Trichlorocyanuric acid: an efficient reagent for one-pot synthesis of *Ptychodiscus brevis* (PB-1) toxin and its derivatives

Arvind K. Gupta, Jyotiranjan Acharya, Devendra K. Dubey and Mahabir P. Kaushik*

Process Technology Development Division, Defence R & D Establishment, Jhansi Road, Gwalior 474002 (MP), India

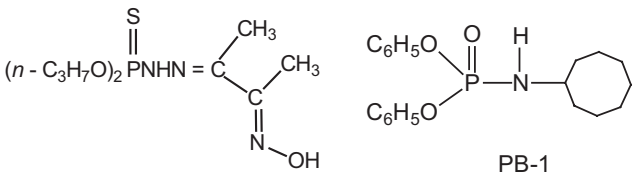
Trichlorocyanuric acid is an efficient regent for simple and one-pot synthesis of dialkyl, *N*-cycloctylphosphoraamidates (PB-1) and its various derivatives in excellent yields. The procedure is operationally simple and involves the reaction of various dialkylphosphites with trichloroisocyanuric acid in acetonitrile and subsequent treatment with amines in presence KF-celite to give PB-1 and derivatives.

Keywords: dialkylphosphites, trichlorocyanuric acid, phosphoramidates, phosphates, *Ptycodiscus brevis* (PB-1)

Marine derived dinoflagellates have become a rich source of structurally novel and pharmacologically active secondary metabolites. Some of the species of dinoflagellates also produce toxic compounds and are responsible for sea food poisoning. This class of marine toxin has attracted the attention of organic chemists due to their involvement in human intoxication and socioeconomic impact brought about by toxic effect of these toxins. *Ptychodiscus brevis* (*Gymnodinium breve)* is a marine dinoflagellate which is the cause of massive fish kills, mollusk poisoning and human food poisoning along the Florida coast and in the Gulf of Mexico.[1]

Several attempts have been made to isolate the toxins from the cultured cells;[2] however, discrepancies exist in the reported physical properties,[1,3-5] the main reason being presumably the difficulty associated with the separation and purification of the toxin mixture. Elucidation of the chemical structure is imperative not only for the understanding of the molecular basis of mechanism of action, but also for the design of proper defensive countermeasures such as detection, protection and decontamination. Over the past decade, G*ymnodinium breve* toxin such as di(propyl) (*E*)-2-[1-methyl-2-oxopropylidene] phosphorohydrazidothiolate (*E*)-oxime[6,7] and diphenyl cyclooctylphosphoramidate (PB-1, **3a**) were isolated from the dinoflagellate[8] and their structure was established by X-ray crystallography and spectroscopic techniques. The structure of PB-1 attracted the attention of the scientists due to its simplicity and high degree of toxicity.[8] Thus, synthesis and chemical modification followed by structure–function relationship studies provide attractive targets for chemists. The structures of these toxins are given in Scheme 1.

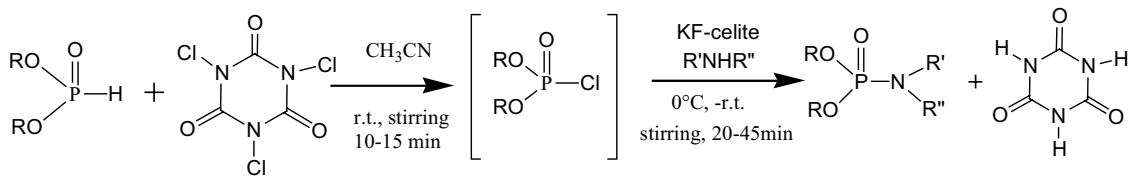
Thus, in order to study the structure–activity relationship of PB-1, there is a need to develop an efficient synthetic procedure which can be applied for the synthesis of large no of compounds in safe mode with short reaction time and under mild reaction conditions. Various methods are known for the synthesis of phosphoramidates (**3**).[8-11] Prominent among them is the reaction of dialkyl chlorophosphate with alkyl/cycloalkyl amines under argon atmosphere in the presence of inert solvent. Although the reaction is straightforward,



