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Synthesis of sterically shielded piperidine nitroxides via acid catalyst heterocyclization of β-aminoketone derivatives with ketones

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Abstract

The capabilities of modern methods for the synthesis of sterically shielded piperidine nitroxides with acyclic substituents are largely limited to symmetrical tetraethyl structures and do not allow the introduction of functional groups into position 2. We propose an alternative approach that allows for variation of substituents adjacent to the nitroxyl group, which significantly expands the potential of sterically hindered nitroxides for promising applications in materials science and structural biology. The new heterocyclization strategy implies construction of 2,2,6-trisubstituted piperidine scaffold from β-aminoketone acetals and dialkyl ketones under acid catalysis. The resulting amines were oxidized to corresponding ketonitrones and subsequent reaction with moderately basic organometallic reagents, such as 2-alkynyl and 2-allyl magnesium halides, enable facile introduction of diverse substituents, including those with functional groups. If necessary, the multiple carbon-carbon bonds in the side chain can be subjected to hydrogenation to give saturated alkyl or functionalized alkyl groups. The study of reduction kinetics for alkyl and allyl substituted piperidine nitroxides in ascorbate/glutathione media (30% EtOH, pH 7.5) yielded second-order rate constants of ~10^{-2} M^{-1} s^{-1}, which is close to that earlier reported for TEEPONE.

Introduction

Since their discovery in 1959 by Lebedev and Kazarnovsky, stable nitroxides of piperidine series (2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) derivatives) hold a prominent position as compounds of significant practical importance. Their applications range widely, from fundamental research to industrial technologies. In the spin labeling technique, these radicals have been extensively used in biophysics and structural biology [1]. Piperidine-based radicals were the first used for measuring distances in proteins by the PELDOR method at room temperature [2]. Piperidine nitroxyl biradicals form the basis of the most efficient commercial agents for dynamic nuclear polarization (DNP) in NMR studies of biomolecules and solid samples [3]. They are also employed as contrast agents for MRI [4, 5] and as spin probes for Overhauser MRI in vivo [6]. Piperidin-1-oxyls played a key role in the development and industrial implementation of controlled polymerization of vinyl monomers (nitroxide-mediated polymerization, NMP) [7]. The unique redox properties of these radicals underpin their use as catalysts for alcohol oxidation [8], electrode active materials in energy storage devices (batteries) [9], as well as antioxidants and superoxide dismutase (SOD) mimetics [10].

Their sterically shielded analogs, such as 2,2,6,6-tetraethylpiperidine-1-oxyl (TEEPO), were initially developed for nitroxide-mediated polymerization (MNP), because shielding with ethyl or bulkier alkyl groups decreases accessibility of the nitroxide moiety and improves the equilibrium parameters in the reversible trapping of alkyl radical of the growing polymer chain [11]. This shielding also alters the redox

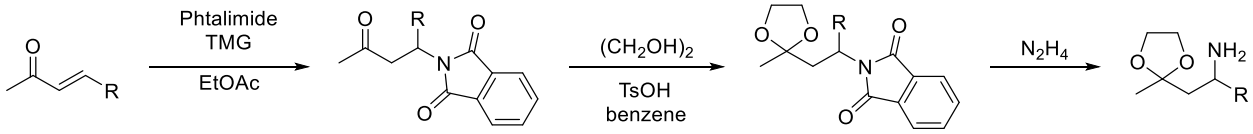
properties of nitroxides and increases their lifetimes in biological systems [12], which makes these radicals promising MRI contrast agents [13], spin probes for in vivo EPRI [14,15] and antioxidant tissue protectors [16].

Existing methods for the synthesis of such sterically hindered piperidine nitroxide radicals are based on approaches employing either the tetraethyl analog of phorone or acetonine [15, 17, 18, 19] or the desulfurization of dispirothiapyranone derivatives [20, 21, 22, 23]. Consequently, the structural diversity of radicals bearing acyclic substituents is practically limited to derivatives of 2,2,6,6-tetraethylpiperidine-1-oxyl. Given the significant interest in this class of compounds, there is a clear need for new synthetic strategies enabling the introduction of diverse acyclic substituents at positions 2 and/or 6 of the piperidine ring.

