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A Convenient Synthesis of 2-Alkoxy-2-oxo-1,4,2-oxazaphosphinanes

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ABSTRACT: *A study on the synthesis of the novel cyclic α-aminophosphonates and 2-alkoxy-2-oxo-1,4,2-oxazaphosphinanes* **4a–r** *has been carried out. The title compounds were obtained in good yields by one-pot procedure using o-aminophenol, alkyl dichlorophosphinite, and ketones or benzaldehyde. One of their geometric stereoisomers was isolated and characterized. Configurations of* **4k** *and one isomer of* **4r** *have been established by X-ray diffraction analysis. The synthetic methods provide an easy access to the organophosphorus heterocycles with the ring system mentioned above. The abnormal chemical shifts of alkyl-substitute protons in ^1H NMR spectra were given reasonable explanation.* Heteroatom Chem 18:65–69, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20258

INTRODUCTION

α-Aminophosphonic acids serve as important analogs of α-aminocarboxylic acids in biological systems such as peptides and proteins. Their utilities as enzyme inhibitors, antibiotics, pharmacological agents, and many other applications have attracted chemists' interests for a long time [1–4]. Moreover, cyclic α-aminophosphonates, one kind of α-aminophosphonates, have some special biological properties [5–8]. In the course of our program aimed at searching for potential and selective organophosphorus inhibitors, virucids, and herbicide, the cyclic α-aminophosphonate and 2-oxo-1,4,2-oxazaphosphinanes stimulated our interest. Because forming this kind of organophosphous heterocycle can introduce a carbon atom with a wide range of substituents at the α-position to the phosphorus atom, which can be applied for asymmetric synthesis of various compounds containing P—C—N fragment, as well as precursor of chiral α-aminophosphorus acid. To the best of our knowledge, some papers deal with 1,4,2-oxazaphosphinane structures [9–15]. They all described the synthesis of this organophosphorus heterocycle starting with imines and different phosphines participate. However, these methods were limited due to low stability and difficult separation of some imines. In our previous work, we have reported the synthesis of 2-phenyl-1,4,2-oxazaphosphinane-2-oxides [16]. We depict herein a convenient and straightforward procedure for the synthesis of 2-alkoxy-2-oxo-1,4,2-oxazaphosphinanes.

RESULTS AND DISCUSSION

As shown in Scheme 1, *o*-aminophenol **1** was allowed to react with alkyl dichlorophosphinite **2** and various substituted ketones or benzaldehyde **3** in anhydrous tetrahydrofuran (THF) containing a small amount of potassium carbonate to give the title compounds **4a–r** in good yields. The reactions were carried out using one-pot procedure. All the products were isolated from the reaction mixture by column chromatography, and their structures were characterized

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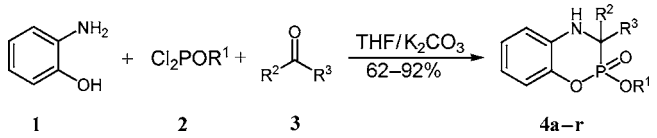

1 2 3 4a–r

4	R^1	R^2	R^3	4	R^1	R^2	R^3
4a	Me	Me	Me	**4j**	Me	$(CH_2)_6$	
4b	Et	Me	Me	**4k**	Et	$(CH_2)_6$	
4c	*i*-Pr	Me	Me	**4l**	*i*-Pr	$(CH_2)_6$	
4d	Me	$(CH_2)_4$		**4m**	Me	Me	Et
4e	Et	$(CH_2)_4$		**4n**	Et	Me	Et
4f	*i*-Pr	$(CH_2)_4$		**4o**	*i*-Pr	Me	Et
4g	Me	$(CH_2)_5$		**4p**	Me	H	Ph
4h	Et	$(CH_2)_5$		**4q**	Et	H	Ph
4i	*i*-Pr	$(CH_2)_5$		**4r**	*i*-Pr	H	Ph

SCHEME 1

by ^{1}H NMR, ^{31}P NMR, mass spectra, refraction and elemental analysis (Tables 1–3).

