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# Synthesis of 2-(arylamino)ethyl phosphonic acids via the aza-Michael addition on diethyl vinylphosphonate

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ABSTRACT

A simple way of synthesising 2-(arylamino)ethyl phosphonic esters and acids via the aza-Michael addition of amines to diethyl vinylphoshonate 'on water' was developed. Various 2-(arylamino)ethyl phosphonates were initially produced through the condensation of primary and secondary amines with diethyl vinylphosphonate, focussing on those bearing one aromatic moiety, giving generally good to high yields (i.e., 75–100%). These phosphonic esters were then hydrolysed in presence of bromomethylsilane to give quantitatively the corresponding phosphonic acids.



## 1. Introduction

Organophosphorus compounds are commonly identified as key intermediates in the study of various biochemical processes.[1] Some of them demonstrated also various biological activity as antibacterial, anti-HIV or protease inhibitors.[1,2] This attractive area has led to the synthesis of numerous so-called 'phosphorus analogues'.[3] Among these, β-aminophosphonic esters and acids represent an important family to which belong naturally occurring molecules isolated from *Celiate protozoa*.[4] Thus the development of useful procedure for the synthesis of β-aminophosphonic esters and acids is of crucial importance, particularly when considering a broad evaluation of their biological properties.

Various synthetic methods[5] have been reported to synthesise 2-(amino)ethylphosphonic esters including carbon–phosphorus,[6–15] carbon–carbon[16–19] or carbon–nitrogen[20,21] bond formations. Among these methods, the aza-Michael reaction leading to the formation of a carbon–nitrogen bond appears to be probably the most versatile. However, the efficiency of this reaction depends on the nature of amines that still constitute a severe limitation in some cases. A wide range of primary and secondary amines has been used in reactions engaging the diethyl vinylphosphonate as a coupling partner in the aza-Michael addition. Without being exhaustive the main contributions refer to the use of cyclodextrine,[22] DBU[23] or $Al_2O_3$[24] as catalyst. Primary amines were shown to react only in the presence of basic catalysts and under extreme temperature conditions and prolonged reaction times.[1] It was also seen that the Michael reaction of primary amines with diethyl vinylphosphonate was complete after 24 h at 70 °C in presence of ethanol.[25] Under these conditions, the reaction between benzylamine and diethyl vinylphosphonate in 1:1 ratio led selectively to the monoaddition. Secondary amines react exothermically with diethyl vinylphosphonate in the absence of solvent; piperidine and dimethylamine constituting relevant examples. Among these substrates, cyclic amines showed good reactivity that was exploited by Baumann et al. for the addition of morpholine to diethyl vinylphosphonate.[26] Improvements were recently reported: in 2007, Brindaban[27] developed a green procedure for the aza-Michael reaction in water without catalyst or organic solvent, using α,β-unsaturated carboxylic esters, ketones, nitriles and amides; in 2008, Matveeva[3,28] showed that water as a solvent accelerates the addition of various amines to diethyl vinylphosphonate to yield β-aminophosphonates. Recently, the procedure was extended to amino acids as suitable *N*-nucleophiles.[28–30] Generally, aromatic amines were shown to be inefficient with regards to Michael addition due to the significant influence of nucleophilic and steric properties on the reaction rate. Therefore, for these substrates, improvement of the aza-Michael reaction constitutes a challenging topic.

If β-aminophosphonic esters represent an interesting class of compounds, their corresponding acids are more desirable when considering biochemical processes and corresponding biological relevance. Unfortunately, acids derivatives are not directly synthesisable via aza-Michael addition due to function incompatibility.

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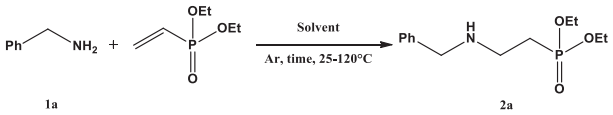
To access this family, hydrolysis of corresponding esters remain the best alternative. Few methods have been reported in the literature. Direct acid catalysed hydrolysis of phosphonic esters requires generally drastic temperature conditions as well as the use of strong hydracids (HI>HBr>HCl).[31] On the other hand, base catalysed reactions led generally to the formation of the corresponding monoester. Thus, while not catalytic, the use of halogenotrimethylsilanes as hydrolysing agents seemingly represents the best choice. Given the balance between the cost and the reactivity, bromotrimethylsilane constitutes the best compromise.[32]

In this paper we report the synthesis of 2-(amino)ethyl phosphonic acids through the aza-Michael addition of amine to diethyl vinylphosphonate followed by hydrolysis, focussing on aromatic amines towards 2-(arylamino)ethylphosphonic compounds.

## 2. Results and discussions

### 2.1. Synthesis of phosphonic esters 2

Initially, we evaluated the influence of various solvents on the aza-Michael equimolar reaction of benzylamine with diethyl vinylphosphonate under inert atmosphere of argon (Scheme 1), a reaction that was previously described in the literature and for which the authors described optimised conditions (water, room temperature, 24 h or water, 100 °C, 45 min).[3]




**Scheme 1.**

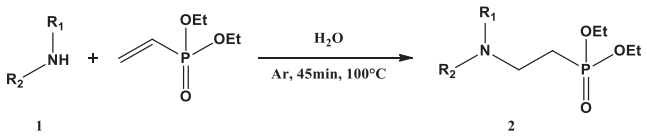
As reported in the Table 1, the presence of water has a strong kinetic effect. While the reaction without solvent proceeded quantitatively at 25 °C within 11 days (Table 1, entry 1) that carried out at 120 °C was completed after 24 h. Thus, increasing the reaction temperature allowed to shorten the reaction time in absence of solvent (Table 1, entries 1–4); however, this was accompanied by the formation of side products that decreased chemical yields and selectivity. The use of dry alcoholic solvents like EtOH or MeOH allowed to improve the reaction conditions (Table 1, entries 6 and 8), nevertheless, despite their polar character better results were obtained by adding water (Table 1, entry 7). But none of these conditions compete with reaction in water that was completed within only 45 min at 100 °C in high chemical yield (Table 1, entry 5).

