Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2023, **33**, 723–725

Mendeleev Communications

Semicarbazones of alkyl 3-nitropyruvates: synthesis and structural features

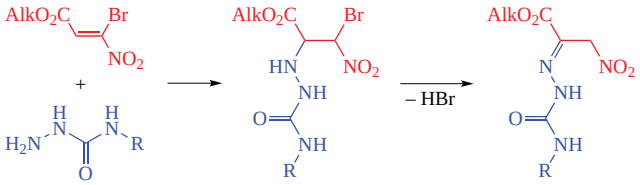
Vasilii V. Pelipko,[a] Ilya A. Pilipenko,[a] Kirill A. Gomonov,[a] Ruslan I. Baichurin,[a] Konstantin A. Lyssenko[b] and Sergey V. Makarenko*[a]

[a] *Herzen State Pedagogical University of Russia, 191186 St. Petersburg, Russian Federation. E-mail: kohrgpu@yandex.ru*

[b] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. E-mail: klyssenko@gmail.com*

DOI: 10.1016/j.mencom.2023.09.042

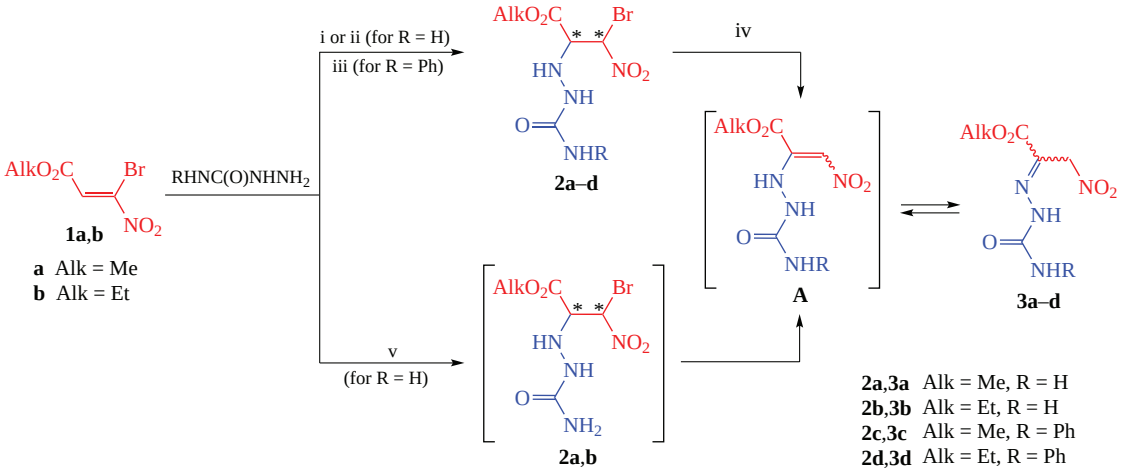
Semicarbazones of alkyl 3-nitropyruvates were obtained by the reaction between alkyl 3-bromo-3-nitroacrylates and semicarbazides. The products were formed as *E*/*Z* isomer mixtures from which some representatives of the individual isomers were isolated. The possibility of their isomerization was shown.



Keywords: nitroacrylates, semicarbazides, nucleophilic addition, aza-Michael adduct, elimination, semicarbazones, nitropyruvates.

Pyruvic acid alkyl esters attract attention due to their anti-inflammatory and antioxidant properties,[1,2] and their 3-nitro-substituted analogs can be used as starting compounds for obtaining heterocyclic substances modulating intracellular calcium.[3] At the same time, semicarbazones and hydrazones of carbonyl[4,5] and α-dicarbonyl compounds[6,7] are of interest as drugs and convenient substrates in the synthesis of heterocycles.[8] A well-known access to alkyl pyruvate semicarbazones is represented by the direct reaction of pyruvic acid esters with semicarbazide.[9] Meantime, highly reactive alkyl 3-bromo-3-nitroacrylates[10–12] would easily form hydrazones in reactions with substituted hydrazines[13] while nitroguanidine-containing hydrazones alkyl 3-nitropyruvates are formed in reactions with 1-amino-2-nitroguanidine.[14]

