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S_N^H Approach in the Synthesis of Nitronyl Nitroxides

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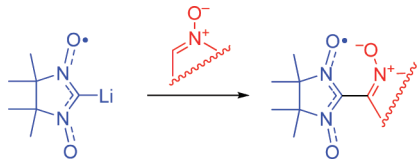

We show that the S_N^H approach opens up new possibilities in the synthesis of hetaryl-substituted nitronyl nitroxides. The reaction of 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl lithium salt with pyridine-, pyrimidine-, pyrazine-, isoquinoline-, phthalazine-, quinoxaline-, and 1,2,4-triazine-*N*-oxides readily gives rise to the corresponding paramagnetic hetarenes. The reaction of this salt with quinoxaline-1,4-dioxide enabled the synthesis of the first nitronyl nitroxide biradical with two spin-labeled fragments *in the vicinal positions* of the heteroaromatic cycle; the persistent biradicals of this type were not known earlier. The characterizations of all persistent radicals obtained by S_N^H synthetic strategy include X-ray crystal structures, EPR investigation, and static magnetic susceptibility measurements.

Persistent nitronyl nitroxides are valuable building blocks for the construction of heterospin exchange-coupled clusters and high-dimension systems with large energies of exchange interaction between the unpaired spins of the paramagnetic centers. The steadily growing interest toward nitronyl nitroxides from the researchers working on the design of molecular magnets[1] leads to substantial extension of the set of available nitroxides. An actively used synthetic strategy in this quest is the classic method[2] employing the interaction of vicinal dihydroxyamine with specifically tailored aldehydes or their synthetic equivalents followed by oxidation of the forming 1,3-dihydroxyimidazolidine into nitroxides. However, this method has a number of inherent limitations: the range of the available vicinal dihydroxyamines is rather limited, certain aldehydes cannot be obtained in principle, and finally the interaction of aldehydes with dihydroxyamine can be accompanied by rearrangements leading away from the target compound.[3] Under these circumstances alternative synthetic approaches based on direct introduction of the substituents into 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (**H1**)[4] to produce polyfunctional nitronyl nitroxides become especially attractive. In our search for these methods we were drawn to the methodology of nucleophilic aromatic substitution of hydrogen and the related S_N^H reactions.[5] This approach turned out to be highly efficient in the reaction of the lithium salt of 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (**Li1**) with quinoline-*N*-oxide leading to formation of 4,4,5,5-tetramethyl-2-(1-oxidoquinoline-2-yl)-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl,[6] which stimulated our investigation into the general applicability of the S_N^H methodology in the synthesis of various spin-labeled hetarenes.

To understand the effect that the structure of azine-*N*-oxide has on its behavior in the S_N^H reaction with **Li1** we prepared an extensive series of these compounds, including monocyclic and bicyclic azine-*N*-oxides, compounds with one or several heteroatoms, with and without substituents, as well as a heterocyclic compound with two *N*-oxide fragments. The S_N^H reaction of **Li1** with azine-*N*-oxides or quinoxaline 1,4-dioxide was performed as follows. A solution of 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (**H1**) in dry THF was prepared in a Schlenk flask, then the flask was placed into a bath with alcohol cooled down to a caramel state. A com-

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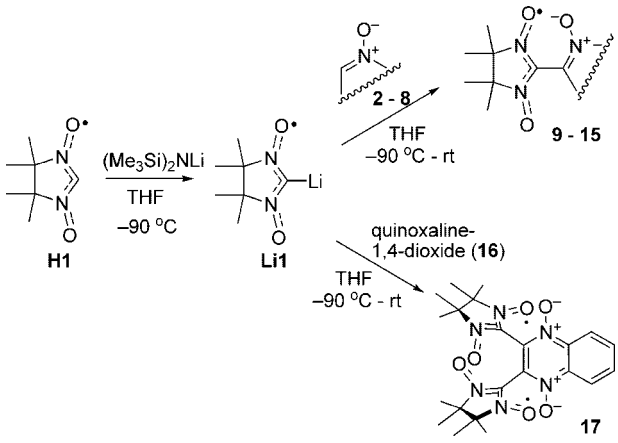
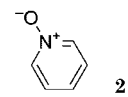
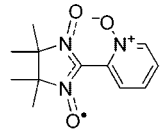
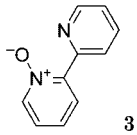
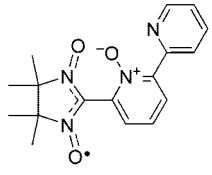
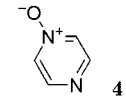
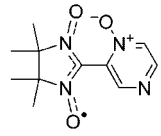
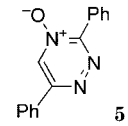
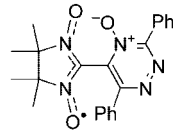
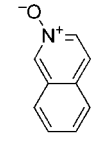
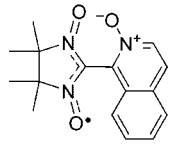
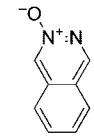
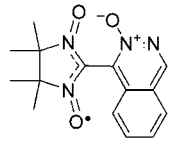
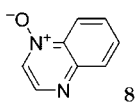
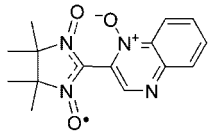
TABLE 1. S_N^H Synthesis of Nitronyl Nitroxides 9−15 and 17



