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# New phosphoroamidate compounds: Synthesis, structural characterization and studies on $ZnCl_2$ assisted hydrolysis of the P–N bond

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ABSTRACT

A variety of phosphorodiamidate compounds were synthesized from the corresponding phosphorodichloridate intermediates and phosphorus oxychloride. These were completely characterized using different spectroscopic methods and single crystal X-ray diffraction studies on one of them. Studies revealed that water in the presence of a mild Lewis acid like $ZnCl_2$ was found to assist the hydrolysis of the P–N linkage. The proof of this concept was effectively realized through the hydrolysis of hexamethylphosphoramide.



## 1. Introduction

Organophosphorus chemistry is indeed intriguing and spans a variety of research areas which include chemical synthesis, studies on their coordination chemistry with different metals and their role in biomedicine [1]. The chemistry of organophosphorus compounds has been a popular research area because of their applications in agriculture [2], pharmaceuticals [3–8], biology [9,10] and chemical agents [11–17]. Organic phosphines, phosphites, phosphinites and amidophosphinites are widely used in homogeneous catalysis as ligands in transition-metal complexes. The very existence of this area, which is of primary importance in today's chemistry, especially in its infancy, was due to the use of phosphine complexes of palladium, platinum, rhodium, etc. The use of transition-metal complexes with chiral phosphine ligands [18–20] as catalysts is of particular interest when performing asymmetric hydrogenation, hydroformylation and many other reactions. These catalysts enabled the syntheses of enantiomerically pure compounds, including the most important pharmaceutical derivatives. Phosphorus containing polymers possess valuable properties, such as fire resistance and inertness to chemical reagents, which make them interesting from a practical point of view [21,22]. Organophosphorus compounds find extensive use in synthetic organic chemistry. This primarily includes well-known olefination reactions: Wittig reaction and P–O olefination that is, the reaction of phosphorus-containing carbanions with carbonyl compounds (Horner–Woodward–Emmons reaction) [23]. Some organophosphonic acids have been implicated as insecticides and sterilizing agents [24] whereas diphosphonic acids have been found useful for anti inflammatory and pain easing activities [25]. Phosphoramidate compounds containing *N*-phosphorylated amino acids have been particularly useful for their antiviral, antitumor and anti HIV properties [26–29]. Quantum chemical calculations on their structure [30,31] and spectroscopic properties [32–34] of these have revealed interesting conclusions. We were inspired to venture into the chemistry of phosphorodiamidates for their potential use as ligands in the coordination chemistry with transition-metals [35–38]. In this regard, we have developed a general route towards the synthesis of various *N,N′*-dibenzylphosphorodiamidates. These compounds were anticipated to provide bidentate ligating environment with different metal synthons. However, the P–N bond is moderately polar and susceptible to attack by nucleophiles. A simple nucleophile like water in the presence of a mild Lewis acid like $ZnCl_2$ was found to cleave this linkage. The work presented is a reflection of our understanding in this context.

## 2. Experimental

### 2.1. General methods

The reactions concerning the synthesis of phosphorodichloridates and phosphoroamidates were performed under dry argon atmosphere using standard Schlenk techniques with rigorous exclusion of moisture and air. Toluene and tetrahydrofuran (THF) were dried by heating under reflux over sodium and benzophenone and distilled fresh prior to use. All the phenols used in this

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study along with phosphorous oxychloride, hexamethylphosphoramide (HMPA) and zinc chloride were purchased from Aldrich and used without subsequent purification. Toluene, hexane, ethyl acetate, methylene chloride, chloroform and tetrahydrofuran were purchased from Ranchem India. $CDCl_3$ used for NMR spectral measurements was purchased from Aldrich. For the spectral characterization of phosphorodichloridates, the $CDCl_3$ used was dried over calcium hydride and distilled.

### 2.2. Instrumentation

$^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker Avance 400 instrument. Chemical shifts for $^1H$ and $^{13}C$ NMR spectra were referenced to residual solvent resonances and are reported as parts per million relative to $SiMe_4$. $^{31}P$ NMR spectra were recorded relative to 85% $H_3PO_4$ as an external standard. Mass spectra of the sample were recorded on a Micro mass QToF instrument, low resolution electro-spray ionization (ESI) mass spectrometer using methanol solvent. GC–MS were recorded using Jeol JMS GC-Mate II instrument. Infrared spectra were recorded using a Nicolet 6700 FTIR instrument. Elemental analyses were done with a Perkin Elmer Series 11 analyzer.

### 2.3. Synthesis of phosphorodichloridates (**1**–**5**)

The required phenol was stirred under reflux with phosphorous oxychloride in the stoichiometric ratio 1:4 and catalytic amount of lithium chloride. The reaction was monitored using TLC (5% ethyl acetate in hexane) against the required phenol. The time required for completion of the reaction was found to be 24 h for **1**, **4** and **5** and 48 h for **2** and **3**. The reaction mixture was purified by distilling the excess $POCl_3$ under reduced pressure to yield the phosphorodichloridates as colorless viscous liquids.

