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Synthesis, Antibacterial and Antifungal Activity of Some Iodo-Substituted 3,5-Diaryl Isoxazolines

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Some iodo-substituted *ortho*-hydroxy chalcones, flavanones and iodo-substituted 3,5-diarylisoxazolines were synthesized and tested for antibacterial activities against *Staphylococcus aureus, Escherichia coli, Proteus mirabilis, Enterobacter aerogenes, Pseudomonas aeruginosa* and antifungal activities against *Curvularia* and *Colletotrichum*. Title compounds were found effective against both bacteria (MIC 25–100 μg/mL) and fungal species (57–100% spore germination inhibition).

INTRODUCTION

Chalcone and its substituted derivatives are reported to have antibacterial[1], antifungal, antiparasitic, antitubercular, antiinflammatory and insect repellent properties[2, 3]. Isoxazolines have been reported to be prepared usually by the action of hydroxylamine hydrochloride on chalcones[4, 5] or flavanones[6, 7] in pyridine solvent. Isomeric trisubstituted isoxazolines were reported from 3-aroyl flavanones[8] in pyridine media. 3,5-Diarylisoxazolines also synthesized[9–11] from chalcones and hydroxylamine hydrochloride in DMSO, pyridine and ethanol solvent.

From the survey of literature, it is clear that iodosubstituted 3,5-diarylisoxazolines have not been so far synthesized. Hence it was thought interesting to synthesize iodosubstituted 3,5-diarylisoxazolines and to study their antibacterial and antifungal activities.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 557 spectrophotometer. ^{1}H NMR spectra ($CDCl_3$) were recorded on Perkin-Elmer R-32 spectrophotometer. Purity of the compounds was checked on silica gel-G TLC plates.

Preparation of 2-hydroxy-3-iodo-5-methylacetophenone

2-Hydroxy-5-methylacetophenone (0.1 mole) was dissolved in acetic acid (40 mL). Sodium acetate (15 g) was added and iodine monochloride in acetic acid (64 mL, 25% w/v) was added dropwise with constant stirring. The temperature was maintained below 25°C. The mixture was allowed to stand for about 30 min, and then poured into cold water. The solid separated was filtered and crystallized from ethanol, m.p. 101°C, yield 10 g. (Scheme-I)

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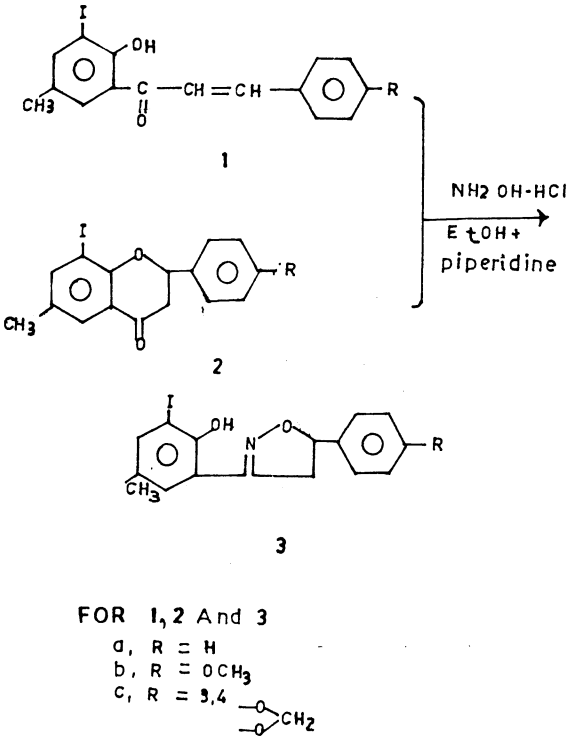

Scheme-I

Chalcones (1)

2-Hydroxy-3-iodo-5-methylacetophenone (0.1 mole) was dissolved in ethanol (100 mL). Aromatic aldehyde 0.1 mole was added and the mixure was heated to boiling. Sodium hydroxide solution (40%, 30 mL) was added slowly with constant stirring. The mixture was kept overnight. It was acidified and the product was crystallised from ethanol-acetic acid mixture.

