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Syntheses and structures of azol-1-yl derivatives of nitronyl and imino nitroxides

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Abstract—2-(Pyrazol-1-yl)-, 2-(imidazol-1-yl)-, 2-([1,2,4]triazol-1-yl)-, and 2-(benzotriazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl were prepared by reactions of 2-bromo-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (NIT-Br) with the corresponding sodium azolides. In prepared 2-(azol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyls, the NIT–N_{Het} bond is readily hydrolyzed. Reduction of imidazole-3-oxide-1-oxyls leads to corresponding 2-(azol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyls, which are much more stable against hydrolysis. The structures of spin-labeled imidazoles, [1,2,4]triazoles and benzotriazoles are confirmed by X-ray analysis, showing that the paramagnetic molecules form packings with motifs from centrosymmetric dimers to topologically linear chains.

1. Introduction

Molecular ferromagnet design based on complexes of paramagnetic metal ions with nitroxides is becoming an area of active interest, as evidenced by the growing number of experimental works and reviews.[1,2] The demand for highly dimensional heterospin structures has stimulated the development of syntheses of polyfunctional nitroxides. For functional groups, it is desirable to use combinations of donor groups, leading to stereochemically non-rigid complexes with potentialities for higher coordination numbers of the metal ion. Thus, nitroxides with polynitrogen heterocyclic substituents such as imidazole,[3] benzimidazole,[4] pyrazole,[5,6] 1,2,4-triazole,[7] and tetrazole[8] have been prepared.

In all known compounds of this type, the nitronyl nitroxide fragment is bonded to the carbon atom of the heterocyclic substituent. The only published exception is 4,4,5,5-tetramethyl-2-(pyrrol-1-yl)-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl,[9] where the nitronyl nitroxide moiety is a poor electron donor. For this reason, we decided to investigate the possibility of synthesizing a series of azol-1-yl derivatives of nitronyl and imino nitroxides containing a nitrogen atom in the *N*-heterocyclic substituent along with the nitrogen atom bonded to the paramagnetic fragment. Nitroxides of this kind are potential polyfunctional spin-labeled ligands. Unexpectedly, we found that nitronyl nitroxides **2a**–**d** are very sensitive to hydrolysis at the C–N_{Het} bond between the heterocycles. Imino nitroxides **3a**–**d** are less liable to this phenomenon. Liability to hydrolysis at the C–N_{Het} bond is an essential obstacle in handling the title nitroxides, and one can think that synthesis of **2b**–**d** and **3b**–**d** in single crystal form, as well as crystal and molecular structure solution, is definite success.

2. Syntheses and structures

The azol-1-yl derivatives of nitronyl and imino nitroxides **2a**–**d** and **3a**–**d** were prepared in a good yield, as shown in Scheme 1. In a typical procedure, an appropriate azole (pyrazole, imidazole, 1,2,4-triazole or benzotriazole) was treated with NaH in DMF, and the resulting sodium azolide was allowed to react with bromoderivative **1**.[9] TLC monitoring indicated that imino nitroxides **3a**–**d** and 4,4,5,5-tetramethylimidazolidin-2-one 1,3-dioxide[10] **4** always formed along with **2a**–**d**. An attempt to isolate **2a**–**d** in individual form led to easy hydrolysis of these nitronyl nitroxides at the C–N_{Het} bond.

Thus, heating in solution above 70 °C or chromatographing on an Al_2O_3 column, or storage in air at room temperature resulted in complete decomposition of **2a**–**d** within 0.5–1.5 h, forming zwitterion **4** and the corresponding heterocycle. Treatment of **2a**–**d** (as well as **4**) with an aqueous alkali or ammonia instantly led to a deep blue solution, whose EPR spectrum is a quintiplet with an unprecedentedly

