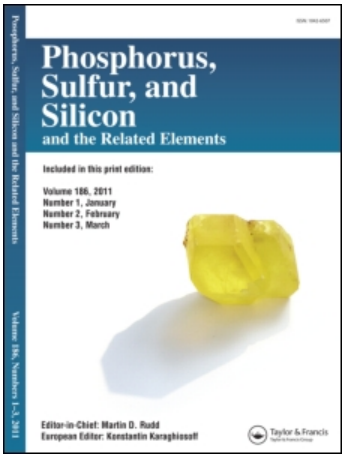


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

UNEXPECTED REACTION OF TRIS(TRIMETHYLSILYL)PHOSPHITE WITH A HINDERED NITRONE

Abdelhamid Zeghdaoui[a]; Nourredine Benali-Cherif[b]; Jean-Pierre Finet[a]; Paul Tordo[a]
[a] Laboratoire Structure et Réactivité des Espèces Paramagnétiques, URA—CNRS 1412, Université de Provence, Centre St-Jérôme, Marseille, Cedex, France [b] Laboratoire de Bioinorganique Structurale, Université d'Aix-Marseille III, Marseille, Cedex, France

To cite this Article Zeghdaoui, Abdelhamid , Benali-Cherif, Nourredine , Finet, Jean-Pierre and Tordo, Paul(1994) 'UNEXPECTED REACTION OF TRIS(TRIMETHYLSILYL)PHOSPHITE WITH A HINDERED NITRONE', Phosphorus, Sulfur, and Silicon and the Related Elements, 91: 1, 219 — 227
To link to this Article: DOI: 10.1080/10426509408021948
URL: http://dx.doi.org/10.1080/10426509408021948

Phosphorus, Sulfur, and Silicon, 1994, Vol. 91, pp. 219–227
Reprints available directly from the publisher
Photocopying permitted by license only

UNEXPECTED REACTION OF TRIS(TRIMETHYLSILYL)PHOSPHITE WITH A HINDERED NITRONE

ABDELHAMID ZEGHDAOUI,* NOURREDINE BENALI-CHERIF,† JEAN-PIERRE FINET* and PAUL TORDO*

**Laboratoire Structure et Réactivité des Espèces Paramagnétiques, URA—CNRS 1412, Université de Provence, Centre St-Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France; †Laboratoire de Bioinorganique Structurale, Université d'Aix-Marseille III, Centre St-Jérôme, 13397 Marseille Cedex 20, France*

(Received July 5, 1994)

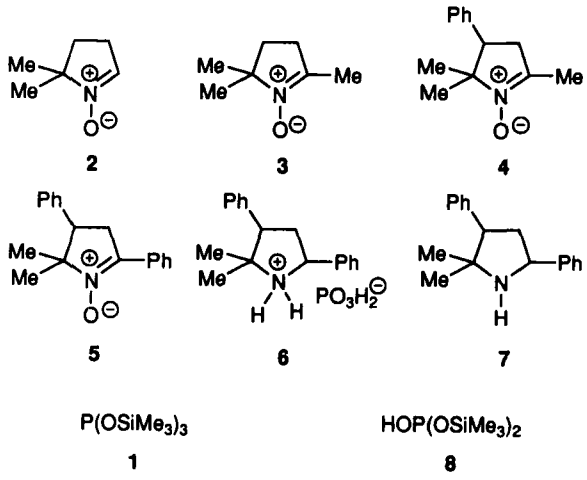
Reaction of 5,5-dimethyl-2,4-diphenylpyrroline N-oxide with *tris*(trimethylsilyl)phosphite gave 2,2-dimethyl-3,5-*trans*-diphenylpyrrolidinium orthophosphite, as the only product, in 90% yield. The absolute structure of the title compound was established by X-ray crystallography. $C_{18}H_{24}NO_3P$ crystallizes in the triclinic space group P_1^- with a = 8.806(4), b = 10.331(1), c = 11.375(5) Å, α = 65.55(6), β = 88.21(4), γ = 67.80(6), V = 866.5(4) Å^3, Z = 2, d_{cal} = 1.28, λ Mo K_α = 0.71069 Å, μ = 1.666 cm^{-1}, F(000) = 356, T = 293 K. The compound presents a *trans* C-3,C-5 diphenylpyrrolidine structure with a dihedral angle = 91.66° between the two phenyl rings.

