The Synthesis of Dialkyl α-Halogenated Methylphosphonates

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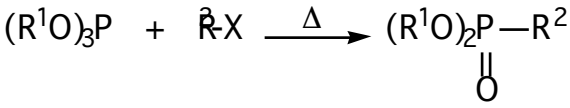
Introduction

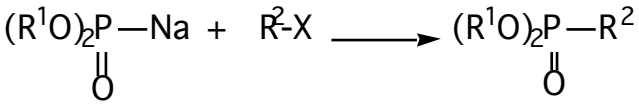
In the realm of organophosphorus chemistry, phosphonates, as both free acids and in their partial and fully esterified forms, are interesting complements to phosphates in terms of biological activity, and have been well documented in the literature.[1-4] Unlike phosphates, the phosphonate linkage is not susceptible to hydrolysis by esterases and is chemically stable. Phosphonates play an important and useful role in our lives from the many and varied biological applications such as antiviral agents (acyclic nucleoside phosphonates),[5-7] as inhibitors of gene expression in mammalian cells (oligonucleoside methylphosphonates)[8] and as antibiotics[4, 9, 10] (phosphonomycin[11]). They have become important in the treatment of bone-disorder (Clodronate[12], Etidronate[13]) and in medical decalcification (e.g. of prosthetics, dental calculus).[14, 15] In the area of agricultural chemistry, they have been developed as insecticides,[4, 10] herbicides (phosphoalanine),[4, 10, 16] fungicides,[10, 17] and plant growth regulators.[16] From their physical properties, phosphonates (as polymer treatments) are also used as fire retardents for materials.[18, 19]

Within this class of compounds there exists an important subdivision, the α-halogenated phosphonates. The functionality at the α-position serves to alter their chemical and physical properties with respect to non-halogenated phosphonates. This alteration of properties is often most apparent when phosphonate mimics of phosphates are closely scrutinised. The presence of the electronegative element on the α-carbon serves to give this carbon more oxygen-like properties, i.e. the α-halogenated phosphonate more closely resembles the parent phosphate but still retains the non-hydrolysable linkage which is important in these applications. Such analogues are said to be bioisosteric with respect to the parent phosphates. Dialkyl α-halogenated methylphosphonates are useful starting materials for the synthesis of a wide variety of phosphonates[1] which can be used in the above described applications.

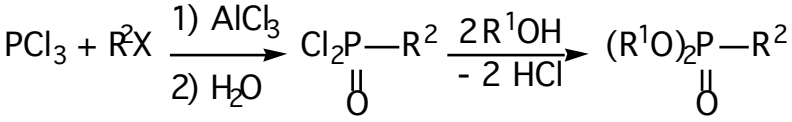
The syntheses of α-halogenated methylphosphonates take many forms and can be classified by their main types such as :

- Michaelis-Arbuzov[20] 

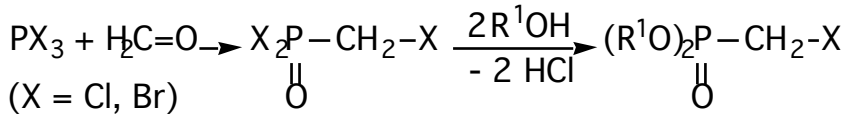
This is the simplest method from a practical point of view. It proceeds without solvent and can be conducted on preparative molar scale. The phosphonates are easily purified by distillation and usually obtained in high yields.

- Michaelis-Becker[21] 

This involves the action of dialkyl phosphite anions on simple alkylhalides. A suitable solvent is needed to modulate the nucleophilicity of the anion. Aromatic solvents, such as toluene or xylene, which provide satisfying nucleophilicity as well as good solubility, are preferably used.

- Kinnear-Perren[22] 

This reaction proceeds in the presence of a Lewis acid (usually $AlCl_3$) with intermediate isolation of the phosphonyl dichloride followed by alcoholysis in a second step. Alternatively the reaction and alcoholysis can be carried out in one step. On laboratory scale, difficulties can arise from the evolution of gaseous hydrochloric acid (2 eq) and precipitation of aluminium hydroxide.

- Kabachnik[23] 

This method is effective with formaldehyde and aromatic aldehydes only, since aliphatic aldehydes lead to poor yields. The reaction occurs without solvent at high temperature in a closed vessel.

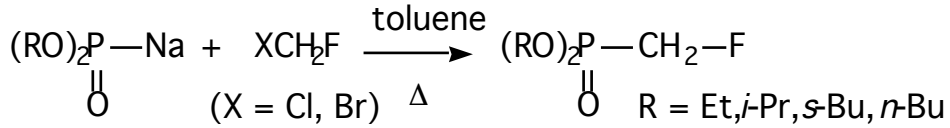
Often specific reactions are also useful, e.g. reductions, oxidations, and substitutions. All these synthetic methods will be examined in the course of this review. The synthesis of mono-, di-, and tri-halogenated methylphosphonates will be presented in separate sections.

I. α-Monohalogenated methylphosphonates

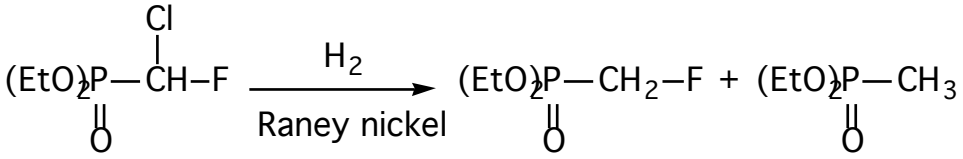
The four monohalogenated methylphosphonates are known. The iodo compounds (see **I. 4.**) were the first described in the literature in 1936. From the number of publications, there is a greater interest in the chloro compounds (see **I. 2.**), but the fluoro derivatives (see **I. 1.**) are becoming more utilised in recent years due to their biological properties.

I. 1. Fluoromethylphosphonates

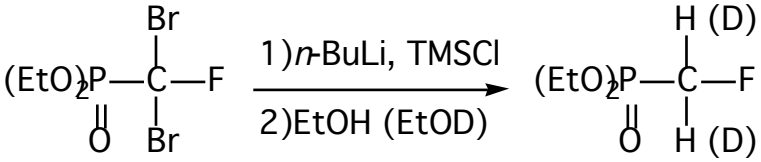
Michaelis-Becker reaction : This oldest[21] and most commonly used method to synthesise fluoromethylphosphonates (ethyl, *i*-propyl, *s*-butyl, and *n*-butyl esters) is based on the reaction between a dialkyl sodiophosphite and chlorofluoromethane[24] or bromofluoromethane* [25] in refluxing toluene. This gives fluoromethylphosphonates in moderate yield : 36 % (*s*-butyl esters) to 50 % (*i*-propyl esters).[24]



Reduction reaction : Reduction of diethyl chlorofluoromethylphosphonate (see **II. 2.**) by means of H_2 / Raney nickel[26] in a water / ethanol mixture (50 / 50) leads to diethyl fluoromethylphosphonate in moderate yield (43 %) together with diethyl methylphosphonate (33 %) resulting from partial hydrogenolysis of the C-F bond. The compounds can be separated from the mixture by column chromatography.



Reduction of diethyl dibromofluoromethylphosphonate (see **III. 6.**) in THF with two equivalents of *n*-butyllithium in the presence of chlorotrimethylsilane as protecting group allows the formation of the stable 1-fluoro-1-lithio-1-(trimethylsilyl)methylphosphonate. Ethanol, when added to this intermediate, acts in turn as protonating and desilylating agent. This facile, one-pot procedure affords diethyl fluoromethylphosphonate in high yield (93 %).[27-30] The diethyl dideuteriofluoromethylphosphonate is synthesised by the same procedure in comparable (92 %) yield.[31]



Diethyl 1-fluoromethylphosphonate[27] **:** To a solution of *n*-BuLi (13.75 mL of a 1.6 M solution in hexane, 22 mmol, 2.2 eq) in THF (30 mL) cooled to -78°C is added a mixture of diethyl 1,1-dibromo-1-fluoromethylphosphonate (3.28 g, 10 mmol) and TMSCl (1.08 g, 10 mmol) in THF (10 mL) *via* a dropping funnel maintaining the temperature at -78°C. The reaction mixture was stirred at this

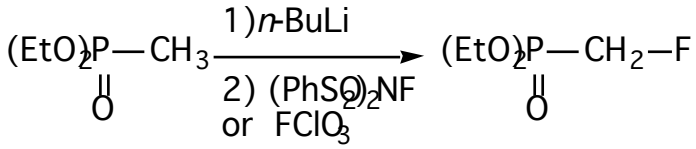
* Bromofluoromethane is no longer available commercially on account of its high mutagenicity.[25]

temperature for 10 min and then allowed to warm to 0°C. A solution of lithium ethoxide in ethanol (15 mL) was added to the reaction mixture and stirred for 10 minutes before the mixture was poured into a beaker of 3M HCl. The phases were separated and the aqueous phase was washed with diethyl ether (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ filtered and evaporated to yield an oil which on distillation gave the title compound as colorless mobile oil.

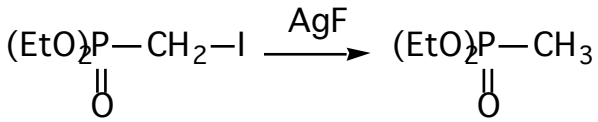
Diethyl 1,1-dideuterio-1-fluoromethylphosphonate[31] was synthesised by the same procedure, by adding ethan[^{2}H]ol (6 mL) at -78°C, instead of lithium ethoxide. Acidic hydrolysis was performed at 0°C.

Diethyl fluoromethylphosphonate was observed by ^{31}P NMR in a mixture obtained from a fluorophilic reaction between diethyl sodiophosphite and dibromofluoromethane or diethyl dichlorofluoromethylphosphonate, but was not isolated.[32]

Oxidation reaction (halogenation) : This involves oxidation of 1-lithiomethylphosphonates in THF solution by electrophilic fluorinating agents. Diethyl fluoromethylphosphonate (or mixed ethyl/methyl esters[33]) was obtained from N-fluorobenzenesulfonimide[34, 35] in 11 % yield and from perchloryl fluoride[36] (mixture of monofluoro and difluoro compounds obtained[33]) in 46 % yield. These fluorinating reactants are explosive compounds and are not easily available.



Halogen-substitution reaction : An unsuccessful attempt to synthesise diethyl fluoromethylphosphonate was made by heating neat diethyl iodomethylphosphonate (see **I. 4.**) in the presence of silver fluoride.[37] Under these conditions, only diethyl methylphosphonate was recovered by reductive cleavage of the C-I bond.

