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First acetylenic derivatives of stable 3-imidazoline nitroxides

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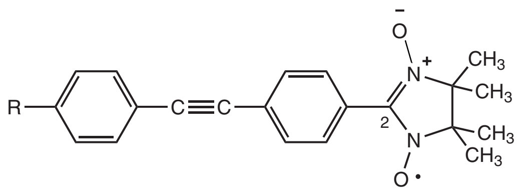
Abstract—The Stephens–Castro reaction of copper(I) salts of 1-aryl(hetaryl)alkynes with 2,2,5,5-tetramethyl-4-[2-(4-iodophenyl)-vinyl]imidazoline-3-oxide-1-ol proved to be a general method for the preparation of 2,2,5,5-tetramethyl-4-[2-(*p*-aryl(hetaryl)ethynyl-phenyl)]vinyl-3-imidazoline-3-oxide-1-oxyles.

We have recently reported the synthesis and properties of a series of spin-labelled charge acceptors that produce three-spin systems in non-polar and non-viscous alkane solutions upon X-ray irradiation.[1] These products are 2-imidazoline-1-oxyl derivatives such as **1**. Although very interesting, the 2-imidazoline derivatives present some drawbacks due to the fact that the radical is conjugated with the lateral chain, which shortens considerably the lifetime of the radical, destroying the spin correlation. To avoid this shortcoming, we thought of compounds having structure **2**; the fact that the chain is now at position 4 of the 3-imidazoline ring interrupts the conjugation and should allow an easier measurement of magnetic and optical properties.

In general, the field of polyfunctional stable nitroxylic radicals together with their coordination chemistry and their physical properties has been often explored.[2–5] We will report in this communication our attempts to synthesize a new family of stable nitroxides of the 3-imidazoline-3-oxide-1-oles series—the acetylenylnitroxides **2**. Although many studies have been devoted to the chemistry of 3-imidazoline-3-oxide-1-oxyls, no acetylenic derivatives of this series have been reported because there were no known procedures for their synthesis.[3,4] Note that an acetylene bridge is a convenient rigid fragment, which allows to obtain compounds with precise distances between functional groups, which is fundamental in the design of high dimensional molecular systems.



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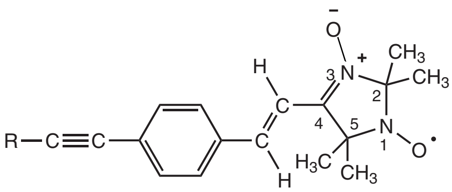

2

Keywords: Imidazoline; Nitroxides; Radicals; Stephens–Castro reaction.

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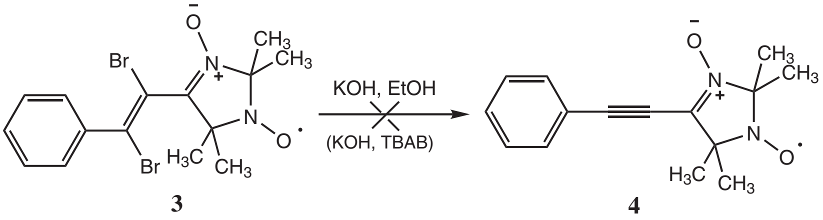
Previously we have developed procedures for the synthesis of spin-labelled acetylenes of the 2-imidazoline-1-oxyl series, for example, **1**, containing either heterocyclic or carbocyclic residues.[1,6,7] Compounds of this general type are useful model systems for the investigation of the phenomenon of spin catalysis in recombination of radical–ion pairs generated upon radiolysis.[1,8] For the reason explained in the introduction, we are interested in developing a method of synthesis of acetylenic derivatives of 3-imidazoline-3-oxide-1-oxyls, like **2**.

