ISSN: 0974 - 7516 Volume 10 Issue 5

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 10(5), 2014 [188-191]

Studies on sulphonamides: Part I: Preparation and antimicrobial activity of 2-arylsulphonamido-4-choloro / hydroxy-6-methylpyrimidines

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ABSTRACT

Some new 2-Arylsulphonamidopyrimidines have been prepared by the condensation of Benzenesulfonylchloride and 2-amino-4-hydroxy/chloro-6-methylpyrimidine in dry pyridine.The structures of the compounds have been delineated by IR, NMR and MASS spectral study. The products have been screened for antimicrobial activity; most of the compounds proved active.

KEYWORDS

2-Amino-4 –chloro/hydroxy-6-methylpyrimidine;
Aryl sulphonyl chlorides;
2 –Arylsulphonamido-4 – chloro / hydroxy - 6 – methylpyrimidine;
Antimicrobial activity.

INTRODUCTION

The study of sulphonamides has revealed valuable drugs for various diseases. Some sulfonamides having pyrimidine nucleus are still the most prescribed drugs used in medicine. Sulphonamidopyrimidines are known for the activities like antitumor[1,7], chemokine receptor modulators[2-5], inflammatory and antimicrobial[6], radio-protective[7], herbicide[8] etc. This led us to synthesize sulphonamides in search of agents having better drug potentiality.

2-Amino-4-chloro/hydroxy-6-methylpyrimidine was condensed with different arylsulphonyl chlorides to get desired product.

The constitution of the products was established by IR, PMR and Mass spectral study. The products were tested for antimicrobial activity. Melting temperatures of all the compounds were taken in open capillary and are uncorrected.

ANTIMICROBIAL ACTIVITY

The antimicrobial testing was carried out by cup-plate method at a concentration of 50 μgm using DMF as solvent. The different strains used for testing the antibacterial and antifungal activity of the products were 24 hours old subculture of *Gram positive bacteria* : B. subtilis, S. pyoqens, *Gram Negative bacteria* : E. coli, K. pneumoniae, *Fungi* : A. niger and S. cerevisiae.

EXPERIMENTAL

Preparation of 2-arylsulphonamido-4-chloro / hydroxy-6-methylpyrimidine

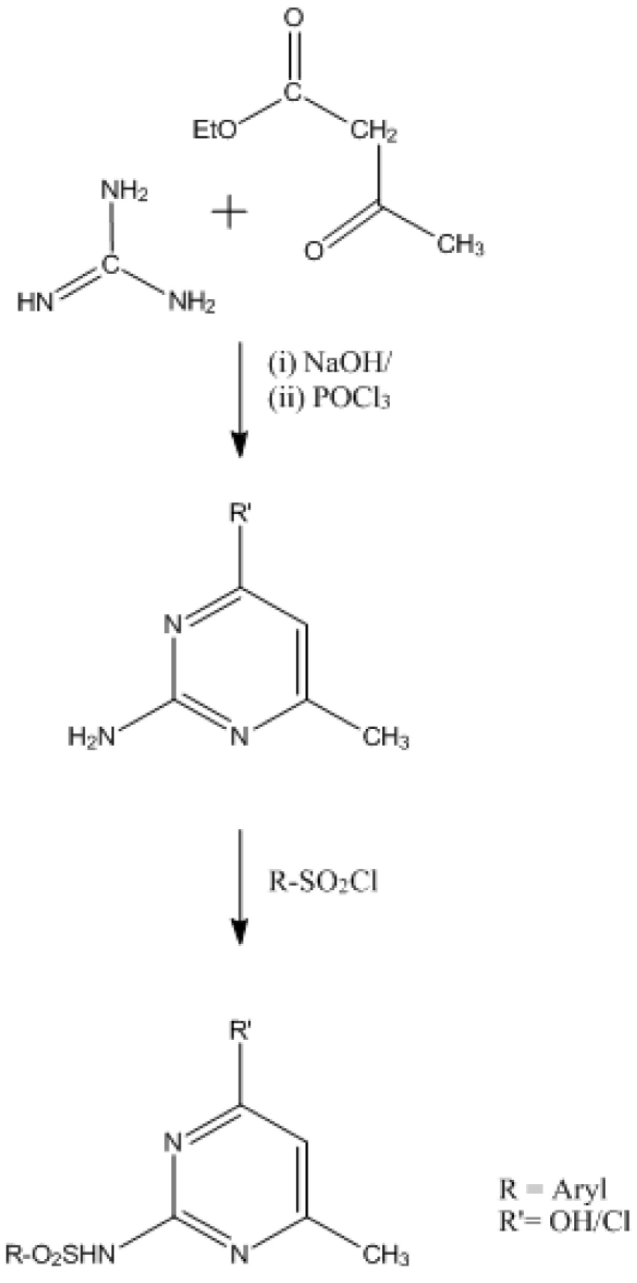
(a) Preparation of 2-Amino-4-hydroxy-6-methylpyrimidine

