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NOTE

Synthesis and Biological Studies of Some Isoxazolines

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3-[3-(2-Hydroxyphenyl)-4,5-dihydro-isoxazol-5-yl]chromen-4-one (**IVa-d**) have been synthesized from appropriate α,β-unsaturated ketones (**IIIa-d**) and hydroxylamine hydrochloride in presence of ethanol as a moistening solvent under microwave irradiation. The compounds have been characterized by elemental analysis and spectral data. The antimicrobial activities of the compounds have also been evaluated.

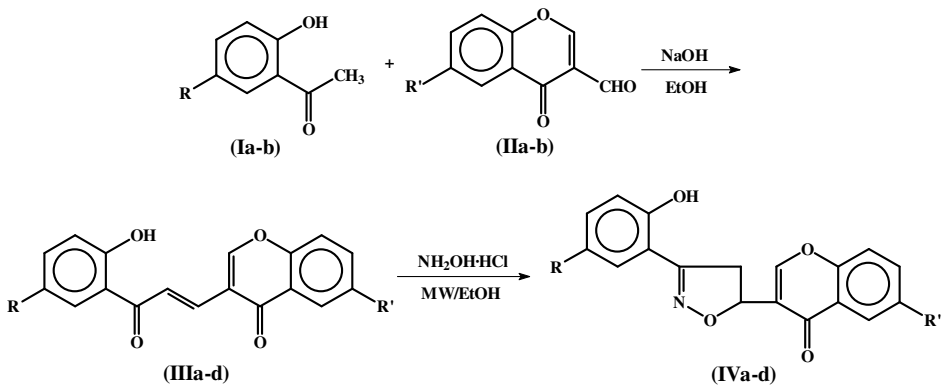
Key Words: Isoxazolines, Microwave, Synthesis, Biological activity.

Isoxazoline nucleus is useful as intermediate in organic synthesis, polymer, pharmacologically active[1], dyes[2], pesticide[3], fungicidal[4], antimicrobial, bactericidal, mutagenic, *etc.* Isoxazolines have been synthesized from chalcone, hydroxylamine hydrochloride in presence of acetic acid and potassium carbonate under microwave irradiation[5]. Microwave assisted reaction have much interest because of the simplicity in operation, greater selectivity and rapid synthesis of variety of heterocyclic compounds[3]. Keeping this in mind, it is worthwhile to develop rapid synthesis of isoxazolines derivatives using microwave irradiation.

The melting points of all the compounds were recorded using hot paraffin bath and are uncorrected. PMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvent. IR spectra were recorded on Perkin-Elmer spectrophotometer using KBr pellets. Purity of compounds was checked on silica gel-G plates by TLC.

Synthesis of α,β-unsaturated ketones (IIIa-d): Aromatic ketones (**Ia-b**) (0.05 mol) were condensed with formyl chromone (**IIa-b**) (0.05 mol) by dissolving them in ethanol and the solution was warmed. To this warm solution 40 % NaOH (0.15 mol) was added. The mixture was stirred mechanically at room temperature to get a red mass. It was kept overnight at room temperature and was decomposed with ice-cold HCI (1:1) to get yellow granules. These were filtered, washed with 10 % $NaHCO_3$ followed by water and crystallized from ethanol-acetic acid to get 2'-hydroxy chalcone. m.p. 85-86 °C; elemental analysis % : (found C, 74.95; H, 4.92; calcd. for $C_{20}H_{16}O_4$, C, 75.00; H, 5.00).

This reaction was extended to synthesize other compounds (**IIIb-d**).



IIIa: R = R′ = CH_3 **IIIb:** R = CH_3; R′ = H
IIIc: R = H; R′ = CH_3 **IIId:** R = R′ = H

Scheme

Synthesis of 3-[(2-hydroxy-5-methyl phenyl)-4,5-dihydroisoxazol-5-yl]-6-methyl chromen-4-one (IVa): 3-[3-(2-Hydroxy-5-methyl phenyl)-3-oxo-propenyl]-6-methyl chromen-4-one (**IIa**) (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) were taken in round-bottom flask with ethanol as a moistening solvent. The reaction mixture was irradiated at 360 watt for 4.5 min in microwave oven. The completion of reaction was checked by TLC. The reaction mixture after cooling treated with water. The product obtained was washed, filtered and recrystallized from ethanol-acetic acid. m.p. 152-153 ºC; elemental analysis %: (found C, 70.95; H, 4.17; N, 3.18; calcd. for $C_{20}H_{17}NO_4$, C, 71.64; H, 5.07; N, 4.17).

