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Synthesis of 1-azaspiro[4.4]nonan-1-oxyls via Intramolecular 1,3-Dipolar Cycloaddition

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Abstract

Sterically shielded nitroxides of pyrrolidine series are known to demonstrate the highest stability to reduction. Here we report on the synthesis of new pyrrolidine nitroxides from 5,5-dialkyl-1-pyrroline *N*-oxides via the introduction of pent-4-enyl group to nitrone atom followed by intramolecular 1,3-dipolar cycloaddition reaction and isoxazolidine ring opening. Kinetics of reduction of the new nitroxides with ascorbate was studied and compared to that of previously published 1*S*,2*R*,3′*S*,4′*S*,5′*S*,2″*R*-dispiro[(2-hydroxymethyl)-cyclopentan-1,2′-(3′,4′-di-*tert*-butoxy)pyrrolidine-5′,1″-(2″-hydroxymethyl)cyclopentane]-1′-oxyl (**1**).

Keywords

Aldonitrones; 1,3-dipolar cycloaddition; DMPO; pyrrolidine nitroxides; sterically shielded nitroxides.

Introduction

Sterically shielded nitroxides currently attracted much attention due to their high stability to bioreduction [1,2]. It has been shown that 2,2,5,5-tetraethyl pyrrolidine nitroxides demonstrate the highest stability, sometimes exceeding that of trityl radicals [1]. Introduction of spiro cyclic moieties was found to produce smaller effect onto reduction rates of nitroxides than the introduction of linear alkyl substituents, however, spirocyclic nitroxides may show much longer spin relaxation times at 70-125 K [3] and even at room temperature [4]. The latter effect may be useful for structural studies using PELDOR or DQC [5]. We have recently reported on the synthesis of a sterically shielded pyrrolidine nitroxide **1**, via stereospecific consecutive assembling of two spiro-(2-hydroxymethyl)-cyclopentane moieties. This was achieved using a repetitive sequence of procedures, including the addition of pent-4-enyl magnesium bromide to corresponding nitrone, oxidation to alkenylnitrone, intramolecular 1,3-dipolar cycloaddition, and isoxazolidine ring opening. This nitroxide showed both unexpectedly low reduction rate [6] and high relaxation times T_1 and T_m at room temperature [4]. Unexpectedly high stability of this nitroxide to chemical reduction results from the configuration of hydroxymethyl groups, which are directed towards the nitroxide group, thereby making it more hampered. It is known that inductive effects of the substituents can strongly affect the rate of nitroxide reduction [8,9], therefore one could expect that removal of electron-withdrawing tert-

butoxy groups at the positions 3 and 4 of pyrrolidine ring of **1** (Fig. 1) should lead to further decrease of the reduction rate of the nitroxide.

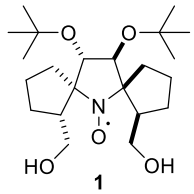

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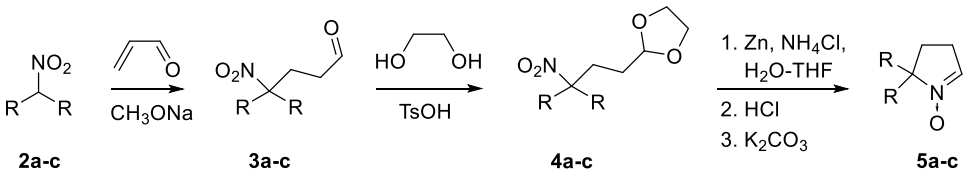
Figure 1: Nitroxide **1** structure.

Here we describe the synthesis of asymmetric 3,4-unsubstituted pyrrolidine nitroxides with only one spiro-(2-hydroxymethyl)-cyclopentane moiety. The rates of reduction of the new nitroxides with ascorbate were measured.

