The development of bisphosphonates for therapeutic uses, and bisphosphonate structure-activity consideration

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Abstract
Recent progress in the synthesis of major constituents of the methyl-1,1-bisphosphonate family is reviewed. These compounds are important precursors of the corresponding bisphosphonic acid with, in many cases, remarkable pharmacologically interesting properties. The literature has been fully covered over the last two decades.

Keywords: Synthesis of bisphosphonic acids; osteoporosis; bone resorption; arthritis; anti-inflammatory

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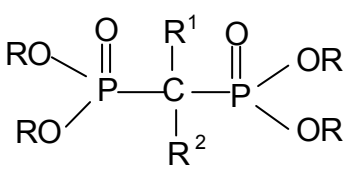
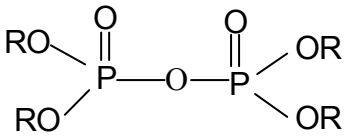
1. Introduction

Recently, the development of organophosphorus chemistry has been characterized by a great interest in bisphosphonates (*BPs*) and bisphosphonic acids.[1-8] The BPs are synthetic organic compounds characterized by a P-C-P backbone structure. They are chemically stable analogues of the endogenous metabolites, inorganic pyrophosphates *(PPi)* (Figure 1). Unlike PPi, BPs are resistant to breakdown by enzymatic hydrolysis. They bind to bone minerals and inhibit the resorption of living bone. The biological effects of BPs on calcium metabolism were originally ascribed to their physicochemical effects to impede the dissolution of hydroxyapatite crystals. Although such effects may contribute to their overall action, their effects on cells are probably of greater importance, particularly for the more potent compounds.[1b,6,8] The marked structure-activity relationship observed among more complex compounds indicate that the pharmacophore required for maximal activity depends not only upon the bisphosphonate moiety but also on key additional features, especially nitrogen- substitution in alkyl or heterocyclic side chains.[6-8]



Bisphosphonates, R = alkyl
Bisphosphonic acids, R = H



Pyrophosphates, R = alkyl
Pyrophosphonic acid, R = H

Figure 1

In clinical medicine, several BPs (e.g., etidronate, clodronate, pamidronate, alendronate, risedronate and ibandronate) are established as effective treatments for bone diseases such as

Paget's disease (a condition in which patches of bone become softened and enlarged), myeloma, and bone metastases. In addition, etidronate and alendronate are approved for the prevention and treatment of osteoporosis. Both can increase bone mass and produce a reduction in fracture rates to approximately half of control rates at the spine, hip and other sites in post-menopausal women.

The clinical pharmacology of BPs is characterized by low intestinal absorption but inhibition of bone resorption by being highly selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of the bone-resorping cells known as *osteoclasts.* It is likely that BPs are internalized by osteoclasts and interfere with specific biochemical processes, and thereby induce programmed cell death or *apoptosis*. The molecular mechanisms by which these effects are brought about are becoming clearer.[9,10]

As is to be expected from their wide spectrum of applications, there are several recent books and reviews that describe the biochemistry, pharmacology, and clinical applications of bisphosphonates.[1-10] Nevertheless, no parallel effort has been placed on reviewing the synthesis of these compounds. In this review, the syntheses and chemical reactions of BPs are thoroughly discussed, whereas biological and technological applications are only indicated briefly. The emphasis is on information added to this topic from 1990 to 2008. The authors have attempted the review to be encyclopedic with respect to the topics and chemistry, but not in citing all examples of every reaction.

2. Technological Applications of Bisphosphonates

The early uses of BPs were industrial, mainly as corrosion inhibitors, as complexing agents in the textile, fertilizer and oil industries, as well as for many other industrial processes.[9] Their use as, "water softeners" was based on their ability to inhibit calcium carbonate precipitation, as do polyphosphates, and has been applied in domestic and industrial water installations. It is only in the past three decades that the BPs have been developed as drugs for use in various diseases of calcium metabolism.

3. Biological Activities of Bisphosphonates

The BPs have been known to chemists since the middle of the 19th century, and the first synthesis dates back to 1865 in Germany.[11] Etidronate-the first BP to be used in humans for the treatment of Paget's disease-[12] was synthesized just over 100 years ago.[13] In the early 1960s, William Neuman and Herbert Fleisch[14] were studying mechanisms of calcification induced by collagen, and showed that body fluids such as plasma and urine contained inhibitors of calcification. Since it had been known since the 1930s that trace amounts of polyphosphates were capable of acting as water softeners by inhibiting the crystallization of calcium salts, such

as calcium carbonate, they proposed that compounds of this type might be natural regulators of calcification under physiological conditions. Fleisch and his colleagues[14,15] showed that inorganic pyrophosphate-a naturally occurring polyphosphate, and a known byproduct of many biosynthetic reactions in the body-was present in serum and urine and could prevent calcification by binding to newly-forming crystals of hydroxyapatite. It was therefore postulated that PPi might be the agent that normally prevents calcification of soft tissues, and regulates bone mineralization. It was also proposed that some pathologic disorder, such as the formation of kidney stones, might be linked to disturbances in PPi metabolism. The concentration of PPi in body fluids would expect to be regulated by hydrolytic enzymes.[16]

4. Chemistry

Diphosphonates and gem-diphosphonates are both correct names for bisphosphonates. However, recently and after the wide application of this class of compounds in therapeutic uses, the single term "bis-" is generally used for compounds characterized by the [P-(R^1)C(R^2)-P] structure. This feature allows a great number of possible variations, mostly by changing the two lateral chains (R^1 and R^2) on the carbon. Small changes in the structure in the R^1 or R^2 moiety can lead to extensive alterations in their physicochemical, biological, therapeutic, and toxicological characteristics. For these reasons, it appears there is a need for more BP-compounds with a greater margin between the inhibitions of mineralization with accompanying increase in toxicity, and improved oral bioavailability with G1 side effects.

4.1 Structural-activity relationships

Studies of the relationships between bisphosphonate structure and anti-resorptive potency suggest that the ability of BPs to inhibit bone resorption is dependent on two separate properties of the bisphosphonate molecule. The two-phosphonate groups, together with a hydroxyl group at the R^1 position, impart high affinity for bone mineral and act as a "bone hook", allowing rapid and efficient targeting of BPs to bone mineral surfaces. Once localized within bone, the structure and three-dimensional conformation of the R^2 side chain (as well as the phosphonate groups in the molecule) determine the biological activity of the molecular targets. The understanding of what these molecular targets might be has become much clearer as a result of recent work. In the following sketch (Figure 2), we summarize the correlation between moieties and the potency, while Table 1 indicates the most BP-drugs on the market.

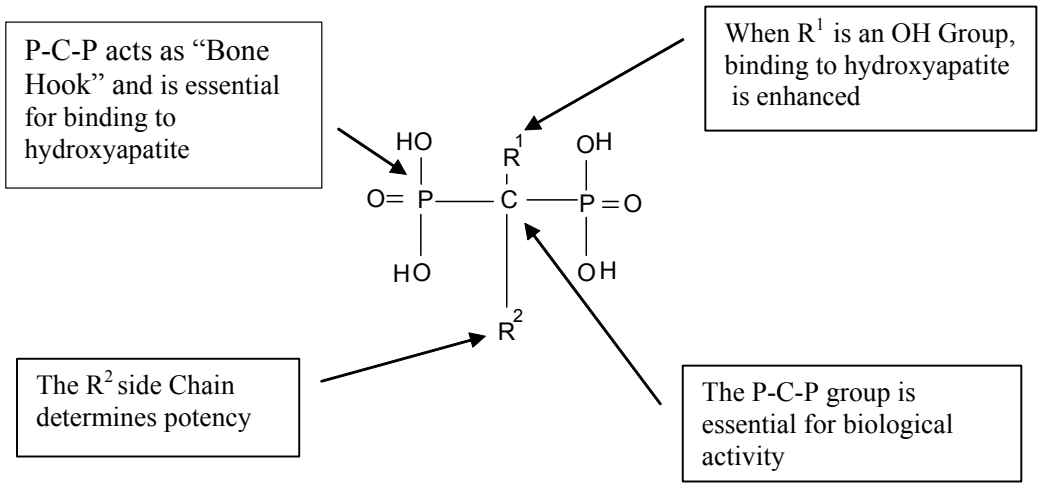


Figure 2

Table 1. Most applicable BP-drugs and their structures

Bisphosphonates	R^1	R^2
Etidronate*	-OH	-Me
Clodronate*	-Cl	-Cl
Pamidronate*	-OH	$-CH_2CH_2NH_2$
Alendronate*	-OH	$-(CH_2)_3NH_2$
Risedronate*	-OH	$-CH_2$-3-pyridine
Tiludronate*	-H	$-CH_2$-S-phenyl-Cl
Ibandronate*	-OH	$-CH_2CH_2N(CH_3)$(pentyl)
Zoledronate	-OH	$-CH_2$-imidazole
YH529	-OH	$-CH_2$-2-imidazolo-pyridinyl
Incadronate	-H	-N-(cycloheptyl)
Olpadronate	-OH	$-CH_2CH_2N(CH_3)_2$
Neridronate	-OH	$-(CH_2)_5NH_2$
EB-1053	-OH	$-CH_2$-1-pyrrolidinyl

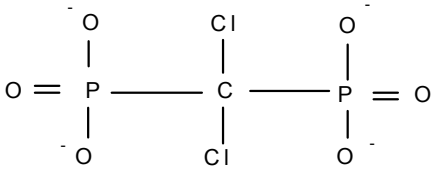
*Indicates BPs already approved for one or more countries. Pamidronate is the most extensively used drug for Paget's disease.

4.2 Biochemical bases for the mechanisms of action of BPs

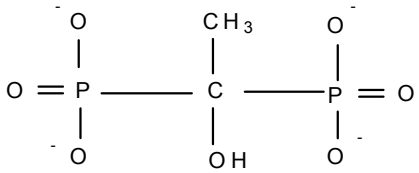
Although our bones seem solid and stable, they actually undergo constant renewal. Specialized cells called osteoclasts draw used calcium out of the bones while other cells called osteoblasts replace it. In some instances (for example after the menopause), this process can get out of balance. Calcium starts to leach out of bones faster than it can be replaced, leading to a brittle-bone disease called osteoporosis. BP-drugs reduce this problem by reducing the activity of osteoclasts and slowing the loss of calcium from the bones. So, it is prescribed for menopausal women to prevent osteoporosis and to strengthen the bones.[17-21] It is also used in the treatment of osteoporosis resulting from therapy with steroidal and other medications incorporated.[22-26] The effect on the osteoclast leads to a decrease in bone turnover, and is secondary to the inhibition of bone resorption.

Several studies[22,24,27-30] indicate that BPs can be classified into at least two groups, with different modes of action. BPs that most closely resemble PPi (such as Clodronate and Etidronate, Figure 3) can be metabolically incorporated into non-hydrolyzable analogues of ATP-dependent intracellular enzymes. The more potent, nitrogen-containing BPs (such as Zoledronate and YH529, Figure 4) are not metabolized in this way but they act on liver-enzymes function, which explains the loss of osteoclast activity and induction of apoptosis.[31,32] These different modes of action might account for subtle differences between compounds in terms of their clinical effects.

4.2.1 BPs that resemble PPi



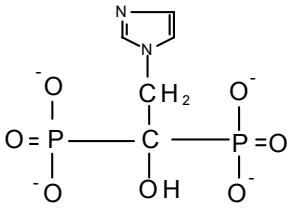
(Dichloromethylidene)-bis-phosphonate (**Clodronate**)



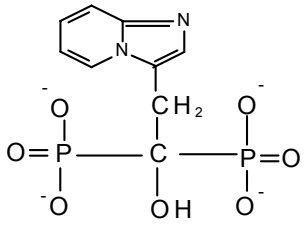
(1-Hydroxyethylidene)-bis-phosphonate (**Etidronate**)

Figure 3

4.2.2 Nitrogen-containing BPs



1-Hydroxy-2-(1H)-imidazol-1-yl)ethylidene bisphosphonate, (**Zoledronate)**



(1-Hydroxy-2-imidazo-(1,2-a)-pyridin-3--3-yl)- ethylidene bisphosphonate, (**YH529)**

Figure 4

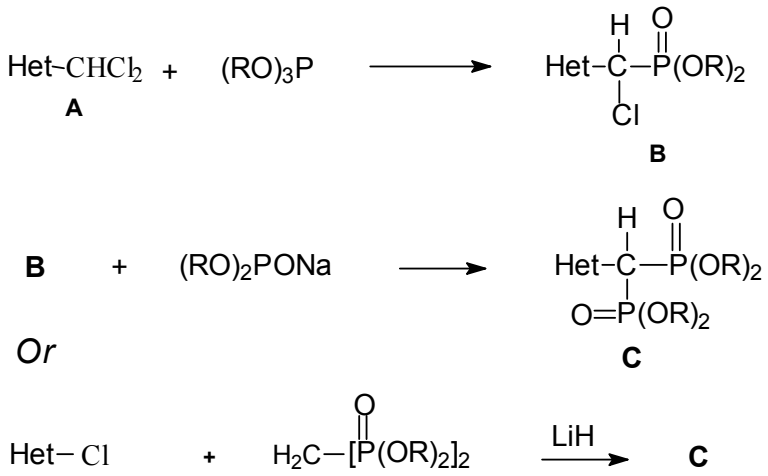
5. Synthesis

The need to develop more powerful anti-resorptive agents has generated a diverse spectrum of BPs with unique pharmacological activities, as well as uses for other purposes. The desire to obtain unique BPs has stimulated numerous synthetic strategies as alternatives to the established methods, namely the Arbusov reaction and the condensation of PCl_3 with an acid. Nevertheless, the preparation of bisphosphonates could be achieved through many available methods *via* application of phosphorus reagents on saturated and unsaturated systems.

