Lithiation of diethyl trichloromethylphosphonate and the transformations of the α-lithiated derivative

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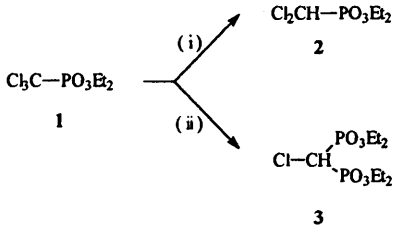
The lithiation of diethyl trichloromethylphosphonate below −100 °C leads to a stable α-lithiated derivative, but at temperatures of about −80 °C the lithiation is accompanied by spontaneous reactions leading to tetraethyl (chloromethylene)bisphosphonate as the exclusive product. Possible mechanisms of the reaction are discussed.

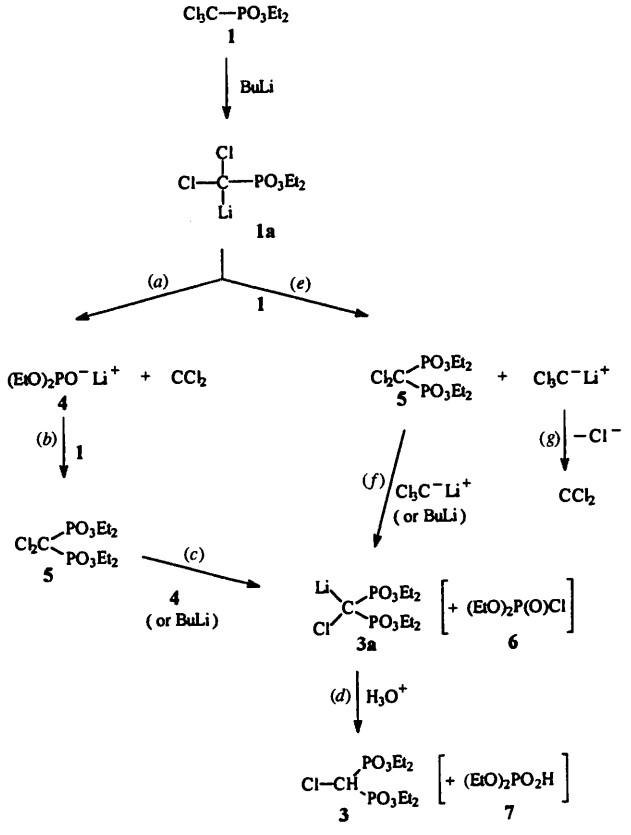
Diethyl trichloromethylphosphonate **1**, easily available *via* the Arbuzov reaction since 1947,[1] proved a useful substrate in various synthetic procedures. The applications, based on a facile metal–halogen exchange leading to the α-phosphoryl, α-chlorocarbanions, were extensively studied by Normant,[2] Savignac[3] and other researchers.[4] Seyferth and Marmor reported that α-lithiated **1** can be quenched by a variety of electrophiles, including water, the latter reaction yielding diethyl dichloromethylphosphonate **2** in 55% yield.[4a] Since we were in need of substrate **2**, we repeated the literature preparation,[4a] and found that the outcome of the reaction depends dramatically on the temperature (Scheme 1). Both products, **2** and **3**, can be prepared with high selectivity, and the latter also represents a valuable substrate for further syntheses.[5] Bisphosphonate **3** was, however, hitherto available only by the functionalisation of previously prepared methylenebisphosphonate systems,[6] while the reaction reported here allows us to prepare it from simple, monophosphonic precursor. While the formation of **2** is obvious (lithiation, followed by protonation), we found the formation of **3** as the practically exclusive product under specific conditions rather intriguing, and we report here our attempts to elucidate the mechanism of the transformation **1**–**3**.



Scheme 1 (i) BuLi, Et_2O. followed by aq. NH_4Cl; all steps at temp. ≤ −100 °C; (ii) as above, but all steps at temp. −70 to −80 °C

Results and discussion

Since the first step of the reaction undoubtedly involves the lithium–chlorine exchange leading to the monolithiated derivative **1a**, the critical feature is the thermal stability of this derivative. At temperatures not higher than −100 °C **1a** is stable and can be converted into **2** when a proton source is added. It seems, however, that at temperatures even as low as −70 to −80 °C, **1a** undergoes fast and irreversible transformations resulting in the formation of a new phosphorus–carbon bond. We propose two plausible mechanisms for the cleavage of one, and the formation of a new P–C bond in the **1**/BuLi system (Scheme 2).



