Synthesis and Reactions of New Nitronyl Nitroxides

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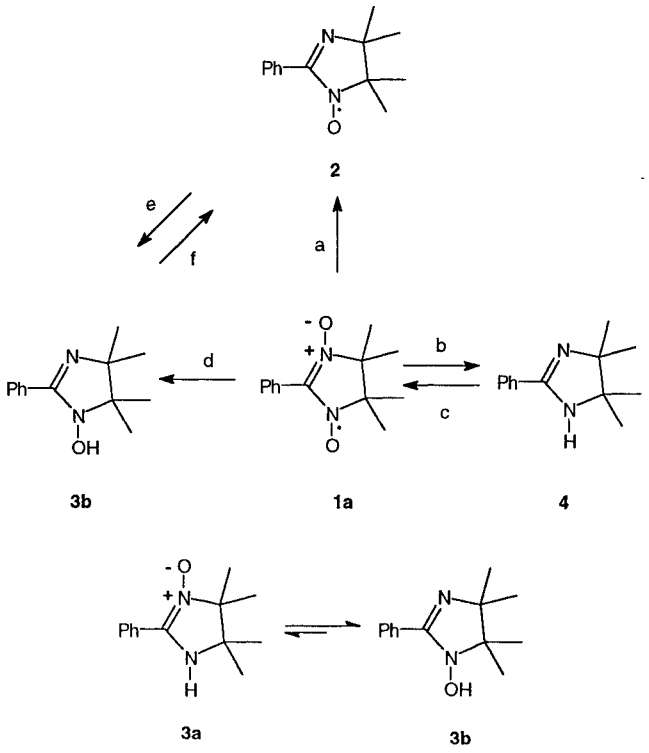
Various new 2-substituted 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-oxide mono- **1b**, **7**, **13a,b**, **14**, **15**, **16**, **17**, **22** and biradicals **8**, **9** were prepared. The nitronyl nitroxide functions were selectively reduced by Fe/HOAc to 1-hydroxyimidazoline derivatives **3b**, **11**, **21**. The reductions by Zn/HCl led to imidazolines **4**, **12**. The nitronyl nitroxide functions remained inert when the 2-phenyl compound was nitrated by H_2SO_4/HNO_3 to give nitrophenyl nitronyl nitroxide derivatives **13a,b**, **14**.

Nitronyl nitroxides were synthesized by Ullman et al. nearly 30 years ago,[1] and in recent years have received considerable attention because of the rapid development in the field of molecular-based magnetic materials. Nitrophenyl,[2] hydroxyphenyl,[3] *N*-alkylpyridinium[4] substituted 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-oxyl 3-oxides behave as ferromagnets or antiferromagnets. Several stable biradicals connected through hydrocarbon π-conjugation,[5] aromatic π-conjugation[6] and heterocyclic π-conjugation[7] were synthesized and investigated as molecules with triplet or singlet ground state. The other reason for the renaissance of nitronyl nitroxides is their capability of trapping NO$^{\bullet}$ radicals,[8] the importance of which in biological systems was discovered a few years ago.[9] Very recently, nitronyl nitroxides were also reported as useful therapeutic ingredients for different virus infections.[10] In continuation of our interest in antiarrhythmic compounds[11] we wished to prepare sterically hindered amines not only from 2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrole derivatives but from nitronyl nitroxide derivatives too. Reduction of nitronyl nitroxide **1a** with Fe powder/acetic acid[12] led to a product which was not the desired 4,4,5,5-tetramethyl-2-phenyl-4,5-dihydro-1*H*-imidazole **(4)** but the 1-hydroxy-4,4,5,5-tetramethyl-2-phenyl-4,5-dihydro-imidazole **(3b)**, prepared earlier by Ullman et al. from radical **1a** by heating it in ethanol containing aqueous hydrochloric acid, and considered as a nitrone **3a**.[1,13] This different behavior is presumably attributed to the fact that the imino nitroxide formed during the reaction is protonated at the imino nitrogen in acetic acid media.[14] Although compound **3b** was reported to exist mainly in nitrone form **3a**, we think that it is an *N*-hydroxyimidazoline compound **3b**, because it could be readily oxidized back to nitroxide **2** with PbO_2 in $CHCl_3$ which is not characteristic for nitrones, neither the fact that compound **2** could be reduced with ascorbic acid to the *N*-hydroxyimidazoline **3b**.

Our assumption was proved by running $^1H\{^{15}N\}$:HSQC experiments optimized by 90 Hz coupling. In case of compound **4** correlation was found between the NH signal at $\delta = 5.5$ and a nitrogen signal at $\delta = -111$. However, we could not observe the same correlation in the case of compound **3b** confirming the dominance of *N*-hydroxyimidazoline form **3b**. Compound **4** could be formed by reduction of radical **1** with aqueous HCl/Zn reagents.[15]

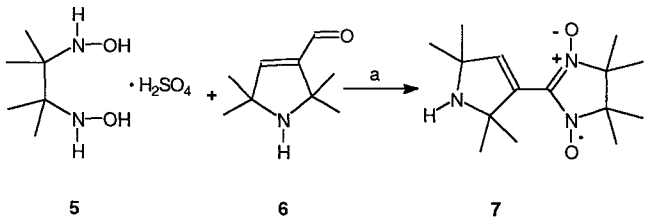


(a) $NaNO_2$/aq. HCl/H_2O/dioxane/r.t./15 min./87%. (b) Zn/aq. HCl/100°C/1.5 h/then NaOH/60%. (c) Na_2WO_4/H_2O/CH_3OH/H_2O_2/r.t./48 h/51%. (d) Fe/HOAc/50°C → r.t./1 h/then K_2CO_3/73%. (e) ascorbic acid/dioxane/H_2O/3 min./N_2/then $KHCO_3$/53%. (f) PbO_2/$CHCl_3$/r.t./10 min./87%.

