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Synthesis and antibacterial activity of some substituted isoxazolines and isothiazolines

CHINNA RAO GANTLA*, Y.SURESH, S.HARIKRISHANA and S.P. SHRIVASTAVA

Department of Chemistry, Dr. H.S. Gour University, Sagar - 470 003 (India).

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ABSTRACT

Some substituted isoxazoline and isothiazolines were synthesized from chalcones. These varied products have been characterized by elemental analysis spectral studies and tested for antibacterial activity against *S. aureus, B.megaterium, A.niger and A.parasitica*

Key words: Synthesis, Isoxazolines, Isothiazolines, Antimicrobial activity.

INTRODUCTION

The heterocyclic nuclei such as isoxazolines possess remarkable biological activity[1-3]. isoxazolines have been prepared usually by the action of hydroxylamine hydrochloride on chalcones[3-5]. Isoxazolines on treatment with phosphorous pentasulphide in pyridine gave isothiazolines[6-7]. In the present work, we have synthesized some substituted isoxazoline and isothizoline derivatives and evaluated their antibacterial activity.

RESULTS AND DISCUSSION

In the present work, we have synthesized some substituted Isoxazolines and Isothiazolines derivatives some synthesized compounds such as VIa, VId, VIId, VIIc are shown moderate biological activities against *B. megaterium, S. aureus, A. niger, A. parasitica*.

EXPERIMENTAL

All melting points were determined in open capillary tubes and are uncorrected. All the compounds are characterized by IR and NMR spectral analysis.

(A) Synthesis of 3-nitro-4-(-3'-Chloro, 4'-methoxy-5'-nitrobenzene sulfonamide) Acetophenone

3-chloro-4-methoxy-5-nitro benzene sulfonyl chloride (0.01mol) was added slowly to a mixture of 3-nitro-4-amino-acetophenone (0.01mol) in methanol (65 ml) and pyridine (5 ml). The reaction mixture was refluxed for 1h then poured into crushed ice and acidified with HCl. The product obtained was re crystallized from methanol yield 83% m.p. 265°C.

(B) Synthesis of V(a-e)

To mixture of compound III (0.05 mol) in methanol and 25% aq NaOH, substituted aromatic aldehydes (0.05 mol) was added drop wise stirred at 32°C for 4.5h. Then reaction mixture was poured in ice cold water and acidifies with HCl. The compound obtained was filtered washed with water and recrystallized from ethanol. The purity of compound was checked by TLC. Compounds V(b-c) were synthesized by above method using respective aldehyde.

Table 1: Physical data of the title compounds

Comp. No.	R	m.p. (°C)	% Yield	Molecular formula
VI_a	P-Cl	120	65	$C_{22}H_{16}O_8Cl_2N_4S$
VI_b	m-NO_2	148	54	$C_{22}H_{16}O_{10}ClN_5S$
VI_c	P-Br	125	56	$C_{22}H_{16}O_8ClN_4SBr$
VI_d	P-CH_3	211	44	$C_{23}H_{19}O_8ClN_4S$
VI_e	P-OCH_3	185	59	$C_{23}H_{19}O_9ClN_4S$
VII_a	P-Cl	128	60	$C_{22}H_{16}O_7Cl_2N_4S_2$
VII_b	m-NO_2	139	58	$C_{22}H_{19}O_9Cl_2N_5S_2$
VII_c	P-Br	148	60	$C_{22}H_{16}O_7Cl_2N_4S_2$
VII_d	P-CH_3	198	49	$C_{23}H_{19}O_7ClN_4S_2$
VII_e	P-OCH_3	210	61	$C_{22}H_{19}O_8ClN_4S_2$

Table 2: I.R. Spectral data of VI a-e (cm^{-1})

Vibration	VII a	VII b	VII c	VII d	VII e
N-H Str.	3425	3438	3428	3430	3480
Ar - H str	3020	3002	3061	3025	3009
C - O Str	1580	1560	1541	1572	1562
C = N Str	1208	1220	1210	1215	1216
C - O - C Str	1150	1140	1148	1152	1160
Ar; C = C Str	1475	1460	1462	1478	1780

Table 3: I..R. Spectral data of VII a-e (cm^{-1})

Vibration	VII a	VII b	VII c	VII d	VII e
N-H Str.	3421	3426	3419	3410	3422
Ar – Hstr	3042	3020	3012	3030	3048
C = N Str	1510	1532	1536	1542	1520
C – C Str	1170	1168	1171	1165	1175

