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New spiro-fused 2-nitrocyclopropanecarboxylates: synthesis and structure

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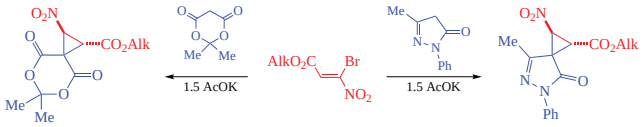
Reactions of alkyl 3-bromo-3-nitroacrylates with cyclic CH-acids, Meldrum's acid or 3-methyl-1-phenylpyrazol-5-one, afford new spiro-fused 2-nitrocyclopropanecarboxylates. In the case of Meldrum's acid, the products are formed as individual diastereomers. The obtained experimental results are confirmed by quantum chemical calculations (B3LYP/6-311+G(d,p) taking into account solvent effects).

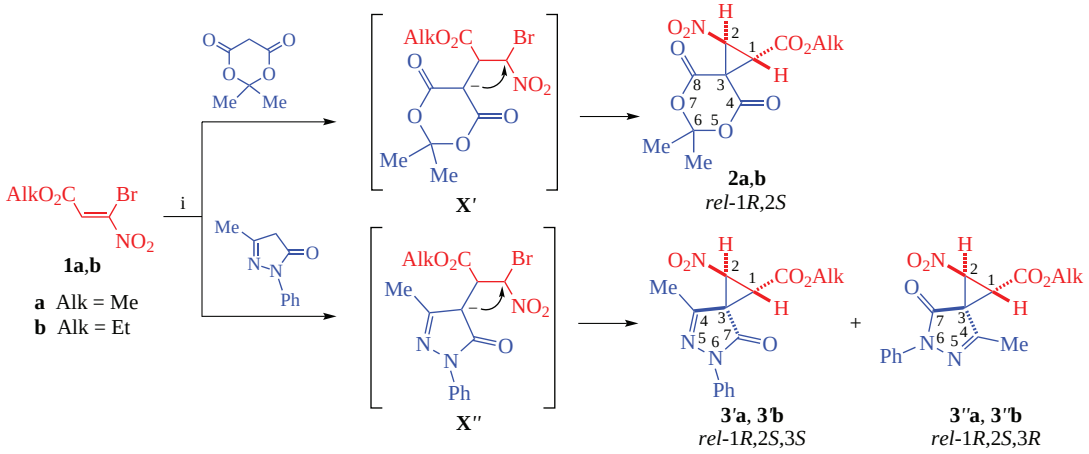


Keywords: 1-halo-1-nitroethenes, 3-bromo-3-nitroacrylates, Meldrum's acid, 3-methyl-1-phenylpyrazol-5-one, nitrocyclopropane, spirocyclopropane.

Nitrocyclopropanes represent an original family[1] among compounds with strained small rings,[2–5] which are of interest for both theory and practice. Nitrocyclopropane fragment is included in the structure of the peptide antibiotic *hormaomycin*.[6] Nitrocyclopropanes can serve as precursors for amino-cyclopropanes found in a number of natural substances.[7,8] The introduction of an ester group into the nitrocyclopropane moiety makes these compounds even more attractive, given the potential possibility of obtaining cyclopropane amino acids from them.[1] 1-Aminocyclopropanecarboxylic acids demonstrate a wide range of biological properties,[7,9–12] they are precursors of ethylene biosynthesis,[7] and are used in the synthesis of peptides.[7,9] 2-Aminocyclopropanecarboxylic acids exhibit pharmacological activity against $GABA_C$ receptors.[13]

Among the known syntheses of 2-nitrocyclopropane-carboxylates, the reactions of nitroalkenes with (halo)-malonates[14–17] as well as α,β-unsaturated carboxylates with halonitromethanes[18–21] have been actively employed. Several known spiro-fused nitrocyclopropanecarboxylates were obtained by the reactions of bromonitroalkanes with 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylates.[18,20] At the same time, available *gem*-halo nitroalkenes would react with cyclic CH-acids to form spironitrocyclopropane structures,[22,23] while 3-bromo-3-nitroacrylates being the representatives of β-functionalized *gem*-bromo nitroalkenes are effective Michael acceptors.[24]

