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Synthesis and Antimicrobial Activity of 3-[(4-Substituted) (2-oxo-1,3-oxazolidin-3-yl) phosphoryl]-1,3-oxazolidin-2-ones

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ABSTRACT

3-[(4-Substituted) (2-oxo-1,3-oxazolidin-3-yl)-phosphoryl]-1,3-oxazolidin-2-ones (4a–j**) were synthesized through a two-step process. Bis-(2-oxo-1,3-oxazolidin-3-yl)-phosphonic chloride (2) prepared by the reaction of two moles of oxazolidin-2-one (1) with phosphorus oxychloride in dry tetrahydrofuran in the presence of triethylamine and treatment with various heterocyclic aromatic and aliphatic amines under the same experimental conditions afforded the title compounds (**4a–j**). They were characterized by elemental analysis, IR, NMR (^{1}H, ^{13}C and ^{31}P) and mass spectroscopy. Their antimicrobial activities were also evaluated.**

KEYWORDS

3-[(4-Substituted) (2-oxo-1,3-oxazolidin-3-yl)-phosphoryl]-1,3-oxazolidin-2-ones, oxazolidin-2-one, bis-(2-oxo-1,3-oxazolidin-3-yl)-phosphonic chloride, antimicrobial activity, spectral studies.

1. Introduction

Organophosphorus compounds are well-known bioactive agents in a wide spectrum of living organisms. Organophosphorus esters are thoroughly proven pesticides and insecticides.[1] Several organophosphorus fungicides such as iprobenfos and edifenphos are used for the control of fungal diseases in plants.[2] Oxazaphosphinine derivatives, cyclophosphamide and its analogues, isophosphamides, are clinically useful anticancer drugs.[3,4]

Recently it was observed that the benzoxazaphosphinine moiety possessed significant antimicrobial activity.[5,6] Polymeric organophosphorus compounds found use as flame retardants[7–9] and in material science. They have increasingly been used as reagents and in a wide range of chemical reactions[10] in asymmetric organic synthesis. Organophosphoramides are used as ligands in Lewis base-catalysed allylation and aldol addition reactions.[11] The chemistry of phosphoramidates has been recently developed due to their biological activity and also their use in coordination chemistry. Some of them with the RC(O)N(H)P(O)R^1_2 formula act as O,O′-donor ligands for metal ions, particularly for rare earth metal cations.[12] In view of this, a series of 3-[(4-substituted-1-yl) (2-oxo-1,3-oxazolidin-3-yl)-phosphoryl]-1,3-oxazolidin-2-one derivatives (**4a–j**) have been synthesized.

2. Results and Discussion

The synthesis of the title compounds (**4a–j**) involves the preparation of the intermediate bis-(2-oxo-1,3-oxazolidin-3-yl)-phosphonic chloride (**2**)[13–14] by the reaction of two moles of 1,3-oxazolidin-2-one (**1**) with one mole of phosphorus oxychloride in dry tetrahydrofuran (THF) in the presence of triethylamine (TEA) at 35 °C for 2 h. The subsequent reaction of **2** with heterocyclic aliphatic and aromatic amines (**3a–j**) at 30–40 °C in THF in the presence of TEA afforded the title compounds in high yields.

Compounds **4a–j** showed characteristic infrared absorption wavenumbers in the ranges 1764–1720, 1252–1220 and 766–745 cm^{-1} for C=O, P=O and P-N groups, respectively[15] (see Table 1). ^{1}H NMR spectra of compounds (**4a–j**) showed complex multiplets for aromatic protons in the range of δ 6.43–8.01 ppm (see Table 2). Methylene protons of oxazolidine 2-one (O-CH_2) resonated as a triplet in the region δ 4.28–4.40 ppm (4H, t, J = 8.2 Hz) due to their coupling with the adjacent protons. Similarly the two protons of the methylene (N-CH_2) group directly linked to nitrogen appeared as a triplet at δ 3.21–3.38 ppm[16] (4H, t, J =8.1 Hz) due to coupling with the neighbouring protons. In all these compounds the protons adjacent to nitrogen in the amino part showed the expected multiplicity in their respective regions.[17]

In the ^{13}C NMR spectra, the carbonyl carbon in **4a–j** exhibited a singlet in the region δ 175.5–180.2 ppm. The C-4 and C-5 carbons of the oxazolidin-2-one moiety gave singlets in the regions δ 27.8–31.0 and 71.8–73.5 ppm respectively. Heterocyclic and cyclic amine carbon exhibited chemical shifts in the expected range[18] (see Table 3). The ^{31}P NMR chemical shifts of the title compounds appeared in the regions δ –13.01 to –18.70 ppm[19,20] (Table 1).

