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Synthesis of α-Aminophosphinates by the Hydrophosphinylation of Imines

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ABSTRACT: *Numerous substituted α-aminophosphinates were synthesized by addition of alkyl and phenyl H-phosphinates to aromatic imines and characterized. Modest diastereoselectivity was observed in the reaction. The size of the substituents exerts a small effect on the diastereoselectivity of P—C bond formation.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:235–240, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10133

INTRODUCTION

In the past decades numerous synthetic methods have been developed for the synthesis of α-aminophosphonic acids to study their biological activity [1–3]. Because of their structural analogy with α-amino carboxylic acids, they are considered to be transition state analogues. Some of them are known as herbicide (e.g. glyphosate), while others as enzyme inhibitor or neuroactive agent (e.g. NMDA receptor agonists) [4].

However, the α-aminophosphinic acids seem to be closer analogues of α-amino carboxylic acids because of the higher stability of P—C bond. Nevertheless, less publications are available on these compounds as there is no convenient and simple method for the synthesis of their phosphorus containing precursors [5–9].

The most obvious way for their synthesis is the Kabachnik–Field type reaction involving the addition of H-phosphinates to a C=N double bond. The addition results in the products as the mixture of diastereomers because of the attack of the chiral H-phosphinate on the prochiral C-centre of C=N bond (Scheme 1).

So far only a few attempts have been made for the separation and determination of the pure diastereomers and enantiomers. Belov et al. [10] isolated a single enantiomer of ethyl α-benzylaminophenylphosphinic acid by repeated recrystallization from a diastereomeric mixture followed by resolution and determined the absolute configuration by X-ray crystallography. A short report was also published on the diastereoselectivity of the addition of ethyl phenyl-*H*-phosphinate on several imines prepared from isobutyraldehyde and different type of benzyl and α-substituted benzylamines [11].

RESULTS AND DISCUSSION

We decided to study the reactions of a series of ethyl alkyl-*H*-phosphinates **1** with imines **2** varying the size of the substituent on the C=N moiety to generate a high diastereoselectivity (Scheme 2).

The imines were prepared by the condensation of the appropriate benzaldehyde with amines. The

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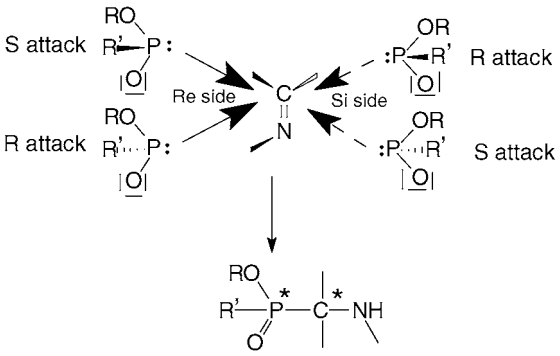


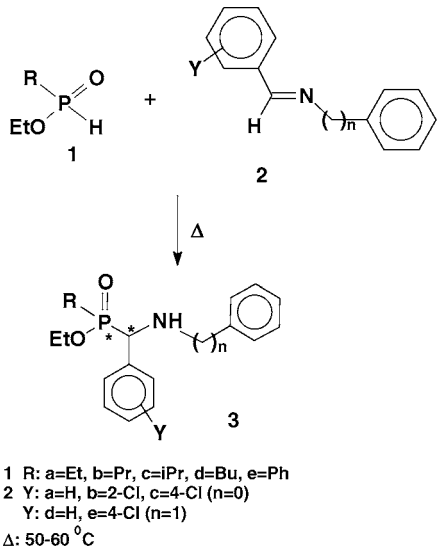
SCHEME 1

α-aminophosphinates **3** were synthesized by the reaction of the imine with the *H*-phosphinate at 50–70°C for 3 h. The conversion was almost quantitative according to TLC. In most cases, the aminophosphinate **3** was crystallized from the reaction mixture. The results are summarized in Table 1.

The ratio of diastereomers was established by means of ^{31}P NMR measurements of the reaction mixtures and confirmed after column chromatography. The ratio of the diastereomers can also be determined from the ^{1}H NMR spectra of ethyl ester groups which gave rise to two distinct triplets.

The results demonstrate in all cases a slight extent of diastereoselectivity, some tendencies can, however, be observed. Comparing the effect on the diastereoselectivity of substituted imines **2**, we found that the imines having ortho chloro-substituent on the α-benzene ring gave better selectivity than para- or unsubstituted ones, probably due to the steric effects during the addition. As it can be seen, the *N*-substituent of the imine (benzyl or phenyl) exerts only a small effect on the diastereoselectivity.

Finally, we report the results of diastereoselectivity observed in different solvents (Table 2). We chose the model reaction of ethyl propyl-*H*-phosphinate (**1b**) with imine **2c**, and examined the ratio of diastereomers formed after 3 and 30 h. It can be seen that both the conversion and diastereoselectivity is low in ethanol, the diastereoselectivity values are lower in acetonitrile and THF, than without solvent. Interestingly, the value of the ratio of diastereomers in toluene is inverted after 3 h compared to the experiment performed without solvent namely from 60/40 to 40/60. After 30 h reaction time the diastereomeric excess is destroyed in all experiments, possibly due to the kinetic control.



