SYNTHESIS OF 3-OXO-3-PHENYL-2,2,5-TRIMETHYL-1,3-OXAPHOSPHORINANES AND THEIR TETRAFLUOROBORATE SALTS

SUSANA LÓPEZ CORTINA*, PERLA ELIZONDO MARTÍNEZ, NANCY PÉREZ RODRIGUEZ, EUGENIO HERNÁNDEZ FERNÁNDEZ
Facultad de Ciencias Químicas, Universidad Autónoma de Nuevo León, Av. Universidad s/n, Cd. Universitaria, 66451, San Nicolás de los Garza, Nuevo León, México.
**e-mail: susalas75@gmail.com*

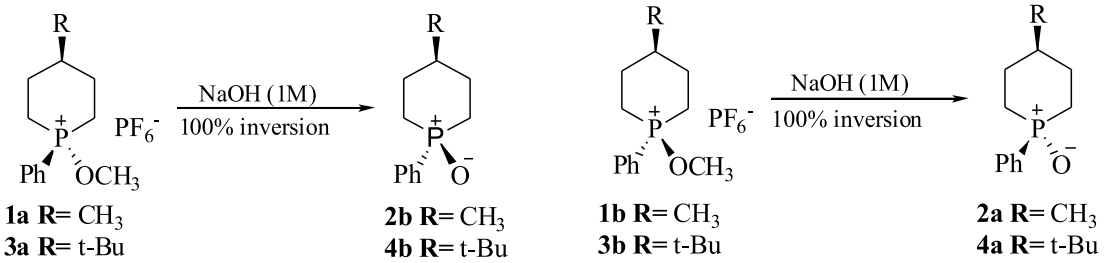
MARIO FERNÁNDEZ ZERTUCHE
Centro de Investigaciones Químicas, Universidad Autónoma del Edo. de Morelos, Av. Universidad 1001, Col. Chamilpa, 62209, Cuernavaca, Morelos, México.

Abstract

The synthesis and characterization of *cis*- and *trans*- 3-oxo-3-phenyl-2,2,5-trimethyl-1,3-oxaphosphorinanes (7a and 7b) and their corresponding tetrafluoroborate salts (3a and 3b), heterocyclic organophosphorus compounds not previously reported in the literature, was accomplished. They were fully characterized by ^{1}H, ^{13}C and ^{31}P NMR. It was established the relative configuration of these compounds on the basis of an X-ray diffraction study of oxide 7a.

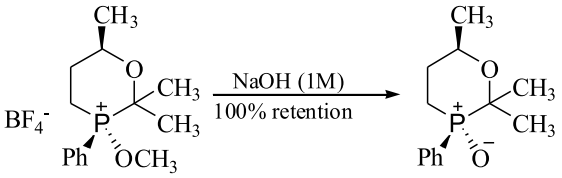
1. Introduction

Phosphorus-containing compounds and their chemistry have gained considerable attention as a result of their biological and chemical profiles [1,2]. The most frequently encountered reactions in phosphorus chemistry are nucleophilic substitutions; such reactions at tetravalent phosphorus centers are involved in a number of cellular energetic and biosynthesis processes [3]. In this context, quaternary phosphonium salts undergo nucleophilic displacement reactions induced by aqueous hydroxide ion to yield phosphine oxides [4] and with few exceptions, these reactions have shown inversion of configuration at phosphorus as the stereochemical course [5]. In cyclic phosphonium salts, however, the stereochemical behavior is much more complex, in six-membered rings the most studied leaving groups have been the benzyl and the methoxy groups attached to the phosphorus atom. When the benzyl group is used as the leaving group, the reaction with base is non-stereospecific yielding phosphine oxides as mixtures of different proportions [6]. However, when the more electronegative methoxy group is used as the leaving group, pure samples of *cis* and *trans* 4-methyl (**1a** and **1b**) or 4-*t*-butyl (**3a** and **3b**) afford the corresponding phosphine oxides **2** or **4** (Scheme 1) with complete inversion of configuration at phosphorus [7].

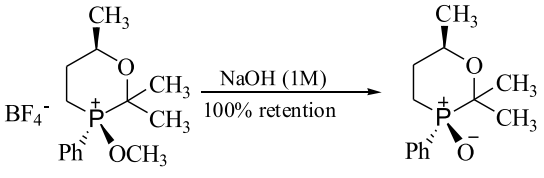


Scheme 1. Stereochemical behavior of phosphorinanium salts.

