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Controlled Reactivity of Phosphonates by Temporary Silicon Connection

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Abstract: In this review a summary of the different syntheses of trimethylsilylphosphonates is given. Their chemical reactivity in the light of their synthetic utility leading to numerous types of functionalized phosphonates is described. The material is presented according to the role played by the trimethylsilyl group.

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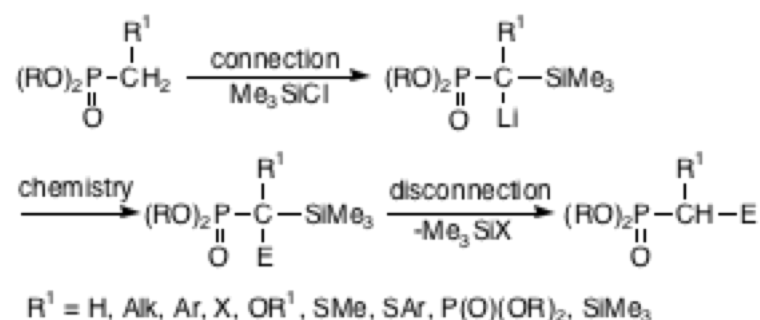
Key words: phosphonate carbanion, Peterson reaction, silicon, halogenation, alkylations

1 Introduction

α -Silylated phosphonates have been known since 1956¹ but their common use as reagents in phosphorus chemistry has become important only in recent years.^{2,7} The first participation of the trimethylsilyl group in phosphonates chemistry was reported in 1972,⁸ as an extension of the Peterson reaction, and the use of trimethylsilyl as protecting group appeared in 1988.⁹ Undoubtedly, the presence of trimethylsilyl on the α -carbon atom to phosphorus has opened a

research area giving rise to new synthetic developments and applications for phosphonates chemistry. Trimethylsilyl has the ability to stabilize and modify the reactivity of the adjacent carbanions and, consequently, their reactivity does not parallel that of other functional phosphonates. The easy connection of the trimethylsilyl group at the α -carbon atom combined with a ready disconnection as trimethylsilanolate or trimethylsilylheteroatom have contributed to confer α -silylated phosphonates upon a role of intermediates to control the reactivity of phosphonate carbanions.

For a number of years we have been engaged in a program to develop novel and efficient routes for the synthesis of phosphonates. In this area, α -silylated phosphonates appear as reagents of significant synthetic importance for the preparation of functionalized phosphonates. The overall operation involving α -silylated phosphonates is depicted in Scheme 1. In this review, the types of reaction they undergo, with an emphasis on their synthetic utility, and various methods of preparation are summarized.

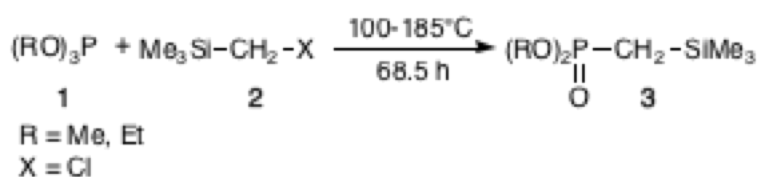


Scheme 1.

2 General Method for the Synthesis of α -Silylated Phosphonates

A. Michaelis-Abuzov Route

Several chloromethylsilanes have been used as silylmethylphosphonate precursors, although few of them have received utility in organic synthesis. The diethyl 1-(trimethylsilyl)methylphosphonate **3** ($\text{R} = \text{Et}$), the most useful reagent, was first prepared in 56.5 % yield by refluxing for 68.5 h at 100–185°C a mixture of triethyl phosphite **1** and (chloromethyl)trimethylsilane **2** (Scheme 2).¹ Reduction of reaction time lowers significantly the yield.¹⁰ Replacement of triethyl phosphite by trimethyl phosphite, to prepare the corresponding dimethyl ester, has little effect on the yield, which is comparable to the previous one (64.5 %).¹¹ By contrast, the use of (bromomethyl)trimethylsilane in reaction with triethyl phosphite decreases dramatically the yield which brings down at 25 %.¹² In further examples, essentially chloromethylsilanes bearing different group (Et, Ph) on the silicon atom have been used for the preparation of the corresponding silylmethylphosphonates in yields ranging from 44 to 75 %.^{13,14} One example of conversion of chloromethyl- to iodomethylsilanes followed by Michaelis-Arbuzov reaction has also been reported.¹⁵

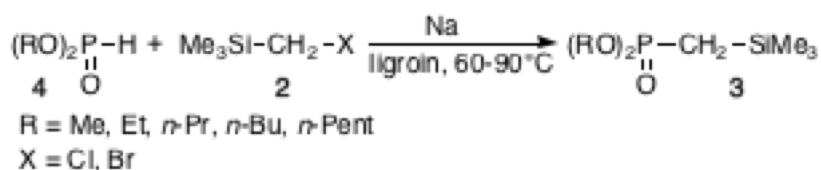


Scheme 2.

Surprisingly, secondary α -silylated bromides were reactive, but the reactions require severe conditions (3-12 h at 170-200°C). Thus by the Michaelis-Arbuzov rearrangement of triethyl phosphite with (α -bromobenzyl)trimethyl- and (α -bromobenzyl)triethylsilanes, the corresponding diethyl (trimethyl)- and (triethylsilyl)benzylphosphonates were obtained in 56 and 24 % yields, respectively.¹⁶

B. Michaelis-Becker Route

(Halogenomethyl)trimethylsilanes **2** ($\text{X} = \text{Cl, Br}$) undergo typical Michaelis-Becker reaction with a variety of dialkylphosphites **4** to give dialkyl 1-(trimethylsilyl)methylphosphonates **3** in modest yields (23-38 %) (Scheme 3).^{11,12,17,18} This method, being not economical in terms of yields, has only limited utility and has never been developed.



Scheme 3.

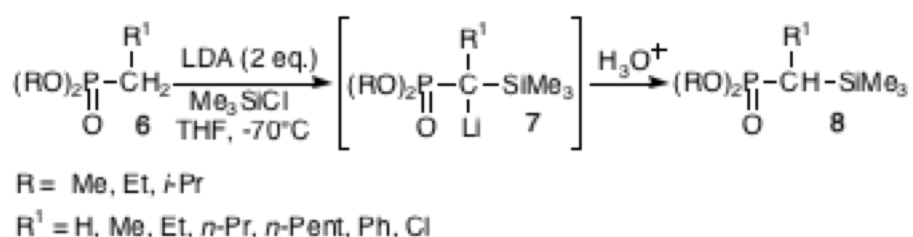
C. Kinnear-Perren Route

The 1-(trimethylsilyl)methylphosphonic dichloride **5** has been prepared on large scale but in modest yield (31 %) by reaction between (chloromethyl)trimethylsilane **2** ($\text{X} = \text{Cl}$), phosphorus trichloride and aluminium trichloride followed by hydrolysis with a limited amount of water. Although this procedure give moderate yields, the large number of phosphonic diesters **3** subsequently prepared in fair to good yields (40-71 %) by alcoholysis of **5** is compensatory (Scheme 4).^{19,20}