Scheme 1

it suffers from several drawbacks, such as long reaction times, poor atom economy (requires extra mole of base as acid scavenger), and use of hazardous solvents.[8] The other route involves high temperature (240°C) which results in the tar formation and reduces the yields of the desired products.[12] In recent years, development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic chemistry.[13] It is evident from the literature that trichlorocyanuric acid[14] (TCCA), an inexpensive and commercially available reagent has found versatile applications in functional group transformations and has been used for the conversion of alcohols into their corresponding alkyl chlorides, oxidation of sulfides into sulfoxides, oxidative coupling of thiols and selenols, cleavage of thioacetals into their corresponding ketones.[15] In spite of availability of large number of synthetic methods, no attempt has been made to synthesise PB-1 and its derivatives by using TCCA as a chlorinating reagent and KF-celite as a solid support. We report herein a new method for the synthesis of *Ptychodiscus brevis (*PB-1) and its analogues in the presence of a mixture of dialkylphosphites (**1**), TCCA (**2**), a primary amine and KF-celite producing high yields of phosphoramidates (**3**) Scheme 2.

Initially the reaction of diphenyl phosphite and cyclooctylamine with TCCA was performed as model reaction in the presence of different solid supports by varying the reaction conditions. The model reaction was monitored by ^{31}P NMR to find out the consumption of diphenylchlorophosphate and formation of the corresponding product. The results are summarised in Table 1. The results of spectral analysis were also compared with authentic sample.[8a]



1 **2** **3** **4**

Scheme 2 Synthesis of phosphoramidates.

* Correspondent. E-mail : mpkaushik@rediffmail.com

Table 1 Conditions optimisation for the synthesis of diphenyl *N*-alkyl phosphoramidates from diphenyl phosphate

Entry	Phosphoramidate (**3**)[a]			Soild support	Time/min	Yield/%[b]
	R	R'	R"			
1	C_6H_5	C_8H_{15}	H	KF-celite)	10	98
2	C_6H_5	C_8H_{15}	H	KF	10	48
3	C_6H_5	C_8H_{15}	H	Celite	10	37
4	C_6H_5	C_8H_{15}	H	Symctone clay	10	50
5	C_6H_5	C_8H_{15}	H	Montmorillonite	10	47
6	C_6H_5	C_8H_{15}	H	KSF clay	10	35
7	C_6H_5	C_8H_{15}	H	Kieselgel	10	29
8	C_6H_5	C_8H_{15}	H	Active charcoal	10	41
9	C_6H_5	C_8H_{15}	H	Active carbon	25	97
10	C_6H_5	C_6H_{11}	C_6H_{11}	KF-celite	10	85
11	C_6H_5	C_6H_{11}	C_6H_{11}	KF-celite	20	85
12	C_6H_5	C_6H_{11}	C_6H_{11}	KF-celite	05	85
13	C_6H_5	C_6H_{11}	C_6H_{11}	KF-celite	10	68
14	C_6H_5	β-naphthyl	H	KF-celite	10	65
15	C_6H_5	β-naphthyl	H	KF-celite	20	80
16	C_6H_5	β-naphthyl	H	KF-celite	20	78
17	C_6H_5	β-naphthyl	H	KF-celite	50	82
18	C_6H_5	C_8H_{15}	H	No solid support	180	32

[a]Reactions were monitored by GC, TLC, 100% conversion is based on ^{31}P NMR; [b]isolated yield; all the reactions were performed at room temperature (except entries 13 and 16 which were performed at 50°C).

It is clear from Table 1 that dicyclohexylamine reacted very rapidly and reaction was complete just after addition of amine. β-Naphthylamine reacted slowly and took a little longer time (20 min) for the reaction to be complete. The effect of the nature of the solid support on the reaction rate was also studied. Various supports such as KF-celite, KF, celite, symctone clay, montmorillonite KSF clay, kieselgel, active charcoal and active carbon were used; KF-celite was found to be superior in terms of conversion and reaction time. All the reactions with KF-celite reached to completion within 20 min under neat condition and at ambient temperature, while without KF-celite, even extended reaction time (up to 3 h) had no significant enhancement in the yields (32%). It was also observed that by increasing the reaction time on KF-celite, there is no significant change in the yield of products. By following the optimised procedure, a series of compounds were prepared and confirmed by spectroscopic techniques (Table 2).

