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RESEARCH ARTICLE

Review on the Synthesis of *α*-Aminophosphonate Derivatives

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Abstract: *α*-Aminophosphonates are bioesters of amino acids and have several pharmacological activities. The high therapeutic properties of these compounds have encouraged researchers to synthesize new *α*-aminophosponate derivatives by Kabachnik field reaction and by Pudovik reaction by using different catalyst, under microwave irradiation, sonication *etc*. This article aims to review the work reported by researchers under different conditions and their biological activities.

Keywords: *α*-Aminophosphonates, Sonication, Kabachnik, Field reaction, Pundovik reaction, Catalyst

Introduction

The growing interest in aminophosphonates is due to their pharmacological activities[1]. *α*-Aminophosphonate are bio-esters of amino acids in which carboxylic group in replaced by phosphoric group, acting as antagonist of amino acids. They inhibit enzymes involved in amino acid metabolism and thus affect the physiological activity of cell.

Alkyl substituted α-aminophosphonate derivatives have antifungal[2], antibacterial[3], antiviral[4] and antitumour[5] activity. They also act as enzyme inhibitors[6], anticancer[7], antitubercular[8], herbicidal[9] pharmaceutical agents[10] and many other applications have attracted the interest of chemist in the synthesis.

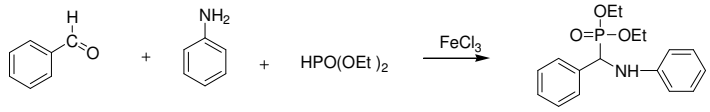
Literature survey reveals different synthetic protocols for the synthesis of these compounds. The most common synthetic route is via

A) Three component reactions is which an aldehyde, an amine and di and trialkyl phosphite is condensed in one setup by Kabachnik -field[11] reaction using Lewis and Bronsted acid catalyst such as $LiclO_4$[12] $Incl_3$,[13] $AlCl_3$[14] lanthanide triflates / magnesium sulphate[15,] $SbCl_3/Al_20_3$[16] $TaCl_2$-Sio_2[17], CF_3COOH[18], Scandium[19] BF_3 Et_2O[20] $M(OTF)_n$[21] and $M(ClO_4)_n$[22].

B) The second pathway is the Pudovik reaction[23] where dialkyl phosphite or trailkyl phosphite are added to the compounds containing imino bond in the presence of either base or Lewis catalyst. Such a glamorous history and novelty in medicinal properties prompted us to review the convenient methods for the synthesis of *α*-aminophosphonate derivatives 2000 onwards.

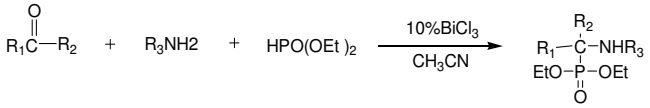
Review

Zahara Rezai and cowokers[24] reported one pot three component synthesis of aldehydes, amines and diethyl phosphite using $FeCl_3$ as catalyst (Scheme 1). Methodology was compared with the synthesis carried by using $CuCl_2$, results showed that $FeCl_3$is more efficient than $CuCl_2$. Synthesized compounds were screened for antifungal activity, it was found Indole containing bis α-aminophosphonates showed activity against *M. Canis*.



Scheme 1

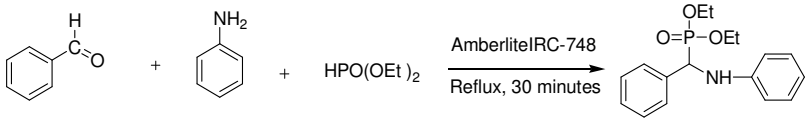
Zhuang ping Zhan and Jun-pingli[25] has reported an efficient protocol from aldehyde, aromatic amine and dialkyl phosphite in the presence of bismuth(III) chloride (Scheme 2).



Scheme 2

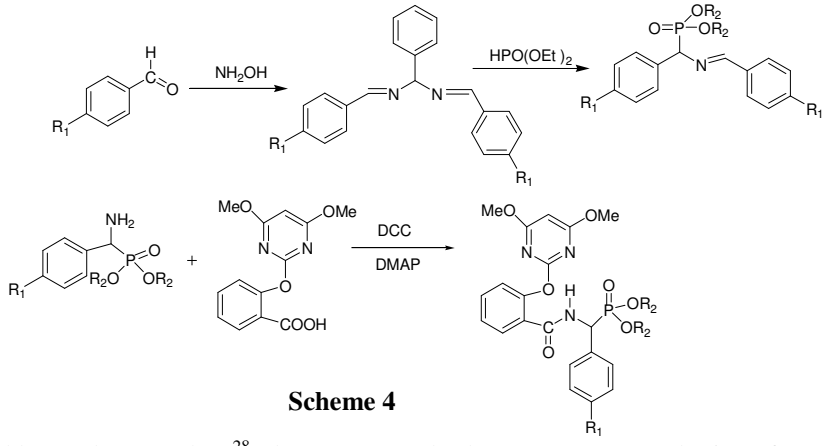
A one pot synthesis of new α-aminophosphonates has been reported by Nellisar Shashikumar[26] from substituted anilines, substituted aromatic aldehydes, and dialkyl phosphite in dry toluene in the presence of recyclable catalyst Ambelite IR-748 in good yield (Scheme 3).

