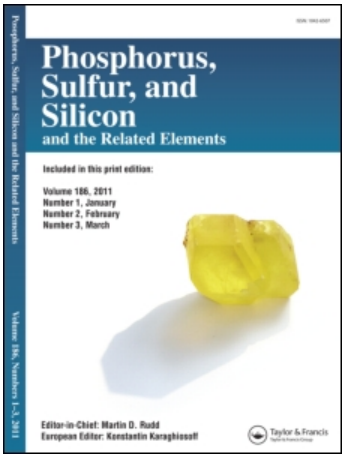

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A FACILE APPROACH FOR THE SYNTHESIS OF α-HALOGENATED ALKYLIDENEDIPHOSPHONATES BY REACTION OF ALKYLLITHIUM WITH CHLOROPHOSPHATE AND HALOGEN REAGENT

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Alkyllithium reacts with chlorophosphate to generate the α-lithio-alkylidenediphosphonate, which further reacts with halogen reagents to afford corresponding α-halogenated alkylidenediphosphonates.

Keywords: α-Lithio-alkylidenediphosphonate; α-halogenoalkylidenediphosphonate; chlorophosphate; halogen reagent; *n*-alkyllithium

As important derivatives of methylenediphosphonate, alkylidenediphosphonates play an important role as precursors of vinylphosphonates in organic synthesis[1–4] and as inhibitors in biological systems.[5] Additionally, α-halogenated alkylidenediphosphonates result in more active compounds than the parent structure in organic synthesis[1,6–11] and particular biological systems.[12–13] Common methods for the preparation of α-monohalogenated methylenediphosphonates include the partial reduction of dihalogenated methylenediphosphonates,[14–17] phosphorylation of lithiated halogenomethylphosphonates,[1,18–19] and the self-condensation of lithiated dihalogenomethylphosphonates.[18,20–22] A limited number of examples exist for the formation of halogenomethylenediphosphonates (such as fluoro- and chloro derivatives).[23–26] Developing general methods for the preparation of elaborated methylenediphosphonates, especially those tolerating substituents such as alkyl group or halogen atom on the α-carbon position is of great interest. The successful application of

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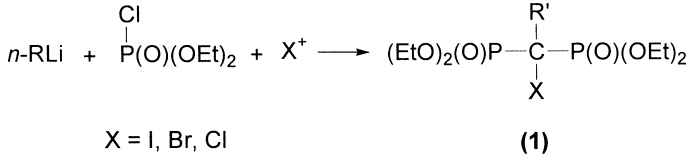
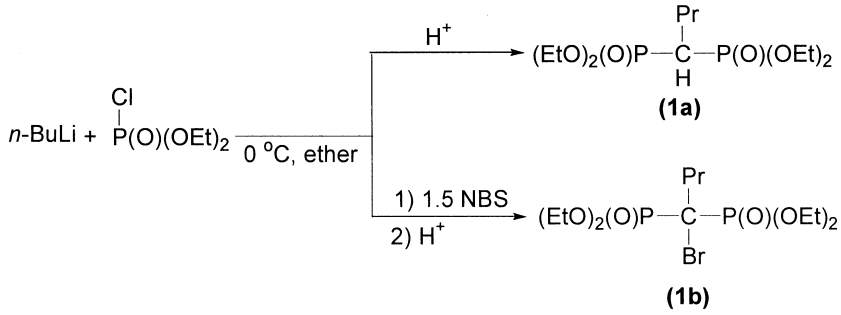
LDA process for the synthesis of α-lithiated alkylidenediphosphonates has confirmed its efficiency in the synthesis of alkylidenediphosphonates and (*E*)-vinylphosphonates with a considerable degree of stereoselectivity.[1–4] In our study, we find a facile approach to obtain α-monohalogenoalkylidenediphosphonates **(1)** based on the one-pot procedure of the reaction of alkyllithium with chlorophosphate and halogen reagent (Scheme 1).



SCHEME 1

RESULTS AND DISCUSSION

The reaction of *n*-butyllithium with chlorophosphate gave product **(1a)** after hydrolysis which was consistent with butylidenediphosphonate.[1,27–28] Furthermore, the reaction mixture was treated with halogen reagents such as NBS to afford final product (**1b**) (Scheme 2).



