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"Synthesis of Some Isoxazolines from Methyl Substituted Acetophenone and Substituted Benzaldehyde Via Chalcone Intermidiate and Their Antimicrobial Studies"

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ABSTRACT

In this paper new series of Isoxazoline IIa-IIg were prepared by condensation of aromatic Hetrocyclic Chalcones Ia-Ig with hydroxylamine hydrochloride and using Pyridine.The synthesized compounds were characterized by using IRspectra,1H NMR spectra C.H.N analysis. The validity of the expected chemical compounds to the prepared compounds in this search was obvious from IR spectra, 1H NMR spectra and C.H.N.results. It also deals with study of the biological activity of the prepared compounds which showed good to moderate biological activities against various micro organisms (P. aeruginosa, S. aureus, C. frundii, E. coli, P. mirabilis and S. typhi) in comparison to the aromatic Hetrocyclic Chalcones Ia-Ig. 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.

Keywords: Isoxazoline, chalcone, antibacterial activity.

I. INTRODUCTION

Compounds incorporating heterocyclic ring systems continue to attract con-siderable interest due to the wide range of their biological activities. Amongst them, five-membered heterocyclic compounds occupy a unique place in the realm of natural and synthetic organic chemistry. Isoxazolines as heterocyclic compounds have found wide application as pharmaceutical and agrochemical agents.For instance, isoxazolines possess biological activities,[1–8] such as insecticidal, antibacterial, antibiotic, antitumour, antifungal, antimicrobial activity, and anti-inflammatory and analgesic. In addition, isoxazoline derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis.[9, 10] Consequently, much attention has been paid to the development of new methodologies for their preparation. Several methods have been reported for the synthesis of isoxazoline derivatives. The synthetic routes for the preparation of isoxazoline derivatives involves the base-catalyzed condensation of substituted aromatic ketone and substituted aldehydes to give α-β-unsaturated ketones (chalcones), which on cyclization with hydroxyl amine hydrochloride in alkaline medium give the corresponding isoxazoline derivatives[11-14]. Depending on the above finding, we decided to synthesize some newly substituted Isoxazoline derivatives.

II. REVIEW OF LITERATURE

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[15].

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 [16].

Muna S. Al-Rawiet al had synthesized 4[5-(3 -nitrophenyl)-4, 5-dihydroisoxazol-3-yl] aniline [II] [17].
Sharma et al. have synthesized 3-phenyl amino-5-(substituted phenyl) isoxazoline and screened for anti-fungal activity [18].

Kh. F. Ali et al had synthesized 3-(4-substituted phenylamido)-5-(3`- nitrophenyl)-4, 5-dihydroisoxazol[19].
Shrikrishna D. Tupare et al had synthesized 6-(3-(4,5-dihydro-5-(4-methoxyphenyl) isoxazol-3-yl) phenyl amino) pyridazin-3 (2H)-one[20].

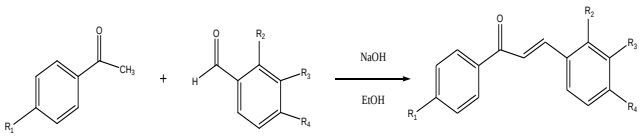
Thus, we had synthesized some isoxazolines from methyl substituted acetophenone and substituted benzaldehyde via chalcone intermediate in pyridine and analyzed their antimicrobial activity.Structures of these compounds have been established by spectral analysis (^{1}H NMR,IR) and elemental analysis. The melting points are uncorrected.

III. EXPERIMENTAL

1. 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.

