Current Chemistry Letters 10 (2021) 221–234

Contents lists available at GrowingScience

Current Chemistry Letters

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A comparative study of metal-catalyzed three-component synthesis of α-aminophosphonates

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C H R O N I C L E

Article history:
Received October 12, 2020
Received in revised form
November 30, 2020
Accepted January 15, 2021
Available online
January 15, 2021

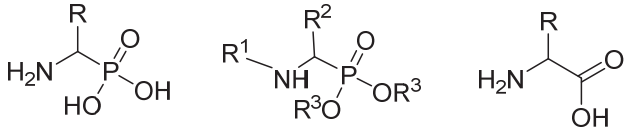
Keywords:
Carbonyl compounds
Amines
Phosphite
Catalyst
α-Aminophosphonates

A B S T R A C T

Different metal catalysts have been tested for the one-pot transformation of carbonyl compounds, amines and phosphites to α-aminophosphonates. The influence of catalyst type, amount, solvent and the substrate electronic factor have been investigated. The results revealed that the carbonyl compounds could be smoothly converted into α-aminophosphonates at room temperature in good to excellent yields, with or without solvent in a reasonable reaction time. These results suggested that among others, lithium perchlorate and metal triflates were proven to be effective catalysts in 10 moles % catalysts. Polar aprotic solvents proved to be the best for the synthesis of α-aminophosphonates. The synthesized compounds' structure characterizations were elucidated by different spectroscopic tools and showed results consistent with the expected structures.

1. Introduction

Organophosphorus compounds especially, α-aminophosphonic acids (I) and their esters (II), have a potential biological activity due to the similarity with α-amino acids (III). They represent an essential analogy to α-amino acids (III) as we replaced a carboxylic group with a phosphonic acid ester moiety (*cf.* **scheme. 1**).[1] The preparation of new derivatives and development of the known synthetic procedures are especially important in the field of organophosphorus chemistry. They have a wide variety and great interest in research in recent years because of the broad spectrum of pharmacological and environmental uses of α-aminophosphonic acids and even their related derivatives.[2, 3]



I II III

Scheme 1: Structures of α-aminophosphonic acids I, α-aminophosphonic esters II, and α -amino acids III

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doi: 10.5267/j.ccl.2021.1.006

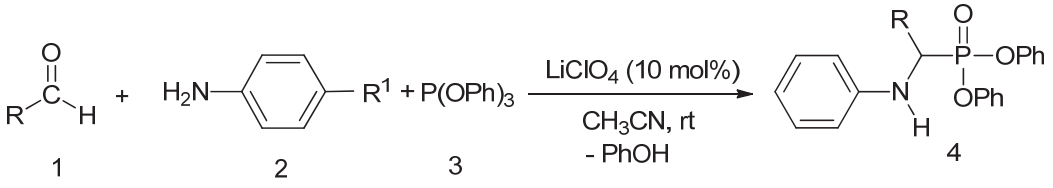
These classes of organophosphorus compounds have elevation biological efficiency, metabolic stability, and tenuous toxicity to mammalian cells.[2] In fact, α-aminophosphonates have demonstrated several therapeutic effects, and they serve as antifungal,[2] herbicides,[4] antibacterial, [5-8] antiviral,[9] enzyme inhibitors,[10,11] and anticancer agents,[12-14]which made them extremely important in medicinal and agricultural chemistry. Recently, it has been reported that functionalized α-aminophosphonates-loaded solid support has industrial and environmental applications in uranium sorption and heavy metals removal.[15-17] The synthesis of α-aminophosphonates has many pathways that depend on the nature of reactants and catalysts[18,19]. In this context, new methods of synthesizing α-aminophosphonates have been discovered and developed to improve their achievability and scalability.[20]In continuation of our efforts to develop a suitable strategy to synthesize and enhance organophosphorus compounds to be used in different biological and environmental applications. We decided to investigate the reactions using different Lewis acid catalysts under different conditions as probable tools for optimizing α-aminophosphonates synthesis with high atom economy.

Herein, we report a convenient approach to the synthesis of diversified α-aminophosphonates in a one-pot reaction with high yields under mild conditions using commercially available starting materials, different catalysts and even under solvent-free conditions.

2. Results and Discussion

The α-aminophosphonates are generally synthesized from the one-pot reaction of aldehydes, ketones or carbamates, amines trialkyl/aryl phosphite with- or without a catalyst. In this study, we have chosen benzaldehyde and its para-substituted analogs with different electron-donating and electron-withdrawing groups or heterocyclic aldehydes with biological importance such as pyrazolaldehyde derivatives as a model example (**Scheme 2)**. In addition, para-substituted anilines with electron-withdrawing substituents were also studied. The main aim is to find an efficient protocol for the synthesis of the bioactive α-aminophosphonates and study the scope and limitation of the reaction. The use of $LiClO_4$ was first used as a catalyst for the reaction in this study.

As model system, the reaction of equimolar ratio of benzaldehyde or its derivatives with aniline or its para-substituted analogues (*cf.* Table 1), triphenylphosphite and 10 mole percent of $LiClO_4$ in acetonitrile at room temperature, afforded α-aminophosphonates **4** as depicted in **Scheme 2**.



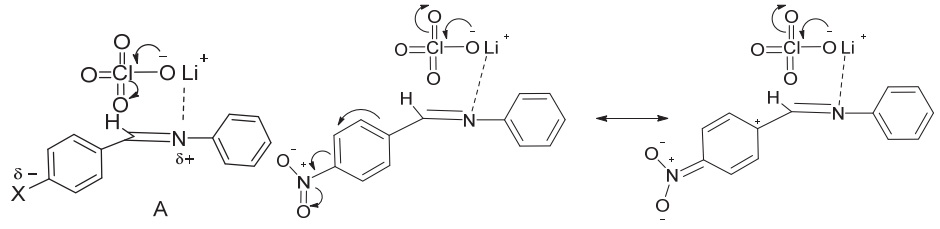
Scheme 2: Model system for a one-pot synthesis of α-aminophosphonates

Table 1. Model system for the synthesis of α-aminophosphonates using different arylaldehydes and $LiClO_4$[a] catalyst

Entry	Compd No.	R	R^1	Yield (%)[b]	Times (hrs)
1	**4a**	C_6H_5-	H	87	4
2	**4b**	4-$CH_3C_6H_4$-	H	90	2.5
3	**4c**	4-HOC_6H_4-	H	93	1.5
4	**4d**	4-ClC_6H_4-	H	56	60
5	**4e**	4-$NO_2C_6H_4$-	H	43	80
6	**4f**	C_6H_5-	4-$NO_2C_6H_4$-	34	87
7	**4g**	C_6H_5-	4-ClC_6H_4-	43	78

