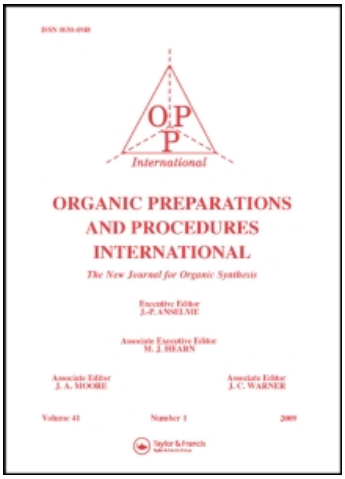

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PRODUCT SELECTIVITY IN THE SYNTHESIS OF THREE NOVEL PHOSPHORUS-CONTAINING HETEROCYCLES FROM ACYCLIC PRECURSORS BY SELECTION OF BASE STRENGTH

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PRODUCT SELECTIVITY IN THE SYNTHESIS OF THREE NOVEL PHOSPHORUS-CONTAINING HETEROCYCLES FROM ACYCLIC PRECURSORS BY SELECTION OF BASE STRENGTH

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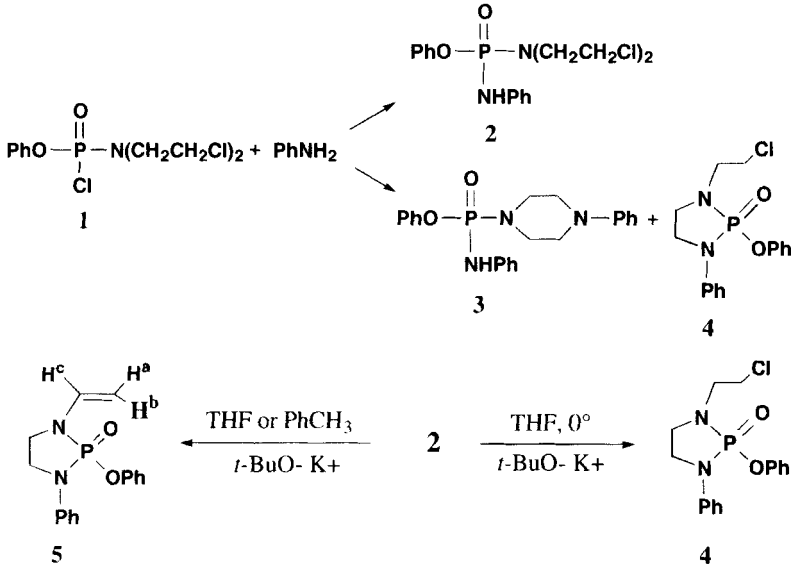
A project was originally designed to synthesize derivatives of phenyl N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**2**) substituted in the anilino group by reaction with readily available phenyl N,N-*bis*(2-chloroethyl)phosphoramidochloridate (**1**) with substituted anilines. In the process of improving the synthesis of **2**, syntheses of three novel heterocyclic compounds (**3-5**) were developed[1] and subsequently individual yields were improved by varying the strengths of the bases used. The results of these studies are presented.

The initial precipitate (2.5%) from the reaction of **1** with aniline was identified from its IR and NMR spectra as phenyl N(4-phenyl)piperazinyl-N'-phenylphosphorodiamidate (**3**). In order to increase the yield of (**3**) by using a stronger base, the phosphorodiamidate (**2**) was reacted with equimolar amounts of aniline and DABCO to give a 34% yield (by ^{31}P analysis; 13% isolated) along with another cyclic product (**4**) (see below) in a ratio of 64:36 for **3** and **4** respectively. The



compounds were separated by a combination of solubility differences and TLC. Signals for only **3**, **4** and starting compound (**2**) appeared in the ^{31}P NMR spectrum of the reaction mixture. When aniline was omitted in the reaction of **2** with DABCO in toluene at reflux, only **4** was formed in 33% yield

with starting material (**2**) appearing in the ^{31}P NMR spectrum besides **4**. In order to improve the yield of **4**, a stronger base than DABCO was used. In the reaction with potassium *tert*-butoxide in toluene or tetrahydrofuran, a 95% yield of **4** was obtained as evidenced from the observation of only a single peak in the ^{31}P NMR spectrum. When two or more molar equivalents of potassium *tert*-butoxide in toluene or THF were used in the above cyclization, the N-vinyl derivative (2-phenoxy-3-phenyl-1-vinyl-1,3,2-diazaphospholidine-2-oxide) of **4** (**5**) was formed as the major product evident in the ^{31}P NMR spectrum of the reaction mixture (98% yield).

