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► **To cite this version:**

Bogdan Iorga, Duncan Carmichael, Philippe Savignac. Phosphonate–phosphonochloridate conversion. Comptes rendus de l'Académie des sciences. Série IIc, Chimie, 2000, 3 (11-12), pp.821-829. <10.1016/s1387-1609(00)01207-x>. <hal-03161486>

HAL Id: hal-03161486

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Submitted on 10 Mar 2021

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Phosphonate-Phosphonochloridate Conversion

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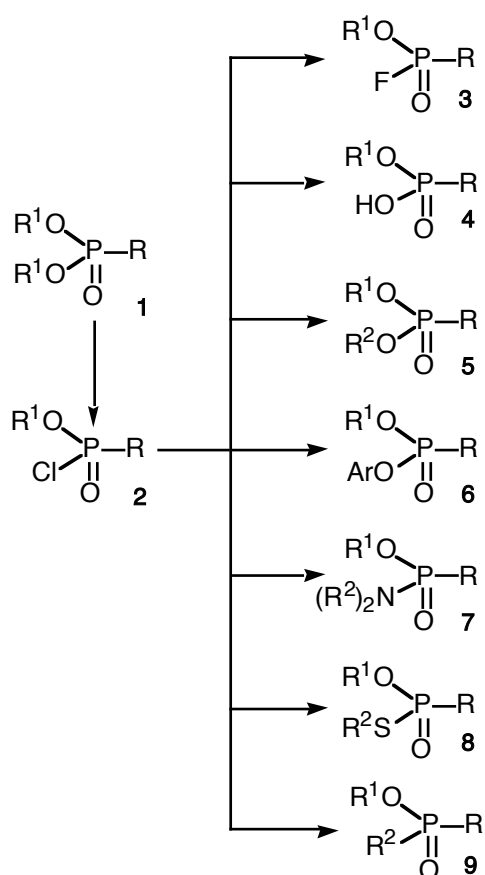
Abstract - This review deals with the phosphonate-phosphonochloridate conversion. The different phosphorus-chlorine bond forming reagents (COCl_2 , $(\text{COCl})_2$, SOCl_2 , PCl_5 , POCl_3 , Ph_3PCl_2 , trichloro(*o*-phenylenedioxy)phosphorane) and the reaction conditions which they impose are considered.

Phosphonates / Phosphonochloridates / Chlorinating Agents

Version française abrégée - Conversion des dialkyl alkylphosphonates en alkyl chloroalkylphosphonates. La transformation des alkylphosphonates en chloroalkylphosphonates est une réaction très utile en chimie du phosphore. Les chloroalkylphosphonates sont de précieux intermédiaires dans la préparation de dérivés phosphorés plus élaborés tels que, fluoroalkylphosphonates, diesters mixtes, phosphoramidate-ester, thiophosphonates et phosphinates. Plusieurs agents de chloration ont été introduits pour réaliser cette transformation: le phosgène, COCl_2 , le chlorure d'oxalyle, $(\text{COCl})_2$, le chlorure de thionyle, SOCl_2 , le pentachlorure de phosphore, PCl_5 , l'oxychlorure de phosphore, POCl_3 , Ph_3PCl_2 et le trichloro(*o*-phenylenedioxy)phosphorane. Les avantages et inconvénients de chaque réactif sont examinés en fonction des critères suivants: disponibilité, efficacité, tolérance, conditions d'emploi, solvant, température, nature des sous-produits. Trois réactifs se détachent, le chlorure d'oxalyle, le pentachlorure et l'oxychlorure de phosphore. Ils réalisent la transformation alkylphosphonates-chloroalkylphosphonates avec efficacité dans des conditions non destructrices et avec des phosphonates d'une grande variété structurale.