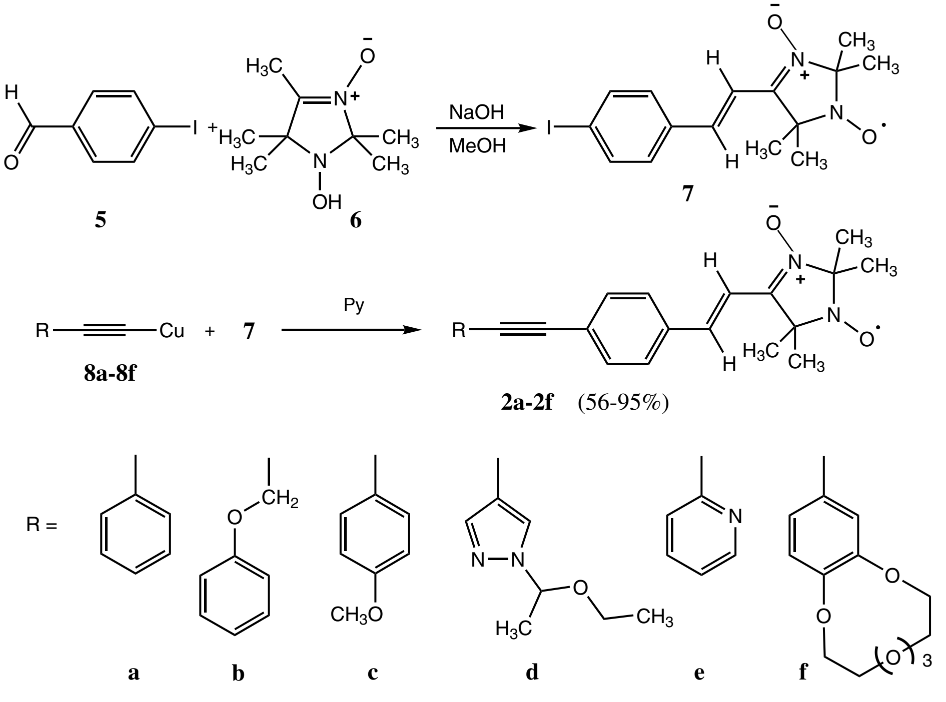
Our first approach aimed at preparing **4** and related compounds. However, all attempts to use a classical method for the synthesis of the desired acetylenes—dehydrobromination of *vic*-dibromoolefins—were unsuccessful. For instance, reaction of dibromoethylene **3** with either KOH in boiling EtOH, KOH in the presence of TBAB (tetrabutylammonium bromide), or KOH in DMSO (Scheme 1) gave a large number of products, from which acetylene **4** could not be isolated.

Another possible way to prepare acetylenic derivatives of 3-imidazoline-3-oxide-1-oxyls could be the condensation of a iodoimidazoline with a terminal acetylene using the $Pd(PPh_3)_2Cl_2$–CuI–NEt_3 system under argon atmosphere.[6] However, all our attempts to carry out the catalytic variant of the cross-coupling of a bromide bearing the spin label with 1-alkynes were also unsuccessful: the reaction resulted in the formation of diamagnetic derivatives, accompanied by the homo-coupling of 1-alkynes.

Probably, the successful application of cross-coupling in the 2-imidazoline series and the negative result of the same reaction for 3-imidazoline ones is related to the strong oxidative properties of the nitroxide group in 3-imidazoline-3-oxide-1-oxyls compared with the corresponding one in 2-imidazoline-3-oxide-1-oxyl derivatives.[5] For this reason, and taking into account the difference in the mechanisms of Cu- and Pd-catalyzed reactions, we supposed that the difficulties could be overcome by using the acetylide synthesis to obtain the desired alkynylnitroxyles.[9,10] Iodoimidazoline (**7**, Scheme 2, note that the transformation of hydroxylamine **6** into the radical **7** implies a concomitant oxidation probably by molecular oxygen),[5] prepared by reacting **5** and **6**, was introduced into the reaction flask with the



Scheme 1.



Scheme 2.