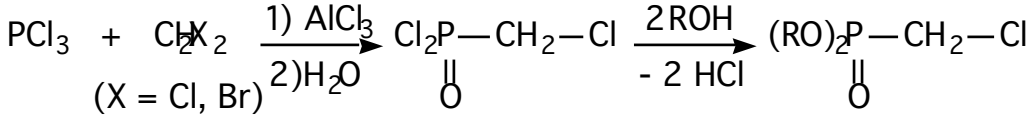


I. 2. Chloromethylphosphonates

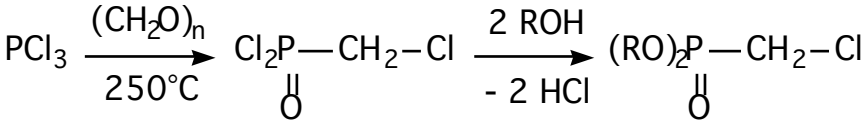
Michaelis-Becker reaction : The Michaelis-Becker reaction cannot be commonly used for the synthesis of chloromethylphosphonates since dichloromethane in the presence of diethyl sodiophosphite yields mainly tetraethyl methylenebisphosphonate (51 %). Diethyl chloromethylphosphonate appears as a side product in 15 % yield.[38] Both products are isolable from the mixture by distillation.

Kinnear-Perren reaction : This method is currently used for the synthesis of alkylphosphonyl dichlorides. The reaction is performed with phosphorus trichloride and dichloromethane in the presence of $AlCl_3$ to give chloromethylphosphonyl dichloride in 85 % yield.[22] With bromochloromethane or dibromomethane in the presence of $AlCl_3$, alkylation and subsequent halogen exchange take place giving the fully chlorinated product in low yield (35 %).

Standard alcoholysis in anhydrous condition yield the dialkyl chloromethylphosphonates (see Table 1).

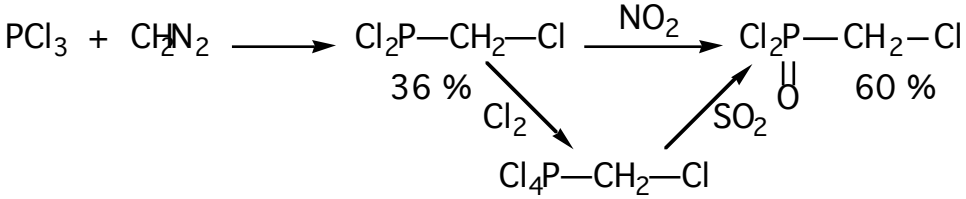


Kabachnik reaction : The reaction between phosphorus trichloride and formaldehyde at 250°C and without solvent, gives the chloromethylphosphonyl dichloride in up to 67 % yield.[23, 37, 39-42] The corresponding dialkyl chloromethylphosphonates are obtained after treatment with the appropriate alcohols (see Table 1).



The reaction also occurs between the more elaborate pyrocatecholchlorophosphite (*o*-$C_6H_4O_2PCl$) and formaldehyde to give pyrocatechol chloromethylphosphonate (*o*-$C_6H_4O_2P(O)CH_2Cl$) in 48 % yield.[23]

In an analogous way, phosphorus trichloride reacts with an ethereal solution of diazomethane to form chloromethyldichlorophosphine (Cl_2P-CH_2Cl) in 36 % yield. This compound gives the chloromethylphosphonyl dichloride in 60 % yield after oxidation. This occurs under anhydrous conditions either with NO_2 or through successive reactions of Cl_2 and SO_2 with the intermediate formation of chloromethyl tetrachlorophosphorane (Cl_4P-CH_2Cl).[43]



Standard alcoholysis yield the dialkyl chloromethylphosphonates (see Table 1).

• Alcoholysis of chloromethylphosphonyl dichloride :

Chloromethylphosphonyl dichloride obtained from either the Kinnear-Perren or Kabachnik reaction reacts with alcohols allowing the corresponding dialkyl chloromethylphosphonates to be obtained in yields ranging from 42 to 96 % (see Table 1). The quenching alcohol can be simply added pure.[44] The removal of the hydrogen chloride formed in the reaction is achieved with a stream of dry air,[45] appliance of occasional slight vacuum,[46] or constant water pump vacuum (for diols only).[47] However, the addition of a tertiary amine (pyridine[48, 49] and

triethylamine[50-55]) remains the most widely used method to trap the hydrogen chloride. The direct addition of sodium alcoholate[56] is also a useful synthetic method.

Table 1 :

Alcohol	Yield (%)[ref.]
methanol	66[53] or 90[45]
ethanol	72-95[39, 44, 45, 53, 55, 57, 58]
2-chloroethanol	66,[42] 72[50]
2,2,2-trichloroethanol	59,[42] 90[55]
2,2,2-trifluoroethanol	92[55]
isopropanol	74-79,[45, 58, 59] 85[55]
butanol	55-94[45, 59, 60]
isopentanol	79[59]
octanol	51[48]
allyl alcohol	60,[59, 61] 92[55`]
3-hydroxy-1-propyne	73[52]
phenol	77-96[42,* 46, 53,** 62]
1,3-propanediol	94[49]
2,2-dimethyl-1,3-propanediol	42[63] or 93[47, 55, 64]
1,4-butanediol	42[41]
pyrocatechol	90[65]

Mixed chloromethylphosphonates ((EtO)(RO)P(O)CH_2Cl) were obtained *via* controled hemi-alcoholysis of chloromethylphosphonyl dichloride with ethanol to first give the ethyl chloromethyl chlorophosphonate intermediate (43 %)[51] followed by further alcoholysis to furnish the mixed ester (R = 2-(ethylmercapto)ethyl[51] or 4-nitrophenyl,[56] 50-56 %). This method was also used in the synthesis of ethyl chloromethylphosphonamides ((EtO)(R_2N)P(O)CH_2Cl, 70 % yield).[54]

Chloromethylphosphonyl dichloride also reacts with one equivalent of water to yield quantitatively the corresponding phosphonic anhydride ($ClCH_2P(O)O_2P(O)CH_2Cl$). The addition of epoxides gives five-membered cyclic esters of chloromethylphosphonate in good yields (63-81 %).[66]

The reaction of chloromethylphosphonyl dichloride with trialkylsilanol acetates yields organosilicon esters of chloromethylphosphonic acids.[67]

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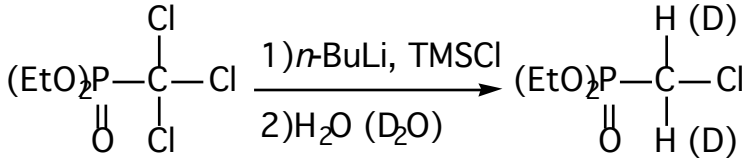
* Mono and dichlorophenols also used as quenching agent

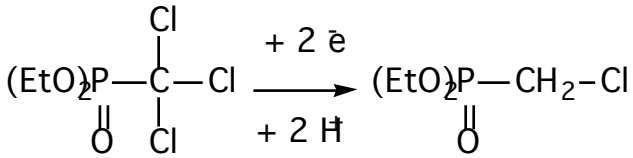
** 4-Methylphenol also used as quenching agent

Reduction reaction : The reduction procedure of diethyl trichloromethylphosphonate to chloromethylphosphonate involves the double exchange of chlorine with *n*-butyllithium in the presence of chlorotrimethylsilane. After protonation and removal of the silicon group with ethanol, diethyl chloromethylphosphonate is obtained pure in almost quantitative yield.[68] Under the same conditions, diethyl dideuteriochloromethylphosphonate was also isolated in comparable (95%) yield.[31]

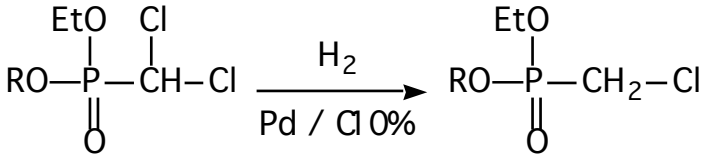


Diethyl 1-chloromethylphosphonate[68] **:** To a solution of *n*-BuLi (73 mL of a 1.5 M solution in hexane, 110 mmol, 2.2 eq) in THF (70 mL) cooled to -78°C is added a mixture of diethyl 1,1,1-trichloromethylphosphonate (12.8 g, 50 mmol) and TMSCl (6 g, 55 mmol) in THF (25 mL) *via* a dropping funnel maintaining the temperature at -78°C. The reaction mixture was stirred at this temperature for 15 min and then allowed to warm to -50°C. Water (30 mL) was added to the reaction mixture and stirred for 1 hour. The phases were separated and the aqueous phase was washed with diethyl ether (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 filtered and evaporated to yield an oil which on distillation gave the title compound as colorless mobile oil.
Diethyl 1,1-dideuterio-1-chloromethylphosphonate[31] was synthetised by hydrolysis with heavy water (25 mL) at -50°C instead of water.

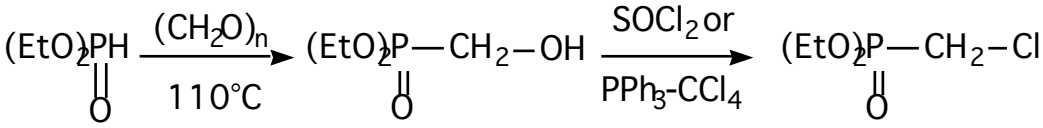
The electrochemical reduction of diethyl trichloromethylphosphonate to diethyl chloromethylphosphonate (20 % yield) was first mentioned in the synthesis of gemdichloroolefins from ketones *via* the Wittig-Horner reaction.[69, 70] This was then successfully applied to the synthesis of diethyl chloromethylphosphonate on preparative scale.[71] Diethyl chloromethylphosphonate was formed with a small amount of diethyl dichloromethylphosphonate (less than 10 %), and was obtained in pure form and high yield (80 %) after distillation. This electrochemical method can compete with chemical reduction which uses strongly basic and expensive alkyllithium reagents, and is currently of increasing use.[72, 73]



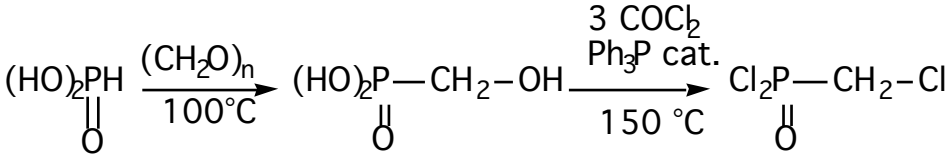
The hydrogenolysis of a C-Cl bond of chiral dialkyl dichloromethylphosphonates under rather mild conditions by means of molecular hydrogen and triethylamine over 10 % palladium-charcoal as catalyst is also reported. This method gives dialkyl chloromethylphosphonates ((EtO)(RO)P(O)CH_2Cl) in 73 % yield (R = phenyl or methyl).[74] The analogous (EtO)(MeS)P(O)CH_2Cl is also obtained in this way.[33, 74]



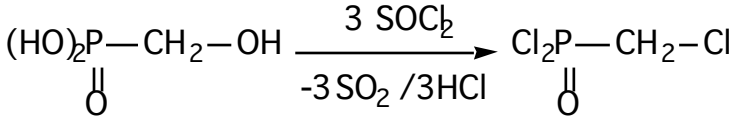
Hydroxy-substitution reaction : Diethyl chloromethylphosphonate is obtained from diethyl hydroxymethylphosphonate which is easily accessible from diethyl phosphite and paraformaldehyde at 110°C in 49-65 % yield.[75, 76] The subsequent chlorination occurs with thionyl chloride at 50°C (42 % yield)[77] or in a much safer procedure involving the triphenylphosphine-tetrachloromethane system (86 % yield).[78]



Chloromethylphosphonyl dichloride was synthesised by Hoechst Chemicals[79] *via* the hydroxymethylphosphonic acid. The latter is obtained by heating phosphorous acid and paraformaldehyde at approximately 100°C. The so-formed hydroxymethylphosphonic acid is converted into chloromethylphosphonyl dichloride under rather drastic conditions ($COCl_2$ at 150°C, in the presence of Ph_3P as catalyst). Yields are almost quantitative in preparative scale reactions (250 g of $Cl_2P(O)CH_2Cl$).



