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Synthesis of some Isoxazolines from chloro substituted Acetophenone and substituted Benzaldehyde via Chalcone intermediate and their Antimicrobial studies

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Abstract **-** Different isoxazolines (IIa-IIg) were synthesized via cyclization of substituted chalcone intermediate in the presence of hydroxylamine hydrochloride. Isoxazoline is a five membered heterocyclic compound having various pharmacological actions. In addition, Isoxazoline derivatives have played a crucial role as intermediates in the organic synthesis of number of heterocyclic pharmacological active compounds. Due to their diverse pharmacological activity, it is found useful in the treatment of antibacterial, anticancer, antiproliferative, antifungal, anti-amoebic, anti-inflammatory agents. They also exhibit analgesic, antimicrobial, antitumor and antidepressant activities. The structures of the isoxazoline derivatives were confirmed by spectral analysis. The derivatives of isoxazoline shows good to moderate activities against number of bacteria and fungus.

Keywords **-** *Isoxazoline, chalcone, antibacterial activity.*

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I. Introduction

The classical synthesis of the title compounds involves the base-catalyzed condensation of substituted aromatic ketone and substituted aldehydes to give α-β-unsaturated ketones (chalcones), which on cyclization with hydroxylamine hydrochloride in alkaline medium give the corresponding isoxazoline derivatives. In recent years, attention has increasingly been given to the synthesis of isoxazoline derivatives as a source of new antibacterial agents. The synthesis of novel isoxazoline derivatives remains a main focus of medicinal research. Isoxazoline derivatives have been reported to possess antifungal[1], antibacterial[2], anticonvulsant[3], antiinflammatory[4], antiviral[5] and analgesic activity[6]. In recent years, fluorinated acetophenones have found an important place in the manufacture of drugs, such as ciprofloxacin[7]. Moreover, In addition, isoxazoline derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis[8–12]. Depending on the above finding, we decided to synthesize some newly substituted Isoxazoline derivatives.

Karthikeyan *et al.* have synthesized pyrazolylisoxazoline and isoxazoles using 1, 3-dipolar cycloaddition of pyrazole derived nitrile oxide with various dipolarophiles such as N-substituted maleimide, diethyl acetylene carboxylate and phenylacetylene.The synthesized compound were evaluated for anti-nociceptive activities [17].

Wei Ming *et al.* synthesized 3, 5-disubstituted isoxazolines by mild deselenenylation reaction of isoxazolinyl substituted phenyl selenide, which on treatment with the organic base 1, 5-diazabicyclo [5, 4, 0]-undec-5-ene (DBU) or NaCN afford 5-methyl-3-substituted isoxazole[18].

Thus, we had synthesized some isoxazolines from chloro substituted acetophenone and substituted benzaldehyde

II. Review of Literature

Shrikrishna D. Tupare *et al* had synthesized 6-(3-(4,5-dihydro-5-(4-methoxyphenyl) isoxazol-3-yl) phenyl amino) pyridazin-3 (2*H*)-one[13].

Kh. F. Ali *et al* had synthesized 3-(4-substituted phenylamido)-5-(3`-nitrophenyl)-4,5-dihydro- isoxazol[14].

Muna S. Al-Rawi *et al* had synthesized 4[5-(3-nitrophenyl)-4, 5-dihydroisoxazol-3-yl] aniline [II] [15].

Sharma *et al.* have synthesized 3-phenyl amino-5-(substituted phenyl) isoxazoline and screened for anti-fungal activity [16].

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via chalcone intermediate in pyridine and analyzed their antimicrobial activity.Structures of these compounds have been established by spectral analysis (^{1}H NMR,IR) and elemental analysis. The melting points are uncorrected.

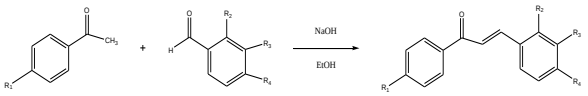
III. Experimental

(I) Preparation of substituted Chalcones.

To a cooled solution of NaOH and ethanol, substituted acetophenone was added followed by substituted benzaldehyde, the reaction mixture was stirred for 2-3 hours till the mixture become viscous and then the mixture was kept overnight in a refrigerator. The obtained product was filtered under suction and washed well with cold water. Then it was recrystallized by rectified spirit. Physical characterization and data of synthesized chalcones (I a-g) is given in table 1.

List of Chalcones prepared is as...

Ia (*E*)-3-(2-chlorophenyl)-1-(4-chlorophenyl)prop-2-en-1-one
Ib (*E*)-1,3-bis(4-chlorophenyl)prop-2-en-1-one
Ic (*E*)-1-(4-chlorophenyl)-3-(3-nitrophenyl)prop-2-en-1-one
Id (*E*)-1-(4-chlorophenyl)-3-*p*-tolylprop-2-en-1-one
Ie (*E*)-1-(4-chlorophenyl)-3-(2-nitrophenyl)prop-2-en-1-one
If (*E*)-1-(4-chlorophenyl)-3-(4-nitrophenyl)prop-2-en-1-one
Ig (*E*)-3-(3-chlorophenyl)-1-(4-chlorophenyl)prop-2-en-1-one

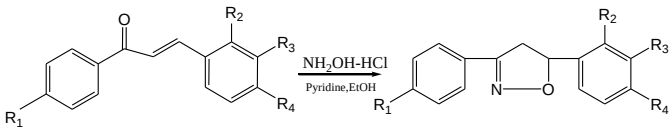


(II) Preparation of substituted Isoxazolines.