In this study, we propose a synthesis of alkyl 3-nitropyruvate semicarbazones based on the reaction of alkyl 3-bromo-3-nitroacrylates **1a**,**b** with semicarbazides (Scheme 1). Bromo-nitroacrylates **1a**,**b** react with semicarbazide (generated from its hydrochloride by the action of aqueous NaOH) or with 4-phenylsemicarbazide in ethanol at room temperature to form aza-Michael adducts, alkyl 3-bromo-2-(2-carbamoylhydrazinyl)-3-nitropropanoates **2a**–**d**, in 31–72% yields (procedures A or C). These products were isolated; according to ^{1}H NMR data, they are mixtures of two diastereomers in the ratios **2a**′/**2a**″ = 1.3 : 1, **2b**′/**2b**″ = 1 : 1.3, **2c**′/**2c**″ = 1.1 : 1, **2d**′/**2d**″ = 6.3 : 1 (diastereomers with more downfileld signals for the methine protons C^2*H* and C^3*H* in the ^{1}H NMR spectra are designated as **2a**′–**d**′ in distinction to upfield resonating **2a**″–**d**″). Refluxing these substances **2a**–**d** in aqueous alcoholic solution in the absence of a base (procedure D) results in alkyl 2-(2-carbamoylhydrazinylidene)-3-nitropropanoates **3a**–**d** in 56–89% yields. Their ^{1}H NMR spectra recorded in DMSO-d_6 contain a double set of signals of all structural fragments, which should indicate their existence as *E*/*Z* isomer mixtures (the *E*/*Z* ratio for **3a** was 1 : 3; for **3b**, 1 : 4; for **3c**, 1 : 30; and for **3d**, 1 : 11.5; see Scheme 1).



Scheme 1 *Reagents and conditions*: i, $H_2NC(O)NHNH_2$·HCl, 1 M NaOH (aq.), EtOH, ~20 °C, 1 h (procedure A); ii, $H_2NC(O)NHNH_2$·HCl–AcONa (1 : 1), EtOH, ~20 °C, 2 h (procedure B); iii, $PhHNC(O)NHNH_2$, EtOH, ~20 °C, 1 h (procedure C); iv, EtOH–H_2O (2 : 1), Δ, 2.5 h (procedure D); v, **1**–$H_2NC(O)NHNH_2$·HCl–AcONa (1 : 2 : 2.8), EtOH, ~20 °C, 1 h (procedure E).

Most probably, the initially generated product of HBr elimination, nitro enamine **A**, undergoes an enamine–imine tautomeric transformation to form the final semicarbazone (see Scheme 1). Quantum-chemical calculations (PBE1PBE/def2-TZVP) performed for nitro enamine **A**, *E*- and *Z*-isomers of semicarbazone **3a** argue for the latter being much more energetically favorable (by 6.7 and 10.1 kcal mol^{-1}).

The synthesis of semicarbazones **3a**,**b** as a mixture of *E*- and *Z*-isomers with yields of 90 and 64%, respectively, can also be carried out in one pot (procedure E) by keeping a mixture of bromonitroacrylates **1a** or **1b**, semicarbazide hydrochloride, and sodium acetate (molar ratio 1:2:2.8) in ethanol at room temperature. Note that the use of an equimolar amount of semicarbazide hydrochloride and sodium acetate (exemplified by bromonitroacrylate **1b**) under these conditions leads to only aza-adduct **2b** in 58% yield (procedure B). Double recrystallization makes it possible to obtain some of *E*- or *Z*-isomers in individual form.

The configuration of the semicarbazones was determined based on the ^{1}H–^{1}H NOESY experiments (variable mixing time τ 1, 1.5, 2 s). For the *E*-**3a** isomer, cross peaks of the signals for the C*H*$_2$NO$_2$ protons (δ 5.61 ppm) and N*H* (δ 10.96 ppm) groups are observed. In turn, for *Z*-**3b** isomer such cross peaks of the signals for C*H*$_2$NO$_2$ protons (δ 5.43 ppm) and N*H* (δ 11.32 ppm) groups are absent (see Online Supplementary Materials).

It turned out that at room temperature in a DMSO-d_6 solution individual compounds *E*-**3a** and *Z*-**3b** would undergo isomerization forming mixtures of the corresponding *E*- and *Z*-isomers. It is known that the *E*-isomer of methyl pyruvate semicarbazone is converted to the *Z*-isomer under irradiation (λ 254 nm, exposure for 2 days),[15] while *N*-acylhydrazones of methyl pyruvate undergo partial isomerization (*E* → *Z*) when heated to 30–40 °C for several hours.[16] The study of the isomerization of *E*-**3a** and *Z*-**3b** in a DMSO-d_6 solution (0.217 M) controlled by ^{1}H NMR spectroscopy shows that their isomerization processes are slightly different (see Online Supplementary Materials). Thus, already after 0.5 h, the solution of *Z*-**3b** contains ~1% of the *E*-isomer, while *E*-**3a** still remains individual. However, the equilibrium of both processes completes after ~105 h (the fraction of the *Z*-isomer for **3a** reaches 37.5%, the fraction of the *E*-isomer for *Z*-**3b** approaches 55%).

