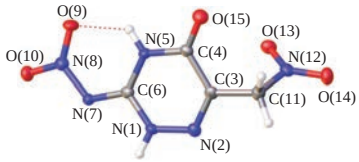


Figure 1 Molecular structure of compound **5** according to X-ray single crystal data.

$^{3}J_{H_BH_X}$ 6.10 Hz), 7.07 (d, 1H, CH_A, $^{3}J_{H_AH_B}$ 3.97 Hz), 7.30 (s, 1H, NH_2), 8.48 (s, 1H, NH_2), 9.63 (s, 1H, NH); **3b**″ 1.21 (m, 3H, *Me*CH_2O), 4.17 (m, 2H, Me*C*H_2O), 4.76 (dd, 1H, CH_B, $^{3}J_{HCNH}$ 6.10, $^{3}J_{HCCH}$ 4.88 Hz), 6.24 (d, 1H, NH_X, $^{3}J_{HCNH}$ 6.10 Hz), 7.11 (d, 1H, CH_A, $^{3}J_{HCCH}$ 4.88 Hz), 7.30 (s, 1H, NH_2), 8.48 (s, 1H, NH_2), 9.56 (s, 1H, NH). ^{13}C NMR, δ: **3b**′ 14.31 (OCH_2*Me*), 62.65 (O*C*H_2Me), 66.11 (CH_B), 81.04 (CH_A), 161.64 (C=NNO_2), 167.77 (C=O); **3b**″ 14.34 (OCH_2*Me*), 62.91 (O*C*H_2Me), 65.67 (CH_B), 80.42 (CH_A), 161.54 (C=NNO_2), 167.43 (C=O). Found (%): C, 20.79; H, 3.38; N, 24.62. Calc. for $C_6H_{11}N_6O_5Br$ (%): C, 20.99; H, 3.20; N, 24.48.

*Methyl 3-nitro-2-[2-(*N′*-nitrocarbamimidoyl)hydrazinylidene]propanoate* **4a**. (*a*) A solution of compound **3a** (0.33 g, 1.0 mmol) in 30 ml of ethanol–water mixture (1 : 2) was refluxed for 2 h and cooled to 18–20 °C. The crystalline precipitate then formed was filtered, washed with water, ethanol and diethyl ether on the filter, and dried in air. Yield 0.13 g (52%), mp 162–165 °C [decomp., water–ethanol (1 : 1.5)]. (*b*) A solution of methyl 3-bromo-3-nitropropenoate **2a** (0.52 g, 2.4 mmol) in ethanol (10 ml) was added dropwise at 80–85 °C to a solution of 1-amino-2-nitroguanidine **1** (0.29 g, 2.4 mmol) in water (20 ml). The mixture was stirred at 80–85 °C for 2.5 h, then cooled to 18–20 °C. The resulting crystalline precipitate was filtered, washed with water, ethanol and diethyl ether on the filter, and dried in air to give 0.26 g (76%) of a mixture of *Z*- and *E*-isomers (6 : 1), mp 164–166 °C [decomp., water–ethanol (1 : 1.5)]. IR (ν/cm^{-1}): 1296, 1416 (NNO_2), 1376, 1558 (CH_2NO_2), 1646 (C=N), 1711 (C=O), 3131, 3325 (NH). ^{1}H NMR, δ: **4a**′ 3.80 (s, 3H, MeO), 5.54 (s, 2H, CH_2NO_2), 8.60 (s, 1H, NH_2), 8.86 (s, 1H, NH_2), 13.12 (s, 1H, NH); **4a**″ 3.77 (s, 3H, Me), 5.71 (s, 2H, CH_2NO_2), 8.47 (s, 1H, NH_2), 9.19 (s, 1H, NH_2), 12.13 (s, 1H, NH). ^{13}C NMR, δ: **4a**′ 53.83 (MeO), 76.81 (CH_2NO_2), 131.13 (C=N), 158.25 (C=NNO_2), 161.00 (C=O); **4a**″ 53.49 (MeO), 69.29 (CH_2NO_2), 132.85 (C=N), 158.73 (C=NNO_2), 163.74 (C=O). UV [λ_{max}/nm (ε)]: 296.0 (23715). Found (%): N, 33.98. Calc. for $C_5H_8N_6O_6$ (%): N, 33.87.

