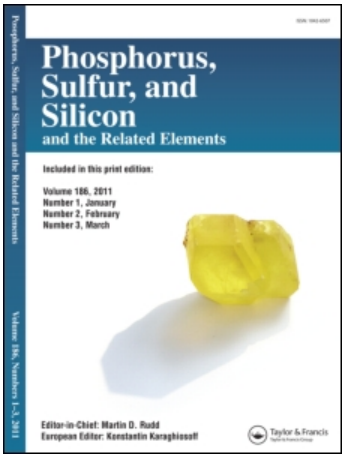

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SYNTHESIS OF PRIMARY α-CHLOROPHOSPHINES BY A CHEMOSELECTIVE REDUCTION OF α-CHLOROPHOSPHONATES

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SYNTHESIS OF PRIMARY α-CHLOROPHOSPHINES BY A CHEMOSELECTIVE REDUCTION OF α-CHLOROPHOSPHONATES

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Reduction of chloromethylphosphonates with lithium aluminium hydride gave a mixture of chloromethylphosphine and methylphosphine, characterized by NMR, IR and mass spectra. Reduction of the same compounds by AlH_3 gave chloromethylphosphine as nearly the only product. Extension of this reaction to the C-substituted derivatives gave the corresponding α-chlorophosphines with good chemoselectivity.

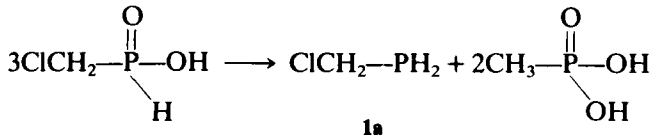
Key words: Reduction of phosphonates; aluminium hydride; chemoselectivity; primary phosphines.

INTRODUCTION

Primary alkyl- or arylphosphines are valuable starting materials in organophosphorus chemistry.[1] The most suitable method for their synthesis is the reduction of various precursors like phosphonous dihalides or phosphonates with lithium aluminium hydride (LAH) or trisubstituted silanes. However, there is still no efficient method for the reduction of phosphonate derivatives bearing a functional group in the α-position.[2] We report here a chemoselective reduction of α-chlorophosphonates to the corresponding α-chlorophosphines which are of particular interest as precursors of unhindered phosphaalkenes.[3]

RESULTS AND DISCUSSION

The only known α-chlorophosphine is the parent compound **1a**. It was synthetized by thermal disproportionation of chloromethylphosphinic acid (Equation 1). This reaction requires a relatively high temperature (150°C), gives a low yield (<35%), and must be carried out with caution owing to the explosive character of the chlorophosphinic acid precursor when heated "in vacuo".[4]

