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Synthesis of Some Cyclophosphorodiamidates Derivatives of *Bis*(2-chloroethyl)amine

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Phenyl phosphorodichloridate (**1**) is readily prepared by reaction of phenol with phosphoryl chloride at low temperature. The crude product is white in colour is subjected to vacuum distillation. However, this reagent reacts only poorly with *bis*(2-chloroethyl)amine hydrochloride at ambient temperature; thus, an alternative route was sought to aniline and to give **2** and **3**, respectively compounds. Compound (**3**) reacted with aniline and diazabicyclo[2,2,2]octane in refluxing toluene to give **4**. Reaction of **3** with diazabicyclo[2,2,2]octane and potassium *tert*-butoxide in refluxing toluene gave **5** and **6**, respectively which compound **6** arised from elimination of HCl from the 2-chloroethyl group of compound **5**. Reactions proceed in high yield, under mild conditions. The structures of prepared compounds were confirmed by ^{1}H, ^{31}P and ^{13}C NMR spectroscopy, mass spectrometry and X-ray crystallography.

Key Words: Phosphoramides, *Bis*(2-chloroethyl)amine, Cyclophosphamide.

INTRODUCTION

Cyclophosphamide, an alkylating agent prepared over 45 years ago by Arnold and Bourseaux[1], has become widely used in cancer chemotherapy[2]. An unique mode of action involves hydroxylation of the heterocyclic compounds, followed by breakdown to generate phosphoramide mustard, which is a potent to DNA alkylator[3]. Other agents containing the masked *bis*(2-chloroethyl)amine group are also in clinical use or pre-clinical evalution. These include the phenylbutyric acid compound chlorambucil[4] and the phenylamine derivative melphalan[5].

Since the first synthesis of phosphoramide mustard and evaluation of its antitumor activites, the investigation of the chemistry and biological activity of phosphoramide mustards has been vigorously pursued in many research laboratories. Friedman and co-workers[6,7] have prepared aliphatic, aromatic and cyclic phosphorodiamidate, phosphorotriamidates, phosphorodiamidic monoesters, phosphoroamidic diesters, as well as various phosphorodiamidic acids and phosphoramidic acid monoesters of N,N-*bis*(2-chloroethyl)amine.

Subsequently, the same authors have reported the synthesis of the diamide derivatives *via* a phosphoramidochloridate prepared by reacting N,N-*bis*(2-chloroethyl)phosphoramidodichloridate with phenols[8-10]. The antitumor activities of these compounds were investigated and it is reported that some of them have shown biological activity.

This work reports the synthesis of phenyl N,N-*bis*(2-chloroethyl)-N'-cyclophosphorodiamidates (**4**), (**5**) and (**6**). These cyclization reactions as a route to interesting heterocyclic ring systems were briefly explored.

EXPERIMENTAL

^{31}P NMR spectra were recorded on a varian DPX300 spectrometer operating at 101.249 MHz and shifts are reported in units of δ relative to 85 % phosphoric acid as external standard, positive shifts are downfield. ^{13}C NMR spectra were recorded on a varian DPX300 spectrometer operating at 62.902 MHz and shifts are reported in units of δ relative to TMS. Both ^{13}C and ^{31}P NMR spectra were proton noise decoupled and all signals were singlets unless otherwise stated. ^{1}H NMR spectra were recorded on a varian DPX300 spectrometer opera-ting at 250.132 MHz and are reported in units of δ relative to TMS. All NMR spectra were recorded in $CDCl_3$ and TMS as internal standard or 85 % H_3PO_4 as external standard unless otherwise stated and all coupling constants are reported in Hz. EI-MS were recorded on a VG7070H spectrometer.

All experiments involving water sensitive reagents were carried out under dry conditions. Where needed, anhydrous solvents and reagents were obtained in the following ways: Et_3N, Et_2O, hexane and CH_2Cl_2, were refluxed over CaH_2 for several hours and distilled. All but Et_3N were further dried over activated 4 Å molecular sieves. All alcohols were distillated onto activated 4 Å molecular sieves. The reactions were monitored by TLC and visualized with UV light followed by development using *n*-hexane and ethyl acetate 7:3 (v/v) and Et_2O:hexane (3 :1) as an eluent.