In our previous works we have shown how the reactions of cyclic nitrones with metalorganic compounds is a fruitful approach for the synthesis of sterically shieled radicals of the pyrrolidine, imidazoline and imidazolidine series,[24] including those with functional groups in the side chains [25]. Here we applied this strategy for the synthesis of sterically hindered piperidine nitroxyl radicals. Six-membered cyclic nitrones - 2,2,6-trialkyl-substituted 2,3,4,5-tetrahydropyridine-1-oxides were prepared via the acid-catalysed reaction of 2-(2-aminoalkyl)-2-methyl-1,3-dioxolanes with ketones in analogy to literature procedures [26, 27, 28, 29], followed by oxidation in the tungstate-hydrogen peroxide system [cf. 30]. It should be noted that no case of heterocyclization has ever been described where the resulting piperidine cycle contained three substituents at the 2- and 6-positions of the heterocycle. Subsequent treatment of these nitrones with alkynyl- or allylmagnesium halides gave 2-alkynyl or 2-allyl-substituted nitroxides. Finally, carbon-carbon multiple bonds were removed via Pd-catalyzed hydrogenation and nitroxide group was recovered by mild oxidation. This approach was used to prepare both symmetric 2,2,6,6-tetraethyl- and 2,2,6,6-tetrapropyl- substituted piperidine nitroxides, and sterically shielded nitroxides with functional groups in the side chain of the heterocycle.

Result and discussion

β-Aminoketones **4a,b** were obtained from enones **1a,b** via a modified literature sequence [31] involving phthalimide Michael addition, dioxolane formation, and hydrazinolysis (Scheme 1). The target 2-(2-aminoalkyl)-1,3-dioxolanes **4a,b** were obtained in pure form after vacuum distillation.



1a R = Et
1b R = Pr

2a 85%
2b 97%

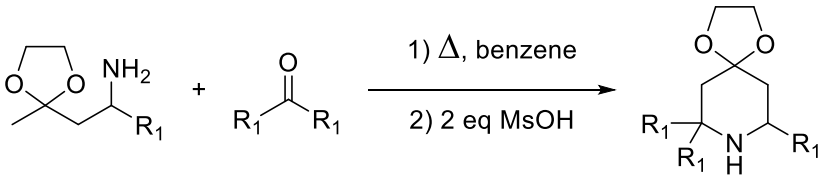
3a 92%
3b 98%

4a 63%
4b 73%

Scheme 1

Conversion of α,β-unsaturated ketones **1a,b** to aminodioxolanes **4a,b** proceeded in 49% and 69% overall yield, respectively. In the ^{1}H NMR spectrum of **4a**, characteristic signals of the dioxolane fragment protons (multiplet, 3.72–3.79 ppm, 4H) and an isolated methyl group (singlet, 1.13 ppm, 3H) were observed. The NH_2 protons appeared as a broad signal at 1.77–1.89 ppm. In addition, eight-spin system comprising the ethyl group resonances (0.71, 1.13, 1.19 ppm), the N-adjacent methine (2.71 ppm), and diastereotopic methylene protons (1.39, 1.58 ppm) supported the assigned structure. Compound **4b** exhibited spectral data identical to those previously described [32].

The aminodioxolanes **4a,b** were subjected to acid-catalyzed heterocyclization with the corresponding diethyl and dipropyl ketones following a reported procedure [30]. In a typical experiment, a mixture of aminodioxolane and ketone was heated in benzene in the presence of pyridinium p-toluenesulfonate (PPTS) using a Dean-Stark apparatus to facilitate Schiff base formation. After cessation of water evolution, methanesulfonic acid (2.0 equiv) was added dropwise to the refluxing mixture, and heating was continued for an additional hour. The reaction was quenched with aqueous sodium carbonate, and the resulting piperidines **5a,b** were purified by vacuum distillation. The target 2,2,6-triethyl- and 2,2,6-tripropyl-substituted piperidines **5a,b** were isolated in approximately 50% yield (Scheme 2).