Chloromethylphosphonyl dichloride was also synthesised in benzene from hydroxymethylphosphonic acid and thionyl chloride at 55°C in 57 % yield.[80]

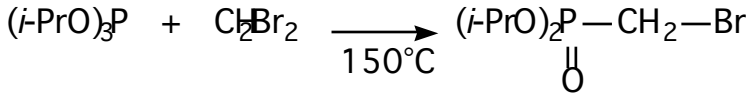


1-Chloromethylphosphonyl dichloride[80] **:** Hydroxymethylphosphonic acid (22.4 g) was suspended in anhydrous benzene (150 mL) and, with stirring and protecting from moisture, pyridine (47.5 g) was added. The phosphonic acid then became syrup-like and deposited on the bottom of the flask. The reaction mixture was heated at 55°C and distilled thionyl chloride (71.4 g) was added dropwise over a period of 30 min maintaining the temperature at 55-65°C. On evolution of sulfur dioxide the mixture became homogeneous and was cooled to 30°C over about 2 hours with stirring. Finally the solution was cooled with an ice bath for a further 30 min and the thus-formed crystals were separated by filtration. The latter were washed with benzene (5 x 60 mL). The filtrates were added together and the benzene was distilled at atmospheric pressure. With fractionation of the residue under vacuum, the chloromethylphosphonyl dichloride distilled at 90-95°C / 18 mmHg (18.9 g, 57 %).

I. 3. Bromomethylphosphonates

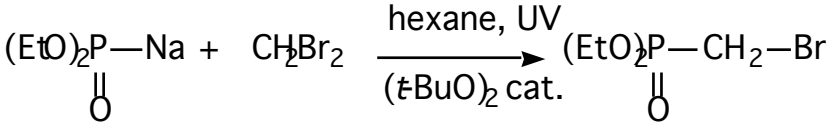
Kabachnik reaction : The first attempt to synthesise these compounds *via* the formation of bromomethylphosphonyl dibromide[23] prior to alcoholysis was not completed, probably due to the low yield (7 %) of the intermediate.

Michaelis-Arbuzov reaction : Triethyl phosphite reacts with dibromomethane to give diethyl bromomethylphosphonate in 13 % yield.[37] Altering the various reaction conditions does not improve the yield.[81, 82] The choice of starting phosphite plays an important role, e.g. triisopropyl phosphite gives a better yield (48 %) given the inert nature of isopropylbromide, generated in the reaction, toward trisopropyl phosphite.[83]

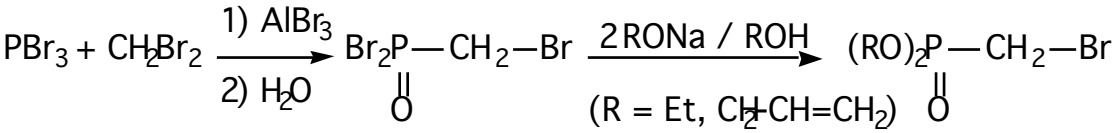


Diisopropyl 1-bromomethylphosphonate[83] **:** Into an apparatus consisting of a round bottomed flask-equipped with an efficient reflux condenser (60 cm long), surmounted with a distillation apparatus with a narrow downward cooler ending in a graduated measuring cylinder are introduced triisopropyl phosphite (52 g, 0.26 mol) and dibromomethane (111 g, 0.64 mol, 150 % excess). The reaction mixture is heated during 47 hours with a metallic bath at 145-150°C with the reflux condenser thermostatted at 62°C during which isopropylbromide distills from the reaction mixture (20.5 mL, 26.6 g, 0.22 mol). Two distillations of the colourless to yellowish reaction mixture yield the excess dibromomethane, and diisopropyl bromomethylphosphonate (31.0 g, 48 %). The second fraction consists of tetraisopropyl methylenebisphosphonate (17.2 g, 40 %).

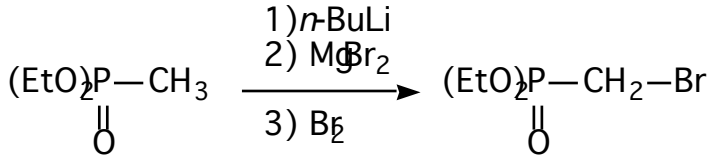
Michaelis-Becker reaction : The UV light-induced Michaelis-Becker reaction between diethyl sodiophosphite and dibromomethane in hexane with $(t\text{-BuO})_2$ as initiator gives the diethyl bromomethylphosphonate which was converted, without isolation, into tetraethyl methylenebisphosphonate (55-87 % yield).[82]



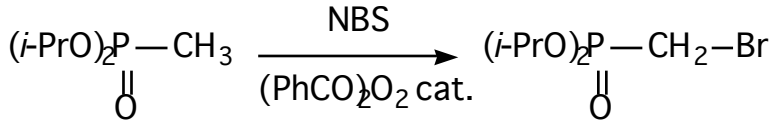
Kinnear-Perren reaction : In the presence of $AlBr_3$, the reaction between dibromomethane and phosphorus tribromide gives bromomethylphosphonyl dibromide in 60 % yield.[61] Further treatment of this acid bromide with a sodium alkoxide in alcohol yields the corresponding dialkyl bromomethylphosphonate (ethanol, 49 % ; allyl alcohol, 43 % overall yield).[61]



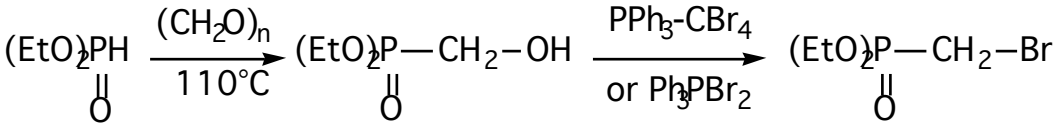
Oxidation reaction (halogenation) : Diethyl methylphosphonate yields 64 % of the corresponding bromomethylphosphonate by addition of bromine to the intermediate 1-magnesium methylphosphonate in THF.[84]



A direct bromination of diisopropyl methylphosphonate in neutral conditions was recently reported involving the use of N-bromosuccinimide as electrophilic brominating reagent and benzoyl peroxide as initiator in CCl_4. Diisopropyl bromomethylphosphonate is thus obtained in moderate yield (42 %).[85]



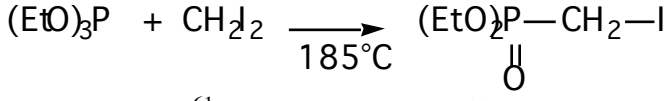
Hydroxy-substitution reaction : Diethyl bromomethylphosphonate is obtained from diethyl hydroxymethylphosphonate (easily accessible from diethyl phosphite and paraformaldehyde at 110°C in 49-65 % yield[75, 76]). This transformation occurs by means of triphenylphosphine-tetrabromomethane or dibromotriphenylphosphorane in the presence of pyridine in 65 and 67 % yield respectively.[86]



I. 4. Iodomethylphosphonates

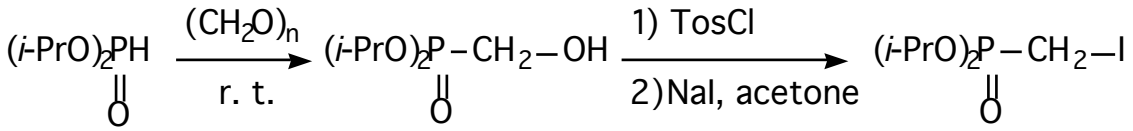
Michaelis-Arbuzov reaction : Diethyl iodomethylphosphonate was described for the first time in 1936 as the product of the reaction between triethylphosphite and diiodomethane (60 % yield claimed after distillation).[20] More recent reports on the same reaction point out the formation of a significant amount of tetraethyl methylenebisphosphonate.[87] Even under optimised experimental conditions, i.e. with continuous removal of ethyliodide by a stream of dry air, diethyl iodomethylphosphonate was obtained with maximum yields of only 30-40 %.[37, 39, 88] Not surprisingly, the reaction with trimethyl phosphite gives dimethyl iodomethylphosphonate in lower yield (27 %).[89]

In an alternative approach to dialkyl iodomethylphosphonates, it was found that yields are improved by adding trialkyl phosphites to an excess of hot diiodomethane. Under these conditions yields of 90 % for diethyl iodomethylphosphonate and 41 % for the diallyl ester are obtained.[61]



Diethyl 1-iodomethylphosphonate[61] **:** Triethyl phosphite (83 g, 1 mol) was added to diiodomethane (200 g, 1.5 mol) at 185° which was refluxing half-way up a column (10") containing glass helices and a condenser set for distillation. The rate of addition was adjusted so that distillation (70-110°) occured steadily and the temperature increased, finally to 220°. Heating was continued for a further 10 min. The products were ethyl iodide (74 g, 95 %), diiodomethane (68 g, 34 %), and diethyl iodomethylphosphonate (120 g, 90 %).

Substitution reaction : For the synthesis of diisopropyl iodomethylphosphonates, the intermediate formation of hydroxymethylphosphonate was prefered. The Pudovik reaction between diisopropyl phosphite and paraformaldehyde at room temperature was used as a first step. This gives diisopropyl hydroxymethylphosphonate in very good yield (92 %) which after tosylation is heated with NaI in dry acetone to give the corresponding diisopropyl iodomethylphosphonate. However no yield is reported.[90]



An attempted halogen-exchange reaction failed to transform the diallyl chloromethylphosphonate into the iodomethyl derivative. Thus, NaI in dry acetone gave allyl iodide as the only identifiable product resulting from a dealkylation reaction of the phosphonate.[61]

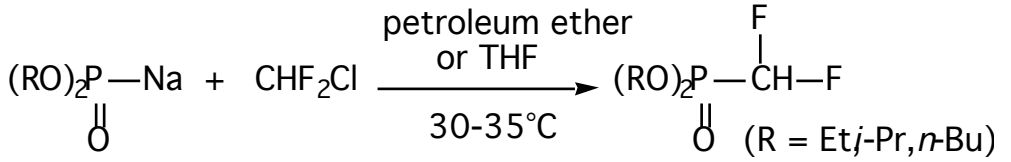
Oxidation reaction (halogenation) : An attempt to iodinate diethyl methylphosphonate by addition of iodine to the intermediate 1-magnesium methylphosphonate in THF yielded 5 % of iodomethylphosphonate.[84]

