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New Strategy for the Synthesis of Functionalized Phosphonic Acids*

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ABSTRACT

Various approaches leading to mono-, di-, and polyfunctionalized phosphonates as well as phosphoryl heterocycles are reported for the systematic study of relationships between chemical structure and biological activity of this most important class of organophosphorus compounds. © 1997 John Wiley & Sons, Inc.

INTRODUCTION

Functionalization of phosphonic acid molecules opens enormous possibilities for structural variation of this important class of organophosphorus compounds with potential biological activity. This is particularly true for 1-aminoalkylphosphonic acids and related peptides for which have been found wide applications as both agrochemicals and medicinal products. Numerous synthetic approaches have been described for the formation of monofunctionalized phosphonic acids, which usually require multistage manipulations. Introduction of additional functionalized groups to these molecules by traditional methods is complicated due to inter- or intramolecular interactions. Consequently, the design of syntheses of mono-, di-, and polyfunctionalized phosphonic acids and study of the structural effects of these compounds on their biological activity are of great interest both in synthetic organophosphorus chemistry and for the development of leads for the structures for biologically active molecules. In this article, our emphasis is placed on the description of new and convenient methods of synthesis.

RESULTS AND DISCUSSION

Monofunctionalized Phosphonic Acids

Alkylidenebisphosphonates. Condensation of aldehydes with diethyl phosphite, followed by sulfonylation of the 1-hydroxy group thereby formed with methanesulfonyl chloride, and subsequent substitution by another molecule of diethyl phosphite provides the corresponding alkylidenebisphosphonates in one pot procedures with good yields [1]. Upon acid hydrolysis, the resultant alkylidenebisphosphonates are converted smoothly to 1-alkylmethylenebisphosphonic acids [2] containing a basic skeleton for compounds with potential therapeutic effects in the treatment of osteoporosis [2,3].

1-Heteroatom-Substituted Phosphonic Acids.

1-Heteroatom-substituted phosphonic acids cover a wide spectrum of important organophosphorus

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compounds. Unfortunately, the conventional synthetic method based on nucleophilic substitution of a 1-haloalkylphosphonate is under great challenge associated with low reactivity of the 1-haloalkyl group, the narrow scope of applications, and the relative inaccessibility of the intermediates. As found by us, substitution of a 1 (methanesulfonyl)alkylphosphonate by a phosphite anion provides an alkylidenebisphosphonate. Since the -OMs group behaves as a good leaving group, this nucleophilic substitution process was extended as a general method of preparation of 1-heteroatom-substituted alkylphosphonates (Scheme 1).

The yields in the reactions were increased with the enhancement of the nucleophilicity of the reagents as shown by the order:

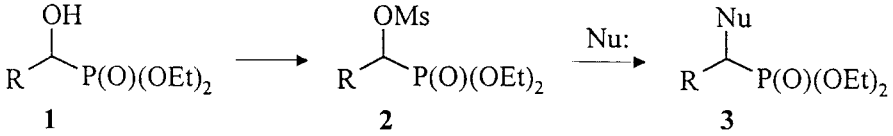
$$n\text{-BuSH} > \text{PhSH} > NH_2NH_2 > \text{PhNHNH}_2 \sim \text{PhCH}_2NH_2 > (EtO)_2POH > \text{PhCONHNH}_2 \gg KCN \gg KF$$

Diethyl 1-hydroxypropylphosphonate provided the products in much higher yields than the corresponding 1-phenyl-1-hydroxymethylphosphonates due to the greater steric hindrance of phenyl over ethyl in these nucleophilic substitution reactions.

1-Aminophosphonic Acids.

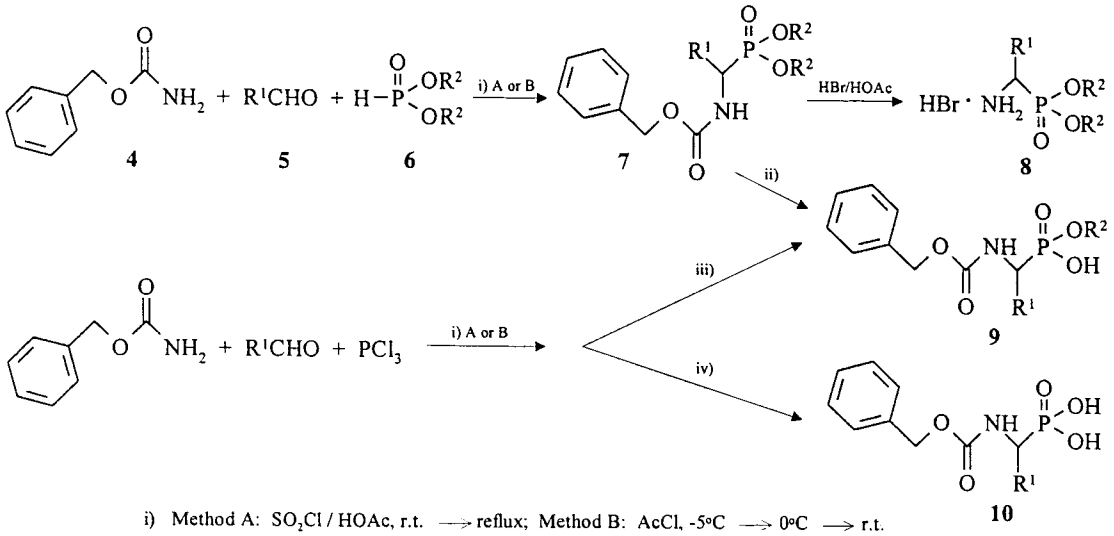
As phosphorus analogues of α-aminocarboxylic acids, 1-aminoalkylphosphonic acids are the most important members of the 1-heteroatom-substituted phosphonic acids because of their potential biological activity. As the mimetic tetrahedral intermediates of hydrolyzed esters, amides, and peptides, 1-aminophosphonic acid derivatives have been used as antibiotics, medicaments, or enzyme inhibitors [4].

Among numerous synthetic methods for the preparation of 1-aminoalkylphosphonic acids, a three-component condensation involving an alde-



R = Et, Ph
Nu = *n*-BuS, PhS, $PhCH_2NH$, $(EtO)_2PO$, PhCONHNH, PhNHNH

SCHEME 1



i) Method A: SO_2Cl / HOAc, r.t. → reflux; Method B: AcCl, -5°C → 0°C → r.t.
ii) NaOH / H_2O / $Bu_4N^+Br^-$ iii) R^2OH iv) H_2O

R^1 = Me, Ph, p-MeC_6H_4, p-$MeOC_6H_4$.
R^2 = H, Et.

SCHEME 2

hyde, an alkyl carbamate, and a trivalent phosphorus reagent is the most attractive. A systematic study is being carried on in our laboratory with the aim of developing new and convenient methods for the synthesis of 1-aminoalkylphosphonic acids based on the investigation of the influence of substrate structure, nature of the catalyst and the type of solvent on the yield of product [5–7].

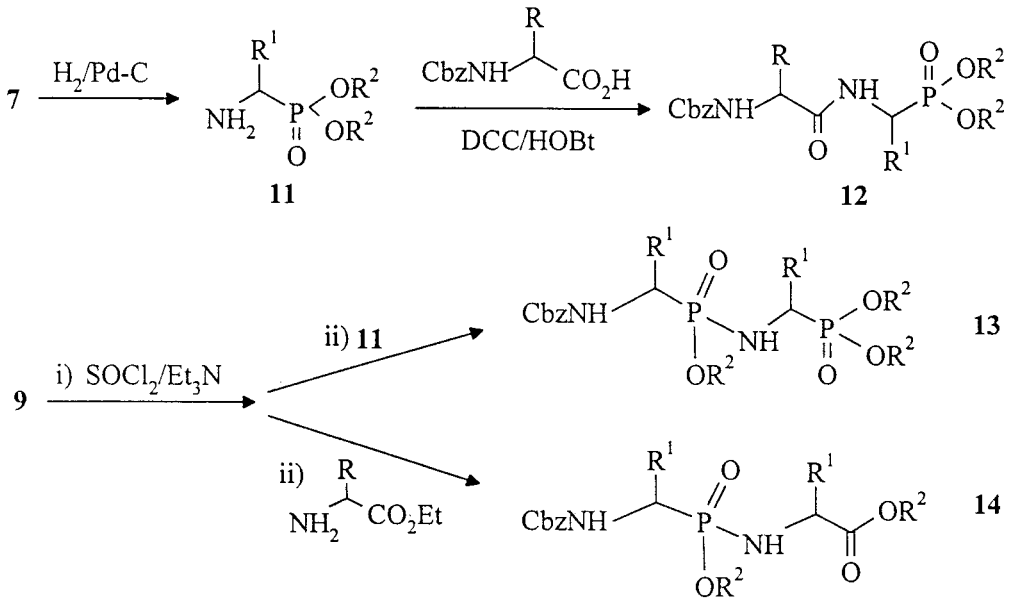
By using acetyl chloride as the solvent, the scope of applications of such three-component condensations can be expanded to include the convenient synthesis of derivatives of 1-aminoalkylphosphonates, key intermediates for phosphonopeptide synthesis [8–10] (Scheme 2).

The application of *N*-protected alkylphosphonic monoesters and diesters in phosphonopeptide synthesis has also been demonstrated by us [11]. Thus, dialkyl 1-(N-benzyloxycarbonylamino)alkylphosphonates were converted to 1-aminoalkylphosphonates in almost quantitative yields upon catalytic hydrogenolysis using palladium on carbon as the catalyst. The latter was directly coupled, without isolation, with an *N*-protected amino acid using dicyclohexylcarbodiimide (DCCI) plus N-hydroxybenzotriazole (HOBt) as condensation agents, producing phosphonopeptides containing a C-terminal aminophosphonic moiety. On the other hand, alkyl hydrogen 1-(N-benzyloxycarbonylamino)alkylphosphonates, upon treatment with thionyl chloride in the presence of triethylamine, followed by condensation with an aminoalkylcarboxylate or aminoalkylphosphonate, afforded phosphonopeptides bearing an N-terminal aminophosphonic moiety (Scheme 3).

When an α-halocarboxamide was used in place of a benzyl carbamate in the above tricomponent condensation, a backbone for the formation of oligophosphonopeptides was established [12]. Thus, condensation of 2-halogenated amides, substituted benzaldehydes, and a dialkyl phosphite in the presence of acetic anhydride containing ethanolic hydrogen chloride provided α-(2-haloacylamino)-substituted benzylphosphonates, which were reacted with phthalimide in the presence of potassium carbonate, using tetraethylammonium bromide as a phase transfer catalyst, followed by hydrazinolysis, to give dipeptides with a free amino group. This type of dipeptide was coupled with another *N*-protected amino acid to form a tripeptide. It is obvious that analogous couplings on both N- and P-terminal moieties should furnish oligophosphonopeptides (Scheme 4).