5.1 Bisphosphonates from halo-substrates

The classical strategy method to synthesize substituted-bisphosphonates has included two steps. The first is an Arbusov reaction between an halo-substrate and trialkyl phosphite, followed by an addition of dialkyl phosphonate on the produced monophosphonate (Scheme 1). Later, this method is developed, and a one-pot synthesis of symmetric bisphosphonic esters could be obtained, without the use of dialkyl phosphonate, by introducing a protic reagent, which would remove the unused monophosphonate.

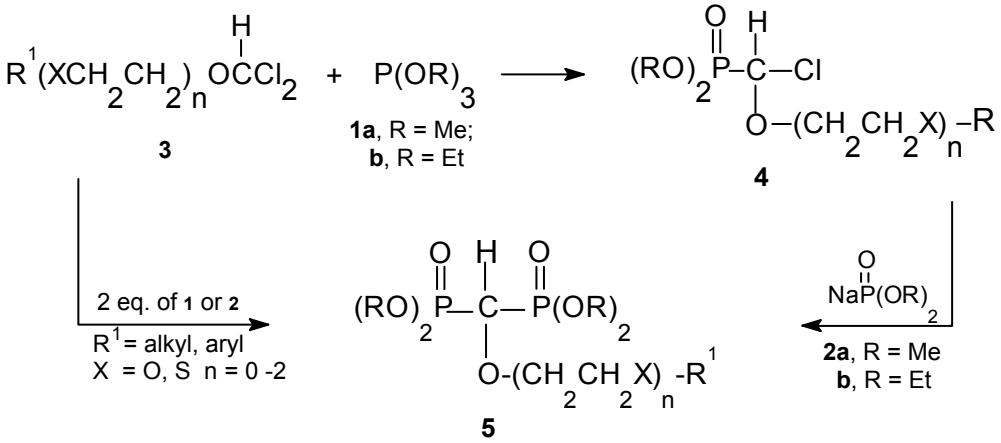
The other methodology is to apply Wittig-Horner reagents, such as tetraalkyl methane-1,1-bisphosphonate, with halo-substrates to synthesize the requested bisphosphonates (Scheme 1).[33-35]



Scheme 1

5.1.1 Application of alkyl phosphites on halo-substrates

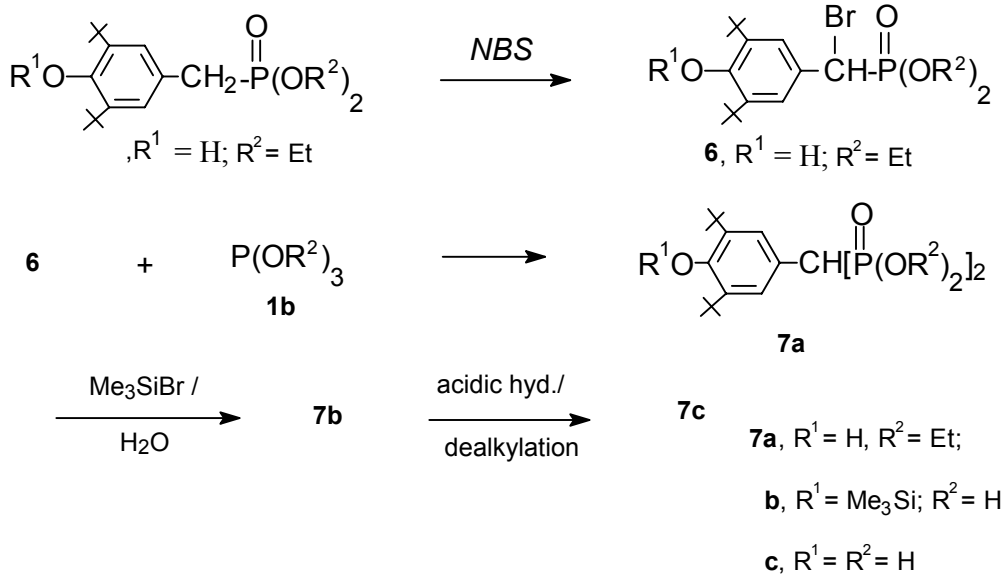
Arbusov reaction of the halo-compounds, **3,** with trialkyl phosphites, **1,** afforded the mono-phosphonates, **4**. Treating compounds **4** with sodium dialkyl phosphonates, **2**, afforded several methylene-1,1-bisphosphonates **5**.[36] Alternatively, bisphosphonates **5** could be obtained from the reactions of compounds **3** with two equivalents of trialkyl phosphites **1** or dialkyl phosphonates, **2,-** the first method giving better yields (Scheme 2).[36]



Scheme 2

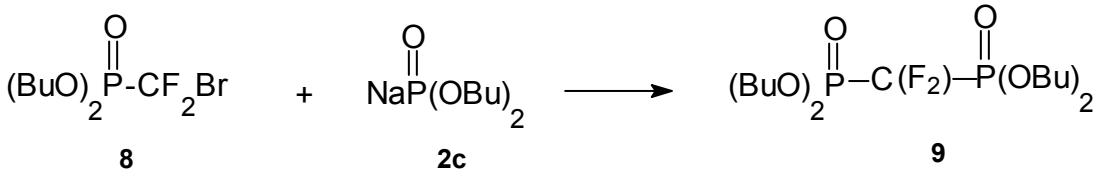
Treatment of 3,5-di-*tert*-butyl-4-hydroxyphenylmethanephosphonic diethyl ester with *N*-bromosuccinimide (*NBS*) gave the benzyl-brominated phosphonates **6**, which could be converted with triethyl phosphite **1b** into the bisphosphonate **7a** in high yield (Scheme 3).[37] The bisphosphonate **7a** was treated with trimethylsilyl bromide to give the *O*–arylsilyated bis-

phosphonic acid, **7b**, which under acidic hydrolysis conditions, 4-hydroxyphenyl-methane-bis-phosphonic acid, **7c**, was formed in nearly quantitative yield.[37]



Scheme 3

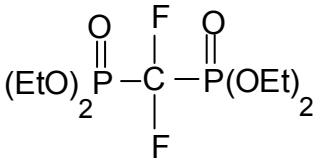
Methane-1,1-bisphosphonates bearing fluorine substituents are widely used in the design of new drugs to improve their lipophilicity and to modify their pharmacological properties. The first preparation of fluorinated bisphosphonates was achieved by Burton *et al*.[38] On treating bromodifluoromethyldibutyl phosphonate, **8**, with sodium dibutyl phosphonate, **2c**, in hexane, the tetrabutyl-difluoromethylene bisphosphonate, **9**, was isolated in 47% yield (Scheme 4).



Scheme 4

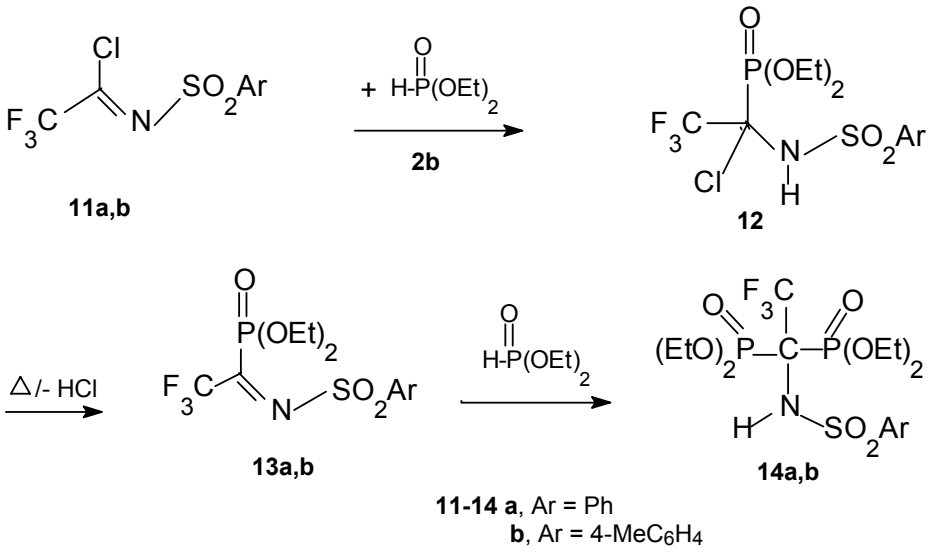
The bisphosphonate **10** (Figure 5), which is an analog of **9**, could also be obtained *via* direct reaction of CF_2Br_2 with excess sodium diethyl phosphonate (**2b**). However, this route gave lower yields, and the product-isolation is more difficult owing to increased formation of side products.[38, 39] Furthermore, a novel type of fluorinated bisphosphonates could be prepared. When the trifluoro-acetimidoyl chlorides **11a,b** were allowed to react with diethyl phosphonate (**2b**), the *α*-(sulfonylamino)trifluoroethylidene-bisphosphonates (**14a,b**) were formed as outlined in

Scheme 5.[40] In the manner shown in Schemes 4 and 5, several BPs and their relevant BP-acids were synthesized in moderate to high yields.[4,41,42]



10

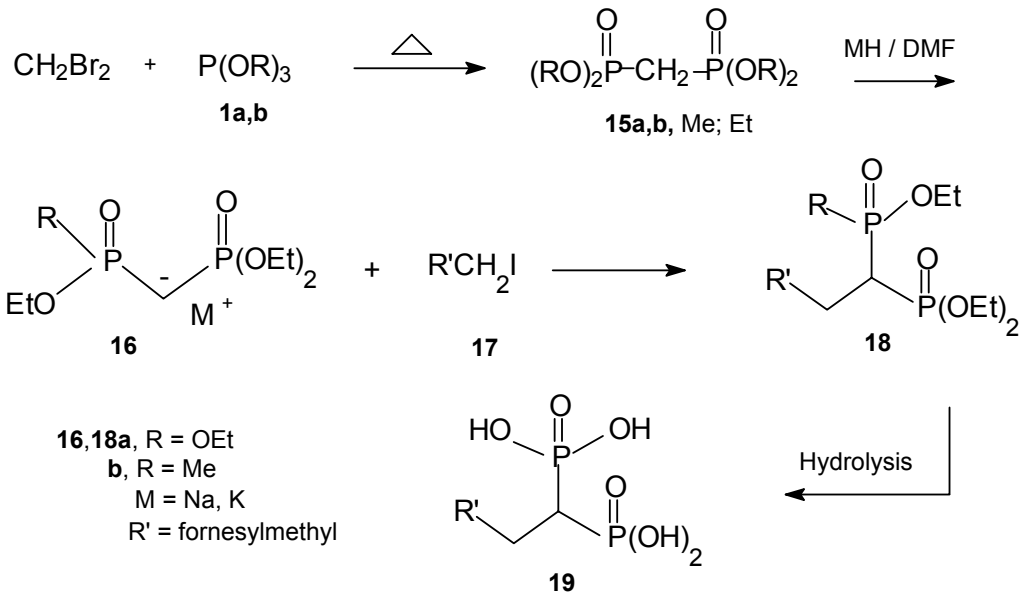
Figure 5



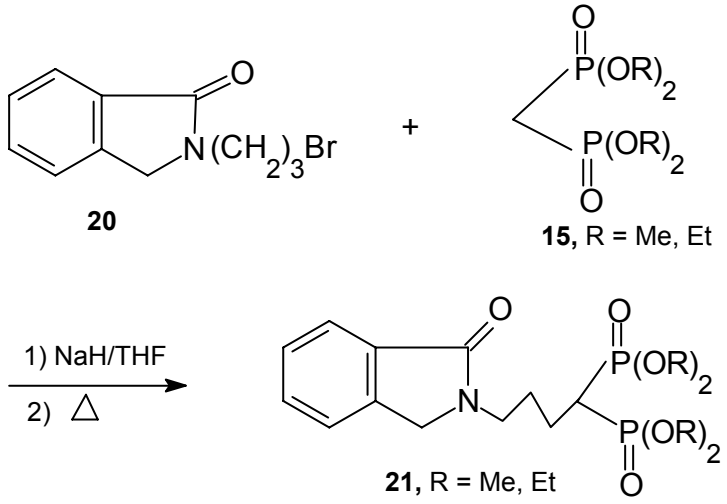
Scheme 5

5.1.2 Application of Wittig-Horner reagents on halo-substrates. The most common Wittig-Horner reagents used for this purpose are tetra-alkylmethane-1,1-bis-phosphonates, **15a,b**, which were prepared easily (~40% yield) by treating a trialkyl phosphite with dibromo-(or di-iodo) methane according to Scheme 6.[43] Then, metallated bisphosphonate esters, **16**, react with a series of alkyl halides **17** to prepare the substituted esters **18**. Dealkylation of the ester moieties was performed by hydrolysis with water or aqueous alkali to give methylene-1,1-bisphosphonic acids **19** as in Scheme 6.[35]

