

NOVEL SYNTHESIS OF BENZOXAPHOSPHACYCLOALKANE DERIVATIVES VIA  
PALLADIUM-CATALYSED INTRAMOLECULAR FORMATION OF CARBON-PHOSPHORUS BOND

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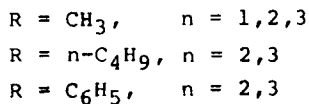
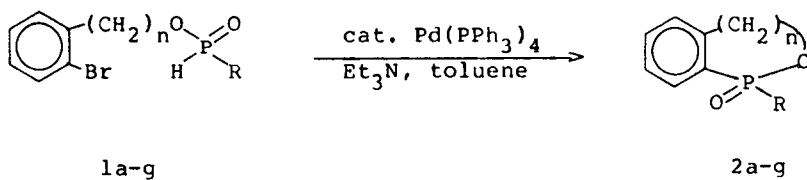
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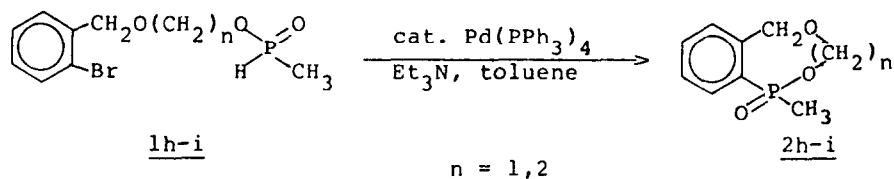
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Summary: A novel synthesis of benzoxaphosphacycloalkane derivatives by palladium-catalysed intramolecular cyclization of the corresponding alkane- or benzenephosphonous acid mono( $\omega$ -o-bromophenylalkyl)ester is presented.

In recent years, the synthesis of heterocyclic compounds using transition metals has attracted much attention<sup>1)</sup>, since the use of transition metal species might well offer advantages over the more conventional routes in terms of milder reaction conditions, better selectivity, novel synthetic routes, and the use of more readily available starting material. Phosphorus heterocycles constitute a class of compounds possessing potent biological activity<sup>2)</sup>, however, to our knowledge, no example on transition metal catalysed or promoted synthesis of phosphorus heterocycles has been reported.

Recently, it is known that aryl- and alkenylphosphonates<sup>3)</sup>, arylphenylphosphinates<sup>4)</sup>, alkylarylphosphinates<sup>5)</sup>, alkylarylphenylphosphine oxides<sup>6)</sup> and also alkenylmethyl- and alkylarylphosphinates<sup>7)</sup> could be synthesized via palladium-catalysed formation of carbon-phosphorus bond. Herein, we wish to describe the first synthesis of benzoxaphosphacycloalkane derivatives via the palladium-catalysed intramolecular formation of carbon-phosphorus bond as shown by the following scheme.



Table. Synthesis of benzoxaphospacycloalkane derivatives<sup>a)</sup>

Run	Alkane- or Benzene- phosphonous Acid Monoester	Reaction Time (h)	Product <sup>b)</sup>	m.p. (°C) or b.p. (°C/mm)	Yield <sup>c)</sup> (%)
1		<u>1a</u> 7		66-68° (lit. 8) 70-72°)	45
2		<u>1b</u> 7		125°/0.1	49
3	<u>1b</u>	7 <sup>d)</sup>	<u>2b</u>	123-124°/0.2	48
4		<u>1c</u> 5		75-77°	41
5		<u>1d</u> 6		83-84°	50
6		<u>1e</u> 7		144-145°	41
7	<u>1e</u>	8 <sup>d)</sup>	<u>2e</u>	144-145°	45
8		<u>1f</u> 5		77-78°	39
9		<u>1g</u> 6		150-152°	45
10		<u>1h</u> 10		114-116°	(34)
11		<u>1i</u> 12		119-121°	(13)

- a) Reaction Conditions: 1 equiv. of alkane- or benzenephosphonite monester, 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> and 3 equiv. of triethylamine in dry toluene at 100°C for 5-12 h under nitrogen, unless otherwise stated.
- b) All new compounds have been fully characterized spectrally (IR, <sup>1</sup>H-NMR, MS) and elemental composition determined by combustion analysis or high-resolution mass spectroscopy<sup>9</sup>).
- c) Isolated yields, GLC yields in parenthesis.
- d) 5 mol% of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> was used as the catalyst.

Transesterification of monoethyl alkane- or benzenephosphonite with the corresponding ω-o-bromophenylalkanols yielded the alkane- or benzenephosphonous acid mono(ω-o-bromophenylalkyl)ester (1a-i) respectively, which on treatment with 5 mol% of tetrakis(triphenylphosphine)palladium in the presence of excess triethylamine in toluene underwent intramolecular cyclization, affording the corresponding benzoxaphosphacycloalkane derivative (2a-i).

