Nitronyl and Imino Nitroxides: Improvement of Ullman's Procedure and Report on a New Efficient Synthetic Route

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Abstract: The synthesis of nitronyl and imino nitroxides has been reexamined with the aim of both increasing yields and of offering opportunities for new structures. The conditions for the formation of 2,3-bis(hydroxyamino)-2,3-dimethylbutane, the key intermediate of Ullman's route, have been carefully studied, and a new procedure is proposed, which affords the free base in a very pure form and up to 60% yield. Full characterization of this intermediate including an X-ray crystal structure is presented. An alternative synthetic route through 2,3-diamino-2,3-dimethylbutane and the corresponding imidazolidines which bypasses the delicate synthesis of the bis(hydroxyamino) compound is described. It is shown that 3-chloroperbenzoic acid is an effective oxidant for the transformation of adequately substituted imidazolidines into nitronyl nitroxides, which are obtained in high yield. An illustration of the potentialities of this new route, a new nitronyl nitroxide with two ethyl substituents in positions 4 and 5 of the imidazoline ring, is reported. The scope and limitations of the two routes are discussed.

Keywords: amines · heterocycles · imidazolidines · imidazolines · nitroxides

Introduction

Nitronyl and imino nitroxide free radicals were described in the seventies by Ullman in his pioneering work,[1–3] and since then they have not attracted much attention until the last decade of the century. This recent renewal of interest mainly stems from the use of these paramagnetic species as building blocks for designing molecular magnetic materials.[4] Successful achievements in this field, such as purely organic ferromagnetically ordered solids[5, 6] and metal-organic exchange-coupled complexes that exhibit versatile magnetic properties,[7, 8] have triggered the synthesis of hundreds of these free radicals.

The synthesis of nitronyl and imino nitroxides relies almost exclusively[9] on the condensation of 2,3-bis(hydroxyamino)-2,3-dimethylbutane (**2**) with an aldehyde and oxidation of the condensation product (Scheme 1).[2] While the condensation and oxidation stages proceed with acceptable yields and are reproducible, preparation of the bis(hydroxyamino) intermediate is poorly reproducible and often leads to frustrating results. Its formation in moderate yield and questionable purity was published over thirty years ago;[10] it is obtained using the classical reduction process with zinc in ammonium chloride buffered solution of the dinitro analogue, **1**.[11] This synthetic procedure has recently received attention, and the understanding of important features of the redox process has led to a new procedure, which affords the sulfate salt of **2** in a fairly good yield; the synthesis of the pure free base however, is still a challenge.[12] Thus, the overall yield of nitroxide from **1** is often less than 50% and mainly reflects the difficulties in preparing the bis(hydroxyamino) compound. However, since the dinitro precursor is readily available in most cases, yield and purity of the bis(hydroxyamino) (**2**) intermediate are not a matter of great concern, and all nitronyl nitroxides reported so far were prepared using this procedure.

However, problems associated with the preparation of this key intermediate are probably the cause of the limited number of developments reported so far that concern structural variations in nitronyl nitroxides. Indeed, while any aldehyde may give a nitronyl nitroxide, uncertainty about purity of the bis(hydroxyamine) may lead to delay or abandonment of attempts to synthesize specific nitroxides that require aldehydes, which are difficult to prepare. Accordingly, we performed a thorough study of the formation of compound **2** and produced a new workup, which affords the

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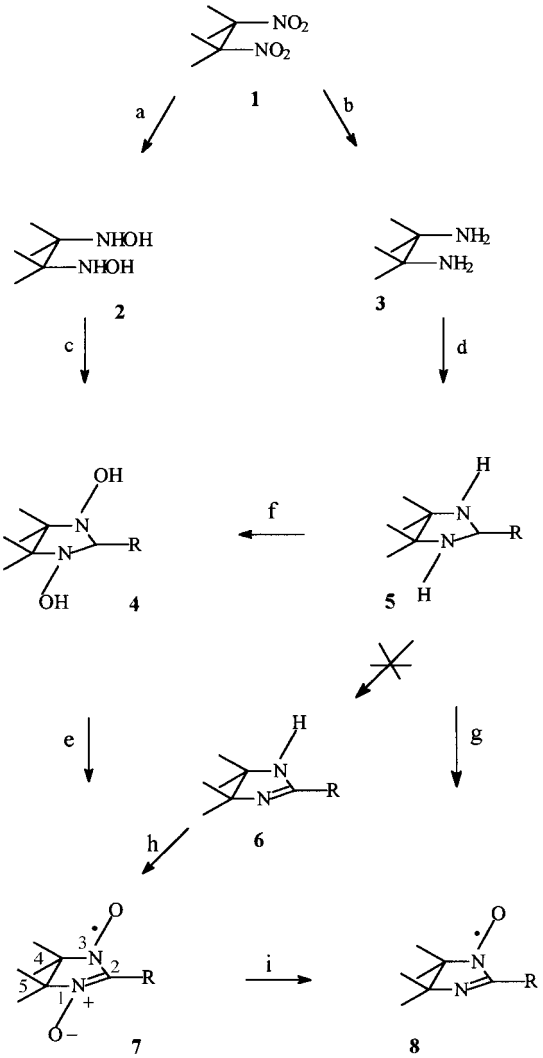