Phosphonates / Chlorophosphonates / Agents de Chloration

The reaction conditions for direct substitution of an alkoxy group by nucleophiles (alcohols, phenols, amines, Grignard reagents) in dialkyl alkylphosphonates **1** are sufficiently drastic that this method is not currently used. Procedures which involve the intermediacy of the highly reactive alkyl alkylphosphonochloridates **2** appear to have greater synthetic utility. For this reason, there has been significant interest in developing efficient procedures for transforming readily available dialkyl alkylphosphonates **1** into alkyl alkylphosphonochloridates **2**.^[1-3] The phosphonate-phosphonochloridate conversion, which replaces a single ester linkage of the dialkyl alkylphosphonate **1** by a chlorine atom, is a widely employed operation. As depicted in Scheme 1, the alkyl alkylphosphonochloridates **2** are pivotal intermediates for the transformation of dialkyl alkylphosphonates **1** into more elaborated phosphorus compounds, such as phosphonofluoridates **3**,^[4-7] monoesters **4**,^[8-10] mixed diesters **5**^[5,11-17] and **6**,^[5,18-20] phosphoramidate esters **7**,^[5,6,9,11,15,19,21-36] thiolphosphonates **8**^[13,15,37,38] and alkylphosphinates **9**.^[39-47] Several chlorinating reagents have been developed for the preparation of alkyl alkylphosphonochloridates **2**. They include two carbon-based chlorinating agents, COCl_2 , $(\text{COCl})_2$, one reagent containing sulfur SOCl_2 , and four containing phosphorus, PCl_5 , POCl_3 , Ph_3PCl_2 and the trichloro(*o*-phenylenedioxy)phosphorane. The structure of the reagents plays an important role in determining the outcome of its reaction with dialkyl alkylphosphonates **1**. The relatively high reactivity of these halogenating reagents means that carefully controlled reaction of dialkyl alkylphosphonates **1** with the appropriate reagents is required to produce in mild conditions clean samples of alkyl alkylphosphonochloridates **2**.

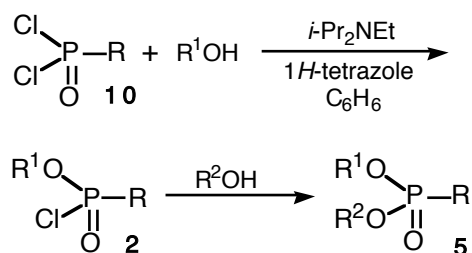


Scheme 1.

Before considering the different phosphorus-chlorine bond-forming reagents and the reaction conditions which they impose, it seems appropriate to briefly review the processes described for preparing alkyl alkylphosphonochloridates **2** from alcohols and alkylphosphonic dichlorides **10**. The difficulties associated with these syntheses illustrate the importance of the phosphonate-phosphonochloridate conversion.

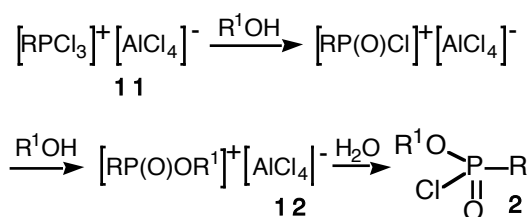
The preparation of alkyl alkylphosphonochloridates **2** from alkylphosphonic dichlorides **10** by selective alcoholysis (1 eq.) of only one phosphorus-chlorine bond presents certain difficulties.[48-53] The reaction is generally too rapid to allow selective mono esterification and experiments have confirmed that alkyl alkylphosphonochloridates **2** are at least as reactive than the starting alkylphosphonic dichlorides **10**. Additionally, many other factors including the nature of alcohols, primary or secondary, hindered or not, the nature of tertiary amine, the solvent and the reaction temperature all influence the degree of the mono esterification at phosphorus. The effect of catalytic amount of base has been investigated and neither imidazole or pyridine have an effect on the ease or course of the reaction. By contrast,

a catalytic amount of 1*H*-tetrazole was found to increase the rate of alcoholysis in the same way for primary or secondary alcohols and hindered alcohols such as menthol or testosterone.[53] Under these conditions the mixed diesters **5** can be obtained almost exclusively *via* alkyl alkylphosphonochloridates **2** (Scheme 2) and the formation of symmetrical diesters **5** ($R^1 = R^2$) was reduced to negligible amounts. 1*H*-tetrazole enhances the reactivity of the phosphonic dichloride **10**, probably by nucleophilic catalysis, but apparently less effectively catalyses reaction of the alkyl alkylphosphonochloridates **2**, perhaps due to increased steric requirements. The alkylphosphonic dichloride route, however, suffers from another drawback in that the synthesis of the starting materials **10** is restricted to compounds bearing a non sensitive R functionality bound to phosphorus (R = alkyl or aryl).



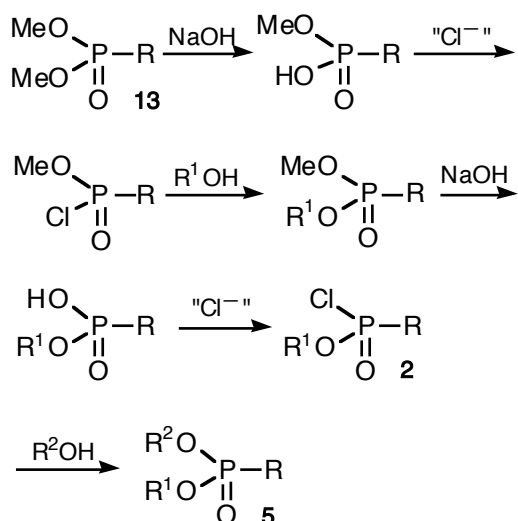
Scheme 2.

