Tetrahedron Letters,Vol.27,No.26,pp 3017-3020,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

PALLADIUM-CATALYZED SYNTHESIS OF 3-METHYLENE-1-OXA-2-PHOSPHACYCLOALKANE-2-OXIDE DERIVATIVES —— THE PHOSPHORUS ANALOGS OF α-METHYLENELACTONES

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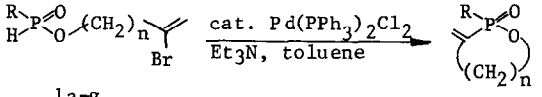
Summary: A novel synthesis of 3-methylene-1-oxa-2-phosphacycloalkane-2-oxide derivatives by palladium-catalysed intramolecular cyclization of the corresponding alkane- or benzenephosphonous acid mono(ω-2-bromovinylalkyl)ester is presented.

α-Methylenelactones represent a major class of biologically active natural products[1]. On the other hand, cyclic organophosphorus compounds have received considerable attention because of their potent biological activity[2]. Therefore, some interest has been aroused recently on the synthesis and investigation of the biological property of the phosphorus analogs of α-methylenelactones and a communication concerning the synthesis of phosphorus analogs of α-methylene-γ-lactones by a Reformatsky reaction has appeared[3].

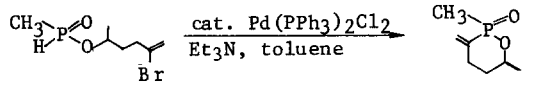
Transition metal catalyzed or promoted synthesis of heterocyclic compounds is a currently active field, which often permits the use of unconventional starting materials to make both conventional and unconventional products via novel synthetic routes under mild reaction conditions with high selectivity. Recently, we have described the palladium-catalyzed synthesis of benzoxaphosphacycloalkane derivatives[4]; herein, we wish to report the synthesis of 3-methylene-1-oxa-2-phosphacycloalkane-2-oxide derivatives via the palladium-catalyzed intramolecular formation of carbon-phosphorus bond as shown in the following scheme.



1a-g

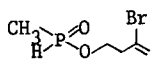
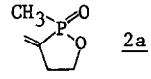
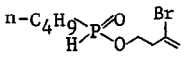
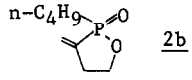
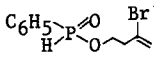
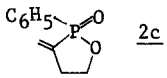
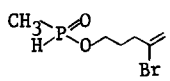
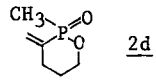
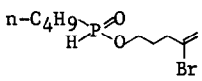
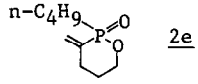
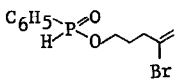
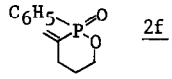
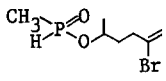
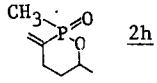
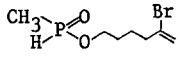
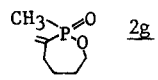
2a-g

R=CH_3, n=2,3,4
R=n-C_4H_9, n=2,3
R=C_6H_5, n=2,3



1h 2h

Table 1. Synthesis of 3-methylene-1-oxa-2-phosphacycloalkane-2-oxide derivatives[a)]

Run	Alkane- or Benzene-phosphonous Acid Monoester		Reaction Time (h)	Product[b)]		b.p. (°C/mm)[c)]	Yield (%)
1		1a	7		2a	80-90°/1	38
2		1b	7		2b	160-170°/1	44
3		1c	3.5		2c	150-160°/0.5	69
4		1d	6		2d	110-120°/1	30
5		1e	12		2e	150-160°/0.3	34
6		1f	1		2f	170-180°/0.5	38
7		1h	6		2h	90-100°/0.5	35
				cis:trans=48:52			
8		1g	5		2g	130-140°/1	17

a) Reaction Conditions: 1 equiv. of alkane- or benzenephosphonous acid monoester, 5 mol% of $Pd(PPh_3)_2Cl_2$ and 3 equiv. of triethylamine in dry toluene at 110° for 1-12 h under nitrogen.

b) All these compounds have been fully characterized spectrally (IR, ^1H NMR) and elemental composition determined by high-resolution mass spectroscopy[5)].

c) Short-path distillation, bath temperature given.

Reaction of dichloroalkyl- or dichlorophenylphosphine with one equivalent of the corresponding ω-2-bromovinylalkanols in the presence of triethylamine followed by hydrolysis yielded the alkane- or benzenephosphonous acid mono-(ω-2-bromovinylalkyl)ester(1a-h)[6)] respectively, which on treatment with 5 mol% of dichlorobis(triphenylphosphine)palladium[7)]

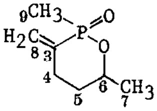
in the presence of excess triethylamine in toluene underwent intramolecular cyclization, affording the corresponding 3-methylene-1-oxa-2-phosphacycloalkane-2-oxide derivative (2a-h) in modest yield.