Ethyl acetoacetate (87 g, 0.67 M) was added to a flask containing powdered guanidine carbonate (58 g, 0.32 M) and the mixture was heated for 2 - 2.5 hrs. at

100 -10^0 C. After heating, water was added and on cooling product got separated. Yield 70%, M. P. 270^0 C (d).

IR (KBr) : 3400 – 3100 (O-H str.), 1385, 1340 (O-H def.), 1180 (C-O str.), 2950 (C-H asym. str.), 1470 (C-H def.), 3400 (N-H str.), 1650 (N-H def.), 1340,1280 (C-N str.),3100 (C-H str.) 1520 (C=C str.) 1480, 1460 (C=N str.), 1180, 1040, 1020 (C-H i.p. def.), 720, 660 (C-H o.o.p.) cm^{-1}.

PMR : 8.00 (s, 1H, O<u>H</u>), 6.45(s, 1H, Py-<u>H</u>), 5.44(s, 2H, -N<u>H</u>$_2$), 2.03(s, 3H, -C<u>H</u>$_3$), δ ppm.



Reaction Scheme

(b) Preparation of 2-amino-4-chloro-6-methylpyrimidine

A mixture of 2-Amino-4-hydroxy-6-methylpyrimidine (5 g, 0.04 M) and phosphorusoxychioride (7 g, 0.046 M) was heated at 100^0 C for 4 hrs. The excess of phosphorusoxychloride was distilled off and the slurry was slowly added to crushed ice. The pH was adjusted between 7 and 9 with concentrated sodiumhydroxide and then with sodiumcarbonate solution. The product was filtered and washed with water, dried and recrystallised from ethanol. Yield 61%; m.p.185^0 C.

IR (KBr) : 2950 (Alkane; C-H asym. str.), 1430 (Alkane; C-H def.), 3350(NH$_2$; N-H str.) 1630 (NH$_2$; N-H def.), 1280 (C-N str.), 3100 (Py; C-H str.), 1580, 1540, 1475, (C=C + C=N str.), 1240, 1160, 1030 (C-H i.p. def.), 620 (C-H o.o.p.), 780 (C-Cl str.), cm^{-1}.

PMR : 6.83 (s, 1H, Py-<u>H</u>), 6.47 (s, 2H, -N<u>H</u>$_2$), 2.24 (s, 3H, -C<u>H</u>$_3$), δ ppm.

(c) Preparation of 2-arylsulphonamido-4-hydroxy-6-methylpyrimidine

A mixture of Benzenesulfonylchloride (1.27 ml, 0.01 M) and 2-amino-4-hydroxy-6-methyl pyrimidine (1.25 g, 0.01 M) in dry pyridine (10 ml) was refluxed for 5 hrs. The product was isolated and recrystallised from ethanol. Yield 68% ; m.p. 222^0 C. Similarly, other arylsulphonylchlorides were condensed. The physical constants are recorded in TABLE 1.