When the two substitutes (R^2, R^3) of carbonyl compound **3** are different, four diastereoisomers should be found, because two stereogenic centers are created. In fact, only a mixture of two diastereoisomers was separated as colorless oil by column chromatography. Subsequently, one isomer was isolated from the above mixture by recrystallization at low temperature. However, owing to the close values of R_f of diastereoisomers, it appeared to be impossible to isolate the other one by column chromatography or by recrystallization. The ratios of geometric isomers given in Table 2 were determined by the integration of suitable signals in the ^{1}H NMR spectra or the ^{31}P NMR spectra of the crude products. A comparison of the spectra of the isomers displayed a consistent difference in the chemical shifts of ^{31}P. The isomer (major) isolated with colorless solid state has a smaller δ value of ^{31}P (shift difference $\Delta\delta = 0.21$–1.49 ppm). In addition, these compounds **4p–r**, with hydrogen at 3-position, also observed the difference in chemical shifts (C3-H $\Delta\delta = 0.12$–0.18 ppm) and coupling constants of $^2J_{PH}$ ($\Delta J = 5.5$–10.6 Hz). The results are in agreement with those of analogs described in the literatures [9,12]. In order to confirm the structure of the major isomer, the isolated one isomer of product **4r** was recrystallized and determined by X-ray diffraction analysis [17] (Fig. 1). Its configuration is unambiguously *cis*, for which the proton of C-3 and the isopropoxy are all axial.

In the ^{1}H NMR spectra of **4d–o** (Table 3), whose alkyl substituents at 3-position are more than one carbon, it is interesting to find two sets of multiple peaks in the field ($\delta = 1.65$–2.50 ppm) with

TABLE 1 Physical Constants of the Synthesized Compounds **4a–l**

Product	*Yield*[a] *(%)*	*M.p.*[b] *(°C)*	*^{31}P NMR $CDCl_3$/ H_3PO_4*	*MS (M^+)*	*Found/Calcd*		
					C (%)	*H (%)*	*N (%)*
4a	75	168–170	18.23	227.07	52.96/52.86	6.18/6.21	6.15/6.17
4b	72	77–79	17.94	241.09	54.60/54.77	6.78/6.69	5.79/5.81
4c	74	99–101	16.59	255.12	56.69/56.47	7.16/7.11	5.74/5.49
4d	88	134–136	19.30	252.11	56.87/56.92	6.43/6.37	5.64/5.53
4e	92	92–94	18.15	267.19	58.33/58.42	6.69/6.79	5.22/5.24
4f	91	138–139	16.80	281.13	59.50/59.78	7.25/7.17	4.68/4.98
4g	86	150–152	18.02	267.14	58.38/58.42	6.73/6.79	5.38/5.24
4h	90	127–129	18.15	281.12	59.60/59.78	7.23/7.17	5.03/4.98
4i	89	135–137	15.73	295.13	60.89/61.01	7.43/7.51	4.72/4.74
4j	78	120–122	17.23	281.12	59.52/59.78	7.15/7.17	4.93/4.98
4k	62	87–89	17.93	295.13	61.12/61.01	7.45/7.51	4.74/4.74
4l	73	156–158	16.25	309.15	63.24/62.12	7.68/7.82	4.40/4.53

[a]Isolated yield.
[b]After recrystallization from proper solvents.

TABLE 2 Physical Constants of the Synthesized Compounds **4m–r**

Product	Yield[a] (%)	M.p.[b] (°C)	^{31}P NMR $CDCl_3/H_3PO_4$ (major/minor)	MS (M^+)	n_D^{20}[c]	Ratio[d]	Found/Calcd C (%)	Found/Calcd H (%)	Found/Calcd N (%)
4m	74	101–103	19.79/20.14	241.09	1.6473	52:48	54.39/54.77	6.72/6.69	5.67/5.81
4n	81	129–131	17.51/17.83	255.10	1.7032	53:47	56.64/56.47	7.33/7.11	5.51/5.49
4o	80	139–141	17.20/17.78	269.12	1.5891	55:45	57.85/57.98	7.87/7.49	5.28/5.20
4p	65	177–179	11.60/12.11	275.10	1.5769	58:42	61.11/61.09	4.89/5.13	4.93/5.09
4q	86	140–142	10.58/10.79	289.09	1.6321	65:35	62.49/62.28	5.51/5.58	4.63/4.84
4r	71	135–137	9.15/10.64	303.10	1.7596	67:33	63.39/63.36	6.01/5.98	4.63/4.62

[a]Overall yield of geometric stereoisomers.
[b]The major isomer isolated.
[c]Refraction of crude products after column chromatography.
[d]Determined by the integration of suitable signals in ^1H NMR or ^{31}P NMR spectra of the crud products.

integration of two protons. We consider the protons of methylene binding to C-3 are magnetically nonequivalent and display two sets of signals, respectively. In contrast, they locate in lower field than the other alkyl-substitute protons. This abnormal chemical shifts can be explained by the following two reasons. (1) The distances between P atom and methylene protons are shorter than that of the other alkyl-substitute protons. The protons of methylene attaching to C-3 locate in the low field because of electronic effect. (2) The rigidity of six-membered phosphorus heterocycle can inhibit the rotational freedom of the methylene, thereby creating difference between the two protons. Moreover, the presence of phenyl group at 5,6-position also strengthens the rigidity of the heterocycle. Further support for these conclusions comes from an X-ray structure determination of compound **4k** [17] (Fig. 2).