The important advantage of this reaction is its occurrence at room temperature. Further interesting observation reveals that the formation of PB-1 and its derivatives from corresponding phosphites require shorter reaction times (30–60 min) as compared to other reported method. Another advantage is that by-product (cyanuric acid) **4** does not react with amines

Table 2 Synthesis of PB-1and its analogues by the reaction of dialkyl phosphite and TCCA on KF-celite

Entry	Phosphoramidates[a]		Yield[b] /%	M.p./b.p.	^{31}P NMR[c] ($CDCl_3$)
	R	R'			
1	C_6H_5	Cyclooctyl	98	112	–1.79
2	C_6H_5	Cycloheptyl	96	106	–1.76
3	C_6H_5	Cyclohexyl	99	102	–1.64
4	C_6H_5	Cyclopentyl	88	98	–1.47
5	C_6H_5	Cyclododecyl	89	138	0.38
6	C_6H_5	n-octyl	90	134	0.63
7	C_6H_5	n-hexyl	95	130	0.56
8	C_6H_5	n-decyl	83	148	0.57
9	C_6H_5	Dicyclohexyl	84	170	–12.97
10	C_6H_5	ß -naphthyl	80	148	–11.34
11	4-$NO_2C_6H_4$	Cyclooctyl	80	168	–12.97
12	4-CN–C_6H_{4l}	Cyclooctyl	82	138	–12.02
13	CH_3	Cyclooctyl	95	145/0.5	10.63
14	CH_3	Cycloheptyl	90	130/1	10.73
15	CH_3	Cyclohexyl	88	136/1	10.88
16	CH_3	Cyclopentyl	88	130/1.5	10.76
17	C_2H_5	Cyclooctyl	89	162/1	9.28
18	C_2H_5	Cycloheptyl	85	158/1	9.09
19	C_2H_5	Cyclohexyl	92	150/0.8	8.89
20	C_2H_5	Cyclopentyl	82	144/1	8.78
21	$CH_3CH_2CH_2$	Cyclooctyl	88	175/1	8.15
22	$CH_3CH_2CH_2$	Cycloheptyl	80	170/0.8	8.21
23	$CH_3CH_2CH_2$	Cyclohexyl	81	168/1	8.27
24	$CH_3CH_2CH_2$	Cyclopentyl	89	159/1	8.38
25	$(CH_3)_2CH$–	Cyclooctyl	82	162/1	6.09
26	$(CH_3)_2CH$–	Cycloheptyl	85	157/1	6.20
27	$(CH_3)_2CH$–	Cyclohexyl	87	148/1	6.29
28	$(CH_3)_2CH$–	Cyclopentyl	88	140/1	6.37

[a]Reactions were monitored by ^{31}P NMR, TLC and GC. [b]isolated yields. [c]NMR spectra of entries 5 and 6 were recorded in DMSO-d_6. All the products had satisfactory IR, NMR and MS data and were compared with authentic samples[16]. Compounds 13–28 are low melting solids.

under these conditions and can be easily separated from the product. The filtrate contains the desired products which can be purified either by crystallisation or by vacuum distillation. The by-product (**4**) was recovered after washing with acetone followed by evaporation of the solvent which could be recycled for the preparation of TCCA (**2**).

To examine the reproducibility and scale-up feasibility of developed procedure, one mole of diethyl phosphite was reacted with 0.33 mol of the reagent (**2**) to generate the diethyl chlorophosphates *in situ*. The heterogeneous reaction mixture was cooled to 0°C and mixture of KF-celite (1.0 mole) was added to the flask. Cycloctyl amine (1 mol) was added slowly into it. After addition of amines, reaction mixture was shaken on vortex shaker at room temperature and monitored by ^{31}P NMR. The results of ^{31}P NMR studies indicated that signal of diethyl chlorophosphate disappeared after the addition of the cycloctyl amine and a new signal appeared at δ –9.28 within 20 min. It clearly demonstrated that the conversion of diethylphosphite to diethyl chlorophosphate followed by the formation of corresponding diethyl *N*-cycloctylphosphoramidates. Filtration of heterogeneous reaction mixture after washing with CH_3CN and removal of the solvent provided the pure product in 89% isolated yield (entry 17, Table 2).

In conclusion, we have developed a simple, rapid, economical and efficient one-pot synthetic method for preparation of PB-1 and its derivatives. This method can be applied for the synthesis of other biologically active phosphoramidates and phosphates and will be a useful and an important addition to existing methodologies.

