A Short Novel Synthesis of the Phosphazene Base Et-P₂

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A novel synthesis of the phosphazene base Et-P₂ 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 P₂ bases the least hindered base Et-P₂ 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 P₁ 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 ¹·HBF₄ available in one batch with routine lab equipment. In our hands the alternative route to C directly from PCl₅ in two steps proved problematic [4].

Results and Discussion

In the original route to phosphazene ¹ the P–N–P alignment was achieved by combining two individual P₁ 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 ³⁺ (or dication ³·H²⁺) which upon dealkylation at the bridging imino group would lead to ¹ (or ¹·H⁺). Such substitutions with subsequent ring-opening have been reported for primary [5] but not for secondary amines, where breakdown into two P₁ fragments was observed [6]. The dealkylation step ³⁺ → ¹ had no precedence in literature.

The synthesis of ² could be considerably improved by utilizing cyclohexane, a compound of low toxicity, instead of CCl₄ [7] or chlorobenzene [8] as a solvent. No ³·H²⁺ 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 P₁ compounds ca. 23% of ¹ could be obtained after treatment of this reaction product with KOMe and distillation. However, dication ³·H²⁺ was obtained in good yield by performing the substitution of ² along a reversed addition mode and with extended reaction periods. The separation of ³·H²⁺ salts from salts of dimethylamine and from NaBF₄ proved prob-
Scheme 2. Novel synthesis of 1 (Et-P$_2$) from PCl$_5$ and ethylammonium chloride.

Dealkylation of 3·H$_2^+$ turned out to be a challenge. Principally three reaction modes of 3·H$_2^+$ or 3$^+$ had to be considered (Scheme 3): Attack at
1) one of the phosphorus atoms with cleavage into two \( P_1 \) fragments;
2) the \( \alpha \)-ethyl carbon of the bridging imino group inducing nucleophilic dealkylation;
3) a \( \beta \)-proton of this ethyl group inducing Hofmann elimination.

Path 1 was in fact dominating with hard nucleophiles like \( \text{MeO}^- \), \( \text{MeCH}_3\text{NH}^+ \), \( \text{tert-amylate} \), and \( \text{KF} \). Soft nucleophiles like \( \text{RS}^- \), \( \text{Cp}^- \) (path 2), and \( \text{KH} \) (path 3) proved more suitable, but all these reagents were basic enough to deprotonate \( 3 \cdot \text{H}^{2+} \) to \( 3^- \) 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 \( \text{Cl}^- \) as nucleophile (Scheme 2), as this anion is the counterion directly arising from the synthesis of \( 3 \cdot \text{H}^{2+} \) and allows a one-pot procedure without need of further reagents.

A trapping experiment showed that no 1,2-dibromomethane was formed on passing a bubbler filled with a solution of bromine in \( \text{CCl}_4 \). Ethyl chloride was detected in the expected amount (\( ^1\text{H} \) NMR spectrum of the solution with \( \alpha \)-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 Monoskop M. IR: Perkin–Elmer 298. Elemental analyses: Perkin–Elmer Elemental Analyzer 240. \(^1\text{H} \) NMR (internal standard TMS = tetramethylsilane; in \( \text{D}_2\text{O}, \text{TSP} = \text{sodium 2,2,3,3-tetradeutero-3-trimethylsilylpropionate} \); 250 MHz Bruker AC 250 and 400 MHz Bruker AM 400. All reactions involving 2 were performed under \( \text{N}_2 \) 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 \( \text{N}_2 \).

Chlorobenzene was distilled over \( \text{P}_2\text{O}_5 \) and stored over molecular sieves 3 Å. Cyclohexane was filtered over a short column of basic alumina. MeCN was stirred over KMnO4 until a persistent violet color appeared, filtered, distilled over \( \text{P}_2\text{O}_5 \) and stored over molecular sieves 3 Å. EtNH\( _2\text{Cl} \) (Fluka Chemie AG/Switzerland, 98%) was dried in high vacuum in the melt at 120 °C for 5 min. Me\( _2\text{NH} \) (Fluka Chemie AG/Switzerland, 99%) was dried over 2 drying towers filled with KOH; KCl and PCl5 were used as purchased by Riedel-deHaën. \( \text{NH}_4\text{BF}_4 \), NaBF4, and Na\( _2\text{SO}_4 \) were used as purchased by Fluka Chemie AG/Switzerland.

