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An Overview of Recent Advances on the Synthesis and Biological Activity of α-Aminophosphonic Acid Derivatives

Junmin Huang and Ruyu Chen

Institute of Elemento-Organic Chemistry, National Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

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ABSTRACT: *As phosphorus analogs of natural α-amino acids, α-aminophosphonic acids and their derivatives have attracted wide attention in chemistry, medicine, and agricultural science. In this report, we provide an overview of our work about the synthesis and biological activity of α-aminophosphonic acid derivatives.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:480–492, 2000

INTRODUCTION

Aminophosphonic acids play an important role in living systems. The amino and phosphono groups in an aminophosphonic acid may be sited in any positions relative to each other on the carbon skeleton. However, those in which the amino group is sited on a carbon atom α to phosphorus have potential biological activity and particular significance as being analogs of the naturally occurring α-amino acids. As the mimetic tetrahedral intermediates of hydrolyzed esters, amides, and peptides, α-aminophosphonic acid derivatives have been used as antibiotics, herbicides, antitumor agents, or enzyme inhibitors with a broad application in many areas of agriculture and medicine [1,2]. By the early 1970s, and at the time of publication of the survey of organophosphorus compounds by Kosolapoff and Maier, only relatively few such compounds had been prepared, even though their natural occurrence and biological importance had already been recognized [3]. During the last 30 years, there has been a considerable growth in interest in the chemistry of this group of compounds, with the emphasis on their synthesis and diverse potential biological significance in metabolic processes of life. In this report, we wish to provide an overview of our work in recent years about the synthesis and biological activity of α-aminophosphonic acid derivatives. By introducing other biologically active groups into the structure of an α-aminophosphonic acid, we aimed to search for novel drugs or agricultural chemicals with high activity and low toxicity.

RESULTS AND DISCUSSION

Study on the Derivatives of α-Aminophosphonic Acids Containing Organogermanium Groups

Germasesquioxides have antitumor and other activities, and recent studies show that the germasesquioxides modified by phosphonic acid groups have high antitumor or antiinflammatory activity [4]. In order to introduce α-aminophosphonates into this kind of organogermanium compound, β-trichlorogermyl propionyl chloride was allowed to react with α-aminophosphonates in the presence of triethylamine to give compounds **1**, which were hydrolyzed

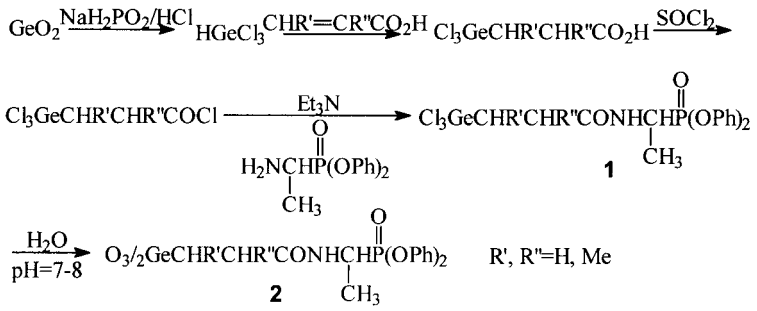
Correspondence to: Ruyu Chen
Contract Grant Sponsor: National Natural Science Foundation of China.

with water to give compounds **2** (Scheme 1). The proper conditions included a pH between 7 and 8 with saturated sodium hydrocarbonate, the use of mixed solvents, and low temperature and lead to easy isolation and high purity of products [5,6].

The study of Mannich-type reactions involving organogermanium compounds (Scheme 2) is significant for two reasons. It not only is the first report of an intramolecular catalytic Mannich-type reaction but also affords a convenient synthetic procedure for the preparation of the germasesquioxides modified by aminophosphonic acid groups.

The Mannich-type reactions of 3-trichlorogermylbutanal are carried out easily and smoothly under mild conditions compared with those of the aldehydes without organogermanium groups involved (Scheme 3, by Birum in 1974 [7]). This can be explained as being due to an intramolecular catalytic mechanism. The germanium atom can easily form a fifth coordinated bond with an electron donor due to the existence of the empty 4d orbitals, especially bonded to electron-withdrawing atoms or groups. The germanium atom in β-trichlorogermylbutanal was bonded to three chlorine atoms. It easily interacted with the oxygen atom of the carbonyl group to render it more reactive and easily attacked by an amine than that of *n*-butanal [8].

It is conceivable that the incorporation of the two moieties of pentacoordinated germanium and α-aminophosphonic acid into one structural unit might produce a synergistic effect on the activity of such a compound and that the studies of this type of novel structure would provide some interesting information of biological importance. Our initial attempts to use the common route via the reaction of **3** with phosphonylation reagents were confirmed to be unsuccessful, even under vigorous conditions (Scheme 4). It may be shown that the nitrogen atom



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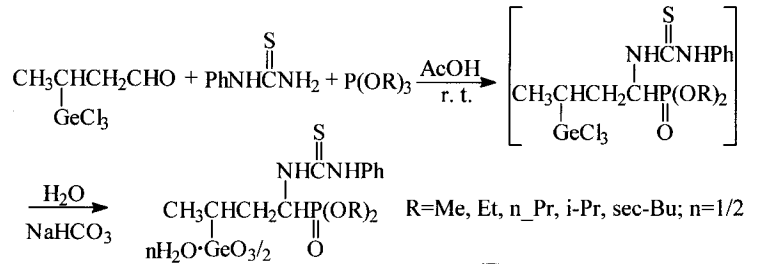

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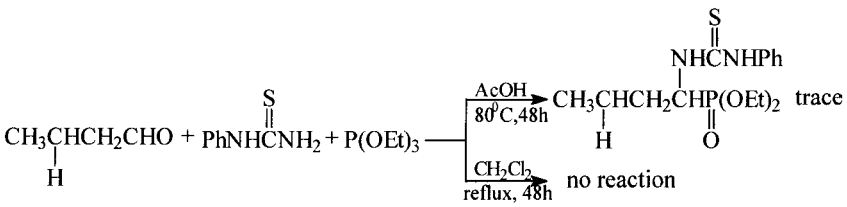

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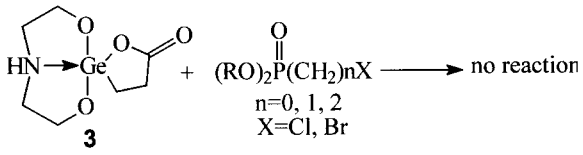


SCHEME 4

of compound **3** exhibits remarkably reduced nucleophilicity because of formation of an N–Ge bond.

