Recent Progress in Three-Component Reactions for Synthesis of α-Aminophosphonates.

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[Received 13th Sept.2014; Revised 23rd Sept.2014; Accepted 24th Sept.2014]

Abstract: Overview of data, obtained in recent years, concerning the mechanistic aspects, the catalyzed versions of α-Aminophosphonates by different reactions namely Kabachnik - Fields reaction, Mannich reaction, Microwave assisted reactions are discussed. Different Schemes for α-aminophosphonates synthesis during recent years are discussed.

Keywords: Kabachnik – Fields reaction, Mannich reaction, Pudovik reaction, Microwave assisted reactions, α-aminophosphonates.

I. INTRODUCTION

Organophosphorus chemistry is exploring the properties and reactivity of organophosphorus in particular aminophosphonic compounds. Aminophosphonates were almost unknown in the 1950[s] but now they are the subject of many publications and reviews. The discovery of aminophosphonic acids in living systems stimulated the interest in this group of compounds and the intensive research directed towards synthesis of α-aminophosphonic acid analogues of protein and non-protein amino acids resulted in a new class of drugs and other bioactive compounds with a great variety of commercial applications ranging from agriculture to medicine. Their utilities as enzyme inhibitors, anticancer agents, antibiotics, euro modulators, plant growth regulators and herbicides, antibacterial, and many other applications have attracted the interests of chemists for a long time [1-5]

α-Aminophosphonic acids occupy an important place among the various compounds containing a P–C bond and an amino group (Fig. 1), because they are analogues of natural a-amino acids, the 'building blocks of peptides and proteins'. Phosphonates or phosphonic acids are organic compounds containing one or more C–$P(O)(OH)_2$ or C–$P(O)(OR)_2$ (with R = alkyl, aryl) groups. Since the work of Schwarzenbach in 1949, phosphonic acids are known as effective chelating agents. The introduction of an amine group into the molecule to obtain –NH_2–C–$P(O)(OH)_2$ increases the metal binding abilities of the phosphonates [6-9]. Phosphonates are highly water-soluble while the phosphonic acids are only sparingly soluble. Phosphonates are not volatile and are poorly soluble in organic solvents [10-13].

Organophosphorus compounds have been extensively used in organic synthesis. Several reviews have been devoted to the synthesis of aminoalkanephosphonic acids [1-3,14] However, most of the described methods for the synthesis of a-aminophosphonic acids use carbonyl compounds such as aldehydes, ketones, or carboxylic acids as starting compounds [15-19]. The impressive array of applications has recently stimulated considerable effort towards the synthesis of aminophosphonic acids and many methods are now available [20-24]. α-Aminophosphonic acids are obtained reacting amides, or 2-oxazolidinone derivatives with formaldehyde and phosphorus trichloride [25-28]. a-Aminophosphonic acids bearing heterocyclic, [29-32] aromatic rings such as furane, anthracene, thiophene, pyrazole, imidazole and pyridine are described [33-36].

Chemistry: synthesis of α-aminophosphonates

The diesters of H-phosphonic acid occupy a major position in organophosphorus chemistry since they are frequently the intermediates in the synthesis of a variety of bioactive products including aminophosphonates, aminophosphonic acids, P–C phosphonates, hydroxyalkyl phosphonates, etc.

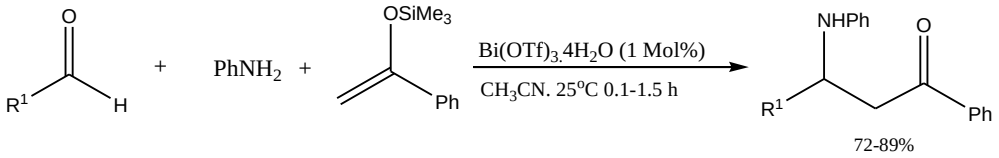
The strongly polar character of the phosphoryl group of the H-phosphonates is responsible to a great extent for the reactivity of this class of S compounds [37-43].

