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New type of spin-labeled aminoenal

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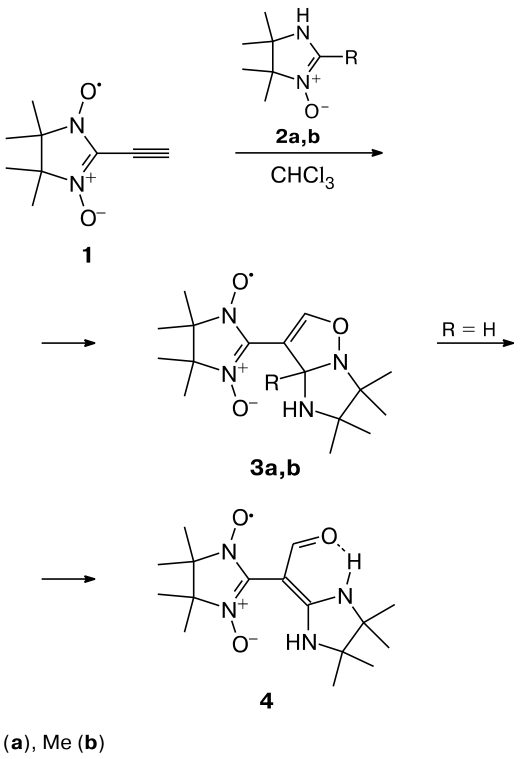
Ethynyl-substituted nitronyl nitroxide is involved in the 1,3-dipolar cycloaddition with cyclic nitrones without affecting the nitronyl nitroxide fragment. The reaction of 2,4,4,5,5-pentamethyl-4,5-dihydro-1*H*-imidazole 3-oxide produces the corresponding 1,2,3,7a-tetrahydroimidazo[1,2-*b*]isoxazole derivative. The analog of the latter derived from 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole 3-oxide is transformed into spin-labeled aminoenal. The solid phase of aminoenal is formed by packing unsymmetrical trimers resulting from the self-assembling of the molecular fragments based on a hydrogen bond network.

Key words: nitroxides, alkynes, nitrones, 1,3-dipolar addition, aminoenal, X-ray diffraction analysis, ESR spectra.

The development of an efficient procedure for the synthesis of 2-ethynyl-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyl 3-oxide**[1,2]** (**1**) stimulated us to use ethynyl-substituted nitronyl nitroxide **1** as a dipolarophile in the 1,3-dipolar cycloaddition reaction with 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole 3-oxides **2**. Based on the known fact that 4,5-dihydro-1*H*-imidazole 3-oxides can be bound at the triple bond of activated alkynes,**[3—6]** we expected that the reaction of **1** with **2** would produce spin-labeled derivatives of the previously unknown type. Actually, the reaction of **1** with **2a** in $CHCl_3$ afforded the only regioisomer of spin-labeled diaminoenal **4** in high yield (>60—65%). The formation of compound **4** is attributed to the spontaneous rearrangement of the initially formed cycloadduct **3a** (Scheme 1). An analogus cycloadduct can be stabilized by performing the reaction of **1** with 2,4,4,5,5-pentamethyl-4,5-dihydro-1*H*-imidazole-3-oxide (**2b**), which produces 1,2,3,7a-tetrahydroimidazo[1,2-*b*]isoxazole **3b** as the only product having a blue color characteristic of conjugated nitronyl nitroxides. It should be noted that the yield of cycloaddition product **3b** is low ($\leq$20%) because nitrone **2b** reacts with **1** much more slowly (under the same conditions) than **2a**, and, under the reaction conditions, compound **1** undergoes gradual deoxygenation to give ethynyl-substituted imino nitroxide, which is not involved in the cycloaddition reaction.

