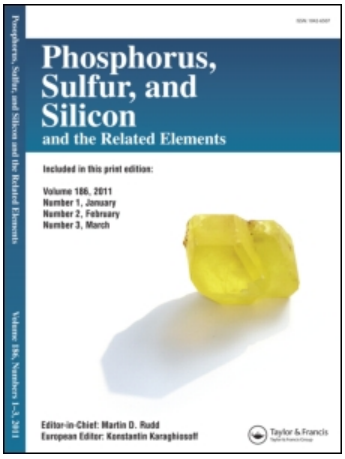

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Synthesis and Antioxidant Properties of Novel 1,3,2-Oxazaphospholanes Incorporating 1,2-Dihydropyridines

Vijaya Kabra[a]; Sonia Sharma[a]; Neelima Gupta[a]; Ashok Kumar[b]; Priyadarshi Meena[b]
[a] Department of Chemistry, University of Rajasthan, Jaipur, India [b] Department of Zoology, University of Rajasthan, Jaipur, India

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SYNTHESIS AND ANTIOXIDANT PROPERTIES OF NOVEL 1,3,2-OXAZAPHOSPHOLANES INCORPORATING 1,2-DIHYDROPYRIDINES

Vijaya Kabra,[1] Sonia Sharma,[1] Neelima Gupta,[1] Ashok Kumar,[2] and Priyadarshi Meena[2]
[1]*Department of Chemistry, University of Rajasthan, Jaipur, India*
[2]*Department of Zoology, University of Rajasthan, Jaipur, India*

Novel chiral 1,3,2-oxazaphospholane-2-sulfides incorporating a dihydropyridine ring have been synthesized via phosphorylation of 2-aminopyridinium salts, followed by in situ oxidation and cyclocondensation with 2-(alkylamino)ethanol. Cyclic organothiophosphates thus obtained have been screened for their antioxidant properties.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Antioxidant property; 1,2-dihydropyridine; 1,3,2-oxazaphospha heterocycles; phospholane ring system

INTRODUCTION

In this article, we report the synthesis and characterization of 1,3,2-oxazaphospholane-2-sulfides incorporating a dihydropyridine ring. In our previous publications, we have utilized substituted pyridinium salts, with active terminal hydrogen atoms, as synthones for various organophosphorus derivatives having a phosphorus in different coordination states.[1–5] Now, a cyclic 1,3,2-oxazaphospholane ring has been formed by cyclocondensation of a phosphorylated intermediate with an appropriate binucleophile, i.e., 2-(alkylamino)ethanol.

Both dihydropyridine[6,7] and 1,3,2-O,N,P heterocyclic derivatives[8,9] are highly valued due to their use as starting materials and intermediates in synthetic organic chemistry and their importance in biological systems. Several review articles have highlighted the importance of dihydropyridine derivatives as "active hydrogen store" in cell systems, as they are responsible for a number of biological reactions as antioxidants.[6,7] In medicinal chemistry,

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Address correspondence to Vijaya Kabra, Department of Chemistry, University of Rajasthan, Jaipur 302004, India. E-mail: kabrasg@hotmail.com

attachment of dihydropyridine unit to a biomolecule is found to enhance lipophilicity of the conjugate, thereby improving drug delivery at the site of the reaction.[7]

The importance of 1,3,2-O,N,P heterocycles has attracted the interest of synthetic organic chemists as well as biochemists due to their valuable pharmacological properties and potential for synthetic applications.[8] Different synthetic strategies for five- and six-membered systems incorporating 1,3,2-O,N,P moiety are available in the literature.[9–11] Reddy et al.[11] and Gazaliev et al.[12] have addressed the conformational aspects of oxazaphosphorinane and phospholane ring systems. The importance of these heterocyclic units is evident by their presence in a number of alkylating anticancer drugs,[8,9] pesticides,[13] and antimicrobial agents.[11] Such compounds are also known to posses matrix metalloproteinase inhibitory[14,15] and synergizing activities.[16] They have been used in the synthesis of phospholipids[17] and asymmetric synthesis.[10,18]