Kabachnik and Fields [15-18] have discovered the first method for the preparation of α-aminophosphonic acids.

Three-component reactions have emerged as useful methods because the combination of three components to generate new products in a single step is extremely economical, among the multi-component reactions [44-48]. The usefulness and importance of these processes is underscored by the large number of publications since our previous review [49] published in early 2005.

Mannich Reaction

The formation of β-aminocarbonyl compounds (Mannich bases) from the reaction of an active methylene compound with formaldehyde and an amine was first recognized by Mannich [50]. Its application in the synthesis of numerous pharmaceuticals and natural products, and the later developments of this reaction [6] are significant. Ollevier and Nadeau [51] have reported a bismuth, triflate-catalyzed, Mannich-type reaction of aldehydes, anilines, and silyl enol ethers to afford the corresponding β-aminoketones (Scheme 1).



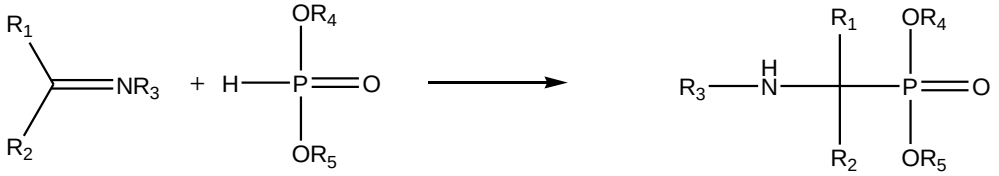
Scheme 1

The advantages are lowcatalyst loading (1%) and no formation of by-products. Probably due to enamine formation, aliphatic aldehydes did not react under these conditions, except cyclohexanecarboxaldehyde, which furnished the corresponding product in good yields. The same group has also developed [52] a bismuth triflate-catalyzed protocol for the reaction of an aldehyde, an amine, and a silyl ketene acetal to furnish β-aminoesters.

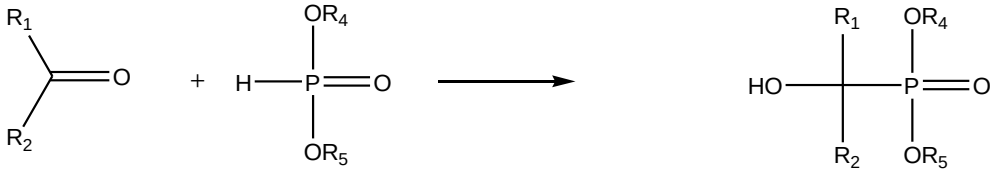
Janda and co-workers [53] have reported the use of molecular iodine (neutral conditions) for the preparation of β-aminoketones via a three-component Mannich reaction. A zinc(II) triflate-promoted reaction of electron-deficient aromatic amines with electron-deficient aromatic aldehydes and diethyl malonate has been described by Wang et al. [54] for the synthesis of β-aminoesters.

Kabachnik-Fields reaction:

Various synthetic methods for α-aminophosphonic acids and α-aminophosphonates have been reported [55-57] and the straightforward one is the addition of the compounds, containing P-H bond to the C=N- bond of imines (Pudovik reaction, [58] Scheme 2A). In fact, dialkyl phosphites are able to undergo many addition reactions, including addition to the C=O bond to give α-hydroxyphosphonates (Abramov reaction [59-61] Scheme 2B).

