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A facile synthesis of aminomethylene bisphosphonates catalyzed by ytterbium perfluorooctanoate under ionic liquid condition

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ABSTRACT

Three-component reactions of amines, triethylorthoformate and diethyl phosphite are efficiently catalyzed by ytterbium perfluorooctanoate [Yb(PFO)$_3$] in 1-butyl-3-methylimidazolium chloride ([bmim][Cl]) ionic liquid, giving the corresponding aminomethylene bisphosphonates in good yields. The catalyst can be recovered and reused for several times without any significant loss of activity.

1. Introduction

Ionic liquids (ILs) are rapidly becoming green alternatives to the conventional and environmentally toxic volatile organic solvents. In recent years, ionic liquids and Lewis acid catalysts combination has received substantial consideration from the organic community for their innumerable advantages over conventional multistep synthesis [1]. These reactions provide instantaneous access to large compound libraries with diverse functionalities. Sang-gi Lee and his co-workers proved that the catalytic activities were very dependent on the ionic liquids and the catalyst immobilized in an ionic liquid was reused several times without any loss of activity. Moreover ionic liquids and Lewis acid catalysts are both atom and step economic as they avoid time consuming costly purification processes in addition to the increase of yield. Recently, ILs have attracted a great deal of attention due to their high thermal stability, good conductivity, non-volatility, non-flammability, suitable polarity, wide electrochemical window, and recyclability [2–6].

Geminal bisphosphonates (BPs) are hydrolytically stable analogs of naturally occurring inorganic pyrophosphates (PPs) and constitute an important class of biologically active compounds. A number of these compounds have found application in treatment of bone diseases such as Paget's, myeloma, bone metastases, and osteoporosis [7]. Recently, BPs have also been used as antiprotozoan [8,9] agents and are found to stimulate human γδ T cells [10]. Classical synthetic routes to aminomethylene bisphosphonates (*N*-BPs) involve acid catalyzed reactions of nitriles with phosphorous acid or phosphites, condensation of amines with triethylorthoformate and phosphites [11–16], Beckmann rearrangement of oximes in the presence of phosphites [17] and reductive amination of carbonyl derivatives with amino methyl diphosphonate [18]. However, the above-mentioned catalysts have one or more disadvantages such as long reaction times [12], require stoichiometric amounts of toxic catalysts [13], give poor product yields and generate large amounts of waste [12]. It is evident from the recent literature that ytterbium perfluorooctanoate [Yb(PFO)$_3$] has invoked enormous interest as a green and potential Lewis acid catalyst to construct carbon–carbon and carbon–heteroatom bonds in various organic transformations such as Doebner reaction [19], Kabachnik–Fields reaction [20] Mannich reaction [21] and Biginelli reaction [22]. It has received considerable attention due to its low toxicity, cost effectiveness, air and water compatibility, ease of handling, good reactivity, recyclable catalyst, experimental simplicity and remarkable ability to suppress side reactions in acid sensitive substrates.

Hence, there is a need to develop a convenient, environmentally benign and practicably feasible method for the synthesis of *N*-BPs. We report for the first time, a simple, one-pot, practical protocol for the synthesis of *N*-BPs by [Yb(PFO)$_3$] in ionic liquid [bmim][Cl] at 100 °C.

2. Results and discussion

In this letter we report an efficient and environmentally benign protocol for the synthesis of *N*-BPs by condensation of aromatic

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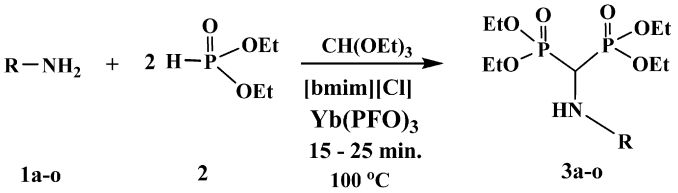

Scheme 1. Synthesis of aminomethylene bisphosphonates catalyzed by $[Yb(PFO)_3]$ in [bmim][Cl].