In this study, we propose a synthesis of new spiro-fused 2-nitrocyclopropanecarboxylates based on the reaction of alkyl 3-bromo-3-nitroacrylates[25] **1a**,**b** with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) or 3-methyl-1-phenylpyrazol-5-one (Scheme 1). The reaction proceeds in anhydrous methanol at room temperature in the presence of fused potassium acetate (bromonitroacrylate/CH-acid/AcOK = 1 : 1 : 1.5) and leads to alkyl 6,6-dimethyl-2-nitro-4,8-dioxo-5,7-dioxaspiro[2.5]octane-



Scheme 1 *Reagents and conditions*: i, AcOK (1.5 equiv.), MeOH, 18–20 °C, 3 h.

1-carboxylates **2a**,**b** or alkyl 4-methyl-2-nitro-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-en-1-carboxylates **3a**,**b**, respectively.† The transformation is a domino process that includes the formation of the Michael adduct (**X′**, **X″**) and its cyclization by intramolecular *C*-alkylation. According to the ^{1}H NMR spectra, nitrocyclopropanecarboxylates **2a**,**b** are formed as single diastereomers. Products **3a**,**b** are formed as mixtures of two diastereomers (ratios **3′a**/**3″a** or **3′b**/**3″b** are 2 : 1), which are easily separated by silica gel column chromatography.

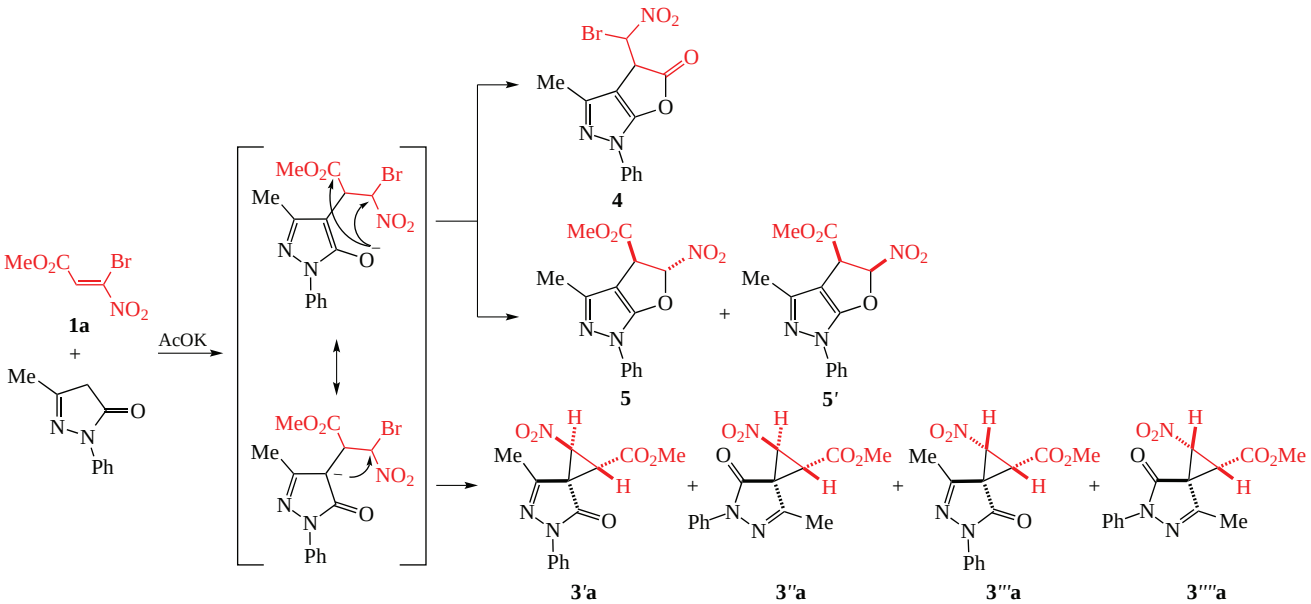
The experimental results obtained in the case of reactions with 3-methyl-1-phenylpyrazol-5-one are of undoubted interest from a theoretical point of view, since this CH-acid is capable of producing both *C*-[26–28] and *O*-alkylation products.[29–31] In addition, it is known that 3-bromo-3-nitroacrylates react with acyclic, carbo- and heterocyclic CH-acids to form furan-3-carboxylates.[32–35] During the domino reaction, the initially formed Michael adduct, in this case, undergoes intramolecular *O*-alkylation and subsequent aromatization of the intermediate dihydrofuran ring.

