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Evalution of Some New 2-Isothiazoline Derivatives from Chalcone and their Antibacterial Activity

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Abstract **- 2-isothiazoline derivatives can be synthesized from the chalcone by the action of hydroxyl amine hydrochloride which was followed by the reaction with phosphorous penta sulphide. These all synthesized derivatives of 2-isothiazoli have been screened for antibacterial activity and characterized by spectral studies.**

Keywords: 2-hydroxy-5-methyl-4,6-dibromoacetophenone, Substituted aldehyde, Chlcones, 2-isoxazolines,2-isothiazoline, Antibacterial activity, IR/NMR Spectroscopy.

INTRODUCTION

Chalcone have many pharmacological activity such as antimicrobial[1], antiviral[2], anti-inflammtory[3], antifungal[4], antispasmodics[5], etc Various chalcones derivatives can be obtained by the condensation of aryl ketone with the various substituted aldehyde[6,7]. Chalcone and its related hetero cyclic derivatives such as isothiazoline, oxazine, pyrazoline, isoxazole, thiazine, pyrimidine, benzthiazepine, quinoxaline etc shows antibacterial activity against various gram positive and gram negative bacteria[8-12]. We report the reaction of 2-hydroxy-5-methyl-4,6-dibromoacetophenone with various substituted aromatic aldehydes to produced corresponding 2'-hydroxy-5'-methyl-4',6'-dibromo chalcones[1A-1J]. Which on treatment with hydroxyl amine hydrochloride gives 2-isoxazoline derivative[2A-2J] and finally reaction with phosphorous pentasulphide produced 2- isothiazoline derivatives[3A-3J]. The constitution of all compounds synthesized was characterized by elemental analysis, IR and H1 NMR spectral study.
Compounds were also evaluated for antibacterial activity.

MATERIAL AND METHODS

All melting points were taken in open capillary tubes and are uncocorrected. IR spectra in KBr were recorded on perkin-Elmer-377 spectrophotometer and H^1 NMR spectra were recorded on Varian NMR spectrophotometer. All compounds gave satisfactory elemental analysis.

General method for the synthesis of 2'-hydroxy-5'-methyl-4',6'-dibromo chalcones[1A-1J]

A mixture of 2-hydroxy-5methyl-4,6-dibromoacetophenone (0.01 mole) and aryl aldehyde (0.01 mole) in ethanol (30 ml) was stirred and to it excess of 40% potassium hydroxide (25 ml) solution was added. The mixture was kept overnight at room temperature. The colour of the reaction mixture was change from yellow to orange. The content was then poured over crushed ice and acidified with hydrochloric acid (1:1). The solid separated was filtered, washed with distilled water, dried and crystallized from ethanol, yield 60-70%.

General method for the synthesis of 3-(2'-hydroxy-5'-methyl-4',6'-dibromophen-1'-yl)-5-(substituted phenyl)-2-isoxazoline[2A-2J]

A mixture of 2'-hydroxy-5'-methyl-4',6'-dibromo chalcone (0.01 mol) and hydroxylamaine hydrochloride (0.02 mol) in ethanol (25 ml) was refluxed on water bath at 60-70°C for 4 hours. The reaction was cooled and acidified with glacial acetic acid. The solid separated was filtered and washed with water, dried and crystallized from ethanol (99%), yield 40-50%.

General method for the synthesis of 3-(2'-hydroxy-5'-methyl-4',6'-dibromophen-1'-yl)-5-(substituted phenyl)-2-isothiazoline[3A-3J]

A mixture of 3-(2'-hydroxy-5'-methyl-4',6'-dibromophen-1'-yl)-5-(substituted phenyl)-2-isoxazoline (0.01 mol) and phosphorous pentasulphide (0.01 mol), was taken in pyridine (20 ml). The reaction mixture was refluxed on water bath at 80-90°C for an hour. The reaction mixture was then cooled and diluted with water. The solid obtained was filtered, washed with water and crystallized from ethanol (99%), yield 40-60%.

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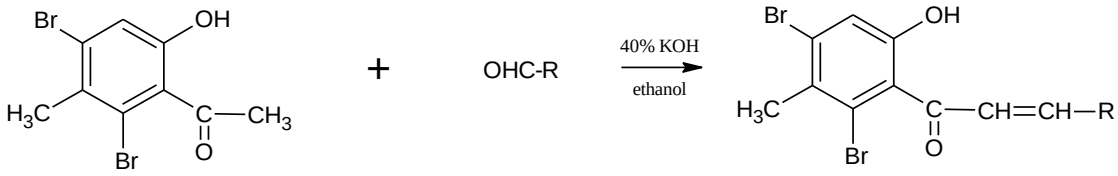
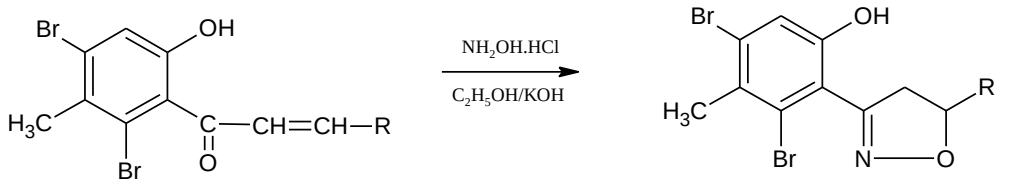
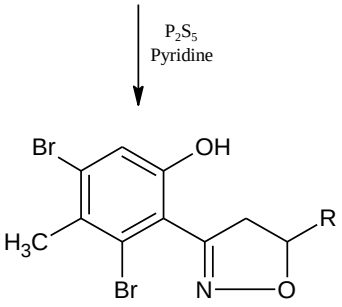
REACTION SCHEME