In another report, the heterocyclic bisphosphonate **21** could be prepared in 78 % yield by the nucleophilic substitution of 2-(3-bromopropyl)-1-iso-indolinone **20** with the bis-phosphonate reagents **15a,b** (Scheme 7).[33]

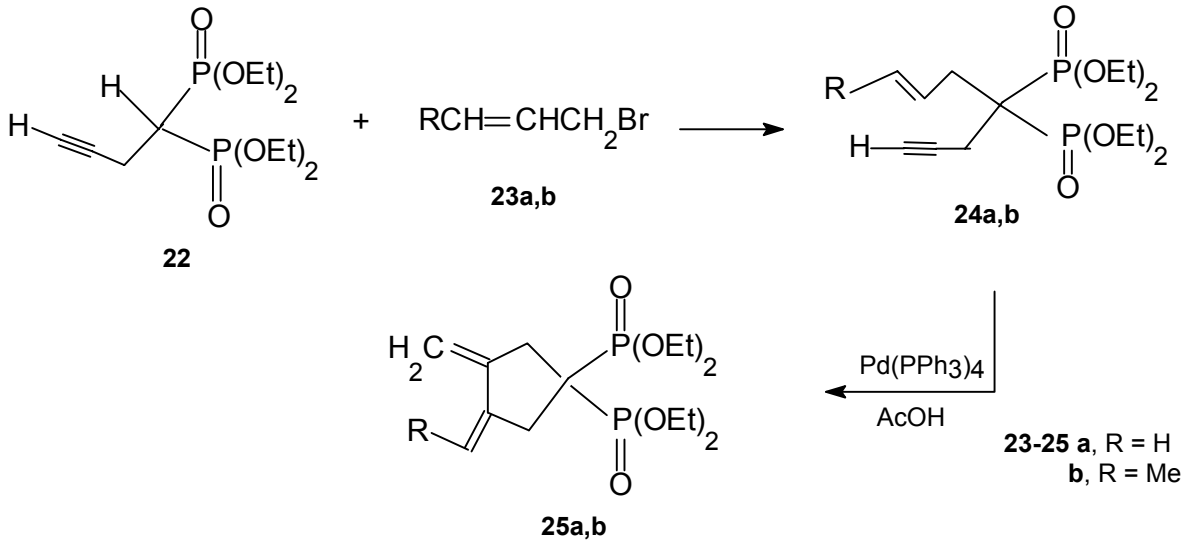


Scheme 6



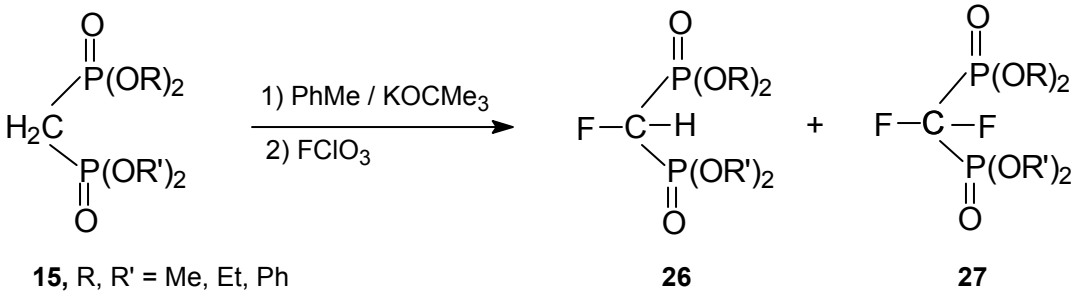
Scheme7

Condensation of tetraethyl but-3-yn-1,1-diyl-bisphosphonate **22** with the allylic bromides **23a,b** gave the BP-derivatives **24a,b**. Furthermore, an intramolecular enyne cyclo-isomerization reaction of **24**, using a palladium phosphonium salt in acetic acid, afforded the cyclic substituted bisphosphonates **25a,b** in good yields (Scheme 8).[34]

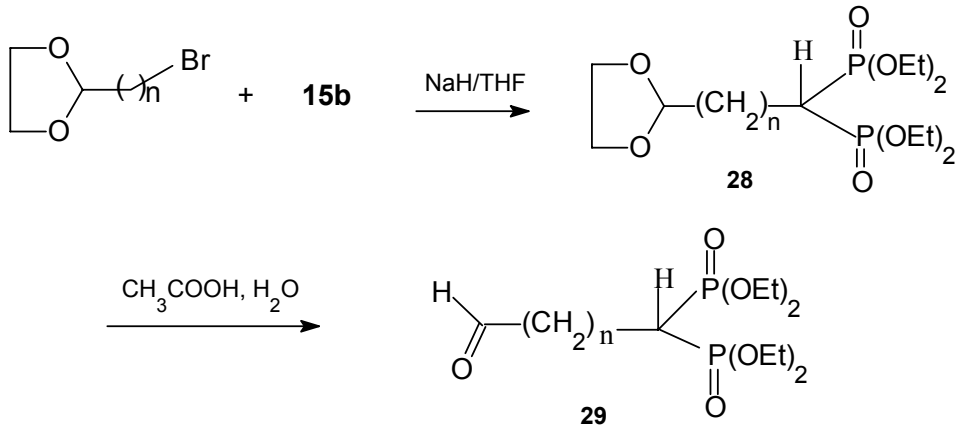


Scheme 8

The methane-1,1-bisphosphonate esters **15** were treated with base ($KOCMe_3$) and then with $FClO_3$ to prepare several mono- **26** and di-α-fluorinated methane-bisphosphonates **27** (Scheme 9).[44] Furthermore, Chaleix and Lecouvey,[45] performed an efficient synthetic route for preparation of a new family of aldehyde-bisphosphonates as shown in Scheme 10.

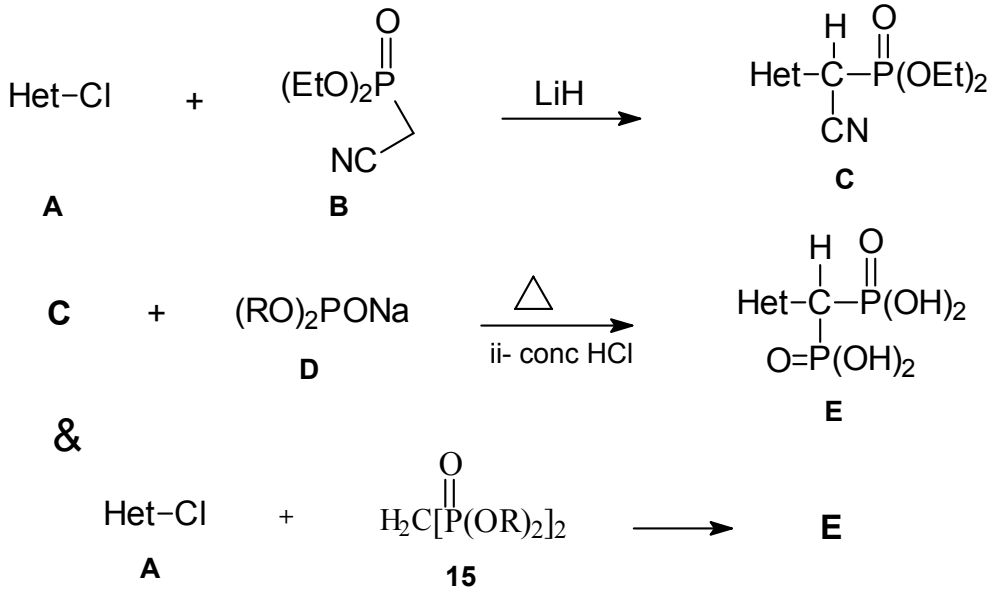


Scheme 9



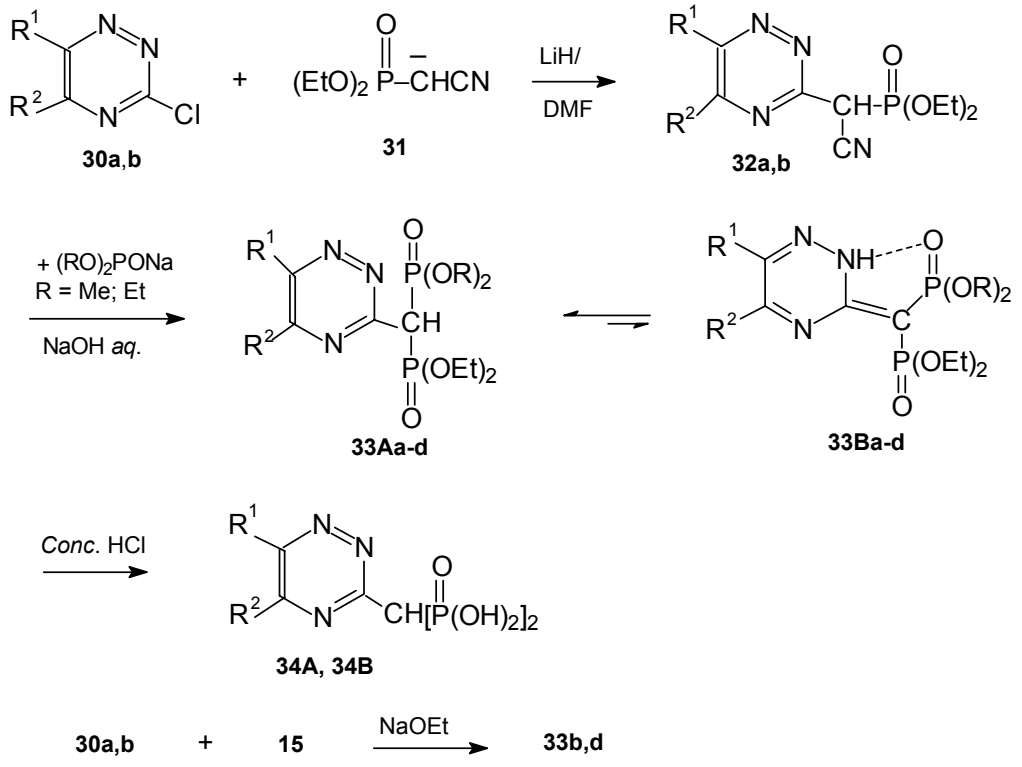
Scheme 10

Two simple and efficient one-pot procedures for the synthesis of a series of α-branched *N*-heterocycle-substituted methane-1,1-bisphosphonates were reported recently by Abdou *et al*.[46] The first method involved two steps. The first was the preparation of the corresponding diethyl cyanomethyl phosphonate derivatives **C** in ~70% yield from the reaction of the lithium salt of diethyl cyanomethyl phosphonate, **B**, with the parent halo-compound **A**. Further reaction of sodium dialkyl phosphonates **D** on these adducts, followed by acid hydrolysis, afforded the corresponding bisphosphonic acids *(BP-acids)* **E** in ~42% (Scheme 11). In a second approach, the same halo-compounds were treated with **15b** to give the requisite *BP*s (Scheme 11). Hydrolysis of the prepared *BP*s to BP-acids was also undertaken.[46]



Scheme 11

Following the first procedure, 3-chlorophenanthro[9,10-*e*]-1,2,4-triazine (or 3-chloro-5,6-diphenyl-1,2,4-triazine (**30a,b**)) was treated with diethyl cyanomethyl phosphonate, **31**, (3 equivalents) in refluxing DMF containing excess of LiH (two equivalents of **31**) to give the corresponding monophosphonates **32a** (74%) or **32b** (71%). Treatment of **32a,b** with the dialkyl phosphonates **2a,b** in toluene containing NaOH solution (0.5 *M*) yielded, via elimination of HCN, the corresponding methane-1,1-bisphosphonates **33**, which could be hydrolyzed to the bisphosphonic acid derivatives by refluxing in *conc.* HCl (Scheme 12).[46] In a second approach, the same halo-compounds reacted with **15b** to give the requisite *BP*s.[46]



Scheme 12

Cpd.	R^1, R^2	R	Cpd.	R^1, R^2	R
33a	R^1, R^2 = phenanthrene	Me	**33d**	$R^1 = R^2$ = Ph	Et
33b	R^1, R^2 = phenanthrene	Et	**34**	R^1, R^2 = phenanthrene	-
33c	$R^1 = R^2$ = Ph	Me			-

According to the approach described in Scheme 12, the BPs **35-37**[46] (Figure 6) and further examples of BPs and BP-acids were also prepared. [47,48]

