A Novel Synthesis of Phosphonates from Diethyl (Trichloromethyl)phosphonate

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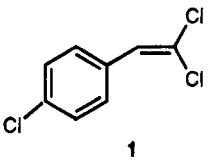
Commercially available diethyl (1,1,1-trichloromethyl)phosphonate was reacted with aldehydes and ketones to generate (chlorovinyl)phosphonates in a single step. These intermediates could be hydrogenated in high yields to the corresponding saturated phosphonates.

Phosphonates are interesting complements to phosphates in terms of biological activity and have been well documented in recent literature. Unlike phosphates, the phosphonate linkage is not susceptible to hydrolysis by esterases and is chemically stable. Acyclic nucleoside phosphonates are a novel class of antiviral agents that exhibit broad-spectrum inhibition of DNA viruses (e.g., adenovirus, Epstein–Barr virus, hepatitis B virus, acyclovir-resistant herpes simplex virus, and ganciclovir-resistant cytomegalovirus)[1–3] and retroviruses (e.g., HIV-1, HIV-2, SIV, and MSV).[2] Oligonucleoside methylphosphonates act effectively as specific antisense inhibitors of gene expression in mammalian cells.[4] Phosphonates also show promise as useful broad-spectrum antibiotics.[5–7] Bisphosphonates have become important in the treatment of hypercalcemia and tumor-induced osteolysis.[5,7,8] In the area of agricultural chemistry, phosphonates have been developed as insecticides,[6,7] herbicides,[6,7,9] fungicides,[7,10] and plant growth regulators.[9] We have discovered a single-step conversion of commercially available diethyl (trichloromethyl)phosphonate into a reactive bisphosphonate intermediate that is known to react with aldehydes and ketones to form vinylphosphonates.

In a search of the literature for methods of converting aldehydes to 1,1-dihaloalkenes, we noticed a procedure by Normant and co-workers.[11] The authors reported that treatment of diethyl trichloromethylphosphonate with 1 equiv of ethereal *n*-butyllithium at −100 °C in a THF–diethyl ether solution, followed by 1 equiv of an aldehyde or ketone, resulted in the formation of a 1,1-dichloroalkene in yields of 75–97%. When we repeated Normant et al.'s procedure on 4-chlorobenzaldehyde (as a model), using *n*-butyllithium (2.5 M in hexanes as our only deviation from his experimental conditions), we obtained a mixture of four compounds—the desired dichloroalkene, **1**, in 58% yield; 4-chlorobenzaldehyde in 16% yield; and two unexpected products in a combined 21% yield that contained phosphorus (by ^{31}P-NMR). Further analysis confirmed the structures of the two products as **2a** and **2b**, a mixture of geometric isomers.



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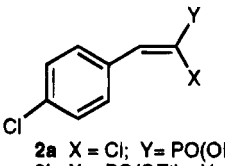

2a X = Cl; Y = $PO(OEt)_2$
2b X = $PO(OEt)_2$; Y = Cl

To determine whether the ratio of products remained the same at a more routine internal temperature of −70 °C (dry ice–acetone bath), the reaction was repeated. The amount of recovered dichloroalkene **1** dropped to 2%, while the amount of **2a** and **2b** rose to a combined 49%.

Normant et al. proposed a mechanism for the reaction involving attack of the lithiodichloro species, **3** (generated by treatment of the diethyl trichloromethylphosphonate with 1 equiv of *n*-butyllithium), on the carbonyl group of an aldehyde or ketone to form a betaine. Elimination provides the desired product (Scheme 1).