The mass spectra of compounds (**4a, 4d, 4g**) showed their respective molecular ion peaks in the expected m/z mass range. Mass spectral data of these compounds are given in Table 4.

3. Experimental

3.1. General Synthetic Procedures

IR spectra ($\bar{\nu}$ cm^{-1}) were recorded on a Perkin Elmer 1600 instrument as KBr pellets. NMR spectra were recorded on a Bruker AMX-300 MHz spectrometer operating at 121.5 MHz for ^{31}P, 300 MHz for ^{1}H, and 75 MHz for ^{13}C. All compounds were dissolved in $CDCl_3$ and chemical shifts were referenced to TMS (^{1}H and ^{13}C) and 85 % H_3PO_4 (^{31}P). Elemental analyses were performed using a Perkin Elmer 2400 instrument at the Central Drug Research Institute (CDRI), Lucknow.

3.2. Preparation of 3-[(Piperidine-1-yl) (2-oxo-1,3-oxazolidin-3-yl) phosphoryl]-1,3-oxazolidin-2-one (4a)

Oxazolidin-2-one, bis-(2-oxo-1,3-oxazolidin-3-yl)-phosphonic chloride (**2**) was prepared by reacting two moles of oxazolidine

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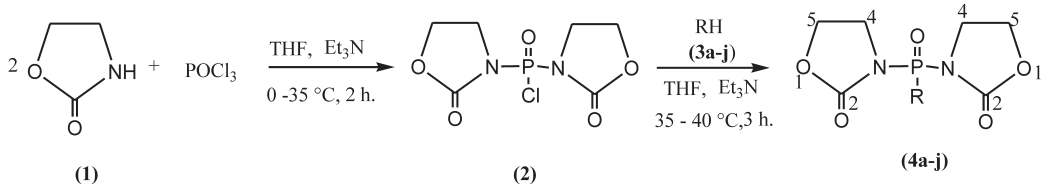
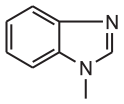
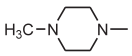
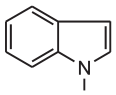
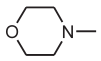
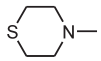
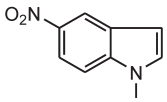


Compound	R	Compound	R
4a		**4f**	
4b		**4g**	
4c		**4h**	
4d		**4i**	
4e		**4j**	

Scheme 1
Synthesis of the title compounds.

with one mole of phosphorus oxychloride in the presence of triethylamine in dry tetrahydrofuran.[13,14]

To the cold (0–5 °C) solution of **2** in THF, TEA (0.61 g, 0.006 mol) and piperidine (0.510 g, 0.006 mol) in 20 mL of dry THF was added dropwise with stirring. After addition, the temperature of the reaction mixture was slowly raised to 35–40 °C and stirring was continued for another 3 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the solvent was removed in a rota-evaporator. The residue was washed with water, followed by 2-propanol

Table 1 Physical, analytical, IR and ^{31}P NMR spectral data of **4a–j**.