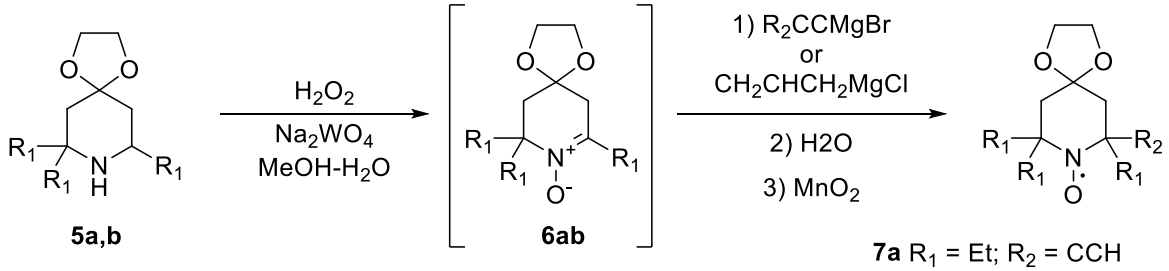
4a R_1 = Et
4b R_1 = Pr

5a 51%
5b 50%

Scheme 2

The ^{1}H NMR spectrum of piperidine **5a** was simulated using full line-shape analysis with gNMR software (version 5.0) [33]; the extracted spin-system parameters were consistent with the proposed structure (see Supporting Information). For compound **5b**, such analysis was not feasible due to extensive overlap of methylene proton resonances associated with the propyl substituents; nevertheless, the spectral characteristics were analogous to those observed for **5a**. Notably, HRMS analysis of **5a,b** exhibited fragment ions corresponding to α-cleavage adjacent to the nitrogen atom, resulting in loss of the 2- or 6-alkyl substituent ([M−R]$^+$) in agreement with established fragmentation patterns for cyclic amines [34].

The 2,2,6-trisubstituted piperidines **5a,b** were oxidized to the corresponding ketonitrones **6a,b** using a sodium tungstate/hydrogen peroxide system. Due to their inherent instability, ketonitrones **6a,b** were used without purification and characterization. It is known that the reaction of sterically hindered nitrones may lead to metalation or deoxygenation of the alkylnitrone group instead of nucleophilic addition [35,36]. Conversely, less basic organometallic reagents, such as vinylmagnesium bromide [35] , ethynylmagnesium bromide [24], or allylmagnesium chloride [37], readily undergo addition, yielding the corresponding nitroxides. Ketonitrone **6a** was treated with various alkynylmagnesiun bromides, generated by deprotonation of acetylene, propargyl alcohol, or N-Boc-protected propargylamine with ethylmagnesium bromide, whereas nitrone **6b** was treated with allylmagnesium bromide. Subsequent quenching of the reaction mixtures with water, followed by oxidation with MnO_2, afforded the corresponding nitroxides **7a-d** in 50–80% overall yield from piperidines **5a,b** (Scheme 3).



5a,b

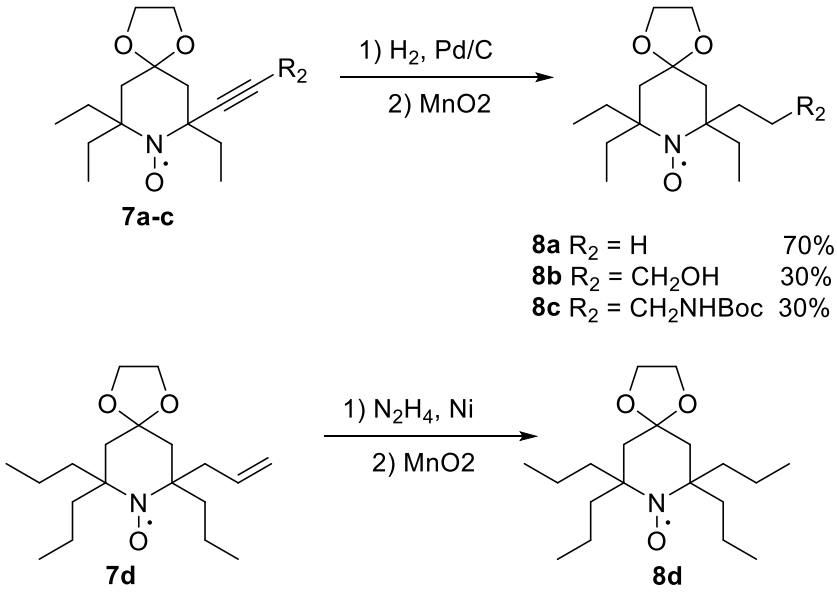
6ab

7a R_1 = Et; R_2 = CCH 72%
7b R_1 = Et; R_2 = $CCCH_2OH$ 60%
7c R_1 = Et; R_2 = $CCCH_2NHBoc$ 50%
7d R_1 = Pr; R_2 = CH_2CHCH_2 80%