*Ethyl 3-nitro-2-[2-(*N′*-nitrocarbamimidoyl)hydrazinylidene]propanoate* **4b**. (*a*) Obtained (0.12 g, 54%) from compound **3b** (0.29 g, 0.84 mmol) in water (20 ml) and ethanol (10 ml) using version (*a*) of the technique for synthesizing compound **4a**; mp 167–170 °C [decomp., water–ethanol (1 : 1.5)]. (*b*) Obtained (0.94 g, 51%) from 1-amino-2-nitroguanidine **1** (0.83 g, 6.97 mmol) in water (30 ml) and ethyl 3-bromo-3-nitropropenoate **2b** (1.58 g, 6.97 mmol) in ethanol (15 ml) using version (*b*) of the technique for synthesizing compound **4a**; mp 168–170 °C [decomp., water–ethanol (1 : 1.5)]. IR (ν/cm^{-1}): 1297, 1417 (NNO_2), 1371, 1560 (CH_2NO_2), 1644 (C=N), 1706 (C=O), 3158, 3332 (NH). ^{1}H NMR, δ: 1.23 (t, 3H, OCH_2*Me*, $^{3}J_{HCCH}$ 7.10 Hz), 4.30 (q, 2H, O*C*H_2Me, $^{3}J_{HCCH}$ 7.10 Hz), 5.57 (s, 2H, CH_2NO_2), 8.60 (s, 1H, NH_2), 8.86 (s, 1H, NH_2), 13.20 (s, 1H, NH). ^{13}C NMR, δ: 14.13 (OCH_2*Me*), 63.20 (O*C*H_2Me), 76.93 (CH_2NO_2), 131.45 (C=N), 158.26 (C=NNO_2), 160.48 (C=O). UV [λ_{max}/nm (ε)]: 299.0 (29150). Found (%): C, 27.33; H, 3.92; N, 32.19. Calc. for $C_6H_{10}N_6O_6$ (%): C, 27.48; H, 3.81; N, 32.06.

*3-Nitroimino-6-nitromethyl-4,5-dihydro-(2*H*)-1,2,4-triazin-5-one* **5**. (*a*) Obtained (0.03 g, 33%) by refluxing compound **4a** (0.1 g, 0.43 mmol) in a water–methanol solution (1 : 1, 10 ml) containing potassium hydroxide (0.02 g, 0.43 mmol) for 2.5 h. The solution was then cooled and acidified with an aqueous HCl solution to pH 3. The resulting precipitate was filtered, washed with water, ethanol and diethyl ether on the filter, and dried in air, mp 138–139 °C [decomp., water–ethanol (1 : 1.5)]. (*b*) Obtained (0.03 g, 52%) by refluxing compound **4b** (0.07 g, 0.27 mmol) in a water–ethanol solution (1 : 1, 10 ml) containing potassium hydroxide (0.015 g, 0.27 mmol) for 2.5 h. The solution was then cooled and acidified with an aqueous HCl solution to pH 3. After that, the mixture was treated analogously to version (*a*) for synthesizing compound **5**; mp 138–139 °C [decomp., water–ethanol (1 : 1.5)]. (*c*) A solution of ethyl 3-bromo-3-nitropropenoate **2b** (0.22 g, 1 mmol) in ethanol (10 ml) was added dropwise to a solution of 1-amino-2-nitroguanidine **1** (0.12 g, 1 mmol) in water (10 ml) at 80–85 °C. The mixture was stirred at 80–85 °C for 2.5 h, potassium hydroxide (0.056 g, 1 mmol) in water (2 ml) was then added, and the mixture was stirred for more 2.5 h. The solution was then cooled and acidified with an aqueous HCl solution to pH 3. The resulting precipitate was filtered, washed with water, ethanol and diethyl ether on the filter, and dried in air to give 0.07 g (33%) of the product, mp 138–139 °C [decomp., water–ethanol (1 : 1.5)]. Mixed samples of products obtained by techniques (*a*) and (*b*), as well as (*b*) and (*c*), do not give a melting point depression. IR (ν/cm^{-1}): 1317, 1415 (NNO_2), 1340, 1553 (CH_2NO_2), 1587 (C=N), 1700 (C=O), 3177 (NH). ^{1}H NMR, δ: 5.77 (s, 2H, CH_2NO_2), 13.90 (br. s, 2H, NH). ^{13}C NMR, δ: 73.91 (CH_2NO_2), 142.98 (*C*CH_2NO_2), 152.96 (C=NNO_2), 153.72 (C=O). UV [λ_{max}/nm (ε)]: 289.0 (15900). Found (%): C, 22.06; H, 1.75. Calc. for $C_4H_4N_6O_5$ (%): C, 22.22; H, 1.85.

