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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 poly-functionalized phosphonates as well as phosphoryl heterocycles were reported for the systematic study of relationship between chemical structure and biological activities of this most important class of organophosphorus compounds.

Introduction

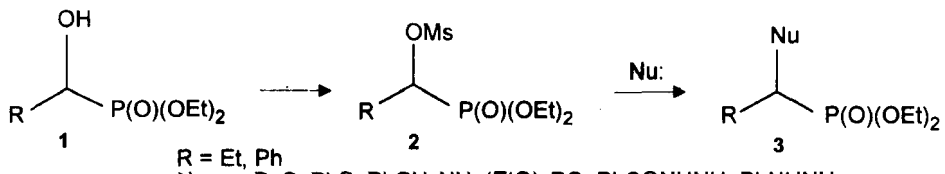
Functionalization of phosphonic acid molecules opens enormous possibilities of structural variation of this important class of organophosphorus compounds with potential biological activities. This is particularly true for 1-aminoalkylphosphonic acid and related peptides which have been found wide applications both as agrochemicals and medicinal products. Numerous synthetic approaches were described for the formation of monofunctionalized phosphonic acid which is usually required multistage manipulation. Introduction of additional functionalized group to these molecules by traditional method is complicated due to inter- or intra- molecular interactions. Consequently, design of synthesis of mono-, di- and polyfunctionalized phosphonic acids and study the structural effect of these compounds on their biological activity are of great interest both in synthetic organophosphorus chemistry and for the development of lead structure for biologically active molecules.

Results and Discussion

1. Monofunctionalized phosphonic acids

1.1 1-Heteroatom substituted phosphonic acids

1-Heteroatom substituted phosphonic acids cover a wide spectrum of important organophosphorus compounds. Unfortunately, the conventional method of preparation based on nucleophilic substitution of 1-halogen-alkylphosphonates is under greater challenge associated with low reactivity of 1-halogen atom, narrow scope of applications as well as inaccessibility of the intermediates. As found by us, upon substitution of 1-methanesulfonyl 1-alkylphosphonate by a phosphite anion provided alkylidene bisphosphonates.[1] Since -OMs behaviours as good leaving group, this nucleophilic substitution was extended as a general way of preparation of 1-heteroatom substituted alkylphosphonate.



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

The yield of reaction was increased as the increase of the nucleophilicity of the reagents as shown by the order:

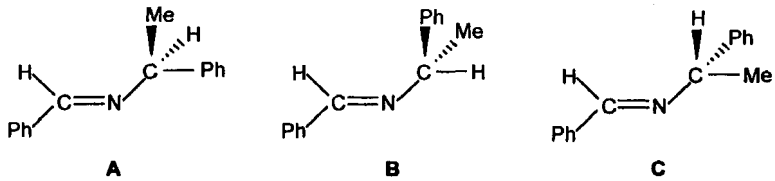
n-BuSH > PhSH > NH_2NH_2 > $PhNHNH_2$ ~ $PhCH_2NH_2$ > $(EtO)_2POH$ > $PhCONHNH_2$ >> CN^- >> F^-

Diethyl 1-ethyl-1-hydroxymethylphosphonate provides much higher yield than corresponding 1-phenyl-1-hydroxymethylphosphonate.

However, substitution of methanesulfonyl group by trifluoromethanesulfonyl moiety failed to give analogous reaction under similar condition.

1.2 1-Aminophosphonic acids

As phosphorus analogs of 1-aminocarboxylic acid, 1-aminoalkylphosphonic acids are most important members of 1-heteroatom substituted phosphonic acids. The asymmetric synthesis of these compounds aroused the interest of organic chemists,[2] nevertheless, direct conversion of 1-amino-carboxylic acid to corresponding phosphonic acid was reported.[3] Since the biological activity of 1-aminophosphonic acid is largely dependent on their absolute configurations. The nucleophilic addition of dialkylphosphite to imines or oxoiminium derivative constituted the majority of asymmetric synthesis of 1-aminophosphonic acid up to date. We have investigated the stereochemical behavior of the addition of diakylphosphites to aldimine, resulting from the condensation of substituted benzaldehyde and (R)-1-phenylethylamine. The structural effect of substrates and reagents, the influence of reaction conditions including the nature of catalyst and solvent on the diastereomeric excess values and induced direction of the asymmetric addition were reported.[4] A molecular machanics study on this type of reaction revealed that the *de* values and the induced direction were controlled by the conformation of the imine substrate.[5]

