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Controlled monohalogenation of phosphonates☆ Part IV. Selective synthesis of monohalogenomethylenediphosphonates

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Dedicated to Professor Jean F. Normant on the occasion of his 65th birthday

Abstract

The preparation of monohalogenated tetraalkyl methylenediphosphonates **5** has been studied. Upon electrophilic halogenation lithiated chloro-, bromo- and iodomethylenediphosphonates **4a–c** are selectively prepared from unprotected lithiated methylenediphosphonates **2** whereas the protected ones **3** are unreactive. Condensation of lithiated dihalogenomethanes with diethyl chlorophosphate **7** leads to the formation of lithiated chloro-, and bromomethylenediphosphonates **4a**,**b**. A possible reaction pathway via intermediate carbenoids is proposed. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Electrophilic halogenation; SNP(V) reaction; Phosphonate; Halogenomethylenediphosphonate

1. Introduction

The tetraalkyl monohalogenomethylenediphosphonates are compounds of great synthetic utility currently employed for the synthesis of the corresponding α-halogenovinylphosphonates [2–8]. Additionally, they present interesting biological properties for the treatment of bone disorders [9]. Owing to their pyrophosphate analogy, the methylenediphosphonates act as inhibitors of RNA polymerase activity of influenza virus A. The halogenation of methylenediphosphonates results in more active compounds than the parent structure in particular biological systems. For example, the chloromethylenediphosphonate is a better inhibitor than methylenediphosphonate itself [10]. The inhibitory power of methylenediphosphonates appears to be related to their ability to chelate with metal anions [10,11].

There are several methods for the preparation of monohalogenomethylenediphosphonates. They include: (a) the partial reduction of dihalogenated methylenediphosphonates [11–17] developed mainly for the chloro and bromo derivatives; (b) the unselective electrophilic halogenation of metalated methylenediphosphonates [18–21] studied with all four halogens; (c) the electrophilic phosphorylation (SNP(V)) of lithiated halogenomethylphosphonates [2,3,22,23] applied to fluoro- and chloro- derivatives; (d) the self-condensation of lithiated dihalogenomethylphosphonates [7,22,24–26] carried out with fluoro- and chloro- derivatives; (e) the Michaelis–Arbuzov reaction of trialkyl phosphites with diethyl dichloromethylphosphonate [27].

There are no known methods for the selective conversion of methylenediphosphonates to monohalogenated methylenediphosphonates by a common route to the four halides. As part of an ongoing study on the selective monohalogenation of phosphonates, we have been interested in the synthesis of monohalogenomethylenediphosphonates. Two complementary approaches have been investigated and compared: the first one by electrophilic halogenation of lithiated

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methylenediphosphonates and the second by nucleophilic substitution at phosphorus [28] with lithiated dihalogenomethanes.

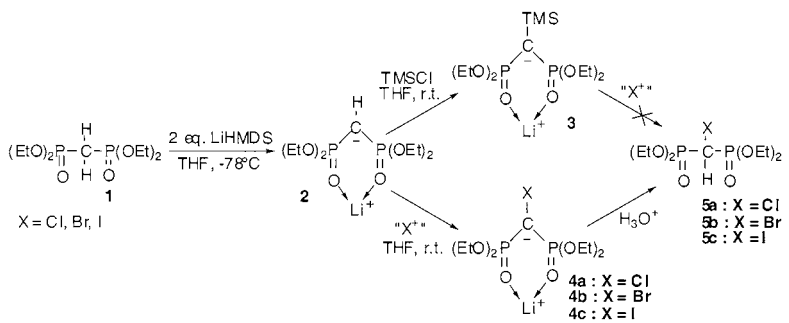
2. Results and discussion

Tetraethyl methylenediphosphonate (**1**) has been used as candidate for electrophilic halogenation. Whereas a significant part of its chemistry has already been described concerning the formation of dihalogenated derivative, neither has been reported on its selective electrophilic monohalogenation. In view of our previous work on the controlled monohalogenation of phosphonates [1,29–31] by temporary silicon connection [32], the tetraethyl 1-lithio-1-trimethylsilylmethylenediphosphonate **3** was a good model for electrophilic halogenation reactions and should lead selectively to the monohalogenated methylenediphosphonate (**5**).

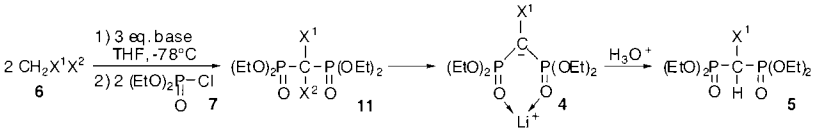
Tetraethyl methylenediphosphonate (**1**) on reaction with TMSCl at room temperature in the presence of LiHMDS (two equivalents) led to the complete formation of **3** (δ ^{31}P(THF) +41.7 ppm) via the unprotected anion **2** (Scheme 1). Unfortunately, the protected anion **3** being too delocalized was unchanged after several hours of exposure to each of the halogenating agents (NFBS, C_2Cl_6, $C_2Cl_4Br_2$, I_2) whatever the temperature. By monitoring (^{31}P-NMR) the reactions, the slow protonation of **3** was the only reaction observed.