SCHEME 2

TABLE 1 α-Aminophosphinates Prepared and Ratio of Diastereomers

	n	*R*	*Y*	*Ratio*	δ ^{31}P
3a	0	Et	H	60/40	54.7, 53.8
3b	0	Et	4-Cl	56/44	56.1, 53.9
3c	0	Pr	H	51/49	55.4, 52.5
3d	0	Pr	4-Cl	58/42	52.9, 52.4
3e	0	Pr	2-Cl	64/36	52.3, 52.1
3f	0	*i*Pr	H	58/42	57.7, 52.3
3g	0	*i*Pr	4-Cl	46/54	55.8, 55.6
3h	0	Bu	H	52/48	53.8, 52.9
3i	0	Bu	4-Cl	54/46	53.2, 52.9
3j	0	Ph	H	55/45	40.9, 38.7
3k	0	Ph	2-Cl	40/60	40.3, 38.2
3l	1	Et	H	52/48	55.8, 55.2
3m	1	Et	4-Cl	52/48	55.2, 54.7
3n	1	Pr	4-Cl	53/47	54.0, 53.3
3o	1	*i*Pr	H	45/55	57.1, 56.7
3p	1	*i*Pr	4-Cl	43/57	56.3, 55.6
3q	1	Bu	H	49/51	54.9, 54.2
3r	1	Bu	4-Cl	53/47	53.4, 53.0

TABLE 2 Ratio of Diastereomers and Conversion (%) in Different Solvents after 3 h and 30 h Reaction Time for **3d**

	Reaction Time (h)			
	3		*30*	
	Ratio	*Conversion (%)*	*Ratio*	*Conversion (%)*
Toluene	40/60	60	51/49	60
Acetonitrile	53/47	54	51/49	84
THF	52/49	48	51/49	48
Ethanol	53/47	5	54/46	15
No solvent	58/42	48	–	–

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 250 instrument, while ^{31}P NMR spectra on a Bruker DRX-500 instrument, using TMS as the internal standard (^{1}H, ^{13}C) and 85% H_3PO_4 as external standard (^{31}P), in $CDCl_3$ solutions.

General Procedure for α-Aminophosphinate **3**

A mixture of the imine **2** (10 mmol) and ethyl alkylphosphinate **1** (30 mmol) was stirred at 50–70°C for 3 h. After cooling to room temperature the aminophosphinates **3a–h** were crystallised from the reaction mixture, then the product was recrystallised from hexane–ethyl acetate 8:2. Compounds **3i–r** were isolated by column chromatography (toluene–acetone 17:3) on silica gel. Products **3i–k** and **3n–p** were isolated as viscous oils whereas **3l, m, q**, and **r** as white solids.

*Ethyl (1-Phenylamino-phenylmethyl)-ethylphosphinate (**3a**).* mp 75°C. Yield: 47%. ^{1}H NMR δ: 1.01 (dt, $J_{HH} = 7.7$ Hz, $J_{PH} = 18$ Hz), 1.19, (dt, $J_{HH} = 7.7$ Hz, $J_{PH} = 18$ Hz) 3H, $PCH_2C\underline{H}_3$, 1.02 (t, $J_{HH} = 7.0$ Hz), 1.28 (t, $J_{HH} = 7.0$ Hz) 3H, $OCH_2C\underline{H}_3$, 1.54 Hz (dq, $J_{HH} = 7.7$ Hz, $J_{PH} = 13$ Hz), 1.88 (dq, $J_{HH} = 7.7$ Hz, $J_{PH} = 13$ Hz) 2H, $PC\underline{H}_2$, 3.26 (dq, $J_{HH} = 7.0$ Hz, $J_{PH} = 10.0$ Hz), 3.75 (dq, $J_{HH} = 7.0$ Hz, $J_{PH} = 10.0$ Hz), 3.97–4.21 (m), 2H, $OC\underline{H}_2$, 4.11 (d, $J_{PH} = 17.3$ Hz, 1H, $PC\underline{H}$), 4.57–4.71 (m, 1H, $N\underline{H}$), 6.58–6.71 (m, $Ar\underline{H}$, 3H), 7.07–7.45 (m, 7H, $Ar\underline{H}$). ^{13}C NMR δ: 5.57 (d, $J_{PC} = 34$ Hz), 5.67 (d, $J_{PC} = 34$ Hz), $\underline{C}H_3CH_2P$, 16.42 (d, $J_{PC} = 5$ Hz), 16.71 (d, $J_{PC} = 5$ Hz), $\underline{C}H_3CH_2O$, 19.16 (d, $J_{PC} = 94$ Hz), 20.68 (d, $J_{PC} = 94$ Hz), $CH_3\underline{C}H_2P$, 56.65 (d, $J_{PC} = 91$ Hz), 57.27 (d, $J_{PC} = 91$ Hz) $\underline{C}HP$. 61.53 (d, $J_{PC} = 7.0$ Hz), 61.87 (d, $J_{PC} = 7.0$ Hz), $CH_3\underline{C}H_2O$, 113.85, 113.97, 118.37, 127.54, 127.62, 127.90, 127.95, 128.01, 128.63, 128.81, 129.19, 136.13, 146.20, 146.36 Ar$\underline{C}$.

*Ethyl (1-Phenylamino-(4-chloro)-phenylmethyl)-ethylphosphinate (**3b**).* mp 78°C. Yield: 59%. ^{1}H NMR δ: 1.03 ppm (dt, $J_{HH} = 7.6$ Hz, $J_{PH} = 18$ Hz), 1.15 (dt, $J_{HH} = 7.6$ Hz, $J_{PH} = 18$ Hz) 3H, $PCH_2C\underline{H}_3$, 1.08 (t, $J_{HH} = 6.8$ Hz), 1.28 (t, $J_{HH} = 6.8$ Hz), 3H, $OCH_2C\underline{H}_3$, 1.60 (dq, $J_{HH} = 7.6$ Hz, $J_{PH} = 15$ Hz), 1.90 (dq, $J_{HH} = 7.6$ Hz, $J_{PH} = 15$ Hz) 2H, $PC\underline{H}_2$, 3.41 (dq, $J_{PH} = 10.0$ Hz), 3.82 (dq, $J_{HH} = 10.0$ Hz), 4.00–4.23 (m), 2H, $OC\underline{H}_2$, 4.10 (d, $J_{PH} = 17.0$ Hz, 1H, $PC\underline{H}$), 4.57–4.71 (m, $J_{HH} = 17.0$ Hz, 1H, $N\underline{H}$), 6.57–6.73 (m, 2H, $Ar\underline{H}$), 7.08–7.41 (m, 7H, $Ar\underline{H}$). ^{13}C NMR δ: 5.46 (d, $J_{PC} = 33.0$ Hz), 5.48 (d, $J_{PC} = 33.0$ Hz), $\underline{C}H_3CH_2P$, 16.33 (d, $J_{PC} = 5.3$ Hz), 16.56 (d, $J_{PC} = 5.3$ Hz), $\underline{C}H_3CH_2O$, 19.43 (d, $J_{PC} = 96$ Hz), 20.37 (d, $J_{PC} = 94$ Hz), $CH_3\underline{C}H_2P$, 55.90 (d, $J_{PC} = 95.2$ Hz), 56.51 (d, $J_{PC} = 95.1$ Hz), $\underline{C}HP$, 61.62 (d, $J_{PC} = 7.1$ Hz), 61.83 (d, $J_{PC} = 7.1$ Hz), $CH_3\underline{C}H_2O$, 113.70, 113.81, 118.45, 118.52, 128.62, 128.74, 128.85, 129.10, 129.18, 129.25, 133.57, 134.08, 134.51, 145.74 Ar$\underline{C}$.

