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Synthesis of 3-Phenylimino-4-[2′-(substituted)alkyl/ benzylidene amino]phenyl-5-arylimino-1,2,4-dithiazolidines and Their Antimicrobial Activity

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Several 3-phenylimino-4-[2′-(substituted)alkyl/benzylidene amino]phenyl-5-arylimino-1,2,4-dithiazolidines have been synthesized by the interaction of 1-phenyl-3-[2′-(substituted)alkyl/benzylidene amino]phenyl thiocarbamides with N-aryl-S-chloro isothiocarbamoyl chlorides. The present compounds in the form of monohydrochlorides have been isolated. These compounds on basification with aqueous ammonia solution afforded free bases. These compounds were successfully brominated into their dibromo derivatives. The structures of these compounds were confirmed on the basis of elemental analysis and spectral data and evaluated for their antimicrobial activity against gram positive and gram negative bacteria.

Key Words: Synthesis, 1,2,4-Dithiazolidine, Antimicrobial activity.

INTRODUCTION

Synthesis of various dithiazolidines are reported in the literature involving methods like oxidative debenzylation[1], oxidation with bromine and iodine of the related 1-substituted-2,4-dithiobiurets as well as oxidative dealkylation[2,3] provide some routes for their synthesis. Dithiazolidines synthesis have also reported from chlorocarbonyl sulphenyl chloride and *o*-dimethyl aminoethyl, N-alkyl thiocarbamates[4]. The present method is useful for the synthesis of 3,4,5-trisubstituted-1,3,4-dithiazolidines.

EXPERIMENTAL

The melting points were recorded using hot paraffin bath and are uncorrected. IR spectra were recorded on Perkin-Elmer spectrophotometer (Nujol mull and as KBr pellets). PMR spectra were recorded with TMS as internal standard using $CDCl_3$ as solvents.

The parent compound 1-phenyl-3-(2-amino)phenyl thiocarbamide (**I**) was prepared by refluxing the mixture of *o*-phenylene diamine (0.01 mol) and phenyl isothiocyanate (0.01 mol) in chloroform medium for 2 h.

Synthesis of 3-phenylimino-4-[2′-(2-hydroxy)benzylidene amino]phenyl -5-phenylimino-1,2,4-dithiazolidine (IVa)

The compound 1-phenyl-3-[2′-(2-hydroxy)benzylidene amino]phenyl thiocarbamide (**IIa**) was prepared by refluxing the mixture of 1-phenyl-3-(2-amino)phenyl thiocarbamide (**I**) (0.01 mol) and 2-hydroxy benzaldehyde (0.01 mol) in 1:1 ratio in chloroform (20 mL) for 2 h. On completion of reaction and distilling off the solvent, the product was isolated, yield 78 %, m.p. 140ºC. It was crystallized from ethanol. This reaction was extended to synthesize the other compounds (**IIb-p**) using different aliphatic and aromatic aldehydes.

1-Phenyl-3-[2′-(2-hydroxy)benzylidene amino]phenyl thiocarbamide (**IIa**) (0.01 mol) was suspended in chloroform (15 mL). To this a solution of N-phenyl-S-chloroisothiocarbamoyl chloride (0.01 mol) in chloroform was added. The reaction mixture was refluxed on water bath for 3 h. The evolution of hydrogen chloride gas was observed. Then chloroform was distilled off, a sticky mass was obtained. It was repeatedly washed with petroleum ether (60-80ºC) followed by addition of ethanol, a solid product was isolated, crystallized from ethanol yield 80 %, m.p. 89ºC. This was identified as monohydrochloride of 3-phenylimino-4-[2′-(2-hydroxy) benzylideneamino]phenyl-5-phenylimino-1,2,4-dithiazolidine (**IIIa**). On basification with dilute ammonium hydroxide it gave the free base. It was crystallized from ethanol and identified as 3-phenylimino-4-[2′-(2-hydroxy)benzylidene amino]phenyl-5-phenylimino-1,2,4-dithiazolidine (**IVa**), m.p. 84ºC. (Found: C 67.40, H, 4.14, N, 11.61, S 13.32, $C_{27}H_{20}N_4OS_2$ requires C 67.5, H 4.16, N 11.66, S 13.42 %). IR[7,8]: (**IVa**) 3754 ν(O–H), 1635 ν(C=N), 1338 ν(C–N), 747 ν(C–S), 511 ν(S–S). PMR: δ 8.83 (1H, =CH), δ 6.66-7.98 (18H, aromatic protons) and δ 13.2 (1H, O–H). A similar procedure was adopted for the synthesis of compounds **IVb-p**. Their characterization data is given in Table-1.

