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Synthesis of α-functionalized phosphonates from α-hydroxyphosphonates

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This paper is dedicated to my mentor, Professor H. Firouzabadi on the occasion of his honorable retirement

Contents

1. Introduction

Considering the enormous significance of organophosphorus compounds in nature, it is surprising that naturally occurring phosphonates, which contain a C–P bond have only been known since 1959 when (aminoethyl)phosphonic acid was isolated from sheep rumen.[1] Since then, numerous compounds of this class have been isolated, synthesized, and tested for their biological activity.[2] In particular, phosphonates bearing heteroatomic substituents in the α- and β-position to the phosphorus atom have shown strong activities as antibiotics, anticancer drugs, and enzyme inhibitors.[3] Their activity may be attributed to the relative stability of the C–P bond, compared to that of the P–O bond. They also play an important and useful role in our lives as antiviral agents and inhibitors of gene expression in mammalian cells. They have become important in the treatment of bone disorders and in medical decalcification.[4] In the area of agricultural chemistry, they have been developed as insecticides, herbicides, fungicides, and plant-growth regulators.[5] From their physical properties, phosphonates are used as fire retardants for materials.[6]

From organic and polymer synthesis to biology and biochemistry, phosphonate derivatives have such a wide range of properties and applications that they have stimulated an enormous amount of study for several decades.[7] In this regard, considerable attention has been focused on the synthesis of phosphonates, particularly the α-functionalized analogs.[2c,8] Within α-functionalized phosphonates, α-hydroxyphosphonates, which are easily prepared from commercially available materials, are useful precursors for the preparation of other types of α-functionalized phosphonates. Although a vast number of publications deal with

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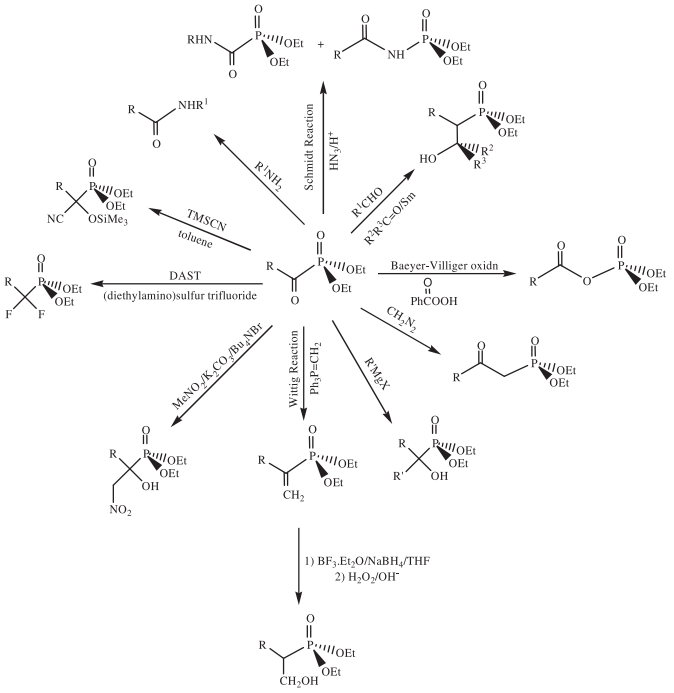
these kinds of transformations, there are no reviews on this subject. The aim of this report is to provide an overview of the strategies employed to prepare different types of α-functionalized phosphonates directly from α-hydroxyphosphonates. We have also compared these methods with the general procedures for the preparation of these important scaffolds.

2. α-Ketophosphonates

α-Ketophosphonates are an important subdivision of organophosphorus compounds. The adjacent phosphorus substituent and carbonyl functional groups in α-ketophosphonates is the main reason that makes them interesting compounds in organic synthesis.[9] For instance, it is possible to convert them into α,α-difluorophosphonates, amides, and β-hydroxyphosphonates and to use them in Wittig, Beyer–Villiger or Schmidt reactions.[10] They react with diazomethane or undergo nucleophilic addition by nitromethane in basic conditions.[11] α-Ketophosphonates can react with alkyl- and aryl- magnesium bromides to give the hydroxyl compounds.[12] α-Ketophosphonates undergo cyanosilylation by trimethylsilyl cyanide to produce the trimethylsilyloxycyanophosphonates[13] (Scheme 1).



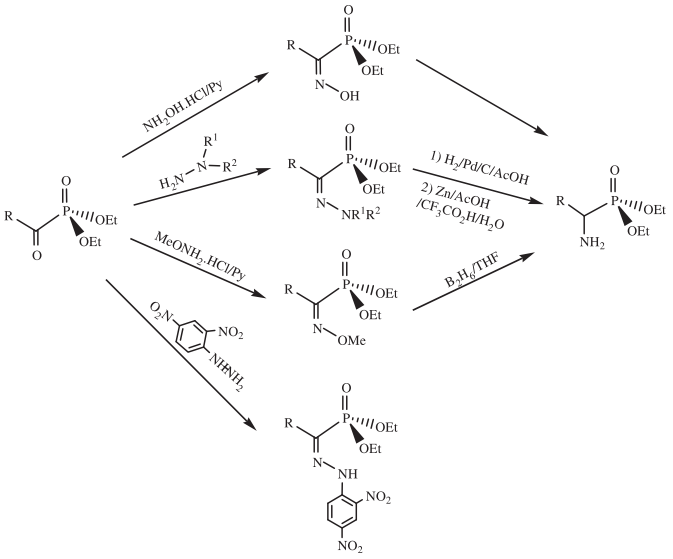
Scheme 1.

α-Ketophosphonates are good precursors for the preparation of α-aminophosphonates by the reduction of their oxime and imine derivatives.[14] Conversion of α-ketophosphonates into their 2,4-dinitrophenylhydrazone derivatives is a good method for their identification (Scheme 2).

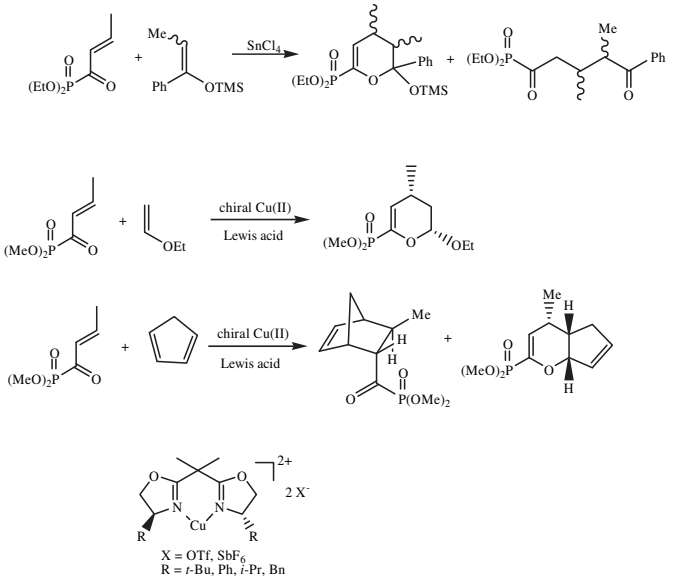
α-Keto-β,γ-unsaturated phosphonates undergo a Mukaiyama–Michael or a Diels–Alder reaction with enol ethers or cyclopentadiene[15] (Scheme 3).

It is also a very well known fact that the carbon–phosphorus bond in α-ketophosphonates is readily cleaved as a result of nucleophilic attack. This property makes α-ketophosphonates potentially useful acylating agents, but also susceptible to hydrolysis and difficult to handle.[16]

The Michaelis–Arbuzov rearrangement, also known as the Arbuzov rearrangement, Arbuzov reaction or Arbuzov

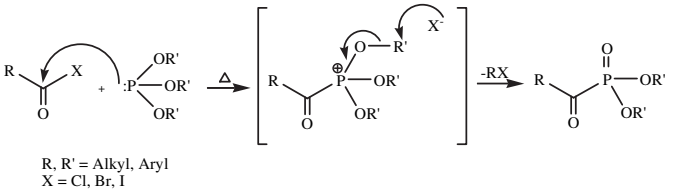


Scheme 2.



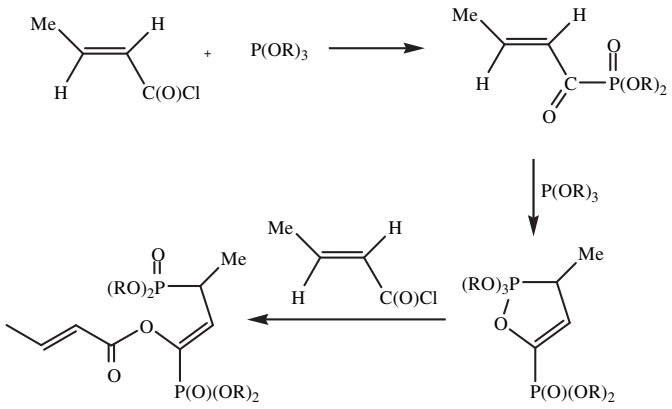
Scheme 3.

transformation, is one of the most versatile pathways for the formation of carbon–phosphorus bonds and involves the reaction of an ester of trivalent phosphorus with acyl halides to produce α-ketophosphonates (Scheme 4).[17]



Scheme 4.

This method works well for the less complex acyl chlorides, but shows less success in the preparation of α-keto-β,γ-unsaturated phosphonates, where multiple addition products are often observed (Scheme 5).[18]



Scheme 5.