**Table 1**
Aza-Michael addition of benzylamine in different solvent and temperature conditions

| Entry | Solvent | T° (°C) | Reaction time | Yield[a] (%) |
|---|---|---|---|---|
| 1 | No solvent | 25 | 11 days | 96 |
| 2 | No solvent | 70 | 18 h | 56 |
| 3 | No solvent | 120 | 18 h | 86 |
| 4 | No solvent | 120 | 24 h | 86 |
| 5 | $H_2O$ | Reflux | 45 min | 94 |
| 6 | EtOH | Reflux | 45 min | 62 |
| 7 | $H_2O$/EtOH 1/1 | Reflux | 45 min | 87 |
| 8 | MeOH | Reflux | 45 min | 66 |

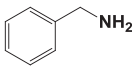
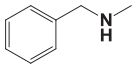
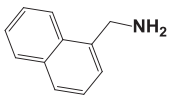
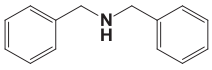
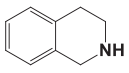
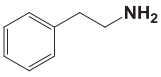
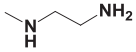
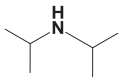
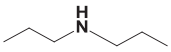
Reaction conditions: 8.4 mmol of amine, 8.4 mmol of diethyl vinylphosphonate, 2 mL solvent, T°C, time. Solvents are degassed before use.
[a] Isolated yields.

Having demonstrated that water is the solvent of choice to perform this reaction (agreeing with reported literature[3,27,33,34]), we next evaluated the aza-Michael additions of primary and secondary amines, focussing particularly on those bearing an aromatic group, to diethyl vinylphosphonate in presence of water (Scheme 2). To begin with, amines **1a**–**i**, namely, benzylamine **1a**, *N*-benzylmethylamine **1b**, *N*-naphthylmethylamine **1c**, dibenzylamine **1d**, 1,2,3,4-tetrahydroisoquinoline **1e**, phenethylamine **1f**, *N*-methylethylenediamine **1g**, diisopropylamine **1h**, and dipropylamine **1i** were selected and evaluated in this reaction (see Table 2).




**Scheme 2.**

**Table 2**
Aza-Michael reaction of diethyl vinylphosphonate and various amines in degassed water according to Scheme 2

| Entry | Amine | | Product | Reaction time | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 |  | **1a** | **2a** | 45 min | 94 |
| 2 |  | **1b** | **2b** | 45 min | 100 |
| 3 |  | **1c** | **2c** | 45 min | 75 |
| 4 |  | **1d** | **2d** | 45 min | 35 |
| 5 |  | **1e** | **2e** | 45 min | 100 |
| 6 |  | **1f** | **2f** | 45 min | 97 |
| 7 |  | **1g** | **2g₁**[b]<br>**2g₂**[c] | 45 min<br>45 min | 100<br>100 |
| 8 |  | **1h** | **2h** | 5 min | 100 |
| 9 |  | **1i** | **2i** | 5 min | 100 |

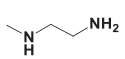
Reaction conditions: 8.4 mmol of amine, 8.4 mmol of diethyl vinylphosphonate, 2 mL of distilled water, reflux, 5–45 min.
[a] Isolated yields.
[b] Mono-adduct; ratio amine/diethyl vinylphosphonate=5:1.
[c] Bis-adduct; ratio amine/diethyl vinylphosphonate=1:5.

As expected secondary amines were more reactive than primary amines resulting in reaction completion within 45 min. Apart from dibenzylamine **1d** (Table 2, entry 4) that gave a poor selectivity and corresponding poor yield due to possible steric effects, all evaluated amines displayed good and repeatable results giving high yields of at least 75%. The reactions involving *N*-benzylmethylamine **1b** (Table 2, entry 2) and 1,2,3,4-tetrahydroisoquinoline **1e** (Table 2, entry 5) were very selective leading to quantitative yields. The reactivities of diisopropylamine **1h** (Table 2, entry 8) and dipropylamine **1i** (Table 2, entry 9) are particularly remarkable as

quantitative conversions are achieved in only 5 min. In all cases, $^{1}$H NMR showed the disappearance of the vinylic protons at $\delta \sim 6$ ppm, and a corresponding appearance of shifts relating to aliphatic protons at $\delta \sim 2$ ppm ($CH_2P$) and $\delta \sim 2.8$ ppm ($CH_2N$), giving proof of reaction. The $^{31}$P NMR showed one phosphorous species at $\delta \sim 30$ ppm attributed to the expected product, differing from the signal of the starting material ($\delta \sim 17$ ppm).

The specific case of *N*-methylethylenediamine **1g** requires more details. While the dual reactivity of ethylene diamine was previously described by Odinets et al.[3] indicating that when the diamine is used in the ratio 1:1, only the mono adducts was formed while bis-addition was observed with a ratio diethyl vinylphosphonate/amine=1:2. To the best of our knowledge, no example concerning the selectivity of the reaction when engaging a diamine in which primary and secondary amine functionality are present was previously reported. In order to answer this question we then engaged *N*-methylethylenediamine **1g**. As reported in Table 3, using a 1:1 ratio between the amine **1g** and the vinylphosphonate resulted in a mixture of mono- and bis-adduct compounds, in favour of the mono-derivative with a 77% selectivity. Increasing the amine loading to 2:1 allowed to enhance the selectivity towards the mono-adduct derivative; the best being achieved by using a ration amine : vinylphosphonate=5:1. Reacting *N*-methylethylenediamine **1g** with diethyl vinylphosphonate in a ratio 1:5 deliver cleanly the expected bis-adduct. Interestingly a lower vinylphosphonate loading allowed already to obtain selectively (i.e., 89%) the bis-adduct.

**Table 3**
Optimisation of the reaction of *N*-methylethylenediamine **1g** with diethyl vinylphosphonate and various amines in degassed water according to Scheme 2

|  (equiv) |  (equiv) | Selectivity (%)[a] | |
|---|---|---|---|
| | | Mono | Bis |
| 1 | 1 | 77 | 23 |
| 1 | 1.5 | 46 | 54 |
| 1 | 2 | 5 | 89 |
| 1 | 5 | 0 | 100 |
| 2 | 1 | 97 | 3 |
| 5 | 1 | 100 | 0 |

Reaction conditions: 8.4 (mmol × equiv) of amine, 8.4 (mmol × equiv) of diethyl vinylphosphonate, 2 mL of distilled water, reflux, 45 min.
[a] Determined by GC after calibrating the signals corresponding to the starting materials and the products using analytically pure samples versus *n*-dodecane.

The structures of both compounds were certified by NMR and Mass analyses. The bis-adduct **2g$_2$** deliver clear signal in $^{31}$P at 30.84 and 30.09 ppm, and $^{13}$C NMR at 26.14 and 23.31 with C–P coupling constant $^{1}J$(C,P)=139.1 and 138.4 Hz, respectively, in full agreement with the structure. Additionally, Mass Spectra with ($m/z$)=403.21 confirm the identification. As for **2g$_2$**, the mono-adduct derivative **2g$_1$** show signal at 30.15 ppm in $^{31}$P NMR and at 23.64 ppm in $^{13}$C NMR with a $^{1}J$(C,P) coupling constant of 139.1 Hz attributed to R(**CH$_3$**)**NCH$_2$CH$_2$P**O(OEt)$_2$ in which the secondary amine function of **1h** reacted with the diethyl vinylphosphonate. This attribution is supported by comparisons to NMR data of **2g$_1$** to **2b** versus **2a** and **2f**. Mass spectra with ($m/z$)=286.15 support mono-addition. In no case the mono-addition due to the reaction of primary amine side (i.e., R-NH$_2$) was observed.