Table 4: NMR Spectral data of compounds VI a-e

Inference	Chemical Shift in δppm and multiplicity				
	VII a	VII b	VII c	VIId	VII e
3-Cl 4- OCH_3 5-NO_2 Ar-Ring	6.2 (m)	6.1 (m)	6.0 (m)	6.4 (m)	6.2 (m)
3-NO2 1, 4 Sub-Ar -Ring	5.8 (m)	5.8 (m)	5.6 (m)	5.8 (m)	5.7 (m)
1,4 Substi Ar Ring	5.2 (m)	5.3 (m)	5.4 (m)	5.2 (m)	5.4(m)
Isoxazolin 4 -CH	3.3 (d)	3.5 (d)	3.6 (m)	3.4 (m)	3.2 (m)
Isoxazolin 5 -CH	2.8 (t)	2.5 (t)	2.7 (t)	2.8 (t)	2.6 (t)
Sulfonamide SO2NH	3.8 (t)	3.9 (t)	4.0 (S)	3.9 (s)	3.6 (t)
Ar-OCH_3	4.3 (s)	4.2 (s)	4.3 (s)	4.8 (s)	4.3 (s)

(C) Synthesis of 3-[3'-nitro-4'-(3''-chloro-4''-methoxy-5''-nitrobenzene sulfonamide) benzene]-5-(substituted aryl)-Isoxazolines (VI a)

A mixture of Va (0.05 mol) hydroxylamine hydrochloride (0.01 mol) and sodium hydroxide (25%, 25 mol) in ethanol (95%, 30 ml) was refluxed on water bath for 3.5 h then cooled and acidified with dil. HCl. The solid obtained was filtered, washed with methanol and recrystallized from 95% ethanol. Compounds V(b-c) was synthesized using respective compound V.

(D) Synthesis of 3-[3'-nitro-4'-(3''-chloro-4''-methoxy-5''-nitrobenzene sulfonamide) benzene]-5-(substituted aryl)-Isothiazolines (VIIa)

Compound VIa (0.001 mol) was treated with P_2S_5 (0.001 mol) in the presence of 20 ml pyridine and refluxed in water bath for 2 h cool and filtered, washed with water and recrystallized from ethanol. Compounds VII(b-c) was synthesized using respective compound VII.

Antimicrobial activity data of the title compounds

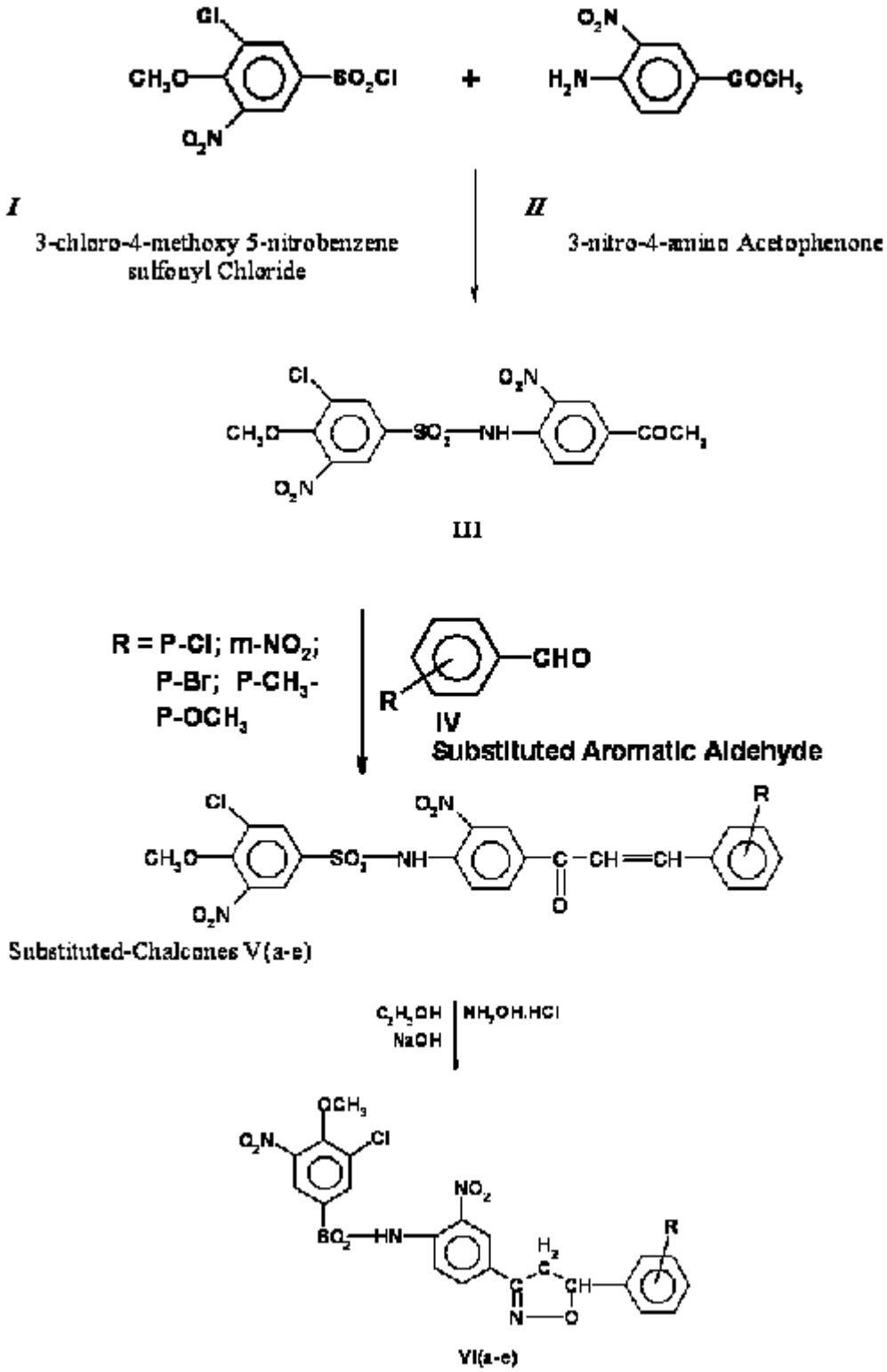
For bacteria nutrient agar medium was used *Bacillus megaterium* and *Staphylococcus aureus* were selected for screening. The