#### 2.3.1. 2-$MeC_6H_4OP(O)Cl_2$ (**1**)

The compound **1** was synthesized from 2-$MeC_6H_4OH$ (1.0 g, 9.2 mmol), $POCl_3$ (5.6 g, 36.8 mmol) and LiCl (8.7 mg, 0. 2 mmol). Yield = 1.2 g (56%). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.34–7.20 (m, 4H, *ortho*, *meta*, *para*), 2.35 (s, 3H, Ar*Me*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 148.84 (Ar–O), 132.03 (Ar–C), 129.49 (Ar–C), 127.43 (Ar–*Me*), 126.94 (Ar–C), 120.04 (Ar–C), 16.32 (Ar–Me). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 3.44 (s). GC–MS: 224.76 $(M+H)^+$. *Anal.* Calc. for $C_7H_7Cl_2O_2P$: C, 37.37; H, 3.14. Found: C, 37.54; H, 3.08%.

#### 2.3.2. 2-$FC_6H_4OP(O)Cl_2$ (**2**)

The compound **2** was synthesized from 2-$FC_6H_4OH$ (1.0 g, 8.9 mmol), $POCl_3$ (5.5 g, 35.6 mmol) and LiCl (8.4 mg, 0. 2 mmol). Yield = 1.1 g (50%). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.43–7.17 (m, 4H, *ortho*, *meta*, *para*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 154.65 (Ar–F), 148.80 (Ar–O), 128.44 (Ar–C), 125.12 (Ar–C), 122.84 (Ar–C), 117.74 (Ar–C). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 3.01 (s). GC–MS: 228.15 $(M+H)^+$. *Anal.* Calc. for $C_6H_4Cl_2FO_2P$: C, 31.47; H, 1.76. Found: C, 31.68; H, 1.44%.

#### 2.3.3. 2-$ClC_6H_4OP(O)Cl_2$ (**3**)

The compound **3** was synthesized from 2-$ClC_6H_4OH$ (1.0 g, 7.8 mmol), $POCl_3$ (4.8 g, 31.2 mmol) and LiCl (8.4 mg, 0.2 mmol). Yield = 1 g (50%). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.51–7.28 (m, 4H, *ortho*, *meta*, *para*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 145.94 (Ar–O), 131.27 (Ar–C), 128.28 (Ar–C), 127.97 (Ar–Cl), 125.92 (Ar–C), 121.92 (Ar–C). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 4.05 (s). GC–MS: 245.06 $(M+H)^+$. *Anal.* Calc. for $C_6H_4Cl_3O_2P$: C, 29.36; H, 1.64. Found: C, 29.65; H, 1.77%.

#### 2.3.4. 4-$MeC_6H_4OP(O)Cl_2$ (**4**)

The compound **4** was synthesized from 4-$MeC_6H_4OH$ (1.0 g, 9.2 mmol), $POCl_3$ (5.6 g, 36.8 mmol) and LiCl (8.7 mg, 0.2 mmol). Yield = 1.3 g (60%). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.18–7.14 (m, 4H, *ortho*, *meta*), 2.31 (s, 3H, Ar*Me*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 147.57 (Ar–O), 137.06 (Ar–C), 130.75 (Ar–Me), 120.30 (Ar–C), 20.76 (Ar–*Me*). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 3.57 (s). GC–MS: 224.30 $(M+H)^+$. *Anal.* Calc. for $C_7H_7Cl_2O_2P$: C, 37.37; H, 3.14. Found: C, 37.51; H, 3.22%.

#### 2.3.5. 4-*t*-$BuC_6H_4OP(O)Cl_2$ (**5**)

The compound **5** was synthesized from 4-*t*$BuC_6H_4OH$ (1.0 g, 6.8 mmol), $POCl_3$ (4.2 g, 27.2 mmol) and LiCl (8.4 mg, 0.2 mmol). Yield = 1.1 g (62%). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.43 (d, 2H, *meta*), 7.19 (d, 2H, *ortho*), 1.31 (s, 9H, Ar–C*Me*$_3$). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 150.21 (Ar–O), 147.38 (Ar–$CMe_3$), 127.03 (Ar–C), 119.84 (Ar–C), 34.55 (*C*Me$_3$), 31.29 (C*Me*$_3$). $^1P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 3.59 (s). GC–MS: 267.36 $(M+H)^+$. *Anal.* Calc. for $C_{10}H_{13}Cl_2O_2P$: C, 44.97; H, 4.91. Found: C, 45.26; H, 4.69%.

### 2.4. Synthesis of *N,N′*-dibenzylphosphorodiamidates (**6**–**10**)

An aryl phosphorodichloridate and benzylamine in a stoichiometric ratio 1:4 were stirred for 12 h in toluene (10 mL) under ambient conditions to produce the corresponding *N,N′*-dibenzylphosphorodiamidate. The reaction mixture was quenched with water and extracted with methylene chloride. Removal of the volatiles gave the crude product which was subsequently purified by column chromatography (70% of chloroform in hexane as eluent) and obtained as a white solid after removal of volatiles.

