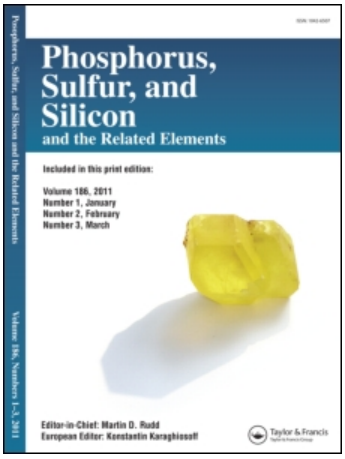

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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Online publication date: 27 October 2010

To cite this Article Reddy, Valluru Krishna , Rao, Lakonda Nagaprasada , Oshikawa, Tatsuo , Takahashi, Masaki and Yamashita, Mitsuji(2002) 'Synthesis of Novel 1-(substituted phenyl)-2-phospholene 1-Oxide Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 177: 6, 1801 — 1806
To link to this Article: DOI: 10.1080/10426500212255
URL: http://dx.doi.org/10.1080/10426500212255

Phosphorus, Sulfur and Silicon, 2002, Vol. 177:1801–1806

1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290093414

SYNTHESIS OF NOVEL 1-(SUBSTITUTED PHENYL)-2-PHOSPHOLENE 1-OXIDE DERIVATIVES

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(Received July 29, 2001; accepted December 25, 2001)

Several novel 1-(substituted phenyl)-2-phospholene 1-oxide 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. Structures of all the synthesized compounds were unequivocally confirmed by IR, ^{1}H, ^{13}C, and ^{31}P NMR spectral, elemental, and X-ray crystallographic analyses.

Keywords: Grignard reactions; ^{1}H, ^{13}C, and ^{31}P NMR analyses; substituted phenyl-2-phospholenes

INTRODUCTION

In recent years focus has increased on the synthesis of bioactive phosphorus compounds. Among these compounds, phospha sugars are very interesting due to their potential biological activities in various fields.[1] In view of their characteristic biological activities, nitro- and/or chloro-substituted phenyl phospha sugar derivatives are expected to have heightened bioactivity because several reports suggested that the molecules containing substituted aromatic groups, being mainly nitro- and/or halo-substituted, are possessing potential bioactivity,[2] and, moreover, chloro- and nitro-subtituted aromatic compounds are more toxic.[3] Thus by incorporating these substituted aromatic moieties into a basically bioactive phospha sugar molecule, the resulting bioactivity is expected to be more enhanced than that of the normal phospha sugar molecules.

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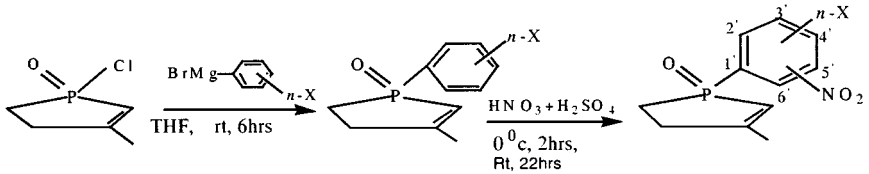
RESULTS AND DISCUSSION

In connection with our greater interest in the synthesis of substituted 1-phenyl-2-phospholene 1-oxide derivatives, compounds **1a–g** were synthesized through Grignard reagent formation.[4] The essence of our synthetic method by using a Grignard reagent is to generate a P-phenyl bond through metal-halogen exchange and then to trap it by nucleophilic addition (Grignard coupling). The Grignard reagent is therefore used in excess. Except for the first entry, all of the products in Table I are new compounds.



1 **2a-g** **3a-g**

X=H, Cl, OMe; n=-*p*, -*m*, -*o*

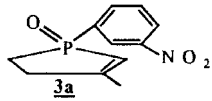
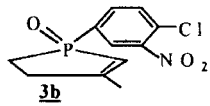
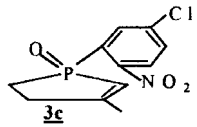
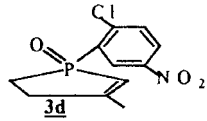
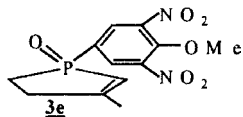
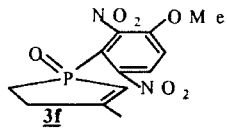
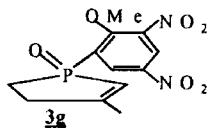
SCHEME 1

