Heteroatom Chemistry
Volume 11, Number 7, 2000

The Reaction of $PhCH_2C(O)NR_2/P(O)Cl_3$ with Phosphites and Hydridophosphorane

Wen-Hu Wang, Guo-Yan Xu, Ru-Zhen Cao, and Lun-Zu Liu

National Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, P.R. China

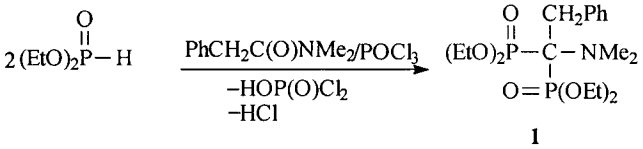
Received 4 April 2000; revised 25 July 2000

ABSTRACT: *The reaction of $PhCH_2C(O)NR_2/P(O)Cl_3$ (R = alkyl) with diethyl or triethyl phosphite afforded E-vinylphosphonates* **3** *with high geometrical stereoselectivity and acceptable yields. The reaction with hydridophosphorane* **8** *gave* **10**, *a novel trisphosphoranylphosphine oxide that can be reduced to the corresponding phosphine* **14**. © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:512–517, 2000

INTRODUCTION

Methylenebiphosphonates featuring a P–C–P linkage constitute not only the basic skeleton of a variety of compounds, but also show interesting biological activities [1]. Likewise, substituted aminomethylene biphosphonates are also an important class of biologically active compounds, and much work has been reported in the recent literature on the synthesis and reactivity of such compounds [2–9].

We have reported previously [10,11,12] that Vilsmeier reagents formed between N,N–disubstituted formamides or N,N-disubstituted acetamides and phosphorus oxychloride react with phosphites or hydridophosphoranes to provide the corresponding aminomethylenebiphosphonates or aminomethylenebiphosphoranes, respectively. Similarly, compound **1** was also obtained by the reaction of $PhCH_2C(O)NMe_2/P(O)Cl_3$ with $(EtO)_2P(O)H$ in a molar ratio of 1:2 without triethylamine (Equation 1) [12]. However, when the reaction of $PhCH_2C(O)NR_2/P(O)Cl_3$ with the phosphite in an equimolar ratio was conducted in the presence of triethylamine, the vinylphosphonates **3** were obtained instead.



1 (1)

It is interesting to note that, when the reaction of $PhCH_2C(O)NR_2/P(O)Cl_3$ with hydridophosphorane **8** was carried out under mild conditions, we obtained an unusual, new trisphosphoranylphosphine oxide **10**, which can readily be reduced to the corresponding phosphine **14** by chloroform.

RESULTS AND DISCUSSION

Reaction of $PhCH_2C(O)NR_2/P(O)Cl_3$ with Diethyl and Triethyl Phosphite

Many methods exist to prepare vinylphosphonates [8,13–16], but there are few routes available for highly stereoselective synthesis of vinylphosphonates. Herein, a novel, simple method for the preparation of *E*-vinylphosphonates is described. This reaction has the advantage of easy availability of the starting materials and a short route (a one-pot reaction, in fact). Particularly, this reaction has high stereoselectivity. $PhCH_2C(O)NR_2/P(O)Cl_3$ reacted

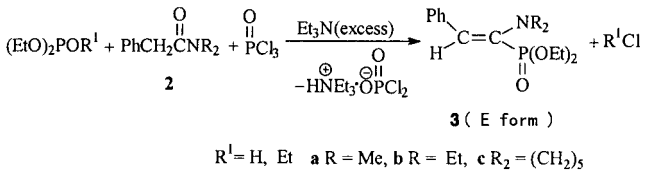
Correspondence to: Lun-Zu Liu.
Contract Grant Sponsor: National Science Foundation of China.
Contract Grant Number: 29972024.