Because of anchoring of phenyl ring at 5,6-position, the P(1), O(2), N(1), C(1), and C(2) are almost coplanar, whose distance from their least-squares plane $(6.957x + 4.236y - 16.333z - 5.9498 = 0)$ is 0.0418, −0.0567, −0.0351, 0.0241, and 0.0258 Å, respectively. The six-membered heterocycle holds the envelope conformation, and to some extent, the confirmation of cycloheptyl substitute cannot invert freely. As a result, protons of C(8) give two sets of multiple peaks in the low field in the ^1H NMR spectra for the reasons mentioned above. The EI-MS spectra of **4a–r** show the existence of strong molecular ion peaks, indicating that the heterocyclic skeletons have some stability.

However, this method appears to be limited to ketones and benzaldehyde, since the attempts to extend the reaction to aliphatic aldehydes failed.

The results obtained show that the synthetic reactions are some stereoselective affording the products, which might be the result of the presence of

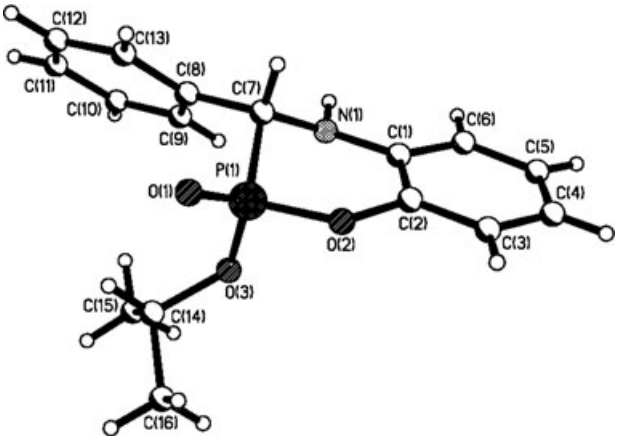

FIGURE 1 The crystal structure of one isomer of **4r**.

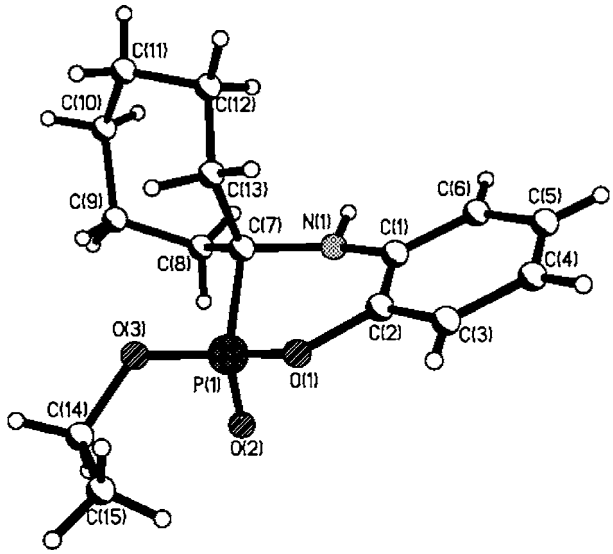

FIGURE 2 The crystal structure of **4k**.