#### 2.4.1. 2-$MeC_6H_4OP(O)(NHBn)_2$ (**6**) (Bn = $PhCH_2$–)

The compound **6** was synthesized from **1** (0.45 g, 2 mmol) and $BnNH_2$ (0.86 g, 8 mmol). Yield = 0.4 g (60%). M.p. = 53 °C. IR (neat, $cm^{-1}$): 3377 (N–H), 1223 (P=O), 697 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.44–7.06 (m, 14H, *ortho*, *meta*, *para*), 4.21 (m, 4H, C*H*$_2$Bn), 3.22 (br, 2H, N*H*), 2.23 (s, 3H, Ar*Me*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 149.79 (Ar–O), 139.64 (Ar–C), 129.03 (Ar–C), 128.40 (Ar–C), 127.36 (Ar–C), 127.28 (Ar–C), 127.19 (Ar–*Me*), 126.90 (Ar–C), 124.11 (Ar–C), 119.83 (Ar–C), 45.25 ($CH_2Ph$), 16.50 (Ar–*Me*). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 10.96. HRMS (ESI) for $C_{21}H_{23}N_2O_2P$ $(M+H)^+$: Calc., 367.1575; Found: 367.1577.

#### 2.4.2. 2-$FC_6H_4OP(O)(NHBn)_2$ (**7**)

The compound **7** was synthesized from **2** (0.46 g, 2 mmol) and $BnNH_2$ (0.86 g, 8 mmol). Yield = 0.4 g (53%). M.p. = 48 °C. IR (neat, $cm^{-1}$): 3199 (N–H), 1260 (P=O), 692 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.38–7.05 (m, 14H, *ortho*, *meta*, *para*), 4.18 (m, 4H, C*H*$_2$Bn), 3.05 (br, 2H, N*H*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 158.23 (Ar–F), 155.17 (Ar–O), 139.49 (Ar–C), 128.77 (Ar–C), 127.50 (Ar–C), 125.49 (Ar–C), 124.73 (Ar–C), 123.30 (Ar–C), 116.86 (Ar–C), 45.35 ($CH_2Ph$). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 11.24. HRMS (ESI) for $C_{20}H_{20}FN_2O_2P$ $(M+Na)^+$: Calc., 393.1144; Found: 393.1140.

#### 2.4.3. 2-$ClC_6H_4OP(O)(NHBn)_2$ (**8**)

The compound **8** was synthesized from **3** (0.49 g, 2 mmol) and $BnNH_2$ (0.86 g, 8 mmol). Yield = 0.4 g (51%). M.p. = 70 °C. IR (neat, $cm^{-1}$): 3229 (N–H), 1259 (P=O), 702 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.57–7.13 (m, 14H, *ortho*, *meta*, *para*), 4.24 (m, 4H, C*H*$_2$Bn), 3.17 (br, 2H, N*H*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 146.92 (Ar–O), 138.75 (Ar–C), 130.68 (Ar–C), 128.71 (Ar–C), 128.07 (Ar–C), 127.66 (Ar–C), 127.53 (Ar–C), 126.04 (Ar–Cl), 125.79 (Ar–C), 122.03 (Ar–C), 45.91 ($CH_2Ph$). $^{31}P\{^1H\}$ NMR

(161 MHz $CDCl_3$, ppm): $\delta$ 11.09. HRMS (ESI) for $C_{20}H_{20}ClN_2O_2P$ $(M+Na)^+$: Calc., 409.0849; Found: 409.0845.

#### 2.4.4. 4-$MeC_6H_4OP(O)(NHBn)_2$ (**9**)

The compound **9** was synthesized from **4** (0.45 g, 2 mmol) and $BnNH_2$ (0.86 g, 8 mmol). Yield = 0.5 g (63%). M.p. = 65 °C. IR (neat, $cm^{-1}$): 3198 (N–H), 1200 (P=O), 690 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.31–7.10 (m, 14H, *ortho*, *meta*, *para*), 4.18 (m, 4H, C*H*$_2$Bn), 2.98 (br, 2H, N*H*), 2.31 (s, 3H, Ar*Me*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 148.89 (Ar–O), 139.58 (Ar–C), 134.18 (Ar–*Me*), 130.23 (Ar–C), 128.74 (Ar–C), 127.61 (Ar–C), 120.23 (Ar–C), 45.39 ($CH_2$Ph), 20.83 (Ar–*Me*). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 10.96. HRMS (ESI) for $C_{21}H_{23}N_2O_2P$ $(M+H)^+$: Calc., 367.1575; Found: 367.1581.

#### 2.4.5. 4-*t*-$BuC_6H_4OP(O)(NHBn)_2$ (**10**)

The compound **10** was synthesized from **5** (0.53 g, 2 mmol) and $BnNH_2$ (0.86 g, 8 mmol). Yield = 0.6 g (72%). M.p. = 40 °C. IR (neat, $cm^{-1}$): 3174 (N–H), 1203 (P=O), 690 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.24–7.05 (m, 14H, *ortho*, *meta*, *para*), 4.11 (m, 4H, C*H*$_2$Bn), 2.79 (br, 2H, N*H*), 1.25 (s, 9H, Ar–C*Me*$_3$). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 148.79 (Ar–O), 147.46 (Ar–$CMe_3$), 139.61 (Ar–C), 128.71 (Ar–C), 127.62 (Ar–C), 127.45 (Ar–C), 126.63 (Ar–C), 119.90 (Ar–C), 45.38 ($CH_2$Ph), 34.46 (Ar–*C*Me$_3$), 31.55 (Ar–C*Me*$_3$). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 11.25. HRMS (ESI) for $C_{24}H_{29}N_2O_2P$ $(M+H)^+$: Calc., 409.2045; Found: 409.2048.

