Zr^{4+}-Catalyzed Efficient Synthesis of α-Aminophosphonates[1]

J. S. Yadav,* B.V. S. Reddy, K. Sarita Raj, K. Bhaskar Reddy, A. R. Prasad

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India
Fax +91(40)7170512; E-mail: yadav@iict.ap.nic.in

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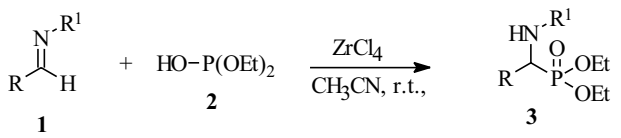
Abstract: Aldimines undergo nucleophilic addition with diethyl phosphite in the presence of a catalytic amount of zirconium tetrachloride at ambient temperature to afford the corresponding α-aminophosphonates in high yields with high selectivity.

Key words: α-aminophosphonates, diethyl phosphite, imines, zirconium reagents

The synthesis of α-aminophosphonates has attracted much interest because of their biological activity and structural analogy to α-amino acids.[2] They also act as peptide mimics,[3] enzyme inhibitors,[4] haptens of catalytic antibodies,[5] antibiotics and pharmacological agents.[6] As a result, a variety of synthetic approaches[7] have been developed for the synthesis of α-aminophosphonates. Of these methods, the nucleophilic addition of phosphites with imines, catalyzed by an acid or a base is one of the most convenient methods. Lewis acids[8,9] are known to catalyze these reactions under mild conditions. Recently, lanthanide triflates[10] are also found to be effective for this transformation. However, many of these procedures involve stoichiometric amount of catalysts, expensive reagents, longer reaction times and low yields of products in the cases of aliphatic aldehydes and amines. Therefore, there is a need to develop a convenient and practically potential method for the synthesis of α-aminophosphonates.

In this report, we describe a novel and efficient protocol for the synthesis of α-aminophosphonates using a catalytic amount of zirconium tetrachloride under mild conditions (Scheme).



Scheme

The treatment of benzaldimine with diethyl phosphite in the presence of 10 mol% $ZrCl_4$ in acetonitrile resulted in the formation of α-aminophosphonate **3** (R = Ph, R^1 = H) in 93% yield. Several aldimines (generated in situ from aldehydes and amines over anhydrous Na_2SO_4) reacted well with diethyl phosphite under similar reaction conditions to afford the corresponding α-aminophosphonates in high yields. In all cases, the reactions proceeded smoothly at ambient temperature with high selectivity. Both aromatic and aliphatic aldimines produced excellent yields of products. However, the reactions of aliphatic aldimines took longer reaction time compared to aromatic imines because of the lower reactivity of aliphatic aldehydes than aromatic. The reactions are clean and complete within 3–7 hours (Table). The reaction conditions are very mild and the α-aminophosphonates are exclusively formed without the formation of any undesired side products. In addition to its simplicity and milder reaction conditions, this method is even effective with aliphatic and α,β-unsaturated aldehydes, which normally produce low yields due to their intrinsic lower reactivity. The present method does not require any additives or promoters[9] to proceed the reaction. Another important feature of this reaction is the survival of a variety of functional groups such as olefins, ethers, hydroxyl, methylenedioxy and halides under the reaction conditions. Similar yields and selectivity was also obtained with bismuth(III) chloride in acetonitrile. Several examples illustrating this novel and efficient protocol for the synthesis of α-aminophosphonates are listed in the Table. Among various Lewis acids such as $YbCl_3$, YCl_3, and $LaCl_3$ used for this transformation, $ZrCl_4$ was found to be more effective than others in terms of yields and reaction time.

In summary, we have demonstrated a novel and efficient protocol for the synthesis of α-aminophosphonates using catalytic amount of zirconium tetrachloride. The method is effective for aromatic, aliphatic, α,β-unsaturated aldehydes and provides excellent yields of the products, which makes it useful and attractive process for the synthesis of α-aminophosphonates.