Keywords: Nitronyl nitroxides; Imino nitroxides; Pyrazole; Imidazole; Triazole; Alkylation.
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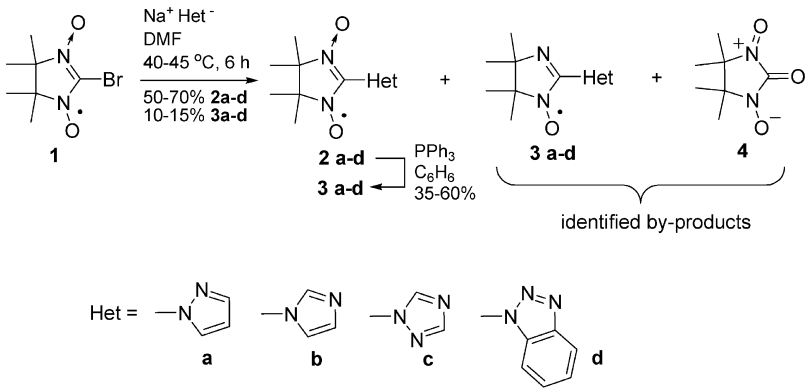
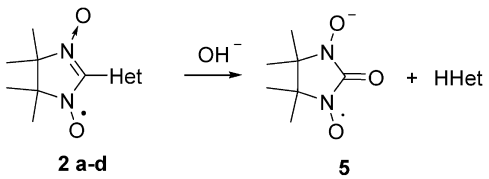


Scheme 1. Preparation of 2-(azol-1-yl)-4,4,5,5-tetramethylimidazoline-3-oxide-1-oxyls **2a–d** and 2-(azol-1-yl)-4,4,5,5-tetramethylimidazoline-1-oxyls **3a–d**.



Scheme 2. Alkaline hydrolysis of nitronyl nitroxides **2a–d**.

high nitrogen coupling constant a_N=8.71 G,[8] which is well known and characteristic of hydroxamic acid anion **5** alone (Scheme 2).

The desired nitronyl nitroxides were isolated by column chromatography on SiO_2. Single crystals **2b–d** suitable for an X-ray diffraction study were grown under 'cold' crystallization conditions, as described in Section 4. Numerous attempts to grow crystals **2a** always gave finely disperse polycrystalline concretions, not suitable for an X-ray diffraction study.

Nitronyl nitroxides **2a–d** were reduced to imino nitroxides **3a–d** using PPh_3 in dry benzene (Scheme 1). Compounds **3a–d** are much more kinetically stable. They are not decomposed by water. They may be purified by chromatography on both SiO_2 and Al_2O_3. Imino nitroxides are stored under normal conditions without taking any special safety measures. Nitroxides **3b–d** were grown as crystals suitable for an X-ray diffraction analysis, except **3a**, which precipitated as an oil at −25 °C from hexane.

The molecular structure of **2b–d** and **3b–d** is shown in Figures 1 and 2. Selected bond lengths are given in Tables 1 and 2.