### 2.5. Synthesis of 4-*t*-Buphenyl *N,N′*-di–methylbenzylphosphorodiamidate (**11**)

A stirred solution of **5** (1.34 g, 5 mmol) in 10 mL toluene was reacted with (±)-α-methylbenzylamine (3.03 g, 25 mmol) under ambient conditions for 12 h. The reaction mixture was quenched with water and extracted with methylene chloride. Removal of the volatiles gave the crude product which was subsequently purified by column chromatography (60% of chloroform in hexane as eluent) and obtained as a colorless viscous solid after removal of volatiles.

Yield = 1.8 g (81%). IR (neat, $cm^{-1}$): 3199 (N–H), 1213 (P=O), 696 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.29–6.99 (m, 14H, *ortho*, *meta*, *para*), 4.53 (q, 2H, C*H*Me), 3.18 (br, 1H, N*H*), 2.99 (br, 1H, N*H*), 1.43 (d, 6H, CH*Me*), 1.30 (s, 9H, Ar*tBu*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 148.95 (Ar–O), 147.01 (Ar–$CMe_3$), 145.17 (Ar–C), 128.62 (Ar–C), 127.09 (Ar–C), 126.38 (Ar–C), 125.94 (Ar–C), 119.78 (Ar–C), 51.39 (*C*HMe), 34.36 (Ar–*C*Me$_3$), 31.53 (Ar–C*Me*$_3$), 25.34 (CH*Me*). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 8.70. HRMS (ESI) for $C_{26}H_{33}N_2O_2P$ $(M+H)^+$: Calc., 437.2358; Found: 437.2355.

### 2.6. Synthesis of phosphonic acid anion (**12**–**17**)

To a stirred solution of *N,N′*-dibenzylphosphorodiamidate/HMPA in THF (10 mL) was added $ZnCl_2$ under ambient conditions in a stoichiometric ratio 1:1. The time required for completion of the reaction was found to be 12 h for **12**, **15**–**17** and 24 h for **13** and **14**. The solvent was removed under reduced pressure and the reaction mixture was extracted with toluene and subsequently filtered. Evaporation of the solvent yielded the crude product which was purified by crystallization from 1:1 methylene chloride and hexane mixture at 0 °C.

#### 2.6.1. [2-$MeC_6H_4OP(O)O(OH)$][$BnNH_3$] (**12**)

The compound **12** was synthesized from **6** (0.10 g, 0.23 mmol) and $ZnCl_2$ (37 mg). Yield = 42 mg (70%). IR (neat, $cm^{-1}$): 3306 (N–H), 1223 (P=O), 696 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.33–7.11 (m, 9H, *ortho*, *meta*, *para*), 4.21 (m, 2H, C*H*$_2$Ph), 3.89 (s, 5H, THF and O*H*), 2.15 (s, 3H, Ar–*Me*), 1.90 (s, 4H, THF). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 148.84 (Ar–O), 138.34 (Ar–C), 131.63 (Ar–C), 128.88 (Ar–C), 128.77 (Ar–C), 127.69 (Ar–C), 127.38 (Ar–C), 127.30 (Ar–Me), 125.26 (Ar–C), 119.83 (Ar–C), 69.28 (THF), 45.32 (*C*H$_2$Ph), 25.48 (THF), 16.62 (Ar–*Me*). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 13.18. HRMS (ESI) for $C_{14}H_{18}NO_4P$ $(M+THF)^+$: Calc., 367.1549; Found: 367.1553.

#### 2.6.2. [2-$FC_6H_4OP(O)O(OH)$][$BnNH_3$] (**13**)

The compound **13** was synthesized from **7** (0.10 g, 0.27 mmol) and $ZnCl_2$ (36 mg). Yield = 56 mg (70%). IR (neat, $cm^{-1}$): 3302 (N–H), 1202 (P=O), 693 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.29–7.09 (m, 9H, *ortho*, *meta*, *para*), 4.19 (m, 2H, C*H*$_2$Ph), 3.91 (br, 1H, O*H*). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 151.01 (Ar–F), 138.48 (Ar–O), 138.42 (Ar–C), 128.81 (Ar–C), 127.69 (Ar–C), 126.26 (Ar–C), 125.01 (Ar–C), 123.29 (Ar–C), 116.89 (Ar–C), 45.26 (*C*H$_2$Ph). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 13.75. HRMS (ESI) for $C_{13}H_{15}FNO_4P$ $(M+THF)^+$: Calc., 371.1298; Found: 371.1290.

#### 2.6.3. [2-$ClC_6H_4OP(O)O(OH)$][$BnNH_3$] (**14**)

The compound **14** was synthesized from **8** (0.10 g, 0.25 mmol) and $ZnCl_2$ (35 mg). Yield = 55 mg (70%). IR (neat, $cm^{-1}$): 3378 (N–H), 1260 (P=O), 692 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.43–7.10 (m, 9H, *ortho*, *meta*, *para*), 5.05 (s, 1H, O*H*), 4.37 (m, 2H, C*H*$_2$Ph), 3.95 (s, 4H, THF), 1.96 (s, 4H, THF). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 152.04 (Ar–O), 137.28 (Ar–C), 128.70 (Ar–C), 127.78 (Ar–C), 127.34 (Ar–C), 127.03 (Ar–C), 126.96 (Ar–C), 124.92 (Ar–Cl), 122.55 (Ar–C), 117.16 (Ar–C), 69.47 (THF), 45.36 (*C*H$_2$Ph), 25.37 (THF). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 13.62. *Anal.* Calc. for $C_{17}H_{23}ClNO_5P$: C, 52.65; H, 5.98; N, 3.61. Found: C, 52.45; H, 6.37; N, 3.99%.