Key words: Nitrone deoxygenation, 2-phenylpyrroline-N-oxide, imine reduction, *bis*(trimethylsilyl)-phosphite.

INTRODUCTION

Aminoxyl radicals have found application as spin labels,[1] MRI[2] and polarization agents.[3] The majority of stable aminoxyl radicals are derived from secondary amines bearing two quaternary sp^3 atoms and exhibit isotropic three lines ESR spectra. Replacement of one of the substituent on one α-atom by a one-half spin nucleus introduces a second very large hyperfine splitting. This is indeed observed in the case of the 2-phosphonylpyrrolidine aminoxyl radicals, which we have developed in recent years.[4]

Two main routes have been studied for their preparation: a) addition of a phosphorus reagent on a nitrone[5,6] and b) oxidation of the appropriate α-aminophosphonic acid derivative.[7] The main problems associated with the reported sequences are the poor overall yields which have been obtained. In the case of addition of a phosphorus reagent on a nitrone, reaction of a phosphorus centered radical leads to mixtures of the aminoxyl and the *O*-phosphonylhydroxylamine ester resulting from subsequent trapping of the aminoxyl by the phosphorus radical. When the phosphorus moiety is introduced by a nucleophilic addition followed by oxidation to the aminoxyl, the reversibility of the addition leads to poor yields of aminoxyl. In view of the observations of Yamada on the addition of trialkylphosphite to cyclic nitrones[8] and of those of Vasella on the easy addition of *tris*(trimethylsilyl)phosphite to linear acyclic nitrones,[9] we decided to investigate the reaction of cyclic nitrones



with *tris*(trimethylsilyl)phosphite **1**, which should lead to hydroxylamine-*O*-silyl ethers, amenable to oxidation under neutral conditions.

RESULTS AND DISCUSSION

Treatment of various substituted pyrrolidine nitrones **2–4**[10] with either diethyl trimethylsilylphosphite or with tris(trimethylsilyl)phosphite (TSP) led only to recovery of unreacted nitrones. However, when the 2-phenyl nitrone **5** was treated with an excess of TSP, a crystalline product **6** was obtained from the aqueous phase. This compound is scarcely soluble in organic solvents. ^{31}P NMR of its solution in CD_3OD indicated the presence of a phosphorus group (δ 4.2 ppm). However, when this compound was studied by EPR, only a four line ESR spectrum (1, 2, 2, 1) was observed, corresponding to a nitroxide with A_N = 14 G and A_H = 14 G, whereas α-phosphonylnitroxides always give six lines ESR spectra. Moreover, microanalyses were in agreement with a molecular formula such as $C_{18}H_{24}NO_3P$. Fortunately, the compound crystallized in such a way that it was well-suited for X-ray structural determinations. Some striking features were observed (Figure 2). Among them, the absence of oxygen carried by the nitrogen, the presence of two C—N bonds of equal length [N(1)—C(2) = 1.514(2) Å, [N(1)—C(5) = 1.514(3) Å] indicative of a sp^3 nitrogen, and the non-bonded nature of the phosphorus group.

A more detailed study showed that the product presented the structure of a saturated 2,4-*trans*-diphenylpyrrolidinium, salified by a P(III) phosphorous derivative. The two protons borne by the nitrogen were localized on a Fourier map, as well as one hydrogen on the oxygen of the phosphorous acid. The dihedral angles are equal to 91.66° between the two phenyl rings, 146.24° between the C-5 phenyl and pyrrolidinium average plane and 62.75° between the C-3 phenyl and pyrrolidinium average plane. The relative positions of the pyrrolidinium ring and the phosphorous acid are shown in Figure 2. The asymmetric unit cell contains two pyrrolidines with the two phosphorous acid molecules close to the symmetry center.