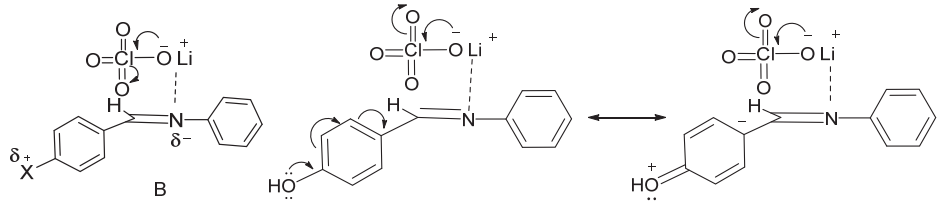
[a] All reactions were carried out at room temperature in the presence of arylaldehyde or its derivatives (1.0 mmol), aniline or its para substituted derivatives (1.0 mmol), triphenyl phosphite (1.0 mmol) and $LiClO_4$ catalyst (10 mol %) under atmospheric conditions. [b] Isolated yield.

In case of 4-hydroxybenzaldehyde and aniline (entry 3), we could isolate the desired α-aminophosphonate **4c** in excellent yield (93%) after 1.5 hours. Depending on that fact, we decided to switch to another substituted benzaldehyde. The reactions were conducted under atmospheric conditions using further derivatives of either benzaldehyde or aniline derivatives, phosphite and $LiClO_4$ (10 mol %) as a catalyst in acetonitrile at room temperature as given in Table 1. We have compared the chemical yields if using electron-donating and electron-withdrawing groups in either benzaldehyde or aniline derivatives, in case of benzaldehyde with electron-donating substituents, give excellent yields (>90) and shorter reaction time, entry **2** and **3** (**Table 1**). In comparison, benzaldehyde derivatives bearing electron-donating such as entry **4** and **5** (**Table 1**) afforded lower yields (56-43%) and longer reaction time. In addition, the same trend was seen in case of aniline containing electron withdrawing substituents (such as NO_2 and Cl) where low yields of the corresponding products were formed (entries 6, 7). As a consequence of the mesomeric or inductive impact of the substituents on the imine, our results may be clarified. In the case of electron- withdrawing groups, the electrophilicity of the imine is increased, resulting in a reduction in its ability to interact with the Lewis acid catalyst, as seen in (**Scheme 3)**.



Scheme 3. Effect of the electron-withdrawing group on the catalytic activity and efficiency of $LiClO_4$ coordination with the intermediate imine.

On the other hand, the nucleophilicity of the imine has increased by electron donation substituents, thereby increasing its contact with the catalyst to promote product formation, as seen in **Scheme 4**.



Scheme 4. Effect of the electron-donating group in the coordination between $LiClO_4$ and imine

In the second model system, we have compared the different catalysts, including nanocatalyst such as nano Ni and nano Pd (entry 7 and **8**, **Table 2**). In this case, various catalysts, such as $LiClO_4$, $ZnCl_2$, $Cu(OTf)_2$, $Zn(OTf)_2$, $TiCl_4$, $SnCl_4$,and $AlCl_3$ as well as nano-catalysis, were screened for the reaction of benzaldehyde and triphenylphosphite. Thus, under the same conditions used in the synthesis of α-aminophosphonate at room temperature in acetonitrile, it was appropriate to compare various catalysts (**Table 2**). Lithium perchlorate ($LiClO_4$), entry **1**, copper triflate $Cu(OSO_2CF_3)_2$, entry **2**, nano Ni, entry **7**, nano Pd, entry **8** were selected according to these findings.

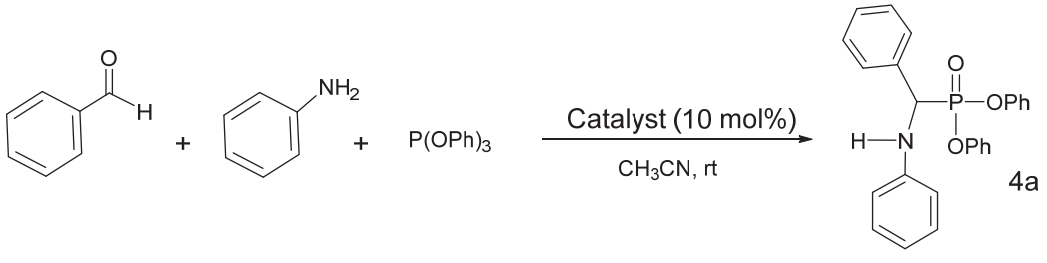


Table 2. Comparison of catalysts[a]

Entry	Catalyst	Yield (%) [b]	Time (hrs)
1	$LiClO_4$	87	4
2	$Cu(OTf)_2$	85	6
3	BF_3	67	30
4	$TiCl_4$	55	30
5	$AlCl_3$	70	30
6	$ZnCl_2$	78	30
7	Nano Ni	81	5
8	Nano Pd	85	3

[a] All reactions have been carried out at room temperature in the presence of benzaldehyde (1.0 mmol), aniline (1.0 mmol), triphenyl phosphite (1.0 mmol) and $LiClO_4$ catalyst (10 mol %) under atmospheric conditions. [b] Isolated yield.

2.1. Screening of solvents in α-aminophosphonates synthesis in the presence of $LiClO_4$ catalyst

After determining that $LiClO_4$ is the catalyst of choice, we then screened different solvents to study the role of solvents to improve the yield of the model reaction. We examined CH_3CN, THF, $CHC1_3$, CH_2C1_2, and EtOEt (**Table 3**).

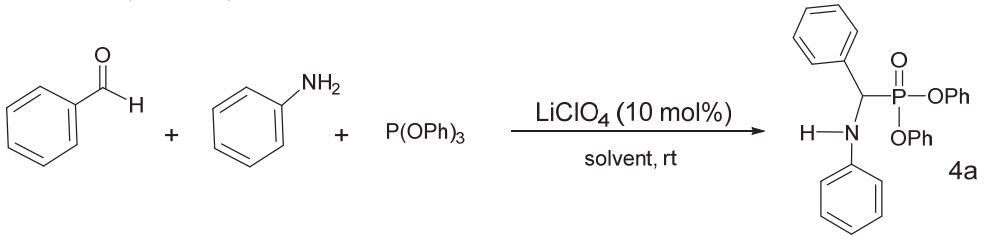


Table 3. Screening of solvents in α-aminophosphonates synthesis in the presence of $LiClO_4$[a] catalyst

Entry	Solvent	Yield[b] (%)	Times (hrs)
1	THF	5	30
2	$CHCl_3$	15	30
3	$(C_2H_5)_2O$	60	30
4	CH_2Cl_2	65	30
5	CH_3CN	87	4

[a] All reactions have been carried out at room temperature in the presence of benzaldehyde (1.0 mmol), aniline (1.0 mmol), triphenyl phosphite (1.0 mmol) and $LiClO_4$ catalyst (10 mol %) under atmospheric conditions. [b] Isolated yield.

