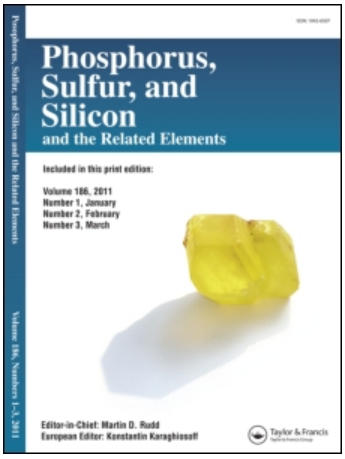

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Dedicated to Professor L. Horner on the occasion of his 80th birthday

(Received January 14, 1992)

Reaction of methylenebisphosphonate with α-nitroalkenes followed by addition of trimethylchlorosilane leads to the formation of ethenylidenebisphosphonates and trimethylsilyl nitronate in almost quantitative yield. These two products, upon prolonged reaction at ambient temperature, provide 2-isoxazoline-5,5-diylbisphosphonates via regioselective 1,3-dipolar cycloaddition in high yield.

Key words: Methylenebisphosphonate; α-nitroalkenes; ethenylidenebisphosphonates; 2-isoxazoline-5,5-diylbisphosphonate; 1,3-dipolar cycloaddition.

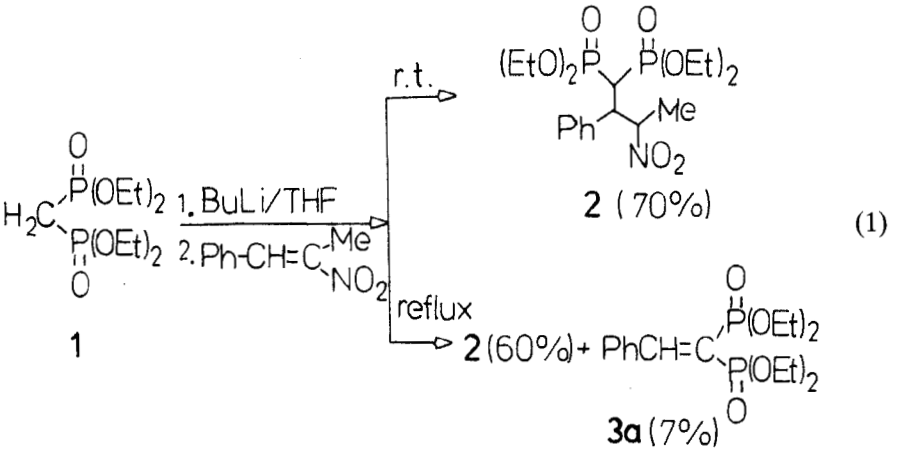
INTRODUCTION

As phosphorus analogue of malonic ester, the chemistry of methylenebisphosphonate is not well developed, although it is of great interest in basic phosphorus chemistry. On the other hand, the medicinal potentials of this class of compounds including antivirus activity,[1] inhibition of osteoclastic bone resorption[2] and application as ligands of ^{99}Tc radiopharmaceuticals[3] show exciting prospects. These situations encourage us to investigate the reactions of tetraethyl methylenebisphosphonate (**1**) and the syntheses of new derivatives thereof. Herein we wish to report the reactions of **1** with α-nitroalkenes which lead to a novel synthesis of ethenylidenebisphosphonates (**3**) and 2-isoxazoline-5,5-diylbisphosphonates (**8**).

RESULTS AND DISCUSSION

α-Nitroalkenes, as Michael acceptors bearing a moderate leaving group, give various Michael addition products with different nucleophiles. For example, Tamura[4] reported the synthesis of α-cyanocyclopropylcarboxylate by reaction of α-cyanoacetate with α-nitroalkenes in high yield. Vankar[5] obtained, however, only the Michael condensation products in the reaction of malonate or thiophenoxyacetate under similar experimental conditions. In our case, as the result of reaction of **1** and 2-nitro-1-phenylpropene in the presence of n-butyllithium, the Michael addition product 2 was obtained when quenched by an acid. When the above reaction was