α-Aminophosphonates 3: General Procedure

A mixture of aldimine **1** (generated in situ from the corresponding aldehyde and the amine, Table) (5 mmol), diethyl phosphite **2** (6 mmol) and $ZrCl_4$ (10 mol%) in MeCN (15 mL) was stirred at r.t. for an appropriate time (Table). After completion of the reaction, as indicated by TLC, the mixture was quenched with H_2O (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 2:8) to afford pure α-aminophosphonate.

3a

Oil.

^{1}H NMR ($CDCl_3$): δ = 1.17 (t, 3 H, *J* = 7.1 Hz), 1.30 (t, 3 H, *J* = 7.1 Hz), 2.18 (s, 3 H), 3.70–3.83 (m, 1 H), 3.95–418 (m, 3 H), 4.70 (dd,

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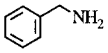
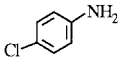
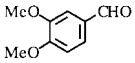
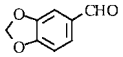
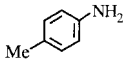
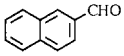
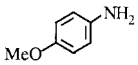
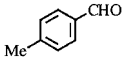
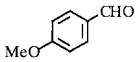
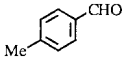
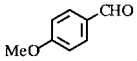
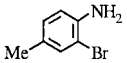
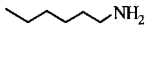
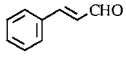
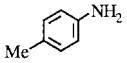
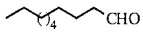
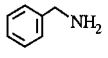
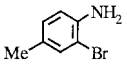
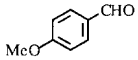
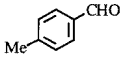
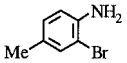
Table $ZrCl_4$-Catalyzed Synthesis of α-Aminophosphonates[a]

Entry	Aldehyde	Amine	Reaction Time (h)	Yield[b] (%)
a			3.5	87
b			5.0	90
c			4.5	89
d			5.5	85
e			4.0	90
f			4.0	92
g			6.0	85
h			3.0	93
i			4.5	88
j			5.0	90
k			4.5	92
l			6.0	89
m			7.0	81
n			5.5	85
o			4.5	82
p			8.0	78
q			5.5	85
r			4.5	90
s			6.0	87

[a] All products were characterized by ^1H NMR, IR and mass spectra.
[b] Isolated and unoptimized yield.

1 H, *J* = 23, 8.1, 7.0 Hz), 5.28 (dd, 1 H, *J* = 7.0, 2.0 Hz), 6.30 (d, 1 H, *J* = 7.8 Hz), 6.78 (d, 1 H, *J* = 7.8 Hz), 7.25–7.50 (m, 6 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.3, 16.5, 56.3, 63.5, 114.0, 118.5 128.0, 128.7, 129.2, 130.0, 136.0, 146.3.

IR (KBr): 3328, 2972, 1618, 1512, 1228, 1012, 968, 758 cm^{-1}.

EIMS: *m*/*z* = 333 (M^+), 196, 105, 91, 77, 51, 43.

Anal. Calcd for $C_{18}H_{24}NO_3P$ (333.4): C, 64.85; H, 7.26; N, 4.20; P, 9.29. Found: C, 64.81; H, 7.30; N, 4.24; P, 9.30.

3b
Oil.

^1H NMR ($CDCl_3$): δ = 1.18 (t, 3 H, *J* = 6.8 Hz), 1.28 (t, 3 H, *J* = 6.8 Hz), 3.90-4.18 (m, 4 H), 4.95 (d, 1 H, *J* = 23. 8 Hz), 6.60–6.78 (m, 3 H), 6.80–6.95 (m, 2 H), 7.10–7.25 (m, 4 H), 8.85 (br s, 1 H, OH).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.3, 16.5, 47.8, 50.5, 62.2, 63.5, 114.0, 115.8, 118.5, 120.0, 129.2, 130.0, 131.8, 132.1, 151.5, 158.8, 159.3.