Another approach to alkyl alkylphosphonochloridates **2** exploits the Kinnear-Perren procedure. Early preparations of alkylphosphonic dichlorides **10** included treatment of corresponding complexes $[\text{RPCl}_3]^+ [\text{AlCl}_4]^-$ **11**, formed from equimolar amount of RCl, AlCl₃ and PCl₃, with a controlled amount of water (7-11 eq.) in methylene chloride solution.[54,55] The reaction has been reinvestigated by replacing the simple hydrolysis step by sequential treatment with alcohols and water.[56] Thus, complexes **11** were converted directly to alkyl alkylphosphonochloridates **2** upon treatment with two moles of alcohol (R¹OH) and cleavage of the new intermediate complexes **12** with a limited amount of water. This reaction sequence permits a simple one-pot conversion of PCl₃ into the readily obtained complexes **11** with subsequent transformation into the alkyl alkylphosphonochloridates **2** (R = Me, Et, *i*-Pr) in acceptable yields (32-79%) (Scheme 3). Unfortunately, the potential of this procedure is often handicapped by the sensitivity of the substrates R to the highly acidic reaction conditions and the method appears to have limited synthetic potential.



Scheme 3.

Another methodology commonly used for the synthesis of alkyl alkylphosphonochloridates **2** involves the selective esterification of phosphonic acids as summarized in Scheme 4. Starting from a dimethyl alkylphosphonate **13**, it proceeds by sequential alkaline hydrolysis, chlorination and esterification to produce mixed diesters **5** via the monoesters **2**. [57-60]



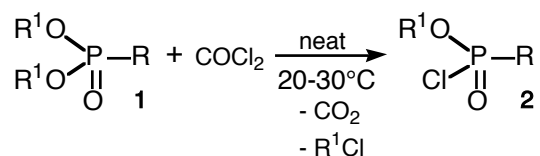
Scheme 4.

Other more straightforward reaction systems are needed and the phosphonate-phosphonochloridate conversion methodology appears to offer a more direct and facile approach to alkyl alkylphosphonochloridates **2** bearing widely varied, functionalised alkyl appendages.

Carbonyl chloride, (phosgene), COCl₂

At the beginning of the 1960's most investigations of the reaction of dialkyl alkylphosphonates **1** with phosgene were directed towards the preparation of products having potent anticholinesterase properties (pesticides, chemical warfare agents). Several alkyl

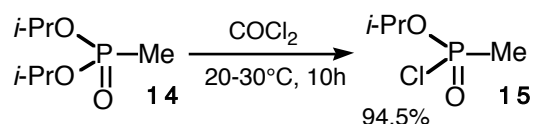
alkylphosphonochloridates **2** were prepared by simply bubbling dried phosgene through neat dialkyl alkylphosphonates **1**, at a temperature below 25°C for relatively long periods (10 to 24 h).[61,62]



Scheme 5.