(1b) IR: ν_{max} (Nujol) 3400 broad ν(OH); 1555 ν(—C—CH=CH); 1265–1260 ν(Ar—O); 1155–1150 ν(C—C); 1025–1020 ν(CH_3—O); 980–975 ν(CH=CH); 710–700 cm^{-1} ν(C—I).

UV-Vis (chloroform): λ_{max} 374 nm (OD = 0.54)

PMR ($CDCl_3$): δ 2.33 (3H, s, Ar—CH_3); 3.92 (3H, s, OCH_3); 7.2–8.5 (6H, m, Ar—H), 6.7 (1H, s, =CH—); 7.10 (1H, s, =CH—); 13.70 (1H, s, CH).

Flavanones (2)

Chalcone (0.1 mol) was refluxed in ethanol (80%, 100 mL) containing conc. H_2SO_4 (1 mL) for about 24 h. Crystals obtained were filtered off and washed with sodium bicarbonate solution (1%) followed by water. The product was recrystallised from ethanol-acetic acid mixture.

(2a) IR: ν_{max} (Nujol) 1700–1552 ν(C=O stretching in cyclic ketones); 1311–1212 ν(Ar—O stretching in aromatic ether); 1091–1064 ν(C—O—C stretching in cyclic ether, 6-membered); 800–711 cm^{-1} ν(C—I stretching).

UV-Vis (chloroform): λ_{max} 270.7 nm and 339.9 nm corresponding to $n \rightarrow \pi^*$ transition.

PMR ($CDCl_3$): 2.31 (3H, s, Ar—CH_3); 0.95 (1H, dd, $CH_{HA}A_{BX}$, J_{AB} = 15 Hz, J_{AX} = 7 Hz); 3.13 (1H, dd, CH_{HB} A_{BX}, J_{AB} = 15 Hz, J_{BX} = 9 Hz); 5.56 (1H, dd, C_H, $A_{BX}J_{AX}$ = 7 Hz, J_{BX} = 9 Hz) 7.21–8.10 (7H, m, Ar—H)

3-5-Diarylisoxazolines (3)

A mixture of chalcone or flavanone (0.01 mol) and hydroxylamine hydrochloride (0.02 mol) was refluxed in ethanol (25 mL) and piperidine (1 mL) for about 1 h. After cooling, the reaction mixture was acidified with dilute hydrochloric acid. The product was crystallised from ethanol (70%). The physical data of the synthesized compounds are presented in Table-1.

TABLE-1
PHYSICAL DATA OF COMPOUNDS*

Compounds No.	R	m.p. (°C)	Yield %	Molecular formula
1a	H	90	80	$C_{16}H_{13}O_2I$
1b	OCH_3	147	85	$C_{17}H_{15}O_3I$
1c	3,4 	163	85	$C_{17}H_{13}O_4I$
2a	H	116	70	$C_{16}H_{13}O_2I$
2b	OCH_3	122	80	$C_{17}H_{15}O_3I$
2c	3,4 	158	75	$C_{17}H_{13}O_4I$
3a	H	176	65	$C_{16}H_{12}O_2NI$
3b	OCH_3	188	75	$C_{17}H_{14}O_3NI$
3c	3,4 	196	85	$C_{17}H_{14}O_4NI$

*All compounds gave satisfactory elemental analyses.

(3B) IR: ν_{max} (Nujol) 3700–3100 ν(O—H); 1700–1550 ν(C=N); 1310–1210 ν(Ar—O in ethers); 1180 ν(C—O stretching in phenols); 950 ν(—N—O) and 700 cm^{-1} ν(C—I).

UV-Vis: λ_{max} 336 nm (OD = 0.78) corresponding to $n \rightarrow \pi^*$ transition.