SCHEME 2

We examined this reaction in detail and found that 1 mmol diethyl chlorophosphate was dropped slowly into ether solution of 1 mmol *n*-butyllithium at -78°C, the exclusive product *n*-butylphosphonate was observed, which was confirmed by ^{31}P NMR ($\delta = 33$ ppm). When 1 mmol diethyl chlorophosphate was dropped slowly to ether solution of 1 mmol *n*-butyllithium at 10°C, three peaks appeared in the ^{31}P NMR

spectrum after the reaction was maintained at 10°C for 1 h. One appeared at 25 ppm that was assigned to butylidenediphosphonate[27–28] and another appeared at 44 ppm which was consistent with α-lithiated methylenediphosphonate[1,27] The third signal at 33 ppm was assigned to the *n*-butylphosphonate. Furthermore, treatment of the reaction with 1 mmol diethyl chlorophosphate and 1.5 mmol *n*-butyllithium at 10°C for 1 h showed only two peaks in ^{31}P NMR spectrum. One strong peak appeared at 44 ppm and another small one at 33 ppm. The peak at 25 ppm completely disappeared compareed with one to one ratio reaction of *n*-butyllithium and chlorophosphate. In this procedure, when the reaction mixture was treated with halogen reagents (such as I_2, NBS, and NCS), the peak at 44 ppm completely disappeared. Instead, in the ^{31}P spectra of these reaction mixtures, a new peak appears at a position appropriate for the product expected from each halogen reagent and these products were obtained in good yield (Table I). It is noteworthy that the reaction was treated with 1.5 mmol *n*-BuLi, small amount of butylphosphonate was still obtained as byproduct about 8% (GC yield) that was easily separated from major product. In addition, α-iodobutylidenephosphonate was not stable since some amount of butylidenephosphonate was observed after the purification.

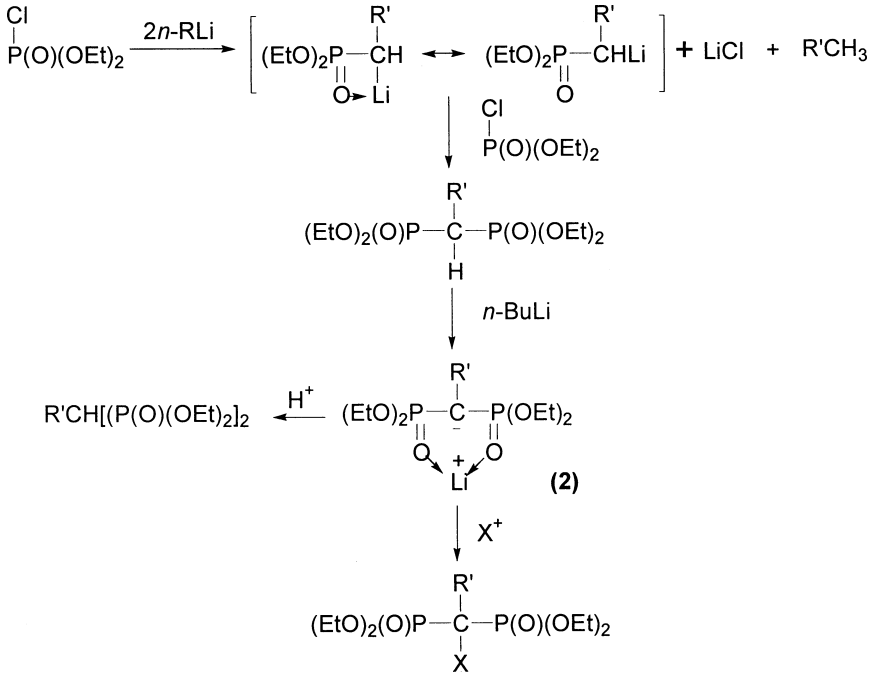
Furthermore, the reaction of other alkyllithium (such as ethyllithium and methyllithium) with chlorophosphate and halogen reagents gave analogous products of α-monohalogenobutylidenediphosphonate in good yield (Table I). It is noteworthy that the reaction mixture of methylithium and chlorophosphate was treated with more than one equiv. of halogen reagents (I_2, NBS, and NCS) to afford some amount of α,α-dihalogenated methylenediphosphonates. When the reaction mixture of methylithium and chlorophosphate was treated with more than two equiv of halogen reagents above, the exclusive product of α,α-dihalogenated methylenediphosphonate was obtained.

TABLE I Formation of α-Halogenated Alkylidenediphosphonates by the Reaction of RLi with Chlorophosphate and Electrophiles

RLi	Electrophile	X	Yield (%)[a]	^{31} P NMR δ(ppm)
BuLi	HCI	H	92 (60) (**1a**)	24.9
BuLi	NBS	Br	90 (55) (**1b**)	16.6
BuLi	I_2	I	85 (42) (**1c**)	19.4
BuLi	NCS	CI	88 (59) (**1d**)	16.7
EtLi	NBS	Br	53 (34) (**1e**)	17.6
MeLi	NBS	Br	89 (60) (**1f**)	14.1
MeLi	I_2	I	85 (45) (**1g**)	16.7

[a]GC yields. Isolated yields are given in parentheses.