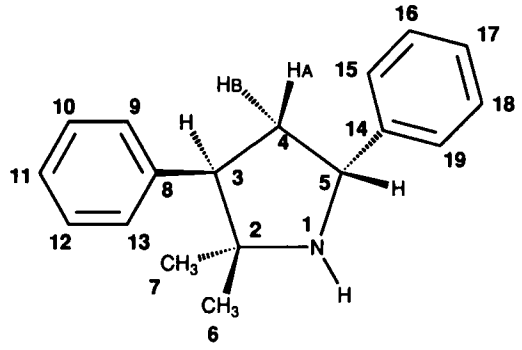


FIGURE 1 Numbering of compound **7**.

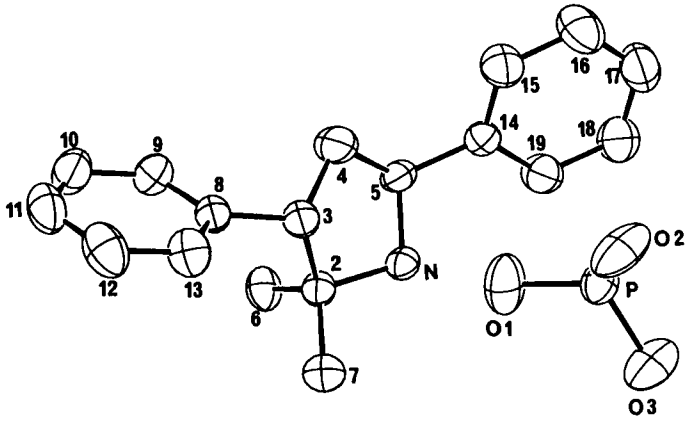


FIGURE 2 Perspective view (ORTEP) of compound **6**.

The $H_2PO_3^-$ anion is weakly co-ordinated to the nitrogen atom [O(1)···N(1) = 2.672 Å). The compound is composed of alignments of discrete ammonium and phosphite groups. The crystal packing is shown in Figure 3, the molecules are stacked in columns as cation-anion-anion-cation. The shortest intermolecular distances between these anions is [$O(2)^{i}\cdots O(3)^{ii}$ = 2.573 Å].

After treatment of the aqueous solution of **6** with base, the free amine was isolated and its relative stereochemistry studied by ^{1}H NMR. The amine was isolated as a solid. Such a compound has already been described by Kloetzel in 1947.[11] Direct examination of the 400 MHz ^{1}H NMR spectra did not allow a complete assignment of all the signals. However, this was realized by the NOESY procedure, which unambiguously confirmed the stereochemistry obtained by X-ray studies of the salt.

The outcome of the reaction between **1** and **5** was partly surprising. Indeed, deoxygenation of nitrones can be efficiently performed by triphenylphosphine and leads to the corresponding imine. Provided the nitrone is easily accessible, that sequence can afford an easy access to imines.[10] By analogy, reduction of the nitrone **5** by TSP would not be surprising. Moreover, the apparently surprising difference of reactivity in the pyrroline-N-oxides as a function of the substitution pattern of