In a typical experiment, the methanephosphonous acid mono(β-o-bromophenylethyl)ester (1b, 9 mmol), tetrakis(triphenylphosphine)palladium (0.45 mmol) and triethylamine (4 ml, 29 mmol) in toluene (25 ml) was placed in a thick-wall tube. The tube was flushed with nitrogen, capped and heated in an oil bath at 100° for 7 h. Ethyl acetate was added and then filtered. The filtrate was concentrated on a rotary evaporator and the residue was purified by column chromatography on silica gel eluting with petroleum ether (b.p. 60-90°)/ethyl acetate. The product thus obtained was further purified by distillation to give 1-methyl-2,1-benzoxaphosphacyclohexane-1-oxide (2b, b.p. 125°C/0.1 mm) in 49% yield; IR(neat) 1220, 1020 cm<sup>-1</sup>; <sup>1</sup>H NMR(CCl<sub>4</sub>, δ) 1.51 (d, 3H, P-CH<sub>3</sub>, J<sub>P,CH<sub>3</sub></sub> = 15 Hz), 3.0 (m, 2H, ArCH<sub>2</sub>), 4.30 (m, 2H, OCH<sub>2</sub>), 7.51 (m, 4H, arom); MS, m/e 182(M<sup>+</sup>). Elem. anal. calcd. for C<sub>9</sub>H<sub>11</sub>O<sub>2</sub>P: C, 59.33; H, 6.09; P, 17.01; found: C, 59.69; H, 6.12; P, 17.11.

The results are summarized in the Table. Those cyclized products with a five membered (run 1) or a six membered ring (runs 2,4,5) are formed with ease in 41-50% yield. Products with seven membered ring are obtained in comparative yields (runs 6,8,9). Interestingly, it is shown that products with eight membered ring (run 10) and nine membered ring (run 11) can also be formed via this palladium route, albeit in much lower yields. Moreover, the cyclization reaction proceeds equally well with dichlorobis(triphenylphosphine)palladium instead of tetrakis(triphenylphosphine)palladium as the catalyst (runs 3,7), implying that the Pd(II) species is reduced in situ to the Pd(0) species by the action of phosphonites with the aid of triethylamine<sup>10</sup>).

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## References and Notes

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- 9) Data for 2a, 2c-i (for 2b, see text). 2a,  $^1\text{H-NMR}$  ( $\text{CCl}_4, \delta$ ), 1.70(d, 3H), 5.25(m, 2H), 7.56(m, 4H). 2c,  $^1\text{H-NMR}$  ( $\text{CCl}_4, \delta$ ), 1.5-2.2(m, 2H), 1.75(d, 3H), 3.03(m, 2H), 4.24(m, 2H), 7.69(m, 4H); calcd. exact mass for  $\text{C}_{12}\text{H}_{17}\text{O}_2\text{P}$ : 224.097, found: 224.096. 2d,  $^1\text{H-NMR}$  ( $\text{CDCl}_3, \delta$ ), 3.15(m, 2H), 4.53(m, 2H), 7.38(m, 9H); calcd. exact mass for  $\text{C}_{14}\text{H}_{13}\text{O}_2\text{P}$ : 244.065, found: 224.064. 2e,  $^1\text{H-NMR}$  ( $\text{CDCl}_3, \delta$ ), 1.5-2.2(m, 2H), 1.75(d, 3H), 3.03(m, 2H), 7.69(m, 4H); MS, 192 ( $\text{M}^+$ ); elem. anal. calcd. for  $\text{C}_{10}\text{H}_{13}\text{O}_2\text{P}$ : C, 61.24; H, 6.68; P, 15.80; found: C, 60.96; H, 6.42; P, 16.00. 2f,  $^1\text{H-NMR}$  ( $\text{CDCl}_3, \delta$ ), 0.88-1.9(m, 9H), 2.01(m, 2H), 2.88(m, 2H), 4.12(m, 2H), 7.47(m, 4H); calcd. exact mass for  $\text{C}_{13}\text{H}_{19}\text{O}_2\text{P}$ : 238.112, found: 238.113. 2g,  $^1\text{H-NMR}$  ( $\text{CDCl}_3, \delta$ ), 2.06(m, 2H), 3.0(m, 2H), 4.29(m, 2H), 7.46(m, 9H); calcd. exact mass for  $\text{C}_{15}\text{H}_{15}\text{O}_2\text{P}$ : 258.081, found: 258.082. 2h,  $^1\text{H-NMR}$  ( $\text{CDCl}_3, \delta$ ), 1.65(d, 3H), 3.89(m, 2H), 4.38(m, 2H), 4.82(d, 2H), 7.71(m, 4H); calcd. exact mass for  $\text{C}_{10}\text{H}_{13}\text{O}_3\text{P}$ : 212.060, found: 212.062. 2i,  $^1\text{H-NMR}$  ( $\text{CDCl}_3, \delta$ ), 1.71(d, 3H), 1.8(m, 2H), 3.73(t, 2H), 4.13(m, 2H), 4.71(d, 2H), 7.74(m, 4H); calcd. exact mass for  $\text{C}_{11}\text{H}_{15}\text{O}_3\text{P}$ : 226.076, found: 226.078.
- 10) In order to verify that  $\text{PdCl}_2(\text{PPh}_3)_2$  is reduced to Pd(0) species by the action of phosphonites with the aid of  $\text{Et}_3\text{N}$ , the following experiment has been performed: equimolar amt. of  $\text{PdCl}_2(\text{PPh}_3)_2$  and monoethyl methanephosphonite was allowed to react in the presence of excess triethylamine and triphenylphosphine in DMSO and the yellow crystalline palladium complex formed was submitted to ESCA determination. It is shown clearly that only the Pd(0) species is present (binding energy for Pd  $3d_{5/2}$  336 eV and for Pd  $3d_{3/2}$  341.3 eV).

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