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Synthesis and properties of the first representatives of terminal acetylenes in 3-imidazoline-1-oxyl 3-oxide series

O. L. Krivenko and S. F. Vasilevskii**

Institute of Chemical Kinetics and Combustion of the Siberian Branch of the Russian Academy of Sciences,
3 ul. Institutskaya, 630090 Novosibirsk, Russian Federation.
Fax: +7 (383) 330 7350. E-mail: vasilev@kinetics.nsc.ru

Method for the synthesis of *m*- and *p*-isomers of 4-[2-(ethynylphenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl 3-oxides by the cross-coupling of 4-[2-(3-iodophenyl)vinyl]- and 4-[2-(4-iodophenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl 3-oxides with (trimethylsilyl)acetylene followed by desilylation was elaborated. The reactions at the CH-fragment of the ethynyl group were performed. The Mannich reaction proceeds with the loss of a spin label, whereas the oxidative homocoupling, with its retention.

Key words: nitroxyl radicals, alkynes, the Sonogashira reaction, 3-imidazolinenitroxides.

The high stability of 3-imidazoline nitroxyl radicals and susceptibility of their ESR spectra pre-determine a wide application of these compounds as spin labels and sondes, analytical reagents, and complex-forming paramagnetic ligands.[1]

A quest for the new materials with the desired magnetic and optical properties is restrained by the strict structural, electronic, and sterical requirements to the substrate. Radicals with ethynyl groups seem to be particularly prospective, since the HC≡C fragment is a rigid, convenient building element for the construction of the spin-labeled molecules with the preliminary set of electronic, geometric, and magnetic parameters. In fact, from one hand, the increased acidity of the acetylene proton allows one to easily functionalize the molecule or to create new C—C bonds. On the other hand, the C≡C unit is able to participate in delocalization of electronic density and to secure a rigid spatial structure of the molecule, providing the necessary factors for studying of various magnetic or optical properties. In addition, the partial hydrogenation of the C≡C bond can lead to *cis*- and *trans*-ethylene derivatives, *i.e.*, to the molecules with the other geometry, but with retention of conjugation. If necessary, a complete hydrogenation of the triple bond gives one an opportunity to partially or completely decrease the exchanging interactions in the molecule of radical. This was the problem occurred during the study of important theoretical questions of the spin catalysis in recombination of spin-correlated ion-radical pairs, generated during radiolysis in the alkane solutions.[2,3] This problem was partially solved on the example of the acetylene derivatives of nitroxyl radicals of 2-imidazoline series, the subsequent hydrogenation of which allowed one for the first time to register a magnetic effect (15%) during recombination of the ion-radical pairs.[4] These works led to a conclusion that for the qualitative studies, it is necessary to additionally decrease the exchanging interaction between the spin center and the ion-radical pair, appearing as a result of radiation. The exchanging interaction can be efficiently decreased by the application of nitroxyls of 3-imidazoline series as the substrates, where the paramagnetic center is separated from the aromatic part of the molecule by two single bonds. In addition, in case of successful synthesis of the acetylene derivatives of 3-imidazolin-1-oxyls, a complete hydrogenation of the acetylene bridge can be achieved, which would lead to the additional decrease in the exchanging interaction.

It should be emphasized that, despite of the well-developed chemistry of 3-imidazolinenitroxyls, there was no information on the synthesis of alkynyl substituted 3-imidazoline-1-oxyl 3-oxides.

Earlier, we have published communications[5,6] on the synthesis of the first representatives of the disubstituted acetylene derivatives of 3-imidazoline-1-oxyl 3-oxides by the Castro method. However, this method is not suitable for the synthesis of terminal alkynes and has a number of restrictions. The essential disadvantage of this method consists in the necessity of the preliminary preparation of explosive copper acetylides. In addition, not all the terminal alkynes can form copper acetylides, for example, they cannot be obtained from 3-morpholinoprop-1-yne or 2-methylbut-3-yn-2-ol (application of the latter could have afforded terminal acetylenes upon base-promoted cleavage according to the retro-Favorsky reaction).