Scheme 2

According to first mechanism, **1a** undergoes fragmentation to the diethyl phosphite anion **4** and dichlorocarbene (step *a*), followed by the reaction between the new nucleophile **4** and the unlithiated **1** to form the (dichloromethylene)bisphosphonate product **5** (step *b*). The latter step can occur either *via* the direct attack of **4** at the α-carbon of **1** with the diplacement of chloride (the Michaelis–Becker reaction[7]), or *via* the attack of **4** at the α-Cl atom of **1**, and the subsequent phosphorylation of the released carbanion **1a** by the diethyl phosphorochloridate formed in the attack. Nucleophilic attack of P^{III} derivatives at halogen is also a common reaction in organophosphorus chemistry.[8] The dichloromethylene

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derivative **5** can next undergo dehalogenation by anion **4** (formation of diethyl phosphorochloridate **6**), or by the excess of BuLi, yielding the lithiated bisphosphonate **3a** (step *c*). Aqueous quenching converts **3a** into the final product **3**, while **6** undergoes fast hydrolysis to diethyl phosphate **7** (step *d*).

The second alternative involves the $S_N2(P)$ displacement at the phosphorus atom of unlithiated **1** by the nucleophilic carbon of its carbanionic derivative **1a**, with the Cl_3C^- acting as the leaving group (step *e*). Hammond and co-workers demonstrated that the P–CCl_3 bond in 4-nitrophenyl phenyl(trichloromethyl)-phosphinate is cleaved by hydroxide ion in preference to the ester P–O function.[9] The trichloromethyl carbanion can decompose to dichlorocarbene (step *g*), or act as a dehalogenating agent with respect to **5**, yielding **3a** (step *f*) and, subsequently, the final product **3**.

Both mechanisms imply the formation of CCl_2 species as a result of the P–C bond fission. Indeed, when the reaction shown in Scheme 1 was carried out at −70 to −80 °C in the presence of 1 equiv. of cyclohexene, the expected 1,1-dichloro[4.1.0]bicycloheptane was isolated and identified by comparison with the authentic material. The feasibility of step (*b*) was confirmed in the next experiment, in which phosphonate **1** was treated at −70 to −80 °C with an equimolar amount of **4**, generated from diethyl phosphite and BuLi in Et_2O. After aqueous work-up, the product was purified by distillation yielding **3** (50%), identical with the product obtained before. Finally, step (*c*) was tested separately by reacting the independently prepared tetraethyl (dichloromethylene)bisphosphonate **5** with an equimolar amount of **4** under the same conditions as above. The organic layer revealed the formation of **3** (70%), while the aqueous (D_2O) layer contained only diethyl phosphate **7**, easily identified by the addition of the authentic material. Similar oxidation of a phosphite to the halophosphate level was reported for the reaction of sodium diethyl phosphite with diethyl bromomalonate,[10] and in the preparation of tetraisopropyl (fluoromethylene)bisphosphonate in the reaction between the corresponding (bromofluoromethylene)bisphosphonate and sodium diisopropyl phosphite.[11] Monodehalogenation of dialkyl esters of (dichloromethylene)bisphosphonic acid by BuLi (steps *c* and *f*) was reported as a necessary step in the preparation of the α-substituted bisphosponate derivatives.[6c]

In conclusion, no experiment has disproved any of the steps proposed in the mechanism of the formation of the product **3** (Scheme 2); at the same time we cannot offer any evidence that would allow to favour unambigously one mechanism over the other. We believe, however, that the mechanism involving the $S_N2(P)$ displacement of the Cl_3CLi as a critical step (step *e*, followed by steps *f*, *g* and *d*) seems a more likely option for the following reasons. First, although the α-lithiated phosphonic derivatives are among the most commonly used synthetic reagents,[12] to our knowledge no reports on their spontaneous fragmentation to phosphite anions and carbene species have been published. Secondly, in the experiments leading to the formation of **3** from **1** and BuLi (Scheme 1), we never observed either **7** or **6** in the final reaction product. Such a result would only be possible if the initial lithiation of **1** (transformation **1** ⟶ **1a**) were much slower than the next steps (*b*) and (*c*). In such case, all phosphite anion would be consumed in step (*b*), and the dehalogenation of **5** (step *c*) would be accomplished by the excess of BuLi alone. We do not see any reason for such a facile fragmentation of **1a** into two reactive species, **4** and CCl_2. We think, however, that the mechanism involving steps (*e*) and (*f*) indicates the synthetic potential of the (trichloromethyl)phosphonic function not only from the point of view of the halogen–metal exchange, but also because of its phosphorylating reactivity due to the presence of the P–CCl_3 function.