We have investigated antioxidant activity of the synthesized 1,3,2-oxazaphospholane derivatives, and a comparison has been made with ascorbic acid, which is a known non-enzymatic antioxidant by adopting a standard DPPH (2,2-diphenyl-1-picrylhydrazyl free radical) method.[19]

RESULTS AND DISCUSSION

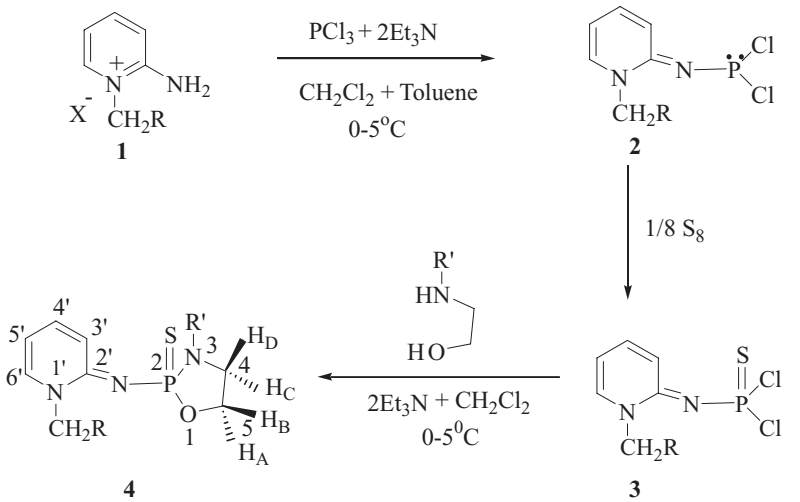
N-Alkyl-2-aminopyridinium halides[1–5] were phosphorylated by using one equivalent of phosphorus trichloride in the presence of two equivalents of triethylamine at 0–5°C in a 2:1 mixture of methylene chloride and toluene under nitrogen atmosphere to generate the corresponding iminodichlorophosphines **2**.[20] The intermediate **2** was oxidized in situ with elemental sulfur (1/8 equivalent) at ambient temperature, which generated the corresponding cycloiminylidenamidothiophosphoryl dichloride **3**, incorporating phosphorus in more stable tetracoordinated state. Cycloiminylidenamidothiophosphoryl dichloride **3**, upon nucleophilic substitution of the labile chlorine atoms with a bifunctional nucleophile, such as 2-(alkylamino)ethanol ($R' = CH_3$, C_2H_5), furnished 2-(*N*-alkylpyridin-2′-ylidenamido)-3-alkyl-[1,3,2]oxazaphospholane-2-sulfide **4** (Scheme 1).

The products are white crystalline solids with sharp melting points, are stable under nitrogen atmosphere, and have been well characterized through elemental analysis; ^1H, ^{31}P, and ^{13}C NMR spectroscopy (Table I); and mass spectrometry.

NMR Studies

The progress of the reaction progress was monitored using ^{31}P NMR spectroscopy. After the addition of sulfur and *N*-(alkylamino)ethanol, the ^{31}P NMR signal which initially appeared at δ146.5–158.3 ppm corresponding to the tri-coordinated iminodichlorophosphine **2** shifted to the higher frequency region of δ69.2–77.1 ppm, which is characteristic for tetracoordinated phosphorus,[21] indicating the completion of the reaction and the formation of **4a–f**.

Cyclic oxazaphospholane derivatives **4** have been further characterized by ^1H NMR spectroscopy (Table I). Due to the presence of chiral phosphorus at the 2-position, methylene protons at the 4 and 5 positions of the oxazaphospholane ring become diastereotopic and an ABCD spin system (Scheme 1) is observed. Due to the higher electronegativity of oxygen, the signals of the AB part in the range of δ4.2–4.3 ppm have been assigned to $O-CH_2$ protons, and the signals in the higher frequency region of δ3.0–3.6 ppm have been assigned to $N-CH_2$ protons as CD part of the spin system. Signals for each individual