IR (KBr): 3360, 3180, 1620, 1560, 1520, 1203, 1080, 760 cm^{-1}.

EIMS: *m*/*z* = 335 (M^+), 178, 77, 65, 53.

Anal. Calcd for $C_{17}H_{22}NO_4P$ (335.3): C, 60.89; H, 6.61; N, 4.18; P, 9.24. Found: C, 60.92; H, 6.70; N, 4.22; P, 9.28.

3c
Liquid.

^1H NMR ($CDCl_3$): δ = 1.15 (t, 3 H, *J* = 6.9 Hz), 1.28 (t, 3 H, *J* = 6.9 Hz), 2.30 (s, 3 H), 3.60–3.78 (m, 1 H), 3.95–4.19 (m, 3 H), 4.60 (br s, 1 H, NH), 4.75 (d, 1 H, *J* = 23.7 Hz), 6.38 (d, 1 H, *J* = 7.8 Hz), 6.60 (t, 1 H, *J* = 7.8 Hz), 6.90 (t, 1 H, *J* = 7.8 Hz), 7.0 (d, 1 H, *J* = 7.8 Hz), 7.25–7.38 (m, 3 H), 7.40–7.50 (m, 2 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 15.8, 15.9, 16.0, 16.1, 17.2, 54.3, 57.4, 62.9, 63.0, 111.0, 117.8, 122.6, 126.6, 127.3, 127.4, 127.5, 127.6, 127.8, 128.2, 128.3, 129.5, 129.9, 135.6, 135.7, 143.9, 144.2.

IR (KBr): 3314, 2978, 1614, 1512, 1224, 1010, 981.3, 758 cm^{-1}.

EIMS: *m*/*z* = 333 (M^+), 196, 155, 122, 105, 77, 43.

Anal. Calcd for $C_{18}H_{24}NO_3P$ (333.4): C, 64.85; H, 7.26; N, 4.20; P, 9.29. Found: C, 64.81; H, 7.30; N, 4.24; P, 9.30.

3d
Liquid.

^1H NMR ($CDCl_3$): δ = 1.18 (t, 3 H, *J* = 7.0 Hz), 1.25 (t, 3 H, *J* = 7.0 Hz), 3.80–3.90 (m, 1 H), 4.05–4.20 (m, 3 H), 4.80 (br s, 1 H, NH), 5.05 (d, 1 H, *J* = 23.9 Hz), 6.58 (d, 2 H, *J* = 7.8 Hz), 6.80 (t, 1 H, *J* = 7.8 Hz), 6.85 (d, 1 H, *J* = 7.8 Hz), 7.05 (d, 1 H, *J* = 7.8 Hz), 7.10 (t, 1 H, *J* = 7.8 Hz), 7.20 (d, 1 H, *J* = 7.8 Hz), 9.05 (br s, 1 H, OH).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.3, 16.5, 46.9, 50.1, 62.5, 63.5, 115.6, 118.5, 120.7 129.2, 130.8, 131.6, 132.5, 150.5, 158.7, 159.5.

IR (KBr): 3301, 3212, 3080, 1680, 1572, 1246, 1082, 986, 888, 774 cm^{-1}.

EIMS: *m*/*z* = 369 (M^+), 278, 233, 128, 112, 65, 43.

Anal. Calcd for $C_{17}H_{21}ClNO_4P$ (369.8): C, 55.22; H, 5.72; Cl, 9.59; N, 3.79; P, 8.38. Found: C, 55.25; H, 5.70; Cl, 9.62; N, 3.81; P, 8.40.

3e
Solid; mp 78–80 °C.