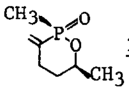
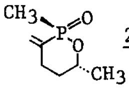
In a typical experiment, the n-butanephosphonous acid mono(3-bromo-3-butenyl)ester (1b, 8 mmol), dichlorobis(triphenylphosphine)palladium (0.4 mmol) and triethylamine (4 ml, 29 mmol) in toluene (25 ml) was placed in a thick-wall tube. The tube was flushed with nitrogen, capped and heated in an oil bath at 110° for 7 h. Ethyl acetate was added and then filtered. The filtrate was concentrated on a rotary evaporator and the residue was distilled in vacuo using a short-path distillation apparatus to give 2-n-butyl-3-methylene-1-oxa-2-phosphacyclopentane-2-oxide (2b, b.p. 160-170°/1 mm) in 44% yield; IR (neat) 1635(C=C), 1230(P=O), 1010(P-O-C) cm^{-1}; ^1H NMR($CDCl_3$, δ) 0.92(t, 3H, CH_3, J=7.2 Hz), 1.51(m, 4H, $CH_3CH_2CH_2$), 1.91(m, 2H, P-CH_2), 2.88(m, 2H, OCH_2CH_2), 4.32(m, 2H, OCH_2), 5.94(d-t, 1H, H/=\P . $J_{P,H}$=41 Hz, $J_{H,H}$=2 Hz), 5.95(d-t, 1H, H\=/P, $J_{P,H}$=20 Hz, $J_{H,H}$=2 Hz); calcd. exact mass for $C_8H_{15}O_2P$: 174.081, found: 174.082.

The results are summarized in Table 1. It is noteworthy that all the cyclized products obtained by the present reaction are those containing an exocyclic double bond, no migration of double bond has been observed. The yields of five membered rings (run 1-3) are better than those of six membered rings (run 4-7), which are in turn better than that of seven membered ring (run 8).

The product 2h (run 7) was a mixture of cis and trans isomers (ratio 48:52) which were individually isolated by preparative GLC. Their configuration is assigned on the basis of their ^{13}C NMR spectra, assuming that the carbon of the methyl group linked to the phosphorus atom and the carbon of the methyl group in the ring being more upfield due to more interactions between the two methyl groups in the cis isomer (2h-I) than those in the trans isomer (2h-II)[8].

Table 2. ^{13}C NMR[a] shifts and the ^{13}C-^{31}P coupling constants[b] of 2h-I and II



Compound	C_3	C_4	C_5	C_6	C_7	C_8	C_9
 2h-I	139.25 (107.24)	31.81 (10.0)	34.55	76.60 (7.9)	22.25 (7.1)	126.09 (6.8)	12.20 (92.7)
 2h-II	141.44 (111.7)	31.48 (5.8)	35.58	72.80 (5.1)	22.30 (8.2)	120.92 (12.1)	12.55 (101.7)

a) The ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer (50.3 MHz), using $CDCl_3$ as internal reference at 76.88 ppm.

b) Coupling constants in parenthesis in hertz.

Acknowledgement: Thanks are due to the Science Fund of Academia Sinica for financial support.

References and Notes

1) H. M. R. Hoffmann, J. Rabe, Angew. Chem. Int. Ed. Eng., 24, 94 (1985).

2) L. D. Quin, "The Heterocyclic Chemistry of Phosphorus", John Wiley and Sons, 1981.

3) J. Collard, C. Benezra, Tetrahedron Lett., 23, 3725 (1982).

4) Yuanyao Xu, Jing Zhang, Tetrahedron Lett., 27, 4771 (1985).