Scheme 3

The structures of nitroxides **7a-d** were confirmed by ^{1}H NMR spectroscopy of their amine derivatives, obtained via Zn/CF_3COOH reduction in CD_3OD, following a reported procedure [32]. The full line-shape analysis of the 1H NMR spectra for reduced nitroxides **7a-c** (see Supporting Information) confirmed the 7,7,9-triethyl-1,4-dioxa-8-azaspiro[4.5]decane core and revealed distinct alkynyl signatures: a singlet at 3.29 ppm (1H) for **7a**, a singlet at 4.28 ppm (2H) for **7b**, and two singlets at 3.89 ppm (2H) and 1.46 ppm (9H) for **7c**. For the allyl derivative **7d**, extensive signal overlap prevented rigorous simulation, but characteristic terminal vinyl protons at 5.83, 5.28, 5.27 ppm were clearly observed. Elemental analysis and HRMS data were in agreement with the proposed structures.

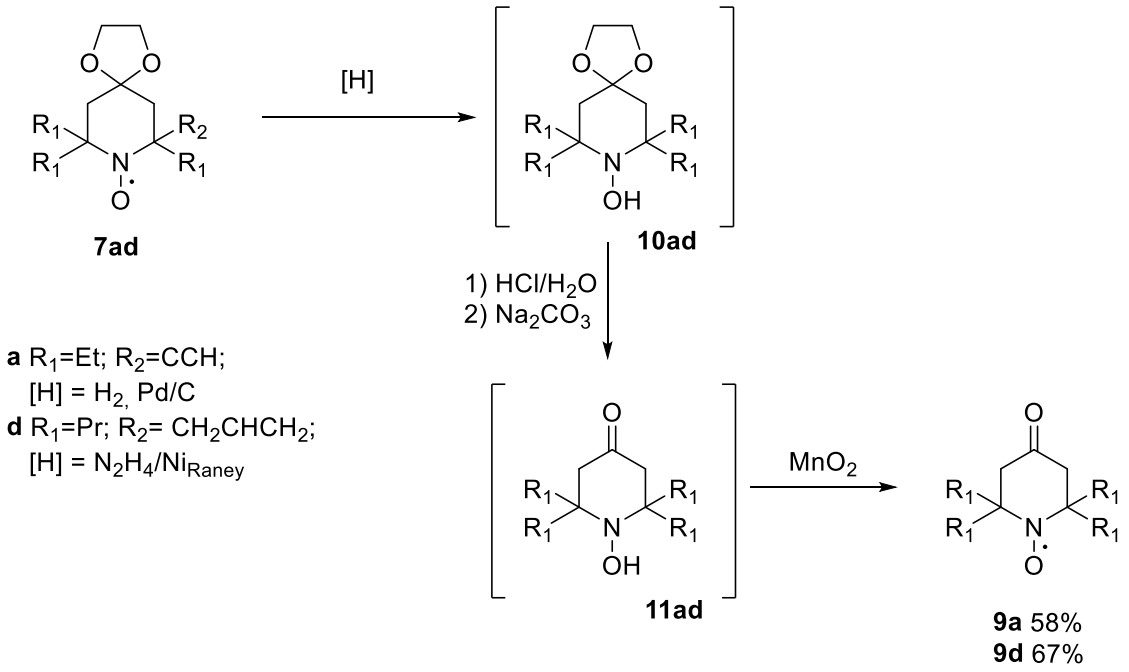
Subsequent hydrogenation of the unsaturated carbon–carbon bonds afforded the corresponding saturated derivatives **8a-d**. Specifically, alkynyl derivatives **7a-c** were hydrogenated with H_2 over a palladium catalyst, while the allyl derivative **7d** was reduced with hydrazine over Raney nickel (Scheme 4). The completeness of hydrogenation was confirmed by the absence of residual signals of protons of ethylene moiety in the ^{1}H NMR spectra of **8a-d**. Elemental analysis and HRMS data were consistent with the proposed molecular formulas.



Scheme 4

Notably, among the alkynyl derivatives, high hydrogenation yields 70% were observed exclusively for the terminal ethynyl derivative **7a**. The lower yields for **7b** and **7c** presumably stem from labile hydrogens in the substituents that promote N–O bond cleavage under hydrogenation conditions, leading to the corresponding amines [38].

In a separate set of experiments, aqueous hydrochloric acid was added to the reaction mixtures after the hydrogenation of **7a,d** was complete. Under these conditions the dioxolane protecting group was removed and nitroxides **9a,d** were isolated in 58% and 67% yield (Scheme 5).