We turned then to the halogenation of the unprotected tetraethyl 1-lithiomethylenediphosphonate **2**, prepared from **1** and LiHMDS (two equivalents) (Scheme 1). In the reaction of **2** with NFBS, no significant difference in the course of the reaction was observed and FHMDS (*N*-fluorohexamethyldisilazane, δ ^{19}F (THF) −176 ppm) represented the only fluorinated product identified in the reaction mixture. This result was consistent with the presence in the reaction mixture of LiHMDS (one equivalent) which, being more reactive than **2,** was completely converted into FHMDS. By contrast, when the reaction of **2** was carried out with chlorinating (C_2Cl_6), brominating ($C_2Cl_4Br_2$) and iodinating (I_2) agents, a clean, rapid reaction occurred and the tetraethyl 1-lithio-1-halogenomethylenediphosphonates (**4a–c**) were obtained quantitatively (δ ^{31}P(THF) +35.3 ppm for Cl and +33.6 ppm for Br or I). After acidic work-up with 3 M HCl, the tetraethyl chloromethylenediphosphonate (**5a**) was isolated in excellent yield (97%). With the same conditions, the bromomethylenediphosphonate (**5b**) undergoes a partial dismutation during work-up in dibromomethylenediphosphonate (**11b**) and methylenediphosphonate (**1**). The dismutation is suppressed by using 2 M H_2SO_4. The bromo- (**5b**) and iodomethylenediphosphonate (**5c**) decomposes slowly in methylenediphosphonate (**1**) by loss of halogen. These experiments and results indicate that only the tetraethyl chloromethylenediphosphonate (**5a**) can be obtained in pure form. However, the electrophilic halogenation of tetraethyl methylenediphosphonate (**1**) is important in allowing the selective preparation of lithiated 1-chloro- (**4a**), 1-bromo- (**4b**) and 1-iodo- (**4c**) methylenediphosphonates which, in the context of the development of their chemistry, can be employed in further reactions.

To enlarge the access to monohalogenomethylenediphosphonates (**5**) we have examined their formation by reaction of dihalogenomethanes (**6**) ($CH_2X^1X^2$) with diethyl chlorophosphate (**7**) using both LDA or LiHMDS as metallating agents. We assume that the lithiated dihalogenomethanes (**8**) undergo a double phosphorylation reaction, via the diethyl 1-lithio-1,1-dihalogenomethylphosphonates (**10**), to produce the dihalogenated tetraethyl methylenediphosphonates (**11**) converted in situ into monohalogenomethylenediphosphonates (**5**) by halogen–metal exchange reaction (Scheme 2). The choice and stoichiometry of the base (LDA, LiHMDS) are very important and depend on the nature of the dihalogenomethane used. The reaction was evaluated with a range of dihalogenomethanes (**6**), symmetrical or unsymmetrical, containing chlorine, bromine or iodine (Table 1). To minimize the decomposition of the carbenoids generated in this process, the dihalogenomethanes **6** and the diethyl chlorophosphate (**7**) were added to the base, LDA or LiHMDS (three



Scheme 1.



Scheme 2.

equivalents), at low temperature under internal quench conditions.

By this methodology, LDA was used to prepare both the chloro- (**5a**) and bromomethylenediphosphonates (**5b**) from the corresponding symmetrical dihalogenomethanes (**6**, $X^1 = X^2 = Cl$ or Br). Similarly, LiHMDS was used to prepare **5b** from dibromomethane. As LiHMDS is not strong enough to deprotonate the dichloromethane, the chloromethylenediphosphonate (**5a**) was efficiently prepared from chloroiodomethane (**6**, $X^1 = Cl$, $X^2 = I$), a relatively expensive reagent. The monohalogenomethylenediphosphonates (**5a**,**b**) were isolated, after work-up, in 85–95% yields. Due to the little difference between the relative rates of halogen–metal exchange, the use of bromochloromethane led to a mixture of **5a** and **5b**. In the same conditions, the diiodomethane gave an unexploitable mixture of compounds.