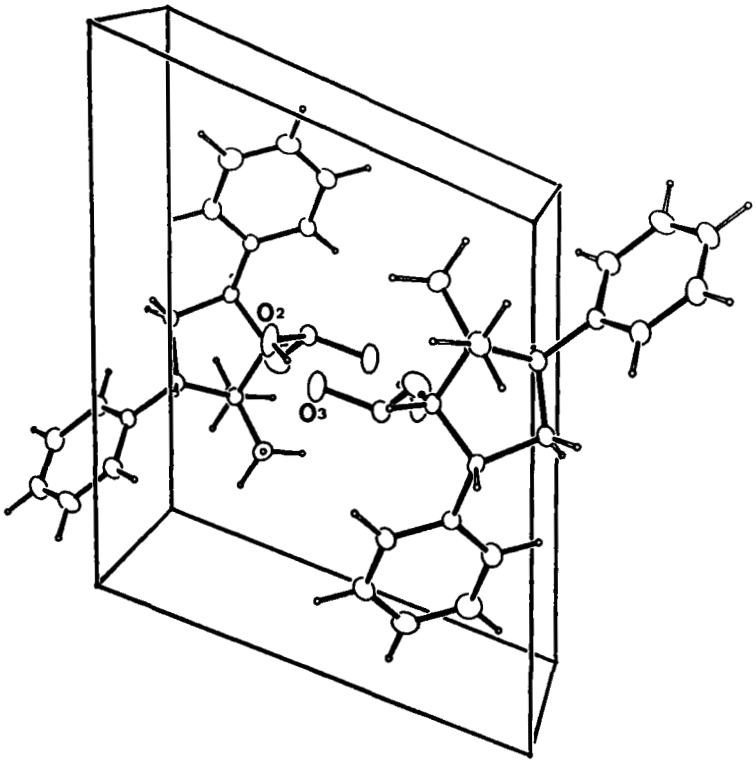
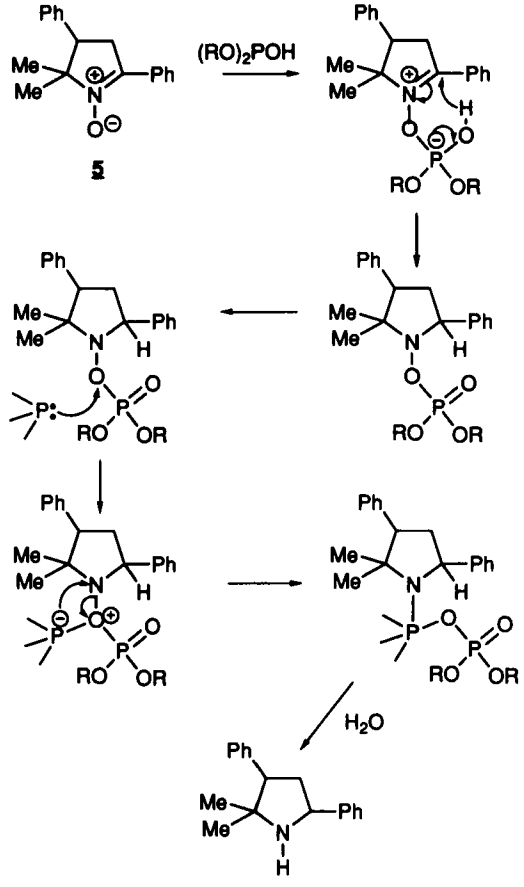


FIGURE 3 Stereopacking diagram of the molecules of **6**.

the C-2 atom had already been described in their reaction with Ph_3P. Nitrones **2–4** were unreactive towards Ph_3P, while **5** was reduced to the imine. In the present study, the only product found in nearly quantitative yield was the amine and not the imine.

^{31}P NMR examination of the $(TMSO)_3P$ reagent, from commercial origin, indicated the presence of two signals: δ 112.6 ppm and a second signal at δ −14.6 ppm indicative of the presence of $(TMSO)_2POH$ **8**.[12] This could explain the origin of the proton introduced on C-2. The presence of the disilyl ester leads to suggest a possible mechanism for this reaction as indicated in Scheme 1. The deoxygenation of the nitrone can be performed by either the phosphite **1** or the disilylphosphite **8**. However, the second step must involve a hydride transfer from the phosphite to the intermediate imine. This can only be performed by **8**, already present in small amounts in the reagent (from the ^{31}P NMR) and which can be produced *in situ* by mild hydrolysis of the trisilyl phosphite by traces of water. Eventually, during the aqueous work-up, the silylphosphite is hydrolyzed and due to the pKa difference (H_3PO_4, pKa 2.12 and H_3PO_3, pKa 1.8), only the orthophosphite salt is formed.

To the best of our knowledge, the reaction we are reporting represents a fairly unique example of hydrogen transfer from a phosphite as a hydride. Indeed, a



SCHEME 1 Mechanism of the phosphite-mediated deoxygenation and reduction.

variety of imines have been shown to react with TMS esters of phosphorus derivatives to lead only to α-aminophosphonic acid derivatives.[13,14]

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AM 400 X spectrometer and the chemical shifts (δ) in ppm referred to internal TMS. Proton-decoupled ^{31}P NMR spectra were recorded on a Bruker AC 100 at 40.54 MHz and the chemical shifts (δ) referred to external 85% H_3PO_4. All J values are given in Hz.

