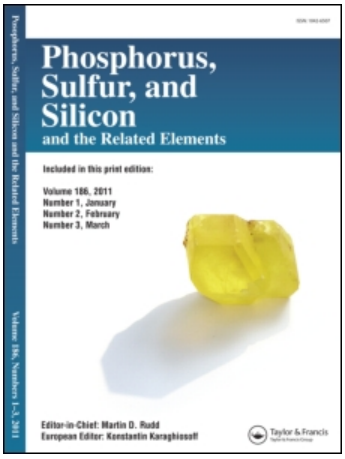

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 100. STEROSELECTIVE SYNTHESIS OF 2-SUBSTITUTed ISOXAZOLINYL METHYLPHOSPHONATES

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 100. STEROSELECTIVE SYNTHESIS OF 2-SUBSTITUTED ISOXAZOLINYL METHYLPHOSPHONATES*

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Reaction of dialkyl 1-hydroxy aminophosphonates with aldehydes leads to a nitrone bearing phosphonate moiety. The phosphoryl nitrone thus obtained provides (Z) 2-substituted isoxazolinyl methylphosphonates upon reaction with maleic anhydride as a 1,3-dipolar cycloaddition product.

Keywords: Phosphoryl nitrone; 1,3-dipolar cycloaddition; stereo-selective; dihydroisoxazole

INTRODUCTION

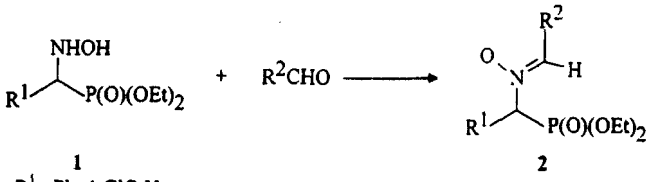
As one of the most important reactive species, nitrones are capable of reaction with carbanions of various types to furnish a Reformatsky product. Another unique chemical feature of nitrone is the ability to undergo [3+2] cycloaddition with a dipolarphile. The synthetic concept related to the formation of five-membered ring heterocycles based on the dipolar cycloaddition of nitrone was extensively reported by Huisgen and coworkers.[1,2] We are very interested in the chemical behavior of a nitrone bearing a phosphonate moiety, since this is capable of providing phosphorylated heterocycles by an analogues reaction pathway. Phosphorylated heterocycles are difficult to obtain because the conventional methods for the formation of carbon-phosphorus bonds have proved to be impractical.[3] Nevertheless, phosphorylated nitrones have not, to the best of our knowledge, been studied yet. In this paper we demonstrate that the reaction of a

* The paper is dedicated to Professor Robert Wolf for his fine contribution to organophosphorus chemistry.

1-hydroxy aminophosphonate and aldehyde will result in a new phosphorylated nitrone which is then to give 2-substituted isoxazolinyl methylphosphonate after reaction with maleic anhydride via 1,3-dipolar cycloaddition.

RESULTS AND DISCUSSION

The reaction of diethyl 1-hydroxyaminoalkyl(aryl)phosphonate (**1**) and an aldehyde under reflux in ethanol for 4-12 hours gave a new phosphorylnitrone, namely 1-alkyl(aryl)-N-[1'-(O,O-diethylphosphoryl)]-1'-aryl methylnitrone (**2**). The latter, as an acyclic aldonitrone, is considered to be in the Z configuration.[4] and obtained in satisfactory yield. The ^{1}H- and ^{31}P-NMR data clearly demonstrated that **2** is the sole Z-isomer. The ^{1}H-NMR gave a singlet for N=C-H located between 7.1 and 8.3 ppm. The ^{31}P-NMR of 2 displayed a single peak in the 15 ppm region. (Scheme 1 and Table I).