The formation of the anions **4** (Scheme 2) can be explained by two competitive pathways, route A and route B, outlined in Scheme 3. In a common step, the dihalogenomethylphosphonate (**9**) is unambiguously formed by the attack of the lithiated dihalogenomethane (**8**) on diethyl chlorophosphate (**7**). Subsequently, the reaction can follow either the route A (deprotonation, condensation and halogen–metal exchange) or the route B (halogen–metal exchange, condensation, deprotonation). We consider that the route B, initiated by an halogen–metal exchange reaction, faster than a deprotonation reaction, is the more probable. Moreover, the 1-lithio-1-halogenomethylphosphonate (**12**) being more reactive than the 1-lithio-1,1-dihalogenomethylphosphonate (**10**) the formation of **5** (route B) is more favoured than the formation of **11** (route A).

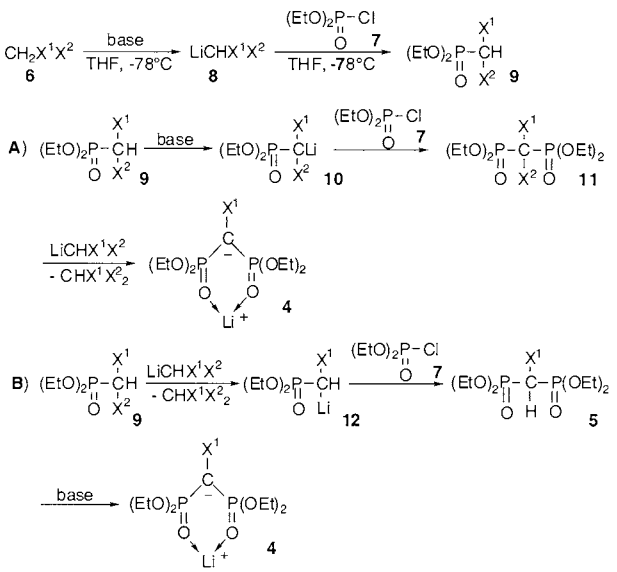
3. Conclusion

The present results confirm the previous ones concerning the electrophilic monohalogenation of functionalized phosphonates [1]. The phosphonates bearing electron-withdrawing groups [CN, $(RO)_2P(O)$] in the α-position can be efficiently monohalogenated without protection of the α-position, the intermediate monohalogenated anion being too stabilized to undergo a second halogenation. In spite of the failure in the synthesis of the monofluorinated methylenediphosphonate using NFBS, we are able to prepare lithiated chloro-, bromo- and iodomethylenediphosphonates from readily available halogenating agents. Moreover, the electrophilic monohalogenation of methylenediphosphonates appears more appropriate on large scale than the use of lithiated dihalogenomethanes which requires a careful control of several successive reactions.

Table 1
Preparation of diethyl halogenomethylene-diphosphonates (**5a**,**b**) from dihalogenomethanes and diethyl chlorophosphate

Base	X^1	X^2	Product
LDA	Cl	Cl	**5a**
	Br	Br	**5b**
LiHMDS	Cl	Cl	– [a]
	Cl	Br	**5a** (70%) + **5b** (30%)
	Cl	I	**5a**
	Br	Br	**5b**
	I	I	– [b]

[a] No reaction.
[b] Complex mixture.



Scheme 3.

4. Experimental

NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz for proton, 50.3 MHz for carbon, 81.01 MHz for phosphorus and 235 MHz for fluorine. ^{31}P downfield shifts (δ) are expressed with a positive sign, in ppm, relative to external 85% H_3PO_4 in H_2O. ^{1}H and ^{13}C chemical shifts (δ) are reported in ppm relative to $CDCl_3$ as internal standard. ^{19}F chemical shifts (δ) are reported in ppm relative to $CFCl_3$ as external standard. Coupling constants (J) are given in Hz. The following abbreviations are used: s, d, t, q, p, m for singlet, doublet, triplet, quadruplet, pentuplet and multiplet, respectively. Low resolution mass spectra were recorded on a Hewlett-Packard 5989 B GC-MS spectrometer (BPX5 column, positive chemical ionization NH_3). Organic solvents were purified by standard procedures. THF was distilled under an inert atmosphere from purple solution of sodium-benzophenone ketyl. The synthesis of all compounds was carried out under dry nitrogen. 'Evaporation' of solvents indicates evaporation under reduced pressure using a rotary evaporator. All drying of solutions was done with anhydrous magnesium sulfate.

*4.1. General procedure for the preparation of diethyl halogenomethylenediphosphonates (**5a–c**) by electrophilic halogenation*

A 250-ml reactor equipped with a mechanical stirrer, thermometer, efficient reflux condenser and an isobar addition funnel was charged with *n*-BuLi (6.9 ml of 1.6 M solution in hexane, 11 mmol) and THF (20 ml). The solution was cooled to -78°C and a solution of diisopropylamine (1.16 g, 11.5 mmol) in THF (10 ml) was added. After 10 min, the tetraethyl methylenediphosphonate **1** (1.44 g, 5 mmol) in THF (10 ml) was slowly added and the reaction mixture was allowed to warm to room temperature (r.t.). The resulting anion **2** was then treated with the halogenating reagent (5.5 mmol) in THF (10 ml). After 15 min, the resulting mixture was poured into an ice-cold stirred mixture of H_2SO_4 (30 ml of 2 M solution) and CH_2Cl_2 (25 ml). The aqueous layer was extracted with CH_2Cl_2 (2×25 ml). The extracts were dried and the solvents evaporated to give the crude products **5a–c** as orange oils.