Spectral data of 2-(4'-methylphenylsulphonamido) -4- hydroxy -6-methylpyrimidine

IR (KBr) : 3300 – 2900 (O-H str.), 1360 (O-H def.), 1170 (C-O str.), 1470 (C-H def.), 3300-2900 (2^0 N-H str.), 1330 (S=O asym. str.), 1170 (S=O sym. str.) 820(N-SO$_2$ str.),1660 (C= N str.) 1540, 1520, 1460, 1440 (C=C str.), 1040, 1020 (C-H i.p. def.), 720, 670 (C-H o.o.p.) cm^{-1}. PMR : 8.85 (s, 1H, O<u>H</u>), 8.22 (s, 1H, SO$_2$-N<u>H</u>), 7.77(s, 1H, Py-<u>H</u>), 7.00-7.60 (m, 4H, Ar-<u>H</u>) 2.50 (s, 3H, ϕ-C<u>H</u>$_3$), 2.19(s, 3H, Py-C<u>H</u>$_3$), δ ppm.

Mass spectral data of 2-phenylsulphonamido-4-hydroxy-6-methylpyrimidine, m/z : 265(M$^+$), 250, 237, 223, 222, 210, 195, 182, 181, 109, 83, 79 (base peak), 66, 54, 40.

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TABLE 1 : Physical data

Sl. No	R	R'	Molecular Formula	M.P. °C	Yield %	% of Nitrogen	
						Calcd.	Found
1.	2.	3.	4.	5.	6.	7.	8.
1	Phenyl	OH	$C_{11}H_{11}N_3O_3S$	222	68	15.85	15.78
2	3-Carboxy-4-Chlorophenyl	OH	$C_{12}H_{10}N_3O_5SCl$	255	63	12.23	12.20
3	3-Carboxy-4-hydroxyphenyl	OH	$C_{12}H_{11}N_3O_6S$	246	65	12.92	12.82
4	3-Carboxy-4-methoxyphenyl	OH	$C_{13}H_{13}N_3O_6S$	238	60	12.39	12.18
5	3-Carboxy-6-methoxyphenyl	OH	$C_{13}H_{13}N_3O_6S$	245	58	12.39	12.22
6	2-Carboxy-4-methylphenyl	OH	$C_{13}H_{13}N_3O_5S$	250	66	13.00	12.89
7	3-Carboxy-6-methylphenyl	OH	$C_{13}H_{13}N_3O_5S$	167	68	13.00	12.81
8	3-Carboxyphenyl	OH	$C_{12}H_{11}N_3O_5S$	243	69	13.59	13.41
9	4-(α'-Carboxy)styryl	OH	$C_{14}H_{13}N_3O_5S$	248	57	12.54	12.39
10	4-Methylphenyl	OH	$C_{12}H_{13}N_3O_3S$	180	70	15.05	14.91
11	Phenyl	Cl	$C_{11}H_{10}N_3O_2SCl$	263	71	14.81	14.73
12	3-Carboxy-4-Chlorophenyl	Cl	$C_{12}H_9N_3O_4SCl_2$	300(d)	72	11.60	11.45
13	3-Carboxy-4-hydroxyphenyl	Cl	$C_{12}H_{10}N_3O_5SCl$	281(d)	69	12.23	12.15
14	3-Carboxy-4-methoxyphenyl	Cl	$C_{13}H_{12}N_3O_5SCl$	>320	67	11.75	11.61
15	3-Carboxy-6-methoxyphenyl	Cl	$C_{13}H_{12}N_3O_5SCl$	>320	68	11.75	11.67
16	2-Carboxy-4-methylphenyl	Cl	$C_{13}H_{12}N_3O_4SCl$	298(d)	57	12.30	12.13
17	3-Carboxy-6-methylphenyl	Cl	$C_{13}H_{12}N_3O_4SCl$	>320	54	12.30	12.14
18	3-Carboxyphenyl	Cl	$C_{12}H_{10}N_3O_4SCl$	279	56	12.82	12.62
19	4-(α'-Carboxy)styryl	Cl	$C_{14}H_{12}N_3O_4SCl$	>320	58	12.88	12.78
20	4-Methylphenyl	Cl	$C_{12}H_{12}N_3O_2SCl$	287	73	14.12	14.00