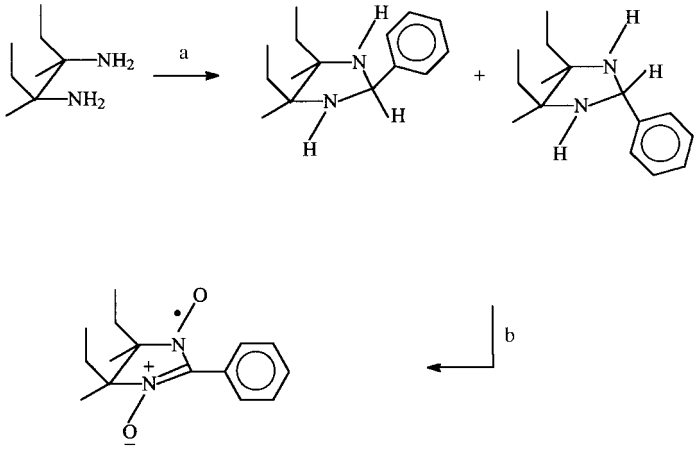
Scheme 1. The bis(hydroxyamino) and diamino routes to nitronyl and imino nitroxides. a) Zn/NH_4Cl, THF/H_2O; b) Sn, HCl, reflux; c) and d) RCHO, methanol, $CHCl_3$ or diethyl ether; e) $NaIO_4$ or MnO_2, CH_2Cl_2/H_2O; f) *m*-chloroperbenzoic acid (2 equivalents)/CH_2Cl_2; g) Na_2WO_4/H_2O_2; h) see ref. [9]; i) $NaNO_2$/HCl, H_2O/CH_2Cl_2. R = phenyl (a), *p*-nitrophenyl (b), 3-pyridyl (c), H (d), methyl (e), and *tert*-butyl (f).

pure free base **2** in a highly pure form and a yield of up to 60%; we report its full characterization including a X-ray diffraction study.

Although tetramethylated nitronyl nitroxides (Scheme 1, **7**) are thus satisfactorily obtained for most purposes, the Ullman route suffers from major drawbacks: i) the delicate synthesis of the bis(hydroxyamino) compound could hardly be transposed to differently substituted dinitro precursors; ii) adequately substituted *vic*-diamines are precursors of nitronyl nitroxides, which, according to this synthetic scheme, would have to be oxidized to dinitro compounds and then reduced to bis(hydroxyamino) compounds with increasing uncertainties about the yield. Accordingly, there are synthetic problems that would be solved only with great difficulty following Ullman's synthetic scheme. For example, the yield is not high enough to trigger the synthesis of perdeuterated nitronyl nitroxides, which would have utility in neutron diffraction studies. More importantly, structural variations that involve enantiotopic methyl groups in positions 4 and 5 (Scheme 1, compound **7**) of the imidazoline ring that would be involved in the preparation of all series of chiral nitronyl nitroxides cannot be envisioned because it would require a tedious study for establishing a reliable synthetic procedure for the corresponding bis(hydroxyamino) intermediate.

Considering that flexible syntheses of new nitronyl nitroxides are central to continued progress in the field of molecular magnetism, we decided to explore other synthetic routes toward these important open-shell intermediates. There are two general methods for obtaining nitroxide free radicals: the first, related to Ullman's procedure, involves oxidation of hydroxyamines by mild oxidizing reagents,[13–15] the second converts amines directly to free radicals by use of strong oxidants.[13, 14, 16–18] Conversion of adequately substituted imidazolines into nitronyl nitroxides by sodium tungstate catalyzed hydrogen peroxide oxidation in a rather low yield has been reported which is a possibility for a new synthetic route.[9]

In addition to a more efficient synthesis of the bis(hydroxyamino) intermediate, we describe in this paper an alternative new synthetic route through 2,3-diamino-2,3-dimethylbutane, **3**, which bypasses the usual bis(hydroxyamino) precursor. Potentialities of this new synthetic route are illustrated by the synthesis of already known free radicals in high yield and by the straightforward preparation of a newly substituted nitronyl nitroxide (Scheme 2). The scope and limitations of this new synthetic route are discussed and compared with those of Ullman's procedure.



Scheme 2. Illustration of the synthetic potentialities of the diamino route: *meso*-4,5-diethyl-4,5-dimethyl-2-phenyl-4,5-dihydro-1H-imidazolyl-3-oxide-1-oxy. a) benzaldehyde/diethyl ether; b) *m*-chloroperbenzoic acid/CH_2Cl_2, $NaIO_4$.

Results and Discussion

The bis(hydroxyamino) route: As stated before, the only delicate step of Ullman's route is the synthesis of compound **2**. Its preparation was performed more than one hundred times in our laboratories using the Lamchem – Mittag procedure,[10] which was progressively modified. These studies ascertained the redox mechanism, established the stability of the bis(hydroxyamino) derivative when pure, and explained the for-

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mation of side products such as 2-methyl-substituted nitronyl nitroxide.[12] Concerning this point, it is worth mentioning that alcohols should not be used as solvent. They are oxidized by the bis(hydroxyamine) into aldehydes, which condense in situ and are air oxidized into nitroxides. Since this process is probably catalyzed by impurities and is unpredictable,[19] use of nonpurified methylene chloride or chloroform, which are usually stabilized with 0.2–0.4% of ethanol may also give the undesirable free radical, when compound **2** is extracted in the presence of a base. The pink color (low concentration of nitroxide) disappears during extraction, but decomposition products contaminate the bis(hydroxyamine), which is far less stable. These observations open questions about catalytic redox reactions that involve hydroxyamines, which are out of the scope of this study.

Use of THF instead of ethanol in the modified Lamchem–Mittag procedure (Procedure A) not only avoids formation of undesired nitroxides but also has a strong influence on the course of the reduction. While in ethanol/water (1:1) ammonium chloride is soluble and the dinitro compound sparingly soluble, the reverse situation is observed when THF/water (2:1) is used. Actually, the kinetics of the reduction are strongly dependent on the concentration of NH_4Cl in the solution. The course of the reaction is thus strongly affected since in the first case there is a rather weak concentration of dinitro compound and a large concentration of NH_4Cl, while in the second case the concentration of dinitro compound is at a maximum, and that of NH_4Cl is monitored by the quantity of water. Formation of side products is thus minimized; in particular, provided that the temperature is kept below 12 °C, formation of the diamine is almost negligible using a 2:1 ratio of THF/water.