Results and Discussion

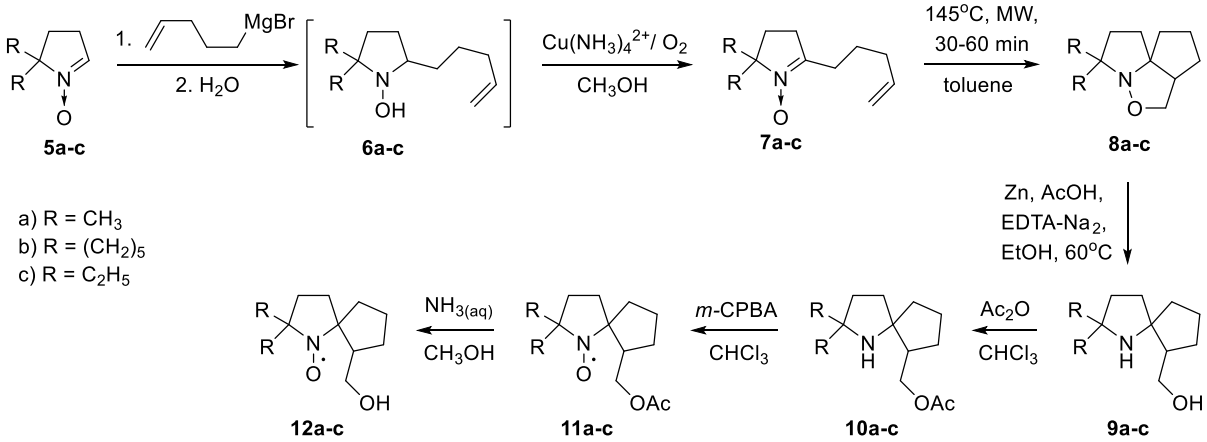
Resulted aldonitrones **5b,c** were prepared in analogy to the well-known synthesis of DMPO (**5a**) [10,11] from nitrocyclohexane and 3-nitropentane (Scheme 1). In brief, the reaction of nitrocyclohexane and acrolein in CH_3ONa/CH_3OH solution afforded corresponding nitroaldehyde **3b** with 70% yield. Surprisingly Michael addition with 3-nitropentane to acrolein was accompanied with remarkable tarring and afforded much lower yield of nitroaldehyde **3c** (25%). The reactive aldehyde groups were protected via 1,3-dioxolane assembling and the resulting compounds were treated with Zn dust and NH_4Cl in water-THF solution to reduce nitro groups. The resulting hydroxylamines were treated with hydrochloric acid to hydrolize dioxolane moieties and careful basification resulted in intramolecular cyclization to give **5b,c** with yields 51% and 42% correspondingly.



a) R = CH_3
b) R = $(CH_2)_5$
c) R = C_2H_5

Scheme 1: Synthesis of aldonitrones **5a-c**.

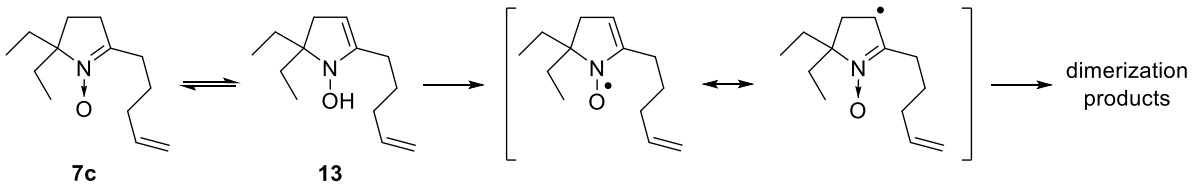
The nitrones **5a-c** readily react with 4-pentenylmagnesium bromide. Quenching of the reaction mixtures with water in aerobic conditions leads to partial oxidation of the resulting *N*-hydroxypyrrolidines **6a-c** to corresponding nitrones **7a-c**, therefore this conversion was finalized via bubbling of air in the presence of $Cu(NH_3)_4^{2+}$(Scheme 2).



Scheme 2: Principal synthetic scheme for nitroxides **12a-c**.

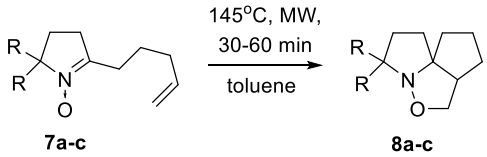
The samples of resulting 2-(pent-4-enyl)nitrones **7a-c** remarkably deteriorate upon storage in aerobic conditions with dark tar formation. The possible pathway of decay may include oxidation of ene-hydroxylamine tautomeric form to vinylnitroxide, similar compounds are prone to various dimerizations (Scheme 3) [cf. 12]. It is interesting to note that in the mass-spectrum of **7c** [M-1$^+$] ion was observed instead of the

molecular ion. Easy loss of hydrogen atom is in line with susceptibility of **9c** to oxidative decay (Scheme 3).



Scheme 3: Possible pathway of ketonitrone **7c** self-transformations.