5) Selected spectral data of 2a, 2c-h (for 2b, see text). 2a, ^{1}H NMR($CDCl_3$, δ), 1.67(d, 3H, P-CH_3, $J_{P,H}$=14.6 Hz), 2.88(m, 2H, CH_2), 4.31(m, 2H, OCH_2), 5.93(d-t, 1H, H/=/P, $J_{P,H}$=42.8 Hz, $J_{H,H}$=2.2 Hz), 5.97(d-t, 1H, H\=/P, $J_{P,H}$=18 Hz, $J_{H,H}$=2.2 Hz); calcd. exact mass for $C_5H_9O_2P$: 132.034, found: 132.034. 2c, ^{1}H NMR($CDCl_3$, δ), 3.01(m, 2H, CH_2), 4.51(m, 2H, OCH_2), 5.15(d-t, 1H, H/=/P, $J_{P,H}$=45 Hz, $J_{H,H}$=2.3 Hz), 5.88(d-t, 1H, H\=/P, $J_{P,H}$=19.1 Hz, $J_{H,H}$=2.3 Hz), 7.70(m, 5Harom); calcd. exact mass for $C_{10}H_{11}O_2P$: 194.050, found: 194.048. 2d, ^{1}H NMR($CDCl_3$, δ), 1.56(d, 3H, P-CH_3, $J_{P,H}$=15 Hz), 1.86(m, 2H, $OCH_2\underline{CH_2}$), 2.64(m, 2H, $OCH_2CH_2\underline{CH_2}$), 4.40(m, 2H, OCH_2), 5.60(d-m, 1H, H/=/P, $J_{P,H}$=43 Hz), 5.62(d-m, 1H, H\=/P, $J_{P,H}$=21 Hz); calcd. exact mass for $C_6H_{11}O_2P$: 146.050, found: 146.050. 2e, ^{1}H NMR($CDCl_3$, δ), 0.93(t, 3H, CH_3, J=7.2 Hz), 1.54(m, 4H, $\underline{CH_2CH_2}CH_3$), 1.87(m, 4H, P-CH_2+$OCH_2\underline{CH_2}$), 2.60(m, 2H, $OCH_2CH_2\underline{CH_2}$), 4.30(m, 2H, OCH_2), 5.66(d-m, 1H, H/=/P, $J_{P,H}$=43 Hz), 5.69(d-m, 1H, H\=/P, $J_{P,H}$=21 Hz); calcd. exact mass for $C_9H_{17}O_2P$: 188.097, found: 188.097. 2f, ^{1}H NMR($CDCl_3$,), 1.90(m, 2H, $OCH_2\underline{CH_2}$), 2.68(m, 2H, $OCH_2CH_2\underline{CH_2}$), 4.43(m, 2H, OCH_2), 5.42 (d-m, 1H, H\=/P, $J_{P,H}$=22 Hz), 5.68(d-m, 1H, H/=/P, $J_{P,H}$=45 Hz), 7.65(m, 5Harom); calcd. exact mass for $C_{11}H_{13}O_2P$; 208.065, found: 208.064. 2g, ^{1}H NMR($CDCl_3$, δ) 1.52(d, 3H, P-CH_3, $J_{P,H}$= 14.5 Hz), 1.70(m, 4H, $OCH_2\underline{CH_2CH_2}$); 2.42(m, 2H, =$\underline{CH_2}$), 4.13(m, 2H, OCH_2), 5.94(d-m, 1H, H/=/P, $J_{P,H}$=40 Hz), 6.12(d-m, 1H, H\=/P, $J_{P,H}$=19.1 Hz); calcd. exact mass for $C_7H_{13}O_2P$: 160.065, found: 160.065. 2h-I, ^{1}H NMR($CDCl_3$, δ), 1.40(d-d, 3H, $OCH\underline{CH_3}$, $J_{H,H}$=6.0 Hz, $J_{P,H}$=1.2 Hz), 1.41(d, 3H, P-CH_3, $J_{P,H}$=16.8 Hz), 1.70(m, 2H, $OCH\underline{CH_2}$), 2.55(m, 2H, =$\underline{CH_2}$), 4.25(m, 1H, OCH), 5.59(d-m, 1H, H/=/P, $J_{P,H}$=39 Hz), 5.82(d-m, 1H, H\=/P, $J_{P,H}$=19.6 Hz); calcd. exact mass for $C_7H_{13}O_2P$: 160.065, found: 160.065. 2h-II, ^{1}H NMR($CDCl_3$, δ), 1.29(d-d, 3H, $OCH\underline{CH_3}$, $J_{H,H}$=6.2 Hz, $J_{P,H}$=1.2 Hz), 1.60(d, 3H, P-CH_3, $J_{P,H}$=14.8 Hz), 1.86(m, 2H, $OCH\underline{CH_2}$), 2.64(m, 2H, =CH_2), 4.68(m, 1H, OCH), 5.45(d-m, 1H, H\=/P, $J_{P,H}$=20.7 Hz), 5.52(d-m, 1H, H/=/P, $J_{P,H}$=46 Hz); calcd. exact mass for $C_7H_{13}O_2P$: 160.065, found: 160.065.

6) Compounds 1a-h were fully characterized spectrally and elemental composition determined by combustion analysis.

7) Dichlorobis(triphenylphosphine)palladium can be reduced in situ to Pd(0) species by the action of phosphonites with the aid of Et_3N; see reference 4.

8) B. Akermark, K. Zetterberg, J. Am. Chem. Soc., 106, 5560 (1984).

(Received in Japan 22 April 1986)