Review on the Synthesis of $\alpha$-Aminophosphonate Derivatives

R.A. SHASTRI

Post Graduate Department of Chemistry, S.B.E.S. College of Science, Aurangabad- 431001 (Maharashtra), India
shastriranjana@yahoo.com

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Abstract: $\alpha$-Aminophosphonates are bioesters of amino acids and have several pharmacological activities. The high therapeutic properties of these compounds have encouraged researchers to synthesize new $\alpha$-aminophosphonate 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: $\alpha$-Aminophosphonates, Sonication, Kabachnik, Field reaction, Pundovik reaction, Catalyst

Introduction

The growing interest in aminophosphonates is due to their pharmacological activities\(^1\). $\alpha$-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 $\alpha$-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$_2$O$_3$\(^16\), TaCl$_5$-SiO$_2$\(^17\), CF$_3$COOH\(^18\), Scandium\(^19\), BF$_3$ Et$_2$O\(^20\), M(OTF)$_n$\(^21\) and M(ClO$_4$)$_n$\(^22\).

B) The second pathway is the Pudovik reaction\(^23\) where dialkyl phosphite or trialkyl 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 $\alpha$-aminophosphonate derivatives 2000 onwards.
Review

Zahara Rezai and coworkers\textsuperscript{24} reported one pot three component synthesis of aldehydes, amines and diethyl phosphite using FeCl\textsubscript{3} as catalyst (Scheme 1). Methodology was compared with the synthesis carried by using CuCl\textsubscript{2}, results showed that FeCl\textsubscript{3} is more efficient than CuCl\textsubscript{2}. Synthesized compounds were screened for antifungal activity, it was found Indole containing bis-\(\alpha\)-aminophosphonates showed activity against \textit{M. Canis}.

\begin{equation}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{C} \\
\text{NH} \\
\text{HPO(OEt)}_2 \\
\end{array} \quad \begin{array}{c}
\text{NH} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{HPO(OEt)}_2 \\
\end{array} \xrightarrow{\text{FeCl}_3} \begin{array}{c}
\text{O} = \text{P} - \text{OEt} \\
\text{OEt} \\
\end{array}
\end{equation}

Scheme 1

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

\begin{equation}
\begin{array}{c}
\text{R}_1\text{C} - \text{R}_2 \\
\end{array} + \begin{array}{c}
\text{R}_3\text{NH}_2 \\
\end{array} + \begin{array}{c}
\text{HPO(OEt)}_2 \\
\end{array} \xrightarrow{10\%\text{BiCl}_3, \text{CH}_3\text{CN}} \begin{array}{c}
\text{R}_2 \text{C} - \text{NHR}_3 \\
\text{OEt} \quad \text{OEt} \\
\end{array}
\end{equation}

Scheme 2

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

All Synthesized compounds exhibit antimicrobial activity

\begin{equation}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{C} \\
\text{NH} \\
\text{HPO(OEt)}_2 \\
\end{array} \quad \begin{array}{c}
\text{NH} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{HPO(OEt)}_2 \\
\end{array} \xrightarrow{\text{AmberliteIR-748}, \text{Reflux, 30 minutes}} \begin{array}{c}
\text{O} = \text{P} - \text{OEt} \\
\text{OEt} \\
\end{array}
\end{equation}

Scheme 3

Chanfei Jin, Yong Ji, Hongwn He and Liwu Fu\textsuperscript{27} synthesized a new series of dialkyl [2-(4, 6-dimethoxy pyrimidin - 2-y1 oxy) benzamido (aryl) methyl phosphonate derivatives. Synthesized compounds were screened for antitumor activity and showed promising activity (Scheme 4).

\begin{equation}
\begin{array}{c}
\text{R}_1\text{C} - \text{O} \\
\end{array} + \begin{array}{c}
\text{NH}_2 \\
\end{array} + \begin{array}{c}
\text{HPO(OEt)}_2 \\
\end{array} \xrightarrow{\text{DMAP, DCC}} \begin{array}{c}
\text{R}_1\text{C} - \text{NH}_2 \\
\text{OEt} \quad \text{OEt} \\
\end{array}
\end{equation}

Scheme 4

Reddy and coworkers\textsuperscript{28} have reported the one pot synthesis of new \(\alpha\)-aminophosphonate derivatives from Indole aldehydes, amines and dialkyl and diaryl phosphite using tetramethyl guanidine as catalysts (Scheme 5).
Naga Raju and coworkers\textsuperscript{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 5