#### 2.6.4. [4-$MeC_6H_4OP(O)O(OH)$][$BnNH_3$] (**15**)

The compound **15** was synthesized from **9** (0.10 g, 0.27 mmol) and $ZnCl_2$ (37 mg). Yield = 42 mg (70%). IR (neat, $cm^{-1}$): 3302 (N–H), 1202 (P=O), 694 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.31–7.28 (m, 9H, *ortho*, *meta*, *para*), 4.18 (m, 2H, C*H*$_2$Ph), 3.90 (s, 5H, THF and O*H*), 2.30 (s, 3H, Ar–*Me*), 1.92 (s, 4H, THF). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 148.64 (Ar–O), 142.30 (Ar–C), 138.47 (Ar–Me), 135.12 (Ar–C), 130.40 (Ar–C), 128.78 (Ar–C), 127.56 (Ar–C), 120.18 (Ar–Me), 69.13 (THF), 45.25 (*C*H$_2$Ph), 25.52 (THF), 20.81 (Ar–*Me*). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 13.44. HRMS (ESI) for $C_{14}H_{18}NO_4P$ $(M+THF)^+$: Calc., 367.1549; Found: 367.1548.

#### 2.6.5. [4-*t*-$BuC_6H_4OP(O)O(OH)$][$BnNH_3$] (**16**)

The compound **16** was synthesized from **10** (0.10 g, 0.24 mmol) and $ZnCl_2$ (33 mg). Yield = 58 mg (70%). IR (neat, $cm^{-1}$): 3316 (N–H), 1211 (P=O), 695 (P–N). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.34–7.04 (m, 9H, *ortho*, *meta*, *para*), 4.22 (m, 2H, C*H*$_2$Ph), 3.89 (s, 5H, THF and O*H*), 1.90 (s, 4H, THF), 1.29 (s, 9H, Ar–C*Me*$_3$). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 148.14 (Ar–O), 147.89 (Ar–C), 138.67 (Ar–$CMe_3$), 138.42 (Ar–C), 128.73 (Ar–C), 127.54 (Ar–C), 126.79 (Ar–C), 119.70 (Ar–C), 68.30 (THF), 45.19 ($CH_2$Ph), 34.46 (Ar–*C*Me$_3$), 31.48 (Ar–C*Me*$_3$), 25.68 (THF). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 13.66. HRMS (ESI) for $C_{17}H_{24}NO_4P$ $(M+THF)^+$: Calc., 409.2018; Found: 409.2016.

#### 2.6.6. [$Me_2NP(O)O(OH)$][$Me_2NH_2$] (**17**)

HMPA (0.10 g, 0.56 mmol) and $ZnCl_2$ (76 mg) were used. Yield = 70 mg (75%). IR (neat, $cm^{-1}$): 3360 (N–H), 1181 (P=O). $^1H$ NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 3.89 (s, 4H, THF), 2.62 (br, 12H, N*Me*), 1.89 (s, 4H, THF). $^{13}C$ NMR (100 MHz $CDCl_3$, ppm): $\delta$ 69.13 (THF), 36.78 (N*Me*), 25.36 (THF). $^{31}P\{^1H\}$ NMR (161 MHz $CDCl_3$, ppm): $\delta$ 27.85. *Anal.* Calc. for $C_8H_{23}N_2O_4P$: C, 39.66; H, 9.57; N, 11.56. Found: C, 40.01; H, 9.39; N, 11.41%.

**Table 1**
Crystal data for the structures **10** and **15**.

| Compound | **10** | **15** |
|---|---|---|
| Empirical formula | $C_{48}H_{58}N_4O_4P_2$ | $C_{28}H_{36}N_2O_8P_2$ |
| Formula weight | 816.92 | 590.53 |
| Crystal system | monoclinic | monoclinic |
| Space group | $P2_1/c$ | $P2_1/c$ |
| $T$ (K) | 173 | 173 |
| Wavelength (Å) | 0.71073 | 0.71073 |
| $a$ (Å) | 20.8933(8) | 12.9529(8) |
| $b$ (Å) | 9.8712(3) | 6.5937(4) |
| $c$ (Å) | 22.5314(8) | 17.3840(11) |
| $\alpha$ (°) | 90 | 90 |
| $\beta$ (°) | 99.200(10) | 90.443(3) |
| $\gamma$ (°) | 90 | 90 |
| $V$ (Å$^3$) | 4587.1(3) | 1484.68(16) |
| $Z$ | 4 | 2 |
| $D_{calc}$ (g cm$^{-3}$) | 1.183 | 1.321 |
| Reflections collected | 31 921 | 10 463 |
| Number of independent reflections | 11 178 | 3620 |
| Goodness-of-fit (GOF) | 1.016 | 0.979 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1 = 0.0505$, $wR_2 = 0.1358$ | $R_1 = 0.0499$, $wR_2 = 0.1293$ |
| $R$ indices (all data) | $R_1 = 0.0914$, $wR_2 = 0.1676$ | $R_1 = 0.0814$, $wR_2 = 0.1563$ |

$R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR_2 = [\sum(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$.