General procedure

Synthesis of phenyl phosphorodichloridate (1): Dry Et_3N (7.48 mL, 53.6 mmol) and C_6H_5OH (5.04 g, 53.6 mmol) in Et_2O (100 mL) were added dropwise with vigorous stirring to phosphoryl chloride (5.0 mL, 53.6 mmol) in Et_2O (100 mL) at -78 ºC under an atmosphere of nitrogen. The mixture was allowed to warm to ambient temperature, stirred for 20 h, then filtered and the solvent removed under reduced pressure to give the crude product. Spectral data: Yield: 87 %; b.p. 241-243 ºC; ^{31}P NMR: δ = 4.33.

Synthesis of phenyl-N, N-*bis*(2-chloroethyl)phosphoramidochloridate (2): *Bis*(2-chloroethyl) amine hydrochloride (51.5 g, 0,288 mol), dry methylene chloride (300 mL) and triethylamine (58.4 g, 0.577 mol) were placed in a 3-necked round bottom flask protected from moisture with a calcium chloride tube. Phenyl phosphorodichloridate (60.8 g, 0.288 mol) was dissolved in dry methylene chloride (73 mL) and added dropwise over 25 min and the mixture was stirred at ambient temperature overnight. The precipitated triethylamine hydrochloride was removed by suction filtration. The filtrate was extracted with 1 M HCl (2 mL × 50 mL). After addition of saturated sodium bicarbonate solution to remove excess acide, the organic layer was washed with distilled water or saturated NaCl solution until the wash liquid was neutral to litmus.

It was dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and then subjected to high vacuum until a constant weight was obtained. The final product is an orange-brown oil which was used without further purification, but which can be decolorized P_2O_5. Yield 81.9 g (89-92 %) and b.p. 232-237 ºC (literature[6] 75 %). Spectral data: ^{1}H NMR ($CDCl_3$) δ: 3.52-3.72 (m, -CH_2CH_2-, 8H), 7.22-7.36 (m, C_6H_5, 5H). ^{13}C NMR ($CDCl_3$) δ: 41.08 (s, C1), 49.20 (d, $^3J_{P\text{-}C}$ = 4.8 Hz, C2), 120.08 (d, $^3J_{P\text{-}C}$ = 5.7 Hz, C3), 125.85 (s, C5), 129.70 (s, C4), 149.30 (d, $^2J_{P\text{-}C}$ = 8.6 Hz, C8). ^{31}P NMR ($CDCl_3$) δ: 11.3.

Synthesis of phenyl-N, N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (3): The reaction was carried out by a slight modification of literature[11] procedure. Phenyl N, N-*bis*(2-chloroethyl)phosphoramidochloridate (**2**) (9.48 g, 29.9 mmol) in toluene (30 mL) was heated to reflux. Aniline (2.76 g, 29.6 mmol) and diazabicyclo[2.2.2]octane (DABCO) (3.41 g, 30.4 mmol) were dissolved in toluene (50 mL) and added to the refluxing solution of phosphoramidochloridate. Refluxing was continued for 2 h following the addition. Methylene chloride (150 mL) was added and the reaction mixture was extracted successively with 1 M HCl (3 mL × 100 mL), saturated sodium bicarbonate solution (3 mL × 50 mL) and water (4 mL × 100 mL). The organic phase was dried with anhydrous sodium sulfate and filtered to give a wine-red solution. The solution was decolorized with activated charcoal and filtered. Removal of solvent *in vacuo* gave 7.09 g (63 %) of syrupy crude. The crude material was dissolved in hot toluene (40 mL) and set aside. On cooling, a solid formed which was recovered by filtration, 0.365 g (4 %). The solid was recrystallized from methanol, m.p. 161-162 ºC. Spectral data: ^{1}H NMR ($CDCl_3$) δ: 3.41-3.56 (m, CH_2, 8H), 6.06 (d, $^2J_{P\text{-}H}$ = 9.0 Hz, N-H, 1H), 6.98-7.35 (m, Ar, 13H). ^{13}C NMR ($CDCl_3$) δ: 41.84 (s, C1), 49.51 (d, $^3J_{P\text{-}C}$ = 4.7 Hz, C2), 117.94 (d, $^3J_{P\text{-}C}$ = 7.2 Hz, C3), 120.38 (d, $^3J_{P\text{-}C}$ = 4.7 Hz, C9), 122.19 (s, C5), 125.07 (s, C11), 128.32 (s, benzene), 129.30 (s, C4), 129.72 (s,C10), 139.15 (d, $^2J_{P\text{-}C}$ = 1.9 Hz, C8), 150.17 (d, $^2J_{P\text{-}C}$ = 6.6 Hz, C14). ^{31}P NMR ($CDCl_3$) δ: 5.60.