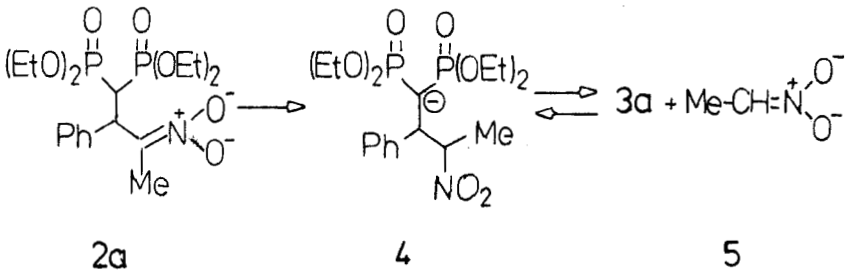
carried out at relatively high temperature, we observed that, in addition to compound **2**, a low yield of ethenylidenebisphosphonate derivative **3a** was isolated, rather than the tetraethyl 3-methyl-2-phenylcylopropane-1,1-diylbisphosphonate as expected.



(1)

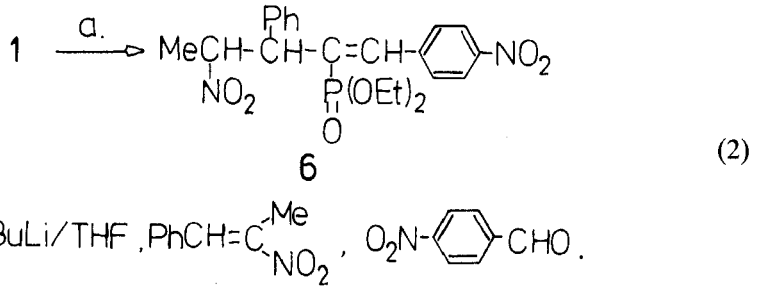
The mechanism of the reactions involved in Equation 1 can be postulated as follows: Compound **1** reacts with 2-nitro-1-phenylpropene to give anion **2a** which undergoes intramolecular proton transfer to form the more stable anion **4**. When the anion **4** is quenched by an acid at low temperature, compound **2** is obtained as the normal Michael condensation product. However, when anion **4** is heated, it splits off an anion **5**, rather than a nitrite ion in the usual manner, to form compound **3a**. The low yield of the product **3a** indicates that the reaction seems to be a reversible process which is in equilibrium with the Michael addition of **3a** by anion **5**. Although Hutchinson[6] reported the inertness of ethenylidenebisphosphonate towards carbanions, Sturtz achieved the Michael condensation product using some carbanions in high yields.[7] These two contradictory results may best be rationalized by an equilibrium process similar to that shown in Scheme I. Different results may be obtained with various carbanions or under different experimental conditions.

In order to verify our suggestion, we added to the reaction solution p-nitrobenzaldehyde, which underwent Wittig-Horner reaction with the anion **4**. As a result, the equilibrium between **4** and **3a** was shifted to the left side completely and product



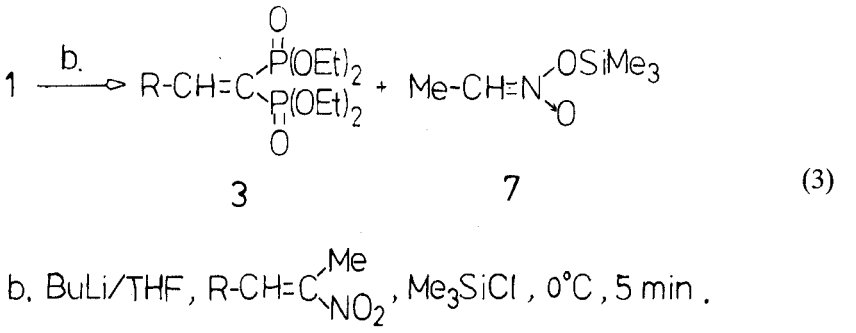
SCHEME I

6 was obtained as the sole product. This is a strong evidence supporting our postulation.