*Ethyl (1-Phenylamino-phenylmethyl)-propylphosphinate (**3c**).* mp 70°C. Yield: 40%. ^{1}H NMR δ: 1.01 (t, $J_{HH} = 7.1$ Hz) $C\underline{H}_3CH_2CH_2$ major, 1.28 (t, $J_{HH} = 7.1$ Hz) 3H, $C\underline{H}_3CH_2CH_2$ minor, 1.50–1.80 (m, 3H, $C\underline{H}_3CH_2O$), 1.68–1.80 (m, 2H, $C\underline{H}_2CH_2P$), 1.80–1.95 (m, $J_{PH} = 13.0$ Hz, 2H, $PC\underline{H}_2CH_2$), 3.26 (dq, $J_{HH} = 7.2$ Hz, $J_{PH} = 10.1$ Hz), 3.74 (dq, $J_{HH} = 7.2$ Hz, $J_{PH} = 10.1$ Hz), 2H, $OC\underline{H}_2$, 4.58 (dd, $J_{HH} = 7.5$ Hz, $J_{PH} = 15.6$ Hz, 1H, $PC\underline{H}$), 4.95 (b, 1H, $N\underline{H}$), 6.58–6.72 (m, 3H, $Ar\underline{H}$), 7.09–7.52 (m, 7H, $Ar\underline{H}$). ^{13}C NMR δ: 15.63 (d, $J_{PC} = 5.1$ Hz, $\underline{C}H_3CH_2O$), 15.82 (d, $J_{PC} = 13.4$ Hz, $\underline{C}H_3CH_2CH_2$), 16.58 (d, $J_{PC} = 5.2$ Hz, $CH_3\underline{C}H_2CH_2$), 29.91 (d, $J_{PC} = 92.0$ Hz, $CH_2\underline{C}H_2P$), 57.38 (d, $J_{PC} = 94.2$ Hz, $\underline{C}HP$), 61.7 (d, $J_{PC} = 6.9$ Hz, $CH_2\underline{C}H_2O$), 114.04, 118.54, 128.05, 128.11, 128.18, 128.77, 128.80, 129.37, 138.25, 138.30, 145.58, 146.01, Ar$\underline{C}$.

*Ethyl (1-Benzylamino-(4-chloro)-phenylmethyl)-propylphosphinate (**3d**).* mp 85°C. Yield: 48%. ^{1}H NMR δ: 1.04 (t, $J_{HH} = 7.0$ Hz, 3H, $C\underline{H}_3CH_2O$), 1.25–1.37 (m, $J_{HH} = 7.0$ Hz, 3H, $C\underline{H}_3CH_2CH_2$), 1.36–1.69 (m, 2H, $C\underline{H}_2CH_2P$), 1.69–1.92 (m, $J_{PH} = 12.2$ Hz, 2H, $PC\underline{H}_2CH_2$), 3.37 (dq, $J_{HH} = 7.0$ Hz, $J_{PH} = 10.0$ Hz), 3.81 (dq, $J_{HH} = 7.0$ Hz, $J_{PH} = 10.0$ Hz), 4.02–4.13 (m, $J_{HH} = 7.0$ Hz) 2H, $OC\underline{H}_2$, 4.09 (d, $J_{PH} = 18.3$ Hz, 1H, $PC\underline{H}$), 4.54–4.68 (m, 1H, $N\underline{H}$), 6.56–6.74 (m, 2H, $Ar\underline{H}$), 7.26–7.40 (m, 7H, $Ar\underline{H}$). ^{13}C NMR δ: 15.38 (d, $J_{PC} = 5.4$ Hz, $\underline{C}H_3CH_2O$), 15.44 (d, $J_{PC} = 13.4$ Hz, $\underline{C}H_3CH_2CH_2$), 16.42 (d, $J_{PC} = 5.0$ Hz, $CH_3\underline{C}H_2CH_2$), 29.48 (d, $J_{PC} = 92$ Hz, $CH_2\underline{C}H_2P$), 56.54 (d, $J_{PC} = 94.5$ Hz, $\underline{C}HP$), 61.7 (d, $J_{PC} = 6.9$ Hz, $CH_2\underline{C}H_2O$), 113.80, 113.91, 118.57, 128.76, 128.94, 129.20, 129.31, 133.67, 134.19, 146.00, Ar$\underline{C}$.

