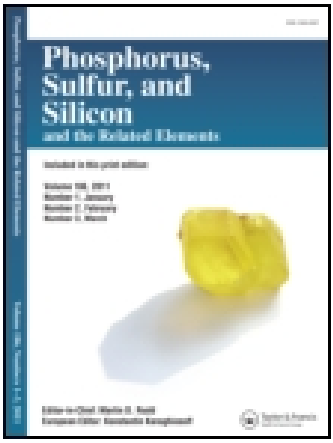

Phosphorus, Sulfur, and Silicon and the Related Elements

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A study on Mannich type reaction synthesis of Diphenyl α-[phenyl N,N-bis(2-chloroethyl) phosphorylamino]methylphosphonates has been carried out. Their geometric stereoisomers were isolated and characterized. The reaction was catalyzed by acetyl chloride and good to excellent yields were obtained under these reaction conditions.

Keywords α-amino phosphonates; acetyl chloride; Mannich type reaction

INTRODUCTION

α-amino phosphonates have received an increasing amount of attention because they are key substrates in the synthesis of phosphonopeptides.[1–3] The use of α-amino phosphonates as enzyme inhibitors,[2–6] antibiotics and pharmacological agents,[7,8] herbicides,[9] and haptens of catalytic antibodies[10,11] are well documented. A number of synthetic methods for the synthesis of α-amino phosphonates has been developed during the past two decades.[12–15] Of these methods, the synthesis of α-amino phosphonates, catalyzed by a base or an acid, is the most convenient.[16,17] The key step in the synthesis of α-amino phosphonates is the nucleophilic addition of an amine to a carbonyl compound followed by the addition of a phosphite to the resulting imine.

Among numerous synthetic methods for the preparation of α-aminophosphonic acids derivatives, the three-component condensation involving substituted amide, aldehyde (or ketone) and phosphorus ester

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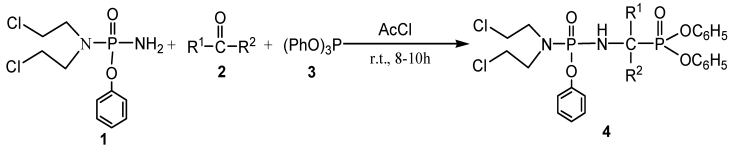
is of significant interest.[18–20] We report here a facile synthetic method for the preparation of α-amino-substituted phosphate-phosphonates derivatives with the aids of a versatile reagent acetyl chloride.

RESULTS AND DISCUSSION

The Mannich-type reaction of trivalent phosphines has proved facile for the preparation of new α-aminoalkanephosphonate compounds. As shown in Scheme 1, (phenyl)bis(2-chloroethyl)amine phosphoramidate (**1**) was allowed to react with triphenyl phosphite (**3**) and various substituted ketones or benzaldehyde (**2**) in acetyl chloride to give the target Diphenyl α-[(phenyl)bis(2-chloroethyl) aminephosphoryl amino]methylphosphonates **4a–e** in moderate to good yields ranging from 56%–90%. It was found that the use of aromatic adehydes led to much better yields than that of ketones. The reactions were carried out using one-pot procedure. All the products were isolated from reaction mixture by column chromatography, and their structures were characterized by ^{1}H NMR, ^{31}P NMR, ^{13}C NMR and mass spectrum.

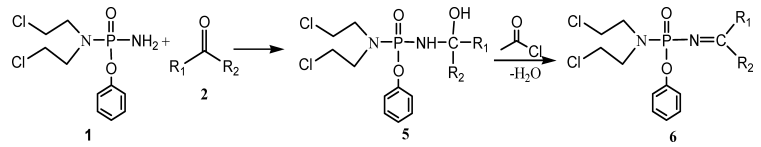


1 **2** **3** **4**

Entry	R^1	R^2	Time/h	Yield(%)	**4**
1	Ph	H	6	94	**4a**
2	*p*- $O_2NC_6H_4$	H	7	95	**4b**
3		H	7	92	**4c**
4	Cyclopentanone		9	88	**4d**
5	Cyclopentanone		9.5	85	**4e**

SCHEME 1

The reactions are aided by using acetyl chloride as a dehydrating agent. It is reasonable to postulate that carbonyl addition of **2** to **1** forms the unstable adduct **5**. Acetyl chloride accelerates the process of intramolecular dehydration of **5** forming the correspond Schiff's base **6** (Scheme 2).