amines, diethylphosphite and triethylorthoformate catalyzed by $[Yb(PFO)_3]$ in ionic liquid [bmim][Cl] at 100 °C (Scheme 1). The products were obtained in high yields by a simple work-up. Initially, we investigated the condensation reaction of *p*-bromoaniline, diethyl phosphite and triethylorthoformate using different catalysts at 100 °C, and the results are listed in Table 1. It was found that $[Yb(PFO)_3]$ showed better catalytic activity among these catalysts. Most excitingly, when $[Yb(PFO)_3]$ was used, the reaction proceeded very smoothly and gave the product 3a in 90% yield (Table 1, entry 9). Moreover, we found that the yields were obviously affected by the amount of $[Yb(PFO)_3]$ loaded. When 1 mol%, 5 mol%, 10 mol%, and 15 mol% of $[Yb(PFO)_3]$ were used, the yields were 35%, 75%, 90%, and 91%, respectively (Table 1, entries 9–12). Therefore, 10 mol% of $[Yb(PFO)_3]$ was sufficient and excessive amount of catalyst did not increase the yields significantly (Table 1, entries 9). The catalytic activity of the recycled $[Yb(PFO)_3]$ was also examined. $[Yb(PFO)_3]$ could be reused three times for the reaction without noticeable loss of activity (Table 1, entry 9).

In order to elucidate the role of $[Yb(PFO)_3]$, a controlled reaction was carried out using aromatic amines, diethylphosphite and triethylorthoformate in ionic liquid without using $[Yb(PFO)_3]$. The reaction proceeds with low yields (40%) even after 8 h. It is to be noted that the reaction proceeded to give 50% yields (and took 12 h) when $[Yb(PFO)_3]$ was used alone in the absence of an ionic liquid. It is important to note that electronic factors played an important role in this $[Yb(PFO)_3]$ mediated condensation reaction in ionic liquid as a reaction media. In order to elucidate the role of the solvents, various solvents were screened to evaluate the scope and limitation of this reaction (Table 2). The results substantiates our hypothesis that the $[Yb(PFO)_3]$ catalyzed synthesis of *N*-BPs would not only be faster but would also results in higher yields in ionic liquids as compared to other conventional solvents. The results indicate that different solvents affected the efficiency of the reaction. Water, PEG, acetonitrile, acetone, nitromethane and chloroform afforded low yields (Table 2, entries 1–6). The use of solvents such as ethanol, DMF, and toluene could improve the yields (Table 2, entries 8–10). Especially, the reaction could be carried out under solvent-free condition and gave moderate yield (Table 2, entry 7). Finally, when [bmim][Cl] was used, the yield increased to 90% (Table 2, entry 11) better than any other solvents examined here. The result substantiates our hypothesis that the $[Yb(PFO)_3]$ catalyzed synthesis of N-BPs would not only be faster but would also result in higher yields in ionic liquids as compared to other conventional solvents. The above results showed that $[Yb(PFO)_3]$ was essential in the reaction, and the best results were obtained when the reaction was carried out with 10 mol% of $[Yb(PFO)_3]$ in [bmim][Cl] at 100 °C (Table 1, entry 9).

The reaction of various aromatic/heteroaromatic amines (**1a–o**) with diethyl phosphite (**2**) and triethylorthoformate in the presence of the optimum quantity of $[Yb(PFO)_3]$ under [bmim][Cl] conditions at 100 °C resulted in the formation of the *N*-BPs (**3a–o**) (Table 3). Here, we have carried out the similar reaction with various aromatic/heteroaromatic amines containing electron donating or electron withdrawing functional groups at different positions but it did not showed any remarkable differences in the yields of product and reaction time. This result provided incentive to extend this process to various substrates. Both aryl and heterocyclic amines worked well in this reaction to give the corresponding *N*-BPs. Reasonable yields were also observed with less-reactive heterocyclic amines (Table 3, entries n and o). In all the cases, the reactions were completed within 15–25 min.

