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The Synthesis of 2,6,7-Trioxa-1,4-diphosphabicyclo[2.2.2]octane Revisited: The Synthesis of 2,6,7-Triphenyl-2*N*,6*N*,7*N*-triaza-1,4-diphosphabicyclo[2.2.2]octane and the Synthesis of 1λ^5-Phosphiranol

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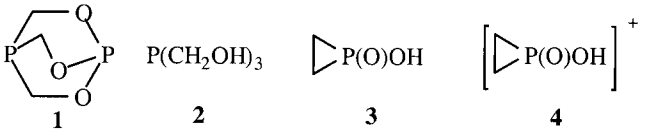
ABSTRACT: *We report herein a reliable synthesis of $P(OCH_2)_3P$ in a study aimed at understanding the factors that control its formation. We also report the serendipitous synthesis of the novel phosphiranol $(CH_2)_2PO_2H$ and the synthesis of $P(PhNCH_2)_3P$ in good yield.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:114–117, 2001

INTRODUCTION

The bicyclic ligand **1** was first reported from our laboratories [1–3] and later by others [4]. Because of anecdotal information gathered from other investigators regarding difficulties in repeating our synthesis of **1** from **2** and indeed our own subsequent problems with consistently repeating the synthesis of **1**, we decided to examine this reaction more closely. The desire to pursue a more reliable synthesis was spurred by the observation that **1** can act as a ligand that forms interesting metal complexes [5]. During the course of the present study, we serendipitously encountered a synthesis for **3**. Although a transient species, **4** analogous to **3** has been reported [6], to our knowledge no mention of a stable phosphiranol has been made in the literature. The only report of a 2*N*,6*N*,7*N*-triaza-1,4-diphosphabicyclo[2.2.2]octane is that for **5**, which was reported from our laboratories to form in low yield via Reaction 1 [7]. Here we describe a more efficient route to this ligand.



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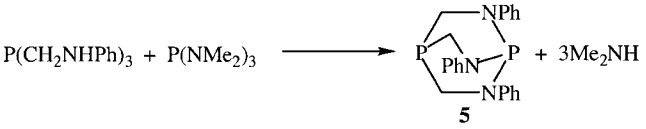

5 (1)

RESULTS AND DISCUSSION

We previously showed that the synthesis of **2** from phosphonium salt **6** in methanol with 1 equiv. of commercial NaOMe is incomplete (Reaction 2) [2]. Here we confirm that this is the case even with the use of up to 2.0 equiv. of commercial NaOMe. Thus, addition of 1.05 equiv. of a methanolic suspension of commercial NaOMe to **6** followed by stirring for 15–

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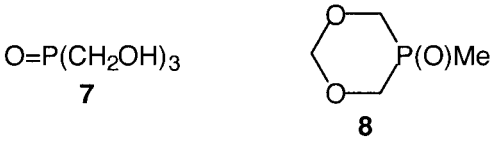
20 minutes resulted in a ca. 65% conversion to **2** as estimated by ^{1}H and ^{31}P NMR integration.

$$\underset{\mathbf{6}}{P(CH_2OH)_4Cl} + NaOMe \rightarrow \underset{\mathbf{2}}{P(CH_2OH)_3} + CH_2O + MeOH + NaCl \quad (2)$$



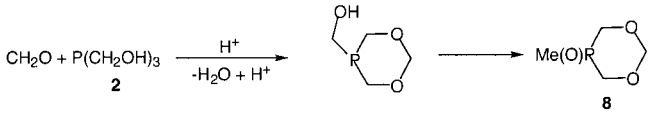
^{1}H NMR spectroscopic analysis showed the reaction mixture obtained (after filtration and removal of solvent from the filtrate) to consist of a mixture of 65% of **2** along with its oxidized form **7**, 30% **6**, and about 5% paraformaldehyde. However, by adding 1.2 equiv. of freshly prepared NaOMe (made by reacting sodium with methanol), **2** was produced from **6** in 74% yield, in addition to 18% of **7** and ca. 8% paraformaldehyde as estimated by ^{1}H NMR integration. Analysis of this reaction mixture by ^{31}P NMR spectroscopy showed it to be free of starting material **6** (δ = 27.0). The presence of **7** is apparently due to the oxidation of **2** with adventitious oxygen. This observation had also been reported previously by Ellis et al [8]. By bubbling air through a CD_3OD solution of **2**, we were able to observe a gradual decrease in the ^{31}P NMR signal corresponding to 2 and a concomitant increase in the signal for **7** (δ ^{31}P = 48.7). Complete conversion to **7** occurred after 72 hours.