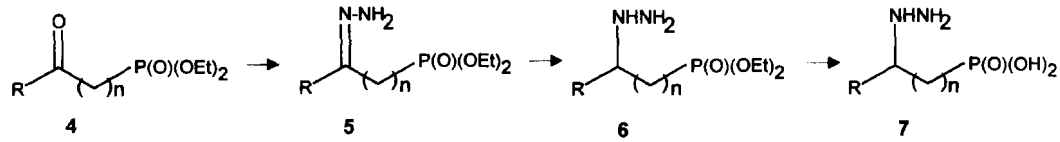


A B C

With the aid of phenylglycine ester as chiral auxiliary, the *de* value of this asymmetric addition is increased to 89% in addition to 84% chemical yield. As a result of the coordination Lewis acid, the comformer C is predominant. In consequence of the steric effect, the attack of diethylphosphite took place from the reface of the imines giving rise to mainly (1R, 1R). Therefore the values were increased with the increase of the coordination ability. This can also be rationalized by the contribution of the ratio of conformer C. This is the first example illustrating the successful trial in asymmetric synthesis of 1-aminophosphonic acids based on molecular mechanics calculation.[6]

1.3 1- and/or 2-Hydrazinoalkylphosphonic Acids

Starting from diethyl 1-ketophosphonates, 1-hydrazonophosphorus can be prepared smoothly, the latter was conveniently reduced to corresponding hydrazino derivatives, as analogous of aminophosphonic acid, upon treatment with $NaBH_4$.[7]



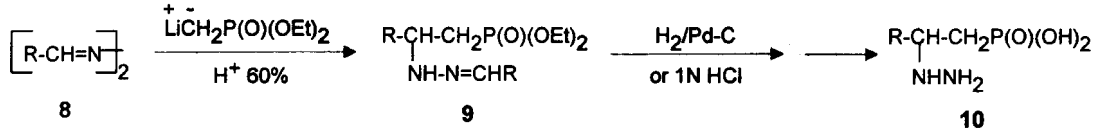
4 5 6 7

n=0, R = Me, $PhCH_2$, p-$MeC_6H_4CH_2$, p-$MeOC_6H_4CH_2$, p-$FC_6H_4CH_2$

n=1, R = Et, cyc-Pr, $PhCH_2$, Ph, p-$MeC_6H_4CH_2$, p-$MeOC_6H_4$, p-MeO-m-BrC_6H_3, p-FC_6H_4, p-ClC_6H_4, p-BrC_6H_4, p-$NO_2C_6H_4$

The β-hydrazinoethylphosphonates were prepared analogously from β-ketoethyl-phosphonate, using BH_4·THF as reducing reagent, which is capable to convert β-hydrazono derivatives to β-hydrazinoethylphosphonates in high yield.

As shown by us, a direct synthetic route to β-hydrazinoethylphosphonic acid was achieved based on the addition of cabanion derived from methylphosphonate to an aldimine prepared conveniently by condensation of aromatic aldehyde with hydrazine. Difficult was encountered during the hydrogenolysis of N=C bond since it is unsully accompanied by N-N bond cleavage to amino-derivative. Removal of CHR- group can be achieved by acid treatment with 1N HCl, though the yield is poor (around 30%). The 2-hydrazino-2-alkyl(aryl)ethylphosphonic acids are easily obtained from the diethyl ester by reaction with Me_3SiBr and followed by subsequent treatment with methanol in the usual manner.

