# Dialkyl 1-Alkynylphosphonates: a Range of Promising Reagents

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This review covers the preparations of 1-alkynylphosphonates by Michaelis–Arbuzov and Michaelis–Becker reactions, by nucleophilic substitutions at phosphorus ($SNP^V$), and by elimination from 1-alkenylphosphonates. The reactivity and versatility of 1-alkynylphosphonates have made them valuable precursors for other phosphonates, and particularly for the synthesis of heterocycles by [2+2], [3+2], and [4+2] cycloaddition reactions.

## I. Introduction

Diethyl 1-propynylphosphonate, the first 1-alkynylphosphonate, was described in 1957[1] and the syntheses forming the basis of modern alkynylphosphonate chemistry were elaborated in the 1960s. The methodologies developed during this period for the synthesis of 1-alkynylphosphonates used synthetic concepts which were new to phosphorus chemistry, such as "charge affinity inversion" and "positive halogen abstraction". There are four main reaction categories useful for the preparation of 1-alkynylphosphonates: the "apparent" Michaelis−Arbuzov and Michaelis−Becker reactions, the phosphite-allenylphosphonate rearrangement, carbanionic displacements at pentavalent phosphorus centers [$S_NP(V)$],[2] and conversions of vinyl- to alkynylphosphonates by addition-elimination reactions. The first three synthetic procedures rely on the preparation of a terminal alkyne, bearing either a proton or a halide, prior to formation of the C−P bond. The fourth procedure offers a complementary and more versatile, multi-step approach invol-

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**MICROREVIEWS:** This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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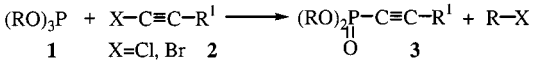
ving the elaboration of suitably substituted vinylphosphonates prior to unmasking the triple bond. In this review, particular emphasis will be placed upon the synthetic methods and chemistry peculiar to 1-alkynylphosphonates.

## II. General Methods of Synthesis

### A. Nucleophilic Displacement Reactions by Phosphorus Nucleophiles

#### 1. Michaelis−Arbuzov Reaction

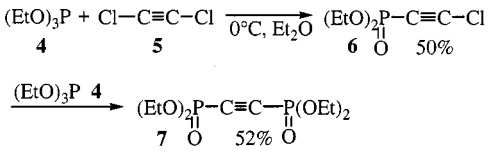
In 1962 it was reported that α-bromoalkynes **2** (X = Br), with a triple bond conjugated to a benzene ring or other multiple bond, react surprisingly easily with trialkyl phosphites **1**. A subsequent Michaelis−Arbuzov-type rearrangement gives dialkyl 1-alkynylphosphonates **3** in fair to good yields (48−67%) (Scheme 1).[3]



Scheme 1

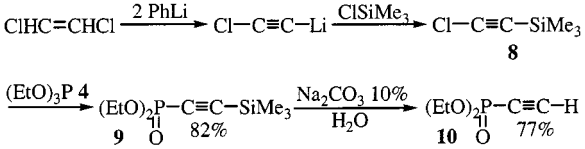
Chloro-, bromo- and iodoalkylacetylenes not conjugated to an unsaturated system do not react. However, the presence of electronegative atoms or groups increases the reactivity of the haloacetylene functionality, so that substituted haloacetylenes **2** (X = Cl or Br) undergo an "apparent" Michaelis−Arbuzov reaction with trialkyl phosphites **1** when $R^1$ is an electron-withdrawing or accommodating group [$R^1$ = Ph,[4] $C_6F_5$,[5] R−C≡C,[6] $CH_2$=CH,[7] Cl,[4,8,9] Br,[9,10] $(EtO)_2P(O)$,[8,11,12] SR,[13,14] $SiMe_3$,[15,16] $SnEt_3$[17,18]].

The Michaelis−Arbuzov rearrangement of dichloroacetylene **5** proceeds under surprisingly mild conditions, even in the cold in ethereal solution, to give mainly the monosubstitution product. For example, the reaction of triethyl phosphite **4** (1 equiv.) with a large excess of dichloroacetylene **5** (5 equiv.) furnishes diethyl 2-chloroethynylphosphonate (**6**) in 50% yield (Scheme 2). A better yield (90%) has been reported if the reaction is carried out at −20 °C.[19] However, the chlorine atom in the product phosphonate **6**, which is rather labile because of the polarization induced by the highly electron-withdrawing phosphoryl group, can undergo a further Michaelis−Arbuzov rearrangement with formation of tetraethyl acetylenediphosphonate **7** in 52% yield.[4]



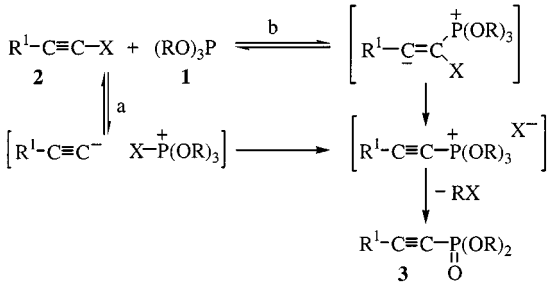
Scheme 2

Dialkyl ethynylphosphonates are the simplest of these compounds, but not the easiest to prepare. Whilst several approaches have been described, no convenient high-yield synthesis appeared until the introduction of the trimethylsilyl functionality as a protecting group for the acetylenic CH linkage. The synthesis of diethyl ethynylphosphonate **(10)**, then, involves an "apparent" Michaelis−Arbuzov reaction between chloroethynyltrimethylsilane **(8)** and triethyl phosphite **(4)**, heating at reflux for 5 h. The trimethylsilyl group is sufficiently electron-accommodating to promote the reaction. The resulting diethyl trimethylsilylethynylphosphonate **(9)**, obtained in high yields (70−82%), may readily be desilylated by 10% aqueous sodium carbonate to give the required diethyl ethynylphosphonate **(10)** in overall yields of up to 77% (Scheme 3).[15]



Scheme 3

In view of the supposed inertness of halo-unsaturated substrates in the Michaelis−Arbuzov reaction, it is remarkable that arylalkynyl halides are more reactive than comparable alkyl, aryl, or vinyl halides towards trialkyl phosphites **1**. The success of the Michaelis−Arbuzov reaction in the synthesis of dialkyl 1-alkynylphosphonates **3** from haloalkynes **2** has provoked a number of mechanistic studies. Three sites have been investigated as the zone of the initial nucleophilic attack by trialkyl phosphites **1**: the halogen, the α-carbon, and the β-carbon. Studies to date suggest that the reaction proceeds by at least two different mechanisms, and that the most important of these probably involves positive halogen abstraction (path a), as outlined in Scheme 4.[20−24]



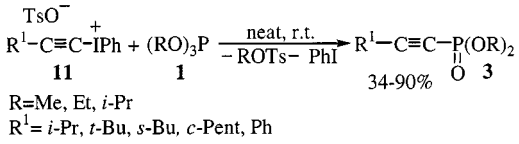
Scheme 4

The second mechanism operating may well be the addition/elimination mechanism (path b), also outlined in Scheme 4. The negative charge developing at the β-carbon in the intermediate is consistent with the requirement for electron-withdrawing or accommodating $R^1$ groups. The first mechanism also satisfies this requirement.