Scheme 5

The IR spectrum of the nitroxide **9a** (TEEPONE) was identical to that reported in literature [22], the IR spectrum of **9d** was similar, with strong absorption band at 1717 cm^{-1}, characteristic of the carbonyl (C=O) stretching vibrations. The ^1H NMR spectra of the reduced derivatives of **9a,d** showed no signals of the dioxolane moiety protons, confirming complete deprotection. The signal intensities for the methylene protons at the 3- and 5-positions of the heterocycle were remarkably diminished due to H/D exchange under the acidic conditions employed for sample preparation.

All nitroxyl radicals showed typical EPR triplets (a_N = 15-16 G)(Table 1). Reduction rate constants for **7d**, **8a,d**, and **9a,d** were measured in 30% EtOH (pH 7.5) using ascorbate/glutathione system, yielding values ~10^{-2} $M^{-1}s^{-1}$, which comparable to that of TEEPONE. Notably, the reduction rate constant determined for TEEPONE in 30% aqueous ethanol are virtually indistinguishable from those reported for pure aqueous solution [12, 22]. The 2-ethynyl-substituted radical **7a** exhibited pronounced susceptibility to glutathione-mediated reduction even in the absence of ascorbate, thereby complicating reliable kinetic analysis (Table 1).

Table 1. EPR spectra parameters and reduction rate constants

Nitroxide	a_N, G ±0.05 G	Hp-p, G ±0.05 G	k_2 $M^{-1}s^{-1}$ × 10^2 in water-ethanol solution
7a	15.48	1.78	nd*
7b	16.00	1.75	-
7c	16.00	1.85	-
7d	15.48	1.88	7.8±0.3
8a	15.63	2.00	4.5±0.5

8b	15.73	1.95	-
8c	15.73	1.98	-
8d	15.52	1.80	5.9±0.1
9a	14.88	1.93	6.2±0.5
9d	15.19	1.66	7.6±0.4

** Accurate quantification of the reduction rate constant proved unattainable owing to the fast reduction process.*

Conclusion

Here we provided yet another demonstration of the synthetic advantages of previously proposed general approach to the synthesis of sterically shielded nitroxides based on the reaction of sterically hindered nitrones with moderately basic organometallic reagents followed by hydrogenation of carbon-carbon multiple bonds.

In this work we applied this method to the synthesis of sterically shielded nitroxides of piperidine series. Along with TEEPONE and its dioxolane-protected derivative, a number of a new nitroxides were prepared, including those with four larger alkyl groups (propyl ones) adjacent to the nitroxide moiety and those with a functional group in the side chain. These functionalized nitroxides can hardly be prepared by any of previously used methods. Taking into account the fact, that piperidine nitroxides are traditionally used as precursors of nitroxyl radicals of other types, especially the pyrroline and pyrrolidine series, this method may open up new possibilities in the chemistry of nitroxide spin labels and nitroxide-based functional materials.

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References

1. Gophane, D. B.; Sigurdsson, S. T. TEMPO-Derived Spin Labels Linked to the Nucleobases Adenine and Cytosine for Probing Local Structural Perturbations in DNA by EPR Spectroscopy. *Beilstein Journal of Organic Chemistry* **2015**, 11, 219–227. https://doi.org/10.3762/bjoc.11.24.
2. Meyer, V.; Swanson, Michael A.; Clouston, Laura J.; Boratyński, Przemysław J.; Stein, Richard A.; Mchaourab, Hassane S.; Rajca, A.; Eaton, Sandra S.; Eaton, Gareth R. Room-Temperature Distance Measurements of Immobilized Spin-Labeled Protein by DEER/PELDOR. *Biophysical Journal* **2015**, 108 (5), 1213–1219. https://doi.org/10.1016/j.bpj.2015.01.015.
3. Casano G., Karoui H., Ouari O. Polarizing agents: evolution and outlook in free radical development for DNP //Handbook of High Field Dynamic Nuclear Polarization. – 2020. – P. 103-120.