A catalytic method for the introduction of the acetylene alcohol residues into derivatives of 2,2,5,5-tetramethyl-3-imidazoline-1-oxyl 3-oxide under the most often used conditions of the Sonogashira reaction

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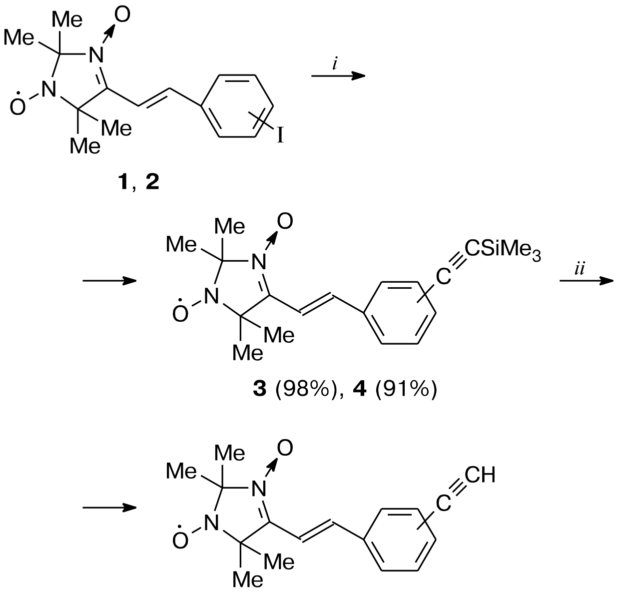
Scheme 1



1, **2**

3 (98%), **4** (91%)

5 (48%), **6** (79%)

Reagents and conditions: *i.* $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, PhH, 45 °C; *ii.* K_2CO_3, MeOH.

Note. Position of substituents in the aromatic ring: *meta* (**1**, **3**, **5**), *para* (**2**, **4**, **6**).

($Pd(PPh_3)_2Cl_2$—CuI—Et_3N, 80 °C) also failed. The reaction of cheap and easily available isomeric 4-[2-(bromophenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl 3-oxides with 2-methylbut-3-yn-2-ol led to a mixture of dehydrodimer of acetylene alcohol with diamagnetic compounds, the corresponding 4-[2-(bromophenyl)vinyl]-1-hydroxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxides, and was accompanied by resinification of the reaction mixture.

To avoid these complications, the more active (trimethylsilyl)acetylene has been chosen as the alkyne component, and the more reactive iodo derivatives **1** and **2**, as the haloarene components. This allowed us to decrease the reaction temperature to 45 °C and successfully accomplish the synthesis of ethynyl derivatives of 3-imidazoline-1-oxyl 3-oxides **3** and **4** in 98 and 91% yield, respectively (Scheme 1).

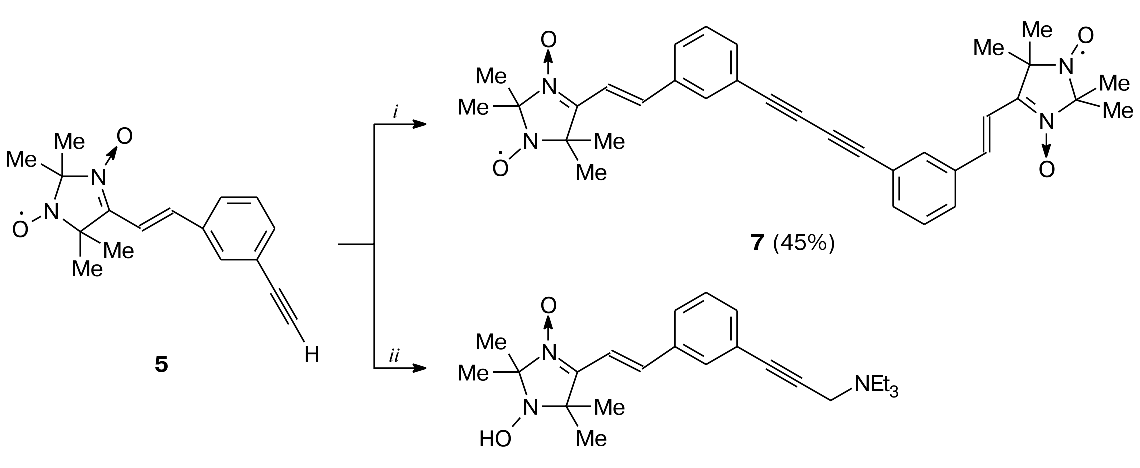
Desilylation of compounds **3** and **4** upon treatment with K_2CO_3 in MeOH leads to the target terminal ethynylimidazolines **5** and **6**.