Based upon the discrepancy of the results that we obtained, we treated diethyl (trichloromethyl)phosphonate in THF at −70 °C with 1 equiv of *n*-butyllithium (1.6 M in hexanes) and quenched with 1 N HCl. We obtained one major product by TLC. Using GC–MS, ^{1}H-NMR, and ^{31}P-NMR we identified this product as tetraethyl (chloromethylene)bisphosphonate, **4**. Aboujaoude et al.[12] reported that **4** can be used to synthesize (chlorovinyl)phosphonates from aldehydes and ketones. With this information, we propose the following mechanism by which diethyl (trichloromethyl)phosphonate reacts with aldehydes and ketones to generate (chlorovinyl)-phosphonates (Scheme 2). Presumably, the initially formed lithiodichloro species, **3**, reacts with a molecule of starting material to form the tetraethyl (dichloromethylene)bisphosphonate, **5**. Given the ability of the trichloromethyl group to stabilize an anionic charge due to the effect of the electronegative chlorine atoms, this step should proceed readily. The well-known haloform reaction occurs by a similar pathway. The second step involves a metal–halogen exchange of one of the chlorines of the bisphosphonate to provide the active phosphorane species, **7**.

Upon further analysis of our results at −70 °C, we found that the 49% combined yield of **2a** and **2b** was in excellent agreement with the 50% yield predicted by the proposed mechanism, since two molecules of diethyl

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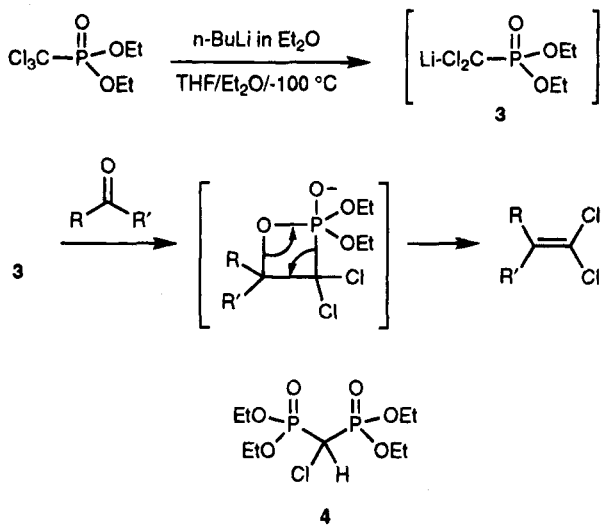
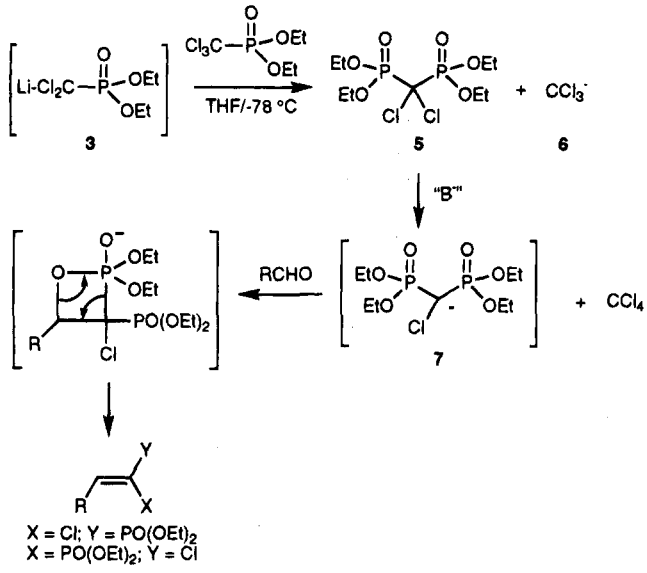
Scheme 1



Scheme 2



(trichloromethyl)phosphonate are consumed for every molecule of 4-chlorobenzaldehyde.

It is interesting to note that an increase of only 30 °C in the internal reaction temperature changed dichloroalkene **1** from being the major product of the reaction to a very minor one. Based upon the proposed mechanism, it seems likely that the warmer reaction temperature accelerates the rate of SN2 attack of the lithiodichloro species, **3**, upon a molecule of starting material phosphonate, thus maximizing the amount of bisphosphonate **5** that is formed and the resulting products **2a** and **2b**. At the colder temperature, the lithiodichloro species, **3**, is relatively unreactive and is the major component in the reaction upon addition of the aldehyde, thus maximizing the amount of dichloroalkene **1** that is formed.