Phenyl N(4-phenylpiperazinyl)-N'-phenylphosphorodiamidate (4): Phenyl N,N-*bis*(2-chloroethyl)phosphoramido chloridate (**2**) (7.90 g, 0.0250 mol) in toluene (13 mL) as stirred at refluxing condition. The refluxing reaction mixture was added a solution of aniline (2.30 g, 0.0250 mol) and diazabicyclo[2.2.2]octane (2.8 g, 0.0250 mol) in toluene (13 mL) over 20-25 min; refluxing was maintained for 18 h. The reaction mixture was allowed to cool and HCl (150 mL) was added and then the mixture was extracted with methylene chloride (300 mL). The combined methylene chloride layer was extracted with HCl (200 mL) followed by saturated sodium bicarbonate solution. The resulting organic phase was washed with water, dried over Na_2SO_4 and filtered. The filtrate was decolorized with activated charcoal. After removal of spent charcoal by filtration, the filtrate was concentrated *in vacuo* to a viscous, orange residue. Examination of the crude [TLC on alumina, Et_2O:hexane (3:1)] showed three main components (R_f = 0, R_f = 0.4 and R_f = 0.6). The residue was suspended in hexane and while heated, toluene was added until a clear solution resulted (procedure hereafter referred to as crystallizing from hexane/toluene). On standing, the title compound precipitated from solution as a white, fluffy solid (TLC, R_f = 0.4). The mother liquor was concentrated to give the target compound as a residue, 0.94 g yield (10 %). The white fluffy solid was recrystallized from toluene (0.24 g, 2.5 %), m.p. 137.5-138.0 ºC. Spectral data: ^{1}H NMR ($CDCl_3$) δ: 2.96-3.00 (m, CH_2, 4H), 3.36-3.41 (m, CH_2, 4H), 5.89(d, $^2J_{P\text{-}H}$ = 9.0 Hz, N-H, 1H), 6.82-7.28 (m, Ar, 15H). ^{13}C NMR ($CDCl_3$) δ: 44.43 (d, J = 10.0 Hz, CH_2), 49.55 (d, J = 6.34 Hz, CH_2); (d PhO): 120.46 (d, $^3J_{P\text{-}C}$ = 4.5 Hz, C_{ortho}), 124.79 (s, C_{para}), 129.20 (s, C_{meta}), 150.53 (d, $^2J_{P\text{-}C}$ = 6.3 Hz, C_{ipso}) ; (d PhN) : 118.06 (d, $^3J_{P\text{-}C}$ = 7.3 Hz, C_{ortho}), 121.90 (s, C_{para}), 129.07 (s, C_{meta}), 139.48 (d, $^2J_{P\text{-}C}$ = 1.8 Hz, C_{ipso}); (d diaza-Ph): 116.48 (s, C_{ortho}), 120.23 (s, C_{para}), 129.66 (s, C_{meta}), 151.23 (s, C_{ipso}). ^{31}P NMR ($CDCl_3$) δ: 3.0; MS (ESI-) expected for $C_{22}H_{24}N_3O_2P$ [M-H]- 393. Found (%) 393.2. Anal. calcd. (%) for $C_{22}H_{24}N_3O_2P$: C, 67.16; H, 6.15; N, 10.68. Found (%): C, 67.18; H, 6.20; N, 10.71.

Synthesis of 1-(2-chloroethyl)-2-phenoxy-3-phenyl-1,3,2-diazaphospholidine-2-oxide (5): Phenyl N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**3**) (3.06 g, 8.20 mmol) and diazabicyclo[2.2.2]octane (0.920 g, 8.20 mmol) were placed in dry toluene (20 mL) and heated liquid. The hydrochloride was triturated with hot toluene. Combined organic layer was concentrated under reduced pressure and subjected to a high vacuum to yield 1.17 g of residue which ^{31}P NMR showed to be a mixcture of 1-(2-chloroethyl)-2-phenoxy-3-phenyl-1,3,2-diazaphospholidine-2-oxide (**5**) and unreacted starting material (**3**) (yields 33 and 67 %, respectively by ^{31}P NMR analysis). The residue was purified by dry column chromatography on silica gel with diethyl ether: acetone (9 :1). Trituration of the silica with methylene chloride and subsequent evaporation of the solvent gave the desired compound as white crystals, 0.35 g yield (26 %), m.p. 114.0-115.0 ºC. Spectral data: ^{1}H NMR ($CDCl_3$) δ: 3.21-3.28 (m,

