

SYNTHESIS OF NOVEL NITRO-SUBSTITUTED 1-PHENOXY-2-PHOSPHOLENES AND PHOSPHOLANES

Mitsuji Yamashita,* Valluru Krishna Reddy, Tatsuo Oshikawa, and
Masaki Takahashi

Department of Materials Chemistry, Faculty of Engineering, Shizuoka University,
Hamamatsu 432-8561, Japan

Abstract: Some nitro-substituted phenoxyphospha sugar derivatives, which are analogs of sugars having a phosphorus atom in place of the ring oxygen of normal sugars, were synthesized from the corresponding 2-phospholenes as the starting materials. Catalytic *cis*-dihydroxylation of the 2-phospholenes with osmium(VIII) oxide, protection of *cis*-diol and some functional group interconversions gave tetraofuranose type phospha sugar derivatives which are possessing phosphorus ester functionality (O=P-O-) with a nitrophenyl group. These derivatives are structurally confirmed by spectral analyses.

Introduction

Replacement of the oxygen atom in the hemiacetal ring of normal sugars by a hetero atom or a carbon atom leads to pseudo sugars, some of which have been widely investigated in the fields of synthetic, biological, and medicinal chemistry. In particular hetero sugars in which the ring oxygen has been replaced by a nitrogen, sulfur, or selenium atom have been extensively studied and widely developed (1). Although aza and thia sugars are known to exist in nature, phospha sugar derivatives, having a P atom in place of the ring oxygen, have not yet been found in naturally occurring products.

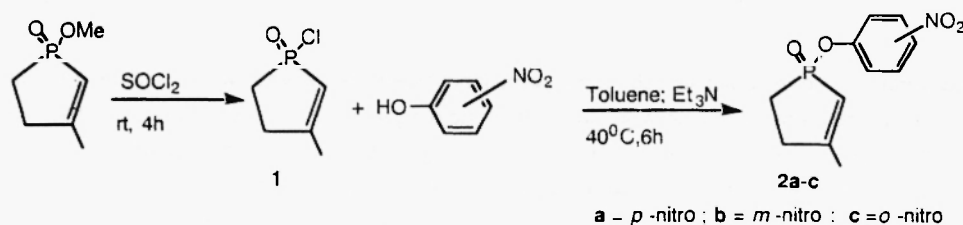
Phospha sugars are of interest because of their potential biological activities (2). Therefore phospha sugar derivatives were of interest in the aspects related not only to synthesis and structures but also to biological activities. Phospha sugars containing a phenoxy groups being mainly nitro-substituted are expected to be possessing potential biological activities suggested by bio-active phosphorus compounds (3).

Addition of phosphorus trihalides or phosphonous dihalides to 1,3-alkadienes is known to produce cyclic unsaturated phosphorus compounds, i.e., phospholenes (4, 5). In our earlier papers (6, 7), we reported the *cis*-dihydroxylation of 2-phospholenes with a catalytic amount of osmium(VIII) oxide and cooxidants (7). The present paper deals with further conversion of phospha sugars into different substituted 1-nitrophenoxy phospholene and phospholane derivatives. Phospha sugars possessing phosphorus ester functionality (O=P-O-) with a nitrophenyl group has not yet been reported so far.