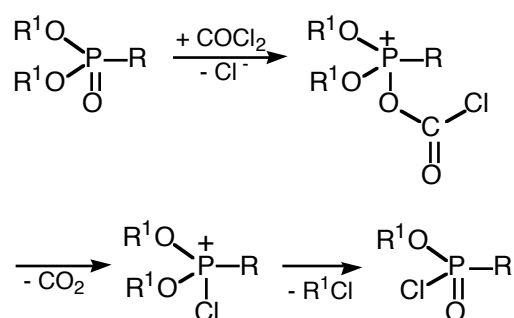
To isolate a pure product cleanly the dialkyl alkylphosphonates **1** must be transformed completely into the target alkyl alkylphosphonochloridates **2**; separation by fractional distillation is difficult because the two compounds have very similar boiling points. Several variations on the preparation of isopropyl alkylphosphonochloridates **2** ($\text{R}^1 = i\text{-Pr}$) from diisopropyl alkylphosphonates **1** ($\text{R}^1 = i\text{-Pr}$) and phosgene have been reported.[63] The best yields are obtained when the R alkyl group has no more than three carbon atoms. Thus, when $\text{R} = \text{Me}, \text{Et}, n\text{-Pr}$, reactions were complete in 24 h and gave uniformly high yields (90%) of pure distilled product. The use of longer chain or more hindered alkyl groups, $\text{R} = i\text{-Pr}, n\text{-Bu}, i\text{-Bu}, s\text{-Bu}, n\text{-C}_5\text{H}_{11}$, implies longer reaction time (four days) and lower yields (26-70%). An influence of the ester group ($\text{R}^1 = \text{Et}, n\text{-Pr}, i\text{-Pr}, n\text{-Bu}, n\text{-C}_5\text{H}_{11}$) has also been observed with several derivatives containing a methyl group bounded to phosphorus.[62] All the corresponding alkyl methylphosphonochloridates **2** ($\text{R} = \text{Me}$) were isolated with roughly comparable yields and considered as sufficiently pure to be used without distillation. This chlorination method appears to be fairly general and has been used for the large-scale synthesis of isopropyl methylphosphonochloridate **15**, an intermediate in the synthesis of isopropyl methylphosphonofluoridate (Sarin), in 91% distilled yield from the reaction of diisopropyl methylphosphonate **14** with phosgene (Scheme 6).[4] Generally, this method allows alkylphosphonochloridates **2** to be isolated in sufficiently pure form to be used without distillation because the only by-products are one equivalent of alkyl chloride R^1Cl and carbon dioxide. Hence, phosgene cleanly and specifically removes only one ester group to give the alkylphosphonochloridates **2** from the corresponding phosphonates. However, the reaction

has been limited to phosphonates containing R alkyl groups and is relatively slow, so it has not been frequently used. Furthermore, the use of phosgene, which requires sophisticated equipment and great care, is strictly controlled in many countries.



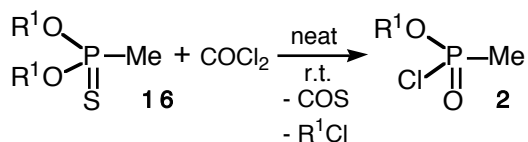
Scheme 6

It seems clear that the reaction occurs by a succession of nucleophilic displacement from a preliminary attack by the phosphoryl oxygen atom, which is the more nucleophilic centre, on the phosgene carbonyl group. After, it was not possible to make a definite decision between the two mechanisms involving either attack at phosphorus or attack on an ester group. However, the first mechanism has appeared as the more probable pathway (Scheme 7). The reaction then evolves by loss of chloroformate ion which rapidly decomposes into carbon dioxide. The final stage of the reaction, which involves the removal of an alkyl group from the quasi-phosphonium intermediate, is similar to the last stage of the Michaelis-Arbuzov reaction.[64] The relative reactivity of a series of phosphoryl oxygen atom has been shown to be: $\text{R}^1\text{R}^2\text{P}(\text{O})\text{OMe} > (\text{R}^1\text{O})\text{R}^2\text{P}(\text{O})\text{OMe} > (\text{R}^1\text{O})_2\text{P}(\text{O})\text{OMe}$.



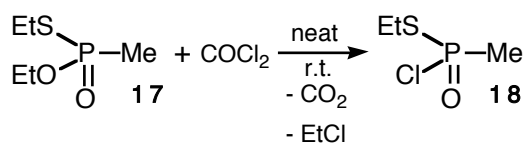
Scheme 7.

The behaviour of the analogous thionophosphonate esters has also been studied. Reaction of carbonyl chloride with diethyl methylphosphonothionate **16** ($\text{R}^1 = \text{Et}$) and its dipropyl homologue **16** ($\text{R}^1 = n\text{-Pr}$), results in the loss of sulphur as carbonyl sulphide with formation of ethyl and propyl methylphosphonochloridate **2** ($\text{R}^1 = \text{Et}, n\text{-Pr}$) (Scheme 8).[65]



Scheme 8.

In contrast, the corresponding thiolate esters, such as the diethyl methylphosphonothiolate **17**, react with carbonyl chloride to give the *S*-ethyl methylphosphonochloridothiolate **18** and carbon dioxide in good yield (Scheme 9).[65]

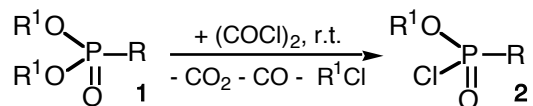


Scheme 9.

