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Phosphate–Phosphonate Conversion: Nucleophilic Displacement Reactions Involving Phosphoric Amides and Alkyllithiums

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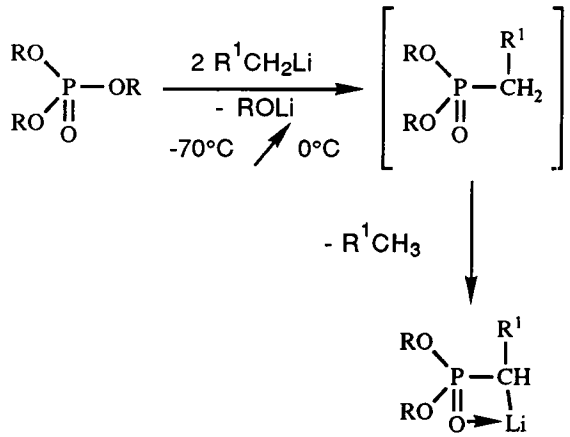
ABSTRACT

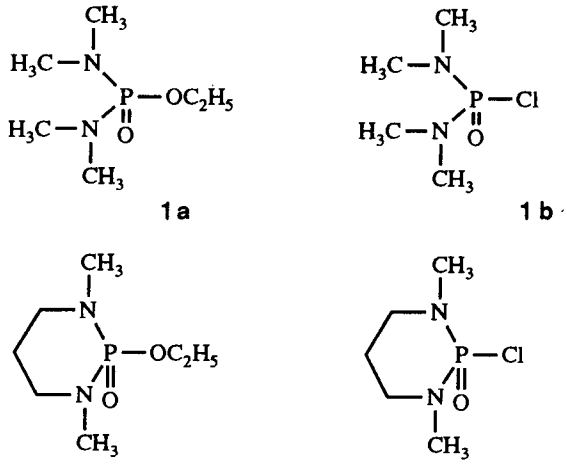
Alkylation at phosphorus with alkyllithiums of acyclic, 5-membered, and 6-membered cyclic phosphoric amides was investigated. The chlorinated derivatives reacted in all cases to afford stable α-(lithioalkyl)phosphonamides. Only 2-ethoxy-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine reacted similarly. The study has shown that steric hindrance at phosphorus is the main control of the reaction.

INTRODUCTION

Action of alkyllithiums upon cyclic and acyclic phosphoric acid esters has already been investigated. Acyclic phosphoric esters lead to α-(lithioalkyl)phosphonates [1] in quantitative yield (Equation 1).

We investigated this reaction in the field of acyclic and cyclic phosphoric amides in order to provide an attractive route to α-lithioalkylphosphonamides and alkyl-phosphonamides [2]. The large variety of available secondary amines and diamines allows a comprehensive evaluation of the different reactivities of the phosphorus atom in acyclic and cyclic phosphoric diamides. We focused on three phosphoramidic moieties (**1**, **2**, and **3**) with decreasing steric hindrance and increasing electrophilicity (Scheme 1). In each case, reactions were performed with the two leaving groups EtO and Cl, which show increasing leaving capability.





SCHEME 1

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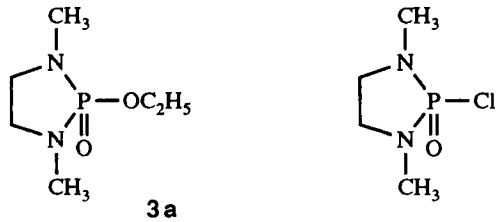
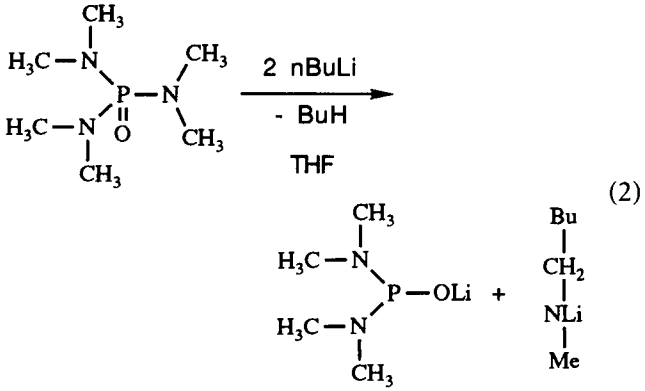