Table 1
Influence of the catalyst on the synthesis of aminomethylene bisphosphonate.[a]

Entry	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	$FeCl_3$ (10)	20	30
2	$ZnCl_2$ (10)	20	45
3	I_2 (10)	20	40
4	$CuCl_2$ (10)	20	55
5	$AlCl_3$(10)	20	50
6	*p*-TSA (10)	20	55
7	Amberlyst 15 (10)	20	60
8	$BF_3{\cdot}SiO_2$ (10)	20	70
9[c]	$[Yb(PFO)_3]$(10)	20	90, 88, 85
10	$[Yb(PFO)_3]$ (1)	20	35
11	$[Yb(PFO)_3]$ (5)	20	75
12	$[Yb(PFO)_3]$(15)	20	91

[a] Reaction of *p*-bromoaniline (1 mmol), diethyl phosphite (2 mmol) and triethylorthoformate (1 mmol) in [bmim][Cl] (2 mL) at 100 °C.
[b] Isolated yield.
[c] Catalyst was reused three times.

Table 2
Influence of the solvent on the synthesis of aminomethylene bisphosphonate.[a]

Entry	Solvent (2 mL)	Time (min)	Yield[b] (%)
1	Water	20	20
2	PEG	20	30
3	CH_3CN	20	30
4	CH_3COCH_3	20	20
5	CH_3NO_2	20	25
6	$CHCl_3$	20	20
7	CH_3CH_2OH	20	50
8	DMF	20	55
9	Toluene	20	62
10	[bmim][Cl]	20	90

[a] Reaction of *p*-bromoaniline (1 mmol), diethyl phosphite (2 mmol) and triethylorthoformate (1 mmol) using 10 mol% $[Yb(PFO)_3]$ at 100 °C.
[b] Isolated yield.

Table 3
Synthesis of aminomethylene bisphosphonates.[a]

Entry	R	Product	Time (min)	Yield[b] (%)
1	4-Br C_6H_4	3a	20	90
2	4-Cl C_6H_4	3b	18	91
3	4-F C_6H_4	3c	18	90
4	4-Me C_6H_4	3d	15	93
5	4-NO_2 C_6H_4	3e	18	92
6	4-*Iso* Propyl-C_6H_4	3f	18	89
7	4-$N(CH_3)_2$ C_6H_4	3g	21	88
8	2-Et C_6H_4	3h	22	85
9	4-Cl, 2-NO_2 C_6H_3	3i	20	90
10	2-Cl C_6H_4	3j	15	92
11	2-Me C_6H_4	3k	18	90
12	1-Naphthyl	3l	25	85
13	PhNH C_6H_4	3m	24	85
14	2-Pyridyl	3n	25	75
15	2-Thiazolyl	3o	25	70

[a] Reaction of *p*-bromoaniline (1 mmol), diethyl phosphite (2 mmol) and triethylorthoformate (1 mmol) using 10 mol% $[Yb(PFO)_3]$ in [bmim][Cl] (2 mL) at 100 °C.
[b] Isolated yield.

3. Conclusion

In conclusion, an efficient three component one-pot synthesis of a variety of *N*-BPs is accomplished using $[Yb(PFO)_3]$ in [bmim][Cl] at 100 °C. Reusable, eco-friendly, inexpensive, efficient catalyst, short reaction times, high yields and easy workup are the advantages of this protocol. This method serves as an alternative procedure for an efficient synthesis of *N*-BPs.

4. Experimental

4.1. Method and apparatus

Chemicals were purchased from Aldrich and Alfaaesar Chemical Companies. NMR spectra were recorded in ppm in DMSO-d_6 on a Jeol JNM ECP 400 NMR instrument using TMS as internal standard. Mass spectra were recorded on a Jeol JMS-700 mass spectrometer. The ionic liquid [bmim][Cl] and $[Yb(PFO)_3]$ were prepared according to procedures from the literature [21,23].

4.2. Synthesis of tetraethyl (4-bromophenylamino) methylenebisphosphonate (3a)

A mixture of *p*-bromolaniline (**1a**, 1 mmol), diethyl phosphite (**2**, 2 mmol), triethylorthoformate (1 mmol), [bmim][Cl] (2 mL) was well stirred with $[Yb(PFO)_3]$ (10 mol%) at 100 °C for appropriate time (Table 3). When the reaction was completed as indicated by TLC, methylene chloride (5 mL) was added. The catalyst was filtered and washed with methylene chloride (5 mL). The filtrate was washed with water. The combined organic layer was dried over anhydrous Na_2SO_4, filtered. The filtrate was evaporated under reduced pressure. The resulting product was purified by column chromatography on silica gel (60–120 mesh, ethylacetate/hexane, 1:2) to afford pure product **3a**. The filter residue, which was the catalyst, was dried under vacuum and reused in the next reaction. This procedure was applied successfully for the preparation of other compounds.