A possible mechanism as follows: alkyllithium reacts with chlorophosphate to yield alkylphosphonate, which is readily trapped by the metallation of another molecular RLi to give α-lithio alkylphosphonate.[28] Furthermore, α-lithio alkylphosphonate reacts with another molecule of chlorophosphonate to give alkylidenediphosphonate,[27–30] which quickly reacts with the third molecule of RLi to produce tetraethyl lithioalkyldenediphosphonate **(2)** that is thermally stable[1a,1b] and shows at 44 ppm in ^{31}P NMR spectrum. The compound **(2)** is quenched with HCl solution to obtain alkylidenediphosphonate. Halogenation of compound **(2)** by NBS, NCS, and I_2 provides α-halogenoalkylidendiphosphonate (Scheme 3).



SCHEME 3

In conclusion, the present procedure is the simplicity and the efficiency for the syntheses of alkylidenediphosphonate and α-halogenoalkylidenediphosphonates. The entire procedure is performed in a single reaction vessel without the solution of purification of intermediates and uses commercial or readily available starting materials.

EXPERIMENTAL

General

All reactions were run under nitrogen with a slightly positive pressure. Unless otherwise noted, all starting materials were commercially available and were used without further purification. Ether was refluxed and distilled from sodium benzophenone ketyl under a nitrogen atmosphere. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL AL-300 MHZ NMR spectrometer. ^{31}P-NMR spectra were recorded on Bruker-200NMR spectrometer. Mass spectra were obtained on Esquire-LC mass spectrometer. GC analysis was performed on SHIMADZU GC-14B equipped with fused silica capillary column. Appropriate alkanes were used as internal standards.

A Representative Procedure for the Reaction of n*-Butyllithium with Chlorophosphate and NBS. Preparation of α-Bromo-Butylidenediphosphonate (1b)*

To a solution of *n*-butyllithium (3 mmol, 191 μl, 1.57 M in hexane) in ether (5 mL) under nitrogen atmosphere was dropped diethyl chlorophosphate (2.0 mmol, 289 μl) at 0°C. The reaction mixture was stirred at 10°C for 1 h. Then the mixture was quenched with 3 M HCl and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and was evaporated in vacuo to give a light yellow liquid. Chromatography using ether/ethanol (10/1) as elute provided the colorless oil product 198 mg. The product was consistent with butylidenediphosphonate,[1,27–28] GC yield 92%, isolated yield 60%. Furthermore, the reaction mixture was treated with NBS (1.5 mmol, 267 mg) instead of 3 M HCl, and stirred for additional 3 h. Then the mixture was quenched with 3 M HCl and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated in vacuo to give a light yellow liquid. Chromatography using ethyl acetate/petroleum ether (3/1) as eluent provided α-bromobutylidenediphosphonate as colorless oil 224 mg. GC yield 90%, isolated yield: 55%. ^{1}H NMR($CDCl_3$, Me_4Si) δ 0.97 (t, $^{3}J_{HH} = 7.2$ Hz, 3H, $CBrCH_2CH_2\underline{CH_3}$), 1.37 (td, $^{3}J_{HH} = 7.2$ Hz, $^{4}J_{PH} = 1.8$ Hz, 12H, $4OCH_2\underline{CH_3}$), 1.65–1.75 (m, 2H, $CBrCH_2\underline{CH_2}CH_3$), 2.13–2.73 (m, 2H, $CBr\underline{CH_2}CH_2CH_3$), 4.05–4.34 (m, 8H, $4O\underline{CH_2}CH_3$); ^{13}C NMR($CDCl_3$, Me_4Si), δ 14.11 (s, $CBrCH_2CH_2\underline{C}H_3$), 16.33–16.23 ($4OCH_2\underline{C}H_3$), 19.38 (t, $^{3}J_{PC} = 6.5$ Hz, $CBrCH_2\underline{C}H_2CH_3$), 38.07 (t, $^{2}J_{PC} = 2.8$ Hz, $CBr\underline{C}H_2CH_2CH_3$), 54.49 (t, $^{1}J_{PC} = 139.7$ Hz, $\underline{CBr}CH_2CH_2CH_3$), 64.39–64.30 ($4xO\underline{C}H_2CH_3$); ^{31}P NMR($CH_2Cl_2$, 85% H_3PO_4) δ16.6; ESI-Ms(+): m/z = 433.1 ($M + Na^+$, ^{81}Br, 100), 431.4 ($M + Na^+$, ^{79}Br, 78); 409.5 ($M + H^+$, ^{79}Br, 13), 411.4 ($M + H^+$, ^{81}Br, 16).