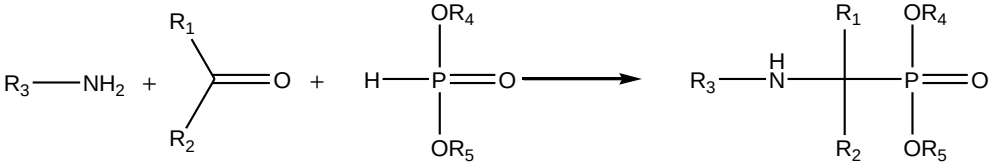


Scheme 2A



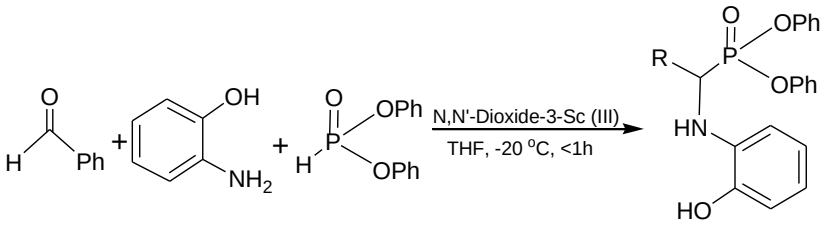
Scheme 2B

However, the most remarkable pathway to the synthesis of α-aminophosphonates is the Kabachnik-Fields reaction, [62-65] which is a one-pot, three-component procedure using carbonyl compound, amine and dialkyl phosphite (Scheme 3).



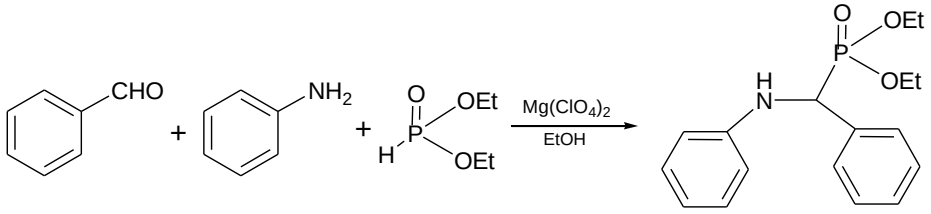
Scheme 3

Xin Zhou et al. [66] applied the N,N′-dioxide-Sc(III) complex in the three-component Kabachnik-Fields reaction of aldehydes, 2-aminophenol and diphenylphosphite (Scheme 4) to give the corresponding α-aminophosphonates in good yields with high enantioselectivities. Kabachnik-Fields reaction proceeded directly with extremely high reactivity under mild conditions and could be explored for large scale synthesis of the α-aminophosphonates.



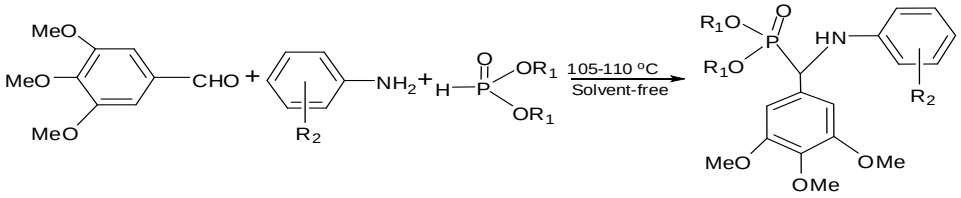
Scheme 4

Jie Wu et al. [67] discussed three component reactions of aldehydes, amines and diethyl phosphitecatalyzed (Scheme 5) by $Mg(ClO_4)_2$ or molecular iodine which afforded the corresponding α-aminophosphonates in excellent yields under mild conditions.



Scheme 5

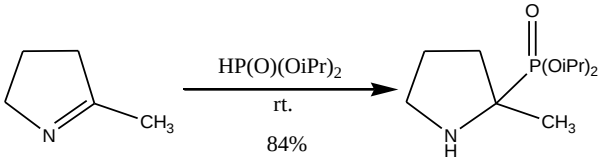
New α-aminophosphonates were synthesized by the Kabachnik-Fields reaction with 3,4,5-trimethoxybezaldehyde, various aromatic anilines and dialkyl phosphate (Scheme 6) under solvent free conditions. Half-leaf method was used to determine the in vivo curative efficacy of the title products against Tobacco Mosaic Virus (TMV) [68].



Scheme 6

Pudovik Reaction

Nucleophilic addition of dialkyl phosphite to cyclic C=N imines is one of the most direct ways to synthesize cyclic α-aminophosphonates of this type. Addition of diisopropyl phosphite to the commercially available 2-methyl-1-pyrroline produced diisopropyl α-aminophosphonate in 84% yield (Scheme 7) [69].