TABLE 3 ^{1}H NMR Data of Synthesized Compounds **4a–r**

Product	*^{1}H NMR ($CDCl_3$/TMS), δ, J (Hz)*
4a	1.57 (d, $^3J_{PCCH} = 12.2$, 3H, CH_3), 1.62 (d, $^3J_{PCCH} = 12.1$, 3H, CH_3), 2.87–3.01 (br, 1H, NH), 3.58 (d, $J =$ 11.1, 3H, OCH_3), 6.72–6.89 (m, 4H, C_6H_4)
4b	1.34 (t, $J = 7.34$, 3H, OCH_2CH_3), 1.45 (d, $^3J_{PCCH} = 15.26$, 3H, CH_3), 1.52 (d, $^3J_{PCCH} = 16.01$, 3H, CH_3), 3.60 (br, 1H, NH), 4.24–4.34 (m, 2H, OCH_2), 6.69–6.97 (m, 4H, C_6H_4)
4c	1.30 (d, $J = 6.41$, 3H, $1/2 \times OCH(CH_3)_2$), 1.36 (d, $J = 6.03$, 3H, $1/2 \times OCH(CH_3)_2$), 1.45 (d, $^3J_{PCCH} =$ 15.45, 3H, CH_3), 1.51 (d, $^3J_{PCCH} = 16.01$, 3H, CH_3), 2.77–2.99 (br, 1H, NH), 4.90–4.97 (m, 1H, OCH), 6.69–6.96 (m, 4H, C_6H_4)
4d	1.70–1.87 (m, 6H, $3 \times CH_2$), 2.17–2.27 (m, 1H, $1/2 \times CH_2$), 2.34–2.50 (m, 1H, $1/2 \times CH_2$), 2.35–2.82 (br, 1H, NH), 3.88 (d, $J = 10.5$, 3H, OCH_3), 6.70–6.99 (m, 4H, C_6H_4)
4e	1.34 (t, $J = 6.97$, 3H, OCH_2CH_3), 1.67–1.89 (m, 6H, $3 \times CH_2$), 2.14–2.25 (m, 1H, $1/2 \times CH_2$), 2.36–2.46 (m, 1H, $1/2 \times CH_2$), 3.41–3.53 (br, 1H, NH), 4.26–4.31 (m, 2H, OCH_2), 6.69–6.98 (m, 4H, C_6H_4)
4f	1.29 (d, $J = 6.22$, 3H, $1/2 \times OCH(CH_3)_2$), 1.36 (d, $J = 6.22$, 3H, $1/2 \times OCH(CH_3)_2$), 1.65–1.96 (m, 6H, $3 \times CH_2$), 1.99–2.12 (m, 1H, $1/2 \times CH_2$), 2.23–2.43 (m, 1H, $1/2 \times CH_2$), 2.69–2.84 (br, 1H, NH), 4.90–4.97 (m, 1H, OCH), 6.70–6.97 (m, 4H, C_6H_4)
4g	1.39–1.85 (m, 8H, $4 \times CH_2$), 1.91–1.96 (m, 1H, $1/2 \times CH_2$), 2.05–2.15 (m, 1H, $1/2 \times CH_2$), 2.81–3.00 (br, 1H, NH), 3.87 (d, $J = 10.8$, 3H, OCH_3), 6.76–6.97 (m, 4H, C_6H_4)
4h	1.32 (t, $J = 6.96$, 3H, OCH_2CH_3), 1.69–1.81 (m, 8H, $4 \times CH_2$), 1.87–1.97 (m, 1H, $1/2 \times (CH)_2$), 2.21–2.49 (m, 1H, $1/2 \times (CH)_2$), 3.41–3.53 (br, 1H, NH), 4.28–4.31 (m, 2H, OCH_2), 6.69–6.98 (m, 4H, C_6H_4)
4i	1.29 (d, $J = 6.22$, 3H, $1/2 \times CH(CH_3)_2$), 1.35 (d, $J = 6.22$, 3H, $1/2 \times CH(CH_3)_2$), 1.44–1.78 (m, 8H, $4 \times CH_2$), 1.87–1.97 (m, 1H, $1/2 \times CH_2$), 1.99–2.07 (m, 1H, $1/2 \times CH_2$), 2.75–2.93 (br, 1H, NH), 4.92–4.96 (m, 1H, OCH), 6.76–6.95 (m, 4H, C_6H_4)
4j	1.52–1.73 (m, 10H, $5 \times CH_2$), 2.14–2.25 (m, 1H, $1/2 \times CH_2$), 2.30–2.46 (m, 1H, $1/2 \times CH_2$), 3.47–3.59 (br, 1H, NH), 4.28 (d, $J = 11.3$, 3H, OCH_3), 6.72–6.96 (m, 4H, C_6H_4)
4k	1.34 (t, $J = 6.97$, 3H, CH_3), 1.54–1.71 (m, 10H, $5 \times CH_2$), 2.16–2.21 (m, 1H, $1/2 \times CH_2$), 2.30–2.43 (m, 1H, $1/2 \times CH_2$), 3.46–3.59 (br, 1H, NH), 4.25–4.31 (m, 2H, OCH_2), 6.72–6.96 (m, 4H, C_6H_4)
4l	1.30 (d, $J = 6.22$, 3H, $1/2 \times CH(CH_3)_2$), 1.34 (d, $J = 6.18$, 3H, $1/2 \times CH(CH_3)_2$), 1.44–1.78 (m, 10H, $5 \times CH_2$), 1.87–1.97 (m, 1H, $1/2 \times CH_2$), 1.99–2.07 (m, 1H, $1/2 \times CH_2$), 2.75–2.93 (br, 1H, NH), 4.92–4.98 (m, 1H, OCH), 6.76–6.96 (m, 4H, C_6H_4)