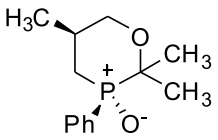
We have reported our results about the hydroxide-induced displacement of the methoxy groups on samples of pure *cis* and *trans* isomers of 3-methoxy-2,2,6-trimethyl-3-phenyl-1,3-oxaphosphorinanium tetrafluoroborate salts 5a and 5b (Scheme 2), systems designed to study the effect of a second heteroatom in the ring system on the stereochemistry of the reaction. In our study, the presence of the oxygen atom induces a different stereochemical outcome since 5a and 5b reacted with base to yield the phosphine oxides 6a and 6b with complete retention of configuration at phosphorus [8]. This study contrasts with the results observed in five-membered rings where the presence of the oxygen has no effect on the stereochemistry of the reaction [9].



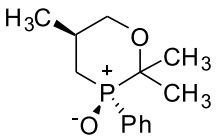
5a **6a**



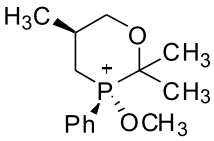
5b **6b**



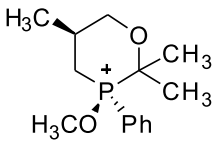
7a



7b



8a



8b

2.1.2 Synthesis and separation of *cis*- and *trans*- 3-oxo-3-phenyl-2,2,5-trimethyl-1,3-oxaphosphorinane, 7. 3-hydroxy-2-methylpropylphenylphosphine, **11** (1g, 5.49 mmol), dissolved in 30 mL of benzene, was mixed with 8.1 mL (0.11 mol) of anhydrous acetone, then 0.05 g (0.29 mmol) of dried *p*-toluensulfonic acidwas added [11]. The reaction mixture was refluxed at 100°C for 42 h using a Dean-Stark trap. At this point an additional portion (5.45 mL, 0.074 mol) of acetone was added and the reaction mixture was kept at reflux for an additional period of 50 h. After removal of the solvent, oxidation of the crude product was carried out by dissolving the material in 20 mL of benzene and adding at 0°C, 1.1 mL (5.54 mmol) of 5.0M *tert*-butylhydroperoxide in decane [12]. After the addition was completed, the reaction was allowed to reach room temperature and was stirred overnight at this temperature. The solvent was evaporated in *vacuo* and the crude product purified by flash column (silica-gel/ dichloromethane-isopropanol 90-10) to give 0.14g (13% yield) of the diasteromeric oxides of **7**. The mixture was separated by chromatographic column (silica gel 230-400/ dichloromethane-isopropanol 95-5), obtaining isomerically pure samples of *cis*- and *trans*- oxides. **3-oxo-*r*-3-phenyl-2,2,*c*-5-trimethyl-1,3-oxaphosphorinane, 7a**. ^{31}P NMR ($CDCl_3$) +30.420; ^{1}H NMR ($CDCl_3$) 1.03 (dd, J = 6.6, J = 2.2, 3H), 1.26 (d, J = 13.6, 3H), 1.40 (d, J = 12 Hz, 3H), 2.12 (m, 2H), 2.73 (m, 1H), 3.51 (dd, J = 12.2, J = 11.8, 1H), 3.81 (m, J = 12.2, J = 4.5, J = 2.05, J = 2.05, 1H), 7.49 (m, 2H), 7.55 (m, 1H), 7.77 (m, 2H); ^{13}C NMR ($CDCl_3$) 19.16 (d, J = 13.77), 21.36 (d, J = 12.26), 23.13 (s), 28.07 (d, J = 4.52), 29.49 (d, J = 61.12), 68.86 (d, J = 4.52), 73.93 (d, J =76.30), 128.79 (d, J = 10.66), 130.18 (s), 131.47 (d, J = 9.15), 132.35 (s). Anal. Calcd for $C_{13}H_{19}O_2P$: C, 65.53; H, 8.037. Found: C, 65.33; H, 7.81. **3-oxo-*r*-3-phenyl-2,2,*t*-5-trimethyl-1,3-oxaphosphorinane, 7b**. ^{31}P NMR ($CDCl_3$) +29.17; ^{1}H NMR ($CDCl_3$) 0.945 (dd, J = 6.4, J = 2.8, 3H), 1.27 (d, J=13.2, 3H), 1.66 (d, J = 11.2, 3H), 2.0 (m, 2H), 2.40 (m, 1H), 3.51 (dd, J = 11.9, 1H), 3.76 (m, J = 12.47, J = 4.28, J = 2.1, J = 2.1, 1H), 7.51 (m, 3H), 8.10 (m, 2H); ^{13}C NMR ($CDCl_3$) 18.81 (d, J = 13.67), 19.86 (d, J = 7.64), 24.12 (d, J = 3.015), 32.0 (d, J = 4.62), 33.06 (d, J = 56.39), 67.89 (d, J = 5.63), 73.72 (d, J =77.81), 128.47 (d, J = 10.66), 131.04 (s), 131.87 (s), 132.21 (s). Anal. Calcd for $C_{13}H_{19}O_2P$: C, 65.53; H, 8.037. Found: C, 65.6; H, 8.15.