It was found that the reaction of germanium sesquioxides **4** or tetraethoxygermane with diethyl *N,N*-bis(2-hydroxylethyl) aminomethyl phosphonate **5** takes place under mild conditions, and the easy work-up makes the method practical (Scheme 5). Crystallographic analysis has shown that the geometry about the germanium atom is a distorted trigonal bipyramid. The electron withdrawing effect of the N–Ge interaction increased the dπ-pπ back donating trend of the P=O bond and led to shielding of the phosphorus resonance (shifted ~8 ppm upfield relative to the signal of δp 26.92 ppm in compound **5**) [9–11].

Study on the Derivatives of α-Aminophosphonic Acid Containing Organoselenium Groups

In recent years, biologically active organoselenium compounds have begun to attract considerable interest due to their unique and diverse potential of pharmacological importance, such as broad spectrum antitumor and antiviral activities, and some of them are even many times more active than their oxygen or thio analogs. On the other hand, N-substituted α-aminophosphonate derivatives represent a class of compounds that tend to exhibit superior biological activities, such as antibacterial, herbicidal, antitumor, and inhibitory activity to enzymes. In order to search for novel antitumor and antiviral agents with high activity and low toxicity, a series of 1-aminoalkanephosphonate derivatives of benzisoselenazolone were designed and synthesized by a multistep route outlined in Scheme 6.

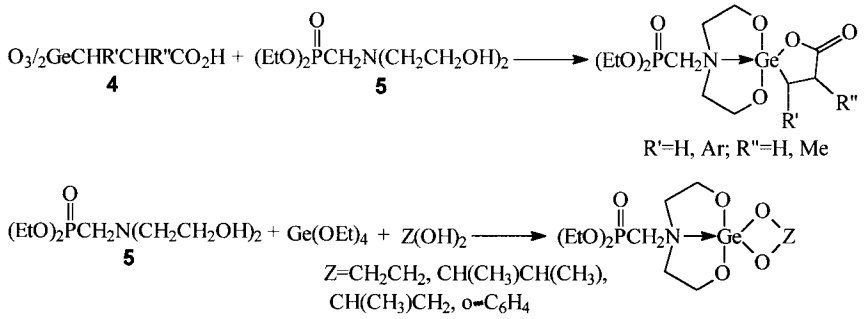
Under the PEG-KBH_4 reaction system, 1 mol of selenium was efficiently reduced to Se_2^{2-} anion by only 1/8 mol of KBH_4 catalyzed by PEG-400 in aqueous NaOH. The reaction of **7** with each α-aminophosphonate hydrobromide **6** was carried out in an ether-water-$KHCO_3$ reaction system in the presence of phase transfer catalyst Bu_4NI to give products **8** in yields of 85–96%. The X-ray analyses showed that the selenium-containing fused ring has a planar structure and that, by the molecular packing of the unit cells, two adjacent molecules are symmetrically linked to each other through Se···O=P bonding interactions with an intermolecular Se···O distance of 2.797 Å. The preliminary anticancer tests in vitro indicated that some of these compounds have high inhibitory effects against human cervix carcinoma (HeLa) cells, human liver carcinoma (BEL-7402) cells, and human lung carcinoma (PG) cells. In contrast, Ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one), which is well known for its good anti-inflammatory activity and glutathione peroxidase-like (GSH-Px) activity, shows little antitumor activity [12,13].

Study on α-Aminophosphonic Acid Derivatives of Glucopyranose

Recently, it was reported in the literature that some organic phosphorus compounds bearing a monosaccharidyl group could be used as antitumor agents, antivirals, or immunomodulators [14]. In order to search for novel anticancer drugs, a series of *O,O*-dialkyl α-(2-deoxy-1, 3, 4, 6-tetra-*O*-acetyl-β-D-glucopyranosyl) amino-*p*-methyl (or methoxyl) phenyl methylphosphonates were synthesized by the addition reactions of phosphite and imines **9**, which were produced from 2-amino-2-deoxy-glucopyranose and aromatic aldehydes (Scheme 7) [15–17]. The configurations of the five chiral carbon atoms of the glucose unit are known, but the newly formed chiral carbon atom from the addition reaction might have two configurations. The content of R-isomers increases as the size of the alkyl groups of the phosphites increases, which is probably due to the difference of steric hindrance of C_1-OAc and C_4-OAc of the glucopyranosyl group to the attack of the phosphite on the imine.

Synthesis of α-Aminophosphonic Acid-Mylabris Derivatives

Mylabris, the dried body of the Chinese blister beetle, has been used as Chinese medicine for over 2000 years. Its active constituent, cantharidin (exo-4a,7a-dimethyl-4,7-epoxyhexahydro isobenzofuran-1,3-dione) has displayed significant antitumor properties in vitro and in vivo. The adverse effects on urinary and gastrointestinal tracts prevent it from being widely accepted by the clinic [18]. The structural modifications of cantharidin were pursued by us with the aim to decrease its toxicity and maintain or increase its efficacy. We designed and synthesized a series of α-aminophosphonate derivatives of norcantharidin **10** and phosphonodipeptide derivatives of norcantharidin **11** (Scheme 8), which might be of interest in the fields of chemistry, biochemistry, and pharmacology [19–21].