Owing to the possibility of coordination with the catalyst, THF leads to a low conversion to product. At the same time, CH_2C1_2 and EtOEt provide products with a medium yield. By comparison, because of its high polarity, CH_3CN was the best solvent, as it lowers the activation energy by a favorable interaction level with the charged transition state. We agreed to improve the yield once we concluded that CH_3CN was the best solvent for the synthesis of α-aminophosphonates. The formation of the imine produces water as a byproduct during the reaction, which can hydrolyze the imine. We, therefore, added molecular sieve $3A^0$ as a dehydrating agent (**Table 4**).

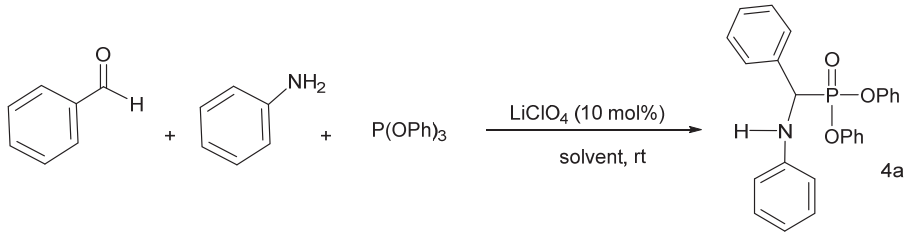


Table 4: Model system for improvement of solvent for the model reaction[a]

Entry	Solvent	Yield (%) [b]	Reaction time (hrs)
1	CH_3CN/3A0 molecular sieves	88	4
2	CH_3CN	87	4

[a] All reactions have been carried out at room temperature in the presence of benzaldehyde (1.0 mmol), aniline (1.0 mmol), triphenyl phosphite (1.0 mmol) and $LiClO_4$ catalyst (10 mol %) under atmospheric conditions. [b] Isolated yield.

Our new target was the control of the amount of the catalyst. In this case, the benzaldehyde, aniline and triphenyl phosphite reaction was used as the design model in the presence of 1, 5 and 10 mol % $LiClO_4$ in CH_3CN at room temperature. The target product was obtained at 73 % yield when we carried out the reaction with 1 mol % $LiClO_4$. In comparison, in the presence of 5 and 10 mol percent of $LiClO_4$, the commodity was supplied with a 90 % yield. Further synthetic experiments in the presence were agreed to be carried out (**Table 5**).

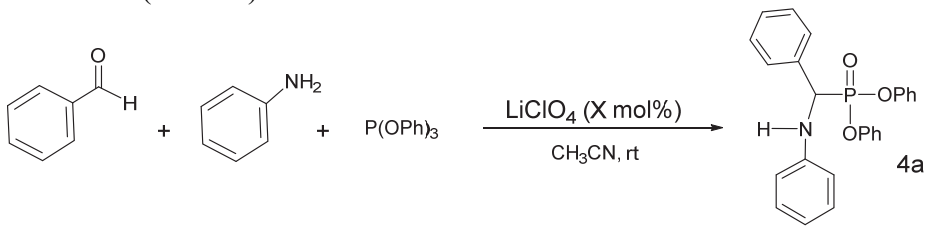
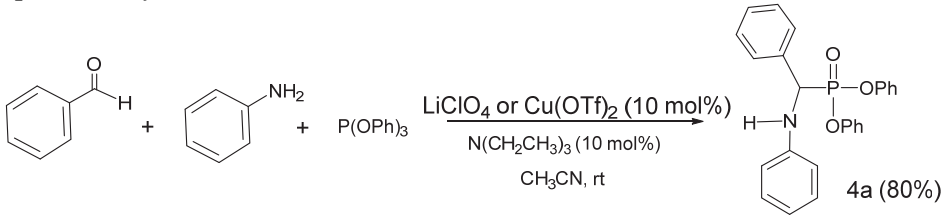


Table 5. Catalyst mol% optimization[a]

Entry	Catalyst (mol%)	Catalyst	Yield (%) [b]	Reaction Time (hrs)
1	1	$LiClO_4$	73	10
2	5	$LiClO_4$	90	6
3	10	$LiClO_4$	87	4

[a] All reactions have been carried out at room temperature in the presence of benzaldehyde (1.0 mmol), aniline (1.0 mmol), triphenyl phosphite (1.0 mmol) and $LiClO_4$ catalyst (10 mol %) under atmospheric conditions. [b] Isolated yield.

In order to clarify whether the actual catalytic activity resulting from the initial metal precursor is used as a catalyst in the case of metal perchlorates or triflates, this has been confirmed, and it excludes the generation in situ of perchloric acid ($HClO_4$) or trifllic acid (TfOH), catalyzing the reaction instead of metal perchlorates or triflates. therefore, it was essential to decide whether Lewis acid, in this case, a metal precursor or Bronsted acid, perchloric acid or triflic acid, was the catalyst. A one-pot experiment has been, therefore, constructed as follows: 0.1 mmol of $LiClO_4$ or $Cu(OTf)_2$ and 0.15 mmol of triethyl amine was stirred in methylene chloride. The reaction mixture was then supplemented with benzaldehyde (1.0 mmol), aniline (1.1 mmol), and triphenyl phosphite (1.0 mmol). The corresponding α-aminophosphonate was isolated at 80 % yield after 4 hours **Scheme 5**. This outcome shows that there has been no catalytic impact on the reaction of perchloric or triflic acid since any triethylamine would have neutralized it, thus blocking its catalytic potential. This research clarifies the true catalyst is Li(I) or Cu(II). These findings show that metal perchlorate and triflates are extremely powerful catalysts for α-aminophosphonates synthesis.



Scheme 5. Catalyst study of α-aminophosphonates synthesis

2.2. Screening of Catalysts under Solvent Free Conditions

Next, under solvent-free conditions, we agreed to analyze or measure the influence of the catalyst. Therefore, under solvent-free conditions for the synthesis of α-aminophosphonates, we agreed to compare catalytic activity against various catalysts used in aminophosphonates synthesis at room temperature. (**Table 6**).