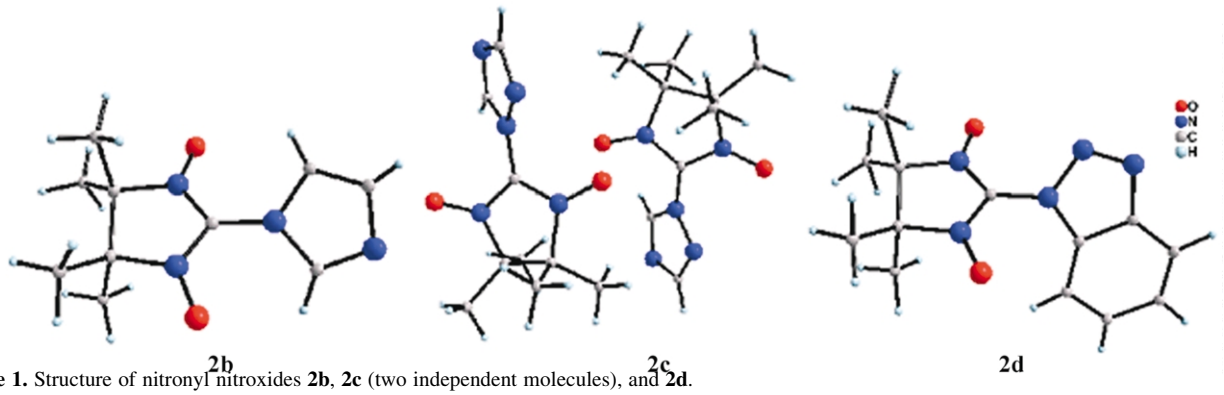


Figure 1. Structure of nitronyl nitroxides **2b**, **2c** (two independent molecules), and **2d**.

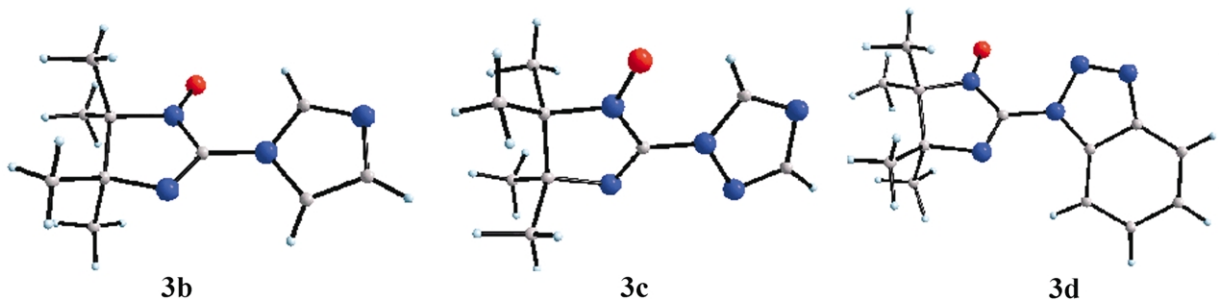


Figure 2. Structure of imino nitroxides **3b**, **3c**, and **3d**.

Table 1. Selected bond lengths (Å) and angles (°) for **2b–d**

Compound	**2b**	**2c**	**2d**
N–O	1.275(2)	1.289(3)	1.282(4)
	1.275(2)	1.267(3)	1.257(5)
C–N	1.333(2)	1.341(4)	1.313(5)
	1.330(2)	1.330(4)	1.346(5)
$C–N_{Het}$	1.374(3)	1.376(4)	1.386(5)
$\angle CN_2–Het$	28.8(2)	44.3(1) 7.8(1)	59.3(2)

Table 2. Selected bond lengths (Å) and angles (°) for **3b–d**, **4**

Compound	**3b**	**3c**	**3d**	**4**
N–O	1.261(3)	1.276(3)	1.265(3)	1.243(4)
				1.249(4)
C–N	1.383(4)	1.383(4)	1.368(3)	1.368(4)
	1.272(4)	1.264(3)	1.257(3)	1.369(4)
$C–N_{Het}$	1.393(4)	1.396(4)	1.387(3)	
$\angle CN_2–Het$	22.2(5)	22.0(4)	36.7(2)	

Note that N–O bond lengths are within the limits characteristic of the nitroxides (~1.27–1.28 Å). The $C–N_{Het}$ bond lengths also vary within a narrow range of values, 1.385±0.015 Å. Within this range of values, however, $C–N_{Het}$ bond lengths for **2d** and **3b–d** markedly exceed those for **2b** and **2c**. This correlates with the significant difference between C–N bond lengths in the imidazoline ring (Tables 1 and 2).

The difference in the C–N bond lengths of the imidazoline ring is quite natural for imino nitroxides **3b–d**, but not for **2d**, for which it proved to be unexpected. This difference in bond lengths must increase polarity of molecules **2d** and **3b–d**. It is not surprising, therefore, that in solids they should typically 'coalesce' into dimers.