2-hydroxy-methyl-4,6-dibromoacetophenone Substituted aldehydes Chalcones
[1A - 1J]



[1A - 1J] [2A - 2J]



[3A - 3J]

Where R = 4-chlorophenyl, 4-hydroxyphenyl, Phenyl, 2,4-dichlorophenyl, 3-phenoxyphenyl, 2,6-dichlorophenyl, 3-nitrophenyl, 3,4,5-trimethoxyphenyl, 4-methoxyphenyl, 4-N,N-dimethylaminophenyl.

SCHEME

TABLE- 1

Characterization Table of 3-(2'-hydroxy-5'-methyl-4',6'-dibromophen-1'-yl)-5-(substituted phenyl)-2-isothiazoline[3A-3J]

Compd. No.	R	Molecular formula	(M. wt.)	Yield (%)	M.P. 0C.
3A	4-chlorophenyl	$C_{16}H_{12}ONSBr_2Cl$	461.59	38	156
3B	4-hydroxyphenyl	$C_{16}H_{13}O_2NSBr_2$	443.15	42	132
3C	Phenyl	$C_{16}H_{13}ONSBr_2$	427.15	44	133
3D	2,4-dichlorophenyl	$C_{16}H_{11}ONSBr_2Cl_2$	496.04	38	128
3E	3-phenoxyphenyl	$C_{22}H_{17}O_2NSBr_2$	519.24	38	143
3F	2,6-dichlorophenyl	$C_{16}H_{11}ONSBr_2Cl_2$	496.04	55	164
3G	3-nitrophenyl	$C_{16}H_{12}O_3N_2SBr_2$	472.15	38	124
3H	3,4,5-trimethoxyphenyl	$C_{19}H_{19}O_4NSBr_2$	517.23	37	168
3I	4-methoxyphenyl	$C_{17}H_{15}O_2NSBr_2$	457.17	42	180
3J	4-N,N-dimethylaminophenyl	$C_{18}H_{18}ON_2SBr_2$	470.22	41	104

^{1}H NMR Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is one of the latest physical methods which is use for the structure determination of organic compounds. PMR spectra of 2-isothiazoline derivatives were recorded on varian spectrophotometer. Spectra were examined in $CDCl_3$ at room temperature using TMS as internal standard.

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TABLE-2

200 MHz PMR spectra of 3-(2'-hydroxy-5'-methyl-4',6'-dibromophen-1'-yl)-5-(4"methoxyphenyl)-2-isothiazoline (Compound no. 3I)

Chemical shift	Relative Number of Protones	Assignment
2.30	3	$-CH_3$
2.57	2	$-CH_2$ of isothiazoline ring
3.82	3	$-OCH_3$
4.32	1	-CH of isothiazoline ring
6.33	1	-OH
6.75-7.80	5	Ar-H

Infrared spectra

Infrared absorption were recorded using potassium bromide pallets method. The spectra were recorded using "Perkin-Elmer" spectrophotometer. The results are describe in table no. 3.

TABLE-3

IR spectra of 3-(2'-hydroxy-5'-methyl-4',6'-dibromophen-1'-yl)-5-(4"chlorophenyl)-2-isothiazoline (Compound no. 3A)

Position of absorption band (cm^{-1})	Intensity	Band and its mode of vibration	Functional group
610	s	C-Br stretching	Bromo compound
780	s	C-Cl stretching	Chloro compound
845	s	N-S stretching	Isothiazoline ring
950	m	C-S stretching	Isothiazoline ring
1385	sh	O-H bending	Ar-OH intramolecular
1470	s	C-H bending	-
1590	v	C=N stretching	Compound containing C=N group
2980	m	C-H stretching	-
3400	sh	O-H stretching	Ar-OH group

S=strong, m=medium, b=broad, w=weak, sh=sharp, v=variable

Antibacterial activity

The synthesized compounds were screened for their antibacterial activity using *S.aureus, E. coli* by cup plate method using DMF as solvent. All the compounds shows mild activity against both bacteria in comparison with ampicilin and gentamycin. The results are describe in table no. 4.

Table-4

Compound No.	Zone of inhabitation in mm Antibacterial (24 hrs.)	
	S.aureus (+ve)	E.coli (-ve)
3A	8	10
3B	12	11
3C	10	8
3D	15	12
3E	N.A.	N.A.
3F	10	10
3G	14	10
3H	11	12
3I	10	17
3J	12	11
Standard Drugs:		
Ampicilin	18	-
Gentamycin	-	21

RESULTS AND DISCUSSION

2-isothiazoline derivatives shown medium activity against both bacteria i.e. S.aureus and E.coli. From the table no. 4, compound no. 3I shown the maximum activity amongst all the compounds towards –ve bacteria i.e. E.coli. The compound no. 3D and 3G haven shown good activity against S.aureus bacteria. The compound no. 3E found inactive against both bacteria while rest of the compounds have shown the medium to poor activity against both bacteria. The activities of synthesized compounds are compared with standard antibiotics like Ampicillin and Gentamicin. It was observed that the synthesized compounds are less active than the standard one.

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