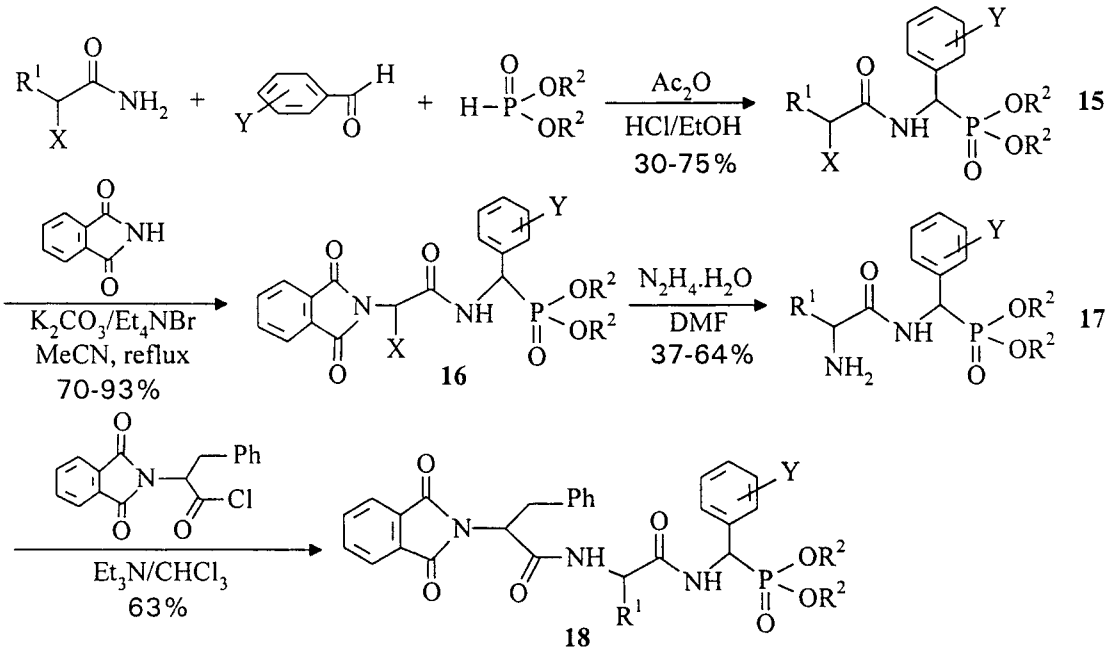
Since the biological activities of 1-aminophosphonic acids are largely dependent on their absolute configurations, the asymmetric synthesis of these compounds has aroused the interest of organic chemists [13]. The nucleophilic addition of a dialkyl phosphite to chiral imines or oxoiminium derivatives have constituted the majority of asymmetric syntheses of 1-aminophosphonic acids to date, although several additional interesting synthetic methods have been developed [14–16].

Gilmore and McBride [17] have briefly investigated the stereochemical behavior of the addition of diakyl phosphites to aldimines resulting from the condensation of substituted benzaldehydes with (R) or (S)-1-phenylethylamine at 140°C. Since a high temperature is not favorable for asymmetric induction, we studied this reaction at ambient temperature in the presence of various catalysts in order to improve stereoselectivity. We found that the nature of catalysts and solvents influenced remarkably the diastereomeric excess (*de*) values attained and the induced direction of the asymmetric addition [18]. The addition reaction of diethyl phosphite to *N*-benzylidene-(*S*)-1-phenylethylamine was examined as a typical example. With $AlCl_3$ or $BF_3 \cdot Et_2O$ as catalyst and CH_2Cl_2 as solvent, the *de* value was found to be 70% or 61%, respectively, based on ^{31}P NMR spectroscopic measurements. Upon hydrolysis to cleave the ester and hydrogenolysis to remove the α-phenylethyl group, the adduct formed by the use of BF_3Et_2O as the catalyst was converted into the α-aminobenzylphosphonic acid with $[\alpha]_D$ − 18.3, which was determined to have the *S*-configuration by comparison with the literature [19] reported value of $[\alpha]_D$ − 17.6. This indicates that the (1S, 1′S) diastereoisomer is the major product of the addition reaction. However, with $ZnCl_2$ or TsOH as catalyst and CH_2Cl_2 as solvent, or $BF_3 \cdot Et_2O$ as catalyst and toluene as solvent, or without use of a catalyst, this reaction gave the (1R, 1′S) diastereoisomers predominantly. These results were reasonably explained by our molecular mechanics studies. Calculation indicates that three stable conformations of the imine are involved in this reaction and the relative energies are shown to be in the order C < A < B. In the absence of catalyst or in the presence of $ZnCl_2$ or TsOH, attack of diethyl phosphite on the favored conformer C takes place from the *re* face of the imine due to a steric interaction, leading to mainly the (1R, 1′S) diastereoisomer. When BF_3Et_2O or $ZnCl_2$ is used as the catalyst, the empty d-orbital of the central atom is used to form an intramolecular chelate complex with the lone pair electrons of nitrogen and the phenyl at C-1′, which renders conformer A predominant. Attack of diethyl phosphite at conformer A from the less hindered direction, namely, the *si* face



R = H, Me, i-Bu, $PhCH_2$.
R^1 = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, p-,m-OCH_2O.
R^2 = Et, Bu.

SCHEME 3

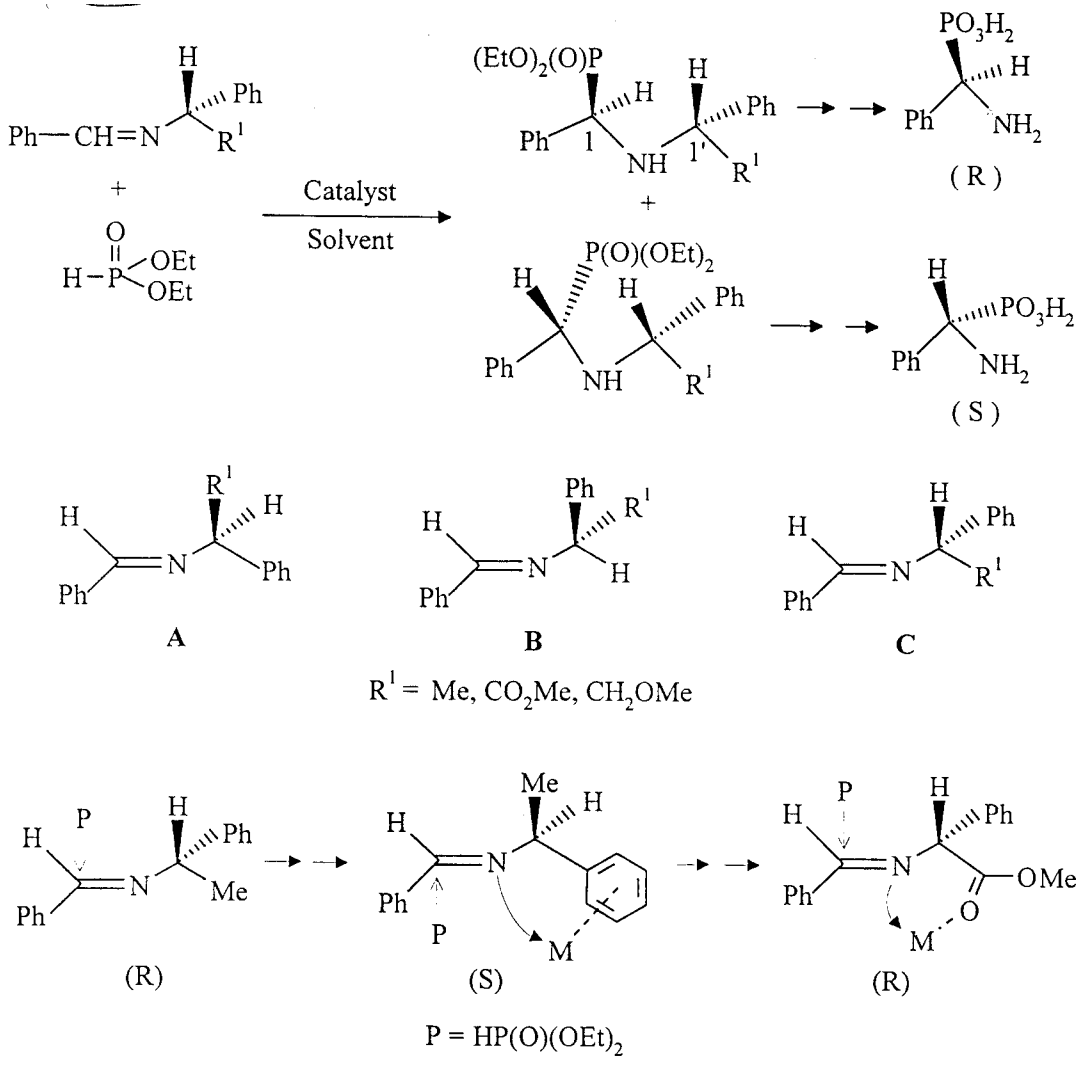


R^1 = H, Me, Et. R^2 = Et, Bu. X = Cl, Br. Y = H, p-Me, p-MeO, m,p-OCH_2O.

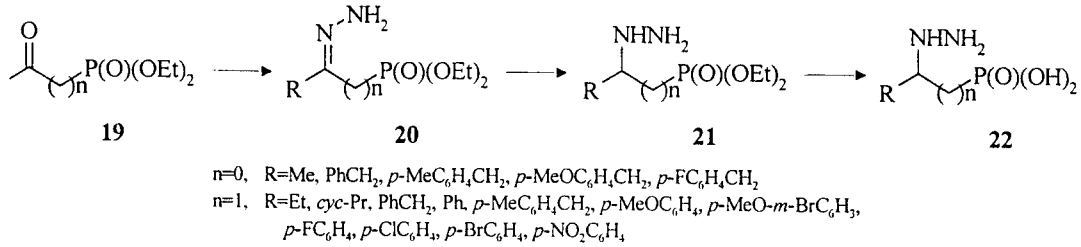
SCHEME 4

of the imine, provides the (1S, 1′S) diastereoisomers. The opposite stereofacial selectivity, with toluene as solvent, can be rationalized by the strong coordination of BF_3 with the solvent that prevents the formation of the intramolecular coordination complex (Scheme 5).

