First example of direct introduction of nucleophiles bearing a stable radical moiety into azaaromatic substrates*

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Addition products of 4-hydroximino-2,2,6,6-tetramethylpiperidine-1-oxyl with 5-aryl-2,3-dicyano-1-ethylpyrazinium salts were isolated for the first time. Crystallographic data on the three-dimensional structures of σ^H-adducts bearing a stable radical moiety were obtained.

Key words: 2,3-dicyano-1-ethyl-5-phenylpyrazinium and 2,3-dicyano-1-ethyl-5-(4-fluorophenyl)pyrazinium tetrafluoroborates, 4-hydroximino-2,2,6,6-tetramethylpiperidine-1-oxyl, σ^H-adducts with *O*-nucleophiles, nitroxide radicals.

The chemistry of azaaromatic compounds is mainly determined by the properties of σ-adducts generated by their reactions with nucleophiles.[1,2] 1,4-Diazines are characterized not only by diverse chemical transformations but also by high stability of their σ^H-adducts.[3,4] Recently, crystallographic data on the structures of relatively stable σ^H-adducts of 2,3-dicyanopyrazinium cations with alcohols have been obtained for the first time.[4] In the present study, we examined the possibility of introducing *O*-nucleophiles containing a free radical center into diazines. Nitroxides are widely used in biophysical studies as spin labels and as contrast agents in NMR tomography.[5—9] In addition, nitroxides can act as antioxidants.[10—12] Therefore, it was of interest to examine the possibility of direct coupling of heterocyclic systems with nucleophiles bearing a nitroxide.

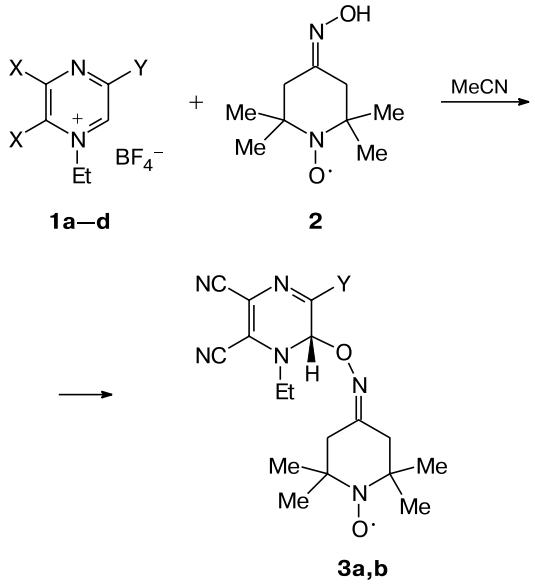
It is known that nitroxides containing the OH group can act as nucleophiles; however, in solution, these compounds are very pH sensitive.[13,14]

At room temperature, 5-aryl-2,3-dicyano-1-ethylpyrazinium tetrafluoroborates **1a,b** readily react with 4-hydroximino-2,2,6,6-tetramethylpiperidine-1-oxyl (**2**) in the absence of bases to form stable σ^H-adducts **3a,b** at the unsubstituted C(6) atom (Scheme 1).

The structure of compound **3a** was established by X-ray diffraction (Fig. 1).

Attempts to prepare analogous products with 2,3-dicyano-1-ethylpyrazinium tetrafluoroborate **1c** and 2,3-dichloro-1-ethylpyrazinium tetrafluoroborate **1d** failed. The formation of complex multicomponent mixtures in the course of the reactions with these salts were detected by TLC.

Scheme 1



1a—d **2** **3a,b**

Compound	X	Y
a	CN	Ph
b	CN	4-FC_6H_4
c	CN	H
d	Cl	H

* Dedicated to Academician O. M. Nefedov on the occasion of his 75th birthday.