SCHEME 2

The ^{31}P NMR spectra of compound **4** showed two doublets due to the P-P splitting, as shown by identical coupling constants. Similar results were reported by C. Y. Yuan.[18–20] The ^{31}P NMR spectra showed at around $\delta = 15$–20 and at $\delta = 7$–10 ppm, the first one being attributable to the P–atom of the diphenoxyphosphinyl group, and the second one to the P–atom of the N–phosphoryl group. In the ^{1}H NMR spectra of **4**, the CHP proton appears as a doublet–doublet-doublet ($\delta = 5.01$–5.28) due to the pair of phosphorus atoms coupling with coupling constant $^{2}J_{P,CH}$ of 22.2 Hz and $^{3}J_{P,CH}$ of 11 Hz and NH coupling with a coupling constant $^{3}J_{NH,CH}$ of 21 Hz. The EI-MS spectra of **4a–e** show the existence of strong molecular ion peaks, indicating that the molecular skeletons have some stability.

CONCLUSION

We have developed an improved route of the synthesis of Diphenyl α-[(phenyl)bis(2-chloroethyl) aminephosphorylamino]methylphosphonates by using acetyl chloride. The reactions take place under mild conditions with good yields, and acetyl chloride accelerates the process of intramolecular dehydration of **5** forming the corresponding Schiff's base **6**.

EXPERIMENTAL

All melting points were determined on a Yanaco apparatus and were uncorrected. NMR spectra were measured on a Varian AS400 NMR instrument in $CDCl_3$ and chemical shifts were expressed as δ. Coupling constants J are given in Hz. Tetramethyl silane was used as an internal standard for ^{1}H NMR, 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. IR Spectra were recorded on a Equinox55 Spectrometer, and band positions were reported in wave numbers (cm^{-1}). Column chromatograghy was performed using silica gel H (10–40 μm, Ocean Chemical Factory of Qingdao).

General Experimental Procedure for the Preparation of Compounds 4a–e

Freshly distilled ketones or benzaldehyde (1 mmol) is added dropwise to a stirred mixture of (phenyl)bis(2-chloroethyl)amine phosphoramide[21] **1** (1 mmol, 0.30 g), triphenyl phosphate (1 mmol, 0.31 g) and acetyl chloride (5 ml) at room temperature. The process of the reaction is monitored by TLC on silica gel. After 8–10 h stirring at r.t., the resulting mixture is filtered and the filtrate concentrated in vacuo. The residue is purified by column chromatography on silica gel, eluting with EtOAc/petroleum ether (bp 60–90 °C, 1:2) to afford pure products.

4a. White solid, mp:151–152°C; υ_{max}(KBr)/cm^{-1} 3218, 1272, 957, 773; ^{31}P NMR (121 MHz, $CDCl_3$): δ (ppm) 14.56 (d, $J = 43.4$ Hz), 9.64 (d, $J = 43.4$ Hz); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53–6.69 (m, 20H, 4C$_6H_5$), 5.11 (ddd, $^{3}J_{PH} = 10.7$, $^{3}J_{NH-CH} = 21.9$, $^{2}J_{PH} = 23.4$ Hz, 1H, C*H*), 4.75–4.54 (br, 1H, N*H*), 3.32–3.19 (m, 8H, 2CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.76, 129.60, 129.53, 128.92, 128.72, 128.64, 125.34, 125.19, 124.64, 120.82, 120.76, 120.31, 120.27 (4C_6H$_5$), 54.50, 52.38 (d, $J_{CP} = 157.4$ Hz, *C*H), 49.24, 49.18 (2CH$_2$*C*H$_2$Cl), 41.91 (2*C*H$_2$CH$_2$Cl); ESI-MS: [M+H]$^+$ m/z 619. (Found: C, 56.10; H, 4.91; N, 4.65. $C_{29}H_{30}N_2O_5P_2Cl_2$ requires C, 56.23; H, 4.88; N, 4.52%).

4b. White solid, mp:188–189°C; υ_{max}(KBr)/cm^{-1} 3260, 1349, 1274, 975, 768; ^{31}P NMR (121 MHz, $CDCl_3$): δ (ppm) 12.79 (d, $J = 40.3$ Hz), 9.46 (d, $J = 40.3$ Hz); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–6.83 (m, 19H, 3C$_6H_5$, C$_6H_4$), 5.28 (ddd, $^{3}J_{PH} = 10.8$, $^{3}J_{NH-CH} = 22.1$, $^{2}J_{PH} = 22.1$ Hz, 1H, C*H*), 5.07-4.97 (br, 1H, N*H*), 3.48–3.21 (m, 8H, 2CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.22, 130.08, 129.92, 129.69, 129.63, 125.99, 125.90, 125.11, 124.06, 120.75, 120.18 (3C_6H$_5$, C_6H$_4$), 54.22, 52.26 (d, $J_{CP} = 161.2$ Hz, *C*H), 49.16 (2CH$_2$*C*H$_2$Cl), 42.17 *C*H$_2$CH$_2$Cl); ESI-MS: [M+H]$^+$ m/z 664. (Found: C, 52.44; H, 4.07; N, 6.34. $C_{29}H_{29}N_3O_7P_2Cl_2$ requires C, 52.42; H, 4.40; N, 6.32%).