II. α-Dihalogenated methylphosphonates

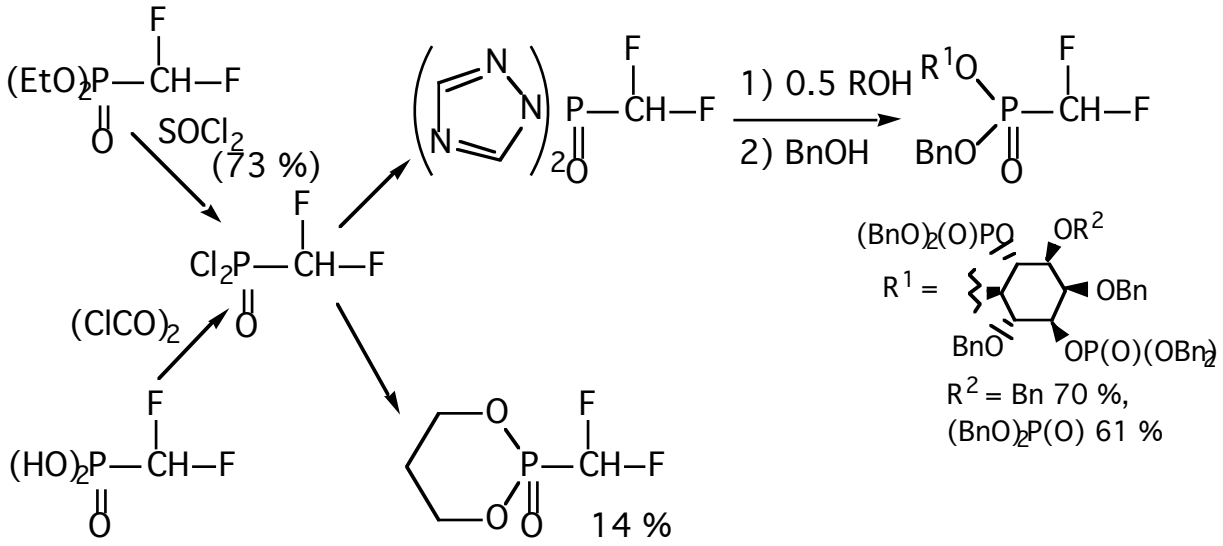
The same trend as for the monohalogenated phosphonates can be noticed i.e. a greater attention to dichloro compounds (see **II. 4.**) and an increasing interest in the difluoro derivatives (see **II. 1.**) in more recent years. No synthesis is currently described for the mixed halogenoiodo compounds.

II. 1. Difluoromethylphosphonates

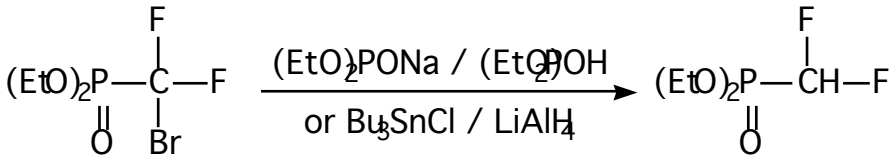
Michaelis-Becker reaction : This reliable reaction takes place between diethyl sodiophosphite and chlorodifluoromethane in petroleum ether or THF at 30-35°C to give diethyl difluoromethylphosphonate in moderate to good yield (49,[21] 54,[91, 92] 77[93] %). Diisopropyl and dibutyl difluoromethylphosphonates were obtained in the same manner in 49 and 68 % yield respectively.[21]



Esterification reaction : Transesterification of diethyl difluoromethylphosphonate was performed in three steps : firstly, difluoromethylphosphonyl dichloride was obtained by chlorination with thionyl chloride and pyridine (73 % yield).[92] This was then converted into difluoromethylphosphonyl di(1,2,4-triazolide) which in turn is displaced to afford the mixed dialkyl difluoromethylphosphonates in 61-70 % yield.[94] The 2-(difluoromethyl)-2-oxo-1,3,2-dioxophosphorinane was obtained in 14 % yield from the corresponding phosphonic acid *via* the phosphonyl dichloride.[49]



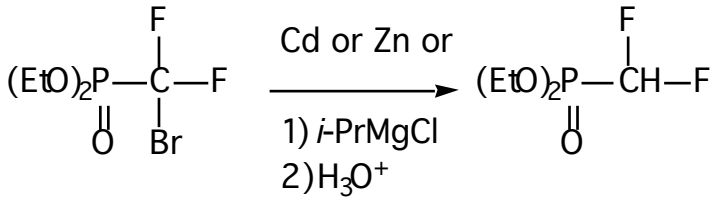
Reduction reaction : The reaction involves the positive halogen abstraction from diethyl bromo-[95] or chlorodifluoromethylphosphonate[29] with diethyl sodiophosphite in diethyl phosphite. The first reaction affords diethyl difluoromethylphosphonate in 75 % yield, while no yield is reported for the second. Reduction with tributyltin chloride-lithium aluminium hydride gives the same product in unknown yield.[96]



Dibutyl difluoromethylphosphonates was formed in the same manner from dibutyl bromodifluoromethylphosphonate. The reaction with dibutyl sodiophosphite gives mostly the bisphosphonate with only 27 % yield of the desired product.[95]

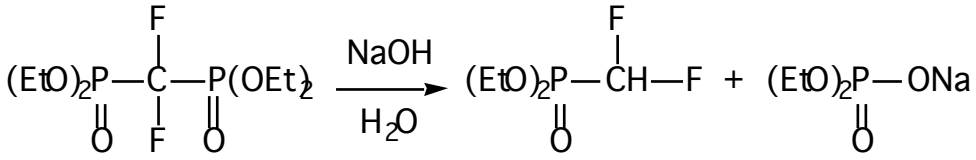
Metal-halogen exchange reactions from bromodifluoromethylphosphonates are more successful. Cadmium[97] or zinc[98] react in quantitative yields with diethyl, diisopropyl and

dibutyl difluoromethylphosphonates. Isopropylmagnesium chloride[99] affords diethyl difluoromethylphosphonate in 85 % yield.

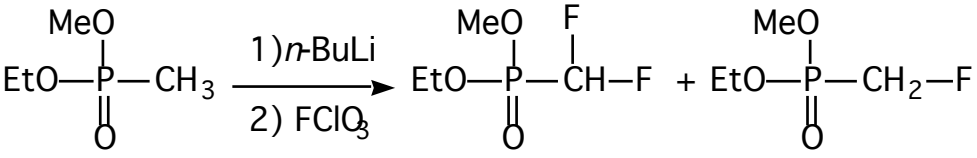


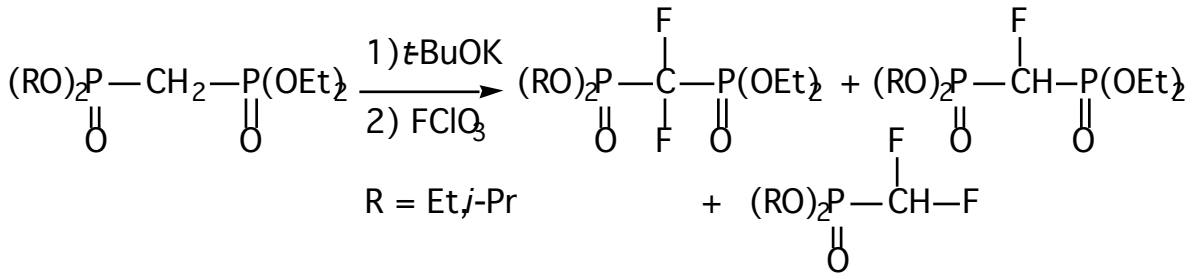
Diethyl 1,1-difluoromethylphosphonate[99] **:** A 500 mL reactor equipped with a mechanical stirrer, thermometer, reflux condenser, and an addition funnel was charged with previously standardised *i*-PrMgCl (29 mL of 1.90 M Et_2O solution, 0.055 mol) and THF (120 mL). The solution was cooled to -78°C and a solution of diethyl bromodifluoromethylphosphonate (13.4 g, 0.05 mol) in THF (50 mL) was added dropwise. The resulting mixture was stirred for 10 min at -78°C then at this temperature a solution of EtOH (10 mL) in THF (10 mL) was added dropwise. The reaction mixture was poured into an ice-cold mixture of HCl (40 mL of 3 M solution) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product which was purified by bulb-to-bulb distillation (b.p. 50-55°C / 0.5 mmHg). Yield = 85 %.

Diethyl difluoromethylphosphonate was also obtained by hydrolysis of tetraethyl difluoromethylenebisphosphonate with sodium hydroxide.[100]



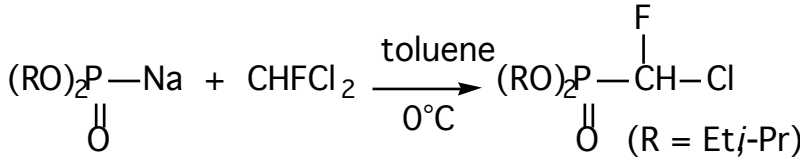
Oxidation reaction : The reaction of chiral ethylmethyl methylphosphonate with successively a strong base (*n*-BuLi) and perchloryl fluoride in THF yields a mixture of the corresponding difluoro and monofluorophosphonate.[33] An analogous process was applied to tetraethyl and tetraisopropyl methylenebisphosphonate with potassium tert-butoxide as a base in toluene. The choice of base is important as is the proportion of starting materials. In this way the reaction can be directed towards either the monofluorobisphosphonate (48 %) or the difluorobisphosphonate (73 %), sometimes accompanied by formation of diethyl or diisopropyl difluoromethylphosphonate (up to 18 %) as side product.[101]





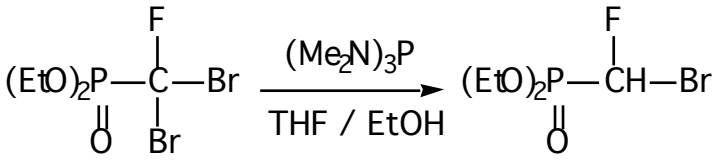
II. 2. Chlorofluoromethylphosphonates

Michaelis-Becker reaction : To date, the Michaelis-Becker reaction seems to be the best way to synthesise chlorofluoromethylphosphonates, although yields are generally low. The reaction between diisopropyl sodiophosphite and dichlorofluoromethane in toluene at 0°C gives 38 % of the corresponding chlorofluoromethylphosphonate.[102] No yield is reported for the analogous synthesis of diethyl chlorofluoromethylphosphonate.[25, 36]

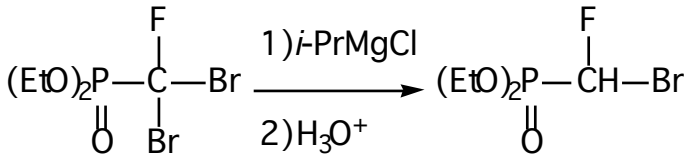


II. 3. Bromofluoromethylphosphonates

Reduction reaction : The only reported synthesis of diethyl bromofluoromethylphosphonate is the reduction of diethyl dibromofluoromethylphosphonate. This occurs with $(Me_2N)_3P$ in THF / ethanol medium at room temperature in 90% yield, but the product is always contaminated with a small amount (6-8 %) of $(Me_2N)_3PO$ which is difficult to remove.[28]