Scheme 1

This method is a generally applicable procedure for the synthesis of new 2-substituted 4,5-dihydro-1*H*-imidazole derivatives among which antihypertensive agents were found.[16]

One of our aims was to synthesize new nitronyl nitroxide mono- and biradicals which are capable of acting as scavangers of the NO$^{\bullet}$ radical[8] and other reactive oxygen intermediates, similar to the previous observation with nitronyl nitroxides and for the metabolic pathway of bioactive pyrrolidines to nitroxide radical.[17] A new compound was obtained in the reaction of 2,3-bis(hydroxyamino)-2,3-dimethylbutane **(5)**[18] with 3-formyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrole **(6)**[19] in the presence of base, then the formed bis(hydroxyamine)imidazolidine was oxidized to 4,4,5,5-tetramethyl-2-(2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-oxide radical **(7)** when aerated in the presence of PbO_2 (Scheme 2).



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(a) $Na_2CO_3/CH_3OH/H_2O$/r.t./24 h/then $PbO_2/CHCl_3$/40 min./ 62%.

Scheme 2

Compound **7** was oxidized with H_2O_2 in the presence of a catalytic amount of Na_2WO_4 to biradical **8**. X-ray structure determination of biradical **8** showed that the pyrroline and imidazoline rings are almost coplanar; the dihedral angle between the two rings is 19° (Figure 1). Reaction of biradical **8** with nitrous acid gave 2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl biradical **(9)** (the crystal structure is depicted in Figure 2). Reaction of compound **7** with nitrous acid gave imino nitroxide **10**. Reduction of compound **7** with HOAc/Fe powder system removed the oxygen atom from the imidazoline ring to give 1-hydroxy-4,4,5,5-tetramethyl-2-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-4,5-dihydroimidazole **(11)**, which could be oxidized to compound **10** with PbO_2 in $CHCl_3$. Reduction of compound **7** with aqueous HCl/Zn powder gave 2-(2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole **(12)**. It is worth noting that biradical **8** could also be reduced to compound **12** with aqueous HCl/Zn powder, which could be oxidized back to biradical **8** with H_2O_2 in the presence of Na_2WO_4 (Scheme 3).

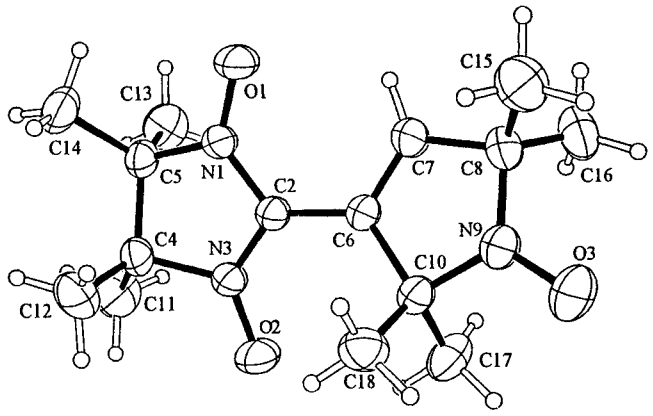


Figure 1. X-ray structure of **8** with the numbering of atoms

Searching for further functionalization of nitronyl nitroxides and imino nitroxides we have investigated the possibility of aromatic electrophilic substitution on the aromatic ring attached to the nitronyl nitroxide ring. In earlier papers we reported nitration of the aromatic ring in the presence of *N*-oxyl radicals.[20] Nitronyl nitroxides attached to the aromatic ring substituted with a nitro group are important from the viewpoint of material science also,[2] and most of them can be formed from the

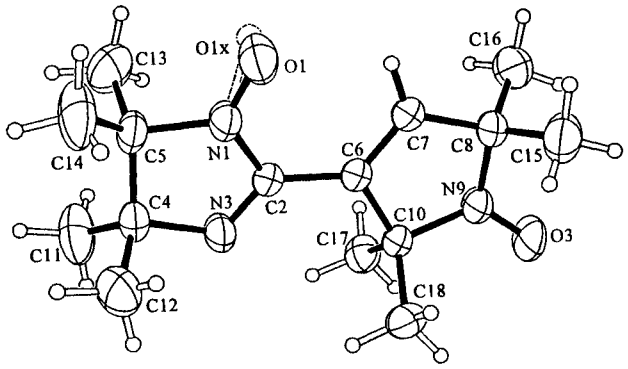
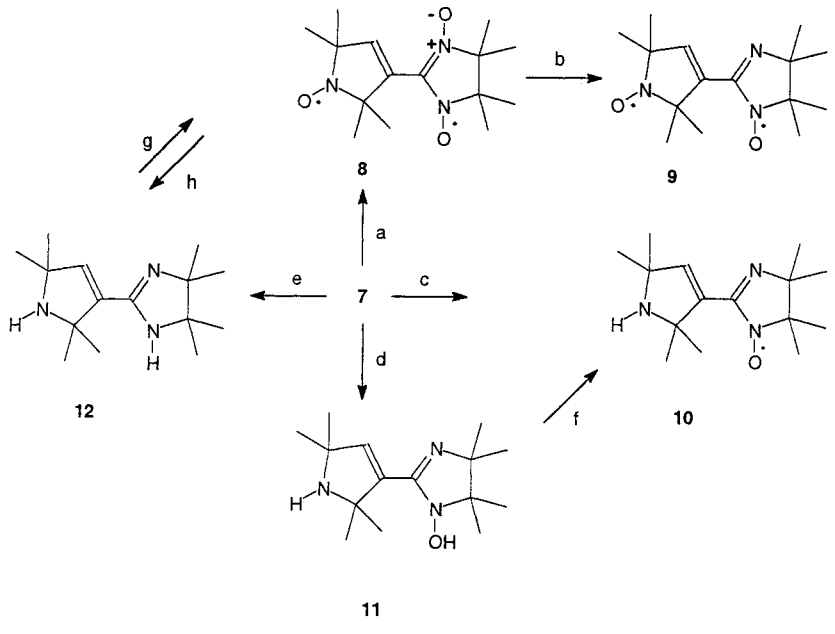