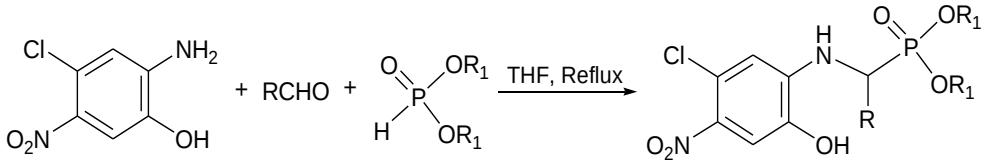
Scheme 7

Synthesis of α-Aminophosphonates by Three-Component Reactions

In recent years, considerable interest and attention have been focused on the synthesis and bio-activity evaluation of α-aminophosphonic acids [70-72] and their derivatives as they have important applications in medicinal chemistry as antibiotics, antiviral agents and enzyme inhibitors. In addition to this, the structural similarity with naturally occurring α-amino acids gave the momentum to synthesize α-aminophosphonic acids and their derivatives and study their applications in biological system. Extensive investigation for the past few decades revealed that they are of particular importance in biological and medicinal research [73] and the application of α-aminophosphonates as enzyme inhibitors, [74-76] antibiotics, pharmacological agents, [77-81] herbicides [82,83] heptants of catalytic antibiotics [84,85] inhibitors of EPSP synthease [86] HIV protease [87] and rennin [88] are well manifested.

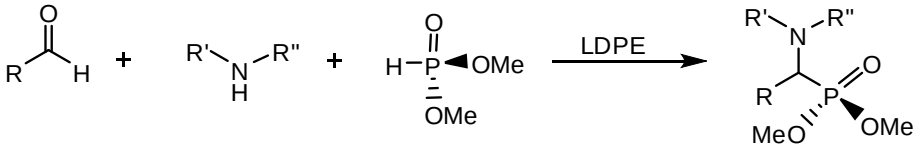
A simple and efficient method for the preparation of α-aminophosphonates have been reported by

Arthanareeswari et al. [89] (Scheme 8) from aldehydes, 2-amino-4-chloro-5-nitrophenol and dimethyl/diethyl phosphate in dry tetrahydrofuran at reflux conditions for 4-5 hours in 63-79% yield.



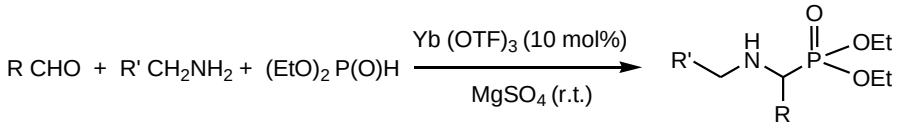
Scheme 8

A simple and convenient method for the preparation of α-aminophosphonates have been reported by Heydari et al. [90] from aldehydes, amines and dimethylphosphite in the presence of lithium perchlorate in diethyl ether (LDPE) (Scheme 9). Under these reaction conditions, both the aliphatic and aromatic aldehydes gave good yields.



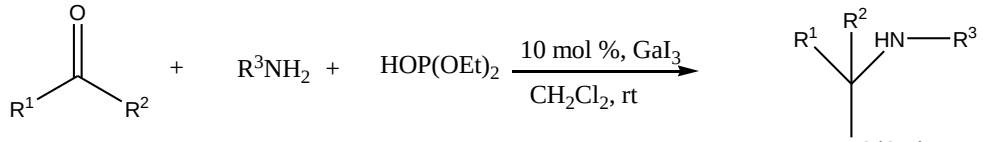
Scheme 9

Recently lanthanide triflate catalysed reactions of aldehydes, amines and dialkylphosphite in an one-pot three component reaction to prepare α-aminophosphonate are documented by Qian et al. [91] For all these reactions, $In(OTF)_3$ and $Yb(OTF)_3$ (Scheme 9) are found to be the effective catalysts. These triflates are also capable of catalyzing the addition of phosphite to imine system.