*Ethyl (1-Benzylamino-(2-chloro)-phenylmethyl)-propylphosphinate (**3e**).* mp 125°C. Yield: 18%. ^{1}H NMR δ: 0.88 (t, $J_{HH} = 6.9$ Hz), 1.30 (t, $J_{HH} = 6.9$ Hz) 3H, $C\underline{H}_3CH_2O$, 0.99 (dt, $J_{HH} = 7.3$ Hz, $J_{PH} = 17.9$ Hz, 3H, $C\underline{H}_3CH_2CH_2$), 1.40–1.70 (m, 2H, $J_{PH} = 12.2$ Hz, $C\underline{H}_2CH_2P$), 1.88–1.97 (m, $J_{PH} = 14.2$ Hz, 2H, $PC\underline{H}_2CH_2$), 3.15 (dq, $J_{HH} = 6.9$ Hz), 3.67 (dq, $J_{HH} = 6.9$ Hz), 4.10–4.27 (m, $J_{HH} = 6.9$ Hz) 2H, $OC\underline{H}_2$, 4.17 (dd, $J_{HH} = 7.3$ Hz, $J_{PH} = 17.4$ Hz, 1H, $PC\underline{H}$), 5.22–5.29 (m, 1H, $N\underline{H}$), 6.56–6.70 (m, 2H, $Ar\underline{H}$), 7.07–7.55 (m, 7H, $Ar\underline{H}$).

*Ethyl (1-Phenylamino-phenylmethyl)-isopropylphosphinate (**3f**).* mp 85°C. Yield: 75%. ^{1}H NMR δ: 0.95 (t, $J_{HH} = 7.0$ Hz), 1.24 (t, $J_{HH} = 7.0$ Hz)

3H, C$\underline{H}_3$CH$_2$O, 1.08 (dd, J_{HH} = 7.0 Hz, J_{PH} = 17.2), 1.09 (dd, J_{HH} = 7.0 Hz, J_{PH} = 17.2 Hz), 1.23 (J_{HH} = 7.0 Hz, J_{PH} = 16.9 Hz), 1.24 (dd, J_{HH} = 7.0 Hz, J_{PH} = 16.9 Hz), 6H, C$\underline{H}_3$CH, 1.70–1.89 (m, J_{PH} = 13.0 Hz) 2.08–2.28 (m, J_{PH} = 13.0 Hz) 1H, CH$_3$C$\underline{H}$, 3.13 (dq, J_{HH} = 7.5 Hz, J_{PH} = 10.0 Hz) 3.68 (dq, J_{HH} = 7.5 Hz, J_{PH} = 10 Hz) 3.92–4.14 (m, J_{HH} = 7.5 Hz) 2H, OC$\underline{H}_2$, 4.05 (dd, J_{HH} = 7.3 Hz, J_{PH} = 17.6 Hz, 1H, PC$\underline{H}$), 4.67–4.79 (m, 1H, N$\underline{H}$), 6.57–6.63 (m, 3H, Ar$\underline{H}$), 7.06–7.12 (m, 2H, Ar$\underline{H}$), 7.25–7.47 (m, 5H, Ar$\underline{H}$). ^{13}C NMR δ: 15.11 (d, J_{PC} = 4.7 Hz), 15.34 (d, J_{PC} = 4.7 Hz), $\underline{C}$H$_3$CH$_2$O, 16.53 (d, J_{PC} = 22.6 Hz), 16.61 (d, J_{PC} = 22.6 Hz) $\underline{C}$H$_3$CH, 25.42 (d, J_{PC} = 107.0 Hz), 26.91 (d, J_{PC} = 107 Hz), CH$_3\underline{C}$HP, 54.58 (d, J_{PC} = 93.0 Hz), 55.73 (J_{PC} = 93.0 Hz), $\underline{C}$HP, 61.63 (d, J_{PC} = 7.3 Hz), 62.13 (d, J_{PC} = 7.3 Hz), O$\underline{C}$H$_2$, 113.54, 113.75, 117.98, 118.20, 127.59, 127.93, 128.32, 128.50, 128.98, 135.73, 145.80, 145.95, Ar$\underline{C}$.

*Ethyl (1-Benzylamino-(4-chloro)-phenylmethyl)-isopropylphosphinate (***3g***).* mp 120°C. Yield: 56%. ^{1}H NMR δ: 1.01 (t, J_{HH} = 6.9 Hz), 1.25 (t, J_{HH} = 6.9 Hz) 3H, C$\underline{H}_3$CH$_2$O, 1.11 (dd, J_{HH} = 7.0 Hz, J_{PH} = 16.9 Hz), 1.13 (dd, J_{HH} = 7.0 Hz, J_{PH} = 16.9 Hz), 1.23 (dd, J_{HH} = 7.0 Hz, J_{PH} = 17.0 Hz), 1.25 (dd, J_{HH} = 7.0 Hz, J_{PH} = 17.0 Hz) 6H, C$\underline{H}_3$CH, 1.87 (heptett,d, J_{HH} = 7.1 Hz, J_{PH} = 12.0 Hz), 2.18 (heptett,d, J_{HH} = 7.1 Hz, J_{PH} = 12.0 Hz) 1H, CH$_3$C$\underline{H}$, 3.24 (dq, J_{HH} = 7.1 Hz, J_{PH} = 10 Hz), 3.76 (dq, J_{HH} = 7.1 Hz, J_{PH} = 10.0 Hz), 3.90–4.20 (m, J_{HH} = 7.3 Hz), 2H, OC$\underline{H}_2$, 4.03 (dd, J_{HH} = 7.3 Hz, J_{PH} = 17.0 Hz 1H, PC$\underline{H}$), 4.66–4.78 (m, 1H, N$\underline{H}$), 6.55–6.72 (m, 2H, Ar$\underline{H}$), 7.07–7.15 (m, 2H, Ar$\underline{H}$), 7.26–7.42 (m, 5H, Ar$\underline{H}$). IR (KBr): 3273, 1205, 1029, 961 cm^{-1}.