3a 3b

SCHEME 1 (*continued*)

RESULTS AND DISCUSSION

It is known that treating tris-(dimethylamino)-phosphate (HMPA) in tetrahydrofuran with salt-free *n*-butyllithium at low temperature affords quantitative yields of bis(dimethylamino)lithiophosphite (δ_P (THF) +133.7) on warming the reaction mixture. Since the phosphorus atom is highly hindered, *n*-butyllithium cannot act as a nucleophile and hence abstracts a proton from a methyl group. Subsequent rearrangement, with cleavage of a P—N bond, affords the parent-lithiated phosphite and *N*-methyl formimine [3] (Equation 2). Two equivalents of *n*-butyllithium were used, one as base, the other as nucleophile; each one reacted with the generated *N*-methylformimine.



(2)

In a previous study [4], we demonstrated the important effect of lithium salts upon the alkylation–metalation reaction involving phosphoric acid esters. In particular, alkyllithiums showed better nucleophilicity toward the phosphorus atom in salt-free solutions. This can be explained by an activation of alkyllithiums through coordination between the phosphoryl group and lithium [5], a reaction that is enhanced in salt-free medium. Thus, when performed in the presence of lithium bromide, the reaction between HMPA and *n*-butyllithium (Equation 2) afforded only 53% of the lithiated phosphite.

Since lithium salts may act as a regulator, reactions reported in this paper were performed with and without salts in order to define the best reaction conditions.

Bis(dimethylamino)ethylphosphate (**1a**) and -chlorophosphate (**1b**)

1a behaved similarly to HMPA when treated at −70°C with 2 equiv of *n*-butyllithium that contained lithium bromide, then warmed up to 0°C. However, the reaction was not complete after 2 h, and the reaction mixture contained about 30% ethyl-(dimethylamino)lithiophosphite (δ_P (THF) +130.6), 5% unidentified compound (δ_P (THF) +97.0), and 65% unreacted **1a**. No product resulting from an alkylation at phosphorus was detected. The abstraction of a proton from **1a** was slow enough to allow the competing attack of the solvent, which consumed the base and hence stopped the reaction.

The same reaction performed in salt-free solution led to analogous results. As deduced from the ^{31}P NMR spectrum, the ratio was 50% (phosphite), 10% (unidentified by-product) and 40% (unconsumed **1a**), respectively. Higher activity of *n*-butyllithium does not induce any alkylation at phosphorus, but only leads to more undesired reactions.

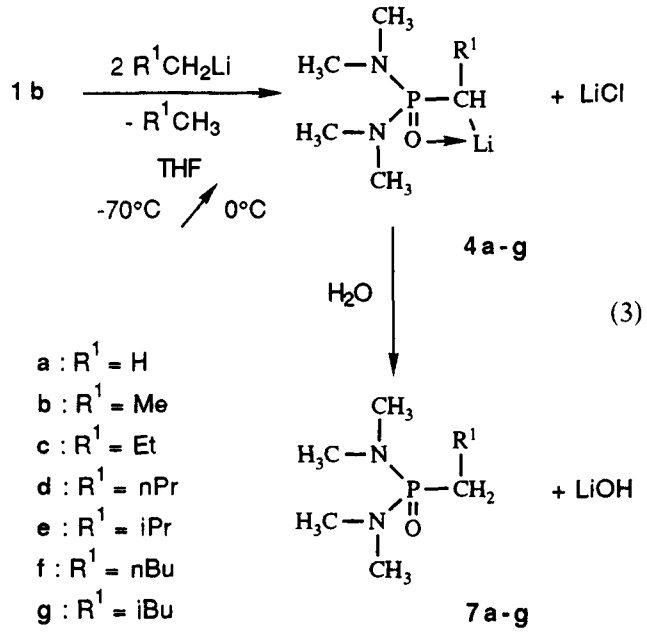
In complete contrast, **1b** reacted cleanly with *n*-butyllithium to give quantitatively the stable α-(lithiobutyl)bis(dimethylamino)phosphonate (**4d**), both with and without the presence of lithium bromide.