Entry	Substrate	Product	Yield (%)[a]
1	 **2**	 **9**	26
2	 **3**	 **10**	62
3	 **4**	 **11**	24
4	 **5**	 **12**	36
5	 **6**	 **13**	32
6	 **7**	 **14**	44
7	 **8**	 **15**	42

[a] Isolated yield based on azine-*N*-oxide.

mercially available solution of $(Me_3Si)_2NLi$ in THF was added to the violet-colored solution of **H1** and the solution changed color to reddish-orange due to formation of **Li1**. Then a solution of azine-*N*-oxide (or quinoxaline 1,4-dioxide) in dry THF was added to the prepared solution of **Li1** observing how the reaction mixture rapidly changed color to different shades of greenish-brown, which as a rule changed further at low temperature,

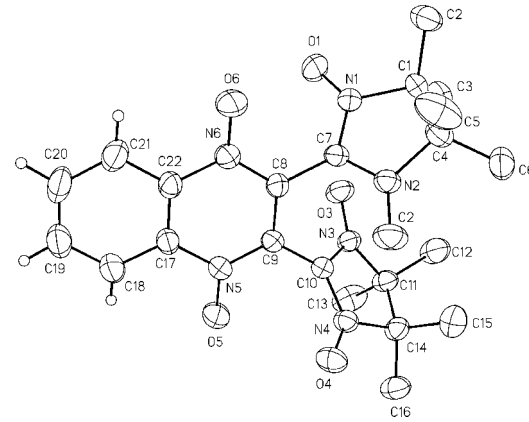


FIGURE 1. Molecular structure of **17**.

gradually approaching the final color of the product of the S_N^H reaction. The only exception was quinoxaline-*N*-oxide, after adding which to **Li1** the reaction mixture turned green and retained this color at low temperatures, but upon raising the temperature closer to room temperature it also changed color to the color of the corresponding product. These color changes, rather convenient for visual control of chemical transformations, come from bright and intense colors of the forming compounds. This circumstance, together with the substantial difference between the R_f values of the products and of the other components of the reaction mixture, simplified the extraction and purification of the products using column chromatography.

The performed identification of the synthesized compounds demonstrated that interaction of **Li1** with azine-*N*-oxides **2**−**8** produced hetaryl-substituted nitronyl nitroxides **9**−**15** (Table 1) in medium yields, with the reaction never completing as indicated by comparable yields of the products **9**−**15** and the initial azine-*N*-oxides and **H1**. The reaction of 2 equiv of **Li1** with quinoxaline 1,4-dioxide produced biradical **17**.

The performed experiments show that rather different azine-*N*-oxides, having one or several nitrogens in the cycle, mono- or bicyclic, can enter the S_N^H reaction with **Li1**. Furthermore, judging by the structure of nitroxide **13**, the direction of the reaction is determined solely by kinetic factors. The nucleophilic attack can consecutively target vicinal hydrogens, as, e.g., in quinoxaline 1,4-dioxide, which can produce biradicals with topology not accessible within the classic nitronyl nitroxide synthesis (Figure 1). This proves the S_N^H reaction to be a reliable method for linking the carbon of the paramagnetic fragment **H1** with the carbon of the nitronyl group of azine-*N*-oxide.