Evaluation of the formation barriers and thermodynamic stability using quantum chemical calculations (B3LYP/6-311+G(d,p) taking into account solvent effects) of all possible configurational isomers of dihydrofuran (**4**, **5**, **5′**) and nitrospirocyclopropane (**3**) structures using the example of reaction between methyl 3-bromo-3-nitroacrylate **1a** and 3-methyl-1-phenylpyrazol-5-one showed that the process is kinetically controlled (Scheme 2, the energy profiles of the considered reactions are given in Online Supplementary Materials).

Indeed, the difference in the thermodynamic stability of the isomers of dihydronitrofuropyrazole carboxylates **5**, **5′** and nitrospirocyclopropane carboxylates **3** is small and amounts to 1.8–2.0 kcal mol^{-1} for *trans*-isomers and 0.3–1.7 kcal mol^{-1} for *cis*-isomers in favor of compounds **3**. At the same time, the calculated energies of transition states in the formation of dihydrofuran derivatives **5**, **5′** turned out to be significantly higher than the corresponding energies for cyclopropanes **3**. Thus, for *trans*-isomers this difference is ~8.9 kcal mol^{-1}, and for *cis*-isomers it is about 5 kcal mol^{-1} in favor of spirocyclopropanes **3** (see Online Supplementary Materials). The formation of furopyrazolone **4** by involving an ester group in the reaction is extremely energetically unfavorable and thus seems to be the least probable process. It should be noted that the *trans*-isomers of nitrospirocyclopropanecarboxylates **3′a**, **3″a** are 4.1–5.7 kcal mol^{-1} more favorable than the *cis*-isomers **3‴a**, **3⁗a**. The energies of the corresponding transition states during the formation of *trans*-isomers also turned out to be lower by 3.4–3.9 kcal mol^{-1}. Thus, the results of quantum chemical modeling of the reaction of alkyl 3-bromo-3-nitroacrylates with 3-methyl-1-phenylpyrazol-5-one indicate that it should selectively lead to *trans*-isomers of spiro-fused 2-nitrospiro-cyclopropanecarboxylates.

Indeed, the spin–spin coupling constants of the methine protons of the cyclopropane ring ($^3J_{H(1)H(2)}$ = 6.3–6.9 Hz) observed in the ^{1}H NMR spectra of compounds **2a**,**b**, **3a**,**b** indicate their transoid arrangement, which agrees with the literature data for structurally similar compounds[21,36] and makes it possible to assign the *rel*-1*R*,2*S* configuration to the C^1 and C^2 atoms. Results of ^{1}H–^{1}H NOESY experiments for individual diastereomers **3a**,**b** obtained with variable values of mixing time (τ 0.5, 1, 1.5, 2 s) demonstrate NOE correlations of C^{1}H/CH$_3$ protons (heterocycle) for diastereomers **3′a**, **3′b** and C^{2}H/CH$_3$ (heterocycle) for diastereomers **3″a**, **3″b** (Figure 1). The presence of these correlations indicates the realization for diastereomers **3′a**, **3′b** of such arrangement of spirocycles, in which the methyl group of pyrazolone and the nitro group lie on the same side of the cyclopropane ring, while for diastereomers **3″a**, **3″b** this position is occupied by the methyl and alkoxycarbonyl groups. Thus, in general, diastereomers **3′a**, **3′b** should possess *rel*-1*R*,2*S*,3*S* configuration while **3″a**, **3″b** the *rel*-1*R*,2*S*,3*R* one.