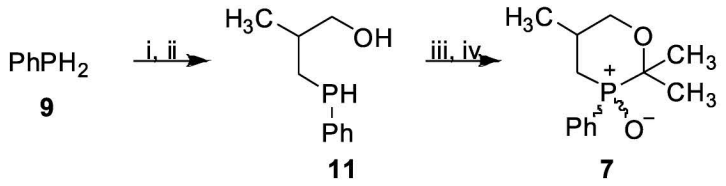
2.1.3 Synthesis of *cis*- and *trans*- 3-methoxy-3-phenyl-2,2,5-trimethyl-1,3-oxaphosphorinanium tetrafluoroborate, 8. For the preparation of the *cis* isomer **8a**, 0.039 g (0.164 mmol) of the *cis* phosphine oxide **7a** was dissolved in 20 mL of dry methylene chloride. This solution was added to a suspension of 0.032 g (0.216 mmol) of trimethyloxonium tetrafluoroborate in dry methylene chloride and the resulting mixture was stirred at room temperature for 6 h. The solution was evaporated to dryness *in vacuo* to give 0.044g (79% yield) of the *cis* isomer, **8a**, ^{31}P NMR ($CDCl_3$) δ +72.43; ^{1}H NMR ($CDCl_3$) 1.09 (dd, J = 6.4, J = 2.8, 3H), 1.31 (d, J = 16.4, 3H), 1.48 (d, J = 12.8, 3H), 2.55 (m, 3H), 3.52 (dd, J = 12.0, J = 11.9, 1H), 4.03 (d, J = 11.4 , 3H), 7.73 (m, 5H). *Trans* isomer **8b**, was prepared in a similar way from **7b** (*trans* oxide), evaporation of the solvent afforded 0.038g (68% yield) of *trans* isomer **8b**, ^{31}P NMR ($CDCl_3$) +68.30; ^{1}H NMR ($CDCl_3$) 1.04 (dd, J = 5.8, J = 3.5, 3H), 1.39 (d, J = 16.6, 3H), 1.8 (d, J = 14.0, 3H), 3.05 (m, 3H), 3.78 (m, 2H), 4.1 (d, J = 11.4, 3H), 7.82 (m, 5H).

2.2 Crystal data of 3-oxo-*r*-3-phenyl-2,2,*c*-5-trimethyl-1,3-oxaphosphorinane, 7a.

Empirical formula	$C_{13}H_{19}O_2P$	
Formula weight	238.25	
Temperature	273(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 9.6486(11) Å	α= 90°
	b = 14.6240(16) Å	β= 92.126(3)°
	c = 18.430(2) Å	γ = 90°
Volume	2598.7(5) $Å^3$	
Z	8	
Density (calculated)	1.218 Mg/m^3	
Absorption coefficient	0.196 mm^{-1}	
F(000)	1024	
Crystal size	0.21 x 0.37 x 0.39 mm^3	
Theta range for data collection	1.78 to 28.25°	
Index ranges	-12<=h<=12, -14<=k<=18, -12<=l<=23	
Reflections collected	10366	
Independent reflections	5734 [R(int) = 0.0147]	
Completeness to theta = 28.25°	89.2 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5734 / 0 / 295	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2sigma(I)]	R1 = 0.0358, wR2 = 0.0973	
R indices (all data)	R1 = 0.0391, wR2 = 0.0997	
Largest diff. peak and hole	0.504 and -0.328 $e.Å^{-3}$	