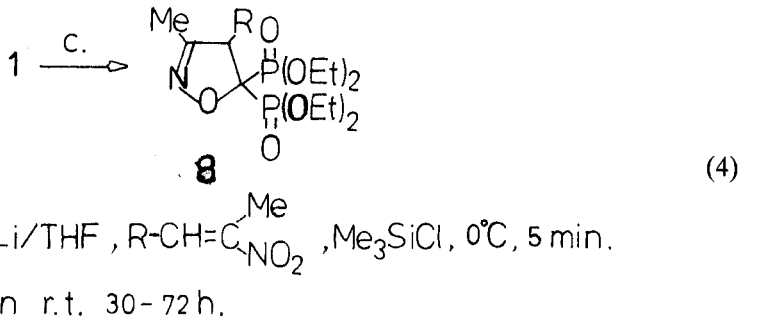


(2)

On the other hand, if we could drive the equilibrium completely towards the formation of compound **3a**, it should be of synthetic importance since only a few methods are available for the preparation of ethenylidenebisphosphonates **3**.[8] However, our trial on just raising the reaction temperature failed to give the expected result. As far as our knowledge is concerned,[9] compound **1** does not react with trimethylchlorosilane in the presence of a base such as butyllithium. Therefore, we added to the equilibrium mixture trimethylchlorosilane, which led to the formation of a nitronate **7**. As the result, the equilibrium is shifted to the right side completely. Thus, compound **3** was isolated in almost quantitative yield upon complete removal of nitronate **7** and solvent Equation (3). Since α-nitroalkenes are easily available,[10] this method is proved to be a convenient and facile route to **3**.



(3)



(4)

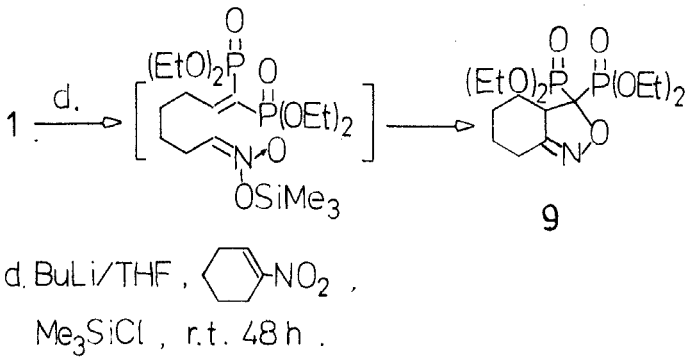
TABLE 1
Compounds **3** and **8** synthesized

Entry	R	3		8	
		Yield(%)*	Lit.	Yield(%)*	Rea.Time(h)
a	Ph	98	8a,13	92	40
b	p-$NO_2C_6H_4$	99	8a,13	90	30
c	p-ClC_6H_4	97	8a,13	77	45
d	o,p-$Cl_2C_6H_3$	95	/	78	50
e	p-$MeOC_6H_4$	95	13	80	36
f	p-$Me_2NC_6H_4$	90	13	80	40
g	Et	93	8c	60	48
h	Pr	94	8c	65	72

* isolated yield based on compound **1**.

As the nitronate **7** is actually a 1,3-dipole,[11] it might undergo 1,3-dipolar cycloaddition with alkenes like compounds **3**. Thus, reaction of **3** and **7**, both formed in situ upon addition of trimethylchlorosilane to the equilibrium shown in Scheme I, at room temperature for 30—72 hours, affords 2-isoxazoline-5,5-diylbisphosphonate **8** in high yield. The cyclo-addition is highly regioselective and no isomeric 2-isoxazoline-4,4-diylbisphosphonate can be detected. A series of compounds **8** thus obtained was unambiguously characterized by ^1H-, ^{31}P- and ^{13}C-NMR spectra. Table I summarizes the compounds **3** and **8** synthesized. Since 2-alkylethenylidenebisphosphonates are less stable than the corresponding 2-aryl derivative,[8c,13] the yields of their products **8** are relatively low (entry g and h).

As an additional illustration, as shown in Equation (5), reaction of **1** with 1-nitrocyclohexene provides compound **9** as the result of the intramolecular 1,3-dipolar cycloaddition.



(5)

EXPERIMENTAL

Infrared spectra were obtained on an IR-440 infrared spectrometer. ^{1}H NMR spectra were recorded on a XL-200 spectrometer. ^{31}P- and ^{13}C-NMR spectra were taken with broad band decoupling on a FX-90Q spectrometer using TMS as the internal reference and 85% phosphoric acid as the external standard for ^{31}P-NMR. Mass spectra were recorded on a Finnigan 4021 mass spectrometer. Butyllithium (2.5 M solution in Hexanes) was purchased from Aldrich Chemical Co. Other reagents were obtained from local commercial source (Shanghai Chemical Co.). Tetraethyl methylenebisphosphonate was prepared according to the literature.[12] 2-Nitro-1-arylpropenes were synthesized according to the literature by Gairaud.[10b] 2-Nitro-2-pentene and 2-nitro-2-hexene were prepared using Melton's method.[10a] 1-Nitrocyclohexene was prepared using Corey's procedure.[10c] Trimethylchlorosilane was distilled prior to use.