The alkylation–metalation reaction of **1b** was extended to both linear lithiated species (methyl-, ethyl-, propyl-, butyl-, and pentyllithium), and branched species (isobutyl- and isopentyllithium) (Table 1). Hydrolysis with water afforded bis(di-

TABLE 1 ^{31}P Chemical Shifts (δ) of Anions **4, 5, 6** (Recorded in THF with LiBr or LiCl) and Parent Protonated Compounds **7** (Recorded in $CDCl_3$), **8, 9** (Recorded in THF).

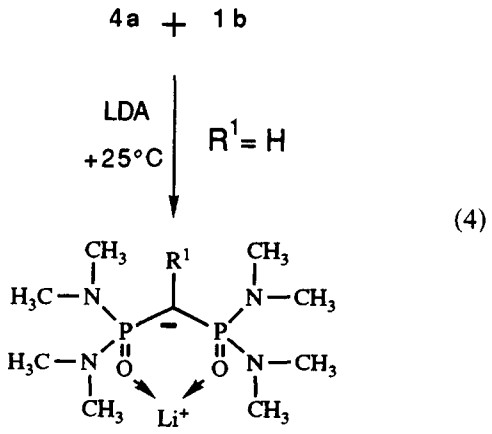
	a	*b*	*c*	*d*	*e*	*f*	*g*
R^1	*H*	*Me*	*Et*	*nPr*	*iPr*	*nBu*	*iBu*
4	+63.7	+57.2	+55.8	+54.2	+51.9	+54.4	+54.3
7	+36.3	+37.6		+36.4	+35.2	+36.3	+36.7
5	+61.3			+50.7			
8	+32.2			+30.7			
6	+66.2	+61.7	+58.5	+57.4	+54.9	+59.8	+58.5
9	+36.7			+39.1			+39.1

methylamino)alkylphosphonates (**7**), which were isolated and purified (Equation 3).



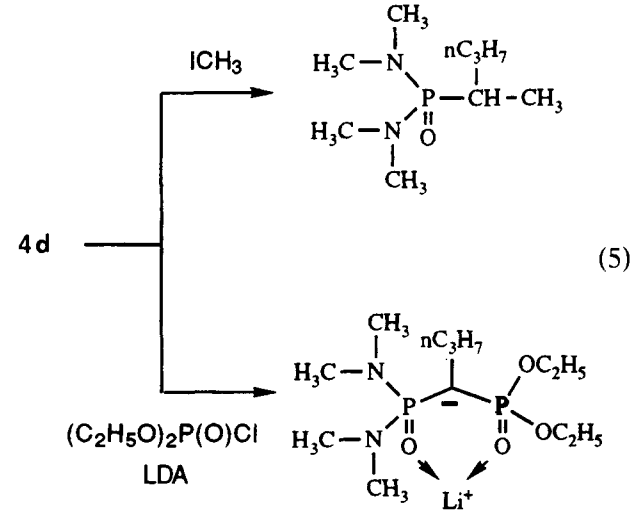
(3)

Unlike diethylchlorophosphate, which was attacked at −70°C by both the alkyllithium and the generated α-lithioalkylphosphonate (diphosphorylation reaction) [4] during the alkylation–metalation reaction, bis(dimethylamino)chlorophosphate (**1b**) did not react with the generated carbanion under the same operating conditions. This reaction could only be observed with the least substituted carbanion **4a** (R^1 = H) at a low rate at 25°C (2.5 h) (Δ_P (THF) +48.4). The structure of the lithiomethylenediphosphonamide thus obtained was identified by comparing its $\delta^{31}P$ with those of previously characterized lithioalkylidenediphosphonates [6] (Equation 4).