1

R^1= Ph, 4-ClC_6H_4
R^2= Et, Ph, 4-$MeOC_6H_4$, 4-FC_6H_4

2

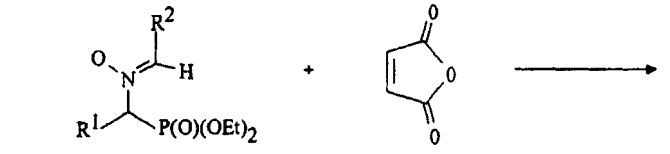
SCHEME 1

TABLE I Synthesis of phosphoryl nitrone

Entry	*Nitrone*	R^1	R^2	*Yield*
1	**2a**	Ph	Et	46
2	**2b**	Ph	Ph	69
3	**2c**	Ph	4-$MeOC_6H_4$	65
4	**2d**	4-ClC_6H_4	4-$MeOC_6H_4$	51
5	**2e**	4-ClC_6H_4	4-FC_6H_4	41

As a characteristic reaction of the nitrone, the phosphoryl nitrone **2** underwent cycloaddition with maleic anhydride to form an isoxazoline derivative stereoselectively, 2-[1'-(O,O-diethylphosphoryl)alkane]-3-aryl-4,5-dicarboxylisoxazoline (**3**). Generally, during 1,3-dipolar cycloadditions, a nitrone is capable of

forming four regeoisomers with unsymmetric alkenes. The symmetric alkene derivative, maleic anhydride, can only give two stereoisomers with a nitrone. As shown in Scheme 2 for **3d**, two stereoisomers, 3,4-(Z) **3d** and 3,4-(E) **3d**, could be formulated. (Scheme 2, Table 2)



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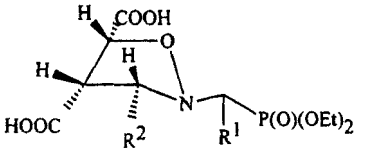
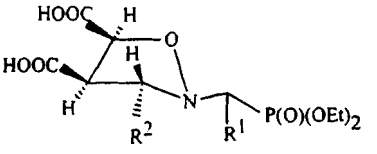


3,4-(Z) **3**



3,4-(E) **3**

b: R^1= Ph, R^2=Ph
c: R^1= Ph, R^2= 4-$MeOC_6H_4$
d: R^1= 4-ClC_6H_4, R^2=4-$MeOC_6H_4$

SCHEME 2

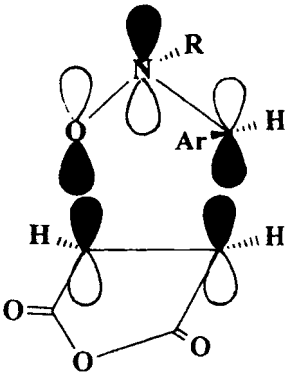
TABLE II Synthesis of 2-substituted isoxazolinyl methylphosphonates

Entry	*Isoxazoines*	R^1	R^2	*Yield(%)*
1	**3b**	Ph	Ph	45
2	**3c**	Ph	4-$MeOC_6H_4$	40
3	**3d**	4-ClC_6H_4	4-$MeOC_6H_4$	46

The structure of 3,4-(Z) **3d** was elucidated as follows. The appearence of a single peak at 18.6 ppm in the ^{31}P-NMR spectrum demonstrated that only one stereoisomer was formed during the cycloaddition.

However, as shown by the ^{1}H-NMR spectrum of the reaction product, the doublet of the proton in CHP was located at a higher field (4.49 ppm) than that in parent nitrone **2d** (5.5ppm). The coupling constants of two protons at positions 5 and 3 are 7.25 and 7.41 Hz respectively. These data differ enormously with the literature values reported for analogues (E) and (Z) isomers of isoxazolines with-

out a phosphoryl group.[5,6] Consequently, the conventional proton NMR spectroscopic investigation was unable to establish the configuration of compound **2d**. However, with the aid of a two dimensional NOESY technique, the configuration of the Z and E isomers was established. A marked enhanced NOE effect of protons at position 3,4,5 should be observed, if **3d** possessed the 3,4 (E) configuration. Unfortunately, experimental spectroscopic data show that there is no enhancement for protons at positions 3, 4 and 5 of compound **3d**. Consequently, those protons located on the 3 and 4 positions have a Z configuration. The high stereoselectivity of this 1,3 dipolar cycloaddition could be rationalized using frontier molecular orbital (FMO) theory as represented by the following diagram.



LUMO

HOMO

This diagram clearly demonstrated that interaction of the LUMO of phosphoryl nitrone **2** with the HOMO of maleic anhydride is favorable to form the thermodynamically more stable 3,4-(Z) **3d** due to the presence of a bulky phosphoryl group.

