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β-Phosphorylated Five Membered Ring Nitroxides, A New Class of Stable Nitroxides. 1. Synthesis by Reaction of Dialkylphosphites with 1-Pyrroline-N-Oxides.

Anne Mercier, Yves Berchadsky, Badrudin[1], Sylvia Pietri and Paul Tordo*.

Laboratoire de Structure et Réactivité des Espèces Paramagnétiques, associé au CNRS, UA 1412, Université de Provence, Faculté de St Jérome, av. Esc. Normandie-Niemen, 13397 Marseille Cedex 13, France.

Key Words: β-Phosphorylated five membered ring nitroxides; 1-pyrroline-N-oxides; α-phosphorylated 1-pyrroline-N-oxides; ESR.

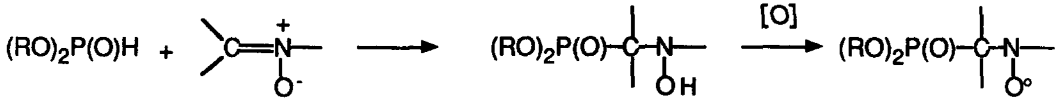
Abstract: Dialkylphosphites add to 2,5,5-trialkyl-1-pyrroline-N-oxides to give, after oxidation with copper(II)acetate, the corresponding β-phosphorylated nitroxides, which are stable in many organic solvents.

For most of stable nitroxide radicals[2], atoms adjacent to the radical center are quaternary carbons, usually bearing alkyl substituents or, in few cases, heteroatoms[3]. New stable nitroxides with a non-zero spin nucleus on one of the α-carbons could be of special interest in the spin-labeling[4] technique, where hyperfine coupling with this nucleus is expected to bring more information on the studied systems. Furthermore, depending on the magnitude of this coupling, these nitroxides could also find interesting applications as relaxation or nuclear polarization[5] agents.

The very long half-lives observed for various β-phosphorylated nitroxides generated in spin-trapping experiments[6] prompted us to investigate the possibility to isolate some of them and we report herein preliminary results on the characterization of the first members of this new class of stable nitroxides.

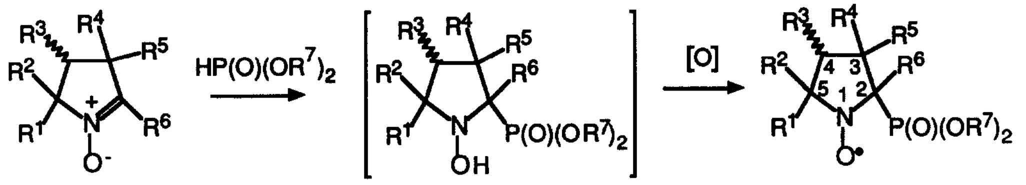
Dialkylphosphites were reported to add to nitrones to yield α-hydroxyamino phosphonates[7], which can be spontaneously oxidized in air into the corresponding nitroxides (Scheme 1).

Scheme 1



On the other hand 2,5,5-trialkyl-1-pyrroline-N-oxides are easy to prepare[8] and thus we anticipated that their use according to Scheme 1 would open a route to nitroxides of the proxyl series, bearing β-dialkoxyphosphoryl substituents (Scheme 2).

Scheme 2



1 ($R^1 = R^2 = R^6 = Me, R^3 = R^4 = R^5 = H$)
2 ($R^1 = R^2 = R^6 = Me, R^3 = Ph, R^4 = R^5 = H$)
3 ($R^1 = R^2 = R^6 = CD_3, R^3 = Ph, R^4 = R^5 = D$)

4 ($R^1 = R^2 = R^6 = Me, R^3 = R^4 = R^5 = H, R^7 = Et$)
5 ($R^1 = R^2 = R^6 = Me, R^3 = Ph, R^4 = R^5 = H, R^7 = Et$)
6*($R^1 = R^2 = R^6 = CD_3, R^3 = Ph, R^4 = R^5 = D, R^7 = Et$)
*From **3** and $DP(O)(OEt)_2$