4m	Major: 1.14 (t, $J = 7.04$, 3H, CH_2CH_3), 1.57 (d, $^3J_{PCCH} = 15.6$, 3H, CH_3), 1.65–1.74 (m, 1H, $1/2 \times CH_2$), 1.79–1.98 (m, 1H, $1/2 \times CH_2$), 2.77–2.99 (br, 1H, NH), 3.61 (d, $J = 11.1$, 3H, OCH_3), 6.75–6.87 (m, 4H, C_6H_4); Minor: 1.02 (t, $J = 9.14$, 3H, CH_2CH_3), 1.57 (d, $^3J_{PCCH} = 19.6$, 3H, CH_3), 1.65–1.74 (m, 1H, $1/2 \times CH_2$), 1.79–1.98 (m, 1H, $1/2 \times CH_2$), 2.77–2.99 (br, 1H, NH), 3.61 (d, $J = 11.1$, 3H, OCH_3), 6.75–6.87 (m, 4H, C_6H_4)
4n	Major: 1.11 (t, $J = 7.54$, 3H, CH_2CH_3), 1.35 (t, $J = 7.16$, 3H, OCH_2CH_3), 1.42 (d, $^3J_{PCCH} = 15.82$, 3H, CH_3), 1.67–1.86 (m, 1H, $1/2 \times CH_2$), 1.91–2.06 (m, 1H, $1/2 \times CH_2$), 3.33–3.49 (br, 1H, NH), 4.24–4.33 (m, 2H, OCH_2CH_3), 6.70–6.97 (m, 4H, C_6H_4); Minor: 0.93 (t, $J = 7.16$, 3H, CH_2CH_3), 1.33 (t, $J = 7.16$, 3H, OCH_2CH_3), 1.37 (d, $^3J_{PCCH} = 18.82$, 3H, CH_3), 1.67–1.86 (m, 1H, $1/2 \times CH_2$), 1.91–2.06 (m, 1H, $1/2 \times CH_2$), 3.33–3.49 (br, 1H, NH), 4.24–4.33 (m, 2H, OCH_2CH_3), 6.70–6.97 (m, 4H, C_6H_4)
4o	Major: 1.09 (t, $J = 7.83$, 3H, CH_2CH_3), 1.30 (d, $J = 6.26$, 3H, $CH(CH_3)_2$), 1.36 (d, $J = 6.26$, 3H, $CH(CH_3)_2$), 1.41 (d, $^3J_{PCCH} = 16.04$, 3H, CH_3), 1.70–1.85 (m, 1H, $1/2 \times CH_2$), 1.93–2.03 (m, 1H, $1/2 \times CH_2$), 2.91–3.14 (br, 1H, NH), 4.91–4.96 (m, 1H, OCH), 6.70–6.99 (m, 4H, C_6H_4); Minor: 0.94 (t, $J = 7.54$, 3H, CH_2CH_3), 1.30 (d, $J = 6.26$, 3H, $1/2 \times CH(CH_3)_2$), 1.36 (d, $J = 6.26$, 3H, $1/2 \times CH(CH_3)_2$), 1.41 (d, $^3J_{PCCH} = 17.05$, 3H, CH_3), 1.70–1.85 (m, 1H, $1/2 \times CH_2$), 1.93–2.03 (m, 1H, $1/2 \times CH_2$), 2.91–3.14 (br, 1H, NH), 4.91–4.96 (m, 1H, OCH), 6.70–6.99 (m, 4H, C_6H_4)
4p	Major: 3.58 (d, $J = 11.1$, 3H, OCH_3), 3.56–4.14 (br, 1H, NH), 4.76 (d, $^2J_{PCH} = 10.2$, 1H, CH), 6.77–7.06 (m, 4H, C_6H_4), 7.41–7.60 (m, 5H, C_6H_5); Minor: 3.58 (d, $J = 11.3$, 3H, OCH_3), 3.56–4.14 (br, 1H, NH), 4.59 (d, $^2J_{PCH} = 19.6$, 1H, CH), 6.77–7.06 (m, 4H, C_6H_4), 7.41–7.60 (m, 5H, C_6H_5)
4q	Major: 1.12 (t, $J = 7.35$, 3H, OCH_2CH_3), 3.83–4.05 (m, 2H, OCH_2), 4.75 (d, $^2J_{PCH} = 10.1$, 1H, CH), 6.76–7.05 (m, 4H, C_6H_4), 7.40–7.61 (m, 5H, C_6H_5); Minor: 1.28 (t, $J = 7.35$, 3H, OCH_2CH_3), 3.90–4.15 (m, 2H, OCH_2), 4.63 (d, $^2J_{PCH} = 20.7$, 1H, CH), 6.76–7.05 (m, 4H, C_6H_4), 7.40–7.61 (m, 5H, C_6H_5)
4r	Major: 1.30 (d, $J = 6.26$, 3H, $1/2 \times CH(CH_3)_2$), 1.36 (d, $J = 6.26$, 3H, $1/2 \times CH(CH_3)_2$), 2.91–3.14 (br, 1H, NH), 4.77 (d, $^2J_{PCH} = 10.7$, 1H, CH), 4.93–4.96 (m, 1H, OCH), 6.70–6.99 (m, 4H, C_6H_4), 7.39–7.62 (m, 5H, C_6H_5); Minor: 1.21 (d, $J = 6.41$, 3H, $1/2 \times CH(CH_3)_2$), 1.30 (d, $J = 6.03$, 3H, $1/2 \times CH(CH_3)_2$), 2.91–3.14 (br, 1H, NH), 4.59 (d, $^2J_{PCH} = 16.2$, 1H, CH), 4.76–4.83 (m, 1H, OCH), 6.70–6.99 (m, 4H, C_6H_4), 7.39–7.62 (m, 5H, C_6H_5)