Experimental

Melting points were determined on a hot stage microscope and are uncorrected. IR spectra were recorded on Bruker FT-IR spectrometer model Tensor 27 on KBr disk. ^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ on Bruker DPX Avance FT- NMR at 400 and 162 MHz respectively using tetramethylsilane as an internal standard for ^{1}H and 85% H_3PO_4 as an external standard for ^{31}P NMR. A Chemito GC model 1000 instrument was used with flame ionisation detector (FID). A capillary column (30 m × 0.25 mm I.D-BP5) packed with 5% phenyl and 95% dimethyl polysiloxane (SGE) coated on fused silica was employed. The injection port and detector block were maintained at 280°C and 260°C respectively and the column oven was at programmed temperature profile started at 50°C, ramped up to 280°C at 25°C/min. Nitrogen was used as carrier gas (at a flow rate of 30 ml/min). Air for FID was supplied at 300 ml/min and hydrogen at 30 ml/min. In all analysis, 0.4 µl sample was injected and peaks recorded on Iris32 data acquisition station. The GC–MS analyses were performed in EI (70 eV) in full scan mode with an Agilent 6890 GC equipped with a model 5973 mass selective detector (Agilent Technologies, USA). An SGE BPX5 capillary column with 30 m length × 0.32 mm internal diameter × 0.25 µm film thickness was used at temperature program of 80°C (2 min)–20°C/min–280°C (3 min). Helium was used as the carrier gas at a constant flow rate of 1.2 ml/min. The samples were analysed in splitless mode at injection temperature.

Preparation and characterisation of KF-celite surface mediated catalyst

KF-celite was prepared by combination of KF (10.0 g, 0.17 mole) and celite (celite 521, 15.0 g, 0.25 mole) in a mortar and pestle by grinding together until a fine, homogenous powder was obtained (10–15 min). It was mixed with 150 ml of distilled water and stirred for 1 h at room temperature and then water was removed under vacuum using Heidolph rotary evaporator till dryness. It was shaken with 100 ml acetonitrile, filtered and washed with 3 × 25 ml acetonitrile. It was further dried under vacuum at 100°C for 2 h and stored in a Stoppard flask under desiccators. However, in order to know nature of KF-celite, micro structural studies were performed by scanning electron microscope (SEM). It was observed that KF was finely and uniformly distributed on the Celite.

General experimental procedure

Dialkyl phosphite (0.01 mole) was added to a solution of TCCA (0.0034 mole) in 10 ml acetonitrile and reaction mixture was stirred for 10–15 min. The progress of the reaction mixture was monitored by ^{31}P NMR by drawing a few milligrams of reaction mixture in a NMR tube. The results of NMR studies indicate that ^{31}P NMR signal of dialkylphosphite is exchanged with the formation of corresponding dialkyl chlorophosphate. It is also physically visualised by appearance of a white amorphous precipitate of cyanuric acid. The reaction mixture was cooled at 0°C and KF-celite 1.30 g (0.015 mole of both KF and celite) was added and sealed with rubber septum. To the reaction mixture was added alkyl amine/cycloalkyl amine (0.01 mol) with the help of a syringe at the same temperature. After the addition, the reaction mixture was brought to room temperature and shaken on vortex shaker. The progress of the reaction was further monitored by ^{31}P NMR. The results of NMR studies indicated that ^{31}P NMR signal of corresponding dialkyl chlorophosphate completely disappeared and a new signal of phosphoramidates appeared within 20–45 min. The reaction mixture was filtered, washed with 3 × 10 ml of CH_3CN, followed by removal of solvent to give the crude product which was purified either by crystallisation or distillation under vacuum to get pure PB-1 or corresponding derivatives.

Spectral data of PB-1 and derivatives:

Diphenyl N-cyclooctylphosphoramidate (**1**): ^{1}H NMR δ: 7.02–7.41 (m, 10H), 3.72 (dd, NH, 1-exchangeable), 3.45(m, 1-H), 1.61(m, 14H for 7 CH_2); IR: (KBr) ν (max) 3219(NH), 2950, 2890(CH), 1410(C–N), 1250 (P=O), 980–965 (P–O–aryl) cm^{-1}. Anal. Calcd for $C_{20}H_{26}NO_3P$ (359): C 66.85, H 7.29, N 3.89 Found: C 66.93, H 7.32, N 3.92%.