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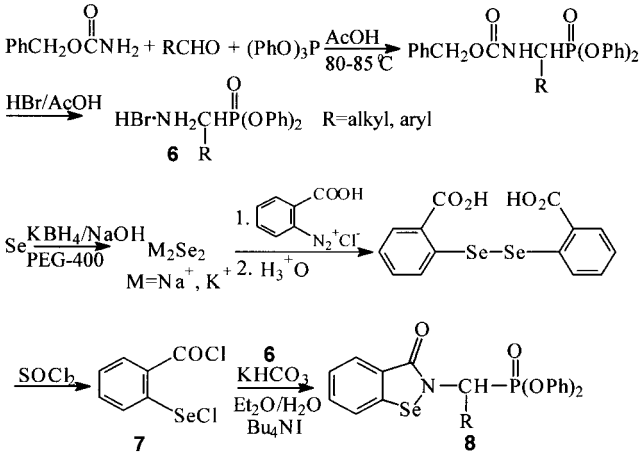


SCHEME 6

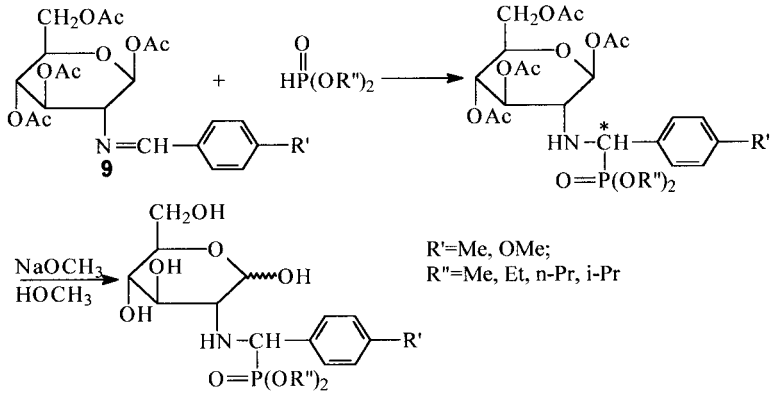
Study on the Derivatives of α-Aminophosphonic Acid Containing a Phosphoryl Mustard Group

The synthesis and the antitumor mechanism of the phosphoryl mustard derivatives have been reported in the literature [22]. For the straight chain phosphoryl mustard derivatives, if the substituents attached to the phosphorus atom are electron-attracting groups, they tend to have good antitumor activity, but instead, if they are electron-donating groups, there is no activity [23–25]. Considering that some thioureidophosphordiamide and phosphoramidate derivatives possess significant antivirus and antitumor activities, we designed and synthesized a number of novel α-phosphoryl(thio)ureido alkanephosphonates **12** and **13** by a convenient, multistep route involving the addition reaction of phosphoryl isothiocyanides with α-aminophosphonates and a homogeneous desulfurization utilizing the Ag^+-H_2O system as key steps shown in Scheme 9. Despite a variety of approaches to the synthesis of N-substituted α-aminophosphonate derivatives are available, to the best of our knowledge, only one general method for the preparation of (thio)ureidoalkanephosphonates has been developed by a three-component Mannich-type reaction involving an aldehyde, a phosphite, and a compound bearing a (thio)ureido function [26]. Significantly, our synthetic strategy as outlined has a great deal of flexibility, providing a new convenient general method for the preparation of a wide variety of structurally related (thio)ureidoalkanephosphonate derivatives [27,28].

The carbodiimide intermediate **14** in the conversion of compounds **12** into **13** was trapped to afford regioselectively the corresponding imino-ether **15** instead of its isomer **16**. The mechanism of desulfurization of **12** has also been studied, and the possible intermediate was trapped using the Ag^+-ROH reaction system (Scheme 10), and the results demonstrate that water or methanol regioselectively attacks the C=N bond linked to the phosphoramidate moiety in the desulfurisation procedure. Preliminary bioassays indicate that compounds **12** and **13** have potent antiphytoviral activities against the tobacco mosaic virus (TMV). In addition, some of compounds **12** possess selective herbicidal activities, and some of **12** and **13** exhibit good fungicidal activities against wheat leaf rust and cucumber grey blight.

Study of α-Aminophosphonic Acid–Phosphonoformic Acid or Phosphonoacetic Acid Derivatives

It is well known that phosphonoformic acid (PFA) and its analog phosphonoacetic acid (PAA) have broad activities against viruses. However, their clinical applications were restricted due to their poor penetration into cells and a by-effect on bone [29]. With PFA and PAA as the starting compounds, α-aminophosphonates were introduced into these structures in order that they might have the improved activity of PFA and PAA and increased liposolubility, and overcome side effects, and that the activity of aminophosphonates might be stimulated by



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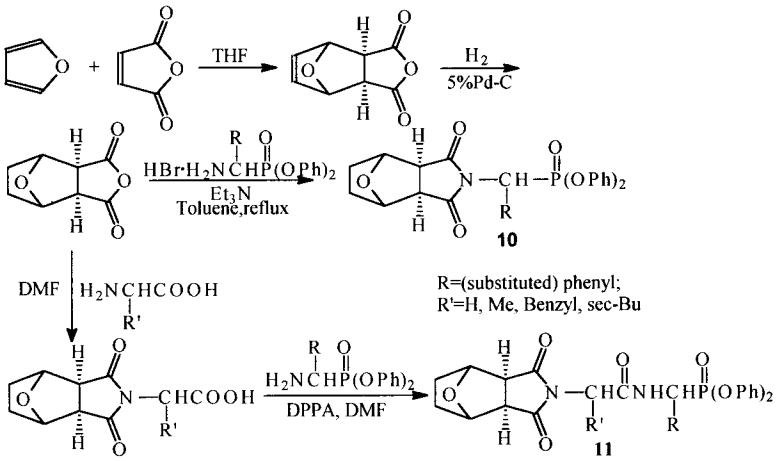

