A Short Novel Synthesis of the Phosphazene Base Et-P_2

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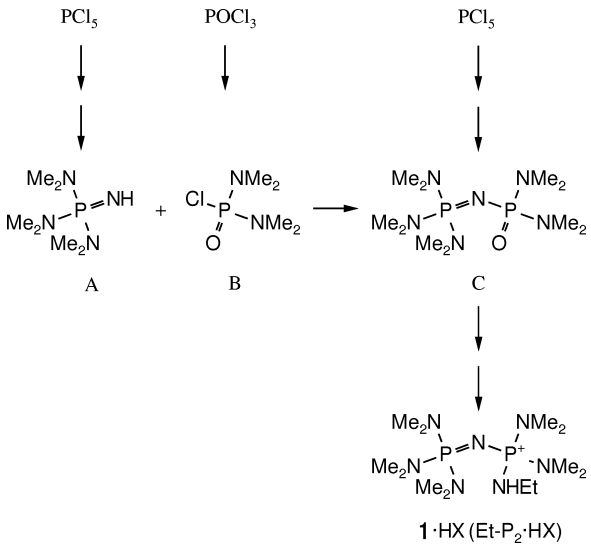
A novel synthesis of the phosphazene base Et-P_2 is presented, which approximately halves the efforts of its production.

Key words: Phosphazenes, Synthetic Methods, Nucleophilic Substitution, Elimination

Introduction

Phosphazene bases [1] span a large range of basicity and have developed into important tools in synthesis [2]. Among the commercially available P_2 bases the least hindered base Et-P_2 **1** has received most attention [3]. The original synthesis [1] requires two steps beyond the coupling product C of two commercially available, but relatively expensive P_1 building blocks A and B (Scheme 1); their syntheses from inexpensive starting materials afford altogether three individual steps and make up to 0.8 mol quantities of $\mathbf{1} \cdot HBF_4$ available in one batch with routine lab equipment. In our hands the alternative route to C directly from PCl_5 in two steps proved problematic [4].