4	a	b	c	d	e	f
R	H	C_6H_5	CO_2CH_3	$CO_2C_2H_5$	H	C_6H_5
R'	CH_3	CH_3	CH_3	CH_3	C_2H_5	C_2H_5

Scheme 1

proton appear as doublet of double doublets (ddd) due to geminal coupling of 12.9–18.3 Hz and vicinal couplings of 5.4–7.5 Hz with cis proton and 6.2–10.8 Hz with trans proton, except O—CH_2 protons of **4a** and **4f**, where additional coupling with phosphorus ($^3J_{PH}$ = 6.1–6.3 Hz) is also observed (Table I). However, in the case of **4d** and **4e**, O—CH_2 protons appear as complex multiplet. Moreover, in the case of **4e**,**f**, N3-methylene protons also become diastereotopic, giving rise to an ABX_3 spin system which shows additional three bond coupling with phosphorus ($^3J_{PH}$ = 7.8–10.8 Hz) (Table I). N3-CH_3 protons in **4a–d** appear as doublet ($^3J_{PH}$ = 11.4–13.2 Hz) at δ2.6–2.7 ppm. In the case of **4c**,**d**, long distance–induced diastereotopicity is observed when N1′-CH_2 protons become anisochronous, giving rise to two doublets in the range of δ4.5–4.7 ppm ($^2J_{HH}$ = 12.3–16.2 Hz).

The signals in the ^{13}C NMR spectra have been assigned according to chemical shift (Table I). C-4 and C-5 carbons of the oxazaphospholane ring appear at δ40.8–55.8 ppm and δ50.0–65.4 ppm ($^2J_{PC}$ = 2.5 Hz), respectively. N3-methyl and ethyl carbon atoms give signals in the range of δ14.2–46.7 ppm ($^2J_{PC}$ = 10.5 Hz). The N1′-methylene carbon absorbs at δ49.9–64.9 ppm, while the N1′-CH_3 carbon absorbs at δ64.8–64.9 ppm. All other carbon atoms appear in the expected regions (Table I).

Mass Spectrum

The mass spectrum of one representative compound **4b** was also recorded. Molecular ion peak M^+ (m/z = 319.36, 2%), a base peak M + 1 (m/z = 320.12, 100%), M + 2 (m/z = 321.13, 19%), and M + 3 (m/z = 322.12, 6%) were observed due to the possible acceptance of one proton by different heteroatoms present in the molecule. Other significant