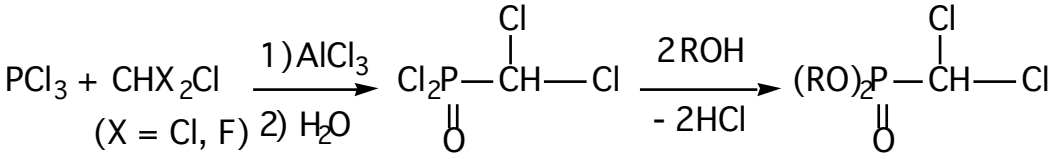
A halogen-metal exchange on diethyl dibromofluoromethylphosphonate with isopropylmagnesium chloride in THF also gives the title compound in 71 % yield but contaminated with fluoromethylphosphonate.[103]



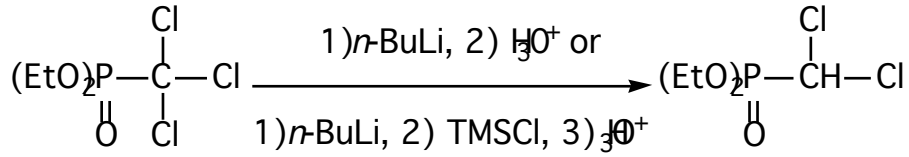
Diethyl 1-bromo-1-fluoromethylphosphonate[103] **:** A 500 mL reactor equipped with a mechanical stirrer, thermometer, reflux condenser, and an addition funnel was charged with previously standardised *i*-PrMgCl (29 mL of 1.90 M Et_2O solution, 0.055 mol) and THF (120 mL). The solution was cooled to -78°C and a solution of diethyl dibromofluoromethylphosphonate (16.4 g, 0.05 mol) in THF (50 mL) was added dropwise. The resulting mixture was stirred for 10 min at -78°C then at this temperature a solution of EtOH (10 mL) in THF (10 mL) was added dropwise. The reaction mixture was poured into an ice-cold mixture of HCl (40 mL of 3 M solution) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product which was purified by bulb-to-bulb distillation.

II. 4. Dichloromethylphosphonates

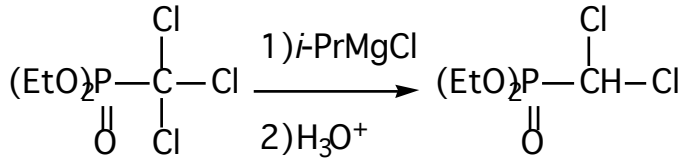
Kinnear-Perren reaction : The Kinnear-Perren reaction between phosphorus trichloride and trichloromethane or chlorodifluoromethane was investigated in the presence of $AlCl_3$. In both cases, the dichloromethylphosphonyl dichloride was exclusively obtained in 63-70 %[22, 104] and 40 % respective yields.[22] Dichloromethylphosphonyl dichloride is esterified under classical conditions (e.g. with phenol / triethylamine[105] or with phenols / pyridine in 70-81 % yield[104]). Hemi-ethanolysis in the presence of triethylamine allows the synthesis of ethyl dichloromethyl chlorophosphonate ($Cl(EtO)P(O)CHCl_2$) and further alcoholysis with 4-nitrophenol gives the mixed dichloromethylphosphonate diester in 57 % yield.[56]



Reduction reaction : The chemical reduction of trichloromethylphosphonate *via* halogen-metal exchange with *n*-butyllithium followed by acidic hydrolysis gives diethyl dichloromethylphosphonate in moderate yield (55 %).[106] The yield was improved to 65 % by trapping the intermediate lithiodichloromethylphosphonate with trimethylsilyl chloride. The C-Si bond is then cleaved in acidic aqueous medium.[107]

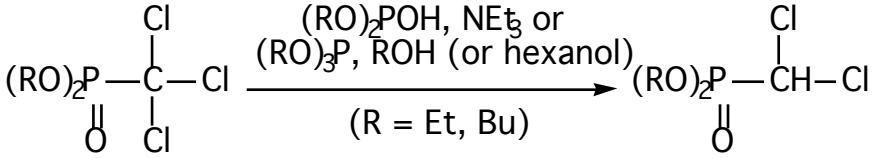


A similar halogen-metal exchange reaction occurs with isopropyl magnesium chloride in THF to give diethyl dichloromethylphosphonate in 94 % yield. The improved yield can be explained by the formation of the more stable magnesium intermediate.[108]

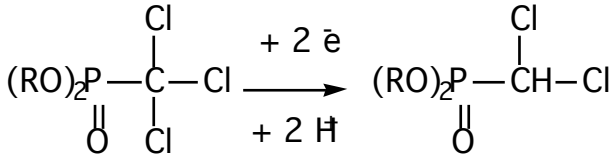


Diethyl 1,1-dichloromethylphosphonate[108] **:** To a stirred mixture of previously standardised 1.9 M solution of isopropylmagnesium chloride (83 mL; 158 mmol) and THF (400 mL) cooled to -78°C, was added dropwise a solution of diethyl 1,1,1-trichloromethylphosphonate (38.3 g; 150 mmol) in THF (50 mL) over a period of 15 min The resulting mixture was stirred at -78°C for a further 15 min and then a solution of absolute ethanol (12 g; 260 mmol) in THF (15 mL) was added dropwise to the reaction mixture. After 5 min the mixture was allowed to warm to -40°C and was then poured into a beaker containing a mixture of 3 M HCl (70 mL), an equal volume of crushed ice, and CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated to yield a yellow oil which when distilled gave the title compound as a colourless oil (32 g, 94%).

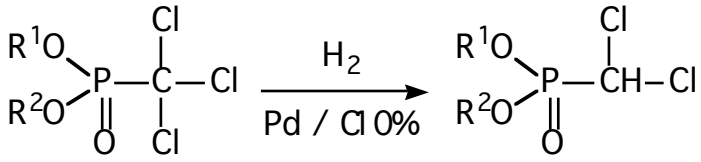
The reaction between dialkyl phosphite and dialkyl trichloromethylphosphonate in the presence of triethylamine gives quantitative yields of diethyl and dibutyl dichloromethylphosphonates in a preparative scale.[109] Similarly, diethyl trichloromethylphosphonate reacts with triethyl phosphite in boiling hexanol (65 % yield)[110] or ethanol[109] to give diethyl dichloromethylphosphonate without formation of the corresponding monochloromethylphosphonate. Analogous reactions have been performed on the dibutyl ester in butanol.[109]



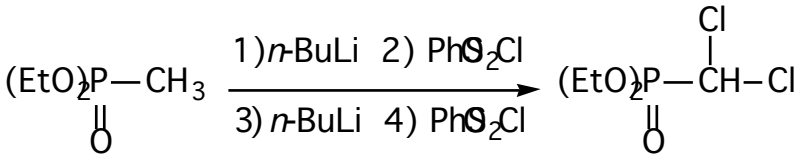
The electrochemical reduction of diethyl trichloromethylphosphonate[72, 73, 111, 112] to give dichloromethylphosphonate appeared for the first time as an intermediate step in the synthesis of gemdichloroolefins from ketones *via* the Wittig-Horner reaction.[69, 70] This method was then successfully optimised for the preparation of diethyl dichloromethylphosphonate.[71] Under the electrochemical conditions, diethyl dichloromethylphosphonate is formed together with a small amount of diethyl chloromethylphosphonate. After distillation diethyl dichloromethylphosphonate was obtained in pure form and high yield (> 80 %). This electrochemical method could compete with chemical reduction which uses strongly basic and expensive alkyllithiums.



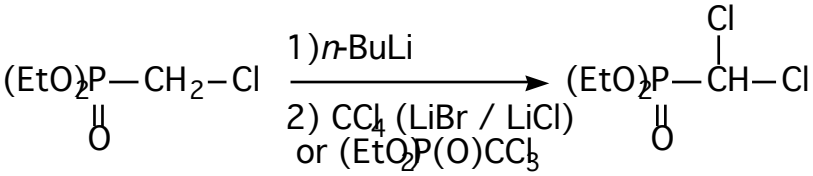
The hydrogenolysis of a C-Cl bond of chiral dialkyl (e.g. ethyl / methyl esters) trichloromethylphosphonate by means of molecular hydrogen, triethylamine and 10 % palladium on charcoal as catalyst is also reported.[33, 74]



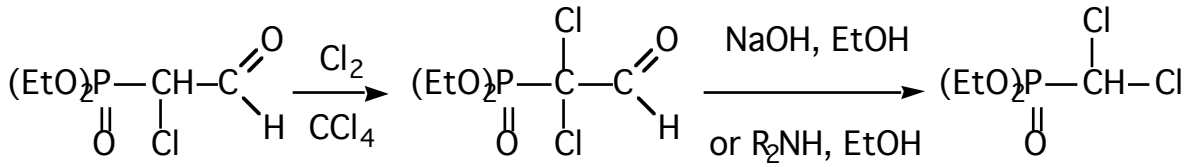
Oxidation reaction : The double oxidation of diethyl methylphosphonate by successive addition of *n*-butyllithium and benzenesulfonyl chloride quantitatively affords diethyl dichloromethylphosphonate.[113]



Under the same conditions, diethyl chloromethylphosphonate was converted into the corresponding dichloro compound in 60-95 % yield in reaction with tetrachloromethane (with,[114] or without[115]lithium salts) or diethyl trichloromethylphosphonate[115] as chlorinating agents.

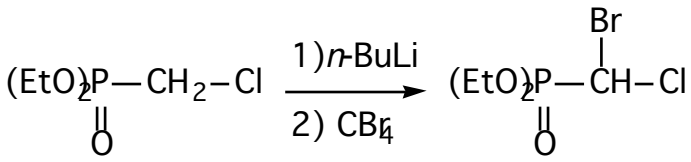


"Substitution" reaction : Diethyl 1-chloro-2-oxoethylphosphonate reacts with chlorine in tetrachloromethane at 0°C to give the corresponding 1,1-dichloro-2-oxoethylphosphonate. The action of a base (sodium hydroxide, dialkylamine) leads to the cleavage of the formyl group and hence the formation of e.g. diethyl dichloromethylphosphonate in 72 % yield.[116]



II. 5. Bromochloromethylphosphonates

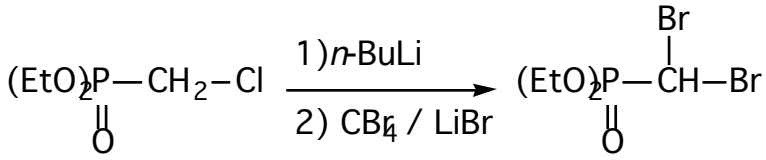
Oxidation reaction (halogenation) : Diethyl chloromethylphosphonate gives the corresponding bromochloromethylphosphonate in 71 % yield by addition of tetrabromomethane to the intermediate 1-lithiochloromethylphosphonate.[117]



Diethyl 1-bromo-1-chloromethylphosphonate[117] **:** This was prepared according to the procedure for the synthesis of diethyl dibromomethylphosphonate[114] (see **II. 6.**), however, the ratio of diethylphosphonate to tetrabromomethane was changed to 3:1. Under these conditions, diethyl bromochloromethylphosphonate could be obtained in a yield of 71 %.