On extending the above reaction the other isoxazolines (**IVb-d**) have been isolated in good yields (Table-1).

TABLE-1
PHYSICAL DATA AND ELEMENTAL ANALYSIS OF **III** AND **IV**

Compd.	m.f.	m.p. (ºC)	Yield (%)	Elemental analysis (%): Calcd. (Found)		
				C	H	N
IIIa	$C_{20}H_{16}O_4$	85-86	78	75.00 (74.95)	5.00 (4.92)	–
IIIb	$C_{19}H_{14}O_4$	100-101	71	74.50 (74.42)	4.57 (4.37)	–
IIIc	$C_{19}H_{14}O_4$	158-161	75	74.50 (74.42)	4.57 (4.37)	–
IIId	$C_{18}H_{12}O_4$	138-141	69	73.97 (73.87)	4.10 (3.98)	–
IVa	$C_{20}H_{17}NO_4$	152-153	82	71.64 (70.95)	5.07 (4.95)	4.17 (3.98)
IVb	$C_{19}H_{15}NO_4$	160-162	79	71.02 (70.93)	4.67 (4.57)	4.36 (4.25)
IVc	$C_{19}H_{15}NO_4$	181-183	81	71.02 (70.93)	4.67 (4.57)	4.36 (4.25)
IVd	$C_{18}H_{13}NO_4$	200-203	74	70.35 (70.28)	4.23 (3.98)	4.56 (4.06)

Compounds were also screened for antimicrobial activity against microorganisms *viz.*, *E. coli, S. aureus, A. aeruginosa* and *P. vulgaris*.

The starting compounds were substituted *o*-hydroxy acetophenones (**Ia-b**) which were prepared from corresponding phenyl acetate by Fries migration using anhydrous $AlCl_3$. Substituted chromones (**IIa-b**) were prepared from *o*-hydroxy acetophenones (**Ia-b**) by Vilsmear Haack reaction using DMF-$POCl_3$.

Based catalyzed condensation reaction between acetophenones (**Ia-b**) and chromones (**IIa-b**) afforded α,β-unsaturated ketones (**IIIa-d**). 2'-Hydroxy chalcones (**IIIa-d**) on treatment with hydroxylamine hydrochloride in few drops of ethanol gave 3-[(2-hydroxy-5-methyl phenyl)-4,5-dihydroisoxazol-5-yl]-6-methyl chromen-4-one (**IVa**) under microwave irradiation, m.p. 152-153 °C.

The other isoxazolines (**IVb-d**) have been prepared by extending this reaction with above procedure. IR spectrum of **IVa** showed ν(O-H) 3333; ν(C=O) 1638; ν(C=N) 1501; ν(=N-O) 958 cm^{-1}. ^1H NMR spectrum of compound showed the peak due to Ar-H (6.8-7.4, m, 6H); Ar-CH_3 (2.41, s, 3H); C-H (7.1, dd, 1H), C-H (73, dd, 1H); C-H (7.6, dd, 1H), *etc*.

Antimicrobial activity: The synthesized compounds (**IVa-d**) were screened for their antimicrobial activity against gram +ve and gram -ve microorganisms like *E. coli*, *S. aureus*, *A. aeruginosa* and *P. vulgaris* using cup-plate method[6]. The concentration was of 1×10^{-5} CIU/mL and each well was of diameter 10 mm. Compounds **IVa** and **IVb** showed enhanced activity against *E. coli*, while other compounds showed moderate activity. Compound **IVc** and **IVd** showed moderate activity against *A. aeroginosa* and *P. vulgaris*. All compounds showed good activity against *S. aureus*.

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