The treatment of propargyl bromide with trialkyl phosphites **1** has been reported to give complex reaction mixtures. From the reaction between triethyl phosphite **(4)** and propargyl bromide at 90 °C, for example, only the diethyl 1-propynylphosphonate **(18)** (R = Et) was isolated, and then only in low yields (15%).[25,26]

Early transformation of trialkyl phosphites **1** and haloalkynes **2** ($R^1C{\equiv}CX$) into dialkyl 1-alkynylphosphonates **3**

was limited to haloalkynes in which $R^1$ was an electron-withdrawing group.[23,27] In 1990, two innovations of merit were reported.[28,29] The first featured alkynylphenyliodonium salts[28] as alkynylating agents, while the second featured $NiCl_2$ as a catalyst.[29] Alkynylphenyliodonium tosylates **11** react with trialkyl phosphites **1** in a formal Michaelis−Arbuzov reaction to give dialkyl 1-alkynylphosphonates **3** (Scheme 5). It seems plausible that the first step in this reaction is a Michael addition of the trimethyl phosphite **1** (R = Me) to the electron-deficient β-carbon to form an ylide, which undergoes loss of iodobenzene and formation of vinylidene. The rearrangement of this carbene affords the alkyne phosphonium salt, which is transformed into **3** and ROTs as in the second step of the Michaelis−Arbuzov reaction.[30] For example, when an excess of neat trimethyl phosphite **(1)** (R = Me) was added to solid (tert-butylethynyl)phenyliodonium tosylate **11** ($R^1$ = *t*Bu) at room temperature, the iodonium salt rapidly disappeared to give 90% yields of dimethyl *tert*-butylethynylphosphonate **3** (R = Me, $R^1$ = *t*Bu) after workup.

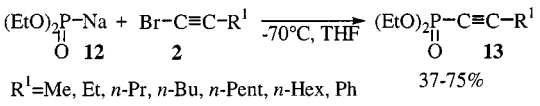



Scheme 5

The reactions of **11** ($R^1$ = *s*Bu, *i*Pr, *c*-Pent, Ph and *p*-Tol) with trimethyl and higher phosphites have been investigated. Dimethyl 1-alkynylphosphonates **3** (R = Me) may be isolated in yields ranging from 34 to 90%. It is clear that the alkynylphenyliodonium ion cleavage induced by trimethyl phosphite is remarkably selective in favor of the alkynyl group. It seems plausible that the alkynylphosphonate formation is initiated by Michael addition of the trimethyl phosphite to the triple bond of **11**, followed by vinylidene formation, rearrangement, and Michaelis−Arbuzov collapse. This preparation of dialkyl 1-alkynylphosphonates **3** from alkynylphenyliodonium tosylates **11** is a useful complement to the traditional Michaelis−Arbuzov synthesis.[28] At the same time, it was reported that 1-*tert*-butyl-2-chloroacetylene reacts with trialkyl phosphites **1** between 110 and 160 °C in the presence of a catalytic amount of anhydrous $NiCl_2$ to give the corresponding alkynyl esters in good yields: 73% for the ethyl ester and 75% for the isopropyl ester.[29]

## 2. Michaelis−Becker Reaction

The first attempt to prepare 1-alkynylphosphonates **3** by a Michaelis−Becker reaction was reported in 1965.[31] However, only 1-octyne was produced when 1-bromo-1-octyne was allowed to react with sodium diethyl phosphite **(12)** in liquid ammonia, with diethyl phosphoramidate as co-product. It seems likely that reduction of the bromo compound occurs by a halogen/metal exchange, with the resulting diethyl bromophosphate immediately being converted into diethyl phosphoramidate by the liquid ammonia.[31] The difficulties associated with this approach — namely the conversion of the bromoalkynes into sodium acetylides and their subsequent reaction with the bromophosphate by-products — may be eliminated by working at low temperature. Thus, sodium diethyl phosphite **(12)** reacts with 1-bromoalkynes **2** in THF at low temperature to give the diethyl 1-alkynylphosphonates **13** in fair to good yields (37−75%) (Scheme 6).[32−34] Usually, yields are improved by lowering the temperature further and by adding the bromoalkyne slowly.[32,34] However, such precautions are not always necessary and fair yields (20−63%) have been observed in the synthesis of a number of heterocycle-containing ethynylphosphonic esters, even in benzene at 80 °C, upon reaction of the corresponding bromoacetylenic alcohols.[35] Likewise, the reaction between diethyl phosphite and 4-chloro-2-methyl-3-butyn-2-ol in dry $Et_2O$ at room temperature in the presence of a catalytic amount of CuCl and diethylamine reportedly gives good yields (60−72%) of dialkyl 3-hydroxy-3-methyl-1-butynylphosphonate.[36] Treatment of alkynyl iodides with copper(I) dimethyl phosphite in a THF suspension subjected to ultrasonic irradiation, forming dimethyl phenylethynylphosphonate in 68% yield, has recently been described.[37] Nevertheless, the Michaelis−Becker route does not always proceed cleanly and the dialkyl 1-alkynylphosphonates **3** frequently contain undesired side products, which are not easily removed. Given the difficulties associated with the use of bromoalkynes **2**, it is unsurprising that this reaction is used infrequently and that the general synthetic utility of the procedure remains to be proven. Haloalkynes are triphilic and the approach of anionic and neutral nucleophiles at the haloalkyne has been discussed and appraised in terms of the three sites.[24]



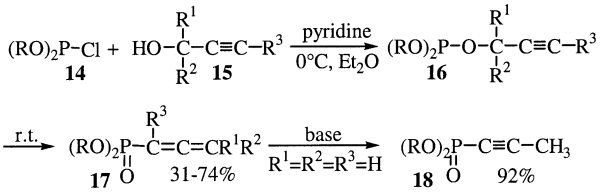

Scheme 6

Propargyl bromide reacts with sodium diethyl phosphite **12** to give diethyl 1-propynylphosphonate **(18)** (R = Et). Unfortunately, irrespective of the reaction conditions (sodium in either refluxing THF[38] or liquid ammonia,[31] potassium carbonate in benzene at 70 °C,[39] or potassium fluoride at 60 °C without solvent[40]), complex mixtures containing diethyl 1-propynylphosphonate **(18)** (R = Et), diethyl 2-propynylphosphonate, and diethyl allenylphosphonate **17** (R = Et, $R^1$ = $R^2$ = $R^3$ = H) are obtained.

## 3. Rearrangement and Isomerization Reactions

In 1962, three laboratories, one in the Soviet Union[41] and two in the United States,[42,43] independently reported the rearrangement of dialkyl 2-alkynylphosphites **16** to dialkyl allenylphosphonates **17**. Propargyl phosphites **16**, readily obtained from propargyl alcohols **15** and dialkyl chlorophosphites **14** in $Et_2O$ at 0 °C in the presence of $Et_3N$ or pyridine, rearrange slowly upon standing at room temperature to give excellent overall yields of readily isolable dial-

kyl allenylphosphonates **17** (Scheme 7). In ethereal solution at room temperature, the rearrangement stops at the stage of the allenylphosphonate **17**. The particular ease with which the acetylenic-allenic rearrangement takes place is evidently due to a combination of the nucleophilic properties of the trivalent phosphorus atom and the rather electrophilic character of the triple bond. This rearrangement has been widely explored because the allenylphosphonates are particularly well suited for elaboration into enaminophosphonates by addition reactions at the allenic carbon atom.