All Synthesized compounds exhibit antimicrobial activity



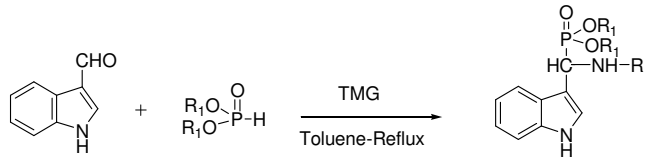
Scheme 3

Chanfei Jin, Yong Ji, Hongwn He and Liwu Fu[27] synthesized a new series of dialkyl [2-(4, 6 -dimethoxy pyrimidin - 2-yl oxy) benzamido (aryl) methyl phosphonate derivatives. Synthesized compounds were screened for antitumor activity and showed promising activity (Scheme 4).



Scheme 4

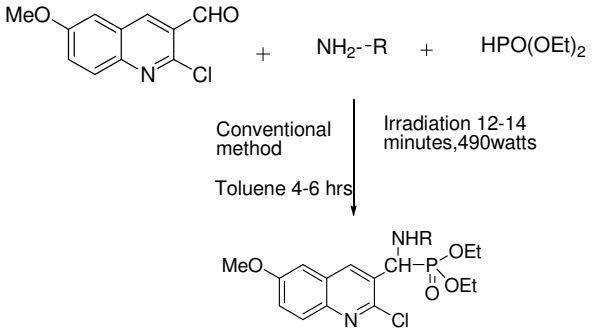
Reddy and coworkers[28] have reported the one pot synthesis of new α-aminophosphonate derivatives from Indole aldehydes, amines and dialkyl and diary phosphite using tetramethyl guanidine as catalysts (Scheme 5).



R_1= CH_3, C_2H_5, C_6H_5

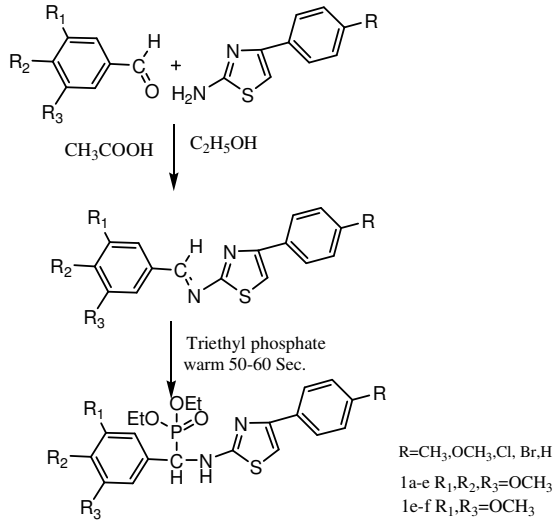
Scheme 5

Naga Raju and coworkers[29] investigated new series of diethyl (2-chloro-6 methoxy quinolin-3 yl) substituted phenylamino methyl phosphonate derivatives by using microwave irradiation at 490 watts for 12-14 minutes. This technique is advantageous over conventional methods due to shorter reaction times, easy workup and minimization of thermal decomposition products. All synthesized compounds exhibited antiviral and antioxidant activity (Scheme 6).



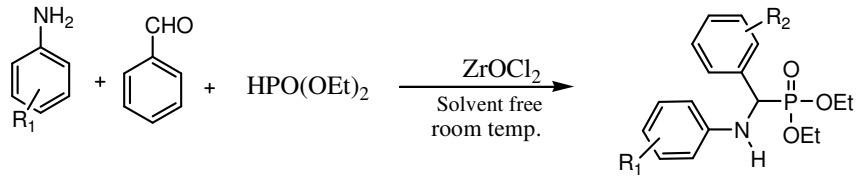
Scheme 6

A solvent free methodology for the synthesis of new series of α-aminophosphonates containing thiazol moiety has been reported by Shastri[30] by warming *N* -(3,4,5, trisubstituted benzylidene - 4 (4-substituted phenyl) thiazol 2-imine with triethyl phosphate for 50-60 seconds yielded α-aminophosphonates within 5-7 minutes (Scheme 7).