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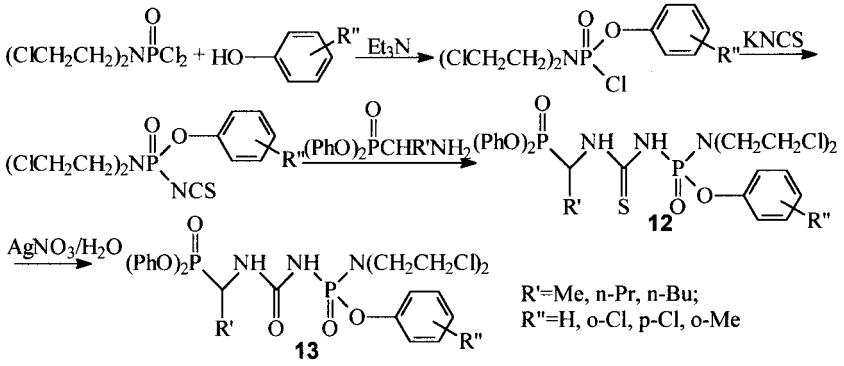
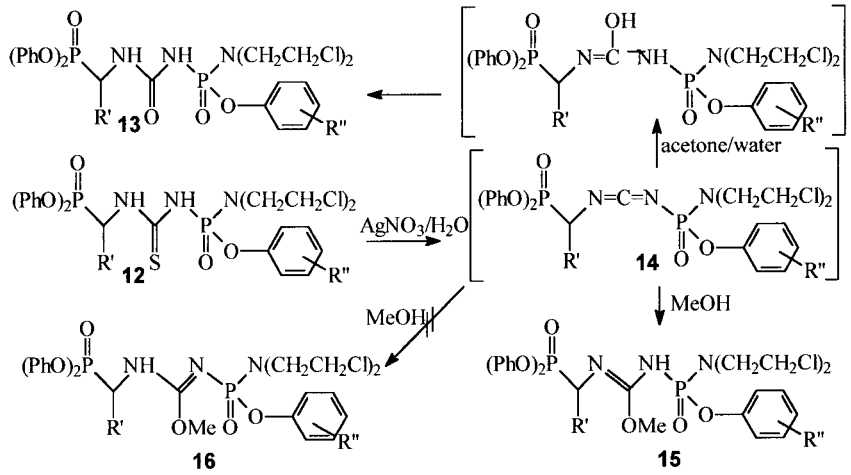


SCHEME 9

phosphonylation. The derivatives of *N*-(alkoxycarbonyl alkoxyphosphonyl)-*α*-aminophosphonates **17** and *N*-(alkoxycarbonyl-methyl-alkoxyphosphonyl)-*α*-aminophosphonates **18** with the *N*-terminal of the amino phosphonates bonding to phosphorus of PFA and PAA, were synthesized via the reaction of the corresponding phosphonyl chloride with *α*-aminophosphonates in the presence of a base (Scheme 11) [30,31]. The preliminary bioassay showed that some of the compounds **17** and **18** have substantial activities against tobacco mosaic virus (TMV). The inhibitory effect was higher than that of DHT (2,4-dioxy-



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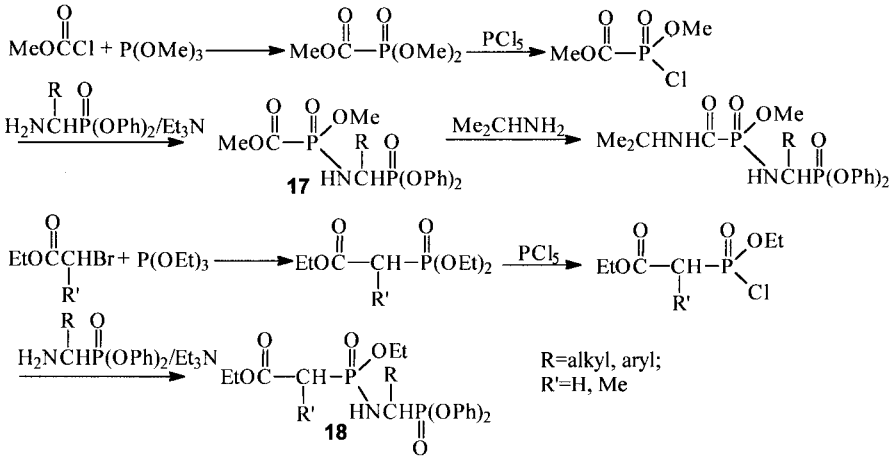


SCHEME 11

hexahydro-1,3,5-triazine). In addition, some of the compounds showed inhibitory effects against cancer cells in vitro.

Study on the Derivatives of α-Aminophosphonic Acid Containing a Sulfonyl Group

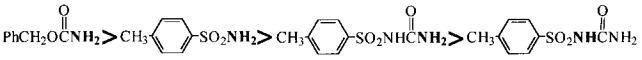
It is revealed that lots of herbicides with high activity possess a sulfonyl group. Some derivatives of α-amino phosphonic acids possess good herbicidal activities, e.g., Glyphosate and Glyphosine are two herbicides that have been commercialized. Based on this idea, we tried to introduce the sulfonyl group in to the structure of α-amino phosphonic acids with the aim of developing novel herbicides of high efficiency and low toxicity.

In 1982, Varaprasad reported that α-(*p*-toluenesulfonamido)phosphonates could be synthesized by the addition reaction of *N*-benzylidene-*p*-toluenesulphonamide with dialkyl phosphites. However, the process was too complicated, and the yields were unsatisfactory [32]. Among numerous synthetic methods for the preparation of α-amino phosphonic acid derivatives, the three-component condensation involving a substituted amide, an aldehyde and a phosphorus reagent is of significant interest [33–35]. By using acetyl chloride as the solvent, *p*-toluenesulfonamide reacted with diethyl phosphite and an aldehyde to give *O*,*O*-diethyl-α-(*p*-toluenesulfonamido)phosphonates **19** readily with good yields of 65–90%. During the reaction, imine **22** was separated out, indicating that the possible mechanism is that shown in Scheme 12. When the mixture of AcOH and Ac_2O is used as the solvent, only **21** and **22** are obtained. The possible reason is that AcOH is unfavorable for step 3 although it can catalyze step 1.