PMR ($CDCl_3$): δ 2.28 (3H, s, Ar—CH_3); 3.86 (s, O—CH_3); 2.83 (1H, dd, CHH_A) 3.56 (1H, dd, CHH_B); 5–18 (1H, dd, C—H); 6.8–7.8 (6H, m, Ar—H) and 7.8–8.2 (1H, br, O—H).

Antibacterial activity

A stock solution (400 μg/mL) of the title compounds was prepared in dimethylformamide and was used within 2 days. The antibacterial activity was then assayed against *Staphylococcus aureus* (NCTC-6571), *Escherichia coli* (NCTC-2562), *Proteus mirabilis, Enterobacter aerogenes* (NCIM-2562) and

Pseudomonas aeruginosa (NCTS-10662) using serial dilution method. The minimum inhibitory concentrations (MICs) were recorded at the end of an incubation period of 24 ± 2 h.

Antifungal activity

It was tested using spores of *Colletotrichum* and *Curvularia* sp. An aliquot (0.05 mL) of the title compound (0.2%) was placed on demarcated area of the microscopic glass slide with the help of a micropipette. The solvent was then allowed to evaporate leaving the deposit of the test compound on the top of the slide. The spore suspension of the fungal species was adjusted in sterile distilled water to get 25–30 conidia per lower field of microscope. 0.1 mL of previously adjusted spore suspension was then deposited over the demarcated area of test compounds using sterile pipette. The demarcated areas were then closed with coverslip and incubated in a moist chamber at 20–25°C for 24 ± 2 h. Controls were run using the solvent dimethylformamide. Percentage of spore germination inhibition was calculated as:

$$\% \text{ of spore germination inhibition} = \frac{\% \text{ of spore germination in treatment}}{\% \text{ of spore germination in control}} \times 100$$

RESULTS AND DISCUSSION

Antibacterial activity of iodo-substituted 3,5-diaryl isoxazolines is shown in Table-2. Table-3 shows the percentage inhibition of fungal spore germination of the title compounds.

TABLE-2
ANTIBACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Compounds No.	R	MIC (μg/mL)				
		S. aureus	*E. coli*	*Pr. mirabilis*	*E. aerogenes*	*Ps. aeruginosa*
1a	H	50	100	50	50	100
1b	OCH_3	50	50	25	50	50
1c	3,4	50	50	25	50	50
2a	H	50	100	50	50	100
2b	OCH_3	25	50	25	25	50
2c	3,4 	25	50	50	25	50
3a	H	25	100	50	25	50
3b	OCH_3	25	50	50	50	50
3c	3,4	25	50	50	25	50
Standard drug Chloramphenicol		12.5	06	12.5	12.5	12.5

TABLE-3
FUNGAL SPORE GERMINATION INHIBITION BY TITLE COMPOUNDS

Compound No.	R	% Spore germination inhibition	
		Colletotrichum	*Curvularia*
1a	H	75.70	60.00
1b	OCH_3	95.90	57.30
1c	3,4 $-O>CH_2$ $-O$	98.00	62.00
2a	H	93.34	59.91
2b	OCH_3	100.00	57.90
2c	3,4 $-O>CH_2$ $-O$	100.00	66.85
3a	H	100.00	97.78
3b	OCH_3	100.00	97.78
3c	3,4 $-O>CH_2$ $-O$	100.00	88.89

The chalcones (1), flavanones (2) and 3,5-diaryl isoxazolines (3) were found effective towards both gram positive and gram negative bacteria. The compounds were active in the MIC range of 25–50 μg/mL (*S.aureus, P. mirabilis* and *E. aerogenes*), and 50–100 μg/mL (*E. coli* and *P. aeruginosa*).

The fungal species used in the present investigation are known plant pathogens. The compounds were more effective against *Colletotrichum* sp. than against *Curvularia* sp. All title compounds were effective in inhibiting 75–100% *Colletotrichum* spore germination and 57–97% *Curvularia* spore germination.

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