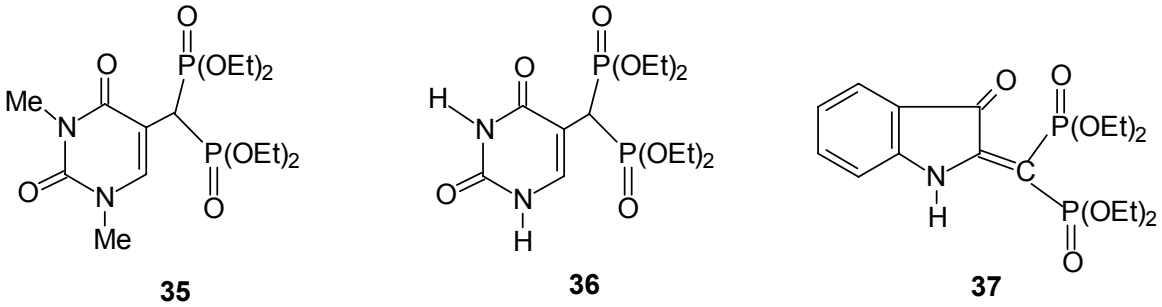
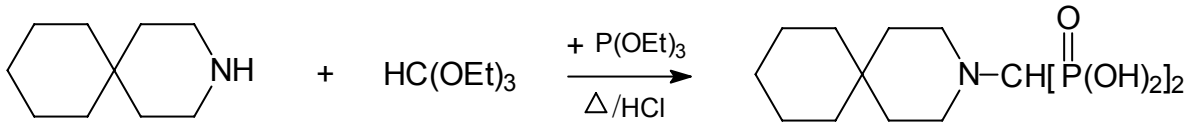


Figure 6

5.2 Bisphosphonates from substrates-bearing nitrogen functions

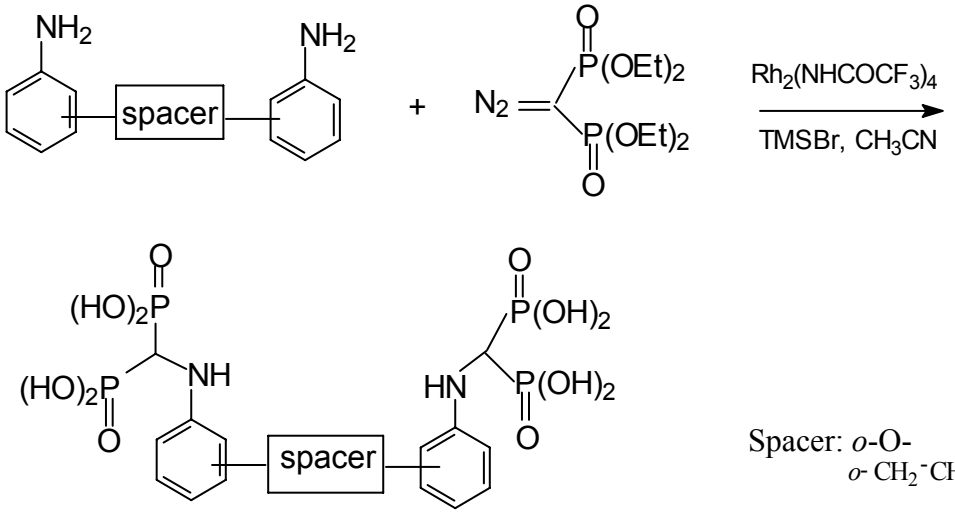
5.2.1 Amines. Substituted aminomethylene bisphosphonates and the corresponding bisphosphonic acids are an important class of biologically active compounds.[1-4] They are powerful inhibitors of the enzyme farnesyl pyrophosphate synthase (FPPS), a key regulatory enzyme in the mevalonate pathway. Thus, they display therapeutic properties for several human pathologies such as osteoporosis, rheumatoid arthritis, and cancer.[4] Respectively, much work has been reported in the literature on the synthesis and the reactivity of such systems.[49-57] *N*-Substituted aminomethylene bisphosphonic acids could be synthesized by reacting the corresponding amine with equivalent quantities of triethyl-orthoformate and diethyl phosphonate (or triethyl phosphite).[52] According to this method, the substituted-aminomethylene bisphosphonic acid, **38**, which has been described as an effective bone resorption inhibitor, useful in treating osteoporosis, could be obtained from 3-azaspiro[5,5]undecane as described in Scheme 13.[51c]

On the other hand, the preparation of aminomethylene bisphosphonic acids **39** through a double-insertion reaction of vinylidene bisphosphonate on diamines, in the presence of dirhodium complex $Rh_2(NHCOCF_3)_4$, is also reported (Scheme 14).[52]



38

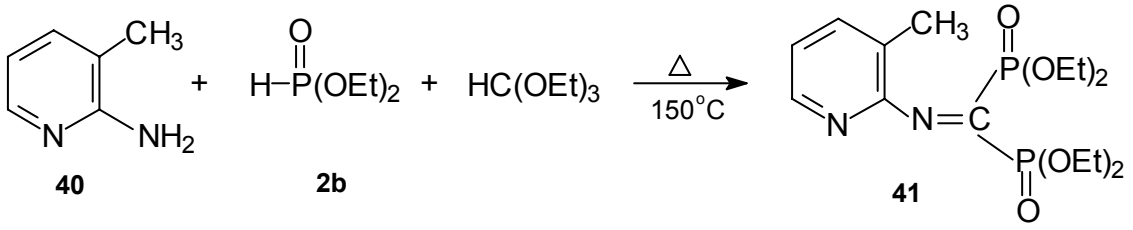
Scheme 13



39

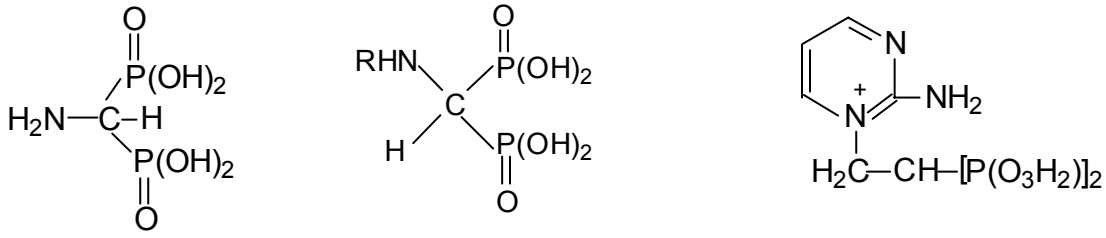
Scheme 14

Tetraethyl [3-methyl-2-pyridinyl-amino]methylidene-bisphosphonate, **41**, was obtained in 49% yield by allowing 2-amino-3-methylpyridine **40**, diethyl phosphonate **2b**, and triethyl-orthoformate to react under heating for 30 minutes (Scheme 15).[53] In the same fashion, BP-acids **42-44** (Figure 7) could be obtained in high yields.[54-57]



40 **2b** **41**

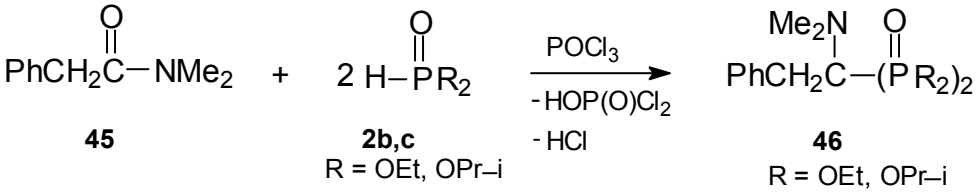
Scheme 15



42 **43** **44**

Figure 7

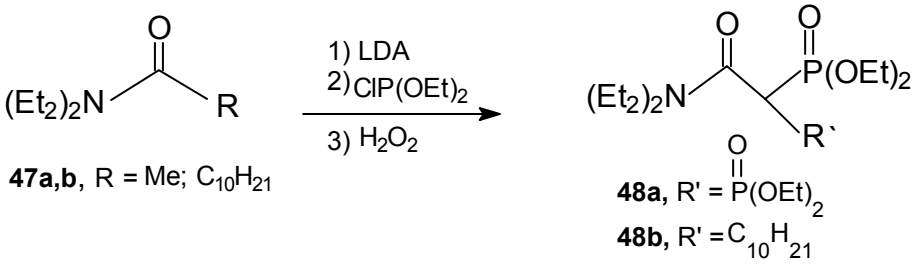
5.2.2. Amides. The *α*-aminomethylene-bisphosphonates, **46**, were prepared by a simple method (one-pot-reaction) by treating *N,N*-disubstituted-formamides (or -acetamides) **45** with two equivalents of dialkyl phosphonates **2b,c** in the presence of phosphorus oxychloride.[58]



45 **2b,c** R = OEt, OPr–i **46** R = OEt, OPr–i

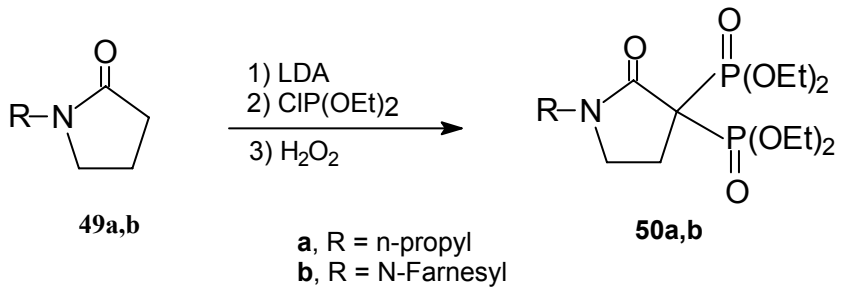
Scheme 16

Treatment of the simple acyclic amide **47a,b** with strong base (LDA), followed by addition of diethyl phosphorochloridite, and oxidation of the immediate product with H_2O_2 afforded the bisphosphonate, **48a,** in 72% yield.[58-61] Unfortunately, when the longer chain amide **47b** was treated under the same reaction conditions, only the mono-phosphonate **48b** was obtained.[49]

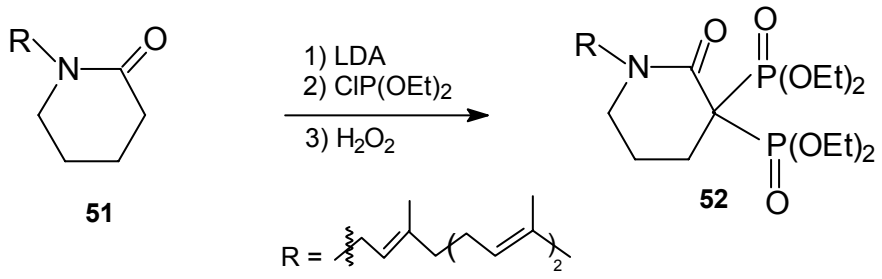


Scheme 17

The treatment of *N*-alkyl lactams **49a,b** with excess LDA, subsequent addition of diethyl phosphorochloridite, and oxidation of the reaction mixture with H_2O_2 allowed synthesis of several lactone bisphosphonates, **50**, in good yield (Scheme 18).[49] Similarly, when the same reaction conditions were applied to the six-membered lactam ring **51**, the bisphosphonate **52** was isolated in a moderate yield as in Scheme 19.[49]

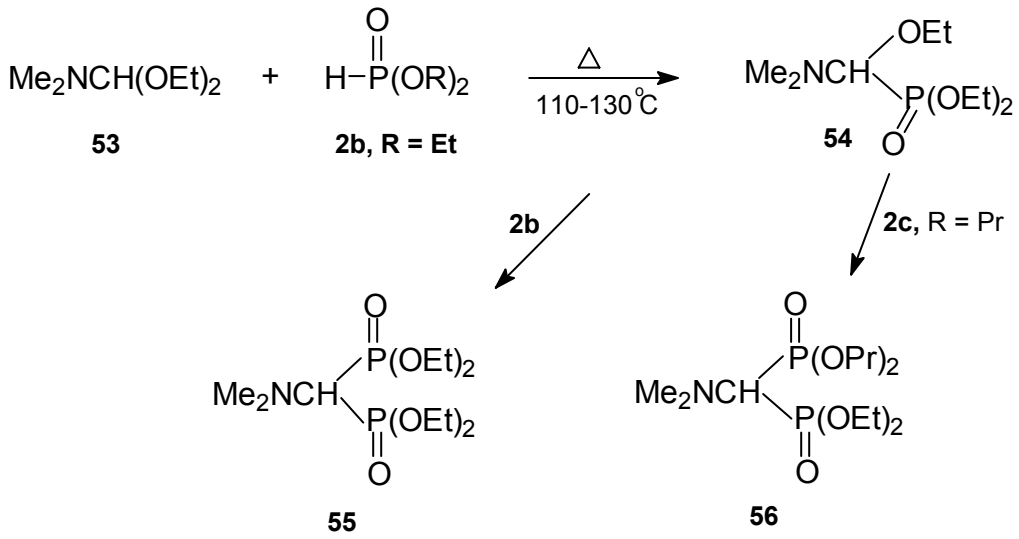


Scheme 18



Scheme 19

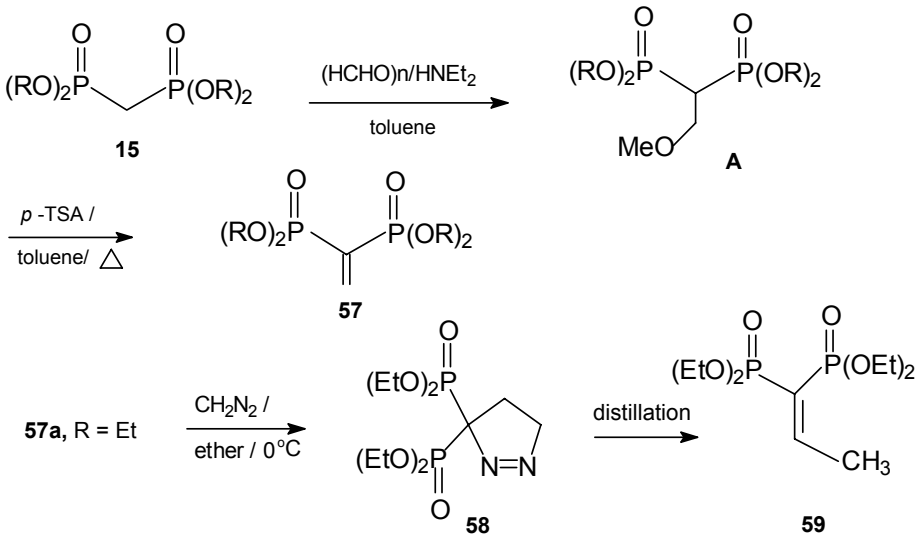
Preparation of bis-aminomethylene bisphosphonates through a double insertion-reaction of **1** on diamines is also reported.[62] Reaction of dimethylformamide diethyl acetal **53** with diethyl phosphonate **2b** at 110-130 ºC gave the monophosphonate, **54**, which when treated with another mole of **2b,c** gave the symmetrical **55** or asymmetrical bisphosphonate **56** (Scheme 20).[62]