Another method, which has been used for the preparation of α-ketophosphonates is the oxidation of α-hydroxyphosphonates.[19] Burke et al. have reported the successful oxidation of di-*tert*-butyl benzylic α-hydroxyphosphonates using 10 equiv of MnO_2 in refluxing toluene.[20] They found that other oxidizing agents including pyridinium chlorochromate[21] (PCC), pyridinium dichromate[22] (PDC), dichloro-dicyanobenzoquinone (DDQ), and Swern oxidation were effective for the oxidative preparation of only di-*tert*-butyl α-ketophosphonates.[20] They observed that methyl and benzyl phosphonate esters could not survive under the above reaction conditions and their corresponding aldehydes were produced by cleavage of the C(O)–P bond.[20] Burke et al., in 1993, has reported that diethyl α-hydroxyphosphonates could also be converted into their corresponding diethyl α-ketophosphonates by Swern oxidation.[10a] On the other hand, Hammond claimed that treatment of diethyl α-hydroxyalkynephosphonates with PDC, PCC, Ag_2O, and Swern oxidation failed to yield the desired diethyl α-ketoalkynephosphonates.[23] Oxidation by other known reagents, such as CrO_2, MnO_2, CrO_3/Al_2O_3, and Pfitzner–Moffatt oxidation conditions requires long reaction times, high molar ratios of oxidant/substrate or special treatments for activating the reagents.[10a,20,24] Due to the sensitivity of C(O)–P bonds in α-ketophosphonates toward acidic hydrolysis, in order to make PCC a successful oxidizing reagent for this important transformation, in 2004, a modification has been carried out on the previously reported procedure for the efficient preparation of diethyl α-ketophosphonates by PCC.[25] In this report, vacuum distillation was successfully applied for the isolation of the diethyl α-ketophosphonate, rather than an acidic work up. Lack of cleavage of the C(O)–P bond in both solvent-free conditions and in solution was an important practical advantage of this method. Although oxidants such as PCC worked efficiently for the conversion of α-hydroxyphosphonates into their corresponding α-ketophosphonates, they suffered from a troublesome work up such as vacuum distillation for the isolation of the α-ketophosphonates from pyridine, which was produced during the reaction. Nicotinium dichromate (NDC), nicotinium chlorochromate (NCC), and isonicotinium dichromate (INDC) are other reported suitable oxidants for the conversion of various types of α-hydroxyphosphonates into their corresponding carbonyl compounds.[26] These reagents, during the progress of the reaction, produce a solid mixture of chromium(III) compound (green) and solid nicotinic or isonicotinic acids, which are isolated by a simple filtration; evaporation of the solvent produced the desired α-ketophosphonates in high yields and purities. $ZnCr_2O_7\cdot 3H_2O$ (ZDC) is another chromium-based oxidant, which has been used for the preparation of α-ketophosphonates from α-hydroxyphosphonates. In the presence of ZDC, various types of α-hydroxybenzylphosphonates were cleanly and immediately converted into their corresponding benzoylphosphonates in excellent yields.[27] In order to avoid the problems of toxicity in using chromium-based oxidants, $KMnO_4$ as an inexpensive and environmentally friendly oxidant was successfully applied for the oxidation of α-hydroxyphosphonates in solution and also under solvent-free conditions.[28]

3. α-Trimethylsilyloxyphosphonates

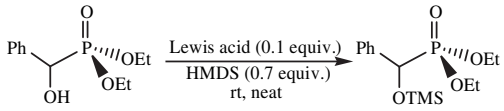
Masked acyl anions have become important synthetic tools in organic synthesis. The practical use of masked acyl anions imposes two general restrictions. First, the anion precursor should be an inexpensive and stable compound and, second, the unmasking of the latent function should be easily and mildly accomplished at the end of the desired synthetic transformation in the same reaction vessel, without prior isolation of an intermediate. The α-acidic hydrogen of α-trimethylsilyloxyphosphonates can be metalated by lithium diisopropylamide (LDA) to afford the relatively stable α-carbanionic species.[29] On the other hand, the C–P and Si–O bonds of α-trimethylsilyloxyphosphonates are readily cleaved under alkaline and acidic conditions.[30] Therefore, α-lithiated α-trimethylsilyloxyphosphonates have become important synthons in organic synthesis as masked acyl anions.[31] They react with various ketones to produce the corresponding α-hydroxy ketones.[32] Unsymmetrical ketones and carboxylic acids can be produced by the reaction of α-lithiated α-trimethylsilyloxyphosphonates with alkylating agents followed by hydrolysis of the C–P and Si–O bonds.[30,33] α-Lithiated α-trimethylsilyloxyphosphonates can also undergo facile acylation with a variety of acylating agents, producing the corresponding α-acylated products. These compounds, in turn, are easily converted into α-hydroxy ketones by cleavage of the Si–O bond and elimination of dialkyl phosphite in alkaline media.[29,31]

The common methods for the preparation of α-trimethylsilyloxyphosphonates include the reaction of aldehydes with diethyl trimethylsilyloxyphosphite or with a mixture of triethyl phosphite and trimethylsilyl chloride.[31,34] The reported procedures need harsh reaction conditions, accompanied by rather long reaction times. The other method used for this purpose is the reaction of a trialkyl phosphite with a silyl phenyl ketone, which requires a long reaction time (12 h) and also proceeds at a high temperature (80 °C).[35]

Direct silylation of α-hydroxyphosphonates is another procedure for the preparation of α-trimethylsilyloxyphosphonates. In one report, hexamethylsilathiane has been used as a silylating agent at 50–70 °C to produce the desired products in moderate yields (55–78%).[36] Recently, a simple procedure for the first general, versatile, and high-yielding synthesis of a variety of α-trimethylsilyloxyphosphonates by direct silylation of α-hydroxyphosphonates with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) has been described. This reaction occurred immediately at room temperature with excellent yields using iodine as the catalyst.[37] $Mg(OTf)_2$, $Al(OTf)_3$, $Cu(OTf)_2$, and $Fe(F_3CCO_2)_3$ are other catalysts, which have been used for the high-yielding preparation of α-trimethylsilyloxyphosphonates by the direct reaction of α-hydroxyphosphonates with HMDS at room temperature in the absence of solvent.[38] The Si–O and C–P bonds usually undergo cleavage and are sensitive toward the reaction conditions. The almost quantitative yields of the products strongly indicate that the Si–O and C–P bonds tolerate these mild reaction conditions, which is an advantage of these methods. Products of high purity were obtained after work up and further purification was not required.[37,38]

The catalytic activity of $Mg(OTf)_2$, $Al(OTf)_3$, and $Cu(OTf)_2$ was compared with that of several metal triflates including LiOTf, $Ce(OTf)_4$, $Hg(OTf)_2$ and some other Lewis acids, such as $ZnCl_2$,[39] $Zn(bipy)_3Cl_2$,[40] $FeCl_3$, $Fe(bipy)Cl_3$,[40] $CuCl_2$, $MgCl_2$, $AlCl_3$, and $ZrOCl_2\cdot 8H_2O$ in the silylation of diethyl α-hydroxybenzylphosphonate as a model compound with HMDS in the absence of solvent at room temperature

(Scheme 6, Table 1). $Mg(OTf)_2$, $Al(OTf)_3$, and $Cu(OTf)_2$ were found to be the most effective catalysts for this purpose and the corresponding silylated product (100%; monitored by TLC and based on ^1H NMR of the reaction mixture) was observed in a short reaction time.



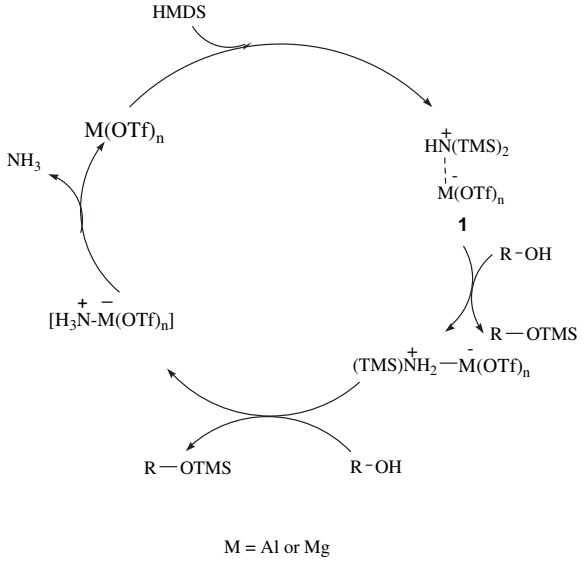
Scheme 6.

Table 1
Silylation of diethyl α-hydroxybenzylphosphonate with HMDS in presence of Lewis acids in neat conditions at room temperature

Entry	Lewis acid[a]	Time (h)	Conversion based on ^1H NMR (%)
1	$Mg(OTf)_2$	[b]	100
2	$Al(OTf)_3$	[b]	100
3	$Cu(OTf)_2$[c]	0.25	100
4	$Ce(OTf)_4$	3	80
5	$Hg(OTf)_2$	10	60
6	LiOTf	1.5	100
7	$ZnCl_2$	1	100
8	$Zn(bipy)_3Cl_2$	24	20
9	$FeCl_3$	1.5	80
10	$Fe(bipy)Cl_3$	1.5	30
11	$ZrOCl_2 \cdot 8H_2O$	1.5	30
12	$AlCl_3$	4.5	80
13	$CuCl_2$	10	20
14	$MgCl_2$	6.5	50

[a] Equivalent ratios of substrate/HMDS/catalyst: 1/0.7/0.1.
[b] Reaction occurred immediately.
[c] Equivalent ratios of substrate/HMDS/catalyst: 1/0.7/0.11.