2,2-Dimethyl-3,5-trans-diphenylpyrrolidinium orthophosphite **6**

Tris(trimethylsilyl)phosphite **1** (1.6 g, 2 ml, 5.35 mmoles) was slowly added over 10 minutes to a solution of 5,5-dimethyl-2,4-diphenylpyrroline N-oxide **5** (0.5 g, 1.8 mmole) in 50 ml of anhydrous dichloromethane under an atmosphere of nitrogen. The mixture was stirred for 4 h at room temperature. Water (50 ml) was added. After extraction, the aqueous phase was kept overnight in the refrigerator. After filtration, white crystals of **6** were obtained (0.6 g, 95%), m.p. 240–241°C, ^{31}P NMR (CD_3OD): δ 4.2 ppm; (Anal. Found C, 64.66; H, 7.18; N, 3.95%. $C_{18}H_{24}NO_3P$ requires C, 64.86; H, 7.20; N, 4.24%).

TABLE I

Crystal data, data collection and refinement parameters

Formula	$C_{18}H_{24}NO_3P$
M	333.37
Crystallization	water
Crystal System	triclinic
Space group	P_1^-
Crystal size/ mm	0.3 x 0.3 x 0.4
a/ Å	8.806 (4)
b/ Å	10.331 (1)
c/ Å	11.375 (5)
α	65.55 (6)
β	88.21 (4)
γ	67.80(6)
V/ Å^3	866.5(4)
Z	2
Dc/ g. cm^{-1}	1.278
F (000)	356
Diffractometer	Enraf-Nonius CAD4
Wavelength	λ Mo K_α/ 0.71069 Å
μ (Mo K_α)/ cm^{-1}	1.666
Monochromator	Graphite
Scan type; Θ_{max}	Θ - 2Θ; 24°
Scan range Θ/ deg.	1 - 24
h,k,l range	-10/ 10; -11/ 11; 0/ 13
Number of reflections:	
- measured	2818
- unique	2543
- used in refinement	2229 (>3σ)
Number of variables	208
R and R_W	0.044; 0.046
W	$1/\sigma^2$, P=0.04
Goodness of fit	0.588
Max shift	0.01
H atoms	NH_2 hydrogen and one hydrogen of PO_3H_2 were localized on a Fourier map and refined. All other hydrogen positions were calculated, not refined.

2,2-Dimethyl-3,5-trans-diphenylpyrrolidine **7**

A cooled solution of **6** (0.1 g, 0.3 mmole) in water (50 ml) was slowly treated with 2 N aqueous sodium hydroxide (10 ml). The mixture was stirred for 1 h at room temperature and then extracted with ether (50 ml). The organic phase was dried over sodium sulfate and evaporated under reduced pressure to afford a white powder. Recrystallisation from light petroleum gave white crystals (0.068 g, 90%), m.p. 70–71°C (lit. 66–70°C), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, s, H-6), 1.29 (3H, s, H-7), 1.87 (1H, br s, NH), 2.24 (1H, ddd, $J_{4A,4B}$ 13.4, $J_{4A,3}$ 8.8, $J_{4A,5}$ 4.7, H-4A), 2.79 (1H, ddd, $J_{4B,4A}$ 13.3, $J_{4B,3}$ 11.9, $J_{4B,5}$ 9.5, H-4B), 3.14 (1H, dd, $J_{3,4B}$ 10.8, $J_{3,4A}$ 8.8, H-3), 4.54 (1H, dd, $J_{5,4B}$ 9.5, $J_{5,4A}$ 4.7, H-5), 7.20–