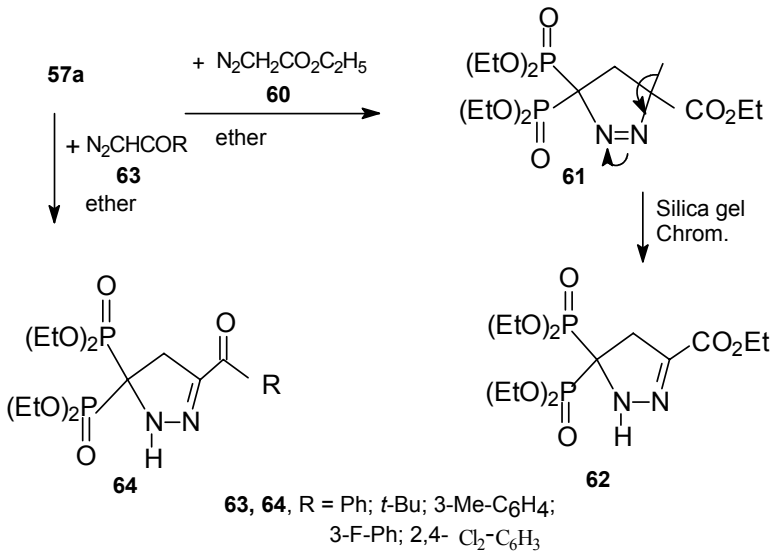
Scheme 20

5.2.3 Diazo-compounds. Vinylidene bisphosphonate **57** is another phosphorus reagent, which could be prepared by heating tetraalkyl methylene-1,1-bisphosphonate in toluene solution of paraformaldehyde and diethylamine to give the methylene bisphosphonate **A**, which when heated for 24 h in toluene in the presence of *p*-TSA converted to ethylidene bisphosphonate **57.** At 0 ºC, the addition of diazomethane to a solution of **57a**, in ether gave, after concentration, the pyrazoline bis-phosphonate, **58**, as the sole product in nearly quantitative yield. However, upon standing for one week at room temperature or during attempted distillation, **58** was converted quantitatively into the propenylidene-diphosphonate **59** as in Scheme 21.[63]

On the other hand, the reaction of ethyl diazo-acetate, **60**, with the vinylidene bis-phosphonate **57a** in ether afforded the un-rearranged pyrazoline **61** as the crude product, but upon silica gel chromatography a 1,3-proton shift occurred to give **62** as shown in Scheme 22.[64] In another report, the diazo-substrates, **63**, combined with **57a** in ether at 22 ºC, and stirring overnight, to give the pyrazoline bisphosphonates, **64**. The latter products were found to be more stable.[64]

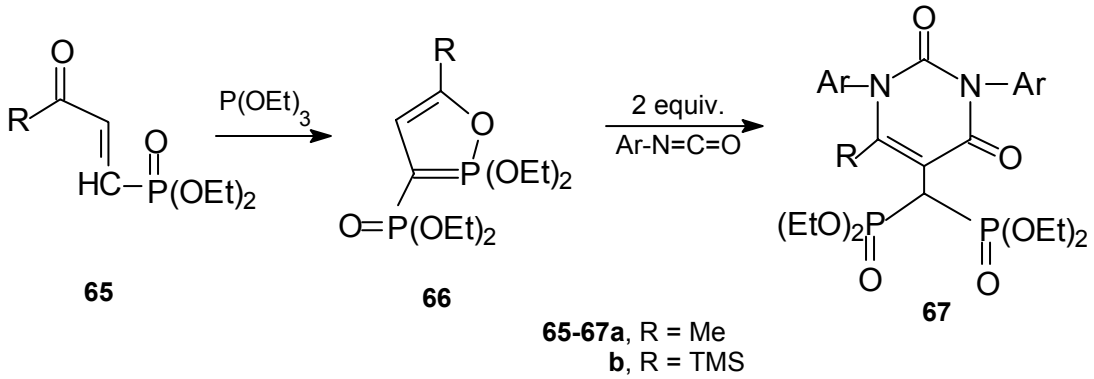


Scheme 21



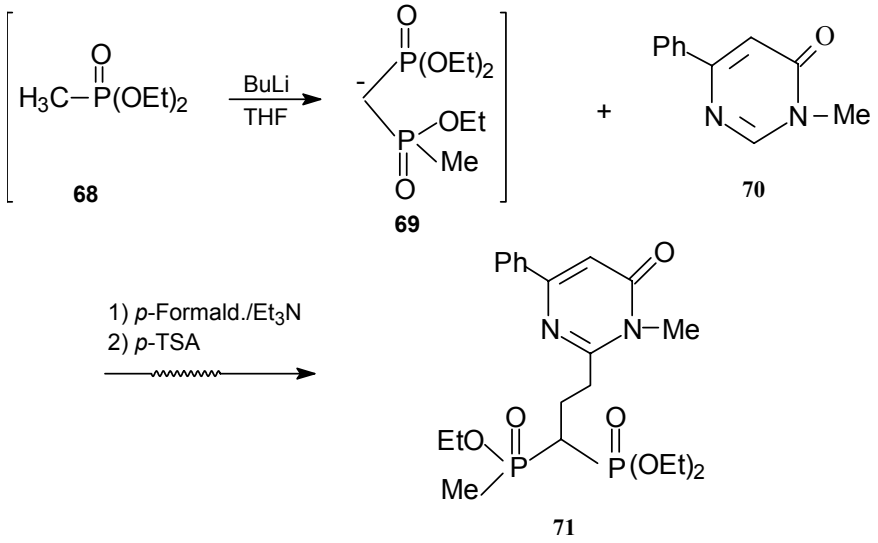
Scheme 22

5.2.4 Isocyanates. Bisphosphonopyrimidinediones **67a,b** could be prepared in moderate to high yields from the condensation of the easily prepared pentacovalent oxaphospholenes **66** with isocyanates as outlined in Scheme 23.[65]



Scheme 23

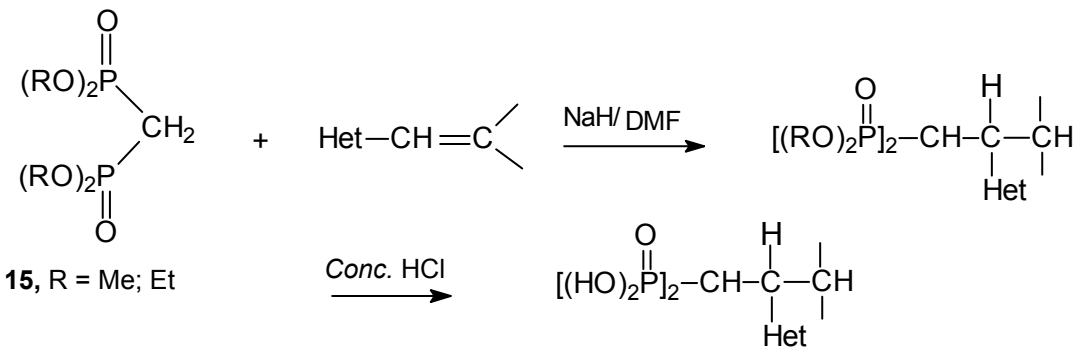
White and Fritzen[66] elaborated the new asymmetrical carbanion **69** for preparation a novel series of pyrimidine bisphosphonate esters. Treatment of the phosphinite **68** with BuLi in tetrahydrofuran gave the dimerization product **69** in 56% yield. This reagent underwent C-methylenation by treatment with paraformaldehyde and triethylamine, followed by *p*-toluenesulfonic acid, and then reaction with the corresponding lithiated pyrimidinone derivatives **70** to give the products **71** (Scheme 24).[66]



Scheme 24

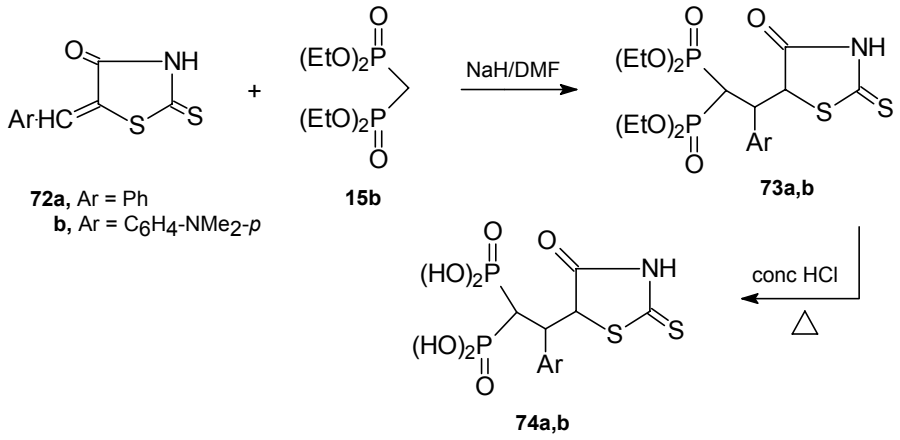
5.3 Bisphosphonates from substrates bearing an activated carbon-carbon double bond

Michael addition reaction of methylene-1,1-bisphosphonate **15** to alkylidene (or arylidene) substrates has been used as a convenient tool for the preparation of the heterocyclic substituted-1,1-bisphosphonates in different yields. Hydrolysis of BP-products by *conc*. hydrochloric acid produced the corresponding 1,1-bisphosphonic acids (Scheme 25).[67-70]



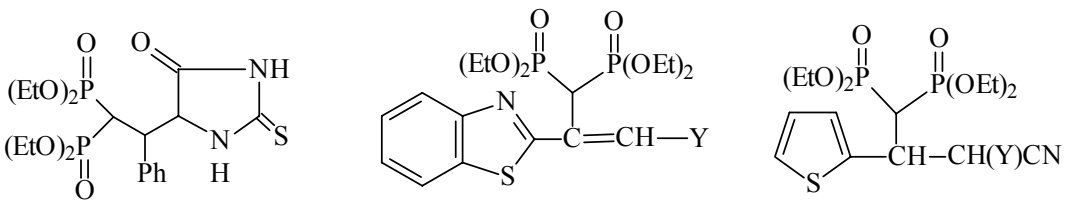
Scheme 25

According to this procedure, 5-phenylmethylene-2-thioxo-4-thiazolidinone **72a** and 5- (4-dimethylaminophenyl)-methylene-2-thioxo-4-thiazolidinone, **72b,** reacted with **15b** (two-fold excess based on the alkenes) in DMF containing excess NaH (two mole equiv of **15**) to give the corresponding 1,1-bisphosphonates **73a,b** as major products.[67] Acidic hydrolysis of the BPs **73a,b** afforded the BP-acids **74a,b** (Scheme 26).[67]



Scheme 26

In a systematic study, 1,1-bisphosphonates bearing *S*-, and *N*-heterocycles (**75-77,** Figure 8) were prepared in reasonable yields (47 to 72%) by a simple one-pot reaction, and were isolated exclusively in the *Z*-configuration.[67]