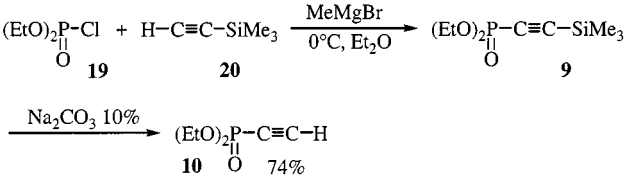
Scheme 7

The prototropic isomerization of the allenylphosphonate **17** into the 1-propynylphosphonate **18** proceeds partially or completely under the influence of the organic base generally present in the reaction mixture in catalytic amounts.[44] When pure dialkyl allenylphosphonates **17** were heated to 200 °C, they remained unchanged (apart from partial polymerization). In the presence of basic catalysts − sodium ethoxide,[45] NaOH[46] and sodium hydride[47] at room temperature, or triethylamine[48−50] and triethylphosphite[48] at high temperature − they more or less readily undergo prototropic isomerization into dialkyl 1-propynylphosphonates **18**. Thus, diethyl propadienylphosphonate **17** (R = Et, $R^1 = R^2 = R^3 = H$) was straightforwardly and almost completely isomerized into diethyl 1-propynylphosphonate **18** (R = Et) in excellent yield (92.5%). This method has enabled a variety of dialkyl 1-propynylphosphonates **18** bearing different R groups at the phosphorus atom to be prepared. The rearrangement of γ-substituted propargyl phosphites is accompanied by inversion of the unsaturated groups, but rearrangement stops at the allenic isomers ($R^3 \neq H$) because of the lack of a labile hydrogen atom at the carbon bound to the phosphoryl group. Similarly, dialkyl γ,γ-dimethylallenylphosphonate **17** ($R^1$, $R^2 \neq H$), which is thermodynamically more stable than the acetylenic isomer, does not undergo prototropic transformation in the presence of base. Not even heating dialkyl γ,γ-dimethylallenylphosphonates in the presence of sodium ethoxide or triethylamine causes prototropic transformation, but instead, according to a kinetic study, induces an intramolecular dimerization of the product. Two variants of this rearrangement have been reported. The first uses triethyl phosphite **4** instead of diethyl chlorophosphite **14** (R = Et).[51] Thus, in the presence of a catalytic amount of para-toluenesulfonic acid, triethyl phosphite **4** reacts with propargyl alcohol in DMF at room temperature to give a mixture of diethyl allenylphosphonate **17** (R = Et, $R^1 = R^2 = R^3 = H$) (51%) and 1-propynylphosphonate **18** (R = Et) (14%). The second variant[52] is based on the conversion of the allenylphosphonates **17** ($R^1$, $R^2 \neq H$, $R^3 = H$) into 1-alkynylphosphonates **18** by a photochemically allowed [1,3s]-sigmatropic shift (in benzene, with 46−50% yields).

## B. Reactions at Electrophilic Phosphorus

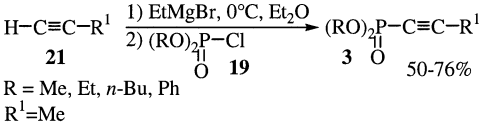
### 1. Alkynylmagnesiums

In the past, interest in the preparation of dialkyl 1-alkynylphosphonates **3** centered upon studies of nucleophilic addition to carbon−carbon triple bonds activated by phosphoryl groups. The parent ethynylphosphonate was prepared in 1960 by the reverse addition of stoichiometric quantities of ethynylmagnesium bromide to the appropriate dialkyl chlorophosphates in THF.[53] The product was obtained in very low yield (12 to 25%), presumably because of side reactions involving the relatively acidic alkynyl proton. The yields can be increased slightly (25 to 35%) by the use of (toxic) dialkyl fluorophosphates.[54] Despite advances in the development of methodology for the elaboration of 1-alkynylphosphonates, the preparation of the parent ethynylphosphonates remained difficult for a long period. Eventually, diethyl ethynylphosphonate **10** became easily accessible through reaction of a protected synthetic equivalent, trimethylsilylethyne **20**, with methylmagnesium bromide in $Et_2O$, followed by addition to a solution of diethyl chlorophosphate **19** [$S_NP(V)$ reaction].[55] The resulting diethyl trimethylsilylethynylphosphonate **9** was deprotected by hydrolysis with 10% $Na_2CO_3$ to give the parent diethyl ethynylphosphonate **10** in a good overall yield of 74% (Scheme 8).



Scheme 8

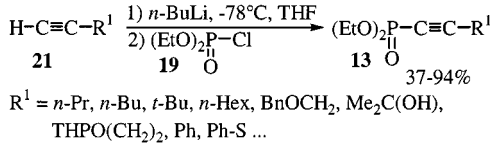
The extension of this principle to higher homologues of acetylene gave better results. These compounds were readily obtained from dialkyl or diphenyl chlorophosphates and the appropriate terminal alkynylmagnesium bromide, which was in turn prepared from the alkyne **21** and ethylmagnesium bromide in $Et_2O$ or THF (Scheme 9).[56] The most widely employed phosphorus reagent is diethyl chlorophosphate **19** (R = Et), which is reacted with the alkynylmagnesium bromide through direct[33,34,57] or inverse[56] addition at 0 °C in $Et_2O$ or at −30 °C in THF. This procedure has successfully been employed for the preparation of a variety of dialkyl 1-alkynylphosphonates **3** in fair to good yields (51 to 76%), with the best results generally obtained by addition of the alkyne salt to the chlorophosphate.



Scheme 9

**2. Alkynyllithiums**

Since lithium reagents are generally more reactive carbanion equivalents than their Grignard counterparts, it might be expected that they would be able to condense more cleanly with chlorophosphates. Furthermore, the facile and quantitative generation of alkynyllithiums under low temperature conditions makes the use of lithium reagents a useful and especially attractive methodology, well developed for both simple and functionalized alkynes, for the generation of dialkyl 1-alkynylphosphonates **3**. Alkynes **21** were metalated with *n*BuLi in THF solution at low temperature, and the resultant lithium acetylides treated with diethyl chlorophosphate **19** at the same temperature. This procedure minimizes side reactions and provides high and reproducible yields of diethyl 1-alkynylphosphonates **13** (Scheme 10).[58−66] The synthesis of diethyl ethynylphosphonate **10** has recently been described, with lithium bis(diisopropylamino)boracetylide serving as the synthetic equivalent for lithium acetylide. After reaction with diethyl chlorophosphate **19** in THF at −78 °C, the protected diethyl ethynylphosphonate was hydrolyzed with a 3 M aqueous HCl solution to produce **10** in a good overall yield of 72%,[67] comparable with those obtained previously.[15,55] The synthesis of **10** in an overall yield of 68% by means of a three-step synthesis has also been reported. This includes the reaction of lithium trimethylsilylacetylide with diethyl chlorophosphite **14** (R = Et) (83%), followed by oxidation with *meta*-chloroperbenzoic acid, and deprotection with KF in EtOH (82%).[68]