Diphenyl N-cycloheptylphosphoramidate (**2**): ^{1}H NMR δ: 6.93–7.12(m, 10-H), 3.74(dd, NH, 1-H exchangeable), 3.46(m, 1-H), 1.75(m, 12-H for 6 CH_2); IR: (KBr) ν (max) 3222(NH), 2955, 2880(CH), 1415(C–N), 1260 (P=O), 990–975(P–O–aryl) cm^{-1}. Anal. Calcd for $C_{19}H_{24}NO_3P$(345): C 66.08, H 7.01, N 4.05 Found: C 66.20, H 7.12, N 4.25%.

Diphenyl N-cyclohexylphosphoramidate (**3**): ^{1}H NMR δ: 7.25 (m, 10-H), 3.72 (dd, NH, 1-H exchangeable), 3.53(m, 1-H), 1.52(m, 10-Hfor5CH_2); IR: (KBr) ν(max) 3220(NH), 2960, 2870(CH), 1420 (C-N), 1255 (P=O), 980–965(P–O–aAryl) cm^{-1}. Anal. Calcd for $C_{18}H_{22}NO_3P$(331): C 65.25, H 6.69, N 4.22 Found: C 65.22, H 6.48, N 4.30%.

Diphenyl N-cyclopentylphosphoramidate (**4**): ^{1}H NMR δ: 7.20 (m, 10-H), 3.77(dd, NH, 1-H exchangeable), 3.43(m, 1-H), 1.55(m, 8-H for 4CH_2); IR: (KBr) ν(max) 3219(NH), 2950, 2890(CH), 1410(C–N), 1250 (P=O), 980-965 (P–O–aryl) cm^{-1}. Anal. Calcd for $C_{17}H_{20}NO_3P$(317): C 64.35, H 6.35, N 4.41 Found: C 64.22, H 6.23, N 4.32%.

Diphenyl N-cyclododecylphosphoramidate **(5)**: ^{1}H NMR δ: 7.24 (m, 10-H), 3.72(dd, NH, 1-H exchangeable), 3.43(m, 1-H), 1.62(m, 24-H for 11 CH_2); IR: (KBr) ν(max) 3225(NH), 2965, 2870(CH), 1425(C–N), 1260(P=O), 980–965(P–O–aryl) cm^{-1}. Anal. Calcd for $C_{24}H_{34}NO_3P$ (415): C 69.39, H 8.25, N 3.37 Found: C 69.43, H 8.42, N 3.58%.

Diphenyl N-octylphosphoramidate (**6**): ^{1}H NMR δ: 7.22 (m, 10-H, Ar), 3.73(dd, NH, 1-exchangeable), 3.54(m, 2-H, CH_2), 1.76 (m, 12H for 6 CH_2), 1.22 (t, 3-H, CH_3); IR: (KBr) ν(max) 3220(NH), 2970, 2880(CH), 1415(C–N), 1260 (P=O), 980–965(P–O–aryl) cm^{-1}. Anal. Calcd for $C_{20}H_{28}NO_3P$ (361): C 66.48, H 7.81, N 3.87 Found: C 66.60, H 7.92, N 4.02%.

Diphenyl N-hexylphosphoramidate (**7**): ^{1}H NMR δ: 7.33(m, 10-H, Ar), 3.72(dd, NH, 1-exchangeable), 3.48(m, 2-H, CH_2), 1.75(m, 8H for 4 CH_2), 1.30 (t, 3-H, CH_3); IR: (KBr) ν(max) 3220(NH), 2970, 2880(CH), 1425(C–N), 1265 (P=O), 988–970(P–O–aryl) cm^{-1}. Anal. Calcd for $C_{18}H_{24}NO_3P$(333): C 64.86, H 7.26, N 4.20 Found: C 64.78, H 7.23, N 4.29%.

Diphenyl N-decylphosphoramidate (**8**): ^{1}H NMR δ: 7.23(m, 10-H, Ar), 3.73(dd, NH, 1-exchangeable), 3.48(m, 2-H, CH_2), 1.76(m, 16H for 8 CH_2), 1.28 (t, 3-H, CH_3); IR: (KBr) ν(max) 3225(NH), 2975, 2885(CH), 1415(C–N), 1260 (P=O), 980–965(P–O–aryl) cm^{-1}. Anal. Calcd for $C_{22}H_{32}NO_3P$ (389): C 67.85, H 8.28, N 3.60 Found: C 67.52, H 7.98, N 3.85%.