Tetraethyl 3-nitro-2-phenylbutylidenebisphosphonate (**2**). Tetraethyl methylenebisphosphonate(**1**) (1.44 g, 5 mmol) is added to dry, freshly distilled THF (25 mL) and the solution is stirred for 1 min under nitrogen in a 100 mL 3-necked flask fitted with a drying tube and a rubber septum. After the solution is cooled down to −60°C, butyllithium (2.0 mL, 5 mmol) is added and stirring is continued for 30 min. The reaction mixture is then allowed to warm to −30°C which is followed by the addition of 2-nitro-1-phenylpropene (0.856g, 5.25 mmol) in THF (4 mL). After being stirred for 30 min, the solution is allowed to warm to r.t. and stirred for an additional 7 h and then again cooled to −30°C. Hydrochloric acid (1 N) is added until the pH of the reaction mixture is acidic. The mixture is extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phase is dried over anhydrous sodium sulfate, the solvent removed under vacuum to give the product, which is purified by flash chromatography on silica with elution with acetone/petroether (1/1, v/v) to give the pure product **2** as a colorless oil. Yield: 1.57g (70%). IR (film) ν 3030, 1590, 1250, 1160, 1025, 970. CIMS: m/e 452 (M^+ + H), 421, 242. ^{31}P-NMR ($CDCl_3$) δ: 21.09 (s), 22.95 (s). ^{1}H-NMR ($CDCl_3$) δ: 1.05, 1.16, 1.36, 1.38 (4 × 3H, 4t, J = 7, 4C$\underline{H}_3$CH$_2$O), 2.08 (1H, dt, J = 7, 22, CHP$_2$), 2.15 (3H, d, J = 9, C$\underline{H}_3$CH), 3.45 (1H, dq, J = 7, 9, CHNO$_2$), 3.64 (1H, dd, J = 7, 6, CH—C$_6$H$_5$), 3.70–4.40 (8H, br, C$\underline{H}_2$O), 7.32 (5H, m, C$_6$H$_5$). Anal. Calcd for $C_{18}H_{31}NO_8P_2$: C,47.90; H,6.92; N,3.10. Found: C,47.67; H,6.99; N,3.01.

Diethyl (E)-4-nitro-3-phenyl-2-diethoxyphosphonyl-1-(4'-nitrophenyl)-1-pentene (**6**). Butyllithium (2.0 mL, 5 mmol) is added to tetraethyl methylenebisphosphonate **1** (1.44 g, 5 mmol) in THF (20 mL) at −60°C and the resulting mixture is stirred for 30 min. 2-Nitro-1-phenylpropene (0.856 g, 5.25 mmol) in THF (4 mL) is then added and the solution stirred at −60°C for 10 min and then at r.t. for 6 h. p-Nitrobenzaldehyde (0.83 g, 5.5 mmol) in THF (3 mL) is added and the solution stirred at r.t. until the TLC shows the completion of the reaction. (Too high reaction temperature may cause the transformation of anion **4** to anion **2**, which leads to the formation of 2-nitro-1-phenylpropene and the Horner reaction product of compound **1** with p-nitrobenzaldehyde.) Hydrochloric acid (1 N) is added until the pH of the reaction mixture is slightly acidic. The mixture is extracted with CH_2Cl_2 (4 × 30 mL), the combined organic layer dried over anhydrous sodium sulfate, the solvent removed to give the crude product, which is purified by column chromatography with elution with acetone/petroether (1/1.5, v/v) to give pure **6** as a colorless oil. Yield: 1.56 g (70%). IR (film) ν 3085, 1615, 1555, 1250, 1025. CIMS: m/e 449 (M^+ + H). ^{31}P-NMR ($CDCl_3$) δ: 19.53. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, t, J = 7, CH$_3$CH$_2$), 2.15 (3H, d, J = 8, C$\underline{H}_3$CH), 3.50 (1H, dd, J = 7,8, CHPh), 4.18 (4H + 1H, m, CH$_2$O + CHNO$_2$), 6.05 (1H, dd, J = 3, 20, CH=), 7.30 (5H, m, C$_6$H$_5$), 7.66, 8.00 (2 2H, 2m, C$_6$H$_4$). Anal. Calcd for $C_{21}H_{25}N_2O_7P$: C,56.25; H,5.62; N,6.25. Found: C,56.02; H,5.43; N,6.11.