It appeared that an internally generated nucleophile was causing metal–halogen exchange on the bisphosphonate, **5**. In the proposed mechanism, the nucleophile would have to be either the anion of chloroform **6** or the lithiodichloro species, **3**. In the first case, carbon tetrachloride would be directly formed. In the second case, the starting material, diethyl (trichloromethyl)phosphonate, would be directly formed. The starting material could, however, react with **6** to regenerate **3** along with carbon tetrachloride to begin the cycle anew. The presence of carbon tetrachloride in the reaction would support either one of the proposed pathways, but since it would be formed in both cases, its presence in the product mixture would not allow for differentiation of one pathway over the other, making it impossible to discern the exact mechanism. When the crude reaction mixture that generated bisphosphonate **4** was carefully analyzed by GC–MS, carbon tetrachloride was detected, but it could not be quantitated.

Table 1

starting material	(chlorovinyl)-phosphonate	satd phosphonate
benzaldehyde	**2**[a]	**13** (78%)
butyraldehyde	**8** (61%)	**14** (72%)
cyclohexanone	**9** (59%)	**15** (90%)
p-anisaldehyde	**10** (92%)	**16** (91%)
3-bromobenzaldehyde	**11** (78%)	97%[b]
acetophenone	**12** (28%)[c]	**17** (94%)
benzoyl chloride		
benzophenone	SM	

[a] Yield = 106%. [b] Product identified as diethyl (2-phenylethyl)phosphonate. [c] Reaction was refluxed for 48 h.

We discovered that the (chlorovinyl)phosphonate mixture could be easily reduced to the corresponding saturated phosphonate by hydrogenation over 10% palladium catalyst in 95% ethanol using sodium acetate as a buffer.

In an effort to explore the scope of the reaction sequence, we tested several carbonyl-containing compounds (Table 1). All of the aldehydes chosen, along with cyclohexanone and acetophenone as the representative ketones, reacted to give phosphonate products. Benzophenone proved to be too sterically hindered to react, and benzoyl chloride failed to give the expected (1,2-dichlorovinyl)phosphonate.

In summary, a novel synthesis of phosphonates from carbonyl compounds and commercially available diethyl (trichloromethyl)phosphonate has been achieved. Experimental evidence indicates that the reaction proceeds through the known bisphosphonate **7**, and we have proposed a mechanism to explain its formation. Based upon the compounds tested, aldehydes and unhindered ketones are reactive substrates, whereas acid chlorides fail to give desired products. Both the initially obtained (chlorovinyl)phosphonates and the saturated phosphonates lend themselves to further chemical modification and thus provide for the synthesis of a number of interesting phosphorus-containing derivatives.

Experimental Section

General. Diethyl (trichloromethyl)phosphonate was purchased from Fluka and was used without further purification. *n*-Butyllithium was purchased from Aldrich as either 1.6 or 2.5 M solutions in hexanes. Anhydrous tetrahydrofuran (THF) was obtained from Aldrich, and anhydrous diethyl ether was used directly from Mallinckrodt's 500-g resealable cans without further drying. The model carbonyl compounds used to generate Table 1 were all purchased from Aldrich. Flash chromatography on silica gel (230–400 mesh) was the method used to purify all products. Characterization of compounds was accomplished by ^{1}H-NMR (d_6-DMSO), ^{31}P-NMR (d_6-DMSO), MS, GC–MS, and microanalysis. Since all products exist as an unseparated *E* and *Z* mixture of geometric isomers, the ^{1}H-NMR data are reported with the number of protons equal to the total for both isomers.