If aza-Michael addition of evaluated amines to diethyl vinylphosphonate is generally exempt of by-products, impurities and side products were observed for that with *N*-naphthylmethylamine **1c** (Table 2, entry 3). This was interpreted as a consequence of the degradation of **1c** under the reaction conditions. In order to identify the causes of formation of side products, we evaluated the influence of both the atmosphere and the reaction time. Thus several experiments were conducted under either air or inert atmosphere of argon, with two different reaction times (Table 4).

**Table 4**
Aza-Michael reaction of diethyl vinylphosphonate with *N*-naphthylmethylamine **1c** in degassed water under different reaction conditions

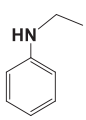
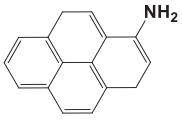
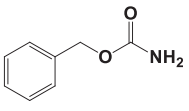
| Entry | Reaction conditions | Conv. (%)[a] | Sel. (%)[a] | Yield[a] (%) |
|---|---|---|---|---|
| 1 | 45 min–Air | 75 | 80 | 60 |
| 2 | 90 min–Air | 92 | 96 | 88 |
| 3 | 45 min–Inert atmosphere | 78 | 96 | 75 |
| 4 | 90 min–Inert atmosphere | 92 | 95 | 87 |

Reaction conditions: 8.4 mmol of amine, 8.4 mmol of diethyl vinylphosphonate, 2 mL of distilled water, reflux, 45 min.
[a] Determined by GC after calibrating the signals corresponding to the starting materials and the products using analytically pure samples versus *n*-dodecane.

If conversion versus diethyl vinylphosphonate is not affected by the nature of the atmosphere for a given reaction time, the selectivity of the reaction does depend on the nature it; however not linearly. Thus, when working at a run time of 45 min the selectivity of the reaction drops from 96% under inert atmosphere to 80% under air, the influence is less marked when working for 90 min as apparently the same selectivity is achieved (i.e., ca. 95%). This indicates that the aforementioned effect would be more pronounced when working at short reaction time (i.e., 45 min) due to the limited conversion. In conclusion, these results showed that the reaction is sensitive towards oxygen, leading probably to the formation of side products due to amine degradation by the dissolved oxygen. To our opinion, this is most likely related to the difficulties in achieving a strictly inert atmosphere when working in water.

With these results in hand, next we evaluated several aromatic amines derived from aniline, as well as carbamates, in order to assess the scopes and limitations of the procedure. Thus, aniline **1k**, ethylaniline **1l**, aminopyrene **1m**, and benzylcarbamate **1n** were engaged in the aza-Michael addition to vinyl diethylphosphonate (Table 5). At first, all reactions were carried out in water.

**Table 5**
Aza-Michael reaction of diethyl vinylphosphonate with **1k**–**n** in degassed water or water/EtOH

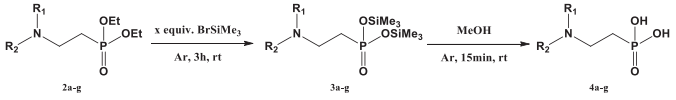
| Entry | Amine | | Solvent | Reaction time |
|---|---|---|---|---|
| 1 |  | **1k** | $H_2O$ | 45 min |
| 2 |  | **1l** | $H_2O$ | 45 min<br>6 h |
| | | | $H_2O$/EtOH | 45 min<br>6 h |
| 3 |  | **1m** | $H_2O$ | 45 min<br>6 h |
| | | | $H_2O$/EtOH | 45 min<br>6 h |
| 4 |  | **1n** | $H_2O$/EtOH | 45 min<br>6 h |

Surprisingly, no product was observed whatever the reaction time. If this assumption agrees with some literature for **1k**,[3] it was somewhat unexpected for **1l** that is supposed to be more nucleophilic. Next we envisioned that the lack of solubility of **1l**–**n** in water could affect their reactivity, encouraging us to evaluate their reactivity in a mixture $H_2O$/EtOH (1:1) were these amines are soluble. Unfortunately, under these conditions no product was formed indicating that the limitation of the procedure is closely linked to the nucleophilic character of the engaged amine in such aza-Michael reaction.

## 2.2. Synthesis of phosphonic acids

As described in introduction, the route to prepare phosphonic acids requires a two step procedure: 1/the synthesis of phosphonic esters; 2/the selective hydrolysis to obtain the corresponding acids.

Thus we evaluated the hydrolysis of the previously prepared phosphonic esters **2a**–**g** towards the corresponding acids **4a**–**g** using bromotrimethylsilane as cleaving agent. As depicted in Scheme 3, this procedure proceed through the trimethylsilyl intermediates, that were in the range of our reaction sets isolated while this is not required. Such an approach allowed us to optimise the reaction conditions.



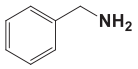
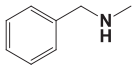
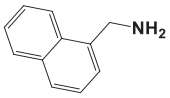
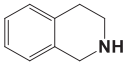
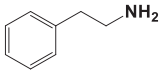
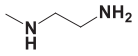

**Scheme 3.**

The reaction was monitored by $^1$H NMR following both the appearance of a signal related to the protons of trimethylsilyl moiety ($\delta \sim 0$ ppm) and the ratio between these protons and those of the aromatic groups ($\delta \sim 7$ ppm). Additionally, the conversion of the phosphonic ethyl esters towards the corresponding silyl and acid derivatives was monitored by the chemical shifts in $^{31}$P NMR at each hydrolysis step.

The results reported in Table 6 indicate that the ratio phosphonic esters/bromotrimethylsilane depends on the nature of the substrate. Thus, while 4.8 equiv of bromotrimethylsilane were sufficient to quantitatively hydrolyse the esters **2a** and **5a**, a larger excess (i.e., 6.8 equiv) should be used when engaging the esters **1a** and **3a**. This is most likely related to the nature of the latter substrates that present a relatively acidic proton on the amine function that can therefore deliver under the reaction conditions the corresponding *N*-silylated compound consuming thus bromotrimethylsilane. Such a hypothesis was confirmed by analysing the crude reaction mixture by $^1$H NMR that present in these cases several signals in the range of −0.5–1 ppm attributed to the various *N*- and *O*-trimethylsilyl groups. Thank to the use of a larger excess of bromotrimethylsilane, such a disappointing partial hydrolysis of the phosphonic ethyl esters could be avoided.

