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Synthesis and Antimicrobial Activity of Some Phenophosphazines

SNEHAL LOKHANDWALA[1,*] and K.R. DESAI[2]

[1]Shroff S.R. Institute of Chemical Technology, Block No. 402, At & Post Vataria-392 002, India
[2]Department of Chemistry, C.G. Bhakta Institute of Biotechnology, Gopal Vidyanagar, Tarsadi-394 350, India

*Corresponding author: E-mail: snehal_sl@yahoo.co.in

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A new family of organophosphorus compounds namely 3-chloro-1-(10-hydroxy-10-oxo-5,10-dihydro-phenophosphazin-2-yl)-4-(substituted phenyl)-azetidin-2-one (**3a-j**) has been synthesized by reaction of 2-[(substituted benzylidene)-amino]-10-oxo-5,10-dihydro-phenophosphazin-10-ol (**2a-j**) with chloro acetyl chloride and triethyl amine. All these compounds were characterized by elemental and spectral analysis. Their antimicrobial activity was also evaluated.

Key Words: Phenophosphazine, Azetidinone, Antimicrobial activity, Spectral analysis.

INTRODUCTION

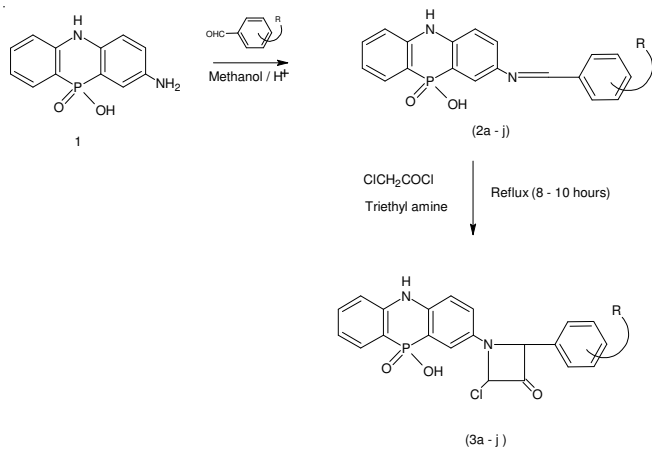
Organophosphorus hetrocycles having O and N in a six membered ring have gained much attention ever since cyclophosphamide was discovered as anticancer drug. Moreover several organophosphorus compounds have been extensively used in treatment of rheumatoid arthritis[1] and as antiviral[2] and antineoplastic agents[3].

Azetidinones also have diversified antibacterial and antifungal activities[4]. In present research, synthesis of compounds containing a six memebered hetero ring of N and P along with a four membered β-lactam ring is accomplished successfully. All compounds were characterized by elemental, IR and NMR analysis. Their antibacterial and antifungal activities were also evaluated.

EXPERIMENTAL

Melting points were determined using an open-ended capillary method and are uncorrected. The purity of synthesized compounds were checked by TLC. IR spectra were recorded in KBr using Perkin Elmer Spectrum BX series spectrophotometer. ^{1}H NMR spectra were carried out on Bruker DRX- 300 MHz (^{1}H). NMR spectrophotometer using TMS as internal standard in $CDCl_3$-DMSO solvent. Microanalytical data were obtained from Central Drug Research Institute, Lucknow, India.

General synthesis of 3-chloro-1-(10-hydroxy-10-oxo-5,10-dihydro-phenophosphazin-2-yl)-4-(substituted phenyl)-azetidin-2-one (3a-j): 2-Amino-5,10-dihydro-phenophosphazin-10-ol-10-oxide (**1**) was allowed to react with different aromatic aldehydes in presence of methanol and acid catalyst to get the corresponding Schiff bases (**2a-j**). The above synthesized Schiff bases and triethyl amine (1:3) were dissolved in DMF in a round bottom flask and chloroacetyl chloride was added slowly with constant stirring. The reaction mixture was stirred at room temperature for 1 h and then refluxed for 8-10 h. Excess of solvent was then removed by distillation. The solid thus separated was filtered, washed and dried. The crude product was then recrystallised with glacial acetic acid (**Scheme-I**).