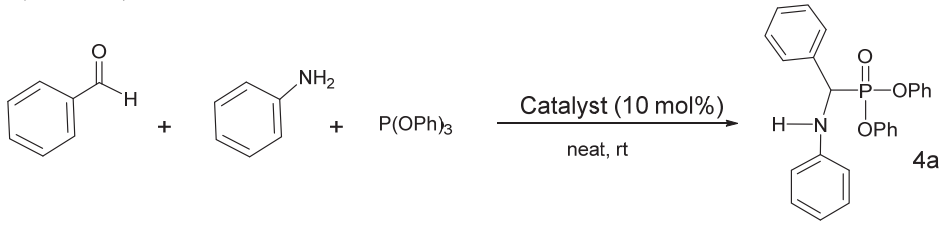
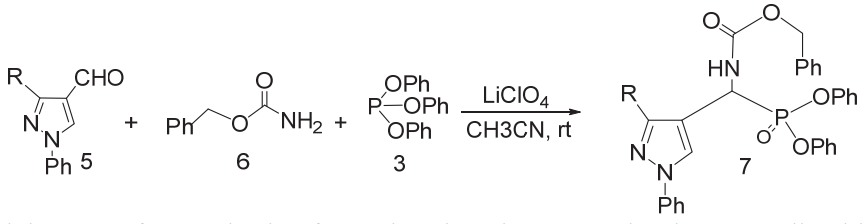


Table 6. Comparison of Catalysts under neat condition[b]

Entry	Catalyst	Yield (%) [b]	Time (hrs)
1	$LiClO_4$	87	5
2	$Cu(OTf)_2$	85	6
3	BF_3	67	30
4	$TiCl_4$	55	30
5	$AlCl_3$	70	30
6	$ZnCl_2$	78	30
7	Nano Ni	79	26
8	Nano Pd	80	22

[a] All reactions have been carried out at room temperature in the presence of benzaldehyde (1.0 mmol), aniline (1.0 mmol), triphenyl phosphite (1.0 mmol) and $LiClO_4$ catalyst (10 mol %) under atmospheric conditions. [b] Isolated yield.

The next model example is to apply the Lewis acid-catalyzed reaction to biologically active heterocyclic α-aminophosphonates of type **7** starting from heterocyclic aldehydes such as *4-* formyl pyrazole derivatives **5** with carbamates component **6** according to **Scheme 6**. All reactions have been performed for 30-90 hours, and yields have been mild to excellent. Following the reaction, pure product **7** was obtained by quenching the reaction mixture in water accompanied by filtration without further purification, thus minimizing purification costs. Different pyrazole aldehydes containing electron-donating and electron-withdrawing substituents have been analyzed in order to gauge the scope of the reaction. It was found that the reaction is effectively undergone within 30-90 hours in all situations (**Table 7**). It was affording the corresponding products, α-aminophosphonate. It also investigated the effect of catalyst concentration. From observation, it was discovered that increasing catalyst concentration up to 10 mmol improves product yield. A further rise in catalyst concentration did not greatly change model reaction yields of up to 20 mmol. The 10 mmol catalyst concentration was sufficient for all reactions. After conditions for the production of α-aminophosphonate from pyrazolaldehydes were identified, a variety of lewis acids and substrates were investigated to determine the nature and limitations of the reaction. Therefore, a range of lewis acid, carbamates, different substituted pyrazolaldehydes and phosphites were examined in order to optimize the yield as well as evaluate the scope and limitations of the reaction and the results are summarized in (**Table 7)**. Slight aldehyde excess (1.1-1.3 equivalent) was observed to increase the predicted product's yield although the higher reaction temperature and longer reaction time did not impact the reaction outcome. It was found that after the reaction was complete, the products could precipitate instantly at room temperature.



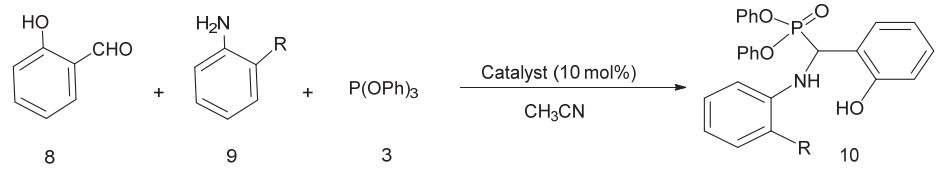
Scheme 6: Model system for synthesis of α-aminophosphonates using heterocyclic aldehyde and $LiClO_4$ as a catalyst

Table 7. Model system for synthesis of α-aminophosphonates using heterocyclic aldehyde and $LiClO_4$[a] as a catalyst

Entry	Compd No.	R	Yield (%) [b]	Reaction time (hrs)
1	7a	C_6H_5	90	48
2	7b	4-$CH_3C_6H_4$	85	30
3	7c	4-ClC_6H_4	80	78
4	7d	4-BrC_6H_4	82	63
5	7e	4-$NO_2C_6H_4$	80	90
6	7f	2-Thinyl	80	68
7	7g	3-Pyridinyl	80	48

[a] The reactions have been carried out under atmospheric conditions at room temperature using $LiClO_4$-catalyzed pyrazolaldehyde (1.0 mmol), benzylcarbamate (1.0 mmol) and triphenyl phosphite (1.0 mmol). [b] Isolated yield.

Furthermore, α-aminophsophonates **10** were synthesized in Great yields from three one-pot reaction of salicaldehyde **8**, amines **9**, and triphenyl phosphite **3** in acetonitrile with different catalysts as depicted in **scheme 7** and **table 8.**



Scheme 7. Schematic routes for the synthesis of functionalized α-aminophosphonates

Table 8. Synthesis of α-aminophosphonates with Different Catalysts and Substrates[a]