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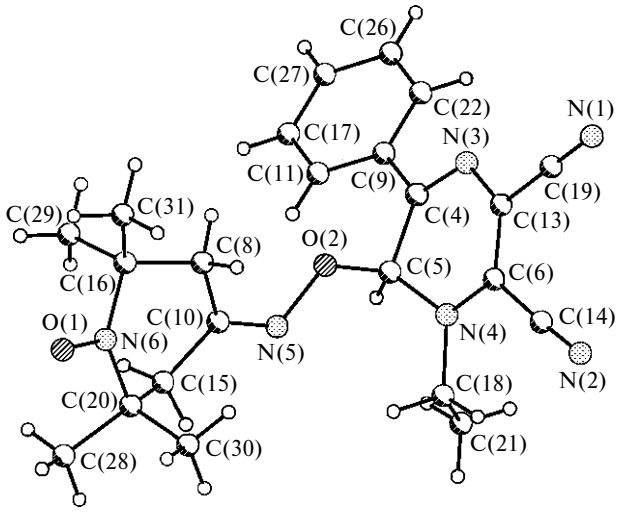

Fig. 1. Geometry of molecule **3a** in the crystal structure.

Compounds **3a,b** were studied by the ESR method. The starting polycrystals of compounds **3a,b** give a single ESR line with a width ΔB = 16.5 mT and g = 2.0061. In solution, the spectrum is completely resolved, and both compounds (**3a,b**) are characterized by identical spectral patterns (Fig. 2).

The ESR signal of compounds **3a** and **3b** (see Fig. 2) consists of three equidistant lines with equal intensities, which is evidence for hyperfine splitting due to anisotropic hyperfine coupling between the unpaired electron of the nitroxide and the nuclear spin I = 1 of the nitrogen atom. The corresponding hyperfine splitting constant A is 14.42 G, and the g factor of the central line is 2.0061, which are in good agreement with the data for the standard nitroxide, *viz.*, 4-hydroxy-2,2,6,6-tetramethylpiperidineoxyl (TEMPO) (g = 2.0070, A = 15.88 G).[15] Since the parameters of the spin state in σ^H-adducts **3a,b** are similar to the corresponding parameters for the nitroxide, it can be concluded that the peripheral molecular structure has no effect on the spin density distribution.

To conclude, we demonstrated that 5-aryl-2,3-dicyano-1-ethylpyrazinium salts form stable σ^H-adducts with oximes of nitroxides.

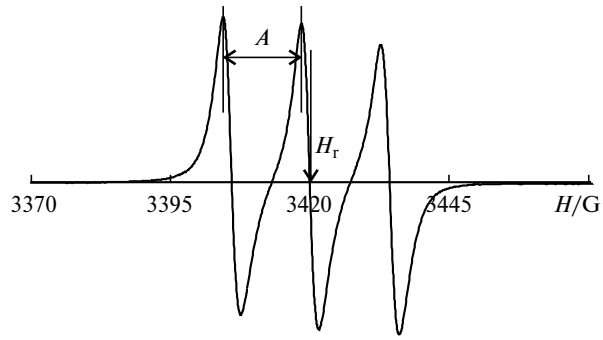

Fig. 2. ESR spectrum of a solution of compound **3a** in chloroform at T = 293 K.

Experimental

Compounds **1a—d** (see Refs 4 and 16) and **2** (see Ref. 17) were synthesized according to procedures described in the literature.

The X-band ESR spectra (~9.4 GHz) were recorded at room temperature on a standard homodyne ESR-231 spectrometer equipped with a TE_{102} rectangular resonator. The experimental conditions: the central field B_0 = 324 mT, the scan range δB_{sr} = 20 mT ($\delta B_{sr} > 5\Delta B$, where ΔB is the peak-peak linewidth),[18] the microwave power P = 2 mW, and the modulation amplitude b = 0.3 mT; the g factor was calibrated with the use of pyrolysate of coal pitch and $CuSO_4 \cdot 5H_2O$. The measurements were carried out for solutions of polycrystals in chloroform at a concentration of ~10^{-5} mol mL^{-1}.