^1H NMR ($CDCl_3$): δ = 1.16 (t, 3 H, *J* = 6.9 Hz), 1.25 (t, 3 H, *J* = 6.9 Hz), 2.30 (s, 3 H), 3.65–3.75 (m, 4 H), 3.80 (s, 6 H), 3.90–4.20), (m, 3 H), 4.70 (d, 1 H, *J* = 23.8 Hz), 6.40 (d, 1 H, *J* = 7.8 Hz), 6.65 (t, 1 H,*J* = 7.8 Hz), 6.80 (d, 1 H, *J* = 7.8 Hz), 6.90–7.08 (m, 4 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 15.9, 16.0, 16.2, 20.0, 54.3, 55.4, 55.5, 57.3, 62.7, 62.8, 110.7, 110.8, 110.9, 113.7, 119.9, 120.0, 127.1, 128.1, 129.3, 143.7, 144.0, 148.4, 148.5, 148.8.

IR (KBr): 3323, 2971, 1560, 1515, 1237, 1028, 963, 756 cm^{-1}.

EIMS: *m*/*z* = 393 (M^+), 256, 210, 151, 118, 91, 65, 41.

Anal. Calcd for $C_{20}H_{28}NO_5P$ (393.4): C, 61.06; H, 7.17; N, 3.56; P, 7.87. Found: C, 61.10; H, 7.12; N, 3.51; P, 7.90.

3f
Solid; mp 102–104 °C.

^{1}H NMR ($CDCl_3$): δ = 1.20 (t, 3 H, *J* = 7.0 Hz), 1.25 (t, 3 H, *J* = 7.0 Hz), 2.25 (s, 3 H), 3.65–3.75 (m, 1 H), 3.85–4.18), (m, 3 H), 4.45 (br s, 1 H, NH), 4.60 (d, 1 H, *J* = 24.0 Hz), 5.85 (s, 2 H), 6.30 (d, 1 H, *J* = 8.0 Hz), 6.57 (t, 1 H, *J* = 8.0 Hz), 6.70 (d, 1 H, *J* = 8.0 Hz), 6.80–7.0 (m, 4 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.0, 16.2, 16.3, 17.3, 54.3, 57.3, 63.0, 63.1, 100.9, 107.9, 108.0, 108.1, 108.2, 111.2, 118.0, 121.0, 121.1, 122.8, 126.8, 129.8, 130.0, 144.0, 144.3, 147.2, 147.8.

IR (KBr): 3331, 2982, 1603,1507, 1444, 1261,1023, 964, 750 cm^{-1}.

EIMS: *m*/*z* = 377 (M^+), 240, 118, 65, 51.

Anal. Calcd for $C_{19}H_{24}NO_5P$ (377.4): C, 60.47; H, 6.41; N, 3.71; P, 8.21. Found: C, 60.50; H, 6.38; N, 3.69; P, 8.24.

3g
Oil.

^{1}H NMR ($CDCl_3$): δ = 1.10 (t, 3 H, *J* = 7.0 Hz), 1.30 (t, 3 H, *J* = 7.0 Hz), 1.80 (br s, 1 H, NH), 3.60 (m, 1 H), 3.90 (m, 1 H), 4.15 (m, 2 H), 4.75 (d, 1 H, *J* = 23.5 Hz), 6.55–6.70 (m, 3 H), 7.0–7.15 (m, 2 H), 7.38–7.50 (m, 2 H) 7.60 (d, 1 H, *J* = 7.8 Hz), 7.75–7.90 (m, 4 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 15.6, 15.7, 16.3, 16.4, 50.0, 53.0, 63.2, 113.5, 118.2, 122.9, 125.3, 125.4, 125.5, 126.1, 128.3, 128.4, 128.9, 129.1, 131.4, 131.7, 133.8, 145.9, 146.2.

IR (KBr): 3382, 2980, 1720, 1470, 1320, 1240, 1100, 870, 820, 760 cm^{-1}.