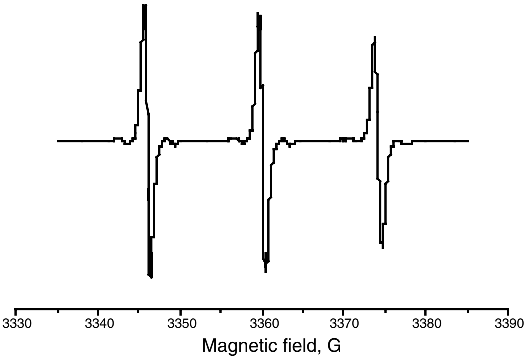


Figure 1. ESR spectrum of 10^{-4} M **2a** in degassed toluene, room temperature, microwave power 2 mW, modulation amplitude 0.005 mT.

previously prepared copper acetylides [**8a–f**: **a**, R = Ph; **b**, R = Ph–O–CH_2; **c**, R = *p*–MeO–C_6H_4; **d**, 1-(1-ethoxyethyl)-1*H*-4-pyrazolyl; **e**, R = 2-pyridyl; **f**, R = crown ether] in boiling pyridine.[7] The structure of all new compounds, obtained in excellent yields—90–95%—save in the case of the crown ether **2f**, were established by elemental analyses and spectroscopic data.[11,12]

The ESR spectra of the nitroxides **2** are typical for a 3-imidazoline radical with spin density localized only at the N(1)–O$^\bullet$ fragment (see Fig. 1) contrary to what happens for 2-imidazoline-1-oxyl derivatives **1** where the spin density is localized on the two equivalent NO fragments and on the C(2).[4–6]

The new compounds **2** show increased stability compared with the previous ones **1**, for instance, **2** remain unaltered after several weeks at room temperature while **1** must be stored in a refrigerator to prevent decomposition. This is consistent with the behaviour of both classes of imidazoline nitroxides.[5]