α-Choloro-butylidenediphosphonate (1c). ^{1}H NMR($CDCl_3$, Me_4Si) δ 0.95 (t, $^{3}J_{HH} = 7.4$ Hz, 3H, $CClCH_2CH_2\underline{CH_3}$), 1.37 (t, $^{3}J_{HH} = 7.1$ Hz, 12H, $4OCH_2\underline{CH_3}$), 1.65–1.77 (m, 2H, $CClCH_2\underline{CH_2}CH_3$), 2.11–2.28 (m, 2H, $CCl\underline{CH_2}CH_2CH_3$), 4.20–4.30 (m, 8H, $4O\underline{CH_2}CH_3$); ^{13}C NMR($CDCl_3$, Me_4Si) δ 14.21 (s, $CClCH_2CH_2\underline{C}H_3$), 16.30–16.37 (m, $4OCH_2\underline{C}H_3$), 17.91 (t,$^{3}J_{PC} = 6.2$ Hz, $CClCH_2\underline{C}H_2CH_3$), 37.73 (t, $^{2}J_{PC} = 2.8$ Hz, $CCl\underline{C}H_2CH_2CH_3$), 62.46 (t, $^{1}J_{PC} = 143.4$ Hz, $\underline{C}ClCH_2CH_2CH_3$), 64.12–64.66 ($4O\underline{C}H_2CH_3$), ^{31}P NMR($CH_2Cl_2$, 85% H_3PO_4) δ 16.7; ESI-MS(+): m/z = 387.2 (M + Na^+, ^{35}Cl, 100), 389.2 (M + Na^+,^{37}Cl, 32); 365.3 (M + H^+, ^{35}Cl, 35), 367.3 (M + H^+, ^{37}Cl, 15).

α-Iodo-butylidenediphosphonate (1d). ^{1}H NMR($CDCl_3$, Me_4Si) δ 0.95 (t, 3H, $^{1}J_{HH} = 7.2$ Hz, $ClCH_2CH_2\underline{CH_3}$), 1.33–1.37 (m, 12H, $4OCH_2\underline{CH_3}$), 1.65–1.69 (m, 2H, $ClCH_2\underline{CH_2}CH_3$), 1.98–2.10 (m, 2H, $ICH_2\underline{CH_2}CH_2CH_3$), 4.09–4.27 (m, 8H, $4O\underline{CH_2}CH_3$); ^{13}C NMR($CDCl_3$, Me_4Si) δ 14.16 (s, $ClCH_2CH_2\underline{CH_3}$), 16.37–16.52 ($4OCH_2\underline{C}H_3$), 22.46 (t, $^{3}J_{PC} = 6.5$ Hz, $ClCH_2\underline{C}H_2CH_3$), 39.34 (t, $^{2}J_{PC} = 3.4$ Hz, $CI\underline{C}H_2CH_2CH_3$,), 34.88 (t, $^{1}J_{PC} = 135.0$ Hz, $\underline{C}ICH_2CH_2CH_3$), 64.46–64.63 (m, $4O\underline{C}H_2CH_3$), ^{31}P NMR(CH_2Cl_2, 85% H_3PO_4) $\delta = 19.4$; ESI-MS(+): m/z = 457.2 (M + H)$^+$, 479.1 (M + Na)$^+$.

α-Bromo-ethylidenediphosphonate (1e). ^{1}H NMR($CDCl_3$, Me_4Si) δ 1.36 (t, $^{3}J_{HH} = 7.5$ Hz, 12H, $4OCH_2\underline{CH_3}$), 2.08 (t, 3H, $^{3}J_{PH} = 15.5$ Hz, $CBr\underline{CH_3}$), 4.29–4.30 (m, 8H, $4xO\underline{CH_2}CH_3$); ^{13}C NMR($CDCl_3$, Me_4Si) δ 16.16 (d,^{3} $J_{PC} = 6.6$ Hz, $4xOCH_2\underline{C}H_3$), 23.94 (t, $^{2}J_{PC} = 3.5$ Hz, $CBr\underline{C}H_3$), 47.68 (t, $^{1}J_{PC} = 143.4$ Hz, $\underline{C}BrCH_3$), 64.62–64.73 (m, $4O\underline{C}H_2CH_3$), ^{31}P NMR(CH_2Cl_2, 85% H_3PO_4) δ 17.6; ESI-Ms(+): m/z = 403.1 (M + Na^+, ^{79}Br, 306), 405.1 (M + Na^+, ^{81}Br, 284).

The dates of spectrum of compounds **(1f, 1g)** are consistent with Iorga and Savigance.[11]

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