ESR spectra of all the synthesized ethynyl substituted nitroxides[5,6] have the typical for 3-imidazoline radicals character, as in case of related disubstituted acetylenes (see data in Ref. 6), and show that the spin density in them is localized only on the $N{-}^{\bullet}O$ fragment. In this connection, we report the ESR spectra parameters for one compound **5** only (spectra for the other compounds will be reported in the next publication). In the spectrum of compound **5**, there are the main triplet on the nitrogen atom in position 1 of the cycle with the splitting of 14.13 Hz (in toluene) and weak satellites from C atoms of four methyl groups (the splitting of 5.82 Hz). There is also weak splitting of 0.23 Hz in value from twelve protons of the methyl groups.

In order to estimate the synthetic potential of the ethynyl substituted nitroxyls, the oxidative homocoupling and the Mannich condensation, two of the most typical reactions for terminal acetylenes, were carried out.

The homodimerization of compound **5** upon treatment with the air oxygen in the presence of copper(I) salts leads to the symmetrical diacetylene **7** (45%)

Scheme 2



5

7 (45%)

8 (85%)

Reagents and conditions: *i.* O_2, CuCl, Py; *ii.* $(CH_2O)_x$, Et_2NH, CuI, Ar.

(Scheme 2). During this, the paramagnetic center was retained.

The Mannich reaction was carried out in its classical version, with secondary amine and paraformaldehyde in the presence of CuI under inert atmosphere. The yield of the Mannich base **8** was 85%, during this, the loss of the spin label occurred, apparently, owing to the reduction by paraformaldehyde. However, the target nitroxyl can be easily recovered by the oxidation of *N*-hydroxy derivative in $NaIO_4$—$CHCl_3$—H_2O system.

In conclusion, a convenient method for the synthesis of terminal acetylene derivatives of 3-imidazoline-1-oxyl 3-oxides is proposed and it is shown that the reaction of paramagnetic alkynes can proceed both with the retention and with the loss of the spin label. The complete set of the spectral data, including ESR and UV spectra, will be published later.

Experimental

IR spectra of the compounds synthesized were recorded on a Bruker IFS 66 spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DPX 400 spectrometer (400.13 MHz) in $CDCl_3$. Mass spectra were obtained on a Finnigan SSQ-710 mass-spectrometer by the direct inlet method (the temperature of the ionization chamber was 220—270 °C, the ionization voltage, 70 eV). Merck 60 (70—230 μm) silica gel was used for the column chromatography; TLC monitoring was carried out on Silufol 60 F254 (Merck, 0.2 mm) plates.