Scheme 7

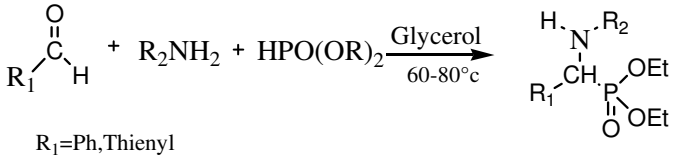
Recently $ZrOCl_2$ catalyzed one pot synthesis of α-aminophosphonates has been reported by Mayur Bhanushail Ninti Nandkumar and cowokers[31] by condensing amine, aldehyde and diethyl phoshite in the presence of environmentally friendly catalyst $ZrOCl_2$ $8H_2O$ in microwave reactor at 120 ^oC (Scheme 8).



R_1=H, CH_3, CLF, CF_3
R_2=H, CH_3, Br, Cl

Scheme 8

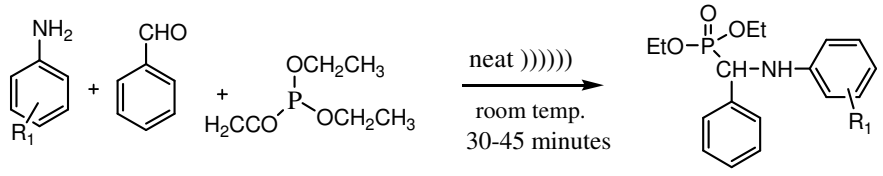
A simple and efficient method for the synthesis of α-aminophosphonates has been developed by Nicolae Onita, Ludovic Kurunezi *et al.*[32]. The one pot three component reaction of aldehyde, amine, dialkyl/diaryl phosphite or phosphonic acid at 100 watts under solvent and catalyst free condition. Under these conditions, microwave irradiation causes a strong acceleration of this process, reaction time was shorten going from 6-24 hours to 3-6 minutes to give α-aminophosphonates. Synthesized α-aminophosphonates were showed antioxidant and herbicidal activity. A one pot synthesis of α-aminophosphonates has been reported by Kobra Aziz, Meghdad, Karimi and Akbari Heydari[33] by condensing aldehyde, amine and phosphite using glycerol as solvent at 60-80 ^oC for 5-30 minutes in high yield (Scheme 9).



R_1=Ph,Thienyl
R_2=Ph,Bu
R=Me,Et,Ph

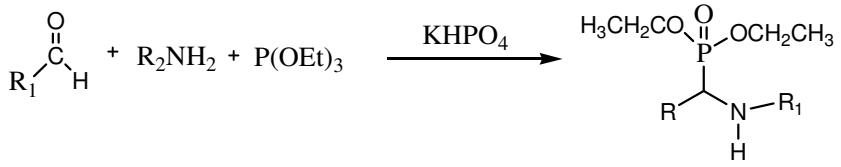
Scheme 9

An ultrasound promoted environment friendly one pot three component condensation of aldehyde, amine and triethyl phosphite under ultrasound irradiation has been reported by Meena Sharma, Baldev Singh *et al.*,[34] This technique in advantageous over conventional methods due to shorter reaction time, solvent free condition and excellent yields (Scheme 10).



Scheme 10

Charansing Gill *et al.,*[35] have reported the use of 5% $KHPO_4$ catalyst for the synthesis of α-aminophosphonates via one pot reaction of aldehydes amines and triethyl phosphite under solvent free condition at room temperature for 30-60 minutes in high yield (Scheme 11).