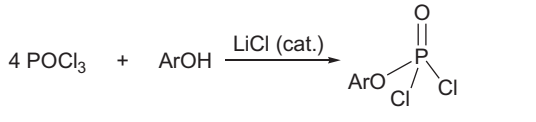
### 2.7. X-ray crystallography

Single crystals of **10** and **15** suitable for structural studies were obtained by crystallization from 1:1 methylene chloride/hexane mixture at 0 °C over a period of one week. X-ray data collection was performed with Bruker AXS (Kappa Apex 2) CCD diffractometer equipped with graphite monochromated Mo (Kα) ($\lambda = 0.7107$ Å) radiation source. The data were collected with 100% completeness for $\theta$ up to 25°. ω and φ scans were employed to collect the data. The frame width for ω was set to 0.5° for data collection. The frames were integrated and data were reduced for Lorentz and polarization corrections using SAINT-NT. The multi-scan absorption correction was applied to the data set. All structures were solved using SIR-92 and refined using SHELXL-97 [39]. The crystal data are summarized in Table 1. The non-hydrogen atoms were refined with anisotropic displacement parameter. All the hydrogen atoms could be located in the difference Fourier map. The hydrogen atoms bonded to carbon atoms were fixed at chemically meaningful positions and were allowed to ride with the parent atom during refinement.

## 3. Results and discussion

### 3.1. Synthesis and characterization

The phosphodichloridates (**1–5**) were synthesized by heating various phenols with excess $POCl_3$ in the presence of catalytic amount of lithium chloride under reflux conditions (Scheme 1).




Ar = 2-$MeC_6H_4$ **1**; 2-$FC_6H_4$ **2**; 2-$ClC_6H_4$ **3**; 4$MeC_6H_4$ **4**; 4-*t*$BuC_6H_4$ **5**

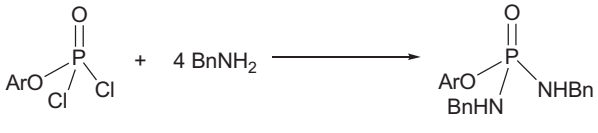
**Scheme 1.** Synthesis of phosphodichloridates.

These were isolated in moderate yields as colorless viscous liquids after distilling off the excess $POCl_3$. The $^1$H NMR of **1–5** contains the signals for all moieties in the required ratio. $^{13}$C NMR reveals that the phenyl carbon atom directly bonded to oxygen is considerably deshielded with respect to the other aromatic peaks with the exception of **2** where the aromatic carbon atom attached to fluorine is even further deshielded. These compounds showed only one signal in their $^{31}$P{$^1$H} NMR as expected from the structure. GC–MS spectra recorded on these compounds reveal the molecular ion peaks as a proton adduct. Finally, their purity was assured through the correct elemental analysis values. Reliable IR spectra could not be obtained as a result of the sensitivity of these compounds to moisture. These compounds have been reported in the literature previously where some were prepared by the reaction of the sodium phenolate salt with $POCl_3$ [40] or reaction of the phenol with $POCl_3$ in the presence of an acid scavenger like $Et_3N$ [41] or direct reaction of phenol with $POCl_3$ in the presence of NaCl [42]. Our contribution has been in the establishment of a reliable synthetic route and thorough unambiguous characterization of these compounds by various spectroscopic methods.

The *N,N′*-dibenzylphosphorodiamidate derivatives (**6–10**) were synthesized by reacting the corresponding aryl phosphorodichloridate (**1–5**) with benzyl amine in toluene (Scheme 2). These compounds were isolated in 50–70% yield after work up and column chromatography as white solids.

The IR spectra of **6–10** reveal peaks due to $\nu_{N-H}$, $\nu_{P=O}$ and $\nu_{P-N}$ with prominent intensities. The $^1$H NMR of **6–10** reveals all the expected signals in the correct ratio of integration. The benzylic protons appear as a complex multiplet in **6–10** as a result of coupling with the neighboring –NH proton and phosphorus with $^2J_{P-N} = 11.9$ Hz [43]. The aromatic signals of these compounds in the $^{13}$C NMR have resemblance to their parent phosphodichloridates. The $^{31}$P{$^1$H} NMR of these **6–10** reveal a single peak at *ca.*11 ppm that is downfield shifted *ca.* 8 ppm with respect to the parent phosphodichloridates compounds. The structural identity and the purity of these compounds were determined using HRMS analysis. The unambiguous structural analysis was performed by measuring the single crystal X-ray structure of **10**. In a similar manner, compound **11** was synthesized using **5** and (±)-α-methylbenzylamine. It is noteworthy to mention that the $^1$H NMR of this compound shows two broad signals corresponding to the –NH moiety. Their authenticity as –NH protons was confirmed using $D_2O$ exchange studies. The $^{31}$P{$^1$H} NMR signal is upfield shifted in comparison to **6–10**. This is attributed as a result of electron donation from the methyl group on the α carbon atom.