Another improvement to the Lamchem–Mittag procedure comes from using eight equivalents of NH_4Cl. This quantity brings just the right number of anions required for four atom grams of Zn. Examination of the literature shows that the quantity of NH_4Cl used (2–4 equivalents) does not rely on any experimental finding except that it is in line with the incorrect belief that NH_4Cl had only the role of buffering the solution. Actually, use of eight equivalents does result in a well-defined Zn complex, $[Zn(NH_3)_2Cl_2]$.[20]

However, although the synthesis does afford the pure free base **2**, the yield is spread over a large range, and the synthesis is not well reproducible. This is likely to be the consequence of adding Zn portionwise, which is a hardly reproducible process and this probably results in a great deal of local heating of the solution. This drawback is overcome in Procedure B, in which the dropwise addition of NH_4Cl in solution allows one to monitor the temperature and the reaction rate by means of a constant and weak concentration of the salt. One observes that the role of NH_4Cl is dramatic: compound **2** appeared at the same time as a few drops of the salt were added.[21] Therefore, since these parameters are well controlled, reproducibility is enhanced, and one obtains a reproducible yield, which was not possible using Procedure A.

Finally, we addressed the problem of the true nature of the solution of **2** in THF/H_2O. One notes that the precipitate of $[Zn(NH_3)_2Cl_2]$ is recovered in only 85–88% yield, and that ⅛ of the added Zn metal should be in solution. This is verified by analyzing the solution content that corresponds to $[Zn(\mathbf{2})_2Cl_2]$. Mass spectrometry analysis of the recovered solid exhibits the expected mass and the characteristic isotopic pattern of Zn complexes, which, with the results of elemental analyses, demonstrate unambiguously that compound **2** is filtered as its Zn^{II} complex.

Accordingly, the reaction should be written as follows [Eq. (1)].

$$2\,C_6H_{12}(NO_2)_2 + 8\,Zn + 16\,NH_4Cl \rightarrow 7\,[Zn(NH_3)_2Cl_2] + [C_6H_{12}(NHOH)_2]_2ZnCl_2 + 4\,H_2O + 2\,NH_3 \quad (1)$$

Hydroxyamino derivatives are known to be unstable and particularly subject to oxidation even on exposure to air. This seemed also true for compound **2**, which, when prepared according to the Lamchen–Mittag procedure, often decomposed at room temperature in a few days. At lower temperature (4–6 °C) decomposition occurs slowly with the production of acetoxime, which sublimes in the flask. Therefore, it clearly appeared that the Lamchen–Mittag workup, mainly the acidification of the crude reaction filtrate before evaporation, was based on the incorrect belief that the desired bis(hydroxyamino) derivative is volatile. This fact gave support to the new workup, which avoids acidification of the crude product and increases the yield.

Although this procedure affords 2,3-bis(hydroxyamino)-2,3-dimethylbutane in pure form and acceptable yield, one should be aware that the use of Zn from another source (different particle size distribution) may result in a different yield and purity. As well, in Procedure B, the use of less or more water than usual may also have the same consequence.

Even when pure, in solution the compound is rather unstable at room temperature and transforms slowly into acetoxime and other nonidentified products.[12] In contrast, in the solid state it seems to be indefinitely stable (up to two years at room temperature without change). Full characterization by X-ray diffraction was performed without precaution, and the data did not show any sign of crystal destruction during data collection at room temperature. The structure (Figure 1) is unexceptional. The molecule adopts a staggered conformation with a NCCN dihedral angle of 71.6(4)°. One of the hydroxyamino groups is statistically disordered on two positions with respective occupancies of 0.1 and 0.9, which

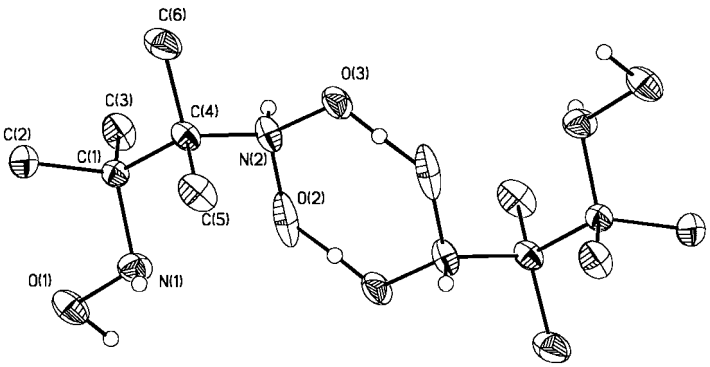

Figure 1. View of the molecular structure of **2**. Relevant bond lengths [Å] and angles [°] are as follows: O(1)–N(1) = 1.451(1), O(2)–N(2) = 1.507(9), C(1)–C(4) = 1.568(1); N(1)–C(1)–C(4)–N(2) = 71.6(4).

each share the hydrogen atom (not disordered) of their hydroxyl group with a neighboring molecule. Therefore, the molecules are arranged into dimers as shown in Figure 1. In addition, the second hydroxyamino group is also engaged in hydrogen bonding with another dimer so that the compound should be viewed as zig-zag chains that run along the *c* axis. All distances and angles are within the expected range and need no further comments.

The production of compound **2** in pure form is important. Indeed, the presence of impurities has dramatic effects on the following steps of the synthesis of nitronyl nitroxides and, in particular, it partly accounts for the presence of imino nitroxides in variable amount in almost all nitronyl nitroxide preparations. Dehydration of the 1,3-dihydroxy-imidazolidine compound **3** (Scheme 1) seems to be promoted not only by sodium periodate during the oxidation stage and SiO_2 if the oxidation is not complete, but also by the presence of impurities during the condensation process.

In conclusion, since the dinitro precursor **1** is a readily available product, and that this new workup brings pure intermediate **2** in acceptable yield, the synthesis of nitronyl nitroxides proceeds with higher yields. In particular, this new method opens up new possibilities when the aldehyde is a rare compound.