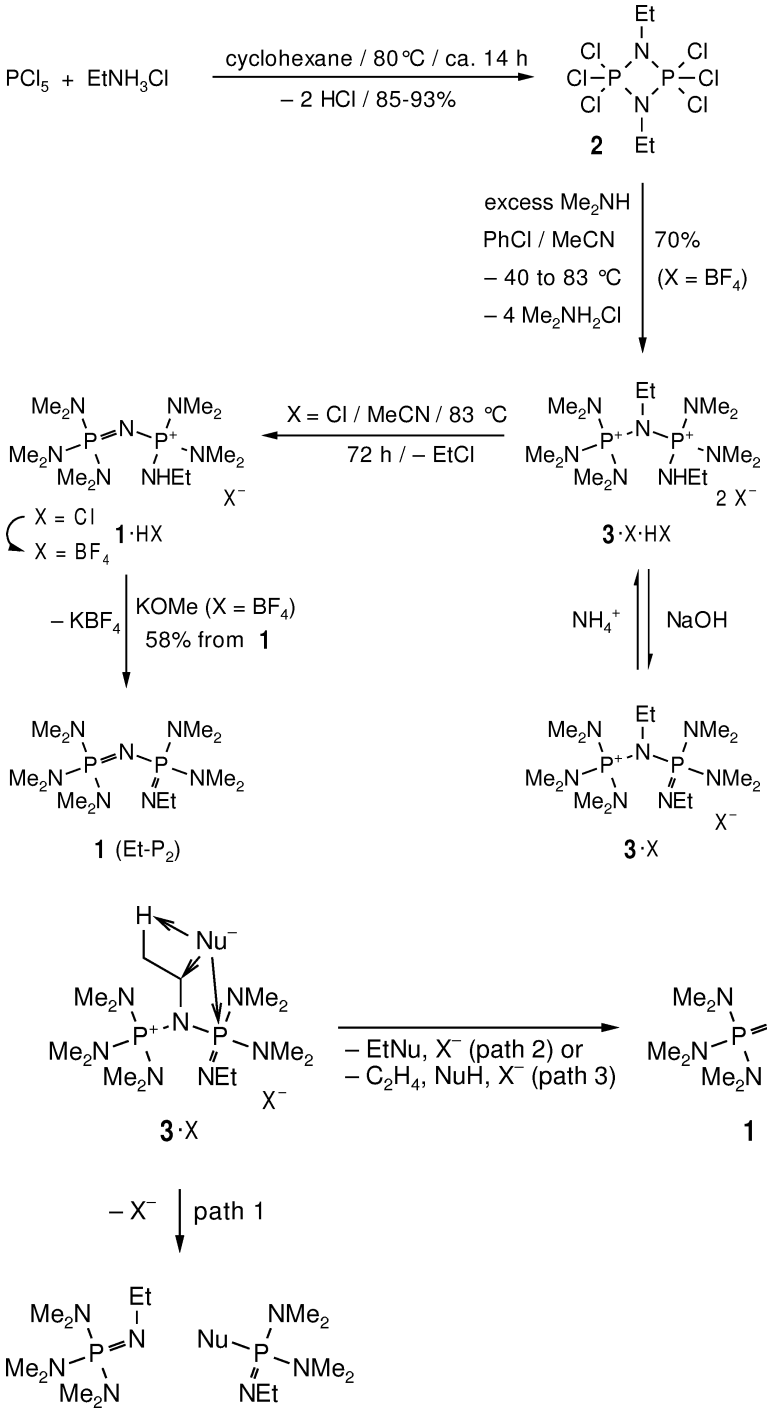


Scheme 1. Schematic original synthesis of $\mathbf{1} \cdot HX$.

Results and Discussion

In the original route to phosphazene **1** the P–N–P alignment was achieved by combining two individual P_1 building blocks A and B. We now started with a compound already having this P–N–P alignment, namely *cyclo*-1,3-diphosphazane **2**. There was hope that nucleophilic substitution of the chlorine atoms of **2** and nucleophilic ring-opening of the strained four-membered ring with dimethylamine would afford $\mathbf{3}^+$ (or dication $\mathbf{3} \cdot H^{2+}$) which upon dealkylation at the bridging imino group would lead to **1** (or $\mathbf{1} \cdot H^+$). Such substitutions with subsequent ring-opening have been reported for primary [5] but not for secondary amines, where breakdown into two P_1 fragments was observed [6]. The dealkylation step $\mathbf{3}^+ \rightarrow \mathbf{1}$ had no precedence in literature.

The synthesis of **2** could be considerably improved by utilizing cyclohexane, a compound of low toxicity, instead of CCl_4 [7] or chlorobenzene [8] as a solvent. No $\mathbf{3} \cdot H^{2+}$ was detected in the reaction mixture when **2** was added to excess dimethylamine as reported for reactions with primary amines [5], but interestingly, in addition to P_1 compounds *ca.* 23% of **1** could be obtained after treatment of this reaction product with KOMe and distillation. However, dication $\mathbf{3} \cdot H^{2+}$ was obtained in good yield by performing the substitution of **2** along a reversed addition mode and with extended reaction periods. The separation of $\mathbf{3} \cdot H^{2+}$ salts from salts of dimethylamine and from $NaBF_4$ proved prob-



Scheme 2. Novel synthesis of **1** (Et-P_2) from PCl_5 and ethylammonium chloride.

Scheme 3. Reaction channels of $\mathbf{3}^+$ with nucleophiles or bases.

lematic. As it turned out, deprotonation of $\mathbf{3}\cdot Cl\cdot HCl$ and anion exchange to give the tetrafluoroborate $\mathbf{3}\cdot BF_4$ allowed a neat separation (Scheme 2).

Dealkylation of $\mathbf{3}\cdot H^{2+}$ turned out to be a challenge. Principally three reaction modes of $\mathbf{3}\cdot H^{2+}$ or $\mathbf{3}^+$ had to be considered (Scheme 3): Attack at

1) one of the phosphorus atoms with cleavage into two P_1 fragments;

2) the α-ethyl carbon of the bridging imino group inducing nucleophilic dealkylation;

3) a β-proton of this ethyl group inducing Hofmann elimination.

Path 1 was in fact dominating with hard nucleophiles like MeO^-, *tert*-amylate, and KF. Soft nucleophiles like RS^-, Cp^- (path 2), and KH (path 3) proved more suitable, but all these reagents were basic enough to deprotonate $\mathbf{3} \cdot H^{2+}$ to $\mathbf{3}^+$ thus hampering the dealkylation for electrostatic reasons. Under the required forcing reaction conditions, if at all, only low to moderate yields of **1** were achieved. A breakthrough came with the utilization of much less basic halide ions as nucleophiles, most conveniently with Cl^- as nucleophile (Scheme 2), as this anion is the counterion directly arising from the synthesis of $\mathbf{3} \cdot H^{2+}$ and allows a one-pot procedure without need of further reagents.

A trapping experiment showed that no 1,2-dibromoethane was formed on passing a bubbler filled with a solution of bromine in CCl_4. Ethyl chloride was detected in the expected amount (^{1}H NMR spectrum of the solution with *o*-dichlorobenzene as standard). Thus the dealkylation proceeds *via* path 2 rather than *via* path 3.