4. Madushani Dharmarwardana; Martins, A. F.; Chen, Z.; Palacios, P.; Nowak, C. M.; Welch, R. P.; Li, S.; Michael Andrew Luzuriaga; Leonidas Bleris; Pierce, B. S.; A Dean Sherry; Gassensmith, J. J. Nitroxyl Modified Tobacco Mosaic Virus as a Metal-Free High-Relaxivity MRI and EPR Active Superoxide Sensor. *Molecular pharmaceutics* **2018**, 15 (8), 2973–2983. https://doi.org/10.1021/acs.molpharmaceut.8b00262.
5. Uddin, M. A.; Geng, Y.; Wang, L.; Yu, H.; Wang, H.; Yuan, X.; Keshta, B. E.; Yuan, X.; Zhu, G.; Teng, L. Metal-Free Nitroxide-Containing T1 Magnetic Resonance Imaging Contrast Agent for Invasive Breast Cancer Diagnosis. *Eur. Polym. J.* **2025**, *239*, 114303. https://doi.org/10.1016/j.eurpolymj.2025.114303.
6. Zhivko Zhelev; Rumiana Bakalova; Aoki, I.; Dessislava Lazarova; Saga, T. Imaging of Superoxide Generation in the Dopaminergic Area of the Brain in Parkinson's Disease, Using Mito-TEMPO. *ACS Chemical Neuroscience* **2013**, 4 (11), 1439–1445. https://doi.org/10.1021/cn400159h.
7. GigmesD. (ed.). Nitroxide mediated polymerization: from fundamentals to applications in materials science. – Royal Society of Chemistry, 2016. – N. 19.
8. Bobbitt, J. M.; BrüCkner, C.; Merbouh, N. Oxoammonium- and Nitroxide-Catalyzed Oxidations of Alcohols. *Organic Reactions* **2009**, 103–424. https://doi.org/10.1002/0471264180.or074.02.
9. Nishide, H.; Oyaizu, K. Toward Flexible Batteries. *Science* **2008**, 319 (5864), 737–738. https://doi.org/10.1126/science.1151831.
10. Soule, B. P.; Hyodo, F.; Matsumoto, K.; Simone, N. L.; Cook, J. A.; Krishna, M. C.; Mitchell, J. B. The Chemistry and Biology of Nitroxide Compounds. *Free radical biology & medicine* **2007**, 42 (11), 1632–1650. https://doi.org/10.1016/j.freeradbiomed.2007.02.030.
11. Wetter, C.; Gierlich, J.; Knoop, C. A.; Müller, C.; Schulte, T.; Studer, A. Steric and Electronic Effects in Cyclic Alkoxyamines—Synthesis and applications as regulators for Controlled/Living Radical Polymerization. *Chemistry - a European Journal* **2004**, *10* (5), 1156–1166. https://doi.org/10.1002/chem.200305427.
12. Jagtap, A. P.; Krstic, I.; Kunjir, N. C.; Hänsel, R.; Prisner, T. F.; Sigurdsson, S. Th. Sterically shielded spin labels for in-cell EPR spectroscopy: Analysis of stability in reducing environment. *Free Radical Research* **2014**, *49* (1), 78–85. https://doi.org/10.3109/10715762.2014.979409.
13. Soikkeli, M.; Kettunen, M. I.; Nivajärvi, R.; Olsson, V.; Rönkkö, S.; Laakkonen, J. P.; Lehto, V.-P.; Kavakka, J.; Heikkinen, S. Assessment of the Relaxation-Enhancing Properties of a Nitroxide-Based Contrast Agent TEEPO-Glc with in Vivo Magnetic Resonance Imaging. *Contrast Media & Mol. Imaging* **2019**, *2019*, 1–8. https://doi.org/10.1155/2019/5629597
14. Emoto, M.; Mito, F.; Yamasaki, T.; Yamada, K.-I.; Sato-Akaba, H.; Hirata, H.; Fujii, H. A Novel Ascorbic Acid-Resistant Nitroxide in Fat Emulsion Is an Efficient Brain Imaging Probe forin VivoEPR Imaging of Mouse. *Free Radical Research* **2011**, 45 (11-12), 1325–1332. https://doi.org/10.3109/10715762.2011.618499.
15. Wang, X.; Emoto, M.; Sugimoto, A.; Miyake, Y.; Itto, K.; Amasaka, M.; Xu, S.; Hirata, H.; Fujii, H.; Arimoto, H. Synthesis of 15N-Labeled 4-Oxo-2,2,6,6-Tetraethylpiperidine Nitroxide for EPR Brain Imaging. *Tetrahedron Letters* **2014**, 55 (13), 2146–2149. https://doi.org/10.1016/j.tetlet.2014.02.063.
16. Kajer, T. B.; Fairfull-Smith, K. E.; Yamasaki, T.; Yamada, K. I.; Fu, S.; Bottle, S. E.; Hawkins, C. L.; Davies, M. J. Inhibition of myeloperoxidase- and neutrophil-mediated oxidant production by tetraethyl and tetramethyl nitroxides. *Free Radical Biology and Medicine* **2014**, *70*, 96–105. https://doi.org/10.1016/j.freeradbiomed.2014.02.011.
17. Babić, N.; Peyrot, F. New Synthetic Route to 2,2,6,6-Tetraethylpiperidin-4-One: A Key-Intermediate towards Tetraethyl Nitroxides. *Tetrahedron Letters* **2019**, 60 (44), 151207. https://doi.org/10.1016/j.tetlet.2019.151207.
18. Schulte, T.; Siegenthaler, K. O.; Luftmann, H.; Letzel, M.; Studer, A. Nitroxide-Mediated Polymerization of N-Isopropylacrylamide: Electrospray Ionization Mass Spectrometry, Matrix-Assisted Laser Desorption Ionization Mass Spectrometry, and Multiple-Angle Laser Light Scattering Studies on Nitroxide-Terminated Poly-N-Isopropylacrylamides. *Macromolecules* **2005**, 38 (16), 6833–6840. https://doi.org/10.1021/ma050343n.