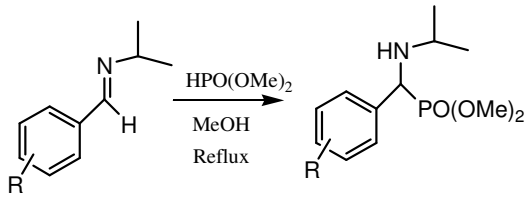


R_1=C_6H_5,$C_6H_4CH_3$,C_6H_4Cl,$C_6H_4NO_2$,C_6H_4OH

R_2= C_6H_5,$C_6H_4CH_3$,C_6H_4Cl,$C_6H_4OCH_3$

Scheme 11

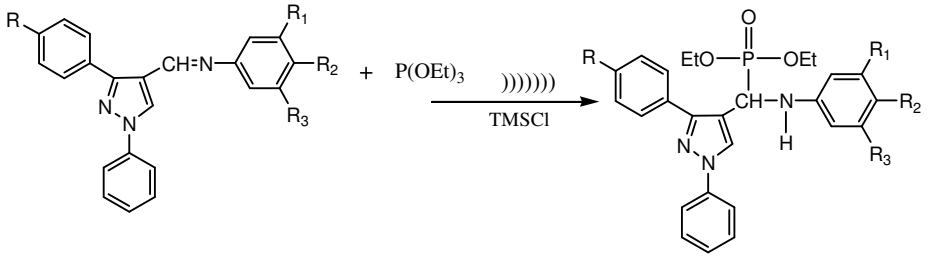
A simple and efficient method for the synthesis of *α*-aminophosphonates has been reported by Christian V. Stevens *et al*.,[36] by the condensation of imines with dialkyl phosphite in microreacter by using methanol (Scheme 12).



Scheme 12

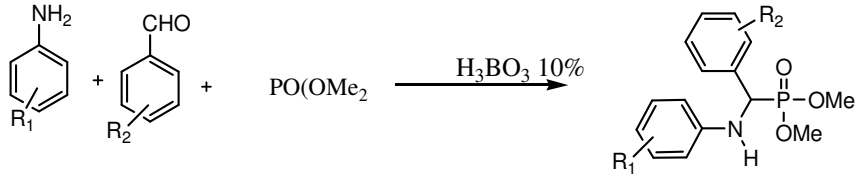
A series of *α*-aminophosphonates have been reported by Deepak Nagargoje *et al*.,[37] from fluorinated pyrazole imines and triethyl phosphite using TMSCl as a catalyst by both conventional and under ultrasound irradiation conditions (Scheme 13).

The non conventional method, ultrasonication is advantageous over conventional process *viz* short time span to complete reaction easy work procedure and excellent yields.



Scheme 13

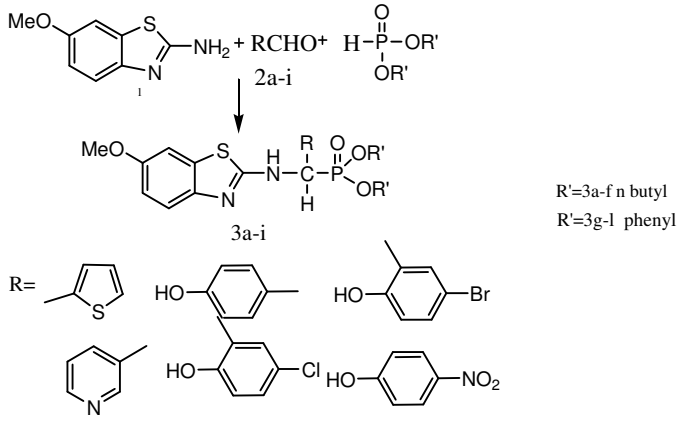
One pot synthesis of *α*-aminophosphonates catalyzed by boric acid at room temperature has been reported by Zahed Karimi Jaberi and Mohammad Amri[38] by the condensation of trimethyl phosphite aldehydes and amines in the presence of boric acid (10 mol %) under solvent free conditions (Scheme 14).



Scheme 14

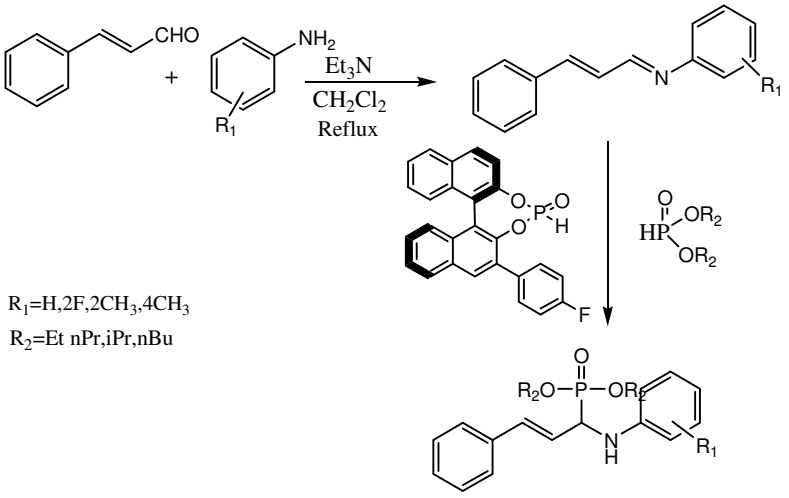
Pasupuleti Visweswara Rao *et al.,*[39] synthesized a series of dibutyl (2-hydroxy phenyl) 6-methoxy bezo[d] thiazol-2-yl-amino) methyl phsphonates and diphemyl (4-hydroxy-phenyl). 6-methoxy benzo[d]thiazol – 2 yl amino) methyl phosphonates by the condensation of various aromatic / heterocyclic aldehydes with dibutyl and diphenyl phsphites by the kabachnik field reaction under microwave irradiation at 700 watt for 12-15 minutes in high yield (Scheme 15).