D. Carbanionic Route

Unquestionably, the most attractive procedure for the preparation of dialkyl 1-(trimethylsilyl)methylphosphonates is the carbanionic route. The obvious difficulties resulting from transmetallation reactions which attend the execution of carbanionic reactions involving activated methylene groups have led to the development of ingenious procedures based on the trapping of 1-lithioalkylphosphonate anions with chlorosilanes in the presence of LDA. For example, the addition at -70°C of trimethylchlorosilane (TMSCl) (1 eq.) to a solution of dialkyl 1-lithioalkylphosphonates prepared from dialkyl alkylphosphonates (1 eq.) **6** and LDA (2 eq.) produces after work-up the dialkyl 1-(trimethylsilyl)alkylphosphonates **8** in 75-90 % yields of isolated product (Scheme 5), *via* the quantitative and clean generation of the stable intermediates, substituted dialkyl 1-lithio-1-(trimethylsilyl)methylphosphonates **7**.^{22,23} By varying the reactants, dialkyl methyl-, alkyl-, halogenomethyl- or benzylphosphonates **6**, a number of dialkyl 1-(trimethylsilyl)phosphonates **8** may be easily obtained, thus extending significantly the scope and synthetic utility of the carbanionic route.^{24,25} This expeditious and versatile technique has largely supplanted the previously reported carbanionic approaches. For example, addition of an excess of dimethyl 1-lithiomethylphosphonate, generated with *n*-BuLi (1 eq.), to a cooled THF solution of TMSCl, or addition of TMSCl in excess to a cooled solution of dimethyl 1-lithiomethylphosphonate resulted in the two cases in low yields (27-31 %) of dimethyl 1-(trimethylsilyl)methylphosphonate **8** (R = Me, R' = H).^{26,27}



Scheme 5.

The synthetic advantages of the carbanionic route are evident. Compared with the Michaelis-Arbuzov and Michaelis-Becker routes involving (chloromethyl)trimethylsilane, an expensive reagent, the carbanionic route uses TMSCl, an inexpensive and readily accessible starting material. Similarly, all the phosphonates are commercially available or accessible on laboratory scale. In addition, the carbanionic route leads to the lithiated α -silylphosphonate intermediates which may be directly used for further transformations. This method of generating carbanions **7** by proton-metal exchange reaction from α -substituted dialkyl methylphosphonates **6** is complemented by the halogen-metal exchange reaction from dialkyl trichloromethylphosphonate. Compared with the carbanionic route using lithiophosphonates, the use of cuprophosphonates provides another synthetic access to dialkyl 1-(trimethylsilyl)alkylphosphonates **8**, but not so attractive.^{28,29}

3 Reactions of α -Silylated Phosphonates

A. Trimethylsilylmethyl as Masked Carbanion

Several groups have demonstrated that desilylation of organosilanes containing a C-SiMe₃ moiety initiated by means of fluoride ion (CsF, KF or TBAF) is an effective way for the transfer of carbanions to electrophilic centers. Some examples involving the fluoride-induced formation of α -phosphonylated carbanions from 1-(trimethylsilyl)methylphosphonates containing a fragile C-Si bond have been described. Cleavage of the carbon-silicon bond under these conditions offers the advantages of neutral conditions and contributes to better yields from sensitive substrates than those obtained under basic conditions.

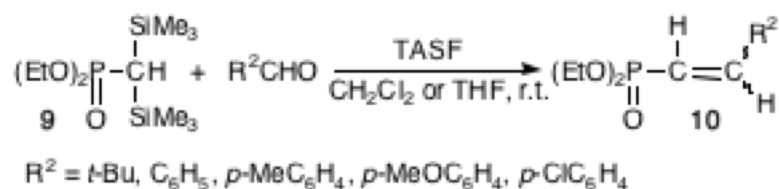
This procedure, appearing operationally simpler and cleaner than traditional protocols, has been applied to the preparation of alkenes^{26,30} and 1-alkenylphosphonates³¹ by Horner-Wadsworth-Emmons (H-W-E) and Peterson reactions, respectively.

When dimethyl 1-(trimethylsilyl)benzylphosphonate was treated with benzaldehyde in the presence of fluoride ion sources (CsF, KF, TBAF), stilbene and dimethyl benzylphosphonate, a protodesilylation product, were produced. The best result of stilbene (85 %) was obtained upon heating in THF for 1 day with freshly dried CsF. Use of MeCN gave a similar result, whereas in toluene the reaction became very slow. KF was less effective even in the presence of 18-crown-6. TBAF was efficient at room temperature, however, the modest yield seems to be due to the difficulty in drying or the existence of acidic hydrogen, easily transmetallated by the resulting carbanion. When CsF or KF were used, only the *E*-stilbene was obtained, while TBAF afforded a mixture of *E*- and *Z*-stilbene in a 90/10 ratio. The formation of dimethyl benzylphosphonate seems to be due to the protonation by water which still remained in the system, and the yield of the olefin becomes water dependent. In the case of reactions with

isobutyraldehyde, the corresponding olefins were obtained in low yield (35 %) as a *E*+*Z* mixture (70/30). By contrast, cinnamaldehyde gave stereochemically pure *E,E*-1,4-diphenyl-1,3-butadiene in 67 % yield.^{26,30}

Several variations on the reaction between diethyl 1-(trimethylsilyl)methylphosphonate **3** (R = Et) and aromatic aldehydes have been reported by solvent-free techniques in a domestic oven. At room temperature in the presence of dried CsF, unsupported or supported on magnesium oxide, the *O*-silylated diethyl 2-hydroxy-2-arylethylphosphonates were produced selectively in 60-80% yields of isolated product. The hygroscopic nature of CsF can complicate the reaction and under non-anhydrous conditions, with non-dried CsF for example, formation of diethyl arylvinylphosphonates is observed.³²

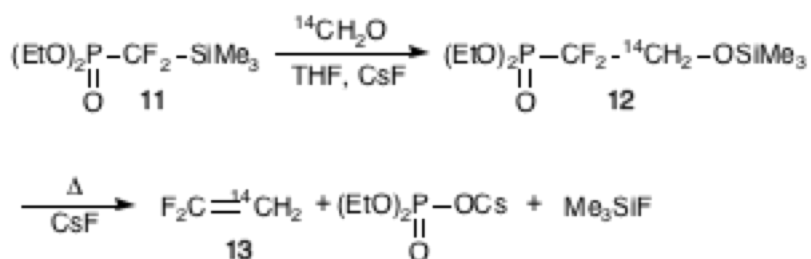
Generation of α -silylated carbanions by fluoride ion from diethyl *bis*(trimethylsilyl)methylphosphonate **9** constitutes a promising extension of the Peterson reaction. Diethyl *bis*(trimethylsilyl)methylphosphonate **9** was reacted for 1 h under *tris*(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) catalysis in THF at room temperature with aromatic aldehydes and in refluxing THF with pivalaldehyde. The reaction gives the diethyl alkenylphosphonates **10** in 60-70 % yield as a mixture of *E* and *Z* isomers in a 85/15 ratio for aromatic aldehydes and 50/50 for pivalaldehyde (Scheme 6).³¹ This chemistry proceeding under mild and almost neutral conditions *via* metal-free carbanionic species appears as the method of choice for preparing compounds possessing base- or acid-sensitive functionalities.