Oxalyl chloride, (COCl)₂

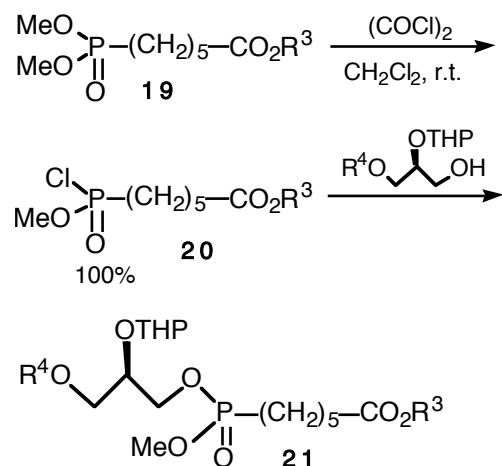
In the search for a more user-friendly reagent, oxalyl chloride has been introduced as an alternative to phosgene. It shows similar reactivity and, being a liquid reagent and more practical to use, has gradually replaced phosgene in laboratory experiments. At room temperature, either neat or in dry solvent (Et₂O, CH₂Cl₂), oxalyl chloride reacts with dialkyl methylphosphonates **1** (R¹ = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu) to give exclusively the corresponding alkyl methylphosphonochloridates **2** in excellent yields (Scheme 10).[66-70] An excess of oxalyl chloride is generally used. As with phosgene, the reaction is relatively long, from 20 to 70 h, but mild and selective. For example, it has been shown that treatment of phosphonates containing the cyclotetrasiloxane ring with PCl₅ or SOCl₂ gave cyclotetrasiloxane cleavage rather than formation of the desired alkylphosphonochloridate. It was only when these phosphonates were treated with oxalyl chloride under mild conditions that the monoesters were successfully prepared with yields of 80-90%.[71] The by-products of the reaction are the alkyl chloride R¹Cl along with carbon monoxide and dioxide, resulting from the decomposition of the chlorooxalate ion. Formation of carbon monoxide necessitates the use of well ventilated hoods. The reaction mechanism is the same as for phosgene. Dimethyl benzylphosphonate was submitted to a comparative treatment with phosphorus pentachloride

and phosgene in CCl₄ at room temperature. The same methyl chlorobenzylphosphonate was obtained in each case but after 12 h for PCl₅ and 48 h for (COCl)₂. [26]



Scheme 10.

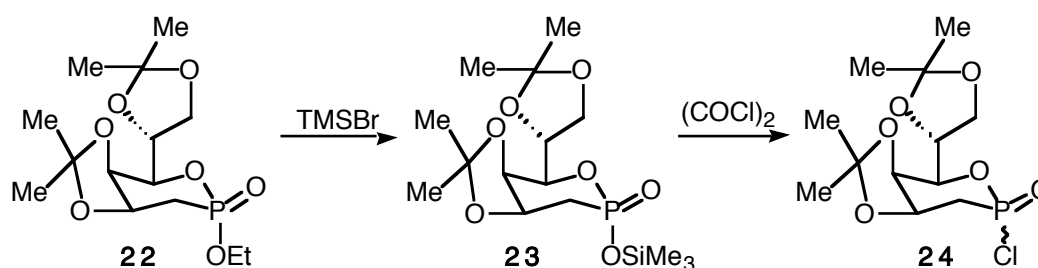
One of the most important applications of oxalyl chloride is the use in the synthesis of haptenic phosphonate transition-state analogues. For example, haptens that possess a phosphonate group **21** bearing a five-carbon spacer as the linker were prepared by phosphorylation of the glycerol derivative. Obtention of the intermediate phosphonochloridate **20** was accomplished in quantitative yield by treatment of dimethyl carboxypentylphosphonates **19** with oxalyl chloride in CH₂Cl₂ at room temperature (Scheme 11). [72,73]



Scheme 11.

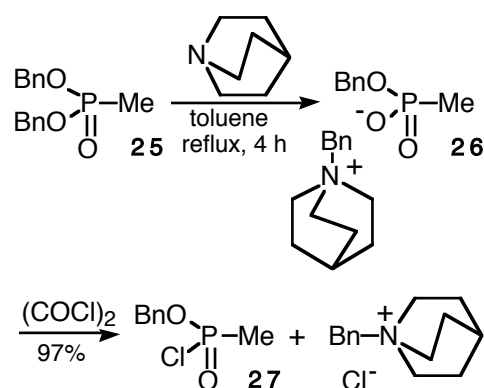
The trimethylsilyl ester of the phosphorus analogue of protected 3-deoxy-β-D-manno-octulopyranosonic acid (β-Kdo) has been found to react smoothly with oxalyl chloride to produce the corresponding phosphonochloridate **24**. In this one-pot reaction sequence, the ethyl ester of the phosphorus analogue of protected 3-deoxy-β-D-manno-octulopyranosonic acid **22** was first converted into the silyl ester **23**, by reaction with bromotrimethylsilane at 50°C for 2.5 h, then treated overnight at room temperature with oxalyl chloride in the

presence of a catalytic amount of imidazole to produce the cyclic phosphonochloridate **24** in good overall yield (90%) (Scheme 12).[74]