Representative Procedure for the Preparation of (Chlorovinyl)phosphonates. To a stirring −70 °C (internal temperature) solution of diethyl (trichloromethyl)phosphonate

(36.6 mmol) in anhydrous THF (150 mL) in a 500-mL three-necked round bottom flask equipped with a septum, a thermometer, and an addition funnel topped by a nitrogen inlet was added dropwise *n*-butyllithium (18.3 mmol) at such a rate that the internal reaction temperature did not exceed −65 °C. The resulting dark red solution was stirred at −70 °C for 1 h before an aldehyde or ketone (16.6 mmol) as a solution in anhydrous THF (20 mL) was added dropwise over 15 min. The reaction was allowed to reach room temperature by stirring for 18 h before saturated ammonium chloride (50 mL) was added followed by diethyl ether (100 mL). The layers were separated, and the organic layer was washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to an oil. Flash chromatography of the crude product over silica gel with a hexane/ethyl acetate eluent system provided the pure (chlorovinyl)phosphonate.

(*E* and *Z*)-Diethyl (1-chloro-2-phenyl)vinylphosphonate (2): yield, 106%; ^{1}H-NMR δ 7.87−7.38 (m, 12H), 4.35−4.02 (m, 8H, 4 CH_2), 1.36−1.20 (m, 12H, 4 Me).

(*E* and *Z*)-Diethyl (1-chloro-1-pentenyl)phosphonate (8): yield, 61%; ^{1}H-NMR δ 6.87 (t, *J* = 7.1 Hz, 1H), 6.80 (t, *J* = 7.1 Hz, 1H), 4.34−3.97 (m, 8H, 4 CH_2), 2.38−2.24 (m, 4H), 1.58−0.87 (m, 22H); ^{31}P-NMR ppm 12.90, 9.72.

(*E* and *Z*)-Diethyl (chlorocyclohexylidenemethyl)-phosphonate (9): yield, 59%; ^{1}H-NMR δ 4.30−3.95 (m, 8H, 4 CH_2), 2.82 (bs, 4H), 2.51 (bs, 4H), 1.76−1.15 (m, 24H); ^{31}P-NMR ppm 13.47, 10.70. Anal. Calcd for $C_{11}H_{20}O_3ClP$ (0.20 $Cl_3CPO(OEt)_2$): C, 45.35; H, 6.98; Cl, 17.85. Found: C, 45.54; H, 7.08; Cl, 17.97.

(E and Z)-Diethyl [1-chloro-2-(4-methoxyphenyl)vinyl]-phosphonate (10): yield, 92%; ^{1}H-NMR δ 7.90−6.93 (m, 10H), 4.14−3.93 (m, 8H, 4 CH_2), 3.81 (s, 3H, OMe), 3.78 (s, 3H, OMe), 1.28 (t, *J* = 7.0 Hz, 6H, 2 Me), 1.14 (t, *J* = 7.0 Hz, 6H, 2 Me); ^{31}P-NMR ppm 11.98, 8.68. Anal. Calcd for $C_{13}H_{18}O_4ClP$ (0.10 $Cl_3CPO(OEt)_2$, 0.10 $CHCl_3$): C, 47.74; H, 5.63; Cl, 16.58. Found: C, 48.04; H, 5.97; Cl, 16.64.

(*E* and *Z*)-Diethyl [1-chloro-2-(3-bromophenyl)vinyl]-phosphonate (11): yield, 78%; ^{1}H-NMR δ 8.06−7.42 (m, 10H), 4.30−4.01 (m, 8H, 4 CH_2), 1.31 (t, *J* = 7.0 Hz, 6H, 2 Me), 1.19 (t, *J* = 7.0 Hz, 6H, 2 Me); ^{31}P-NMR ppm 12.90, 9.97.