The syntheses described above can obviously be extended to the preparation of a variety of heterocyclic analogs by using substituted anilines and phenols.

EXPERIMENTAL SECTION

All reactions were run in three-necked round-bottom flasks under a positive argon pressure. ^{1}H, ^{13}C, and ^{31}P NMR spectra were taken on a Bruker AMX 360 MHz spectrometer operated in the FT mode. Positive ^{31}P chemical shifts (δ) are reported downfield from 85% H_3PO_4. Chemical shifts (δ) for ^{1}H and ^{13}C NMR spectra run in $CDCl_3$ are relative to internal TMS. Those run in DMSO-d_6 are calibrated with the characteristic ^{1}H and ^{13}C peaks of the solvent. IR spectra were run on a Mattson FT-IR instrument using matched 0.1 mm sodium chloride cells for 5% solution spectra of solids in dry methylene chloride. Mass spectra were obtained on Finnigan 1020, and VG ProSpec mass spectrometers. Melting points were determined on a Thomas Hoover Unimelt apparatus and are corrected. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, Georgia. Aniline was freshly distilled over Zn dust; methylene chloride was distilled over P_2O_5; THF was distilled over potassium and benzophenone; benzene, toluene and hexane were distilled over sodium. Potassium *tert*-butoxide, a 1.0 M solution in THF, was used as purchased. Other reagents were used as supplied.

Phenyl N,N-*bis*(2-Chloroethyl)phosphoramidochloridate (1).- The phosphoramidochloridate (**1**) was prepared by a slight modification of literature procedures.[2-4] *bis*(2-Chloroethylamine) hydrochloride (52 g, 0.29 mol), dry methylene chloride (300 mL) and triethylamine (58 g, 0.58 mol) were placed in a 3-necked round-bottom flask protected from moisture with a calcium chloride tube. Phenyl phosphorodichloridate (61 g, 0.29 mol) dissolved in dry methylene chloride (73 mL) was added dropwise over 25 m and the mixture was stirred at ambient temperature overnight. The precipitated triethylamine hydrochloride was removed by suction filtration. The filtrate was extracted with two 50 mL portions of 1 M HCl. The organic layer was extracted with saturated sodium bicarbonate solution to remove excess acid and washed with distilled water or saturated NaCl solution until it was neutral to litmus. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and then subjected to high vacuum until a constant weight (82 g, 90%). Yields up to 92% (lit.[3] 75%) were obtained in other preparations using the same procedure. The product was an orange-brown oil which was pure enough for the subsequent reaction, but which can be decolorized with P_2O_5. ^{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, CH_2), 49.20 (d, $^{3}J_{P-C}$ = 4.8 Hz, CH_2), 120.08 (d, $^{3}J_{P-C}$ = 5.7 Hz, C_{ortho}), 125.85 (s, C_{para}), 129.70 (s, C_{meta}), 149.30 (d, $^{2}J_{P-C}$ = 8.6 Hz, C_{ipso}); ^{31}P NMR ($CDCl_3$): δ

11.3; IR (cm^{-1}): 945 (P-O-C), 1285(P=O), 1490 (P-O-C).

Isolation of Phenyl N(4-Phenyl)piperazinyl-N'-phenylphosphorodiamidate (3) from Reaction of 1 with Aniline using DABCO as Base.- A solution of aniline (2.3 g, 0.025 mol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (2.8 g, 0.025 mol) in toluene (13 mL), was added over 20-25 m to a refluxing mixture of phenyl N,N-*bis*(2-chloroethyl)phosphor-amidochloridate (**1**) (7.9 g, 0.025 mol) in toluene (13 mL) and the reaction mixture maintained at reflux for 18 hrs. It was allowed to cool to ambient temperature and HCl (2M) (150 mL) was added. The mixture was extracted with methylene chloride (2 x 150 mL). The combined methylene chloride layer was extracted with HCl (2M) (2 x 100 mL). The organic layer was extracted with saturated sodium bicarbonate solution, washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was decolorized with activated charcoal and the resultant solution concentrated to a viscous, orange-colored oil. The oil was suspended in hexane and while heated, toluene was added until a solution resulted (procedure hereafter referred to as crystallizing from hexane/toluene). On standing, a white fluffy substance (0.24 g, 2.5%), mp. 137.5-138°, identified as **3** precipitated.