*Ethyl (1-Phenylamino-phenylmethyl)-butylphosphinate (***3h***).* mp 68°C. Yield: 94%. ^{1}H NMR δ: 0.81 (t, J_{HH} = 7.2 Hz), 0.9 (t, J_{HH} = 7.2 Hz) 3H, C$\underline{H}_3$CH$_2$, 1.01 (t, J_{HH} = 7.0 Hz), 1.28 (t, J_{HH} = 7.0 Hz) 3H, C$\underline{H}_3$CH$_2$O, 1.34–1.47 (m, J_{HH} = 7.3 Hz, 2H, CH$_3$C$\underline{H}_2$), 1.47–1.64 (m, J_{HH} = 7.0 Hz, 2H, CH$_2$C$\underline{H}_2$), 1.75–1.98 (m, J_{PH} = 13.1 Hz, 2H, C$\underline{H}_2$P), 3.24 (dq, J_{HH} = 7.1 Hz, J_{PH} = 10.0 Hz), 3.75 (dq, J_{HH} = 7.1 Hz, J_{PH} = 10.0 Hz), 3.95–4.21 (m, J_{HH} = 7.1 Hz) 2H, OC$\underline{H}_2$, 4.1 (d, J_{PH} = 18.0 Hz, 1H, PC$\underline{H}$), 4.54–4.72 (m, 1H, N$\underline{H}$), 6.58–6.71 (m, 3H, Ar$\underline{H}$), 7.07–7.44 (m, 7H, Ar$\underline{H}$). ^{13}C NMR: δ: 13.56 (d, J_{PC} = 7.0 Hz, $\underline{C}$H$_3$CH$_2$CH$_2$), 16.42 (d, J_{PC} = 5.4 Hz), 16.62 (J_{PC} = 5.4 Hz), $\underline{C}$H$_3$CH$_2$O, 23.23 (d, J_{PC} = 4.7 Hz), 23.97 (d, J_{PC} = 4.7 Hz) CH$_3$CH$_2\underline{C}$H$_2$, 23.72 (CH$_3\underline{C}$H$_2$CH$_2$), 26.16 (d, J_{PC} = 94.9 Hz), 27.33 (d, J_{PC} = 94.8 Hz) CH$_2\underline{C}$H$_2$P, 57.37 (d, J_{PC} = 94.5 Hz), 57.58 (d, J_{PC} = 94.5 Hz) $\underline{C}$HP, 61.50 (d, J_{PC} = 7.1 Hz), 61.83 (d, J_{PC} = 7.1 Hz) CH$_2\underline{C}$H$_2$O, 113.80, 114.0, 118.31, 127.56, 127.63, 127.87, 128.06, 128.58, 128.78, 129.17, 135.73, 135.79, 136.18, 146.26, 146.46, Ar$\underline{C}$.

*Ethyl (1-Phenylamino-phenylmethyl)-butylphosphinate (***3i***).* oil. Yield: 82%. ^{1}H NMR δ: 0.75 (t, J_{HH} = 7.2 Hz), 0.81 (t, J_{HH} = 7.2 Hz) 3H, C$\underline{H}_3$CH$_2$, 0.96 (t, J_{HH} = 7.0 Hz), 1.18 (t, J_{HH} = 7.0 Hz) 3H, C$\underline{H}_3$CH$_2$O, 1.20–1.39 (m, J_{HH} = 7.2 Hz, 2H, CH$_3$C$\underline{H}_2$), 1.39–1.69 (m, J_{HH} = 7.0 Hz, 2H, CH$_3$CH$_2$C$\underline{H}_2$), 1.63–1.93 (m, J_{PH} = 13.0 Hz, 2H, C$\underline{H}_2$P), 3.23–3.38 (m, J_{HH} = 7.0 Hz), 3.60–3.81 (m, J_{HH} = 7.0 Hz), 3.87–4.15 (m, J_{HH} = 7.0 Hz), 2H, OC$\underline{H}_2$, 4.00 (d, J_{PH} = 17.6 Hz, 1H, PC$\underline{H}$), 4.48–4.62 (m, 1H, N$\underline{H}$), 6.49–6.63 (m, 3H, Ar$\underline{H}$), 6.98–7.04 (m, 2H, Ar$\underline{H}$), 7.19–8.04 (m, 4H, Ar$\underline{H}$).

*Ethyl (1-Phenylamino-phenylmethyl)-phenylphosphinate (***3j***).* mp <25°C. Yield: 57%. ^{1}H NMR δ: 1.13 (t, J_{HH} = 7.0 Hz), 1.34 (t, J_{HH} = 7.0 Hz) 3H, OCH$_2$C$\underline{H}_3$, 3.74 (dq, J_{HH} = 7.0 Hz, J_{PH} = 14.0 Hz), 3.87 (dq, J_{HH} = 7.0 Hz, J_{PH} = 14.0 Hz), 4.04–4.25 (m, J_{HH} = 7.0 Hz), 2H, OC$\underline{H}_2$, 4.11 (d, J_{PH} = 19.1 Hz), 4.14 (d, J_{PH} = 19.1 Hz), 1H, PC$\underline{H}$, 4.83 (b, 1H, N$\underline{H}$), 6.50–6.70 (m, 2H), 7.00–7.14 (m, 4H), 7.25–8.54 (m, 8H), 7.75–7.82 (m, 1H) Ar$\underline{H}$. ^{13}C NMR δ: 16.35 (d, J_{PC} = 5.9 Hz), 16.60 (d, J_{PC} = 5.9 Hz) $\underline{C}$H$_3$CH$_2$O, 58.45 (d, J_{PC} = 105.0 Hz), 59.0 (d, J_{PC} = 105.0 Hz) $\underline{C}$HP, 61.9 (d, J_{PC} = 6.8), 62.15 (d, J_{PC} = 6.8) CH$_2\underline{C}$H$_2$O, 113.9, 118.3, 127.3, 127.6, 127.8, 128.2, 128.2, 128.3, 128.4, 128.5, 128.6, 129.1, 131.9, 132.2, 132.5, 132.6, Ar$\underline{C}$, 134.1 (d, J_{PC} = 190.0 Hz, P$\underline{C}_{Ar}$), 146.4 (d, J_{PC} = 16.7 Hz), 146.6 (d, J_{PC} = 13 Hz) NH$\underline{C}_{Ar}$. IR (neat): 3403, 1211, 1038, 956 cm^{-1}.