Diphenyl N, N-dicyclohexylphosphoramidate (**9**): ^{1}H NMR δ: 7.23(m, 10-H), 3.52(m, 2-H), 1.51 (m, 20-H for 10 CH_2); IR: (KBr) ν(max) 2970, 2880(CH), 1410(C–N), 1260 (P=O), 980–960(P–O–aryl) cm^{-1}. Anal. Calcd for $C_{24}H_{32}NO_3P$ (413): C 69.73, H 7.80, N 3.38 Found: C 69.93, H 7.93, N 3.49%.

Diphenyl N-ß-naphthylphosphoramidate (**10**): ^{1}H NMR δ: 7.63 (m, 17-H), 3.70 (dd, NH, 1-exchangeable); IR: (KBr) ν(max) 3220(NH),

2900, 2860(CH), 1410(C–N), 1250 (P=O), 980–965(P–O–aryl) cm-1. Anal. Calcd for $C_{22}H_{18}NO_3P$ (375): C 70.40, H 4.83, N 3.73 Found: C 70.53, H 4.93, N 3.69%.

Di-4-nitrophenyl N-cyclooctylphosphoramidate (**11**): ^{1}H NMR δ: 7.21(m, 8-H, Phenyl), 3.71(dd, NH, 1-H exchangeable), 3.45(m, 1-H), 1.62(m, 14-H for 7 CH_2 groups); IR: (KBr) ν(max) 3270(NH), 3000, 2950(CH), 1500 and 1340(NO_2), 1290(P=O), 1200–1210(P–O–C), 1180–1175(P–O–aryl) cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_3O_7P$ (452): C 53.45, H 5.35, N 9.35 Found: C 53.88, H 5.12, N 9.47%.

Di-4-cyanophenyl N-cyclooctylphosphoramidate (**12**): ^{1}H NMR δ: 7.22(m, 8-H, Phenyl), 3.71(dd, NH, 1-H exchangeable), 3.45(m, 1-H), 1.62(m, 14-H for 7 CH_2 groups); IR: (KBr) ν(max) 3255(NH), 2990, 2950(CH), 2250 (C≡N), 1430(C–N), 1260(P=O), 1160–1150 (P–O–aryl) cm^{-1}. Anal. Calcd for $C_{22}H_{24}N_3O_3P$ (409): C 64.55, H 5.91, N 10.27 Found: C 64.52, H 5.83, N 10.49%.

Dimethyl N-cyclooctylphosphoramidate (**13**): ^{1}H NMR δ: 3.80(d, d 1-H exchangeable), 3.72 (d, 6-H, $J_{H\text{-}P}$ = 12.0 Hz), 3.45(m, 1-H), 1.62(m, 14-H 7 CH_2); IR: (KBr) ν(max) 3220(NH), 2950, 2890 (C–H), 1250, (P=O), 1090, 1050 (P–O–C) cm^{-1}. Anal. Calcd for $C_{10}H_{22}NO_3P$ (235): C 51.06, H 9.43, N 5.95 Found: C 51.17, H 9.38, N 5.98%.

Dimethyl N-cycloheptylphosphoramidate (**14**): ^{1}H NMR δ: 3.76 (d, 6-H, $J_{H\text{-}P}$ = 12.0 Hz), 3.72(dd, NH, 1-H exchangeable), 3.46 (m, 1-H); IR: (KBr) ν(max) 3220(NH), 2950, 2890(C–H), 1250, (P=O), 1090, 1050(P–O–C) cm^{-1}. Anal. Calcd for $C_9H_{20}NO_3P$ (221): C 48.86, H 9.12, N 6.33 Found: C 48.71, H 9.18, N 6.18%.

Dimethyl N-cyclohexylphosphoramidate (**15**): ^{1}H NMR δ: 3.78 (d, 6-H, $J_{H\text{-}H}$ = 12.0 Hz), 3.73(dd, NH, 1-H exchangeable), 3.45(m, 1-H), 1.62(m, 10-H for 5 CH_2 Protons) 1.55(m, 12-H for 6 CH_2) IR: (KBr) ν(max) 3230(NH), 2945, 2877(C–H), 1260, (P=O), 1080, 1040(P–O–C) cm^{-1}. Anal. Calcd for $C_8H_{18}NO_3P$ (207): C 46.37, H 8.76, N 6.76 Found: C 46.49, H 8.88, N 6.98%.