Scheme 12

A procedure that allows for selective chlorination of various mono- and dibenzylphosphonates via an intermediate quinuclidinium salt **26** has been described. The sequence is initiated by the nucleophilic attack of quinuclidine on an activated benzylic position of benzylphosphonate **25** to give the phosphonate quinuclidinium salt **26** (Scheme 13). This dealkylation reaction is analogue to that involving trialkylphosphate and tertiary amine.[75] Treatment of salt **26** with oxalyl chloride, leads to benzyl methylphosphonochloridate **27** in good overall yields (97%).[76,77]

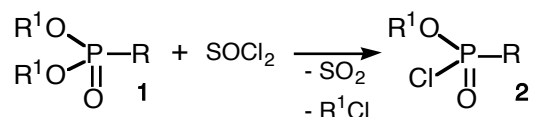


Scheme 13.

Thionyl chloride, SOCl_2

The reaction of dialkyl alkylphosphonates **1** with thionyl chloride to give the alkyl alkylphosphonochloridates **2**, generally requires heating, with the thionyl chloride being used as solvent and reagent (Scheme 14).[66,78] A variation using benzene as the solvent has also

been reported.[66] In spite of heating the chlorination of dialkyl alkylphosphonates **1** stops at the half-ester. However, some sensitive alkylphosphonochloridates **2** do not survive the necessary reaction conditions, and polymeric mixtures frequently result, thereby excluding this conversion for synthetic purposes.



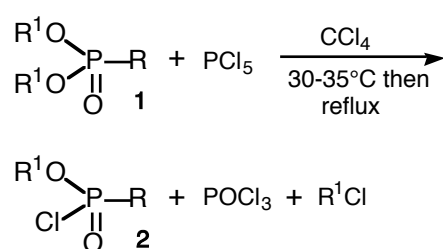
Scheme 14.

This method, having only limited utility for the synthesis of alkylphosphonochloridates **2**, has found applications in the transformation of dialkyl alkylphosphonates **1** into alkylphosphonic dichlorides **10** (R = Me, Et, CH₂CH₂Cl, *n*-C₁₂H₂₅), provided that excess of thionyl chloride, prolonged reaction time and suitable catalysts such as DMF, N-formylpyrrolidine or N-formylpiperidine are used.[79]

Phosphorus pentachloride, PCl₅

Historically, phosphorus pentachloride was the first halogenating reagent to be introduced in phosphonate chemistry. It is the most frequently used and most widely known chlorinating reagent and undoubtedly PCl₅ has several advantages. Treatment of phosphonates with this reagent gives a rather rapid reaction with removal of only one of the ester groups. However, whilst removal of the second ester group is difficult, the treatment can proceed too far to give the dichloridate. Thus, the major difficulty in this reaction often arises from the formation of mixtures containing phosphonochloridates and dichloridates. Only two of the chlorides of PCl₅ are used in this conversion, so this difficulty is overcome when the chlorinating agent and the phosphonates **1** are used in stoichiometric amounts with reaction temperatures held between 30-35°C. However, when PCl₅ is introduced in excess, it can be destroyed by bubbling SO₂ into the reaction mixture.[16,17,21,37,80-82] The role played by reaction solvents is important in progressively solubilising solid PCl₅ as the reaction evolves. For example, CCl₄, in which PCl₅ is soluble, is the most convenient and more frequently used solvent (Scheme 15);[9,10,12,17-19,24-26,28,29,31,37,41,83-86] benzene and toluene are