II. 6. Dibromomethylphosphonates

Oxidation / substitution reaction : The single reported synthesis of diethyl dibromomethylphosphonate proceeds *via* a halogen exchange reaction. The 1-lithiochloromethylphosphonate obtained from diethyl chloromethylphosphonate (see **I. 2.**) on treatment with tetrachloromethane yields the 1-lithiodichloromethylphosphonate and chloroform resulting from a trans-metallation with (trichloromethyl)lithium. A halogen exchange then occurs with lithium bromide and affords a mixture of the corresponding bromochloromethylphosphonate (30 %) and dibromomethylphosphonate (10 %). When the reaction is performed with tetrabromomethane and lithium bromide, formation of diethyl dibromomethylphosphonate occurs in 90 % yield contaminated with a small amount of diethyl bromochloromethylphosphonate.[114, 118]

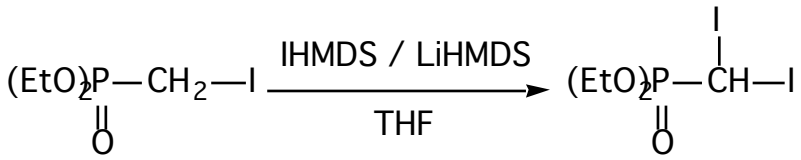


Diethyl 1,1-dibromomethylphosphonate[114] **:** Anhydrous lithium bromide (3.5 g, 0.04 mol) is dissolved under nitrogen in tetrahydrofuran (100 mL), butyllithium (0.02 mol + 10 %) in ether is added at - 10°, the mixture is cooled to - 75°, and diethyl chloromethylphosphonate (3.7 g, 0.02 mol) in tetrahydrofuran (20 mL) is added dropwise with stirring. After 8 min stirring at - 75°, tetrabromomethane (6.6 g, 0.02 mol) in tetrahydrofuran (30 mL) is added at - 70° (sometimes the solution acquires a darkish colour). The stirring is continued for 40 min and water (40 mL) is then added. The resultant mixture is extracted with dichloromethane (2 x 50 mL). The organic layers are dried with anhydrous magnesium sulfate and the solvent and tribromomethane formed are removed under vacuum to leave a crude mixture of diethyl dibromo- and bromochloromethylphosphonate which was used as such.

II. 7. Diiodomethylphosphonates

Oxidation reaction (halogenation) : The only reported synthesis of diethyl diiodomethylphosphonate occurs by simply reacting diethyl iodomethylphosphonate with a

mixture of lithiumbis(trimethylsilyl)amide (LiHMDS) and iodobis(trimethylsilyl)amide (IHMDS). This leads to the formation of diethyl diiodomethylphosphonate in 98 % yield.[119]



Diethyl 1,1-diiodomethylphosphonate[119] **:** BuLi (0.90 mL of a 2.5 M solution in hexane, 2.23 mmol), freshly titrated, was added at 0°C to a solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (0.36 g, 2.23 mmol) in THF (6 mL). The solution of I_2 (0.26 g, 1.02 mmol) in THF (2mL) was added, then after 5 min, a solution of diethyl iodomethylphosphonate (0.28 g, 1.02 mmol) in THF (2 mL) was added. After 90 min at -70°C, a sat. aq NaCl solution (3 mL) was added. After usual workup, the crude diiodophosphonate was isolated as a yellow oil. (yield : 98 %)

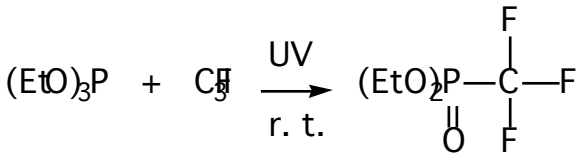
III. α-Trihalogenated methylphosphonates

From the number of publications, the trichloro compound (see **III. 1.**) is of far greater interest than others. Moreover, one can notice an increasing interest in the bromodifluoro compounds (see **III. 3.**) together with dibromofluoro (see **III. 6.**), trifluoro (see **III. 1.**) and difluoroiodo (see **III. 4.**) -methylphosphonates (ranged in order of decreasing number of publications) with practically no mention of other compounds.

III. 1. Trifluoromethylphosphonates

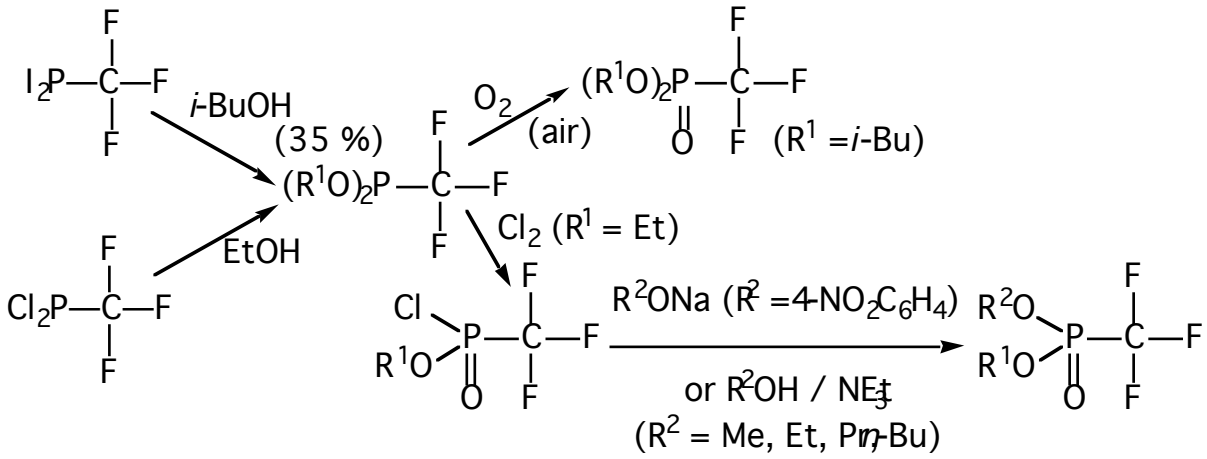
Michaelis-Becker reaction : The diisopropyl trifluoromethylphosphonate was observed by ^{31}P NMR (12 %) in a mixture obtained from a fluorophilic reaction between diisopropyl sodiophosphite and bromotrifluoromethane, but was not isolated.[32]

Michaelis-Arbuzov reaction : Due to the relatively high volatility of CF_3Br (b.p. -59°C) and established inertness of CF_3Cl and CF_3I in thermal Michaelis-Arbuzov reactions,[25] a photolytic pathway was investigated. A mixture of triethyl phosphite and trifluoroiodomethane was irradiated with an ultraviolet source and gave diethyl trifluoromethylphosphonate in 51 %[120] to quantitative[121] yield.

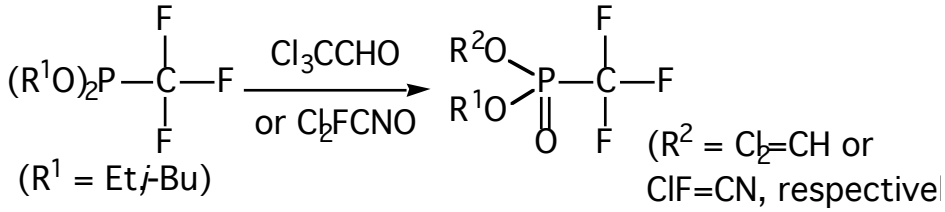


Diethyl 1,1,1-trifluoromethylphosphonate[121] **:** Triethyl phosphite (9.65 g, 58 mmol) which has been freshly distilled over sodium was transfered into a thick walled Pyrex glass tube in an anhydrous atmosphere box. Into the tube that was evacuated at -196°C, CF_3I (23.6 g, 116 mmol) was condensed, and the tube sealed off with care. The glass seal must be done carefully to avoid leaving a weak point in the tube wall. The tube was allowed to warm to 25°C and then exposed to UV radiation (Hanovia Utility lamp) for 48 h. The tube was cooled to -196°C and the C_2H_5I and any unreacted CF_3I were distilled away. The nonvolatile liquid diethyl trifluoromethylphosphonate remained in the Pyrex tube in ~ 100 % yield.

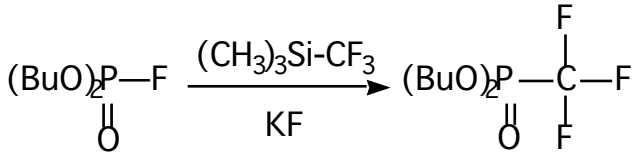
Oxidation reaction : Dialkyl trifluoromethylphosphonates are prepared from trifluoromethylphosphonous dihalides *via* multistep convergent syntheses. Trifluoromethylphosphonous diiodide[122] or dichloride[56] in reaction with respectively isobutanol or ethanol gives the corresponding dialkyl trifluoromethylphosphonite ($(R^1O)_2PCF_3$) in 35 % yield (from the diiodo compound).[122] Oxidation with atmospheric air allows the formation of dialkyl trifluoromethylphosphonates (e.g. diisobutyl in 58 % yield)[122] whereas oxidation with chlorine yields the corresponding alkyl (e.g. ethyl) trifluoromethyl chlorophosphonate which after reaction with sodium 4-nitrophenolate or alcohol (methanol, ethanol, propanol, butanol) / triethylamine leads to the fully esterified trifluoromethylphosphonate in 41 to 59 % yield.[56, 123]



Dialkyl trifluoromethylphosphonite ($(R^1O)_2P\text{-}CF_3$, R^1 = Et, *i*-Bu) can also react in a Perkow manner with chloral or with dichlorofluoronitrosomethane to give, in both cases, the expected mixed dialkyl trifluoromethylphosphonate with respectively 32-66 %[124] and 84-86 %[125] yields.



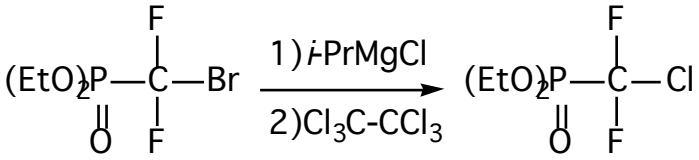
Alkylation reaction at phosphorus : Dibutyl fluorophosphate reacts without solvent at 60°C with trimethyl(trifluoromethyl)silane in the presence of potassium fluoride to give dibutyl trifluoromethylphosphonate in 93 % yield.[126]



III. 2. Chlorodifluoromethylphosphonates

Michaelis-Becker reaction : The reaction of diethyl sodiophosphite and dichlorodifluoromethane gives a mixture of tetraethyl difluoromethylenebisphosphonate (major product) and diethyl chlorodifluoromethylphosphonate (minor product).[25] Both products are isolable from the mixture by distillation.