Dimethyl N-cyclopentylphosphoramidate (**16**): ^{1}H NMR δ: 3.80 (d, 6-H, $J_{H\text{-}H}$ = 12.0 Hz), 3.72(dd, NH, 1-H exchangeable), 3.45(m, 1-H), 1.62(m, 8-H for 4 CH_2 Protons); IR: (KBr) ν(max) 3225(NH), 2955, 2880(C–H), 1255, (P=O), 1090, 1050(P–O–C) cm^{-1}. Anal. Calcd for $C7H_{16}NO_3P$ (193): C 43.52, H 8.35, N 7.25 Found: C 43.49, H 8.48, N 7.38%.

Diethyl N-cyclooctylphosphoramidate (**17**): ^{1}H NMR δ: 4.25 (m, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 3.72(dd, NH, 1-H exchangeable), 3.45(m, 1-H), 1.65(m, 14-H for 7 CH_2) 1.33 (t, 6-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max) 3220(NH), 2950, 2890(C–H), 1250, (P=O), 1090, 1050 (P–O–C) cm^{-1}. Anal. Calcd for $C_{12}H_{26}NO_3P$ (263): C 54.75, H 9.96, N 5.32 Found: C 54.79, H 9.78, N 3.48%.

Diethyl N-cycloheptylphosphoramidate (**18**): ^{1}H NMR δ: 4.31(dq, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 3.72(dd, NH, 1-H exchangeable), 3.45(m, 1-H), 1.55(m, 12-H for 6 CH_2 Protons), 1.33(t, 6-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max)3230(NH), 2960, 2880(C–H), 1265, (P=O), 1080, 1045 (P–O–C) cm^{-1}. Anal. Calcd for $C_{11}H_{24}NO_3P$ (249): C 53.01, H 9.71, N 5.62 Found: C 53.17, H 9.58, N 5.80%.

Diethyl N-cyclohexylphosphoramidate (**19**): ^{1}H NMR δ: 4.34(m, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 3.71(dd, NH, 1-H exchangeable), 3.46(m, 1-H), 1.5(m, 10-H for 5 CH_2 Protons), 1.33(t, 6-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max) 3220(NH), 2950, 2890(C–H), 1250, (P=O), 1090, 1050 (P–O–C) cm^{-1}. Anal. Calcd for $C_{10}H_{22}NO_3P$ (235): C 51.06, H 9.43, N 5.95 Found: C 51.21, H 9.43, N 6.18%.

Diethyl N-cyclopentylphosphoramidate (**20**): ^{1}H NMR δ: 4.35(m, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45(m, 1-H), 1.6(m, 8-H for 4 CH_2 Protons), 1.33(t, 6-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max) 3220(NH), 2950, 2890(C–H), 1250, (P=O), 1090, 1050 (P–O–C) cm^{-1}. Anal. Calcd for $C_9H_{20}NO_3P$ (221): C 48.86, H 9.12, N 6.33 Found: C 49.05, H 9.30, N 6.49%.

Dipropyl N-cyclooctylphosphoramidate (**21**): ^{1}H NMR δ: 4.05(m, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.74 (m, 4H, 2 CH_2), 1.65(m, 14-H for 7CH_2 Protons) 0.97(t, 6-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max) 3230(NH), 2966, 2890(C–H), 1250, (P=O), 1090, 1045(P–O–C) cm^{-1}. Anal. Calcd for $C_{14}H_{30}NO_3P$ (291): C 57.73, H 10.39, N 4.81 Found: C 57.97, H 10.42, N 5.08%.

Dipropyl N-cycloheptylphosphoramidate (**22**): ^{1}H NMR δ: 4.03 (m, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 3.72(dd, NH, 1-H exchangeable), 3.46(m, 1-H), 1.72 (m, 4H, 2 CH_2, J = 7.04 Hz), 1.58(m, 12-H for 6 CH_2 Protons) 0.96(t, 6-H, $J_{H\text{-}H}$ = 7.48); IR: (KBr) ν(max) 3230(NH), 2960, 2895(C–H), 1265, (P=O), 1090, 1050(P–O–C) cm^{-1}. Anal. Calcd for $C_{13}H_{28}NO_3P$ (277): C 56.31, H 10.18, N 5.05 Found: C 56.50, H 10.34, N 5.25%.