Figure 2. X-ray structure of **9** with numbering of atoms. Site occupation factors: 0.898 for O1 and 0.102 for O1x. The best planes for five-membered rings are coplanar with a dihedral angle of 6°

corresponding aromatic aldehyde.[21] We thought it was worth considering their synthesis with direct nitration. Nitration of compound **1a** with H_2SO_4/HNO_3 gave the 3-nitrophenyl derivative **13a** as main product and 2-nitrophenyl derivative **14** as byproduct, following our expectation that the protonated nitronyl nitroxide ring[1] behaves as a *meta* director group under conditions of aromatic electrophilic substitution. While nitrous acid with nitronyl nitroxide resulted in imino nitroxide, then by avoiding warming of the reaction mixture above 40 °C during nitration and workup we observed formation of imino nitroxide only in traces.

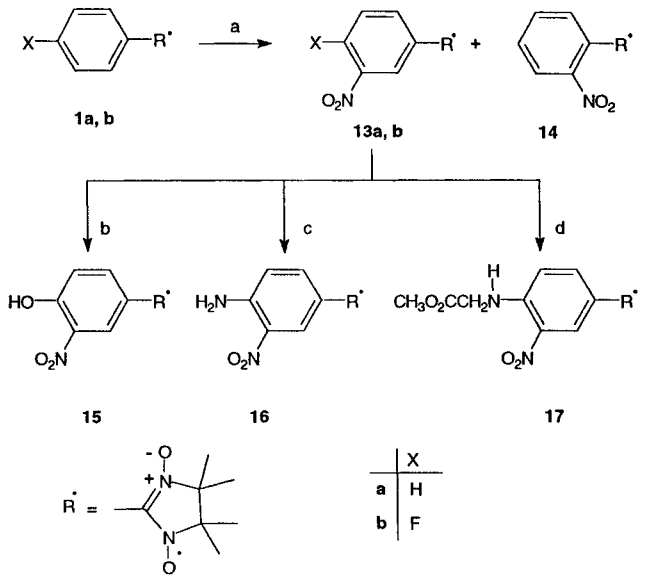
Structures of compounds **13a** and **14** were confirmed by Ullman's procedure from 3-nitrobenzaldehyde and 2-nitrobenzaldehyde, respectively. Nitration of the fluorinated derivative **1b** gave only nitronyl nitroxide **13b**. In the resulting compound fluorine could be involved in aromatic nucleophilic substitution reaction analogous to 2,4-dinitrofluorobenzene (DNFB) utilised by Sanger.[22] Fluorine could be replaced under mild phase-transfer conditions for the OH group and for the NH_2 group yielding compounds **15** and **16**, respectively, and with glycine methyl ester solution we got the α-paramagnetically labelled α-amino acid **17** (Scheme 4).[23] So **13b** may also serve as a new, potentially useful reagent both for monitoring nitric oxide release and spin labelling of proteins at nucleophilic side-chain functions.

A series of papers demonstrate the utilization of free nitroxide radicals attached to a fluorophore as fluorescent radical scavengers.[24] Other spin-labelled fluorophores were used as optical sensors of redox/radical reactions[25] and as donor–acceptor pair.[26] Our studies offered the possibility of connecting the nitronyl nitroxide radical as NO˙ trap to a fluorophore; this to the best of our knowledge have not been reported yet. The 4-nitrophenyl derivative **18** was reduced with HOAc/Fe powder, which removed not only one oxygen from the nitronyl nitroxide ring but reduced the nitro group as well. The resulting hydroxylamine was not isolated, but oxidized immediately to imino nitroxide **19**. This compound was dansylated at the aromatic amino group[27] to give the paramagnetic compound **20** with low fluorescence. The reduction of



(a) $Na_2WO_4/H_2O/CH_3OH/H_2O_2$/r.t./5 days/57%. (b) $NaNO_2$/aq. HCl/H_2O/dioxane/r.t./15 min./65%. (c) $NaNO_2$/aq. HCl/H_2O/dioxane/r.t./15 min./52%. (d) Fe/HOAc/50°C → r.t./1 h/then K_2CO_3/71%. (e) Zn/aq. HCl/100°C/1.5 h/thenNaOH/50%. (f) $PbO_2/CHCl_3$/r.t./10 min./91%. (g) $Na_2WO_4/H_2O/CH_3OH/H_2O_2$/r.t./5 days/50%. (h) Zn/aq. HCl/100°C/1.5 h/then NaOH/42%.