Compound	Molecular formula	M.p./°C	Yield/%	Elemental analysis found (calculated)			$\bar{\nu}$/cm^{-1}			δ(^{31}P)/ppm
				C	H	N	P=O	P-N	C=O	
4a	$C_{11}H_{18}N_3O_5P$	220–221	70	43.61 (43.57	6.10 5.98	14.01 13.86)	1233	766	1764	–13.58
4b	$C_{11}H_{19}N_4O_5P$	211–212	65	41.59 (41.51	6.10 6.02	17.69 17.60)	1220	745	1720	–13.68
4c	$C_{10}H_{16}N_3O_6P$	230–231	68	39.40 (39.35	5.36 5.28	13.82 13.77)	1228	747	1728	–14.01
4d	$C_{10}H_{16}N_3O_5PS$	240–241	70	37.42 (37.38	5.09 5.02	13.12 13.08)	1232	755	1730	–15.02
4e	$C_{10}H_{16}N_3O_5P$	210–211	65	41.59 (41.53	5.64 5.58	14.61 14.53)	1245	758	1735	–14.76
4f	$C_{13}H_{13}N_4O_5P$	215–216	68	46.50 (46.44	3.95 3.90	16.72 16.66)	1238	753	1745	–18.70
4g	$C_{14}H_{14}N_3O_5P$	220–221	65	50.20 (50.16	4.26 4.21	12.60 12.53)	1242	758	1753	–16.02
4h	$C_{10}H_{12}N_3O_5P$	225–226	60	42.18 (42.11	4.30 4.24	14.10 14.73)	1250	760	1740	–13.02
4i	$C_9H_{11}N_4O_5P$	227–228	65	37.82 (37.77	3.92 3.87	19.63 19.58)	1240	763	1750	–15.60
4j	$C_{14}H_{13}N_4O_7P$	230–231	65	44.26 (44.22	3.50 3.45	14.78 14.73)	1252	762	1725	–14.06

Table 2. ^{1}H NMR spectral data [a,b] of **4a-j**.

Compound	Ar-H	N-CH_2	O-CH_2	C-CH_2	S-CH_2	N-CH_3
4a	–	3.24 (4H, t, J = 8.2 Hz) 2.75 (4H, t, J = 7.8 Hz)	4.36 (4H, t, J = 8.5 Hz)	1.56 (6H t, J = 8.1 Hz)	–	–
4b	–	3.34 (4H, t, J = 8.1 Hz) 2.70 (4H, t, J = 7.9 Hz) 2.40 (4H, t, J = 8.2 Hz)	4.20 (4H, t, J = 8.4 Hz)	–	–	2.30 (s, 3H)
4c	–	3.21 (4H, t, J = 8.2 Hz) 3.10 (4H, t, J = 7.7 Hz)	4.38 (4H, t, J = 8.0 Hz) 3.68 (4H, t, J = 7.9 Hz)	–	–	–
4d	–	3.28 (4H, t, J = 8.0 Hz) 3.01 (4H, t, J = 7.8 Hz)	4.28 (4H, t, J = 8.2 Hz)	–	2.60 (4H, t, J = 8.0 Hz)	–
4e	–	3.21 (4H, t, J = 8.1 Hz) 2.90 (4H, t, J = 8.0 Hz)	4.39 (4H, t, J = 8.3 Hz)	1.7 (4H, t, J = 7.9 Hz)	–	–
4f	7.20–8.10 (m, 5H)	3.35 4H, t, J = 8.2 Hz)	4.38 (4H, t, J = 8.2 Hz)	–	–	–
4g	6.90–7.50 (m, 6H)	3.37 (4H, t, J = 8.1 Hz)	4.29 (4H, t, J = 8.6 Hz)	–	–	–
4h	6.20–6.80 (m, 4H)	3.38 4H, t, J = 7.9 Hz)	4.26 (4H, t, J = 8.0 Hz)	–	–	–
4i	7.10–7.80	3.29 (4H, t, J = 8.2 Hz)	4.35 (4H, t, J = 8.2 Hz)	–	–	–
4j	6.50–8.10 (m, 5H)	3.32 (4H, t, J = 7.8 Hz)	4.40 (4H, t, J = 8.1 Hz)	–	–	–

[a] Recorded in $CDCl_3$.
[b] Chemical shifts in ppm.

Table 3 ^{13}C NMR spectral data [a] for the compounds **4a, 4d, 4e, 4g** and **4i**.

Compound	δ/ppm
4a	178.8 (C2), 31.0 (C-4), 71.6 (C-5), 40.5 (C-2′), 27.1 (C-3′), 25.6 (C-4′), 27.1 (C-5′), 40.5 (C-6′).
4d	180.2 (C2), 29.5 (C-4), 71.8 (C-5), 35.8 (C-2′), 47.5 (C-3′), 47.5 (C-5′), 35.8 (C6′).
4e	178.5 (C2), 29.0 (C-4), 72.1 (C-5), 38.0 (C-2′), 24.8 (C-3′), 24.8 (C-4′), 38.0 (C-5′).
4g	176.9 (C2), 27.8 (C-4), 73.5 (C-5), 125.0 (C-2′), 102.8 (C-3′), 120.8 (C-4′), 122.0 (C-5′), 120.1 (C-6′), 113.8 (C-7′), 130.8 (C-8′), 138.1 (C-9′).
4i	175.5 (C2), 28.6 (C-4), 70.8 (C-5), 136.5 (C-2′), 122.5 (C-4′), 122.8 (C-5′).