All the synthesized compounds were screened for antibacterial and antioxidant activity. These compounds showed promising activitiy depending upon the nature of bioactive group at α-carbon.



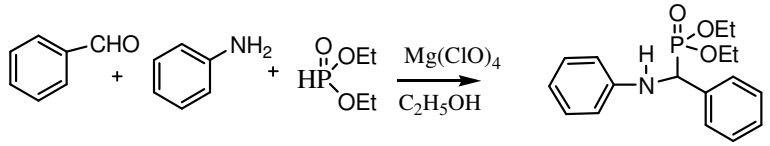
Scheme 15

Song yang *et al*.,[40] have described the asymmetric addition of dialkyl phosphites on aldimines derived from cinnamaldetyde catalysed by the chiral organo catalyst (R) -3, 3',-(4-Flurophenyl)1-1' binaphthol phosphate to yield α-aminophosphonates (Scheme 16).



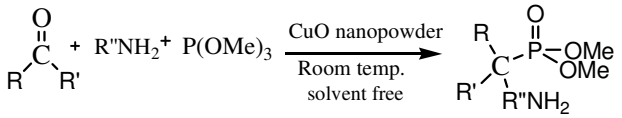
Scheme 16

A convenient synthesis of α-aminophosphonates have been developed by Jie Wu *et al*.,[42] via three component reactions catalyed by Mg $(ClO_4)_2$ or molecular iodine which yielded the corresponding α-aminophosphonates in high yield (Scheme 17).



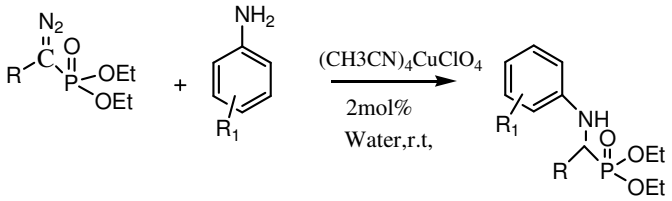
Scheme 17

A highly efficient one pot synthesis of *α*-aminophosphonates using CuO nano powder as catalysts under solvent free conditions is developed by Julie Banerji and coworkers[42]. The merit of this synthesis is excellent yield and recyclable catalyst (Scheme 18).



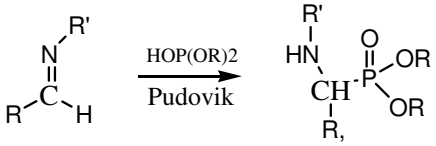
Scheme 18

A green approach to the synthesis of *α*-aminophosphonates in aqueous medium has been reported by chinnappan sivasankar and coworkers[43] method involves, synthesis of different kinds of *α*-aminophosphonates via phosphonate substituted carbene insertion in to N-H bond of aniline catalyzed by, copper transition metal catalyst $(CH_3CN)_4CuClO_4$ in water. The advantages of this methodology are use of environmentally benign catalysts, clean products and high yields (Scheme 19).



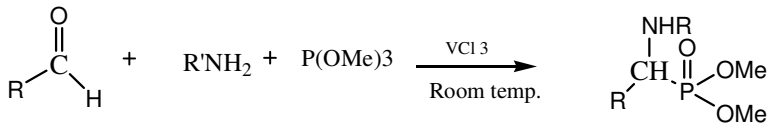
Scheme 19

α-Aryl *α*-aryl phosphonates and *α*-aryl *α*-aminophosphine oxides were synthesized by the microware assisted Pudovik reaction by the condensation of dialkyl phosphite and diphenylphosphine oxide to imines which is formed from benzaldehyde and primary amines (Scheme 20).



Scheme 20

Rajitha and coworkers[46] developed an efficient protocol for the one pot synthesis of and α-aminophosphonates by the condensation of aldehyde, amine and trimethyl phosphite in acetonitrile using VCL_3 as catalyst. The products were obtained in 5-15 minutes at room termperature (Scheme 21).



Scheme 21

Conclusion

α-Aminophosphonate derivatives are well known and important bioesters of amino acids in medicinal field; hence various derivatives have been synthesized. The *α*-aminophosphonates scaffold and its analogues are important pharmacophores which are found in biologically active compounds which stimulated the research activity in this field. The manuscript is a brief review about different methods, for the synthesis *α*-aminophosphonates derivatives.

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