K_2CO_3. There are low yields and much insoluble solid in the reaction mixture found in the absence of K_2CO_3. Future development of asymmetric synthesis of 2-alkoxy-2-oxo-1,4,2-oxazaphosphinanes is in progress.

EXPERIMENTAL

Instruments and Reagents

All melting points were determined on a Yanaco apparatus and are uncorrected. NMR spectra were measured on a Bruker AVANCE 300 NMR instrument in $CDCl_3$, and chemical shifts are expressed as δ. Coupling constants *J* are given in Hertz. Tetramethyl silane was used as an internal standard for ^1H NMR spectroscopy and 85% H_3PO_4 as an external standard for ^{31}P NMR spectroscopy. Mass spectra were recorded on a Polaris-Q instrument of Thermofinnigan. Elemental analysis was carried out on a Yanaco CHNCORDER MT-3 Analyzer. X-ray analysis was done on a Bruker SMART 1000 CCD diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å). Column chromatography was performed using silica gel H (10–40 μm; Haiyang Chemical Factory of Qingdao). The solvent was dried with sodium and redistilled. All the ketones and benzaldehyde were redistilled before use. Alkyl dichlorophosphinite was synthesized according to the document [18].

General Procedure for Synthesis of 2-Alkoxyl-2-oxo-1,4,2-oxazaphosphinanes **4a–r**

o-Aminophenol (10 mmol, 1.09 g) and alkyl dichlorophosphinite (10 mmol) were dissolved in anhydrous THF (30 mL). Then K_2CO_3 (0.02 g) was added at room temperature with stirring. Fifteen minutes later, the ketones or benzaldehyde (10 mmol) was added. After an additional 4 h, the mixture was refluxed for 2 h. The resulting mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with EtOAc/petroleum ether (b.p. 60–90°C, 1:1) to afford analytically pure products. The major isomers of product **4m–r** were recrystallized from ether and hexane at low temperature.

In summary, we have developed a convenient and efficient method for the synthesis of 2-alkoxy-2-oxo-1,4,2-oxazaphosphinane derivatives. A wide range of ketones and benzaldehyde were converted to the corresponding cyclic α-aminophosphonates using this method. The specific structure features give a good explanation of the methylene protons located in the low field in the ^1H NMR spectra. The structure of **4k** and one isomer of **4r** were determined by X-ray analysis.

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