Scheme 10

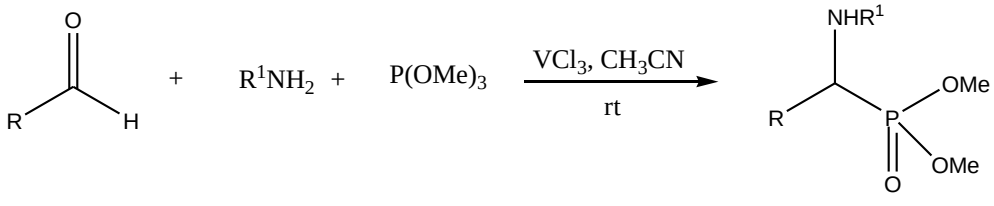
A convenient synthesis of α-aminophosphonates has been developed by Sun et al. [92] via gallium triiodide-catalyzed coupling of carbonyl compounds, amines, and diethylphosphite in dichloromethane (Scheme 110). The catalyst, gallium triiodide, was generated in situ very easily by the reaction of gallium metal and iodine. The methodology is applicable for both primary and secondary amines. The reactivity of ketones is slower than that of the aldehydes.



R= aryl, R^1=alkyl; R^2= H, Me; R^3= aryl

Scheme 11

Rajitha et al. [93] have reported an efficient protocol for the one-pot synthesis of α-aminophosphonates (Scheme 12) by the condensation of aldehydes, amines, and trimethylphosphite in acetonitrile using VCl_3 as a catalyst. The products were obtained in high yields with short reaction times (5–15 min) at room temperature. The catalyst is inexpensive and the method does not require any additive for promoting the reaction.



R^1= aryl, alkyl; R= aryl

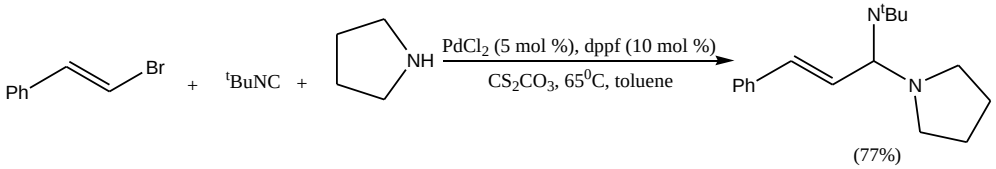
(90-95%)

Scheme 12

A one-pot synthesis of polysubstituted 4-(phenoxymethyl)-3-pyrrolines and their isomers has been reported by Balme and co-workers [94] via coupling of propargyl amines, vinyl sulfones (or nitro alkenes), and phenols. The same group [95] has also achieved the onepot synthesis of highly functionalized 4-benzyl-(and allyl-)pyrrolidines by the palladiumcatalyzed coupling reaction of allylic amines, gem-deactivated alkenes, and unsaturated halides (or triflates). A novel and diverse route to 3-

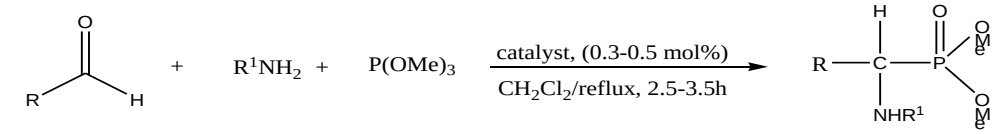
aryl/heteroaryl/vinyl substituted heterocycles has also been developed [96] via a sequential three-component Pd-cascade / RCM process.