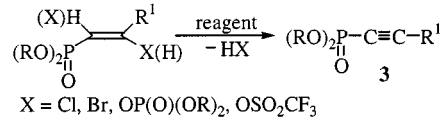

Scheme 10

The advantages of lithium acetylides over haloalkynes (Michaelis−Arbuzov or Michaelis−Becker routes) have been clearly demonstrated in several comparable syntheses. In 1976, the preparation of diethyl 3,3-diethoxy-1-propynylphosphonate by condensation of 3,3-diethoxy-1-lithio-1-propyne with diethyl chlorophosphate **19** at −65 °C was described.[58] The product was easily purified and obtained in 70−80% yield. In contrast, the reaction of 1-bromo-3,3-diethoxy-1-propyne with potassium or sodium diethyl phosphite **12** (Michaelis−Becker reaction) gave only 30−40% yields of product, from which impurities could not easily be removed by distillation. A comparison of the reaction sequences between magnesium and lithium acetylides, with respect to diethyl chlorophosphate **19**, has also been performed under the same experimental conditions. It reveals that, in all cases, the use of lithium acetylides in place of their Grignard counterparts results in significantly higher yields.[34]

Dialkyl 1-alkynylphosphonates **3** can also be synthesized by reaction of lithium tetraorganoaluminates with dialkyl chlorophosphates. However, the reaction of these lithium tetraorganoaluminates, prepared from $LiAlH_4$ and the corresponding substituted alkynes in a pyridine medium, are often sluggish, requiring high temperatures (105 °C) and lengthy reaction times (5 h). However, they do produce dialkyl 1-alkynylphosphonates **3** in good yields (60 to 80%).[69]

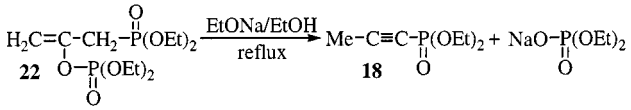
**C. β-Elimination Reactions**

Since heteroatom-substituted vinylphosphonates such as enol phosphates and vinyl halides are masked acetylenic compounds, a variety of methods have been developed for their elaboration and subsequent use in the synthesis of 1-alkynylphosphonates **3**. These β-eliminations usually have the leaving group β to the phosphoryl group, although cases where the leaving group is α to the phosphorus center are also known (Scheme 11).




Scheme 11

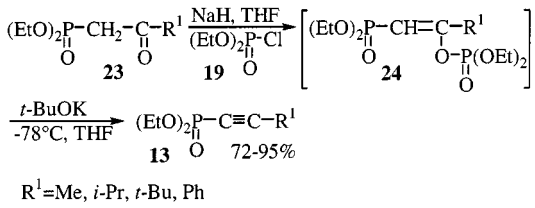
The preparation of 1-alkynylphosphonates **3** by an appropriate β-elimination procedure was first recorded in 1957, when it was reported that the action of sodium ethoxide on diethyl 3-diethylphosphonoisoprenyl phosphate **22** in refluxing EtOH led to diethyl 1-propynylphosphonate **18** (R = Et) in 69% yield (Scheme 12).[1,70] The experimental conditions are crucial, and it has been shown that successful elimination of phosphate takes place to the exclusion of the ethanolysis reaction only at elevated temperature. At room temperature, the enol phosphate **22** was reported to undergo competing ethanolysis to triethyl phosphate and diethyl 2-oxopropylphosphonate. Given the drastic reaction conditions required for the subsequent conversion into 1-alkynylphosphonates, this method was rarely used and remained underdeveloped for a significant period of time. Fortunately, many efforts have been made to find bases which might effect elimination of the phosphate from the enol without also bringing about isomerization or hydrolysis. The development of a variety of milder alternative methods has led to much more widespread adoption of this elimination sequence.[71]




Scheme 12

Recently, the conversion of diethyl 2-oxoalkylphosphonates **23** into 1-alkynylphosphonates **13** via transient enol phosphates **24** has been shown to occur in good yields. Thus, treatment of diethyl 2-oxoalkylphosphonates **23** with NaH in THF followed by addition of diethyl chlorophosphate **19** gave the enol phosphate **24**. The β-elimination reaction from the enol phosphate was carried out at low temperature using *t*BuOK. The reaction proceeds satisfactorily in 72 to 95% overall yield with 2-oxoalkylphosphonates (Scheme 13).[72] In the case of long chain substituents (**24**, $R^1$ = Et), the product underwent a prototropic isomeriz-

ation to give a mixture of diethyl 1-butynylphosphonate **13** ($R^1$ = Et) and diethyl 2-butynylphosphonate.

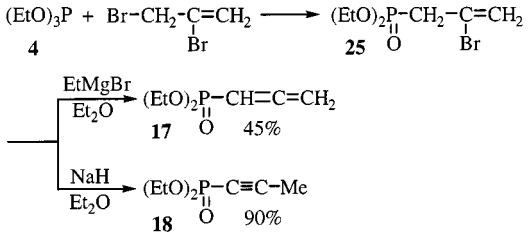


Scheme 13

This approach has been adapted to the preparation of dialkyl fluoroethynylphosphonate in 65−80% yields, by trifluoromethanesulfonylation of the dialkyl trifluoro-2-hydroxypropenylphosphonate, using trifluoromethanesulfonic anhydride in the presence of diisopropylethylamine (3 equiv.).[73]

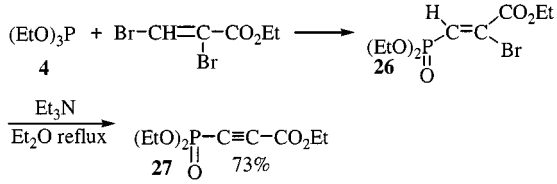
Procedures for the conversion of enol phosphates into the corresponding alkynes involve strongly basic conditions, but several milder methods have been reported in the related case of vinyl halides, which are ideal precursors for triple bond generation by means of a β-elimination reaction. Two complementary approaches have been developed for the synthesis of 1-alkynylphosphonates **3**. One uses simple dehydrochlorination of 2-chlorovinylphosphonates, and the other uses dehydrochlorination with subsequent double bond isomerization of 2-haloallylphosphonates. For example, dialkyl 2-chlorovinylphosphonates undergo a β-elimination on heating with an equimolar amount of KOH in absolute EtOH, to give the corresponding 1-alkynylphosphonates **3** in 73−85% yields.[74,75] Similarly, by the judicious selection of base, 2-haloallylphosphonates, obtained from 2,3-dihalo-1-propenes and trialkyl phosphites **1** by a Michaelis−Arbuzov reaction, may be converted into allenylphosphonates **17** or 1-propynylphosphonates **18**. Thus, treatment of diethyl 2-bromopropenylphosphonate **25** with ethylmagnesium bromide in $Et_2O$ at room temperature produces the diethyl allenylphosphonate **17** (R = Et, $R^1$ = $R^2$ = $R^3$ = H) in 45% yield, while treatment with the more basic NaH under the same conditions gives the diethyl 1-propynylphosphonate **18** (R = Et) in 90% yield (Scheme 14).[47b] Similarly, treatment of diisopropyl 2-chloroallylphosphonate with 10% aqueous methanolic sodium carbonate at room temperature induced facile dehydrochlorination with subsequent double bond isomerization to afford diisopropyl 1-propynylphosphonate **18** (R = *i*Pr) in essentially quantitative yields.[76] In the case of 2-chlorovinylphosphonic dichlorides, the conversion into 1-alkynylphosphonic dichlorides is effected by triethylamine in refluxing benzene.[77]

Another procedure for the synthesis of dialkyl 1-propynylphosphonate **18** is based either upon a simple dehydrochlorination of dialkyl 1-chloro-*cis*-propenylphosphonate or upon a double dehydrochlorination-detosylation of dialkyl 1-chloro-2-mesityloxypropylphosphonates. The reaction conditions for the elimination, which involves alkali metal hydroxides or amides in MeOH at room temperature, are relatively mild.[78]



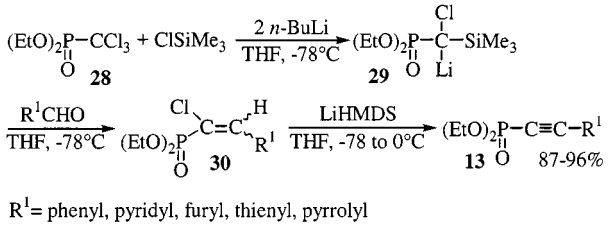
Scheme 14

An even gentler method for the dehydrochlorination of the diethyl 2-bromopropenoate **26** to the (diethoxyphosphoryl)propynoate **27**, employs triethylamine in refluxing $Et_2O$[79] or DBU in $Et_2O$ at low temperature.[80] The results are better with the former reagent (Scheme 15).