(*E* and *Z*)-Diethyl (1-chloro-2-phenyl-1-propenyl)phosphonate (12). In preparing the product, it was necessary to reflux the reaction mixture for 48 h before the quench was done with saturated ammonium chloride: yield, 28%; ^{1}H-NMR δ 7.44−7.27 (m, 10H), 4.66−3.71 (m, 8H, 4 CH_2), 2.30 (s, 3H, Me), 2.29 (s, 3H, Me), 1.26 (t, *J* = 7.0 Hz, 6H, 2 Me), 1.04 (t, *J* = 7.0 Hz, 6H, 2 Me); ^{31}P-NMR ppm 8.24, 7.07.

Representative Procedure for the Preparation of the Diethyl Ethylphosphonates. A solution of the diethyl (chlorovinyl)phosphonate (25 mmol) and sodium acetate (30 mmol) in 95% ethanol (100 mL) in a 500-mL Parr bottle was mixed with 10% palladium on carbon (3 g) and agitated under a hydrogen gas atmosphere (35 psi) for 17 h. Excess hydrogen was removed and the reaction was filtered through Celite. The cake was washed with 95% ethanol (100 mL), and the combined filtrate was concentrated in vacuo. Ethyl acetate (200 mL) and water (75 mL) were added to the residue, and the layers were separated. The organic layer was washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the crude product over silica gel with a hexane/ethyl acetate eluent system provided the pure diethyl ethylphosphonate.

Diethyl (2-phenylethyl)phosphonate (13): yield, 78%; ^{1}H-NMR δ 7.35−7.17 (m, 5H), 4.06−3.91 (m, 4H, 2 CH_2), 2.86−2.72 (m, 2H), 2.13−1.96 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 6H, 2 Me); ^{31}P-NMR ppm 31.7. Anal. Calcd for $C_{12}H_{19}O_3P$ (0.7 H_2O): C, 56.55; H, 8.07. Found: C, 56.40; H, 7.94.

Diethyl pentylphosphonate (14): yield, 72%; ^{1}H-NMR δ 4.11−3.90 (m, 4H, 2 CH_2), 1.77−0.83 (m, 11H), 1.23 (t, *J* = 7.0 Hz, 6H, 2 Me); ^{31}P-NMR ppm 33.2. Anal. Calcd for $C_9H_{21}O_3P$ (0.20 H_2O): C, 51.03; H, 10.18. Found: C, 50.83; H, 9.89.

Diethyl (cyclohexylmethyl)phosphonate (15): yield, 90%; ^{1}H-NMR δ 4.14−3.90 (m, 4H, 2 CH_2), 1.94−0.90 (m, 13H), 1.23 (t, *J* = 7.0 Hz, 6H, 2 Me); ^{31}P-NMR ppm 31.7. Anal. Calcd for $C_{11}H_{23}O_3P$ (0.10 $CHCl_3$, 0.30 H_2O): C, 52.99; H, 9.49. Found: C, 52.79; H, 9.35.

Diethyl [2-(4-methoxyphenyl)ethyl]phosphonate (16): yield, 91%; ^{1}H-NMR δ 7.18 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.07−3.91 (m, 4H, 2 CH_2), 3.73 (s, 3H, OMe), 2.80−2.66 (m, 2H), 2.09−1.95 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 6H, 2 Me); ^{31}P-NMR ppm 31.8. Anal. Calcd for $C_{13}H_{21}O_4P$ (0.90 H_2O): C, 54.12; H, 7.97. Found: C, 54.13; H, 7.84.

Diethyl (2-phenylpropyl)phosphonate (17): yield, 94%; ^{1}H-NMR δ 7.35−7.17 (m, 5H), 3.99−3.75 (m, 4H, 2 CH_2), 3.15−2.99 (m, 1H), 2.14−2.00 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H, Me), 1.21−1.08 (m, 6H, 2 Me); ^{31}P-NMR ppm 30.5. Anal. Calcd for $C_{13}H_{21}O_3P$ (0.50 H_2O): C, 58.86; H, 8.36. Found: C, 58.79; H, 8.16.

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