Akiyama et al. [97] have described the three-component synthesis of optically active 4-arylated dehydroprolines. A synthesis of highly fluorescent indolizines and bisindolizines has also been reported [98] via a consecutive one-pot, three-component process involving a coupling/1,3-dipolar cycloaddition sequence. The synthesis of α,β unsaturated amidines and imidates has been reported [99] by the palladium-catalyzed coupling of an alkenyl bromide, an isonitrile, and an amine (or alkoxide/phenoxide) (Scheme 13). In the synthesis of lkenylamidines, the attempts to replace tert-butyl isonitrile with n-butyl-, cyclohexyl- or benzyl isonitriles was unsuccessful, even though a variety of primary and secondary amines were tried under the reaction conditions. But, in the synthesis of alkenylimidates, not only tert-butyl isonitrile, but n-butyl and cyclohexyl isonitriles also furnished the desired imidates.



Scheme 13

Reddy et al. [100] have reported the use of butyldimethyl(1-phenylethyl) ammonium bromide as a catalyst for the synthesis of α-aminophosphonates (Scheme 14) via the one-pot reaction of an aldehyde, an aromatic amine, and trimethylphosphite in refluxing CH_2Cl_2. The catalyst is not sensitive to moisture unlike the other conventional Lewis acid catalysts and can be prepared easily in the laboratory. The reaction was even extended to ketones and secondary amines.

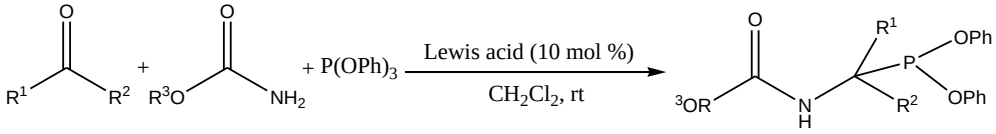


R= aryl, alkyl; R^1= aryl

(81-92%)

Scheme 14

Haemers et al. [101] have reported the Lewis acid catalyzed Birum-Oleksyszyn reaction [102-104] (one-pot condensation reaction of an aldehyde with benzyl carbamate and triphenyl phosphite) for the synthesis of N-protected diphenyl 1-aminoalkylphosphonates (Scheme 15). Yields were comparatively higher than the yields obtained using the usual protocol (heating in acetic acid). The reaction has been extended to ketones also, but required longer reaction times and resulted in lower yields than those obtained with aldehydes.



R^1= H, alkyl, aryl, aralkyl

R^2= alkyl, aryl, aralkenyl, aralkyl, cycloalkyl

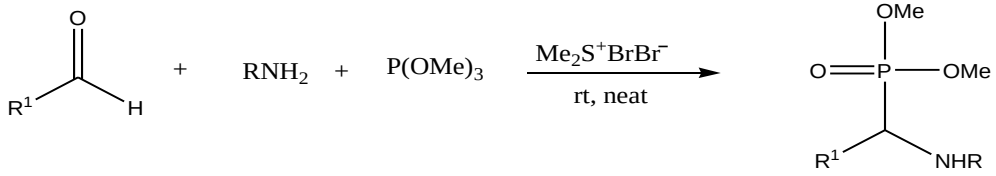
R^3= $PhCH_2$, ^tBu

(44-94%)

Scheme 15

A solvent-free protocol for the preparation of α-aminophosphonates has been reported by Wu et al. [105] via NBS or CBr_4 catalyzed reaction of aldehydes, amines, and diethyl phosphite.

A solvent-free method for the one-pot synthesis of α-aminophosphonates has been developed [106] in the presence of catalytic (bromodimethyl) sulfonium bromide at room temperature (Scheme 16). Using this catalyst, aromatic as well as α,β-unsaturated aldehydes participated in the reaction to give products without the bromination of the aromatic rings.