FAB Mass: *m*/*z*: 369 (M^+), 322, 244, 182, 167, 152, 141, 136, 115.

Anal. Calcd for $C_{21}H_{24}NO_3P$ (369.4): C, 68.28; H, 6.55; N, 3.79; P, 8.38. Found: C, 68.24; H, 6.57; N, 3.80; P, 8.42.

3h
Oil.

^{1}H NMR ($CDCl_3$): δ = 1.15 (t, 3 H, *J* = 6.9 Hz), 1.25 (t, 3 H, *J* = 6.9 Hz), 3.65 (s, 3 H), 3.60–4.18 (m, 4 H), 4.65 (d, 1 H, *J* = 24.0 Hz), 6.50 (d, 2 H, *J* = 8.0 Hz), 6.65 (d, 2 H, *J* = 8.0 Hz), 7.20–7.38 (m, 3 H), 7.40–7.50 (m, 2 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 15.6, 15.7, 15.9, 16.0, 20.4, 54.9, 58.0, 62.3, 62.8, 62.9, 113.4, 114.3, 114.8, 121.9, 127.1, 127.3, 127.4, 127.5, 127.6, 127.7, 128.0, 129.5, 132.2, 135.6, 139.8, 140.1,152.

IR (KBr): 3378, 3080, 2896, 1786, 1506, 1246, 1096, 794, 732 cm^{-1}.

EIMS: *m*/*z* = 349 (M^+), 292, 212, 168, 134, 81, 45.

Anal. Calcd for $C_{18}H_{24}NO_4P$ (349.364): C, 61.88; H, 6.92; N, 4.01; P, 8.87. Found: C, 61.90; H, 6.95; N, 4.08; P, 8.90.

3i
Liquid.

^{1}H NMR ($CDCl_3$): δ = 1.19 (t, 3 H, *J* = 7.0 Hz), 1.28 (t, 3 H, *J* = 7.0 Hz), 2.25 (s, 3 H), 2.30 (s, 3 H), 3.60–3.80 (m, 1 H), 4.05–4.18 (m, 2 H), 4.60 (br s, 1 H, NH), 4.70 (d, 1 H, *J* = 23.8 Hz), 6.38 (d, 1 H, *J* = 8.0 Hz), 6.60 (t, 1 H, *J* = 8.0 Hz), (t, 1 H, *J* = 8.0 Hz), 7.0 (t, 1 H, *J* = 8.0 Hz), 7.10 (d, 2 H, *J* = 8.0 Hz), 7.38 (d, 2 H, *J* = 8.0 Hz).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 15.9, 16.0, 16.1, 16.2, 17.2, 20.8, 54.1, 57.1, 62.9, 63.0, 111.1, 117.7, 122.6, 126.6,127.3, 127.4, 129.0, 129.1, 129.8, 132.5, 132.6, 137.2, 137.3, 144.0, 144.3.

IR (KBr): 3397, 3008, 1680, 1540, 1260, 1080, 971.2, 762, 560 cm^{-1}.

EIMS: *m*/*z* = 347 (M^+), 210, 118, 91, 65, 51.

Anal. Calcd for $C_{19}H_{26}NO_3P$ (347.4): C, 65.69; H, 7.54; N, 4.03; P, 8.92. Found: C, 65.72; H, 7.58; N, 4.14; P, 8.93.

3j
Oil.

^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3 H, *J* = 7.0 Hz), 1.30 (t, 3 H, *J* = 7.0 Hz), 3.68 (s, 3 H), 3.95–4.18 (m, 4 H), 4.80 (d, 1 H, *J* = 23.8 Hz), 6.60–6.70 (m, 5 H), 6.80–6.95 (m, 2 H), 7.10–7.20 (m, 2 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.3, 16.4, 55.4, 55.6, 63.3, 114.1, 118.2, 120.3, 125.1, 127.7, 129.0, 132.6, 146.5, 159.3.