TABLE II

Bond angles in degrees with e.s.d.s

O(1)-P(1)-O(2)	111.2 (1)	C(3)-C(8)-C(9)	123.2 (2)
O(1)-P(1)-O(3)	108.7 (1)	C(3)-C(8)-C(13)	118.8 (2)
O(2)-P(1)-O(3)	117.6 (1)	C(9)-C(8)-C(13)	118.0 (2)
C(2)-N(1)-C(5)	106.2 (1)	C(8)-C(9)-C(10)	120.4 (2)
N(1)-C(2)-C(3)	98.8 (2)	C(9)-C(10)-C(11)	120.4 (2)
N(1)-C(2)-C(6)	109.4 (2)	C(10)-C(11)-C(12)	119.8 (2)
N(1)-C(2)-C(7)	108.8 (1)	C(11)-C(12)-C(13)	120.2 (3)
C(3)-C(2)-C(6)	114.3 (2)	C(8)-C(13)-C(12)	121.1 (2)
C(3)-C(2)-C(7)	113.6 (2)	C(5)-C(14)-C(15)	121.8 (2)
C(6)-C(2)-C(7)	111.1 (2)	C(5)-C(14)-C(19)	119.8 (3)
C(2)-C(3)-C(4)	104.5 (2)	C(15)-C(14)-C(19)	118.3 (2)
C(2)-C(3)-C(8)	115.6 (2)	C(14)-C(15)-C(16)	120.3 (2)
C(4)-C(3)-C(8)	116.6 (2)	C(15)-C(16)-C(17)	121.1 (3)
C(3)-C(4)-C(5)	106.2 (2)	C(16)-C(17)-C(18)	118.7 (3)
N(1)-C(5)-C(4)	103.6 (2)	C(17)-C(18)-C(19)	120.7 (2)
N(1)-C(5)-C(14)	110.0 (1)	C(14)-C(19)-C(18)	120.8 (3)
C(4)-C(5)-C(14)	118.4 (2)		

Numbers in parentheses are estimated standard deviations in the least significant digit.

7.38 (8H, m, ArH) and 7.40–7.50 (2H, m, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 63.03 (C-2), 58.85 (C-5), 55.8 (C-3), 39.48 (C-4); (Anal. Found C, 86.0; H, 8.43; N, 5.50%. $C_{18}H_{21}N$ requires C, 86.05; H, 8.36; N, 5.57%).

X-ray determination: Intensity data were obtained on an Enraf-Nonius CAD4 diffractometer with a graphite incident-beam monochromator using Mo K_α radiation for a white crystal of **6** at room temperature. The cell parameters of triclinic unit cell were calculated by least squares from the setting angles of 25 reflections. Two reference reflections measured every 60 min showed no decay during the X-ray exposure time, total loss of gain intensity was -1.5%. The data were corrected for Lp but not for absorption and secondary extinction, resulting in the unique set of 2229 with $I > 3\sigma(I)$ used in the structure determination.

All non-H atoms were found by direct methods (Frenz, 1978)[15] and the structure was refined successfully, with space group P_1^-, by full matrix least squares procedure using anisotropic thermal parameters for all non-H atoms. Atomic scattering factors are taken from *International Tables for X-ray crystallography* (Vol. IV, 1974).[16] The weighting scheme used was $1/\sigma^2(F_{obs})$ being derived from: $\sigma(I_{obs}) = [\sigma^2(I_{obs}) + (0.04I_{obs})^2]^{1/2}$. Final convergence was reached at $R = 0.044$, $R_w = 0.046$; $w = 1/\sigma^2(F)$; $(\Delta/\sigma)_{max} = 0.01$; number of refined parameters = 208 Residual $\Delta\rho_{max} = +0.524, -0.420$ eÅ^{-3} in a final Fourier-Difference synthesis. Further details of the crystal and data collection are reported in Table I. The bond angles are given in Table II, and the bond distances are summarized in Table III.

