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Phosphate-Phosphonate Conversion: Nucleophilic Displacement Reactions Involving Phosphoric Esters and Methyllithium

Philippe Savignac, Marie-Paule Teulade, and Carl Patois*
Laboratoire de Chimie du Phosphore et des Métaux de Transition, DCPH, Ecole Polytechnique, 91128 Palaiseau Cedex, France

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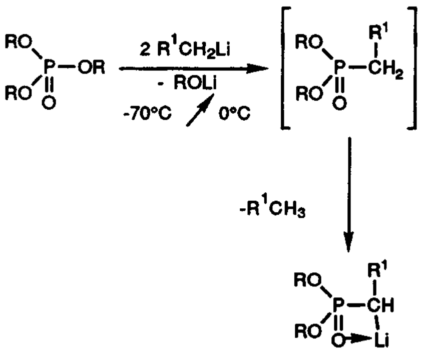
ABSTRACT

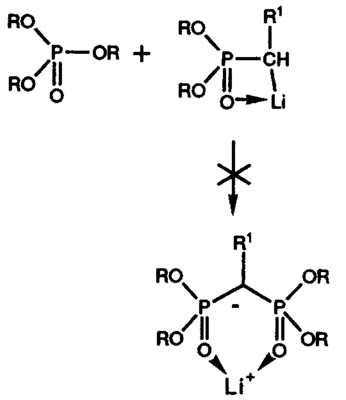
The alkylation-metalation reaction of phosphoric esters depends on the way the lithium reagent has been prepared. With salt-containing methyllithium (LiBr or LiI), the alkylation is never complete. On the contrary, with salt-free methyllithium, the alkylation is completed at −10°C. This reaction is performed independently of the substituents at the phosphoryl group.

INTRODUCTION

The alkylation-metalation reaction of a phosphoric acid triester with alkyllithium reagents is one of the simplest methods to prepare α-(lithioalkyl)phosphonates [1] (Equation 1). It is noteworthy that the generated α-(lithioalkyl)phosphonate is a weaker nucleophile than the alkyllithium. Thus the undesired formation of alkylidene-diphosphonate was never observed (Equation 2).



(1)



(2)

As previously reported [2], this process works very well with linear or ramified alkyllithium reagents except methyllithium. In order to overcome this limitation, the reaction of methyllithium has been further explored, by varying temperature and added salts.

RESULTS

To follow the progress of the alkylation-metalation of a phosphoric acid triester, we have used ^{31}P nuclear magnetic resonance (NMR) spectroscopy be-

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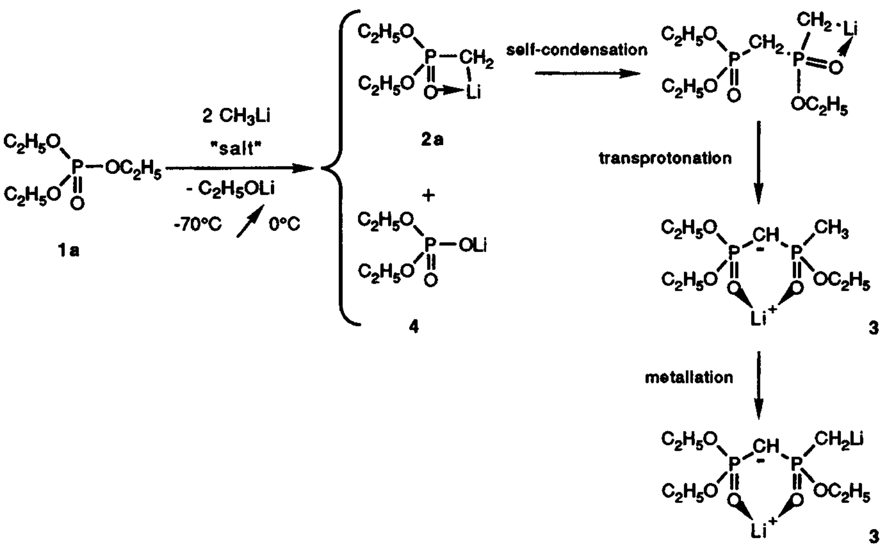
* To whom correspondence should be addressed.