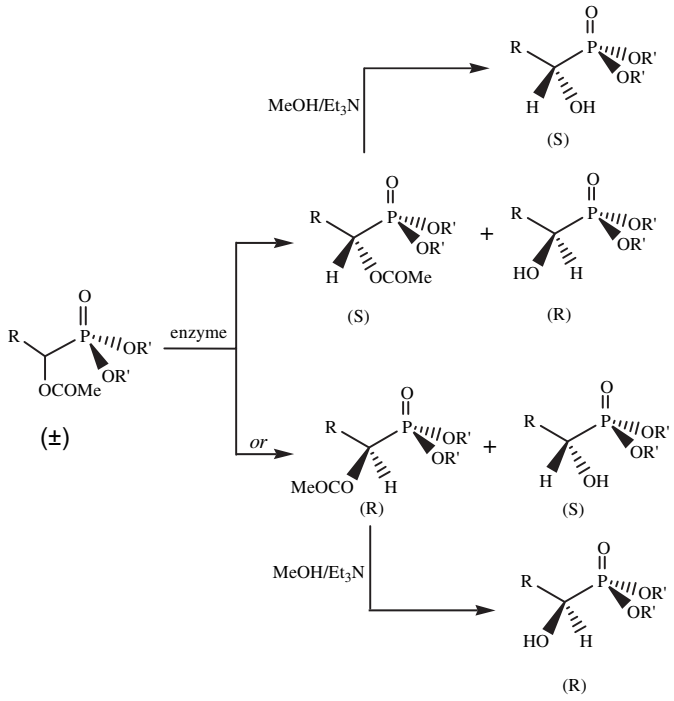
A proposed mechanism was reported for the catalytic role of $Mg(OTf)_2$ and $Al(OTf)_3$ in silylation reactions of α-hydroxyphosphonates with HMDS (Scheme 7). In this mechanism, it is suggested that a Lewis acid–base interaction between the metal triflate and the nitrogen atom of HMDS polarizes the N–Si bond of HMDS to produce a reactive silylating agent (**1**).



Scheme 7.

4. α-Carboxyphosphonates

α-Acetyloxyphosphonates are considered to be important and valuable phosphorus compounds for the synthesis of optically active α-hydroxyphosphonates. Enzymatic systems have been introduced for the enantioselective hydrolysis of racemic α-acetyloxyphosphonates (Scheme 8).[41]



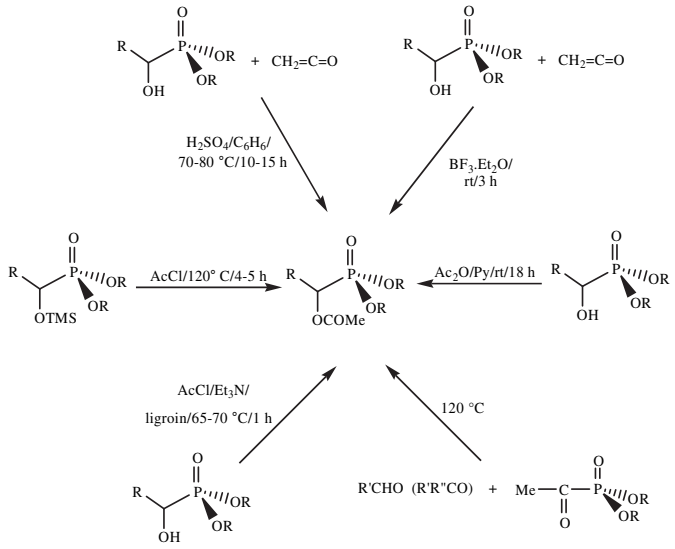
Scheme 8.

Chiral and non-racemic α-hydroxyphosphonates are useful precursors for a variety of α-substituted Phosphonates, especially α-aminophosphonic acids, which have received considerable attention in medicinal, bioorganic and, organic chemistry, owing to their potential activities as analogs of α-amino acids.[3a,42]

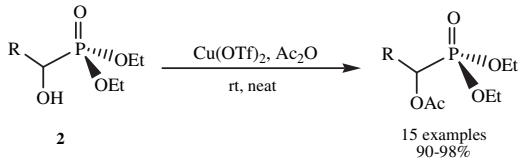
The reactions of aldehydes and ketones with acyl phosphites have been reported for the preparation of α-acetyloxyphosphonates at 120 °C to produce the desired products in low yields (Scheme 9).[43] The other reported procedures for this purpose include the direct acetylation of α-hydroxyphosphonates with ketene catalyzed by $BF_3 \cdot Et_2O$[44] or H_2SO_4 (Scheme 9).[45] These protocols suffer from usually low yields[44] and require rather high temperatures (70–80 °C) and long reaction times (10–15 h).[45] Acetylation of α-hydroxyphosphonates with Ac_2O or AcCl in the presence of Et_3N or pyridine has been conducted at room temperature in 1–18 h with low-to-excellent yields (Scheme 15).[41b,c,46] In the other reported procedure, AcCl has been used for the acetylation of α-trimethylsilyloxyphosphonates at a rather high temperature (120 °C) to produce α-acetyloxyphosphonates in moderate yields (55–70%) (Scheme 9).[36]

Recently, $Cu(OTf)_2$ has been used as a mild Lewis acid for the preparation of a variety of α-acetyloxyphosphonates by the direct acetylation of α-hydroxyphosphonates **2** with Ac_2O.[47] This reaction proceeded at room temperature under solvent-free conditions and produced the desired products in excellent yields and with short reaction times (Scheme 10).

Acetylation of α-hydroxyphosphonates with Ac_2O under solvent-free conditions using microwave irradiation is another procedure for the preparation of a variety of α-acetyloxyphosphonates.[48] A combination of solvent-free conditions and microwave irradiation in this method led to a noticeable reduction in the reaction time and an enhancement of the efficiency of the reactions, which could be considered as an eco-friendly approach (green chemistry).

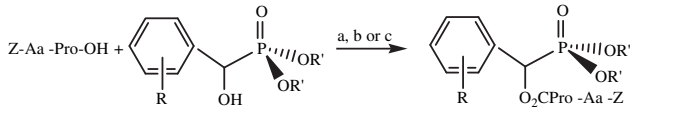


Scheme 9.



Scheme 10.

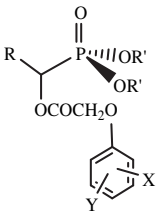
The dipeptidylcarboxyphosphonates (**4**) as carboxyester pseudopeptide analogs were synthesized by a coupling reaction of α-hydroxyphosphonates to substrate-derived dipeptides (**3**) (Scheme 11). The coupling reagents used were: (a) *N*,*N*′-carbonyldiimidazole (CDI) in the presence of allyl bromide or methyl iodide; (b) 1-hydroxybenzotriazole (HOBt) in the presence of dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide (DCC); and (c) 1-hydroxy-7-azabenzotriazole (HOAt) in the presence of DMAP and DCC.[49]



Scheme 11.

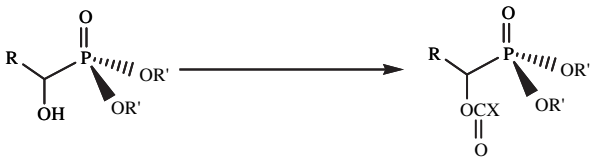
He and co-workers, in 2006, synthesized a series of fluorine-containing phenoxyacetoxyalkylphosphonates by the acetylation of α-hydroxyphosphonates with fluorophenoxyacetyl chloride in the presence of Et_3N (Scheme 12).[50] They investigated the influence of a fluorine moiety on the biological activity of these compounds by screening them for herbicidal activity in a greenhouse. Their studies showed that, by introducing a fluorine moiety into the parent structure of phenoxyacetoxyalkylphosphonates, a series of new compounds with satisfactory herbicidal activity could be synthesized.[50]

A variety of ester derivatives of α-hydroxyphosphonates were also prepared by the He groups and by Russian workers (Scheme 13).[51]



X, Y = F, CF_3; R' = Me, Et; R = Me, CCl_3, Ph, (substituted) Ph

Scheme 12.

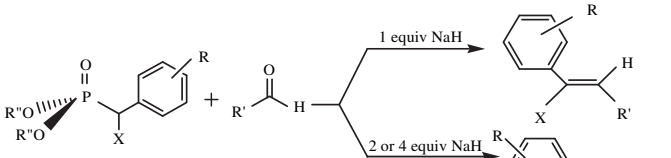


X = R", CH_2Cl, CH_2OR", $NHC(O)NH_2$, NHC(O)R", NHR"
R = H, Me, Et, *n*-Pr, Ph, 2-ClC_6H_4, 4-ClC_6H_4, CCl_3
R' = Me, Et, *n*-Pr, *iso*-Pr
R" = 3-$CF_3C_6H_4$, 2-$O_2NC_6H_4$, 2-MeC_6H_4, Ph, 3,4-$Cl_2C_6H_3$, $PhSO_2$, 4-$MeC_6H_4SO_2$

Scheme 13.

5. α-Halophosphonates

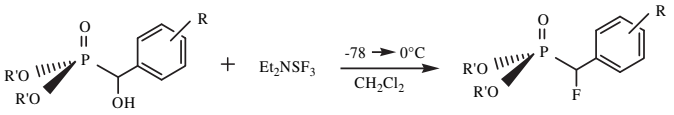
The preparation of biologically active diethyl α-halogenated phosphonates, which are also good precursors for the preparation of heavily substituted olefins via the Horner–Wadsworth–Emmons (HWE) olefination reaction, is an interesting reaction in organic chemistry (Scheme 14).[52] On the other hand, substitution of a hydrogen atom in the α-CH_2 position by fluorine in enzyme substrate phosphonic analogs is widely practiced in various areas of bioorganic and medicinal chemistry with the aim of preparing better mimics of the phosphate parents.[8]



Scheme 14.

A number of approaches for the introduction of a halogen atom at the α-CH_2 position of phosphonates have been reported. However, electrophilic approaches are not highly selective and mixtures of non-halogenated and bis-halogenated phosphonates could result.[53] Therefore, the search for a reaction sequence that may be conveniently executed to produce a large variety of α-monohalogenophosphonates in a pure form has received a large amount of attention from organic chemists. In this regard, a -nucleophilic approach is an especially useful synthetic method for the introduction of one halogen atom at the α-position of phosphonates.