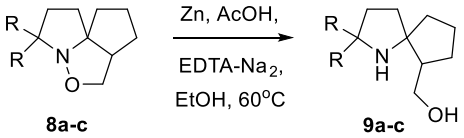
Intramolecular cycloaddition of similar nitrones is known to lead to hexahydro-1*H*-cyclopenta[*c*]isoxazoles [6, 7]. Indeed, heating of **7a-c** at 145 °C in toluene for 30-60 min in microwave oven afforded **8a-c** (racemic mixtures) (Scheme 4). The structure assignment was performed on the basis of ^{1}H and ^{13}C NMR spectra and ^{1}H-^{1}H and ^{13}C-^{1}H correlations (see SI); the spectral data coincide with literature data for similar systems [6].



Scheme 4: Intramolecular 1,3-dipolar cycloaddition of alkenylnitrones **7a-c**.

To decrease tarring the reaction was carried out in the presence of TEMPO. It should be noted that heating of alkenyl nitrones **7a** and **7b** gives the corresponding cycloadducts with yields close to quantitative, whereas for nitrone **7c**, a complete conversion could not be achieved neither at 145°C nor at the higher temperature. According to the ^{1}H NMR spectra, the ratio **7c**/**8c** never exceeded 3/1. Heating of pure sample of **8c** in similar conditions resulted in the appearance of signals at 5.70,

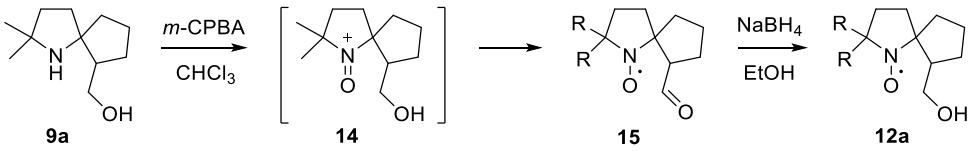
4.92 and 4.87 ppm in ^{1}H NMR spectra, which were attributed to terminal vinyl group protons of **7c**. 1,3-Dipolar cycloaddition of nitrones to alkenes is known to be reversible [13, 14]. We have recently reported on similar reversibility of intramolecular cyclization of sterically shielded pent-4-enylnitrone of 2*H*-imidazole series [15]. Treatment with Zn in AcOH-EtOH-EDTA-Na_2 mixture was used for reductive isoxazolidine ring opening [cf. 15, 16] affording aminoalcohols **9a-c** with yields 85-95% (Scheme 5).



Scheme 5: Isoxazolidine ring opening.

We have previously reported that H_2O_2/WO_4^{2-} system is inefficient for the oxidation of secondary amines with spiro-(2-hydroxymethyl)-cyclopentane moiety at α-carbon to nitroxides, while this oxidation can be easily performed using *m*-CPBA [6, 15]. Treatment of **9a** with *m*-CPBA in dry chloroform at -10 °C afforded a nitroxide, which was isolated as an orange oil with the yield 73% (Scheme 6). IR spectrum of the isolated compound showed strong absorption band at 1725 cm^{-1} typical for carbonyl compounds and no absorption in 3100-3500 cm^{-1}, indicating that the hydroxymethyl group was affected in the reaction. Mass-spectrum showed molecular ion $[M^+]$= 196.1335. corresponding to molecular formula $C_{11}H_{18}NO_2$, which coincide with element analysis data. This allowed assigning to the nitroxide the structure of aldehyde **15**. Indeed, oxidation of amines with peracids is known to proceed via oxoammonium cation formation [17,18], and the latter is known to oxidize alcohols to carbonyl compounds [19]. The close proximity of the hydroxymethyl group to

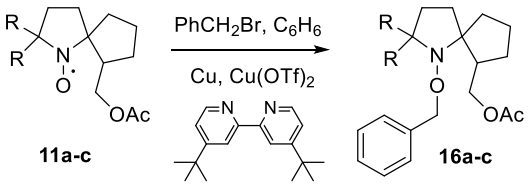
oxoammonium one favours the reaction. Treatment of **15** with $NaBH_4$ in EtOH resulted in a quantitative reduction of the aldehyde group to hydroxymethyl one to give **12a**, identical to that prepared using the alternative method (see below).



Scheme 6: Oxidation of aminoalcohol **9a**.

To prevent oxidative reactions in the side chain, the hydroxymethyl group in **9a-c** was protected via acylation. Heating of **9a-c** with an excess of acetic anhydride in chloroform quantitatively afforded corresponding esters **10a-c**. Products of acylation of the sterically hindered amino group were not detected.