Table I Physical and spectral data of the compounds **4a–c**

Compound	Mol. formula (Mol. wt.)	Yield (%)	Mp (°C)	Elemental analysis (%) Calcd. (Found) C	H	N	^{31}P NMR δ ppm	^{1}H NMR	^{13}C NMR
4a	$C_9H_{14}ON_3SP$ (243.269)	68	125°C	44.39 (44.34)	5.75 (5.74)	17.26 (17.25)	77.1	2.7(d, $^{3}J_{HP}$ = 13.2, N3-CH_3); CD part of ABCD spin system (δ_{HC} = 3.2 (ddd), δ_{HD} = 3.1 (ddd), $^{2}J_{HC\text{-}HD}$ = 18.3, $^{3}J_{HC\text{-}HB}$ = 9.0, $^{3}J_{HC\text{-}HA}$ = 6.3, $^{3}J_{HD\text{-}HA}$ = 6.2, $^{3}J_{HD\text{-}HB}$ = 6.0, 4-CH_2); 3.6(s, 3H, N1′-CH_3); AB part of ABCD spin system (δ_{HA} = 4.3 (dddd), δ_{HB} = 4.2 (dddd), $^{2}J_{HA\text{-}HB}$ = 12.1, $^{3}J_{HA\text{-}HD}$ = 6.2, $^{3}J_{HA\text{-}HC}$ = 6.3, $^{3}J_{HA\text{-}P}$ = 6.1, $^{3}J_{HB\text{-}HC}$ = 9.0, $^{3}J_{HB\text{-}HD}$ = 6.0, $^{3}J_{HB\text{-}P}$ = 6.1, 5-CH_2); 6.4(ddd, 1H, $^{3}J_{HH}$ = 6.1, $^{3}J_{HH}$ = 6.2, $^{4}J_{HH}$ = 3.1, H-4′); 7.3(dd, 1H, $^{3}J_{HH}$ = 6.2, $^{4}J_{HH}$ = 3.3, H-5′); 7.5(d, 1H, $^{3}J_{HH}$ = 6.1, H-3′); 7.6(dd, 1H, $^{3}J_{HH}$ = 6.2, $^{4}J_{HH}$ = 3.1, H-6′).	64.8(s, N1′-CH_3); 33.0(s, N3-CH_3); 40.8(s, C-4); 50.0(s, C-5); 109.3(s, C-5′); 120.8(s, C-4′); 138.9(s, C-6′); 139.4(s, C-2′)
4b	$C_{15}H_{18}ON_3SP$ (319.367)	73	137°C	56.36 (56.35)	5.63 (5.64)	13.15 (13.12)	75.0	2.6(d, $^{3}J_{HP}$ = 12.9, N3-CH_3); CD part of ABCD spin system (δ_{HC} = 3.2 (ddd), δ_{HD} = 3.1 (ddd), $^{2}J_{HC\text{-}HD}$ = 13.8, $^{3}J_{HC\text{-}HB}$ = 7.5, $^{3}J_{HC\text{-}HA}$ = 5.4, $^{3}J_{HD\text{-}HA}$ = 8.7, $^{3}J_{HD\text{-}HB}$ = 7.2, 4-CH_2); AB part of ABCD spin system (δ_{HA} = 4.3 (ddd), δ_{HB} = 4.1 (ddd), $^{2}J_{HA\text{-}HB}$ = 14.7, $^{3}J_{HA\text{-}HD}$ = 8.7, $^{3}J_{HA\text{-}HC}$ = 5.4, $^{3}J_{HB\text{-}HC}$ = 7.5, $^{3}J_{HB\text{-}HD}$ = 7.2, 5-CH_2); 5.3(s, 2H, N1′-CH_2); 6.4(dd, 1H, $^{3}J_{HH}$ = 7.4,$^{3}J_{HH}$ = 6.6, H-5′); 7.3(d, 1H, $^{3}J_{HH}$ = 6.4, H-3′); 7.3–7.4(m, 5H, Ar); 7.4(dd, 1H, $^{3}J_{HH}$ = 6.6, $^{3}J_{HH}$ = 6.4, H-4′); 7.7(d, 1H, $^{3}J_{HH}$ = 7.4, H-6′).	32.7(s, N3-CH_3); 49.9(s, N1′-CH_2); 54.5(s, C-4); 64.8(s, C-5); 109.3(s, C-5′); 120.5(s, C-3′); 120.9(s, C_o); 128.2(s, C_m); 128.9(s, C_p); 129.1 (s, C_i); 135.5(s, C-4′); 137.9(s, C-6′); 138.7(s, C-2′)
4c	$C_{11}H_{16}O_3N_3SP$ (301.306)	66	105°C	43.80 (43.79)	5.31 (5.29)	13.93 (13.89)	74.7	2.7(d, $^{3}J_{HP}$ = 12.9, N3-CH_3); CD part of ABCD spin system (δ_{HC}= 3.2 (ddd), δ_{HD} = 3.2 (ddd), $^{2}J_{HC\text{-}HD}$ = 18.3, $^{3}J_{HC\text{-}HB}$ = 8.4, $^{3}J_{HC\text{-}HA}$ = 6.9, $^{3}J_{HD\text{-}HA}$ = 10.8, $^{3}J_{HD\text{-}HB}$ = 7.2, 4-CH_2); 3.8(s, 3H, $CO_2\mathbf{CH_3}$); AB part of ABCD spin system (δ_{HA} = 4.3 (ddd), δ_{HB} = 4.2 (ddd), $^{2}J_{HA\text{-}HB}$ = 15.3, $^{3}J_{HA\text{-}HD}$ = 10.8, $^{3}J_{HA\text{-}HC}$ = 6.9, $^{3}J_{HB\text{-}HC}$ = 8.4, $^{3}J_{HB\text{-}HD}$ = 7.2, 5-CH_2); 4.5(d, 1H, $^{2}J_{Ha}$ = 16.2, N3′-CH_2); 4.7(d, 1H, $^{2}J_{Hb}$ = 16.2, N3′-CH_2); 6.4(dd, 1H, $^{3}J_{HH}$ = 8.7, $^{3}J_{HH}$ = 8.1, H-5′); 7.3(d, 1H, $^{3}J_{HH}$ = 6.0, H-3′); 7.4(dd, 1H, $^{3}J_{HH}$ = 8.1, $^{3}J_{HH}$ = 6.0, H-4′); 7.7(d, 1H, $^{3}J_{HH}$ = 8.7, H-6′).	32.3(s, N3-CH_3); 49.8(s, C-4); 64.8(s, N1′-CH_2); 53.8(s, C-5); 29.6(s, CO_2-$\mathbf{CH_3}$); 108.9(s, C-4′); 120.2(s, C-3′); 120.4(s, C-6′); 138.5(s, C-2′); 139.3(s, C=O)