19. Wetter, C.; Gierlich, J.; Knoop, C. A.; Müller, C.; Schulte, T.; Studer, A. Steric and Electronic Effects in Cyclic Alkoxyamines—Synthesis and Applications as Regulators for Controlled/Living Radical Polymerization. *Chem. - Eur. J.* **2004**, *10* (5), 1156–1166. https://doi.org/10.1002/chem.200305427.
20. Kinoshita, Y.; Yamada, K.-I.; Yamasaki, T.; Sadasue, H.; Sakai, K.; Utsumi, H. Development of Novel Nitroxyl Radicals for Controlling Reactivity with Ascorbic Acid. *Free Radical Research* **2009**, 43 (6), 565–571. https://doi.org/10.1080/10715760902914575.
21. Sakai, K.; Yamada, K.; Yamasaki, T.; Kinoshita, Y.; Mito, F.; Utsumi, H. Effective 2,6-Substitution of Piperidine Nitroxyl Radical by Carbonyl Compound. *Tetrahedron* **2010**, 66 (13), 2311–2315. https://doi.org/10.1016/j.tet.2010.02.004.
22. Paletta, J. T.; Pink, M.; Foley, B.; Rajca, S.; Rajca, A. Synthesis and Reduction Kinetics of Sterically Shielded Pyrrolidine Nitroxides. *Organic Letters* **2012**, 14 (20), 5322–5325. https://doi.org/10.1021/ol302506f.
23. Kinoshita, Y.; Yamada, K.; Yamasaki, T.; Mito, F.; Yamato, M.; Kosem, N.; Deguchi, H.; Shirahama, C.; Ito, Y.; Kitagawa, K.; Okukado, N.; Sakai, K.; Utsumi, H. In Vivo Evaluation of Novel Nitroxyl Radicals with Reduction Stability. *Free Radical Biology and Medicine* **2010**, 49 (11), 1703–1709. https://doi.org/10.1016/j.freeradbiomed.2010.08.027.
24. Dobrynin, S. A.; Gulman, M. M.; Morozov, D. A.; Zhurko, I. F.; Taratayko, A. I.; Sotnikova, Y. S.; Glazachev, Y. I.; Gatilov, Y. V.; Kirilyuk, I. A. Synthesis of Sterically Shielded Nitroxides Using the Reaction of Nitrones with Alkynylmagnesium Bromides. *Molecules* **2022**, 27 (21), 7626–7626. https://doi.org/10.3390/molecules27217626.
25. Taratayko, A. I.; Glazachev, Y. I.; Eltsov, I. V.; Chernyak, E. I.; Kirilyuk, I. A. 3,4-Unsubstituted 2-Tert-Butyl-Pyrrolidine-1-Oxyls with Hydrophilic Functional Groups in the Side Chains. *Molecules* **2022**, *27* (6), 1922. https://doi.org/10.3390/molecules27061922.
26. Guillaumet, G.; Pavé, G.; Chalard, P.; Viaud-Massuard, M.-C.; Troin, Y. A new efficient synthesis of spirocyclic benzopyrans. *Synthesis* **2003**, *2004* (01), 121–127. https://doi.org/10.1055/s-2003-44353.
27. Ciblat, S.; Canet, J.; Troin, Y. ChemInform Abstract: A New Route to 2-Spiropiperidines. *ChemInform* **2001**, 32 (41). https://doi.org/10.1002/chin.200141166.
28. Heathcock, C. H.; Davidsen, S. K.; Mills, Sander.; Sanner, M. A. Total synthesis of (.+-.)-methyl homodaphniphyllate. *Journal of the American Chemical Society* **1986**, *108* (18), 5650–5651. https://doi.org/10.1021/ja00278a061.
29. Bariau, A.; Jatoi, W. B.; Calinaud, P.; Troin, Y.; Canet, J. A simple stereoselective route to A-Trifluoromethyl analogues of piperidine alkaloids. *European Journal of Organic Chemistry* **2006**, *2006* (15), 3421–3433. https://doi.org/10.1002/ejoc.200600157.
30. Rogovoy M.I., Dobrynin S.A., Glazachev Y.I., Kirilyuk I.A. Synthesis of 8-[(hydroxy)methyl]-13,13-diethyl-1,4-dioxa12-azadispiro[4.1.4.3]tetradecane-12-oxyl. Chem. Sustainable Dev. 2025. 33 (5), 570-577
31. Islam, A. M.; Raphael, R. A. A Direct Transformation of Cyclohexanones into Bicyclo[5 : 3 : 0]Dec-7-En-9-Ones. *Journal of the Chemical Society (Resumed)* **1955**, 3151. https://doi.org/10.1039/jr9550003151.
32. Bariau, A.; Canet, J.-L.; Chalard, P.; Troin, Y. Asymmetric Synthesis of 1,3-Aminoketals. *Tetrahedron: Asymmetry* **2005**, 16 (22), 3650–3660. https://doi.org/10.1016/j.tetasy.2005.09.024.
33. Rummey, J. M.; Boyce, M. C. Introducing the GNMR Program in an Introductory NMR Spectrometry Course to Parallel Its Use by Spectroscopists. *Journal of Chemical Education* **2004**, 81 (5), 762–762. https://doi.org/10.1021/ed081p762.
34. Pretsch, E.; Bühlmann, P.; Affolter, C. Mass Spectrometry. *Structure Determination of Organic Compounds* **2000**, 313–383. https://doi.org/10.1007/978-3-662-04201-4_7.
35. Dobrynin, S. A.; Glazachev, Y. I.; Gatilov, Y. V.; Chernyak, E. I.; Salnikov, G. E.; Kirilyuk, I. A. Synthesis of 3,4-bis(hydroxymethyl)-2,2,5,5-tetraethylpyrrolidin-1-oxyl via 1,3-dipolar cycloaddition of azomethine ylide to activated alkene. *J. Org. Chem.* **2018**, 83, 5392– 5397, https://doi.org/10.1021/acs.joc.8b00085