IR (KBr): 3360, 2894, 1680, 1548, 1342, 1080, 969, 732 cm^{-1}.

EIMS: *m*/*z* = 349 (M^+), 228, 214, 91, 65, 46.

Anal. Calcd for $C_{18}H_{24}NO_4P$ (349.4): C, 61.88; H, 6.92; N, 4.01; P, 8.87. Found: C, 61.95; H, 7.03; N, 4.08; P, 8.85.

3k
Solid; mp 62–64 °C.

^{1}H NMR ($CDCl_3$): δ = 1.50 (t, 3 H, *J* = 6.8 Hz), 2.18 (t, 3 H, *J* = 6.8 Hz), 2.35 (s, 3 H), 3.60–3.75 (m, 1 H), 3.85–4.18 (m, 3 H), 4.60 (br s, 1 H, NH), 4.78 (d, 1 H, *J* = 24.7 Hz), 6.58 (d, 2 H, *J* = 8.0 Hz), 6.68 (t, 1 H, *J* = 8.0 Hz), 7.05–7.18 (m, 4 H), 7.27 (d, 2 H, *J* = 8.0 Hz).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.3, 16.5, 21.2, 55.8, 63.3, 113.9, 118.4, 127.7, 129.4, 132.7, 137.7, 146.3, 146.5.

IR (KBr): 3324, 2984, 1604, 1502, 1234, 1020, 971, 748 cm^{-1}.

EIMS: *m*/*z* = 333 (M^+), 197,142,105,78.

Anal. Calcd for $C_{18}H_{24}NO_3P$ (333.4): C, 64.85; H, 7.26; N, 4.20; P, 9.29. Found: C, 64.81; H, 7.30; N, 4.24; P, 9.30.

3l
Liquid.

^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3 H, *J* = 7.0 Hz), 1.29 (t, 3 H, *J* = 7.0 Hz), 2.20 (s, 3 H), 3.78 (s, 3 H), 3.80–4.18 (m, 4 H), 4.70 (dd, 1 H, *J* = 24, 7.1 Hz), 5.20 (dd, 1 H, *J* = 7.1, 2.0 Hz), 6.28 (d, 1 H, *J* = 7.8 Hz), 6.70–6.90 (m, 3 H), 7.25–7.40 (m, 3 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.3, 16.5, 20.9, 55.7, 62.3, 62.5, 63.2, 113.5, 113.8, 115.0, 118.5, 119.0, 129.2, 131.0, 131.5, 131.7, 134.8, 147.3, 147.8, 160.7.

IR (KBr): 3386, 3050, 2980, 1600, 1560, 1272, 1080, 800, 589 cm^{-1}.

EIMS: *m*/*z* = 441 (M^+), 304, 302, 224, 196, 180, 168, 141, 121, 83, 77, 65, 47.

Anal. Calcd for $C_{19}H_{25}BrNO_4P$ (442.3): C, 51.60; H, 5.70; Br, 18.07; N, 3.17; P, 7.0. Found: C, 51.64; H, 5.72; Br, 18.12; N, 3.20; P, 6.97.

3m
Oil.

^{1}H NMR ($CDCl_3$): δ = 0.90 (t, 3 H, *J* = 6.8 Hz), 1.15 (t, 3 H, *J* = 7.0 Hz), 1.20–1.55 (m, 11 H), 2.40–2.55 (m, 2 H), 3.50 (br s, 1 H, NH), 3.75–4.15 (m, 5 H), 7.30–7.45 (m, 5 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 11.4, 16.2, 16.7, 29.7, 32.37, 48.4, 48.7, 60.9, 61.2, 62.0, 63.1,128.5, 129.0, 129.5, 129.5, 132.7, 135.7.

IR (KBr): 3368, 3270, 2848, 1768, 1460, 1338, 1242, 1050, 732.4 cm^{-1}.

EIMS: *m*/*z* = 327 (M^+), 190, 105, 77, 65, 51.

