

Synthesis and Antimicrobial Activity of Novel 3 Substituted 1,5-Dihydro-2,4,3-Benzodioxaphosphepine 3-Oxides

P. Haranath, M. F. Stephen Babu, U. Anasuyamma,
C. Naga Raju, and C. Suresh Reddy

Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, India

Received 27 September 2004; revised 7 April 2005

ABSTRACT: Novel 3 substituted 1,5-dihydro-2,4,3-benzodioxaphosphepine 3-oxides (**5a–h**) were synthesized by reacting 1,2-benzenedimethanol (**1**) with phosphorus tribromide in the presence of triethylamine at 0–30°C and subsequent reaction of the monobromide (**2**) with different Grignard reagents (**3**) at room temperature. The products (**4**) were converted to corresponding oxides **5a–i** by oxidation with H₂O₂ at room temperature. The chemical structures of all the products were confirmed by analytical, IR and NMR (¹H, ¹³C, and ³¹P) spectral data. Their antifungal and antibacterial activity is also evaluated. Most of these compounds exhibited moderate antimicrobial activity in the assay. © 2005 Wiley Periodicals, Inc. *Heteroatom Chem* 16:572–575, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20154

INTRODUCTION

Organophosphate moiety is an important pharmacophore in agricultural and pharmaceutical compounds [1]. Phosphocin/phosphepine and their related derivatives containing this group represent an important class of pesticides, antibiotics, herbicides,

and antiviral agents [2]. Some of them are well known for their insecticidal activities [3] and are known to degrade hydrolytically and enzymatically to nontoxic residues. Discovery of their fungicidal properties constitutes a recent development [4].

RESULTS AND DISCUSSION

The synthetic route (Scheme 1) involves the cyclization of equimolar quantities of 1,2-benzenedimethanol (**1**) with phosphorus tribromide in the presence of triethylamine in toluene to form phosphorobromodite (**2**). On subsequent reaction of **2** with different substituted Grignard reagents (**3**) formed **4a–i**, which were converted to corresponding oxides (**5a–i**) by oxidation with H₂O₂ at room temperature.

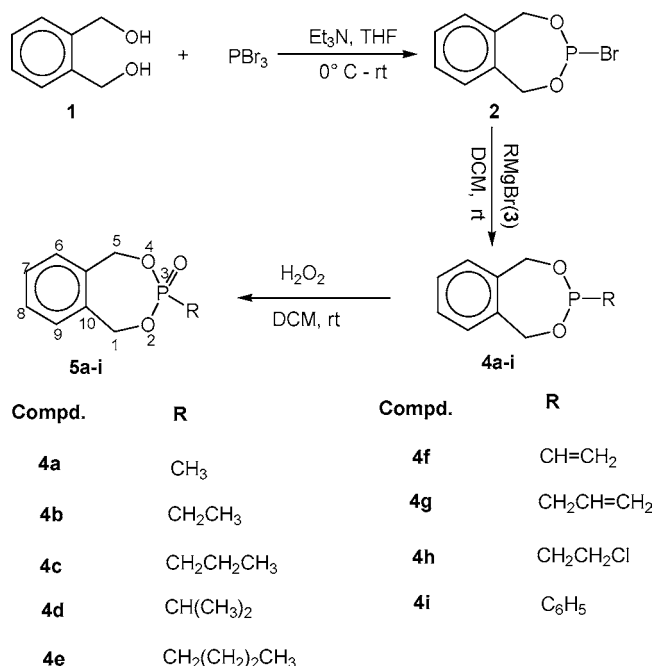
Product yields and elemental analysis, IR [5–7] and ³¹P NMR [8] data, ¹H [7] and ¹³C NMR [7] data of **5a–i** are given in Tables 1, 2, 3, and 4 respectively, and the data agreed with the proposed chemical structures.

ANTIMICROBIAL ACTIVITY

The compounds **5a–i** (Table 5) were screened for their antifungal activity against *Aspergillus niger* and *Helminthosporium* species along with the standard fungicide Bavestien. Disc diffusion method [9] was followed for screening the compounds at three

Correspondence to: C. Suresh Reddy; e-mail: csureshsvu@yahoo.com.