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded on a Shimadzu IR-440 or Perkin-Elmer 983G or Digilab FTS/20E spectrophotometer. ^{1}H-NMR Spectra were taken on a Varian EM-360L (60 MHz), FX90Q (90MHz), XL-200 or Bruker AM-300 using TMS as an external standard. Proton decoupled ^{31}P-NMR spectra were measured on a Varian FX-90Q or Bruker AM-300 ; 85 % H_3PO_4 was used as an internal reference standard. Both ^{13}C-NMR and 2-D NOE spectra (NOESY) were recorded on a BrukerAM-300 apparatus. MS was taken on a Finnigan MAT 4201 mass spectmeter (EI or FAB technique).

Synthesis of phosphoryl nitrones by condensation of 1-hydroxyaminoalkyl(aryl)phosphonates with an aldehyde.

(Z) **2a** A solution of diethyl 1-(hydroxyamino)-benzylphosphonate[7] (**1a**) (1.5 g, 5.8 mmole) and freshly distilled n-propylaldehyde (11.5 mmole) in ethanol (20 mL) was heated under stirring at 47°C for 24 h. Removal of solvent gave a viscous liquid which was then separated by silica-gel(200-300 mesh) column chromatography. Upon eluction with ethyl acetate and methanol a colorless powder (0.8 g) was obtained. Yield 46 %, mp 82-84°C. IR(KCl) ν ; 1580(C=N), 1250(P=O), 1145(N-O), 1015(P-O-C)cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0,8-1.75 (m, 9H), 2.2-2.95 (m, 2H), 3.95-4.6(m, 4H), 5.4(d, 1H, $^2J_{PH}$=19Hz), 7.1(t, 1H, J=6 Hz, CH=N), 7.3-7.65 (m, $3H_{arom}$), 7.68-8.0 (m, $2H_{arom}$). ^{31}P-NMR δ : 15.34 ppm. MS(EI) m/z=299. Elemental analyses $C_{14}H_{22}NO_4P$. Calc. % C 56.17, H 7.41, N 4.68. Found % C 55.79, H 7.37, N 4.56.

(Z) **2b** An equimolecular (6 mmole) **1a** and freshly distilled aromatic aldehyde was dissolved in anhydrous ethanol (20 mL) and the mixture was heated with stirring for 4h. Removal of solvent resulted colorless solid which was then recrystallized from ethylacetate and petroleum ether. (Z) **2b** yield 69 %, mp 159-161°C. IR(KBr) ν : 1620(C=N), 1240(P=O), 1140(N-O), 1010(P-O-C)cm^{-1}. ^{1}H-NMR($CDCl_3$) δ : 1.1-1.45 (m, 6H), 3.9-4.5 (m, 4H), 5.5 (d, 1H, J=20 Hz), 7.2-7.6 (m, 8H), 7.7-8.1 (m, 2H), 8.3 (s, 1H, CH=N)ppm. Elemental analyses $C_{18}H_{22}NO_4P$(347.4) Calc. % C 62.23, H 6.40, N 4.03. Found % C 61.89, H 6.22, N 3.84.

(Z) **2c** By reaction of **1a** and p-methoxybenzyl aldehtde, (Z)**2c** was obtained in 65 % yield. Method analogous to that for (Z) **2b**. mp.149-151°C IR (KCl) ν : 1610(C=N), 1240(P=O), 1135(N-O), 1025(P-O-C)cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 Hz) δ : 1.0-1.4 (m, 6H), 3.8 (s, 3H), 3.9-4.4 (m, 4H), 5.4 (d, 1H, J=19 Hz), 6.85 (d, 2H, J=9 Hz), 7.2-7.5 (m, 3H), 7.55-7.9 (m, 3H, CH=N,$2H_{arom}$), 8.2 (d, 2H, J=9Hz) ppm. ^{31}P-NMR($CDCl_3$) 15.78 ppm. MS(EI 70ev) m/z=377. Elemental Analyses $C_{19}H_{24}NO_5P$(378.4) Calc. % C 60.31, H 6.34, N 6.37. Found % C 60.25, H 6.27, N 3.64.