Scheme 1



The crystallization of compound **4** from a mixture of CH_2Cl_2 and heptane afforded intergrowths of bulk and plate-like crystals. The X-ray diffraction study showed that the bulk and plate-like crystals belong to the mono-

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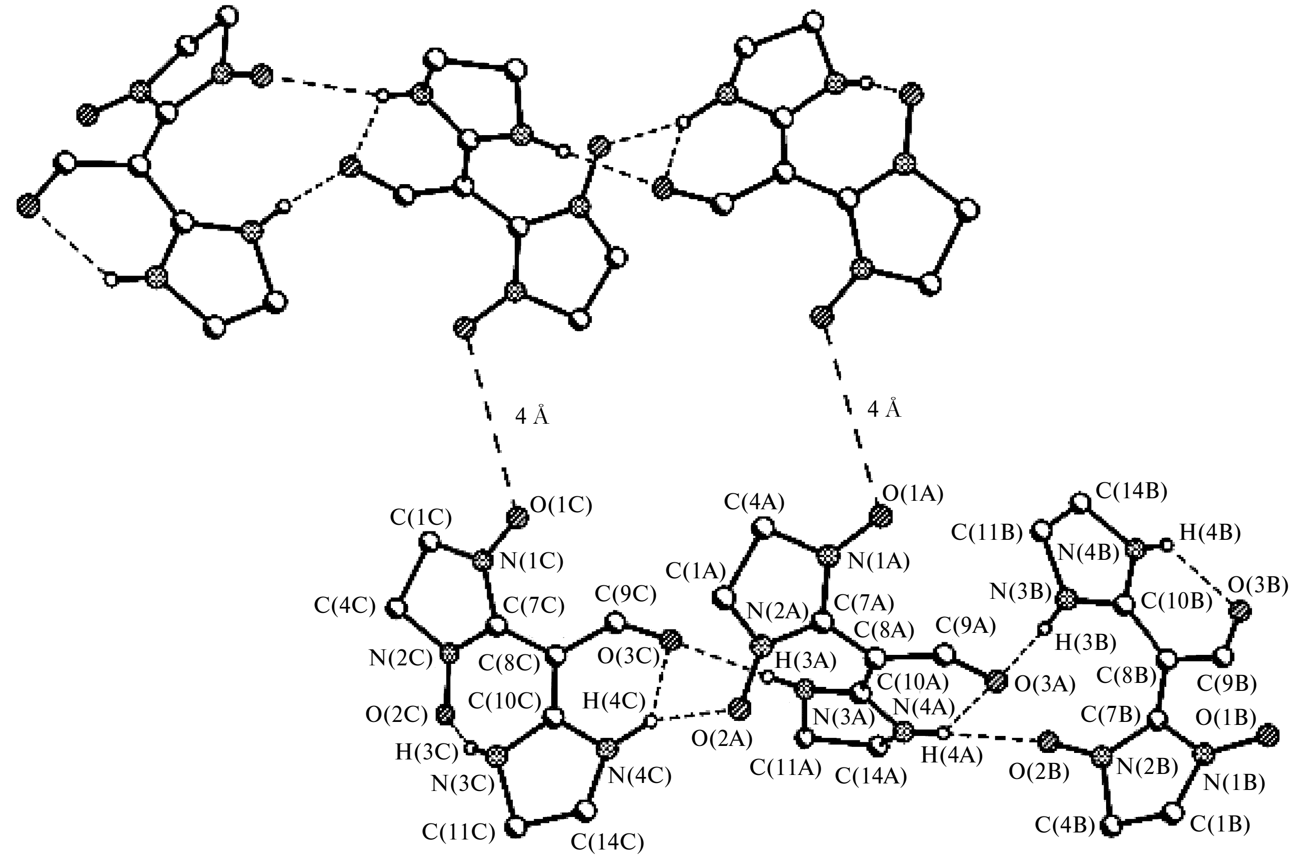

Fig. 1. Structure of trimer $(\mathbf{4})_3$ with the atomic labeling and the shortest distance between the O atoms of the >N—O groups of the adjacent trimers (the CH_3 groups and the H atoms of the aldehyde groups are omitted).

clinic and triclinic systems, respectively, and are polymorphs of **4**.