Anal. Calcd for $C_{17}H_{30}NO_3P$ (327.4): C, 62.37; H, 9.24; N, 4.28; P, 9.46. Found: C, 62.40; H, 9.20; N, 4.31; P, 9. 47.

3n
Liquid.

^{1}H NMR ($CDCl_3$): δ = 1.12 (t, 3 H, *J* = 7.0 Hz), 1.28 (t, 3 H, *J* = 7.0 Hz), 1.30–1.85 (m, 1 H), 8.63 (dd, 1 H, *J* = 19.0, 2.0 Hz), 3.95–4.15 (m, 4 H), 6.65–7.15 (m, 5 H). ^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.4, 22.0, 27.0, 28.3, 29.7, 31.0, 39.9, 56.1, 62.6, 113.2, 117.8, 129.3, 129.7, 147.8.

IR (KBr): 3324, 2980, 2750, 1760, 1618, 1490, 1228, 960, 830, 780, 550 cm^{-1}.

EIMS: *m*/*z* = 325 (M^+), 188, 97, 77, 65, 43.

Anal. Calcd for $C_{17}H_{28}NO_3P$ (325.4): C, 62.75; H, 8.67; N, 4.30; P, 9.52.Found: C, 62.71; H, 8.71; N, 4.29; P, 9.55.

3o
Oil.

^{1}H NMR ($CDCl_3$): δ = 1.23–1.38 (m, 6 H), 2.25 (s, 3 H), 3.18 (br s, 1 H, NH), 4.15–4.22 (m, 4 H), 4.45 (dd, 1 H, *J* = 2.15, 2.1 Hz), 6.18–6.35 (m, 1 H), 6.58–6.65 (m, 3 H), 6.85–6.95 (m, 2 H), 7.20–7.38 (m, 4 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.3, 20.1, 52.7, 55.7, 62.7, 62.8, 63.2, 113.8, 123.5, 126.3, 127.5, 128.3, 129.5, 132.6, 132.9, 136.1, 143.9.

IR (KBr): 3306, 2984, 2922, 1615, 1591, 1238, 1026, 967, 808, 702 cm^{-1}.

EIMS: *m*/*z* = 360 (M^+), 222, 196, 97, 91, 83, 69, 55, 43.

Anal. Calcd for $C_{20}H_{26}NO_3P$ (359.4): C, 66.84; H, 7.29; N, 3.90; P, 8.62. Found: C, 66.81; H, 7.33; N, 3.93; P, 8.60.

3p
Oil.

^{1}H NMR ($CDCl_3$): δ = 0.95 (t, 3 H, *J* = 6.8 Hz), 1.15 (t, 3 H, *J* = 7.0 Hz), 1.17–1.60 (m, 20 H), 3.85–4.40 (m, 7 H), 7.35–7.48 (m, 5 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 14.1, 16.7, 22.7, 29.0, 29.3, 29.7, 30.5, 31.8, 32.3, 38.2, 53.7, 61.8, 127.1, 127.7, 128.7, 129.8, 144.4.

IR (KBr): 3352, 3280, 2850, 1786, 1460, 1320, 1224, 1050, 720 cm^{-1}.

EIMS: *m*/*z* = 383 (M^+), 246, 139, 107, 91, 77, 51, 43.

Anal. Calcd for $C_{21}H_{38}NO_3P$ (383.5): C, 65.77; H, 9.99; N, 3.65; P, 8.05. Found: C, 65.81; H, 9.97; N, 3.68; P, 8.07.

3q
Solid; mp 76–78 °C.