[a] Recorded in $CDCl_3$.

and recrystallized from 2-propanol to afford pure compound (**4a**) with good yield (70 %), m.p. 220–221 °C. All other compounds (**4b–j**) were prepared by adopting the same procedure. All compounds were recrystallized from 2-propanol.

4. Biological Activity

4.1. Experimental Method

All the title compounds were tested for their antimicrobial activity by adopting the experimental method of Benson.[21]

Whatman No. 1 filter paper discs of 6 mm diameter, placed in a dry Petri dish, were autoclaved. The test compounds in measured quantities (1.0 mg, 0.5 mg) were dissolved in 5 mL of dimethylformamide to produce 200 ppm and 100 ppm solutions, respectively. The filter paper discs were allowed to dry and the amount of the substance per disc was taken as 500 and 250 μg. The bacterial (24 h) and fungal (48 h) cultures from the slants were diluted with sterile water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were uniformly spread on solidified agar (nutrient and potato dextrose agar) medium. The filter paper discs prepared from dimethylformamide medium were carefully placed over the spreaded cultures and incubated at 37 °C for 24 h for bacteria and at 28–30 °C for 48 h for fungi. Paper discs treated with dimethylformamide alone served as control. After the incubation period the plates were examined for inhibition zones. The diameters of inhibition zones (including the diameter of the disc) were measured. All determinations were made in triplicate for each of the compounds and the average value was taken.

Table 4 Mass spectral data of **4a**, **4d** and **4g**.

Compound	M/z/%
4a	303 (M^+, 60), 275 (25), 247 (34), 219 (80), 133 (45)
4d	321 (M^+, 45), 265 (40), 235 (28), 220 (45), 149 (22)
4g	336 (M^{+1}, 25), 311 (65), 280 (35), 250 (40), 144 (65), 118 (33)

4.2. Antimicrobial/fungal Activity

The antibacterial activity of compounds **4a–j** was assayed against the growth of *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) at three concentrations (100, 50 and 25 ppm) taking penicillin as the standard (see Table 5). The majority of the compounds exhibited significant activity against both bacteria but **4a** and **4g** showed equal antibacterial activity to that of penicillin.

The compounds **4a–j** were screened for their antifungal activity against *Aspergillus niger* and *Helminthosporium oryzae* species along with the standard fungicide griseofulvin (see Table 6). The disc diffusion method was followed for screening the compounds at three different concentrations (100, 50 and 25 ppm). All the compounds exhibited good antifungal activity. However,

Table 5 Antibacterial activity of **4a–j**.

Compound	Zone of inhibition/mm					
	Escherichia coli			*Staphylococcus aureus*		
	100 ppm	50 ppm	25 ppm	100 ppm	50 ppm	25 ppm
4a	12	9	3	10	8	6
4b	11	5	4	10	7	6
4c	10	8	4	9	8	5
4d	9	7	5	8	7	5
4e	11	7	8	10	8	5
4f	10	6	4	11	6	5
4g	12	5	5	10	8	5
4h	7	8	6	–	–	–
4i	9	7	6	–	–	–
4j	10	5	5	10	7	5
Penicillin	12	8	–	10	7	–

Table 6 Antifungal activity of **4a–j**.

Compound	Zone of inhibition/mm					
	Aspergillus niger			*Helminthosporium oryzae*		
	100 ppm	50 ppm	25 ppm	100 ppm	50 ppm	25 ppm
4a	11	6	4	11	6	5
4b	10	7	4	10	8	6
4c	10	8	7	11	9	5
4d	11	10	6	9	8	4
4e	10	5	4	10	8	6
4f	9	7	6	9	8	–
4g	12	11	8	11	10	7
4h	10	8	6	8	5	3
4i	11	7	5	9	6	5
4j	10	8	7	10	7	5
Griseofulvin	12	8	–	10	7	–

compound **4g** showed equal antifungal activity when compared with that of the reference compound.

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