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

^1H NMR ($CDCl_3$): δ 2.96-3.00 (m, CH_2, 4H), 3.36-3.41 (m, CH_2, 4H), 5.89 (d, $^2J_{P-H}$ = 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); (δ PhO): 120.46 (d, $^3J_{P-C}$ = 4.5 Hz, C_{ortho}), 124.79 (s, C_{para}), 129.20 (s, C_{meta}), 150.53 (d, $^2J_{P-C}$ = 6.3 Hz, C_{ipso}); (δ PhN): 118.06 (d, $^3J_{P-C}$ = 7.3 Hz, C_{ortho}), 121.90 (s, C_{para}), 129.07 (s, C_{meta}), 139.48 (d, $^2J_{P-C}$ = 1.8 Hz, C_{ipso}); (δ 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: M^+ 393.

The evidence is consistent with structure **3** for this compound. The mother liquor was concentrated to give **2** as a residue (0.94 g, 10%).

Synthesis of Phenyl N(4-Phenyl)piperazinyl N'-Phenylphosphorodiamidate (3) from Reaction of 2 with Aniline Using DABCO as Base.- Phenyl N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**2**) (4.20 g, 11.3 mmol), DABCO (1.27 g, 11.3 mmol), aniline (1.05 g, 11.3 mmol), and dry toluene (52 mL) were heated at reflux for 18 hrs. A ^{31}P NMR spectrum showed the following product distribution: **2** (δ = 5), 49.3%; **3** (δ = 3), 34.3%; unknown (δ = 14), 3.3%; and compound (**4**) (see below) (δ = 13), 13.0%. Toluene was removed under reduced pressure and the crude reaction mixture was transferred to a separatory funnel. HCl (2M) (100 mL) was added and the mixture extracted with methylene chloride (2x150 mL). The combined methylene chloride layer was washed once with HCl (100 mL). After neutralization of excess acid (saturated sodium bicarbonate solution), the mixture was washed with brine until the wash was neutral to litmus, dried (anhydrous sodium sulfate), and filtered. The filtrate was concentrated under reduced pressure and later subjected to high vacuum overnight to yield a highly viscous orange-brown mass (3.0 g). The crude product was crystallized from hexane/ether from which **2** precipitated as the first crop of crystals (0.61 g). The solvent was removed from the filtrate to leave a residue of 2.11 g which was dissolved in ether. The solution was placed on a dry silica column (ca. 0.5 g), and the column was eluted with ether:acetone (9:1) until coloring

matter eluted with the solvent front. The silica was triturated repeatedly with ether to recover the product. The ether solution was concentrated and hexane added. On seeding, **3** precipitated from solution (0.36 g). The filtrate was again concentrated and dissolved in ether/hexane; on standing more crystals precipitated (0.23 g) giving a combined yield of **3** of 13%.

Isolation of 1-(2-Chloroethyl)-2-phenoxy-3-phenyl-1,3,2-diazaphospholidine-2-oxide (4).- The residue from above (0.48 g) was separated by preparative thin-layer chromatography on silica, [Analtech 1000μ, 20 x 20 cm plates] using diethyl ether:acetone (9:1). The bands were scraped off and the silica triturated with methylene chloride. Evaporation of the solvent gave **2**, 0.064 g, R_F = 0.84; and **4**, R_F = 0.40. Compound **4** was recrystallized from toluene/hexane as white needles, mp. 114.5-115.0°; 0.036 g (3.4%).

Anal. Calcd for $C_{16}H_{18}ClN_2O_2P$: 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

^1H 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, CH2); (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^3 J_{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: M^+336.

Synthesis of 1-(2-Chloroethyl)-2-phenoxy-3-phenyl-1,3,2-diazaphospholidine-2-oxide(4): (A) Using DABCO as Base.- Phenyl N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**2**) (3.1 g, 8.2 mmol) and DABCO (0.92 g, 8.2 mmol) were placed in dry toluene (20 mL) and heated under reflux for 54 hrs. The precipitated DABCO hydrochloride was separated from the liquid. The hydrochloride was triturated with hot toluene. The combined organic layer was concentrated under reduced pressure and subjected to a high vacuum to yield 1.2 g of residue which ^{31}P NMR showed to be a mixture of **4** and unreacted **2** (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 **4** as white crystals, 0.19 g yield (7%). Compound **2** (0.68 g) was recovered.