Based on the above results, we reasoned that if the methyl group were replaced by the methoxymethylene or methoxycarbonyl group, introduction of catalysts that coordinated strongly with an oxygen atom would bring about a greater contribution of conformer C, and the asymmetric induction effect would be improved significantly. Consequently, we investigated the reaction using (*R*)-2-methoxy-1-



SCHEME 5



SCHEME 6

phenylethylamine or (*R*)-phenylglycine methyl ester as chiral auxiliaries instead of (*S*)-1-phenylethylamine. Here, the relative spatial arrangements of the groups linked to the chiral carbon remain unchanged, and the conformational analysis mentioned previously should be applicable.

With (*R*)-phenylglycine methyl ester as the chiral auxiliary, this asymmetric addition with BF_3Et_2O as catalyst and CH_2Cl_2 as solvent gave a *de* value of 89% with (1R, 1′R) as the major configuration of the product, in addition to an 84% chemical yield. Other catalysts, such as $AlCl_3$, $TiCl_4$, and $ZnCl_2$, furnished (1R, 1′R)-diastereoisomers predominantly with good to excellent *de* values regardless of the existence or nonexistence of an empty *d*-orbital of the central metal atom. These results can be explained by predominant contribution of conformer C as a result of the coordination of the Lewis acid with the carbonyl group. The *de* values are dependent on the coordination ability of the catalysts, and therefore, $BF_3 \cdot Et_2O$ gives the best *de* values.

Analogous results were obtained with (*R*)-2-methoxy-1-phenylethylamine as chiral auxiliary. Our investigations represent the first successful trial of molecular mechanics calculations as a guide in asymmetric syntheses of 1-aminophosphonic acids [19,20]. These experimental data were strongly supported by Smith's report [14].

It is interesting to note that, as one of the heterobimetallic asymmetric catalysts, the Lanthaniod-Potassium-BINOL complex was used in an effective asymmetric hydrophosphonylation of an imine with excellent, up to 96%, *de* values [21].

1- and/or 2-Hydrazinoalkylphosphonic Acids.

As derivatives of aminoalkylphosphonic acids, hydrazinoalkylphosphonic acids are of considerable interest as compounds with potential biological activity. These compounds have been prepared by the addition of dialkyl phosphites to aldazines, followed by acid hydrolysis [22]. However, this method is not applicable to the synthesis of the esters of 1-hydrazinoalkylphosphonic acids since acid hydrolysis leads to the cleavage of the ester linkage, while catalytic hydrogenolysis to remove the *N*-protective group usually results in N–N bond splitting to form the 1-aminoalkylphosphonic ester [23]. Another synthetic route to these compounds was based on the addition of a dialkyl phosphite to the hydrazone resulting from condensation of formaldehyde with N-(benzyloxycarbonyl)hydrazine. The adducts thus formed, upon removal of the benzyloxycarbonyl group by catalytic hydrogenation, gave the 1-hydrazinomethylphosphonates [24]. Unfortunately, other substituted hydrazones are inert to nucleophilic addition of a dialkyl phosphite [25].

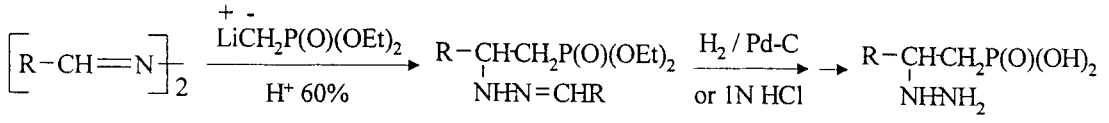
As found by us, starting from diethyl 1-ketophosphonates, 1-hydrazonophosphonates can be prepared smoothly. In this reaction, the presence of glacial acetic acid is critical since direct condensation of hydrazine or hydrazine hydrate with 1-ketophosphonates usually results in cleavage of the P–C bond to form acyl hydrazines and the dialkyl phosphite. 1-Hydrazonophosphonates, upon treatment with $NaBH_3CN$, were conveniently reduced to the corresponding hydrazino derivatives that were isolated as their oxalates due to their air sensitivity. The free 1-hydrazinoalkylphosphonic acids were obtained from the hydrazinophosphonates upon acid hydrolysis [26] (Scheme 6).

The 2-hydrazinoethylphosphonates were prepared analogously from 2-ketoethylphosphonates using BH_3THF as the reducing reagent, which is able to convert 2-hydrazono derivatives to 2-hydrazinoethylphosphonates in high yield.

As shown by us, a direct synthetic route to 2-hydrazinoethylphosphonic acids was achieved based on the addition of the carbanion derived from diethyl methylphosphonate to the aldimine prepared conveniently by condensation of an aromatic aldehyde with hydrazine. Difficulty was encountered during the hydrogenolysis of the N = C bond since it is usually accompanied by N–N bond cleavage. However, removal of the =CHR group can be achieved by acid treatment with 1N HCl, although the yield is poor (around 30%). The corresponding 2-hydrazino-2-alkyl(aryl)ethylphosphonic acids are easily obtained from the diethyl esters by reaction with Me_3SiBr and subsequent treatment with methanol in the usual manner (Scheme 7).

1-Hydroxyamino-alkylphosphonic Acids.

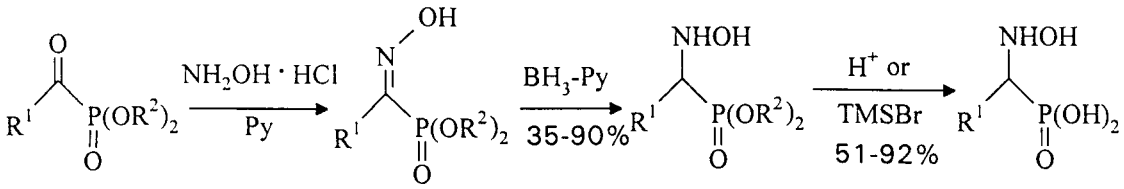
1-(Hydroxyamino)alkylphosphonic acids are a class of important compounds possessing strong antibacterial activity [27]. A number of syntheses have been developed to provide a convenient route to this class of compounds, including the controlled reduction of 1-nitroalkylphosphonates with zinc and ammonium chloride [28], the addition of a dialkyl phosphite to a 1-oxoaldoxime at an elevated temperature [29], the nucleophilic addition of a lithium or potassium dialkyl phosphite to N-glycosylnitrone followed by glycoside cleavage and hydrolysis [30], and the condensation of 1-(benzyloxyamino)alkylphosphonic acid with an O-alkylisourea, followed by treatment with boron tris(trifluoroacetate) [31]. These methods are,



23 **24** **25**

R = Ph, MeC_6H_4, $MeOC_6H_4$, FC_6H_4, ClC_6H_4, $NO_2C_6H_4$

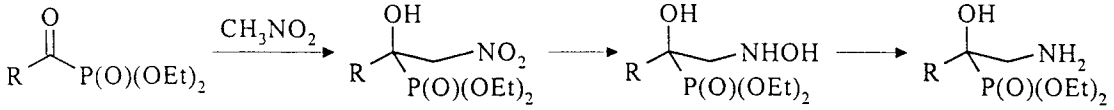
SCHEME 7



26 **27** **28** **29**

R^1 =Me, i-Pr, $PhCH_2$, p-$FC_6H_4CH_2$, Ph, p-MeC_6H_4, o-MeC_6H_4, m-MeC_6H_4, p-FC_6H_4, p-ClC_6H_4.
R^2 = Me, Et, i-Pr.

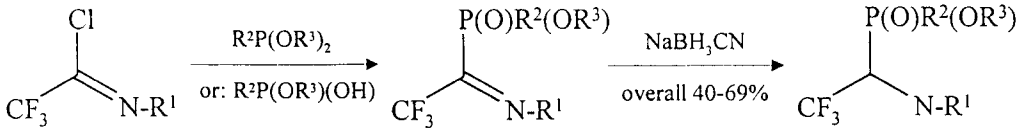
SCHEME 8



26 **30** **31** **32**

R = Me, Et, Pr, C_5H_{11}, Ph.

SCHEME 9



33 **34** **35**

R^1 = *n*-C_8H_{17}, *cyclo*-C_6H_{11}, $PhCH_2CH_2$, Ph, *p*-MeC_6H_4, *o,p*-$Me_2C_6H_3$, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$.
R^2 = MeO, EtO, *i*-PrO, *i*-BuO, *i*-Pr, Ph.
R^3 = Me, Et, *i*-Pr, *n*-Bu.

SCHEME 10

however, limited by their narrow scope, other competitive reactions, and relatively inaccessible starting materials. We established a new and facile approach to 1-(hydroxyamino)alkylphosphonic acids by controlled reduction of 1-(hydroxyimino) alkylphosphonates with the borane-pyridine complex [32].

Standard Arbuzov reactions of acyl chlorides with trialkyl phosphites gave 1-oxophosphonates, which were converted into 1-(hydroxyimino)-alkylphosphonates in almost quantitative yield by oximation with hydroxylamine hydrochloride in the presence of pyridine. Reduction of the oximes in alcoholic hydrogen chloride with an excess of the borane-pyridine complex provided 1-(hydroxyamino)alkylphosphonates as crystalline hydrochloride salts that were converted into the corresponding free acids either by hydrolysis with 6N HCl at 90°C

for 4 hours in 45–86% yield or by dealkylation with Me_3SiBr in acetonitrile, followed by treatment with aqueous methanol (Scheme 8).

DIFUNCTIONALIZED PHOSPHONIC ACIDS

1-Hydroxy-2-aminoalkylphosphonic Acid and Derivatives Thereof

As a phosphorus analogue of an isomer of serine, 1-hydroxy-2-aminoethylphosphonic acid has been isolated from a living organism [33]. This awakened an increased interest in the synthesis of this unusual aminophosphonic acid containing a hydroxyl group. 1-Alkyl derivatives of 1-hydroxy-2-aminoethylphosphonic acid were prepared either by addition of dimethyl phosphite to N-(2-oxoethyl)phthalimide, followed by hydrazinolysis [34], or by aminative cleavage of the ethylene oxide ring of phosphomycin derivatives, followed by subsequent hydrolysis [35]. A serious drawback of these methods is associated with starting materials attainable only with difficulty, and therefore, a new approach is necessary. We found that careful reduction of 1-hydroxy-2-nitroalkylphosphonates could achieve this goal.