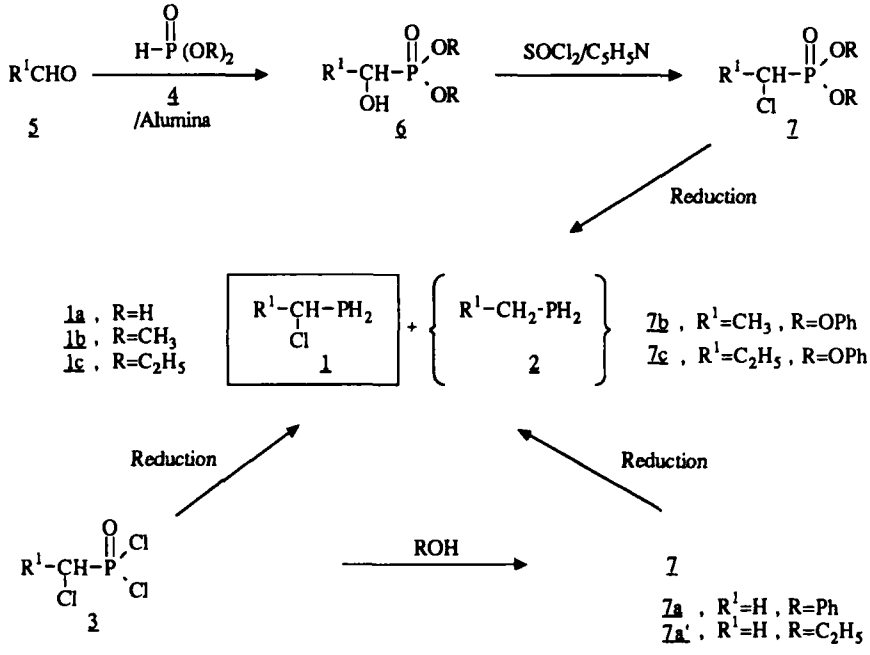


$$3ClCH_2{-}P(=O)(H){-}OH \longrightarrow \underset{\textbf{1a}}{ClCH_2{-}PH_2} + 2CH_3{-}P(=O)(OH){-}OH \qquad (1)$$

We show that the chemoselective reduction of various α-chlorophosphonyl derivatives gives the best results and can be generalized to the C-substituted compounds, although this reaction has been found more challenging than expected.

In order to easily purify the phosphines **1**, tetraglyme was chosen in all the reductions as the polar non-volatile solvent. The suspension containing the reducing agent was stirred continuously and pumped (10^{-3} mm) during the reduction. The new phosphines **1** prepared herein were purified by standard vacuum line techniques and characterized by ^{1}H, ^{13}C, ^{31}P NMR, IR and Mass Spectra.

We investigated the efficiency and selectivity of some reducing agents towards various precursors of $ClCH_2PH_2$ (Scheme 1). The results are summarized in Table I. LAH reduction of chlorophosphonate **7a'**[5] proceeds smoothly at −20°C to afford a mixture of **1a**, methylphosphine, and ethanol (entry 1). Purification of **1a** is not possible owing to the presence of ethanol. A slightly cleaner product can be obtained with phosphonyl derivatives substituted by better electron-withdrawing groups such as $—P(O)(OPh)_2$ or $—P(O)Cl_2$ (entries 2 and 3). Chloromethylphosphine **1a** can be purified on the vacuum line but the yield is always poor. Thus, LAH gives primary phosphines but gives no chemoselectivity when a C—Cl bond is in an α-position to the phosphonyl group. Other hydride reagents like sodium borohydride or trimethylsilylhydride were inefficient. The reduction problem was finally solved using aluminium hydride (AlH_3).[6] Reduc-



SCHEME 1

TABLE I

Product distribution and yield from reduction of **3.7** under selected conditions

Entry	Reactant	Product distribution[a] with L A H (%)		Product Yield(%)[a]	Entry	Products distribution[a] with AlH_3 (%)		Product Yield(%)[a]
		1	2			1	2	
1	**7a'**	**1a** (26)	**2a** (74)	**1a** (7)[b]	4	**1a** (78)	**2a** (22)	**1a** (65)
2	**7a**	**1a** (41)	**2a** (59)	**1a** (32)	5	**1a** (>95)	**2a** (<5)	**1a** (80)
3	**3**	**1a** (60)	**2a** (40)	**1a** (35)	6	**1a** (67)	**2a** (23)	**1a** (27)
	7b				7	**1b** (95)	**2b** (5)	**1b** (88)
	7c				8	**1c** (97)	**2c** (3)	**1c** (92)

[a] Determined using an internal reference (entries 1–4, 6). For preparative scale (entries 5,7,8), all yields refer to purified matérial. [b] Presence of EtOH (<20%).