The triclinic phase of **4** has an unusual structure. The crystals of compound **4** are built of trimers $(\mathbf{4})_3$, which are formed as a result of the self-assembly of the molecular fragments based on a complex hydrogen bond network (Fig. 1). The parameters of these hydrogen bonds are given in Table 1. In the crystal, trimers $(\mathbf{4})_3$ form centrosymmetric pairs; the shortest distance between the O atoms of the >N—O groups of the adjacent trimers is 4.000 Å (see Fig. 1), Consequently, the paramagnetic centers in the solid phase of **4** are substantially spaced from each other.

It should be noted that the geometric parameters of the individual molecules in trimer $(\mathbf{4})_3$ are different. In Table 2 and Fig. 1 (in the atomic labeling), these molecules are denoted by **A**, **B** and **C**. The largest difference in the bond length is observed for the imidazolidinyl-

Table 1. Hydrogen bond parameters in trimer $(\mathbf{4})_3$

Fragment N—H...O	*d*/Å			Angle/deg N—H—O
	N—H	H...O	N...O	
N(3A)—H(3A)...O(3C)	0.86(5)	2.13(5)	2.921(5)	152(5)
N(4A)—H(4A)...O(3A)	0.84(4)	2.14(4)	2.772(5)	132(4)
N(4A)—H(4A)...O(2B)$^{\#1}$	0.84(4)	2.37(4)	3.040(5)	138(4)
N(3C)—H(3C)...O(2C)	0.97(4)	1.86(5)	2.766(6)	154(4)
N(4C)—H(4C)...O(3C)	1.06(5)	2.14(5)	2.797(5)	118(3)
N(4C)—H(4C)...O(2A)	1.06(5)	2.00(5)	2.943(5)	146(4)
N(3B)—H(3B)...O(3A)$^{\#1}$	1.00(5)	1.90(5)	2.893(5)	171(4)
N(4B)—H(4B)...O(3B)	0.89(4)	2.06(4)	2.717(5)	130(4)

Note. The equivalent atoms are generated by the symmetry operation $^{\#1}$ $-x, -y + 2, -z$.

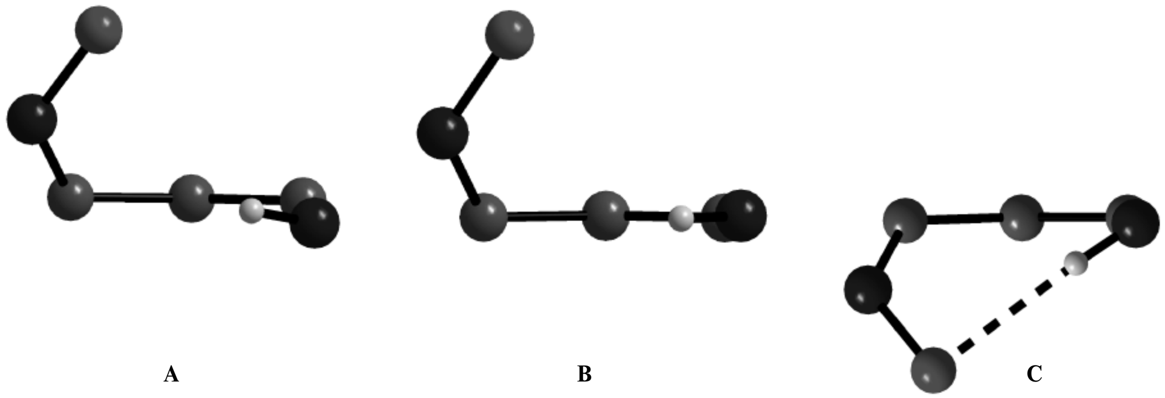

Fig. 2. Structural difference in the O(2)—N(2)—C(7)—C(8)—C(10)—N(3)—H(3) fragments in molecules **A**, **B**, and **C** (the projection along the C(8)—C(9) axis with the C(7)—C(8)—C(10) groups in the parallel orientation).