Scheme 3



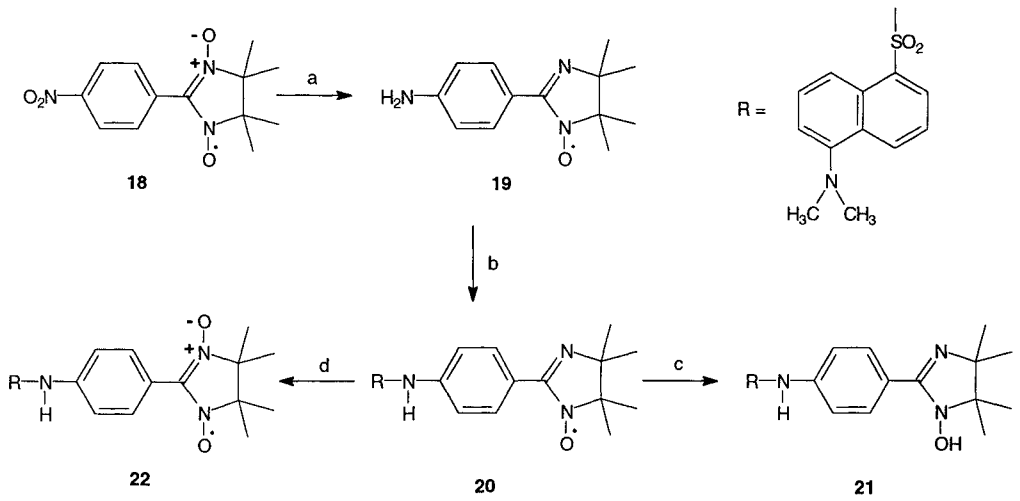
(a) HNO_3/H_2SO_4/15 min./0°C → r.t./then K_2CO_3/11–63%. (b) KOH/18-crown-6/H_2O/dioxane/2 h/r.t./51%. (c) NH_4OH/H_2O/dioxane/24 h/r.t./68%. (d) Glycine methyl ester hydrochloride/$KHCO_3/H_2O$/dioxane/24 h/r.t./70%.

Scheme 4

compound **20** with Fe/HOAc reagents gave the highly fluorescent diamagnetic compound **21** while oxidation of compound **20** with Na_2WO_4/H_2O_2 gave the nonfluorescent nitronyl nitroxide **22**.

In conclusion, a new approach was described for synthesis of biradicals. A convenient methodology was also developed for selective reduction of nitronyl nitroxides to *N*-hydroxyimidazolines and imidazolines. Introduction of adequate substituents onto the aromatic ring served also as a synthon for synthesizing fluorescent nitronyl nitroxide as double amplifier (fluorescent and spin label) reagents.

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N, S) were performed on a Fisons EA 1110 CHNS elemental analyzer. The IR (Specord 75) spectra were in each case consistent with the assigned structure. ^1H NMR spectra were recorded on a VARIAN-GEMINI 200 spectrometer at 200 MHz. Chemical shifts are given in ppm,



(a) Fe/HOAc/50 °C → r.t./1 h/then K_2CO_3/then $PbO_2/CHCl_3$/15 min./r.t./47%. (b) Dansyl chloride/pyr./30 min./60 °C/29%. (c) Ascorbic acid/dioxane/H_2O/N_2/3 min./r.t./then $KHCO_3$/55%. (d) $Na_2WO_4/H_2O/CH_3OH/H_2O_2$/r.t./10 days/53%.

Scheme 5

relative to TMS internal standard. The $^1H\{^{15}N\}$: HSQC experiments were run on a VARIAN UNITY INOVA 400 instrument at 400 MHz using a PFG ID probe head at 303 K in $CDCl_3$. The ^{15}N chemical shift is referenced to the chemical shift of external piperidine. Mass spectra were recorded on a VG TRIO-2 instrument in the EI mode (70 eV, direct inlet) or with thermospray technique. Samples were analyzed in the bypass mode. 10 μL of the sample solution in CH_3OH was introduced via the thermospray interface. The mobile phase was CH_3OH/H_2O, 1 : 1 solution containing 0.1 M NH_4OAc. The capillary tip temperature was 230 °C, the electrode voltage was 180 V and the source temperature was 210 °C. The ESR spectra were obtained from 10^{-5} molar solution ($CHCl_3$), using a BRUKER 300-E spectrometer. The ESR spectra of nitronyl nitroxides consisted of a five-line pattern with intensity ratios of 1:2:3:2:1. These spectra are attributed to an electron interacting with two equivalent nitrogens (a_N = 7.2–8.0 G). Imino nitroxides exhibited a seven-line spectrum resulting from coupling with the two nonequivalent nitrogen nuclei (a_N^1 = 4.1–4.5 G, a_N^2 = 9.1–10.0 G). The ESR spectra of compounds **8** and **9** were poorly resolved due to large electron–electron exchange interaction.[5]

Flash-column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm). Quantitative TLC was carried out on commercially prepared plates (20 × 20 × 0.2 cm) coated with Merck Kieselgel GF_{254}. Dansyl chloride was purchased from Aldrich, compounds **1a**,[1] **2**,[1] **5**,[17] **6**,[12] **18**[5] were prepared according to published procedures. The physical and spectral data of all new compounds are listed in the Table.