‡ *Crystal data for* **5**. To perform an X-ray diffraction experiment, a crystal of compound **5** was mounted on a micro holder and placed into a Bruker Smart Apex II single crystal diffractometer equipped with a CCD (charge-coupled device) flat detector of reflected X-rays. The measurements were carried out at 150 K using monochromatic MoKα radiation (λ = = 0.71073 Å). Unit cell parameters [$C_4H_4N_6O_5$, monoclinic, space group $P2_1/c$, a = 5.2937(10), b = 9.7054(17) and c = 15.059(3) Å, β = 96.012(3)°, V = 769.4(2) Å^3, Z = 4] were refined by least squares method based on 7004 reflexes with 2θ within 5.00–54.98°. The structure was solved by direct methods and refined to R_1 = 0.036 (wR_2 = 0.068) for 1105 independent reflexes with $|F_0| \geqslant 4\sigma_F$ using SHELXL-97 program[14] within the OLEX2 software complex.[15] The absorption correction was applied in SADABS program.[16] The positions of hydrogen atoms were calculated using the algorithms available in the SHELX software complex. U_{iso}(H) was set as 1.2 U_{eq}(C) and C–H 0.97 Å for CH_2 groups. U_{iso}(H) was set as 1.2 U_{eq}(N) and N–H 0.86 Å for NH groups.

CCDC 1444513 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.

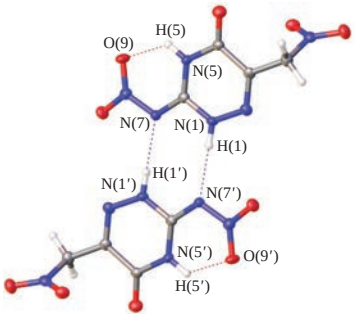


Figure 2 Association of adjacent equivalent molecules of compound **5** into dimers by a system of hydrogen bonds (dotted lines) [N(1)–H(1)···N(7′)].

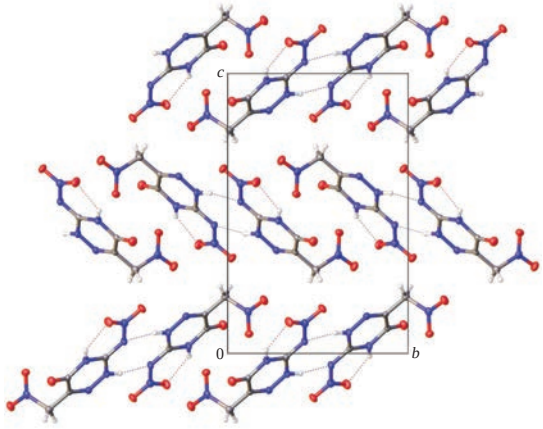


Figure 3 Packing of dimers of compound **5** molecules in a crystal.

an O(9)···H(5)–N(5) intramolecular hydrogen bond is formed between an oxygen atom in the nitro group and the hydrogen atom at the adjacent nitrogen atom in the ring. Furthermore, adjacent molecules are combined into dimers (Figure 2) due to formation of a set of intramolecular hydrogen bonds N(1)–H(1)···N(7′) and N(1′)–H(1′)···N(7). Dimers are packed into bundles parallel to plane (001) (Figure 3).‡

In conclusion, we have pioneered in a synthesis of a hitherto unknown nitroimino derivative of 1,2,4-triazin-5-one using condensation of 1-amino-2-nitroguanidine with alkyl 3-bromo-3-nitropropenoates. This procedure does not require sophisticated equipment and allows the syntheses to be carried out by multistage or one-pot techniques.

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The physicochemical studies of the compounds synthesized were carried out at the Center for Collective Use of A. I. Herzen State Pedagogical University of Russia. Structural studies of compound **5** were performed using equipment of the 'X-ray diffraction research methods' Resource Center at St. Petersburg State University.

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