(d) Preparation of 2-arylsulphonamido-4-chloro-6-methylpyrimidine

A mixture of Benzenesulfonylchloride (1.27ml, 0.01M) and 2-amino-4-chloro-6-methylpyrimidine (1.43g, 0.01 M) in pyridine (10 ml) was refluxed for 2 to 2.5 hrs. And the excess of pyridine was removed by distillation. Remaining mass was poured into ice water, filtered and washed with dilute hydrochloric acid and with water successively. It was recrystallised from ethanol. Yield71%; m.p. 263^{0}C. Similarly, other arylsulphonylchlorides were condensed. The physical constants are recorded in TABLE 1.

Spectral data of 2-(4'-methylphenylsulphonamido)-4-chloro-6-methylpyrimidine

IR (KBr) : 1170 (C-O str.), 1470 (C-H def.), 3300-2900 (2^0 N-H str.), 1380, 1310 (S=O asym. str.), 1140 (S=O sym. str.), 3300 (N-H str.), 910, 800 (N-SO_2 str.),1600, 1570 (C= N str.) 1540, 1500, 1460 (C=C str.), 3050 (C-H str.)1030, 1090, 1020 (C-H i.p. def.), 700, 680 (C-H o.o.p.) 2950 (Alkane C-H str.), 1420 (alkane C-H def.), 660 (C-Cl str.) cm^{-1}.

PMR : 8.08 (s, 1H, SO_2-N<u>H</u>), 7.67(s, 1H, Py-<u>H</u>), 7.10-7.51 (m, 4H, Ar-<u>H</u>) 2.53 (s, 3H, ϕ-C<u>H</u>$_3$), 2.11 (s, 3H, Py-C<u>H</u>$_3$), δ ppm.

CONCLUSION

It has been concluded from the experimental data that all the sulphonamides are moderately active against different strains of Gram-positive and Gram-neqative bacteria.

The significant antibacterial activity was observed in compounds bearing R' = OH; R = 3-carboxy-4-chlorophenyl, 3-carboxy-4-hydroxyphenyl, 3-carboxy-4-methoxyphenyl, 3-carboxyphenyl and R' = Cl; R = 4-methylphenyl against B. subtilis. R' = OH; R = 3-carboxy-6-methylphenyl, 4-methylphenyl and R' = C1; R = 2-carboxy-4-methylphenylagainst S. pyoqens.

Maximum antibacterial activity was observed in compounds having R' = OH; R = 3-carboxy-4-chlorophenyl, 4-(α'-carboxy)styryl and R' = Cl; R =

3-carboxy-4-chlorophenyl against E. coli. The significant activity was observed against K. pneumoniae in compounds bearing R' = OH; R = 3-carboxy-4-chlorophenyl and R' = Cl; R = 3-carboxy-6-methoxyphenyl.

All the compounds have displayed significant antifungal activity except compounds bearing R' = OH; R = phenyl and R' = Cl; R = 3-carboxy-6-methoxyphenyl against A. niger; while compounds were inactive against S. cerevisiae except compounds bearing R' = OH; R= 3-carboxy-6-methylphenyl, 4-(α'-carboxy)styryl and R' = Cl; R = 3-carboxy-6-methylphenyl.

The antimicrobial activity was less as compared to that of displayed by known antibiotics like Norfloxacin, Ampicillin, Griseofulvin, Chloramphanicol.

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