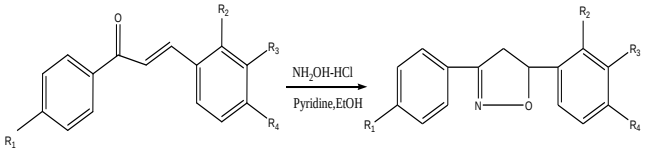
List of Chalcones prepared is as.
Ia (E)-3-(2-chlorophenyl)-1-p-tolylprop-2-en-1-one
Ib (E)-3-(4-chlorophenyl)-1-p-tolylprop-2-en-1-one
Ic (E)-3-(3-nitrophenyl)-1-p-tolylprop-2-en-1-one
Id (E)-1,3-dip-tolylprop-2-en-1-one
Ie (E)-3-(2-nitrophenyl)-1-p-tolylprop-2-en-1-one
If (E)-3-(4-nitrophenyl)-1-p-tolylprop-2-en-1-one
Ig (E)-3-(3-chlorophenyl)-1-p-tolylprop-2-en-1-one



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

Comp	R_1	R_2	R_3	R_4	Molecular Formula	Mol. Wt.	%N Cal. (Found)	MP^{O}C	% Yield
Ia	CH_3	Cl	H	H	$C_{16}H_{13}ClO$	257	-	131	79
Ib	CH_3	H	H	Cl	$C_{16}H_{13}ClO$	257	-	130	77
Ic	CH_3	H	NO_2	H	$C_{16}H_{13}NO_3$	267	5.24 (5.18)	142	71
Id	CH_3	H	H	CH_3	$C_{17}H_{16}O$	236	-	132	78
Ie	CH_3	NO_2	H	H	$C_{16}H_{13}NO_3$	267	5.24 (5.21)	143	76
If	CH_3	H	H	NO_2	$C_{16}H_{13}NO_3$	267	5.24 (5.20)	140	76
Ig	CH_3	H	Cl	H	$C_{16}H_{13}ClO$	257	-	138	78

Table 2. Physical Characterization and data of synthesized Isoxazolines.

Comp	R_1	R_2	R_3	R_4	Molecular Formula	Mol. Wt.	%N Cal. (Found)	MP^{O}C	%Yield
IIa	CH_3	Cl	H	H	$C_{16}H_{14}ClNO$	272	5.15 (5.10)	311	69
IIb	CH_3	H	H	Cl	$C_{16}H_{14}ClNO$	272	5.15 (5.11)	310	70
IIc	CH_3	H	NO_2	H	$C_{16}H_{14}N_2O_3$	282	9.92 (9.40)	313	72
IId	CH_3	H	H	CH_3	$C_{17}H_{17}NO$	251	5.57 (5.30)	308	73
IIe	CH_3	NO_2	H	H	$C_{16}H_{14}N_2O_3$	282	9.92 (9.70)	322	60
IIf	CH_3	H	H	NO_2	$C_{16}H_{14}N_2O_3$	282	9.92 (9.65)	320	71
IIg	CH_3	H	Cl	H	$C_{16}H_{14}ClNO$	272	5.15 (5.12)	319	77

1. Spectral determination of IIa

IR (V_{max}): 720 cm^{-1}v(C-Cl); 1490 cm^{-1}v(C-C); 1510 cm^{-1}v (N-O); 1480 cm^{-1}v (C-C); 3050 cm^{-1}v (C-H), 1270 cm^{-1}v (C-N), 3100 cm^{-1}v (C-H).

^{1}H NMR (δppm):δ 2.34(s, H, -CH_3); δ 3.31 (dd, H, -CH_2); δ 3.06 (dd, H, -CH_2); δ 4.5 (t, H, -CH);
δ 7.18 (m,1H, Ar-H); δ 7.5 (d,1H, Ar-H); δ 7.20 (m,1H, Ar-H); δ 7.0 (m,1H, Ar-H).

Further development on this subject to understand their mechanistic interaction and Spectral determination of IIb-IIg are currently in progress.

2. 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	12	11	13	11	12	10	13
S. aureus	13	14	12	10	13	12	14
C. frundii	13	12	12	10	12	11	14
E. coli	14	13	11	09	12	10	14
P. mirabilis	13	14	13	10	11	12	13
S. typhi	13	13	11	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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