Scheme 6.

The readily available diethyl 1,1-difluoro-1-(trimethylsilyl)methylphosphonate **11** is particularly suited to fluoride ion-catalyzed reactions. The reaction of **11** with aromatic or heteroaromatic aldehydes in the presence of CsF proceeds easily at room temperature in THF to produce the silylated adducts which are readily hydrolyzed to diethyl 1,1-difluoro-2-hydroxy-2-arylethylphosphonates in 57-87 % yields.³³ Further application of diethyl 1,1-difluoro-1-(trimethylsilyl)methylphosphonate **11** has been demonstrated in the synthesis of [1-¹⁴C]-2,2-difluoroethene **13**. In search of a ¹⁴C-radiolabelled form of 1,1-difluoroethene, the fluoride ion-induced desilylation has been accomplished using diethyl 1,1-difluoro-1-(trimethylsilyl)methylphosphonate **11** and commercial [¹⁴C]-formaldehyde in the presence of catalytic amount of anhydrous CsF (Scheme 7). The key intermediate **12** undergoes a H-W-E

reaction to give the highly volatile [1-¹⁴C]-2,2-difluoroethene **13** which was collected with yields of 10-15 % in a purity exceeding 97%.³⁴

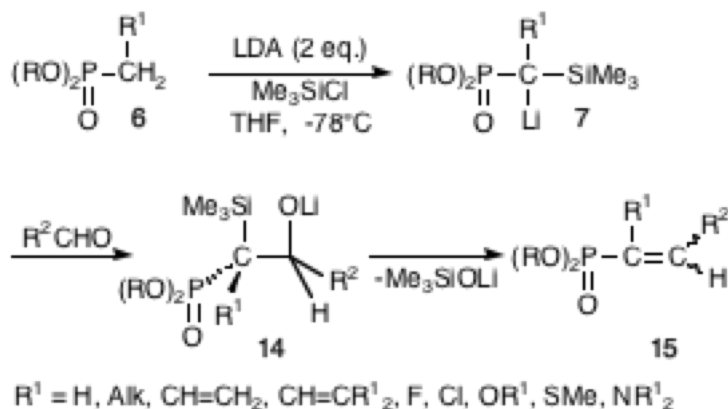


Scheme 7.

B. Trimethylsilyl as Directing Group

In 1968 Peterson made the important discovery that the anions resulting from lithiation of (methylthio)methyltrimethylsilane and (trimethylsilyl)methyldiphenylphosphine sulfide reacted with benzophenone to afford β-oxidosilanes which decompose to give olefins by loss of Me₃SiOLi. This olefination reaction resulting in functionally substituted alkenes has been extended to phosphonates and can be considered as an alternative to the H-W-E reaction.³⁵

The reaction has been investigated with dialkyl 1-(trimethylsilyl)alkylphosphonates **8**, unsubstituted (R¹ = H) or substituted (R¹ ≠ H) at the α-carbon, and aldehydes or ketones, although aldehydes were the most frequently employed in this transformation. The phosphonate version of the Peterson reaction has given the opportunity to develop a one-pot reaction sequence which includes the successive formation of 1-lithio-1-(trimethylsilyl)alkylphosphonates **7**, β-oxidosilanes **14** and 1-alkenylphosphonates **15** (Scheme 8). Unfortunately, as the Peterson reaction is under kinetic control and irreversible, the phosphonate version shows little stereoselectivity and, compared to the H-W-E reaction, mixtures of *E* and *Z* isomers are frequently obtained. Fortunately, the two isomers are chromatographically separable thereby proving a useful route to both isomers.³⁶



Scheme 8.

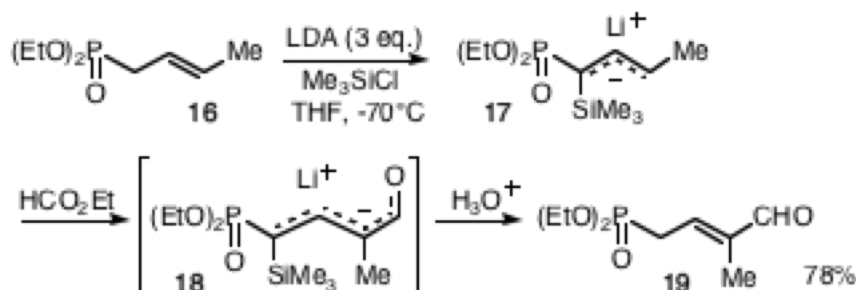
Despite a large number of investigations, a systematic study of the Peterson reaction including solvent, temperature, additives, nature and size of the α -substituents is lacking. Although the reported reactions have not all been effected under the same experimental conditions, it is possible to consider the nature of the carbonyl compounds (aldehydes or ketones) and of the group attached to the α -carbon atom (H,^{8,22,25} alkyl,^{8,22,23,37} OR,³⁸ SR,^{39,40} NR₂,⁴¹ F,⁴²⁻⁴⁶ Cl⁹) as experimental variables which affect the stereoselectivity. However, since aldehydes have been more systematically used than ketones, the comparison is best limited to this class of carbonyl compounds. Thus, the reaction of dialkyl 1-(trimethylsilyl)methylphosphonates **3** with aromatic aldehydes favours the *E* isomer (*cis* P(O)/H relationship) while aliphatic aldehydes give a mixture of the *E* and *Z* isomers in approximately equal amounts.^{8,22,25} Similarly, the presence of a fluorine atom at the α -carbon atom promotes the *E* isomer with aromatic aldehydes and a mixture of *E* and *Z* isomers with aliphatic aldehydes.⁴²⁻⁴⁶ With a chlorine substituent, the two isomers are formed in approximately equal amounts.⁹ Introduction of an alkyl group (Me, Et, *n*-Pr, *n*-Pent, *neo*-Pent) at the α -carbon atom leads predominantly to the *Z* isomer (*trans* P(O)/H relationship) with aromatic aldehydes whilst a mixture of *E* and *Z* isomers is produced with aliphatic aldehydes.^{8,22,23,37} The presence of a NR₂ group at the α -carbon atom strongly favours *Z*-configured products with both aromatic and aliphatic aldehydes.⁴¹ Introduction of a SMe group at the α -carbon atom leads exclusively to the *E* isomer (*trans* P(O)/H relationship) with aromatic aldehydes and predominantly to the same isomer with aliphatic ones. □ PROGCOMP ENRfu □□40□

□

Figure 1.