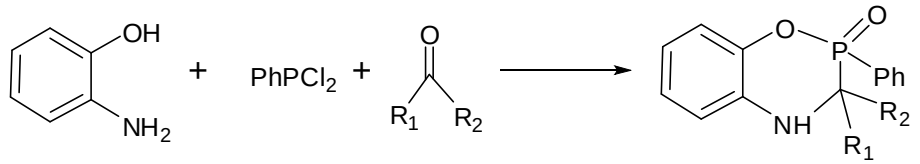


R^1= aryl, R= aryl

(87-95%)

Scheme 16

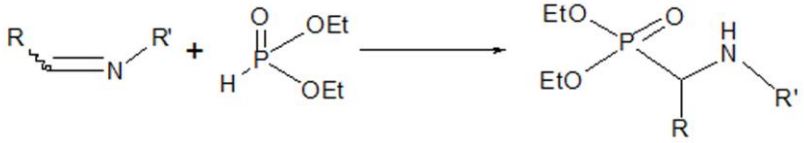
α-aminophosphonic acid derivatives as analogues of naturally occurring α-amino acids have unique and diverse potential biological properties [107]. These compounds have much importance in pharmacy and organic synthesis. [108,109] Zhou et al. [110] prepared some of these compounds by Mannich type of reaction of trivalent phosphine derivatives with α-aminophenol and various substituted aldehydes/ketones.



R_1 = H, Me, Et
R_2 = Me, Et, i-Pr, Ph, 4-MeC_6H_4, 4-$PhOC_6H_4$

Scheme 17

Kraicheva et al. [110] synthesized novel α-aminophosphonic acid diesters through an addition of diethyl phosphate to N,N-dimethyl-N′-furfurylidene-1,3-diaminopropanes.



Scheme 18

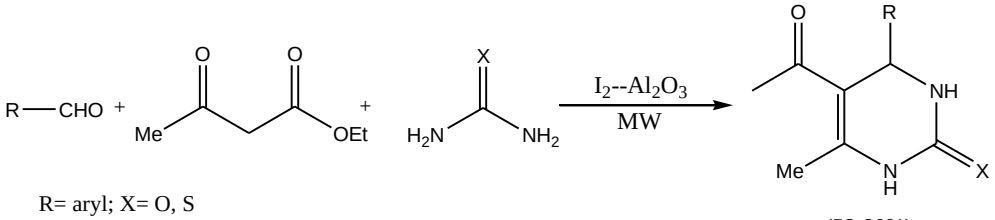
Microwave-assisted Synthesis of α- Aminophosphonates under Solvent and Catalyst Free-conditions

In recent years, the application of microwave energy to accelerate organic reactions has gained popularity after Gedye's [112] pioneering report on the use of microwave irradiation as a thermal source to carry out organic reactions in 1986. This technique [113,114] is advantageous over conventional methods due to shorter reaction times, dry media (thus avoiding the use of harmful solvents), cleaner reactions, easy work up, and minimization of thermal decomposition products.

Gaurao D. et al investigated the "one-pot" three-component reaction of benzaldehyde with (S)-α-methylbenzylamine 4 [(S)-MBA] and dimethyl phosphite at 80 ^{o}C and 60 watts under solvent and catalyst free-conditions [115]. Under these conditions, we found that microwave irradiation causes a strong acceleration of this process (reaction time was shorten, going from 5-8 h to just a 12 min) to give the (R,S)- and (S,S)-α-aminophosphonates 10a in 81% yield as a 75:25 diastereoisomeric ratio (dr), which was determined according to their ^{31}P NMR signals at 27.54 and 27.21 ppm, respectively.

In summary, Gaurao D. et al found a high diastereoselective "one-pot" three-component reaction of aldehydes, chiral amines and dimethyl phosphite under solvent and catalyst free-conditions using microwave irradiation. We also established that Schiff bases intermediates derived from (S)-3,3-dimethyl-2-butylamine 9 shows higher C=N π-facial selectivities than those found in the Schiff bases derived from commonly used (S)-α-methylbenzylamine 4 or the chiral amines 5-8. This procedure could be used in the synthesis of large amounts of α-aminophosphonates in short reaction times.