TABLE 1 Yields and Characterization Data of Compounds **3**

R^1	R	Reaction Time (h)	Yield (%)	δ^1H (CH=C)[a]	$\delta^{31}P$	$\delta^{31}P$ (E-form) [16]
H	Me	24	38.4	6.66 (d, $^3J_{PH}$ = 14.6Hz)[b]	17.31[c]	17.03
H	Et	24	37.1	6.23 (d, $^3J_{PH}$ = 15.3Hz)	17.55	17.40
H	$(CH_2)_4$	48	2[d]		17.41	17.41
Et	Me	24	35.2		17.33	
Et	Et	24	49.6		17.57	
Et	$(CH_2)_4$	48	3[d]		17.41	

[a]Data of other groups were omitted.
[b]In the literature [12], ^{1}H NMR data for *E*-**3a**, δ: 6.66 (d, CH=C, $^3J_{PH}$ = 14.6 Hz); for *Z*-**3a**, δ: 6.30 (d, CH=C, $^3J_{PH}$ = 40.66 Hz).
[c]In literature [12], ^{31}P NMR data, for *E*-**3a**, 17.30; for *Z*-**3a**, 14.10.
[d]Not separated yield; the yield was evaluated by ^{31}P NMR spectra.

with diethyl or triethyl phosphite in the presence of excess triethylamine giving *E*-vinylphosphonates **3** (Equation 2 and Table 1).

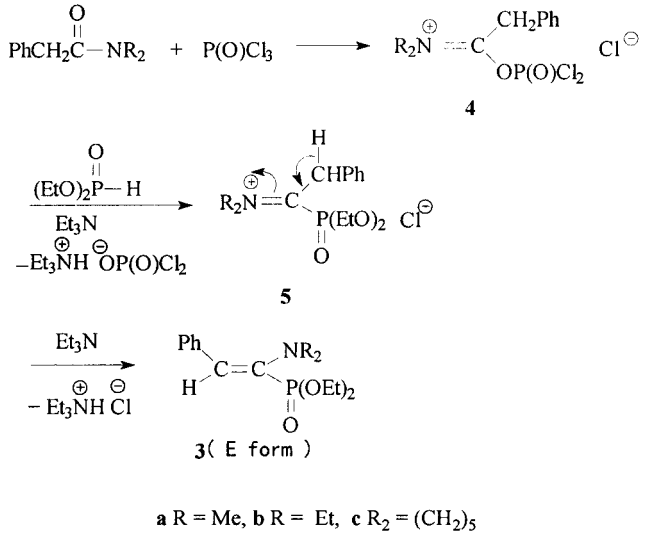


(2)

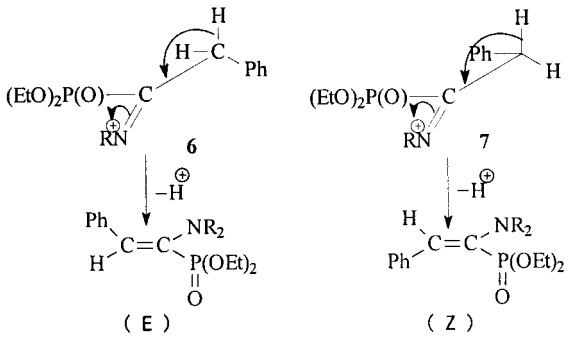
Vilsmeier reagents formed from $PhCH_2C(O)NR_2/P(O)Cl_3$ act in the form of the iminium chloride **4** [12]. Based on this point, we suggest a plausible pathway (Scheme 1) for the reaction described in Equation 2. The phosphorus atom of diethyl phosphite attacks the electrophilic central carbon of **4** with elimination of $HOP(O)Cl_2$ to give the intermediate **5**, which then gives the product with elimination of HCl. In the absence of triethylamine, the intermediate **5a** will react further with another mole of phosphite to give the corresponding biphosphonate **1** [12].

From this reaction, only the *E*-vinylphosphonate was obtained. This may be connected with the conformations **6** and **7** of **5**. Conformation **6** gives the *E*-form and **7** gives the *Z*-form (Scheme 2). With consideration of energy relationships, conformation **6** is more stable than **7** because **7** is more sterically crowded than **6**. An early report from our laboratory [12] pointed out that the *Z*-vinylphosphonate could be converted to the *E*-isomer in refluxing ethyl acetate. Thus, the *Z*-form produced in the third step of Scheme 1 should be transformed to the *E*-form when the reaction mixture is refluxed for a considerable length of time (24 hours). Therefore, the result that only the *E*-isomer is obtained is reasonable.