36. Zhurko, I. F.; Dobrynin, S.; Gorodetskii, A. A.; Glazachev, Y. I.; Rybalova, T. V.; Chernyak, E. I.; Asanbaeva, N.; Bagryanskaya, E. G.; Kirilyuk, I. A. 2-Butyl-2-tert-butyl-5,5-diethylpyrrolidine-1-oxyls: Synthesis and properties. *Molecules* **2020**, 25, 845, https://doi.org/10.3390/molecules25040845
37. Lampp, L.; Morgenstern, U.; Merzweiler, K.; Imming, P.; Seidel, R. W. Synthesis and characterization of sterically and electrostatically shielded pyrrolidine nitroxide radicals. *J. Mol. Struct.* **2019**, 1182, 87– 94, https://doi.org/10.1016/j.molstruc.2019.01.015
38. Dobrynin, S. A.; Usatov, M. S.; Zhurko, I. F.; Morozov, D. A.; Polienko, Y. F.; Glazachev, Y. I.; Parkhomenko, D. A.; Tyumentsev, M. A.; Gatilov, Y. V.; Chernyak, E. I.; Bagryanskaya, E. G.; Kirilyuk, I. A. A Simple Method of Synthesis of 3-Carboxy-2,2,5,5-Tetraethylpyrrolidine-1-Oxyl and Preparation of Reduction-Resistant Spin Labels and Probes of Pyrrolidine Series. *Molecules* **2021**, 26 (19), 5761–5761. https://doi.org/10.3390/molecules26195761.