Preparation of 1-hydroxy-2-nitroethylphosphonates by nucleophilic addition of nitromethane to acetylphosphonates in the presence of di- or triethylamine has been reported [36]. We found that this procedure is not applicable to the synthesis of diethyl 1-hydroxy-2-nitro-2-phenylethylphosphonates since the electron-withdrawing ability of the benzene ring destabilizes the molecule toward alkali and results in C–P or C–C bond cleavage. We achieved an effective and general procedure for the preparation of 1-hydroxy-2-nitroalkylphosphonates based on the addition of nitromethane to acyl- or aroylphosphonates under phase transfer catalysis conditions, using potassium carbonate/tetrabutylammonium bromide as the catalyst [37].

The conversion of the nitro group into an amino functionality by catalytic hydrogenation over Raney-Nickel in acetic acid provided 1-hydroxy-2-aminoalkylphosphonates. Here, acetic acid plays an important and interesting role. It serves not only as solvent but also as an accelerator of the hydrogenation process. It also prevents the decomposition of the reaction products since the basicity of the formed amino group is strong enough to initiate the C–P and C–C cleavage of the resultant molecule. Without isolation, each generated 1-hydroxy-2-aminoalkylphosphonate was directly refluxed in 8N HCl at 100°C to give the corresponding 1-hydroxy-2-aminoalkylphosphonic acid [38].

The controlled reduction of 1-hydroxy-2-nitroalkylphosphonates to 1-hydroxy-2-(hydroxylamino)-alkylphosphonates was also realized by treatment either with aluminum amalgam in ethyl acetate or with stannous chloride in hydrochloric acid solution [39]. The yield is very much dependent on the structure of the substrate and the reactivity of the Al–Hg. However, reduction with $SnCl_2$ usually provided better yields at low temperature (<10°C), regardless of the structure of the substrates (Scheme 9).

Aminophosphonic Acids Bearing a Trifluoromethyl Moiety

Introduction of a fluorine atom, a difluoromethylene group, or a trifluoromethyl group into organic molecules is the subject of active investigation due to some special properties of the fluorine atom compared with the hydrogen atom. For the purpose of changing the biological activity, a series of trifluoromethyl-amino-alkylphosphonic acids was synthesized by us. Our synthetic approach is based on the chemical reactivity of trifluoroacetimidoyl chloride. Thus, Arbuzov-type reactions of trialkyl phosphites with this reagent, followed by subsequent reduction to the imine intermediates, provided 1-(N-aryl/alkylamino)-2,2,2-trifluoroethylphosphonates, the trifluoromethylated phosphorus analogues of N-protected alanine [40] (Scheme 10).

The reaction of triethyl phosphite with N-phenyltrifluoroacetimidoyl chloride was carried out at 80°C without solvent. The ^{19}F NMR chemical shift for the starting imidoyl chloride is 4.8 while that for the compound that was formed is 9.7. After 6 hours, the imidoyl chloride disappeared completely, and the mixture was worked up to give the iminophosphonate in 95% yield. Signals in the ^{31}P NMR spectra at $\delta = 7.37$ (q, $J = 9.2$ Hz) definitely revealed the formation of the Arbuzov reaction product. The subsequent reduction was achieved by treatment with $NaBH_3CN$ as indicated by the ^{31}P NMR resonance at $\delta = 15.2$ (q, $J = 8.7$ Hz), much downfield from that of the iminophosphonate, because the phosphonate moiety in the product is linked to an sp^3-hybridized carbon, while in the iminophosphonate, it is linked to an sp^2 carbon.

We also extended the above reaction to various N-substituted trifluoroacetimidoyl chlorides and other trivalent phosphorus reagents. N-substituents in the imidoyl chlorides caused a remarkable effect on the reaction. When R^1 was alkyl, prolongation of reaction time was found to be necessary. When R^1 was aryl, the more powerful the electron-withdrawing group on the benzene ring, the more rapidly the reaction occurred. When N-(*p*-nitrophen-

yl)trifluoroacetimidoyl chloride was used, the reaction was performed under 0°C because of its high reactivity. Diethyl phenylphosphonite reacted more rapidly than a typical trialkyl phosphite. These results indicate that the Arbuzov-type reaction is initiated by the nucleophilic attack of the trivalent phosphorus species on the imidoyl chloride. Highly electrophilic imidoyl chlorides and more nucleophilic phosphorus reagents promote the reaction markedly. Dialkyl phosphites also reacted with the imidoyl chlorides. In such cases, addition of Et_3N was necessary in order to remove HCl generated. Monoethyl phenylphosphonite reacted similarly.

On the other hand, as a reactive intermediate, trifluoroacetimidoyl chloride underwent a substitution reaction with the carbanion obtained by deprotonation of an appropriate alkyl phosphonate. Subsequent reduction gave the 2-trifluoromethyl-2-(substituted amino)ethylphosphonate, a trifluoromethyl-2-AEP [41] (Scheme 11).

Depending on the nature of R^2, an appropriate base should be used. Replacement of the chlorine of the imidoyl chloride by a carbanion provides, as a rule, a mixture of the iminophosphonate and its isomeric enaminophosphonate, which are very difficult to separate by column chromatography but are easily identified by ^1H NMR spectroscopy. The ratio of the imine to the enamine is dependent on the structure of the substituent. The mixture of intermediates was subjected to reduction without isolation. The reduction proceeded smoothly with $NaBH_3CN$ in acetic acid. Besides its role as a solvent, HOAc enhanced the electrophilicity of the substrate by the protonation of the imino and amino nitrogens.

POLYFUNCTIONALIZED PHOSPHONIC ACIDS

Phosphonostatine-Containing Difluoromethyl Moiety

As an unusual amino acid 4(S)-amino-3(S)-hydroxy-5-methylheptanoic acid (statine) is an essential component of pepstatin, so it is a naturally occurring peptide possessing an inhibitory effect on proteolytic enzymes such as renin [42]. Some synthetic peptides derived from difluorostatin are potent renin inhibitors and show promising new therapeutic possibilities for the treatment of high blood pressure [43]. Replacement of a carboxyl group in a biologically active molecule by a phosphonic moiety often results in an interesting change in the biological activity. Recently, the difluoromethylphosphonate moiety has attracted much attention because it offers significant advantages over its nonfluorinated counterpart as an enzyme inhibitor due to a small steric disparity but a great polarity difference between the difluoromethylene and methylene group [44]. This situation aroused our interest in the synthesis of a phosphorus analogue of statine bearing a difluoromethylene moiety [45].

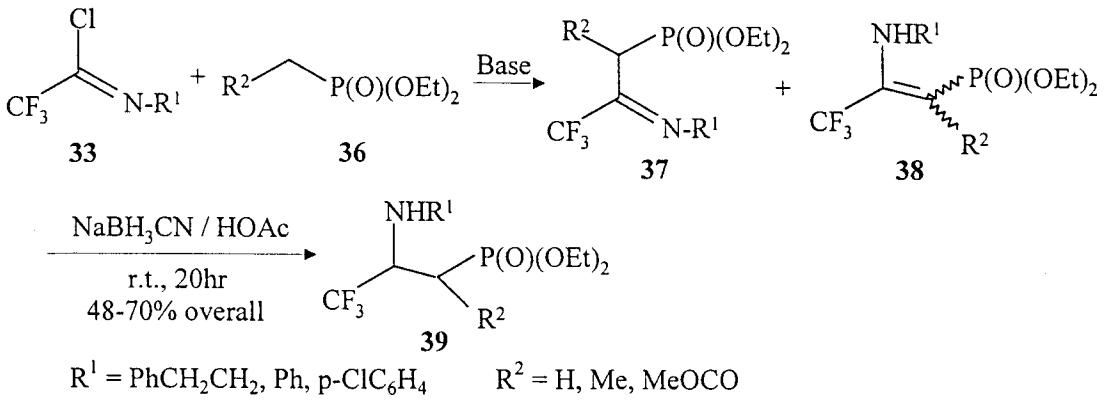
Thus, an *N*-phthalimido-protected *L*-amino acid was converted into its corresponding acyl chloride that was reacted with $BrZnCF_2P(O)(OEt)_2$, derived by the action of zinc powder on diethyl 1-bromo-1,1-difluoromethylphosphonate, providing the 3-(*N*-phthalimido)-2-oxo-1,1-difluoroalkylphosphonate **40**. Owing to the chiral induction of C-3, diastereoselective reduction of compound **40** with $NaBH_3CN$ in acidic medium afforded a mixture of 2*R*,3*S*- (**41**) and 2*S*,3*S*-(**42**) diastereoisomers. The diastereomeric excess value was determined by HPLC. Deprotection at both the *N* and *P* terminals of these diastereoisomers in the usual manner furnished the α,α-difluorophosphonic analogues of statine (Scheme 12).

Peptides Containing the 1-Hydroxy-2-aminophosphonic Acid Residue

1-Hydroxy-2-aminoethylphosphonic acid (HAEP) is another naturally found C–P compound; the 2-alkyl-substituted HAEP and its peptide derivatives were reported to be an inhibitor of renin [46]. Therefore, we devoted our efforts to the synthesis of a new type of phosphonopeptide containing a 1-alkyl-substituted HAEP unit [23]. Since the mixed carboxylic-carbonic acid anhydride method (MCCA), the most popular procedure for peptide bond formation, is unsuitable for the synthesis of phosphonopeptides bearing a free hydroxyl function, we tried to use an active ester in situ, one formed by the reaction of N-hydroxyphthalimide (HONPht) and the N-protected amino acid, in the preparation of phosphonopeptides. In this reaction, apart from its role in accelerating the coupling process via an active ester, HONPht also acted as an acid to prevent the alkalilabile **44** from decomposing. The free peptides **46** were obtained after deprotection of the phosphonopeptides **45** in the usual manner [47] (Scheme 13).

PHOSPHORYLATED HETEROCYCLES

Phosphorylated heterocycles can be regarded as a special class of polyfunctionalized phosphonic acids. The successful clinical application of Fosfomycine and Cyclophosphonamide as wide spectrum antibiotics and anti-cancer drugs, respectively, aroused our interest in structure-activity studies of hetero-



SCHEME 11

cyclic compounds bearing the phosphonate moiety for evaluation of their biological activities. At the same time, a synthetic study of phosphorylated heterocyclic compounds deserves considerable attention because of their extensive applications in organic synthesis.