(4)

This shows that **1b** is a hindered electrophilic species, and that its reactivity essentially depends on steric factors. Carbanion **4d** was successfully methylated and phosphorylated. In this latter case, the phosphoramidate phosphonate anion obtained at −70°C (δ_P (THF) +48.5, +40.2; J_{PP} 88) was identified by comparing it with compounds already synthesized [4] (Equation 5).



(5)

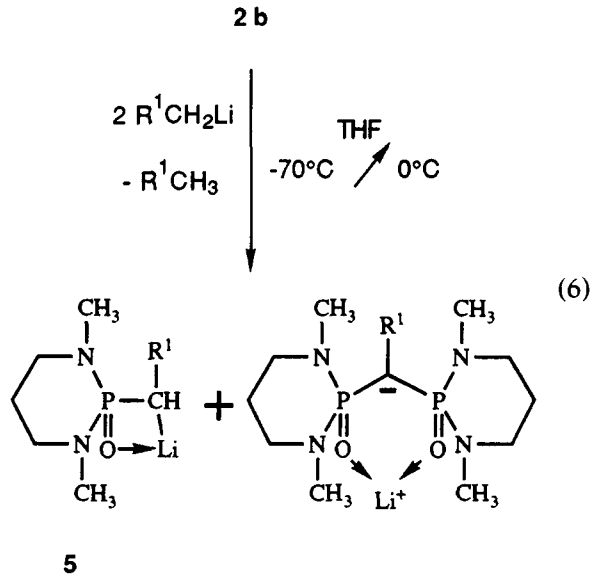
2-Ethoxy- (**2a**) *and 2-Chloro-* (**2b**) *2-Oxo-1,3-dimethyl-1,3,2-diazaphosphorinanes*

Compounds **2a** and **2b** exhibit better access to the phosphorus atom than does **1**, this access is provided by the six-membered ring. However, **2a** was not alkylated at the phosphorus atom by 2 equiv of *n*-butyllithium, whether or not lithium bromide was present. As deduced from the ^{31}P NMR spectrum, the reaction mixture contained 90% unreacted **2a** and 10% unidentified by-product (δ_P (THF) + 124.6). This must be the result of a reaction similar to the reaction between HMPA and *n*-butyllithium.

As expected, the initial reaction of **2b** with *n*-butyllithium (salt-free or not) at −70°C afforded quantitatively the metalated and alkylated product **5d** (δ_P (THF) +50.8) when the mixture was warmed (Table 1).

The lower steric hindrance of **2b** was evidenced by the reaction with methyllithium containing lithium iodide. This reaction afforded the expected carbanion **5a** and 8% diphosphorylation product (δ_P (THF) +46.8, to be compared with that obtained by phosphorylation of **1b**, +48.4) (Equation 6). It is noteworthy that diphosphorylation took place on warming the reaction mixture to 0°C, whereas in **1b** it occurred only at 25°C.

The corresponding phosphonates **8a** and **8d** could only be characterized by ^{31}P NMR spectroscopy, because all attempts to isolate those compounds, in either basic or neutral medium, failed because of their hydrophilic properties.



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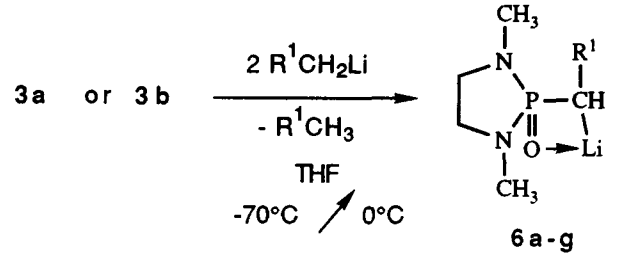
(6)

2-Ethoxy- (**3a**) *and 2-Chloro-* (**3b**) *2-Oxo-1,3-dimethyl-1,3,2-diazaphospholidine*

Unlike **1** and **2**, both **3a** and **3b** reacted readily with linear and branched alkyllithiums to afford quantitatively stable α-(lithioalkyl)diazaphospholidines (**6**) (Table 1) (Equation 7).