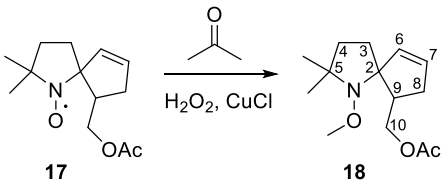
Oxidation of **10a-c** with *m*-CPBA afforded desired nitroxides **11a-c** as orange oils. IR spectra of the new nitroxides showed no absorption bands in the region of 3000-3600 cm^{-1}, and intense band at 1740 cm^{-1}, characteristic of the ester C=O group. To confirm the structure of the nitroxides the alkoxyamines **16a-c** were prepared using Matjaszhewsky's method (Scheme 7) [20].



Scheme 7: Alkoxyamines **16a-c** synthesis.

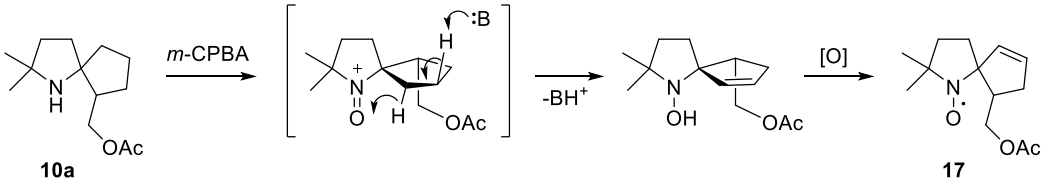
Oxidation of aminoacetate **10a** along with the expected formation of the nitroxyl radical **11a**, afforded another nitroxide **17**. The IR spectra of nitroxyl radicals **11a** and

17 are very similar, showing the bands typical for ester group vibrations and no bands which could be attributed to vibrations of OH or NH groups. However, in the spectrum of compound **17** there are also absorption bands in the region of 3054 and 1620 cm^{-1}, which denote the presence of a double C=C bond. To elucidate the structure, the nitroxyl radical **17** was converted into alkoxyamine **18** (Scheme 8) using the literature method [21] and ^{1}H, ^{13}C NMR spectra, as well as two-dimensional ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC and HMBC were recorded (see SI). Signals at 4.14 and 4.45 ppm in ^{1}H NMR were assigned to the hydrogen atoms of the O-$^{10}CH_2$-group. Analysis of the ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC NMR spectra allows us to unambiguously assign a signal at 2.26 ppm in ^{1}H NMR to the methine proton at the ^{9}C carbon atom (see SI). This signal in ^{1}H-^{1}H COSY has two cross-peaks with hydrogens of O-$^{10}CH_2$-group and two additional cross-peaks with signals at 2.11 and 2.36 ppm, which were assigned to the $^{8}CH_2$-group. The chemical shifts and character of the splitting of this group of signals correspond to structural fragment O-$^{10}CH_2$-^{9}CH-$^{8}CH_2$. The signals of the $^{8}CH_2$ group in COSY spectrum have only 2 additional cross-peaks with the signals at 5.64 and 5.86 ppm. Analysis of the ^{1}H-^{13}C HSQC spectrum showed that the latter protons are bound to carbon atoms with chemical shifts 135.3 and 131.1 ppm correspondingly, and this allows for the assignment of these signals to 1,2-disubstituted alkene moiety. Thus, the NMR data shown above indicate the presence of an isolated spin system O-CH_2-CH-CH_2-CH=CH. A similar analysis of the remaining complex multiplets at 1.56, 1.77 and 1.93 ppm, as well as their correlation with the signals of carbon atoms in the ^{1}H-^{13}C HSQC spectra, allowed us to assign these signals to isolated CH_2-CH_2 system. All these data unambiguously support the assignment of the structure **18** to the isolated alkoxyamine and structure **17** to the corresponding nitroxide.



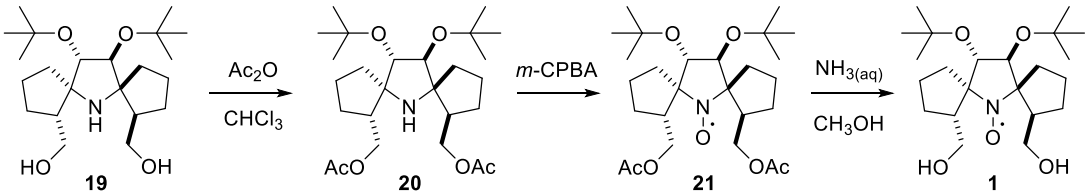
Scheme 8: Alkoxyamine **18** synthesis.