Tables 1 and 2 also give the angles between the plane of the N–C–N fragment of the imidazoline ring and the plane of the azole ring, denoted as $\angle CN_2–Het$. They differ substantially from 0° in all compounds, which hinders effective conjugation between the π-systems of the heterocycles.

As noted above, zwitterion **4** is one of hydrolysis products. It was also isolated as qualitative single crystals. As compound **4** was not found in CCDC, here we give its main structural data. Solid compound **4** is formed from two crystallographically independent molecules (Fig. 3), each possessing C_2 symmetry. The N–O distances in the NO groups are virtually the same and equal, on the average, 1.246 Å; i.e. they are much shorter than the typical N–O distances of nitroxides. Molecules **4** also intrinsically have very short C=O distances, 1.200(6) and 1.207(6) Å.

3. Conclusions

In this study, we have synthesized a series of 1-hetaryl derivatives of nitronyl and imino nitroxides and determined their crystal and molecular structure. It has been found that nitronyl nitroxides of this kind are liable to hydrolysis at the

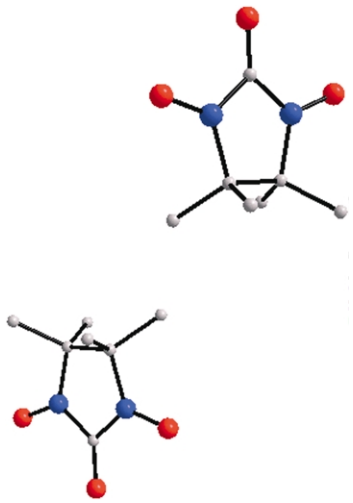


Figure 3. Structure of **4**.

$C–N_{Het}$ bond. This specific feature of nitroxides under study should be taken into account in design of new magnetoactive systems, because, as mentioned in Section 1, synthesis of polyfunctional nitroxides is generally developed for their subsequent application to synthesis of molecular magnets from transition metal heterospin complexes with stable radicals.

4. Experimental

4.1. General

The reactions were monitored by TLC on Silica gel 60 F_{254} aluminum sheets (Merck) using ethyl acetate as eluent. Silica gel 'Merck' (Silica gel 60 0.063–0.200 mm for column chromatography) and Al_2O_3 (neutral, analytical grade, for chromatography, Russia) were used for column chromatography. IR spectra were recorded for KBr pellets on a Vector 22 (Bruker) spectrometer. All reagents and organic solvents were analytical quality and used as purchased. 2-Bromo-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (**1**) was prepared by the procedure described previously.[11]

4.2. General procedure for the preparation of compounds 2a–d

The compounds were synthesized under argon. Azole (4.70 mmol) and DMF (5 mL) were placed in a 50 mL round-bottom flask. To the resulting solution, NaH (60% in mineral oil, 0.20 g, 5.0 mmol) was added with stirring, and the reaction mixture was stirred at room temperature for 10 min. Then **1** (1.0 g, 4.20 mmol) was added, and the reaction mixture stirred at 40–45 °C for 6 h. The flask was connected to a vacuum pump via a trap cooled with liquid nitrogen, and DMF was distilled off at $p<1$ Torr and bath temperature 40–45 °C. The residue was dissolved in benzene (15 mL), and the solid was filtered off. The filtrate was placed on a benzene-wetted SiO_2 column (1.5×30 cm) and chromatographed using a 1:1 mixture of ethyl acetate and benzene as eluent.

The fraction which was collected first was orange colored and contained imino nitroxides **3a–d** and zwitterion **4** (TLC data). This fraction was evaporated on a rotary evaporator and chromatographed on Al_2O_3 (1.5×20 cm) using benzene as eluent. Zwitterion **4** formed a static layer colored blue on Al_2O_3. Imino nitroxides **3a–d** were eluted and recrystallized from hexane. The yields of imino nitroxides **3a–d** were 10–15%.