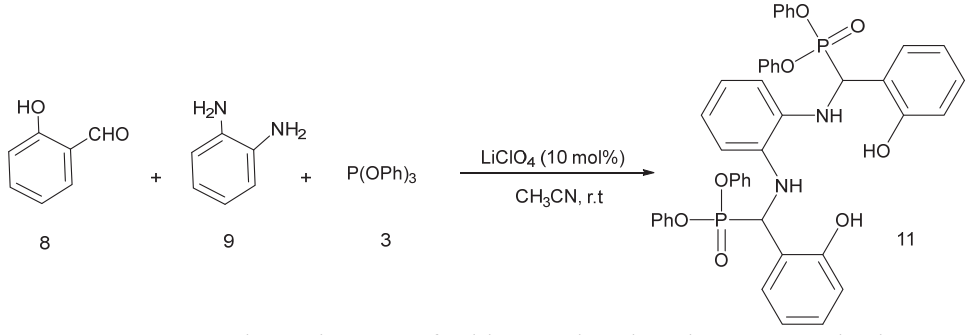
Entry	Compd No.	R	Catalyst (10 mol%)	Reaction time (hrs)[a]	Yield (%) [b]
1	**10**a	H	$LiClO_4$	36	75
2	**10**a	H	$ZnCl_2$	48	69
3	**10**a	H	Nano Ni	26	79
4	**10**a	H	Nano Pd	22	80
5	**10**b	COOH	$LiClO_4$	30	76
6	**10**b	COOH	$ZnCl_2$	48	70
7	**10**b	COOH	Nano Ni	24	80
8	**10**b	COOH	Nano Pd	21	83
9	**10**c	NH_2	$LiClO_4$	38	77
10	**10**c	NH_2	$ZnCl_2$	40	70
11	**10**c	NH_2	Nano Ni	26	79
12	**10**c	NH_2	Nano Pd	22	80

[a] All reactions have been conducted at room temperature using, salicaldehyde (1.0 mmol), amines (1.0 mmol) and triphenyl phosphite (1.0 mmol) catalyst (10 mol%) under atmospheric condition. [b] Isolated yield.

In a comparative study between the use of Lewis acid (LA) and nanocatalyst, it is worthy to note that the reaction with LA requires a longer reaction time and gives mild yields compared with nanocatalyst. To rationalize this result and explain the high efficiency of nanocatalyst compared with LA, it might be explained based on increasing the catalytic surface area as well as improving the stability (**Table 8**)

2.3. Synthesis of bis-α-aminophosphonates from 1,2-Phenylenediamine

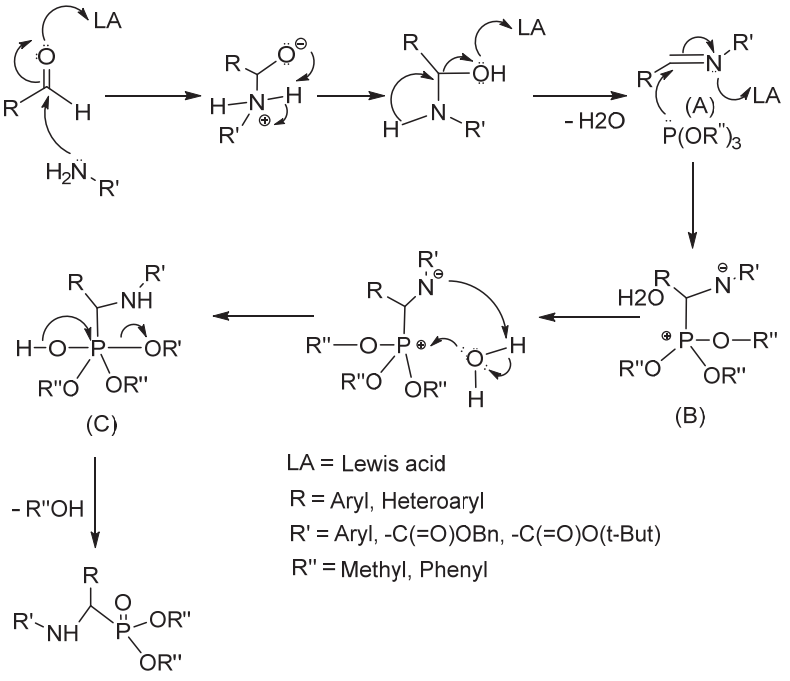
The treatment of 1,4-phenylenediamine **9** with 2 salicaldehyde equivalents **8** and 2triphenyl phosphite equivalents **3** provided a good yield to the target product **11** in the presence of an acetonitrile solvent and $LiClO_4$ as a Lewis acid catalyst, as seen in (**scheme 8**).



Scheme 8. Schematic routes for bis α-aminophosphonates synthesis

The IR spectra revealed a wide absorption band of 3000-3651cm^{-1} in the structural characterization of 11, which is typical of 2 OH groups, while the peak at 3310 cm^{-1} corresponds to 2 NH groups, and the peak at 1213 cm^{-1} corresponds to P = O. For (CH-P) chiral 2 protons, the ^{1}H NMR spectra illustrated a triplet signal at 4,985 ppm.

Scheme 9 indicates the possible mechanism for the creation of α-aminophosphonates. The first step involved the formation of Schiff base **A** via condensation of aldehydes with amine component through dehydration, this was achieved by activation of the formyl group by Lewis acid (LA). The subsequent nucleophilic addition of amine nitrogen to the electrophilic carbon in aldehyde followed by water elimination afforded the Schiff based **A**. The second step was initiated by the addition of the nucleophilic phosphorus of phosphite to the imine carbon of **A** to give the intermediate phosphonium salt **B**. The addition of water to the intermediated **B** followed by hydration to yield the intermediate **C** followed by immediate elimination of phenol to afford the corresponding end product, α-aminophosphonates.



Scheme 9. Suggested mechanism of α-aminophosphonates.

In structure characterization of **10a-c**, the IR spectra of 10a showed a broad absorption band at 2888-3119 cm^{-1}which is characteristic of OH group, while the peak at 3409 cm^{-1} corresponds to NH, and the peak at 1234 cm^{-1} correspond to P=O. While the NH, OH, C=O, and P=O absorption for 10b appeared at 3338, 2760-3342, 1662, and 1253 cm^{-1} respectively. On the other hand, 10c showed a characteristic band at 3323, 3307, 2858-3420, and 1210 cm^{-1} for NH_2, NH, OH, and P=O respectively. The ^1H NMR spectra of 10a showed a doublet of doublet signals at 5.25 ppm for (CH-P) chiral proton with J= 2.5 & 3.0 Hz. NH, OH not visible may be due to either its overlapping with aromatic protons or exchangeable with deuterium for DMSO-d6, in addition, the ^{31}P NMR showed a singlet at 17.72 ppm. On the other hand, the ^1H NMR spectra of 10b showed a doublet of doublet signals at 5.79 ppm for (CH-P) chiral proton with J= 9 Hz. In addition, the ^{31}P NMR showed a singlet at 16.00 ppm. while the ^1H NMR spectra of 10c showed a doublet signal at 4.90 ppm for (CH-P) chiral proton with J= 24.5 Hz. In addition, the ^{31}P NMR showed a singlet at 17.27 ppm. Affirming the creation of α-aminophosphonates. The absence of the aldehyde group (CHO) in ^1H NMR indicated the production of α-aminophosphonates by intramolecular cyclization accompanied by the removal of water.