For lithiated allylic phosphonates, the substitution pattern about the carbon skeleton affects the regioselectivity of the initial silylation as well as the reactivity of the resulting silylated anion. □ PROGCOMP ENRfu □□47□ In the case of α -silylated allylic phosphonates, the trimethylsilyl group has been shown to be useful both as directing and protecting group to control the regioselectivity of the system. For example, the lithiated diethyl allylphosphonate reacts with TMSCl to give diethyl 1-(trimethylsilyl)allylphosphonate in 47 % yield. It has been shown that the 1-sodio-1-(trimethylsilyl)allylphosphonate reacts with paraformaldehyde on heating in THF to give a mixture of 2-trimethylsilyl-1,3-butadiene (H-W-E reaction, 36 %) and 2-diethoxyphosphonyl-1,3-butadiene (Peterson reaction, 12 %). By contrast, the corresponding lithiated anion reacts with paraformaldehyde in hexane at low temperature to give only the Peterson product in 32 % yield. □ PROGCOMP ENRfu □□48,49□ Additionally, treatment of diethyl crotylphosphonate **16** at low temperature with LDA (3 eq.) followed by addition of TMSCl provide exclusively the □-silylated crotylphosphonate anion **17**. By virtue of the

trimethylsilyl group, this anion reacts with ethyl formate in the α -position to give **18**. On acidic hydrolysis, the desilylated diethyl (2E)-3-formyl-2-butenylphosphonate **19** was isolated in 78 % yield (Scheme 9). □ PROGCOMP ENRfu □□50□

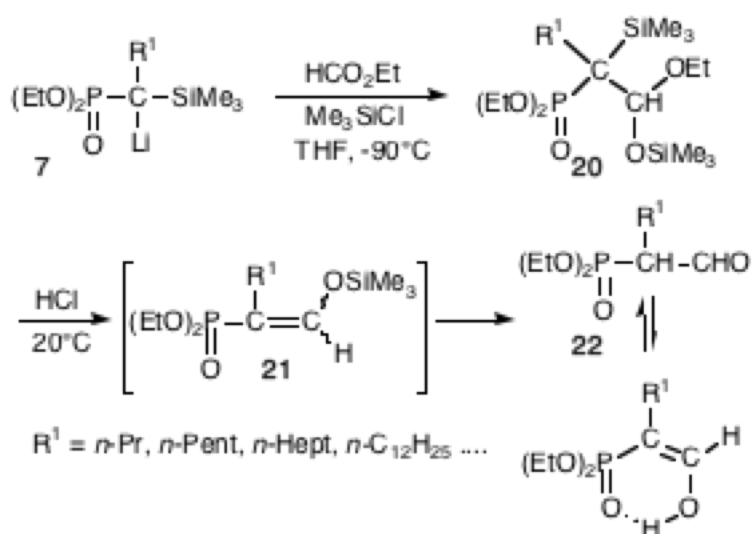


Scheme 9.

By contrast, the α -silylated carbanion generated from diethyl prenylphosphonate, on reaction with alkyl formates, behaves as a Peterson reagent leading to 1-*Z*-2-diethoxyphosphonyl-1-alkoxy-3-methylpenta-1,3-dienes in high yields (72-92 %).⁵¹ The presence of the two methyl groups at the γ -position determines the α -regioselectivity of this anion towards the alkyl formates and favours the fast decomposition of the hindered kinetic *erythro*-adduct, leading to the *Z* enol ether, after a Peterson *syn*-elimination of the oxophilic silylated moiety.⁵¹

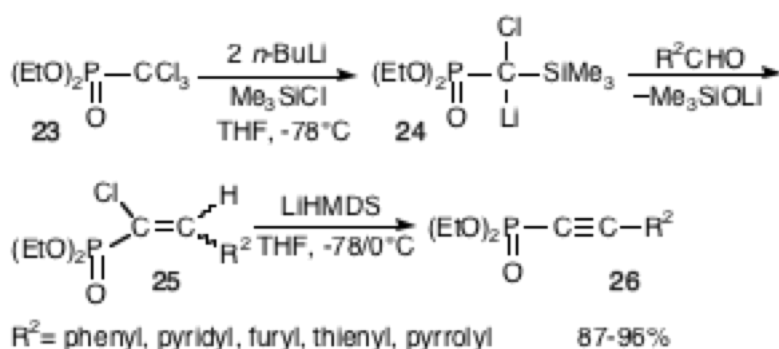
The reaction of lithiated 1-(trimethylsilyl)cinnamyl-, prenyl- and crotylphosphonates with aldehydes was also studied. The cinnamyl derivative undergoes Peterson reaction with aromatic or aliphatic aldehydes to give phosphonodienes in high yield and with high stereoselectivity. Thus, with aromatic aldehydes almost stereomerically pure *E,E*-phosphonodienes were obtained, whereas predominantly *Z,E*-phosphonodienes resulted from reaction with aliphatic aldehydes. In contrast, the prenyl derivative undergoes a strict γ -regioselectivity in its reaction with aromatic aldehydes leading to phosphonolactones and to a mixture of phosphonolactones (major product) and *Z,E*-phosphonodienes (minor product) on reaction with aliphatic aldehydes.⁵²

Decomposition at low temperature of the adduct **14** to 1-alkenylphosphonates **15** can be avoided by trapping the β -oxidosilanes **14** *in situ* at -90°C with an excess of TMSCl. For example, treatment of the diethyl 1-lithio-1-(trimethylsilyl)alkylphosphonate **7** ($\text{R} = \text{Et}$) with ethyl formate followed by addition of TMSCl (1.5 eq.) provided the mixed acetal **20** as the major product. While there are some difficulties encountered in the hydrolysis of enol ethers, the mixed acetals **20** may be easily and completely hydrolyzed in few minutes at room temperature with diluted HCl, *via* the sensitive silylated enol ethers **21**, to give the α -substituted formylphosphonates **22** as a mixture of aldehyde and enol forms. The silylated enol ethers **21** can be used advantageously in place of the traditional enol ethers, thus offering an efficient approach to the synthesis of diethyl 1-formylalkylphosphonates **22** (Scheme 10).⁵³



Scheme 10.