4.2.1. Tetraethyl (4-bromophenylamino) methylenebisphosphonate (3a)

White solid; Mp: 137–139 °C [14]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.09 (t, J = 7.0 Hz, 6H), 1.30 (t, J = 6.8 Hz, 6H), 3.96–3.86 (m, 4H), 4.19–4.05 (m, 4H), 4.65 (dt, J = 21.5, 10.5 Hz, 1H), 5.95 (d, J = 10.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 2H) 7.19 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 145.5, 132.2, 117.2, 108.5, 63.5 (dd, J = 30.5, 7.6 Hz), 50.7 (t, J = 141.4 Hz), 16.3 (dd, J = 28.2, 5.6 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 20.5.

4.2.2. Tetraethyl (4-chlorophenylamino) methylenebisphosphonate (3b)

White solid; Mp: 134–136 °C [14]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.09 (t, J = 7.2 Hz, 6H), 1.25 (t, J = 7.2 Hz, 6H), 3.85–4.05 (m, 8H), 4.80 (dt, J = 22.5, 10.5 Hz, 1H), 5.2 (d, J = 9.5 Hz, 1H), 6.25 (dd, J = 2.2, 10.2 Hz, 2H) 7.10 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 147.5, 128.2, 119.2, 114.9, 63.5 (dd, J = 28.2, 5.5 Hz), 50.2 (t, J = 144.4 Hz), 16.4 (dd, J = 24.2, 5.4 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 19.2.

4.2.3. Tetraethyl (4-fluorophenylamino) methylenebisphosphonate (3c)

White solid; Mp: 60–62 °C [15]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, J = 7.0 Hz, 6H), 1.23 (t, J = 7.0 Hz, 6H), 3.75–3.85 (m, 2H), 3.90–4.01 (m, 2H), 4.05–4.20 (m, 4H) 4.90 (dt, J = 22.5, 10.1 Hz, 1H), 5.50 (d, J = 9.5 Hz, 1H), 6.35 (dd, J = 2.2, 10.2 Hz, 2H), 6.80 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 150.2, 143.5, 118.2, 114.9, 63.5 (dd, J = 28.2, 5.5 Hz), 51.5 (t, J = 144.4 Hz), 16.2 (dd, J = 24.2, 6.4 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 20.2.

4.2.4. Tetraethyl (p-tolylamino) methylenebisphosphonate (3d)

White solid; Mp: 70–72 °C [14]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14 (t, J = 6.8 Hz, 6H), 1.30 (t, J = 6.8 Hz, 6H), 2.2 (s, 3H), 3.75–3.85 (m, 2H), 3.90–4.03 (m, 2H), 4.09–4.19 (m, 4H), 4.65 (dt, J = 21.5, 10.0 Hz, 1H), 4.95 (d, J =10.2 Hz, 1H), 6.70 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 4.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 143.4, 128.2, 124.5, 113.9, 63.5 (dd, J = 28.2, 5.0 Hz), 52.2 (t, J = 141.4 Hz), 20.5, 17.1 (dd, J = 5.4, 30.2 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 20.5.

4.2.5. Tetraethyl (4-nitrophenylamino) methylenebisphosphonate (3e)

Yellow solid; Mp: 205–207 °C [16]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10 (t, J = 7.0 Hz, 6H), 1.16 (t, J = 7.0 6H), 3.85–4.01 (m, 8H), 4.88 (dt, J = 21.5, 10.5 Hz, 1H), 5.20 (d, J = 10.2 Hz, 1H), 7.08 (d, J = 9.2 Hz, 2H), 7.90 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.5, 135.4 126.0, 112.8, 63.3 (dd, 28.5, 7.2 Hz), 48.4 (t, J = 145.1 Hz), 16.7 (dd, J = 28.9, 5.5 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 18.2.