Tetraethyl 2-phenylethenylidenebisphosphonate (**3a**). **General Procedure:** Butyllithium (2.0 mL, 5 mmol) is added to tetraethyl methylenebisphosphonate (1.44 g, 5 mmol) in THF (20 mL) at −60°C and the mixture is stirred for 30 min. 2-Nitro-1-phenylpropene (0.856 g, 5.25 mmol) is added and the solution stirred at −60°C for 10 min and then at r.t. for 6 h. The solution is again cooled down to 0°C and trimethylchlorosilane (0.67 mL, 5.5 mmol) is added. After 5 min, the solution is concentrated at 0°C/0.01Torr for 1 h to allow the complete removal of the solvent and trimethylsilyl nitronate **7**. Chloroform (30 mL) is added to the residue and the resulting mixture is filtered. The filtrate, after flash chromatography on silica (eluent: acetone/petroether = 1/1, v/v), gives the pure product **3a** as a colorless oil, yield: 1.73 g (92%). The spectral data are identical with those reported in the literature.[13]

Compounds **3b,c,e–h** are similarly prepared and give satisfactory analyses which are identical with those reported in the literature[8a,c,13] (Table I).

Tetraethyl 2-(2',4'-dichlorophenyl)ethenylidenebisphosphonate (**3d**). Yellowish oil. IR (film) ν 3080, 1620, 1610, 1580, 1250, 1025. CIMS: m/e 445, 447, 449 (9:6:1, M^+ + H). ^{31}P-NMR ($CDCl_3$) δ: 10.39 (d, J = 49.3), 14.96 (d, J = 49.3). ^{1}H-NMR ($CDCl_3$) δ: 1.12, 1.38 (2 × 6H, 2t, J = 7, CH$_3$), 4.02, 4.17 (2 4H, 2m, CH$_2$O), 7.20–7.65 (3H, m, C$_6$H$_3$), 8.10 (1H, dd, J = 28, CH=). Anal. Calcd for $C_{16}H_{24}Cl_2O_6P_2$: C,43.17; H,5.43. Found: C,43.01; H,5.32.

Tetraethyl 3-methyl-4-phenyl-2-isoxazoline-5,5-diylbisphosphonate (**8a**). **General Procedure:** The same procedure as for the preparation of compound **3a** is followed. When trimethylchlorosilane is added, the solution is stirred for 5 min at 0°C and then for 40 h at r.t. The solution is concentrated in vacuo. Chloroform (30 mL) is added to the residue and the resulting mixture is filtered. The filtrate is concentrated to give the crude product, which is purified by flash chromatography on silica with eluent of acetone/petroether (1.5/1, v/v) to give the pure product **8a** as a white solid. Yield: 1.99 g (92%), m.p. 80–82°C. IR (film) ν 1240, 1220, 1025, 975, 750. CIMS: m/e 434 ($M^+ + H$). ^{31}P-NMR ($CDCl_3$) δ: 21.36 (s), 23.11 (s). ^{1}H-NMR ($CDCl_3$) δ: 1.04, 1.10, 1.28, 1.31 (4 × 3H, 4t, J = 7, 4C$\underline{H}_3$CH$_2$O), 1.70 (3H, s, CH_3C=N), 3.59 (1H, dd, J = 7, 9, CH), 3.70–4.24 (8H, br, CH_2O), 7.22 (3H, m, C_6H_5), 7.37 (2H, m, C_6H_5). ^{13}C-NMR ($CDCl_3$) δ: 14.29 (s, $\underline{C}H_3CN$), 15.90, 16.13, 16.37 (3s, 4$\underline{C}H_3CH_2O$), 39.76 (dd, J = 130, 134, CP_2), 49.09 (s, CPh), 61.72, 62.02, 62.32, 62.61 (4s, 4$\overline{C}H_2O$), 127.21 (s, 4′-C), 127.57 (s, 3′,5′-C), 130.61 (s, 2′,6′-C), 137.40 (dd, J = 4, 12, 1′-C), 156.17 (t, J = 10, C=N). Anal. Calcd for $C_{18}H_{29}NO_7P_2$: C,49.89; H,6.75; N,3.23. Found: C,49.88; H,6.73; N,3.17.