The ^1H NMR spectra were recorded on a Bruker DRX-400 instrument with Me_4Si as the internal standard. The mass spectra were measured on a Shimadzu LCMS-2010 quadrupole liquid GLC-mass spectrometer in acetonitrile at a scan rate of 0.25 mL min^{-1} using a Supelco LC-18 column (4.6×250 mm). The positive-ion electrospray ionization mass spectra were obtained at an operating voltage of 4.5 kV using tunings according to the autotuning file (nitrogen as the carrier gas, the flow rate was 2.5 L min^{-1}). The elemental analysis was carried out on an automated Carlo Erba 1108 analyzer. The melting points were determined on a combined Boetius hot-stage apparatus and are uncorrected. Flash chromatography was performed using Lancaster silica gel (0.040—0.063 mm, 230—400 mesh).

The course of the reactions was monitored and the purity of the products was checked by TLC on Silufol UV-254 plates; the spots were visualized with iodine vapor.

The results of X-ray diffraction study of compound **3a** were deposited with the Cambridge Crystallographic Data Centre (CCDC refcode 622011).*

4-(5,6-Dicyano-1-ethyl-3-phenyl-1,2-dihydropyrazin-2-yl-oximino)-2,2,6,6-tetramethylpiperidine-1-oxyl (3a). A solution of 2,3-dicyano-5-phenylpyrazinium tetrafluoroborate (**1a**) (322 mg, 1 mmol) and 4-hydroximino-2,2,6,6-tetramethylpiperidine-1-oxyl (**2**) (185 mg, 1 mmol) in CH_3CN (5 mL) was stirred for 1 h and then concentrated. The residue was separated on silica gel using a 1 : 2 acetone—hexane mixture as the eluent. Dihydropyrazine **3a** was obtained in a yield of 113 mg (27%) as a crystalline yellow precipitate, m.p. 153—155 °C (decomp). Found (%): C, 66.05; H, 6.63; N, 20.07. $C_{23}H_{27}N_6O_2$. Calculated (%): C, 65.85; H, 6.49; N, 20.03. ^1H NMR (CD_3Cl), δ: 7.97 (br.m, 2 H, Ph); 7.49 (br.m, 3 H, Ph); 6.65 (br.s, 1 H, C(6)H); 3.99 and 3.82 (both br.s, 2 H each, NCH_2); 1.42—1.26 (br.m, 5 H, CH_2, CH_3). GLC-MS, m/z (I_{rel} (%)): 405 $[M + H - O]^+$ (100), 421 $[M + H]^+$ (87.45), 446 $[M + H + CH_3CN]^+$ (25.29), 462 $[M + H - O + CH_3CN]^+$ (37.22). ESR: g = 2.0061, a_H(1 H) = 16.5 mT.

4-[5,6-Dicyano-1-ethyl-3-(4-fluorophenyl)-1,2-dihydropyrazin-2-yloximino]-2,2,6,6-tetramethylpiperidine-1-oxyl (3b). Product **3b** was synthesized analogously to compound **3a** as a yellow oil. The yield was 198 mg (45%). Found (%): C, 62.90; H, 5.91; N, 18.97. $C_{23}H_{26}FN_6O_2$. Calculated (%): C, 63.14; H, 5.99; N, 19.21. ^1H NMR (CD_3Cl), δ: 7.98 (br.m, 4 H, Ph); 6.61 (br.s, 1 H, C(6)H); 3.99 and 3.82 (both br.s, 2 H each,

* These data can be obtained, free of charge, on application to *www.ccdc.cam.ac.uk/data_request/cif.*

NCH_2); 1.43—1.10 (br.m, 12 H, CH_2, CH_3); 0.89—0.87 (br.m, 3 H, CH_3). GLC-MS, m/z (I_{rel} (%)): 423 $[M + H - O]^+$ (100), 439 $[M + H]^+$ (3.61), 464 $[M + H - O + CH_3CN]^+$ (91.15). ESR: $g = 2.0061$, $a_H(1\ H) = 16.5$ mT.