Scheme 15

Diethyl (trichloromethyl)phosphonate (**28**) appears to be a very useful reagent for the generation of a triple bond from an α-chlorovinylphosphonate **30**. The lithiated β-hydroxyphosphonates, which are obtained by the addition of the diethyl 1-lithiochloro(trimethylsilyl)methylphosphonate **29** to aromatic or heteroaromatic aldehydes, undergo a Peterson reaction to give α-chlorovinylphosphonates **32** as a mixture of *Z* and *E* isomers. These readily undergo dehydrochlorination at low temperature with LiHMDS or LDA, to produce high overall yields (89−96%) of a wide range of novel diethyl 1-alkynylphosphonates **13**, bearing an aromatic or heteroaromatic ring in the β position (Scheme 16).[81]

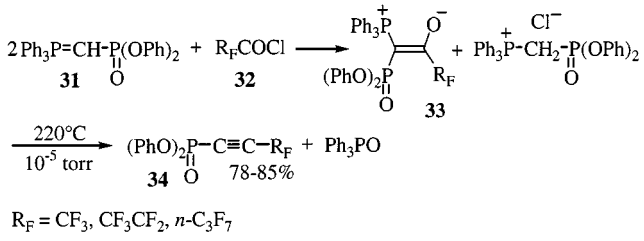


$R^1$= phenyl, pyridyl, furyl, thienyl, pyrrolyl

Scheme 16

An intramolecular Wittig reaction has successfully been applied to the synthesis of 1-alkynylphosphonates **34** by pyrolysis of perfluoroacyl diphenoxyphosphorylmethylenetriphenylphosphoranes **33**. These are prepared by means of a transylidation reaction between the phosphonium salt of **33** and the ylide **31**. In general, this phosphonium salt is obtained by action of the perfluoroacetyl chloride **32** (in excess) on the ylide **31** at 50 °C in benzene. Pyrolysis of the resulting β-ketoylides **33** under nitrogen at reduced pressure (220 °C/$10^{-5}$ Torr) then produces the diphenyl perfluoroal-

kynylphosphonates **34** in good yield (78−85%) (Scheme 17).[82]



Scheme 17

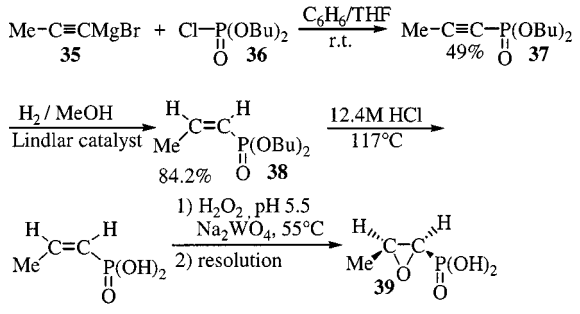
The thermal *syn*-elimination of selenoxide from α-phosphorylvinyl selenoxides in refluxing benzene solution, giving 1-alkynylphosphonates, has also been reported. However, the thermolysis reaction, which eliminates by-products containing selenium, only takes place with the *E* isomers of α-phosphorylvinyl selenoxides.[83]

## III. Chemistry

### A. Reactions of the Triple Bond

#### 1. Reduction

Partial reduction of the triple bond has been used for the selective conversion of 1-alkynylphosphonates into *cis*-1-alkenylphosphonates. The first racemic synthesis of the antibiotic fosfomycin **39** in 1969 serves as an illustration. The methodology is based on the stereospecific reduction of dibutyl 1-propynylphosphonate **37** into dibutyl *(Z)*-1-propenylphosphonate (**38**), using the Lindlar catalyst (Pd/$CaCO_3$ poisoned with lead acetate) in MeOH.[66,84] Dibutyl 1-propynylphosphonate **37** is obtained in reasonable yield (49%) by reaction of propynylmagnesium bromide (**35**) with dibutyl chlorophosphate **36** in a $C_6H_6$/THF solution (section B. 1) (Scheme 18).[84,85]

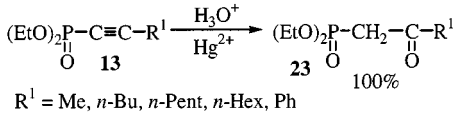


Scheme 18

Unfortunately, the subsequent step using the Lindlar catalyst met with little success and nonstereoselective partial reduction of the triple bond is observed.[86] It was reported that, using 5% Pd/$CaCO_3$ poisoned with quinoline in EtOH, most catalytic hydrogenations of 1-alkynylphosphonates **3** give mixtures composed of *cis*- and *trans*-1-alkenylphosphonate and starting material, from which the predominant *cis* isomer is isolated.[86,87] On the basis of these results, a systematic analysis was undertaken of the relative formation of these three products from the reduction of tetraethyl acetylenediphosphonate **7,** using a range of catalysts (Pd/$CaCO_3$, Lindlar, Pd/$BaSO_4$/Pb, Pd/$BaSO_4$, Pd/$BaCO_3$, Pd/$SrCO_3$).[88] It appeared that quinoline-poisoned Pd/$BaSO_4$ was superior to the other catalysts for the selective reduction of the alkyne to the desired *cis*-alkenediphosphonate. Hydrogenation of di-*n*-butyl-3-hydroxy-1-propynylphosphonate using Pd/$BaSO_4$ and quinoline in MeOH affords the desired *cis*-olefin in 95% yield.[89] Similarly, diethyl 4-methanesulfonyl-1-butenylphosphonate can be partially hydrogenated in 63% yield using Pd/$BaSO_4$ in THF/pyridine.[90]

#### 2. Hydration

The effectiveness of 1-alkynylphosphonates **3** as acetonyl equivalents for the preparation of 2-oxoalkylphosphonates has long been established. Since 2-oxoalkylphosphonates themselves are versatile synthetic intermediates, especially as the reagents of choice for promoting a number of Horner−Wadsworth−Emmons cyclization reactions, procedures that effect the direct conversion of dialkyl 1-alkynylphosphonates **3** into 2-oxoalkylphosphonates are of special importance. The procedure for the hydration of 1-alkynylphosphonates **3** has remained unchanged since the first report in 1966 (Scheme 19).[32] Thus, treatment of diethyl 1-alkynylphosphonates **13** with aqueous $H_2SO_4$ in MeOH in the presence of $HgSO_4$ gives, after reflux for 15 h[32] or at room temperature for 48 h,[60,91] a quantitative yield of pure diethyl 2-oxoalkylphosphonates **23**. In all cases studied, the acetylenic phosphonates are transformed without formation of the isomeric ketophosphonates. When the phosphorus substrate contains an acid-sensitive group, the hydration reaction can be performed in good yield at room temperature in aqueous THF in the presence of $HgCl_2$ (1 equiv.) and pyridine (1.5 equiv.).[92]