3. Conclusions

In summary, the influence of the type of substrates. metal catalysts, catalytic amount, solvent and electronic factor on the yield and reaction time of one-pot synthesis of α-aminophosphonates have been investigated. Among the different screened catalysts, lithium perchlorate and copper (II) triflate, were proven to be the best catalysts in terms of yields and reaction time. The present method represents an

environmentally friendly approach to the green synthesis of α-aminophosphonates with recyclability of the nanocatalyst.

4. Experimental

4.1. Materials and Methods

All Both ^{1}H NMR and ^{13}C NMR (solvent DMSO-d6) tests were performed at the University of Mansoura with a JEOL ECA-500 II spectrometer at (500 MHz or 125 MHz, respectively) chemical shifts stated in relation to the respective solvent in part per million (ppm). ^{31}P NMR (DMSO-d6) spectra were obtained using a BRUKER spectrometer 162 MHz, at the Analytical Lab., Zagazig University, Egypt. With a Thermo Fisher Nicolete IS10, USA spectrometer (Mansoura University), Egypt, the IR spectroscopy was directly acquired within 400-4000 cm^{-1}. An automatic analyzer (CHNS Vario EL III-Elementar Analyzer, Germany) at the Micro Analytical Unit (Al-Azhar University) was used to classify the elemental analysis (C, H, and N). Melting points (m.p) were recorded, on the Stuart Science melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) on Kiesel gel F254 precoated plates (Merck). Solvents such as acetonitrile and diethyl ether were purchased and used without further purification. The nanocatalyst was prepared according to the literature.[21] The starting materials were either purchased (Sigma-Aldrich) or prepared as reported in the literature.[23]

4.2. General procedure for synthesis of α-aminophosphonates

Aldehydes (1.2 mmol), amines (1 mmol), triphenylphosphite (1 mmol) either dissolved in an appropriate solvent (10 mL) or used neat are stirred for about 15 mins., then the catalyst was added in one portion. At room temperature, the reaction mixture was stirred until TLC revealed the completion of the reaction after 1.5-90 hrs. Precipitated products were purified out, washed and dried with acetonitrile. The pure products were obtained in good yields by recrystallization from methanol and cooling.

4.2.1 Synthesis of bis-α-aminophosphonate: Tetraphenyl((1,2-phenylenebis(azanediyl))bis((2-hydroxyphenyl) methylene))bis(phosphonate) 11

Salicylaldehyde (294 mg, 2.2 mmol), 1,2-phenylenediamine (108 mg, 1 mmol), triphenylphosphite (620 mg, 2 mmol), were dissolved in acetonitrile (10 mL) and stirred for about 15 min. Then catalyst 10 mol % was added in one portion. The reaction mixture was stirred further at room temperature until TLC showed the completeness of the reaction after 30 hrs. The work-up of the reaction and the purification of **11** was carried out as described in general the procedure.

4.3. Physical and spectral data

Diphenyl (phenyl(phenylamino) methyl) phosphonate ***(4a)***[22]

White solid. Yield: (87%). ^{1}H NMR (DMSO-d$_6$, δ ppm): 5.06 (dd, 1H, CHP), 6.56 (d, 2H, J = 6.00–7.50 (m, 15H, Ar-H), 8.85 (br.s, 1H). ^{31}P NMR (DMSO, 162.0 MHz): 16.64 ppm.

Diphenyl(phenylamino) (p- tolyl) methyl) phosphonate ***(4b)***[22]

White solid. Yield (90%). ^{1}H NMR (DMSO-d6, 500 MHz): 2.33 (3H, s, CH$_3$), 5.12 (1H, d, JH-P = 24.3 Hz, CH), 6.65 (2H, m, Ar-H), 6.74 (1H, m, Ar-H), 6.88 (2H, m, Ar-H), 7.07-7.31 (12H, m, Ar-H), δ 7.44 (2H, m, Ar-H), NH not seen.

Diphenyl ((4-hydroxyphenyl) (phenylamino) methyl) phosphonate ***(4c)***

White solid. Yield (93%). ^{1}H NMR (DMSO-d6, 500 MHz), δ 5.35 (1H, d, JH-P = 24 Hz, CH), 6.75 (2H, d, J = 8 Hz, Ar-H), 6.79-6.90 (3H, m, Ar-H), 6.98 (2H, d, J = 8 Hz, Ar-H), 7.04 (2H, d, J = 8 Hz, Ar-H), 7.13-7.19 (5H, m, Ar-H), 7.23-7.32 (5H, m, Ar-H), NH not seen. ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ (ppm): 58.9 (CHP), 113.2 (2C), 114.8 (2C), 120.2(2C), 120.3(2C), 120.9, 121.6, 121.7, 128.2(2C), 128.9, 129.2(2C), 130.3, 130.4, 150.5, 150.7, 147.1, 156.1 (COH).

Diphenyl (((4-chlorophenyl) amino) (phenyl) methyl) phosphonate ***(4d)***[22]

White solid. Yield (56%). ^{1}H NMR (DMSO-d6, 500 MHz): δ 5.07 (1H, d, JH-P = 27 Hz, CH), 6.56 (2H, m, Ar-H), 6.82 (2H, m, Ar-H), 7.17 (12H, m, Ar-H), 7.52 (2H, m, Ar-H), NH not seen.

Diphenyl (4-nitrophenyl) (phenylamino) methyl) phosphonate ***(4e)***[22]

Sandy-yellow solid. Yield (43%). ^{1}H NMR (DMSO-d6, 500 MHz): δ 5.23 (1H, d, JH-P = 24.3 Hz, CH), 6.58 (2H, m, Ar-H), 6.79 (1H, m, Ar-H), 6.95 (2H, m, Ar-H), 7.75 (2H, m, Ar-H), 7.32-7.06 (10H, m, Ar-H), 8.21 (2H, m, Ar-H), NH not seen.

Diphenyl[(4-nitrophenyl)amino](phenyl)methyl]phosphonate ***4f****:*

Yellow solid; yield: 0.32 g (34%); mp: 148–149 °C.IR (KBr): 3328.7 (N–H), 1257.9 (P–O), 770.4 (C–P) cm–1. 1H NMR (500 MHz, CDCl3): δ = 8.34–8.20 (m, 2 H), 8.05–7.96 (m, 2 H),7.77–7.75 (m, 2 H), 7.44–6.62 (m, 14 H), 5.93 (dd, JH–P = 24.6 Hz, 1 H, N–CH–P). ^{13}C NMR (125 MHz, CDCl3): δ = 153.2, 153.1, 149.9, 149.8, 149.6, 137.3, 134.4, 129.7, 126.3, 125.7, 125.3, 125.2, 120.4, 120.2, 115.2, 112.3, 54.8, 52.8, 40.2, 39.9, 39.7, 39.1, 38.8 and 38.5 (d, JC–P = 155.7 Hz). MS: m/z = 461 [M + 1]+.