The resulting derivatives were nitrated by using nitrating mixed acids, and interesting observations were carried out that all members of the **2a–g** (Scheme 1) afforded a variety of positional isomeric products (Table II) due to the electrophilic aromatic substitution reaction on mono- and di-substituted benzene rings of **2a–g**, since the P=O is a *deactivating* group. In the first case of compound **2a**, mono substituted substitution of electrophile NO_2^+ was oriented to the meta position to the meta directing (P=O) group, giving product 1-(3′-nitrophenyl)-3-methyl-2-phospholene 1-oxide (**3a**). However, it was somewhat surprising to observe that compounds **2b–d** are

TABLE I Physical Properties and ^{31}P-NMR Shifts of **2a–g**

Compd	*n*-X	Yield (%)	^{31}P-NMR (ppm)
2a	H	60	60.68
2b	*p*-chloro	62	60.39
2c	*m*-chloro	58	60.68
2d	*o*-chloro	52	63.59
2e	*p*-methoxy	71	61.75
2f	*m*-methoxy	69	62.33
2g	*o*-methoxy	66	60.19

TABLE II Product Structures, Physical, and ^{31}P NMR Data of **3a–g**

Entry	Substrate	Product	Yield (%)	MP (°C)	^{31}P-NMR (ppm)
1	**2a**	 **3a**	80	117–120	59.90
2	**2b**	 **3b**	56	ND	77.28
3	**2c**	 **3c**	55	ND	76.57
4	**2d**	 **3d**	50	ND	77.92
5	**2e**	 **3e**	75	170–173	57.96
6	**2f**	 **3f**	71	162–166	56.65
7	**2g**	 **3g**	70	155–159	58.18

*ND, not determined due to syrupy state.

disubstituted with P=O (meta directing) and Cl (ortho-para directing) groups. Nitration occurred, and the incoming group (NO_2^+) was oriented to the favorable position, i.e., either ortho or para to the chloro and meta to the P=O group, giving products 1-(4′-chloro-3′-nitrophenyl)-3-methyl-2-phospholene 1-oxide (**3b**) and 1-(2′-chloro-5′-nitrophenyl)-3-methyl-2-phosphospholene 1-oxide (**3d**), while in the case of compound **2c**, i.e., when a meta-directing group P=O located meta to an ortho-para directing group (Cl), NO_2^+ was oriented to the ortho to the P=O group rather than para and gave the product 1-(5′-chloro-2′-nitrophenyl)-3-methyl-2-phospholene 1-oxide (**3c**), as according to the *ortho effect* principle. Members of **2e–g** are also disubstituted with a

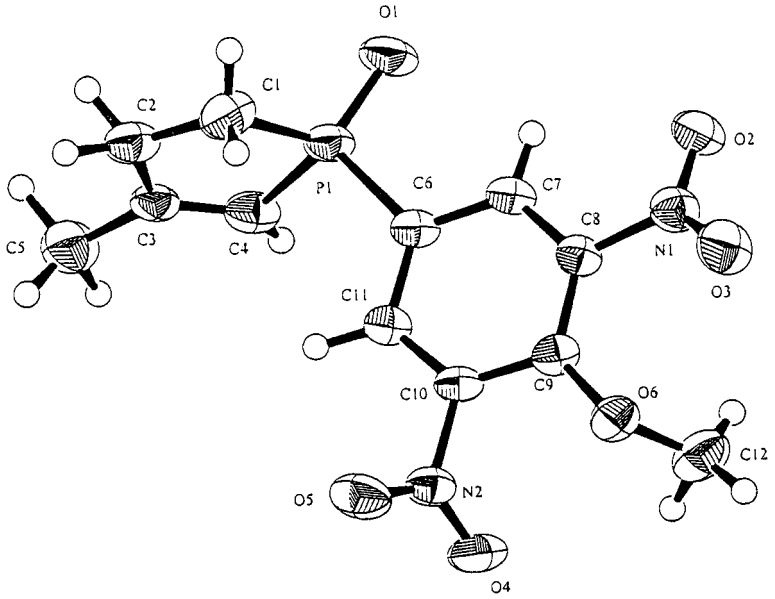


FIGURE 1 ORTEP of compound **3e**.

strong ortho-para activating group (OCH_3), the rate of nitration was enhanced, and dinitration occurred at the same reaction conditions of members **2a–d**. The orientation effect is similar to that of products **3a–d**. All of these products were purified by fractional recrystallization method from EtOAc and *n*-hexane, and single crystal was developed from EtOAc by slow evaporation method for compound **3e**. The ORTEP diagram is shown in Figure 1.