Synthesis of 3-phenylimino-4-[2′-(2-hydroxy){N-bormo-bromo benzylideneamino}phenyl-5-phenylimino-1,2,4-dithiazolidine (Va)

To the solution of 3-phenylimino-4-[2′-(2-hydroxy)benzylidene amino] phenyl-5-phenylimino-1,2,4-dithiazolidine (**IVa**) (0.01 mol) in acetic acid, was added bromine in glacial acetic acid with vigorous shaking, within 0.5 h the reaction mixture solidifies. On pouring the reaction mixture in a little crushed ice with water, the granular solid was obtained (yield 70 %). It was crystallized from aqueous ethanol and identified as 3-phenylimino-4-[2′-(2-hydroxy){N-bromo-bromo benzylidene amino}]phenyl-5-phenylimino-1,2,4-dithiazolidine (**Va**), m.p. 160ºC. (Found: C 58.85, H, 3.60, N, 10.17, S 11.60, $C_{27}H_{20}N_4OS_2Br_2$ requires C 58.90, H 3.63, N 10.18, S 11.63 %). IR[7,8]: (**Va**) 3752 ν(O–H), 1654 ν(C=N), 1349 ν(C–N), 746 ν(C–S), 527

TABLE-1
PHYSICAL DATA OF COMPOUNDS (**IIIa-p**) AND (**IVa-p**)

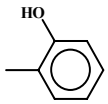
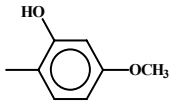
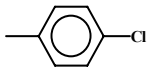
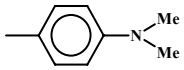
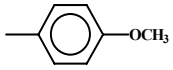
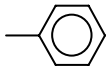
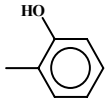
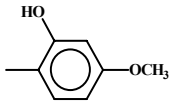
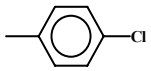
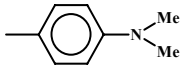
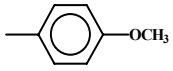
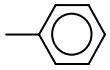
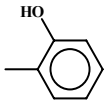
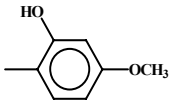
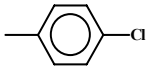
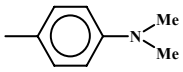
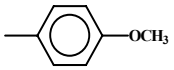
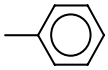
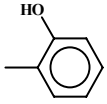
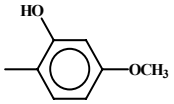
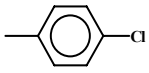
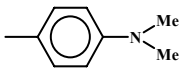
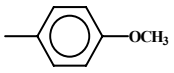
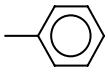
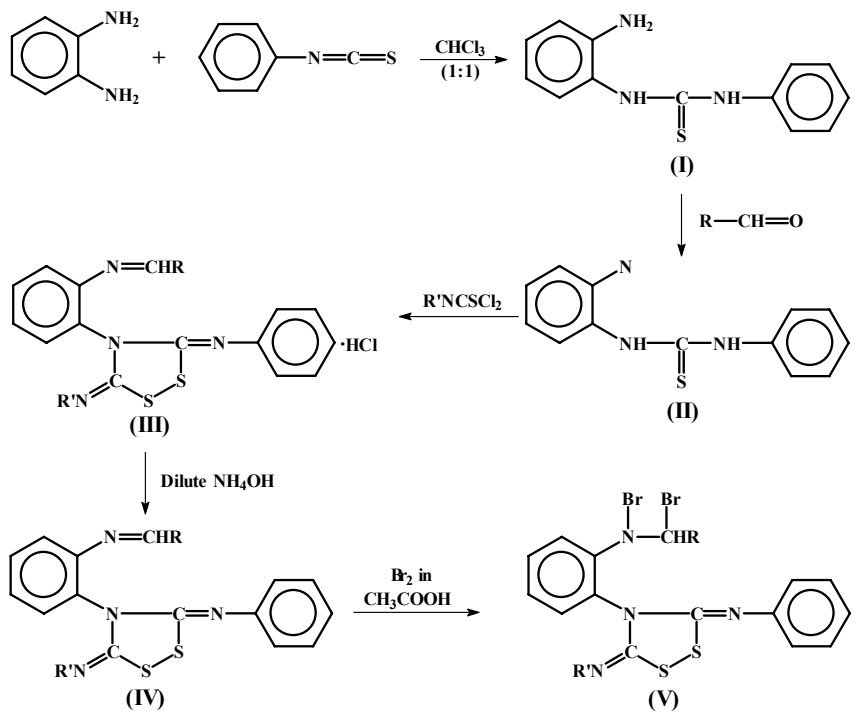
Compd.	R	Yield (%)	m.p. (ºC)		S % Found (Calcd.)	N % Found (Calcd.)
			III	**IV**		
a		78	89	84	13.32 (13.33)	11.61 (11.66)
b		74	87	85	12.48 (12.54)	10.91 (10.98)
c		72	92	90	12.76 (12.85)	11.18 (11.24)
d		75	122	108	12.57 (12.62)	13.72 (13.80)
e		78	112	102	12.92 (12.95)	11.28 (11.33)
f		80	126	121	13.79 (13.73)	12.01 (12.06)
g	—CH_3	77	108	105	15.85 (15.92)	13.87 (13.93)
h		69	87	85	13.97 (14.06)	12.22 (12.30)
i		78	98	91	12.87 (12.95)	11.30 (11.33)
j		70	95	85	12.18 (12.21)	10.60 (10.68)
k		75	102	100	11.78 (11.76)	10.18 (10.29)
l		77	118	104	12.22 (12.28)	13.41 (13.43)
m		79	108	99	12.55 (12.59)	(10.97) 11.02
n		86	118	97	13.31 (13.38)	(11.65) (11.71)
o	—CH_3	76	97	91	15.31 (15.38)	13.38 (13.46)
p		69	95	88	13.61 (13.60)	11.84 (11.94)