*4.1.1. Diethyl chloromethylenediphosphonate (**5a**) [3,11,13,17,24]*

Pale yellow oil, yield 1.56 g (97%). ^{31}P-NMR ($CDCl_3$), δ: 13.5 (s); ^{1}H-NMR ($CDCl_3$), δ: 1.28 (t, 12H, $^{3}J_{HH} = 7.1$, C*H*$_3$CH$_2$O), 3.96 (t, 1H, $^{2}J_{PH} = 17.6$, C*H*Cl), 4.10–4.27 (m, 8H, CH$_3$C*H*$_2$O); ^{13}C-NMR ($CDCl_3$), δ: 16.7 (s, *C*H$_3$CH$_2$O), 43.9 (t, $^{1}J_{PC} = 144.8$, *C*HCl), 64.7 (d, $^{2}J_{PC} = 16.7$, CH$_3$*C*H$_2$O); *m*/*z* (CI): 323 (M + 1 ^{35}Cl, 100), 325 (M + 1 ^{37}Cl, 38), 340 (M + 18 ^{35}Cl, 22), 342 (M + 18 ^{37}Cl, 7).

*4.1.2. Diethyl bromomethylenediphosphonate (**5b**) [11,12]*

Pale yellow oil; decomposes on distillation; crude yield 1.72 g (94%); ^{31}P-NMR ($CDCl_3$), δ: 13.4 (s); ^{1}H-NMR ($CDCl_3$), δ: 1.27 (t, 12H, $^{3}J_{HH} = 7.0$, C*H*$_3$CH$_2$O), 3.81 (t, 1H, $^{2}J_{PH} = 17.0$, C*H*Br), 3.91–4.35 (m, 8H, CH$_3$C*H*$_2$O); ^{13}C-NMR ($CDCl_3$), δ: 16.7 (d, $^{3}J_{PC} = 2.6$, *C*H$_3$CH$_2$O), 29.9 (t, $^{1}J_{PC} = 142.2$, *C*HBr), 64.7 (d, $^{2}J_{PC} = 11.9$, CH$_3$*C*H$_2$O); *m*/*z* (CI): 367 (M + 1 ^{79}Br, 100), 369 (M + 1 ^{81}Br, 100), 384 (M + 18 ^{79}Br, 20), 386 (M + 18 ^{81}Br, 20).

*4.1.3. Diethyl iodomethylenediphosphonate (**5c**)*

Brownish oil; decomposes slowly at room temperature; crude yield 1.86 g (90%). ^{31}P-NMR ($CDCl_3$), δ: 15.5 (s); ^{1}H-NMR ($CDCl_3$), δ: 1.31 (t, 12H, $^{3}J_{HH} = 7.0$, C*H*$_3$CH$_2$O), 3.81 (t, 1H, $^{2}J_{PH} = 17.5$, C*H*I), 4.01–4.28 (m, 8H, CH$_3$C*H*$_2$O); ^{13}C-NMR ($CDCl_3$), δ: 16.8 (s, *C*H$_3$CH$_2$O), 25.4 (t, $^{1}J_{PC} = 136.6$, *C*HI), 65.0 (d, $^{2}J_{PC} = 9.9$, CH$_3$*C*H$_2$O); *m*/*z* (CI): 415 (M + 1, 100), 417 (M + 18, 22).

*4.2. General procedure for the preparation of diethyl halogenomethylenediphosphonates (**5a,b**) from dihalogenomethanes and diethyl chlorophosphate*

A 250-ml reactor equipped with a mechanical stirrer, thermometer, efficient reflux condenser and an isobar addition funnel was charged with *n*-BuLi (10 ml of 1.6 M solution in hexane, 16 mmol) and THF (20 ml). The solution was cooled to -78°C and a solution of diisopropylamine (1.72 g, 17 mmol) in THF (10 ml) was added. After 10 min, a mixture of diethyl chlorophosphate (1.73 g, 10 mmol) and dihalogenomethane (11 mmol) in THF (15 ml) was slowly added at -90°C and after 20 min the reaction mixture was allowed to warm to room temperature. The resulting solution of anions **4a,b** was then poured into an ice-cold stirred mixture of H_2SO_4 (30 ml of 2 M solution) and CH_2Cl_2 (25 ml). The aqueous layer was extracted with CH_2Cl_2 (2×25 ml). The extracts were dried and the solvents evaporated to give the crude products **5a,b** in 85–95% yields.

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