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References and notes

1. Sviridenko, F. B.; Stass, D. V.; Kobzeva, T. V.; Tretyakov, E. V.; Klyatskaya, S. V.; Mshvidobadze, E. V.; Vasilevsky, S. F.; Molin, Y. N. *J. Am. Chem. Soc.* **2004**, *126*, 2807.
2. Caneschi, A.; Gatteschi, D.; Rey, P. *Prog. Inorg. Chem.* **1991**, *39*, 331.
3. Voldarsky, L. B.; Reznikov, V. A.; Ovcharenko, V. I. *Synthetic Chemistry of Stable Nitroxides*; CRC: Boca Raton, 1994; p 221.
4. Kahn, O. *Molecular Magnetism*; VCH: New York, 1993.
5. *Imidazoline Nitroxides*; Volodarsky, L. B., Ed.; CRC: Boca Raton, Florida, 1988, *Synthesis and Properties*, Vol. 1, 222 pp and *Applications*, Vol. 2, 160 pp.
6. Vasilevsky, S. F.; Tretyakov, E. V.; Usov, O. M.; Molin, Yu. N.; Fokin, S. V.; Shwedenkov, Yu. G.; Ikorskii, V. N.; Romanenko, G. V.; Sagdeev, R. Z.; Ovcharenko, V. I. *Mendeleev Commun.* **1998**, *6*, 216.
7. Tretyakov, E. V.; Samoilova, R. I.; Ivanov, Yu. V.; Plyusnin, V. F.; Pashchenko, S. V.; Vasilevsky, S. F. *Mendeleev Commun.* **1999**, *3*, 92.
8. Tretyakov, E. V.; Novikova, T. V.; Korolev, V. V.; Usov, O. M.; Vasilevsky, S. F.; Molin, Yu. N. *Russ. Chem. Bull. Int. Ed.* **2000**, *49*, 1409.
9. Tretyakov, E. V.; Knight, D. W.; Vasilevsky, S. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3713.
10. Vasilevsky, S. F.; Tretyakov, E. V.; Elguero, J. *Adv. Heterocycl. Chem.* **2002**, *82*, 1.
11. Full analytical and spectroscopic data consistent with the proposed structures have been obtained for all compounds reported herein. In all cases the ESR spectra were measured in toluene with 10^{-5}–10^{-4} M concentration of radicals. For example, 4-(2-{4-[1-(1-ethoxyethyl)-1*H*-pyrazol-4-ylethynyl]-phenyl}-vinyl)-2,2,5,5-tetramethyl-3-oxide-3-imidazoline-1-oxyl (**2d**): yield 111 mg (94%), mp 169.1–169.9 °C (from benzene). IR, cm^{-1}: ν_{max} = 2214 (CC); 2935, 2984, 3047 (CH_3); 3438 (br); ^1H NMR (200 MHz, $CDCl_3$) δ, 1.67 (t, OCH_2CH_3, *J* = 7 Hz), 1.65 (d, CH–CH_3, *J* = 6 Hz), 3.33–3.53 (m, O$CH_2$$CH_3$), 5.51 (q, *CH*–$CH_3$, *J* = 6 Hz), 6.72 (br s, Ph–CH═*CH*), 7.35–7.73 (m, 3- and 5-H Pz), 7.83 (br s, Ph–*CH*═CH). Anal. Calcd for $C_{24}H_{29}N_4O_3$: C, 68.39; H, 6.93; N, 11.39. Found: C, 66.35; H, 7.07; N, 12.09. ESR, G: g_{iso} = 2.0058 A_N = 14.11 $A_{H(CH_3)}$ (12H) = 0.23, $A(^{13}C)$ = 5.93. The yield of compound **2a** is 91%, mp 197.3–198.5 °C (from benzene); that of **2b** is 92%, mp 161.5–163.3 °C (from benzene–hexane); finally that of **2c** is 90%, mp 165.8–167.3 °C (from benzene–hexane mixture).
   Compound **2e**: yield 84 mg (93%), mp 179.9–180.0 °C (from benzene–hexane). IR, cm^{-1}: ν_{max} = 2221 (C≡C); 2862, 2936, 2981 (CH_3); 3423 (br); ^1H NMR (200 MHz, $CDCl_3$) δ, 6.70 (br s, 1H, Ph–CH═*CH*), 7.16–7.22 (m, 4H, H_{Ar}), 7.47 (d, 1H, H-3(Py), *J* = 7 Hz), 7.71 [t, 1H, H-4(Py), *J* = 6 Hz], 7.97 (br s, 1H, Ph–*CH*═CH), 8.64 [d, 1H, H-6(Py), *J* = 5 Hz]. Anal. Calcd for $C_{22}H_{22}N_3O_3$: C, 73.31; H, 6.15; N, 11.66. ESR, G: g_{iso} = 2.0058 A_N = 14.11 $A_{H(CH_3)}$ (12H) = 0.23, $A(^{13}C)$ = 5.93.
   Compound **2f**: yield 90 mg (56%), mp 178.8–180 °C (from benzene–hexane). IR, cm^{-1}: ν_{max} = 2205 (C≡C); 2868, 2934, 2930, 2983 (CH_3); 3440 (br); ^1H NMR (200 MHz, $CDCl_3$) δ, 7.75 (s, 8H, OCH_2–CH_2O),3.89–3.92 (m, 4H, OCH_2–CH_2O), 4.11–4.15 (m, 4H, OCH_2–CH_2O), 6.91 (d, 1H, Ph–CH═*CH*), 7.35 (s, 7H, H_{Ar}), 7.78 (br s, 1H, Ph–*CH*═CH). ESR, G: g_{iso} = 2.0058 A_N = 14.11 $A_{H(CH_3)}$ (12H) = 0.23, $A(^{13}C)$ = 5.93.
12. *General procedures of cross-coupling reaction*: A stirred mixture of copper(I) salt of acetylenes **8a–f** (0.36 mmol) and iodide **7** (130 mg, 0.33 mmol) in 10 mL of pyridine is heated to 80–85 °C in an argon stream. The heating is continued for next 3.5–4 h until no more iodide **7** is left (TLC-control). Then $CHCl_3$ (30 mL) and water (40 mL) were added. The organic layer is separated and the water layer is extracted with $CHCl_3$ (2 × 25 mL), the combined organic extracts were washed with 25% NH_3 (aq) and then the organic phase was dried over sodium sulfate, filtered and evaporated to dryness under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (elution with chloroform) followed by crystallization gave the corresponding compounds **2a–f**.