(Z) **2d** Method analogous to that for the preparation of (Z) **2b**. From diethyl 1-hydroxyamino-p-chlorobenzylphosphonate[7](**1d**) and p-methoxy-benzylaldehyde, (Z) **2d** was obtained in 51 % yield. mp. 139-140°C. IR (KCl) ν : 1610(C=N), 1135 (N-O), 1250(P=O), 1030(P-O-C) cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ : 1.25 (t, 6H, J=7 Hz), 3.89 (s, 3H), 4.0-4.7 (m, 4H), 5.5 (d, 1H, $^2J_{PH}$=20), 6.95 (d, $2H_{arom}$, J=8Hz), 7.69 (s, 1H, CH=N), 7.8 (d, $2H_{arom}$, J=9Hz), 8.3 (d, $2H_{arom}$, J=9Hz) ppm. ^{31}P-NMR($CDCl_3$) δ : 15.7 ppm. Elemental analyses $C_{19}H_{23}NClO_5P$ (411.8) Calc. % C 55.41, H 5.63, N 3.40. Found % C 54.97, H 5.54, N 3.41.

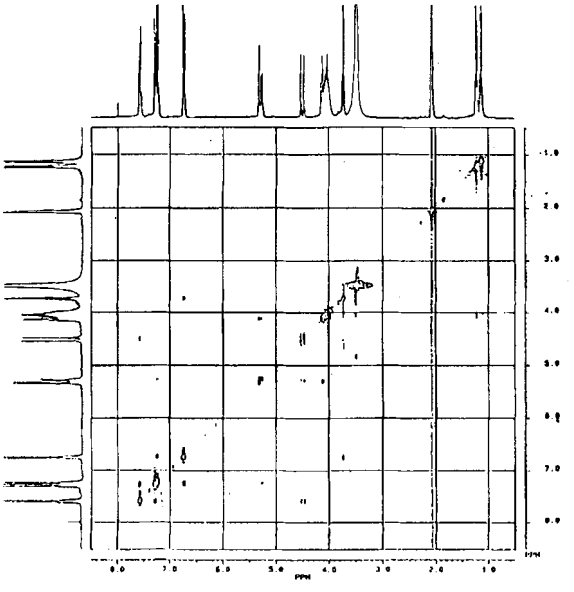
(Z) **2e** Analogues to method for (Z) **2b**, from diethyl 1-hydroxyamino-p-chlorobenzylphosphonate[6] **(1d)** and p-fluorobenzaldehyde, (Z) **2e** was obtained in 41 % yield, mp. 142-143°C. IR(KCl) ν : 1610(C=N), 1260(P=O), 1230, 1140, 1030(P-O-C)cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 1.25 (t, 6H, J=7 Hz), 3.85-4.95 (m, 4H), 5.55 (d, 1H, $^2J_{PH}$=20 Hz, CHP), 6.8-7.9 (m, $6H_{arom}$), 7.75 (s, 1H, CH=N), 8.05-8.45 (q, $2H_{arom}$) ppm. Elemental analyses $C_{18}H_{20}NClFO_4P$ (399.8) Calc. % C 54.07, H 5.05, N 3.50. Found % C 53.88, H 4.94, N 3.25.

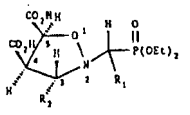
Synthesis of 2-substituted isoxazolinyl methylphosphonates (3) by 1,3-dipolar cycloaddition of nitrone 2 to maleic anhydride. Typical procedure: A mixture of **2** (3 mmole) and maleic anhydride (0.32 g. 3.3 mmole) in anhydrous benzene (15 mL) was heated under reflux for 12 h. Subsequently 2 drops of distilled water was introduced and stirring was conducted for additional 15 minutes. The solvent was then removed and the residue thus obtained was treated with ether (10 mL). After removal of ether in vacuo, the yellowish residue was purified by thin-layer chromatography on a silica gel(10-40u GF254) loaded plate. Elution with $CHCl_3$: EtOH (16:1 by volume) afforded the corresponding isoxazolinyl methylphosphonates 3.

3b A mixture of **2b** (1.04g, 3mmole) and maleic anhydride (0.32 g, 3.3 mmole in anhydrous benzene (15 mL) was treated as described by the typical procedure. **3b** was obtained as colorless crystalline powder mp 158-160°c (dec). Yield 45 %. IR(KBr) ν : 3350(COOH), 1710(C=O), 1220(P=O), 1185(N-O), 1010(P-O-C), cm^{-1}. ^{1}H-NMR(acetone-d_6, 90MHz) δ : 1,0-1.34(m,6H) 3.64-4.28 (m, 5H, $2CH_2O$+H_4), 4.54 (d, 1H, $^2J_{ph}$=18 Hz,CHP), 5.2 (d, 1H, $^3J_{3,4H}$ =7.2 Hz, H_5), 7.0-7.6 (m, $10H_{arom}$) ppm. MS(FAB) m/z 464 (M+1). Elemental analyses $C_{22}H_{26}NO_8P$(463.5) Calc. % C 57.00, H 5.66, N 3.02. Found % C 56.65, H 5.43, N 3.11.