*Ethyl (1-Phenylamino-(2-chloro)-phenylmethyl)-phenylphosphinate (***3k***).* mp <25°C. Yield: 64%. ^{1}H NMR δ 1.06 (t, J_{HH} = 7.1 Hz), 1.38 (t, J_{HH} = 7.1 Hz) 3H, OCH$_2$C$\underline{H}_3$, 3.64 (dq, J_{HH} = 7.0 Hz, J_{PH} = 17 Hz), 3.78 (dq, J_{HH} = 7.0 Hz, J_{PH} = 17 Hz), 4.14–4.33 (m, J_{HH} = 7.0 Hz), 2H, OC$\underline{H}_2$, 5.12 (b), 5.23 (b) 1H, N$\underline{H}$, 5.41 (d, J_{PH} = 17.4 Hz), 5.44 (d, J_{PH} = 17.4 Hz), 1H, PC$\underline{H}$, 6.48–6.63 (m, 1H), 7.00–7.56 (m, 11H), 7.82–8.02 (m, 2H) Ar$\underline{H}$. ^{13}C NMR δ: 16.33 (d, J_{PC} = 6.3 Hz), 16.76 (d, J_{PC} = 6.3 Hz) $\underline{C}$H$_3$CH$_2$O, 53.93 (d, J_{PC} = 106.7 Hz) 54.17 (d, J_{PC} = 102.5 Hz) $\underline{C}$HP, 62.0 (d, J_{PC} = 7.0), 62.52 (d, J_{PC} = 7.0) CH$_2\underline{C}$H$_2$O, 113.7, 118.5, 127.5, 128.0, 128.2, 128.7, 128.9, 129.1, 129.3, 129.4, 131.8, 132.0, 132.3, 132.5, 132.7, 132.8, Ar$\underline{C}$, 113.7 (d, J_{PC} = 128.1 Hz, P$\underline{C}_{Ar}$), 145.9 (d, J_{PC} = 16.7 Hz, NH$\underline{C}_{Ar}$).

*Ethyl (1-Benzylamino-phenylmethyl)-ethylphosphinate (***3l***).* mp 52°C. Yield: 53%. ^{1}H NMR δ: 0.98 (t, J_{HH} = 7.6 Hz, J_{PH} = 17.6 Hz), 1.06 (t, J_{HH} = 7.6 Hz, J_{PH} = 17.6 Hz) 3H, PCH$_2$C$\underline{H}_3$, 1.03 (t, J_{HH} = 7.2 Hz), 1.28 (t, J_{HH} = 7.2 Hz) 3H, OCH$_2$C$\underline{H}_3$, 1.42–1.64 (m, J_{PH} = 13.9 Hz), 1.78 (dq, J_{HH} = 7.6 Hz, J_{PH} = 13.9 Hz) 2H, PC$\underline{H}_2$, 2.77 (s, 1H, N$\underline{H}$), 3.44–3.57 (m, J_{HH} = 7.2), 3.78–4.20 (m, J_{HH} = 7.2 Hz), 2H, OC$\underline{H}_2$, 3.46 (d, J_{AB} = 9.6 Hz), 3.54 (d, J_{AB} = 9.6 Hz),

1H. C$\underline{H}_{2A}$NH, 3.81 (d, J_{AB} = 9.6 Hz), 3.86 (d, J_{AB} = 9.6 Hz), 1H, C$\underline{H}_{2B}$NH, 3.81 (d, J_{PH} = 17.0 Hz, 1H, PC$\underline{H}$), 7.21–7.27 (m, 4H, Ar$\underline{H}$), 7.29–7.40 (m, 6H, Ar$\underline{H}$). ^{13}C NMR δ: 5.37 ($\underline{C}H_3CH_2P$), 16.10 (d, J_{PC} = 5.3 Hz), 16.59 (d, J_{PC} = 5.3 Hz) $\underline{C}H_3CH_2O$, 18.50 (d, J_{PC} = 94 Hz), 19.10 (d, J_{PC} = 94 Hz) $CH_3\underline{C}H_2P$, 50.77 (d, J_{PC} = 15.6 Hz), 51.02 (d, J_{PC} = 5.3 Hz) $\underline{C}H_2NH$, 60.06 (d, J_{PC} = 94.0 Hz), 60.17 (d, J_{PC} = 94.0 Hz) $\underline{C}HP$, 61.28 (d, J_{PC} = 7.0 Hz), 61.82 (d, J_{PC} = 7.0 Hz) $CH_3\underline{C}H_2O$, 126.90, 127.67, 128.06, 128.13, 128.37, 128.53, 135.44, 135.51, 135.72, 139.15, Ar$\underline{C}$.