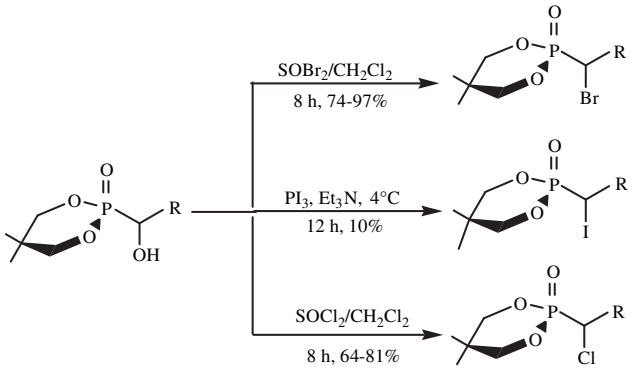
$CHFCl\text{-}CF_2NEt_2$[54] and diethylaminosulfur trifluoride (DAST)[55] are the reported reagents for the preparation of α-fluorophosphonates by replacement of the hydroxyl functional group in α-hydroxyphosphonates. The substitution of the α-hydroxyl group by fluorine generally proceeded smoothly by reaction with a small excess of DAST in CH_2Cl_2 solution at sub-zero temperatures (Scheme 15).



R = H, 4-Me, 3-Cl, 4-Cl, 2,4,6-Me_3
R' = H, Et

Scheme 15.

Allyl bromide/carbonyldiimidazole (CDI) and MeI/CDI have been successfully applied for the preparation of diethyl α-bromo- and α-iodophosphonates, respectively, from diethyl α-hydroxyphosphonates at 150 °C.[56] PPh_3/CBr_4 in refluxing benzene and PPh_3/Br_2/Py in MeCN at room temperature are the reported procedures that have been used for the preparation of diethyl α-bromophosphonates in 42–90% yields.[57] $SOBr_2$ is another reported brominating agent that has been applied for this purpose.[58] In this report, iodination of diethyl α-hydroxyphosphonates has also been tried in the presence of phosphorus triiodide (PI_3).[58] However, attempts to obtain α-iodophosphonates in reasonable yields failed and the desired products were obtained in poor yields (~10%) (Scheme 16).[58] α-Hydroxyphosphonates has been converted into α-chlorophosphonates generally in modest yields using $SOCl_2$/Py,[59] SO_2Cl_2[60] or $POCl_3$.[61] Most of these methods suffer from drawbacks such as low yields, formation of side products, difficulty in separating the product from the reaction mixture or limitations in the type of substrates. $SOCl_2$ is reported to be a useful reagent for the preparation of α-chlorophosphonates in 64–81% yields from their corresponding α-hydroxyphosphonates.[58] Any side-product formation was not detected in these transformations (Scheme 16).



R = Ph, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-MeC_6H_4, 3-MeC_6H_4

Scheme 16.

PPh_3 in refluxing CCl_4 is another reported procedure for the preparation of α-chlorophosphonates in 81–90% yields from the direct chlorination of α-hydroxyphosphonates.[62]

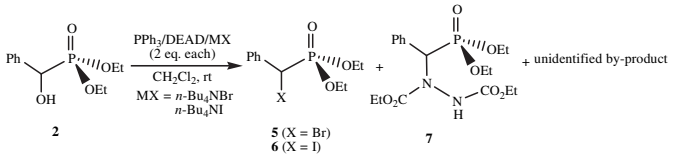
In 2004, the PPh_3/DDQ/*n*-Bu_4NX (X=Br, I) system has been used for the preparation of a variety of diethyl α-bromo- and α-iodophosphonates from the corresponding diethyl α-hydroxyphosphonates in good-to-high yields (Tables 2 and 3).[63] Attempts at chlorination and fluorination of diethyl α-hydroxyphosphonates in the presence of this system with *n*-$Bu_4NCl\cdot H_2O$, *n*-Hex_4NCl, and *n*-$Bu_4NF\cdot 3H_2O$ failed and the starting materials remained intact. In order to show the unique behavior of the PPh_3/DDQ system for the preparation of α-functionalized phosphonates, the bromination, and iodination of **2** with *n*-Bu_4NBr and *n*-Bu_4NI under Mitsunobu reaction conditions (PPh_3/DEAD) were studied (Scheme 17). The results indicate that, under Mitsunobu reaction conditions, besides the formation of the desired products **5** in 41% yield and **6** in 33% yield, two other by-products were also isolated in bromination and iodination. One of the by-products **7** was identified as the alkylated hydrazine derivative and isolated in 5–7% yield for the bromination and iodination reactions (Scheme 17). The presence of a peak as a doublet for the α-CH proton at 5.87 ppm with $^2J_{P,H}$=13.6 Hz in its ^{1}H NMR spectra and two peaks at 3250 and 1730 cm^{-1} for N–H and C(O)OEt in its IR spectra confirmed the formation of **7**. This type of product is quite familiar in Mitsunobu reactions.[64] The other by-product was not identified.

Table 2
Preparation of diethyl α-bromophosphonates from diethyl α-hydroxyphosphonates using PPh_3/DDQ/*n*-Bu_4NBr in CH_2Cl_2 at room temperature

Entry	R	Time (h)	Isolated yield (%)	^{1}H NMR ($CDCl_3$) $\delta_{\alpha CH}$ (ppm)/ $^2J_{P,H}$ (Hz)	^{13}C NMR ($CDCl_3$) $\delta_{\alpha C}$ (ppm)/ $^1J_{P,C}$ (Hz)	Ref.
1	Ph	5	98	4.79/12.5	41.85/159.2	53
2	4-MeC_6H_4	5.5	97	4.85/12.8	41.80/159.1	53
3	4-$MeOC_6H_4$	6	97	4.80/12.7	41.9/162.0	
4	2,4,6-$Me_3C_6H_2$	5.5	90	5.65/14.8	36.19/163.2	
5	2-ClC_6H_4	7	97	5.53/13.8	36.29/161.6	
6	3-ClC_6H_4	9	95	5.36/13.6	36.67/161.5	
7	4-ClC_6H_4	8.5	98	5.86/13.8	40.91/159.5	53
8	2,6-$Cl_2C_6H_3$	6	97	6.1/13.9	38.76/158.0	
9	2-$O_2NC_6H_4$	6.5	95	6.01/14.8	34.06/158.2	
10	3-$O_2NC_6H_4$	7	94	5.98/14.6	38.77/158.0	
11	4-$O_2NC_6H_4$	8.5	96	6.3/14.8	40.12/157.2	52b
12	2-Naphthyl	5	94	5.10/13.9	41.92/159.7	
13	3-Pyridyl	5.5	92	4.91/13.5	38.28/159.5	

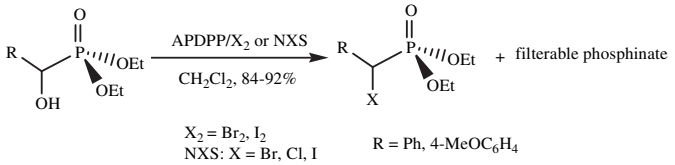
Table 3
Preparation of diethyl α-iodophosphonates from diethyl α-hydroxyphosphonates using PPh_3/DDQ/*n*-Bu_4NI in CH_2Cl_2 at room temperature

Entry	R	Time (h)	Isolated yield (%)	^{1}H NMR ($CDCl_3$) $\delta_{\alpha CH}$ (ppm)/ $^2J_{P,H}$ (Hz)	^{13}C NMR ($CDCl_3$) $\delta_{\alpha C}$ (ppm)/ $^1J_{P,C}$ (Hz)	Ref.
1	Ph	3	84	4.98/13.4	15.41/139.9	53
2	2-ClC_6H_4	5	68	4.63/13.2	9.97/158.2	
3	3-ClC_6H_4	4.5	69	4.92/13.8	9.96/158.5	
4	4-ClC_6H_4	3.5	65	4.87/13.6	14.28/156.3	
5	2-$O_2NC_6H_4$	5	63	6.16/15.0	7.00/155.8	
6	3-$O_2NC_6H_4$	4.5	60	6.05/14.8	13.0/155.1	
7	4-$O_2NC_6H_4$	5.5	61	5.80/13.9	12.98/154.6	52b



Scheme 17.

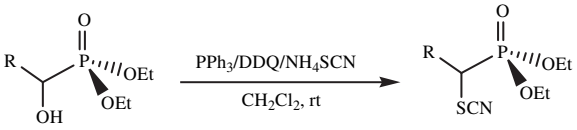
Recently, 4-aminophenyldiphenylphosphinite (APDPP) as a new heterogeneous phosphinite was applied successfully for the conversion of α-hydroxyphosphonates into their corresponding α-halophosphonates in the presence of molecular halogens or *N*-halosuccinimides (Scheme 18).[65] The presence of an acid-scavenging amino group in the structure of APDPP for the conversion of α-hydroxyphosphonates into their corresponding α-halophosphonates eliminates the use of toxic pyridine, as reported in the lit.[66]



Scheme 18.