Table 2. Selected bond lengths in trimer (**4**)$_3$

Bond	Molecule		
	A	**B**	**C**
N(1)—O(1)	1.280(4)	1.291(4)	1.276(4)
O(2)—N(2)	1.310(4)	1.300(4)	1.307(4)
N(1)—C(7)	1.359(5)	1.364(5)	1.374(5)
N(2)—C(7)	1.348(5)	1.351(5)	1.340(5)
O(3)—C(9)	1.245(5)	1.253(5)	1.242(5)
N(3)—C(10)	1.349(5)	1.347(5)	1.351(5)
N(4)—C(10)	1.365(5)	1.334(5)	1.338(5)
C(7)—C(8)	1.445(6)	1.441(6)	1.453(5)
C(8)—C(10)	1.393(6)	1.425(6)	1.422(6)
C(8)—C(9)	1.413(6)	1.408(6)	1.412(6)

idene fragments. The angles between the planes of the CN$_2$ fragments of the heterocycles in molecules **A**, **B** and **C** are also different (56.0(4), 51.6(4), and 44.0(6)°, respectively). Figure 2 shows the resulting synchronous appearance of the spatial difference in the mutual orientation of the heterocycles. Due to a large angle of twist of the heterocycles in molecules **A** and **B**, the N(3A)—H and N(3B)—H groups and the O(2B) and O(2A) atoms of the N—O groups are involved in intermolecular hydrogen bonding (see Table 1), because the H......O distances (2.49(5) and 2.73(5) Å, respectively) are too large for intramolecular hydrogen bonding. A decrease in the distance between the N(3C)—H fragment and the oxygen atom of the N—O group in molecule **C** due to a smaller angle between the planes of the CN$_2$ fragments of the heterocycles leads to the involvement of the N(3C)—H group in intramolecular hydrogen bonding ($d_{\mathrm{H...O}}$ = 1.86(5) Å), which is responsible for the termination of polymerization in the step of formation of the trimer.

The experimental effective magnetic moments (1.73±0.01 μ_B) for polycrystalline samples of **3b** and **4** at room temperature correspond to the theoretical value for monoradicals, which confirms high purity of the nitronyl nitroxides. The magnetic moment μ_{eff} decreases upon cooling of the samples to temperatures below 25 K, which is evidence of weak antiferromagnetic exchange interactions between the paramagnetic centers in the solid phases of **3b** and **4**.

The ESR spectrum of nitroxide **4** (Fig. 3) consists of a triplet of triplets associated with splitting due to the presence of two nonequivalent ^{14}N nitrogen nuclei (a_{N^1} = 0.823 mT, a_{N^2} = 0.696 mT). The substructure of the lines is virtually unresolved and was simulated by standard signals of 12 protons from the methyl groups of the imidazoline ring; $a_{12\mathrm{H}}$ = 0.02 mT with a uniform linewidth somewhat larger than is generally observed (0.024 mT instead of 0.01 mT). The isotropic g factor (g_{iso} = 2.0061) was determined with the use of solid diphenylpicrylhydrazyl as the standard (the accuracy of the determination of the spin-spin coupling constants and the g factors is 0.005 mT and 0.0001, respectively). The magnetic nonequivalence of the ^{14}N nuclei of the imidazoline ring indicates that the substituent in the second position is rather rigidly fixed in an unsymmetrical orientation with respect to the nitronyl nitroxide fragment due to a strong hydrogen bond between the N—H group of the substitu-

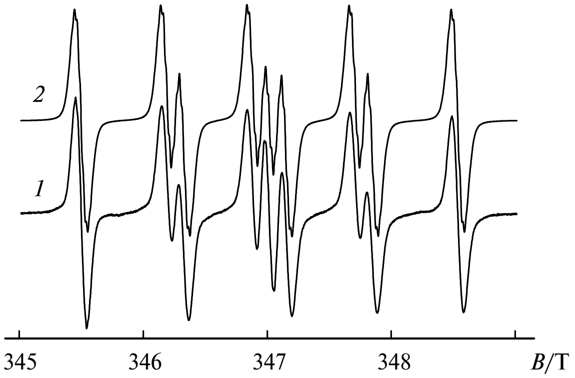

Fig. 3. Experimental (*1*) and simulated (*2*) ESR spectra of compound **4** in toluene at room temperature.