NMR analyses of the compounds **4a**–**n** gave data in accordance with the proposed structure. Particularly, in $^1$H NMR, the shifts at $\delta \sim -0.5$–0.5 ppm related to the appearance of the 18 protons of the trimethylsilyl groups. $^{31}$P NMR showed a shift at $\delta \sim 9$–11 ppm attributed to the phosphonic trimethylester group, differing from the signal in the starting material ($\delta \sim 17$ ppm). Concerning the target acids **4a**–**g**, $^{31}$P NMR presented a shift at $\delta \sim 19$ ppm attributed to the phosphonic acid group. For these compounds, IR analyses showed characteristic large absorption bands between 2500 and 3000 cm$^{-1}$. Unexpectedly, the double adduct **2g$_2$** on *N*-methylethylenediamine **1g** did not deliver the corresponding double acid leading to the formation of a single compound those mass spectra and NMR analyses did not correspond to the expected structure. Further characterisations are necessary in order to identify the obtained molecule.

**Table 6**
Hydrolysis of β-aminophosphonic ethyl esters according to Scheme 3

| Entry | Amine | Equiv $BrSiMe_3$ | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  | 4.8<br>6.8 | **4a** | 67<br>100 |
| 2 |  | 4.8 | **4b** | 100 |
| 3 |  | 4.8<br>6.8 | **4c** | 52<br>100 |
| 4 |  | 4.8 | **4e** | 100 |
| 6 |  | 4.8 | **4f** | 100 |
| 7 |  | 4.8 | **4g$_1$** | 100 |

## 3. Conclusion

Novel 2-(arylamino)ethyl phosphonic ethyl esters bearing an aromatic moiety were synthesised via a direct aza-Michael addition of the corresponding amines to diethyl vinylphosphonate. Once optimised the reaction gave nearly quantitative yields towards the expected compounds, except for dibenzylamine that led to low yield due to steric hindrance. These compounds were then further quantitatively transformed to the corresponding acids via an optimised two step hydrolysis.

## 4. Experimental section

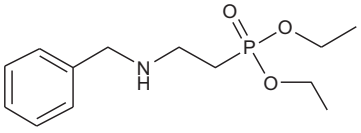
### 4.1. General

All commercial materials were used without further purification. Analytical thin layer chromatography (TLC) was performed on Fluka Silica Gel 60 $F_{254}$. GC analyses were performed on a HP 4890 chromatograph equipped with a FID detector, a HP 6890 autosampler and a HP-5 column (cross-linked 5% phenylmethylsiloxane, 30 m×0.25 mm i.d.×0.25 μm film thickness) with nitrogen as carrier gas. GC–MS analyses were obtained on a Shimadzu GC–MS-QP2010S equipped with a Sulpelco SLB-5MS column (95% methylpolysiloxane+5% phenylpolysiloxane, 30 m×0.25 mm×0.25 μm) with Helium as carrier gas. Ionisation was done by electronic impact at 70 eV. Conversions were determined by GC based on the relative area of GC-signals referred to an internal standard (biphenyl) calibrated to the corresponding pure compounds. The experimental error was estimated to be $\Delta_{rel}=\pm 5\%$. Chemical yields refer to pure isolated substances. Purification of products was accomplished by flash chromatography performed at a pressure slightly greater than atmospheric pressure using silica (Macherey–Nagel Silica Gel 60, 230–400 mesh) with the indicated solvent system. Liquid NMR spectra were recorded on a BRUKER AC-250 spectrometer. All chemical shifts were measured relative to residual $^1$H or $^{13}$C NMR resonances in the deuterated

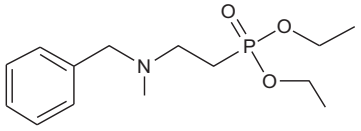
solvents: $CDCl_3$, $\delta$: 7.25 ppm for $^1H$, 77.0 ppm for $^{13}C$; $D_2O$, $\delta$: 4.79 ppm for $^1H$; MeOD, $\delta$: 3.31 ppm (quintet) for $^1H$, 49.0 ppm for $^{13}C$. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad). High resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT 95 XL spectrometer, with isobutan as reactant gas for CI at the 'Centre Commun de Spectrométrie de Masse, UMR5246 CNRS-Université Claude Bernard Lyon 1'. Compound **2h** gave analytical analyses in agreement with reported data (CAS Number [500882-07-05]).

### 4.2. General procedure for the preparation of phosphonic esters

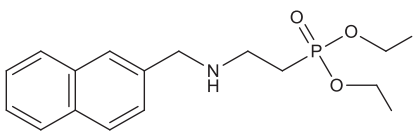
To a 50 mL round bottom flask fitted with a reflux condenser was added $8.4\times10^{-3}$ mol of amine, $8.4\times10^{-3}$ mol of diethyl vinylphosphonate and 2 mL of degassed distilled water. The reaction mixture was heated under reflux at 100 °C for 45 min and the water subsequently removed by freeze drying delivering thus analytically pure compounds. The product were characterised by GC, GC–MS, $^1H$, $^{13}C$ and $^{31}P$ NMR, HRMS.



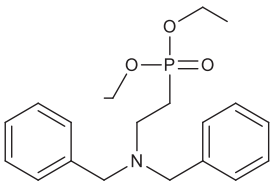
Compound **2a** was obtained as yellow oil (94%). $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 7.29–7.14 (m, 5H, $C_6H_5$), 4.02 (q, $J$=7.28 Hz, 4H, $CH_2O$), 3.73 (s, 2H, $C_6H_5CH_2$), 2.89 (t, $J$=7.42 Hz, 1H, $CH_2NH$), 2.83 (t, $J$=7.34 Hz, 1H, $CH_2NH$), 2.31 (s, 1H, N*H*), 1.99 (t, $J$=7.16 Hz, 1H, $CH_2P$), 1.91 (t, $J$=7.24 Hz, 1H, $CH_2P$), 1.23 (t, $J$=7.00 Hz, 6H, $CH_3$). $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$: 138.63 (Cq–$C_6H_5$), 128.40 (*C*H–$C_6H_5$), 128.10 (*C*H–$C_6H_5$), 127.08 (*C*H–$C_6H_5$), 61.53 (d, $J$=6.44 Hz, $CH_2O$), 53.40 ($CH_2$–$C_6H_5$), 42.6 (d, $J$=3.4 Hz, $CH_2N$), 26.24 (d, $J$=137.95 Hz, $CH_2P$), 16.39 (d, $J$=6.00 Hz, $CH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 30.35. HR ESIMS: calcd for $C_{13}H_{22}NO_3P$ $[M+H]^+$ 272.1410, found $m/z$ 272.1409.