2-(4-Fluorophenyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (1b):

To a stirred solution of **5** (4.92 g, 20 mmol) in H_2O (20 mL) and MeOH (20 mL), 4-fluorobenzaldehyde (2.48 g, 20.0 mmol) was added and the pH was adjusted to 8 with 10% Na_2CO_3 solution and the mixture was stirred for 40 h at r.t. under N_2. The white precipitate was filtered off, washed with Et_2O (10 mL) to give 2-(4-fluorophenyl)-1,3-dihydroxy-4,4,5,5-tetramethylimidazolidine (3.1 g, 61%) which was oxidized further immediately by stirring with PbO_2 (20.0 g, 83.6 mmol) in $CHCl_3$ (50 mL). The PbO_2 was filtered off, the blue solution was evaporated off and purified with flash-column chromatography (hexane/EtOAc). Yield: 2.80 g (55%); R_f 0.31 (hexane/EtOAc, 2:1); blue crystals mp 92 °C.

1-Hydroxy-4,4,5,5-tetramethyl-2-phenyl-4,5-dihydroimidazole (3b); General Procedure:

Method A (from nitronyl nitroxide **1a**): To a solution of **1a** (1.0 g, 4.29 mmol) in glacial HOAc (10 mL) was added Fe powder (1.4 g, 25.0 mmol) and the mixture was stirred and warmed up to 50 °C until the vigorous reaction started. The mixture was stirred for 1 h at r.t., then diluted with H_2O (30 mL), decanted and basified by adding solid K_2CO_3. The mixture was filtered off, the filtrate was extracted with $CHCl_3$ (3 × 20 mL), dried ($MgSO_4$), the solvent was evaporated and the residue was crystallized from hexane/Et_2O to give a white solid; yield: 685 mg (73%); R_f 0.34 ($CHCl_3/CH_3OH$, 9:1); mp 189–190 °C.

^1H NMR: δ = 1.27 (s, 6H); 1.32 (s, 6H); 4.60 (br s, 1H); 7.40 (m, 3H); 8.25 (m, 2H).

Method B (from imino nitroxide **2**): To a stirred solution of compound **2** (0.5 g, 2.30 mmol) in H_2O (5 mL) and dioxane (5 mL), ascorbic acid (880 mg, 5.0 mmol) was added and the mixture was stirred under N_2 for 3 min. Then $KHCO_3$ (600 mg, 6.0 mmol) was added and extracted with $CHCl_3$ (3 × 10 mL), dried ($MgSO_4$) and the solvent was evaporated off in vacuo. The residue was crystallized from hexane-Et_2O to give compound **3b** as a white solid 265 mg (53%).

4,4,5,5-Tetramethyl-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yloxyl Radical (2); General Procedure:

Method A (from nitronyl nitroxide **1a**): To a stirred solution of compound **1a** (0.5 g, 2.1 mmol), $NaNO_2$ (0.69 g, 10.0 mmol) in dioxane (5 mL) and H_2O (5 mL) was added 1 M aq HCl solution (1.0 mL) and the mixture was stirred for 15 min at r.t. The solvents were evaporated off in vacuo, the residue was dissolved in $CHCl_3$ and purified further with flash-column chromatography (hexane/Et_2O) to give compound **2** as red crystals; yield: 400 mg (87%). The analytical data were identical with the product described previously.[1]

Method B (from *N*-hydroxyimidazoline **3b**): To a stirred solution of compound **3b** (109 mg, 0.5 mmol) in $CHCl_3$ (10 mL) was added PbO_2 (100 mg, 0.4 mmol) and the mixture was stirred for 10 min at r.t. The PbO_2 was filtered off, the solution was evaporated in vacuo, the residue was chromatographed (hexane/Et_2O) to give orange-red crystals; yield: 95 mg (87%). The analytical data were identical with the product described previously.[1]

4,4,5,5-Tetramethyl-2-phenyl-4,5-dihydro-1*H*-imidazole (4); General Procedure:

To a stirred solution of **1a** (1.0 g, 4.29 mmol) in 10% aq HCl (25 mL) was added Zn powder (3.0 g, 45.9 mmol) and the mixture was stirred and refluxed for 1.5 h. After cooling, the solution was made basic with 30% aq NaOH and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$),

filtered, evaporated to afford compound **4**; yield: 520 mg, (60%) as a white solid; R_f 0.13 ($CHCl_3/CH_3OH$, 1:1); mp 166–167°C.

^1H NMR: δ = 1.22 (s, 12H); 5.50 (br s, 1H); 7.36 (m, 3H); 7.73 (m, 2H).

4,4,5,5-Tetramethyl-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (1a):

To a solution of **4** (202 mg, 1.0 mmol), $Na_2WO_4 \cdot 2H_2O$ (33 mg, 0.1 mmol) in MeOH (5 mL) and H_2O (5 mL) was added 30% H_2O_2 (1 mL), then the mixture was allowed to stand at r.t. for 48 h. The blue solution was extracted with $CHCl_3$ (2 × 10 mL), the organic phase was dried ($MgSO_4$), filtered, evaporated and the residue was chromatographed (hexane/EtOAc) to give blue crystals; yield: 120 mg (51%). The analytical data were identical with the product described previously.[1]

4,4,5,5,-Tetramethyl-2-(2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (7):

To a stirred solution of **5** (4.92 g, 20 mmol) in H_2O (20 mL) and MeOH (20 mL) was added compound **6** (3.06 g, 20.0 mmol) and the pH was adjusted to 8 with 10% aq Na_2CO_3 and the mixture was stirred for 24 h under N_2. The precipitated white solid was filtered off and the mother liquor was extracted with $CHCl_3$ (3 × 30 mL). The precipitated solid was dissolved in the organic phase, dried ($MgSO_4$), PbO_2 (20.0 g, 83.6 mmol) was added and the solution stirred for 40 min. The PbO_2 was filtered off, the blue solution was evaporated and chromatographed ($CHCl_3/Et_2O$, $CHCl_3/CH_3OH$) to give blue crystals; yield: 3.5 g, (62%); R_f 0.46 ($CHCl_3/CH_3OH$, 9:1); mp 125°C.