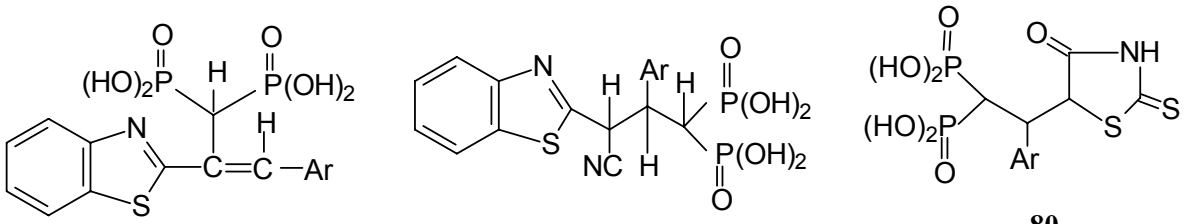
75 **76,** Y = Ph, 2'-furyl **77**, Y = CO_2Et; CN

Figure 8

Later, the same authors used the same route to introduce another series of heteroaryl-methylene-bisphosphonates (BPs) *via* Michael addition reaction of substituted arylidene thiazoles with the Wittig-Horner reagent **15b**. The article was offered to generalize an easy route for the transformation of easily available starting materials to the title BPs and the related BP-acids (**78-80**, Figure 9) in satisfactory yields. In addition, the protocol demonstrates an efficient site selective method for making addition products in high yields from arylidenes and methyl-1,1-bisphosphonate under microwave conditions.[68]

On the other hand, 2-substituted 1,1-cyclopropanediyl-bisphosphonates, **82,** were prepared by reacting bromomethylene bisphosphonate **81** with electron deficient alkenes, as Michael acceptors, in the presence of thallium-(I) ethoxide. Bisphosphonates, **82,** were converted into the corresponding free acids **83** by treatment with chlorotrimethylsilane in the presence of potassium iodide followed by treatment with water (Scheme 27).[69]

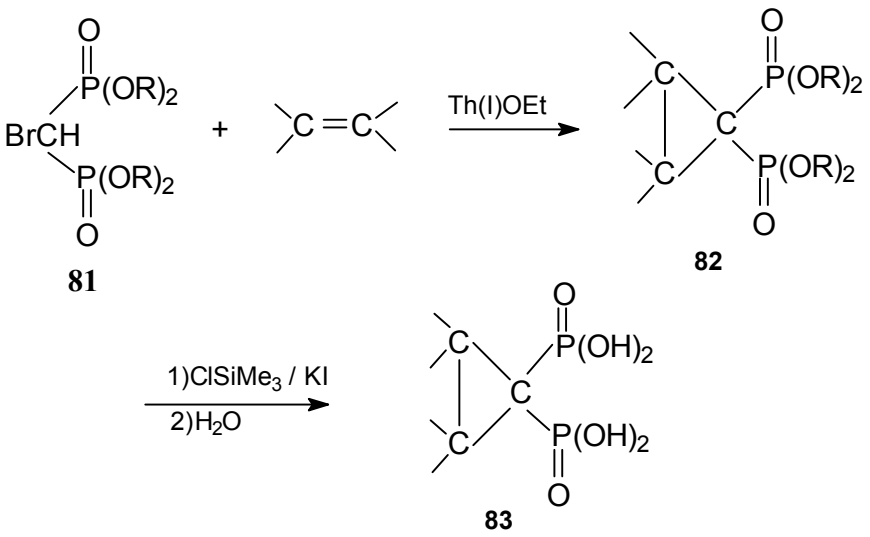
The synthesis of geminal bisphosphonates **85** could also be attained through the photochemical radical addition of tetraethyl phenylselenomethylene bisphosphonate, **84**, prepared *in situ* from deprotonation of tetraethyl methylene bisphosphonate **15b** with NaH, followed by addition of phenylselenium chloride (PhSeCl), to a variety of monosubstituted alkenes (Scheme 28).[70]



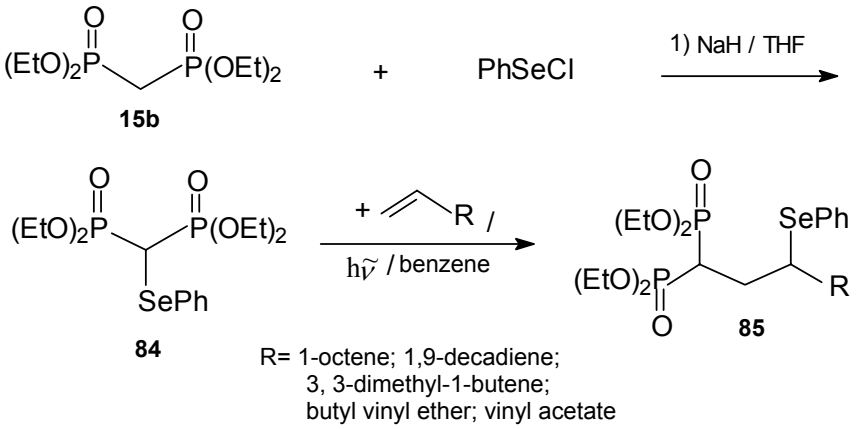
78 **79** **80**

78-80, a, Ar = $PhNMe_2$-*p*; **b,** Ar = $PhCH_3$-*p*
c, Ar = $PhNO_2$-*o*; **d,** Ar = $PhNO_2$-*p*
e, Ar = PhCl-*o*; f = Ar = PhCl-*p*

Figure 9



Scheme 27

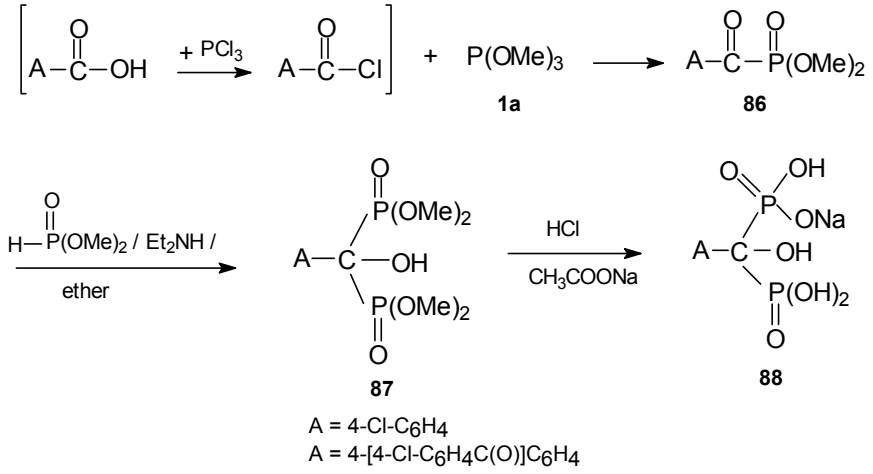


Scheme 28

5.4 Bisphosphonates from substrates-bearing carbonyl functions

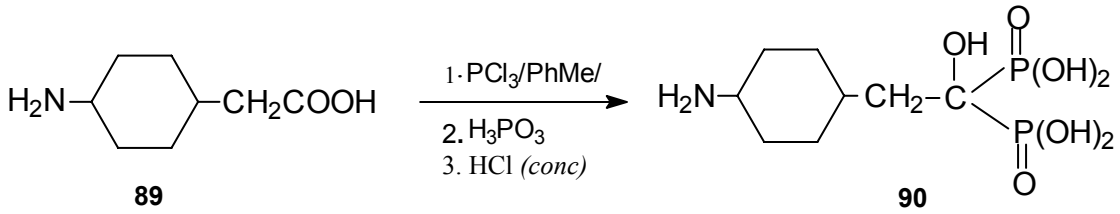
Bisphosphonates derived from substrates bearing carbonyl functions, in most cases, are α-hydroxy-bisphosphonates. These BPs have much biological interest since it is well known that when the R1 side chain (attached to the geminal carbon atom of the P-(R1)C(R2)-P group) is a hydroxyl group, the ability of the BPs to bind to the hydroxyapatite crystals, and to prevent both crystal growth, and dissolution is enhanced. Furthermore, the presence of a hydroxyl group at the R1-position increases the affinity for calcium (and thus for bone mineral), due to the ability of BPs to chelate calcium ions by tridentate rather than bidentate binding.[71a]

5.4.1 Acids, acid chlorides, acid anhydrides, and esters. The synthesis of α-hydroxy bisphosphonic esters *(HBP)* involved three steps. The first is the formation of the acid chloride, which by an Arbusov reaction with a trialkyl phosphite produced an *α*-keto-phosphonate **86**. Further dialkyl phosphonate (or another mole of trialkyl phosphite) to the keto-phosphonate yielded the hydroxy-bisphosphonates **87**. Acidic hydrolysis yields the corresponding bisphosphonic acid (BP-acid) **88.** In some cases, phosphorous acid (H_3PO_3) added to the acid chloride to give, directly, the BP-acids (Scheme 29).[71]

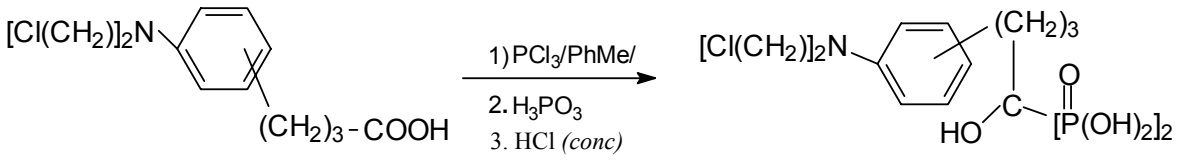


Scheme 29

2-(4-Aminocyclohexyl)-1-hydroxyethane-1,1-bisphosphonic acid, **90**, was readily prepared from the parent acid. Thus, when a mixture of (4-aminocyclohexyl)acetic acid **89** and phosphorus trichloride (PCl_3) in toluene was treated with phosphonic acid afforded **90** in 45% yield (Scheme 30).[72] Similarly, the bisphosphonic acid **92** was prepared from the substituted acid **91** (Scheme 31).[73]



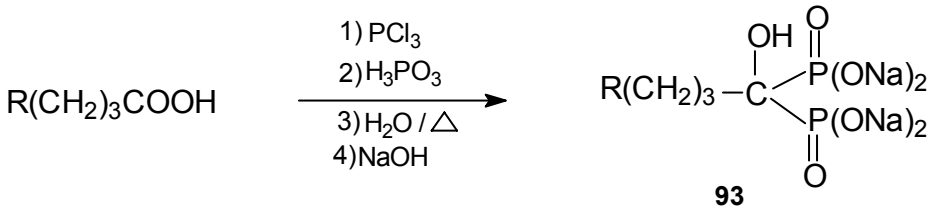
Scheme 30



91 **92**

Scheme 31

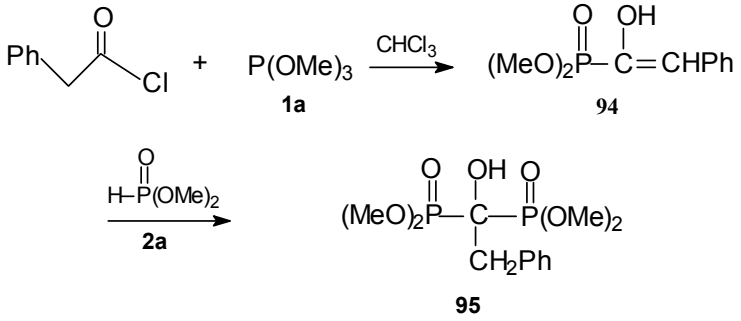
Particularly pure 1-hydroxy-1,1-bisphosphonic acids or their sodium salts **93** were prepared in a high- yield, one-pot procedure (Scheme 32).[74,75] The hydroxyvinyl phosphonate **94** with dimethyl phosphonate **2a** gave the hydroxy-bisphosphonates *(HBP)* **95** (Scheme 33).[76]



93

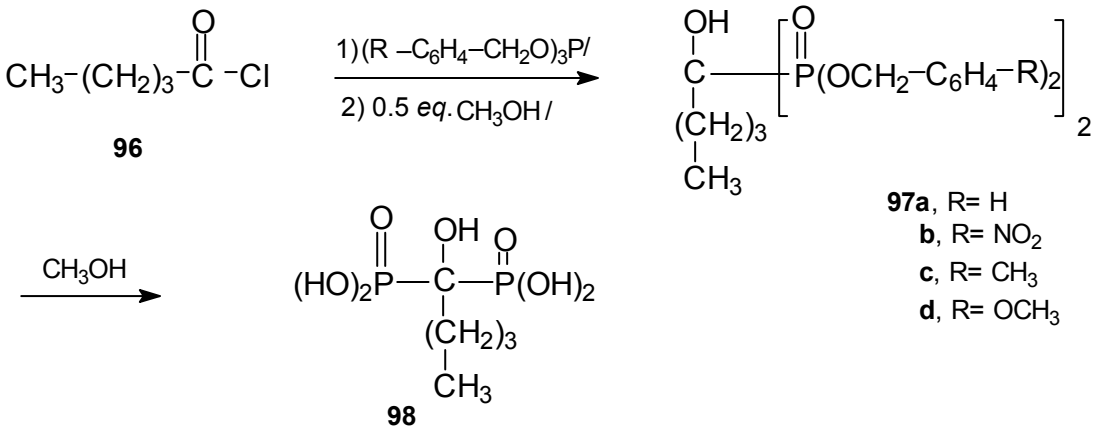
R = NH_2, CH_3, 3-imidazoyl, 3- pyridyl, 4-aminophenyl, Cl

Scheme 32



Scheme 33

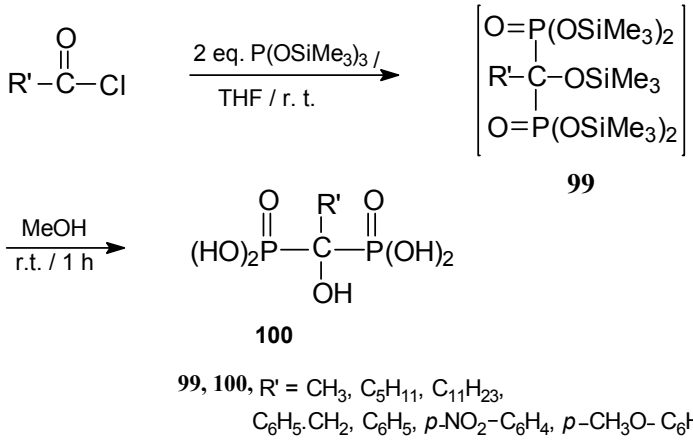
A modified, efficient one-pot method to prepare hydroxy bisphosphonic esters without using a dialkyl phosphonate, by introducing a protic reagent, was reported. Valeryl chloride **96** was added to benzyl phosphite derivatives to give the hydroxy bis-phosphonate benzyl esters **97a-d.** A protic reagent such as methanol was then added, and the solution stirred for one hour at ambient temperature to give BP-acids **98** (Scheme 34).[77] This allowed the synthesis of **97a-d** in excellent yields, except for **97d,** R= OCH_3, where a 35% yield was obtained.