CH_2, 2H), 3.35-3.48 (m, CH_2, 2H), 3.51-3.57(m, CH_2, 2H), 3.66 (t, CH_2, 2H), 6.91-7.34 (m, Ar, 10H). ^{13}C NMR ($CDCl_3$) δ: 42.33(d, J_{P-C} = 3.62 Hz, CH_2), 42.74 (d, J_{P-C} = 13.58 Hz, CH_2), 43.96 (d, J_{P-C} = 12.7 Hz, CH_2), 47.21 (d, J_{P-C} = 5.4 Hz, CH_2); (δ PhO): 120.90 (d, $^3J_{P-C}$ = 4.5 Hz, C_{ortho}), 124.89 (d, $^5J_{P-C}$ = 1.8 Hz, C_{para}), 129.33 (d, $^4J_{P-C}$ = 1.8 Hz, C_{meta}), 150.68 (d, $^2J_{P-C}$ = 9.1 Hz, C_{ipso}); (δ PhN): 115.97 (d, $^3J_{P-C}$ = 4.5 Hz, C_{ortho}), 121.74 (s, C_{para}), 129.19 (s, C_{meta}), 140.67 (d, $^2J_{P-C}$ = 6.3 Hz, C_{ipso}) ; ^{31}P NMR ($CDCl_3$) δ: 13.47; MS (ESI-) expected for $C_{16}H_{18}ClN_2O_2P$ [M-H]- 336. Found (%) 336.2. Anal. calcd. (%) for $C_{16}H_{18}N_2O_2PCl$: C, 57.06; H, 5.39;Cl, 10.53; N, 8.32. Found (%): C, 57.08; H, 5.35;Cl, 10.62; N, 8.31.

Synthesis of 2-phenoxy-3-phenyl-1-vinyl-1,3,2-diazaphospholidine 2-oxide (6): While phenyl N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**2**) (6.34 g, 0.0170 mol) in dry toluene (20 mL) was stirred at reflux, potassium tert-butoxide (34 mL, 0.0340 mol) was added dropwise by syringe at such a rate as to maintain gentle reflux. The reaction mixture was allowed to cool. ^{31}P NMR showed a quantitative conversion of starting material to product. Water (100 mL) was added and the mixture was extracted with methylene chloride (300 mL). The combined methylene chloride layer was washed with water (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vaccuo* to a viscous, light-yellow oil which crystallized under high vacuum overnight, 4.99 g yield (98 %). The crude material was crystallized from hexane/toluene, 4.29 g yield (84 %); m.p. 84.0-85.0 ºC. Spectral data: ^1H NMR ($CDCl_3$) δ: 3.04-3.11 (m, CH_2, 1H), 3.21-3.29 (m, CH_2, 1H), 3.40-3.49 (m, CH_2, 1H), 3.60-3.69 (m, CH_2, 1H), 4.21 (d, vinyl-H^a, 1H), 4.38 (ddd, vinyl-H^b, 1H), 6.70-6.78 (m, vinyl-H^c-1H), 6.85-7.39 (m, Ar, 10H). ^{13}C NMR ($CDCl_3$) δ: 39.73 (d, $^2J_{P-C}$ = 10.78 Hz, CH_2), 42.03 (d, $^2J_{P-C}$ = 12.68 Hz, CH_2), 91.50 (d, $^3J_{P-C}$ = 10.0 Hz, vinyl CH_2); (δ OhO): 121.26 (δ, $^3J_{P-C}$ = 3.6 Hz, C_{ortho}), 125.37 (s, C_{para}), 129.53 (s, C_{meta}), 140.48 (d, $^2J_{P-C}$ = 6.3 Hz, C_{ipso}); (δ PhN): 116.24 (d, $^3J_{P-C}$ = 5.4 Hz, C_{ortho}), 122.18 (s, C_{para}), 129.48 (s, C_{meta}), 150.44 (d, $^2J_{P-C}$ = 9.1 Hz, C_{ipso}); ^{31}P NMR ($CDCl_3$) δ: 8.00.