3. Results and discussion

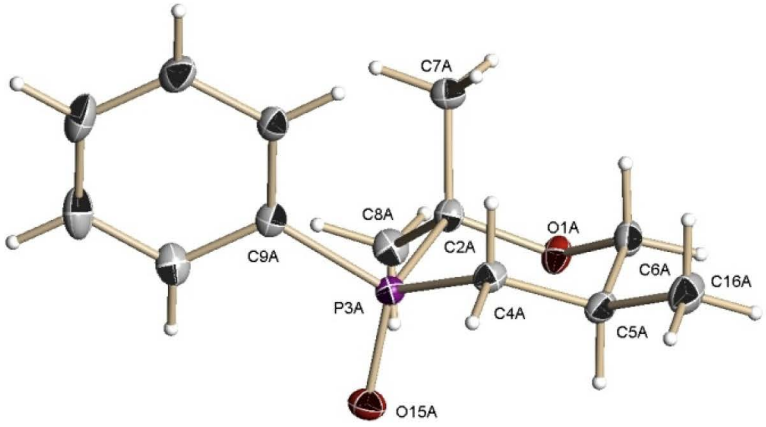
The synthesis of 1,3-oxaphosphorinane oxides 7 was accomplished following the proposed synthetic route (Scheme 3) in which 3-hydroxy-2-methylpropylphenylphosphine was prepared by the ring opening reaction of 3-methyloxetane, 10, (prepared by an adaptation of the Searles' procedure [13]), by the lithium salt of phenylphosphine, 9 (synthesized by reduction of dichlorophenylphospine [14]). This procedure allowed us to obtain compound 11 (38 % yield). The following cyclization toward phosphorinanes oxides 7, was carried out by an adaptation of Oheme's procedure [15], as we have previously published for the synthesis of 1,3-oxaphosphorinane oxides using acetone as dimethyl group provider in the presence of *p*-toluensulphonic acid, followed by an oxidation using *tert*-butylhydroperoxide in benzene. The mixture of *cis*- and - diastereoisomers of the desired 1,3-oxaphosphorinanes was obtained (13 % yield).



(i) *n*-BuLi, THF, 0°C; (ii) 3-methyloxetane, **10**, -78°C;
(iii) *p*-TsOH, acetone, C_6H_6; (iv) *t*-BuOOH, C_6H_6

The separation of the diastereomeric mixture of oxides 7 was accomplished by column chromatography (Scheme 4) leading to diastereoisomers 7a and 7b in a very pure form.

Both compounds were fully characterized by NMR spectroscopy; however, the relative stereochemistry of these diastereoisomers 7a and 7b were established by X-ray crystal structure determinations on isomer 7a. Figure 2 shows the X-ray crystal structure of this compound (*cis* isomer). Unfortunately, an appropriate crystal of 7b could not be obtained for X-ray studies, however, its relative configuration (*trans* isomer) was established indirectly by the crystal structure of isomer 7a.



In the X-ray crystal structure of 7a (Figure 2) it can be observed the methyl group at C(5) and the phenyl substituent at phosphorus both oriented in equatorial position, establishing a *cis* relationship between them. It is then assumed that in isomer 7b, these groups must have a *trans* relationship. The fact that the six-membered ring adopts a flattened chair conformation at the phosphorus end, is suggested by the analysis of this region based on the torsional angles that involves the central fragment P(3)-C(2), which shows angles of approximately 20° degrees far from the ideal gauche conformation angle (60°) or anti conformation angle (180°).

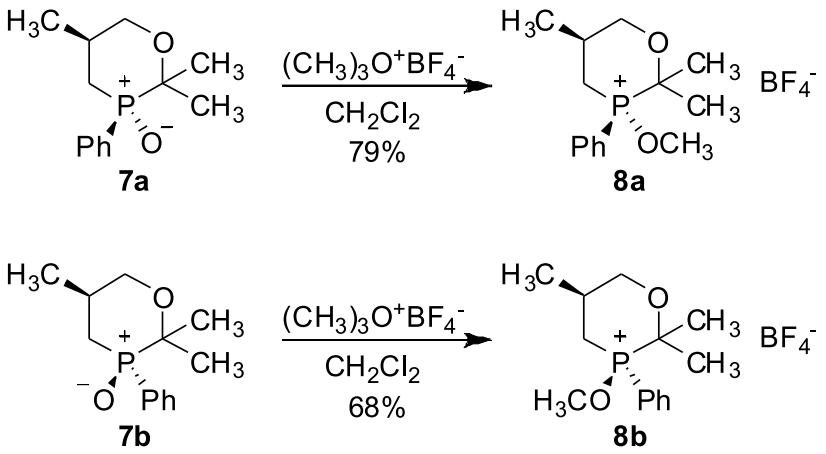
In addition, the O(1)-C(6)-C(5)-C(4) torsion angle at nearly 60° (63.64°) and the C(16)-C(5)-C(6)-O(1) torsion angle at nearly 180° show a normal chair-like conformation at C(5) and C(6). Incidentally, this latter angle (174.26°) also proves that the methyl group at C(5) occupies an equatorial position in 7a.