tion of chlorophosphonates **7a'**, **7a** in tetraglyme leads to the chloromethylphosphine **1a** in good yield with only a small amount of **2a** as a by-product.[7] The diphenyl ester **7a** gives the best results (entry 5). In contrast, a poor yield was observed in the reduction of 3 (entry 6). Complexation between the reducing agent AlH_3 and the phosphonate group can explain this chemoselectivity. A similar and significant difference has also been observed in this reduction of α-chlorocarboxylic acid or ester groups.[6b] Of particular interest is the fact that a combination of the two reagents, trimethylsilyl chloride/LAH in 1:1 molar ratio[8] gave, after vacuum elimination of the resulting $HSiMe_3$, similar results. The infrared spectrum (Et_2O) of this reducing agent presents two bands at 1790 cm^{-1} (ν_{Al-H}) and 760 cm^{-1} (δ_{Al-H}) in good agreement with those observed with an authentic AlH_3 sample.[9] Consequently, the three preparative methods for AlH_3 (LAH/$AlCl_3$;[6a] LAH/H_2SO_4[6b] and LAH/$ClSiMe_3$[8]) can be independently used.[10]

We have extended this reduction to the chloroalkyldiphenylphosphonates **7b** and **7c** (Scheme 1). The synthesis of α-hydroxyphosphonates is well documented.[11] Treatment of aldehyde **5** with diphenylphosphonate **4** on alumina in dry media[11b] leads to the corresponding hydroxyphosphonate **6**, which is then chlorinated using thionyl chloride/pyridine in a 1:1 molar ratio. Reduction of **7** with AlH_3 in tetraglyme gives the corresponding α-chlorophosphine **1** in excellent yield (entries 7 and 8). These reactions can be easily extended on a preparative scale (>10 g). α-Chlorophosphines polymerize slowly at room temperature. However, they can be kept without decomposition for several months with a catalytic amount of hydroquinone.

The reduction of α-chloroalkylphosphonyl derivatives with metal hydride has been explored. Aluminium hydride appears to be the best reagent. The search for other valuable α-functionalized primary and secondary phosphines is continuing in our laboratory.

(Caution: All reactions and handling of phosphines should be carried out under an inert atmosphere in a well-ventilated hood).

EXPERIMENTAL SECTION

All reactions were carried out under an inert atmosphere of dried nitrogen using a two-necked round-bottom flask equipped with a gas-inlet tube, a rubber septum and a stirring bar. All glassware was flamed before use. Tetraglyme was purified by refluxing over and distillation from sodium/benzophenone under reduced pressure (0.01 mmHg). Chlorotrimethylsilane and thionyl chloride were distilled from magnesium and pyridine was distilled from potassium hydroxyde pellets. IR spectra of the phosphines were obtained on a Perkin–Elmer Model 157G using a KBr window cooled with liquid nitrogen. ^{1}H, ^{31}P, ^{13}C NMR spectra were recorded on a Brucker WP 80 DS or Brucker WP 80 spectrometer Chemical shifts are given in p.p.m. relative to internal $SiMe_4$ for ^{1}H and ^{13}C spectra and external 85% H_3PO_4 for ^{31}P NMR spectra. Chemical shifts upfield to the standard are defined as negative. High resolution mass spectra were recorded on a Varian MAT 311 spectrometer.

1-Hydroxyalkyldiphenylphosphonates **6b** *and* **6c** were prepared according to the literature.[11b] Inexpensive γ-alumina (Merck) gave satisfactory results.