(Continued on next page)

Table I Physical and spectral data of the compounds **4a–c** *(Continued)*

Compound	Mol. formula (Mol. wt.)	Yield (%)	Mp (°C)	Elemental analysis (%) Calcd. (Found) C	H	N	^{31}P NMR δ ppm	^{1}H NMR	^{13}C NMR
4d	$C_{12}H_{18}O_3N_3SP$ (315.333)	69	103°C	45.66 (45.64)	5.70 (5.69)	13.31 (13.29)	69.2	1.5(t, 3H, $^3J_{HH}$ = 7.2, $CO_2CH_2\mathbf{CH_3}$); 2.7(d, 3H, $^3J_{HP}$ = 11.4, N3-CH_3); CD part of ABCD spin system (δ_{HC} = 3.6 (ddd), δ_{HD} = 3.5 (ddd), $^2J_{HC\text{-}HD}$ = 12.9, $^3J_{HC\text{-}HB}$ = 6.3, $^3J_{HC\text{-}HA}$ = 5.4, $^3J_{HD\text{-}HA}$ = 9.3, $^3J_{HD\text{-}HB}$ = 6.9, 4-CH_2); 4.4(q, 2H, $^3J_{HH}$ = 5.7, $CO_2\mathbf{CH2}CH_3$); 4.4–4.6(m, 2H, 5-CH_2); 4.5(d, 1H, $^2J_{Ha}$ = 12.3, N3′-CH_2); 4.5(d, 1H, $^2J_{Hb}$ = 12.3, N3′-CH_2); 6.9(d, 1H, $^3J_{HH}$ = 6.5, H-5′); 7.3(d, 1H, $^3J_{HH}$ = 7.2, H-3′); 7.4(dd, 1H, $^3J_{HH}$ = 7.2, $^3J_{HH}$ = 6.5, H-4′); 7.5(d, 1H, $^3J_{HH}$ = 8.7, H-6′).	15.0(s, $CO_2CH_2\mathbf{CH_3}$); 31.0(d, $^2J_{PC}$ = 0.5, N3-CH_3); 49.5 (s, C-4); 64.7(s, N1′-CH_2); 65.4 (d, $^2J_{PC}$ = 2.5, C-5); 29.7(s, CO_2-$\mathbf{CH_2}CH_3$); 112.6(s, C-4′); 115.5(s, C-3′); 127.4(s,C-6′); 145.2(s, C-2′); 162.9(s, C=O)
4e	$C_{10}H_{16}ON_3SP$ (257.296)	75	134°C	46.63 (46.61)	6.21 (6.19)	16.32 (16.29)	76.1	X_3 part of ABX_3 spin system (δX_3 = 1.3 (t), 3H, $^3J_{HA\text{-}HB}$ = 6.0, 3N-CH_2-$\mathbf{CH_3}$); AB part of ABX_3 spin system (δ_{HA} = 3.3 (ddq), δ_{HB} = 3.2 (ddq), $^2J_{HA\text{-}HB}$ = 12.3, $^3J_{HA\text{-}P}$ = 10.8, $^3J_{HA\text{-}X3}$ = 6.6, $^3J_{HB\text{-}P}$ = 7.8, $^3J_{HB\text{-}X3}$ = 6.3, 3N-$\mathbf{CH_2}$-CH_3); CD part of ABCD spin system (δ_{HC} = 3.2 (ddd), δ_{HD} = 3.1 (ddd), $^2J_{HC\text{-}HD}$ = 15.0, $^3J_{HC\text{-}HB}$ = 9.0, $^3J_{HC\text{-}HA}$ = 7.5, $^3J_{HD\text{-}HA}$ = 9.4, $^3J_{HD\text{-}HB}$ = 7.2, 4-CH_2); 3.61(s, 3H, N1′-CH_3); 4.2–4.3(m, 2H, 5-CH_2); 6.4(dd, 1H, $^3J_{HH}$ = 9.6, $^3J_{HH}$ = 6.2, H-5′); 7.3(d, 1H, $^3J_{HH}$ = 7.2, H-3′); 7.4(dd, 1H, $^3J_{HH}$ = 7.2, $^3J_{HH}$ = 6.2, H-4′); 7.6(d, 1H, $^3J_{HH}$ = 9.6, H-6′).	