Dipropyl N-cyclohexylphosphoramidate (**23**): ^{1}H NMR δ: 4.06 (m, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz) 3.71 (dd, NH, 1-H exchangeable), 3.44(m, 1-H), 1.72 (m, 4H, 2 CH_2, J = 7.04 Hz), 1.5(m, 10-H for 5 CH_2 Protons), 0.99(t, 6-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max) 3235(NH), 2965, 2890(C–H), 1250, (P=O), 1090, 1050(P–O–C) cm^{-1}. Anal. Calcd for $C_{12}H_{26}NO_3P$ (263): C 54.77, H 9.96, N 5.32 Found: C 54.60, H 9.54, N 5.47%.

Dipropyl N-cyclopentylphosphoramidate (**24**): ^{1}H NMR δ: 4.05 (m, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 3.72(dd, NH, 1-H exchangeable) 3.45(m, 1-H), 1.74 (m, 4H, 2 CH_2, J = 7.04 Hz), 1.6(m, 8-H for4CH_2 Protons) 0.98(t, 6-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max) 3220(NH), 2950, 2890(C–H), 1250, (P=O), 1090, 1050(P–O–C) cm^{-1}. Anal. Calcd for $C_{11}H_{24}NO_3P$ (249): C 53.01, H 9.71, N 5.62 Found: C 52.90, H 9.45, N 5.58%.

Diisopropyl N-cyclooctylphosphoramidate (**25**): ^{1}H NMR δ: 4.55 (sept, 2-H, $J_{H\text{-}H}$ = 6.0 $J_{H\text{-}P}$ = 6.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.65(m, 14-H for 7 CH_2 Protons) 1.25(d, 12-H, $J_{H\text{-}H}$ = 6.0); IR: (KBr) ν(max)3225(NH), 2965, 2890(C–H), 1260 (P=O), 1090, 1050(P–O–C)cm^{-1}. Anal. Calcd for $C_{14}H_{30}NO_3P$ (291): C 57.71, H 10.39, N 4.81 Found: C 57.43, H 10.35, N 5.20%.

Diisopropyl N-cycloheptylphosphoramidate (**26**): ^{1}H NMR δ: 4.53(sept, 2-H, $J_{H\text{-}H}$ = 6.0 $J_{H\text{-}P}$ = 6.0 Hz), 3.72(dd, NH, 1-H exchangeable), 3.45(m, 1-H), 1.55(m, 12-H for 6 CH_2 Protons) 1.26(d, 12-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max) 3220(NH), 2950, 2890(C–H), 1250 (P=O), 1090, 1050 (P–O–C) cm^{-1}. Anal. Calcd for $C_{13}H_{28}NO_3P$ (277): C 56.31, H 10.18, N 5.05 Found: C 56.53, H 10.27, N 5.30%.

Diisopropyl N-cyclohexylphosphoramidate (**27**): ^{1}H NMR δ: 4.34 (m, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 3.71(dd, NH, 1-H exchangeable), 3.46(m, 1-H), 1.5(m, 10-H for 5 CH_2 Protons) 1.33(t, 6-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max) 3230(NH), 2945, 2877(C–H), 1260, (P=O), 1080, 1040(P–O–C) cm^{-1}. Anal. Calcd for $C_{12}H_{26}NO_3P$ (263): C 54.77, H 9.96, N 5.32 Found: C 54.60, H 9.54, N 5.47%.

Diisopropyl N-cyclopentylphosphoramidate (**28**): ^{1}H NMR δ: 4.35(m, 4-H, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 3.72(dd, NH, 1-H exchangeable)3.45(m, 1-H), 1.6(m, 8-H for 4 CH_2 Protons) 1.33(t, 6-H, $J_{H\text{-}H}$ = 7.0); IR: (KBr) ν(max) 3220(NH), 2950, 2890(C–H), 1250, (P=O), 1090, 1050(P–O–C) cm^{-1}. Anal. Calcd for $C_{11}H_{24}NO_3P$ (249): C 53.01, H 9.71, N 5.62 Found: C 52.90, H 9.45, N 5.58%.

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