Scheme 19

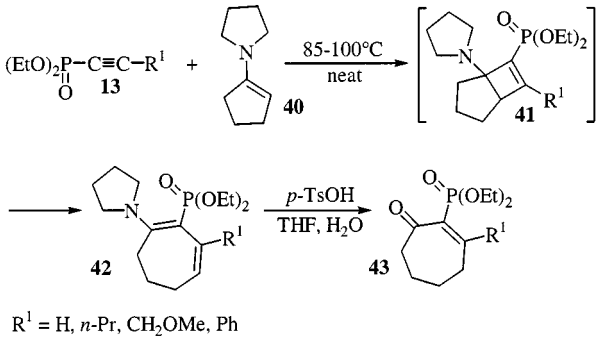
Sensitive enyne phosphonates have been converted into γ,δ-ethylene-β-ketophosphonates in reasonable yields (25−70%) by treatment with a mixture of HgO/$ClCH_2CO_2H/BF_3{\cdot}Et_2O$/ROH in refluxing EtOH.[93]

#### 3. Cycloaddition Reactions

##### a. [2+2] Cycloadditions

The cycloaddition of enamines **40** with activated alkynes, such as dimethyl acetylenedicarboxylate, is reported to occur at room temperature. In contrast, the less reactive diethyl 1-alkynylphosphonates **13** require reaction temperatures of at least 85 °C to undergo cycloaddition. Under such conditions, spontaneous ring opening of the thermally unstable cyclobutene intermediate **41** affords the ring-enlarged product **42**. Acid hydrolysis of the product enamine gives the unsaturated β-ketophosphonate **43** (Scheme 20).[63] The best results for the cycloaddition are

obtained with rigorous exclusion of moisture and with temperatures below 100 °C. Reaction times vary from 24 h ($R^1$ = H) to eight days ($R^1$ = $CH_2OMe$).[63]

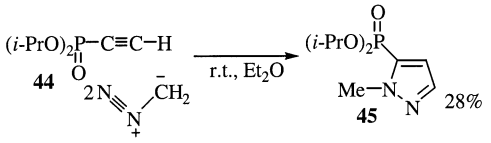



Scheme 20

The reaction must be carefully controlled in order to optimize the yield. Cycloadditions with substituted diethyl 1-alkynylphosphonates **13** are less satisfactory; for example, $R^1$ = H, yield = 77% and $R^1$ = Ph, yield = 17% (for n = 1).

**b. [3+2] Cycloadditions**

Cycloadditions of diazo and azido compounds with acetylenes constitute a well-established method for the synthesis of pyrazoles and triazoles. Addition of diazomethane to ethynylphosphonates provides a convenient method for synthesizing phosphonopyrazoles.[54,94] Thus, diisopropyl ethynylphosphonate **44** reacts smoothly with an excess of diazomethane to give the 1-methyl-5-phosphonopyrazole **45** in 28% yield, with the diazomethane acting as an *N*-methylation reagent for the initially formed phosphonopyrazole (Scheme 21).[54] The tetramethyl acetylenediphosphonate **54** reacts spontaneously with diazomethane in cooled $Et_2O$ to give the 4,5-diphosphonopyrazole **46** in 95% yield (Figure 1).[11]




Scheme 21

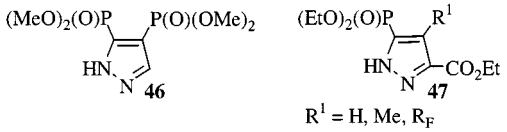



Figure 1. 5-Phosphonopyrazoles obtained from [3+2] cycloadditions

Cycloadditions of ethyl diazoacetate with 1-alkynylphosphonates **3** have also been studied.[84–86] The data indicate that the cycloaddition of ethyl diazoacetate with diethyl ethynylphosphonates **10**, diethyl 1-propynylphosphonates **18** (R = Et), and diethyl perfluoroalkynylphosphonates **34**, in which the imino group participates in a strong intermolecular hydrogen bond, gives tautomeric pyrazolylphosphonates **47** in 58–92% yields, as mixtures of regioisomers. Because of its instability, the intermediate 3*H*-pyrazole is rapidly isomerized to the 1*H*-pyrazole. The electron-accepting ethoxycarbonyl group, by conferring acidic character on the $C_3$–H bond, facilitates this aromatization to give the 1*H*-pyrazole **47**. A study of the influence of the phosphorus substituent (Cl, EtO, *i*PrO, *n*BuO, Et, Ph) upon the cycloaddition reaction has appeared. Ethyl diazoacetate reacts most easily with 1-alkynylphosphonates bearing dichloro substituents at phosphorus, while more severe conditions are required with diethyl substituents.[95]

Other 1,3-dipoles such as *C*-aryl-*N*-phenylnitrones,[98] *para*-substituted phenylazides,[99,100] azidoalkylcarboxylates[97,101] and azidoalkylphosphonates,[102] *C*-substituted-*N*-arylnitrilimines,[103] *para*-substituted benzonitrile oxide,[57,97] and *N*-phenylsydnone[104] react with diethyl 1-alkynylphosphonates **13**. They give, respectively, 5-isoxazolinephosphonates **48** in 42–72% yield,[98] 1-aryl-4-triazolylphosphonates **49**,[95–97] 1-carboxyalkyl-[97,101] and 1-phosphonoalkyl-4-triazolylphosphonates,[102] 4- or 5-pyrazolylphosphonates **50** and **51**,[103] 4-isoxazolinephosphonate in 80–92% yields,[57,97] and 3-pyrazolylphosphonates in 53% yield[104] (Figure 2). The reactivity of phosphorylated propynes and the chemo- and regioselectivity of these reactions is controlled both by donor-acceptor interactions between the reactants and the steric requirements of their substituents.

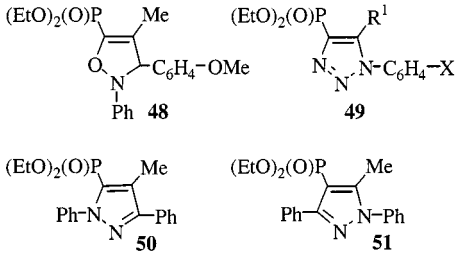



Figure 2. Selected 5-membered ring heterocycles obtained from [3+2] cycloadditions

**c. [4+2] Cycloadditions**

The facile Diels–Alder reaction of dialkyl 1-alkynylphosphonates **3** means that organophosphorus-substituted acetylenes are potentially useful precursors for introducing organophosphorus substituents into diverse organic structures. This chemistry has been developed mainly with dienophiles such as ethynyl,[61] haloethynyl,[10,11] formylethynyl,[86] sulfonylethynyl,[61] sulfoxylethynyl,[61] and phenylethynyl[105] derivatives of phosphonates and acetylenebisphosphonates.[11,19] Only one activating group on the alkyne is necessary for the cycloaddition to occur, and the monophosphorylated acetylene reacts as readily as the diphosphorylated one. Dienes such as isoprene,[86] 2,3-dimethyl-1,3-butadiene,[10] cyclopentadiene,[11] 1,3-cyclohexadiene,[10] anthracene,[61] 9-methylanthracene,[61] 1-phe-

nyl-3,4-dimethylphosphole,[105] and α-pyrone[19] have been employed (Figure 3).