*Ethyl (1-Benzylamino-(4-chloro)-phenylmethyl)-ethylphosphinate (***3m***).* mp 58°C. Yield: 92%. ^{1}H NMR δ: 0.90 (dt, J_{HH} = 7.7 Hz, J_{PH} = 13.6 Hz, 3H, $PCH_2C\underline{H}_3$), 0.98 (t, J_{HH} = 7.1 Hz), 1.19 (t, J_{HH} = 7.1 Hz) 3H, $OCH_2C\underline{H}_3$, 1.26–1.56 (m, J_{PH} = 15.4 Hz), 1.59–1.75 (m, J_{PH} = 15.4 Hz) 2H, PC$\underline{H}_2$, 2.34 (b, 1H, N$\underline{H}$), 3.35 (d, J_{AB} = 12.7 Hz), 3.40 (d, J_{AB} = 12.7 Hz) 1H, C$\underline{H}_{2A}$NH, 3.69 (d, J_{AB} = 12.7 Hz), 3.70 (d, J_{AB} = 12.7 Hz), 1H, C$\underline{H}_{2B}$NH, 3.46–3.59 (m, J_{HH} = 7.1), 3.66–4.01 (m, J_{HH} = 7.1 Hz), 2H, OC$\underline{H}_2$, 3.85 (d, J_{PH} = 17 Hz, 1H, PC$\underline{H}$), 7.20–7.40 (m, 9H, Ar$\underline{H}$). ^{13}C NMR δ: 4.99 (d, J_{PC} = 15.3 Hz) 5.08 (d, J_{PC} = 15.4 Hz), $\underline{C}H_3CH_2P$, 16.09 (d, J_{PC} = 5.2 Hz), 16.33 (d, J_{PC} = 5.2 Hz), $\underline{C}H_3CH_2O$, 18.23 (d, J_{PC} = 94.0 Hz), 18.76 (d, J_{PC} = 94.0 Hz) $CH_3\underline{C}H_2P$, 50.49 (d, J_{PC} = 15.4 Hz), 50.75 (d, J_{PC} = 15.4 Hz) $\underline{C}H_2NH$, 59.23 (d, J_{PC} = 99.0 Hz), 60.14 (d, J_{PC} = 97.0 Hz), $\underline{C}HP$, 60.75 (d, J_{PC} = 7.0 Hz), 61.17 (d, J_{PC} = 7.0 Hz) $CH_3\underline{C}H_2O$, 126.81, 127.93, 127.99, 128.33, 128.47, 129.20, 129.28, 129.61, 129.69, 133.21, 133.91, 133.97, 134.21, Ar$\underline{C}$.

*Ethyl (1-Benzylamino-(4-chloro)-phenylmethyl)-propylphosphinate (***3n***).* mp <25°C. Yield: 61%. ^{1}H NMR δ: 0.92 (t, J_{HH} = 6.9 Hz), 0.95 (t, J_{HH} = 6.9 Hz) 3H, $C\underline{H}_3CH_2CH_2$, 1.07 (t, J_{HH} = 7.2 Hz), 1.26 (t, J_{HH} = 7.2 Hz), 3H, $C\underline{H}_3CH_2O$, 1.41–1.58 (m, J_{HH} = 7.5 Hz, 2H, $C\underline{H}_2CH_2P$), 1.63 (b, 1H, N$\underline{H}$), 1.67–1.84 (m, J_{PH} = 12.7 Hz, 2H, $PC\underline{H}_2CH_2$), 3.49 (d, J_{AB} = 13.2 Hz), 3.57 (d, J_{AB} = 13.2 Hz) 1H, C$\underline{H}_{2A}$NH, 3.81 (d, J_{AB} = 13.2 Hz), 3.95 (d, J_{AB} = 13.2 Hz), 1H, C$\underline{H}_{2B}$NH, 3.51–3.66 (m, J_{HH} = 7.1 Hz), 3.79–4.15 (m, J_{HH} = 7.1 Hz), 2H, OC$\underline{H}_2$, 3.91 (d, J_{PH} = 16.0 Hz, 1H, PC$\underline{H}$), 7.10–7.30 (m, 7H, Ar$\underline{H}$), 7.34–7.36 (m, 2H, Ar$\underline{H}$).

*Ethyl (1-Benzylamino-phenylmethyl)-isopropylphosphinate (***3o***).* oil. Yield: 53%. ^{1}H NMR δ: 0.83–1.12 (m, J_{HH} = 7.0 Hz, 6H, C$\underline{H}_3$CH), 1.03 (t, J_{HH} = 7.0 Hz), 1.19 (t, J_{HH} = 7.0 Hz), 3H, $C\underline{H}_3CH_2O$, 1.61–1.83 (m, J_{HH} = 7.0 Hz,), 2.03–2.23 (m, J_{HH} = 7.0 Hz), 1H, $CH_3C\underline{H}$, 2.44 (b, 1H, N$\underline{H}$), 3.23–3.56 (m, J_{HH} = 7.1 Hz), 3.61–4.17 (m, J_{HH} = 7.1 Hz) 2H, OC$\underline{H}_2$, 3.45 (d, J_{AB} = 12.0 Hz, 1H, C$\underline{H}_{2A}$-Ar), 3.72 (d, J_{HH} = 12.7 Hz, 1H, C$\underline{H}_{2B}$-Ar), 3.92 (d, J_{PH} = 14.5 Hz, 1H, PC$\underline{H}$), 7.17–7.40 (m, 10H, Ar$\underline{H}$).

*Ethyl (1-Benzylamino-(4-chloro)-phenylmethyl)-isopropylphosphinate (***3p***).* mp <25°C. Yield: 68%. ^{1}H NMR δ: 0.80–0.99 (m, J_{HH} = 6.9 Hz, 6H, C$\underline{H}_3$CH), 1.03 (t, J_{HH} = 7.1 Hz), 1.15 (t, J_{HH} = 7.1 Hz), 2H, $C\underline{H}_3CH_2O$, 1.69 (heptett,d, J_{HH} = 7.1 Hz, J_{PH} = 11.6 Hz), 2.06 (heptett,d, J_{HH} = 7.1 Hz, J_{PH} = 11.6 Hz), 1H, $CH_3CH_3C\underline{H}$, 2.21 (b, 1H, N$\underline{H}$), 3.27–3.41 (m, J_{HH} = 7.1 Hz), 3.60–4.08 (m, J_{HH} = 7.1 Hz) 2H, $CH_3C\underline{H}_2O$, 3.30 (d, J_{AB} = 13.4 Hz), 3.35 (d, J_{AB} = 13.4 Hz), 1H, C$\underline{H}_{2A}$NH, 3.66 (d, J_{AB} = 13.0 Hz), 3.82 (d, J_{AB} = 13.2), 1H, C$\underline{H}_{2B}$NH, 3.88 (d, J_{PH} = 19.6 Hz, 1H, C$\underline{H}$), 6.91–7.28 (m, 9H, Ar$\underline{H}$). ^{13}C NMR δ: 14.57 (d, J_{PC} = 4.7 Hz), 14.65 (d, J_{PC} = 4.7 Hz) $\underline{C}H_3\underline{C}H_3CH$, 15.52 (d, J_{PC} = 4.9 Hz), 16.35 (d, J_{PC} = 4.9 Hz) $\underline{C}H_3CH_2O$, 24.76 (d, J_{PC} = 93.4 Hz), 25.55 (d, J_{PC} = 82.0 Hz) $CH_3\underline{C}HP$, 50.37 (d, J_{PC} = 17 Hz), 50.65 (d, J_{PC} = 18.3 Hz) $\underline{C}H_2NH$, 57.50 (d, J_{PC} = 96.3 Hz), 59.00 (d, J_{PC} = 93.0 Hz), $\underline{C}HP$, 62.35 (d, J_{PC} = 6.9 Hz), 62.54 (J_{PC} = 6.9 Hz) $CH_3\underline{C}H_2O$, 127.73, 127.81, 127.87, 128.18, 128.52, 129.53, 129.62, 133.93, 134.20, 138.55, 138.61, Ar$\underline{C}$.