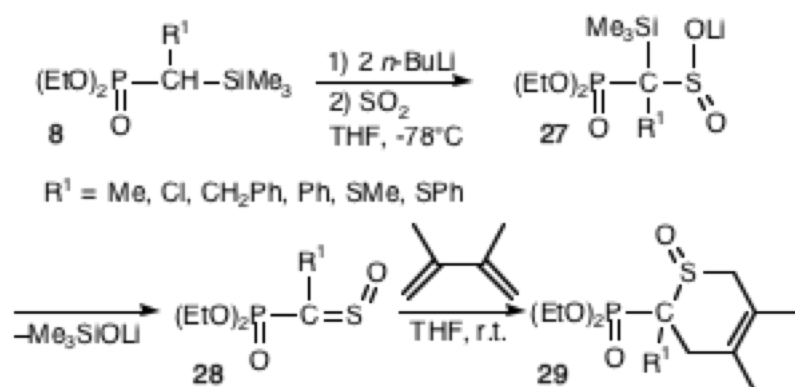
Another interesting feature of the Peterson olefination reaction concerns the subsequent transformation of 1-alkenylphosphonates to new functionalized phosphonates. For example, the diethyl 1-lithio-1-chloro-1-(trimethylsilyl)methylphosphonate **24**, resulting from the treatment of diethyl trichloromethylphosphonate **23** with *n*-BuLi (2 eq.) in the presence of TMSCl, reacts at low temperature with aldehydes to produce a mixture of *E*- and *Z*-1-alkenylphosphonates **25**. When the carbonyl compound is an aromatic or heteroaromatic aldehyde, the diethyl 1-alkenylphosphonates **25** are readily converted into diethyl 1-alkynylphosphonates **26** in high yields (87-96 %) in a one-pot process by treatment at low temperature with LiHMDS and subsequent elimination of LiCl (Scheme 11).⁵⁴ This class of 1-alkynylphosphonates **26** is difficult to prepare by other methods which, generally, are depending on the availability of the terminal alkyne.



Scheme 11.

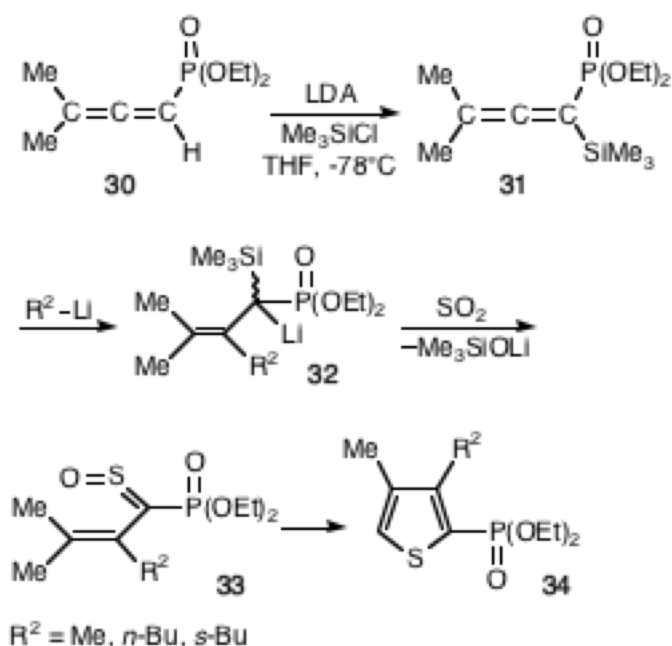
In further examples, diethyl 1-(trimethylsilyl)alkylphosphonates **8** (R = Et) are efficiently converted into sulfoxes **28** after deprotonation with *n*-BuLi at low temperature and subsequent

treatment with sulfur dioxide. Two conditions are crucial to circumvent side reactions: the reaction must be performed at -78°C and the anion must be added to an excess of sulfur dioxide. This reaction appears to be fairly general and, by decomposition of the adducts **27**, a large number of sulfines **28** having various substituents R^1 at the α -carbon atom were isolated in good yields. In these compounds the $\text{S}=\text{O}$ function is positioned *syn* with respect to R^1 . The sulfines **28** were converted into [4+2] cycloadducts **29** by Diels-Alder reaction with 2,3-dimethyl-1,3-butadiene (Scheme 12).⁵⁵



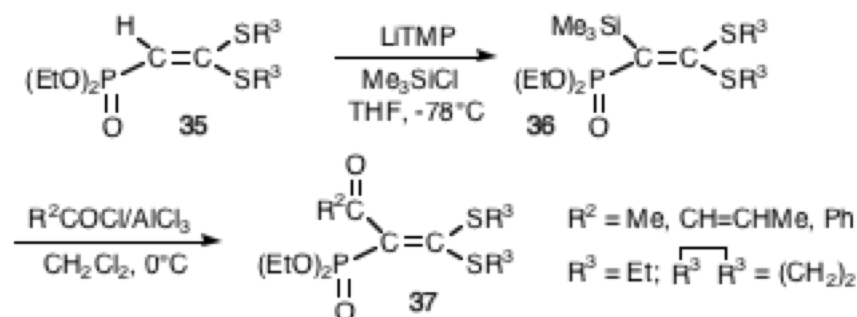
Scheme 12.

More recently, another example involving the intermediacy of phosphorylated sulfines has been reported. Treatment of diethyl allenylphosphonates **30** with LDA at low temperature followed by reaction with TMSCl leads to the desired α -silylated allenylphosphonate **31**. This very unstable compound is directly added to a solution of $\text{R}^1\text{-Li}$ ($\text{R} = \text{Me}, n\text{-Bu}, s\text{-Bu}$) (1 eq.) in THF at -78°C to give the α -phosphonylated carbanions **32**. When the anions **32** were allowed to react with an excess of sulfur dioxide and the resulting sulfines **33** stirred overnight, only poor yields of diethyl 2-thienylphosphonates **34** (12-25 %), contaminated with the protonated form of **32**, were obtained. The separation of these two compounds proved to be problematic (Scheme 13).⁵⁶ The major disadvantage of the method is the incomplete reaction of **32** with sulfur dioxide.



Scheme 13.

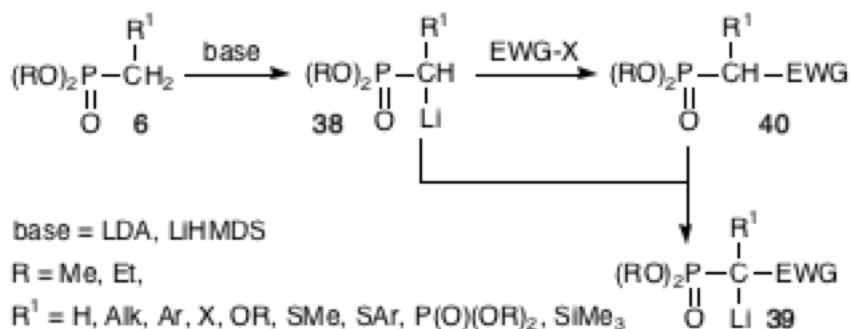
α -Silylvinylphosphonates have proved to be effective precursors of more elaborated phosphonates by Friedel-Crafts-type reactions (Scheme 14).⁵⁷ Thus, α -silylated phosphonoketene dithioacetals **36** react with acid chlorides to produce α -acetylated phosphonoketene dithioacetals **37**. In the case of acyclic dithioacetals **35** ($\text{R}^3 = \text{Et}$), the α -silylated intermediates **36** were prepared in fair yields by addition of LiTMP to a mixture of **35** and TMSCl at -78°C , in order to prevent elimination of a thiolate anion. Replacement of acyclic dithioacetal in **35** by a cyclic dithioacetal ($\text{R}^3\text{-R}^3 = (\text{CH}_2)_2$) provided, in the same experimental conditions, a better yield of α -silylated phosphonoketene cyclic dithioacetals **36** (81 %). Reaction of cyclic dithioacetals **35** ($\text{R}^3\text{-R}^3 = (\text{CH}_2)_2$) with a mixture of acid chlorides (2 eq.) and AlCl_3 (2 eq.) in CH_2Cl_2 at 0°C for 1-3 h gives α -acylated phosphonoketene dithioacetals **37** in satisfactory yields (68-89 %). A comparative study between silylated **36** and unsilylated **35** phosphonoketenes dithioacetals has demonstrated that the α -trimethylsilyl substituent was essential to increase reaction rate and yields.⁵⁷



Scheme 14.