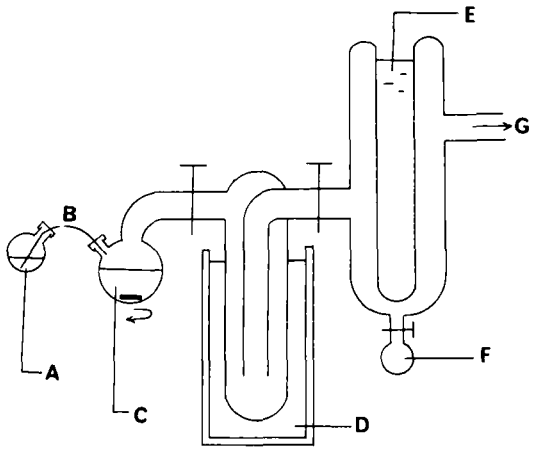
1-Hydroxyethyldiphenylphosphonate **6b** (92% isolated yield, mp 63°C) ^{1}H NMR ($CDCl_3$) δ 1.57 (dd, 3H, $^{3}J_{HH} = 7.5$ Hz, $^{3}J_{HP} = 18.0$ Hz), 4.3 (qd, 1H, $^{2}J_{HP} = 2.4$ Hz), 4.65 (s, 1H), 7.2 (m, 10H); ^{31}P NMR (THF) 13.1 IR (cm^{-1}) (nujol): $\nu_{P\rightarrow O}$, 1220 (vs); ν_{P-O-C} 1205 (s); 940 (s). Anal. after recrystallisation from cyclohexane calc. for $C_{14}H_{15}O_4P$: C, 60.48; H, 5.43; P, 11.94. Found: C, 60.50; H, 5.51; P, 11.14. *1-Hydroxypropyldiphenylphosphonate* **6c** (90% isolated yield, mp 89°C) ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3H, $^{3}J_{HH} = 7.6$ Hz), 1.65–2.35 (m, 2H), 4.10 (m, 1H, $^{3}J_{HH} = 3.5$ Hz, $^{3}J_{HH'} = 3.5$ Hz, $^{3}J_{HH'} = 4.9$ Hz, $^{3}J_{HP} = 8.7$ Hz), 7.16 (m, 10H); ^{31}P NMR (THF) δ 17.5. IR (cm^{-1})(nujol): $\nu_{P\rightarrow O}$, 1225 (vs); ν_{P-O-C}, 1200 (s), 950 (s). Anal. after recrystallisation from cyclohexane calc. for $C_{15}H_{17}O_4P$: C, 61.64; H, 5.86; P, 10.60. Found: C, 61.64; H, 5.87; P, 10.62.

Preparation of 1-chloroalkyldiphenylphosphonates **6.** *General procedure* In a 500 ml round-bottom-flask were placed the phosphonate **6** (0.05 M), toluene (200 mL) and pyridine (6.5 mL, 0.08 M). Thionyl chloride (6 mL, 0.08 M) was added at room temperature over 3 min. and the mixture was heated at toluene reflux for 5 hours and then allowed to cool to room temperature. After several washings (1.0 N HCl solution), water (30 mL), sodium carbonate 10% (30 mL), water (30 mL), saturated NaCl (30 mL), water (30 mL)), the solution was dried over $MgSO_4$. The toluene was evaporated under reduced pressure (20 mmHg, 60°C) and the residue was dried under vacuum (0.01 mm) during 10 hours. This crude product (purity higher than 90%) can be used for the following reductions. Pure crystallized product was obtained after purification on bone black. *1-chloroéthyldiphenylphosphonate* **7b** (91% in crude product, mp 47°C) ^{1}H NMR ($CDCl_3$) 1.85 (dd, $^{3}J_{HH} = 7.6$ Hz, $^{3}J_{HP} = 16.0$ Hz), 4.25 (m, 1H, $^{3}J_{HP} = 10$ Hz), 7.25 (m, 10H); ^{31}P NMR (THF) δ 7.5; ^{13}C NMR ($CDCl_3$) δ 19.2 (q, $^{1}J = 132$ Hz, $^{2}J_{CP} = 3$ Hz), 46.0 (dd, $^{1}J_{CP} = 163$ Hz, $^{1}J_{CH} = 150$ Hz), 120.5 (d, $^{1}J = 163$ Hz), 120.7 (d, $^{1}J_{CP} = 163$ Hz), 125.7 (d, $^{1}J = 150$ Hz), 125.7 (d, $^{1}J = 163$ Hz), 130.0 (d, $^{1}J = 162$ Hz), 150.1 (d, $^{2}J_{CP} = 3$ Hz), 150.7 (d, $^{2}J_{CP} = 3$ Hz); IR (cm^{-1})(nujol): $\nu_{P\rightarrow O}$, 1290 (s); ν_{P-O-C}, 1195 (s), 945 (s). Anal. after recrystallization from cyclohexane/ether. calc. for $C_{14}H_{14}O_3P$: H, 4.72; Cl, 11.97; P, 10.44. Found: H, 4.69; Cl, 12.52; P, 9.89.