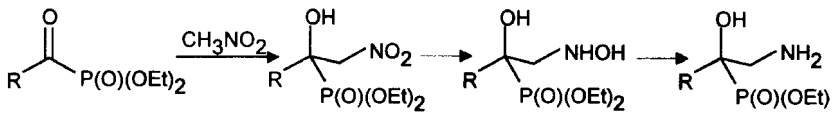


8 9 10

2. Difunctionalized phosphonic acids

2.1 1-Hydroxy-2-nitroalkylphosphonic acid and derivatives there of

Addition of nitromethane to 1-ketophosphonate provides a convenient route to 1-hydroxy-2-nitrophosphonate in which the nitro function can be converted smoothly to hydroxylamino, amino- and hydrazino group.[8,9]

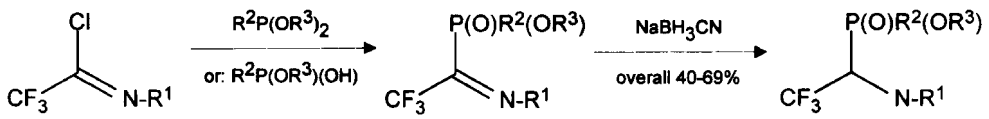


11 12 13 14

The conversion of nitro group into other functionalities depends largely on the reducing agents used. These 1-hydroxyl-2-heteroatom substituted phosphonic acids derivatives are of great interest as compounds of potential biological activity.

2.2 Aminophosphonic acid bearing trifluoromethyl moiety

Introduction of trifluoromethyl group to organic molecule is the subject of active investigation. For the purpose of enhancing the biological acitivity, a series of trifluoromethyl-amino-alkylphosphonic acids was synthesized by us. Our synthetic approach is based on the chemical conversion of trifluoroacetimidoyl chloride. Thus by Arbuzov-type reaction of trialkyl phosphite followed by subsequent reduction to the imine intermediates, leading to (N-aryl/alkylamino)2,2,2-trifluoroethyl-phosphonates, the trifluoromethylated phosphorus analogues of N-protected alanine.



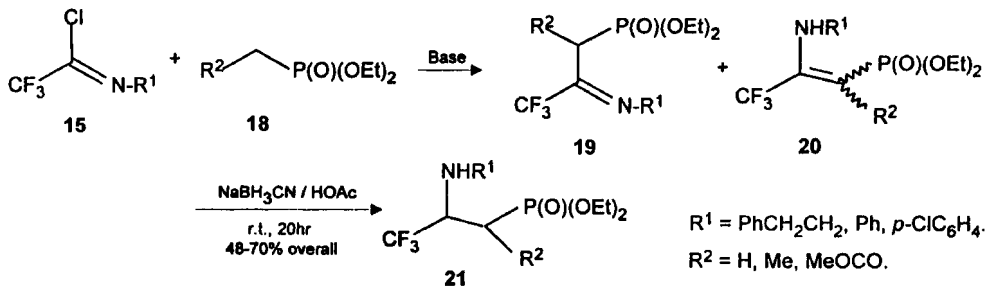
15 16 17

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.

The reaction of triethylphosphite with N-phenyltrifluoroacetimidoyl chloride was carried on at 80°C without solvent. ^{19}F Chemical shift for the starting **15** is 4.8ppm while for the resulted new compound is 9.7ppm. After 6hrs, the imidoyl chloride disappeared completely and the mixture was worked up to give the iminophosphonate in 95% yield. Signals in ^{31}P NMR spectra at δ=7.37ppm (q, J=9.2Hz) definitely revealed the formation of Arbuzov reaction product. The subsequent reduction was achieved by treatment with $NaBH_4CN$ as indicated by ^{31}P NMR at δ=15.2ppm (q, J=8.7Hz), much down field from that of iminophosphonate, because phosphonate moiety in the product is linked to a sp^3 hybridized carbon, while for iminophosphonate, it links to a sp^2 carbon.

We also extended the above reaction to various N-substituted trifluoroacetimidoyl chloride and other trivalent phosphorus reagents as shown below. N-substituents in **15** cause remarkable effect on the reaction. When R^1 was alkyl, prolongation of reaction time is necessary. While R^1 was aryl, the more powerful electron withdrawing group on the benzene ring, the more rapidly the reaction occurred. When N-(p-nitrophenyl)trifluoroacetimidyl chloride was used, the reaction was performed under 0°C for its high reactivity. Diethylphenylphosphonite reacted more rapidly than trialkylphosphite. These results indicated that the above Arbuzov-type reaction initiates to the nucleophilic attack of trivalent phosphorus species to **15**. Highly electrophilic imidoyl chloride and more nucleophilic phosphorus reagent promoted the reaction markedly. Dialkylphosphite also reacted to **15**; in such case addition of Et_3N is necessary in order to remove HCl generated. Monoethylphenylphosphate reacted similarly.