Different nitrones and dialkylphosphites were tested using various experimental procedures[9]. Nitrones **1**, **2** and **3**[10] led to nitroxides **4**, **5** and **6**, which were isolated, although yields remained low (5-10%)[11,12]. The reaction of **2** with diethylphosphite, according to Scheme 2, led to a mixture of two radicals **5a** (major product) and **5b** (minor product), which were separated by flash column chromatography. According to their high resolution mass spectra, **5a** and **5b** correspond to the same mass and were assigned to the diasteomeric structures shown on Scheme 3. The ESR parameters of these new stable nitroxides are reported in Table 1. The diastereomeric nitroxides **5a** and **5b** were shown to exhibit very different phosphorus splittings.

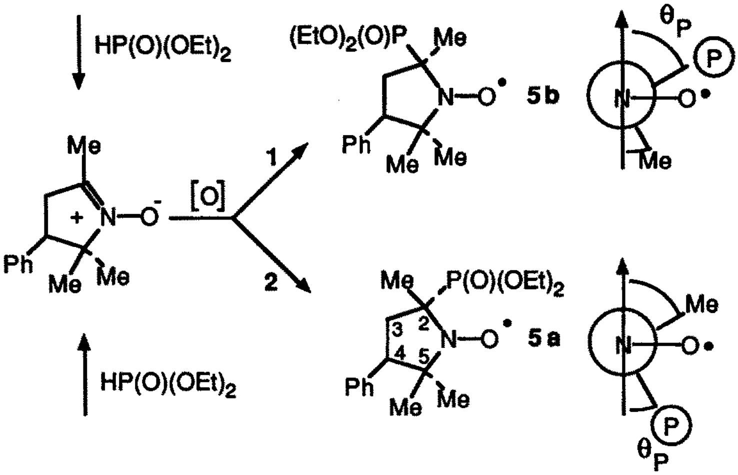
Table 1: ESR Parameters of Stable β-Phosphorylated Nitroxides in Oxygen-Free Benzene at Room Temperature.

Nitroxide	a_N (G)	a_P (G)	a_H $a_{^{13}C}$	g
4	13.75	50.00	–	2.0059
5a	13.75	52.98	0.45 (6H) 0.43 (3H) 7.6 (^{13}C) 5.0 (^{13}C)	2.0059
5b	13.75	36.00	–	2.0059
6a	13.75	52.60	–	2.0059
6b	14.00	35.90	–	2.0059

It is reasonable to assume that the major diastereomer **5a** corresponds to the attack of diethylphosphite on the less hindered face of nitrone **2**, thus diastereomers **5a** and **5b** should have the stereochemistry shown on Scheme 3. ESR studies indicated that for the diastereomeric nitroxides obtained by reacting nitrone **2** with various dialkylphosphites (R^7 = Me, Et, nBu, Bz), the formation of the diastereomer exhibiting the highest phosphorus-hfs is favoured by the steric hindrance of the phosphoryl group. Furthermore, the phosphorus-hfs value in β-phosphorylated nitroxides is linked to the θ_P angle by the relation $a_P = B_P \cos^2\theta_P$[6]. For **5a** the pseudo syn 1-3 interaction between the phenyl and the methyl group attached to C_2 is expected to favour the overlap between the C-P bond and the SOMO, thus leading to a higher phosphorus-hfs than for **5b**.