Compound **2b** was obtained as orange oil (100%). $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 7.31–7.08 (m, 5H, $C_6H_5$), 3.98 (q, $J$=7.34 Hz, 4H, $CH_2O$), 3.42 (s, 2H, $C_6H_5CH_2$), 2.72–2.57 (m, 2H, $CH_2N$), 2.12 (s, 3H, $NCH_3$), 2.03–1.80 (m, 2H, $CH_2P$), 1.19 (t, $J$=7.07 Hz, 6H, $CH_3$). $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$: 138.28 (Cq–$C_6H_5$), 128.92 (*C*H–$C_6H_5$), 128.18 (*C*H–$C_6H_5$), 127.05 (*C*H–$C_6H_5$), 61.47 ($CH_2N$), 61.41 (d, $J$=6.7 Hz, $CH_2O$), 50.30 ($CH_2$–$C_6H_5$), 41.34 ($CH_3N$), 23.6 (d, $J$=138.29 Hz, $CH_2P$), 16.35 (d, $J$=6.02 Hz, $CH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 30.48. HR ESIMS: calcd for $C_{14}H_{24}NO_3P$ $[M+H]^+$ 286.1567, found $m/z$ 286.1572.

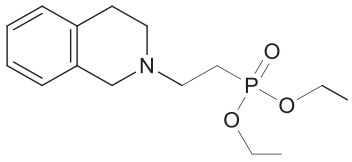


Compound **2c** was obtained as yellow oil (88%). Noteworthy, the reaction mixture was heated under reflux at 100 °C for 90 min and under an inert atmosphere. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 8.24–7.24 (m, 7H, $C_{10}H_7$), 4.24 (s, 2H, $C_{10}H_7CH_2$), 4.04 (q, $J$=7.12 Hz, 4H, $CH_2O$), 3.11 (s, 1H, N*H*), 3.05 (t, $J$=7.27 Hz, 1H, $CH_2N$), 2.99 (t, $J$=7.43 Hz, 1H, $CH_2N$), 2.09 (t, $J$=7.32 Hz, 1H, $CH_2P$), 2.02 (t, $J$=7.37 Hz, 1H, $CH_2P$), 1.25 (t, $J$=7.03 Hz, 6H, $CH_3$). $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$: 134.20 (Cq–$C_{10}H_7$), 133.82 (Cq–$C_{10}H_7$), 131.64 (Cq–$C_{10}H_7$), 128.72 (*C*H–$C_{10}H_7$), 128.06 (*C*H–$C_{10}H_7$), 126.37 (*C*H–$C_{10}H_7$), 126.32 (*C*H–$C_{10}H_7$), 125.71 (*C*H–$C_{10}H_7$), 125.38 (*C*H–$C_{10}H_7$), 123,51 (*C*H–$C_{10}H_7$), 61.7 (d, $J$=6.44 Hz, $CH_2O$), 50.73 (d, $J$=6.9 Hz, $CH_2$–$C_{10}H_7$), 42.99 (d, $J$=3.2 Hz, $CH_2N$), 25.97 (d, $J$=139.43 Hz, $CH_2P$), 16.33 (d, $J$=6 Hz, $CH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 30.20. HR ESIMS: calcd for $C_{17}H_{24}NO_3P$ $[M+H]^+$ 322.1567, found $m/z$ 322.1571.

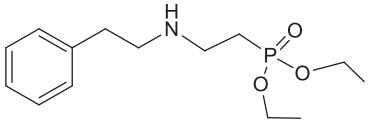


Compound **2d** was obtained as orange oil (35%). $C_{20}H_{28}NO_3P$ (361.18) $m/z$ (GC–MS)=362 $[MH^+]$.

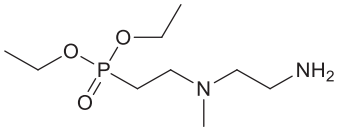
$^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 7.52–7.13 (m, 10H, $C_6H_5$), 4.14–3.91 (m, 4H, $CH_2O$), 3.83 (s, 4H, $C_6H_5CH_2$), 2.80 (ddd, $J$=10.8 Hz, 7.5, 5.4 Hz, 2H, $CH_2N$), 2.46 (d, $J$=34.5 Hz, 2H, $CH_2P$), 1.35–1.11 (m, 6H, $CH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 31.03.



Compound **2e** was obtained as yellow oil (100%). $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 7.14–6.96 (m, 4H, $C_6H_4$), 4.07 (q, $J$=7.11 Hz, 4H, $CH_2O$), 3.63 (s, 2H, $CH_2N$), 2.97–2.69 (m, 6H, $CH_2N$ and $CH_2$), 2.17–1.97 (m, 2H, $CH_2P$), 1.28 (t, $J$=7.1 Hz, 6H, $CH_3$). $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$: 133.93 (Cq–$C_6H_4$), 133.82 (Cq–$C_6H_4$), 128.62 (*C*H–$C_6H_4$), 126.53 (*C*H–$C_6H_4$), 126.28 (*C*H–$C_6H_4$), 125.70 (*C*H–$C_6H_4$), 61.62 (d, $J$=6.46 Hz, $CH_2O$), 55.31 ($CH_2N$), 51.29 ($CH_2N$), 50.47 ($CH_2N$), 28.83 ($CH_2$), 23.98 (d, $J$=139.13 Hz, $CH_2P$), 16.43 (d, $J$=6.10 Hz, $CH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 30.18. HR ESIMS: calcd for $C_{15}H_{24}NO_3P$ $[M+H]^+$ 298.1567, found $m/z$ 298.1572.

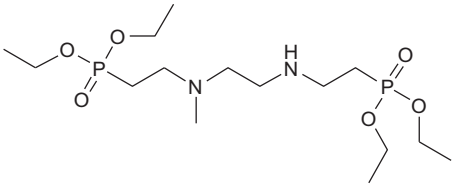


Compound **2f** was obtained as yellow oil (100%). $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 7.25–7.05 (m, 5H, $C_6H_5$), 3.96 (t, $J$=7.09 Hz, 4H, $CH_2O$), 2.91–2.66 (m, 6H, $C_6H_5CH_2$ and $CH_2NH$), 2.50 (s, N*H*), 1.90 (t, $J$=7.35 Hz, 1H, $CH_2P$), 1.83 (t, $J$=7.43 Hz, 1H, $CH_2P$), 1.19 (t, $J$=7.24 Hz, 6H, $CH_3$). $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$: 139.65 (Cq–$C_6H_5$), 128.57 (*C*H–$C_6H_5$), 128.37 (*C*H–$C_6H_5$), 126.10 (*C*H–$C_6H_5$), 61.46 (d, $J$=6.46 Hz, $CH_2O$), 50.67 ($CH_2$–NH), 43.11 (d, $J$=3.25 Hz, $CH_2N$), 36.09 ($CH_2$–$C_6H_5$), 26.27 (d, $J$=139.32 Hz, $CH_2P$), 16.33 (d, $J$=5.97 Hz, $CH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 30.15. HR ESIMS: calcd for $C_{14}H_{24}NO_3P$ $[M+H]^+$ 286.3231, found $m/z$ 286.3235.