The diamino route: In contrast to the bis(hydroxyamino) derivative **2**, the diamino compound **3** is easily prepared. Corresponding to the full reduction of the dinitro precursor, it is obtained pure and in high yield by using drastic reducing conditions.[11, 22] Condensation with aldehydes is quantitative, and the resulting imidazolidines are easily oxidized by 3-chloroperbenzoic acid. We have investigated this new route for a few representatives of aromatic- (**7a–c**) and aliphatic- (**7d–f**) substituted nitronyl nitroxides.

Although the condensation of aldehydes with α-diamines is a well-known preparation of imidazolidines (**5**),[23–26] surprisingly, no investigations have been reported that involve tetramethyl-substituted fragments suitable for the preparation of stable nitronyl nitroxides. Despite the steric crowding of the *gem*-dimethyl groups, the condensation is fast in diethyl ether or chloroform; it is likely that steric hindrance is overcompensated for by the basicity of the amino groups, which is magnified by the presence of these methyl groups. However, electronic or steric effects of the substituent are reflected in the formation of **5b** (*p*-nitrophenyl) and **5f** (*tert*-butyl), which required boiling in chloroform to reach completion. These effects are also probably the cause of the low yields reported by Ullman (bis(hydroxyamino) route)[1] for the corresponding two nitroxides **7b** and **7f** (24 and 47%, respectively, from the corresponding aldehydes), and one can note the efficiency of the new route, which produces these radicals in 66 and 64% yield from **1**.

Being aminals, imidazolidines (cyclic form) are also expected to exist as amino-imines (open form).[27] At room temperature however, ^1H and ^{13}C NMR spectra performed in D_2O in the pH range 1–10 are consistent only with the cyclic form. Moreover, imidazolidines that are described as being hydrolyzed in acidic medium[28] are formed in good yield when acetals are used instead of aldehydes and hydrolyzed in situ (see Experimental Section). This extension of the new route has been investigated for both an aromatic (**5a**) and an alkyl (**5e**)[29] dimethyl acetal with equal success. These heterocycles are oils or solids that have a low melting point; there are a few exceptions like **5b**, which crystallizes from methanol and whose structure was determined by X-ray diffraction, which gave us the opportunity of fully characterizing these new compounds.[30]

While hydroxyamines are oxidized into nitroxides by several mild oxidants such as PbO_2, $NaIO_4$, or Ag_2O,[13–15] conversion of amines into nitroxides requires more powerful oxidizing agents.[16–18] As mentioned before, a few reports describe attempts for synthesizing tetramethylated imidazolines (**6**), which were converted to nitroxides through phosphotungstic acid or $NaWO_4$ catalyzed oxidation with hydrogen peroxide in a rather low yield.[9] In our laboratory, these oxidizing systems converted imidazolidines (**5**) into imino nitroxides (**8**) with a similar low yield. Nevertheless, we have found that 3-chloroperbenzoic acid, introduced in the seventies for converting substituted amines into the corresponding aliphatic nitroxides,[17, 18] was effective also for efficiently transforming imidazolidines into nitronyl nitroxides. This reaction is carried out at low temperature (6–8 °C) in the presence of a base ($NaHCO_3$), which removes *m*-chlorobenzoic acid from the organic phase. However, we have observed that in this basic medium compound **7d** (R = H) is not stable. As described previously by Ullman,[31, 32] $NaHCO_3$ is a strong enough base to convert the nitronyl nitroxide into the corresponding carbanion, which disproportionates into diamagnetic compounds. This compound is better prepared without the use of a base and purified by chromatography on alumina.

Formally, oxidation of imidazolidines **5** into nitronyl nitroxides **7** requires 3.5 equivalents of peracid and should involve several steps. Susceptibility of these heterocycles to oxidizing agents is well-documented; they have even been used as reducing agents for activated double bonds.[33] Consistently, one observes the presence of a weak $[M-2]$ peak in the mass spectra of all compounds **5a–f**, which corresponds to imidazolines **6a–f**. However, peracid oxidation of amines is known to proceed by nucleophilic attack of the amine on a hydroxy group of the peracid, which would afford a mono- or dihydroxyimidazolidine as an intermediate.[34] In order to ascertain the oxidation pathway (**5** → **6** → **7** or **5** → **4** → **7**), we have reacted imidazolidines **5a**,**b** (aromatic-substituted) with two equivalents of 3-chloroperbenzoic acid at low temperature (6 °C). One does not observe the appearance of the characteristic color of nitroxides nor the formation of **6a**,**b** but the production of the corresponding 1,3-dihydroxyimidazolidine **4a**,**b**. It is noteworthy that under the same conditions aliphatic-substituted imidazolidines (**5d–f**) are more rapidly converted into free radicals as are aliphatic amines; in this case, the dihydroxy compounds could not be characterized. Finally, neither PbO_2 nor $NaIO_4$ were able to perform these transformations.

As observed for compound **2**, when pure in the solid state these bis(hydroxyamines) are stable enough to be crystallized in methanol and analyzed by X-ray diffraction at room temperature. The structure of **4b** (*p*-nitrophenyl) is displayed in Figure 2. The imidazolidine ring is highly distorted (atoms

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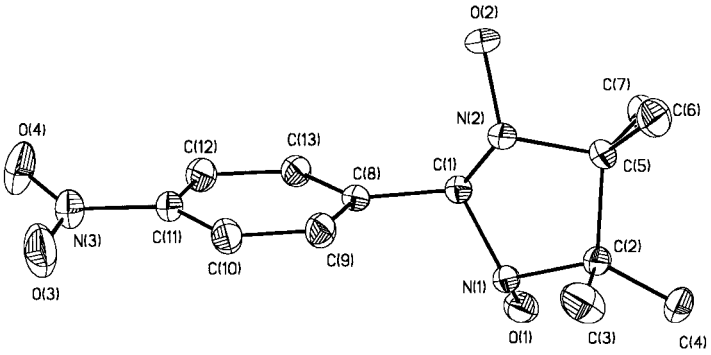


Figure 2. View of the molecular structure of **4b**. Relevant bond lengths [Å] and angles [°] are as follows: O(1)–N(1) = 1.440(2), O(2)–N(2) = 1.454(2), N(1)–C(1) = 1.478(3), N(2)–C(2) = 1.454(3).