Phosphorylated Heterocycles from Isocyanomethylphosphonates

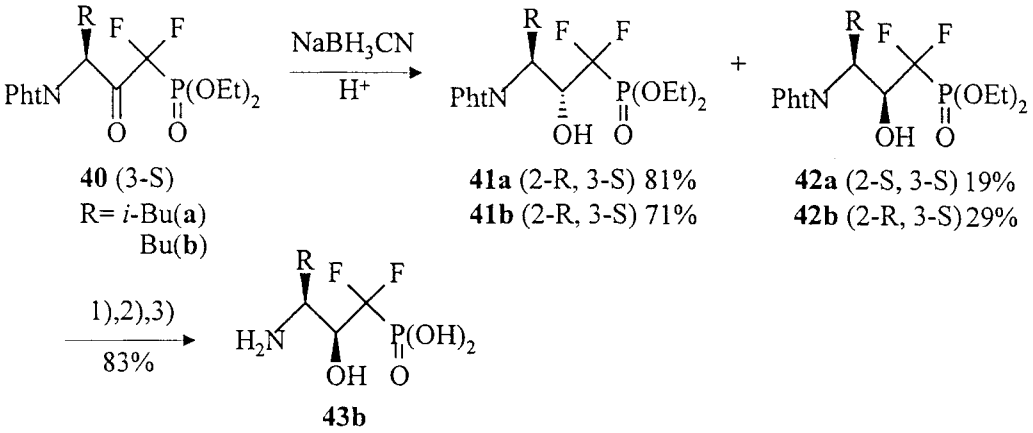
Although alkyl or aryl phosphonates can be prepared from alkyl or aryl halides and trivalent phosphorus reagents, unfortunately, these methods cannot be used for the synthesis of heterocyclic compounds in which the phosphoryl group is directly linked to the ring. However, the building-block strategy can be exploited to solve this problem. Isocyanomethylphosphonates serve as a promising building block owing to the versatile reactivity of the isocyano group. Schollkopf and co-workers [48,49] synthesized phosphorylated oxazoline, oxazole, and thiazole by cycloaddition of an isocyanomethylphosphonate to an aldehyde, acyl chloride or carbon disulfide, namely, the C=O or C=S bond, respectively. We first reported cycloaddition of an isocyanomethylphosphonate to electron-deficient alkenes or imidoyl chlorides, namely, to the C=C or C=N bond, to prepare phosphorylated pyrroles and imidazoles.

Phosphorylated Pyrrole and Dihydropyrrole. Reactions of nitroalkenes with diethyl isocyanomethylphosphonate using *t*-BuOK, *n*-BuLi, or LDA as base provided 3,4-disubstituted pyrrole-2-phosphonates in moderate yields [50]. Reaction of *β*-nitrostyrene with diethyl isocyanomethylphosphonate gave a complicated mixture that demonstrated that the existence of a substituent geminal to the nitro group was essential in this reaction. Aliphatic nitroalkenes furnished the products in lower yields than aromatic nitroalkenes owing to the base-catalyzed polymerization of the alkenes (Scheme 14). A tentative reaction mechanism was postulated by us. The addition of a carbanion derived from diethyl isocyanomethylphosphonate to a nitroalkene generated a nitronate anion that cyclized by intramolecular addition to the isocyano group. Elimination of the nitro group on the tertiary carbon, followed by subsequent allylic proton transfer, afforded the 3,4-disubstituted pyrrole-2-phosphonates. This is an interesting reaction in which the nitro function acts as both an activating and a leaving group (Scheme 15).

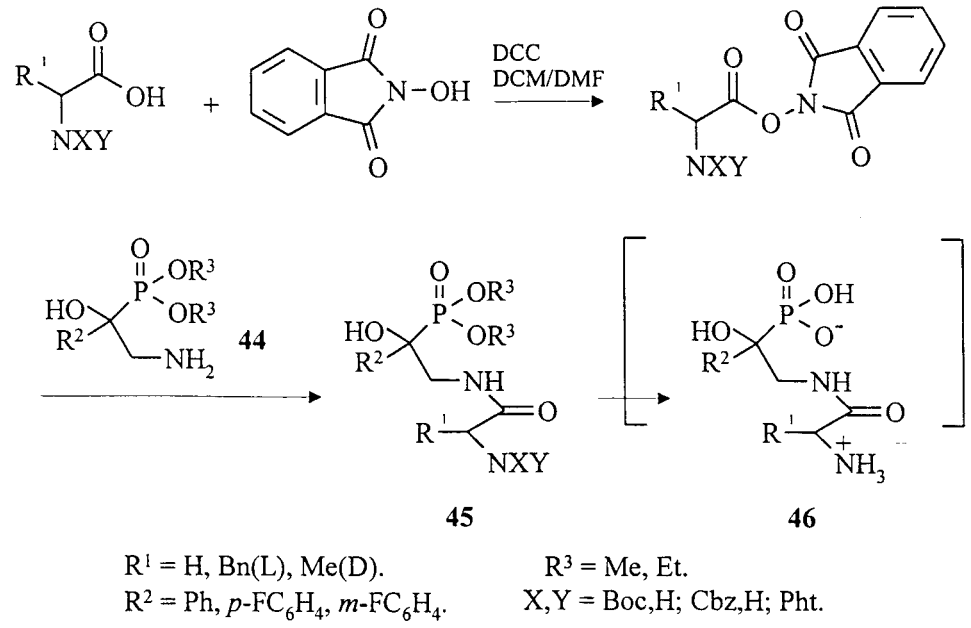
Cuprous oxide catalyzed reactions of diethyl isocyanomethylphosphonate with methyl methacrylate or methacrylonitrile produced 3,4-dihydro-2H-pyrrole-2-phosphonates. In this case, Cu_2O activates the methylene group or the isocyanomethylphosphonate to form a species with a C–Cu bond, which, being similar to a carbanion, attacks the Michael acceptor and then cyclizes to give the product [51]. In spite of its low stereoselectivity, this reaction is a good example of atom economy (Scheme 16).

Phosphorylated Imidazoles. We also investigated the reaction of diethyl isocyanomethylphosphonate with the C=N bond. Unsuccessful trials on reaction with imines or *O*-trimethylsilyl oxime impelled us to study the reaction with imidoyl chlorides. Keeping the role of the nitro group in the aforementioned formation of the pyrrole-2-phosphonate in mind, we supposed that the presence of a leaving group at the imino carbon should facilitate the reaction with the C=N bond. However, imidoyl chlorides are not easy to handle due to their high sensitivity to moisture. We chose trifluoroacetimidoyl chlorides as starting materials because of their stability resulting from the presence of the strong electron-withdrawing trifluoromethyl group.

As shown in Scheme 17, the carbanion derived

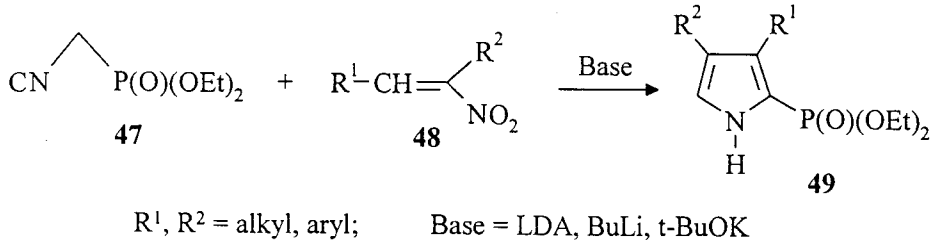


SCHEME 12

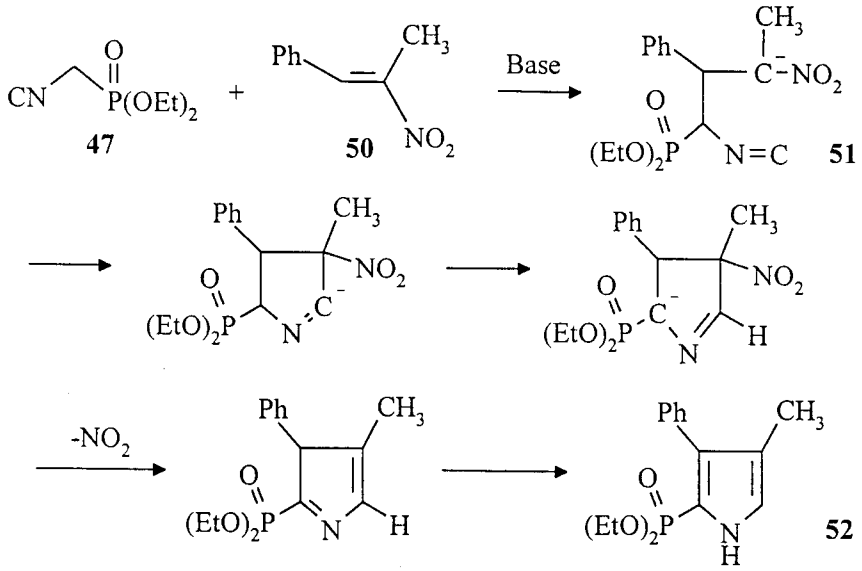


SCHEME 13

from diethyl isocyanomethylphosphonate at −70°C displaced smoothly the chlorine of N-substituted trifluoroacetimidoyl chlorides to form an imine intermediate, which, upon rearrangement, followed by cyclization, gave 1-substituted 5-trifluoromethylimidazole-4-phosphonates in moderate to good yields. Signals at δ = 7.60–7.79 (N=CHN) in ^{1}H NMR spectra definitely revealed the formation of the imidazole. When R was an alkyl group, the yields of imidazoles were somewhat lower than when R was an aryl group, possibly owing to the base-induced isomerization of imidoyl chlorides in the former case [52]. Usually, the addition of amines to an isocyano carbon requires the participation of a catalyst. The driving force of such cyclization seems to be the tendency toward aromatization. Attempts to isolate the imine or the enamine intermediate were not successful.