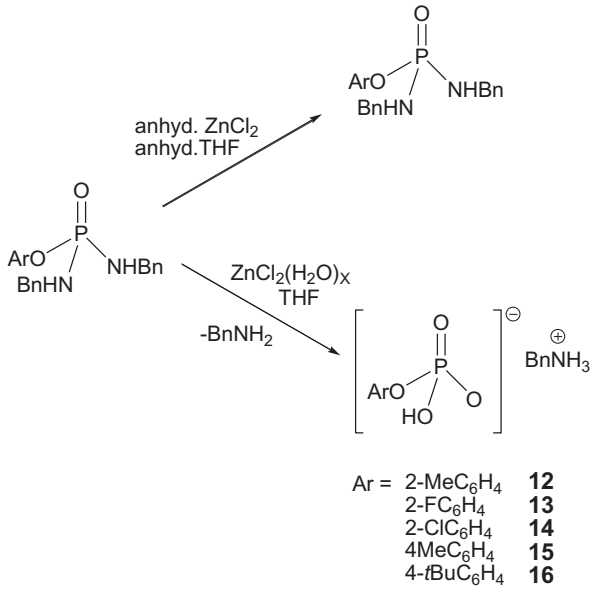
Our initial studies aimed at exploring the reactions of anhydrous $ZnCl_2$ with **6–10**. These reactions were performed with the rigorous exclusion of moisture and air in dry THF at ambient temperature. To our surprise, there was no reaction. Such an observation remained consistent when dioxane was used as a solvent and the reaction mixture were heated to reflux. This observations may be rationalized by reasoning that the acidity of the –NH proton is




Ar = 2-$MeC_6H_4$ **6**; 2-$FC_6H_4$ **7**; 2-$ClC_6H_4$ **8**; 4$MeC_6H_4$ **9**; 4-*t*$BuC_6H_4$ **10**

**Scheme 2.** Synthesis of *N,N′*-dibenzylphosphorodiamidate.

lower than that of the –OH proton. Interestingly, when such reaction mixtures were exposed to air over prolonged periods of time, a white precipitate appeared. Analysis of such reaction mixtures using $^1$H NMR after removal of volatiles clearly revealed that some definite change may have taken place. The –NH signal disappeared completely. $^1$H NMR signals corresponding to $BnNH_2$ was seen. These observations prompted us to reinvestigate these reactions under ordinary conditions by using regular reagent grade THF that was not dried previously and exposing them to air. The initial clear solution containing the reactants became slightly turbid. The volatiles were removed and $^1$H of the reaction mixture had the same characteristics as before. In each case the results were identical resulting in a puzzle. This mystery was solved by treatment of **9** with $ZnCl_2$ and isolating the product. This was subsequently crystallized using methylene chloride/hexane mixture at 0 °C and subjected to single crystal X-ray diffraction studies. Our understanding has been depicted in Scheme 3.




**Scheme 3.** Reaction of *N,N′*-dibenzylphosphorodiamidate with $ZnCl_2$.

It is clear that there is cleavage of the P–N bond which is assisted by mild Lewis acid like $ZnCl_2$, leading to the formation of phosphonic acid. Literature reports such a P–N bond cleavage initiated by strong mineral acids under reflux conditions [44,45]. It is also believed that the P–N bond can be cleaved using Pd salts where the product is not as simple as this [46]. Our method may be considered superior since the transformation is brought about using an environmentally benign cheap salt like $ZnCl_2$, in the complete absence of mineral acids.

Compounds **12–16** were isolated in good yields using the above method. The spectral characteristics are similar to those observed for the *N,N′*-dibenzylphosphorodiamidate precursors **6–10**, respectively.

As an application to this concept we decided to carry out a similar strategy with HMPA with the hope of cleaving the P–N bond. To our surprise, we found that the concept was viable and the expected acid $[Me_2NP(O)O(OH)][Me_2NH_2]$ (**17**) was isolated in good yield. This method may be considered a way to detoxify HMPA. This hydrolysis works equally well with other halide salts of zinc like $ZnBr_2$ but we preferred $ZnCl_2$ because of its lower cost and ease of availability. The reaction with other transition-metal divalent cations like $Cu^{2+}$, $Mn^{2+}$ and $Ni^{2+}$ is extremely slow and appreciable product could not be isolated under comparable conditions with $ZnCl_2$.

**Table 2**
Selected bond lengths [Å] and bond angles [°] for compound **10**.

| | |
|---|---|
| P(1)–O(1) | 1.477(13) |
| P(2)–O(2) | 1.607(14) |
| P(1)–N(1) | 1.621(18) |
| P(1)–N(2) | 1.620(17) |
| N(1)–P(1)–N(2) | 111.91(9) |
| O(1)–P(1)–N(2) | 113.76(9) |
| O(1)–P(1)–O(2) | 113.80(8) |
| O(2)–P(1)–N(1) | 103.57(8) |