Contract grant sponsor: UGC, New Delhi, India.
© 2005 Wiley Periodicals, Inc.



SCHEME 1

different concentrations (25, 50, 100 ppm). Their antibacterial activity was also evaluated according to the disc diffusion method [10,11] at three different concentrations against *Escherichia coli* and *Staphylococcus aureus* by comparing with standards streptomycin.

It is interesting to observe that all compounds **5a-i** exhibited moderate antifungal and antibacterial activity when compared with that of standards. The highlight is that all the compounds exhibited moderate activity against bacteria, and some compounds were more effective than the standard streptomycin. Similarly it is gratifying to observe that these com-

pounds are extremely more effective against fungi *Bavestein*.

EXPERIMENTAL

The melting points were determined on a Mel-Temp apparatus and were uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. All IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 unit. ¹H, ¹³C, and ³¹P NMR spectra were recorded on AMX 400 MHz spectrometer, operating at 400 MHz for ¹H, 100 MHz for ¹³C and 161.9 MHz for ³¹P as solution in CDCl₃, and the chemical shifts were referenced to TMS (¹H & ¹³C) and 85% H₃PO₄ (³¹P).

1,2-Benzenedimethanol was procured from Lancaster Chemical Company, Inc., USA and used without further purification.

Preparation of Ethyl Magnesium Bromide (3b)

Caution: Because of the sensitivity of the reagents and products to moisture and oxygen, all manipulations were performed in an anhydrous inert nitrogen atmosphere.

In a dry 100 mL three-necked round-bottomed flask fitted with dropping funnel, a reflux condenser with a calcium chloride tube, a nitrogen inlet, and a thermometer were placed magnesium turnings (0.12 g, 0.005 mol) and 5 mL dry THF. The reaction mixture was kept under stirring, and 2 mL of ethyl bromide (0.54 g, 0.005 mol) in 10 mL of dry THF is added at 10–15°C for 10 min. When the reaction started the temperature increased to 40–45°C. The mixture was cooled to room temperature, and stirring was continued until the magnesium metal is dissolved to form ethyl magnesium bromide (**3b**).

TABLE 1 Physical Data of **5a-i**

Compd.	mp (°C)	Yield (%) ^a	Mol. Formula (Mol. Wt)	Elemental Analysis Found (Calcd) %	
				C	H
5a	135–136	67	C ₉ H ₁₁ O ₃ P (198.16)	54.55 (54.37)	5.60 (5.61)
5b	119–120	76	C ₁₀ H ₁₃ O ₃ P (212.18)	56.61 (56.80)	6.18 (5.99)
5c	156–157	74	C ₁₁ H ₁₅ O ₃ P (226.12)	58.41 (58.52)	6.68 (6.67)
5d	112–113	71	C ₁₁ H ₁₅ O ₃ P (226.12)	58.41 (58.60)	6.68 (6.67)
5e	147–148	69	C ₁₂ H ₁₇ O ₃ P (240.24)	59.99 (59.82)	7.13 (7.15)
5f	162–163	56	C ₁₀ H ₁₁ O ₃ P (210.17)	57.15 (57.30)	5.28 (5.26)
5g	123–124	59	C ₁₁ H ₁₃ O ₃ P (224.19)	58.93 (58.81)	5.84 (5.85)
5h	181–182	61	C ₁₀ H ₁₂ ClO ₃ P (246.63)	48.70 (48.80)	4.90 (4.88)
5i	130–131	68	C ₁₄ H ₁₃ O ₃ P (260.23)	64.62 (64.79)	5.04 (5.03)

^aRecrystallized from ethanol.

TABLE 2 ^{31}P NMR Data of **4a–i** and **5a–i** and Infrared Spectral Data (cm^{-1})^a **5a–i**

Compd.	^{31}P NMR ^{b,c}	Compd.	IR		^{31}P NMR
			P=O	P–C _(aliphatic)	
4a	123.2	5a	1221	750	1.29
4b	121.2	5b	1226	752	1.47
4c	122.6	5c	1231	756	1.37
4d	124.2	5d	1225	753	1.35, 0.28
4e	119.6	5e	1232	753	1.67
4f	129.2	5f	1228	746	4.38, 0.31
4g	126.2	5g	1226	752	3.19, 0.84
4h	120.3	5h	1227	750	2.31
4i	141.2	5i	1229	761	23.17