$$\underset{\mathbf{6}}{P(CH_2OH)_4Cl} + NaOH \rightarrow \underset{\mathbf{2}}{P(CH_2OH)_3} + CH_2O + H_2O + NaCl \quad (3)$$

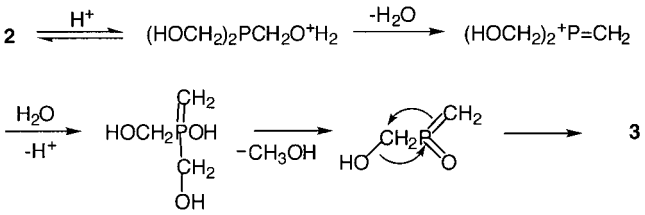
The reaction of an ethanolic solution of **6** with one equiv. of ethanolic NaOH was complete in 15 minutes at room temperature as shown by both ^{1}H and ^{13}C NMR spectroscopic analysis. Even though water is formed in this reaction as well as paraformaldehyde (Reaction 3), we selected this route for the synthesis of **2** because of its simplicity and complete conversion of **6** to product **2**. Thus, after filtration of the reaction mixture under vacuum, the filtrate was passed through anhydrous potassium carbonate onto 4Å molecular sieves. The solvent was removed under vacuum at room temperature to afford **2**, which was then transesterified with $P(OMe)_3$ in refluxing tetrahydrofuran (THF) to give **1** in yields consistently in the range of 29–32%, which is comparable to the 32% yield that we reported originally [1,2]. A sample of **2** prepared by the method reported by Ellis and coworkers [8] (i.e., treatment of anhydrous **6** with dry triethylamine) led to a 42% yield of **1** when transesterified with $P(OMe)_3$ in refluxing THF. Compound **2** prepared in this way contained less than 5% of **7** as the only impurity. When 0.25 equiv. of **6** was deliberately added to a sample of **2** produced by the method of Ellis et al. [8] and the reaction with $P(OMe)_3$ was attempted, a 46% isolated yield of **3** was obtained. This suggests that the formation of **3** stems from **2** and not its oxide **7**, which under these circumstances would be expected to produce only trace amounts of **3** because the concentration of **7** is so low after the first step (<5%).

To study the effect of other potentially damaging impurities on the formation of **1**, water was added to **2** (freshly made by the method of Ellis et al. [8]) in increasing amounts before the reaction with trimethyl phosphite in refluxing THF. In the presence of two drops of water, the reaction of 0.1 mol of **2** afforded a 21% yield of **1**. This yield decreased to 9% when the amount of water was increased to 0.5 mol equiv, and only trace amounts of **1** were isolated when the amount of water was increased to 1.0 equiv. When small amounts (two drops) of dilute HCl were added to 0.1 mol of **2** followed by the trimethyl phosphite reaction in refluxing THF for 16 hours, a 1:1 mixture of **3** and **8** was obtained in a total yield of 37%. This experiment indicated a possible role for H^+ in the formation of **3**. A rationale for the formation of **8** in this reaction is suggested in Scheme 1, wherein formaldehyde originates from the preparation of **2** (Reactions 2 and 3).

When a formaldehyde-free sample of **2** (prepared by a procedure from the literature [8]) was allowed to react with trimethyl phosphite in the presence of catalytic amounts of dilute HCl, the only product obtained upon sublimation was **3**. To further support the role of the acid in the formation of **3**, compound **2** was reacted with trimethyl phosphite in THF in the presence of catalytic amounts (5%) of *p*-toluene sulfonic acid (PTSA). After removal of the volatiles and sublimation of the residue, a 36% isolated yield of **3** was obtained. We have so far found no evidence for the formation of **3** in the absence of acid, **6** or $P(OMe_3)$. This suggests that in the presence of **6**, HCl is perhaps produced as shown in Reaction 4. The sequence of reactions in Scheme 2 represents a highly speculative attempt to rationalize the for-