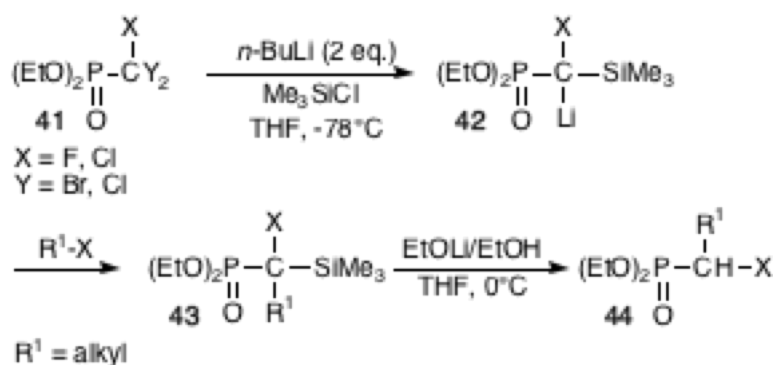
C. Trimethylsilyl as Protecting Group

In the carbanionic route, lithiated phosphonates **38** on reaction with electrophiles having electron withdrawing group (EWG-X) produce new species **40** containing a more acidic methylene group. Consequently, the initially formed carbanion **38** undergoes a facile *trans*-protonation by the new species **40** to produce a substituted lithiated carbanion **39** which can in turn undergo further reactions. The resulting crude product is unavoidably a complex mixture of expected **40**, starting **6** and undesired phosphonates which cannot be usefully separated (Scheme 15).⁴³ These disadvantages are overcome when a proton of the methylene group is replaced with a trimethylsilyl group which stabilizes the adjacent carbanion and control its reaction with electrophiles. Removal of the trimethylsilyl group as trimethylsilanolate or fluorotrimethylsilane results in formation of functionally substituted phosphonates. Each of the steps of this reaction sequence may be conveniently executed in one pot without the isolation of intermediates.



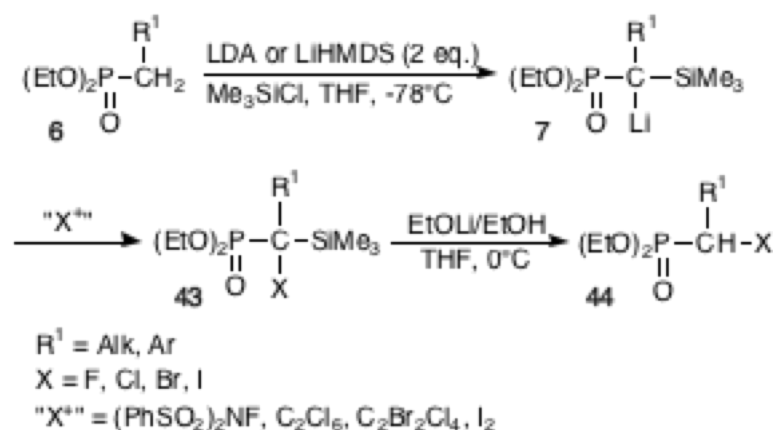
Scheme 15.

Together with these innovations, the use of α -silylated phosphonate carbanions has become one of the most useful and general method available for the synthesis of pure diethyl α -monohalogenoalkylphosphonates **44** in high yields. Two different procedures may be employed for the obtention of α -monohalogenomethylphosphonates, one by nucleophilic phosphonohalogenomethylation of substrates (Scheme 16),^{9,58-63} the other by electrophilic halogenation of phosphonates (Scheme 17).⁶⁴⁻⁶⁶ The former, using trihalogenomethylphosphonates as starting materials, has been developed for fluorine and chlorine substituents, whereas the latter, which appears to be fairly general, has greater synthetic utility and has been employed for the four halogens.



Scheme 16.

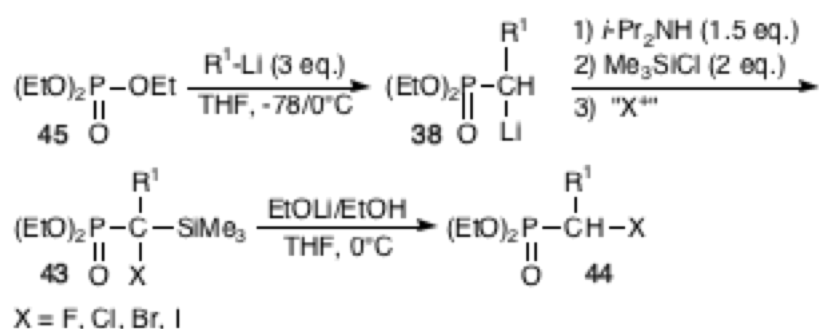
Diethyl trihalogenomethylphosphonates **41** were submitted to a double halogen-metal reaction with *n*-BuLi in the presence of TMSCl to give the diethyl 1-lithio-1-halogeno-1-(trimethylsilyl)methylphosphonates **42**. Under these conditions, the resulting stable carbanions **42** undergo safely alkylation reactions leading to trisubstituted phosphonates **43**. Owing to the presence of activating atoms (F, Cl), the C-Si bond is very sensitive and the trimethylsilyl group easily eliminated with EtOLi in EtOH to produce the substituted α -monofluoro- or α -monochloroalkylphosphonates **44** in high yields and free of byproducts (Scheme 16).⁹⁵⁸⁻⁶⁰⁶³



Scheme 17.

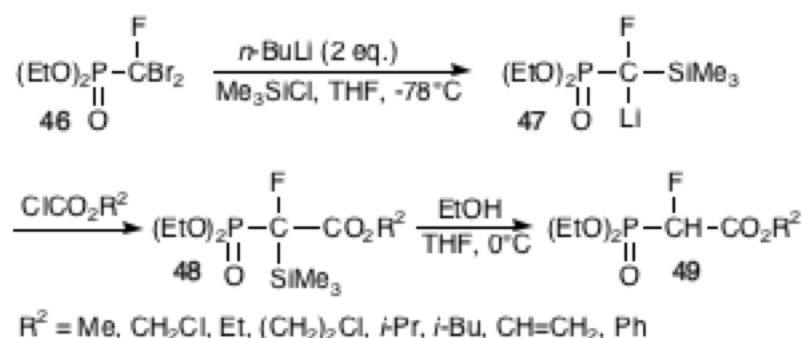
In the second approach, the substituted diethyl 1-lithio-1-(trimethylsilyl)methylphosphonates **7** (R = Et) result from a double proton-metal exchange from the corresponding phosphonates **6** (R = Et) with LDA in the presence of TMSCl. At low temperature, these carbanions undergo halogenation at carbon with commercial electrophilic halogenating reagents: *N*-fluorobenzenesulfonimide (NFBS), hexachloroethane, dibromotetrachloroethane or dibromotetrafluoroethane and iodine to give cleanly the quantitative formation of the halogenated derivatives **43**. After removal of the trimethylsilyl group with EtOLi in EtOH, the diethyl α -monohalogenoalkylphosphonates **44** are isolated in pure form and practically quantitative yields (Scheme 17).⁶⁴⁻⁶⁶