*Ethyl (1-Benzylamino-phenylmethyl)-butylphosphinate (***3q***).* mp 56°C. Yield: 74%. ^{1}H NMR δ: 0.8 (t, J_{HH} = 7.1 Hz), 0.87 (t, J_{HH} = 7.1 Hz) 3H, $C\underline{H}_3CH_2$, 1.03 (t, J_{HH} = 7.0 Hz), 1.28 (t, J_{HH} = 7.0 Hz) 3H, $C\underline{H}_3CH_2O$, 1.30–1.46 (m, J_{HH} = 7.4 Hz, 2H, $CH_3C\underline{H}_2$), 1.46–1.61 (m, 2H, $CH_3CH_2C\underline{H}_2$), 1.70–1.76 (m, J_{PH} = 13.0 Hz, 2H, $C\underline{H}_2P$), 2.53 (b, 1H, N$\underline{H}$), 3.42–3.55 (m, J_{HH} = 7.1 Hz), 3.70–4.12 (m, J_{HH} = 7.1 Hz) 2H, OC$\underline{H}_2$, 3.46 (d, J_{AB} = 13.0 Hz), 3.50 (d, J_{AB} = 13.0 Hz) 1H, C$\underline{H}_{2A}$NH, 3.80 (d, J_{AB} = 13.0 Hz), 3.82 (d, J_{AB} = 13.0 Hz) 1H, C$\underline{H}_{2B}$NH, 3.95 (d, J_{PH} = 17.0 Hz, 1H, PC$\underline{H}$), 7.25–7.38 (m, 10H, Ar$\underline{H}$).

*Ethyl (1-Benzylamino-(4-chloro)-phenylmethyl)-butylphosphinate (***3r***).* mp 61°C. Yield: 88%. ^{1}H NMR δ: 0.83 (t, J_{HH} = 6.9 Hz), 0.88 (t, J_{HH} = 6.9 Hz) 3H, $C\underline{H}_3CH_2$, 1.07 (t, J_{HH} = 7.2 Hz), 1.28 (t, J_{HH} = 7.2 Hz) 3H, $C\underline{H}_3CH_2O$, 1.33–1.45 (m, J_{HH} = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 1.45–1.65 (m, J_{HH} = 7.2 Hz, 2H, $CH_3CH_2C\underline{H}_2$), 1.76 (dt, J_{HH} = 7.2 Hz, J_{PH} = 13.6 Hz, 2H, $C\underline{H}_2P$), 2.43 (b, 1H, N$\underline{H}$), 3.44 (d, J_{AB} = 12.6 Hz), 3.49 (d, J_{AB} = 12.6 Hz), 1H, C$\underline{H}_{2A}$NH, 3.79 (d, J_{AB} = 12.6 Hz), 3.81 (d, J_{AB} = 12.6 Hz), 1H, C$\underline{H}_{2B}$NH, 3.50–3.67 (m, J_{HH} = 7.2 Hz), 3.77–4.16 (m, J_{HH} = 7.2 Hz) 2H, OC$\underline{H}_2$, 3.93 (d, J_{PH} = 17.0 Hz, 1H, PC$\underline{H}$), 7.25–7.35 (m, 9H, Ar$\underline{H}$). ^{13}C NMR δ: 13.56 (d, J_{PC} = 3.5 Hz, $\underline{C}H_3CH_2CH_2$), 16.49 (d, J_{PC} = 5.5 Hz), 16.73 (J_{PC} = 5.5 Hz) $\underline{C}H_3CH_2O$, 23.21 (d, J_{PC} = 4.8 Hz), 23.49 (J_{PC} = 5.1 Hz) $CH_3CH_2\underline{C}H_2$, 23.89 (d, J_{PC} = 15.9 Hz, $CH_3CH_2\underline{C}H_2$), 25.20 (d, J_{PC} = 92.6 Hz), 25.80 (d, J_{PC} =

92.6 Hz) $CH_2\underline{C}H_2P$, 50.91 (d, $J_{PC} = 19.2$ Hz), 51.18 (d, $J_{PC} = 19.2$ Hz) $NH\underline{C}H_2$, 60.00 (d, $J_{PC} = 98.4$ Hz), 60.80 (d, $J_{PC} = 96.0$ Hz) $\underline{C}HP$, 61.08 (d, $J_{PC} = 6.9$ Hz), 61.42 (d, $J_{PC} = 6.9$ Hz) $CH_2\underline{C}H_2O$, 127.20, 127.23, 128.38, 128.41, 128.76, 128.84, 128.87, 129.55, 129.63, 130.05, 133.55, 133.60, 134.47, 134.54, 139.09, Ar$\underline{C}$.

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