1-chloropropyldiphenylphosphonate **7c** (85% in crude yield, mp 53°C) ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3H, $^{3}J = 7$ Hz), 1.80–2.67 (m, 2H), 4.10 (td, 1H, $^{3}J_{HH} = 8$ Hz, $^{2}J_{HP} = 5$ Hz), 7.17 (m, 10 Hz); ^{13}C NMR ($CDCl_3$) δ 11.3 (q, $^{1}J = 124$ Hz, $^{3}J_{CP} = 13.6$ Hz), 25.0 (t, $^{1}J = 131$ Hz, $^{2}J_{CP} = 3$ Hz), 53.3 (t, $^{1}J_{CP} = 160$ Hz, $^{1}J_{CH} = 147$ Hz), 120.5 (d, $^{1}J = 163$ Hz), 120.7 (d, $^{1}J = 163$ Hz), 129.9 (d, $^{1}J = 162.1$), 150.2 (d, $^{2}J_{CP} = 3$ Hz), 150.6 (s, $^{2}J_{CP} = 3$ Hz); IR (cm^{-1})(nujol): $\nu_{P\rightarrow O}$, 1290 (s); ν_{P-O-C}, 1195 (s), 945 (s). Anal. after recrystallization from cyclohexane/ether. Calc. for $C_{15}H_{16}ClO_3P$: H, 5.15; Cl, 11.43; P, 9.98. Found: H, 5.29; Cl, 11.61; P, 10.09.

Reduction of 1-chloromethyldiethylphosphonate **7a'**; In a 50 mL round-bottomed flask was placed LAH (100 mg, 2.64 mM) in 25 mL of tetraglyme. After cooling to −30°C, 1-chloromethyldiethylphosphonate **7a'** (0.55 g, 3.51 mM) was added with stirring and this temperature was maintained for 4 hours. The volatile products were distilled from tetraglyme under vacuum (10^{-2} mm g) and condensed on a liquid nitrogen trap (Scheme 2). The observed products **1a**, **2a** accompanied with traces of tetraglyme and ethanol, are identified by comparison with authentic samples. Separation of chloromethylphosphine **1a** from ethanol was impossible by trap-to-trap distillation.

Preparation of AlH_3: Method A. Preparation by modification of the procedure described by Ashby.[6a] In a 50 mL round-bottomed flask, LAH (125 mg, 3.29 mM) was diluted in tetraglyme (25 mL). $AlCl_3$ (144 mg, 1.08 mM) was added portion by portion at room temperature over 5 min under a nitrogen blanket. Then the mixture was stirred for 30 min. *Method B. Preparation by reaction of $ClSiMe_3$ with*



SCHEME 2. Apparatus used for preparative reductions of α-chlorophosphonates: A, introduction of the precursor on the reducing mixture; B, flex-needle; C, reducing mixture; D, cold trap (−120°C); E, cold finger (liquid nitrogen); F, flask; G, vacuum line.