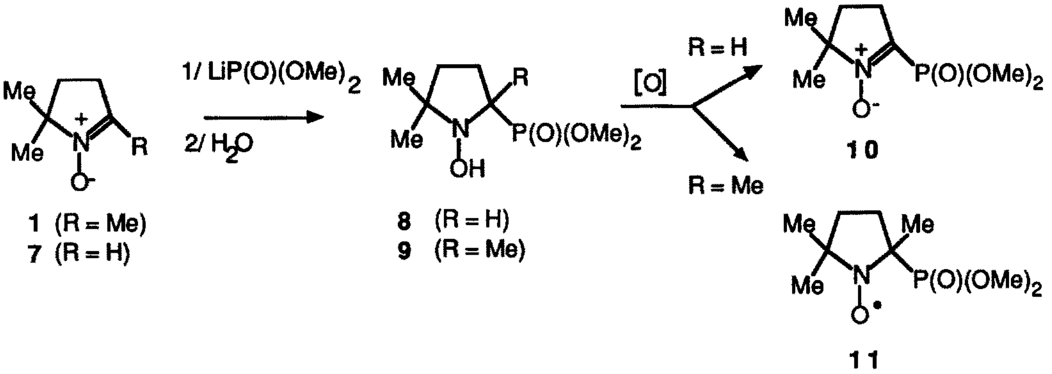
In the case of nitroxide **5a**, hyperfine splittings due to γ-hydrogens are observed (Table 1), which disappear in the corresponding deuterated nitroxide **6a**.

Scheme 3



Isolation of the intermediate N-hydroxyamines resulting from the addition of lithium salts of dialkylphosphites on nitrones **1** and **7** was attempted (Scheme 4)[7a]. Starting from nitrone **7**, we were able to isolate in 23% yield the pure phosphorylated N-hydroxyamine **8**[12] (δ ^{31}P = 29.35 ppm) which can be converted in·65% yield to the α-phosphorylated nitrone **10**[12] (δ ^{31}P = 9.1 ppm) by oxidation with copper(II)acetate.

Scheme 4



However in the case of nitrone **1** all our attempts to isolate the intermediate N-hydroxyamine **9** failed. When R = Me, the steric strain in the intermediate N-hydroxyamine **9** is very large, which presumably makes the addition of the phosphite reversible. This reversibility explains the lack of stability of **9** and the formation of nitroxides **4**, **5** and **6** in very poor yields.

This work allowed us to isolate for the first time β-phosphorylated nitroxides, a new class of stable organic free radicals. We are currently developping a new synthetic scheme to obtain these radicals in reasonable yields[5].

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9. The best results were obtained with the following procedure: nitrone (4.5 mmol) and dialkylphosphite (7.8 mmol) are vigourously stirred at 35-45°C during 7-12 h and the reaction progress controlled by ESR. The excess of dialkylphosphite is removed under reduced pressure by bulb-to-bulb distillation (5.10^{-3} mbar, 25-30°C). The residual material is extracted with dry benzene (50 mL) and powdered copper(II)acetate (0.09 mmol) is then added. After filtration and concentration, the crude product is chromatographied over silica gel.
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11. Nitroxides **4**, **5** and **6** were isolated as orange oils and were purified by column chromatography over silica gel 60 H, eluting in 10% petroleum ether-diethyl ether. They were shown to be stable in many organic solvents (PhH, THF, $PhCH_3$) and their solutions did not show any decrease of their ESR signal over periods of years. These solutions were used in different successful studies of dynamic nuclear polarization[5] and relaxation effects.
12. **3**: ^1H NMR ($CDCl_3$) 3.32 (1H, s), 7.2 (5H, m); D NMR ($CHCl_3$, external reference $CDCl_3$) 0.95 (3D, s), 1.49 (3D, s), 2.13 (3D, s), 2.95 (2D, m); **4**: UV (CH_3CN) 240 nm; HRMS calcd for $C_{11}H_{23}NO_4P$ 264.1364, found 264.1363; **5a,b**: UV (CH_3CN) 240 nm; HRMS calcd for $C_{17}H_{27}NO_4P$ 340.1676, found 340.1679 (**5a**) and 340.1672 (**5b**); **8**: ^1H NMR ($CDCl_3$) 1.46 (6H, s), 2.08 (2H, t), 2.65 (2H, m), 3.32 (1H, m), 3.8 (6H, d); ^{31}P NMR ($CDCl_3$) 29.35; **10**: ^1H NMR ($CDCl_3$) 1.30 (6H, s), 1.72 (2H, t), 2.82 (2H, t), 3.78 (6H, d); ^{31}P NMR ($CDCl_3$) 9.1.

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