^aRecorded as KBr pellets.^bRecorded in CDCl_3 .^cChemical shifts in ppm from 85% phosphoric acid.TABLE 3 ^1H NMR Chemical Shift^a Data of **5a–i**^b

Compd.	CH_2 (1&5)	Ar-H	R1	R2	R3	R
5a	5.20–5.42 (m, 4H)	7.36–7.52 (m, 4H)	1.13 (s, 3H)			
5b	5.21–5.39 (m, 4H)	7.24–7.63 (m, 4H)	1.72–1.80 (m, 2H)	1.12–1.21 (m, 3H)		
5c	5.16–5.40 (m, 4H)	6.88–7.48 (m, 4H)	2.25–2.40 (m, 2H)	1.30–1.50 (m, 5H)		
5d	5.18–5.41 (m, 4H)	7.14–7.53 (m, 4H)	2.10–2.23 (m, 1H)	1.20–1.50 (m, 6H)		
5e	5.03–5.33 (m, 4H)	7.26–7.49 (m, 4H)	2.09–2.30 (m, 2H)	1.51–1.66 (m, 2H)	1.28–1.30 (m, 2H)	0.87–0.90 (m, 3H)
5f	5.11–5.39 (m, 4H)	7.18–7.61 (m, 4H)	5.72–5.86 (m, 1H)	5.23–5.32 (m, 2H)		
5g	5.10–5.42 (m, 4H)	7.15–7.59 (m, 4H)	3.07–3.12 (m, 2H)	5.92–6.02 (m, 1H)	5.39–5.40 (m, 2H)	
5h	5.16–5.32 (m, 4H)	6.98–7.46 (m, 4H)	3.05 (m, 2H)	3.24 (m, 2H)		
5i	5.22–5.41 (m, 4H)	6.61–7.48 (m, 9H)				

^aChemical shifts in δ and J (Hz) in parenthesis.^bRecorded in CDCl_3 .TABLE 4 ^{13}C NMR Chemical Shift^a Data of Some of **5**^{b,c}

Carbon Atoms	5a	5b	5c	5d	5e	5f	5g
C-1 and 5	70.2 (6.6)	69.6 (7.2)	70.7 (6.9)	70.9 (7.1)	70.0 (7.4)	69.6 (6.9)	69.8 (7.2)
C-6 and 9	128.3 (2.9)	128.2 (2.6)	128.3 (2.7)	127.8 (2.7)	127.5	128.3 (2.6)	128.1 (2.6)
C-7 and 8	126.9	126.4	126.2	126.6	126.7	127.2	126.8
C-10 and 11	139.1	138.2	136.2	137.2	136.5	138.7	139.6
C-1'	13.8 (136.0)	27.6 (139.4)	28.4 (140.2)	26.8 (140.7)	34.6 (138.2)	123.4 (131.6)	36.5 (132.8)
C-2'	—	7.1 (14.5)	26.1 (4.7)	16.7 (4.7)	30.4 (4.7)	116.2 (4.6)	134.2
C-3'	—	—	16.15 (15.6)	16.0 (4.7)	22.6 (14.7)	—	119.8 (17.6)
C-4'	—	—	—	—	12.9	—	—

^aChemical shifts in ppm.^bRecorded in CDCl_3 .^c J (Hz) in parenthesis.

Synthesis of 3-(Ethyl)1,5-dihydro-2,4,3-benzodioxaphosphepin 3-oxide **5b**

To a cooled (0°C) and stirred solution of 1,2-benzenedimethanol (**1**, 0.69 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in 25 mL dry toluene under N_2 gas, a solution of phosphorus tribromide (1.35 g, 0.005 mol) in 10 mL of dry toluene was

added over a period of 20 min. After completion of the addition, the temperature of the reaction mixture was raised to room temperature and stirred for 1 h to form the intermediate phosphorobromodite (**2**). The progress of the reaction was judged by the TLC analysis. The reaction mixture was filtered under nitrogen atmosphere to remove triethylamine hydrobromide.