Experimental

All solvents and commercialy available reagents were purified by conventional methods before use. Reactions involving lithiated reagents were carried out in an atmosphere of dry nitrogen. Mass spectra were recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at an ionization potential of 70 eV. NMR spectra were recorded on a Bruker AC300 spectrometer for solutions in $CDCl_3$, and the chemical-shift values are given relative to the solvent (δ_H 7.24 δ_C 77.0). ^{31}P NMR chemical shift values are given relative to 85% H_3PO_4 as external standard. *J* values in Hz.

Diethyl trichloromethylphosphonate 1

Compound **1** was prepared according to the literature procedure;[1] δ_P 5.96.

Tetraethyl (dichloromethylene)bisphosphonate 5

Compound **5** was prepared according to the modified literature procedure.[6d] A solution of tetraethyl methylenebisphosphonate[13] (1.50 g, 5.2 mmol) in CCl_4 (4.5 cm^3) was added dropwise at 0 °C to a stirred solution of $NaHCO_3$ (3.77 g, 44.9 mmol) and Bu_4NCl (0.41 g, 1,47 mmol) in aqueous solution of NaOCl (14%, 45 cm^3). The mixture was stirred at 0 °C for 7 h, the organic layer was separated and the aqueous layer was extracted with CCl_4 (3 × 45 cm^3). The combined organic layers were extracted with sat. aq. NaCl (4.5 cm^3), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Crude product (95%) was purified by distillation (bp 120–123 °C at 0.1 mmHg), followed by column chromatography (SiO_2, CH_2Cl_2/AcOEt, 1:1); δ_H 1.36 (12 H, t, J_{HH} 7.1, 4 × Me of POEt), 4.32–4.40 (8 H, m, 4 × CH_2 of POEt); δ_P 8.87 (lit.,[6d] δ_P 8.82).

1,1-Dichloro[4.1.0]bicycloheptane

This compound was prepared according to the literature procedure.[14] δ_H 1.11–1.37 (4 H, m, 4-H_2, 5-H_2), 1.60–1.72 (4 H, m, 3-H_2, 6-H_2), 1.87–1.99 (2 H, m, 2-H, 7-H); δ_C 18.80 (C-4, C-5), 20.15 (C-3, C-6), 25.76 (C-2, C-7), 67.20 (C-1).

Diethyl dichloromethylphosphonate 2

BuLi (1.6 mol dm^3 solution in hexane; 3.4 cm^3, 5.5 mmol) was added at −105 °C during 15 min to a solution of **1** (1.30 g, 5.0 mmol) and anhydrous LiCl (0.44 g, 5.0 mmol) in dry Et_2O (30 cm^3) with stirring. The mixture was stirred at −105 to −100 °C for 1 h and aq. NH_4Cl (10 cm^3) was added to the solution kept at the same temperature. The mixture was warmed to room temp., the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 cm^3). The organic solution was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the product was purified by bulb-to-bulb distillation (0.82 g, 74%); oven temp. 90–95 °C at 0.15 mmHg; δ_H 1.35 (6 H, t, J_{HH} 7.2, 2 × Me of POEt), 4.28 (4 H, dq, J_{HP}, J_{HH} 14.2, 7.1, 2 × CH_2 of POEt), 5.62 (1 H, d, J_{HP} 2.7, α-CH); δ_P 11.08.