The results of X-ray diffraction analysis performed for compounds **2b**, **3″a**, **3′b** convincingly confirm the accepted structures, the arrangement of cyclopropane protons, and the



Scheme 2

† *General procedure for the synthesis of alkyl 6,6-dimethyl-2-nitro-4,8-dioxo-5,7-dioxaspiro[2.5]octane- and 4-methyl-2-nitro-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1-carboxylates* **2**, **3**. To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione or 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (1.43 mmol) and freshly fused AcOK (2.14 mmol) in anhydrous MeOH (10 ml), a solution of the corresponding 3-bromo-3-nitroacrylate **1a**,**b** (1.43 mmol) in anhydrous MeOH (5 ml) was added dropwise. The resulted mixture was stirred for 3 h at 18–20 °C and then poured into crushed ice. The product was extracted with $CHCl_3$ (3 × 20 ml). The combined extracts were dried over $MgSO_4$, filtered and evaporated to dryness to give compounds **2**, **3** as crystalline substances.

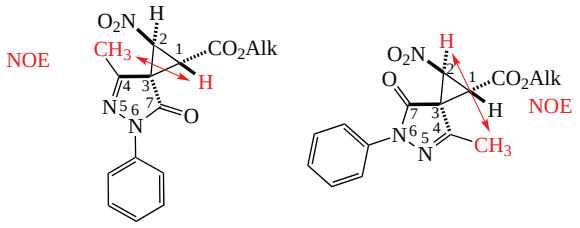


Figure 1 Main correlations in the ^{1}H–^{1}H NOESY spectra of compounds **3a**,**b**.

relative configuration of stereocenters (Figure 2).‡ It should be noted that the lengths of C^1–C^2 bonds [1.464(1)–1.474(2) Å] and C^2–NO_2 [1.482(1)–1.485(1) Å] in the molecules **2b**, **3″a** and **3′b** are close to those in the molecules of spirocyclopropanes [C^1–C^2, 1.4751–1.4782(15) Å][37,38] and condensed nitrocyclopropane [C^1–C^2, 1.4903(19) Å and C^2–NO_2, 1.4811(17) Å].[37]

In summary, we have proposed a convenient synthesis of new spiro-fused diastereohomogeneous *rel*-1*R*,2*S* 2-nitrocyclopropanecarboxylates based on the reaction of alkyl 3-bromo-3-nitroacrylates with cyclic CH-acids (Meldrum's acid and 3-methyl-1-phenylpyrazol-5-one). The structure of isolated individual diastereomeric products was characterized by IR, ^{1}H, ^{13}C, ^{15}N NMR spectroscopy and confirmed by the results of X-ray diffraction analysis.

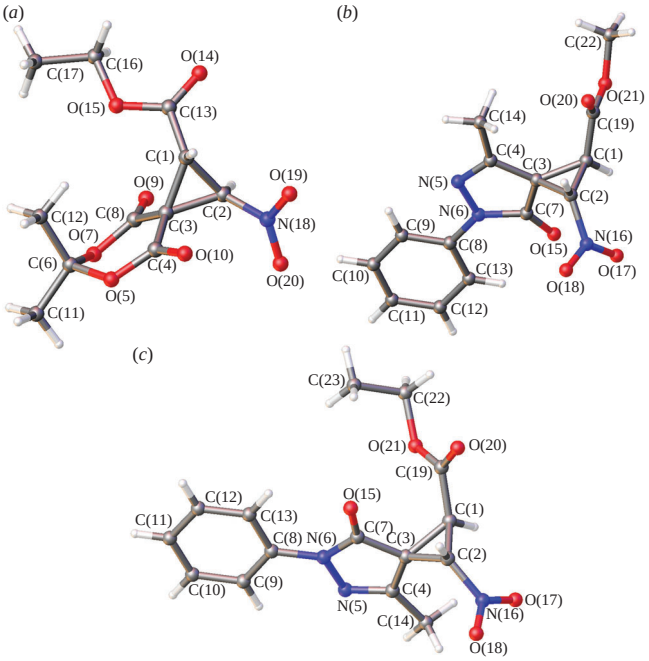


Figure 2 Perspective views of (*a*) compound **2b**, (*b*) compound **3″a** and (*c*) compound **3′b** (X-ray data).