6a-g

(7)

These reactions were very salt-dependent. We observed a dramatic variation in the alkylation rate (decreasing in the presence of lithium salts). We also observed two signals in the ^{31}P NMR spectrum for each of carbanions **6** in salt-free solution, whereas only one was detected when lithium bromide (1 equiv) was present. We examined **6a** that was generated by action of n-butyllithium in a 1:1 mixture of tetrahydrofuran and hexane upon 2-methyl-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine at variable temperature with respect to ^{31}P NMR spectroscopy. We observed a complex multiplet (δ_P (THF) +63.0–+70.0) at any temperature between −80°C and 0°C, which suggested that the anion was aggregated. This is supported by the observation that this salt precipitated on warming. Addition of lithium bromide at 0°C caused the dissolution of the precipitated salt, and the ^{31}P NMR spectrum became a singlet (δ_P (THF) +67.2). We suggest that the two signals observed in the presence of lithium ethylate are the result of a partially aggregated carbanion, which is completely disassociated by the action of 1 equiv of lithium halide.

3a was alkylated at phosphorus at −70°C by a salt-free *n*-butyllithium solution (δ_P (THF), 2 signals in 75:25 ratio, +57.6 and +61.0), but remained unaffected at low temperature by *n*-butyllithium containing lithium bromide. In this case, the alkylation took place only on warming the reaction mixture to 0°C (δ_P (THF) +57.6).

As for **3b**, the alkylation with salt-free *n*-butyllithium was also complete at −70°C (δ_P (THF) +57.5), and the ^{31}P spectrum showed only one singlet because lithium chloride was generated during the reaction.

Methyllithium, being far less reactive than other alkyllithiums, reacted completely with **3a** at phosphorus in salt-free solution at −20°C (δ_P (THF) +65.4 and +68.7) and incompletely in the presence of lithium iodide, even at 0°C.

By contrast, **3b** was completely methylated at phosphorus between −70°C and 0°C, both with and without the presence of lithium iodide (δ_P (THF) +68.2 and +66.2 respectively).

Compounds **3** are sufficiently electrohilic (more deshielded phosphorus atoms) and less hindered to provide them with a greater reactivity toward alkyllithiums, sufficient to prevent diphosphorylation kinetically.

The alkylated products **9** were not isolated after hydrolysis. Isolation was very disappointing because these 5-membered ring compounds are very soluble in water and subject to ring-opening. This is not a major drawback for our future investigation, since the phosphorus moiety is eliminated when used in synthesis. Although both **3a** and **3b** are reactive, we suggest the use of **3b** because the generated LiCl is a "softer" species than EtOLi.

CONCLUSION

This study has demonstrated a general route to acyclic and cyclic alkylphosphonamides after selection of the best leaving group (NR_2 < EtO < Cl). It has also confirmed the important role that lithium salts play in alkylation–metalation reactions as regulators for the substitutions at phosphorus. It has shown that the steric environment at phosphorus mainly controls this first reaction in the phosphoramide series. Since **1b** and **2b** behaved similarly, in our future studies we will focus attention on the phosphoramide precursors (**1b, 3a, 3b**), which are easily acccessible on a large scale and are stable materials. We are now investigating their potential in synthesis.

EXPERIMENTAL

All reactions were performed under nitrogen. Nuclear magnetic resonance spectra were recorded on multinuclear WP 80 SY and AC 200 Bruker spec-

trometers operating at 20.15 and 50.32 (^{13}C) and 32.44 (^{31}P) MHz. Chemical shifts are in parts per million with $CDCl_3$ as internal standard (^{13}C) and with 85% H_3PO_4 as external standard (^{31}P). Coupling constants are in hertz. All alkyllithiums except methyllithium were titrated just before use with 2,2'-bi-quinoline as color indicator and with a 1 M solution of benzyl alcohol in toluene. Methyllithium required the use of *N*-(1-naphthyl) aniline.