RESULTS AND DISCUSSION

The reaction of phenol with phosphoryl chloride in diethyl ether in the presence of triethylamine at -78 ºC gave ethyl phosphorodichloridate (**1**) as a crude product with 87 % yield. Phenyl N,N-*bis*(2-chloroethyl)phosphoramidochloramidate (**2**) was prepared in 89-92 % yield by the reaction of phenylphosphorodichloridate with N,N-*bis*(2-chloroethyl)-amine hydrochloride in methylene chloride at ambient temperature. Compound **2** reacted with various aniline in THF to give phenyl N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**3**) which crystallized from benzene. The ^1H and ^{13}C NMR spectra of **3** had pointed to the incorporation of benzene in the crystal lattice. In order to prove this, single crystals of the compound were obtained by slow evaporation of a benzene solution of the sample. An X-ray crystal structure analysis of the compound was done. The position of benzene in the solvent crystal is shown in the crystal structure (Fig. 1).

Compound **3** reacted with aniline and DABCO in refluxing toluene to give phenyl N-(4-phenyl)piperazinyl-N'-phenylphosphorodiamidate (**4**) and a 1,5-cyclization reaction product, 1-(2-chloroethyl)-2-phenoxy-3-phenyl-1,3,2-diazaphospholidine 2-oxide (**5**). A comparison of the ^1H NMR spectrum of (**5**) with the ^1H NMR spectrum of **3** shows that the doublet at δ = 5.87 due to the aniline hydrogen is absent from (**5**). Compound (**5**) was also prepared in 35 % yield by reaction of (**3**) with DABCO. Reaction (**3**) with one molar equivalent of potassium *tert*-butoxide in refluxing toluene gave (**5**) and 2-phenoxy-3-phenyl-1-vinyl-1,3,2-diazaphospholidine 2-oxide (**6**) which arises from elimination of HCl from the 2-chloroethyl group of (**5**) (**Scheme-I**).