2-(1-Oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (8):

Method A (from nitronyl nitroxide **7**): Compound **7** (2.80 g, 10.0 mmol) was reacted with 30% H_2O_2 (10 mL) in the presence of $Na_2WO_4 \cdot 2H_2O$ (329 mg, 1.0 mmol) for 5 d under the same reaction conditions and procedure for the synthesis of **1a**. The precipitated blue crystals were filtered off and the mother liquor was extracted with $CHCl_3$ (3 × 30 mL). The organic phase was dried ($MgSO_4$), evaporated and chromatographed (hexane/EtOAc, $CHCl_3/Et_2O$) to give dark blue shiny crystals; yield: 1.68 g (57%); R_f 0.29 (hexane/EtOAc, 2:1); mp 170°C.

Method B (from imidazoline **12**): Compound **12** (249 mg, 1.0 mmol) was oxidized with 30% H_2O_2 (1 mL) in the presence of $Na_2WO_4 \cdot 2H_2O$ (33 mg, 0.1 mmol) in MeOH (5 mL) and H_2O (5 mL) for 5 d under the same conditions and procedure as for the synthesis of compound **1a** to give compound **8** after chromatography (hexane/EtOAc, $CHCl_3/Et_2O$); yield: 147 mg (50%).

2-(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl Biradical (9):

Compound **8** (0.5 g, 1.7 mmol) was reacted with $NaNO_2$ (0.5 g, 7.2 mmol), 1 M aq HCl solution (0.7 mL) in dioxane (5 mL) and H_2O (5 mL) to give compound **9** as red crystals after chromatography (hexane/EtOAc); yield: 310 mg (65%); R_f 0.65 (hexane/EtOAc, 2:1); mp 157°C.

2-(2,5-Dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl Radical (10):

Method A (from nitronyl nitroxide **7**): Compound **7** (0.5 g, 1.8 mmol) was reacted with $NaNO_2$/HCl under the same reaction conditions and procedure as for the synthesis of **9** and gave compound **10** after chromatography ($CHCl_3/Et_2O$) as red crystals; yield: 250 mg (52%); R_f 0.60 ($CHCl_3/CH_3OH$, 9:1); mp 83–84°C.

Method B (from *N*-hydroxyimidazoline **11**): Compound **11** (132 mg, 0.5 mmol) was oxidized in the presence of PbO_2 (100 mg, 0.4 mmol) under the same conditions and procedure as for the synthesis of compound **2** (Method B) to give compound **10** after chromatography ($CHCl_3/Et_2O$); yield: 120 mg (91%).

1-Hydroxy-4,4,5,5-tetramethyl-2-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-4,5-dihydroimidazole (11):

Compound **7** (1.0 g, 3.5 mmol) was reduced in HOAc (10 mL) with Fe powder (3.0 g, 53.9 mmol) under the same conditions and procedure as for the syntheses of compound **3b** to give compound **11**; yield: 680 mg (71%); R_f 0.5 ($CHCl_3/CH_3OH$, 1:1); mp 167°C.

^1H NMR: δ = 1.25 (s, 6H); 1.30 (s, 6H); 1.31 (s, 6H); 1.40 (s, 6H); 7.25 (s, 1H); 7.85 (br, 1H).

2-(2,5-Dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole (12):

Method A (from nitronyl nitroxide **7**): Compound **7** (1.0 g, 3.5 mmol) was reduced in 10% aq HCl (25 mL) with Zn powder (2.25 g, 40.0 mmol) under the same conditions and procedure as for synthesis of compound **4** to give compound **12**; yield: 450 mg (50%); R_f 0.17 (CH_3OH); mp 138–140°C.

^1H NMR: δ = 1.19 (s, 12H); 1.32 (s, 6H); 1.41 (s, 6H); 5.50 (br s, 1H); 7.26 (s, 1H).

Method B (from nitronyl nitroxide **8**): Compound **8** (1.0 g, 3.3 mmol) was reduced in 10% aq HCl (25 mL) with Zn powder (2.25 g, 40.0 mmol) under the same conditions and procedure as for the synthesis of compound **4** to give compound **12**; yield: 345 mg (42%).

4,4,5,5-Tetramethyl-2-(3-nitrophenyl)-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (13a), 4,4,5,5-Tetramethyl-2-(2-nitrophenyl)-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (14); General Procedure:

To a stirred solution of **1a** (1.5 g, 6.4 mmol) in concd H_2SO_4 (8 mL) at 0°C, 65% HNO_3 (4 mL) was added dropwise and the mixture was stirred for a further 15 min at this temperature. Then the mixture was allowed to stand at r.t. for 15 min, poured onto crushed ice (100 g), the pH of the solution was adjusted to 9 with K_2CO_3 then extracted with $CHCl_3$ (3 × 30 mL). The organic phase was dried ($MgSO_4$), filtered, evaporated and the residue was chromatographed (hexane/EtOAc, $CHCl_3/Et_2O$) to give compound **13a** as dark green crystals; yield: 1.12 g (63%); R_f 0.30 (hexane/EtOAc); mp 162°C, and **14** as dark purple crystals; yield: 200 mg (11%); R_f 0.35 ($CHCl_3/Et_2O$, 2:1); mp 145–147°C.