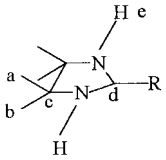
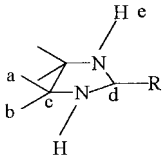
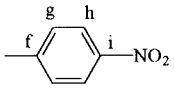
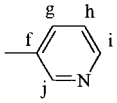
are distributed in a −0.27, +0.30 Å range from the mean plane), and the phenyl ring is almost orthogonal to the mean plane (86°). The molecules are arranged in head-to-tail dimers through hydrogen bonds between one hydroxyl group of one molecule and the nitro group of the second molecule; the dimers exhibit double hydrogen bonding between the second NOH group of each molecule (six-membered ring) that leads to sheets parallel to the *ab* plane. As expected, the intermolecular arrangement and the molecular structure as well are very different from the imidazolidine **5b** and nitroxide analogues.[5]

Surprisingly, conversion of the bis(hydroxy)-imidazolidines (**4**) into nitroxides by *m*-chloroperbenzoic acid is exceedingly slow and almost ineffective for aromatic-substituted representatives in the absence of air or heating. There are two reasons for this behavior: i) *m*-chloroperbenzoic acid is a better oxidizing agent for strong nucleophilic substrates like amines;[17, 18] this is in line with the fairly rapid oxidation of alkyl-substituted species; ii) in our oxidizing procedure, hydroxylated intermediates such as **4** are likely to be very soluble in the aqueous phase, in which *m*-chloroperbenzoic acid is almost absent. This drawback is easily overcome by using sodium periodate, which insures completion of the last oxidation step (**4** → **7**).

Finally, it should be noted that oxidation of **5c** (R = 3-pyridyl) proceeds with the formation of a small amount (8%) of pyridyl-*N*-oxide-substituted nitronyl nitroxide, which shows that the use of *m*-chloroperbenzoic acid might be a severe limitation to this new route. Indeed, many functional groups are sensitive to this reagent and would probably be oxidized during the synthesis. This problem has not been thoroughly investigated.

Examination of Table 1 shows that this new synthetic route, which proceeds through well-established pathways and affords nitronyl nitroxides in good yield. Moreover, it can be extended in a straightforward way to other systems. As an example, we performed the synthesis of nitroxide **9** (Scheme 2) derived from *meso*-3,4-dimethyl-3,4-dinitrohexane, which illustrates the synthetic potentialities of this new route.[35] The structural (Figure 3) and magnetic properties (Curie law) of this new nitroxide are unexceptional and will be discussed in a forthcoming paper with those of chiral nitroxides based on the closely related (*R*,*R*)- or (*S*,*S*)-precursors.

Table 1. NMR ($CDCl_3$, δ) characteristics of imidazolidines and yield of corresponding nitronyl nitroxides based on **1**.

Compound	m.p. [°C]	^{1}H NMR	^{13}C NMR	yield
				
	38–40	s 1.13, 1.04 (a,b) s 2.38 (e), s 5.12 (d) m 7.2–7.6 (g,h,i)	24.1, 24.9 (a,b) 63.2, 73.6 (d) 126.8 (i), 127.7 (h) 128.3 (g), 144.5 (f)	81
	138–139	s 1.12, 1.23 (a,b) s 2.10 (e), s 5.28 (d) q 7.77–7.82, q 8.20–8.26 (g,h)	24.1, 25.8 (a,b) 63.6 (c), 73.1 (d) 124.0, 128.0 (f,g,h,i)	73
	< −12	s 1.12, 1.21 (a,b) s 2.37 (e), s 5.22 (d) m 7.9–8.9 (f,g,h,i,j) 149.3, 149.4 (f,g,h,i,j)	24.1, 25.9 (a,b) 63.4 (c), 71.8 (d) 123.6, 134.5, 140.1	77
H	98–100	s 1.06, 1.07 (a,b) s 2.09 (e), s 3.9 (H)	24.3 (a,b), 61.0 (c) 61.9 (d)	71
CH_3		s 1.06, 1.07 (a,b) d 1.24 (CH_3), s 1.9 (e) q 4.17 (d)	24.3, 24.6 (a,b) 26.1 (CH_3), 63.1 (c) 67.6 (d)	82
	oil	s 0.93 (*tert*-butyl) s 1.07, 1.13 (a,b) s 2.02 (e), s 3.83 (d)	24.6 (*tert*-butyl), 26.4, 26.6 (a,b), 62.2 (c), 80.1 (d)	65

Conclusion

During the last ten years Ullman's route towards nitronyl nitroxides has shown its broad scope through the diversity of free radicals that have been prepared. As stated before, any aldehyde may condense with compound **2** and give a nitronyl nitroxide. The generality of the synthesis is illustrated by several recent reports that show that protected aldehydes (dialkyl acetals) are also suitable for the synthesis.[36] Moreover, formation of the corresponding nitroxides requires only mild oxidants that are expected to preserve the integrity of the