When a more powerful acetylizing reagent AcCl is used as the solvent, it can not only acetylate **20** quickly, but also react with the AcOH produced in step 3 to give Ac_2O. Furthermore, the HCl produced in step 2 can also catalyze step 1, and thus the whole reaction can proceed easily [36–38]. The ^1H NMR spectrum of **19** showed that the two ethoxyl groups are nonequivalent, which could be explained by the X-ray diffraction data (R = *p*-chlorobenzyl). One ethoxyl group is in the shielding area of an α-benzene ring while the other is far from it [39]. Moreover, the nonequivalence disappears when the α-benzene ring is replaced by α-alkyl. Herbicidal preliminary bioassays of **19** showed that the activities by foliar spraying were higher than those by soil application; the activities of these compounds towards grass weeds were higher than those to broadleaf weeds by foliar spraying. The rate of their inhibition came up to 60% at the dosage of 2.25 kg/ha.

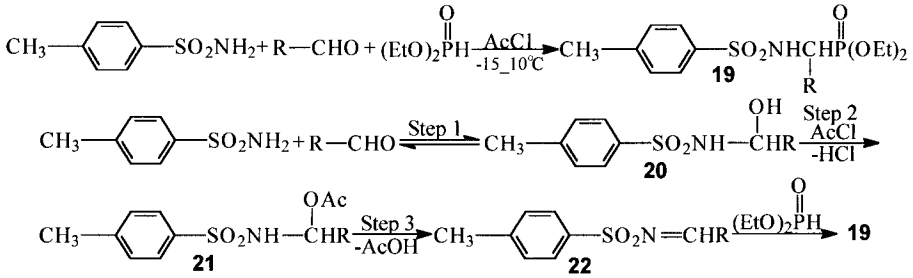
In the same solvent (acetyl chloride), *p*-toluenesulfonurea reacted readily with aromatic aldehydes and phosphites (R = alkyl and phenyl) to give α-(*p*-toluenesulfonureido)phosphonates. The reaction took place selectively at the N atom of the NH_2 group (Scheme 13). The results of bioassay showed that some products had good herbicidal activity (the inhibiting rate could reach 93% at the dosage of 1.5 kg/ha). In addition, we found that some of them possess good anti-TMV activity. The quantitative structure-activity relationship (QSAR) showed that the activity was mainly affected by the steric effect of R. The best result was attained when R is Et, meanwhile, the activity is also related to $\Sigma\pi$ and the steric effect of the para substituting group of the α-benzene ring. More or less, these results are of some significance for predicting anti-TMV activity of new compounds and may help in designing some novel anti-TMV pesticides [40,41].

In order to compare the relative reaction activities of benzyl carbamate **23,** *p*-toluenesulfonamide **24** and *p*-toluenesulfonurea **25,** equal molar quantities of **23, 24, 25,** aromatic aldehyde (A = p-ClC_6H_4) and dialkyl phosphite (R = Et) were reacted in one system. After all the diethyl phosphite was used up, the ratio of the three possible products was checked by ^{31}P NMR spectra. It was found that 90.3% of **23** was converted to diethyl 1-(benzyloxycarbonylamido) *p*-cholrophenylmethyl phosphonate, and 9.3% of **24** was converted to diethyl 1-(benzyloxycarbonyl amido) *p*-cholrophenylmethyl phosphonate while there was no corresponding products from **25.** Obviously, the reactivity order is shown as follows:

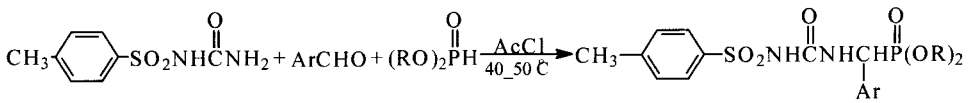


It could be seen that the higher the nucleophilicity of the N atom, the easier was the reaction. However, if the nucleophilicity of the N atom were too high, the N atom would be acetylated by the solvent. For example, when *N*-methyl *p*-toluenesulfonamide was used instead of **24,** the by-product *N*-acetyl *N*-methyl *p*-toluenesulfonamide was formed immediately even below 0°C. Obviously, with acetyl chloride as the solvent, amines could not be used as the nucleophilic reagents.

Because *N*-substituted *p*-toluenesulfonamide **26** can react easily with AcCl, the mixture of AcOH and Ac_2O was used as the solvent instead of acetyl chloride. Thus, **26** reacted with paraformaldehyde at 80°C for 2 hours to give **27,** which reacted with triphenylphosphite to produce **28.** Compound **27** can



SCHEME 12



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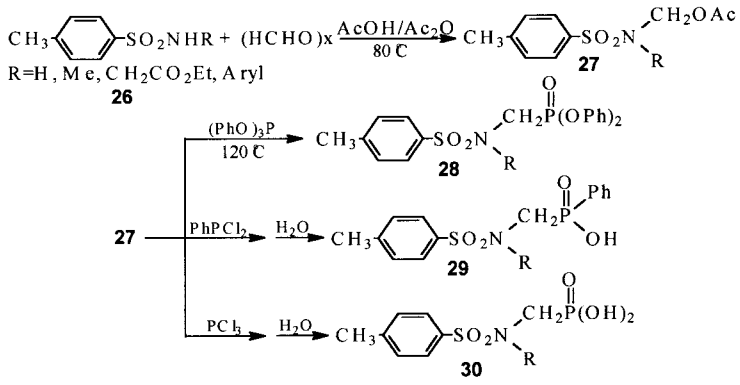