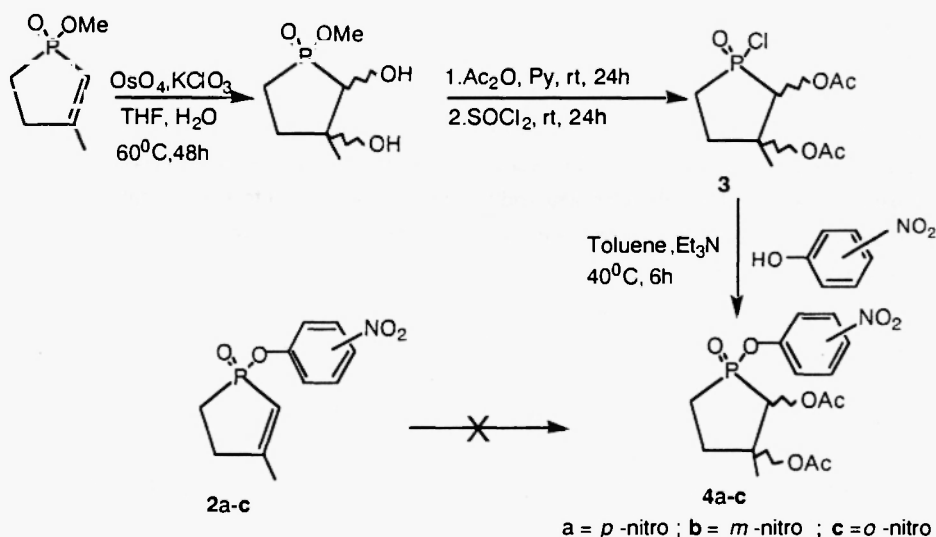
Results and Discussion

A pure compound of 1-chloro-3-methyl-2-phospholene 1-oxide (1) was prepared from 1-methoxy-3-methyl-2-phospholene 1-oxide. Compound (1) was refluxed in dry toluene with nitro-substituted phenols afforded 3-methyl-1-(nitro-substituted phenoxy)-2-phospholene 1-oxides (2a-c) (Scheme 1). In the same way 2,3-diacetoxy-3-methyl-1-(nitro-substituted phenoxy)-phospholane 1-oxides (4a-c) (Scheme 2) were prepared from 2,3-diacetoxy-1-chloro-3-methyl-phospholane 1-oxide (3). The products were purified by column chromatography on silica gel and the isomer ratios are calculated on the basis of ^{31}P NMR. Attempts to prepare phospholanes

(4a-c) from phospholenes (2a-c) were failed because of P-O-C bond was easily broken in aqueous medium due to strong electron withdrawing nature of P=O bond (7) and negative inductive effect of nitrophenyl group. The alternative synthetic method shown in Scheme 2 was followed. These are the first phospho sugar derivatives which are possessing phosphorus ester functional moiety (O=P-O-) with a nitrophenyl group prepared from 2-phospholenes as the starting materials. The structure of 1-(nitro-substituted phenoxy)-2-phospholene and phospholane derivatives is supported by spectral data shown in Tables 1 and 2.



Scheme 1



Scheme 2

Experimental

Preparation of 3-methyl-1-(nitro-substituted phenoxy)-2-phospholene 1-oxides (2a-c): To dry toluene of 15 ml nitrophenols 0.75g (5.0 mmol) and dry triethylamine 1ml (5.0 mmol) 1-chloro-3-methyl-2-phospholene 1-oxide (1) 0.75g (5.0 mmol) in toluene 15 ml was added dropwise for 30 min and the mixture was stirred for 6 h at 40 °C, filtered and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded products 2a-c being purified by column chromatography on silica gel; yield of 2a 80%, 2b 75%, and 2c 78%. The boiling point of products: 2a, bp 155-157 °C/0.1 mmHg; 2b, bp 158-160 °C/0.1 mmHg, and 2c, bp 160-163 °C/0.1 mmHg. Mass: Products 2a-c; m/z 253 (M^+). IR (neat): Products 2a-c: ν (cm⁻¹) 1650 (C=C), 1245 (P=O), and 750 (P-C).

Table 1. NMR data of compound 2a.

¹ H NMR (CDCl ₃)	¹³ C NMR (CDCl ₃)	³¹ P NMR (CDCl ₃)
δ (ppm)	δ (ppm)	δ (ppm)
2.05 (s, 3H, CH ₃)	20.5 (d, ³ J _{CP} =8 Hz, CH ₃)	76.3
2.13-2.30 (m, 2H, H-4,4')	24.4 (d, J _{CP} =27.2 Hz, C-5)	
2.60-2.67 (m, 2H, H-5,5')	31.2 (d, ² J _{CP} =13.3 Hz, C-4)	
5.92 (dd, 1H, J _{PH} =24.4 Hz, J _{HH} =1.3 Hz)	119.19 (d, J _{CP} =128.3 Hz, C-2)	
7.3 (dt, 2H, J _{HH} =9.2 Hz, 3.1 Hz & J _{PH} =2.1 Hz, 1.1 Hz)	120.49 (d, ³ J _{CP} =5.3 Hz, Ph C-2)	
8.2 (dd, 2H, J _{HH} =6.9 Hz & 2.1 Hz)	125.15 (s, Ph C-3)	
	143.59 (s, Ph C-4)	
	156.12 (d, ² J _{CP} =8 Hz, Ph C-1)	
	166.8 (d, ² J _{CP} =34.7 Hz, C-3)	

Table 2. NMR data of compound 4a.