Tetraethyl 3-methyl-4-(4′-nitrophenyl-2-isoxazoline-5,5-diylbisphosphonate (**8b**). Yellowish oil. IR (film) ν 1555, 1525, 1253, 1023, 978. CIMS m/e: 479 ($M^+ + H$), 450, 422, 258. ^{31}P-NMR ($CDCl_3$) δ: 20.55 (s), 22.13 (s). H-NMR ($CDCl_3$) δ: 1.06, 1.11, 1.18, 1.24 (4 × 3H, 4t, J = 7, 4C$\underline{H}_3$CH$_2$O), 1.75 (3H, s, CH_3C=N), 3.80–4.25 (8H + 1H, br, CH_2O + CHPh), 7.68, 8.02 (2 2H, 2d, J = 8, C_6H_4). ^{13}C-NMR ($CDCl_3$) δ: 14.83 (s, CH_3C=N), 15.65, 16.41, 17.16 (3s, 4CH_3CH_2O), 40.81 (dd, J = 120, 128, CP_2), 49.20 (s, CPh), 63.28, 63.58, 63.81, 64.01 (4s, 4CH_2O), 123.25 (s, 3′,5′-C), 131.55 (s, 2′,6′-C), 144.21 (s, 4′-C), 148.15 (s, 1′-C, 156.15 (s, C=N). Anal. Calcd for $C_{18}H_{28}N_2O_9P_2$: C,45.20; H,5.90; N,5.86. Found: C,44.91; H,5.99; N,5.64.

Tetraethyl 3-methyl-4-(4′-chlorophenyl)-2-isoxazoline-5,5-diylbisphosphonate (**8c**). White solid, m.p.82–84°C. IR (film) ν 1253, 1242, 1025, 978. CIMS: m/e 470/468 (1/3, $M^+ + H$), 408/406 (1/3), 277/275 (1/3), 221/219 (1/3). ^{31}P-NMR ($CDCl_3$) δ: 21.22 (s), 22.80 (s). ^{1}H-NMR ($CDCl_3$) δ: 0.76, 0.80, 0.92, 1.01 (4 × 3 H, 4t, J = 7, 4CH_3CH_2O) 1.42 (3H, s, CH3-C=N), 3.56 (1H, dd, J = 6, 8, CHC_6H_4), 3.60–4.20 (8H, br, CH_2O), 7.28 (2H, d, J = 8, C_6H_4), 7.42 (2H, d, J = 8, C_6H_4). ^{13}C-NMR ($CDCl_3$) δ: 14.60 (s, $\underline{C}H_3$C=N), 15.69, 16.59, 17.14 (3s, 4$\underline{C}H_3CH_2$), 39.74 (dd, J = 125, 130, CP_2), 48.78 (s, CPh), 62.57, 62.98, 63.61 (3s, 4CH_2O), 128.07 (s, 3′,5′-C), 132.42 (s, 2′,6′-C), 133.56 (s, 4′-C), 136.42 (s, 1′-C), 156.07 (s, C=N). Anal. Calcd for $C_{18}H_{28}ClNO_7P_2$: C,46.22; H,6.03; N,2.99. Found: C,46.33; H,6.34; N, 3.12.