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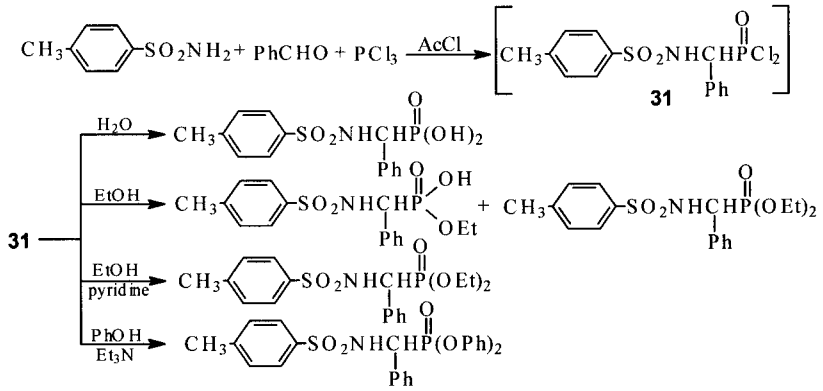

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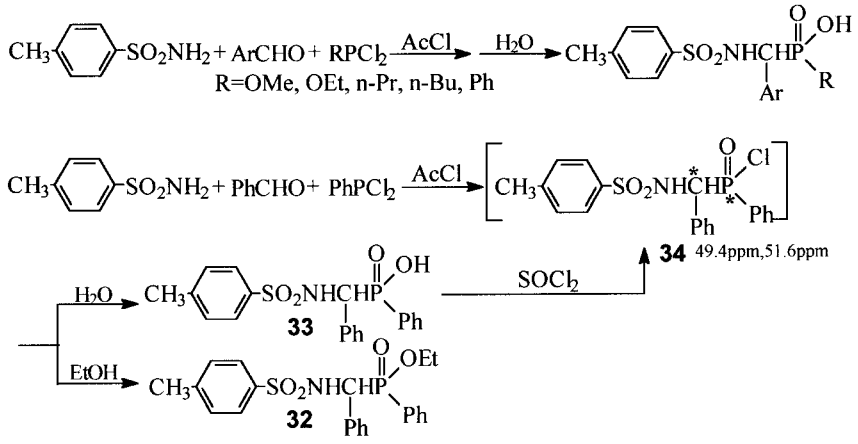
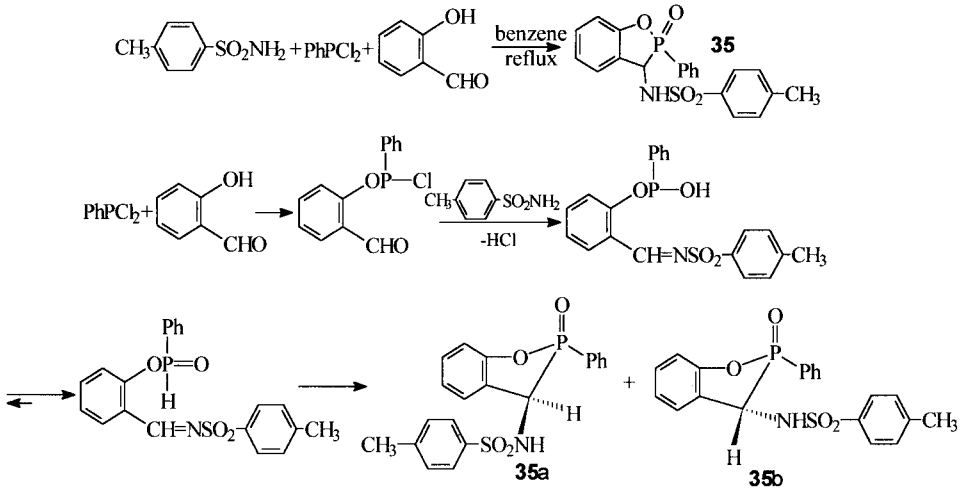


SCHEME 16

also react with $PhPCl_2$ or PCl_3, and then, after hydrolysis with water, **29** and **30** are obtained, respectively (Scheme 14) [42].

The Mannich-type reactions of *p*-toluenesulfonamide and an aldehyde with PCl_3, or $RPCl_2$ (R = OMe, OEt, *n*-Pr, *n*-Bu, Ph) were also studied by using acetyl chloride as the solvent. The proposed mechanism for this type of three-component reaction of *p*-toluenesulfonamide, an aldehyde and a phosphorus reagent suggests that two conditions are necessary for the reaction to proceed smoothly. (1) There must exist a P–H bond in the molecule of the



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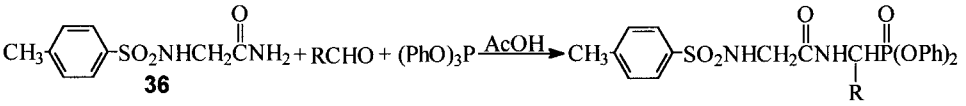

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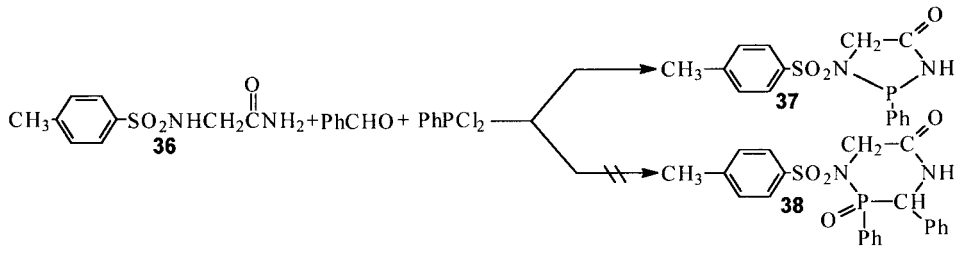