EXPERIMENTAL

Preparation of 1-(Substituted Phenyl)-3-methyl-2-phospholene 1-Oxide Derivatives (2a–g) via Grignard Reaction

A general procedure for members of **2a–g** is illustrated with that of **2b**. A suspension of 1-chloro-3-methyl-2-phospholene 1-oxide (**1**, 0.60 g, 4.0 mmol) in 6 mL of dry THF was added dropwise over 30 min to a solution of *p*-chlorophenylmagnesium bromide (which was prepared from 1.0 g (5.2 mmol) of *p*-chlorobromobenzene, 0.13 g (5.2 mmol) of magnesium in 15 mL of dry THF stirred vigorously for 40 min at 0°C), and the mixture was stirred for an additional 6 h at room

temperature. The reaction mixture was quenched with ice and dilute hydrochloric acid, and the aqueous mixture was extracted with chloroform. The organic layer was dried, and the solvent was evaporated under *vaccuo* to give an oily mixture. This mixture was purified by column chromatography on silica gel by using ethyl acetate and methanol (20:1) as the mixture of eluent, gave 0.60 g, 50% of **2b**. **^{1}H-NMR** (δ in ppm): 2.08 (s, 3H, CH_3), 2.00–2.40 (m, 2H, H-4,4′), 2.50–3.00 (m, 2H, H-5,5′), 5.92 (d, 1H, H-2, J_{PCH} = 25.2 Hz), and 7.35–8.20 (m, 4H, Ph); **^{13}C-NMR** (δ in ppm): 21.00 (d, CH_3, $^3J_{PC}$ = 17.3 Hz), 27.47 (d, C-5, J_{PC} = 69.5 Hz), 34.08 (d, C-4, $^2J_{PC}$ = 8.7 Hz), 120.32 (d, C-2, J_{PC} = 100.2 Hz), 128.8 (d, C-3′, $^3J_{PC}$ = 12.1 Hz), 131.97 (d, C-2′, $^2J_{PC}$ = 11.3 Hz), 132.69 (d, C-1′, J_{PC} = 98.2 Hz), 138.15 (d, C-4′, $^4J_{PC}$ = 3.4 Hz), and 165.31 (d, C-3, $^2J_{PC}$ = 25.4 Hz); Anal. Calcd for $C_{11}H_{12}OPCl$: C, 58.30; H, 5.34. Found: C, 58.12; H, 5.01.

Preparation of 1-(Substituted Nitrophenyl)-3-methyl-2-phospholene 1-Oxide Derivatives (3a–g)

A general procedure of the members of **3a–g** is illustrated with that of **3e**. A solution of 1.0 g (4.5 mmol) of **2e** in 3.5 mL of con. H_2SO_4, the reaction mixture was cooled to 0°C and added dropwise 0.5 mL of fuming HNO_3, stirred for 2 h at 0°C and for 22 h at room temperature. The reaction mixture was poured onto a 100 g of crushed ice, the aqueous solution was extracted with chlorofrom (20 mL × 3), the organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under *vaccuo* to give yellow crude solid. The crude product was purified by fractional recrystallization from ethyl acetate and *n*-hexane to give pure **3e** (0.70 g, 50%), mp 168–170°C. IR (potassium bromide): Products **3e**: ν (cm^{-1}) 1640 (C=C), 1530 and 1350 (NO_2), and 1245 (P=O); **^{1}H-NMR** (δ in ppm): 2.16 (s, 3H, CH_3), 2.66–2.78 (m, 2H, H-4,4′), 2.89–2.97 (m, 2H, H-5,5′), 3.98 (s, 3H, OCH_3), 5.91 (d, 1H, H-2, J_{PCH} = 25.8 Hz), 8.32 (d, 2H, H-2′, 6′, $^2J_{PCH}$ = 10.9 Hz); **^{13}C-NMR** (δ in ppm): 21.20 (d, CH_3, $^3J_{PC}$ = 17.4 Hz), 26.49 (d, C-5, J_{PC} = 71.5 Hz), 33.95 (d, C-4, $^2J_{PC}$ = 9.3 Hz), 64.82 (s, OCH_3), 118.01 (d, C-2, J_{PC} = 102.6 Hz), 145.11 (d, C-3′, $^3J_{PC}$ = 13.6 Hz), 130.75 (d, C-2′, $^2J_{PC}$ = 11.8 Hz), 131.26 (d, C-1′, J_{PC} = 92.6 Hz), 149.56 (d, C-4′, $^4J_{PC}$ = 2.4 Hz), and 168.57 (d, C-3, $^2J_{PC}$ = 27.3 Hz); Anal. Calcd for $C_{12}H_{13}O_6N_2P$ (**3e**): C, 46.16; H, 4.20; N, 8.97. Found: C, 46.05; H, 4.15; N, 8.88.

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