Tetraethyl 3-methyl-4-(2′-dichlorophenyl)-2-isoxazoline-5,5-diylbisphosphonate (**8d**). Colorless oil. IR (film) ν 1240, 1025, 975, 730. CIMS m/e 502/504/506 (9/6/1, $M^+ + H$). ^{31}P-NMR ($CDCl_3$) δ: 20.67 (d, J = 4.5), 22.27 (d, J = 4.5). ^{1}H-NMR ($CDCl_3$) δ: 1.02, 1.10, 1.19, 1.22 (4 × 3H, 4t, 4C$\underline{H}_3$CH$_2$), 2.00 (3H, s, CH3C=N), 3.60 (1H, m, CH), 3.65–4.20 (8H, br, CH_2O), 7.00–7.30 (3H, m, C_6H_3). ^{13}C-NMR ($CDCl_3$) δ: 14.57 (s, CH_3C=N), 15.59, 16.32, 17.06 (3s, 4$\underline{C}H_3CH_2O$), 40.39 (dd, J = 120, 135, CP_2), 48.85 (s, CPh), 62.66, 63.11, 63.27 (3s, 4CH_2O), 126.91, 128.90, 129.44, 133.90, 135.64, 136.07 (6s, C_6H_3), 156.21 (s, C=N). Anal. Calcd for $C_{18}H_{27}Cl_2NO_7P_2$: C,43.25; H,5.42; N,2.79. Found: C, 43.51; H,5.21; N, 2.55.

Tetraethyl 3-methyl-4-(4′-methoxyphenyl)-2-isoxazoline-5,5-diylbisphosphonate (**8e**). White solid, m.p.74–76°C. IR (film) ν 1520, 1250, 1220, 1030, 980, 760. CIMS: m/e 464 ($M^+ + H$), 420, 402, 294, 161. ^{31}P-NMR ($CDCl_3$) δ: 21.51 (s), 23.19 (s). ^{1}H-NMR ($CDCl_3$) δ: 1.06, 1.12, 1.28, 1.31 (4 × 3H, 4t, J = 7, 4C$\underline{H}_3$CH$_2$O), 1.70 (3H, s, CH_3C=N), 3.62 (1H, dd, J = 6, 7, CHC_6H_4), 3.74 (3H, s, OCH_3), 3.75–4.25 (8H, br, CH_2O), 6.76, 7.26 (2 2H, 2d, J = 8, C_6H_4). ^{13}C-NMR ($CDCl_3$) δ: 14.53 (s, $\underline{C}H_3$C=N), 15.83, 16.56, 17.38 (3s, 4$\underline{C}H_3CH_2$), 39.75 (dd, J = 120, 125, CP_2), 48.61 (s, CPh), 55.63 (s, OCH_3), 62.79, 63.00, 63.61 (3s, 4$\overline{C}H_2O$), 113.31 (s, 3′,5′-C), 129.70 (s, 4′-C), 132.03 (s, 2′,6′-C), 156.68 (s, C=N), 159.21 (s, 1′-C). Anal. Calcd for $C_{19}H_{31}NO_8P_2$: C,49.25; H,6.74; N,3.02. Found: C,49.00; H,6.78; N,2.86.

Tetraethyl 3-methyl-4-(4′-dimethylaminophenyl)-2-isoxazoline-5,5-diylbisphosphonate (**8f**). Yellowish oil. IR (film) ν 3085, 1555, 1255, 1024. CIMS: m/e 477 ($M^+ + H$). ^{31}P-NMR ($CDCl_3$) δ: 21.61 (s), 23.24 (s). ^{1}H-NMR ($CDCl_3$) δ: 0.98, 1.04, 1.18, 1.22 (4 × 3H, 4t, J = 7, 4C$\underline{H}_3$CH$_2$), 1.80 (3H, s, CH_3C=N), 2.80 (6H, s, CH_3N), 3.50 (1H, dd, J = 6, 7, C$\underline{H}C_6H_4$), 3.60–4.20 (8H, br, CH_2O), 6.55, 7.10 (2 2H, 2d, J = 9, C_6H_4). ^{13}C-NMR ($CDCl_3$) δ: 14.79 (s, $\underline{C}H_3$C=N), 15.89, 16.63, 17.15 (3s, 4$\underline{C}H_3CH_2O$), 29.80 (s, 2CH_3N), 41.50 (dd, J = 110, 120, CP_2), 48.71 (s, CPh), 62.91, 63.26, 63.52 (3s, 4$\overline{C}H_2O$), 112.90 (s, 3′,4′-C), 126.39 (s, 4′-C), 131.74 (2′,6′-C), 149.86 (s, 1′-C), 157.30 (s, C=N). Anal. Calcd for $C_{20}H_{34}N_2O_7P_2$: C,50.42; H,7.19; N,5.88. Found: C,50.32; H, 7.27; N,5.74.