6. α-Thiocyanatophosphonates

Thiocyanates are considered as important and valuable sulfur-containing compounds for the synthesis of heterocyclic compounds and have traditionally been used as pesticides.[66] A practical and general method for the direct preparation of diethyl α-thiocyanatophosphonates from α-hydroxyphosphonates was not described until 2004 and KSCN was the sole reagent used for the preparation of α-thiocyanatophosphonates from diethyl α-sulfonylated phosphonates.[66c,d] In 2004, PPh_3/DDQ/NH_4SCN was used as an efficient system for the thiocyanation of α-hydroxyphosphonates in CH_2Cl_2 at room temperature (Scheme 19, Table 4).[67] Using this method, different types of diethyl α-hydroxyphosphonates were converted into their corresponding diethyl α-thiocyanatophosphonates in good-to-high yields (Table 4). In the cases such as diethyl α-hydroxy-4-methylbenzyl-, 4-methoxybenzyl-, 2,4,6-trimethylbenzyl-, and 2-naphthyl- phosphonates, the formation of diethyl α-isothiocyanatophosphonates as by-products have also been observed (Table 4, entries 2–4 and 11). Recently, the preparation of α-isothiocyanatophosphonates from α-azidophosphonates using PPh_3/CS_2 has been reported.[68]



Scheme 19.

Table 4
Preparation of diethyl α-thiocyanatophosphonates from diethyl α-hydroxyphosphonates in presence of Ph_3P/DDQ/NH_4SCN in CH_2Cl_2 at room temperature

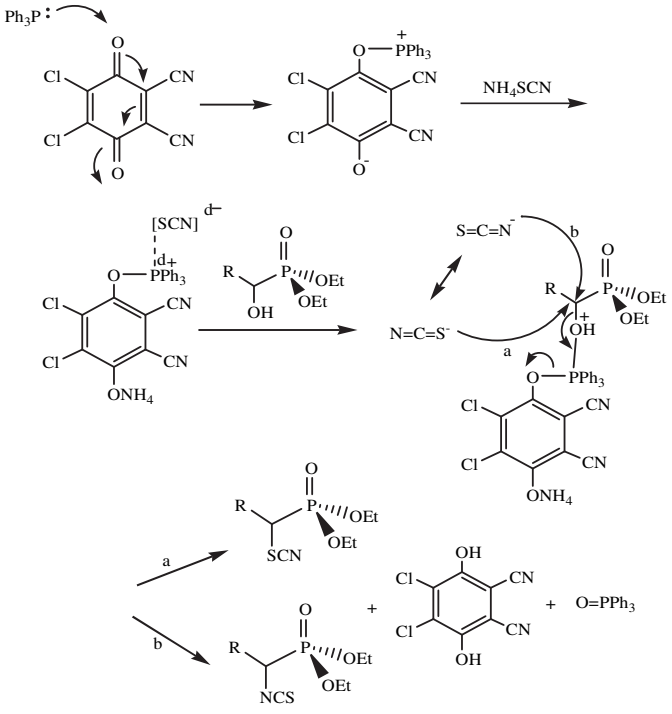
Entry	R	Time (h)	Isolated yield (%)	^1H NMR ($CDCl_3$) $\delta_{\alpha CH}$ (ppm)/ $^2J_{P,H}$ (Hz)	IR (neat) ν_{SCN} (cm^{-1})
1	Ph	9	90	4.49/17.8	2156
2	4-MeC_6H_4	7	79	4.47/17.5	2154
3	4-$MeOC_6H_4$	10	77	4.54/17.5	2154
4	2,4,6-$Me_3C_6H_2$	12	60	5.13/23.1	2153
5	2-ClC_6H_4	13	70	4.60/18.3	2156
6	3-ClC_6H_4	15	75	4.48/18.3	2156
7	4-ClC_6H_4	14	80	4.57/18.2	2152
8	2-$O_2NC_6H_4$	17	65	4.65/20.4	2158
9	3-$O_2NC_6H_4$	21	68	4.60/18.9	2158
10	4-$O_2NC_6H_4$	15	78	4.71/19.0	2158
11	2-Naphthyl	10	80	4.76/17.8	2154

The mechanism shown in Scheme 20 was postulated for these transformations.

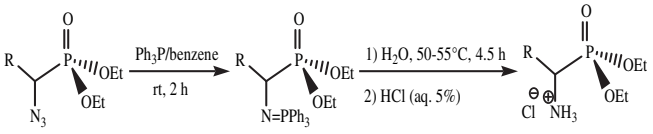
7. α-Azidophosphonates

α-Azidophosphonates are important precursors for the preparation of heterocyclic compounds via 1,3-cycloaddition reactions[69] and also for the preparation of their primary amines.[42a,70] In this respect, α-aminophosphonates, which are phosphorous analogs of the corresponding α-amino acids, are successfully obtained by catalytic hydrogenation of α-azidophosphonates,[42a] or by the Staudinger reaction of the azido compounds with PPh_3 (Scheme 21).[42a,70]

Azidation of diethyl α-chloromethylphosphonates[71] and α-tosylated benzylphosphonates[72] by means of sodium azide in dimethylformamide (DMF) or dimethylsulfoxide (DMSO), respectively, are the reported methods for the preparation of diethyl α-azidophosphonates. Azidation of triethylphosphonoacetate with trifluromethanesulfonyl azide in the presence of Et_3N is the other reported procedure that has been used for this purpose.[73]



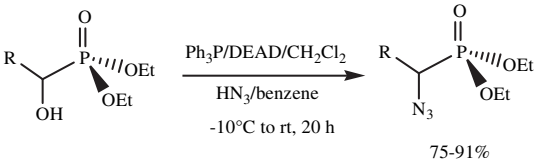
Scheme 20.



R = H, Me, Et, Ph, Bn, $BnOCH_2$, Pr, *iso*-Pr, 4-$MeOC_6H_4$, 4-BrC_6H_4

Scheme 21.

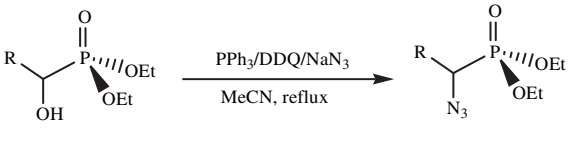
Until 2004, methods for the direct preparation of diethyl α-azidophosphonates from diethyl α-hydroxyphosphonates were limited to Mitsunobu reactions using PPh_3/diethyl azodicarboxylate (DEAD) and HN_3 as a source of azide anion (Scheme 22).[74] Handling of diethyl azodicarboxylate (DEAD) and HN_3 is hazardous and these compounds should be considered as a real problem in this procedure. In addition, this reaction requires long reaction times.



R = H, Me, Et, Pr, *iso*-Pr, $PhCH_2$, Ph

Scheme 22.

In 2004, the PPh_3/DDQ system was used for the azidation reaction of diethyl α-hydroxyphosphonates in the presence of NaN_3 as a nucleophilic source.[69] Using these reaction conditions, replacement of the hydroxyl functional group of a variety of α-hydroxyphosphonates by an azido group progressed well in good-to-high yields (Scheme 23, Table 5).



2

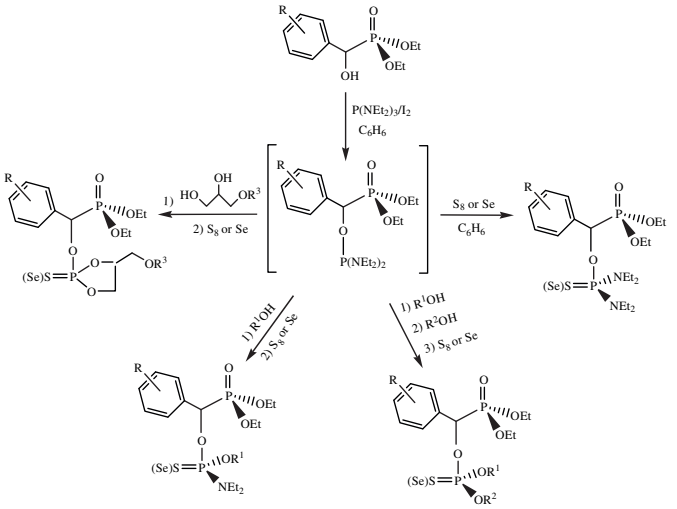
Scheme 23.

Table 5
Preparation of diethyl α-azidophosphonates from diethyl α-hydroxyphosphonates using PPh_3/DDQ/NaN_3 in refluxing MeCN

Entry	R	Time (h)	Isolated yield (%)	IR (neat) ν_{N3} (cm^{-1})	^1H NMR ($CDCl_3$) $\delta_{\alpha CH}$ (ppm)/ $^2J_{P,H}$ (Hz)	^{13}C NMR ($CDCl_3$) $\delta_{\alpha C}$ (ppm)/ $^1J_{P,C}$ (Hz)
1	Ph	3	95	2100	4.74/16.5	61.96/158.2
2	2-ClC_6H_4	6	83	2150	5.29/17.0	56.35/161.1
3	3-ClC_6H_4	7.5	89	2123	5.02/16.4	47.86/162.2
4	4-ClC_6H_4	7	80	2110	4.65/17.0	61.28/158.3
5	2-$O_2NC_6H_4$	8.5	76	2125	4.73/16.4	56.46/157.5
6	3-$O_2NC_6H_4$	7.5	83	2140	4.90/16.4	61.10/156.2
7	4-$O_2NC_6H_4$	5.5	75	2134	4.83/16.7	61.36/155.0

8. α-Phosphate/phosphite-phosphonates

α-Phosphate-phosphonate derivatives have received considerable attention in medicinal and synthetic organic chemistry, due to their potential biological activities, such as herbicidal and antiphytoviral activities against the tobacco mosaic virus (TMV). In addition, some of them exhibit significant fungicidal activities against *R. solani* and *P. piricola* (Scheme 24).[75]