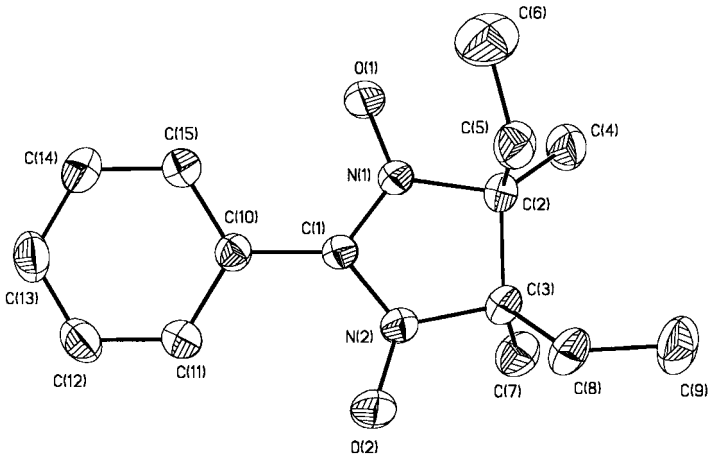


Figure 3. View of the molecular structure of **9**. Relevant bond lengths [Å] and angles [°] are as follows: N(1)–O(1) = 1.287(1), N(2)–O(2) = 1.283(2), N(1)–C(1) = 1.346(2), N(2)–C(1) = 1.344(2); phenyl-imidazoline = 33.8(4).

majority of functional groups that one would wish to introduce in the free radical. In this respect, this route is of general use.

In contrast, the diamino route might be considered as of less general use because the use of 3-chloroperbenzoic acid could be a severe disadvantage for the exclusion of oxidant sensitive groups such as amino groups, double bonds, and thioether in the final free radical. However, it proceeds with higher yields and it opens new perspectives for the design of new nitronyl nitroxides because it bypasses the delicate synthesis of 2,3-bis(hydroxyamino)-2,3-dimethylbutane and can be easily extended to any adequately substituted α-diamino compound as shown for 3,4-diamino-3,4-dimethylhexane.

Experimental Section

Synthesis: Compound 2,3-dimethyl-2,3-dinitrobutane was prepared according to the reported procedure and crystallized from methanol (10 mL g^{-1}).[11] Compound 3-chloroperbenzoic acid and Zn (< 10 μm) were purchased from Aldrich. The former was washed with a phosphate buffer (pH 7.5), dissolved in CH_2Cl_2, the solution dried over sodium sulfate and evaporated, and the resulting solid dried again by evaporation of pentane; iodometric assay indicated 99% purity. The latter was activated by successive washings with HCl (2%), H_2O, ethanol, and diethyl ether. Methylene chloride and chloroform were purified by filtration through alumina (Activity 1). All other reagents were used as received.

2,3-Bis(hydroxyamino)-2,3-dimethylbutane

Procedure A: Compound 2,3-dimethyl-2,3-dinitrobutane (17.6 g, 0.1 mol) was dissolved in tetrahydrofuran (THF, 300 mL). NH_4Cl (43 g, 0.8 mole) in water (150 mL) was added to this solution (precipitation of finely divided NH_4Cl occurred). The two-phase system was cooled in a ice bath (8 – 12 °C), and oxygen was excluded by Ar bubbling. Then, Zn powder (27 g, 4 atom grams) was added by portions over 100 min (≈3 g/10 min), while the temperature was kept below 12 °C. Stirring was continued for 90 min, and the flask placed for 15 hours (a night) in a refrigerator (4 – 6 °C).[37] Then, the mixture was filtered, the precipitate carefully washed with THF until compound **2** was not detected in the washings[21] (4 × 100 mL), and the solution concentrated in vacuo until a waxy solid was obtained. Note that this solid may be used directly in the synthesis of nitroxide free radicals, particularly for condensation with commercially available and inexpensive aldehydes. It contained ≈30 – 50% of the free base.

H_2O (20 mL), sodium carbonate (30 g), sodium chloride (20 g), and anhydrous sodium sulfate (20 g) were added to this solid. The resulting powder was continuously extracted in a Soxlet apparatus protected from air for 16 hours with methylene chloride (400 mL). Slow cooling of the organic phase to room temperature afforded 5.6 g of white crystals (m.p. 181 – 183 °C), which were suitable for a X-ray diffraction study.

Elemental analysis calcd (%) for $C_6H_{16}N_2O_2$: C 48.63, H 10.88, N 18.90, O 21.59; found C 48.76, H 11.13, N 18.87, O 21.31. The rest of the solution was concentrated in vacuo to 100 mL, and pentane (500 mL) was added; this caused crystallization of a further 5.8 g crop (elemental analysis calcd (%): C 48.63, H 10.88, N 18.90, O 21.59; found C 42.28, H 9.35, N 15.23, O 17.85), which was recrystallized from THF (100 mL) at 4 °C to yield the pure compound **2** (3.7 g, yield 63%).

^{1}H NMR (200 MHz, 20 °C, D_2O): $\delta = 1.25$ (s); ^{13}C NMR (200 MHz, 20 °C, D_2O): $\delta = 21.5$ (CH_3), 63.3 (CH_3–C–CH_3). Yields of five different runs were as follows: 43, 35, 56, 63, and 68%.

Procedure B: Compound 2,3-dimethyl-2,3-dinitrobutane (17.6 g, 0.1 mol) was dissolved in a mixture of tetrahydrofuran (300 mL) and water (50 mL). Zn powder (27 g) was added all at once to this solution cooled to 8 – 10 °C in an ice bath. A solution of NH_4Cl (43 g, 0.8 mol) in H_2O (150 mL) was added dropwise to this slurry at such a rate (≈two hours) that the temperature of the reaction did not exceed 12 °C. Then stirring was continued at 10 °C for one hour, and the flask stored in a fridge (4 – 6 °C) for 16 hours. As for Procedure A, the slurry was filtered, and the precipitate carefully washed with THF (4 × 100 mL). The precipitate was then dried by three washings with diethyl ether and carefully collected (59 g, Zn content: 22.6 g, 0.346 atom grams). The solution was evaporated under vacuo until THF ceased to distill off. Then the solution was protected from air, and sodium carbonate (50 g) and sodium chloride (30 g) were added with cooling. Continuous extraction with chloroform (400 mL) was performed over 18 hours. A white powder was obtained (9.4 g, 63%, m.p. 182 °C).