96 **98**

Scheme 34

In another instance, the hydroxymethylene-bisphosphonic acids **100** were prepared by a simple and efficient one-pot procedure.[78,79] Thus, treatment of acyl chlorides with two equivalents of tris-(trimethylsilyl) phosphite at RT leads to the tetrakis-(trimethylsilyl) ester of 1-trimethylsiloxy-1,1-bisphosphonic acids **99**. Hydrolysis of **99** was carried out in methanol at room temperature for 1 h, to produce the free acids, **100**, as in Scheme 35.

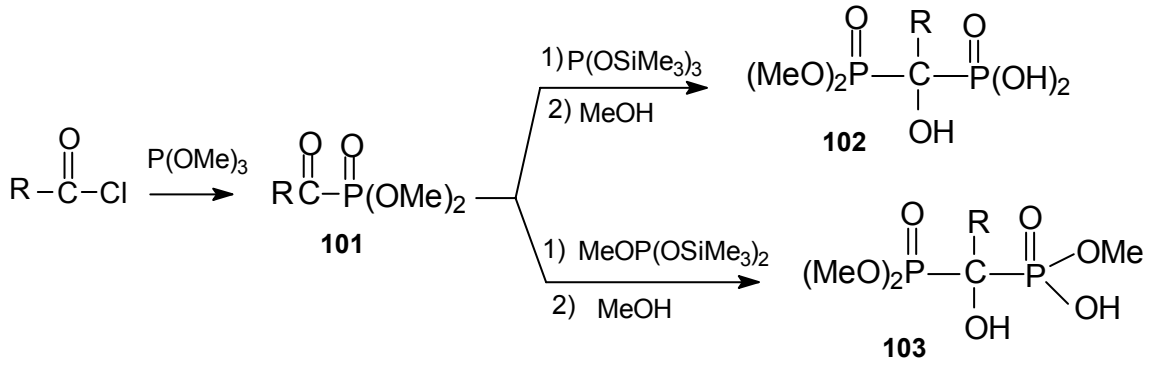


99 **100**

99, 100, R' = CH_3, C_5H_{11}, $C_{11}H_{23}$, $C_6H_5.CH_2$, C_6H_5, *p*-NO_2–C_6H_4, *p*–CH_3O- C_6H_4

Scheme 35

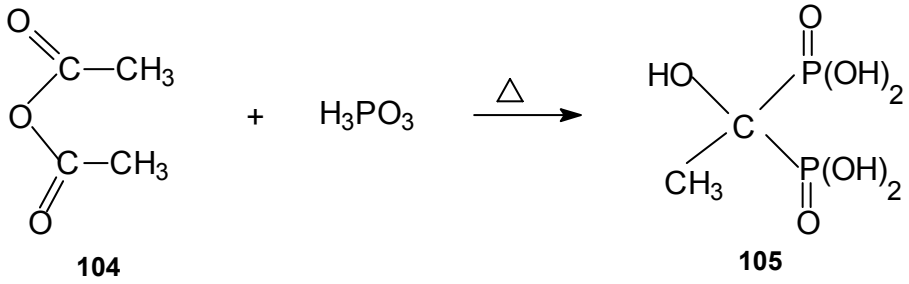
The HBP-diesters **102** and the HBP- triesters **103** were prepared from α-keto-phosphonates **101** (Scheme 36).[79] In the same fashion, a variety of α-hydroxy-bisphosphonic esters *(HBP)* w*ere* synthesized using classical methodology of applying trialkyl phosphites and/or dialkyl phosphonates to the acids or amino acids.[80-83]



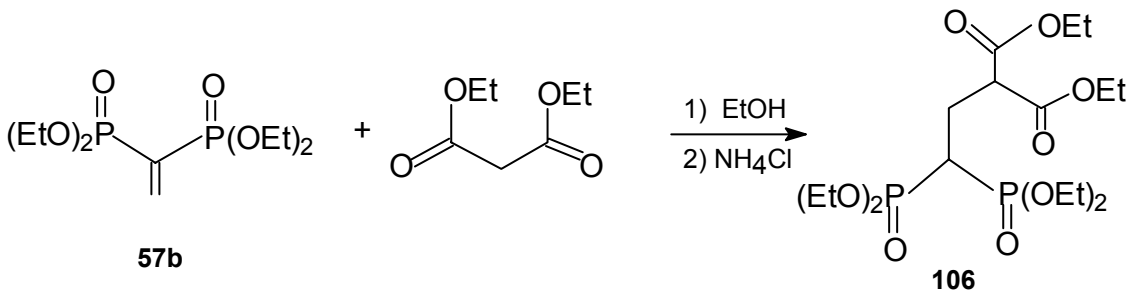
101-103, R= Me, Pr, iso- Pr, Bu, Ph, *p*- Br-C_6H_4, *p*-H_3C-C_6H_4, *p*-H_3CO-C_6H_4, *p*-O_2N-Ph

Scheme 36

Furthermore, acid anhydrides and esters were also used for the synthesis of BPs as indicated in Scheme 37; and Schemes 38-40, respectively. Thus, the synthesis of α-hydroxy-bis-phosphonic acids **105** was performed by the reaction of acetic anhydride **104** with H_3PO_3 (Scheme 37).[84] On the other hand, the methylene-bisphosphonate **106** was obtained from the reaction of tetraethyl ethylidene-1,1-bisphosphonate **57b** with the malonate ester (Scheme 38).[85] Similarly, reaction of **57b** with the cyclic malonate, 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in the presence of a base (DBU) in THF at room temperature afforded the cyclic bisphosphonates **107** (Scheme 39).[86]

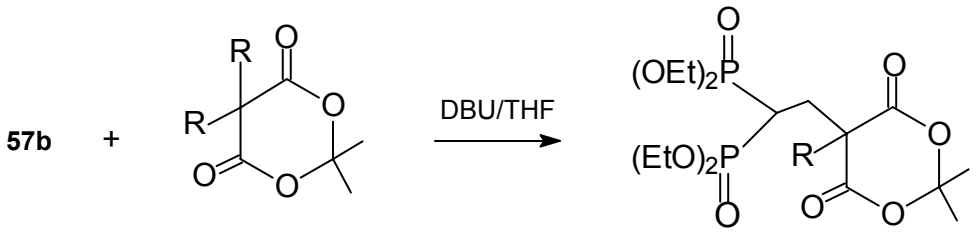


Scheme 37



57b **106**

Scheme 38

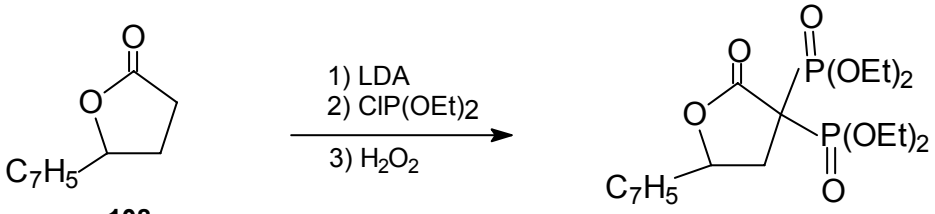


Meldrum's acid deriv. **107,** ,R = H; Me

Scheme 39

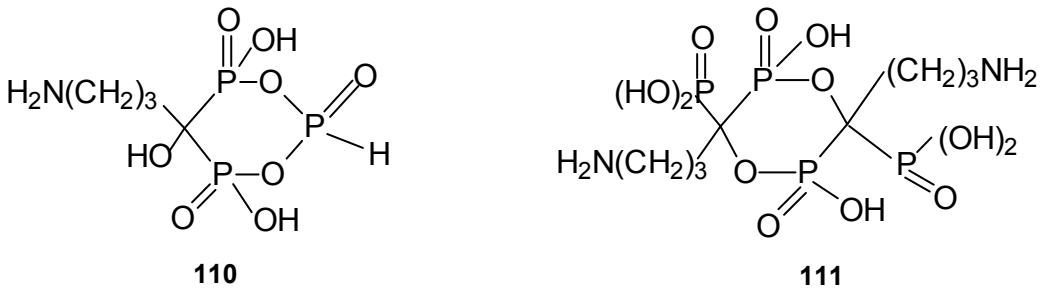
Treatment of the γ- lactone **108** with strong base (LDA), followed by addition of diethyl phosphorochloridite, and finally oxidation of the reaction mixture with hydrogen peroxide, afforded the lactone bisphosphonate **109** (Scheme 40).[49]

Conversely, a process for producing alkylpyrophosphonates, alkylpyrophosphates, and for producing 4-amino-1-hydroxyalkylidene-1,1-bisphosphonic acids or their salts was reported by Dauer *et al*.[87] Thus, the reaction of 4-aminobutyric acid with phosphorous acid in the presence of methanesulfonic acid gave the products **110** and **111**[87] (Figure 10)**.**



108 **109**

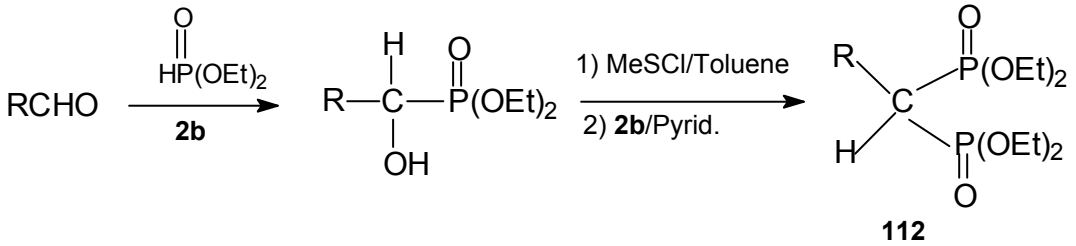
Scheme 40



110 **111**

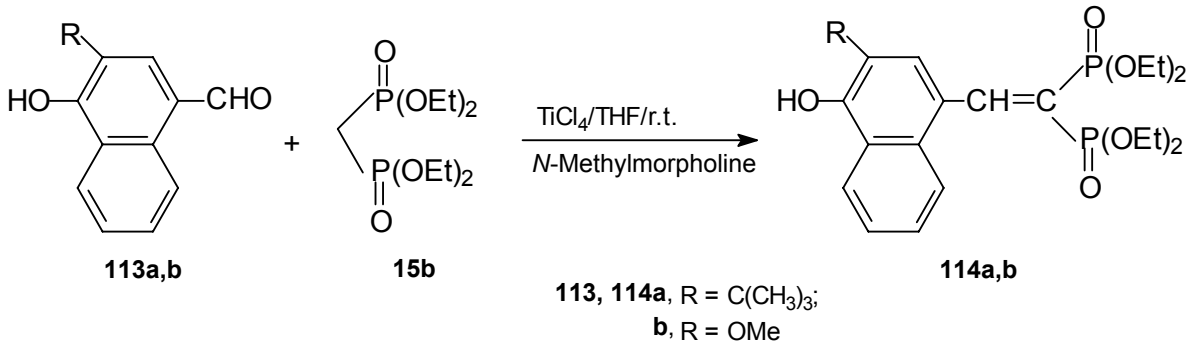
Figure 10

5.4.2 Aldehydes. A simple synthetic approach to tetra-alkylene bisphosphonates from aldehydes and phosphorus reagents was reported.[88-91] Thus, condensation of aldehydes with diethyl phosphonate, followed by sulfonylation of the α-OH with methanesulfonyl chloride and subsequent substitution by another molecule of diethyl phosphonate provides the corresponding bisphosphonates **112** (Scheme 41) in a one-pot procedure.[89] In another report, addition of tetraethyl methylene-bis-phosphonate **15b** to 3-*tert*-butyl-4-hydroxy-1-naphthaldehyde **113a** afforded 2-[3-*tert*-butyl-4-hydroxynaphthyl]ethenylidene-1,1-bisphosphonate, **114a**.[90] In similar instance, 3-methoxy-4-hydroxy-1-naphthaldehyde **113b** gave the corresponding bisphosphonate **114b** (Scheme 42).[91]