TABLE III

Bond distances in angstroems

P(1)-O(1)	1.558 (2)	C(8)-C(13)	1.388 (4)
P(1)-O(2)	1.468 (2)	C(9)-C(10)	1.401 (3)
P(1)-O(3)	1.500 (2)	C(10)-C(11)	1.364 (4)
N(1)-C(2)	1.514 (2)	C(11)-C(12)	1.362 (4)
N(1)-C(5)	1.514 (3)	C(12)-C(13)	1.385 (3)
C(2)-C(6)	1.516 (4)	C(14)-C(15)	1.378 (4)
C(2)-C(7)	1.515 (4)	C(14)-C(19)	1.384 (3)
C(3)-C(4)	1.539 (4)	C(15)-C(16)	1.396 (4)
C(3)-C(8)	1.510 (2)	C(16)-C(17)	1.361 (4)
C(4)-C(5)	1.535 (3)	C(17)-C(18)	1.378 (6)
C(5)-C(14)	1.521 (3)	C(18)-C(19)	1.380 (4)
C(8)-C(9)	1.375 (3)	H-H'	1.59 (4)

Numbers in parentheses are estimated standard deviations in the least significant digit.

ACKNOWLEDGEMENTS

We thank the "Ministère Algérien de l'Enseignement Supérieur" and the "Ministère Français des Affaires Etrangères" for financial support. We thank Dr. R. Faure for the NMR spectra and Dr. M. Pierrot (Université d'Aix-Marseille III) for his interest in this work.

REFERENCES

1. E. G. Janzen and R. A. Towner, *A critical review of spin trapping in biological systems*, in "Bioactive Spin Labels," R. I. Zhdanov, Ed., Springer Verlag, Heidelberg, pp. 573–583 (1992).
2. J. F. W. Keana, L. Lex, J. S. Mann, J. M. May, J. H. Park, S. Pou, V. S. Prabhu, G. M. Rosen, B. J. Sweetman and Y. Wu, *Pure Appl. Chem.*, **62,** 201 (1990).
3. W. Müller-Warmuth and K. Meise-Gresh, *Molecular motions and interactions as studied by dynamic nuclear polarization (DNP) in free radical solutions*, in "Advances in Magnetic Resonance," J. S. Waught, Ed., Academic Press, New York (1983).
4. P. Stipa, J.-P. Finet, F. Le Moigne and P. Tordo, *J. Org. Chem.*, **58,** 4465 (1993) and references therein.
5. P. Tordo, M. Boyer, A. Friedmann, O. Santero and L. Pujol, *J. Phys. Chem.*, **82,** 1742 (1978).
6. A. Mercier, Y. Berchadsky, Badrudin, S. Pietri and P. Tordo, *Tetrahedron Lett.*, **32,** 2125 (1991).
7. F. Le Moigne, A. Mercier and P. Tordo, *Tetrahedron Lett.*, **32,** 3841 (1991).
8. Y. Yamada and K. Mukai, *Tetrahedron Lett.*, **29,** 663 (1988).
9. R. Huber and A. Vasella, *Helv. Chim. Acta*, **70,** 1461 (1987); R. Huber and A. Vasella, *Tetrahedron*, **46,** 33 (1990).
10. J. B. Bapat and D. St. C. Black, *Aust. J. Chem.*, **21,** 2483 (1968).
11. M. C. Kloetzel, *J. Am. Chem. Soc.*, **69,** 2271 (1947).
12. L. Wozniak and J. Chojnowski, *Tetrahedron*, **45,** 2465 (1989).

13. K. Afarinkia, C. W. Rees and J. I. G. Cadogan, *Tetrahedron*, **46,** 7175 (1990).
14. K. Afarinkia, J. I. G. Cadogan and C. W. Rees, *Synlett*, 123 (1992); K. Afarinkia, J. I. G. Cadogan and C. W. Rees, *Synlett*, 124 (1992).
15. B. A. Frenz, *The Enraf-Nonius CAD-4 SDP-A Real Time System for Concurrent X-ray Data Collection and Crystal Structure Solution*, in "Computing in Crystallography," edited by H. Schenk, R. Olthof-Hazekamp, H. Van Konigsveld and G. C. Bassl, Delft University Press (1978).
16. J. Ibers and W. C. Hamilton, Eds. *International Tables for X-ray Crystallography*. Vol. IV. Kynoch Press, Birmingham (Present distributor Kluwer Academic Publishers, Dordecht) (1974).