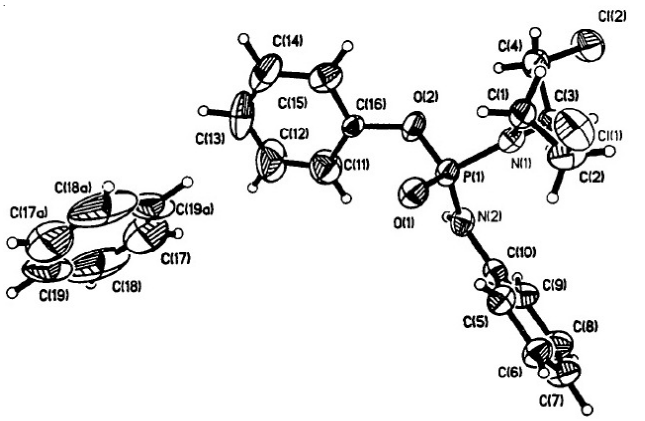


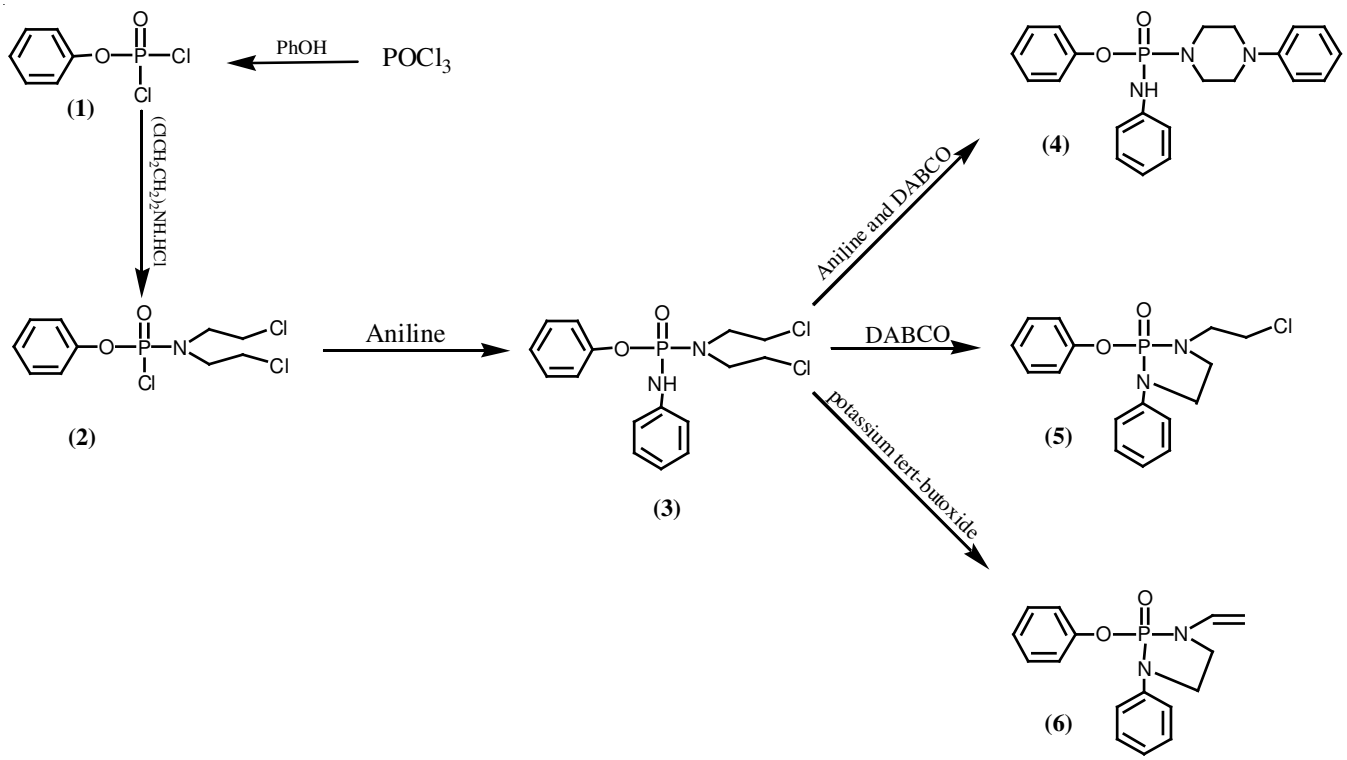
Fig. 1. X-Ray crystal structure of solvented phenyl N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**3**) in $CDCl_3$

The refluxing solution of **3** in toluene, an equimolar amount of potassium tert-butoxide in THF was added dropwise by syringe. ^{31}P NMR examination of the reaction mixture showed that in addition to the expected (**5**) (δ = 13), there was another product formed in this reaction (δ = 8). ^{31}P NMR also showed the presence of unreacted starting material (**3**) (δ = 5). Addition of more potassium *tert*-butoxide (2 mmol) led to consumption of the remaining starting material and an increase in the proportion of the new product to the cyclic compound (**5**). The crude product obtained after workup was dissolved in hexane/toluene solvent mixture from which (**5**) crystallized as a first crop of crystals in 26 % isolated yield. The hitherto unknown compound was crystallized as a second crop of crystals in 48 % yield. The new product was isolated and based on spectra was characterized as 2-phenoxy-3-phenyl-1-vinyl-1,3,2-diazaphospholidine-2-oxide (**6**) arising from elimination of HCl from the 2-chloroethyl group in compound **5**.

The structures of all prepared compounds were confirmed by ^1H, ^{31}P and ^{13}C NMR spectroscopy, also mass spectrometry for compounds **4** and **5** and X-ray crystallography for compound **3** and comparison with literature data[12,13].

Conclusion

The reaction of phenyl phosphorodichloridates with *bis*(2-chloroethyl)amine give the corresponding phosphorochloridate in a good yield and these three react with aniline to afford phenyl-N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**3**). The compound **4** is produced by a DABCO-promoted reaction of **3** *in situ*, with aniline present in the reaction medium. The formation of **5** is understandable because in **3**, the N-H hydrogen is acidic by virtue of its proximity to a phosphoryl phosphorus atom. Abstraction of this hydrogen by



Scheme-I: Reaction path for the preparation of target compounds **4**, **5** and **6**

DABCO produces an anion with the negative charge on nitrogen. If the negatively charge center displaces chloride ion from the 2-chloroethyl group in an SN_2 reaction, the result is the cyclization and formation of compound **5**. Compound **6** arises from elimination of HCl from the 2-chloroethyl group in compound **5**.

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