The second, violet-colored fraction from the SiO_2 column was evaporated on a rotary evaporator at a bath temperature of 25–27 °C. Hexane (~5 mL) was added to the residue, and the product was completely dissolved at room temperature by treatment with ultrasound and benzene addition in sequence. The solution was filtered and stored at −15 °C. Nitronyl nitroxide crystals **2a–d** were filtered off, quickly dried on a filter, and stored in a refrigerator under argon. For an X-ray diffraction study, nitronyl nitroxide crystals **2b–d** were extracted from under the layer of the mother solution and immediately coated with a layer of water-proof glue.

4.2.1. 4,4,5,5-Tetramethyl-2-(pyrazol-1-yl)-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (2a). Yield 0.48 g (51%), violet crystals, mp 96–97 °C. μ_{eff}/β=1.68 (295 K). IR (KBr): [cm^{-1}] 612, 635, 766, 871, 913, 940, 972, 1043, 1078, 1144, 1175, 1201, 1288, 1373, 1399, 1425, 1466, 1576, 1695, 2998, 3118. Anal. found: C, 54.5; H, 6.8; N, 25.0. Calcd for $C_{10}H_{15}N_4O_2$: C, 53.8; H, 6.8; N, 25.1. MS, *m*/*z* (%): 223.11963 (M^+, 44, calcd for $C_{10}H_{15}N_4O_2$ 223.11949), 114 (9), 109 (12), 86 (83), 84 (69), 83 (42), 69 (100), 68 (9), 67 (10), 58 (54).

4.2.2. 2-(Imidazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (2b). Yield 0.45 g (48%), violet crystals, mp 125–128 °C. μ_{eff}/β=1.71 (295 K). IR (KBr): [cm^{-1}] 609, 649, 739, 836, 816, 836, 869, 896, 997, 1016, 1067, 1101, 1144, 1173, 1217, 1246, 1273, 1335, 1376, 1409, 1458, 1528, 1582, 1694, 2990, 3148. MS, *m*/*z* (%): 223.11985 (M^+, 73, calcd for $C_{10}H_{15}N_4O_2$ 223.11949), 86 (23), 84 (100), 83 (29), 79 (5), 69 (89), 67 (10), 58 (20). Anal. found: C, 52.5; H, 6.8; N, 24.3. Calcd for $C_{10}H_{15}N_4O_2$: C, 53.8; H, 6.8; N, 25.1.

4.2.3. 4,4,5,5-Tetramethyl-2-([1,2,4]triazol-1-yl)-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (2c). Yield 0.48 g (51%), violet crystals, mp 113–114 °C. μ_{eff}/β=1.68 (295 K). IR (KBr): [cm^{-1}] 626, 644, 666, 737, 756, 817, 867, 947, 991, 1119, 1140, 1173, 1212, 1271, 1324, 1379, 1421, 1458, 1509, 1578, 1762, 2980, 3095. MS, *m*/*z* (%): 224.11448 (M^+, 71, calcd for $C_9H_{14}N_5O_2$ 224.11474), 157 (22), 110 (28), 84 (100), 83 (29), 70 (27), 69 (80), 56 (86). Anal. found: C, 47.8; H, 6.5; N, 31.2. Calcd for $C_9H_{14}N_5O_2$: C, 48.2; H, 6.3; N, 31.2.

4.2.4. 2-(Benzotriazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (2d). Yield 0.80 g (70%), violet crystals, mp 148–150 °C. μ_{eff}/β=1.73 (295 K). IR (KBr): [cm^{-1}] 609, 756, 766, 780, 845, 865, 919, 972, 998, 1030, 1154, 1177, 1232, 1298, 1312, 1377, 1395, 1426, 1454, 1564, 1612, 2995, 3121. Anal. found: C, 57.1; H, 6.2; N, 25.9. Calcd for $C_{13}H_{16}N_5O_2$: C, 56.9; H, 5.9; N, 25.5.