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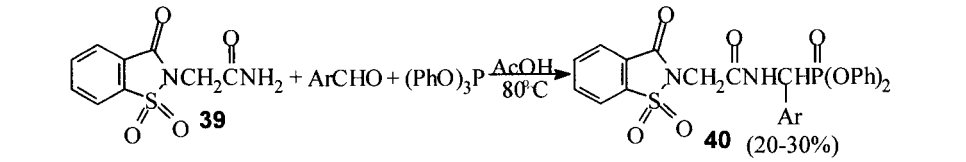

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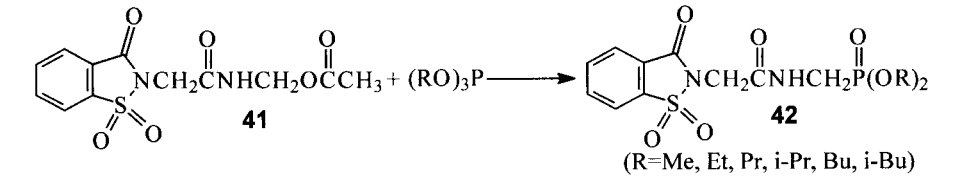


SCHEME 21

phosphorus reagent, or else a P–H bond can be formed readily in the course of the reaction. (2) An imine intermediate can be formed smoothly. The *p*-toluenesulfonamide reacted with benzaldehyde and trichlorophosphine at $-10 \sim 10$°C for 8 hours to give a pale solid, the ^{31}P NMR spectrum of which showed only one peak with the chemical shift of 44.0 ppm. Then the solid was treated with phenol, ethanol, and water to give the corresponding phosphonic diester, monoester and acid respectively. Obviously, the intermediate is the compound **31**, as shown in Scheme 15 [43].

When benzaldehyde was dropped slowly into a mixture of *p*-toluenesulfonamide and phenyldichlorophosphine maintained in an ice-salt bath, 6 hours later a white solid that had formed was filtered off. Its ^{31}P NMR spectrum showed two peaks at 51.6 ppm and 49.4 ppm, indicating that there are at least two kinds of phosphorus compounds in the solid. After treatment with ethanol or water, the corresponding ester **32** and acid **33** were produced respectively. Compound **33** was chloridized with $SOCl_2$ to give the corresponding phosphonyl chloride **34,** whose ^{31}P NMR also showed two peaks at 51.6 ppm and 49.4 ppm, indicating that the two kinds of phosphorus compounds were diastereoisomers of **34** (Scheme 16). By using anhydrous benzene as the solvent, this reaction only gave an imine (p-$CH_3C_6H_4SO_2N=CHC_6H_5$) instead of the product **34,** while replacement of benzaldehyde by salicylaldehyde gave two cyclic products **35a** and **35b** as shown in Scheme 17. Our experiment revealed that the longer reaction time gave the greater ratio of **35a/35b,** indicating **35a** is a thermodynamically controlled product, and **35b** is a kinetically controlled product [44].

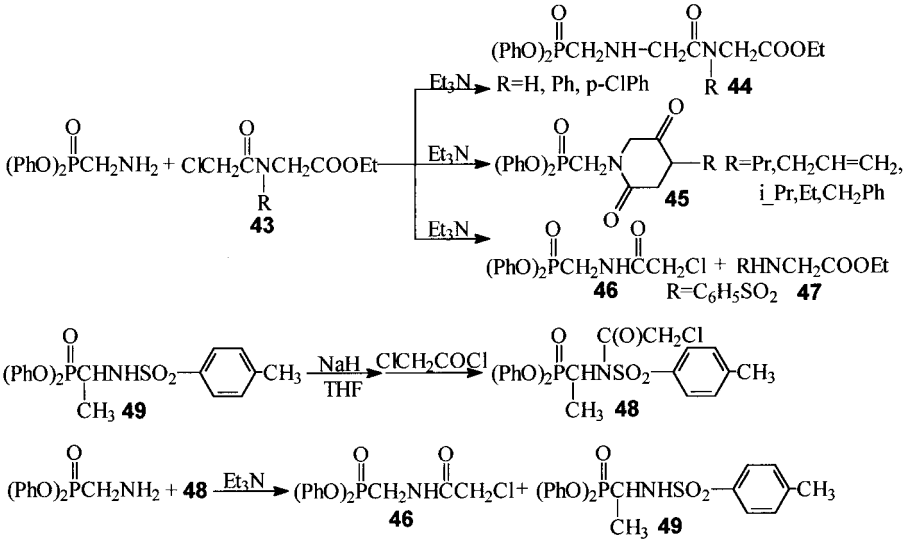
Study on the Synthesis of Phosphonopeptide Derivatives

The derivatives of phosphonopeptides with an α-aminophosphonic acid in the C-terminal position possess many kinds of biological activities. For example, Alaphosphin (L-ala-alap) shows remarkable fungicidal activity in very low concentration, while Bialaphos is a good herbicide. There have been many articles concerning the synthesis of phosphonopeptides with an α-aminophosphonic acid in the C-terminal position, including the acid chloride method, activated ester method, condensation method, mixed anhydride method, and so on. All these methods, however, required an α-aminophosphonic ester to be synthesized as an intermediate, which often required multistep reactions to effectuate. The Mannich-type reaction of an easily obtained material **36** with aldehydes and triphenyl phosphite as shown in Scheme 18 was designed for the purpose of introducing the arylsulfonureido group, which played an important role in the famous sulfonurea-type herbicides, into the structure of phosphonopeptides [45]. However, there are two reactive sites in **36** making the reaction too complicated as evidenced by the fact that the ^{31}P NMR spectrum of the solution exhibits four peaks, and their chemical shifts are 14.0, 13.3, 9.8, and 5.2, respectively. The compound **36** reacted with $PhPCl_2$ and PhCHO in benzene to give a cyclic by-product **37** (45.5%) instead of the expected compound **38** (Scheme 19) [46].