TABLE-2
PHYSICAL DATA OF COMPOUNDS **Va-p**

Compd.	R	Yield (%)	m.p. (ºC)	S % Found (Calcd.)	N % Found (Calcd.)
a		78	160	11.60 (11.63)	10.17 (10.18)
b		72	141	10.95 (11.03)	9.42 (9.65)
c			Not isolated	–	–
d		77	145	12.55 (12.62)	13.78 (13.80)
e		79	148	11.22 (11.34)	9.80 (9.92)
f		77	138	11.85 (11.98)	10.34 (10.48)
g	—CH_3	70	155	13.42 (13.55)	11.79 (11.86)
h		67	143	12.09 (12.19)	10.52 (10.66)
i		77	154	11.32 (11.42)	9.92 (10.00)
j		70	138	10.06 (10.77)	9.40 (9.42)
k			Not isolated	–	–
l		72	148	10.79 (10.82)	11.81 (11.84)
m		80	152	11.01 (11.07)	9.57 (9.68)
n		78	141	11.52 (11.67)	10.18 (10.21)
o	—CH_3	74	157	13.09 (13.16)	13.13 (13.16)
p		70	162	11.75 (11.87)	10.31 (10.38)

ν(S–S). PMR: δ 11.53 (1H, O–H), δ 6.86-7.98 (18H, aromatic protons). Similarly, other acetyl derivatives (**Vb-p**) were prepared, their characterization data is given in Table-2.



where, R - (Va-p)
R : 2-hydroxy benzaldehyde
R : 2-hydroxy-4-methoxy benzaldehyde
R : 4-chloro benzaldehyde
R : 4-N',N-dimethylamino benzaldehyde
R : 4-methoxy benzaldehyde
R : benzaldehyde
R : acetaldehyde
R : furfuraldehyde

R' : phenyl
R' : *p*-tolyl

Scheme-I

RESULTS AND DISCUSSION

The parent compound 1-phenyl-3-(2-amino)phenyl thiocarbamide (**I**) was prepared by refluxing the mixture *o*-phenylene diamine and phenyl isothiocyanate in 1:1 ratio in chloroform medium. This was transformed into 1-phenyl-3-[2′-(2-hydroxy)benzylidene amino]phenyl thiocarbamide (**IIa**) by condensing with 2-hydroxy benzaldehyde in refluxing chloroform medium. It was crystallized in ethanol. The other thiocarbamides (**II**) were prepared by extending this reaction to other aliphatic and aromatic aldehydes.

1-Phenyl-3-[2′-(2-hydroxy)benzylidene amino]phenyl thiocarbamide (**IIa**) was then reacted with N-phenyl-S-chloroisothiocarbamoyl chloride[7] in boiling chloroform for 3 h. The evolution of hydrogen chloride gas was clearly noticed as tested with moist blue litmus paper. Cooling the reaction mixture and distilling off chloroform giving monohydrochloride (**IIIa**) which was basified with dilute ammonium hydroxide solution to give (**IVa**).

The dibromo derivative (**Va**) of present compound was prepared by shaking 3-phenylimino-4-[2′-(2-hydroxy)benzylideneamino]phenyl-5-phenylimino-1,2,4-dithiazolidine (**IVa**) in acetic acid, was added bromine in glacial acetic acid. The structures of all these compounds were assigned on the basis of elemental analysis, PMR and IR spectral data.

Antimicrobial activity: The present compound (**Va-p**) were screened for their antimicrobial activity using cup-plate diffusion method[8]. The bacterial organisms used included both gram positive and gram negative strains like *E. coli*, *S. aureus*, *B. subtilis*, *P. vulgaris* and *Shigella*. Sensitivity plates were seeded with a bacterial inoculum of 1×10^6 CIU/mL and each well (diameter 10 mm) was loaded with 0.1 mL of test compound solution (1000 µg/mL) in DMF. So that concentration of each test compound was 100 µg/mL. The zones of inhibition were recorded after incubation for 24 h using vernier calliper. Inhibition zones recorded of the compounds clearly indicated that **Va**, **Vb** and **Vm** were highly active against *E. coli*, *B. subtilis* and majority of the compounds were found inactive against *P. vulgaris* and *Shigella*.

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