2-(4-Fluoro-3-nitrophenyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (13b):

Compound **1b** (3.0 g, 11.9 mmol) was nitrated with H_2SO_4 (10 mL) and HNO_3 (5 mL) under the same reaction conditions and procedure as for the synthesis of **13a**. Chromatography (hexane/EtOAc) gave dark blue crystals; yield: 2.2 g (62%); R_f 0.28 (hexane/EtOAc, 2:1); mp 127°C.

2-(4-Hydroxy-3-nitrophenyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (15):

A mixture of **13b** (296 mg, 1.0 mmol), 18-crown-6 (53 mg, 0.2 mmol) and 20% aq KOH (3 mL) in dioxane (10 mL) was vigorously stirred at r.t. for 2 h. Then the solvents were evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (2 × 15 mL), the organic phase was washed with brine (10 mL), dried ($MgSO_4$), and purified by flash-column chromatography ($CHCl_3/Et_2O$) to give **15** as green crystals; yield: 150 mg (51%); R_f 0.59 ($CHCl_3/Et_2O$, 2:1); mp 142–144°C.

2-(4-Amino-3-nitrophenyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (16):

A mixture of **13b** (296 mg, 1.0 mmol) and 27% NH_4OH solution (5 mL) in dioxane (10 mL) was allowed to stand at r.t. for 24 h. Then the solvents were evaporated in vacuo, the residue was dissolved in $CHCl_3$ (2 × 15 mL), the organic phase was washed with brine (10 mL), dried ($MgSO_4$), and purified by flash-column chromatography ($CHCl_3/Et_2O$) to give **16** as green crystals; yield: 200 mg (68%); R_f 0.29 ($CHCl_3/Et_2O$, 2:1); mp 192°C.

2-(3-Nitro-4-[*N*-(Methoxycarbonylmethyl)aminophenyl])-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (17):

A mixture of **13b** (592 mg, 2.0 mmol), glycine methyl ester hydrochloride (1.25 g, 10.0 mmol) and $KHCO_3$ (1.0 g, 10.0 mmol) in H_2O (10 mL) and dioxane (15 mL) was allowed to stand at r.t. for 24 h. Then the solvents were evaporated off in vacuo, the residue was dissolved in $CHCl_3$ (3 × 15 mL), the organic phase was washed with brine (10 mL), dried ($MgSO_4$), and purified by flash-column chro-

matography ($CHCl_3/Et_2O$) to give **17** as green crystals; yield: 515 mg (70%); R_f 0.35 ($CHCl_3/Et_2O$, 2:1); mp 156–158 °C.

2-(4-Aminophenyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl Radical (19):

To a solution of **18** (2.78 g, 10.0 mmol) in glacial HOAc (15 mL) was added Fe powder (3.0 g, 53.7 mmol) and the mixture was stirred and warmed to 50 °C until a vigorous reaction started. The mixture was stirred for 1 h at r.t., then diluted with H_2O (30 mL) decanted and basified by adding solid K_2CO_3. The mixture was filtered off, the filtrate was extracted with $CHCl_3$ (3 × 20 mL), dried ($MgSO_4$), PbO_2 (239 mg, 1.0 mmol) was added and the mixture was stirred at r.t. for 15 min. The PbO_2 and $MgSO_4$ were filtered off, the solvent was evaporated in vacuo and the residue was purified by flash-column chromatography ($CHCl_3/CH_3OH$) to give **19** as wine-red crystals; yield: 1.10 g (47%); R_f 0.31 ($CHCl_3/Et_2O$, 2:1); mp 102 °C.

2-(4-Dansylaminophenyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl Radical (20):

To a solution of compound **19** (232 mg, 1.0 mmol) in anhyd pyridine (5 mL), dansyl chloride (270 mg, 1.0 mmol) was added and the mixture was kept at 60 °C for 30 min. Then pyridine was evaporated, the residue was dissolved in $CHCl_3$ (15 mL), washed with brine (10 mL), dried ($MgSO_4$), and purified by flash-column chromatography ($CHCl_3/Et_2O$) to give compound **20**; yield: 137 mg (29%) as orange crystals; R_f 0.40 ($CHCl_3$-Et_2O, 2:1); mp 96 °C.

2-(4-Dansylaminophenyl)-1-hydroxy-4,4,5,5-tetramethyl-4,5-dihydroimidazole (21):

Compound **20** (93 mg, 0.2 mmol) was reduced with ascorbic acid (176 mg, 1.0 mmol) in H_2O (4 mL) and dioxane (2 mL) under the same conditions and procedure as for the synthesis of compound **3b** (method B) to give compound **21** as greenish-white crystals; yield: 52 mg (55%); R_f 0.64 ($CHCl_3/CH_3OH$, 9:1); mp 184–186 °C. ^{1}H NMR: δ = 1.25 (s, 12H); 2.82 (s, 6H); 6.90–7.20 (m, 4H); 7.30–7.80 (m, 3H); 8.20–8.60 (m, 3H).

2-(4-Dansylaminophenyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-yloxyl 3-Oxide Radical (22):

Compound **20** (93 mg, 0.2 mmol) was oxidized with 30% H_2O_2 (2 mL) in the presence of $Na_2WO_4 \cdot 2H_2O$ (33 mg, 0.1 mmol) in MeOH (5 mL) and H_2O (5 mL) for 10 d under the same conditions and procedure as for the synthesis of compound **1a** to give compound **22** after chromatography ($CHCl_3/CH_3OH$); yield: 51 mg (53%); R_f 0.37 ($CHCl_3/CH_3OH$, 9:1); mp 175 °C (dec.).