^{1}H NMR ($CDCl_3$): δ = 1.15 (m, 3 H *J* = 7.0 Hz), 1.28 (m, 3 H, *J* = 6.8 Hz), 2.25 (br s, 1 H, NH), 3.50 (d, 1 H, *J* = 11.8 Hz), 370–4.15 (m, 6 H), 7.20–7.45 (m, 6 H), 7.20–7.45 (m, 10 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.1, 16.2, 16,3, 16.4, 19.8, 55.5, 57.0, 63.1, 63.3, 63.4, 110.3, 112.5, 127.5, 127.6, 127.8, 127.9, 128.4, 128.5, 128.7, 132.7, 135.3, 135.4, 140.8, 141.0.

IR (KBr): 3376, 3112, 2904, 1640, 1536, 1296, 1082, 962, 796, 562 cm^{-1}.

EIMS: *m*/*z* = 411 (M^+), 276, 274, 196, 155, 137, 109, 91, 77, 51, 43.

Anal. Calcd for $C_{18}H_{23}NO_3P$ (412.3): C, 52.44; H, 5.62; Br, 19.38; N, 3.40; P, 7.51. Found: C, 52.43; H, 5.65; Br, 19.37; N, 3.43; P, 7.54.

3r
Solid; mp 64–66 °C.

^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3 H, *J* = 6.9 Hz), 1.28 (t, 3 H, *J* = 6.9 Hz), 2.28 (s, 3 H), 3.60–3.75 (m, 1 H), 3.78 (s, 3 H), 3.85–4.18 (m, 3 H), 4.55 (br s, 1 H, NH), 4.70 (d, 1 H, *J* = 23.7 Hz), 6.38 (d, 1 H, *J* = 7.8 Hz), 6.60 (t, 1 H, *J* = 7.8 Hz), 6.80–7.05 (m, 4 H), 7.38 (d, 2 H, *J* = 7.8 Hz).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 15.7, 15.9, 16.0, 16.1, 17.0, 53.5, 54.6, 56.6, 62.6, 62.7, 111.0, 113.6, 113.7, 117.6, 122.4, 126.5, 127.3, 128.3, 128.4, 129.7, 143.8, 144.1, 158.9.

IR(KBr): 3386, 3012, 2860, 1680, 1560, 1280, 1068, 973, 783, 572 cm^{-1}.

EIMS: *m*/*z* = 363 (M^+), 226, 182, 91, 65, 43.

Anal. Calcd for $C_{19}H_{26}NO_4P$ (363.4): C, 62.80; H, 7.21; N, 3.85; P, 8.52. Found: C, 62.83; H, 7.19; N, 3.87; P, 8.50.

3s
Solid; mp 78–80 °C.

^{1}H NMR ($CDCl_3$): δ = 1.80 (t, 3 H, 7.0 Hz), 1.29 (t, 3 H, *J* = 7.0 Hz), 2.18 (s, 3 H), 2.37 (s, 3 H), 3.70–3.85 (m, 1 H), 3.90–4.18 (m, 3 H), 4.70 (dd, 1 H, *J* = 24, 7.1 Hz), 5.20 (dd, 1 H, 7.1, 2.0 Hz), 6.30 (d, 1 H, *J* = 7.8 Hz), 6.80 (d, 1 H, *J* = 7.8 Hz), 7.10 (d, 2 H, *J* = 7.8 Hz), 7.20–7.38 (m, 3 H).

^{13}C NMR ($CDCl_3$, proton decoupled): δ = 16.3, 16.5, 20.8, 21.3, 59.3, 62.5, 62.8, 63.0, 114.0, 118.5 129.4, 129.7, 130.0, 130.4, 135.0, 136.4, 146.3, 147.9.

IR (KBr): 3397, 1515, 1254, 1022, 973 cm^{-1}.

EIMS: *m*/*z* = 425 (M^+), 289, 273, 193, 154, 140, 91, 43.

Anal. Calcd for $C_{19}H_{25}NO_3P$ (426.3): C, 53.53; H, 5.91; Br, 18.74; N, 3.29; P, 7.27. Found: C, 53.50; H, 5.93; N, 3.27; P, 7.30.

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