14.2(s, N3-CH_2-$\mathbf{CH_3}$); 40.7(d, $^2J_{PC}$ = 13.6, N3-$\mathbf{CH_2}$-CH_3); 64.9(s, N1′-CH_3); 46.9(s, C-4); 62.0(s,C-5); 109.0(s, C-5′); 112.5(s, C-3′); 120.8(s, C-4′); 138.7(s, C-6′); 141.0(s, C-2′)
4f	$C_{16}H_{20}ON_3SP$ (333.394)	77	130°C	57.58 (57.56)	5.99 (5.97)	12.59 (12.57)	74.0	X_3 part of ABX_3 spin system (δX_3 = 1.2 (t), 3H, $^3J_{HA\text{-}HB}$ = 6.0, N3-CH_2-$\mathbf{CH_3}$); AB part of ABX_3 spin system (δ_{HA} = 3.2 (ddq), δ_{HB} = 3.1 (ddq), $^2J_{HA\text{-}HB}$ = 12.9, $^3J_{HA\text{-}P}$ = 9.3, $^3J_{HA\text{-}X3}$ = 7.2, $^3J_{HB\text{-}P}$ = 8.7, $^3J_{HB\text{-}X3}$ = 6.3, N3-$\mathbf{CH_2}$-CH_3); CD part of ABCD spin system (δ_{HC} = 3.1 (ddd), δ_{HD} = 3.0 (ddd), $^2J_{HC\text{-}HD}$ = 14.4, $^3J_{HC\text{-}HB}$ = 9.3, $^3J_{HC\text{-}HA}$ = 7.2, $^3J_{HD\text{-}A}$ = 8.1, $^3J_{HD\text{-}HB}$ = 6.6, 4-CH_2); AB part of ABCD spin system (δ_{HA} = 4.3 (dddd), δ_{HB} = 4.1 (dddd), $^2J_{HA\text{-}HB}$ = 12.3, $^3J_{HA\text{-}HD}$ = 8.1,$^3J_{HA\text{-}HC}$ = 7.2, $^3J_{HA\text{-}P}$ = 6.3, $^3J_{HB\text{-}HC}$ = 9.3, $^3J_{HB\text{-}HD}$ = 6.6, $^3J_{HB\text{-}P}$ = 6.3, 5-CH_2); 5.3(s, 2H, N1′-CH_2-C_6H_5); 6.4(dd, 1H, $^3J_{HH}$ = 6.6, $^3J_{HH}$ = 7.8, H-5′); 7.3(d, 1H, $^3J_{HH}$ = 6.3, H-3′); 7.3–7.4(m, 5H, Ar); 7.4(dd, 1H, $^3J_{HH}$ = 6.6, $^3J_{HH}$ = 5.1, H-4′); 7.7(dd, 1H, $^3J_{HH}$ = 5.1, $^3J_{HH}$ = 7.8, H-6′).	14.2(s, N3-CH_2-$\mathbf{CH_3}$); 46.7(d, $^2J_{PC}$ = 10.5,N3-$\mathbf{CH_2}$-CH_3); 64.9(s, N1′-$\mathbf{CH_2}$-C_6H_5); 55.8(s, C-4); 62.1(s, C-5); 112.6(s, C-5′); 128.2(s, C-3′); 128.9(s,C_o); 129.0(s,C_m); 129.2(s,Cp); 129.9(s, C_i); 138.0(s, C-4′); 138.9(s,C-6′); 141.0(s, C-2′)

peaks were observed at 304.14 (30%), 288.15 (24%), 186.13 (6%), 185.13 (49%), 115.10 (3%), 99.11 (17%), and 61.06 (10%).