Thus, the concomitant product in oxidation **10a** is formed due to hydrogen abstraction in the spiro-cyclopentane ring. To the best of our knowledge, similar transformations were never observed before. Formation of **17** may occur due to the close proximity of N^+=O group in intermediate strained oxoammonium cation to the hydrogen atom of adjacent methylene group of cyclopentane ring (Scheme 9).



Scheme 9: Possible mechanism of nitroxide **17** formation.

The ester groups in **11a-c** were easily cleaved in an aqueous-methanol solution of ammonia. The nitroxides **12a-c** were isolated as an orange colored compounds, moderately soluble in water. Overall yields of these radicals via acylation-oxidation-deprotection pathway were in the range of 54-75%. Remarkably, the use of similar three-step procedure for the synthesis of **1** from **19** allowed to increase the yield of this nitroxide from 20 to 60% (Scheme 10).



Scheme 10: Optimizations of nitroxide **1** synthesis.

The EPR spectra of the nitroxides **12a-c** and **1** acquired in deoxygenated buffer solution showed a significant difference in line widths (see Table 1 and Fig. 7SI-10SI), the broadest lines expectedly being shown by **12b**. Introduction of spiro cyclohexane-moieties to α-carbons of pyrrolidine nitroxides was shown to result in a strong broadening of lines in the EPR spectra, presumably due to unresolved *hfc* on the hydrogens at the positions 2 and 6 of cyclohexane ring [22]. It has been reported that EPR spectra of pyrrolidine or imidazolidine nitroxides with pair(s) of geminal ethyl groups at α-carbon atoms may demonstrate large doublet hyperfine splittings [23-25]. For imidazolidine nitroxides, these splittings were unambiguously attributed to *hfc* on one of four methylene hydrogens of each pair of ethyls [23]. The difference in a_H on these hydrogens occurs due to substituent at the positions 3 or 4 of the ring, which hinders rotation and affects population of conformations of neighbouring geminal ethyl groups, preventing averaging. In agreement to this conclusion, there are no large splittings in the EPR spectrum of **12c** and the line width is a bit higher than in the spectra of similar non-spirocyclic 3,4-unsubstituted 2,2-diethyl-pyrrolidine nitroxides [26], implying free rotation of ethyl groups.

Table 1: Parameters of EPR spectra (hyperfine coupling constants, a_N; peak-to-peak linewidths, $\Delta B_{p\text{-}p}$; *g*-factors), second order rate constants of reduction with ascorbate and partition coefficients octanol-water (K_p) for nitroxides **1** and **12a-c**.

Nitroxide	a_N, mT	$\Delta B_{p\text{-}p}$, mT	g-factor	k_2, $M^{-1}s^{-1}$	K_p
1	1.481	0.29	2.00553(±2)	$(3.6\pm0.2)*10^{-3}$	600
12a	1.595	0.21	2.00549(±2)	$(7.3\pm0.2)*10^{-2}$	12
12b	1.586	0.34	2.00553(±2)	$(4.6\pm0.5)*10^{-2}$	130
12c	1.570	0.24	2.00552(±2)	$(2.2\pm0.4)*10^{-2}$	80

The initial rates of EPR signal decay were used to obtain the rate constants of the nitroxides reduction by ascorbic acid (Fig. 2).