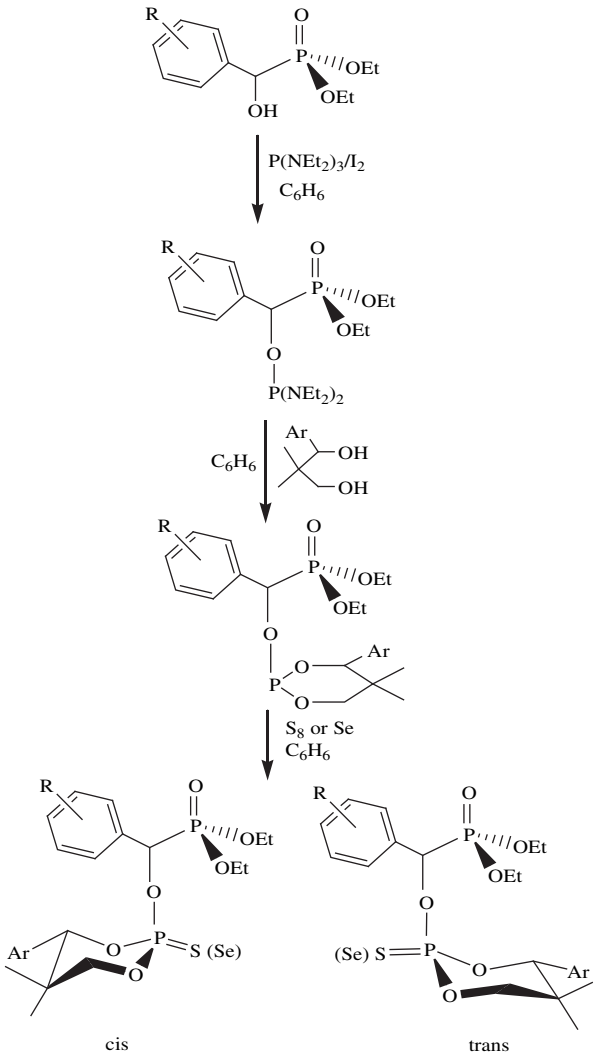
Scheme 24.

Zhou et al. prepared α-thio(seleno) phosphate-phosphonates by a multistep, one-pot reaction from α-hydroxyphosphonates in 1998.[76] In the first step, they prepared phosphite-phosphonates from the reaction of α-hydroxyphosphonates with tris(diethylamino)-phosphine activated by iodine. They then obtained α-thio(seleno) phosphate-phosphonates by successive alcoholysis/or phenolysis with subsequent treatment with sulfur or gray selenium in moderate-to-good yields (Scheme 25).

α-Phosphite-phosphonates were also prepared by treating α-hydroxyphosphonates with $ClP(OR)_2$, R_2PO_2CMe or $(EtO)_2PCl/Et_3N$ in moderate-to-high yields.[77]

9. α-Aminophosphonates

α-Aminophosphonates are probably the most important substitutes for the corresponding amino acids in biological systems.[3a,78] Indeed, a number of potent antibiotics,[79] enzyme inhibitors,[80] and pharmacological agents[81] are α-aminophosphonates as well as their derivatives, notably peptides. α-Aminophosphonates are also found as constituents of natural products. These important compounds have been synthesized by various routes: (a) addition of a P-H function to imines and enamines,[82] (b) addition of a P-H function to nitriles,[83] (c) Arbuzov and Michaelis–Becker reactions,[84] (d) condensation of X-NH_2 with acyl phosphorus species,[85] (e) Curtius and Hofmann rearrangement of substituted phosphonoacetic esters[86] and (f) alkylation of nucleophilic precursors such as Schiff bases.[87] Despite this wide range of synthetic methods for the synthesis of α-aminophosphonates,[88] little attempt has been made to convert the readily accessible α-hydroxyphosphonates into α-aminophosphonates. In 2003, for the first time, a variety of α-aminophosphonates were synthesized from α-hydroxyphosphonates in the presence of acidic alumina using microwave irradiation.[89]

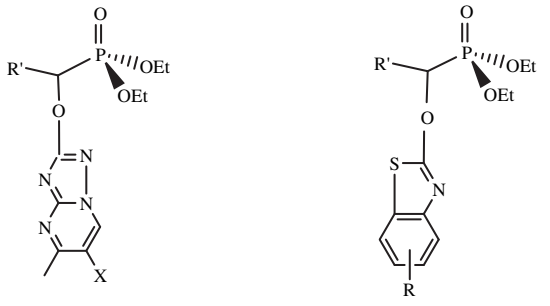


Scheme 25.

10. Miscellaneous

A series of phosphonate derivatives containing triazolo[1,5-*a*]pyrimidine[90] and benzothiazole[91] moieties were synthesized in an attempt to discover organophosphorus compounds with high biological activity (Scheme 26).

α-(1,2,4-Triazolo[1,5-*a*]pyrimidin-2-oxyl) phosphonates were synthesized by a nucleophilic substitution between α-hydroxyphosphonates and 2-methanesulfonyl-1,2,4-triazolo[1,5-*a*]pyrimidines and showed certain selective herbicidal activity against rape and also, to some extent, inhibition of acetolactase synthase activity.[90] On treating α-hydroxyphosphonates with substituted 2-chlorobenzothiazoles in the presence of KI, *n*-Bu_4NBr and/or



Scheme 26.

KOH, α-(substituted benzothiazol-2-oxyl)phosphonates were prepared in 42–95% yields.[91] These compounds showed plant-growth stimulating and herbicidal activities.

11. Concluding remarks

In summary, given the ubiquitous use of phosphonates as pharmacological agents and as crucial synthetic intermediates, considerable attention has been focused on the synthesis of phosphonates, particularly the α-functionalized analogs. Within the α-functionalized phosphonates, α-hydroxyphosphonates, which are easily prepared from commercially available materials, are useful precursors for the preparation of other types of α-functionalized phosphonates. The C–P bond of α-hydroxyphosphonates and also other α-functionalized phosphonates is susceptible to the reaction conditions. Cleavage of the C–P bond in these compounds produces aldehydes or carboxylic acids. Therefore, the introduction of suitable methods for the preparation of α-functionalized phosphonates by the replacement of hydroxyl functional groups without affecting the C–P bonds in these molecules will be an important synthetic achievement in organic synthesis. In this review, we have illustrated the progress that has been achieved in the strategies for the synthesis of α-functionalized phosphonates by the replacement of hydroxyl functional groups in α-hydroxyphosphonates.

It is necessary to note that, despite the impressive progress achieved in the synthesis of α-functionalized phosphonates directly from α-hydroxyphosphonates, there are still many different types of α-functionalized phosphonates, which could be synthesized from α-hydroxyphosphonates. On the other hand, the wide application of α-functionalized phosphonates as pharmaceuticals and biologically active compounds provides the driving force for the future development of the synthesis of new types of α-functionalized phosphonates from α-hydroxyphosphonates. With an increase in the development of new and efficient methods for the conversion of the hydroxyl functional group in ordinary alcohols into different types of functional groups, the prospects for the development of these kinds of chemical transformations in α-hydroxyphosphonates are far from exhausted. Therefore, it is easy to predict that one part of the basic efforts in studying the chemistry of α-hydroxyphosphonates will be concentrated in this direction.