4c. White solid, mp:140–141°C; υ_{max}(KBr)/cm^{-1} 3215, 1269, 952, 772; ^{31}P NMR (121 MHz, $CDCl_3$): δ (ppm) 14.51 (d, $J = 42.9$ Hz), 9.42 (d, $J = 42.9$ Hz); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–6.75 (m, 18H, 3C$_6H_5$, C$_6H_3$), 5.95 (s, 2H, OCH_2O), 5.01 (ddd, $^{3}J_{PH} = 9.1$, $^{3}J_{NH-CH} = 20.2$, $^{2}J_{PH} = 21.5$ Hz, 1H, C*H*), 4.34–4.24 (br, 1H, N*H*), 3.40–3.27 (m, 8H, 2CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.55, 122.47, 120.94, 120.91, 120.51, 120.47, 120.43, 120.38, 109.09, 109.03, 108.73, 101.53 (3C_6H$_5$, C_6H$_3$), 54.01, 52.51 (d, $J_{CP} = 161.3$ Hz, *C*H), 49.44, 49.41 (2CH$_2$*C*H$_2$Cl), 42.28 (2*C*H$_2$CH$_2$Cl); ESI-MS: [M+Na]$^+$ m/z 685. HRMS (ESI-MS) [M+Na]$^+$ Calcd for $C_{30}H_{30}N_2O_7P_2Cl_2Na^+$ 685.0798, found 685.0794.

4d. White oil; υ_{max}(KBr)/cm^{-1} 3267, 1265, 968, 783; ^{31}P NMR (121 MHz, $CDCl_3$): δ (ppm) 20.09(d, J = 11.4 Hz), 7.51 (d, J = 11.4 Hz); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.11 (m, 15H, 3C$_6H_5$), 4.12 (dd, $^2J_{P-NH} = 14.3$, $^3J_{P-NH} = 7.1$ Hz, 1H, NH), 3.64–3.50 (m, 8H, 2CH_2CH_2), 2.37–2.27 (m, 2H, CH_2), 2.18–2.06 (m, 2H, CH_2), 1.89–1.62 (m, 6H, 3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.94, 129.91, 125.25, 124.89, 120.83, 120.78, 120.74, 120.35, 120.31 (3C_6H$_5$), 58.11, 56.52 (d, J_{CP} = 159.8 Hz, CH), 49.56 (2CH$_2C$H$_2$Cl), 42.78 (2CH$_2$CH$_2$Cl), 31.89, 31.41, 25.26, 20.74, 20.64(5CH$_2$); ESI-MS: [M+H$^+$] m/z 611. HRMS (ESI-MS) [M+Na]$^+$ Calcd for $C_{28}H_{34}N_2O_5P_2Cl_2Na^+$ 633.1212, found 633.1204.

4e. White oil; υ_{max}(KBr)/cm^{-1} 3271, 1259, 981, 785; ^{31}P NMR (121 MHz, $CDCl_3$): δ (ppm) 21.47 (d, J = 22.7 Hz), 7.56 (d, J = 22.7 Hz); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.17 (m, 15H, 3C$_6H_5$), 4.12 (dd, $^2J_{PH}$ = 14.3, $^3J_{PH}$ = 7.1 Hz, 1H, NH), 3.66–3.44 (m, 8H, 2CH_2CH_2), 2.50-2.36 (m, 4H, 2CH_2), 2.10–2.01 (m, 2H, CH_2), 1.93–1.81 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.79, 129.73, 125.15, 124.71, 120.63, 120.59, 120.05, 119.98 (3C_6H$_5$), 63.57, 61.38 (d, J_{CP} = 165.1 Hz, CH), 49.42, 49.36 (2CH$_2C$H$_2$Cl), 42.43 (2CH$_2$CH$_2$Cl), 36.02, 35.83, 29.70, 24.64 (4CH$_2$); ESI-MS: [M+H]$^+$ m/z 597. HRMS (ESI-MS) [M+Na]$^+$ Calcd for $C_{27}H_{32}N_2O_5P_2Cl_2Na^+$ 619.1056, found 619.1051.

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