As noted above, quantum-chemical calculations for the individual *E*- and *Z*-isomers of **3a** indicate that isomer *Z*-**3a** is more favorable in the isolated state (for the calculation methods, see refs. 17–22). Its antipode *E*-**3a** is 3.8 kcal mol^{-1} less energy-efficient. Additional stabilization of *Z*-**3a** can be achieved due to the presence of an intramolecular hydrogen bond N–H···O (N···O 2.655 Å) leading to a planar six-membered cycle, while in case of *E*-**3a** an intramolecular hydrogen bond is incorporated into a seven-membered cycle and is much longer (N···O 2.878 Å, see Online Supplementary Materials). The topological analysis of the electron density distribution function, followed by the evaluation of interactions based on the semi-quantitative Espinosa–Lecomte correlation,[23] showed that the energy of the intramolecular hydrogen bond in *Z*-**3a** and *E*-**3a** is 3.7 and 8.9 kcal mol^{-1}, respectively.

At the same time, when considering the stability of the *E*- and *Z*-isomers of **3a** in solution, it should be taken into account that the *E*-**3a** (4.97 D) isomer exceeds *Z*-**3a** (3.3 D) in terms of the dipole moment. Based on this, the high polarity of DMSO-d_6 could lead to a decrease in the energy difference; however, taking into account nonspecific solvation (SCRF = PCM) in quantum-chemical calculations, only slight changes in the difference in the energies of *Z*-**3b** and *E*-**3b** are found, which amount to ~3.45 kcal mol^{-1}. In view of the observed difference in the ratio of *E*- and *Z*-isomers for **3a** and **3b** in solution, additional quantum-chemical calculations taking into account the specific solvation for **3b** showed that the *Z*-isomer is more favorable, and the difference in energy (3.21 kcal mol^{-1}) is only slightly different from **3a**.

The structure of isolated individual isomers of semicarbazones *E*-**3a**, *Z*-**3b**, and *Z*-**3d** was studied by X-ray diffraction analysis (Figure 1).[†] It turned out that the intramolecular hydrogen bond in the *E*-**3a** crystal supposed from quantum-chemical calculations does not actually occur, since the molecules are probably involved in the formation of intermolecular hydrogen bonds leading to a change in their conformations. On the contrary, an intramolecular hydrogen bond is realized in the *Z*-**3b** crystal; however, due to the presence of intermolecular interactions, the distance between the proton donor and acceptor in the crystal is longer (2.750 Å) than that derived from the calculation. To estimate the hydrogen bond energy in the *Z*-**3b** crystal, we used the invariom model[26] which allowed us to obtain a pseudostatic electron density function using tabulated multipole parameters for certain types of atoms and functional groups. Based on the obtained electron density function, we carried out its topological analysis and estimated the energy in the framework of the Espinosa–Lecomte correlation, which turned out to be ~3 kcal mol^{-1} less than in the isolated state. Thus, taking into account the real solvation of a molecule in solution, its stabilization by intramolecular hydrogen bond can be significantly less than in an isolated state. Thus, the evaluation of the strength of the intramolecular hydrogen bond in *Z*-**3b** for an

[†] Crystals of compounds **3a** were obtained from MeOH, and crystals of compounds **3b** and **3d** from EtOH by slow solutions evaporation.

Crystal data for **3a**. $C_5H_8N_4O_5$, M = 204.15, monoclinic, space group $P2_1/n$ (no. 14), 120(2) K, a = 8.0712(9), b = 7.4649(8) and c = 14.5531(15) Å, α = 90°, β = 99.506(2)°, γ = 90°, Z = 4, V = 864.79(16) Å^3, d_{calc} = 1.568 mg mm^{-3}, F(000) = 424.0. A single crystal with dimensions 0.32 × 0.18 × 0.17 mm was selected and intensities of 9589 reflections were measured using a Bruker D8 Quest with Photon III detector diffractometer [ω-scans, μ(MoK$_\alpha$) = 0.140 mm^{-1}, $2\theta_{max}$ = 58°]. After merging of equivalents and absorption correction, 2286 unique reflections (R_{int} = 0.024) were used for the structure solution and refinement. Final R factors: R_1 = 0.0328 [reflections with $I > 2\sigma(I)$], wR_2 = 0.0850 (all reflections), GOOF = 1.054.