Acknowledgements

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References and notes

1. (a) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237–12273; (b) Hildebrand, R. L.; Henderson, T. O. In *The Role of Phosphonates in Living Systems*; Hilderbrand, R. L., Ed.; CRC: Boca Raton, FL, 1983; pp 5–29; (c) Horiguchi, M.; Kandatsu, M. *Nature* **1959**, *184*, 901–902.
2. (a) Wiemer, D. F. *Tetrahedron* **1997**, *53*, 16609–16644; (b) Freedman, L. D.; Doak, G. O. *Chem. Rev.* **1954**, *54*, 479–523; (c) Engel, R. *Chem. Rev.* **1977**, *77*, 349–367; (d) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2005**, *16*, 3295–3340.
3. (a) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193–215; (b) Stowasser, B.; Budt, K. H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetraherdon Lett.* **1992**, *33*, 6625–6628.
4. (a) Conrad, K. A.; Lee, S. M. *Clin. Pharmacol. Ther.* **1981**, *30*, 114–120; (b) Kasting, G. B.; Francis, M. D. *J. Bone Miner. Res.* **1992**, *7*, 513–522; (c) Silvestrini, G.; Zini, N.; Sabatelli, P.; Mocetti, P.; Maraldi, N. M.; Bonucci, E. *Bone* **1996**, *18*, 559–565.
5. Smith, J. D. In *The Role of Phosphonates in Living Systems*; Hilderbrand, R. L., Ed.; CRC: Boca Raton, FL, 1983; pp 31–53.
6. (a) Allen, D. W.; Anderton, E. C.; Bradley, C.; Shiel, L. E. *Polym. Degrad. Stab.* **1995**, *47*, 67–72; (b) Catala, J. M.; Brossas, J. *Makromolekular Chemie- Makromolekular Symposia* **1993**, *74*, 147–153.
7. (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99; (b) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7616–7625; (c) Biller, S. A.; Forster, C. *Tetrahedron* **1990**, *46*, 6645–6658.
8. Hildebrand, R. *The Role of Phosphonates in Living Systems*; CRC: Boca Raton, FL, 1983.
9. Burnaeva, L. M.; Romanov, S. V.; Mironov, V. F.; Konovalova, I. V.; Ivkova, G. A.; Azancheev, N. M.; Cherkasov, R. A. *Russ. J. Gen. Chem.* **1997**, *67*, 1310–1311.
10. (a) Burke, T. R.; Smyth, M. S.; Otaka, A.; Roller, P. P. *Tetrahedron Lett.* **1993**, *34*, 4125–4128; (b) Sekine, M.; Satoh, M.; Yamagata, H.; Hata, T. *J. Org. Chem.* **1980**, *45*, 4162–4167; (c) Takaki, K.; Itono, Y.; Nagafuji, A.; Naito, Y.; Shishido, T.; Takehira, K.; Makioka, Y.; Taniguchi, Y.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 475–481; (d) Yamashita, M.; Kojima, M.; Yoshida, H.; Ogata, T.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1625–1628; (e) Sprecher, M.; Nativ, E. *Tetrahedron Lett.* **1968**, *9*, 4405–4408; (f) Sprecher, M.; Kost, D. *J. Am. Chem. Soc.* **1994**, *116*, 1016–1026.
11. (a) Kost, D.; Sprecher, M. S. *Tetrahedron Lett.* **1975**, *16*, 4483–4486; (b) Yuan, C.; Cui, S.; Wang, G.; Feng, H.; Chen, D.; Li, C.; Maier, L. *Synthesis* **1992**, 258–260; (c) Samanta, S.; Zhao, C.-G. *ARKIVOK* **2007**, *xiii*, 218–226.
12. Shahak, I.; Bergmann, E. D. *Isr. J. Chem.* **1966**, *4*, 225–231.
13. Demir, A. S.; Reis, Ö.; Kayalar, M.; Eymur, S.; Reis, B. *Synlett* **2006**, 3329–3333.
14. (a) Berlin, K. D.; Claunch, R. T.; Gaudy, E. T. *J. Org. Chem.* **1968**, *33*, 3090–3095; (b) Kudzin, Z. H.; Kotynski, A. *Synthesis* **1980**, 1028–1031; (c) Berlin, K. D.; Roy, N. K.; Clauach, R. T.; Bude, D. *J. Am. Chem. Soc.* **1968**, *90*, 4494–4495; (d) Berlin, K. D.; Taylor, H. A. *J. Am. Chem. Soc.* **1964**, *86*, 3862–3866.
15. (a) Telan, L. A.; Poon, C.-D.; Evans, S. A. *J. Org. Chem.* **1996**, *61*, 7455–7462; (b) Evans, D. V.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895–4896.
16. (a) Ackerman, B.; Jordan, T. A.; Eddy, C. R.; Swern, D. *J. Am. Chem. Soc.* **1956**, *78*, 4444–4447; (b) Jugelt, W.; Andreae, S.; Schubert, G. *J. Prakt. Chem.* **1971**, 83–98; (c) Kluger, R.; Pick, D. C.; Chin, J. *Can. J. Chem.* **1978**, *56*, 1792–1795; (d) Breuer, E.; Karaman, R.; Goldblum, A.; Leader, H. *J. Chem. Soc., Perkin Trans. 2* **1988**, 2029–2034.
17. Berlin, K. D.; Hellwege, D. M.; Nagabhushanam, M. *J. Org. Chem.* **1965**, *30*, 1265–1267.
18. Szpala, A.; Tebby, J. C.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1363–1366.
19. (a) Texier-Boullet, F.; Foucaud, A. *Synthesis* **1982**, 916; (b) Baraldi, P. G.; Guarneri, M.; Moroder, F.; Polloni, G. P.; Simoni, D. *Synthesis* **1982**, 653–654.
20. Smyth, M. S.; Ford, H.; Burke, T. R. *Tetrahedron Lett.* **1992**, *33*, 4137–4140.
21. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647–2650.
22. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399–402.
23. Benayound, F.; Hammond, G. B. *Chem. Commun.* **1996**, 1447–1448.
24. (a) Kaboudin, B. *Tetrahedron Lett.* **2000**, *41*, 3169–3171; (b) Liao, Y.; Shabany, H.; Christopher, D. S. *Tetrahedron Lett.* **1998**, *39*, 8389–8392.
25. Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Phosphorus Sulfur Silicon* **2004**, *179*, 1483–1491.
26. Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synth. Commun.* **2004**, *34*, 1463–1471.
27. Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Sardarian, A. R. *Tetrahedron Lett.* **2001**, *42*, 4369–4371.
28. Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett.* **2002**, *43*, 477–480.
29. Sekine, M.; Nakajima, M.; Hata, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 218–223.
30. Hata, T.; Hashisume, A.; Nakajima, M.; Sekine, M. *Tetrahedron Lett.* **1978**, *19*, 363–366.
31. Olah, G. A.; Wu, A. *J. Org. Chem.* **1991**, *56*, 902–904.
32. Koenigkramer, R. E.; Zimmer, H. *Tetrahedron Lett.* **1980**, *21*, 1017–1020.
33. (a) Sekine, M.; Nakajima, M.; Hata, T. *Tetrahedron Lett.* **1979**, *20*, 4475–4478; (b) Sekine, M.; Nakajima, M.; Kume, A.; Hashizume, A.; Hata, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 224–238.
34. Evans, D. A.; Hurst, K. M.; Truesdale, L. K.; Takacs, J. M. *Tetrahedron Lett.* **1977**, *18*, 2495–2498.
35. Sekiguchi, A.; Ikeno, M.; Ando, W. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 337–338.
36. Lebedev, E. P.; Mizhiritskii, M. D.; Baburina, V. A.; Mironov, V. F.; Ofitserov, E. N. *Zh. Obshch. Khim.* **1979**, *49*, 1731–1737.
37. Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett.* **2002**, *43*, 3653–3655.
38. (a) Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Ghassamipour, S.; Ammoozgar, Z. *Tetrahedron Lett.* **2003**, *44*, 891–893; (b) Firouzabadi, H.; Iranpoor, N.; Sobhani, S.;