¹ H NMR (CDCl ₃)	¹³ C NMR (CDCl ₃)	³¹ P NMR (CDCl ₃)
δ (ppm)	δ (ppm)	δ (ppm)
1.96 & 1.97 (2s, 6H, 2CH ₃)	15.63 & 16.16 (2s, 2CH ₃)	55.2 (major)
2.12 (s, 3H, CH ₃)	19.8 (d, ³ J _{CP} =6 Hz, CH ₃)	62.3 (minor)
2.2-2.5 (m, 2H, CH ₂ , H-4,4')	25.9 (d, ² J _{CP} =6 Hz, C-3)	
2.7-3.1 (m, 2H, CH ₂ , H-5,5')	26.9 (d, J _{CP} =64.1 Hz, C-5)	
4.4-4.9 (m, 1H, H-2)	31.2 (d, ² J _{CP} =12 Hz, C-4)	
7.2 (dt, 2H, J _{HH} =9.1 Hz, 3.2 Hz & J _{PH} =2.2 Hz, 1.3 Hz)	67.6 (d, J _{CP} =170 Hz, C-2)	
8.1 (dd, 2H, J _{HH} =7.1 Hz, & 2.2 Hz)	121.2 (d, ³ J _{CP} =5.3 Hz, Ph C-2)	
	125.7 (s, Ph C-3), 145 (s, Ph C-4)	
	156.65 (d, ² J _{CP} =9 Hz, Ph C-1)	
	166.6 & 166.7 (2s, 2 C=O)	

Preparation of 2,3-diacetoxy-3-methyl-1-(nitro-substituted phenoxy)-phospholane 1-oxides (4a-c): Products 4a-c were also prepared under the same experimental procedure as for compounds 2a-c from 1-chloro-2,3-diacetoxy-3-methyl-phospholane 1-oxide (3); yield of 4a 70%, 4b 67%, and 4c 68%. The boiling point of products: 4a, bp 135-138 °C/0.1 mmHg; 4b, bp 139-140 °C/0.1 mmHg, and 4c, bp 140-142 °C/0.1 mmHg. The isomer ratios of products: 4a, 7.7 : 1.0; 4b, 5.4 : 1.0, and 4c, 4.9 : 1.0 based on ³¹P NMR. Mass: Products 4a-c; m/z 371 (M⁺). IR (neat): Products 4a-c: ν (cm⁻¹) 1740 (C=O), 1380 (O-CO-CH₃), 1250 (P=O), and 750 (P-C).

References and Notes

- (1) R. Goto, S. Inokawa, A. Sera, and S. Otani in *Tantori no Kagaku (Chemistry of Monosaccharides)*, Maruzen, Tokyo, 1988.
- (2) a) M. Yamashita, Y. Nakatsukasa, M. Yoshikane, H. Yoshida, T. Ogata, and S. Inokawa, *Carbohydr. Res.*, 59, C12 (1977); b) M. Yamashita, Y. Nakatsukasa, H.

- Yoshida, T. Ogata, S. Inokawa, K. Hirotsu, and J. Clardy, *Ibid.*, **70**, 247 (1979); c) M. Yamada and M. Yamashita, *Ibid.*, **95**, C9 (1981); d) M. Yamashita, M. Yamada, K. Tsunekawa, T. Oshikawa, K. Seo, and S. Inokawa, *Ibid.*, **121**, C4 (1983); e) Idem., *Ibid.*, **122**, C1 (1983); f) M. Yamashita, M. Yamada, M. Sugiura, H. Nomoto, and T. Oshikawa, *Nippon Kagaku Kaishi*, 1207 (1987); g) H. Yamamoto and S. Inokawa, *Adv. Carbohydr. Chem. Biochem.*, **42**, 135 (1984).
- (3) S. Budavari, *The Merck Index*, Twelfth Edition, Merck & Co., Inc., Whitehouse Station, N.J., pp. 1208-1209 (1996). Examples for nitro-substituted phosphorus compounds as bio-active materials: Paraoxon (*diethyl 4-nitrophenyl phosphate*) and Parathion (*diethyl 4-nitrophenyl thiophosphate*).
- (4) a) J. Emsley and D. Hall, in *The Chemistry of Phosphorus*, Harper & Row, London, 1976, p.157; b) L. D. Quin and T. P. Barket, *J. Chem. Soc., Chem. Commun.*, 788 (1967).
- (5) L. D. Quin, J. P. Gratz, and T. P. Barket, *J. Org. Chem.*, **33**, 1034 (1968).
- (6) M. Yamashita, M. Uchimura, A. Iida, L. Parkanayi, and J. Clardy, *J. Chem. Soc., Chem. Commun.*, 569 (1988).
- (7) M. Yamashita, A. Yabui, K. Suzuki, Y. Kato, M. Uchimura, A. Iida, H. Mizuno, K. Ikai, T. Oshikawa, L. Parkanayi, and J. Clardy, *J. Carbohydr. Chem.*, **16**, 499 (1997).

Received on February 22, 2000