Thus in this work we developed a general approach to functionally substituted nitroxides based on the S_N^H reaction of the lithium salt of nitronyl nitroxide with azine-*N*-oxides. The value of this synthetic methodology was demonstrated by the preparation of a representative series of heterocycles bearing a paramagnetic moiety. We especially stress that the suggested S_N^H reaction allowed introducing two paramagnetic substituents in the vicinal positions of the heterocycle. The performed syntheses demonstrate the potential of the S_N^H strategy that can be very useful in planning retrosyntheses of certain nitronyl nitroxides.

Experiment Section

General Procedure for the Synthesis of Nitronyl Nitroxides Based on the S_N^H Methodology (with 9 and 17 as examples). $(Me_3Si)_2NLi$ (1.1 mmol, 1.04 mL of a 1.06 M solution in THF)

was added dropwise to 4 mL of a stirred THF solution of **H1** (157 mg, 1 mmol) at −90 °C under argon. The reaction mixture was stirred for 0.5 h at the same temperature and then treated with *N*-oxide (1.1 mmol in the case of **2**–**8** and 0.55 mmol in the case of **16**) in dry THF (6 mL) under argon. The resulting reaction mixture was allowed to warm to room temperature and was then stirred for 2 h. Finally, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with use of the relevant solvents as the eluent. The eluate was concentrated to dryness in vacuo.

4,4,5,5-Tetramethyl-2-(1-oxidopyridin-2-yl)-4,5-dihydro-1*H*-imidazole 3-Oxide 1-Oxyl (9). This material was prepared following the general procedure. Purification by column chromatography (ethylacetate, then 8:2 ethylacetate−MeOH) gave **9** as claret-colored crystals (65 mg, 26%): mp 172−174 °C (from a mixture of CH_2Cl_2 with *n*-heptane); R_f 0.18 (EtOAc); UV/vis (EtOH) λ_{max} (ϵ, M^{-1} cm^{-1}) 217 (13 300), 267 (11 200), 304 (8 900), 369 (4 000), 542 (480) nm; IR ν 541, 564, 719, 779, 820, 871, 1135, 1156, 1176, 1216, 1267, 1307, 1373, 1387, 1413, 1454, 1561, 1637, 2989, 3023, 3058 cm^{-1}. $\mu_{eff} \approx 1.73\mu_B$ (5−300 K). $C_{12}H_{16}N_3O_3$ (250.27) calcd: C 57.6, H 6.4, N 16.8. Found: C 57.5, H 6.7, N 17.0.

2,3-Bis(4,4,5,5-tetramethyl-3-oxido-1-oxyl-4,5-dihydro-1*H*-imidazol-2-yl)quinoxaline 1,4-Dioxide (17). This material was prepared following the general procedure. Purification by column chromatography (ethylacetate, then 8:2 EtOAc−MeOH) gave **17** as orange-brown crystals (66 mg, 14%): mp 198−200 °C (from a mixture of CH_2Cl_2 with *n*-heptane); R_f 0.17 (ethylacetate); UV/vis ($CHCl_3$) λ_{max} (ϵ, M^{-1} cm^{-1}) 246 (27 500), 310 (26 800), 390 (14 200) nm; IR ν 540, 587, 657, 711, 729, 776, 852, 895, 954, 1035, 1137, 1170, 1217, 1262, 1340, 1372, 1400, 1427, 1452, 1496, 1538, 1599, 2941, 2999, 3107 cm^{-1}. $\mu_{eff} = 2.25\mu_B$ (50−300 K). $C_{22}H_{28}N_6O_6$ (472.49) calcd: C 55.9, H 6.0, N 17.8. Found: C 55.8, H 5.9, N 17.7.

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Supporting Information Available: General experimental details and characterization of **10**−**15**, discussion of the crystal structures, the ORTEP diagrams, X-ray crystallographic data for **9**−**15**, and **17**, and CIF files, and EPR investigation and static magnetic susceptibility measurements for **9**−**15** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org. Files CCDC-715928 (α-**9**), CCDC-715929 (*β*-**9**), CCDC-715930 (**10**), CCDC-715931 (**11**), CCDC-715932 (**12**), CCDC-715933 (**13**), CCDC-715934 (**14**), CCDC-715935 (**15**), and CCDC-715936 (**17**) containing the supplementary crystallographic data for this paper can be obtained free of charge via www.ccdc.cam.ak.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (Fax +44-1233-336-033; E-mail data_request@ccdc.cam.ac.uk), on quoting the deposition number.

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