It should be pointed out that when the iminium chloride **4c** was used, a very low yield of **3c** was obtained (see Table 1). As can be deduced from Scheme 1, the transition state leading to **5** should be very sterically congested. Thus, for the iminium chloride



SCHEME 1

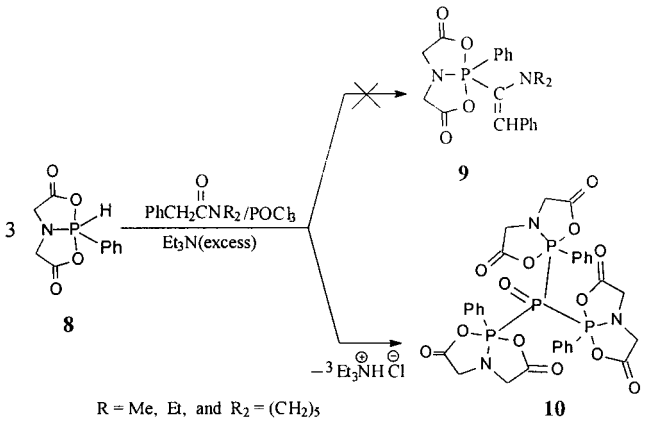


SCHEME 2

4c, the corresponding intermediate **5** might be difficult to be formed because four relatively large groups would be attached to the central carbon atom in the corresponding transition states.

Reaction of $PhCH_2C(O)NR_2/P(O)Cl_3$ with Hydridophosphorane **8** [17]

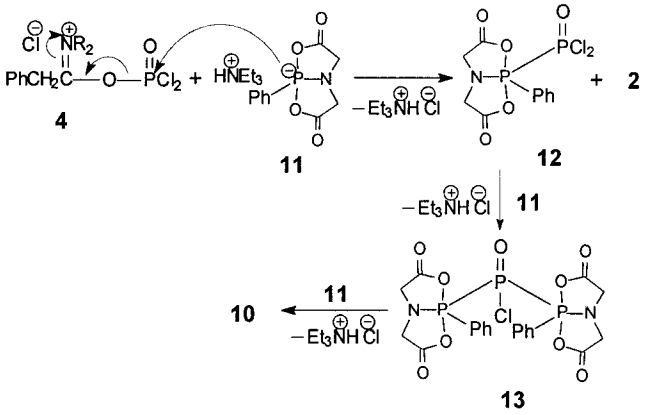
Unlike the reaction previously mentioned, the reaction of hydridophosphorane **8** with $PhCH_2C(O)NR_2/P(O)Cl_3$ did not afford the vinylphosphorane **9**. A new kind of trisphosphoranylphosphine oxide **10** was obtained instead (Equation 3). After a survey of the literature, we found that much work [18–27] has been reported on the synthesis of phosphoranes bearing P–P bonds. The trisphosphoranylphosphine oxide and the corresponding phosphine, however, have not been reported.



(3)

Treatment of $PhCH_2C(O)NR_2/P(O)Cl_3$ with the hydridophosphorane **8** and excess triethylamine gives **10** in ~58–63% yield. Compound **10** is stable to both air and moisture; thermal decomposition takes place only at a temperature over 240°C.

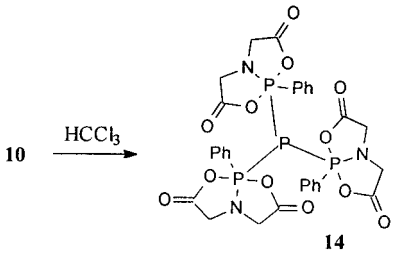
We also found that, if hydridophosphorane **8** was reacted with phosphorus oxychloride in the absence of phenylacetamide **2**, the yield of **10** was very poor, and the purification of the product was rather difficult. Therefore, the suggestion that phenylacetamide **2** may play an important role may be reasonable. Moreover, taking the formation of P–P bonds (in compound **10**) rather than a P–C bond (in compound **9**) into consideration, a plausible mechanism was suggested (Scheme 3). Nucleophilic phosphoranide anion **11** [28] attacks the phosphorus atom of iminium chloride **4** to give **12** with the elimination of hydrogen chloride and phenyl acetamide **2**. Then, **12** reacts with 2-fold amount of **11** to give compound **10**. The reformed **2** has been separated and examined by thin-layer chromatography (TLC) and ^1H NMR spectroscopy. The first step in Scheme 3 might be the rate-determination step.