(3)

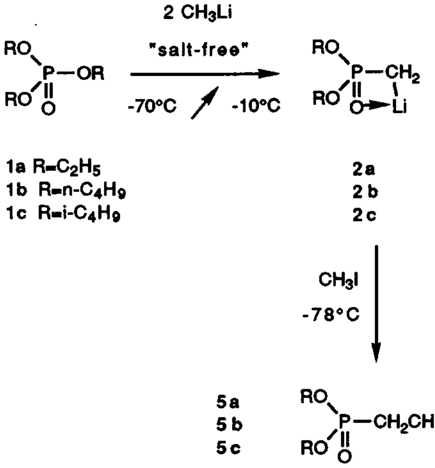
cause it allows the instantaneous and simultaneous observation of ionic and covalent species in the medium. Every 30 min a sample of the reacting solution was collected, and cooled to −78°C. Then an excess of methyl iodide was added to trap all lithiated species. After the reaction mixture had been allowed to warm, we observed and integrated by ^{31}P NMR spectroscopy the signals of the generated phosphonate and of the starting phosphate (if there was any left).

Alkylation-metalation of phosphoric esters and amides with alkyllithium is salt-dependent and is slowed by the presence of lithium salts [1]. Reaction of salt-free *n*-butyllithium with triethyl phosphate **1a** in tetrahydrofuran (THF) solution is 85% complete after 30 min at −40°C, whereas in the presence of lithium bromide only 5% of the phosphate is consumed.

As for methyllithium, the salt-effect, in addition to a weaker reactivity compared with alkyllithium homologues [3], is so critical that the alkylation-metalation process cannot be achieved. The alkylation step is so slow at low temperature that we have to carry out the reaction at around 0°C, where the generated primary carbanion begins to undergo self-condensation [4].

Typically, addition of triethyl phosphate **1a** to a THF/ether solution of methyllithium (which also contains LiBr or LiI) at −70°C, with subsequent warming, yields a mixture containing the expected carbanion **2a**, the methylene-phosphono-phosphinate **3** (which is the self-condensation product), lithium diethylphosphate **4** resulting from a C-methylation at the oxygen-bonded carbon atom, and some starting phosphate **1a** (Equation 3). The self-condensation product **3**, having two acidic protons, consumes part of the starting methyllithium to give the dilithio salt **3′**. The phosphate conversion does not exceed 80%.

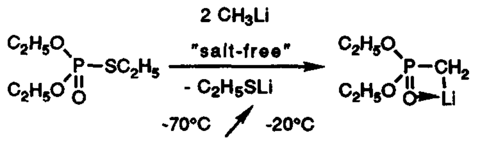
By contrast, when performed in salt-free medium, alkylation-metalation of triethyl phosphate **1a** was half-completed after 30 min at −20°C, and completed quantitatively after another 30 min at −10°C, to yield the primary carbanion **2a** $[\delta_P(\mathrm{THF}) = +58.2]$. Subsequent treatment with methyl iodide at −78°C yielded diethyl ethylphosphonate **5a** $[\delta_P(\mathrm{THF}) = +30.7]$ without any diethyl methylphosphonate. The more hindered phosphates tri-*n*-butyl phosphate **1b** and tri-isobutyl phosphate **1c** were again quantitatively converted to $(\mathrm{nBuO})_2\mathrm{P(O)CH_2Li}$ **2b** $[\delta_P(\mathrm{THF}) = +59.2]$ and $(\mathrm{iBuO})_2\mathrm{P(O)CH_2Li}$ **2c** $[\delta_P(\mathrm{THF}) = +58.6]$ (Equation 4). When treated with methyl iodide, these carbanions gave the parent phosphonates **5b** $[\delta_P(\mathrm{THF}) = +30.9]$ and **5c** $[\delta_P(\mathrm{THF}) = +30.7]$, respectively.



(4)

With O,O-diethyl-S-ethylthiophosphate **6**, which contains a better leaving group than phosphates **1**, the alkylation at the phosphorus atom in salt-free solution was complete after 30 min at −20°C, yielding **2a** quantitatively (Equation 5). No

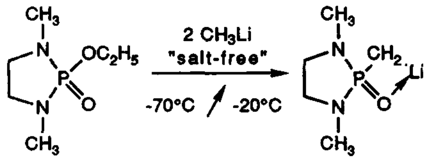
O-ethyl-S-ethyl-ethylthiophosphonate was detected.



(5)

6 2a

A less hindered phosphorus atom, such as that found in 2-ethoxy-2-oxo-1,3-dimethyl-1,3,2-diazaphospholidine **7**, as expected, led to complete alkylation in salt-free solution after 30 min at −20°C (Equation 6).