X-ray Structure Determination of 8:

Crystal data of compound **8**: $C_{15}H_{25}N_3O_3$, space group $P\bar{1}$ (2), a = 7.181(1), b = 11.032(2), c = 11.945(2) Å, α = 106.71(1), β = 105.93(1), γ = 104.02(1)°, Z = 2, V = 816.8(2) Å^3, M_r = 295.38, ϱ_{cal} = 1.201 Mg/m^3, $F(000)$ = 320. Data for a crystal of dimensions 0.5 × 0.35 × 0.20 mm were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å) using ω-θ scans at r.t. 4066 reflections were collected, 3744 unique [R(int) = 0.0157; 2.22° ≤ θ ≤ 27.50°]. The structure was solved by direct methods[28] and was refined by full matrix least squares[29] on F^2. Hydrogen atomic positions were generated from assumed geometries and the riding model was applied to them. The final R values are $R1$ = 0.046, $wR2$ = 0.121 for 2959 [$I > 2\sigma(I)$] data. No absorption correction was applied ($\mu(MO\text{-}K_\alpha)$ = 0.084 mm^{-1}).

X-ray Structure Determination of 9:

Crystal data of compound **9**: $C_{15}H_{25}N_3O_2$, space group $P2_1/c$ (14), a = 6.206(1), b = 13.389(1), c = 19.523(1) Å, β = 94.20(1)°, Z = 4, V = 1617.9(3) Å^3, M_r = 279.38, ϱ_{cal} = 1.147 Mg/m^3, $F(000)$ = 608. Data for a crystal of dimensions 0.35 × 0.20 × 0.15 mm were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu-K_α radiation (λ = 1.54184 Å) using ω-θ scans at r.t. 3968 reflections were collected, 3366 unique [R(int) = 0.0243; to 4.01° ≤ θ ≤ 75.7°]. The structure was solved by direct methods[28] and was refined by full matrix least squares[29] on F^2. Hydrogen atomic positions were generated from assumed geometries and the riding model was applied to them. The final R values are $R1$ = 0.0467, $wR2$ = 0.1274 for 2698 [$I > 2\sigma(I)$] data. Empirical absorption correction (psi-scans) was applied (max. and min. transmission coefficients 1.000 and 0.914).

Atomic coordinates, bond lengths and angles, and thermal parameters for **8** and **9** have been deposited with the Cambridge Crystallographic Data Centre (CCDC).

Table.

Product[a]	Yield (Method) (%)	mp (°C)	IR (Nujol) ν (cm^{-1})	MS m/z (%)
1b	55	92	1630, 1590 (C=C)	251 (M$^+$, 15), 163 (8), 122 (19), 84 (100)
3b	73 (A), 53 (B)	189–190	3400 (OH), 1610, 1580 (C=C)	218 (M$^+$, 5), 201 (19), 145 (84), 104 (100)
4	60	166–167	3370 (NH), 1580 (C=C)	202 (M$^+$, 14), 187 (6), 145 (100), 104 (69)
7	62	125	3340 (NH), 1620 (C=C)	280 (M$^+$, 7), 265 (14), 249 (21), 135 (49), 84 (100)
8	57 (A), 50 (B)	170	1620 (C=C)	295 (M$^+$, 2), 279 (3), 265 (8), 135 (11), 84 (100)
9	65	157	1620 (C=C)	279 (M$^+$, 3), 249 (6), 135 (11), 84 (100)
10	52 (A), 91 (B)	83–84	3310 (NH), 1625 (C=C)	264 (M$^+$, 3), 249 (35), 234 (53), 135 (82), 84 (100)
11	71	167	3500–3280 (NH, OH), 1630 (C=C)	265 (M$^+$, 12), 250 (82), 234 (68), 135 (100)
12	50 (A), 42 (B)	138–140	3450, 3320 (NH), 1600 (C=C)	249 (M$^+$, 12), 234 (100), 195 (47), 135 (62)
13a	63	162	1600 (C=C), 1530 (NO_2)	278 (M$^+$, 2), 247 (13), 207 (32), 190 (83), 150 (100)
13b	62	127	1605 (C=C), 1530 (NO_2)	296 (M$^+$, 32), 208 (16), 167 (9), 84 (100)
14	11	145–147	1610 (C=C), 1530 (NO_2)	278 (M$^+$, 3), 246 (2), 134 (18), 104 (24), 84 (100)
15	51	142–144	3330 (OH), 1615 (C=C), 1540 (NO_2)	294 (M$^+$, 4), 262 (3), 206 (16), 84 (100)
16	68	192	3420, 3330 (NH_2), 1620 (C=C), 1540 (NO_2)	293 (M$^+$, 4), 262 (4), 205 (23), 84 (100)
17	70	156–158	3370 (NH), 1730 (C=O), 1620 (C=C), 1550 (NO_2)	365 (M$^+$, 1), 334 (8), 277 (54), 84 (100)
19	47	102	3400, 3320 (NH_2), 1630, 1580 (C=C)	232 (M$^+$, 2), 217 (21), 160 (98), 84 (100)
20	29	96	3280 (NH), 1605, 1580 (C=C)	TSP: 466 (M + H)$^+$
21	55	184–186	3360 (OH), 3280 (NH), 1610, 1580 (C=C)	TSP: 467 (M + H)$^+$
22	53	175 (dec.)	3280 (NH), 1600, 1580 (C=C)	TSP: 482 (M + H)$^+$

[a] All compounds gave satisfactory elemental analyses: C ± 0.19, H ± 0.15, N ± 0.17, S ± 0.26.

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