Crystal data for **3b**. $C_6H_{10}N_4O_5$, M = 218.17, monoclinic, space group $P2_1/n$ (no. 14), 120.15 K, a = 12.4559(11), b = 4.6090(4) and c = 16.7955(15) Å, α = 90°, β = 99.660(2)°, γ = 90°, Z = 4, V = 950.55(15) Å^3, d_{calc} = 1.525 mg mm^{-3}, F(000) = 456.4. A single crystal with dimensions 0.32 × 0.25 × 0.18 mm was selected and intensities of 11846 reflections were measured using a Bruker D8 Quest with Photon III detector diffractometer [ω-scans, μ(MoK$_\alpha$) = 0.133 mm^{-1}, $2\theta_{max}$ = 61°]. After merging of equivalents and absorption correction, 2873 unique reflections (R_{int} = 0.033) were used for the structure solution and refinement. Final R factors: R_1 = 0.0380 [reflections with $I > 2\sigma(I)$], wR_2 = 0.0973 (all reflections), GOOF = 1.044.

Crystal data for **3d**. $C_{12}H_{14}N_4O_5$, M = 294.27, triclinic, space group $P\bar{1}$ (no. 2), 110(2) K, a = 6.6733(5), b = 7.8870(7) and c = 14.5043(12) Å, α = 90°, β =80.112(3)°, γ = 90°, Z = 2, V = 681.19(10) Å^3, d_{calc} = 1.435 mg mm^{-3}, F(000) = 308.0. A single crystal with dimensions 0.16 × 0.14 × 0.12 mm was selected and intensities of 10048 reflections were measured using a Bruker D8 Quest with Photon III detector diffractometer [ω-scans, μ(MoK$_\alpha$) = 0.114 mm^{-1}, $2\theta_{max}$ = 58°]. After merging of equivalents and absorption correction, 3612 unique reflections (R_{int} = 0.0479) were used for the structure solution and refinement. Final R factors: R_1 = 0.0523 [reflections with $I > 2\sigma(I)$], wR_2 = 0.1266 (all reflections), GOOF = 1.058.

Semi-empirical corrections for absorption were performed in the SADABS program.[24] The structure was solved by the direct method using the SHELXT software package.[25]

CCDC 1881853 (for **3a**), 1881854 (for **3b**) and 2260564 (for **3d**) contain 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.

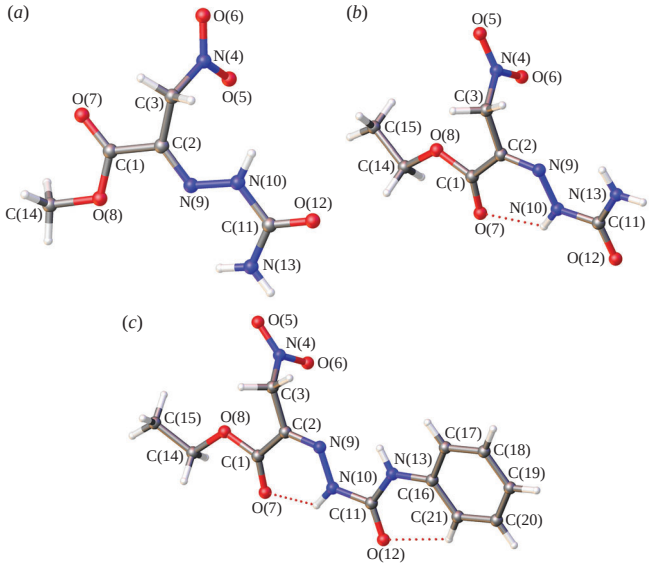


Figure 1 Perspective views of (*a*) compound **3a**, (*b*) compound **3b**, and (*c*) compound **3d** according to X-ray data.

associate with one DMSO molecule showed the formation of the amino group of the bifurcate hydrogen bond by protons and, as a result, the weakening of the intramolecular hydrogen bond (N···O 2.770Å, energy 4.8 kcal mol^{-1}, see Online Supplementary Materials).

Thus, the obtained results of X-ray diffraction studies and quantum-chemical calculations indicate that the stabilization of the *Z*-isomer observed in the isolated state in the cases of **3a** and **3b** can be significantly leveled due to the weakening of the intramolecular hydrogen bond. The observed differences in the isomerization dynamics of **3a** and **3b** is the consequence of moving from methyl group in **3a** to ethyl one in **3b**, which is enough to affect the interaction with solvate molecules.