SCHEME 14



SCHEME 15

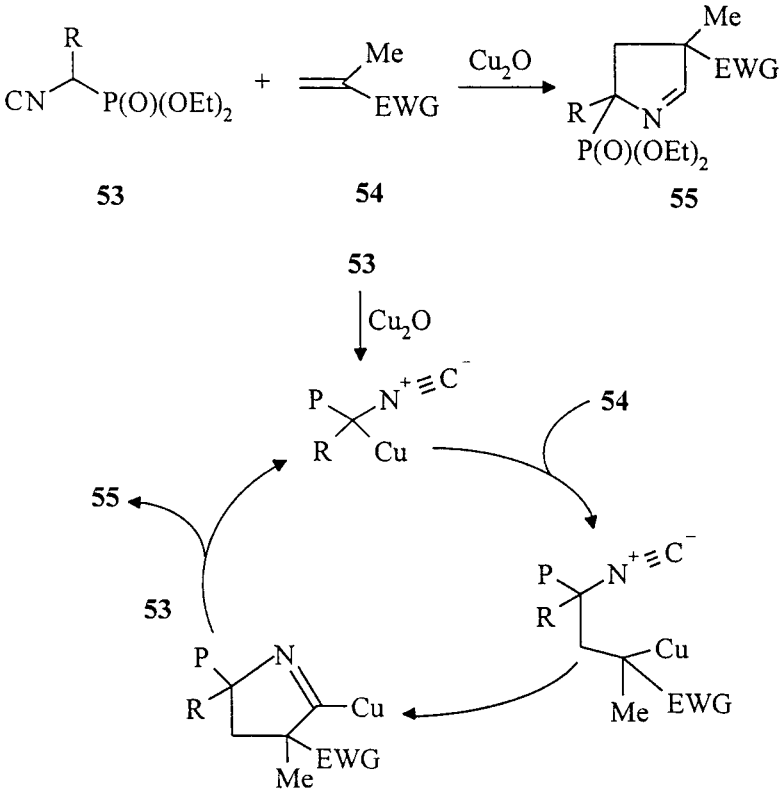
Replacement of BuLi by NaH in this reaction failed to give imidazole compounds. Quenching of the reaction produced a complex that was difficult to purify by column chromatography.

The regiochemistry of this reaction deserves more attention. The single chemical shift in the ^{31}P NMR and ^{19}F NMR spectra demonstrated the sole structure of the products. The regioisomers, 1-substituted 5-trifluoromethylimidazole-2-phosphonates, which conceivably could have resulted from a 1,3-dipolar cycloaddition, were not detected. The ^{13}C NMR spectra confirmed the regiochemistry. The doublets assigned to C-2 and C-4 and the *dq* signals of C-5 indicated that the phosphoryl group was linked to C-4.

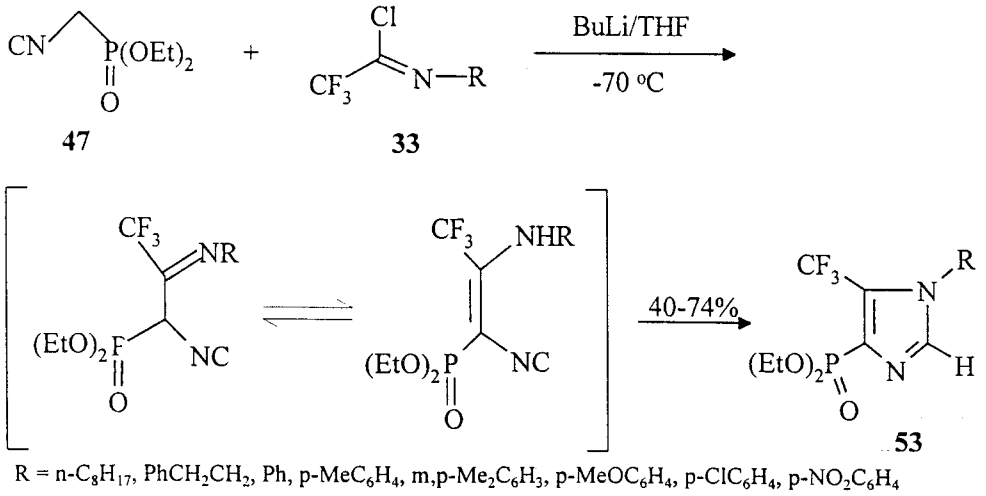
As shown in Scheme 18, another pathway in which cyclization precedes the elimination of chlorine may be postulated [53]. This addition-cyclization-prototropic-elimination process, however, was precluded since the reaction of diethyl 1-isocyanoethylphosphonate with N-phenyltrifluoroacetimidoyl chloride gave a 1-isocyano-2-iminophosphonate rather than the cyclized imidazoline derivative. This result means that the elimination of chloride ion from the N-anion is more rapid than the cyclization (Scheme 19).

It is noted that this reaction provides 1-arylimidazoles [54] that are otherwise not easily attainable due to the fact that nucleophilic alkylation at N-1 by an aryl halide is not possible. Moreover, fluorinated heterocycles are the subject of active investigation, and some fluorinated imidazoles have been found to function as xanthine oxidase inhibitors or have been used as drugs.

Nucleophilicity of Isocyanomethylphosphonate. As demonstrated by Huckel, MNDO, and ab initio MO calculations, the predominant contribution to the valence-bond description of alkyl isocyanides is made by the polar structure $RN^+ = C^-$, an iminocarbene resonance hybrid [55]. The isocyano carbon atom thus carries a nonbonding (*n*) electron pair with a formal negative charge. A nucleophilic character is therefore not unexpected. An evidence for such a property is the [1 + 4] cycloaddition reaction of alkyl isocyanides with conjugated nitroalkenes



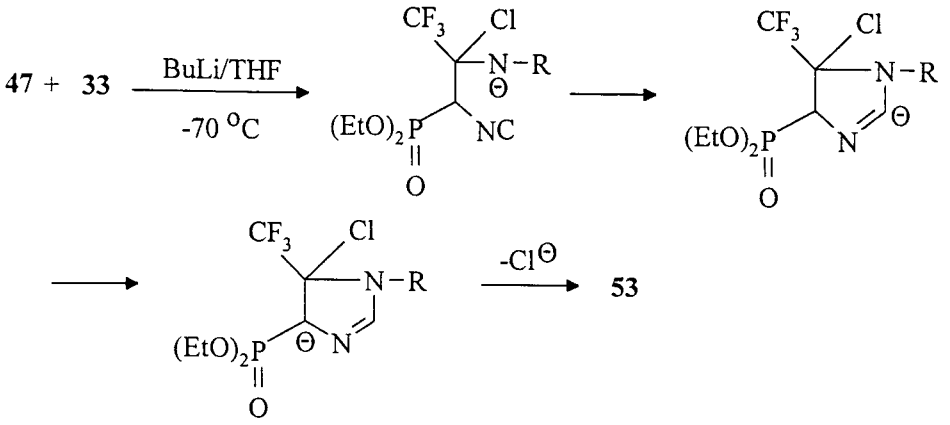
SCHEME 16



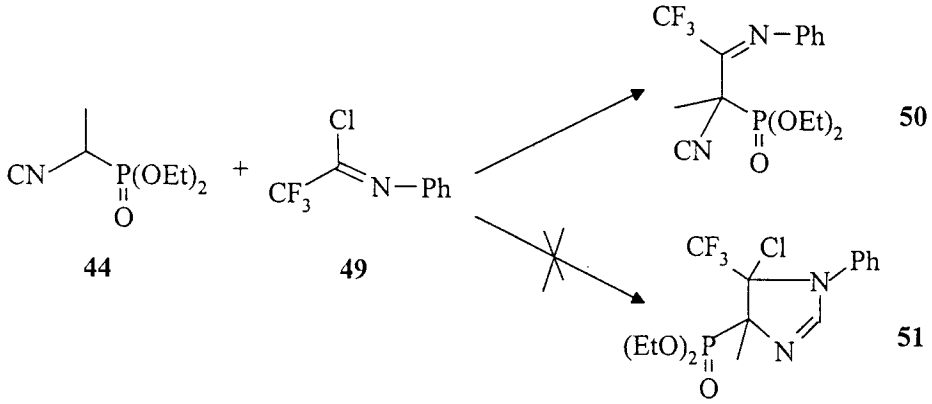
SCHEME 17

[56]. However, we found that diethyl isocyanomethylphosphonate does not react similarly with nitroalkenes, which is attributed to the reduced nucleophilicity of its isocyano carbon atom caused by the electron-withdrawing phosphoryl group. It can be envisaged that the weak nucleophilicity of diethyl isocyanomethylphosphonate can be demonstrated by its reaction with a strong electrophile. Thus, we investigated the α-addition reaction of trifluoroacetic anhydride and acyl chlorides to diethyl isocyanomethylphosphonate [57].

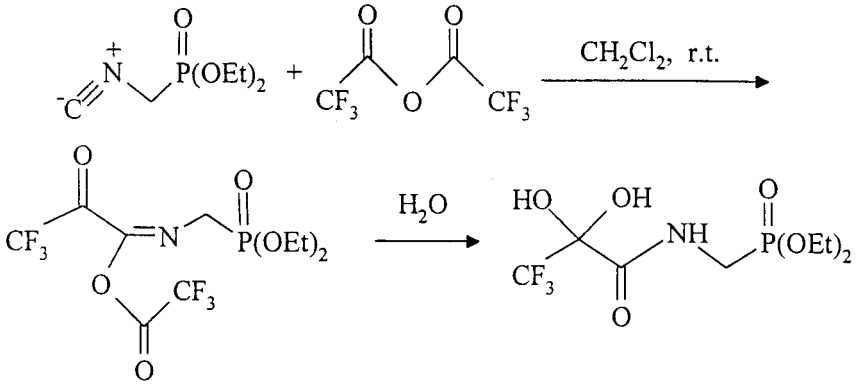
Diethyl isocyanomethylphosphonate was first allowed to react with the highly electrophilic trifluoroacetic anhydride. As shown in Scheme 20, this exothermic reaction occurred at room temperature in dichloromethane, giving (*N*-diethoxyphosphoryl-



SCHEME 18



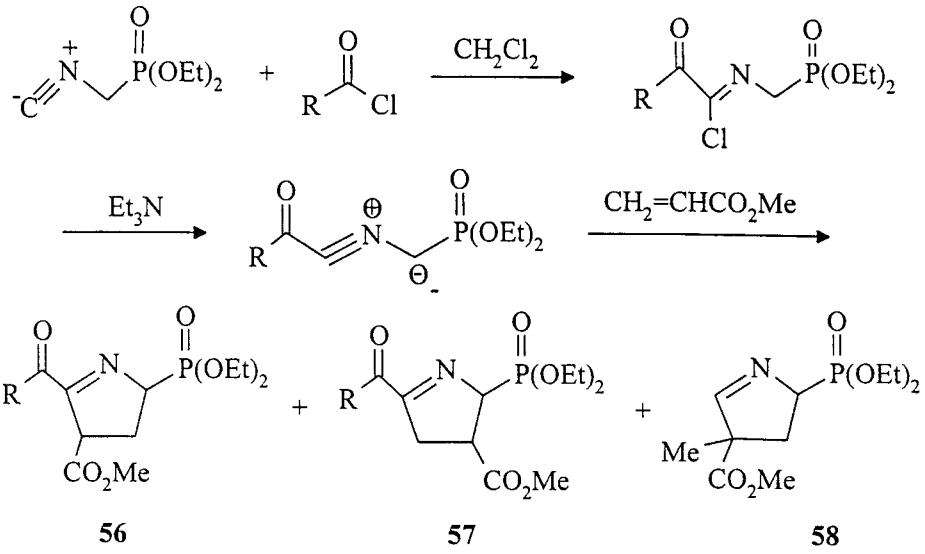
SCHEME 19



SCHEME 20

methyl)trifluoropyruvamide hydrate after hydrolysis of the α-adduct. The resonances at δ_H 3.24 (br, 3H, NH, 2OH), δ_F −6.3 (s), and combustion microanalysis confirmed the structure.