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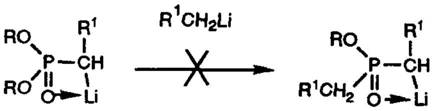
DISCUSSION

The low reactivity of methyllithium when compared with other alkyllithiums is mainly due to its exceptionally strong aggregation [3, 5]. Methyllithium is subject to an oligomerization equilibrium just as any other alkyllithium. However, the equilibrium constant is particularly small in the methyllithium case.

To explain the great salt-effect encountered, we suggest that the phosphate activates the alkyllithium by coordination of the metal [6]. In the presence of salts, the phosphate prefers to coordinate with lithium cations of the salts. The alkyllithium is less activated, which retards the alkylation step. This point is corroborated by the following experiment. To an α-(lithioalkyl)phosphonate was added one more equivalent of the alkyllithium. No further alkylation at phosphorus was observed. The phosphoryl group of the generated α-(lithioalkyl)phosphonate, being intramolecularly engaged with the α-lithium cation (Equation 7), is no more available to activate the alkyl-lithium. Thus, one substitution only occurs at phosphorus.



(7)

In the case of methyllithium, this latter point is essential. The phosphoryl group has to be fully available in order to activate the methyllithium and allow the nucleophilic displacement at the phosphorus atom to occur.

CONCLUSION

The alkylation-metalation reaction of trialkyl phosphates with alkyllithium compounds is now better understood. The salt-effect encountered, albeit important, is problem-free except for methyllithium which has to be used in a salt-free state.

EXPERIMENTAL

All reactions were performed under nitrogen. NMR resonance spectra were recorded on multinuclear WP 80 SY and AC 200 Bruker spectrometers 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 (^{31}P) as external standard, and coupling constants are in Hertz. Mass spectra were recorded on a Shimadzu GC-MS QP 1000 instrument at 70 eV under electronic impact. All commercially available phosphoric acid esters were used as received from the suppliers. Methyllithium was titrated just before use with *N*-(1-naphthyl)aniline as a color indicator, and a 1 M solution of benzyl alcohol in toluene.

Typical working procedure: e.g. Preparation of ***5b****, O,O-di-n-butyl ethylphosphonate*

Tributyl phosphate **1b** (0.020 mol, 5.3g) in tetrahydrofuran (15 mL) was added at −78°C with stirring to salt-free methyllithium (1.4 N in ether; 5% excess) (0.042 mol, 31.5 mL) in a 1 : 1 mixture of ether and tetrahydrofuran. The solution was slowly warmed to −10°C and kept at this temperature for 40 min. Then, after having been recooled to −78°C, methyl iodide (0.022 mol, 3.3 g) was introduced. The solution was brought to 25°C, hydrolyzed with water (25 mL), and extracted with ether/methylene chloride (1 : 1). The organic layers were dried (Na_2SO_4) and evaporated under vacuum. The resulting colorless oil has been proved to be identical with an authentic sample. Yield: 80%. $\delta_P(CDCl_3)$ 30.8, δ_c ($CDCl_3$) 5.5 (CH_3, s, PCH_2CH_3), 12.4 (CH_3, s, $PO(CH_2)_3CH_3$), 17.4 (CH_2, d, J 143.0, PCH_2), 17.6 (CH_2, s, $PO(CH_2)_2CH_2$), 31.6 (CH_2, s, $POCH_2CH_2$), 64.1 (CH_2, s, $POCH_2$).

Analogously, O,O-diethyl ethylphosphonate **5a** and O,O-diisobutyl ethylphosphonate **5c** were obtained.

5a: yield 81%; δ_P ($CDCl_3$) 30.6, δ_c ($CDCl_3$) 5.0 (CH_3, s, PCH_2CH_3), 14.9 (CH_3, s, $POCH_2CH_3$), 16.8 (CH_2, d, J 143.0, PCH_2), 59.7 (CH_2, s, $POCH_2$).

5c: yield 83%; δ_P ($CDCl_3$) 30.6, δ_c ($CDCl_3$) 5.6 (CH_3, s, PCH_2CH_3), 17.6 (CH_2, d, J 147.4, PCH_2), 17.8 (CH_3, s, $POCH_2CH(CH_3)_2$), 28.4 (CH, s, $POCH_2CH$), 70.5 (CH_2, s, $POCH_2$).

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