SCHEME 3

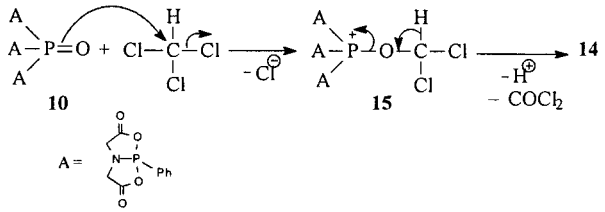
The reason why phosphine oxide **10** rather than vinylphosphorane **9** was formed might be due to steric hindrance. We have shown previously [10] that *N*,*N*-dimethylacetamide (DMA) cannot be used to synthesis N,N-disubstituted amino bisphosphoranyl methane because of steric hindrance. In contrast to the iminium chloride derived from N,N-disubstituted formamide and phosphorus oxychloride, the environment of the iminium carbon in **4** is much more crowded. Thus, a comparatively bulky phosphoranyl anion attacks the phosphorus atom rather than the iminium carbon of **4**. It is well known that a good leaving group in a nucleophilic substitution reaction must readily take on a negative charge [29]. Thus, in this regard, $R_2N^+=C(CH_2Ph)O$ can be expected to be a good leaving group.

We found that compound **10** could be reduced to phosphine **14** by treatment with chloroform at room temperature (Equation 4).



(4)

Many reagents, for example, $LiAlH_4$, $Ca(AlH_4)_2$, CaH_2, silanes, boranes and alanes, have been successfully used to reduce tertiary phosphine oxides to the corresponding tertiary phosphines [30]. However, much experimental data have proved that chloroform could not reduce a common phosphine oxide (like Ph_3PO, Bu_3PO) to a phosphine. We think that the facile reduction of **10** by chloroform may be



SCHEME 4

closely related to the existence of three $\sigma^5\lambda^5$P–$\sigma^4\lambda^5$P bonds. Owing to the three strong electronegative phosphoranyl groups, the nucleophilic reactivity of the P=O oxygen atom in **10** might be stronger than that in ordinary phosphine oxides. A possible mechanism is shown in Scheme 4. The oxygen atom of P=O attacks the carbon atom of $CHCl_3$ with elimination of Cl^- to give the intermediate **15**, which gives **14** with elimination of phosgene. This pathway is different to that in the reduction reaction of a tertiary phosphine oxide by trichlorosilane [31].

The structure of **10** and **14** can be deduced from their ^{31}P NMR spectra, which show an AB_3 spin pattern (see Experimental). Since the $^1J_{PP}$ value both for **10** and **14** are relatively small compared with the $\Delta\delta$ value between the chemical shift of a $\sigma^5\lambda^5$P and that of the central phosphorus atoms ($J/\Delta\delta \cdot \nu_0 \approx 0.06$), the ^{31}P NMR spectra are close to first order [32]. The ^{31}P NMR spectrum of compound **14** is shown in Figure 1.