(B) Using Potassium *tert*-Butoxide as Base.- By the use of a stronger base, potassium *tert*-butoxide[5], the yield of **4** was improved. To a refluxing solution of phenyl N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**2**) (1.5 g, 4.1 mmol) in toluene (10 mL) was added slowly, by syringe, potassium *tert*-butoxide (4.1 mmol). Examination of the reaction mixture by ^{31}P NMR showed three peaks **2** (δ = 5); **4** (δ = 13); and a new compound **5** (δ = 8). Additional potassium *tert*-butoxide (2.0 mmol) was added after which ^{31}P NMR confirmed the absence of **2**. The reaction was allowed to cool. Water (100 mL) was added. The mixture was extracted with methylene chloride (2 x 100 mL), washed once with water, dried with anhydrous sodium sulfate, filtered, and the filtrate concentrated under reduced pressure to yield crude product, 1.1 g. The crude material was crystallized from hexane/toluene. From the solution, **4** crystallized as the first crop of crystals, 0.35 g yield (26%). Compound **5** precipitated

as a second crop of crystals, 0.58 g yield (48%). Similarly, to a stirred, ice-cooled solution of **2** (0.27 g, 0.70 mmol) in THF (7 mL), potassium *tert*-butoxide (0.7 mL) was added slowly by a syringe inserted through a septum. The solution turned turbid. Water (100 mL) was added, and the resulting mixture was extracted with methylene chloride (2 x 100 mL), washed with water (100 mL), dried with anhydrous sodium sulfate, filtered, and the filtrate evaporated under reduced pressure to give compound **4**, 0.22 g (89% yield isolated, 95% by ^{31}P NMR).

Isolation and Characterization of 2-Phenoxy-3-phenyl-1-vinyl-1,3,2-diazaphospholidine-2-oxide (5).- The sample of **5** obtained above was recrystallized from toluene/hexane, mp. 84.0-85.0°. ^{1}H 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, $^{2}J_{P-C}$ = 10.87 Hz, CH_2), 42.03 (d, $^{2}J_{P-C}$ = 12.68 Hz, CH_2), 91.50 (d, $^{3}J_{P-C}$ = 10.0 Hz, vinyl CH_2); (δ PhO): 121.26 (d,$^{3}J_{P-C}$ = 3.6 Hz, C_{ortho}), 125.37 (s, C_{para}), 129.53 (s,C_{meta}), 140.48 (d,$^{2}J_{P-C}$ = 6.3 Hz, C_{ipso}); (δ PhN): 116.24 (d, $^{3}J_{P-C}$ = 5.4 Hz, C_{ortho}), 122.18 (s, C_{para}), 129.48 (s, C_{meta}), 150.44 (d, $^{2}J_{P-C}$ = 9.1 Hz, C_{ipso}; ^{31}P NMR ($CDCl_3$): δ 8.00; MS: M^+300. Since **5** decomposed on attempts at recrystallization from various solvents, preparation of a pure sample for elemental analysis was not possible. Characterization is based on NMR and mass spectra which are in accord with the expected structure from the base-promoted elimination from **4**.

Synthesis of 2-Phenoxy-3-phenyl-1-vinyl-1,3,2-diazaphospholidine-2-oxide (5).- While phenyl N,N-*bis*(2-chloroethyl)-N'-phenylphosphorodiamidate (**1**) (6.3 g, 0.020 mol) in dry toluene (20 mL) was stirred at reflux, potassium *tert*-butoxide (34 mL, 0.034 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 **1** to **5**. Water (100 mL) was added and the mixture extracted with methylene chloride (3x100 mL). The combined methylene chloride layer was washed with water (100 mL), dried with anhydrous sodium sulfate, filtered, and the filtrate concentrated under reduced pressure to a viscous, slightly yellow oil which crystallized under high vacuum overnight (5.0 g, 98%). The crude material was recrystallized from hexane/toluene (4.3 g, 84%); mp. 84.0-85.0°.

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