Materials

n-Butyllithium in hexane, and methyllithium in ether, salt-free, or containing lithium iodide, are commercially available. All other akyllithiums used in this paper were prepared from the appropriate alkyl bromide and lithium metal in ether. Compounds **1a** [7] and **1b** [8] were prepared by known methods; **2a, 2b, 3a,** and **3b** were prepared by the improved procedures described hereafter [9].

Preparation of 2-ethoxy-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine (**3a**). *N,N'*-dimethylethylenediamine (8.6 g, 0.1 mol) and triethylamine (22.2 g, 0.22 mol) dissolved in 300 mL of tetrahydrofuran were placed in a 500-mL flask. Ethyl dichlorophosphate (16.3 g, 0.1 mol) in 100 mL of tetrahydrofuran was added dropwise at +10°C with vigorous stirring. The solution was then stirred for an additional 1 h at room temperature. The resulting triethylamine hydrochloride was collected by filtration and washed (THF), and the organic filtrate was concentrated until the residue attained a constant weight. The crude product was dissolved in a mixture of dichloromethane and ether (1:1), then washed with small quantities (about 2 × 5 mL) of water, dried ($MgSO_4$), and evaporated to afford 12.6 g (70%) of a pale yellow oil; bp 82–84 (0.3 mm Hg); δ_P ($CDCl_3$) +22.3, δ_H ($CDCl_3$) 1.18 (t, 3H), 2.5 (d, 6H, J_{3PH} 10), 3.0 (d, 4H, J_{3PH} 10), 3.85 (dq, 2H); δ_C ($CDCl_3$) 16.1 (CH_3, s, OCH_2CH_3), 31.4 (CH_3, s, NCH_3), 46.6 (CH_2, d, *J* 13, NCH_2), 62.0 (CH_2, s, OCH_2).

Preparation of 2-ethoxy-2-oxo-1,3-dimethyl-1,3,2-diazaphosphorinane (**2a**). Preparation is identical to that of **3a**. This colorless oil was dissolved in ether to eliminate the remaining salts. Yield 82% after filtration and concentration under vacuum. δ_P ($CDCl_3$) +13.0; δ_H ($CDCl_3$) 1.18 (t, 3H), 1.6–2.2 (m, 2H), 2.56 (d, J_{3PH} 10.5, 6H), 2.6–3.2 (m, 4H), 3.87 (qi, 2H); δ_C ($CDCl_3$) 15.5 (CH_3, s, OCH_2CH_3), 22.0 (CH_2, s, CH_2), 34.7 (CH_3, s, NCH_3), 50.3 (CH_2, s, NCH_2), 60.3 (CH_2, s, OCH_2CH_3).

Preparation of 2-chloro-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine (**3b**). Phosphorus oxychloride (15.3 g, 0.1 mol) in 100 mL of tetrahydrofuran was added under stirring at +5°C to *N,N'*-dimethyl ethylenediamine (8.6 g, 0.1 mol) and triethylamine (22.2 g, 0.22 mol) in 300 mL of tetrahydrofuran contained in a 500-mL flask. After 1 h at room temperature, the mixture was filtered, the hydrochloride washed (THF), and the organic solution concentrated under vacuum to afford a very hygroscopic, pale yellow solid, which was dried and stored in vacuo. The crude product was subsequently used without any purification. Yield 85%; mp 76°C, δ_P ($CDCl_3$) +26.4 (major signal) and +28.1 (minor signal); δ_H ($CDCl_3$) 2.6 (d, J_{3PH} 12.7, 6H), 2.8–3.6 (m, 4H); δ_C ($CDCl_3$) 30.6 (CH_3, s), 45.0 (CH_2, d, *J* 13.7).

Preparation of 2-chloro-2-oxo-1,3-dimethyl-1,3,2-diazaphosphorinane (**2b**). Preparation is identical to that of **3b**. The product was not isolated and was used immediately in further reactions. δ_P (THF) +25.4.