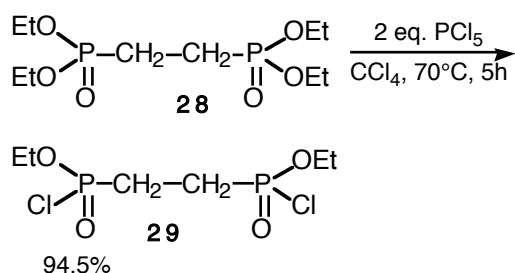
also frequently employed[14,15,23,27,32-34,39,40,43,87] but CH_2Cl_2 and CHCl_3 are used more rarely.[11,16,22,36,38,42] The chlorination has been also described in the absence of solvent.[5-8,13,20,21,80,81,88-90] In that case the reagents are mixed then heated for about 4 h at temperatures between 60 and 90°C, but yields are a little lower and less predictable. No important variations have been made with the ester groups which are invariably methyl or ethyl groups, scarcely higher homologues, and sometimes benzyl groups.[34] The use of cyclic esters has also been reported. The reaction of 2-butoxymethyl-4-methyl-2-oxo-1,3,2-dioxaphospholane with solid PCl_5 in benzene goes exothermically and leads to the phosphonochloridate in 81% yield by spontaneous opening of the dioxaphospholane ring. [82] The R groups bound to phosphorus are represented by alkyl,[9,13-15,18,34,38-40,42,84,85,88] aryl,[32] benzyl,[16,26,28,36,43] norbornyl,[87] halogenoalkyl,[8,12,22,24,31,41,83],vinyl,[11,37,42] phtalimido-methyl[23,30] and -ethyl,[27,33,35] phosphonoethyl,[19] formic,[17,21,80,86] acetic,[5,20,21,29] propionic[21] and butanoic[29] esters, ethyl-[25] and benzyliocyanate,[7] enamides[90] and alcoxymethyl.[6,82] Also formed in this reaction are an equivalent of the corresponding alkyl chloride and phosphorus oxychloride.



Scheme 15.

The best yields, between 70 and 95%, are generally obtained by working in CCl_4 with one equivalent of PCl_5 for one equivalent of phosphonate. The reaction is initiated at 30-35°C during the addition of PCl_5 , then heated at reflux (from 1 to 5 h) to complete the reaction (Scheme 16). The use of benzene also requires heating at reflux for few hours and the yields are roughly comparable to those obtained with CCl_4 (80 to 90%). In these conditions, the reaction generally proceeds in good yields and generates the expected phosphonochloridate. For example, the symmetrical dichloride of the diethyl ester of ethylene-1,2-diphosphonic

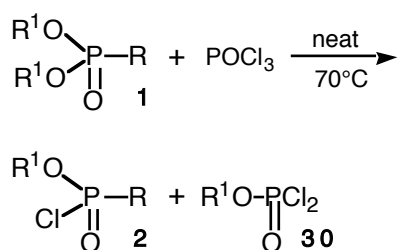
acid **29** was produced in 94.5% yield by the reaction of the tetraethyl ester of ethylene-1,2-diphosphonic acid **28** with PCl_5 in refluxing CCl_4 . [19]



Scheme 16.

Phosphorus oxychloride, POCl_3

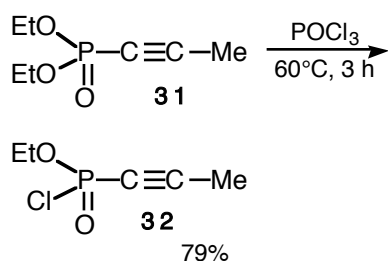
Phosphorus pentachloride, whilst being a useful reagent, is often handicapped by its notorious aggressiveness and suffers from a tendency to give disubstitution products if reaction conditions are not carefully controlled. These problems may be overcome if it is replaced by POCl_3 being used as solvent and reagent. [44-47,91,92] Only one of the chlorines of this reagent is used in the phosphonate-phosphonochloridate conversion and the monochlorination reactions render it a safe and convenient substitute to PCl_5 . The by-product is one equivalent of the corresponding alkyl dichlorophosphate **30** (Scheme 17).



Scheme 17.

A relatively general procedure for the conversion of diethyl alkylphosphonates **1** ($\text{R}^1 = \text{Et}$) to alkylphosphonochloridates **2**, in yields ranging from 38 to 86%, has been developed from POCl_3 and the method has been applied to a large variety of substrates whose R groups comprise alkyl, halogenoalkyl, benzyl, alkenyl, alkynyl and carboxyl groups. In a typical reaction, diethyl 1-propynylphosphonate **31** (1 eq.) was mixed with an excess of freshly purified POCl_3 (1.5 eq.) and heated at 70-80°C for 3-4 h, to cleanly give ethyl 1-

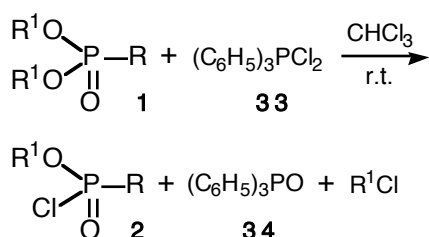
propynylphosphonochloridate **32** in pure form with 79% yield (Scheme 18). After elimination of the excess of POCl₃ and ethyl dichlorophosphate **30** (R¹ = Et), the 1-propynylphosphonochloridate **32** was purified by fractional distillation.[91]



Scheme 18.