Scheme-I

Antimicrobial activity: All the synthesized compounds were screened for *in vitro* and antimicrobial activities. The antibacterial activity was tested using cup plate method against *S. aureus*, *B. subtilis*, *E. coli* and *S. typhi*. Whereas antifungal

activity was tested using Sabourard Dextrose medium against *A. niger* and *C. albicans*. The impregnated dose of the drug for both the analysis was 100 µg/mL. The plates were incubated at 35 ºC and examined for zone of inhibition around each disc after 24 h. Results were compared with the activity of standard drugs like Streptomycin and Cotrimazole. All the compounds exhibited moderated antibacterial and antifungal activities (Table-1).

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF THE SYNTHESIZED COMPOUNDS

Compounds	Zone of inhibition (mm)					
	E. coli	*S. typhi*	*S. aureus*	*B. subtilis*	*A. niger*	*C. albicans*
3a	9	8	9.5	10.5	8.5	5.5
3b	9.5	9.5	10	12	9	7
3c	8	12	8.5	14.5	7.5	9.5
3d	8.5	15	9	17.5	8	12.5
3e	11	8	11.5	10.5	10.5	5.5
3f	10	9.5	10.5	12	9.5	7
3g	10.5	6	11	8.5	10	3.5
3h	6.5	6.5	7	9	6	4
3i	9.5	8	10	10.5	9	5.5
3j	6.5	9	7	11.5	6	6.5
Streptomycin	30	30	30	30	–	–

TABLE-2
PHYSICAL CONSTANTS OF THE SYNTHESIZED COMPOUNDS

Compound	R	Yield (%)	m.p. (ºC)	m.f.	Elemental analysis (%): Found (calcd.)		
					C	H	N
3a	4-OCH_3	81.5	> 300	$C_{22}H_{18}O_4N_2PCl$	59.95 (59.94)	4.11 (4.12)	6.34 (6.35)
3b	3-Cl	79.6	288	$C_{21}H_{15}O_3N_2PCl_2$	56.66 (56.65)	3.42 (3.40)	6.20 (6.21)
3c	3-Br	80.2	170	$C_{21}H_{15}O_3N_2PClBr$	51.52 (51.51)	3.08 (3.09)	5.74 (5.72)
3d	1 CH=CH	85.6	>300	$C_{23}H_{18}O_3N_2PCl$	63.26 (63.24)	4.14 (4.15)	6.40 (6.41)
3e	2-NO_2	84.9	279	$C_{21}H_{15}O_5N_3PCl$	55.32 (55.34)	3.33 (3.32)	9.21 (9.22)
3f	3-OC_6H_5	83.5	>300	$C_{27}H_{20}O_5N_2PCl$	64.50 (64.49)	4.02 (4.01)	5.55 (5.57)
3g	3-OC_6H_5, 4-OH	69.9	272	$C_{23}H_{20}O_5N_2PCl$	58.66 (58.67)	4.30 (4.28)	5.96 (5.95)
3h	3-OCH_3, 4-OH	70.2	>300	$C_{22}H_{18}O_5N_2PCl$	57.85 (57.84)	3.99 (3.97)	6.14 (6.13)
3i	- H	75.6	260	$C_{21}H_{16}O_3N_2PCl$	61.41 (61.40)	3.94 (3.93)	6.81 (6.82)
3j	3,5-OCH_3, 4-OH	81.9	>300	$C_{23}H_{20}O_6N_2PCl$	56.75 (56.74)	4.12 (4.14)	5.75 (5.77)