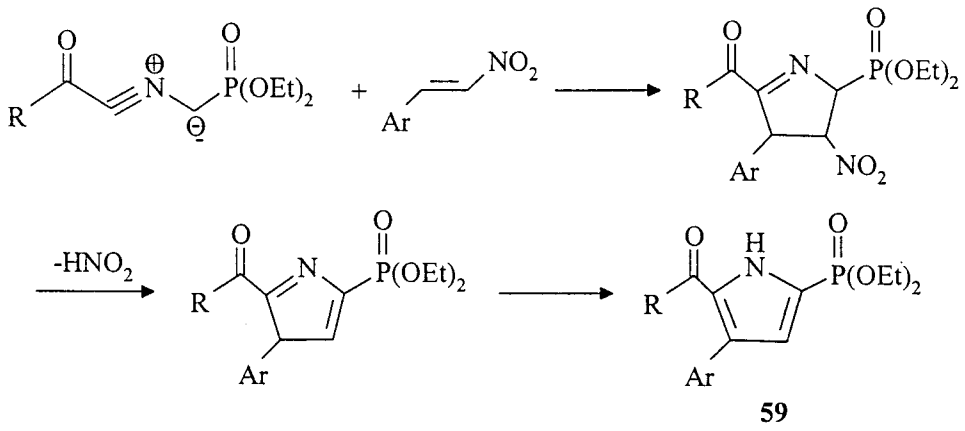
We next examined the reaction of acyl chlorides with an isocyanomethylphosphonate ester. As shown in Scheme 21, the acyl chlorides, derived from the corresponding primary, secondary, and tertiary alkanoic acids, reacted with the isocyanide functional group in refluxing dichloromethane over 20 hours (via TLC monitoring). The α-adduct with the structure of an α-ketoimidoyl chloride can be easily distinguished from the starting materials on a TLC plate by its ultraviolet absorption due to the conju-



56 **57** **58**

R = C_2H_5 (**56a**, **57a**); *cyclo*-C_6H_{11} (**56b**, **57b**); $(CH_3)_3C$ (**56c**, **57c**)

SCHEME 21



59

59a R=C_2H_5, Ar=Ph; **59b** R=C_2H_5, Ar=*p*-ClC_6H_4;
59c R=*t*-Butyl, Ar=Ph; **59d** R=*t*-Butyl, Ar=p-ClC_6H_4

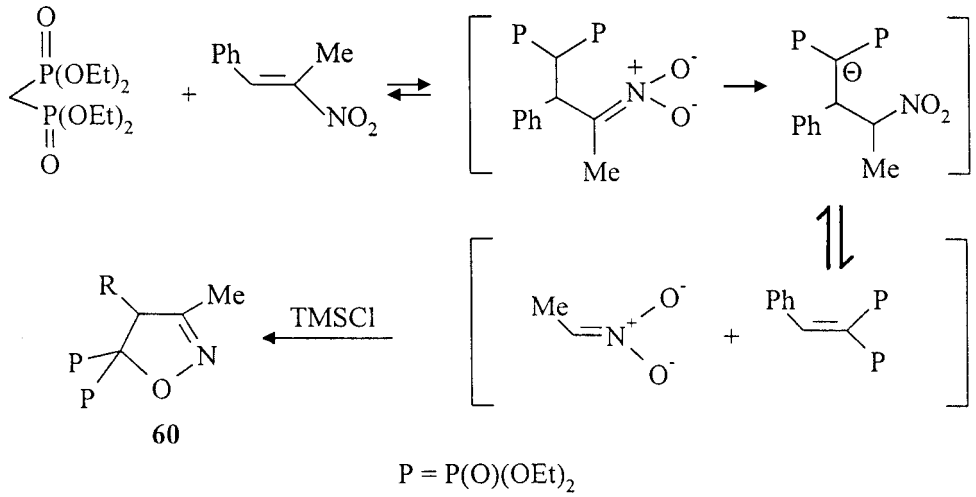
SCHEME 22

4.2 Phosphorylated 4,5-dihydroisoxazoles

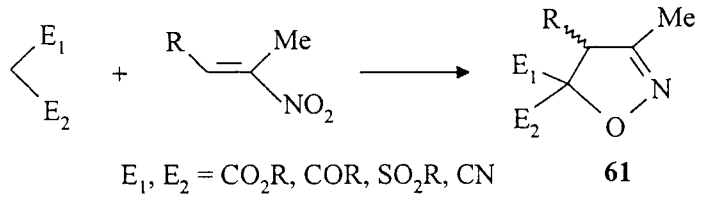
gation between the carbonyl and the imine group. The observed difference between trifluoroacetic anhydride and acyl chlorides when they reacted with diethyl isocyanomethylphosphonate, was attributed to the weaker electrophilicity of acyl chlorides as against that of trifluoroacetic anhydride.

1,3-Dipolar cycloaddition of an α-phosphoryl nitrile oxide to olefins has been reported [58]; however, reactions of phosphorylated nitrile ylides have, to the best of our knowledge, not yet been studied. We demonstrated that the α-ketoimidoyl chlorides, generated by the α-addition reaction of acyl chlorides to the isocyanomethylphosphonate ester, may serve as precursors to phosphorylated nitrile ylides.

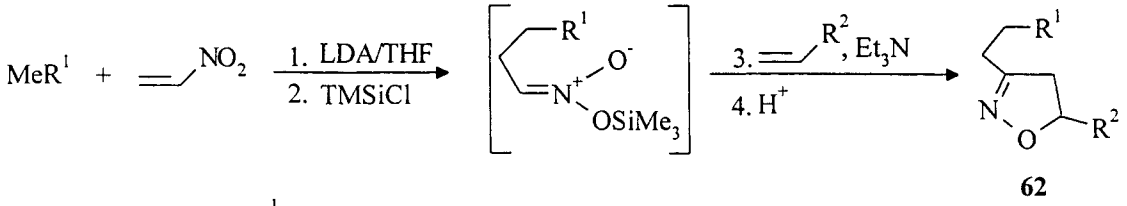
Thus, the α-ketoimidoyl chlorides formed in the above manner were treated with triethylamine without isolation, providing a 1,3-dipolar species upon 1,3-dehydrochlorination. This 1,3-dipolar intermediate was then trapped in situ with methyl acrylate to give the cycloadducts as a mixture of 3- and 4-methoxycarbonylpyrrolines, showing a lack of regioselectivity (Scheme 21).