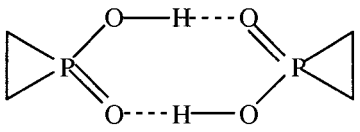
SCHEME 1



SCHEME 2

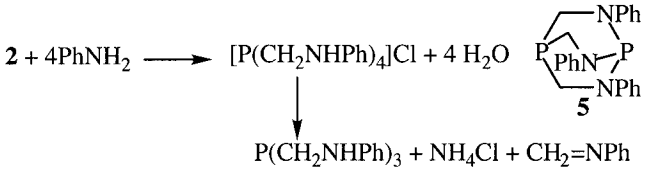
mation of the novel phosphiranol **3** from **2**, which is facilitated by a source of aqueous acid. The formation of methanol in this reaction was confirmed by ^{1}H and ^{13}C NMR spectroscopy and by observation of the growth in the ^{1}H NMR resonances assigned to the methanol OH and CH_3 protons upon adding methanol to the reaction mixture. Although the formation of **3** could in part be attributed to resonance stabilization of its anion formed on proton dissociation of **3**, it should be noted that water solutions of **3** are neutral to litmus, indicating that **3** is a very weak acid. This accords with our failure to separate a mixture of **3** and **8** using aqueous NaOH. On the other hand, stability for **3** may be achieved via H-bonding as depicted in dimer $(\mathbf{3})_2$ or perhaps an analogous trimer.

$$[P(CH_2OH)_4Cl + P(OMe)_3 \rightarrow \underset{\mathbf{6}}{P(CH_2OH)_3} \quad \underset{\mathbf{2}}{} + Me(O)P(OMe)_2 + CH_2O + HCl \qquad (4)$$

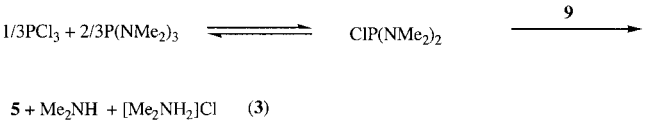


$(\mathbf{3})_2$

Because of the poor yield we obtained previously for **5** [7], we sought a more practical synthesis. The required triamine $P(CH_2NHPh)_3$ **9** (Scheme 3) was easily prepared in 83% yield by the method reported by Frank and Drake [9]. However, the conversion of **9** to **5** proved to be challenging. The attempted transamination of $P(NMe_2)_3$ with **9** at 90°C followed by heating for 72 hours afforded only 18% of **5** as a white solid with a melting point of 194–196°C, which agreed favorably with that previously observed in our laboratories [7]. We were disappointed by the low yield, however. A 70% yield of **5** was achieved using $ClP(NMe_2)_2$ as a reagent as shown in Scheme 4. Thus far, we have been unable by the first step in Scheme 3 to obtain more than very small yields of $P(CH_2NHR)_3$, which is required to form trialkyl an-



SCHEME 3



SCHEME 4

alogues of **5**. The products of such reactions with methyl or ethylamine, for example, consist mainly of uncharacterized oligomers.

EXPERIMENTAL

All reactions were carried out under nitrogen. All solvents were dried according to standard procedures.

Preparation of Chloride-Free **2** *Containing 20%* **7**

Compound **2** was prepared according to a published method using ethanolic sodium hydroxide [1]. After stirring of the solution for 15 minutes, it was allowed to settle for 1 hour. The clear ethanolic solution was vacuum transferred by means of a cannula, through a fritted filter tube packed with anhydrous potassium carbonate into a Schlenk flask containing activated 4Å molecular sieves. The solution was stored over the sieves for 6 hours after which it was transferred by means of a cannula into a round-bottomed flask. Upon removal of the solvent by distillation under reduced pressure at 40°C, a clear viscous liquid was obtained that consisted of **2** plus ca. 20% of its oxidized form **7** and about 7% of paraformaldehyde as determined by ^{1}H NMR integration.