2,2,5,5-Tetramethyl-4-{2-[3-(trimethylsilylethynyl)phenyl]ethen-1-yl}-3-imidazoline-1-oxyl 3-oxide (3). A mixture of iodo derivative **1** (4.45 g, 11.58 mmol), Et_3N (3 mL), PPh_3 (0.08 g), CuI (0.02 g), $Pd(PPh_3)_2Cl_2$ (0.04 g), and (trimethylsilyl)acetylene (1.4 mL, 13.9 mmol) in C_6H_6 (75 mL) was kept for 8 h under Ar atmosphere at 45 °C until iodide **1** disappeared (TLC monitoring, $CHCl_3$). After cooling, the reaction mixture was filtered through a layer of Al_2O_3 (1×2 cm), the solvent was evaporated under reduced pressure, the residue was chromatographed on Al_2O_3 with C_6H_6 as the eluent. Compound **3** (4.02 g, 98%) was obtained, m.p. 144.0—144.5 °C (from C_6H_{14}—C_6H_6). IR ν/cm^{-1}: 1258 (N→O), 1368 (N—$^\bullet$O), 2156 (C≡C). MS, *m/z* (I_{rel} (%)): 355.3 $[M]^+$ (6.86), 325.3 (63.96), 310.3 (42.52), 308.3 (46.73), 267.3 (21.41), 266.3 (27.17), 252.2 (18.93), 211.1 (17.67). Found: *m/z* 355.18373 $[M]^+$. $C_{20}H_{27}N_2O_2Si$. Calculated: M = 355.18417.

2,2,5,5-Tetramethyl-4-{2-[4-(trimethylsilylethynyl)phenyl]ethen-1-yl}-3-imidazoline-1-oxyl 3-oxide (4) was obtained similarly to **3**. The yield was 0.51 g (91%) from iodide **2** (0.61 g, 1.58 mmol), m.p. 184.0—185.0 °C (from C_6H_6—C_6H_{14}). IR, ν/cm^{-1}: 1252 (N→O), 1362 (N—$^\bullet$O), 2157 (C≡C). MS, *m/z* (I_{rel} (%)): 355.1 $[M]^+$ (22.84), 325.1 (43.98), 310.1 (56.54), 309.1 (22.75), 308.1 (73.41), 267.1 (38.07), 266.1 (33.91), 252.1 (24.26), 211.0 (16.03). Found: *m/z* 355.18055 $[M]^+$. $C_{20}H_{27}N_2O_2Si$. Calculated: M = 355.18417.

4-[2-(3-Ethynylphenyl)ethen-1-yl]-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl 3-oxide (5). A mixture of compound **3** (0.33 g, 0.9 mmol) and finely powdered precalcined K_2CO_3 (0.12 g, 0.9 mmol) was stirred in MeOH (15 mL) under argon atmosphere at ~20 °C for 4.5 h. Then, the reaction mixture was diluted by saturated aqueous $NaHCO_3$ (20 mL), extracted with $CHCl_3$ (3×20 mL), dried with Na_2SO_4, and filtered through a layer of Al_2O_3 (1×2 cm). The solvent was evaporated under reduced pressure, the residue was chromatographed on Al_2O_3 with C_6H_6 as the eluent. The product was recrystallized from C_6H_{14}—C_6H_6. The yield of product **5** was 0.12 g (48%), m.p. 141.5—142.0 °C. IR, ν/cm^{-1}: 1253 (N→O), 1362 (N—$^\bullet$O), 2103 (C≡C), 3270 (C≡CH). MS, *m/z* (I_{rel} %)): 283.1 $[M]^+$ (11.92), 253.2 (100.00), 238.2 (42.99), 236.2 (44.49), 194.1 (54.97), 165.1 (64.51), 149.0 (37.29), 139.1 (71.73). Found: *m/z* 283.14521 $[M]^+$. $C_{17}H_{19}N_2O_2$. Calculated: M = 283.14464.

4-[2-(4-Ethynylphenyl)ethen-1-yl]-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl 3-oxide (6) was synthesized similarly to **5**. Compound **6** (0.15 g, 79%) was obtained from **4** (0.23 g, 0.6 mmol), m.p. 176.0—176.6 °C (decomp., from C_6H_{14}—C_6H_6). IR, ν/cm^{-1}: 1254 (N→O), 1361 (N—$^\bullet$O), 2110 (C≡C), 3225 (C≡CH). MS, *m/z* (I_{rel} %)): 283.1 $[M]^+$ (33.31), 253.0 (100.00), 238.0 (72.42), 236.1 (84.63), 194.9 (47.73), 193.9 (75.10), 179.9 (48.82), 165.9 (54.81), 164.9 (70.52), 152.9 (40.80), 138.9 (97.80). Found: *m/z* 283.14430 $[M]^+$. $C_{17}H_{19}N_2O_2$. Calculated: M = 283.14463.