Any attempts to efficiently apply this synthetic route to modified P_2 bases failed. Neither with other primary ammonium chlorides (methylammonium chloride, isopropylammonium chloride; fragmentation along path 1 was observed, in the case of isopropylammonium chloride already during the reaction with dimethylamine), nor with pyrrolidine (low yields of a badly crystallizing P_2 base salt) as secondary amine modified P_2 bases could be secured in reasonable yield.

Conclusion

The new three-step synthesis of oxygen-insensitive distillable liquid **1** constitutes a major improvement and will certainly further establish **1** as a very stable and easy-to-handle auxiliary base in a basicity range which is not covered by other easily handled and easily available or low cost bases [9].

Experimental Section

General

Melting points (m. p.; uncorrected): Bock Monoscop M. IR: Perkin–Elmer 298. Elemental analyses: Perkin–Elmer Elemental Analyzer 240. ^{1}H NMR (internal standard TMS = tetramethylsilane; in D_2O, TSP = sodium 2,2,3,3-tetradeutero-3-trimethylsilylpropionate): 250 MHz Bruker AC 250 and 400 MHz Bruker AM 400. All reactions involving **2** were performed under N_2 with exclusion of moisture; glassware for these reactions was dried for at least 30 min at 100 °C and cooled in a stream of dry N_2.

Chlorobenzene was distilled over P_2O_5 and stored over molecular sieves 3 Å. Cyclohexane was filtered over a short column of basic alumina. MeCN was stirred over $KMnO_4$ until a persistent violet color appeared, filtered, distilled over P_2O_5 and stored over molecular sieves 3 Å. $EtNH_3Cl$ (Fluka Chemie AG/Switzerland, 98%) was dried in high vacuum in the melt at 120 °C for 5 min. Me_2NH (Fluka Chemie AG/Switzerland, 99%) was dried over 2 drying towers filled with KOH; KCl and PCl_5 were used as purchased by Riedel-deHaën. NH_4BF_4, $NaBF_4$, and Na_2SO_4 were used as purchased by Fluka Chemie AG/Switzerland.

*2,2,2,4,4,4-Hexachloro-1,3-diethyl-cyclo-1,3-diphosphazane (**2**)*

$EtNH_3Cl$ (8.20 g, 100 mmol) was added to a suspension of PCl_5 (20.8 g, 100 mmol) in cyclohexane (60 ml) and the mixture was refluxed until the evolution of HCl ceased (*ca.* 14 h). The mixture was cooled to r. t. and the precipitate of insoluble oligomers was filtered off under N_2. The filtrate was concentrated *in vacuo* leaving 2 as a colorless crystalline material (15.4 – 16.8 g, 85 – 93%, lit. [7]: 57.5%. lit. [8]: 70%), m. p. 122 °C (lit. [7]: 119 – 122 °C; lit. [8]: 122 – 124 °C). – ^{1}H NMR (250 MHz, $CDCl_3$, 30 °C): $\delta = 1.41$ (t, ^3J(H,H) = 6.7 Hz, 6 H, CH_3), 3.49 (m, ^3J(H,H) = 7.0 Hz, 4 H, CH_2).

*Pentakis(dimethylamino)-ethylamino-ethyliminobisphosphonium tetrafluoroborate (**3** · BF_4 · HBF_4)*

2 (56.0 g, 155 mmol) was dissolved in chlorobenzene (150 ml) and cooled to −40 °C in a dry ice bath. At this temperature gaseous Me_2NH was added *via* a gas-inlet tube to the mechanically stirred solution until the strongly exothermic reaction slowed down; MeCN (totally 300 ml) was added as needed to keep the mixture stirrable. The mixture was then allowed to warm to −10 °C. Me_2NH (totally *ca.* 135 g, 3.00 mol) was added and the mixture was allowed to warm to r. t. The mechanical stirrer was replaced by a magnetical stirring bar and the gas inlet tube by a dry-ice condenser; the mixture was then gently heated to reflux (to about 40 °C) and held at reflux for 12 h with stirring. Then excess Me_2NH was distilled off over a period of 4 h until the boiling point of MeCN had been reached.

To isolate $\mathbf{3} \cdot BF_4 \cdot HBF_4$ the mixture was concentrated *in vacuo* to dryness and Me_2NH_2Cl was removed from the residue by addition of 50% aqueous NaOH (50.0 g, 620 mmol) and again concentrating *in vacuo* to dryness.