Crystallographic data for compound 3a. X-ray diffraction data were collected on an Xcalibur-3 X-ray diffractometer equipped with a CCD detector (λ-Mo-Kα, graphite monochromator, ω-scanning technique).

Crystals of **3a** were grown from a 1 : 2 acetone—hexane mixture. Crystals of compound **3a**, $C_{23}H_{27}N_6O_2$, are monoclinic, space group $P2_1/n$. At 295 K, the unit cell parameters: a = 13.616(2) Å, b = 11.830(1) Å, c = 14.356(1) Å, β = 102.994(10)°, V = 2253.4(4) Å^3, Z = 4. The structure was solved by direct methods with the use of the SHELXS-97 program package and refined with the use of the SHELXL-97 program package. The final R factor was 0.0468 ($wR(F^2) = 0.0799$) for 2810 reflections with $F_0 > 2\sigma(I)$.

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References

1. O. N. Chupakhin, V. N. Charushin, and H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego, New York, 1994, 376 pp.
2. F. Terrier, *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group*, in *Organic Nitro Chemistry Series*, VCH Publishers, Inc., New York, 1991, 500 pp.
3. G. B. Barlin, *Pyrazines*, in *The Chemistry of Heterocyclic Compounds*, Eds A. Weissberger and E. C. Taylor, Vol. **41**, Wiley Intersci., 1982.
4. P. A. Slepukhin, G. L. Rusinov, V. N. Charushin, V. I. Filyakova, N. S. Karpenko, D. B. Krivolapov, and I. A. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 1 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 1].
5. A. Ueda, S. Nagse, H. Yokoyama, M. Tada, H. Noda, H. Ohya, H. Kamada, A. Hirayama, and A. Koyama, *Molecular and Cellular Biochemistry*, 2003, **244**, 119.
6. P. Twomey, J. Taira, W. DeGraff, J. B. Mitchell, A. Russo, M. C. Krishna, O. H. Hankovszky, L. Frank, and K. Hideg, *Free Radical Biology and Medicine*, 1997, **22**, 909.
7. C. Risso-de Faverney, M. Lafaurie, J. P. Girard, and R. Rahmani, *Toxicology Lett.*, 2000, **111**, 219.
8. H. Yokoyama, T. Sato, H. Ohya-Nishiguchi, and H. Kamada, *Magnetic Resonance Materials in Physics, Biology and Medicine*, 1998, **7**, 63.
9. T. Matsuo, H. Shinzawa, H. Togashi, M. Aoki, K. Sugahara, K. Saito, T. Saito, T. Takahashi, I. Yamaguchi, M. Aoyama, and H. Kamada, *Free Radical Biology and Medicine*, 1998, **25**, 929.
10. C. Charloux, M. Paul, D. Loisance, and A. Astier, *Free Radical Biology and Medicine*, 1995, **19**, 699.
11. J. Fuchs, N. Groth, T. Herring, and G. Zimmer, *Free Radical Biology and Medicine*, 1997, **22**, 967.
12. A. M. Samuni and Y. Barenholz, *Free Radical Biology and Medicine*, 2003, **34**, 177.
13. E. G. Rozantsev, *Svobodnye iminoksil´nye radikaly* [*Free Iminoxyl Radicals*], Khimiya, Moscow, 1970, 216 pp. (in Russian).
14. M. Baskett, P. M. Lahti, and F. Palacio, *Polyhedron*, 2003, **22**, 2363.
15. E. Yoshida and A. Sugita, *Macromolecules*, 1996, **29**, 6422.
16. G. L. Rusinov, P. A. Slepukhin, V. N. Charushin, and O. N. Chupakhin, *Mendeleev Commun.*, 2001, **2**, 43.
17. E. G. Rozantzev and M. B. Neiman, *Tetrahedron*, 1964, **20**, 1, 131.
18. C. P. Poole, Jr. and H. A. Farach, *Theory of Magnetic Resonance*, 2nd ed., Wiley, New York, 1987.

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