The $^1J_{PP}$ values in **10** and **14** fall in the range of directly bonded σ^5P and σ^4P atoms [18,19] and of directly bonded σ^5P and σ^3P atoms [21,27]. Roesky et al. [19,20] previously reported compounds in which relatively small spin–spin coupling constants between directly bonded σ^5P and σ^3P atoms were found. However, the two phosphorus atoms in those compounds were included in a cyclic structure. It is quite abnormal, however, that **10** and **14** have, not only very similar ^{31}P chemical shifts, but also a very similar $^1J_{PP}$ value. In order further to confirm the structure of phosphine **14**, the crystal structure of **14** was determined (Figure 2). As can be seen from this figure, it is true that the central phosphorus atom is a $\sigma^3\lambda^3$ phosphorus atom, and the geometry is pyramidal. The crystal structure also shows that all three σ^5P atoms around the central σ^3P atom are equivalent, and the geometry around the σ^5P atoms are strongly distorted trigonalbipyramidal. Selected bond lengths and bond angles are shown in Table 2.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus, and the thermometer was not standardized. ^{1}H NMR spectra were recorded with a Bruker AC-P200 instrument using tetramethylsilane as an internal standard. ^{31}P NMR spectra were determined by a Bruker AC-P200 instrument, 85% H_3PO_4 being used as an external standard. ES mass spectra were obtained with an HP5988A mass spectrometer. FAB mass spectra were obtained on a VG ZAB-HS mass spectrometer. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyzer. All operations were carried out under a nitrogen atmosphere. The N,N-dialkyl phenylacetamides were prepared using a literature method [33]. Tetrahydrofuran was dried over sodium and then distilled from $LiAlH_4$ before use. Commercial chloroform was purified by the usual method prior to use.

General Procedure for Preparation of Compounds **3**

After a mixture of 3.0 mmol phenylacetamide **2** and 0.46 g (3.0 mmol) of phosphorus oxychloride in 15 mL of THF had been stirred at room temperature for 1 hour, 3.0 mmol of diethyl phosphite (or triethyl phosphite) and 0.91 g (9.0 mmol) of triethylamine were added to the mixture with continued stirring. The reaction mixture was then refluxed for 24 hours, cooled by immersion of the flask in cold water and filtered. The filtrate was concentrated under vacuum and the residue was dissolved in 20 mL of di-

TABLE 2 Selected Bond Lengths (A) and Bond Angles (°)

P(1)–P(4)	2.245(3)	P(3)–N(3)	1.648(5)	P(3)–O(9)	1.758(4)	C(1)–N(1)	1.456(8)
P(2)–P(4)	2.244(2)	P(1)–O(1)	1.750(5)	P(3)–O(10)	1.758(4)	C(2)–N(1)	1.441(8)
P(3)–P(4)	2.244(3)	P(1)–O(2)	1.769(5)	P(1)–C(11)	1.813(4)	C(3)–N(2)	1.417(8)
P(1)–N(1)	1.646(5)	P(2)–O(6)	1.749(5)	P(2)–C(21)	1.809(4)	C(4)–N(2)	1.447(8)
P(2)–N(2)	1.646(6)	P(2)–O(5)	1.769(5)	P(3)–C(31)	1.790(4)	C(5)–N(3)	1.469(7)
P(3)–P(4)–P(2)	105.7(1)	O(9)–P(3)–O(10)	172.6(2)	N(2)–P(2)–C(21)			116.7(2)
P(3)–P(4)–P(1)	104.8(1)	N(1)–P(1)–C(11)	118.6(3)	C(21)–P(2)–P(4)			107.7(2)
P(2)–P(4)–P(1)	105.4(1)	N(1)–P(1)–P(4)	136.0(2)	N(3)–P(3)–P(4)			136.6(2)
O(1)–P(1)–O(2)	171.5(2)	C(11)–P(1)–P(4)	105.0(2)	N(3)–P(3)–C(31)			115.8(3)
O(6)–P(2)–O(5)	170.8(2)	N(2)–P(2)–P(4)	135.3(2)	C(31)–P(3)–P(4)			107.4(2)