LAH (1:1). The procedure described by Kyba[8] was modified. Chlorotrimethylsilane (0.45 mL, 3.5 mM) was added to a stirred suspension of LAH (125 mg, 3.28 mM) in 25 mL of tetraglyme cooled at −30°C. The reducing mixture was allowed to warm to room temperature (2 hours). Then $HSiMe_3$ was removed under vacuum (10^{-2} mmHg, 10 min). IR (Et_2O)(cm^{-1}): ν_{Al-H}, 1790; δ_{Al-H} 760. These values are in agreement with those described in the literature.[9] *Method C. Preparation of AlH_3 by reaction of LAH with H_2SO_4 according to Brown's procedure.*[6b]

Reduction of 1-chloromethyldiphenylphosphonate **7a** *with AlH_3 (analytical scale).* The flask containing the reducing mixture was placed in C on the vacuum line (Scheme 2) and the phosphonate **7a** (0.55 g, 2 mM) in 5 mL of tetraglyme was added slowly at room temperature with a flex-needle in the flash through the septum. As soon as they were formed, volatile compounds were distilled from the tetraglyme under vacuum (10^{-2} mmHg) and collected on the liquid nitrogen cold finger. The major product is the chloromethylphosphine **1a** accompanied by a small amount of methylphosphine and tetraglyme. Tetraglyme can be eliminated using a −80°C trap between the reduction flask and the liquid nitrogen finger (entry 5).

Reduction of 1-chloroalkyldiphenylphosphonate **7** (*preparative scale*). *General procedure.*[10] AlH_3 (0.17 M) was prepared starting from a LAH/$ClSiMe_3$ mixture in 250 mL of tetraglyme. A Schlenk flask containing 0.2 g of hydroquinone was fitted on the vacuum line at F (Scheme 1). The phosphonate **7** (0.1 M) was dissolved in 150 mL of tetraglyme and added under vacuum through the septum to the flask containing the reducing mixture over 60 min at room temperature. The vacuum was maintained one more hour. During and after the addition, chloroalkylphosphine **1** and accompanying tetraglyme were condensed in a −120°C cold trap while the by-product alkylphosphine **2** was eliminated. After the reaction, the cold trap was allowed to warm slowly to room temperature to avoid carrying away some tetraglyme during this trap-to-trap distillation. Thus, the chloroalkylphosphine **1** was condensed on the liquid nitrogen trap then collected in the Schlenk flask.

1-Chloromethylphosphine **1a** 80% yield, purity >95% (^1H NMR) Ref. 4 *1-chloroethylphosphine* **1b**: 88% yield, purity >95% ^1H NMR ($CDCl_3$) δ 1.77 (dd, 3H, $^3J_{HH} = 7$ Hz, $^3J_{HP} = 14$ Hz), 3.3 (dd, 2H, $^1J = 198$ Hz, $^3J = 6$ Hz), 4.3 (m, 1H, $^3J = 7$ Hz, $^2H = 6$ Hz); ^{13}C NMR ($CDCl_3$) δ 28.0 (q, $^2J = 9.8$ Hz, $^1J = 130$ Hz), 45.3 (d, $^1J = 152.3$ Hz, $^1J_{CP} = 14.7$ Hz); ^{31}P NMR (THF) δ −98.0; IR (cm^{-1})(film) ν_{PH}, 2305 (vs); ν_{C-Cl}, 705 (vs). High-resolution mass spectrum for C_2H_6ClP, Calcd; 95.9895, found: 95.9895. *1-chloropropylphosphine* **1c**: 92% yield, purity >95% ^1H NMR ($CDCl_3$) δ 1.1 (t, 3H, $^3J_{HH} = 7$ Hz), 1.92 (m, 2H, $^3J_{HH} = 7$ Hz), 3.5 (s, 2H, $^3J_{HH} = 6$ Hz), 4.2 (s, 1H, $^2J_{HP} = 6$ Hz, $^3J_{HH} = 6$ Hz); ^{13}C NMR ($CDCl_3$) δ 12.0 (qd, $^1J = 122$, $^3J_{CP} = 6.8$ Hz), 34.1 (td, $^1J = 131$ Hz); ^{31}P NMR (THF) δ −104.0; IR (cm^{-1})(film): ν_{PH}, 2285 (vs); ν_{CCl}, 720 (s). High-resolution mass spectrum for C_3H_8ClP, Calcd: 110.0052, found: 110.0051.

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