It has been known that an equatorial phenyl group assumes a conformation in which it is parallel to the symmetry plane of the chair-shaped cyclohexane ring [16]. This could also applies for some 1-phenyl-phosphorinane derivatives [17]. In compound 7a, torsional angles having P(3)-C(9) as central fragment show values close to the expected conformation with the phenyl group parallel to the phosphorinane ring. Although transferring this behavior for the isomers in solution is not possible, one might expect that equatorial phenyl rings in 7a are almost free to rotate, presumably, the presence of the methyl groups at C(2) and the ring oxygen both placed near to the phenyl group, should be noticed in order to propose a conformational behavior in solution, however, this cannot be determined based only on the data reported here.

The ^{1}H NMR spectra of these compounds support a configurational assignment in which the methyl group at C(5) occupies an equatorial position in both isomers since a four bond coupling constants for the CH_3 protons and phosphorus atom are observed, with values of 2.2 Hz for 7a and of 2.8 Hz for 7b. Additionaly, the coupling constants involving H_{6axial} in both isomers support the equatorial position of methyl group at C(5), in *cis* isomer, 7a, it could be clearly observed a geminal coupling with $H_{6equatorial}$ of 12.2 Hz and an axial-axial coupling with H_{5axial} of 11.8 Hz, values closed to the reported data of ciclohexanes. Special attention was given to $H_{6equatorial}$ signal at 3.81ppm, which presents a clear multiplicity of dddd, the first doublet of 12.2 Hz was assigned for the $H_{6equatorial}$-H_{6axial} coupling also observed in H6axial signal, the second doublet of 4.5 Hz corresponds to the $H_{6equatorial}$-H_{5axial} coupling; it was also possible to observe a *W type* four bond coupling of 2.1 Hz for $H_{6equatorial}$-$H_{4equatorial}$ and finally another four bond coupling of 2.1 Hz for $H_{6equatorial-P}$. Similar analysis of the protons on C(6) could be made for *trans* isomer 7b.

The relationship between the C(2) methyl groups and the P=O group, provides additional support to our stereochemical assignment. The coupling constant (^{3}J) between these methyl groups and the phosphorus atom on the P=O function should have a lower magnitude when they have a *cis* disposition than when they have a *trans* disposition. In addition, the chemical shift of the methyl groups *cis* to the P=O functionality should be downfield than the chemical shift of the methyl groups *trans* to the P=O group [18].

Once the configurations of the phosphine oxides 7a and 7b were established, compounds 8a and 8b were obtained by direct methylation of 7a and 7b with trimethyloxonium tetrafluoroborate. The configuration of 8a and 8b was assigned based on the established configuration of their parents 7a and 7b and the known fact that methylation of phosphine oxides with trimethyloxonium tetrafluoroborate preceeds with retention of configuration at phosphorus (Scheme 5) [19]. Some key NMR signals were used for the structural determination of these compounds; for example, the signals for the methoxy groups on both isomers appear as doublets centered around 4.0 ppm as a result of the coupling of these protons with the adjacent phosphorus atom. Likewise, the $^{3}J_{P-OCH3)}$ coupling constants of 11.4 Hz for both isomers are in agreement with the values previously reported by Marsi for phosphorus cyclic compounds [7]. Finally, the ^{31}P NMR signals for each isomer appear at +72.43ppm for 8a and +68.3 ppm for 8b.



4. Conclusions

In this work, we have accomplished the synthesis of *cis*- and *trans*- 3-oxo-3-phenyl-2,2,5-trimethyl-1,3-oxaphosphorinanes (7a and 7b) and their corresponding tetrafluoroborate salts (8a and 8b), heterocyclic organophosphorus compounds not previously reported in the literature. They were fully characterized by ^{1}H, ^{13}C and ^{31}P NMR. A very important part in the characterization of 7a and 7b and indirectly of 8a and 8a was the establishment of the relative configuration of these compounds on the basis of an X-ray diffraction study of oxide 7a. Finally, tetrafluoroborate salts 8a and 8b reported here, could be considered as new target molecules for stereochemical behavior studies of base-induced cleavage, in order to determine the effect of the position of the methyl group on C(5) instead of on C(6) which was previously reported with complete retention of configuration at phosphorus [8].

5. Acknowledgments

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6. Appendix

Includes the following data: atomic coordinates and equivalent isotropic displacement parameters; bond lengths and angles; anisotropic displacement parameters; hydrogen coordinates and isotropic displacement parameters; torsion angles. This section is available at http://www.fcq.uanl.mx

7. References

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