A solution of $NaBF_4$ (20.0 g, 180 mmol) in H_2O (20 ml) was added followed by a volume of 50% aqueous NaOH, which was sufficient to affect a phase-separation (deprotonation to $\mathbf{3} \cdot BF_4$). The aqueous (lower) layer was separated from the product-containing upper layer and was extracted with chlorobenzene (2×50 ml). The combined organic layers were concentrated *in vacuo* to dryness. For reprotonation of $\mathbf{3} \cdot BF_4$ a solution of NH_4BF_4 (16.2 g, 155 mmol) in H_2O (60 ml) was added and the mixture was again concentrated *in vacuo* to dryness. The residue was recrystallized from MeOH and dried at r.t. at 0.05 Torr, affording $\mathbf{3} \cdot BF_4 \cdot HBF_4$ as colorless needles (58.9 g, 70%), m.p. 205 °C. – IR (KBr): ν = 3390, 2900, 1620, 1463, 1400, 1305, 1156, 1069, 991, 934, 911, 775 cm^{-1}. – ^{1}H NMR (250 MHz, D_2O, 30 °C): δ = 1.27 (m, ^3J(H,H) = 7.3 Hz, ^4J(P,H) = 1.5 Hz, 3 H, CH_3CH_2), 1.37 (m, ^3J(H,H) = 7.3 Hz, 3 H, CH_3CH_2), 2.89 (d, ^3J(P,H) = 10.4 Hz, 18 H, $(CH_3)_2N$), 2.90 (d, ^3J(P,H) = 10.4 Hz, 12 H, $(CH_3)_2N$), 3.23 (m, ^3J(P,H) = 3.0 Hz, 2 H, CH_3CH_2), 3.23 (m, ^3J(P,H) = 3.0 Hz, 2 H, CH_3CH_2). – $C_{14}H_{41}B_2F_8N_7P_2$ (543.1): calcd. C 30.96, H 7.61, N 18.05; found C 30.87 H 7.50; N 18.03.

*1,1,1,3,3-Pentakis(dimethylamino)-3-ethylamino-1λ^5,3λ^5-diphosphazenium tetrafluoroborate (**1** ·HBF_4)*

To a solution of $\mathbf{3} \cdot BF_4HBF_4$ (18.06 g, 33.25 mmol) in H_2O (30 ml) a solution of KCl (4.96 g, 66.5 mmol) in H_2O (20 ml) was added. The precipitate (KBF_4) was filtered off and the solution was concentrated *in vacuo* to dryness and dried at 0.05 Torr. MeCN (60 ml) was added and the solution was refluxed for 72 h. The solution was cooled to r.t. and concentrated *in vacuo* to dryness. The chloride anion was exchanged by dissolving the residue in CH_2Cl_2 (30 ml) and shaking with a solution of $NaBF_4$ (7.3 g, 66 mmol) in H_2O (30 ml). The organic phase was dried with Na_2SO_4, concentrated *in vacuo*, and dried at 0.05 Torr, leaving a colorless crystalline material, pure by ^{1}H NMR (14.2 g, 100%). – ^{1}H NMR (250 MHz, D_2O, 30 °C): δ = 1.13 (m, ^3J(H,H) = 7.0 Hz, ^4J(P,H) = 1.2 Hz, 3 H,CH_3CH_2), 2.67 (d, ^3J(P,H) = 10.4 Hz, 30 H, $(CH_3)_2N$), 2.91 (m, ^3J(H,H) = 7.3 Hz, ^3J(P,H) = 9.5 Hz, 2 H, CH_3CH_2).

Liberation of the base and distillation according to literature yielded pure **1** [1].

*One-pot procedure for the conversion of **2** to crude 1,1,1,3,3-pentakis(dimethylamino)-3-ethylamino-1λ^5,3λ^5-diphosphazenium tetrafluoroborate (**1** ·HBF_4)*

The solution obtained from **2** (56.0 g, 155 mmol) after removing excess Me_2NH (see above) was refluxed for 72 h. After cooling to r.t. the bulk of MeCN was removed *in vacuo*, and the precipitated Me_2NH_2Cl was filtered off. CH_2Cl_2 (100 ml) was added and the anion was exchanged by shaking with a solution of $NaBF_4$ (20 g, 180 mmol) in H_2O (50 ml). The aqueous phase was extracted with CH_2Cl_2 (2×20 ml) and the combined organic phases were concentrated *in vacuo*. The residue was dried at 0.05 Torr, yielding a brownish viscous residue of crude $\mathbf{1} \cdot HBF_4$ (52.0 g). Liberation of the base and fractional distillation yielded almost pure **1** (30.0 g, 58% based on **3**) [1].

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