A mixture of chalcone and hydroxylamine hydrochloride was refluxed with pyridine for 2 hours. The reaction mixture was cooled and poured into ice-cold water. The product obtained was filtered, washed with water and recrystallized for purity from alcohol. Physical characterization and data of synthesized Isoxazolines (II a-g) is given in table 2.

List of Isoxazolines prepared is as..

IIa 5-(2-chlorophenyl)-3-(4-chlorophenyl)-4,5-dihydroisoxazole
IIb 3,5-bis(4-chlorophenyl)-4,5-dihydroisoxazole
IIc 3-(4-chlorophenyl)-5-(3-nitrophenyl)-4,5-dihydroisoxazole
IId 3-(4-chlorophenyl)-5-*p*-tolyl-4,5-dihydroisoxazole
IIe 3-(4-chlorophenyl)-5-(2-nitrophenyl)-4,5-dihydroisoxazole
IIf 3-(4-chlorophenyl)-5-(4-nitrophenyl)-4,5-dihydroisoxazole
IIg 5-(3-chlorophenyl)-3-(4-chlorophenyl)-4,5-dihydroisoxazole



IV. Result and Discussion

The Melting points of all compounds were recorded by using Paraffin bath. ^{1}H NMR Spectra and IR Spectra of compound IIa were use for its structural elucidation.

Table 1: *Physical characterization and data of synthesized chalcones.*

Compound	*R_1*	*R_2*	*R_3*	*R_4*	*Mol. Formula*	*Mol. weight*	*%N Cal. (Found)*	*MP^{O}C*	*%Yield*
Ia	Cl	Cl	H	H	$C_{15}H_{10}Cl_2O$	277	-	132	77
Ib	Cl	H	H	Cl	$C_{15}H_{10}Cl_2O$	277	-	133	74
Ic	Cl	H	NO_2	H	$C_{15}H_{10}ClNO_3$	288	4.87(4.43)	142	69
Id	Cl	H	H	CH_3	$C_{16}H_{13}ClO$	257	-	139	78
Ie	Cl	NO_2	H	H	$C_{15}H_{10}ClNO_3$	288	4.87(4.43)	142	75
If	Cl	H	H	NO_2	$C_{15}H_{10}ClNO_3$	288	4.87(4.33)	143	76
Ig	Cl	H	Cl	H	$C_{15}H_{10}Cl_2O$	277	-	132	78

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Table 2 : *Physical Characterization and data of synthesized Isoxazolines.*

Compound	R_1	R_2	R_3	R_4	*Mol. Formula*	*Mol. weight*	*%N Cal (Found)*	*MP^{O}C*	*%Yield*
IIa	Cl	Cl	H	H	$C_{15}H_{11}Cl_2NO$	292	4.79 (4.72)	320	68
IIb	Cl	H	H	Cl	$C_{15}H_{11}Cl_2NO$	292	4.79 (4.72)	321	66
IIc	Cl	H	NO_2	H	$C_{15}H_{11}ClN_2O_3$	303	9.25 (9.10)	319	65
IId	Cl	H	H	CH_3	$C_{16}H_{14}ClNO$	272	5.15 (5.12)	321	66
IIe	Cl	NO_2	H	H	$C_{15}H_{11}ClN_2O_3$	303	9.25 (9.10)	320	67
IIf	Cl	H	H	NO_2	$C_{15}H_{11}ClN_2O_3$	303	9.25 (9.10)	320	71
IIg	Cl	H	Cl	H	$C_{15}H_{11}Cl_2NO$	292	4.79 (4.72)	318	65

i) Spectral determination of IIa

IR (V_{max}): 560 cm^{-1}*v*(C-Cl); 1490 cm^{-1}*v*(C-C); 1510 cm^{-1}*v* (N-O); 1260 cm^{-1}*v* (C-O);. 3040 cm^{-1}*v* (C-H), 1270 cm^{-1}*v* (C-N),

^{1}H NMR (δppm): δ 3.3(m, 2H, -CH_2); δ 4.4 (d, H, -CH); δ 7.02 (m, 1H, -Ar-H); δ 7.1 (dd,1H,Ar-H);δ 7.20 (m,1H, Ar-H); δ 7.3 (m,1H, Ar-H); δ 7.6- (m,1H, Ar-H).
Further development on this subject, to understand their mechanistic interaction and Spectral determination of IIb-IIg are currently in progress.

ii) Antimicrobial Screening of synthesized Isoxazolines

Antimicrobial screening was done by using cup plate method at a concentration of 100µg/ml. The compounds were evaluated for their antimicrobial activity against *P. aeruginosa, S. aureus, C. frundii, E. coli, P. mirabilis and S. typhi.* The results of antimicrobial data are summarized in table 3.All compounds show the moderate to good activity. (Zone of inhibitions in mm)

Table 3: *Antimicrobial Screening synthesized Isoxazolines*

Organisms	*IIa*	*IIb*	*IIc*	*IId*	*IIe*	*IIf*	*IIg*
P. aeruginosa	13	12	12	10	13	12	14
S. aureus	14	13	13	10	12	11	12
C. frundii	12	12	12	09	11	13	15
E. coli	12	14	13	11	12	12	11
P. mirabilis	13	13	11	09	13	12	12
S. typhi	14	13	12	12	12	11	12

Strongly active range >12mm, moderately active range 8-12mm, weakly active range <8mm.

V. Conclusions

Compounds IIa, IIb and IIg are more active due to presence of more electronegative chloro group as compaired to Nitro substituted isoxazoline against the microorganism mention above. These compounds show the moderate to good antimicrobial activity.

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