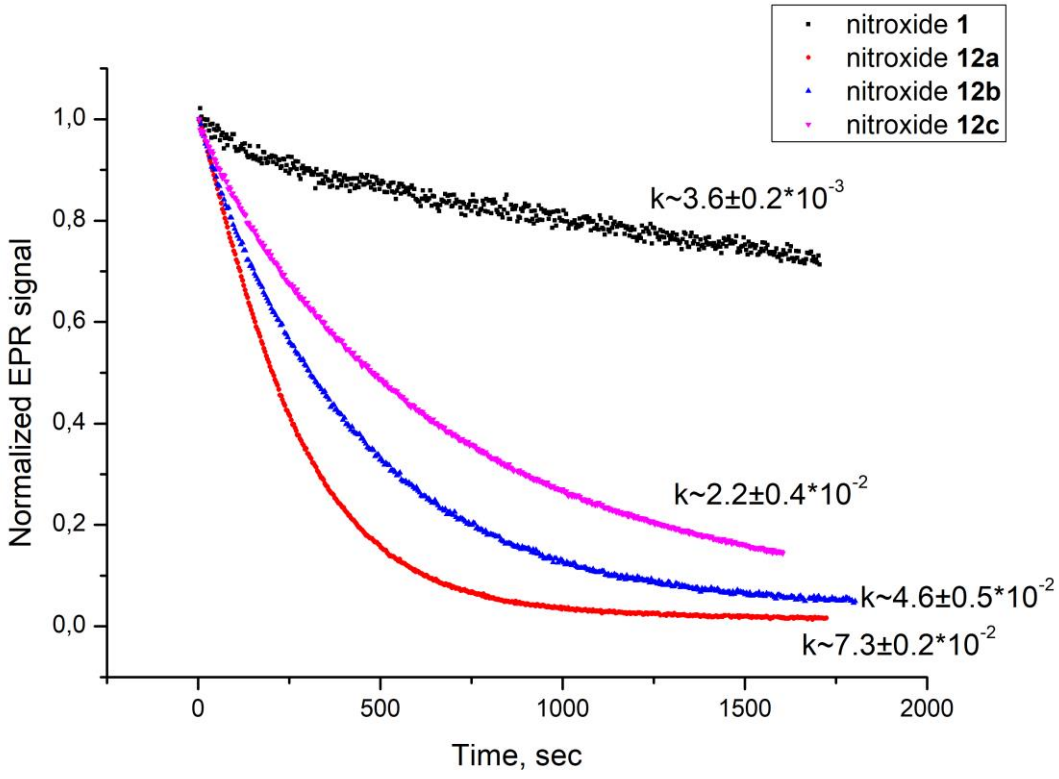


Figure 2: Kinetics of reduction of nitroxides **1** and **12a-c** (0.3 mM) with ascorbate (50 mM) in 50 mM phosphate buffer in presence of glutathione (2 mM), pH=7.4, temperature 293 K. Second-order rate constants, k ($M^{-1}s^{-1}$), for the initial rates of reduction are shown.

The rate constants for all these nitroxides are remarkably higher than that of nitroxide **1**. Even the nitroxide **12c**, which is the most stable among the new pyrrolidine nitroxides shows ca. 6 times higher reduction rate than **1** and both of them are less stable towards reduction then 2,2,5,5-tetraethyl-substituted pyrrolidine nitroxides. Rate of reduction of **12a** is close to that of 3-carboxy-PROXYL [24]. Obviously, single spiro-(2-hydroxymethyl)-cyclopentane moiety can't provide higher reduction resistance than geminal ethyl groups. Thus, estimation of the steric effect of neighbouring substituents can't account for the relative reduction resistance of **1**. Presumably, symmetric structure with bulky substituents at the positions 3 and 4 is an important factor for nitroxide stability. Due to steric repulsion of trans-oriented *tert*-butoxy groups and spiro cyclopentane moieties in the symmetric structure of **1** the (2-hydroxymethyl)-cyclopentane fragments tightly embrace the nitroxide group making it less accessible for reductants. It is also important that symmetric repulsion from both sides of the pyrrolidine ring favors planar nitroxide group and destabilize the corresponding hydroxylamine with sp^3-hybridized nitrogen. Recently we observed similar effect for (3*S*(*R*),4*S*(*R*))-2,2,5,5-tetraethyl-3,4-bis(hydroxymethyl)pyrrolidine 1-oxyl, which showed the highest stability to reduction among known nitroxides [25]. In contrary, the structures **12a-c** are asymmetric and corresponding hydroxylamines could be additionally stabilized with hydrogen bonding of nitrogen to the proton of hydroxymethyl group.

Conclusion

In this paper, we again demonstrated the feasibility of the general synthetic approach to sterically hindered spiro cyclic nitroxides based on intramolecular 1,3-dipolar cycloaddition reaction in alkenylnirones followed by isoxazolidine ring opening. The

resulting asymmetric pyrrolidine nitroxides showed unexpectedly high rates of reduction with ascorbate. This study leads us to the assumption that symmetric structures with bulky substituents at the positions 3 and 4 should be favoured for achieving higher resistance to reduction.

Supporting Information

Full experimental details and analytical data (UV, IR, ^{1}H NMR, ^{13}C NMR, EPR experiments, microanalysis) are provided in the SI file.

Acknowledgements

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