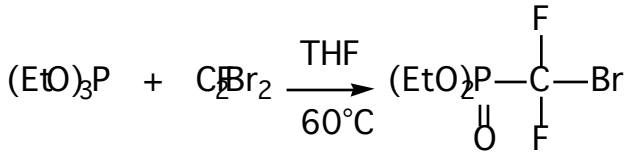
Halogen-substitution reaction : The Grignard reagent obtained from bromodifluoromethylphosphonate *via* an halogen-metal exchange reacts with hexachloroethane to give diethyl chlorodifluoromethylphosphonate in 60 % yield.[99]



Diethyl 1-chloro-1,1-difluoromethylphosphonate[99] **:** A 250 mL reactor was charged with *i*-PrMgCl (5.5 mL of 2.0 M Et_2O solution, 0.011 mol) and THF (10 mL). The solution was cooled to -78°C and a solution of diethyl 1-bromo-1,1-difluoromethylphosphonate (2.67 g, 0.01 mol) in THF (15 mL) was added dropwise. The resulting mixture was stirred for 5 min at -78°C. Then a solution of hexachloroethane (2.61 g, 0.011 mol) in THF (20 mL) was added dropwise. The resulting mixture was stirred for 5 min at -78°C and then allowed to warm up to 0°C within 2 hours. It was poured into an ice-cold mixture of HCl (20 mL of 3 M solution) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product which was purified by bulb-to-bulb distillation (b.p. 50-55°C / 0.5 mm Hg). Yield = 60 %.

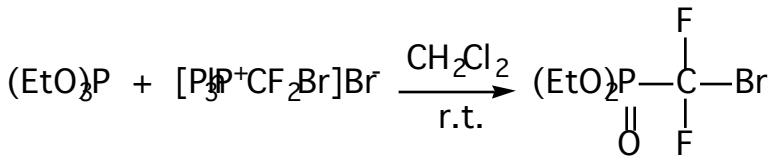
III. 3. Bromodifluoromethylphosphonates

Michaelis-Arbuzov reaction : Diethyl bromodifluoromethylphosphonate is commonly obtained by reaction between triethyl phosphite and dibromodifluoromethane in diethyl ether in yields ranging upward from 90 %.[127, 128] This method is now widely used.[96, 129-132] The initial reaction involved a 24 hours reflux, but this was recently shortened to one and an half hours with a slight modification in the conditions (refluxing solvent).[99] Other dialkyl bromodifluoromethylphosphonates were obtained in the same way (dimethyl, 55 %[127] ; diisopropyl, 42 %[127] ; dibutyl, 65 %[127] to quantitative yield[95, 121]).



Diethyl 1-bromo-1,1-difluoromethylphosphonate[99] **:** A 1 L reactor equipped with a mechanical stirrer, thermometer, efficient reflux condenser, and an addition funnel was charged with dibromodifluoromethane (115 g, 0.55 mol) and THF (300 mL) and flushed with nitrogen. Stirring was initiated and the solution was warmed by immersing the flask in an oil bath heated at 60°C, triethyl phosphite (83 g, 0.5 mol) was then added dropwise over 1 h. After an additional 30 min at 60°C, the reaction mixture was cooled and the solvent was removed under reduced pressure. The crude product (99 %) was purified by bulb-to-bulb distillation (b.p. 145-155°C / 0.5 mm Hg). Yield = 96 %.

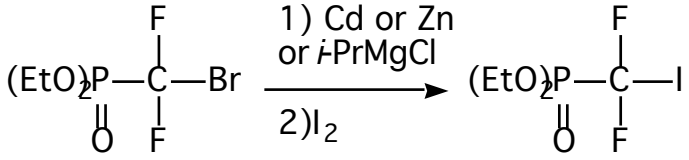
It has been shown that bromodifluoromethyl triphenylphosphonium bromide ($[Ph_3P^+CF_2Br]Br^-$) undergoes facile exchange of the bromodifluoromethyl group with triethyl phosphite. Thus, together in dichloromethane at room temperature in a Michaelis-Arbuzov type reaction they give diethyl bromodifluoromethylphosphonate in 92 % yield.[133]



Michaelis-Becker reaction : Mixtures of products containing the diisopropyl difluoromethylphosphonate (29 %) were observed, by ^{31}P NMR, in a fluorophilic reaction between diisopropyl sodiophosphite and bromotrifluoromethane.[32]

III. 4. Iododifluoromethylphosphonates

Halogen-substitution reaction : Diethyl iododifluoromethylphosphonate was obtained from diethyl bromodifluoromethylphosphonate in a two-step procedure. Firstly, a halogen-metal exchange occurs with cadmium, secondly the so-formed diethoxyphosphinyl difluoromethylcadmium derivative reacts with iodine to give diethyl iododifluoromethylphosphonate in 57 % yield.[97, 134, 135] The analogous reactions based on halogen-metal exchanges with zinc[131, 134, 136] or magnesium[99] give up to 70 % and 48 % yields respectively.



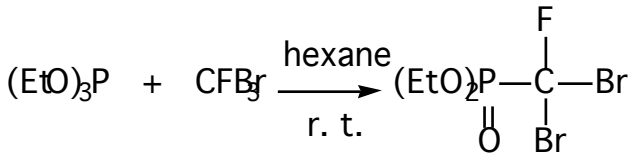
Diethyl 1-iodo-1,1-difluoromethylphosphonate[136] **:** To a stirred suspension of acid-washed Zn powder (34.3 g, 0.52 mol) in monoglyme (300 mL) under N_2 was added diethyl bromodifluoromethylphosphonate (133.5 g, 0.5 g) *via* syringe. (After the addition of ~30 mL, a few crystals of I_2 were added to the stirred reaction mixture to initiate the reaction. The reaction mixture became warm, and the remaining phosphonate was added over a period of 25 min). The reaction mixture was stirred for 2 h and filtered through a medium-frit Schlenk funnel, under N_2. To the clear filtrate was added I_2 (140 g, 0.55 mol) and the mixture stirred for 24 h under N_2. The resultant reaction mixture was concentrated to about half its volume on a rotary evaporator and poured into a mixture of water (400 mL) and $CHCl_3$ (400 mL). Saturated $NaHSO_3$ was carefully added with swirling until the iodine color disappeared. The $CHCl_3$ layer was separated and the aqueous layer extracted with $CHCl_3$ (4 x 150 mL). The combined organic layers were washed with saturated $NaHSO_3$ (100 mL), 2 % HCl (100 mL), and brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was distilled at reduced pressure through a 10-cm Vigreux column to give 111.0 g of title compond (70 %).

III. 5. Dichlorofluoromethylphosphonates

Michaelis-Arbuzov reaction : Diethyl dichlorofluoromethylphosphonate was prepared in 29 % yield from the reaction of trichlorofluoromethane with triethyl phosphite in an autoclave at 180°C. It was contaminated by diethyl ethylphosphonate (8 %).[25]

III. 6. Dibromofluoromethylphosphonates

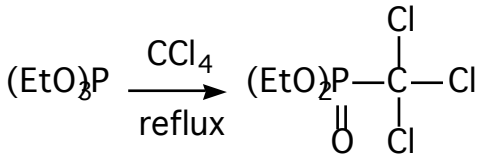
Michaelis-Arbuzov reaction : The synthesis of dibromofluoromethylphosphonates was first described in 1977. They are obtained by reaction between trialkyl phosphites and fluorotribromomethane in boiling diethyl ether in low to good yields depending on the nature of the alkyl group (isopropyl, 22 % ; ethyl, 78 %).[95, 127, 137] The synthesis of the diethyl compound has recently been improved by performing the reaction in hexane, in sunlight and at room temperature. This gives yields ranging upward from 90 %.[29, 138, 139]



Diethyl 1,1-dibromo-1-fluoromethylphosphonate[139] **:** A 500 mL flask was charged with tribromofluoromethane (50 g, 0.185 mol) and dry hexane (100 mL). Triethyl phosphite (29.9 g, 0.18 mol) was added in one portion. The reaction mixture became turbid and few hours later returned clear. The flask was kept in the light for 11-12 d at rt. The reaction can be monitored by ^{31}P NMR spectroscopy. When all the triethyl phosphite has been consumed, hexane was evaporated under reduced pressure to afford the crude product (58.5 g, 97 %). A bulb-to-bulb distillation (170-175°C / 20 mmHg) gave the title compound.

III. 7. Trichloromethylphosphonates

Michaelis-Arbuzov reaction : Trichloromethylphosphonates are commonly obtained by reaction between trialkyl phosphites (methyl, ethyl, propyl, *i*-propyl, allyl, *n*-butyl, *i*-butyl) and excess tetrachloromethane in yields ranging upward from 50 %.[140] Particularly good yields (>82 %) are obtained from triethyl phosphite.[73, 145-150] In the case of ethyl, *n*-butyl, hexyl, octyl, decyl, dodecyl phosphonates,[141] the reaction goes to completion after a 3 hours reflux and after 8 hours in the case of methyl phosphonate (49 %).[142] This method is now widely used.[71, 109, 112, 143, 144]



Diethyl 1,1,1-trichloromethylphosphonate[145] **:** Triethyl phosphite (50 g) was refluxed overnight with dry tetrachloromethane (25 mL, large excess). The colorless solution was distilled under reduced pressure to yield 72 g (93.6 %) of diethyl trichloromethylphosphonate, as a colorless mobile liquid, b.p. 135-137° at 16 mmHg.

Diethyl trichloromethylphosphonate was also obtained from diethyltrimethylsilyl phosphite in 60 % yield,[151] and from benzyldiethyl phosphite in the presence of dibenzoyl peroxide and an ultraviolet source in a radical induced reaction in 87 % yield (compared to 26 % without the dibenzoyl peroxide).[146]

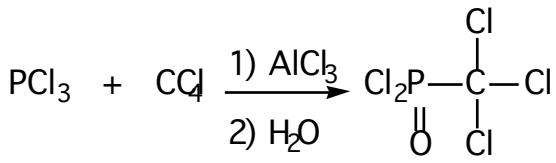
The reaction of tris(2-chloroethyl) phosphite with bromotrichloromethane yields 63 % of the corresponding trichloromethylphosphonate,[152] whereas tricyclopropyl phosphite with tetrachloromethane gives the corresponding trichloromethylphosphonate in 80 % yield.[149] With mixed trialkyl phosphites ($P(OR^1)(OR^2)(OR^3)$), dialkyl trichloromethylphosphonates ($(R^1O)(R^2O)P(O)CCl_3$) were obtained in yields ranging from 31 to 95 %, depending on the nature of the alkyl groups[153] :

R^1	Me	*i*-Pr	*n*-Pr	*i*-Bu	*n*-Bu	*i*-Pent	Me	Et	*i*-Bu	*i*-Pent
R^2	Et	*i*-Pr	*n*-Pr	*i*-Bu	*n*-Bu	*i*-Pent	*n*-Bu	*n*-Bu	*n*-Bu	*n*-Bu
R^3	Me	Et	Et	Et	Et	Et	Me	Et	*i*-Bu	*i*-Pent
Yield	60 %	95 %	36 %	70 %	45 %	45 %	31 %	45 %	50 %	84 %

The Michaelis-Arbuzov reaction was also conducted with more elaborate phosphites such as :

- esters of pyrophosphorous acid ($(RO)_2P\text{-}O\text{-}P(OR)_2$) to yield 15 % of the corresponding trichloromethylphosphonate (R = Et, Pr, Bu).[154]
- diethylphenyl phosphite to form the mixed ethylphenyl phosphonate in 44 % yield.[155]
- adamantyldiethyl phosphite to give a mixture of diethyl and adamantylethyl phosphonate in a 15 / 75 ratio. After purification 46 % of the mixed adamantylethyl trichloromethylphosphonate was obtained.[156]
- tris(1-adamantyl) phosphite to yield 59 % of the corresponding phosphonate, whereas tris(2-adamantyl) phosphite forms the title phosphonate in 80 % yield.[157]