4.2.6. Tetraethyl (4-isopropylphenylamino) methylenebisphosphonate (3f)

Colorless oil. IR (KBr) (ν_{max} cm^{-1}): 3390 (NH), 1244 (P=O), 746 (P–$C_{aliphatic}$). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.09 (t, J = 7.0 Hz, 6H), 1.19 (d, J = 5.6, Hz, 6H), 1.30 (t, J = 6.8 Hz, 6H), 2.91–2.98 (m, 1H), 3.86–3.96 (m, 4H), 4.05–4.19 (m, 4H), 4.65 (dt, J = 21.5, 10.5 Hz, 1H), 5.95 (d, J = 10.2 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.34(dd, J = 2.2, 10.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 138.2, 118.3, 127.6, 132.6, 63.5 (dd, J = 30.2, 7.6 Hz), 47.7 (t, J = 142.4 Hz), 33.7, 23.8, 16.3 (dd, J = 28.2, 5.6 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 20.5; MS: 421 ($M^{\bullet+}$); Anal. calcd for $C_{18}H_{33}NO_6P_2$: C, 51.30; H, 7.89; N, 3.32. Found: C, 51.25; H, 7.83; N, 3.18.

4.2.7. Tetraethyl (4-(dimethylamino)phenylamino) methylenebisphosphonate (3g)

Colorless oil. IR (KBr) (ν_{max} cm^{-1}): 3290 (NH), 1240 (P=O), 740 (P–$C_{aliphatic}$). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.08 (t, J = 7.0 Hz, 6H), 1.28 (t, J = 6.8 Hz, 6H), 2.84 (s, 6H), 3.70–3.74 (m, 2H), 3.80–3.92 (m, 2H), 3.98–4.12 (m, 4H), 4.85 (dt, J = 21.5, 10.5 Hz, 1H), 5.20 (d, J = 10.2 Hz, 1H), 6.55 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 140.2, 116.3, 120.6, 63.0 (dd, J = 29.2, 7.0 Hz), 48.5 (t, J = 144.0 Hz), 42.8, 16.3 (dd, J = 25.5, 5.6 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 18.5; MS: 422 ($M^{\bullet+}$); Anal. calcd for $C_{17}H_{32}N_2O_6P_2$: C, 48.34; H, 7.64; N, 6.63. Found: C, 48.29; H, 7.60; N, 6.59.

4.2.8. Tetraethyl (2-ethylphenylamino) methylenebisphosphonate (3h)

Colorless oil [14]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.09 (t, J = 7.0 Hz, 6H), 1.20 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 6.8 Hz, 6H), 2.41–2.49 (q, 2H), 3.75–4.09 (m, 8H), 4.35 (d, J = 10.2 Hz, 1H), 4.95 (dt, J = 21.5, 10.5 Hz, 1H), 7.60–7.10 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 143.4, 128.2, 127.9, 126.5, 118.9, 112.0 62.5 (dd, J = 28.2, 5.5 Hz), 50.2 (t, J = 144.4 Hz), 24.2, 16.2 (dd, J = 24.2, 5.1 Hz), 14.5; ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 18.2.

4.2.9. Tetraethyl (4-chloro-2-nitrophenylamino) methylenebisphosphonate (3i)

Colorless oil [14]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.08 (t, J = 6.9 Hz, 6H), 1.29 (t, J = 6.9 Hz, 6H), 3.80–4.10 (m, 8H), 4.60 (dt, J = 20.5, 9.5 Hz, 1H), 5.5 (d, J = 10.5 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 1H), 8.10 (d, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz,

DMSO-d_6) δ: 143.5, 136.2, 132.5, 125.0, 119.9, 117.5, 64.5 (dd, J = 28.2, 5.5 Hz), 48.2 (t, J = 144.4 Hz), 16.0 (dd, J = 30.2, 5.4, Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 17.5.

*4.2.10. Tetraethyl (2-chlorophenylamino) methylenebisphosphonate (**3j**)*

Colorless oil [15]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, J = 7.2 Hz, 6H), 1.30 (t, J = 7.2 Hz, 6H), 3.70–4.02 (m, 8H), 4.65 (dt, J = 21.5, 10.5 Hz, 1H), 4.75 (d, J = 9.5 Hz, 1H), 6.40–7.05 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 142.5, 128.2, 127.5, 123.0, 119.2, 114.9, 63.2 (dd, J = 28.2, 6.5, Hz), 48.5 (t, J = 144.4 Hz), 16.4 (dd, J = 27.2, 5.4 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 18.5.