Sarma et al. [116] have reported a quick method for the condensation reaction of an aldehyde, ethyl acetoacetate, and urea or thiourea to synthesize substituted 3,4-dihydropyrimidin-2(1H)-ones using iodine-alumina as the catalyst under microwave irradiation and solvent-free conditions (Scheme 19). The method is quick (1 min) with a variety of aromatic, substituted aromatic, and heterocyclic aldehydes; however, no aliphatic aldehyde has been used. Microwave-assisted synthesis of 3,4-dihydropyrimidinones from an aldehyde, a keto ester and urea or thiourea using ferric chloride hexahydrate as a catalyst under solvent-free conditions has been described by Mirza-Aghayan et al. [117]



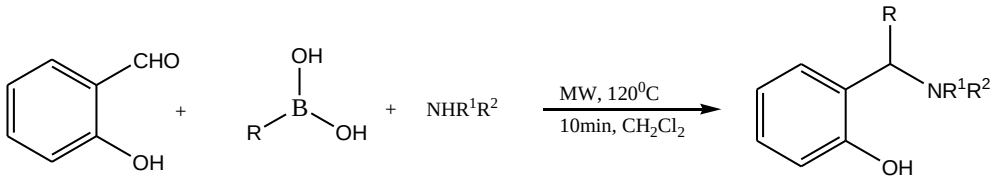
R= aryl; X= O, S

(58-90%)

Scheme 19

Follmann et al. [118] have described a rapid and straightforward, microwave-inducedprotocol for the Petasis reaction of electron-poor aromatic amines such as aminopyridines and compared it with conventional

heating. The utility of the design of experiments (DOE) approach has been reported by Tye et al. [119] to optimize a microwave-assisted protocol for the Petasis boronic-Mannich reaction employing either glyoxylic acid or salicylaldehyde as the carbonyl component along with a wide range of aryl/heteroarylboronic acids and amine components (Scheme 20).



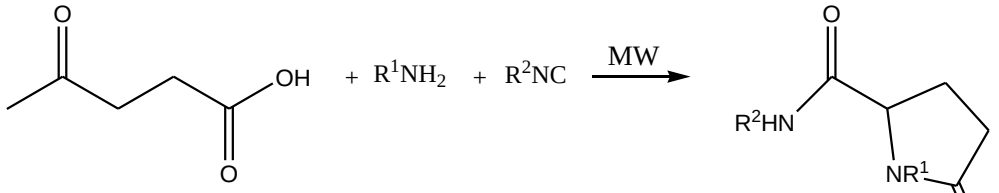
R= aryl

R^1R^2= morpholine, aminodiphenylmethane, p-ansidine, dibenzyl

(10-83%)

Scheme 20

In the case of reaction with salicylaldehyde, only secondary amines gave the desired products. The advantage of this method is the shorter reaction time (10 mins) when compared to several hours required in the other reported methods at room temperature. The same group has also demonstrated [120] the utility of the DOE approach for the rapid and efficient optimization of a microwave-assisted procedure for the Ugi three component condensation of levulinic acid with an amine and an iso nitrile to afford lactam derivatives (Scheme 21) in shorter reaction times (30 min) compared to the conventional procedure (48 h) in methanol as a solvent. Ethanol was also used as a solvent in the case of ethyl isocyanoacetate substrate to avoid problems with transesterification.



R^1= $PhCH_2$, cyclohexyl, 3-methylthiophene-2-methyl, 3-methoxy propyl

R^2= $PhCH_2$, ethyl isocyanoacetate

(17-90%)

Scheme 21

Synthesis of α- Aminophosphonates under Catalyst conditions

A very simple protocol was followed in the reaction process for one-pot synthesis of α-aminophosphonates over CuO nanopowder by Bikash Karmakar et al. [121]. A mixture of a carbonyl compound, an amine, and trimethyl phosphite was stirred in the presence of CuO nanopowder at solvent-free and ambient condition. The catalyst was found to promote the reaction efficiently, affording the corresponding aminophosphonates in high yield. No base or other additives were required in this process. After standard work up, the crude product obtained was passed through a neutral alumina column to isolate the pure compound.

CONCLUSION

This review has covered the three-component methodologies and about α-aminophosphonates reported during recent years. The recent progress in these important and convenient procedures provides a platform for future innovation because of the versatility, molecular economy, and exciting potential for the synthesis of complex organic compounds.

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