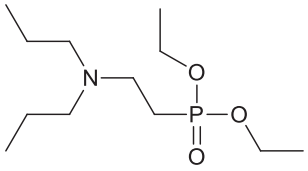


Compound **2g$_1$** was obtained as a colourless viscous oil (100%). $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 4.17–3.97 (m, 4H, $CH_2O$), 3.02 (s, 2H,

$NH_2$), 2.84–2.74 (m, 2H, $CH_2NH_2$), 2.73–2.59 (m, 2H, $CH_2NCH_3$), 2.44 (t, $J$=5.98 Hz, 2H, $CH_2NCH_3$), 2.21 (s, 3H, $CH_3N$), 2.00–1.86 (m, 2H, $CH_2P$), 1.30 (t, $J$=7.13 Hz, 6H, $CH_3$). $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$: 61.58 (d, $J$=6.48 Hz, $CH_2O$), 58.65 ($CH_2N(CH_3)CH_2$), 50.58 (d, $J$=2 Hz, $CH_2N(CH_3)CH_2$), 41.54 ($CH_3N$), 38.91 ($CH_2NH_2$), 23.64 (d, $J$=139.12 Hz, $CH_2P$), 16.42 (d, $J$=6.02 Hz, $CH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 30.15. HR ESIMS: calcd for $C_9H_{23}N_2O_3P$ $[M+H]^+$ 239.1519, found $m/z$ 239.1516.



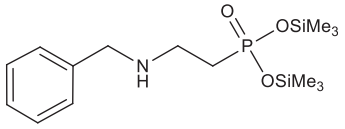
Compound **2g$_2$** was obtained as a colourless viscous oil (100%). $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 4.05–3.85 (m, 8H, $CH_2O$), 3.00 (s, 1H, N$H$), 2.85–2.7 (m, 2H, $CH_2NH$), 2.62–2.48 (m, 4H, $CH_2NH$ and $CH_2NCH_3$), 2.45–2.32 (m, 2H, $CH_2NCH_3$), 2.08 (s, 3H, $CH_3N$), 1.98–1.68 (m, 4H, $CH_2P$), 1.18 (t, $J$=7.11 Hz, 12H, $CH_3$). $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$: 61.42 (d, $J$=6.45 Hz, $CH_2O$), 61.37 (d, $J$=6.46 Hz, $CH_2O$), 55.9 ($CH_2N(CH_3)CH_2$), 50.42 (d, $J$=1.45 Hz, $CH_2N(CH_3)CH_2$), 46.45 ($CH_2NHCH_2$), 43.19 (d, $J$=2.71 Hz, $CH_2NHCH_2$), 41.37 ($CH_3N$), 26.14 (d, $J$=139.07 Hz, $CH_2P$), 23.31 (d, $J$=138.36 Hz, $CH_2P$), 16.27 (d, $J$=5.90 Hz, $CH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 30.84; 30.09. HR ESIMS: calcd for $C_{15}H_{36}N_2O_6P_2$ $[M+H]^+$ 403.2121, found $m/z$ 403.2120.



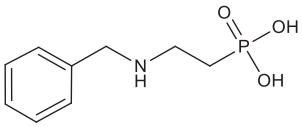
Compound **2i** was obtained as yellow oil (100%). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$: 4.08–3.95 (m, 4H, $CH_2O$), 2.75–2.66 (m, 2H, $(CH_2)_2NCH_2$), 2.31–2.25 (m, 4H, $CH_2N(CH_2)CH_2$), 1.88–1.76 (m, 2H, $CH_2P$), 1.43–1.31 (m, 4H, $CH_2CH_2CH_3$), 1.251 (t, $J$=7.15 Hz, 6H, $OCH_2CH_3$), 0.802 (t, $J$=7.44 Hz, 6H, $CH_2CH_3$). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$: 61.63 (d, $J$=6.28 Hz, $CH_2O$), 55.68 ($CH_2NCH_2$), 46.93 ($(CH_2)_2NCH_2$), 22.90 (d, $J$=137.00 Hz, $CH_2P$), 20.54 ($CH_2CH_2CH_3$), 16.63 (d, $J$=6.33 Hz, $OCH_2CH_3$), 12.05 (d, $J$=6.33 Hz, $CH_2CH_2CH_3$). $^{31}P$ NMR (160 MHz, $CDCl_3$): $\delta$: 32.40. GC–MS: calcd for $C_{12}H_{28}NO_3P$ $M^+$ 265.32; found $m/z$ [$M^+$] 265.20 (7.5%); [$M-C_2H_5$]=236.15 (100%); [$M-PO(OC_2H_5)_2$]=114.15 (70%); [$N(C_3H_7)_2$]=100.15 (65%).

### 4.3. General procedure for the preparation of phosphonic acids

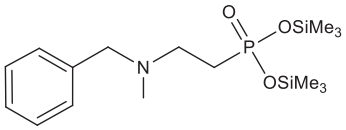
To a three necked round bottom flask fitted with a reflux condenser, an argon bubbler and a dropping funnel was added $8.4\times10^{-3}$ mol β-aminophosphonic ethyl ester and the system was purged under an argon flow for 5 min. Following this, 2.4 equiv of bromotrimethylsilane ($2.0\times10^{-2}$ mol, 2.64 mL) for the synthesis involving secondary amines or 3.4 equiv of bromotrimethylsilane ($2.86\times10^{-2}$ mol, 3.77 mL) for the synthesis involving primary amines were added dropwise to the reaction mixture. The reaction mixture was subsequently stirred at room temperature for 3 h. The air and moisture sensitive intermediate **b** was characterised by $^1H$ and $^{31}P$ NMR. To the reaction mixture was added an excess of methanol (10 mL) at room temperature over 15 min under inert atmosphere. After removing the volatile compounds (solvent, silylated side products), the analytically pure phosphonic acid **1**–**5c** were obtained and characterised by $^1H$, $^{13}C$ and $^{31}P$ NMR, and IR.