Tetraethyl 3-methyl-4-ethyl-2-isoxazoline-5,5-diylbisphosphonate (**8g**). Colorless oil. IR (film) ν 1400, 1370, 1245, 1025, 970. CIMS m/e 386 ($M^+ + H$), 324, 250, 193, 159, 152. ^{31}P-NMR ($CDCl_3$) δ: 20.73

(s). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J = 8, $C\underline{H}_3CH_2C$), 1.24 (12H, t, J = 7, $C\underline{H}_3CH_2O$), 1.80 (2H, m, $C\underline{H}_2CH$), 2.08 (3H, dd, J = 7, 8, $CH_3C{=}N$), 2.70 (1H, m, CH), 4.15 (8H, m, CH_2O). ^{13}C-NMR ($CDCl_3$) δ: 13.53 (s, $\underline{C}H_3CH_2C$), 14.83 (s, $\underline{C}H_3C{=}N$), 15.83, 16.58, 17.37 (3s, $4\underline{C}H_3CH_2O$), 24.50 (s, $\underline{C}H_2C$), 30.00 (s, 4-C), 40.05 (dd, J = 110, 118, CO_2), 63.55, 63.88, 64.20 (3s, $4CH_2O$), 157.15 (s, $\underline{C}{=}N$). Anal. Calcd for $C_{14}H_{29}NO_7P_2$: C,43.63; H,7.59; N,3.64. Found: C,43.66; H,7.48; N,3.84.

Tetraethyl 3-methyl-4-propyl-2-isoxazoline-5,5-diylbisphosphonate (**8h**). Colorless oil. IR (film) ν 1395, 1370, 1250, 1020, 970. CIMS m/e 400 (M^+ + H), 348, 264, 166. ^{31}P-NMR ($CDCl_3$) δ: 20.81 (s). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J = 7, CH_3 of propyl), 1.27 (2H, m, CH_2 of propyl), 1.31, 1.34 (2 × 6H, 2t, J = 7, $C\underline{H}_3CH_2O$), 1.88 (2H, m, CH_2 of propyl), 2.25 (3H, s, $CH_3C{=}N$), 3.00 (1H, m, CH), 4.18 (8H, m, CH_2O). ^{13}C-NMR ($CDCl_3$) δ: 13.35 (s, CH_3 of Pr), 14.83 (s, $\underline{C}H_3C{=}N$), 15.83, 16.55, 17.23 (3s, $4\underline{C}H_3CH_2O$), 24.35, 24.96 (2s, $2CH_2$ of Pr), 30.24 (s, 4-C), 40.12 (dd, J = 112, 115, CP_2), 63.45, 63.89, 64.21 (3s, $4CH_2O$), 157.15 (s, $C{=}N$). Anal. Calcd for $C_{15}H_{31}NO_7P_2$: C,45.12; H,7.83; N,3.51. Found: C,45.03; H,7.95; N,3.23.

Tetraethyl bicyclo[4,3,0]-nonane-9-isoxazoline-7,7-diylbisphosphonate (**9**). Colorless oil. IR (film) ν 1395, 1370, 1245, 1025, 970. CIMS m/e 398 (M^+ + H), 354, 336, 159, 152. ^{31}P-NMR ($CDCl_3$) δ: 21.07 (s), 23.63 (s). ^{1}H-NMR ($CDCl_3$) δ: 1.08, 1.11 (2 × 6H, 2t, J = 7, $4CH_3$), 1.30–1.80 (6H, br, 3,4,5-CH_2), 2.65 (2H, m, 2-CH_2), 3.20 (IH, m, 6-CH), 3.95 (8H, m, CH_2O). ^{13}C-NMR ($CDCl_3$) δ: 15.75, 16.49, 17.23 (3s, $4\underline{C}H_3CH_2O$), 25.02, 25.33, 25.95 (3s, 3,4,5-C), 29.54, 30.61 (2s, 2,6-C), 35.25 (dd, J = 125, 130, CP_2), 62.34, 62.92, 63.56 (3s, $4CH_2O$), 156.20 (s, $C{=}N$). Anal. Calcd for $C_{15}H_{29}NO_7P_2$: C,45.35; H,7.36; N,3.53. Found: C,45.12; H,7.23; N,3.26.

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