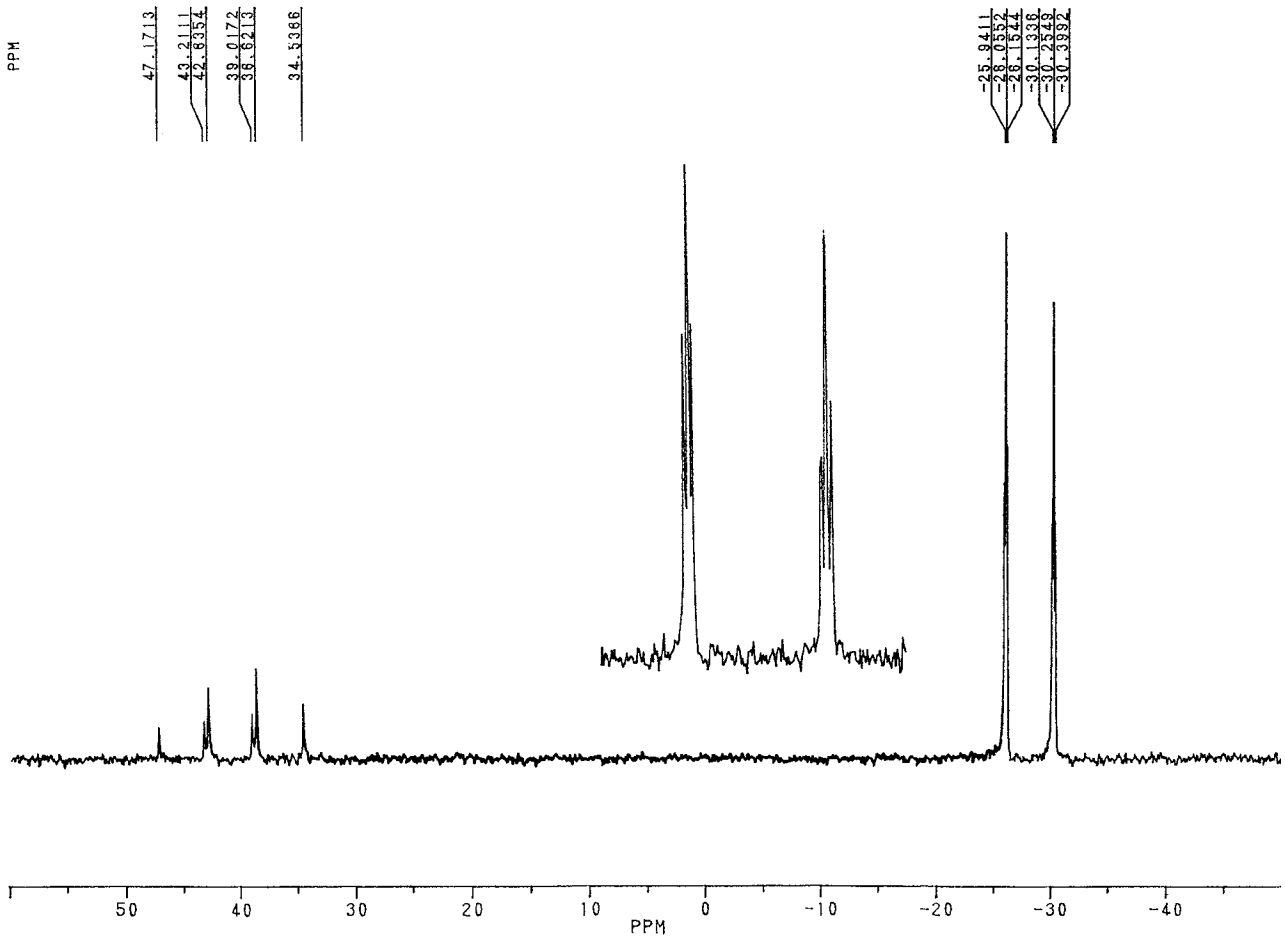


FIGURE 1 ^{31}P NMR spectrum of compound **14**.

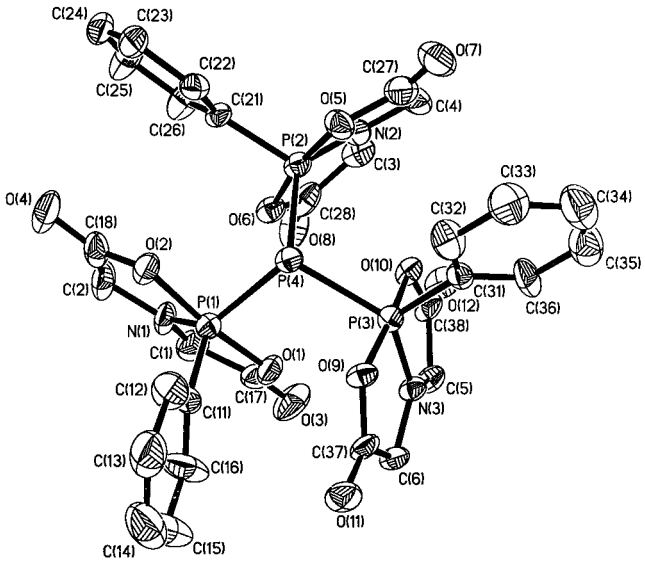


FIGURE 2 Crystal structure of **14**. The hydrogen atoms are omitted for clarity.