TABLE-3
ASSIGNMENTS OF KEY IR BANDS (cm^{-1}) FOR THE SYNTHESIZED COMPOUNDS

Comp. No.	(C=O) str.	(C-Cl) str.	(C-N) str.	(CH=CH) str.	(N-H) str.	(P=O) str.	(N=O) str.	(P-OH) str.	(C-Br) str.
3a	1696	722	1153	1411	3352	1238	–	1024	–
3b	1680	726	1156	1416	3354	1241	–	1042	–
3c	1691	730	1162	1419	3352	1212	–	1011	589
3d	1700	735	1151	1420	3361	1245	–	928	–
3e	1697	728	1146	1421	3319	1237	1525	1021	–
3f	1692	722	1159	1413	3325	1231	–	1024	–
3g	1679	715	1153	1414	3359	1234	–	922	–
3h	1698	725	1151	1411	3360	1238	–	1020	–
3i	1685	712	1152	1415	3371	1238	–	1025	–
3j	1693	736	1158	1426	3324	1218	–	1035	–

TABLE-4
^{1}H NMR DATA FOR THE SYNTHESIZED COMPOUNDS

Compound No.	Assignments
3a	1.9 (s, 1H, P-OH); 5.4(s, 1H, CH-Cl); 3.8(s, 1H, N-H); 3.72 (t, 3H, C-OCH_3); 6.4-7.6 (m, 11H, aromatic)
3b	2.0 (s, 1H, P-OH); 5.2 (s, 1H, CH-Cl); 3.7(s, 1H, N-H); 6.5-7.7(m, 11H, aromatic)
3c	1.9 (s, 1H, P-OH); 5.4 (s, 1H, CH-Cl); 3.9(s, 1H, N-H); 6.4-7.7 (m, 11H, aromatic)
3d	2.0 (s, 1H, P-OH); 4.9 (s, 1H, CH-Cl); 4.1 (s, 1H, N-H); 5.5 (s, 1H, C-H); 6.7 (s, 1H, C-H); 6.5-7.3 (m, 12H, aromatic)
3e	1.7(s, 1H, P-OH); 5.3 (s, 1H, CH-Cl); 4.0 (s, 1H, N-H); 6.4-8.2 (m, 11H, aromatic)
3f	1.9 (s, 1H, P-OH); 5.4 (s, 1H, CH-Cl); 4.0 (s, 1H, N-H); 6.4-7.3 (m, 16H, aromatic)
3g	1.9 (s, 1H, P-OH); 5.4 (s, 1H, CH-Cl); 3.9(s, 1H, N-H); 1.34 (t, 3H, C-OCH_3); 5.1 (1H, s, C-OH); 6.5-7.1 (m, 10H, aromatic)
3h	2.0 (s, 1H, P-OH); 5.1(s, 1H, CH-Cl); 3.92 (s, 1H, N-H); 3.75(t, 3H, C-OCH_3); 3.99 (d, 2H, C-CH_2); 5.0 (1H, s, C-OH); 6.4-7.0 (m, 10H, aromatic)
3i	1.8 (s, 1H, P-OH); 5.5 (s, 1H, CH-Cl); 4.0 (s, 1H, N-H); 6.4-7.6 (m, 12H, aromatic)
3j	2.1 (s, 1H, P-OH); 5.4 (s, 1H, CH-Cl); 3.93 (s, 1H, N-H); 3.72 (t, 3H, C-OCH_3); 5.0 (1H, s, C-OH); 6.5-7.0 (m, 9H, aromatic)

RESULTS AND DISCUSSION

In the present study Schiff bases (**2a-j**) of 2-amino-5,10-dihydrophenophosphazin-10-ol-10-oxide were synthesized by condensation of its amino group with different substituted aromatic aldehydes. The azetidinone derivatives (**3a-j**) of above synthesized Schiff bases were synthesized by reaction of imino with chloroacetyl chloride in presence of triethyl amine. The previous reports revealed that 2-azetidinone derivatives possess antiinflammatory[5], antidegenerative[6], fungicidal[7], antibacterial[8-10] *etc*., activities. In present work we have synthesized several azetidinone derivatives having a spiro structure. All the compounds gave satisfactory elemental analysis (Table-2). IR and NMR analysis were consistent with assigned structures (Tables 3 and 4).

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