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.2023.06.003.

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‡ Crystals of compounds **2b** and **3′b** were obtained from EtOH, and crystals of compound **3″a** from MeOH by slow solutions evaporation.

Crystal data for **2b**. $C_{11}H_{13}NO_8$, M = 287.22, monoclinic, space group $P2_{1/c}$ (no. 14), 120(2) K, a = 10.3640(4), b = 10.6108(4) and c = 11.6311(4) Å, α = 90°, β = 92.6370(10)°, γ = 90°, Z = 4, V = 1277.72(8) Å^3, d_{calc} = 1.493 mg mm^{-3}, $F(000)$ = 600.0. A single crystal with dimensions 0.32 × 0.13 × 0.11 mm was selected and intensities of 15569 reflections were measured using a Bruker APEX II CCD diffractometer [ω-scans, μ(MoK$_\alpha$) = 0.130 mm^{-1}, $2\theta_{max}$ = 58°]. After merging of equivalents and absorption correction, 3385 unique reflections (R_{int} = 0.0229) were used for the structure solution and refinement. Final R factors: R_1 = 0.0334 [3034 reflections with $I > 2\sigma(I)$], wR_2 = 0.0955 (all reflections), GOF = 0.984.

Crystal data for **3″a**. $C_{14}H_{13}N_3O_5$, M = 303.27, monoclinic, space group Cc, 120(2) K, a = 10.2121(14), b = 18.342(3) and c = 8.4035(9) Å, α = 90°, β = 118.069(2)°, γ = 90°, Z = 4, V = 1388.9(3) Å^3, d_{calc} = 1.450 mg mm^{-3}, $F(000)$ = 632.0. A single crystal with dimensions 0.415×0.325×0.1 mm was selected and intensities of 10368 reflections were measured using a Bruker APEX II CCD diffractometer [ω-scans, μ(MoK$_\alpha$) = 0.112 mm^{-1}, $2\theta_{max}$ = 63°]. After merging of equivalents and absorption correction, 4960 unique reflections (R_{int} = 0.0264) were used for the structure solution and refinement. Final R factors: R_1 = 0.0377 [4411 reflections with $I > 2\sigma(I)$], wR_2 = 0.0947 (all reflections), GOF = 1.045.

Crystal data for **3′b**. $C_{15}H_{15}N_3O_5$, M = 317.30, triclinic, space group $P\bar{1}$, 120(2) K, a = 7.5295(3), b = 10.3992(4) and c = 11.0314(4) Å, α = 65.5050(10)°, β = 70.6410(10)°, γ = 79.8960(10)°, Z = 2, V = 740.86(5) Å^3, d_{calc} = 1.422 mg mm^{-3}, $F(000)$ = 332.0. A single crystal with dimensions 0.34 × 0.21 × 0.2 mm was selected and intensities of 16670 reflections were measured using a Bruker APEX II CCD diffractometer [ω-scans, μ(MoK$_\alpha$) = 0.109 mm^{-1}, $2\theta_{max}$ = 60°]. After merging of equivalents and absorption correction, 4338 unique reflections (R_{int} = 0.0440) were used for the structure solution and refinement. Final R factors: R_1 = 0.0401 [3690 reflections with $I > 2\sigma(I)$], wR_2 = 0.1120 (all reflections), GOF = 1.042. Semi-empirical corrections for absorption were performed in the SADABS program.[39] The structure was solved by the direct method using the SHELXT software package.[40] The quantum-chemical calculations were performed using the Gaussian 09 software suite.[41]

CCDC 2164322 (for **2b**), 1845522 (for **3″a**) and 1845521 (for **3′b**) 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.

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