*4.2.11. Tetraethyl (o-tolylamino) methylenebisphosphonate (**3k**)*

Colorless oil [15]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (t, J = 7.0 Hz, 6H), 1.20 (t, J = 7.0 Hz, 6H), 2.2 (s, 3H), 3.85–4.09 (m, 8H), 4.55 (dt, J = 20.5, 10.5 Hz, 1H), 5.95 (d, J = 9.5 Hz, 1H), 6.42–7.05 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 143.2, 128.5, 126.5, 122.0, 118.2, 114.2, 62.5 (dd, J = 28.2, 5.5, Hz), 49.5 (t, J = 140.4 Hz), 19.8, 15.9 (dd, J = 25.2, 5.4 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 18.5.

*4.2.12. Tetraethyl (naphthalene-1-ylamino) methylenebisphosphonate (**3l**)*

White solid; Mp: 62–64 °C [14]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14 (t, J = 7.2 Hz, 6H), 1.30 (t, J = 7.2 Hz, 6H), 3.85–4.09 (m, 8H), 4.35 (d, J = 9.2 Hz, 1H), 5.10 (dt, J = 21.5, 10.5 Hz, 1H), 7.01–8.05 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 142.3, 135.0, 127.9, 126.5, 126.1, 125.0, 122.9, 120.5, 118.9, 108.0 62.5 (dd, J = 28.2, 5.5 Hz), 49.5 (t, J = 145.4 Hz), 16.7 (dd, J = 28.2, 6.2 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 18.2.

*4.2.13. Tetraethyl (4-(phenylamino)phenylamino) methylenebisphosphonate (**3m**)*

White solid; Mp: 82–84 °C [14]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.09 (t, J = 7.0 Hz, 6H), 1.30 (t, J = 7.0 Hz, 6H), 3.85–4.09 (m, 8H), 4.58 (dt, J = 22.5, 10.9 Hz, 1H), 5.10 (d, J = 10.8 Hz, 1H), 6.66 (t, J = 7.2 Hz, 1H), 6.77–7.05 (m, 6H), 7.12 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 141.3, 133.0, 128.9, 120.5, 118.9, 113.9, 113.2, 63.5 (dd, J = 32.5, 7.2 Hz), 49.5 (t, J = 145.4 Hz), 16.0 (dd, J = 24.5, 5.4 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 19.5.

*4.2.14. Tetraethyl (pyridine-2-ylamino) methylenebisphosphonate (**3n**)*

Colorless oil [15]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (t, J = 6.9 Hz, 6H), 1.28 (t, J = 6.9 Hz, 6H), 3.94–3.84 (m, 2H), 4.19–3.99 (m, 6H), 4.75 (dt, J = 21.5, 10.5 Hz, 1H), 5.37 (d, J = 10.2 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 7.23 (t, J = 6.2 Hz, 1H), 7.48 (dd, J = 8.8, 1.0 Hz, 1H), 8.60 (dd, J = 5.8, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.1, 149.3, 136.6, 112.8, 108.1, 63.5 (dd, J = 30.0, 7.0 Hz), 50.6 (t, J = 142.7 Hz), 16.4 (dd, J = 23.0, 5.5 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 21.1.

*4.2.15. Tetraethyl (thiazol-2-ylamino) methylenebisphosphonate (**3o**)*

Colorless oil [15]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10 (t, J = 6.9 Hz, 6H), 1.29 (t, J = 6.9 Hz, 6H), 3.94–3.84 (m, 4H), 4.19–3.99 (m, 4H), 4.55 (dt, J = 22.5, 10.5 Hz, 1H), 5.25 (d, J = 10.2 Hz, 1H), 6.40 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.2, 136.5, 108.1, 63.0 (dd, J = 30.0, 7.2 Hz), 50.6 (d, J = 145.7 Hz), 16.3 (dd, J = 23.0, 5.5 Hz); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 19.2.

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