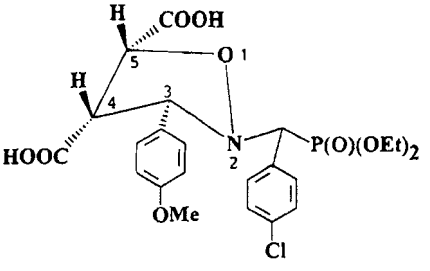
3c A mixture of **2c** (1.14 g, 3 mmole) and maleic anhydride (0.32 g, 3.3 mmole) in anhydrous benzene (15 mL) was treated as described in the typical procedure except to use acetone-diethyl ether as eluent. IR(KCl) ν : 3350(COOH), 1785(C=O), 1230(P=O), 960(P-O-C)cm^{-1} ^{1}H-NMR(300MHz, acetone-d_6) δ : 1.08-1.23 (m, 6H), 3.79 (s, 3H), 3.93-4.12 (m, 4H), 4.26-4.34 (m, 2H, CHP+H_4), 5.50 (d, 1H, $^3J_{4,5H}$=8.85 Hz, H_3), 5.68 (d, 1H, $^3J_{4,5H}$=7.57 Hz, H_5), 6.91 (d, $2H_{arom}$, J=8.8 Hz), 7.18 (d, $2H_{arom}$ J=8.8 Hz) 7.29-7.33 (m, $3H_{arom}$), 7.44-7.47 (m, $2H_{arom}$) ppm. ^{31}P-NMR(300 MHz, acetone-d_6) δ : 25.1 ppm. Elemental analyses $C_{23}H_{28}NO_9P$493.5) Calc. % C 55.97, H 5.73, N 2.84. Found % C 55.81, H 5.92, N 2.73.

3d A mixture of **2d** (1.24 g, 3 mmole) and maleic anhydride (0.32 g, 3.3 mmole in anhydrous benzene (15 mL) was treated as described in the typical procedure. **3d** was obtained as colorless powder mp 113-115°C. Yield 46 % IR(KCl) ν : 3300(COOH), 1780(C=O), 1250(P=O), 1030(P-O-C) cm^{-1}. ^{1}H-NMR(300 MHz, acetone-d_6) δ : 1.13 (t, 3H), 1.23 (t, 3H), 3.73 (s, 3H), 3.97-4.14 (m, 5H,

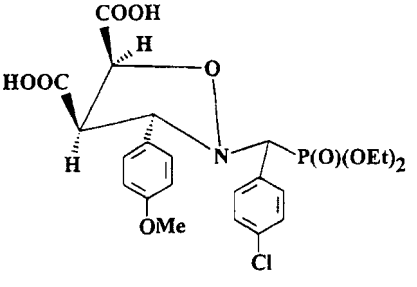




2D NOESY Spectrum of 2-substituted isoxazolino phosphonate



3,4-(Z)**3d**



3,4-(E)**3d**

2CHO+H_4), 4.49 (d, 1H, $^2J_{pH}$=19.0 Hz, CHP), 5.27 (d, 1H, $^3J_{3,4H}$=7.52 Hz, H_3), 5.32 (d, H, $^3J_{4,5H}$ = 7.41 Hz, H_5), 6.74 (d, 2H_{arom}, J=8,74 Hz), 7.22-7.30 (m, 4H_{arom}), 7.58 (d, 2H_{arom}, J=10.54 Hz) ppm. ^{31}P-NMR (300 MHz, $CDCl_3$) δ : 18.65 ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ : 16.85($POCH_2CH_3$), 4.47 (C_4), 5.71 (C_5), 55.8 (C_3), 62.8 (OCH_3), 64.3 ($POCH_2$), 62.9 (d, CP, $^1J_{pC}$ =136 HZ), 126-134 (C_{arom}), 172.7, 173.6 (2 COOH) ppm. MS (FAB)m/z=528(M^+). Elemental analyses $C_{23}H_{27}NClO_9P$ (527.88) Calc. % C 52.33, H 5.17, N 2.65. Found C 52.01, H 4.85, N 2.66.

Acknowledgements

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