Preparation of **2** *Containing* $[P(CH_2OH)_4]Cl$ (**6**)

To a round-bottomed flask containing 1 equiv. of **6** dissolved in 250 mL of methanol was added 1 equiv. of commercial NaOMe (Aldrich) suspended in 65 mL of methanol. The reaction mixture was stirred at room temperature for 15 minutes. The precipitated NaCl was removed by filtration without protection from the atmosphere, and the volatiles were removed under reduced pressure to afford 15.2 g of

impure **2** (as shown by ^{1}H and ^{31}P NMR spectroscopy) that was used for the preparation of **3** without further purification.

Preparation of **1** *from Chloride-Free* **2**

This was achieved using the sample of **2** described previously using a procedure detailed elsewhere [1,2].

Preparation of **3** *from Chloride-Free* **2**

To a round-bottomed flask connected to a water condenser was added 1.5 g of **6** (7.8 mmol) under nitrogen. Using a syringe, 4.5 g (37.5 mmol) of chloride-free **2** was added, followed by 30 mL of dry THF. The flask was then warmed to 50°C, 6.0 g (0.05 mol) of trimethyl phosphite was added dropwise, and the reaction mixture was refluxed for 16 hours. Removal of the volatiles under reduced pressure followed by sublimation afforded a white solid that was purified by recrystallization from benzene to afford 1.4 g (34%) of **3**. ^{1}H NMR ($CDCl_3$): δ 1.47 (dd, 4H), 8.96 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 18.01 (d, J = 69 Hz). ^{31}P NMR ($CDCl_3$): δ 39.76. LRMS Calcd. for $C_2H_6O_2P$, 93.04; observed *m/e* ($M + H^+$) 93.02. Phosphiranol **3** is a white crystalline solid that melts at 142–143°C. It is soluble in most organic solvents but not in pentane. When left in air, **3** slowly absorbed water to form a clear colorless solution that showed no change in either its ^{1}H or ^{31}P NMR spectrum. Attempts to grow crystals of **3** suitable for X-ray diffraction failed.

Preparation of **3** *Using* **2** *Containing* **6**

To a round-bottomed flask connected to a condenser was added 6.2 g of impure **2** containing **6**. Dry THF was then added, and the flask was warmed to 50°C after which 6.0 g (0.05 mol) of trimethyl phosphite was added. The reaction was continued as detailed in the previous paragraph to afford 1.2 g (26%) of **3**.

Preparation of **3** *Using PTSA*

To 0.55 g (4.4 mmol) of **2** (prepared by the method reported by Ellis and co-workers) [8] in a round-bottomed flask was added 30 mL of dry THF under nitrogen. The flask was warmed to 50°C with constant stirring followed by the addition of 5.0 mg PTSA dissolved in 2 mL of THF. The reaction mixture was refluxed for 48 hours, after which it was allowed to cool to room temperature. The volatiles were removed under reduced pressure, and the residue was sublimed under vacuum to afford 0.15 g (36% yield) of **3** after recrystallization of the sublimate from benzene.

Preparation of **5**

To ca. 8.6 mmol of $ClP(NMe_2)_2$ prepared in situ in the equilibrium reaction of 2.8 mmol of PCl_3 with 5.73 mmol of $P(NMe_2)_3$ in 5 mL of acetonitrile at 0°C was syringed 3.0 g (8.6 mmol) of $P(CH_2NHPh)_3$ [9] dissolved in 10 mL of dry acetonitrile, whereupon a white precipitate formed immediately. The reaction mixture was allowed to stir for 2 hours at room temperature, after which it was filtered and the precipitate was washed twice with 5 mL portions of cold dry acetonitrile. Drying of the residue under vacuum afforded 2.30 g (71%) of **5**. ^{1}H NMR ($CDCl_3$): δ 3.63 (dd, 6H), 6.88 (t, 3H), 7.08 (m, 6H), 7.24 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 148.6 (d, J = 21 Hz), 148.5, 129.3, 120.4, 116.0, 115.9 (d, J = 14 Hz), 40.4 (d, J = 13 Hz). ^{31}P NMR ($CDCl_3$): δ 49.7 (d), −45.32 (d). HRMS Calcd. for $C_{21}H_{21}N_3P_2$ 377.1211, observed *m/e* (M^+) 377.1210.

ACKNOWLEDGMENT

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