**Table 3**
Selected bond lengths [Å] and bond angles [°] for compound **15**.

| | |
|---|---|
| P(1)–O(1) | 1.612(16) |
| P(1)–O(2) | 1.562(16) |
| P(1)–O(3) | 1.497(16) |
| P(1)–O(4) | 1.490(14) |
| O(2)–H(2A) | 0.8270(3) |
| O(1)–P(1)–O(2) | 106.20(8) |
| O(1)–P(1)–O(3) | 103.40(9) |
| O(3)–P(1)–O(4) | 118.15(8) |
| O(2)–P(1)–O(4) | 107.92(9) |

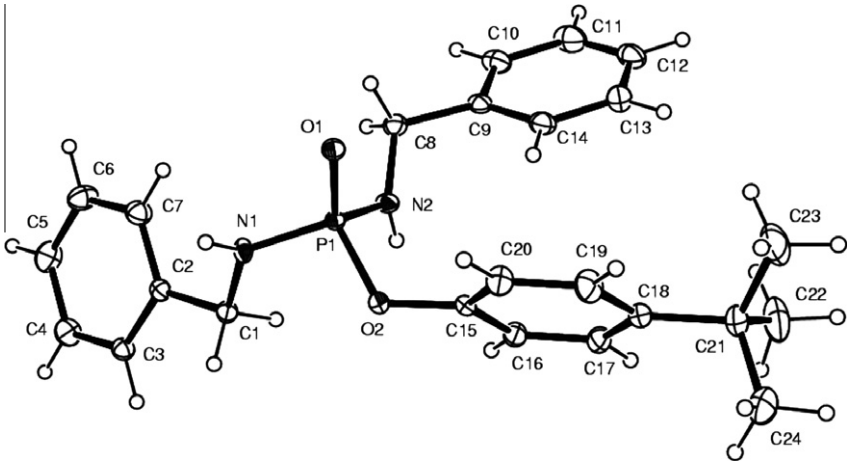



**Fig. 1.** Molecular structure of **10**; thermal ellipsoids were drawn at 30% probability level.

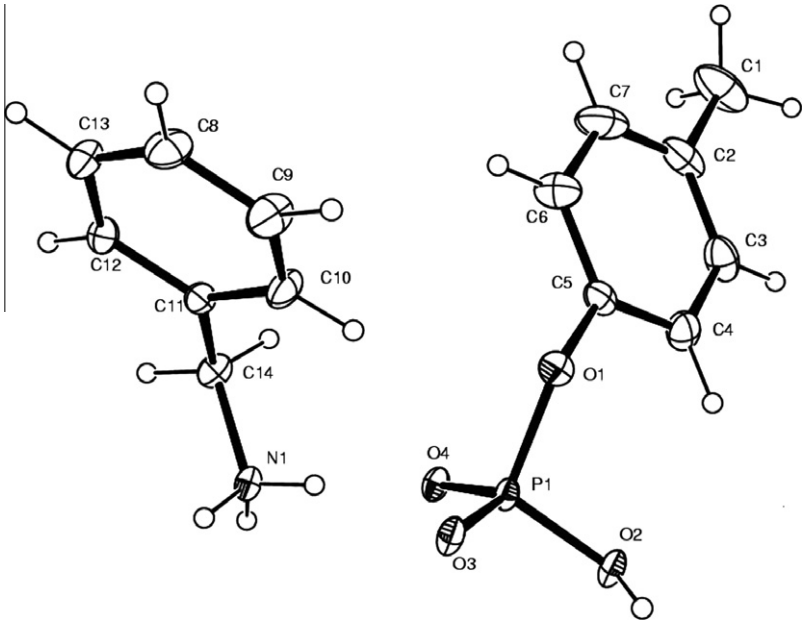



**Fig. 2.** Molecular structure of **15**; thermal ellipsoids were drawn at 30% probability level.

*3.2. Single crystal X-ray diffraction studies*

Among the several compounds synthesized in this study, suitable crystals for X-ray diffraction studies could be obtained from **10** and **15**. Single crystals were grown from dilute solutions of these compounds in 1:1 methylene chloride/hexane mixture at 0 °C over a period of one week. Compound **10** crystallizes in the monoclinic space group $P2_1/c$ with two molecules in the unit cell. Selected bond lengths and angles are listed in Table 2 and the molecular structure is depicted in Fig. 1.

As seen from the bond lengths and angles, the phosphorus center is in a distorted pyramidal environment. The P═O bond length is slightly shorter than the P–O length. The P–N bonds are nearly identical.

Compound **15** crystallizes in the monoclinic space group $P2_1/c$. Selected bond lengths and angles are given in Table 3 and the molecular structure is depicted in Fig. 2.

The bond lengths reveal that the lengths of the P═O and P–O moieties are almost identical suggesting delocalization in these bonds. The structure of the anion resembles that of a distorted pyramid. There is interaction between one of the delocalized P–O bonds and one of the N–H protons of the cation. These are separated by 1.954(2) Å.

## 4. Conclusions

In summary, we have developed reliable synthetic routes and characterization for the preparation of phosphorodichloridates and *N*,*N*′-dibenzylphosphorodiamidates. These compounds were synthesized in moderate yields and good purity. We have described the $ZnCl_2$ assisted cleavage of the P–N bond.

## Acknowledgements

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## Appendix A. Supplementary data

CCDC 750875 and 750876 contain the supplementary crystallographic data for **10** and **15**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.poly.2010.04.002.

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