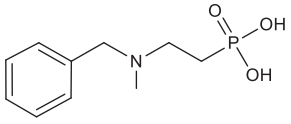
Compound **3a** $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 7.42–6.84 (m, 5H, $C_6H_5$), 3.93–3.58 (m, 2H, $C_6H_5CH_2$), 3.17 (q, $J$=7.22 Hz, 2H, $CH_2NH$), 2.97–2.55 (m, 2H, $CH_2P$), 0.13–0.34 (m, 18H, $SiCH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 21.43.



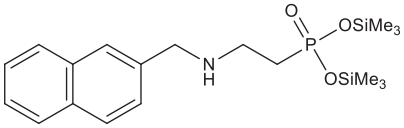
Compound **4a** was obtained as a white solid (100%). $C_9H_{14}NO_3P$ (215.29). FT-IR (KBr) ($cm^{-1}$): 3600–3300m ($\nu$N–H); 2960–2850s ($\nu$C–H); 2700–2560m ($\nu$O–H); 1600m ($\nu$C=C); 1470–1430m ($\delta$C–H), 1240–1180s ($\nu$P=O), 1167–1006m ($\nu$P–O, P–C); 720w ($\nu$C–H), 710–685s (mono-substituted benzene ring). $^1H$ NMR (250 MHz, MeOD): $\delta$: 7.46–7.15 (m, 5H, $C_6H_5$), 4.14 (s, 2H, $C_6H_5CH_2$), 3.19 (dt, $J$=16.8, 5.3 Hz, 2H, $CH_2NH$), 2.04–1.80 (m, 2H, $CH_2P$). $^{13}C$ NMR (62.9 MHz, MeOD): $\delta_{ppm}$: 130.66 (Cq–$C_6H_5$), 129.38 ($CH$–$C_6H_5$), 128.97 ($CH$–$C_6H_5$), 128.56 ($CH$–$C_6H_5$), 50.38 ($CH_2$–$C_6H_5$), 41.92 ($CH_2N$), 23.91 (d, $J$=138.35 Hz, $CH_2P$). $^{31}P$ NMR (101 MHz, MeOD): $\delta$: 19.91. Elemental Analysis: calcd: C, 50.23; H, 6.56; N, 6.51; O, 22.31; P, 14.39; found: C, 50.53; H, 6.58; N, 6.48; P, 14.34.



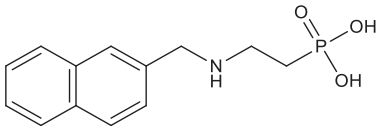
Compound **3b** $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$: 7.10–7.58 (m, 5H, $C_6H_5$), 3.14 (s, 2H, $C_6H_5CH_2$), 2.45 (dt, $J$=7.3, 5.4 Hz, 2H, $CH_2N$), 2.02 (s, 3H, $CH_3N$), 1.74 (m, 2H, $CH_2P$), −0.11 (d, $J$=52.9 Hz, 18H, $SiCH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 11.32.



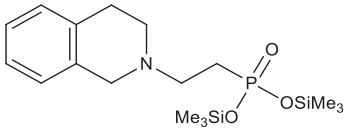
Compound **4b** was obtained as viscous colourless oil (100%). $C_{10}H_{16}NO_3P$ (229.21). FT-IR (KBr) ($cm^{-1}$): 3002–2823s ($\nu$C–H); 2749–2625m ($\nu$O–H); 1652m ($\nu$C=C); 1489–1436m ($\delta$C–H), 1262–1138s ($\nu$P=O), 1138–999m ($\nu$P–O, P–C); 740w ($\nu$C–H), 727–688s (mono-substituted benzene ring). $^1H$ NMR (250 MHz, $D_2O$): $\delta$: 7.53–7.26 (m, 5H, $C_6H_5$), 4.35 (dd, $J$=14.7, 8.2 Hz, 1H, $CH_2N$), 4.21–4.02 (m, 1H, $CH_2N$), 3.48–3.06 (m, 2H, $C_6H_5CH_2$), 2.68 (d, $J$=5.7 Hz, 2H, $CH_2P$). $^{13}C$ NMR (62.9 MHz, MeOD): $\delta$: 130.41 (Cq–$C_6H_5$), 129.42 ($CH$–$C_6H_5$), 129.39 ($CH$–$C_6H_5$), 128.73 ($CH$–$C_6H_5$), 58.65 ($CH_2$–$C_6H_5$), 51.87 ($CH_2N$), 37.78 ($CH_3N$), 23.00 (d, $J$=130.46 Hz, $CH_2P$). $^{31}P$ NMR (101 MHz, $D_2O$): $\delta$: 18.00. Elemental Analysis: calcd: C, 52.40; H, 7.04; N, 6.11; O, 20.94; P, 13.51; found: C, 52.34; H, 7.00; N, 6.07; P, 13.48.



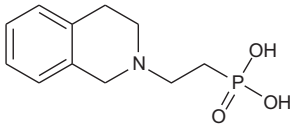
Compound **3c** $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$: 8.22 (s, 1H, $C_{10}H_7$), 8.00–7.61 (m, 2H, $C_{10}H_7$), 7.61–7.18 (m, 4H, $C_{10}H_7$), 4.46–4.22 (m, 2H, $C_{10}H_7CH_2$), 3.12–2.80 (m, 2H, $CH_2NH$), 2.28–1.95 (m, 2H, $CH_2P$), 0.34–0.35 (m, 18H, $SiCH_3$). $^{31}P$ NMR (101 MHz, $CDCl_3$): $\delta$: 9.11.



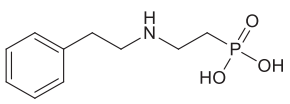
Compound **4c** was obtained as orange solid (100%). $C_{13}H_{16}NO_3P$ (265.35). FT-IR (KBr) ($cm^{-1}$): 3630–3250m ($\nu$N–H); 2960–2850s ($\nu$C–H); 2700–2560m ($\nu$O–H); 1574m ($\nu$C=C); 1479–1450m ($\delta$C–H), 1123–1003m ($\nu$P–O, P–C); 1239–1179s ($\nu$P=O), 766s (naphthalene), 795m (mono-substituted benzene ring). $^1$H NMR (250 MHz, MeOD): $\delta$: 8.21 (s, 1H, $C_{10}H_7$), 8.05 (dd, $J$=28.7, 20.9 Hz, 2H, $C_{10}H_7$), 7.73–7.47 (m, 4H, $C_{10}H_7$), 4.76 (d, $J$=3.4 Hz, 2H, $C_{10}H_7CH_2$), 2.12 (ddd, $J$=36.1, 22.1, 14.2 Hz, 2H, $CH_2N$), 1.29 (ddd, $J$=28.4, 17.8, 10.7 Hz, 2H, $CH_2P$). $^{13}$C NMR (62.9 MHz, MeOD): $\delta$: 135.43 (Cq–$C_{10}H_7$), 132.61 (Cq–$C_{10}H_7$), 131.70 (Cq–$C_{10}H_7$), 130.49 (CH–$C_{10}H_7$), 130.14 (CH–$C_{10}H_7$), 128.58 (CH–$C_{10}H_7$), 128.32 (CH–$C_{10}H_7$), 127.67 (CH–$C_{10}H_7$), 126.55 (CH–$C_{10}H_7$), 123,96 (CH–$C_{10}H_7$), 49.92 ($CH_2$–$C_{10}H_7$), 44.19 ($CH_2N$), 25.53 (d, $J$=139.10 Hz, $CH_2P$). $^{31}$P NMR (101 MHz, MeOD): $\delta$: 20.52. Elemental Analysis: calcd: C, 58.87; H, 6.08; N, 5.28; O, 18.10; P, 11.68; found: C, 58.83; H, 6.02; N, 5.24; P, 11.63.