A solvent free methodology for the synthesis of new series of $\alpha$-aminophosphonates containing thiazol moiety has been reported by Shastri\textsuperscript{30} by warming $N$-(3,4,5-trisubstituted benzylidene-4-(4-substituted phenyl) thiazol-2-imine with triethyl phosphate for 50-60 seconds yielded $\alpha$-aminophosphonates within 5-7 minutes (Scheme 7).
Recently ZrOCl$_2$ catalyzed one pot synthesis of $\alpha$-aminophosphonates has been reported by Mayur Bhanushail Ninti Nandkumar and cowokers$^{31}$ by condensing amine, aldehyde and diethyl phosphite in the presence of environmentally friendly catalyst ZrOCl$_2$ 8H$_2$O in microwave reactor at 120 °C (Scheme 8).

$$\begin{align*}
\text{NH}_2 & + \text{CHO} + \text{HPO(OEt)}_2 \xrightarrow{\text{ZrOCl}_2} \text{NH}^+ \text{P}^\text{OEt}^- \\
\text{R}_1=\text{H, CH}_3, \text{ClF, CF}_3 & \quad \text{R}_2=\text{H, CH}_3, \text{Br, Cl}
\end{align*}$$

**Scheme 8**

A simple and efficient method for the synthesis of $\alpha$-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 $\alpha$-aminophosphonates. Synthesized $\alpha$-aminophosphonates were showed antioxidant and herbicidal activity. A one pot synthesis of $\alpha$-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 °C for 5-30 minutes in high yield (Scheme 9).

$$\begin{align*}
\text{NH}_2 & + \text{R}_2\text{NH}_2 + \text{HPO(OR)}_2 \xrightarrow{\text{Glycerol, 60-80°C}} \text{H}^+ \text{N}^+ \text{R}_2 \\
\text{R}_1=\text{Ph, Thienyl} & \quad \text{R}_2=\text{Ph, Bu} \\
\text{R} = \text{Me, Et, Ph}
\end{align*}$$

**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).

$$\begin{align*}
\text{NH}_2 & + \text{CHO} + \text{H}_2\text{CCOCH}_3 \xrightarrow{\text{neat, room temp.}} \text{EtO}^- \text{R}^\text{OEt}^- \\
\text{R}_1=\text{H, CH}_3 & \quad \text{30-45 minutes}
\end{align*}$$

**Scheme 10**

Charansing Gill et al.$^{35}$ have reported the use of 5% KHPO$_4$ catalyst for the synthesis of $\alpha$-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).
A simple and efficient method for the synthesis of α-aminophosphonates has been reported by Christian V. Stevens et al.,\textsuperscript{36} by the condensation of imines with dialkyl phosphite in microreactor by using methanol (Scheme 12).

A series of α-aminophosphonates have been reported by Deepak Nagargoje et al.,\textsuperscript{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 \textit{viz} short time span to complete reaction easy work procedure and excellent yields.

One pot synthesis of α-aminophosphonates catalyzed by boric acid at room temperature has been reported by Zahed Karimi Jaberi and Mohammad Amri\textsuperscript{38} by the condensation of trimethyl phosphate aldehydes and amines in the presence of boric acid (10 mol %) under solvent free conditions (Scheme 14).
Pasupuleti Visweswara Rao et al., synthesized a series of dibutyl (2-hydroxy phenyl) 6-methoxy benzo[d]thiazol-2-yl-amino) methyl phosphonates and diphenyl (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 phosphites 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 activity depending upon the nature of bioactive group at α-carbon.

Song yang et al., 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).

A convenient synthesis of α-aminophosphonates have been developed by Jie Wu et al., via three component reactions catalyzed by Mg (ClO₄)₂ or molecular iodine which yielded the corresponding α-aminophosphonates in high yield (Scheme 17).
A highly efficient one pot synthesis of $\alpha$-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).

A green approach to the synthesis of $\alpha$-aminophosphonates in aqueous medium has been reported by Chinnappan Sivasankar and coworkers$^{43}$ method involves, synthesis of different kinds of $\alpha$-aminophosphonates via phosphonate substituted carbene insertion in to N-H bond of aniline catalyzed by, copper transition metal catalyst (CH$_3$CN)$_2$CuClO$_4$ in water. The advantages of this methodology are use of environmentally benign catalysts, clean products and high yields (Scheme 19).

$\alpha$-Aryl $\alpha$-aryl phosphonates and $\alpha$-aryl $\alpha$-aminophosphate oxides were synthesized by the microwave assisted Pudovik reaction by the condensation of dialkyl phosphite and diphenylphosphine oxide to imines which is formed from benzaldehyde and primary amines (Scheme 20).

Rajitha and coworkers$^{46}$ developed an efficient protocol for the one pot synthesis of and $\alpha$-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 temerature (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.

Reference
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