Kinnear-Perren reaction : This reaction is performed in the presence of aluminium trichloride with either bromotrichloromethane, tetrachloromethane or dichlorodifluoromethane to obtain the trichloromethylphosphonyl dichloride in respectively 90 %, 85 % and 50 % yield.[22, 37]

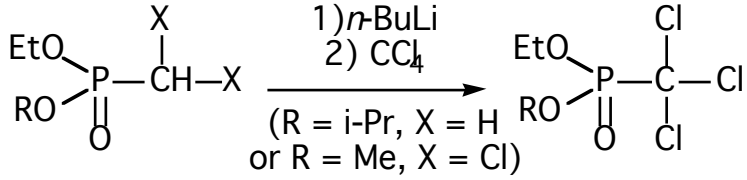


1,1,1-Trichloromethylphosphonyl dichloride[158] **:** In a 2-L. round bottomed three-necked flask, fitted with an efficient reflux condenser, mechanical stirrer, and dropping funnel, are placed anhydrous powered aluminium trichloride (133.3 g, 1 mol), phosphorus trichloride (137.4 g, 1 mol), and tetrachloromethane (184.6 g, 1.2 mol). The reactants are stirred slowly until they are thoroughly mixed, and then heat is applied carefully until the reaction begins. At this point the liquid boils vigorously, and the reaction mixture becomes thicker so that faster stirring is necessary. Finally, the stirrer is stopped when the mixture becomes solid. After the reaction has cooled for 30 minutes, dichloromethane (1 L) is run into the flask, and the solvent is stirred vigorously until the solid is finely suspended. The reflux condenser is replaced by a low-temperature thermometer which dips into the reaction mixture, the suspension is cooled in a dry ice-acetone bath, and the temperature is kept at -10 to -20°C as distilled water (180 g, 10 mol) is added dropwise with vigorous stirring over a period of about 25 min. After the water addition is

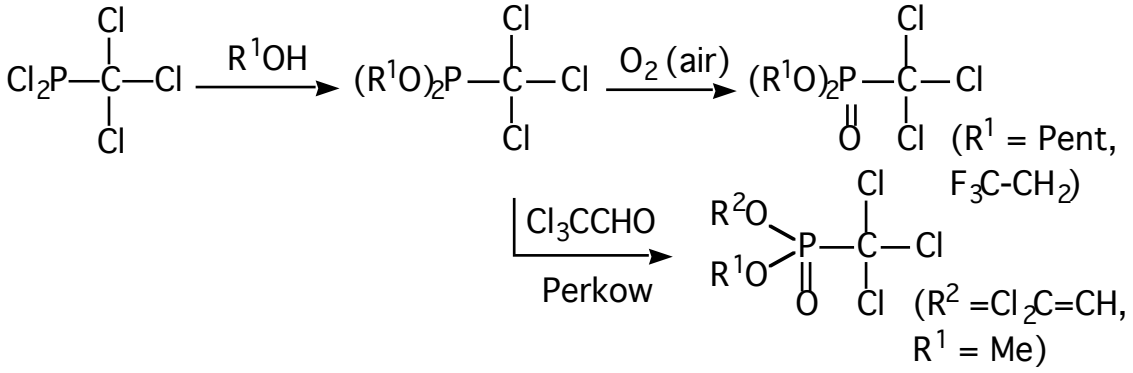
complete, stirring is continued for 15 minutes without the cold bath. The apparatus is dismantled, and the reaction mixture is filtered quickly by suction through a 1.5-cm layer of filter aid on an 11-cm Büchner funnel placed on a 2-L filter flask. The filter cake is pressed down well and washed with three 50-mL portions of dichloromethane. The filtrate is immediately protected from moisture by calcium chloride tubes, and the solvent is removed by distillation from a 2-L flask. After the solution has been concentrated to about 225 mL, the hot liquid is poured into a suitable container, and the remaining solvent is removed under reduced pressure. The yield is 192-199 g (81-84 %) of a white, crystalline solid which melts at 155-156°.

On treatment with an alcohol, this phosphonyl dichloride leads to the corresponding dialkyl chloromethylphosphonate in 68[159] to 95 % yields with phenol or ethanol,[160] and in 40 to 60 % yields with diols such as ethanediol,[161] 2,2-dimethylpropanediol,[162] 1,5-pentanediol and its derivatives.[163] Overall yields of 41-53 % (from phosphorus trichloride) were given for the Kinnear-Perren reaction and its subsequent treatment with ethanol[164] or fluorinated alcohols.[165] The alcoholysis of ethyl (trichloromethyl)chlorophosphonate with 4-nitrophenol yields 40 % of the mixed dialkyl trichloromethylphosphonate.[56]

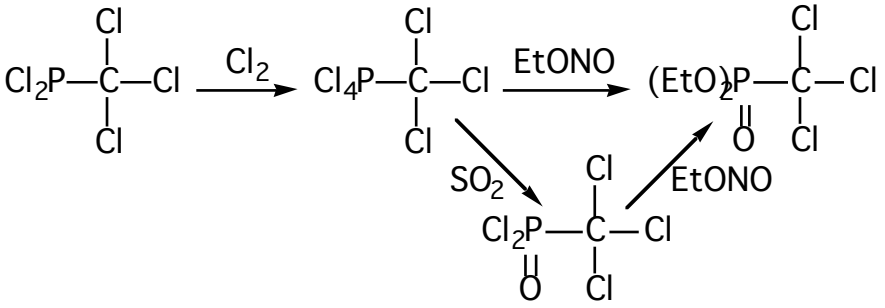
Oxidation reactions : Ethyl isopropyl methylphosphonate successively reacts with *n*-butyllithium and tetrachloromethane[33] to give the corresponding trichloromethylphosphonate in 21 % yield. In the same manner, ethylmethyl dichloromethylphosphonate gives 12 % yield of the trichloro compound.[74]



Dialkyl trichloromethylphosphonate was also prepared from trichloromethylphosphonous dichloride in a multistep synthesis. Trichloromethylphosphonous dichloride in reaction with an alcohol (methanol, pentanol, 2,2,2-trifluoroethanol) gives the dialkyl trichloromethylphosphonite ($(R^1O)_2P\text{-}CCl_3$) in 66-78 % yield. Oxidation of this phosphonite with air leads to a 25 % yield[166] of the dipentyl ester and 50 % yield[167] of bis(2,2,2-trifluoroethyl) trichloromethylphosphonate whereas the Perkow reaction with chloral gives a 70 % yield of methyl (2,2-dichloroethenyl) trichloromethylphosphonate.[166]



Trichloromethylphosphonous dichloride also leads to diethyl trichloromethylphosphonate *via* successive oxidation reactions. The addition of chlorine allows the formation of trichloromethyl tetrachlorophosphorane (Cl_4P-CCl_3) which on reaction with ethyl nitrite gives diethyl trichloromethylphosphonate in 63 % yield. Trichloromethyl tetrachlorophosphorane also reacts with sulfur dioxide to form the intermediate trichloromethylphosphonyl dichloride which on reaction with ethyl nitrite yields diethyl trichloromethylphosphonate (no yield mentioned).[168]



III. 8. Tribromomethylphosphonates

Michaelis-Arbuzov reaction : The only synthesis of this compound currently described is the reaction between triethyl phosphite and tetrabromomethane in benzene at 20°C. The main product is tetraethyl dibromomethylenebisphosphonate (63%) but diethyl tribromomethylphosphonate is also isolated in 15 % yield after distillation.[169]

Recapitulative table of synthetic methods

Method - Yield (%)[Reference] for the synthesis of $(R^1O)_2P(O)-R^2$

R^2	$X^2\backslash X^1$	F	Cl	Br	I
CX^1H_2		(see **I. 1.**) **B**-U[21, 25] 50[24] **E**-31[32] 43[26] 92[* 31] 93[27-30] **F**-11[34, 35] 46[33, 36] **G**-0[37]	(see **I. 2.**) **B**-15[38] **C**-85[22] **D**-60[43] 67[23, 37, 39-42] **C, D quench**- <96[39, 41, 42, 44-67] **E**-20[69] 73[33, 74] 80[71-73] 95[* 31] Q[68] **G**-(65[75, 76]) 42[77] 57[80] 86[78] Q[79]	(see **I. 3.**) **A**-13[37, 81, 82] 48[83] **B**-[U82] **C**-50[61] **D**-8[23] **F**-42[85] 64[84] **G**-(65[75, 76]) 67[86]	(see **I. 4.**) **A**-U[87] 30- 40[37, 39, 88, 89] 60[20] 90[61] **F**-5[84] **G**-0[61] <92[90]
CX^1X^2H	F	(see **II. 1.**) **B**-50-77[21, 91-93] **E**-U[29,96,100] 75[95] 85[99] Q[97, 98] **F**-<18[33, 101] **H**-<51[92, 94, 49]	(see **II. 2.**) **B**-U[36, 25] 38[102]	(see **II. 3.**) **E**-71[103] 90[28]	
	Cl	(see **II. 2.**)	(see **II. 4.**) **C**-60[56] 70[22, 104, 105] **E**-U[33, 70-74, 111, 112] 26[69] 55[106] 65[107, 110] 80[71] 94[108] Q[109] **F**-60[114] 95[115] Q[113] **G**-38[116]	(see **II. 5.**) **F**-30[114] 71[117]	
	Br	(see **II. 3.**)	(see **II. 5.**)	(see **II. 6.**) **F**-90[114, 118]	
	I				(see **II. 7.**) **F**-98[119]
$CX^1X^2X^3$	F	X^3= F (see **III. 1.**) **A**-51[120] Q[121] **B**-12[32] **F**-49[123] 59[56, 122] 66[124] 86[125] **G**-93[126]	X^3= F (see **III. 2.**) **B**-15[25] **G**-60[99]	X^3= F (see **III. 3.**) **A**->90[96,127-132] 92[133] 96[99] Q[95, 121] **B**-29[32]	X^3= F (see **III. 4.**) **G**-48[99] 57[97, 134, 135] <70[131, 136]
		(see **III. 2.**)	X^3= Cl (see **III. 5.**) **A**-29[25]		
		(see **III. 3.**)		X^3= Br (see **III. 6.**) **A**-78[95, 127, 137] >90[29, 138, 139]	

[*] Deuteriated compound
[U] Unknown yield
[Q] Quantitative yield

$CX^1X^2X^3$ (continuation)	Cl		X^3= Cl (see **III. 7.**) **A**-15[154] 44[155] 46[156] >50[71, 109, 112, 140-144] 60[151] 63[152] 80[157] >82[73, 145-150] 95[153] **C**-90[22, 37, 158 164, 165] **C quench**-40[56, 150] 60[161-163] 68[159] 95[160] **F**-21[33,74] 40[166,167] 63[168]		
	Br			X^3= Br (see **III. 8.**) **A**-15[169]	

A : Michaelis-Arbuzov reaction[20]
B : Michaelis-Becker reaction[21]
C : Kinnear-Perren reaction[22]
D : Kabachnik reaction[23]
E : Reduction reaction
F : Oxidation reaction
G : Substitution reaction
H : Other reactions

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