2.2,2,4,4,4-Hexachloro-1,3-diethyl-cyclo-1,3-diphosphazene (2)

EtNH\( _2\text{Cl} \) (8.20 g, 100 mmol) was added to a suspension of PCl5 (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 \( \text{N}_2 \). 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 ºC (lit. [7]: 119 – 122 ºC; lit. [8]: 122 – 124 ºC). \(^1\text{H} \) NMR (250 MHz, CDCl3, 30 °C): \( \delta = 1.41 \) (t, \( \text{J(H,H)} = 6.7 \text{Hz} \), 6 H, CH3), 3.49 (m, \( \text{J(H,H)} = 7.0 \text{Hz} \), 4 H, CH2).

Pentarakis(dimethylamino)-ethylamino-ethylaminobispophosphonium tetrafluoroborate (3 \( \cdot \)BF\(_4\) \( \cdot \)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\( _2\text{NH} \) was added \( \text{via} \) 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\( _2\text{NH} \) (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 magnetic 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\( _2\text{NH} \) was distilled off over a period of 4 h until the boiling point of MeCN had been reached.

To isolate 3 \( \cdot \)BF\(_4\) \( \cdot \)HBF\(_4\) the mixture was concentrated in vacuo to dryness and Me\( _2\text{NH} \)Cl 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 NaBF₄ (20.0 g, 180 mmol) in H₂O (20 ml) was added followed by a volume of 50% aqueous NaOH, which was sufficient to affect a phase-separation (deprotonation to 3·BF₄). 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 to 3·BF₄ a solution of NH₄BF₄ (16.2 g, 155 mmol) in H₂O (P,H) = 1.27 (m, 3J(H,H) = 7.3 Hz, 4J(P,H) = 1.5 Hz, 3 H, CH₃(CH₂)), 1.37 (m, 3J(H,H) = 7.3 Hz, 3 H, CH₃(CH₂)), 2.89 (d, 3J(P,H) = 10.4 Hz, 18 H, (CH₃)₂N), 2.90 (d, 3J(P,H) = 10.4 Hz, 12 H, (CH₃)₂N), 3.23 (m, 3J(P,H) = 3.0 Hz, 2 H, CH₃(CH₂)), 3.23 (m, 3J(P,H) = 3.0 Hz, 2 H, CH₃(CH₂)) – C₁₄H₂₃BF₃N₂P₂ (543.1): calcld. 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-1κ₅,3λ₅-diphosphazenium tetrafluoroborate (I·HBF₄)

To a solution of 3·BF₄HBF₄ (18.06 g, 33.25 mmol) in H₂O (30 ml) a solution of KCl (46.6, 65.5 mmol) in H₂O (20 ml) was added. The precipitate (KBF₄) 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 CH₂Cl₂ (30 ml) and shaking with a solution of NaBF₄ (7.3 g, 66 mmol) in H₂O (30 ml). The organic phase was dried with Na₂SO₄, concentrated in vacuo, and dried at 0.05 Torr, leaving a colorless crystalline material, pure by ¹H NMR (14.2 g, 100%). – ¹H NMR (250 MHz, D₂O, 30 °C): δ = 1.13 (m, 3J(H,H) = 7.0 Hz, 4J(H,H) = 1.2 Hz, 3 H,CH₃(CH₂)), 2.67 (d, 3J(P,H) = 10.4 Hz, 30 H, (CH₃)₂N), 2.91 (m, 3J(H,H) = 7.3 Hz, 3J(P,H) = 9.5 Hz, 2 H, CH₃(CH₂)).

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-1κ₅,3λ₅-diphosphazenium tetrafluoroborate (I·HBF₄)

The solution obtained from 2 (56.0 g, 155 mmol) after removing excess Me₂NH (see above) was refluxed for 72 h. After cooling to r.t. the bulk of MeCN was removed in vacuo, and the precipitated Me₂NHCl was filtered off. CH₂Cl₂ (100 ml) was added and the anion was exchanged by shaking with a solution of NaBF₄ (20 g, 180 mmol) in H₂O (50 ml). The aqueous phase was extracted with CH₂Cl₂ (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 1·HBF₄ (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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