Diphenyl [(4-chlorophenyl)amino](phenyl)methyl]phosphonate ***4g****:*

White solid; yield: 0.40 g (43%); mp: 148–153 °C. IR (KBr): 3336.2 (N–H), 1185.5 (P=O), 775.7 (C–P) cm–1. 1H NMR (500 MHz, CDCl3): δ = 6.33–6.28 (m, 2 H), 6.17–5.84 (m, 14H), 5.64–5.60 (m, 2 H), 5.37–5.32 (m, 2 H), 3.86 (d, JH–P = 24.6 Hz, 1 H, N–CH–P). ^{13}C NMR (125 MHz, CDCl3): δ = 150.1, 144.5, 144.2, 134.3, 129.7, 129.6, 129.1, 128.9, 128.8, 128.5, 128.1, 128.0, 125.5, 125.2, 123.5, 120.6,120.5, 120.2, 115.1, 76.5, 57.1 and 55.0 (d, JC–P = 160.5 Hz). MS: m/z = 450 $[M + 1]^+$.

Diphenyl [(benzyloxycarbonyl) amino] (1,3-diphenylpyrazole) methyl phosphonate ***(7a)***[23]

Yield =90 %, M.p = 230-232 °C, $C_{36}H_{30}N_3O_5P$, IR (KBr) cm^{-1}:3421 (NH), 1261 (P=O), 1068 (POC).^{1}H NMR (DMSO, 500 MHz): δ = 5.08– 5.2 (m, 2H, CH_2OC). 5.5 – 5.6 (m, 1H, CHP), 6.81 – 6.84 (S, 1H, NH), 8.3 (S, 1H, CH pyrazole), 7.09 – 7.3 (12H, m, Ar-H), 7.4 – 7.5 (5H, m, Ar-H), 7.5 – 7.76 (12H, m, Ar-H). Mass spect. m/e = 615 (0.5 %), the ion peak at m/e = 91 (M^+– C_{30} $H_{25}N_2O_5P$, 88.3%), the ion Peak at m/e = 107 (M^+– $C_{29}H_{23}N_3O_4P$, 11.4 %), the ion peak at m/e = 77 (M^+– $C_{30}H_{25}N_3O_5P$, 90.1 %).

Diphenyl [(benzyloxycarbonyl) amino] [1- phenyl (3) tolyl pyrazole) methyl phosphonate ***(7b)*** [23]

Yield = 85 %, M.p = 243 – 244 °C, $C_{37}H_{32}N_3O_5P$,^{1}H NMR (DMSO, 500 MHz): δ = 5.0 – 5.05 (m, 2H, CH_2OC). 5.43 -5.44 (m, 1H, CHP), 6.63 – 6.66 (s, 1H, NH), 8.4 (s, 1H, CH pyrazole), 3.41 (s, 3H, CH_3), 7.4 – 7.7 (m, 12H arom), 7.2 – 7.3 (m, 5H arom), 7.37 – 7.6 (m, 12H arom). Mass spect. m/e = 628 (M^+, 0.2 %), 58 (- CO2N) (M^+ - $C_{36}H_{32}N_2O_3P$, 0.4 %), 60 (- CO_2, NH_2) (M^+ - $C_{36}H_{3o}NO_3P$, 0.4 %), The base ion peak at m/e = 77 (- C_6H_5) (M^+ - $C_{31}H_{27}N_3O_5P$, 100 %), 91 (- C_6H_5N) (M^+ - $C_{31}H_{27}N_2O_5P$, 62 %), 92 (- C_6H_5 –CH_3).

Diphenyl [(benzyloxycarbonyl) amino] (1-phenyl (3) chlorobenzene pyrazole) methyl phosphonate ***(7c)*** [23]

Yield = 80 %, M.p = 270 –271°C, $C_{36}H_{29}N_3O_5ClP$, ^{1}H NMR (DMSO, 500 MHz): δ = 5. 08 – 5.2 (m, 2H, CH_2OC), 5.7 – 5.99 (m, 1H, CHP), 6.80 – 6.83 (s, 1H, NH), 8.5 – 8.65 (s, 1H, CH pyrazole), 7.04 – 7.17 (m, 12H arom), 7.2 – 7.3 (m, 5H arom), 7.5 – 7.68 (m, 12H arom). Mass spect. m/e = 648 (83.3 %), the base ion peak 78 (M^+- C_{30} $H_{24}N_3O_5ClP$).

Diphenyl [(benzyloxycarbonyl)amino](1– phenyl 3– bromobenzene) pyrazole methyl phosphonate ***(7d)***[23]

Yield = 82 %, M.p = 288 – 290 °C, $C_{36}H_{29}N_3O_5BrP$, ^{1}H NMR (DMSO, 500 MHz): δ = 5.06 – 5.2 (m, 2H, CH_2OC), 5.72 – 5.88 (m, 1H, CHP), 6.82 – 6.86 (s, 1H, NH), 8.3 (s, 1H, CH pyrazole), 7.04 – 7.1(m,12H arom) ,7.22 – 7.32 (m, 5H arom) ,7.42 –7.6 (m,12H arom). Mass spect. m/e = 694 (M^{+} ^{1},

5.4 %), 77 (- C_6H_5) (M^+ - $C_{30}H_{24}N_3O_5BrP$, 25.5 %), 81 (- Br) (M^+ - $C_{36}H_{29}N_3O_5P$, 3.4 %), The base ion peak at m/e = 91 (- C_6H_5N) (M^+- $C_{30}H_{24}N_2O_5BrP$, 100 %).

Diphenyl [(benzyloxycarbonyl) amino] [1-phenyl-3-nitrobenzene] pyrazole methyl phosphonate ***(7e)*** [23]

Yield = 80 %, M.p = 278- 281°C, $C_{36}H_{29}N_4O_7P$, ^{1}H NMR (DMSO, 500 MHz): δ = 5.1 – 5.2 (m, 2H, CH_2OC) 5.84 – 5.99 (m, 1H, CHP), 6.81 – 6.84 (s, 1H, NH), 8.2 – 8.33 (s, H, CH pyrazole), 7.07 (m, 12H arom), 7.16 – 7.32 (m, 5H arom), 7.34 – 7.62 (m, 12H arom).