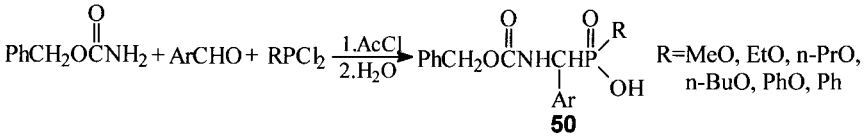
In order to protect the sulfonamido group, saccharinyl acetamide **39** was used to replace compound **36**. The Mannich-type reaction of **39** with aromatic aldehydes and triphenyl phosphite gave phosphonopeptide **40** directly as shown in Scheme 20. The Arbuzov-type reaction has widely been used in the formation of a P–C bond. It was first applied to synthesize phosphonodipeptides in our research. We found that **41** could react readily with $P(OR)_3$ to produce **42** in good yields of 86.6–93.1% (Scheme 21) [47].

Treatment of diphenyl aminomethanephosphonate with *N*-chloroacetyl-*N*-alkyl (aryl or hydrogen or phenylsulfonyl) glycine ethyl ester **43** in the presence of triethylamine gave various products, depending on the substituent R on the N atom of compounds **43.** When R = aryl or hydrogen, the chain dipeptides **44** were formed. When R = alkyl, the products were the cyclic dipeptides **45.** However, when R = phenylsulfonyl, the products **46** and **47** were obtained, resulting from the cleavage of the C–N bond. Similarly, the reaction of diphenyl aminomethanephosphonate with **48** produced esters **46** and **49** via cleavage of the C–N bond [48,49]. This is probably due to the fact that the strong electron-withdrawing groups, phenylsulfonyl and *p*-tolylsulfonyl, decrease the electron density at N so that the C–N bond becomes weak (Scheme 22) [50,51].

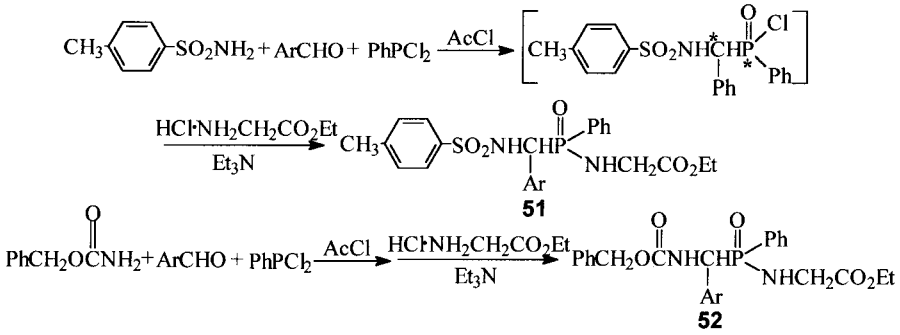
Phosphonopeptides with P–N bonds are of significant interest due to the fact that they are excellent mimetics of the tetrahedral transition state of enzymatic peptide hydrolysis and consequently are potential inhibitors of proteases. The phosphonopeptides containing the P–N bond could not be formed by the usual method used in the synthesis of peptides. The N-protected aminoalkylphosphonic acids did not condense with amino acid esters by use of dicyclohexylcarbodiimide (DCC). Several methods have been described in the literature to synthesize this type of phosphonopeptide, and the main problem in the synthesis of a peptide containing the P–N bond was how to form the P–N bond from an amino phosphonic acid and an amino acid efficiently



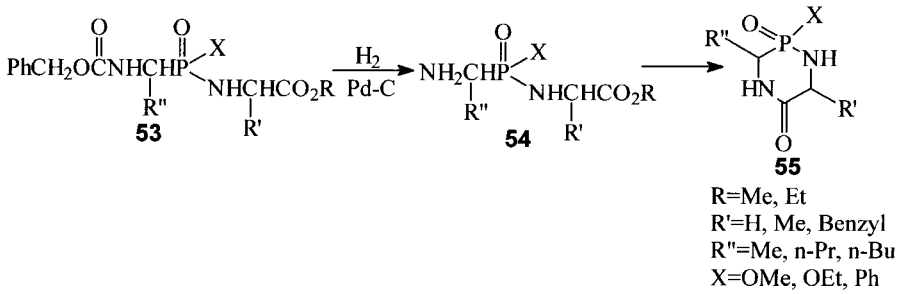
SCHEME 22



SCHEME 23



SCHEME 24



SCHEME 25

[52,53]. Of these literature methods, the most convenient one is to prepare the monoesters of N-protected amionalkylphosphonic acid first, followed by chloridization with thionyl chloride to form the corresponding phosphonyl chloride, which is then reacted with an amino acid ester. Obviously, the monoesters of N-protected aminoalkylphosphonic acids are the key intermediates for the synthesis of peptides having a phosphonamide linkage [54]. By using acetyl chloride as the solvent, benzyl carbamate was found to react with $RPCl_2$ and aromatic aldehydes, then hydrolyzed with water to give **50** readily with satisfactory yields of 60–80%, as shown in Scheme 23 [55,56]. However, in the course of studying the reaction process, the ^{31}P NMR spectrum showed that the reactive phosphorus intermediates were the two diastereoisomers of **34.** Therefore, with acetyl chloride as the solvent, the condensation reaction gives a reactive intermediate, α-(*p*-toluenesulfonyl) aminobenzyl phosphinic chloride or phenyl 1-arylmethylphosphinic chloride, which reacts with the amino acid ester to give the corresponding phosphinopeptide derivatives **51** or **52** containing a P–N bond directly (Scheme 24) [57,58].

Catalytic hydrogenation of **53** by using 5% palladium-active charcoal removed the carbobenzyloxy group and produced the corresponding dipeptide **54** quantitatively. Most of these dipeptides were cyclized directly by reflux in *n*-butanol/toluene (3:1) or by being allowed to stand for 30 to 60 hours at room temperature to give cyclophosphonodipeptides **55** without further purification as shown in Scheme 25 [59–61]. X-ray diffraction studies showed that cyclophosphonodipeptides **55** have a boat conformation, in which the phenyl group on the P atom and the alkyl group on the α-C atom are *cis* to each other.

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