Triphenylphosphine dichloride, Ph₃PCl₂

Triphenylphosphine dichloride **33** is a monochlorination reagent which was introduced in 1988. The reactions between dialkyl alkylphosphonates **1** and triphenylphosphine dichloride **33** were conducted in CHCl₃ solution at room temperature with reaction times from 2 to 22 h. Other solvents such as THF, CCl₄ and Et₂O were found to give less favorable results. A series of dimethyl alkylphosphonates **1** (R¹ = Me) involving simple R alkyl groups or more sophisticated groups (R = Me, *n*-Pr, CH₂CH=CH₂, CO₂Me, CO₂*i*-Pr, CO₂Ph) bound to phosphorus have been studied (Scheme 19).[93] Conversions were found to vary between 73 and 97%. No formation of dihalide product was detected.



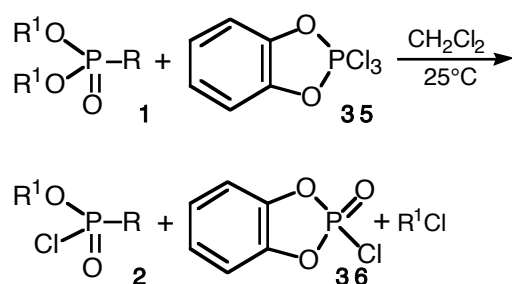
Scheme 19.

The formation of Ph₃PO **34** as a by-product of these reactions presents a fundamental experimental drawback and poses serious difficulties in isolating the pure alkylphosphonochloridates **2**. To obviate this difficulty a polymer-bound tertiary phosphine dichloride reagent was used. Chloromethylated polystyrene was treated with an excess of

ethyl diphenylphosphonite in toluene. The ensuing Michaelis-Arbuzov reaction results in the formation of a polymer-linked diphenylphosphine oxide which may be converted to the tertiary phosphine dichloride by treatment with phosgene. Using one equivalent amount of the polymer reagent in chloroform solution, conversions of 76% and 97% were found for various dimethyl alkylphosphonates after 4 h.[93]

Trichloro(*o*-phenylenedioxy)phosphorane, C₆H₄O₂PCl₃

Trichloro(*o*-phenylenedioxy)phosphorane **35** has been introduced as a chlorinating agent more recently.[94,95] Reactions of dialkyl alkylphosphonates **1** (R¹ = Et, R = Et, CH=CH₂, C≡C-Me) with an equimolar amount of **35** for 24 h at room temperature result in the replacement of one phosphonate alkoxy group with formation of alkylphosphonochloridates **2** in fair yields (56-70%). Also formed in the reaction is *o*-phenylene chlorophosphate **36** (Scheme 20). With a three fold excess of phosphorane **35**, the product alkylphosphonochloridate **2** evolves slowly to give small amounts of the corresponding phosphonic dichloride. Presumably, the replacement of the second alkoxy group by chlorine in the reaction with the phosphorane is facilitated by the presence of the donor alkyl group at phosphorus. Consistently, electron-acceptor substituents on the phosphoryl hamper further replacement of the alkoxy groups. Thus, excess phosphorane **35** reacts with diethyl vinyl- or alkynylphosphonate to yield vinyl- or alkynylphosphonochloridate selectively.[95]



Scheme 20.

Once more, the method suffers from the difficulties encountered in separating the product alkylphosphonochloridate **2** from the *o*-phenylene chlorophosphate **36** by-product. Whilst this may be achieved by fractional distillation, the difference in boiling points is relatively small

and a mixture of products may be obtained. The general synthetic utility of phosphorane **35** remains to be demonstrated.

Conclusion

Three chlorinating reagents, $(\text{COCl})_2$, PCl_5 and POCl_3 , appear particularly valuable for the phosphonate-phosphonochloridate conversion. Oxalyl chloride is clearly preferable to phosgene, whose desirability in purely chemical terms is compromised by practical difficulties when working at higher temperatures and by its very high toxicity. The versatility of PCl_5 is well documented and it seems likely that this reagent will continue to find applications. Whilst phosphoryl chloride has not been widely employed to date, it seems to have great potential and may eventually become the reagent of choice for this conversion.

Acknowledgements

We are grateful to ATO-FINA for financial support to B. I., M. Multan from the Ecole Polytechnique (BCX) for assistance in collecting the literature and the Centre National de la Recherche Scientifique (CNRS).

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