chloromethane, washed with water, dried over magnesium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was chromatographed on a column of silica gel using ethyl acetate and petroleum ether as eluant to afford compounds **3**. The yields and ^{1}H NMR and ^{31}P NMR data are shown in Table 1.

Preparation of Compound **10**

A mixture of 2.1 mmol of phenylacetamide **2** and 0.33 g (2.1 mmol) of phosphorus oxychloride in 15 mL of THF was stirred at room temperature for 1 hour. Then a THF solution of 0.5 g (2.1 mmol) of hydridophosphorane **8** and 0.63 g (6.3 mmol) of triethylamine was dropped into the mixture with cooling in an ice-water bath. The reaction mixture was then stirred at room temperature for 30 minutes and filtered. The filtrate was concentrated under vacuum and the residue was dissolved in 20 mL of dichloromethane, washed with water, dried over magnesium sulfate, and filtered. The volatile components were distilled under reduced pressure. Recrystalli-

zation of the residue from dichloromethane ether afforded compound **10** (~0.30–0.34 g, ~58–63%, based on **8**) as white powder, m.p. 240°C (dec.) (Found: C, 47.04; H, 3.50; N, 5.33. $C_{30}H_{27}N_3O_{13}P_4$ requires C, 47.32; H, 3.57; N, 5.52. %); ^{1}H NMR (DMSO-d_6): 3.85 (12H, br., CH_2), ~7.51–7.72(15H, m, Ph); ^{31}P NMR (DMSO-d_6): −23.67 ($\sigma^5\lambda^5$P, m, $^1J_{P\text{-}P}$ = 329.7 Hz), +37.88 ($\sigma^4\lambda^5$P, m, $^1J_{P\text{-}P}$ = 329.7 Hz); *m/z* (ESMS) 762[(M + 1)$^+$].

Preparation of Compound **14**

Compound **10** (100 mg) was dissolved in 5 mL of chloroform contained in a 50 mL round bottomed flask, and the flask was allowed to stand for 30 minutes. Then 5 mL of ether was added and colorless crystals of **14** precipitated gradually. After 24 hours, the crystals of **14** were filtered off and dried in a nitrogen atmosphere. The yield of **14** was 45 mg, 46%; m.p: 216°C, (dec. sealed, N_2) (Found: C, 48.42; H, 3.47; N, 5.41. $C_{30}H_{27}N_3O_{12}P_4$ requires C, 48.30; H, 3.65; N, 5.63%); ^{1}H NMR: 3.34 ~ 4.53 (m, 12H, CH_2); 7.48 ~ 7.73 (15H, m, Ph); ^{31}P NMR: −28.16($\sigma^5\lambda^5$P, m, $^1J_{P\text{-}P}$ = 341.3 Hz), +40.85($\sigma^3\lambda^3$P, m, $^1J_{P\text{-}P}$ = 341.3 Hz); *m/z* (FABMS) 746 [(M + 1)$^+$].

REFERENCES

[1] Ebetino, F. H.; Dansereau, S. M. Bisphosphonate on Bones; Bijvoet, O.; Fleisch, H. A.; Canfield, R. E.; Russell, G., Eds.; Elsevier Science: Amsterdam, 1995; Chapter 9, pp 139–154.

[2] Ebetino, F. H.; Jamieson, L. A. Phosphorus Sulfur Silicon Relat Elem 1990, 51, (1–4), 23.

[3] Ebetino, F. H.; Kaas, S. M.; Crawford, R. J. Phosphorus Sulfur Silicon Relat Elem 1993, 76, (1–4), 411.

[4] Degenhardt, C. R. Synth Commun 1982, 12, (6), 415.