Alkylation–metalation of compound **1b**. In accordance with a typical working procedure (e.g. preparation of *P*-butyl-*N,N,N',N'*-tetramethylphosphonic diamide (**7d**)), Bis-(dimethylamino) chlorophosphate (**1b**) (0.020 mol, 3.4 g) in tetrahydrofuran (15 mL) was added at −78°C with stirring to *n*-butyllithium (1.6 N in hexane, 5% excess; 0.042 mol, 27 mL) in a 1:1 mixture of hexane and tetrahydrofuran. The solution was stirred for 15 min at this temperature and then slowly warmed to 0°C. Then it was hydrolyzed with water (25 mL) and extracted with methylene chloride (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and evaporated under vacuum. The resulting colorless oil was distilled under vacuum. Yield 84%; bp 92–95°C (1 mm Hg); δ_P ($CDCl_3$) +36.2; δ_C ($CDCl_3$) 12.3 (CH_3, s), 22.5 (CH_2, s), 22.9 (CH_2, s), 23.3 (CH_2, d, *J* 115, PCH_2), 34.5 (CH_3, s, NCH_3).

Analogously, *P*-methyl-*N,N,N',N'*-tetramethylphosphonic diamide (**7b**), *P*-pentyl-*N,N,N',N'*-tetramethylphosphonic diamide (**7f**), and *P*-(3-methylbutyl)-*N,N,N',N'*-tetramethylphosphonic diamide (**7g**) were obtained.

7b: yield 76%; bp 74–77°C (1 mm Hg); δ_P ($CDCl_3$) +37.6; δ_C ($CDCl_3$) 5.4 (CH_3, s), 16.9 (CH_2, d, *J* 116.3), 35.0 (CH_3, s, NCH_3).

7f: yield 81%; bp 100–104°C (1 mm Hg); δ_P ($CDCl_3$) +36.3; δ_C ($CDCl_3$) 13.0 (CH_3, s), 21.1 (CH_2, s), 21.4 (CH_2, s), 24.2 (CH_2, d, *J* 114.8, PCH_2), 32.4 (CH_2, s), 35.2 (CH_3, s, NCH_3).

7g: yield 82%; bp 98–102°C (1 mm Hg); δ_P ($CDCl_3$) +36.7; δ_C ($CDCl_3$) 21.2 (CH_3, s), 21.9 (CH_2, d, *J* 115.4, PCH_2), 28.2 (CH_2, d, *J* 16), 30.0 (CH, s), 35.0 (CH_3, s, NCH_3).

Alkylation–metalation of compound **2b**. Preparation was identical to that of **1b**. However, attempts to isolate the protonated compounds **8** were unsuccessful. Hydrolysis with dilute HCl until the pH was neutral, or with a stoichiometric amount of formic acid, did not allow isolation of the product that remained in the aqueous phase.

Alkylation–metalation of compound **3a**. In accordance with a typical working procedure (e.g. preparation of 2 α-lithiobutyl-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine (**6d**)), 2-ethoxy-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine (**3a**) (0.020 mol, 3.6 g) in tetrahydrofuran (15 mL) was added at −70°C with stirring to *n*-butyllithium (1.6 N in hexane, 5% excess; 0.042 mol, 27 mL) in a 1:1 mixture of hexane and tetrahydrofuran. The solution was slowly warmed to 0°C and was kept at this temperature for 15 min. The resulting carbanion was ready to be used (quantitative as deduced from ^{31}P NMR).

Under the same operating conditions, **6b**, **6c**, and **6e** were obtained from the corresponding alkyllithiums in ether with lithium salts. **6a** was obtained from salt-free methyllithium.

Carbanion **6a** was obtained independently by direct metalation of 2-methyl-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine.

The protonated compound **9** could not be isolated. The difficulties encountered were similar to that encountered with compound **8**.