112

Scheme 41



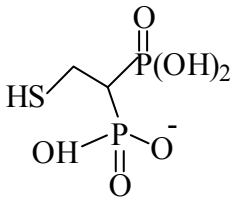
113a,b **15b** **114a,b**

113, 114a, R = $C(CH_3)_3$;
b, R = OMe

Scheme 42

5.5 Miscellaneous methods

The need to develop more powerful BP- drugs has generated a diverse spectrum of compounds with unique pharmacological activities, as well as uses for other industrial purposes. The desire to obtain unique BPs has stimulated numerous synthetic strategies as alternatives to the previous established methods. Recently, it has been focused on the sulfur- containing bisphosphonic acids as a chondroprotective therapy for the treatment of arthritis, particularly rheumatoid arthritis. The first example in this area is mercapto-ethyl-1,1-bisphosphonic acid (HSEDP®, Figure 11), which has demonstrated remarkable activity.[92]

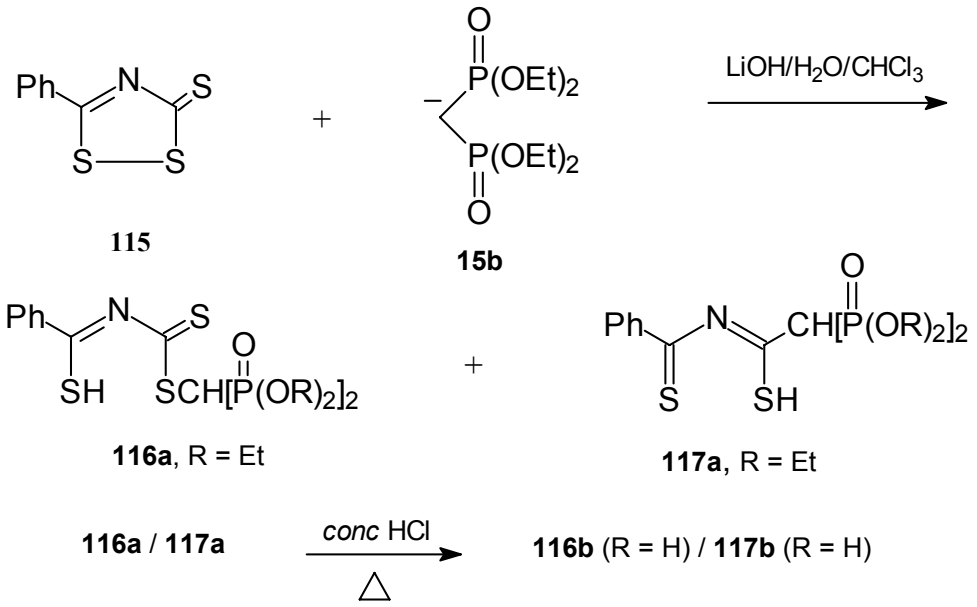


HSDEP

Figure 11

Later, a series of novel *S*-BP-acids-that contain a latent (or free) thiol group with other chemical moieties of potential anti-catabolic pharmacology were designed and synthesized by a one-pot approach. The properties of these products in the rat adjuvant model of arthritis, and the synthetic routes to these and related compounds were described in detail.[93] For example, 5-phenyl-*3H*-3-thioxo-1,2,4-dithiazole (**115**) was treated with three equivalents of **15**b in a mixture of $CHCl_3$ containing LiOH solution (0.5 *M*) at room temperature, to give BPs-acids **116b** and **117b** after treatment of the produced BPs **116a** and **117a** with *conc*. HCl (Scheme 43).[93]

Synthesis of the bisphosphonates **118a-121a** (Figure 12), and their relevant acids **118b-121b**, were also accomplished by applying **15b** on cyclic-, and acyclic *cis*-disulfide, as well as on electron deficient N=C- function in anils, under phase-transfer basic catalysis.[93]



Scheme 43

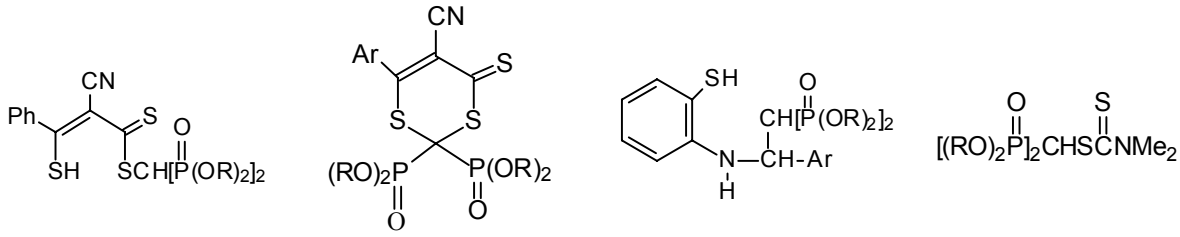
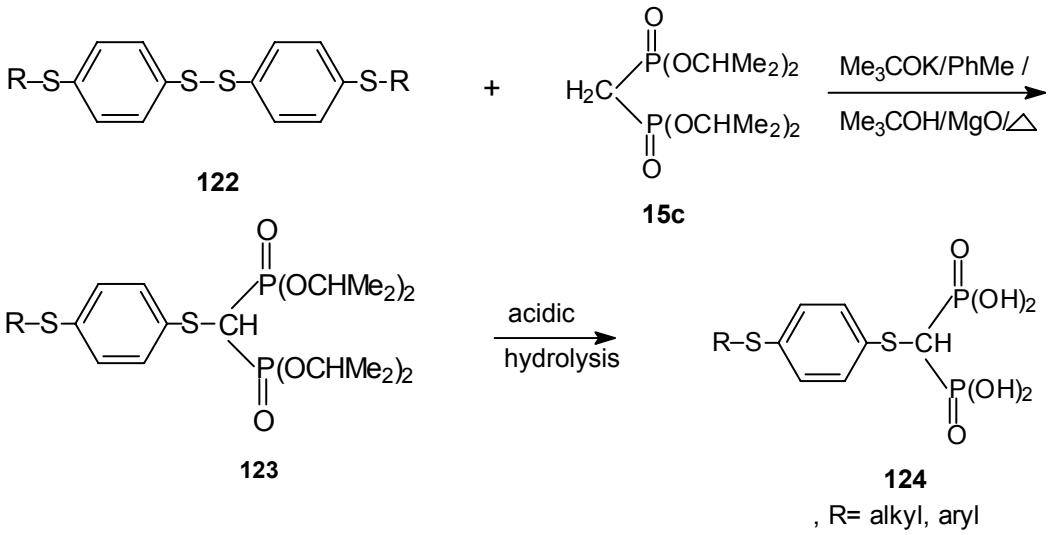
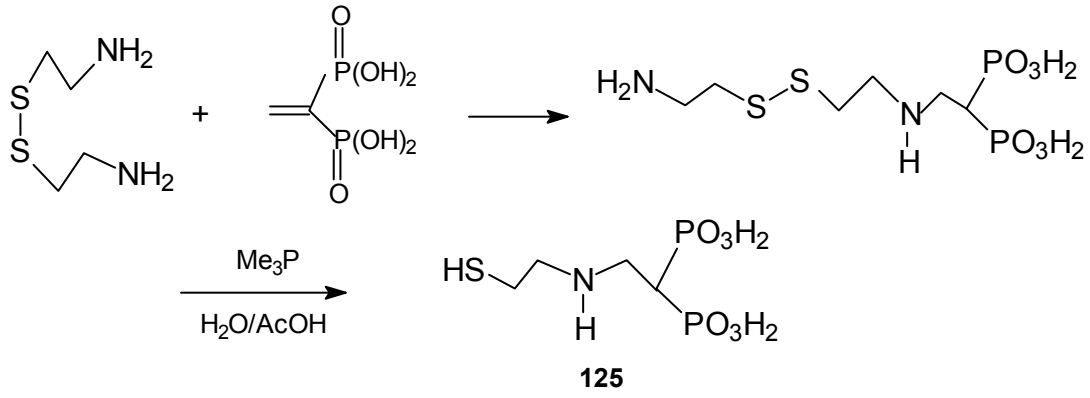


Figure 12

Furthermore, a process for producing a 1-alkylthio- or arylthio- methane-bisphosphonic acids **124** by conducting the coupling reaction of the disulfides **122** with Horner reagent **15c** in the presence of a metallic oxide (MgO), followed by acidic hydrolysis of the formed BPs, **123,** was reported (Scheme 44).[94] On the other hand, the synthesis of 2-(2-mercaptoethylamino)-ethylidene-1,1-bis-phosphonic acid (**125**) is described by Alferiev *et al.*[95] *via* nucleophilic addition of cystamine to vinylidine-bisphosphonic acids followed by reduction of disulfide bond with trimethylphosphine (Scheme 45).



Scheme 44



Scheme 45

6. Major Current Uses of Bisphosphonates

The pronounced selectivity of BPs for bone rather than other tissues is the basis of their value in clinical practice. Their preferential uptake by and adsorption to mineral surfaces in bone brings them into close contact with osteoclasts that lead to the loss of osteoclast activity and induction of apoptosis and death of osteoclasts.[96,97] So, they are used in the following applications:

- Bone scanning.[1,4]
- Inhibition of calcification, e.g., heterotopic bone formation, and dental calculus.[2,5]

- Reducing bone resorption,[1-7] e.g., Paget's disease, hyper-calcemia of malignancy, multiple myeloma,[1,3, 98, 99] bone metastases, especially breast cancer, osteoporosis, as well as treatment and prevention of postmenopausal bone loss.
- And recently in the prevention of bone loss and erosions in rheumatoid arthritis.[92, 99]
- BPs can reduce the pain associated with a variety of painful diseases.[100, 101]

7. Newer and Potential Clinical Indications for Uses of BPs

- Extended use in specific indications, e.g., osteoporosis in men.[100-102]
- Use in children with osteogenesis imperfect and other osteopenic disorders.[102]
- Use after cardiac or liver transplantation.
- Extended use in cancers to optimize anti-tumor effects and survival.
- Prevention of bone loss and erosions in rheumatoid arthritis.[92]
- Possible applications in other joint diseases, such as osteoarthritis.[92]
- Reduction of bone loss associated with periodontal disease.
- Prevention of loosening of joint prostheses.
- BPs appear to be useful lead compounds of novel anti-amebic and anti-malarial drugs.[103]
- BPs can provide benefits to patients with prostate cancer throughout the course of their disease.[104]
- Bioassay results raise the possibility that BP inhibit cancer growth in organs other than bone.[105]

8. Conclusions

In summary, the discovery and the development of the BPs as a major class of drugs for treatment of bone diseases has been a fascinating saga that is not yet completed. Despite the synthesis of hundreds of compounds, no clear-cut structure-effect relationship has been un-ravelled up to now, we can shed light on some results of several studies on structure-activity consideration:

- Even though all BPs are similar in terms of their inhibitory effects on bone resorption, the nitrogen containing analogs, have been demonstrated to be potent inhibitors of bone resorption, and highly selective bone targeting agents.[1-4]
- It was generally found that high anti-resorptive potency required a hydroxyl group at the carbon atom between phosphonate groups (C1).[17]
- The Sulfur containing analogs, have demonstrated remarkable activity in the rat adjuvant arthritis model.[92,93]
- The results suggested that BPs can be divided into two distinct categories in terms of their effects on inflammatory macrophages: (1) BPs that can metabolized and which inhibit the inflammatory response of macrophages, that possessing potential anti-arthritics properties, and

(2) amino-bisphosphonates, which sensitize macrophages to an inflammatory stimulus and may consequently induce an acute phase response.[106]

There has been a return to laboratory studies that are helping to unravel how these drugs work at a cellular level. As a result, their full therapeutic potential is gradually being realized. The journey, as usual started with chemistry, which led on to laboratory studies related to the mechanisms of biological calcification and bone metabolism, and was followed later by exploration of BPs as inhibitors of bone resorption. At the time being, there has been a return to laboratory studies that are helping to solve how these drugs work at a cellular level.

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Biographical Sketches

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Through several research grants, Prof. Abdou got the opportunities to carry out her research work in the United States of America, Germany, Britain, and Poland. She has 142 publications, mainly in Phosphorus Chemistry, and she cooperates, eventually in solving industrial problems for Egyptian Companies producing medicine, chemical or pesticides, as well. Her research interests include bio-, and organophosphorus-, heterocyclic-, and photochemistry. We mostly investigate some fundamental chemistry that deals with phosphorus chemistry leading to new phosphorylated compounds or -heterocycles, which are likely to be biologically active and have potential in the areas of medicine and agriculture.

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