On the other hand, as an reactive intermediate, **15** underwent displacement reaction with cabanion deprotonated from appropriate alkylphosphonate. Subsequent reduction gave 2-trifluoromethyl-2-(substituted amino)ethylphosphonate, a trifluoromethyl-2-AEP.



Depending on the nature of R^2, appropriate base should be used. Replacement of Cl in **15** by carbanions provides, as a rule, a mixture of imino phosphonate (**19**) and enamine (**20**) which are very difficult to separate but are easily identified by ^1H NMR. The ratio of **19** and **20** is dependent on the structure of substituent. The mixture of intermediates was subjected to reduction without isolation. The reduction proceeded smoothly with $NaBH_3CN$ in acetic acid. Besides as a solvent, HAc enhanced the electrophilicity of the substrate by the protonation of the imino and amino nitrogens.

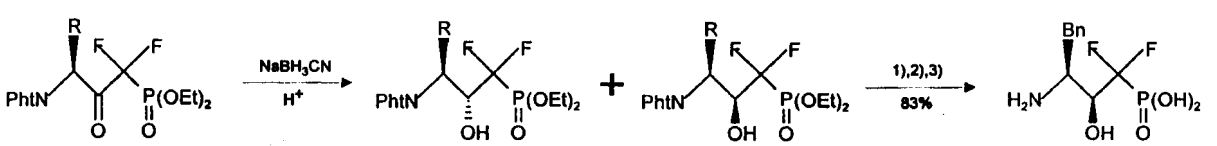
3. Polyfunctionalized phosphonic acids

3.1 Phosphonostatine containing difluoromethyl moiety

As an unusual amino acid 3(S)-amino-2(S)-hydroxy-5-methylheptanoic acid (statine) is an essential component of pepstatin, a naturally occurring peptide possessing inhibitory effect on proteolytic enzymes such as renin. Some synthetic peptides derived from difluorostatin are potent renin inhibitors and show promising new therapeutic possibilities for the treatment of high blood pressure. Recently, the difluoromethylphosphonate moiety has attracted much attention bacause it offered significant advantages over its nonfluoroinated counter parts as enzyme inhibitors.

The building block strategy was introduced by us for the synthesis of functionalized 1,1-difluoromethylphosphonates namely 3(S)-amino-2(S)-hydroxyl-1,1-difluoromethyl-alkylphosphonic acid by the following suquence of reactions.

The stereochemistry involved in these reactions was examined.[10]



22 (3-S)
R=*i*-Bu(a)
Bn(b)