BIOACTIVITY

The world of free radicals in biological systems was first explored by Denham Harman, who proposed the role of free radicals in the aging process.[22] This work gradually triggered intense research into the field of free radicals in biological systems. The harmful effects of free radicals are termed as oxidative and nitrosative stress,[23,24] which develop due to the deficiency of enzymatic and nonenzymatic antioxidants. The antioxidant property of a compound is related to its ability to scavenge deleterious free radicals and also to modulate cell signaling pathways.[25]

Synthesized phospholane derivatives have been screened for antioxidant activity by adopting a standard DPPH technique,[19] where vitamin C, a known non enzymatic antioxidant, has been selected as a standard. Results have been presented in Figure S1 (see the Supplemental Materials, available online).

CONCLUSION

Novel 1,3,2-oxazaphospholane derivatives incorporating 1,2-dihydropyridine ring have been synthesized and well characterized. The presence of a chiral phosphorus center induces distereotopicity in the methylene groups of the oxazaphospholane ring as well as pyridinic *N*-methylene substituent. Upon screening their antioxidant properties, moderate activity in comparison to ascorbic acid has been observed. Compounds **4a** and **4c**, which have larger number of methyl substitutents, show increased activity.

EXPERIMENTAL

The synthesized products are stable in an inert atmosphere and are sensitive towards moisture and atmospheric oxygen. Solvents were carefully dried prior to use, and fine chemicals were used as obtained from Aldrich, Lancaster, and Merck. All the reactions were carried out and products stored under pure dry nitrogen atmosphere. Melting points were determined by capillary method and are uncorrected. Elemental analyses were carried out on a Heraeus Carlo Erba1108 analyzer. NMR spectra were recorded on a Jeol AL300 ^{31}P NMR at 121.50 MHz (Obset 156 KHz) using 85% H_3PO_4 as an external standard, and ^{1}H NMR spectra at 300.4 MHz (Obset 130 KHz) using TMS as internal reference. The DART-MS was recorded on a Jeol AccuTOF JMS-T100LC mass spectrometer having a direct analysis in real time (DART) source, and the antioxidant property was determined by the DPPH method.[19] *N*-Alkyl-2-aminopyridinium halides **1a–f** were synthesized by reported methods[1–5] and were used without recrystallization.

Synthesis of 2-(*N*-Alkylpyridin-2′-ylidenamido)-3-alkyl-[1,3,2]oxazaphospholane-2-sulfides 4a–f

To a well stirred solution of *N*-alkyl-2-aminopyridinium halides (15 mmol) in a mixture of methylene chloride and toluene (40 mL + 20 mL), PCl_3 (15 mmol) was added, followed by the dropwise addition of triethylamine (30 mmol) at 0–5°C. After stirring the resulting mixture for 24 h, sulfur powder (15 mmol) was added, and stirring was continued for

24 h, after which triethylamine (30 mmol) and a solution of 2-(ethyl/methylamino)ethanol (15 mmol) in methylene chloride (20 mL) were added dropwise at 0–5°C. The stirring was further continued for another day. After that, the solvent was removed in vacuo, and the residue was extracted with diethylether (2 × 25 mL) and kept in refrigerator. The white solid thus separated was filtered and dried.

Determination of DPPH Radical Scavenging Activity

The antioxidant activity of the compounds on the basis of the scavenging activity of the stable DPPH was determined by the method described by Braca et al.[19] with slight modification. The 0.1 mL (1 mg/mL) compound was added to 3 mL of 0.1 M DPPH in methanol.

Absorbance at 517 nm was read after 30 min incubation and% inhibition of activity was calculated as% inhibition = [(Ao–Ae)/Ao] × 100 (Ao = absorbance without extract, Ae = absorbance with extract). Ascorbic acid was used as antioxidant standard. The statistically evaluated results and standard deviation have been presented in Figure S1 (Supplemental Materials).

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