Table 5: NMR Spectral data of VII a-e

Inference	Chemical Shift in δppm and multiplicity				
	VII a	VII b	VII c	VIId	VII e
3-Cl 4- OCH_3-5-NO_2 - Ar-Ring	6.2 (m)	6.0 (m)	6.4 (m)	6.1 (m)	6.19 (m)
3-NO_2 1, 4 Sub- Stituted Ar –Ring	5.7 (m)	5.6 (m)	5.3 (m)	5.6 (m)	5.4 0 (m)
1,4 Substituted Ar Ring	5.1 (m)	3.1 (m)	4.9 (m)	5.0 (m)	4.8 (m)
Isothiazolin 4 - CH	3.1 (d)	3.2 (d)	3.0 (d)	3.4 (t)	3.3 (t)
I sothiazolin 5 - CH	2.3 (t)	2.1 (t)	2.3 (t)	2.4 (t)	2.3 (t)
Sulfonimide SO_2 - NH	3.6 (s)	3.4 (s)	3.5 (s)	3.6 (s)	3.8 (s)
Ar-O-CH_3	4.2 (s)	4.1 (s)	4.3 (s)	4.8 (s)	5.9 (s)

Table 6: Biological activity of synthesized compounds

Compound No.	Zone of Inhibition (mm)			
	Bacteria		Fungi	
	B.megaterium	*S.aureus*	*A. niger*	*A.parasitica*
VIa	22	18	19	18
VIb	15	15	17	18
VIc	18	15	21	19
VId	22	18	23	18
VIe	17	13	17	18
VIIa	20	19	21	16
VIIb	21	16	17	18
VIIc	22	15	20	18
VIId	21	18	20	18
VIIe	17	13	17	18
Streptomycin	30	28	-	-
Greseofulvin	-	-	29	30



Scheme 1: 3-[3'-nitro-4'-(3''-chloro-4''-methoxy-5''-nitrobenzene sulfonamide) benzene]-5-(substituted aryl)-Isothiazolines [VII(a-e)]

antibacterial activity was compared with standard *streptomycin* and zone of inhibition (in mm) of antibacterial activity was determined by using filter paper disc diffusion method[8] .

The antifungal activity has been determined by using filter paper disc diffusion method in (P.D.A) medium, selected fungi were *A. niger and A,parasitica* The antifungal activity was compared with standard drug *greseofulvin* and zone of inhibition measured in mm[8].

CONCLUSION

From this study, we concluded that 5th poison of isoxazolines and isothiazolines should be substituted with para substituted phenyl group for better antimicrobial activity. This substitution of phenyl ring at para position should be less steric, lipophilic and hydrogen bond acceptor group like – Cl, Br, NO_2, CH_3, OCH_3 for better antibacterial activity. Synthesis of some other derivatives isoxazoline and isothiazoline are in progress to get some more active antimicrobial agents.

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