23a (2-R, 3-S) 81%
23b (2-R, 3-S) 71%

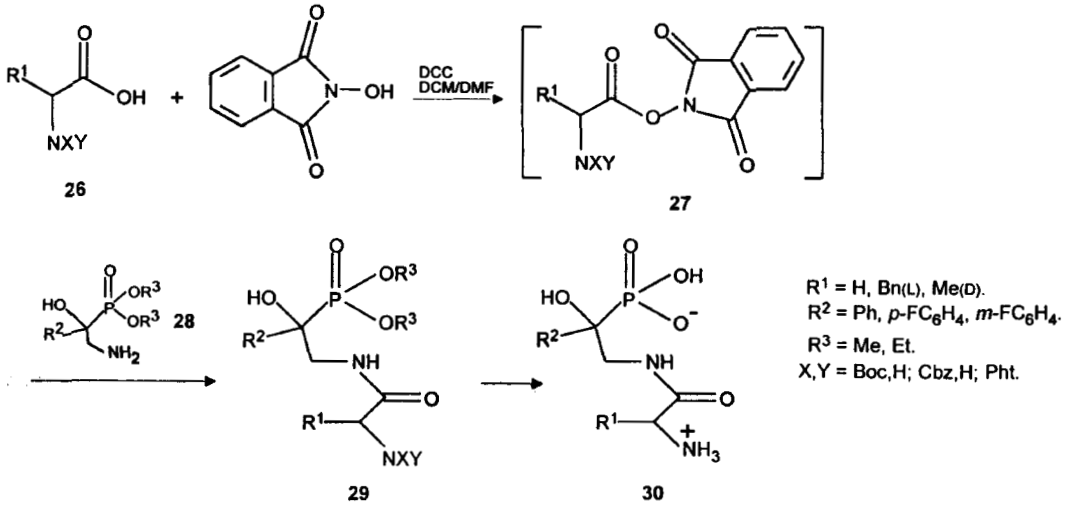
24a (2-S, 3-S) 19%
24b (2-R, 3-S) 29%

25

1) $N_2H_4 \cdot H_2O$, EtOH, reflux, 12h.
2) TMSBr, $CHCl_3$, r.t., 24h.
3) MeOH, 15min.,  , pH=6.

3.2 Peptides containing 1-hydroxyl-2-aminophosphonic acid residue

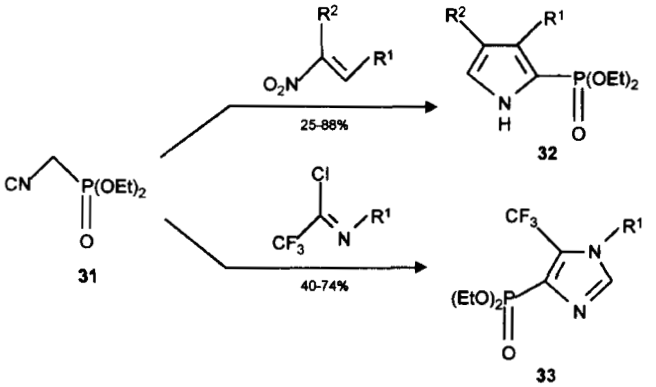
Since 2-amino-1-hydroxyethylphosphonic acid (HAEP) is the fifth C-P compound found in nature, the 2-alkyl substituted HAEP and its peptide derivatives were also reported as an inhibitor of renin. We have reported the use of in situ active ester formed by reaction of HONPht and N-protected amino acid in the synthesis of new type of phosphonopeptide containing a 1-alkyl-substituted HAEP unit.[11]



4. Phosphoryl Heterocycles

Synthetic study of heterocyclic compounds deserve considerable attention because of their potential biological activity and extensive application in organic synthesis. Phosphoryl heterocycles can be regarded as a special class of polyfuntionalized phosphonic acid.

Starting from isocyanomethylphosphonate we were able to synthesize phosphoryl pyrrole and imidazoles.[12]



Nucleophilic addition of nitroethylene to various carbanions followed by treatment with Me_3SiCl gave the corresponding silyl nitronate as a 1,3-dipole, which reacted with a monosubstituted alkene to give 4,5-dihydroisoxazole in a one-pot procedure.[13-15]

With substituted nitroalkene, diethylphosphite offered similar phosphorylisoxazole derivatives.[16]

Stereoselective condensation of alk-3-en-1-ylphosphonates with α-nitroalkenes gave the corresponding nitro compounds, which led to the stereoselective synthesis of 6-aryl-3,3a,4,5,6-penta-hydrocyclo-pent[C]-isoxazole-5-ylphosphonates via intramolecular nitrile oxide - olefin cyclo-addition in fair yield. Cyclohex-2'-en-1'-ylmethylphosphonates behaviours analogously.[17]

Reaction of methylene bisphosphonate with α-nitroalkene followed by addition of TMSiCl lead to the formation of ethenylidenebisphosphonates and trimethylsilyl nitronate in almost quantitative yields. These two products, upon prolonged reaction at ambient temperature, provide 2-isoxazoline-5,5-diylbisphosphonate via regioselective 1,3-dipolar-cycloaddition in high yield.[18]

1,3-Dipolar addition of nitrone was established by Huisgen as one of the important routes to heterocycles.[19] By the reaction of 1-hydroxylaminoalkylphosphonate with aldehyde we obtained a phosphoryl nitrons with exclusively Z-configuration which gave (Z)N-phosphorylisoxazoline via 4+2 dipolar cycloadition with moleic anhydride. the structure of resulting (Z)N-phosphorylisoxazoline was illustrated by 2D NOESY NMR and rationalized by FMO theory.

Acknowledgements

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