ent and the O atom of the N—O group. This is why nitroxide **3b** capable of forming an analogous hydrogen bond also gave the ESR spectrum with the parameters virtually identical to those observed for **4**. The spin-spin coupling constants are also indicative of a slight spin density delocalization from the imidazoline fragment to the substituent in the side chain.

To conclude, our investigation showed that 2-ethynyl-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyl 3-oxide (**1**) can be involved as a dipolarophile in the 1,3-dipolar cycloaddition reaction with 2-*R*-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole 3-oxides **2**. If R = H, the reaction produces spin-labeled aminoenal **4**. This result deserves notice as both a methodological approach to the synthesis of this group of aminoenals and a new method for preparing kinetically stable spin-labeled derivatives, which can form high-dimensional heterospin systems in reactions with metal ions. This will be the subject of our further studies.

Experimental

The IR spectra were recorded in the 400—4000 cm^{-1} region on a Bruker VECTOR-22 spectrophotometer in KBr pellets. The melting points were determined on a Boetius hot-stage microscope. The microanalyses were carried out on a Carlo Erba 1106 analyzer at the N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Russian Academy of Sciences. The electron impact mass spectra were obtained on a Finnigan MAT-8200 mass spectrometer (70 eV). The X-band steady state ESR spectra of **3b** and **4** were recorded in a dilute toluene solution at room temperature on a Bruker EMX spectrometer and were simulated with the use of the Winsim v.0.96 program package.[7] The magnetochemical measurements were carried out on a SQUID Quantum Design MPMS-5S magnetometer in the temperature range of 2—300 K. 2-(Ethynyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyl 3-oxide[1,8] (**1**), 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole 3-oxide[9] (**2a**), and 2,4,4,5,5-pentamethyl-4,5-dihydro-1*H*-imidazole 3-oxide[10] (**2b**) were synthesized according to procedures published earlier.

4,4,5,5-Tetramethyl-2-[2-oxo-1-(4,4,5,5-tetramethylimidazolidin-2-ylidene)ethyl]-4,5-dihydro-1*H*-imidazole-1-oxyl 3-oxide (4). A solution of compounds **1** (25 mg, 0.14 mmol) and **2a** (20 mg, 0.14 mmol) in CHCl$_3$ (5 mL) was stirred at 25 °C for 1 h. Then the reaction mixture was kept at 5 °C for 12 h and chromatographed on a 1.5×5 cm silica gel column using ethyl acetate as the eluent. The blue fraction was collected and concentrated. The residue was recrystallized from a mixture of heptane and CH$_2$Cl$_2$. The yield was 30 mg (67%), m.p. 180—182 °C. IR, ν/cm^{-1}: 700, 735, 868, 890, 988, 1020, 1139, 1177, 1204, 1257, 1303, 1336, 1370, 1394, 1454, 1571, 1627, 2976, 3285. High-resolution mass spectrum. Found: *m/z* 323.2084 [M]$^+$. C$_{16}$H$_{27}$N$_4$O$_3$. Calculated: M = 323.2083. MS, *m/z* (I_{rel} (%)): 324 (20) [M + 1]$^+$, 323 (100) [M]$^+$, 291 (17), 247 (26), 210 (23), 209 (30), 206 (32), 204 (17), 194 (43), 193 (42), 192 (48), 190 (16), 176 (30), 166 (22), 165 (31), 150 (15), 149 (17), 148 (18), 124 (17), 109 (11), 108 (11), 107 (22), 100 (61), 98 (30), 85 (15), 84 (88), 83 (41), 69 (55), 58 (74), 56 (24), 55 (42), 43 (21), 42 (40), 41 (57). Found (%): C, 60.4; H, 8.4; N, 16.9. C$_{16}$H$_{27}$N$_4$O$_3$. Calculated (%): C, 59.4; H, 8.4; N, 17.3.