The electrophilic halogenation can be coupled with the phosphate-phosphonate transformation to provide a convenient one-pot procedure applicable for the construction of α -monohalogenoalkylphosphonates **44** bearing widely varied alkyl appendages R^1 (Scheme 18).⁶⁶ Thus, the addition of alkyllithiums, R^1Li , to triethyl phosphate **45** proceeds as expected to give the intermediate diethyl 1-lithioalkylphosphonate **38** ($R = Et$) which was subjected to sequential silylation and halogenation to afford the monohalogenated derivatives **44** in 85-97 % yields after desilylation. The overall result is that prior nucleophilic substitution of triethyl phosphate with alkyllithiums constitutes a route to diethyl α -monohalogenoalkylphosphonates **44**.⁶⁶



Scheme 18.

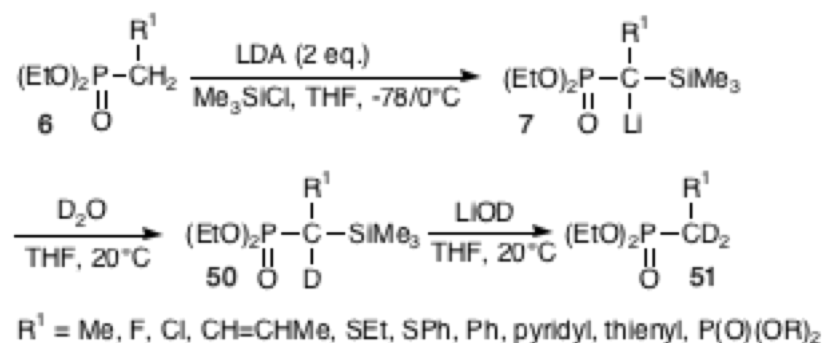
Of great synthetic importance is the preparation of diethyl α -fluorophosphonocarboxylates **49** which are valuable precursors of fluoroacrylates. They are readily obtained in high yields from diethyl dibromofluoromethylphosphonate **46** *via* diethyl 1-lithio-1-fluoro-1-(trimethylsilyl)methylphosphonate **47** as described in Scheme 16. Removal of the trimethylsilyl group is highly dependent upon the nature of the substituents of the carbon atom. In the case of **48**, anhydrous EtOH was the preferred reagent to cleave the C-Si bond, whereas the use of alcoholic lithium ethoxide results in exclusive cleavage of the sensitive C-P bond (Scheme 19).^{61,62}



Scheme 19.

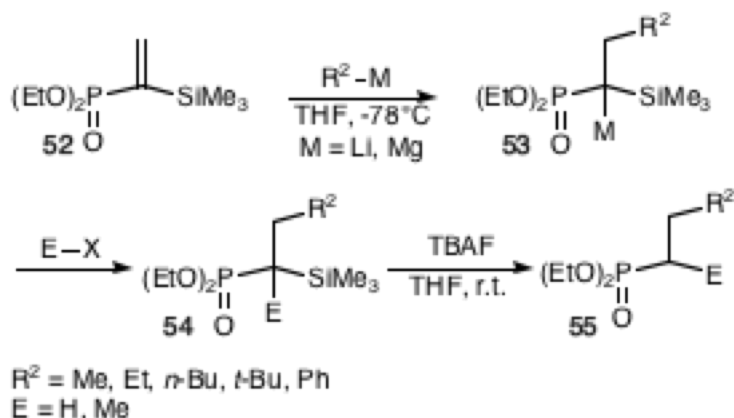
The principle of protection of a proton of the methylene group by the trimethylsilyl has been applied to the preparation of functionalized tetraethyl methylenediphosphonates.⁶⁷ The

extension of this work provides an efficient method for the incorporation of deuterium into phosphonates **51**.^{68,69} Deuteriolysis with heavy water of functionalized dialkyl 1-lithio-1-(trimethylsilyl)methylphosphonates **7** (R = Et) followed by desilylation with LiOD generated *in situ* was effected with a number of compounds **50** containing a variety of functional groups R¹ including alkyl, aryl, heteroaryl, thioalkyl, thioaryl, halogen, phosphoryl, etc... Incorporation of deuterium and chemical yields are good to excellent, and the reaction conditions are mild enough to preserve functionality at phosphorus (Scheme 20).^{68,69}



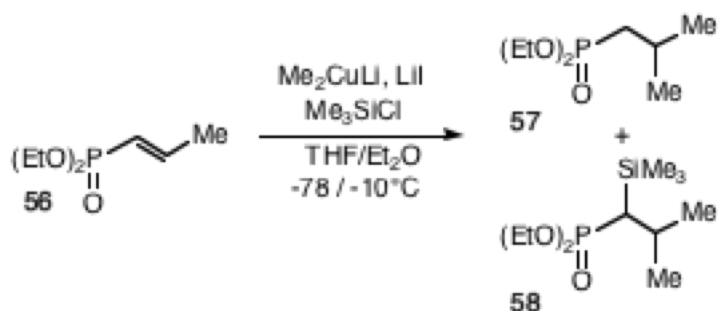
Scheme 20.

Another illustration of the advantages of trimethylsilylphosphonate reagents is provided by the transformations involving the readily available diethyl 1-(trimethylsilyl)vinylphosphonate **52**.^{37,70} This one has been found to be a valuable reagent for the facile conversion of vinylphosphonates into alkyl-,³⁷ alkenyl-,³⁷ β-keto-⁷⁰ and β-amidophosphonates⁷⁰ in high yields. Owing to the trimethylsilyl group, which activates the vinylphosphonates towards the nucleophilic addition of organometallic reagents by virtue of its polarizing effect, Grignard reagents R³MgX, as well as alkyllithiums R³Li, add to the double bond at low temperature to give stable carbanions **53**. They undergo a variety of reactions with electrophiles as alkyl halides,³⁷ acid chlorides,⁷⁰ carbonyl compounds³⁷ and isocyanates⁷⁰ to form functionalized diethyl 1-(trimethylsilyl)alkylphosphonates **54**. All the intermediates **54** are successfully protodesilylated by TBAF in moist THF in near quantitative yields to give the functionalized phosphonates **55** (Scheme 21).



Scheme 21.