Elemental analysis calcd (%) for $C_6H_{16}N_2O_2$: C 48.63, H 10.88, N 18.90, O 21.59; found 48.79, H 11.01, N 18.91, O 21.47.

Dichloro-bis[2,3-bis(hydroxyamino)-2,3-dimethylbutane]-zinc: The reduction was performed as described above except that the solution in THF/water was evaporated under vacuum at room temperature to dryness. The resulting solid was dissolved in hot CH_2Cl_2 and filtered, and the solution evaporated again to a solid phase, which was dried several times with pentane. A white solid was obtained (yield 16.9 g, 76%).

Elemental analysis calcd (%) for $C_{12}H_{32}N_4O_4Cl_2Zn$: C 33.48, H 7.50, N 13.02, Cl 16.26, Zn 14.86; found C 33.60, H 7.81, N 12.91, Cl 15.97, Zn 15.03; MS: *m*/*z* (%): $[Zn(\mathbf{2})_2Cl]^+$, 397; the isotopic pattern of Zn complexes was successfully modeled.

2,3-Diamino-2,3-dimethylbutane (3): This was obtained by a slight modification of reported procedures.[11, 22] Compound 2,3-dimethyl-2,3-dinitrobutane **1** (17.6 g, 0.1 mole) was suspended in concentrated hydrochloric acid (37%, 150 mL). Then, granular Sn (100 g) was added by portions, and the mixture refluxed for three hours. After cooling, the clear solution was extracted with diethyl ether, and the aqueous phase made strongly basic with sodium hydroxide pellets (60 g) and centrifuged to get rid of a sticky precipitate. The solution was extracted with methylene chloride (4 × 50 mL), the solvent distilled off, and the residual oil dried with pentane. Compound 2,3-diamino-2,3-dimethylbutane (9.4 g, 81%) was obtained as a colorless solid with a low melting point.

^{1}H NMR (200 MHz, 20 °C, $CDCl_3$): $\delta = 1.07$ (s, CH_3), 1.26 (br s, NH_2); ^{13}C NMR (200 MHz, 20 °C, $CDCl_3$): $\delta = 26.9$ (CH_3), 55.2 (CH_3–C–CH_3). Dry HCl was bubbled through the methylene chloride distillate, and an additional crop of the chlorhydrate (1.9 g, 10%) was obtained (overall yield 91%).

2-(*R*)-4,4,5,5-Tetramethylimidazolidines (5)

From benzaldehyde: General procedure was used as for **5a**. Benzaldehyde (1.85 g, 0.017 mole) in diethyl ether (10 mL) was added dropwise to a ice cooled solution of 2,3-diamino-2,3-dimethylbutane **3** (2 g, 0.017 mol) in diethyl ether (20 mL). Condensation was complete in a few minutes. The solution was dried over Na_2SO_4 and evaporated (**5a**: 3.5 g, 99%; **5b**:[38] 92%; **5c**: 95%; **5d**: 89%; **5e**: 78%; **5f**:[38] 95%). Single crystals of **5b** were obtained from solutions in methanol at 6 °C.

From benzaldehyde dimethylacetal: General procedure was used as for **5a**. Benzaldehyde dimethylacetal (2.6 g) was added to a solution of diamine **3** (2 g) in methanol (20 mL). Then, the pH of the solution was adjusted to 3 – 4 by dropwise addition of sulfuric acid (1N). Stirring was continued for one

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hour at room temperature, the methanol evaporated, and the residue dissolved with cooling in sodium hydroxide (6 N, 50 mL). Extraction with methylene chloride (4 × 50 mL), drying, and evaporation gave a thick oil (2.76 g, 78 %), which crystallized in the refrigerator (**5a**: 78 %; **5e**: 67 %).

Characteristics of imidazolidines **5a–f** are reported in Table 1. NMR spectra showed that the imidazolidines did not need to be purified for use in the following synthetic steps.

1,3-Dihydroxy-2-(*R*)-4,4,5,5-tetramethylimidazolines (4): Saturated $NaHCO_3$ (30 mL) and, dropwise, 3-chloroperbenzoic acid (860 mg, 0.005 mole) in methylene chloride (50 mL) were added to a ice cooled solution of 2-phenyl-4,4,5,5-tetramethylimidazolidine **5a** (500 mg, 0.0025 mol) in methylene chloride (50 mL). One did not observe any color change. The mixture was stirred for half an hour at low temperature, filtered, and the organic phase dried (Na_2SO_4) and evaporated under vacuum (406 mg, 70 %, m.p. 224–226 °C).

Elemental analysis calcd (%) for $C_{13}H_{20}N_2O_2$: C 66.07, H 8.53, N 11.85, O 13.54; found C 66.25, H 8.56, N 11.95, O 13.84; ^{1}H NMR (200 MHz, 20 °C, $CDCl_3$): $\delta = 1.18$ (s, 6H; CH_3), 1.19 (s, 6H; CH_3), 1.62 (br s, 2H; OH), 4.82 (s, 1H; CH), 7.36–7.59 (m, 5H; phenyl).

Mass spectra showed the presence of traces of mono-hydroxylated imidazolidines, which were not detected in NMR spectra. Crystallization from methanol afforded colorless single crystals of **4b**.