1,4-Bis{3-[2-(2,2,5,5-tetramethyl-3-oxide-1-oxyl-3-imidazolin-4-yl)ethen-1-yl]phenyl}buta-1,3-diyne (7). Air was bubbled through a solution of compound **5** (0.11 g, 0.38 mmol) and CuCl (0.01 g) in pyridine (10 mL) for 45 min until the starting **5** disappeared (TLC monitoring, $CHCl_3$). The reaction mixture was diluted with $CHCl_3$ (20 mL) and washed with 25% aq. NH_3 until the blue color disappeared, dried with K_2CO_3 and passed through a layer of Al_2O_3 (1×2 cm). The solvent was evaporated under reduced pressure, the residue was recrystallized from C_6H_{14}—C_6H_6. Compound **7** was obtained (0.05 g, 45%), m.p. 138.5—139.2 °C. IR, ν/cm^{-1}: 1256 (N→O), 1362 (N—$^\bullet$O), 2147, 2223 (C≡C—C≡C). Found (%): C, 72.74; H, 6.30; N, 8.59. $C_{34}H_{36}N_4O_4$. Calculated (%): C, 72.31; H, 6.42; N, 9.92.

4-[2-{3-[3-(*N*,*N*-Diethylamino)prop-1-yn-1-yl]phenyl}ethen-1-yl]-1-hydroxy-2,2,5,5-tetramethyl-3-imidazoline 3-oxide (8). A mixture of paraformldehyde (0.022 g, 1.63 mmol) and Et_2NH (0.054 mL, 0.742 mmol) in dioxane (7 mL) was stirred for 40 min at 45 °C under Ar atmosphere. Then, CuCl (0.005 g, 0.05 mmol) was added to the reaction mixture, and a solution of compound **5** (0.21 g, 0.742 mmol) in dioxane (5 mL) was added dropwise to this. The mixture was stirred for 3 h at 80 °C until the starting compound **5** disappeared, cooled, filtered through a layer of Al_2O_3 (1×2 cm), and the solvent was evaporated under reduced pressure. The residue was chromatographed on Al_2O_3 with C_6H_6 as the eluent. Product **8** (0.23 g, 85%) was obtained as viscous dark yellow oil. IR, ν/cm^{-1} (neat): 1257 (N→O), 1365 (N—$^\bullet$O), 2117 (C≡C), 3294 (OH). ^{1}H NMR ($CDCl_3$), δ: 1.08—1.13 (t, 6 H, $\underline{CH_3}CH_2N$, *J* = 7 Hz); 1.49 (s, 6 H, 2,2-Me); 1.58 (s, 6 H, 5,5-Me); 2.58—2.65 (q, 4 H, $N\underline{CH_2}Me$, *J* = 7 Hz); 3.63 (s, 2 H, $C\underline{CH_2}N$); 5.35 (v.br.s, 1 H, OH); 6.72—6.78 (d, 1 H, $\underline{CH}$=CHAr, *J* = 16 Hz); 7.33 (s, 4 H, Ar); 8.10—8.16 (d, 1 H, CH=$\underline{CH}$Ar, *J* = 16 Hz). MS, *m/z* (I_{rel} (%)): 369.4 $[M]^+$ (11.54), 353.3 (40.39), 336.3 (40.13), 295.2 (23.61), 281.2 (16.25), 266.2 (13.18), 224.2 (11.28), 194.2 (21.70), 193.2 (86.55), 179.3 (33.88), 178.3 (53.20). Found: *m/z* 369.24169 $[M]^+$. $C_{22}H_{31}N_3O_2$. Calculated: M = 369.24161.

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