4.3. General procedure for the preparation of compounds 3a–d

A solution of nitroxide **3a–d** (0.54 mmol) and PPh_3 (140 mg, 0.54 mmol) in benzene (3 mL) was stirred at room temperature for 24 h. TLC (SiO_2, Al_2O_3) showed that the reaction mixture contained Ph_3PO, zwitterion **4**, and iminonitroxide **3a–d**. Ph_3PO was removed from the mixture by chromatography on a silica gel column (1.5×10 cm) with $CHCl_3$. The orange colored fraction was evaporated on a rotary evaporator, and the residue was chromatographed on Al_2O_3 (1.5×15 cm) using benzene as eluent to give nitroxide **3a–d**. An analytical sample was obtained by recrystallization of the product from hexane.

4.3.1. 4,4,5,5-Tetramethyl-2-(pyrazol-1-yl)-4,5-dihydro-1*H*-imidazole-1-oxyl (3a). Yield 61 mg (55%), orange oil. μ_{eff}/β=1.63 (295 K). IR (KBr): [cm^{-1}] 643, 661, 760, 876, 914, 935, 1039, 1073, 1143, 1171, 1201, 1226, 1261, 1347, 1390, 1453, 1531, 1602, 1740, 2935, 2981, 3133. Anal. found: C, 57.3; H, 7.3; N, 26.3. Calcd for $C_{10}H_{15}N_4O$: C, 58.0; H, 7.3; N, 27.1. MS, *m*/*z* (%): 207.12479 (M^+, 5, calcd for $C_{10}H_{15}N_4O$ 207.12458), 152 (10), 134 (10), 124 (5), 120 (18), 114 (12), 109 (38), 94 (8), 85 (6), 84 (95), 83 (10), 79 (15), 70 (5), 69 (100), 68 (12), 67 (15).

4.3.2. 2-(Imidazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyl (3b). Yield 40 mg (36%), red crystals, mp 66–67 °C. μ_{eff}/β=1.70 (295 K). IR (KBr): [cm^{-1}] 649, 663, 764, 835, 874, 897, 940, 958, 1002, 1014, 1061, 1108, 1138, 1169, 1221, 1251, 1281, 1318, 1375, 1474, 1524, 1601, 2982, 3126, 3146. Anal. found: C, 58.4; H, 7.4; N, 27.1. Calcd for $C_{10}H_{15}N_4O$: C, 58.0; H, 7.3; N, 27.1.

4.3.3. 4,4,5,5-Tetramethyl-2-([1,2,4]triazol-1-yl)-4,5-dihydro-1*H*-imidazole-1-oxyl (3c). Yield 44 mg (59%), red crystals, mp 75–76 °C. μ_{eff}/β=1.71 (295 K). IR (KBr): [cm^{-1}] 656, 671, 871, 885, 948, 962, 989, 1114, 1139, 1214, 1277, 1308, 1373, 1391, 1454, 1515, 1601, 2977, 3111, 3131. Anal. found: C, 51.8; H, 6.9; N, 33.6. Calcd for $C_9H_{14}N_5O$: C, 51.9; H, 6.8; N, 33.6.

4.3.4. 2-(Benzotriazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyl (3d). Yield 36 mg (48%), red crystals, mp 113–114 °C. μ_{eff}/β=1.68 (295 K). IR (KBr): [cm^{-1}] 605, 758, 772, 782, 871, 935, 963, 1001, 1049, 1140, 1156, 1219, 1250, 1287, 1371, 1400, 1449, 1490, 1586, 2980, 3121. Anal. found: C, 60.5; H, 6.4; N, 27.4. Calcd for $C_{13}H_{16}N_5O$: C, 60.5; H, 6.2; N, 27.1.

5. Supplementary material

Crystal data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 217336 for **2b**, 217332 for **2c**, 217333 for **2d**, 217334 for **3b**, 217335 for **3c**, 217331 for **3d**, 217337 for **4**. Copies of this information may be obtained from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1233-336033; e-mail: deposit@ccdc.cam.ac.uk or http://ccdc.cam.ak.uk).

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