Diphenyl [(benzyloxycarbonyl) amino] (1-phenyl-3-thinyl pyrazole) methyl phosphonate ***(7f)*** [23]

Yield = 80 %, M.p = 312 – 314°C, $C_{34}H_{28}N_3O_5SP$. ^{1}H NMR (DMSO, 500 MHz): δ = 5.09 – 5.2 (m, 2H, CH_2OC), 5.7 – 5.84 (m, 1H, CHP), 6.814 – 6.84 (s, 1H, NH), 8.25 (s, 1H, CH pyrazole). 2.41 (s, 3H, CH_3), 7.05 – 7.1 (m, 12H arom), 7.1 – 7.3 (m, 5H arom), 7.37 – 7.6 (m, 12H arom). Mass spect. t m/e = 621 (3.1 %). The base ion peak at m/e = 91 (M^+ - $C_{28}H_{23}N_2O_5PS$), 107 (M^+– $C_{27}H_{21}N_3O_4PS$, 5.3 %), 122 (M – $C_{27}H_{20}N_2O_4PS$, 2.5%), 150 (M^+ – $C_{26}H_{20}N_2O_3PS$, 0.9%).

Diphenyl [(benzyloxycarbonyl) amino] (1-phenyl-3-pyridyl pyrazole) methyl phosphonate ***(7g)*** [23]

Yield = 80 %, M.p = 208-209 °C, $C_{35}H_{29}N_4O_5P$, ^{1}H NMR (DMSO, 500 MHz): δ = 5.0 – 5.1 (m, 2H, CH_2OC), 5.6 – 5.8 (m, 1H, CHP), 6.8 (s, 1H, NH), 7.1 – 7.29 (m, 9H arom), 7.3 – 7. 5 (m, 10H arom), 8.4 (s, 1H, CH pyrazole). Mass spect. m/e = 619 (20.0 %), The base ion peak at m/e = 77 (M^+- $C_{29}H_{24}N_4O_5P$), 91 corresponding to (M^+ - $C_{28}H_{22}N_4O_5P$).

Diphenyl ((2-hydroxyphenyl) (phenylamino)methyl) phosphonate ***(10a)***[24]

White solid. Yield (75%). IR (KBr) cm-^{1}: 2888-3119 broad, OH overlapped, 3409 (NH) ,1592 (C=C Ar), 1234 (P=O), 916 (P–O–C), 756(P–CH). ^{1}H NMR (DMSO-d6, 500 MHz) δ: 5.25 (m,1H, CH-aliphatic), δ 6.5–7.27 (m, 19H, Ar–H), In the ^{31}P NMR (DMSO, 162.0 MHz) δ = 17.72 ppm, Anal Calcd for $C_{25}H_{22}NO_4P$ (431.42): C, 69.54; H, 3.25; N, 5.10; P, 7.19. Found: C, 63.92; H, 4.03; N, 4.93; P, 7.754.

2-(((diphenoxy phosphino) (2-hydroxyphenyl) methyl) amino) benzoic acid ***(10b)***

yellow solid Yield (76%). IR (KBr) cm-^{1}: 3338 (NH), 2760-3342 broad, OH overlapped, 1662 (C=O), 1582 (C=C Ar),1253 (P=O), 943 (P–O–C), 755(P–CH). ^{1}H NMR (DMSO-d6, 500 MHz): δ 5.79 (m, 1H, CH-aliphatic), δ 7.14-7.83 (m, 18H, Ar–H), δ 12.98 (br s, 1 H, COOH), δ 9.19 (multiple singlets, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d6) δ (ppm): 52.8 (CHP), 107.1, 113.6, 115.1, 116.8, 120.5(2C), 121.1(2C), 121.3, 121.4, 121.6, 122.1, 128.1, 128.3, 130.5(2C), 130.6(2C), 131.8, 134.2, 149.3, 149.1, 148.9,151.3 (COH), 163.5 (COOH). ^{31}P NMR (DMSO, 162.0 MHz) δ =16.00 ppm. Anal Calcd for $C_{26}H_{22}NO$ P (475.43): C, 65.62; H, 2.94; N, 4.63; P, 6.52. Found: C, 62.8; H, 3.62; N, 4.02; P, 7.246.

Diphenyl (((2-aminophenyl) amino) (2-hydroxyphenyl) methyl) phosphonate ***(10c)***

Brownish red. Yield (77%). IR(KBr) cm-^{1}: 3323(NH_2), 3307 (NH), 2858-3420 broad, OH overlapped, 1597 (C=CAr), 1210 (P=O), 918 (P–O–C), 749 (P–CH). ^{1}H NMR (DMSO-d6, 500 MHz): δ 4.90 (d, 1H, J = 24.5 Hz, CH-aliphatic), δ 5.42 (br s, 1 H, NH), δ 6.76-8.06 (m, 18H, Ar–H), δ 4.22 (s, 2 H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 53.7 (CHP), 110.6, 114.9, 115.3, 117.3, 119.4, 120.6 (2C), 120.9 (2C), 128.3, 128.7, 121.1, 121.3, 121.5, 121.9, 130.1(2C), 130.3(2C), 133.8, 134.8, 150.1, 150.3, 150.3 (C-OH). ^{31}P NMR (DMSO, 162.0 MHz) δ =17.27 ppm. Anal: Calcd for $C_{25}H_{23}N_2O_4P$ (446.43): C, 67.20; H, 6.27; N, 5.15; P, 6.94. Found: C, 61.16; H, 5.63; N, 5.01; P, 7.589.

Diphenyl ((2-hydroxyphenyl) (phenylamino)methyl) phosphonate ***(11)***

Pale brown. Yield (79%). IR(KBr) cm^{-1}: 3000-3651 broad, OH + NH, 1594 (C=CAr), 1213 (P=O), 921 (P–O–C), 750 (P–CH). ^{1}H NMR (DMSO-d6, 500 MHz): δ 4.985 (m, 2H, Hz, CH-aliphatic), δ 60.8-8.08 (m, 32H, Ar–H), δ 8.058 (br s, 2 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 52.3 (2 CHP), 115.1, 115.3 (2C), 115.9, 116.8, 116.9, 120.1(2C), 120.3(2C), 120.4(2C), 120.5(2C), 121.1 (2C), 121.2 (2C), 121.3, 121.4, 121.5, 121.7, 128.3 (2C), 128.4 (2C), 130.1 (2C), 130.2(2C), 130.3 (2C), 130.4(2C), 131.7, 131.8, 151.1, 151.2, 151.3, 151.4, 154.7 (2 C-OH).

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