[5] Schrader, T.; Kober, R.; Steglich, W. Synthesis 1986, (5), 372.

[6] Nesterov, L. V.; Krepysheva, N. E.; Aleksandrova, N. A. Zh Obshch Khim 1989, 59, (3), 725.

[7] Prishchenko, A. A.; Livantsov, M. V.; Boganova, N. V.; Zhutskii, P. V.; Lutsenko, I. F. Zh Obshch Khim 1989, 59, (10), 2381.

[8] Costisella, B.; Keitel, I.; Gross, H. Tetrahedron 1981, 37, 1227.

[9] Gross, H.; Costisella, B.; Gnauk, T.; Brennecke, L. J Prakt Chem 1976, 318, 116.

[10] Qian, Dingquan; Zeng, Xingzhong; Shi, Xiaodong; Cao, Ruzhen; Liu, Lunzu. Heteroat Chem 1997, 8 (6), 517–520.

[11] Qian, Dingquan; Shi, Xiaodong; Zeng, Xingzhong; Cao, Ruzhen; Liu, Lunzu. Tetrahedron Lett 1997, 38, 6245–6246.

[12] Qian, Dingquan; Shi, Xiaodong; Cao, Ruzhen; Liu, Lunzu. Heteroat Chem 1999, 10 (4), 271–276.

[13] Fukuda, M.; Kan, K.; Okamoto, Y.; Sajurai, H. Bull Chem Soc Jpn 1975, 48, 2103–2105.

[14] Ahlbrecht, H.; Farnung, W. Synthesis 1977, 336–338.

[15] Schindler, N.; Ploger, W. Chem Ber 1971, 104, 2021–2026.

[16] Maier, L.; Diel, P. J. Ger Offen D.E. 4029444 1989; Ciba-Geigy A.-G. Chem Abstr 1991, 115, 24380.

[17] Liu, L. Z.; Li, G. W.; Huang, M. Z. Phosphorus Sulfur Silicon Relat Elem 1992, 69, 1–4.

[18] Schomburg, D.; Weferling, N.; Schmutzler, R. J Chem Soc Chem Commun 1981, 609–610.

[19] Roesky, H. W.; Djarrah, H. Inorg Chem 1982, 21, 844–845.

[20] Roesky, H. W.; Ambrosius, K.; Sheldrick, W. S. Chem Ber 1979, 112, 1365–1371.

[21] Roesky, H. W.; Ambrosius, K.; Banek, M.; Sheldrick, W. S. Chem Ber 1980, 113, 1847–1854.

[22] Schiebel, H. M.; Schmutzler, R.; Schomburg, D.; Wermuth, U. Z Naturforsch Teil B 1983, 38, 702–704.

[23] Richman, J. E.; Day, R. O.; Holmes, R. R. J Am Chem Soc 1980, 102, 3955.

[24] Roesky, H. W.; Amirzadeh-Asl, D.; Sheldrick, W. S. J Am Chem Soc 1982, 104, 2919–2920.

[25] Bettermann, G.; Schmutzler, R. Polyhetron, 1987, 6 (10), 1823–1831.

[26] Vogt, R.; Schmutzler, R. Z Naturforsch Teil B 1989, 44, 690–698.

[27] Lamande, L.; Munoz, A. Tetrahedron 1990, 46, 3527–3534.

[28] Garrigues, B.; Boyer, D.; Munoz, A. Can J Chem 1984, 62, 2170–2178.

[29] Lowry, T. H.; Richardson, K. S. Mechanism and Theory in Organic Chemistry; Harper & Row: New York, 1981; p 339.

[30] Kosolapoff, G. M.; Maier, L. Organic Phosphorus Compounds; Wiley-Interscience: New York, 1972; Vol. 1, p 45.

[31] Kosolapoff, G. M.; Maier, L. Organic Phosphorus Compounds; Wiley-Interscience: New York, 1972; Vol. 3, p 410–411 and references therein.

[32] Corio, P. L. Chem Rev 1960, 60, 363–420.

[33] Adams, R.; Albert, A. A. J Am Chem Soc 1942, 64, 1475–1478.