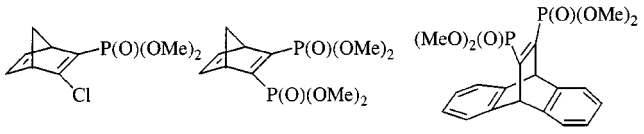
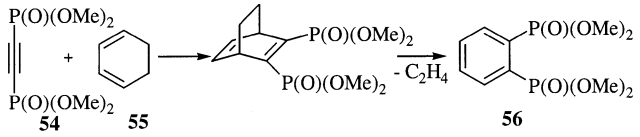



Figure 3. Selected adducts obtained from [4+2] cycloadditions

The reactions may be conducted with or, more rarely, without a solvent. Benzene, toluene, or xylene at reflux are generally preferred and yields are usually good to excellent (65−93%). The strong points of this synthetic procedure are clearly illustrated by the preparation of *ortho*-phenylenediphosphonate **54** in 93% yield (Scheme 22)[11] from the reaction of **52** with 1,3-cyclohexadiene **53** at 150 °C. For 9-methylanthracene, the reaction is highly selective and the cycloadduct contains only one isomer.[61] The Diels−Alder reaction has been investigated in particular detail for sulfonylethynyl- and sulfoxylethynylphosphonates.[61]

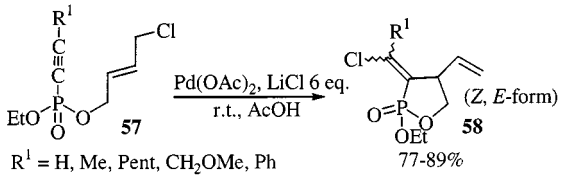



Scheme 22

**d. Intramolecular Ene Reaction**

Depending upon the site of unsaturation, two different examples of intramolecular ene-type reactions of enynes have been described. The first involves an intramolecular ene reaction of 1,6-enynes whose triple and double bonds comprise part of the same phosphorus substituent. Catalytic amounts of $Pd(OAc)_2$ in the presence of $PPh_3$ were used for the cyclization. In toluene, slight heating (60 °C) for four hours allows complete reaction at a reasonable rate. Comparative tests showed that $Pd(OAc)_2$ and $PPh_3$ give the best results of all the ligands employed. The yield of isolated methylcyclopentylidenephosphonate was 68%, from a gram-scale reaction.[62]

In the second reaction type, the ene and yne functionalities form part of two different phosphorus substituents (Scheme 23). The 1-alkynylphosphonate **55** undergoes a facile $Pd(OAc)_2$/LiCl-catalyzed cyclization to give the oxaphospholanes **56** in good (77−89%) yield but with low stereoselectivity (Z to *E* ratios at the *exo* double bonds are approximately 60:40).[106]




Scheme 23

The best solvent appears to be AcOH, and the reaction does not proceed particularly well in MeCN, $C_6H_6$, EtOH, THF or $MeNO_2$. The mechanism may involve *cis*- and *trans*-halopalladation of the triple bond, followed by insertion of the double bond into the C−Pd bond, followed by dehalopalladation to regenerate the catalyst.[106]

**4. Addition Reactions**

Three types of compounds predominate within this category; these are dialkyl ethynylphosphonates, dialkyl 1-alkynylphosphonates, and dialkyl 2-chloroethynylphosphonates. Treatment of diethyl ethynylphosphonates **10** with chlorine in $CCl_4$ [9] or bromine in $Et_2O$[54] leads to the formation of isomeric (E)- and *(Z)*-1,2-dihalovinylphosphonates in good yields. By selecting the correct conditions, either one or two molecules of EtOH may, in the presence of NaOEt, be added across the triple bond to give the 2-ethoxyvinylphosphonates and 2,2-diethoxyethylphosphonates, respectively.[54] The related addition of EtSH gives 2-ethylthiovinylphosphonates, but the product is most conveniently obtained as a mixture of both isomers by adding the ethynyl compound to an excess of the thiol containing dissolved sodium.[54]

Recently, an efficient stereoselective hydrohalogenation reaction of dialkyl ethynylphosphonates, affording the *(Z)*-halovinylphosphonates, has been reported.[107] Thus, heating diethyl ethynylphosphonate **10** with LiI in AcOH at 70 °C for 14 h affords diethyl 2-iodovinylphosphonate as the sole product in 85% yield. The corresponding bromo and chloro analogues were also prepared with high regiostereoselectivity, although in lower yields: 50% for the bromo and 30% for the chloro derivatives.[107] A Michael addition to the triple bond has also been utilized to prepare alkenylphosphonic acid analogues of nucleosides. Thus, the conjugate addition of heterocyclic bases (adenine, uracil, cytosine, thymine) to diethyl ethynylphosphonate **10** has been investigated in depth. Using *t*BuOK as base, 18-crown-6 as catalyst, and MeCN or DMF as solvents, the alkylation of heterocyclic bases leads to two isomers (*Z* and *E*) in moderate yields (32−41%) with the *Z* isomer predominant. The yields are improved to 70−80% by using $K_2CO_3$ as base in DMF at room temperature.[16,108]

A relatively general procedure has been developed for the conversion of diethyl 1-alkynylphosphonates **13** into diethyl 2-oxoalkylphosphonates **23**, using enaminophosphonates. When 1-alkynylphosphonates **13** were heated under reflux with a ten mol excess of primary or secondary amine, enaminophosphonates were produced in fair to good yields.[109] The addition to the triple bond was complete in 20 h for $Et_2NH$[110] and in 3−5 days for *n*$BuNH_2$.[109] Subsequent hydrolysis of the resulting enaminophosphonates with oxalic acid in a two-phase system at room temperature afforded the diethyl 2-oxoalkylphosphonates **23** in excellent yields (76−94%).[109] Dialkyl 1-alkynylphosphonates **3** are capable of adding other nucleophilic reagents, in particular diethyl phosphite[111] and ethyl mercaptan,[112] forming products of the addition of one or two molecules of the reagent at the triple bond.[111] For example, 1-*tert*-butylacetylenephosphonate is subject to nucleophilic attack by the sodium diethyl phosphite **12** (in THF at room temperature for 24 h) to give a triphosphonate in good yield.[29] A decrease in the activity of sodium diethyl phosphite **12** was

observed in ethanolic solutions. The triple bond is attacked by the sodium diethyl phosphite **12** at the β-position with respect to the bulky group, rather than β to the phosphoryl group, steric hindrance predominating over the electronic directing influence of the phosphoryl group. The addition of mercaptans proceeds more readily and, in the presence of excess mercaptans, addition results in the formation only of 2,2-dithioalkoxypropanes.[112] In contrast, heating equimolar amounts of dialkyl 1-propynylphosphonates **3** with alcohols in the presence of sodium alkoxide at 60−70 °C leads to only one addition product: 2-alkoxypropene.[112] In the reaction of benzenesulfenyl chloride with diethyl 1-propynylphosphonate **18** (R = Et), the two regioisomeric adducts with an *E* configuration of the phenylthio group and the chlorine atom about the double bond are obtained.[113] Alkyl or aryl chalcogenate (S, Se, Te) anions add to diethyl 1-alkynylphosphonates **13** to give diethyl 2-chalcogenylvinylphosphonates in satisfactory yields (26−70%). The reaction is stereoselective, giving the *Z* stereoisomer either predominantly or exclusively.[114] Diethyl 1-alkynylphosphonates **13** react readily with an excess of alkyl- or arylmagnesium halides in the presence of CuCl at −30 °C in $Et_2O$ to provide high yields (75−95%) of β-alkylated or arylated diethyl 1-alkenylphosphonates. The addition is highly stereoselective, producing the *cis* addition product almost exclusively. Stoichiometric lithium dialkyl- or diarylcuprates can also react with **13** in $Et_2O$ at low temperature to produce 1-alkenylphosphonates with high regio- and stereoselectivity. The intermediate alkenylcuprates are particularly suited for providing trisubstituted diethyl 1-alkenylphosphonates by reaction with a wide range of electrophiles.[87]