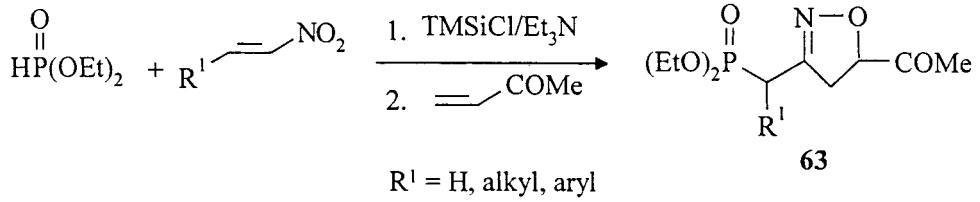
SCHEME 23



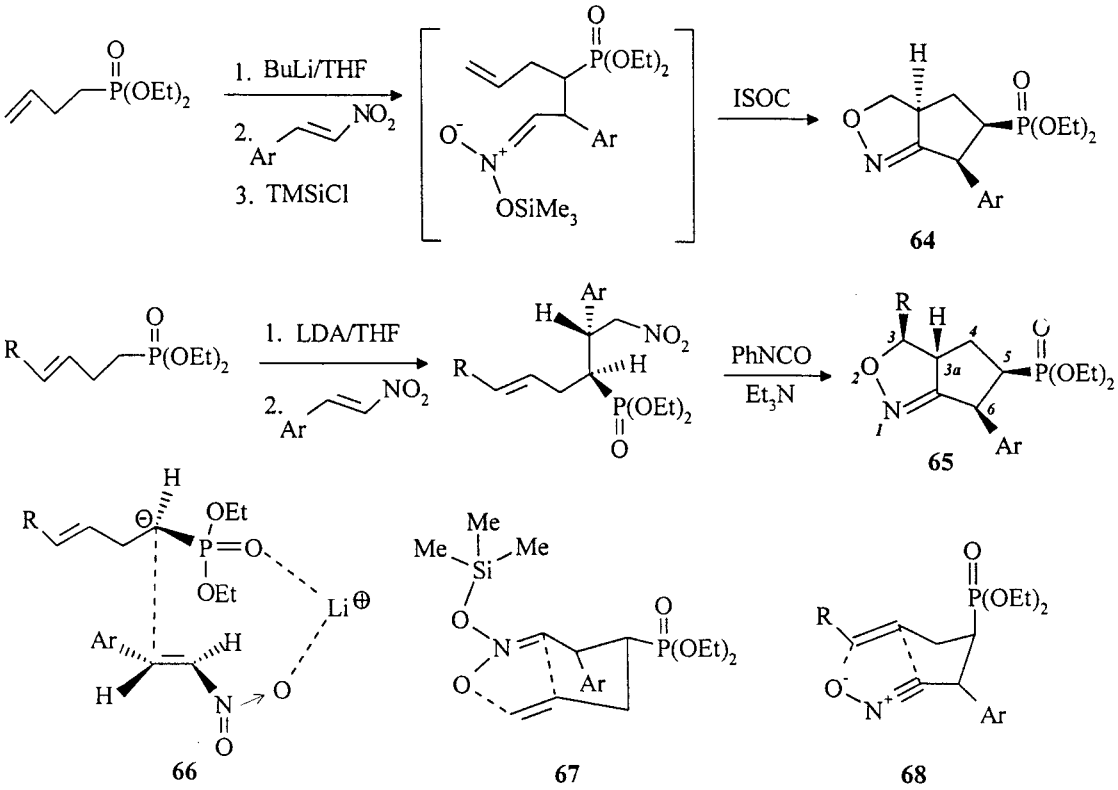
SCHEME 24



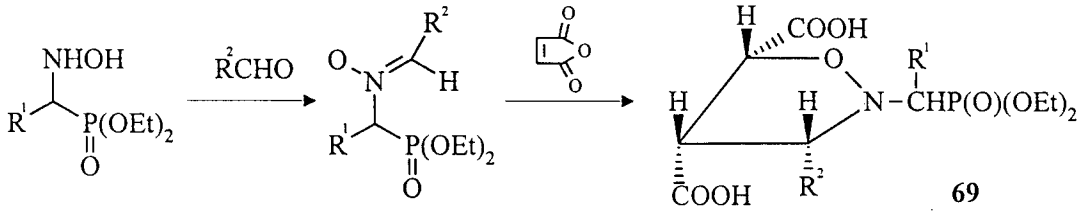
SCHEME 25



SCHEME 26



SCHEME 27



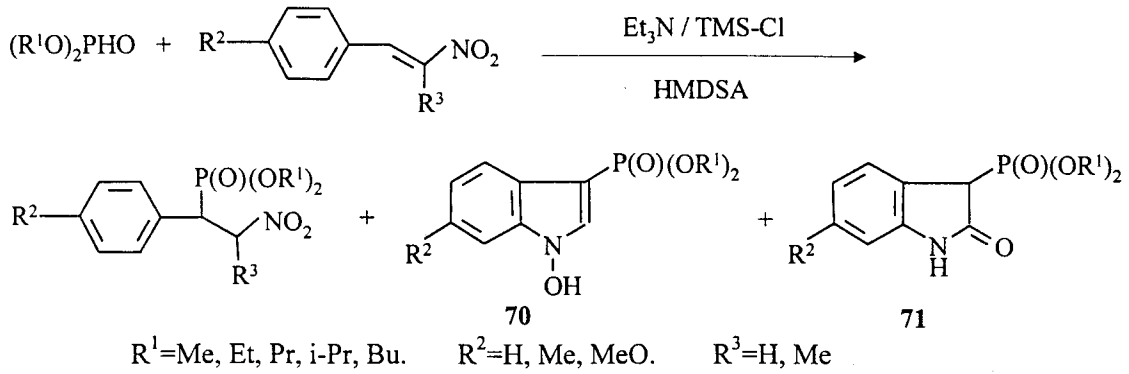
R^1=Ph, p-ClC_6H_4. R^2=Et, Ph, p-$MeOC_6H_4$, p-FC_6H_4.

SCHEME 28

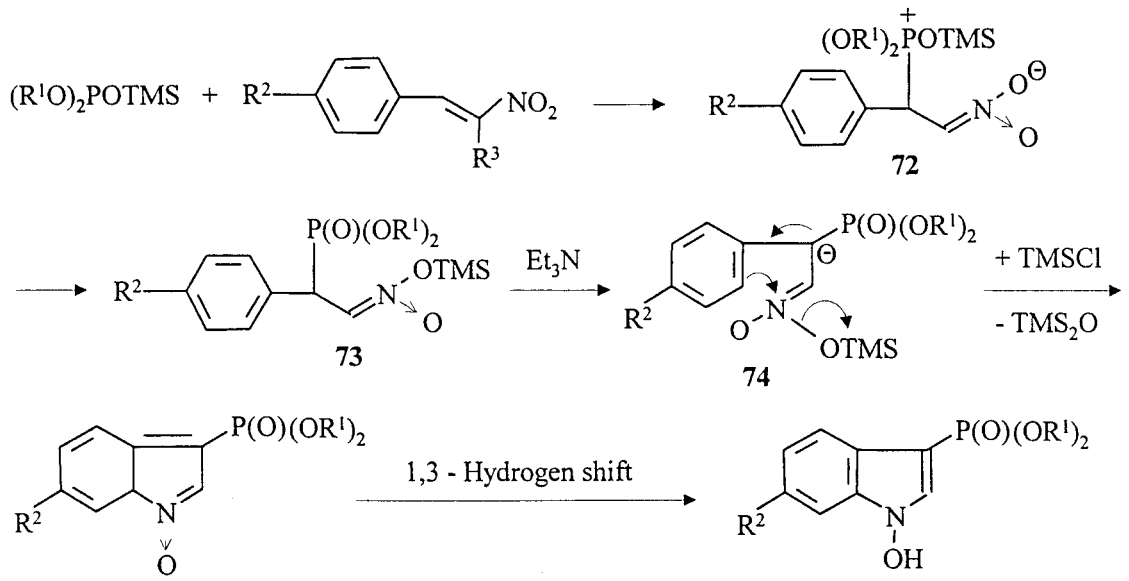
When nitroalkenes were used as dipolarophiles to capture the above 1,3-dipolar intermediates, 5-acylpyrrole-2-phosphonates were obtained in moderate yields, together with some unidentified components. As illustrated in Scheme 22, the pyrroles 59 are produced via a regioselective 1,3-dipolar cycloaddition followed by elimination of nitrous acid and subsequent aromatization (Scheme 22).

Phosphorylated 4,5-Dihydroisoxazoles

In our continuing study of the chemistry of nitroalkenes, we observed that reaction of tetraethyl methylenebisphosphonate with *β*-methyl-*β*-nitrostyrene in the presence of *n*-BuLi in refluxing THF afforded a 7% yield of an ethenylidenebisphosphonate in addition to the normal Michael addition product. We reasoned that the equilibrium shown in Scheme 23 may be involved in this Michael addition. This suggestion was verified by the following: (1) Addition of *p*-nitrobenzaldehyde to the reaction mixture provided the Horner-Emmons reaction product solely. (2) Addition of trimethylchlorosilane (TMSiCl), followed by immediate quenching with acid, furnished the ethenylidenebisphosphonate quantitatively, because TMSiCl reacted with lithium nitromethane to form the silyl nitronate, shifting the equilibrium to the right side completely. (3) Addition of TMSiCl followed by allowing the mixture to stand for two days and subsequent quenching with acid produced the



SCHEME 29



SCHEME 30

2-isoxazoline-5,5-dilylbisphosphonate, resulting from 1,3-dipolar addition of the silyl nitronate to the ethenylidenebisphosphonate. Extension of this reaction to other nitroalkenes led to the development of a useful route to 3,4-disubstituted 4,5-dihydroisoxazole-5,5-diylbisphosphonates [59] (Scheme 23).

Other compounds with an active methylene group reacted analogously with nitroalkenes and then TMSiCl, giving 4,5-dihydroisoxazoles with two electron-withdrawing substituents at C-5 of the ring [60]. Generation of alkenes and nitronates in these reactions was thought to result from a 1,7-silicon migration, which is, however, quite different behavior from that of bisphosphonates (Scheme 24).

The Michael addition of carbanions derived from methylphosphonates to nitroethylene, followed by reaction with TMSiCl, gave the corresponding silyl nitronates that reacted with electron-deficient alkenes to give 4,5-dihydroisoxazoles in a one-pot procedure [61]. Electron-rich alkenes such as styrene or 1-hexene did not undergo this reaction due to the low reactivity of the silyl nitronate. Other carbanions stabilized by an electron-withdrawing group behaved analogously (Scheme 25). Similar reactions using lithium diethyl phosphites as the nucleophile offered 3-diethoxyphoshorylmethyl-4,5-dihydroisoxazole derivatives [62], which have been reported by others to be useful synthetic intermediates (Scheme 26).

Intramolecular silyl nitronate-olefin cycloadditions (ISOC) and intramolecular nitrile oxide-olefin cycloadditions (INOC) were also investigated by us. The Michael addition of carbanions derived from alk-3-en-1-ylphosphonates to 2-aryl-1-nitroethylenes, followed by reactions with TMSiCl, gave the corresponding intermediates of silyl nitronates, which

underwent the ISOC reaction. This led to the stereoselective synthesis of 6-aryl-3,3a,4,5,6-pentahydrocyclopent[C]isoxazole-5-ylphosphonates [63]. The spatial structures of the products were unambiguously characterized by ^{1}H, ^{13}C, and ^{31}P NMR, NOESY, and ^{1}H–^{13}C COSY spectra. The hydrogen at C-3a is *trans* to both the phosphonate group at C-5 and the aryl group at C-6. The Michael addition products were isolated in the absence of TMSiCl and were then allowed to undergo the INOC reaction by treatment with phenyl isocyanate and triethylamine to provide the products where the hydrogen at C-3a is *cis* to both the phosphonate group at C-5 and the aryl group at C-6 [64]. The Michael addition proceeded via the transition state **66** of least steric hindrance in both reactions. The opposite stereoselectivity of ISOC and INOC reactions may be rationalized by the difference of their transition states. In the transition state **67** of an ISOC reaction, the aryl and trimethylsilyl groups have to be *trans* due to the steric interaction, which renders the hydrogen at C-3a *trans* to the aryl group at C-6; on the other hand, the transition state **68** of INOC leads to the *cis* relationship between the hydrogen at C-3a and the aryl group at C-6 (Scheme 27).

Phosphorylisoxazoline Derivatives

1,3-Dipolar addition of nitrones was established by Huisgen [65] as one of the important routes to heterocycles. By the reaction of 1-(hydroxylamino)alkylphosphonates with aldehydes we obtained phosphoryl nitrones with exclusively the Z-configuration that gave (Z)N-phosphorylisoxazolines via 4 + 2 dipolar cycloadditions with maleic anhydride (Scheme 28).

The configuration of the product was demonstrated by 2D NOESY NMR spectroscopy and rationalized by FMO theory [66].

Phosphorylated Indoles

Reactions of dialkyl phosphites with 2-nitrostyrenes in the presence of triethylamine, trimethylsilyl chloride and hexamethyldisilazane provides a one-pot procedure for the synthesis of N-hydroxy-indole-3-phosphonates (**70**) and indole-2-one-3-phosphonates (**71**) as well as the normal addition products, 1-aryl-2-nitroalkylphosphonates [67] (Scheme 29). A tentative reaction mechanism was postulated by us (Scheme 30).

An active nucleophile, a tri-coordinated silylated phosphite, is formed by reaction of a dialkyl phosphite with TMSCl/Et_3N. This species attacks the β-carbon of a 2-nitrostyrene to give a dipolar intermediate (**72**), which undergoes fast 1,6-silyl migration to form the intermediate **73**. α-Proton abstraction by Et_3N from the latter gives **74**. Nucleophilic attack of an ortho-carbanionic center of **74** on the nitrogen atom with loss of TMSO, followed by a 1,3-shift of hydrogen from carbon to oxygen, yields an N-hydroxy-indole-3-phosphonate.

ACKNOWLEDGMENT

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