4,4,5,5-Tetramethyl-2-(2,2,3,3,7a-pentamethyl-1,2,3,7a-tetrahydroimidazo[1,2-*b*]isoxazol-7-yl)-4,5-dihydro-1*H*-imidazole-1-oxyl 3-oxide (3b). A solution of compounds **1** (15 mg, 0.084 mmol) and **2b** (13 mg, 0.084 mmol) in CHCl$_3$ (3 mL) was stirred at 25 °C for 1 h. Then the reaction mixture was kept at 5 °C for 48 h and chromatographed as described above. The column was eluted with ethyl acetate. The blue fraction was collected and concentrated. The residue was dissolved at room temperature in hexane (3 mL), and the resulting solution was kept at −15 °C for 24 h, after which a precipitate was obtained. The solvent was decanted, and the precipitate was dried under a slow argon flow. The yield was 6 mg (21%), m.p. 124—125 °C. IR, ν/cm^{-1}: 749, 802, 830, 869, 887, 914, 937, 1083, 1121, 1163, 1214, 1276, 1360, 1387, 1425, 1449, 1571, 1604, 2984, 3133, 3366. High-resolution mass spectrum. Found: *m/z* 337.2241 [M]$^+$. C$_{17}$H$_{29}$N$_4$O$_3$. Calculated: M = 337.2240. MS, *m/z* (I_{rel} (%)): 338 (5) [M + 1]$^+$, 337 (24) [M]$^+$, 156 (65), 100 (13), 98 (13), 84 (100), 82 (12), 69 (42), 58 (18), 55 (20), 43 (13), 42 (62), 41 (38). Found (%): C, 60.4; H, 8.6; N, 16.5. C$_{17}$H$_{29}$N$_4$O$_3$. Calculated (%): C, 60.5; H, 8.7; N, 16.6.

X-ray diffraction study. The crystallization of **4** from a CH$_2$Cl$_2$—heptane mixture afforded a mixture of plate-like crystals and (predominantly) intergrowths of bulk crystals. The crystallization of **4** from a toluene—CH$_2$Cl$_2$ mixture gave rise only to intergrowths of bulk crystals, *i.e.*, the latter were more suitable for investigation than plate-like crystals. However, in spite of repeated X-ray diffraction studies of bulk crystals, the structure refinement of the monoclinic modification was converged to the R factor of no lower than 11%.

X-ray diffraction data were collected on a SMART APEX CCD Bruker AXS diffractometer (Mo-Kα, λ = 0.71073 Å, T = 240 K, the absorption correction was applied using the Bruker SADABS software, version 2.10). The structure was solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for all non-hydrogen atoms. The H atoms were positioned geometrically and refined using a riding model. All calculations associated with the structure solution and refinement were carried out with the use of the Bruker SHELXTL program package, version 6.14.

Plate-like crystals of trimer (**4**)$_3$: C$_{16}$H$_{27}$N$_4$O$_3$, M = 323.42, triclinic crystals, space group $P1^{-}$, a = 9.672(5) Å, b = 15.212(7) Å, c = 20.782(10) Å, α = 69.303(9)°, β = 80.487(9)°, γ = 72.189(10)°, V = 2718(2) Å^3; Z = 6, 24691 measured reflections (1.52 < θ < 25.00°), of which 9571 reflections are independent, ρ_{calc} = 1.186 g cm^{-3}, μ = 0.83 cm^{-1}, R_1 = 0.0760, wR_2 = 0.1389.

Bulk crystals of **4**: C$_{16}$H$_{27}$N$_4$O$_3$, M = 323.42, crystals are monoclinic, space group Pc, a = 10.933(7) Å, b = 26.898(17) Å, c = 12.657(8) Å, β = 93.499(12)°, V = 3715(4) Å^3; Z = 4.

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