TABLE 5 Antifungal and Antibacterial Activities of Compounds **5** in Terms of Zone of Inhibition (mm)

Compd.	Fungi						Bacteria					
	<i>Aspergillus niger</i>			<i>Helminthosporium oryzae</i>			<i>Escherichia coli</i>			<i>Staphylococcus aureus</i>		
	100	50	25	100	50	25	100	50	25	100	50	25
5a	12	5	2	12	6	2	10	—	—	7	—	—
5b	12	6	2	14	7	4	10	—	—	8	3	—
5c	11	5	2	14	6	2	9	2	—	7	4	2
5d	14	7	3	12	5	—	11	4	2	8	3	—
5e	11	6	3	14	6	—	8	—	—	8	3	—
5f	13	7	4	12	5	2	10	5	2	6	—	—
5g	16	8	3	15	5	2	9	3	—	9	4	2
5h	18	7	2	14	6	2	9	5	—	8	3	—
5i	19	8	4	15	7	3	11	5	2	8	4	2
Bavistin Streptomycin	18	8	4	16	7	3	10	6	—	9	5	—

All concentrations expressed in ppm.

— indicates no activity.

The Grignard reagent **3b** was cooled to 15°C, and phosphorobromodite (**2**) was added to it in 15 min under nitrogen. After the addition, the reaction mixture was brought to room temperature and stirred for 90 min. The progress of the reaction was monitored by TLC (ethyl acetate: hexane) analysis. After completion of the reaction, the mixture was cooled to 5°C and then hydrolyzed by slow addition of saturated aqueous NH₄Cl solution with cooling. The solvent was removed under vacuum, and the residue was extracted with ethyl acetate. The extract after washing with brine solution and drying over anhydrous MgSO₄ was evaporated in rotaevaporator. The crude product (**4b**) obtained was dissolved in dichloromethane (30 mL) and hydrogen peroxide (30% H₂O₂, 0.2 mL, 0.005 mol) was added to it dropwise at 0–5°C. The reaction mixture was brought to room temperature and kept with stirring for 2 h for the completion of oxidation as indicated by the TLC analysis. The reaction mixture was washed with saturated NaCl solution, dried over anhydrous MgSO₄, and the solvent was evaporated in a rotaevaporator. The resulting crude product was recrystallized from 2-propanol to yield 1.46 g (76%) of **5b**, mp 119–120°C.

ACKNOWLEDGMENTS

The authors express their thanks to Professor C. Devendranath Reddy for his helpful guidance and

discussions and the Director of CDRI, Lucknow and SIF, IISC, Bangalore for the elemental and spectral data.

REFERENCES

- [1] (a) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J Chem Soc, Perkin Trans I* 1984, 2845; (b) Demir, A. S.; Tanyeli, C.; Sesenoglu, O.; Demic, S.; Evin, O. O. *Tetrahedron Lett* 1996, 37, 407.
- [2] (a) Schlemminger, I.; Willecke, A.; Maison, W.; Koch, R.; Lutzen, A.; Martens, J. *J Chem Soc, Perkin Trans I* 2001, 2804; (b) Huang, J.; Chen, R. *Heteroatom Chem* 2000, 11, 480.
- [3] Schrader, *Angew Chem* 1958, 69, 86.
- [4] Anuradha, K.; Rajasekhar, A.; Reddy, T. K. K. *Indian J Phytopathol* 1991, 44, 411.
- [5] Thomas, L. C.; Chittenden, R. A. *Chem Soc (London)* 1961, 1913.
- [6] Thomas, L. C. *The Interpretation of the Infrared Spectral of Organophosphorus Compounds*; Heydon: London, 1974.
- [7] Silverstein, R. M.; Bassler, G. C.; Morill, T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; Wiley: New York, 1991.
- [8] Quin, L. D.; Verkade, J. G. *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*; VCH: New York, 1994.
- [9] Benson, H. J. *Microbiological Applications*, 5th ed.; WC Brown, 1990; p. 134.
- [10] Cruickshank, R. *Medical Microbiology, A Guide to Diagnosis and Control of Infection*, 2nd ed.; E & S Livingston: Edinburgh, 1968; p. 888.
- [11] Beuer, A. W.; Kirby, M. M.; Sherries, J. C.; Truck, A. *Am J Clin Pathol* 1969, 45, 493.