In summary, varying the conditions for the reaction of alkyl 3-bromo-3-nitroacrylates with semicarbazides makes it possible to obtain both aza-Michael adducts in the form of a mixture of diastereoisomers and semicarbazones of alkyl 3-nitropyruvates in the form of a mixture of *E*- and *Z*-isomers, one of which in each case can be isolated by recrystallization.

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).

Physicochemical studies were carried out using the equipment of the Center for Collective Use ‘Physical and chemical methods for the study of nitro compounds, coordination, biologically active substances and nanostructured materials’ of the Interdisciplinary Resource Center for Collective Use ‘Modern physical and chemical methods for the formation and study of materials for the needs of industry, science and education’ of Herzen State Pedagogical University of Russia.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.042.

References

1 M. P. Fink, *J. Int. Med.*, 2007, **261**, 349.
2 U. N. Das, *Med. Sci. Monit.*, 2006, **12**, RA79.
3 G. Velicelebi, K. A. Stauderman, F. King, Y. Pei and J. P. Whitten, *Patent WO 2009/076454A2*, 2009.
4 S. Thota, D. A. Rodrigues, P. D. S. M. Pinheiro, L. M. Lima, C. A. Fraga and E. J. Barreiro, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 2797.
5 Y. Demir, F. S. Tokalı, E. Kalay, C. Türkeş, P. Tokalı, O. N. Aslan, K. Şendil and Ş. Beydemir, *Mol. Diversity*, 2022, **6**, 1.
6 Yu. P. Kitaev and B. I. Buzykin, *Gidrazony* (*Hydrazones)*, Nauka, Moscow, 1974 (in Russian).
7 M. D. Mashkovsky, *Lekarstvennye sredstva* (*Medicines*), 16th edn., Novaya Volna, Moscow, 2012, vol. 2, pp. 457, 849 (in Russian).
8 V. V. Pelipko and K. A. Gomonov, *Chem. Heterocycl. Compd.*, 2021, **57**, 624.
9 G. Just and S. Kim, *Can. J. Chem.*, 1977, **55**, 427.
10 M. A. Kuritsyna, V. V. Pelipko, O. N. Kataeva, R. I. Baichurin, K. D. Sadikov, A. S. Smirnov and S. V. Makarenko, *Russ. Chem. Bull.*, 2021, **70**, 1605.
11 V. V. Pelipko, R. I. Baichurin, K. A. Lyssenko, V. V. Dotsenko and S. V. Makarenko, *Mendeleev Commun.*, 2022, **32**, 454.
12 V. V. Pelipko, R. I. Baichurin, K. A. Lyssenko, E. V. Kondrashov and S. V. Makarenko, *Mendeleev Commun.*, 2023, **33**, 451.
13 V. V. Pelipko, K. A. Gomonov, I. A. Litvinov, R. I. Baichurin and S. V. Makarenko, *Russ. Chem. Bull.*, 2022, **71**, 740.
14 V. M. Berestovitskaya, O. Yu. Ozerova, T. P. Efimova, V. V. Gurzhiy and T. A. Novikova, *Mendeleev Commun.*, 2016, **26**, 323.
15 G. Just and S. Kim, *Can. J. Chem.*, 1976, **54**, 2935.
16 G. Palla, G. Predieri, P. Domiano, C. Vignali and W. Turner, *Tetrahedron*, 1986, **42**, 3649.
17 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision C.01*, Gaussian, Wallingford, CT, 2010.
18 J. Perdew, M. Ernzerhof and K. Burke, *J. Chem. Phys.*, 1996, **105**, 9982.
19 S. Grimme, J. Antony, S. Ehrlich and H. Krieg, *J. Chem. Phys.*, 2010, **132**, 154104.
20 S. Grimme, S. Ehrlich and L. Goerigk, *J. Comput. Chem.*, 2011, **32**, 1456.
21 S. Miertuš, E. Scrocco and J. Tomasi, *Chem. Phys.*, 1981, **55**, 117.
22 T. A. Keith, *AIMAll, Version 16.08.17, TK Gristmill Software*, Overland Park, KS, USA, 2016.
23 E. Espinosa, E. Molins and C. Lecomte, *Chem. Phys. Lett.*, 1998, **285**, 170.
24 G. M. Sheldrick, *SADABS*, Göttingen, Germany, 2004.
25 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Adv.*, 2015, **71**, 3.
26 B. Dittrich, C. B. Hübschle, M. Messerschmidt, R. Kalinowski, D. Girnt and P. Luger, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2005, **61**, 314.

Received: 15th May 2023; Com. 23/7171