Preparation of 2-methyl-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine. *N,N'*-dimethylethylenediamine (8.6 g, 0.1 mol) and triethylamine (22.2 g, 0.22 mol) dissolved in 300 mL of tetrahydrofuran were placed in a 500-mL flask. Methyldichlorophosphonate (13.3 g, 0.1 mol) in 50 mL of tetrahydrofuran was added dropwise at +10°C with vigorous stirring. Then the solution was stirred for an additional 1 h at room temperature. The resulting triethylamine hydrochloride was collected by filtration and washed (THF), and the combined organic filtrate was concentrated until the residue attained constant weight. The crude product was redissolved in ether (350 mL) to eliminate remaining salts. Subsequent filtration and evaporation of the filtrate under vacuum afforded 12.6 g (86%) of a pale yellow oil that crystallized spontaneously; mp 38–40°C. Caution, this compound is very hygroscopic. δ_P ($CDCl_3$) + 36.9; δ_H ($CDCl_3$) 1.34 (d, J_{2PH} 15, 3H), 2.56 (d, J_{3PH} 10, 6H), 2.45–3.45 (m, 4H); δ_C ($CDCl_3$) 10.1 (CH_3, d, J 117.5, PCH_3), 30.1 (CH_3, s, NCH_3), 46.5 (CH_2, d, J 9).

Metalation of 2-methyl-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine was performed in tetrahydrofuran at −70°C with *n*-butyllithium in hexane.

REFERENCES

[1] M. P. Teulade, P. Savignac, *Tetrahedron Lett., 28,* 1987, 4, 405; M. P. Teulade, P. Savignac, *Janssen Chimica Acta, 15,* 1988, 6 (2), 3.

[2] M. Regitz, in *Houben-Weyl, Methoden der Organischen Chemie, Phosphorverbindungen II,* Georg Thieme Verlag, Stuttgart, Germany, 1982, pp. 411–14.

[3] H. Normant, T. Cuvigny, G. J. Martin, *Bull, Soc. Chim. Fr.,* 1965, 1605; K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, D. K. Roe, *J. Am. Chem. Soc., 98,* 1970, 5747; E. M. Kaiser, J. D. Petty, L. E. Solter, *J. Organomet. Chem., 61,* 1973, 1; A. E. Abatjoglou, E. L. Eliel, *J. Org. Chem., 39,* 1974, 3042.

[4] P. Savignac, M. P. Teulade, C. Patois, *Heteroatom Chemistry,* in press.

[5] D. A. Lee, W. L. Taylor, W. J. MacDowell, J. S. Drury, *J. Inorg. Nucl. Chem., 30,* 1968, 2807; T. V. Healy, *J. Inorg. Nucl. Chem., 31,* 1969, 499; S. Kusukabe, T. Sekno, *Bull. Chem. Soc. Jpn, 53,* 1980, 2081; H. B. Flora, Ph.D. Thesis, Univ. of S. Carolina, 1971; *Diss. Abstr., 32,* 1971–1972, 6947; B. D. Seebach, *Angew. Chem. Int. Ed. Engl., 27,* 1988, 1624; D. Barr, W. Clegg, R. E. Mulvey, R. Snaith, *J. Chem. Soc., Chem. Commun., 1984,* 226. L. M. Jackman, L. M. Scarmoutzos, W. Porter, *J. Am. Chem. Soc., 109,* 1987, 6524; H. J. Reich, D. P. Green, *J. Am. Chem. Soc., 111,* 1989, 8729.

[6] M. P. Teulade, P. Savignac, E. E. Aboujaoude, S. Lièrge, N. Collignon, *J. Organomet. Chem., 304,* 1986, 283.

[7] K. Sasse, in *Houben-Weyl, Methoden der Organischen Chemie, Organische Phosphorverbindungen, XII/2,* Georg Thieme Verlag, Stuttgart, Germany 1963, p. 457.

[8] P. Lester. U.S. 2,678,335 (1953).

[9] H. Ulrich, B. Tucker, A. A. R. Sayigh, *J. Org. Chem., 32,* 1967, 1360.