Ghassamipour, S. *J. Organomet. Chem.* **2004**, *689*, 3197–3202; (c) Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Ghassamipour, S. *Synthesis* **2005**, 595–599; (d) Firouzabadi, H.; Iranpoor, N.; Jafari, A. A.; Jafari, M. R. *J. Organomet. Chem.* **2008**, *693*, 2711–2714.
39. Firouzabadi, H.; Karimi, B. *Synth. Commun.* **1993**, *23*, 1633–1641.
40. Firouzabadi, H.; Sardarian, A. R.; Khayat, Z.; Karimi, B.; Tangestaninejad, S. *Synth. Commun.* **1997**, *27*, 2709–2719.
41. (a) Li, Y.-F.; Hammerschmidt, F. *Tetrahedron* **1995**, *51*, 4933–4946; (b) Li, Y.-F.; Hammerschmidt, F. *Tetrahedron: Asymmetry* **1993**, *4*, 109–120; (c) Drescher, M.; Hammerschmidt, F.; Kahlig, H. *Synthesis* **1995**, 1267–1272; (d) Eidenhammer, G.; Hammerschmidt, F. *Synthesis* **1996**, 748–754; (e) Heisler, A.; Rabiller, C.; Douillard, R.; Goalou, N.; Hagele, G.; Levayer, F. *Tetrahedron: Asymmetry* **1993**, *4*, 959–960; (f) Khushi, T.; O'Toole, K. J.; Sime, J. T. *Tetrahedron* **1993**, *34*, 2375–2378; (g) Zhang, Y.; Li, J.-F.; Yuan, C.-Y. *Tetrahedron* **2003**, *59*, 473–479.
42. (a) Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem.* **2000**, *65*, 6121–6131; (b) Groth, U.; Richter, L.; Schollkopf, U. *Tetrahedron* **1992**, *48*, 117–122; (c) Lschat, S.; Kunz, H. *Synthesis* **1992**, 90–94.
43. Nesterov, L. V.; Sabirova, R. A.; Krepysheva, N. E. *Zh. Obshch. Khim.* **1969**, *39*, 1943–1948.
44. McConnell, R. L.; Coover, H. W., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 1961–1963.
45. Pudovik, A. N.; Gozman, I. P.; Nikitina, V. I. *Zh. Obshch. Khim.* **1963**, *33*, 3201–3205.
46. (a) Alimov, P. I.; Cheplanova, I. V. *Iz. Akad. Nauk. SSSR, Otdelenie Khim. Nauk* **1956**, 939–942; (b) Strepikheev, Y. A.; Kovalenko, L. V.; Batalina, A. V.; Shvetsova, L. A. *Deposited Doc., VINITI* **1976**, 2264–2276.
47. Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Amoozgar, Z. *Synthesis* **2004**, 295–297.
48. Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Amoozgar, Z. *Synthesis* **2004**, 1771–1774.
49. Green, D.; Elgendy, S.; Patel, G.; Skordalakes, E.; Goodwin, Ch. A.; Scully, M. F.; Kakkar, V. V.; Deadman, J. J. *Phosphorus Sulfur Silicon.* **2000**, *156*, 151–155.
50. He, H.-W.; Li, Y.; Shen, P.; Chen, T. *Phosphorus Sulfur and Silicon.* **2006**, *181*, 2135–2145.
51. (a) Zhang, Y.; Liu, Z.-J.; He, H.-W. *Guangzhou Huaxue* **2000**, *25*, 21–25; (b) He, H.-W.; Liu, Z.-J.; Wang, J. *Yingyong Huaxue* **1998**, *15*, 88–90; (c) He, H.-W.; Zhang, Y.; Liu, Z.-J. *Huaxue Shiji* **1996**, *18*, 70–72; (d) He, H.-W; Chen, T.; Wang, T.; Li, Y.; Shen, P. Faming Zhuanli Shenquing Gongkai Shumingshu Patent 10,012,773, 2004. *Chem. Abstr.* **2005**, *143*, 367398; (e) Cao, H.; Lu, S.-M.; Hu, L.- M.; Liu, Z.-J. *Yingyong Huaxue* **2004**, *21*, 442–445; (f) Cao, H.; Wang, H.; Yang, F.; Wang, J.; Liu, Z.-J. *Nongyaoxue Xuebao* **2003**, *5*, 21–26; (g) Shi, D.-Q.; Sheng, Z.-L.; Wu, H.; Chen, R.- Y. *Huazhong Shifan Daxue Xuebao Ziranke Xueban* **2001**, *35*, 296–300; (h) Fan, X.-E.; Fu, Y.-Q.; Wang, J.-G.; Du, Q.-Y.; Chen, Q.-H. *Chin. J. Chem.* **2002**, *20*, 1340–1346; (i) Hu, L.; Zhang, Y.; He, H.-W.; Liu, Z.-J. *Hecheng Huaxue* **1997**, *5*, 287–291; (j) He, H.-W.; Wang, S.; Liu, Z.-J.; Zhou, Q.; Chen, W. *Yingyong Huaxue* **1998**, *15*, 89–91; (k) He, H.-W.; Wang, S.; Chen, W.; Liu, Z.-J. *Chin. Chem. Lett.* **1998**, *9*, 415–416; (l) He, H.-W.; Wang, J.; Liu, Z.-J. *Chin. Chem. Lett.* **1994**, *5*, 35–38; (m) Tarasova, R. I.; Bikeev, G. L. *Zh. Obshch. Khim.* **1989**, *59*, 961–962; (n) Prokofeva, A. F.; Gryaznova, L. P.; Melnikov, N. N. *Zh. Obshch. Khim.* **1983**, *53*, 1517–1525; (o) Azerbaev, I. N.; Gafurov, E. K.; Dosmukhambetova, K. K.; Vyugova, A. I. *Eksp. Issled. Khim. Biol.* **1974**, 3–8.
52. (a) William, P. T.; Zhong-Yin, Z.; Theodores, W. *Bioorg. Med. Chem.* **1996**, *4*, 1515–1520; (b) Akihiro, Y.; Mitsuo, O. *Nippon Kagaku Kaishi* **1972**, 2103–2107; (c) Kumaraswamy, S.; Swamy, K. *Tetrahedron Lett.* **1997**, *38*, 2183–2184; (d) Zimmer, H.; Bercz, P. J.; Maltenieks, O. J.; Moore, M. W. *J. Am. Chem. Soc.* **1965**, *87*, 2777–2778; (e) Gallagher, M. J.; Noerdin, H. *Aust. J. Chem.* **1985**, *38*, 997–1005; (f) Kondo, K.; Ohnishi, N.; Takemoto, K.; Yoshida, H.; Yoshida, K. *J. Org. Chem.* **1992**, *57*, 1622–1625.
53. Iorga, B.; Eymery, F.; Savignac, P. *Tetrahedron* **1999**, *55*, 2671–2686.
54. Bergmann, E. D.; Shahak, I.; Appelbaum, J. *Isr. J. Chem.* **1968**, *6*, 73–74.
55. (a) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Chem. Commun.* **1981**, 511–513; (b) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin. Trans. 1* **1986**, 913–917.
56. Green, D.; Elgendy, S.; Patel, G.; Baban, J. A.; Skordalakes, E.; Husman, W.; Kakkar, V. V.; Deadman, J. *Tetrahedron* **1996**, *52*, 10215–10224.
57. Gajda, T. *Phosphorus Sulfur Silicon Relat. Elem.* **1990**, *53*, 327–331.
58. Kumaraswamy, S.; Senthamizh Selvi, R.; Kumaraswamy, K. C. *Synthesis* **1997**, 207–212.
59. Gomyo, T.; Yoshida, H.; Ogata, T.; Inokawa, H.; Inokawa, S. *Nippon Kagaku Kaishi* **1974**, 1093; *Chem. Abstr.* **1974**, *81*, 91649.
60. Yamashita, M.; Morizane, T.; Fujita, K.; Nakatani, K.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 812–814.
61. Otten, P. A.; Davies, H. M.; van der Gen, A. *Tetrahedron Lett.* **1995**, *36*, 781–784.
62. (a) Gajda, T. *Synthesis* **1990**, 717–718; (b) Huang, G.-L.; He, H.-W.; Li, M.-q.; Liu, Z.-J. *Hunan Huagong* **2000**, *30*, 27–28.
63. Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron* **2004**, *60*, 203–210.
64. (a) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639–1642; (b) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935–939.
65. Iranpoor, N.; Firouzabadi, H.; Gholinejad, M. *Can. J. Chem.* **2006**, *84*, 1006–1012.
66. (a) Leblanc, B. L.; Jursic, B. C. *Synth. Commun.* **1998**, *28*, 3591–3599; (b) Newman, A. A. *Chemistry and Biochemistry of Thiocyanic Acid and Its Derivatives*, 1st ed.; Academic: New York, NY, 1975; (c) Kashemirov, B. A.; Osipov, V. N.; Savenkov, N. F.; Chvertkin, B. Y.; Khokhlov, P. S. *Zh. Obshch. Khim.* **1992**, *62*, 1268–1271; (d) Gulea, M.; Hammerschmidt, F.; Marchand, P.; Masson, S.; Pisljagic, V.; Wuggenig, F. *Tetrahedron: Asymmetry* **2003**, *14*, 1829–1836.
67. Firouzabadi, H.; Hassani, H.; Sobhani, S. *Synthesis* **2004**, 290–294.
68. Sikora, D.; Gajda, T. *Phosphorus Sulfur Silicon Relat. Elem.* **2000**, *157*, 201–210.
69. (a) Palacios, F.; Choa de Retana, A. M.; Pogalday, J. *Org. Prep. Proced. Int.* **1995**, *27*, 625–635; (b) Palacios, F.; Choa de Retana, A. M.; Pogalday, J. *Heterocycles* **1995**, *40*, 543–550.
70. Gajda, T.; Matusiak, M. *Synth. Commun.* **1992**, *22*, 2193–2203.
71. Commonwealth Scientific and Industrial Research Organization and Imperial Chemical Industries of Australia and New Zealand Ltd.; British Patent 1087066, 1967; *Chem. Abstr.* **1968**, *68*, 95956.
72. Khokhlov, P. S.; Osipov, V. N.; Kolesova, B. A. *Zh. Obshch. Khim.* **1990**, *60*, 1669–1670.
73. Hakiemelahi, G. H.; Just, G. *Synth. Commun.* **1980**, *10*, 429.
74. Gajda, T.; Matusiak, M. *Synthesis* **1992**, 367–368.
75. Zhou, J.; Chen, R.; Yang, X. *Heteroatom Chem.* **1998**, *9*, 369–375.
76. Zhou, J.; Chen, R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2917–2921.
77. (a) Konovalova, I. V.; Mironov, V. F.; Ofitserova, E. K.; Pudovik, A. N. *Zh. Obshch. Khim.* **1981**, *51*, 1667–1668; (b) Konovalova, I. V.; Mironov, V. F.; Ofitserova, E. K.; Pudovik, A. N. *Zh. Obshch. Khim.* **1979**, *49*, 1424–1425.
78. (a) Giannousi, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603–1609; (b) Maier, L.; Lea, P. J. *Phosphorus Sulfur Silicon Relat. Elem.* **1983**, *17*, 1–19; (c) Hanessian, S.; Bennani, Y. L. *Synthesis* **1994**, 1272–1274; (d) Redmore, D. In *Topics in Phosphorus Chemistry*; Griffith, E. J., Grayson, M., Eds.; John Wiley & Sons: New York, NY, 1976; Vol. 8.
79. Atherton, F. R.; Hassal, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29–40.
80. Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652–1661.
81. Hassal, C. H. In *Antibiotics*; Hahn, F. E., Ed.; Springer: Berlin, 1983; Vol. VI, pp 1–11.
82. (a) Rogozhin, S. V.; Davankov, V. A.; Belov, Y. P. *Izu Akad Nauk SSSR* **1973**, *4*, 955–956; (b) Haffmann, H.; Foerster, H. *Monatsh. Chem.* **1968**, *99*, 380–388; (c) Hyun-Joon, H.; Gong-Sil, N. *Synth. Commun.* **1992**, *22*, 1143–1148.
83. Gancarz, R.; Wieczorek, J. S. *Synthesis* **1977**, 625.
84. Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379–1386.
85. Worms, K. H.; Schmidt-Dunker, M. In *Organic Phosphorus Compounds*; Kosolapo, G. M., Marier, L., Eds.; John Wiley: New York, NY, 1976; Vol. 7, p 1.
86. Barycki, J.; Mastalers, P. *Tetrahedron Lett.* **1970**, *11*, 3147–3150.
87. (a) Genet, J. P.; Uziel, J.; Port, M.; Touzin, A. M.; Roland, S.; Thorimbert, S.; Tanier, S. *Tetrahedron Lett.* **1992**, *33*, 77–80; (b) Qian, C.; Huang, T. *J. Org. Chem.* **1998**, *63*, 4125–4128; (c) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141–1143; (d) Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669–670; (e) Chanderasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, C. *Tetrahedron Lett.* **2001**, *42*, 5561–5563.
88. (a) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, 2692–2696; (b) Sobhani, S.; Safaei, E.; Asadi, M.; Jalili, F.; Tashrifi, Z. *J. Porphyr. Phthalocyanines* **2008**, *12*, 849–856; (c) Sobhani, S.; Safaei, E.; Asadi, M.; Jalili, F. *J. Organomet. Chem.* **2008**, *693*, 3313–3317; (d) Sobhani, S.; Tashrifi, Z. *Synth. Commun.* **2009**, *39*, 120–131; (e) Sobhani, S.; Vafaee, A. *Synthesis* **2009**, 1909–1915.
89. Kaboudin, B. *Tetrahedron Lett.* **2003**, *44*, 1051–1053.
90. (a) Yang, G.; Liu, Z.; Liu, J.; Yang, H. *Heteroatom Chem.* **2000**, *11*, 313–316; (b) Yang, G.; Yang, H. *Heterocycl. Commun.* **1999**, *5*, 355–358.
91. (a) He, H.-W.; Hong, X.; Liu, Z.-J. *Chin. Chem. Lett.* **1992**, *3*, 707–710; (b) He, H.-W.; Hong, X.; Wan, S.; Liu, Z.-J. *Youji Huaxue* **1993**, *13*, 269–272; (c) He, H.-W.; Hong, X.; Wan, S.; Liu, Z.-J. *YingYong Huaxue* **1993**, *10*, 20–23.

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