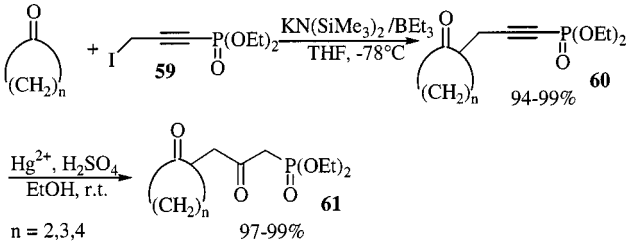
The phosphorus-containing ynamines have been prepared through the reaction of diethyl 2-chloroethynylphosphonates **6** with dialkylamines.[115] Some of these compounds were also prepared by heating **6** with trimethylamine (100% excess) in a sealed tube at 150−160 °C.[116] Formation of ynaminophosphonates by electrochemical synthesis has also been reported.[117] The ynaminophosphonates readily undergo reactions characteristic of ynamines: hydration by water with the formation of acetamides, and addition of alcohol with the formation of the corresponding vinyl ethers.[115] The use of *tert*-butylamine in the reaction with **6** also induces the replacement of halogen, but the reaction is accompanied by isomerization, giving almost quantitative yields of stable ketenimines.[118,119] The presence of two hydrogen atoms at the nitrogen in the amines permits subsequent prototropic isomerization, with the formation of ketenimines. In contrast, reactions with primary phosphanes lead to halogen-substituted products with the retention of the C≡C and P−H bonds.[119] The reaction of ketenimines with water in the presence of catalytic amounts of HCl proceeds smoothly and leads to a high yield of the corresponding amide.[120] Reactions of 2-chloroethynylphosphonates **6** have also been studied with a number of charged ($EtO^-$, $tBuO^-$, $PhO^-$)[121] and neutral[122] nucleophiles containing one or two nucleophilic centers. Treatment of diethyl 2-chloroethynylphosphonate **6** with binucleophilic reagents such as *ortho*-phenylenediamine, *ortho*-aminophenol, and 2-aminoethanol leads to phosphorylated benzimidazoles, benzoxazoles and 4,5-dihydroxazoles, by a mechanism involving initial substitution of the halogen followed by addition of the second nucleophilic center at the same carbon atom.[122]

### B. Isomerization of 1-Alkynylphosphonates

Because of the ready accessibility of 1-alkynylphosphonates **13**, their isomerization to conjugated dienes represents a useful synthetic transformation. In the presence of $[Pd_2(dba)_3CHCl_3]$, the thermal isomerization of diethyl 1-alkynylphosphonates **13** ($R^1$ = Me, Et, *n*Pr, *n*Bu) into diethyl (1*E*,3*E*)-1,3-alkadienylphosphonates occurs at 30 °C in toluene, whereas at 110 °C isomeric (2*E*,3*E*)-2,3-alkadienylphosphonates are formed. The transformation is effected with good yields (79−92%), but requires lengthy reaction times (24−69 h).[123] The same isomerization reaction has been effected with $PBu_3$.[124]

### C. Reactions of 3-Halopropynylphosphonates

3-Halopropynylphosphonates have been used as phosphonate-containing acetonyl equivalents. 3-Hydroxypropynylphosphonate intermediates, readily obtained from the reaction of lithiated derivatives of protected propargyl alcohol with chlorophosphate (section B. 2), were converted into mesylates, and then either into iodides **57** by displacement with sodium iodide,[60] or bromides by use of $Ph_3P/CBr_4$ in $CH_2Cl_2$.[125] Subsequent treatment of the diethyl 3-iodopropynylphosphonate **57** with ketone enolates (formed using KHMDS/triethylborane in THF) gives the corresponding alkylation products **58**, which were then hydrolyzed to the expected β-ketophosphonates **59** (Scheme 24).[60] This reaction has been successfully extended to the preparation of diketophosphonates,[92] and also amino derivatives of phosphonopentynoic acid.[125]




Scheme 24

Metalation of diethyl 1-propynylphosphonate **18** (R = Et) has been achieved by treatment with alkaline amides (Li, Na, K) and calcium in liquid ammonia, and with isopropylmagnesium chloride in $Et_2O$. Metal exchange from the potassium derivative of diethyl 1-propynylphosphonate **18** (R = Et) has been performed with copper(I)- and cobalt(II) chlorides. Alkylation of the potassium derivative with alkyl halides, and hydroxyalkylation with benzaldehyde, both occur in low yields at the γ-position of the parent compound.[126]

### D. Reactions at Phosphorus

Bromo- and iodotrimethylsilane reagents compatible with alkyne and other functionalities are suitable for the mild P−O dealkylation of symmetrical 1-alkynylphosphonates **3** to give the corresponding phosphonic acids.[127−129] The greater reactivity of iodotrimethylsilane will probably prove advantageous for the low-temperature dealkylation of phosphonates possessing triple bonds. Transesterification of diethyl 2-propynylphosphonate with iodotrimethylsilane, followed by solvolysis with MeOH, leads quantitatively to the 1-propynylphosphonic acid.[128]

Two procedures for the transformation of diesters of 1-alkynylphosphonates **3** into monoesters have been described. They involve the selective replacement of one ethoxy group by chlorine, without addition to the triple bond. Treatment of diethyl 1-propynylphosphonate **18** (R = Et) with neat $POCl_3$ (1.2 equiv.) at 60 °C for 3 h gives the ethyl 1-propynylphosphonochloridate **60** in 79% yield.[130] Similarly, treatment of **18** (R = Et) with trichloro(*ortho*-phenylenedioxy)phosphorane for 24 h gives **60** in 74% yield.[131] Transformation into phosphonic dichlorides **61** was achieved by the reaction of **18** (R = Et) with $PCl_5$, heating at 110−135 °C for one hour (Figure 4).

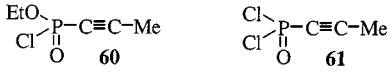



Figure 4. Products obtained from **18** by reaction with $POCl_3$ (**60**) and $PCl_5$ (**61**)

## IV. Conclusion

Methodologies for the preparation of 1-alkynylphosphonates constitute a valuable class of synthetic reactions. Regardless of the nature of the alkyne, the elimination route seems to be the most flexible and promising. It would be of interest to apply these approaches to the development of a general procedure, giving access to 1-alkynylphosphonates containing alkyl or aryl groups irrespectively. 1-Alkynylphosphonates possess remarkable potential and, in addition to the useful transformations involving simple reduction and hydration of the triple bond, cycloaddition reactions appear to offer some very attractive synthetic procedures. The use of 1-alkynylphosphonates might profitably be more widely developed in [2+2] and [4+2] reactions and employed in [2+2+2] enynes reactions for the preparation of new phosphorus reagents and new phosphorus-containing heterocycles.

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