Tetraethyl(chloromethylene)bisphosphonate 3

A solution of **1** (5.1 g, 20.0 mmol) in ether (60 cm^3) was cooled to −80 °C and treated at that temperature with 1.1 equiv. of BuLi; the same procedure was then followed as described for the preparation of **2**, except that the temperature of the reaction mixture was maintained at −70 to −80 °C. Bulb-to-bulb distillation afforded pure **3** (3.0 g, 95%); oven temp. 130–135 °C at 0.2 mmHg; δ_H 1.34 (12 H, t, J_{HH} 7.1, 4 × Me of POEt), 3.97 (1 H, t, J_{HP} 17.5, α-CH), 4.24 (8 H, dq, J_{HP}, J_{HH} 14.2, 7.0, 4 × CH_2 of POEt); δ_C 16.11 (s, 4 × Me of POEt), 43.43 (t, J_{CP} 144.6, α-C), 63.98 (s, 2 × CH_2 of POEt), 64.30 (s, 2 × CH_2 of POEt); ^1H coupled ^{13}C NMR spectrum confirmed the assignment; δ_P 13.90; *m/z* 323, 325 ($M^+ + 1$, 21%, 7%), 322, 324 (M^+, 10%, 7%), 295, 297 ($M^+ + 1 - C_2H_4$, 47%, 14%), 294, 296 ($M^+ - C_2H_4$, 18%, 6%), 267, 269 ($M^+ + 1 - 2C_2H_4$, 57%,

20%), 266, 268 ($M^+ - 2C_2H_4$, 11%, 9%), 239, 241 ($M^+ + 1 - 3C_2H_4$, 53%, 17%), 238, 240 ($M^+ - 3C_2H_4$, 29%, 11%), 211, 213 ($M^+ + 1 - 4C_2H_4$, 50%, 18%), 210, 212 ($M^+ - 4C_2H_4$, 90%, 31%), 193, 195 ($M^+ + 1 - 4C_2H_4 - H_2O$, 57%, 20%), 192, 194 ($M^+ - 4C_2H_4 - H_2O$, 5%, 9%), 99 ($H_4PO_4^+$, 61%), 81 ($H_3PO_3^+$, 36%), 65 ($H_2PO_2^+$, 70%), 29 ($C_2H_5^+$, 100%).

Reaction of 1 with lithium diethyl phosphite 4

A solution of diethyl phosphite (1.38 g, 10 mmol) in diethyl ether (60 cm^3) was cooled to −30 °C and the solution of BuLi (11 mmol) was added with stirring. The solution was stirred at −30 °C for 30 min, cooled to −80 °C, and the solution of **1** (2.60 g, 10 mmol) in diethyl ether (10 cm^3) was added dropwise. The mixture was stirred for 30 min at −80 °C, for another 30 min at −40 °C, warmed to −10 °C, and quenched with aq. NH_4Cl (20 cm^3). After the usual work-up, the ^{31}P NMR spectrum of the crude product revealed the presence of two major phosphorus-containing compounds: **3** (δ_P 13.85) and **7** (δ_P −0.3), together with a few minor signals of unidentified products. Bulb-to-bulb distillation afforded pure **3** and pure **7**, easily identified by the addition of the authentic samples.

Reaction of 5 with 4

The reaction was carried out as described above, using **5** (0.178 g, 0.5 mmol) instead of **1** as a starting material, and using a solution of NH_4Cl in D_2O in the quenching step. The crude product obtained after evaporation of the organic solvent was dissolved in $CDCl_3$ and examined by ^{31}P NMR spectroscopy which revealed the presence of only two phosphorus-containing products: unreacted **5** (δ_P 8.89, 30%) and **3** (δ_P 13.92, 70%). ^1H NMR spectrum was in full agreement with that composition and showed no presence of other products. ^{31}P and ^1H NMR spectra of the D_2O solution revealed the presence of only one product, **7** (δ_P 1.37), identified by the addition of the authentic sample.

Reaction of 1 with BuLi in the presence of cyclohexene

Substrate **1** (1.50 g, 5.87 mmol) was treated with BuLi (1.1 equiv.) in the same manner as described before, but cyclohexene (7.4 g, 90 mmol) was added to the initial solution of **1**. After the usual work-up, the crude product was separated by bulb-to-bulb distillation allowing to separate 1,1-dichloro-[4.1.0]bicycloheptane as a first fraction (0.194 g, 20%); oven temp. 100–120 °C/11 mmHg. The ^1H and ^{13}C NMR spectra of the product were identified to those obtained for the authentic compound.

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