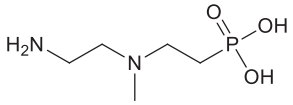
Compound **3e** $^1$H NMR (250 MHz, $CDCl_3$): $\delta$: 7.10 (m, 4H, $C_6H_4$), 4.10 (m, 3H, $CH_2N$ and $CH^aH^bN$), 3.03 (m, 5H, $CH_2N$, $CH^aH^bN$ and $CH_2$), 2.11 (m, 2H, $CH_2P$), 0.38–0.11 (m, 18H, $SiCH_3$). $^{31}$P NMR (101 MHz, $CDCl_3$). $^{31}$P NMR (101 MHz, $CDCl_3$) $\delta$ 11.50.



Compound **4e** was obtained as orange solid (100%). $C_{11}H_{16}NO_3P$ (245.25). FT-IR (KBr) ($cm^{-1}$): 3033–2854s ($\nu$C–H); 2784–2519m ($\nu$O–H); 1650m ($\nu$C=C); 1469–1401m ($\delta$C–H), 1229–1181s ($\nu$P=O), 1180–1090m ($\nu$P–O, P–C); 765–724w (bisubstituted aromatic ring). $^1$H NMR (250 MHz, MeOD): $\delta$: 7.11–7.38 (m, 4H, $C_6H_4$), 4.38 (s, 2H, $CH_2N$), 3.82 (t, $J$=16.6 Hz, 1H, $CH^aH^bN$), 3.64–3.30 (m, 3H, $CH^aH^bN$ and $CH_2$), 2.00 (ddd, $J$=22.3, 15.0, 7.2 Hz, 2H, $CH_2P$). $^{13}$C NMR (62.9 MHz, MeOD): $\delta$: 132.04 (Cq–$C_6H_4$), 129.90 (Cq–$C_6H_4$), 129.52 (CH–$C_6H_4$), 128.84 (CH–$C_6H_4H$), 128.31 (CH–$C_6H_4$), 127.88 (CH–$C_6H_4$), 54.08 ($CH_2N$), 52.82 ($CH_2N$), 51.01 ($CH_2N$), 26.53 ($CH_2$), 24.18 (d, $J$=136.94 Hz, $CH_2P$). $^{31}$P NMR (101 MHz, MeOD): $\delta$: 11.39. Elemental Analysis: calcd: C, 54.77; H, 6.69; N, 5.81; O, 19.90; P, 12.84; found: C, 54.73; H, 6.65; N, 5.78; P, 12.81.



Compound **4f** was obtained as yellow oil (100%). $C_{10}H_{16}NO_3P$ (229.21). FT-IR (KBr) ($cm^{-1}$): 3600–3280m ($\nu$N–H); 2902–2850s ($\nu$C–H); 2700–2560m ($\nu$O–H); 1644m ($\nu$C=C); 1482–1440m ($\delta$C–H), 1248–1180s ($\nu$P=O), 1167–1012m ($\nu$P–O, P–C); 765w ($\nu$C-H), 710–685s (mono-substituted benzene ring). $^1$H NMR (250 MHz, MeOD): $\delta$: 7.36–7.12 (m, 5H, $C_6H_5$), 2.95–2.85 (m, 6H, $C_6H_5CH_2$ and $CH_2NH$), 2.56 (s, NH), 1.85–1.62 (m, 2H, $CH_2P$). $^{13}$C NMR (62.9 MHz, MeOD): $\delta$: 137.57 (Cq–$C_6H_5$), 130.03 (CH–$C_6H_5$), 129.80 (CH–$C_6H_5$), 128.35 (CH–$C_6H_5$), 49.87 ($CH_2NH$), 44.19 ($CH_2NH$), 33.43 ($CH_2$–$C_6H_5$), 25.62 (d, $J$=139.59 Hz, $CH_2P$). $^{31}$P NMR (101 MHz, $CDCl_3$): $\delta$: 21.58. Elemental Analysis: calcd: C, 52.40; H, 7.04; N, 6.11; O, 20.94; P, 13.51; found: C, 52.39; H, 7.08; N, 6.13; P, 13.49.



Compound **4g$_1$** was obtained as yellow oil (100%). $C_5H_{15}N_2O_3P$ (182.15) FT-IR (KBr) ($cm^{-1}$): 3600–3280m ($\nu$N–H); 3035–2852s ($\nu$C–H); 2710–2583m ($\nu$O–H); 1620–1556m ($\delta NH_2$); 1482–1440m ($\delta$C–H), 1246–1176s ($\nu$P=O), 1175–998m ($\nu$P–O, P–C); 743w ($\nu$C–H). $^1$H NMR (250 MHz, MeOD): $\delta$: 2.98 (s, 2H, $NH_2$), 2.88–2.65 (m, 2H, $CH_2NH_2$), 2.69–2.58 (m, 2H, $CH_2NCH_3$), 2.55–2.41 (m, 2H, $CH_2NCH_3$), 2.12 (s, 3H, $CH_3N$), 1.98–1.79 (m, 2H, $CH_2P$). $^{13}$C NMR (62.9 MHz, MeOD): $\delta$: 58.05 ($CH_2N(CH_3)CH_2$), 51.58 ($CH_2N(CH_3)CH_2$), 42.03 ($CH_3N$), 38.93 ($CH_2NH_2$), 21.18 (d, $J$=138.91 Hz, $CH_2P$). $^{31}$P NMR (101 MHz, MeOD): $\delta$: 21.32. Elemental Analysis: calcd: C, 32.97; H, 8.30; N, 15.38; O, 26.35; P, 17.00; found: C, 32.95; H, 8.29; N, 15.40; P, 17.05.

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