Nitronyl nitroxides: A solution of *m*-chloroperbenzoic acid (4.25 g, 0.025 mol) in methylene chloride (50 mL) was added dropwise to a mixture of 2-phenyl-4,4,5,5-tetramethylimidazolidine **5a** (2 g, ≈0.01 mol) in methylene chloride (100 mL) and saturated $NaHCO_3$ (60 mL) in an ice bath. The typical nitronyl nitroxide purple (or red for aliphatic-substituted) color slowly developed. Stirring was continued for one hour, and a solution of $NaIO_4$ (3.1 g, ≈0.015 mol) in water (50 mL) was added dropwise. Appearance of the nitronyl nitroxide was followed by TLC (SiO_2, ethyl acetate). Drying (Na_2SO_4), evaporation of the organic phase, and chromatography (SiO_2, ethyl acetate) led to pure nitronyl nitroxide (1.8 g, 78 %) and the corresponding imino nitroxide (278 mg, 12 %). This procedure did not work for preparing nitroxide **5d**, for which oxidation should be conducted in absence of $NaHCO_3$ (see preceding section). All free radicals **7a–f** were identical to authentic samples prepared according to Ullman's procedure.[1–3]

***meso*-4,5-Diethyl-4,5-dimethyl-2-phenyl-4,5-dihydro-1H-imidazolyl-3-oxide-1-oxy**: Benzaldehyde (750 mg, 7 mmol) was added to *meso*-3,4-diamino-3,4-dimethylhexane (1 g, 7 mmol), obtained as described elsewhere,[35] in diethyl ether (50 mL), and the solution stirred at room temperature for 15 hours. Drying (Na_2SO_4) and evaporation of the solvent afforded the corresponding imidazolidine (1.5 g, 92 %) as a mixture of both isomers. Since oxidation of both compounds resulted in the same nitroxide, the crude product was dissolved in CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). Then, a solution of *m*-chloroperbenzoic acid (3 g, 17 mmol) in CH_2Cl_2 (30 mL) was added dropwise to the cooled mixture (6 °C), and after stirring for one hour a solution (H_2O, 20 mL) of $NaIO_4$ (2.25 g, 10 mmol) was added. Stirring was continued for one hour at 6 °C, and the organic phase was dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography (SiO_2, ethyl acetate). Nitroxide **9** (1.373 g, 83 %, m.p. 70–71 °C) was crystallized from petroleum ether to afford single crystals suitable for a X-ray diffraction study.

Elemental analysis calcd (%) for $C_{15}H_{21}N_2O_2$: C 68.94, H 8.10, N 10.72; found C 68.83, H 7.96, N 10.89.

Imino nitroxides: Na_2WO_4 (100 mg) and **5a** (500 mg) were dissolved in water/methanol (1:1, 10 mL). Then, H_2O_2 (1 mL, 30 %) was added, and the solution was stirred at room temperature for 12 hours. Extraction with CH_2Cl_2 followed by chromatography (SiO_2, ethyl acetate) afforded the corresponding imino nitroxide **8a** (223 mg, 41 %). Imino nitroxides were obtained quantitatively from the nitronyl nitroxides (**7**) using the reported procedures.[39, 40]

Crystal structure determination: Selected crystals of **2**, **4b**, **5b**, and **9** were analyzed using a Siemens SMART CCD area detector three-circle diffractometer ($Mo_{K\alpha}$ radiation, graphite monochromator, $\lambda = 0.71073$ Å). The cell parameters were determined with intensities detected on three batches of 15 frames with a 10 s exposure time for each. For three settings of Φ and 2Θ, 1200 narrow data frames were collected for successive increments of 0.3° in ω. A full hemisphere of data was collected. At the end of collection, the first 50 data frames were recollected in order to check eventual decay during collection. Unique intensities with $I > 10\sigma(I)$ selected within all data frames using the SAINT program were used to refine the cell parameters.[41] The substantial redundancy in data allowed empirical absorption corrections to be applied using multiple measurements of equivalent reflections with the SADABS program. Space groups were derived from systematic absences and were confirmed by the successful solution of the structure determination. Complete information regarding crystal data and data collection parameters is found in the CCDC data (see below).

Crystal structure determinations ***2***: System monoclinic, space group $C2/c$; $T = 293$ K, $a = 23.644(2)$ Å, $b = 6.134(1)$ Å, $c = 13.462(1)$ Å, $\beta = 121.868(2)°$, $V = 1658.2(3)$ Å^3, 1992 unique reflections, 165 parameters refined, $R(F) = 0.052$, $R_w(F) = 0.145$.

Crystal structure determinations ***4b***: System monoclinic, space group $P2_1/c$; $T = 293$ K, $a = 6.604(1)$ Å, $b = 10.873(1)$ Å, $c = 20.030(3)$, $\beta = 92.220(4)°$, $V = 1437.2(4)$ Å^3, 3473 unique reflections, 257 parameters refined, $R(F) = 0.063$, $R_w(F) = 0.144$, residual electron density 0.27, −0.30.

Crystal structure determinations ***5b***: System monoclinic, space group $P2_1/n$; $T = 293$ K, $a = 7.493(1)$ Å, $b = 8.038(6)$ Å, $c = 21.939(2)$ Å, $\beta = 91.943(2)°$, $V = 1320.6(1)$ Å^3, 3203 unique reflections, (1020 with $I > 2\sigma(I)$), 239 parameters refined, $R(F) = 0.040$, $R_w(F) = 0.089$; residual electron density 0.33, −0.37.

Crystal structure determinations ***9***: System monoclinic, space group $P2_1/c$, $T = 293$ K, $a = 10.060(1)$, $b = 8.761(1)$, $c = 16.554(3)$, $\beta = 102.116(3)°$, $V = 1426.5(4)$ Å^3, 3451 unique reflections, 256 parameters refined, $R(F) = 0.05$, $R_w(F) = 0.118$, residual electron density 0.193, −0.242.

The data were processed by the SAINT data reduction software, and the structures were solved by direct methods included in the SHELXTL 5.03 package.[42] All atoms were located on difference Fourier syntheses. Non-hydrogen atoms were refined anisotropically on F^2 while hydrogen atoms, located by calculations, were refined isotropically. Final results (R factors, coefficients of the weighting scheme, and final residual electron densities) are found in the CCDC data (see below).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-149144, CCDC-149195, CCDC-149196, and CCDC-152832 for compounds **2**, **4–5b**, and **9**, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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