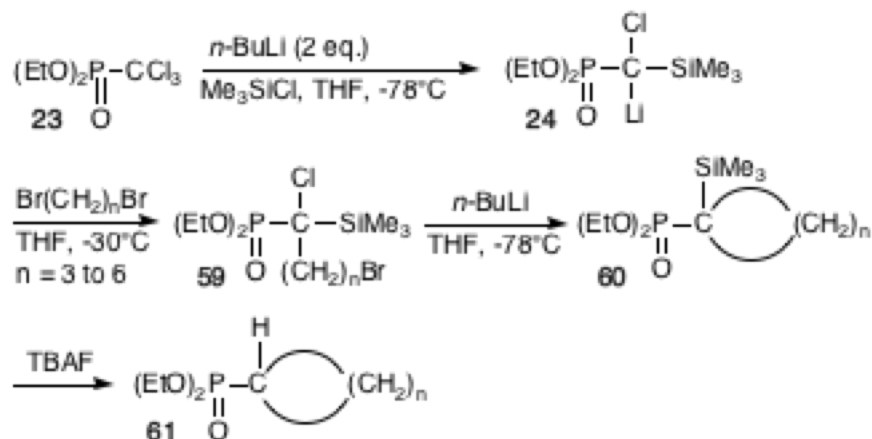
Recently it has been reported that the presence of TMSCl significantly enhances the rate of the conjugate nucleophilic addition of cuprates (R_3CuLi with $R = Me, n-Bu, s-Bu, Ph$) to 1-alkenylphosphonates. The study has shown that the rate of nucleophilic addition of dimethylcuprate to diethyl 1-propenylphosphonates **56** was at least ten times faster at $-78^\circ C$ in the presence of TMSCl than in its absence. A typical reaction between cuprate and 1-alkenylphosphonate in the presence of TMSCl was complete in half an hour at $-78^\circ C$ whereas only traces of diethyl 3-methylbutylphosphonate **57** were observed after three hours in the absence of this reagent. A common by-product of the additions to diethyl vinylphosphonates was the α -silylated phosphonate **58** whose formation occurs subsequent to the nucleophilic addition (Scheme 22).⁷¹



Scheme 22.

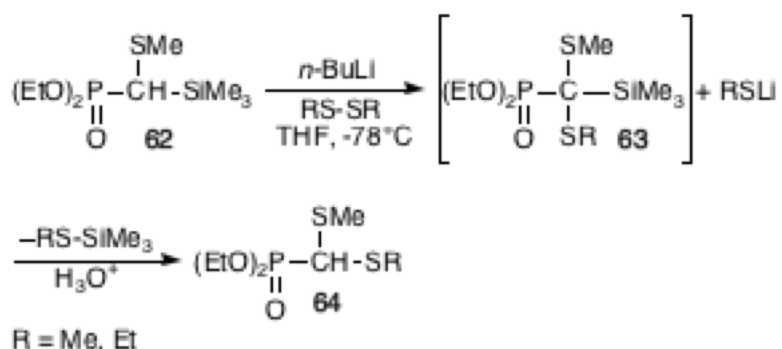
Other applications of 1-(trimethylsilyl)methylphosphonates include the reaction with bielelectrophilic reagents for the preparation of three-, four-, five- and six-membered cycloalkylphosphonates **61**.⁷² The diethyl trichloromethylphosphonate **23** is particularly well suited to this approach and the exchange of the three halogen atoms with $n-BuLi$ followed by sequential addition of TMSCl and ω -dibromoalkanes **59** results in the formation of a series of silylated cycloalkylphosphonates **60**. The C-Si bond not being activated by the presence of an electron withdrawing group, the trimethylsilyl group of **60** was removed by the use of moist

TBAF in THF solution (Scheme 23).⁷² The same principle has been applied to the synthesis of phosphonates bearing two symmetrical or unsymmetrical, saturated or unsaturated, alkyl groups on the α -carbon atom.⁷³



Scheme 23.

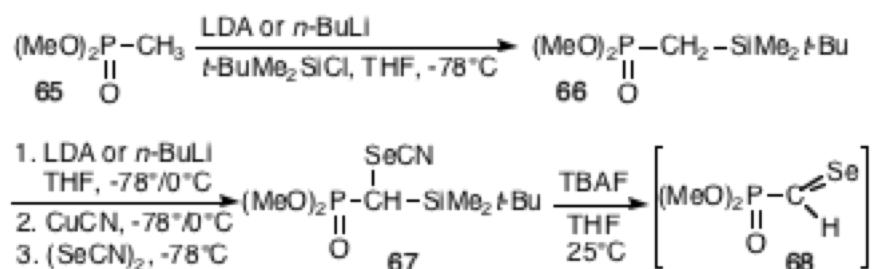
An interesting case of autodesilylation has been observed with the diethyl 1-(methylthio)-1-(trimethylsilyl)methylphosphonate **62** which appears as a useful precursor of symmetrical or unsymmetrical diethyl *bis*(alkylthio)methylphosphonates **64** (Scheme 24). The lithiated derivative of **62**, owing to its high stability within a wide range of temperature, reacts smoothly with dimethyl or diethyl disulfide to give the *bis*(alkylthio)methylphosphonates **64** in 62-75 % (R = Me) and 65 % (R = Et) yields. At low temperature, the 1,1-*bis*(alkylthio)-1-(trimethylsilyl)methylphosphonates intermediate **63** suffer facile desilylation by the lithium alkanethiolates generated in the reaction medium to provide the diethyl *bis*(alkylthio)methylphosphonates **64**.⁴⁰



Scheme 24.

In search for acceptor-substituted selenals, the dimethyl (*tert*-butyldimethylsilyl)methylphosphonate **66** has been elaborated as precursor. It was prepared in 85-95 % yield by carbanionic route from dimethyl methylphosphonate **65** and *tert*-

butyldimethylchlorosilane. To attenuate the reactivity of the lithium derivative of **66**, lower order cyanocuprate were prepared by treatment with copper (I) cyanide in THF. Addition of this cyanocuprate to selenocyanogen, (SeCN)₂, at low temperature resulted in efficient and rapid generation of dimethyl 1-selenocyano-1-(*tert*-butyldimethylsilyl)methylphosphonate **67** in 73 % yield. Dimethyl selenaliphosphonate **68** was subsequently generated by desilylation of **67** on treatment with TBAF in THF at room temperature and reacted *in situ* with suitable [4+2] cycloaddition trapping reagents (Scheme 25).⁷⁴⁻⁷⁷



Scheme 25.

4 Conclusion

(Trimethylsilyl)methylphosphonates constitute a valuable new class of reagents for the preparation of functionalized phosphonates in high yield and pure form. The temporary connection of the trimethylsilyl group provides a clean method for permitting specific monometallation reactions and thus avoiding formation of secondary products. The methodology for the synthesis of 1-(trimethylsilyl)methylphosphonates from simple alkylphosphonates by C-Si bond forming reactions represents currently the most general and versatile approach. Moreover, it can be easily adapted to suit the phosphonate skeleton. Other methodologies are worthy of mention and the particularly attractive vinylphosphonate route merits development. Continued investigations in this area will uncover new reactions to provide still more versatility.

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