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Synthesis and characterization of flavanone derivatives and 3,5-diaryl-4-aroyl isoxazolines

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ABSTRACT

A series of 3, 5-diaryl-4-aroyl isoxazolines (5 $_{a-f}$) have been synthesized by cyclization of bromo nitro substituted Flavanones (4 $_{a-f}$) with hydroxylaminehydrochloride in pyridine containing few drops piperidine. These substituted flavanones have been prepared by interaction of 1-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-3-phenyl-1, 3-propanedione with different substituted aromatic aldehydes refluxing in ethanol with 0.5 ml piperidine. Constitutions of synthesized compounds have been confirmed on the basis of elemental analysis (CHN), MASS, IR and ^{1}H NMR spectral analysis.

Key words: Synthesis, flavanones, 3, 5-diaryl-4-aroyl isoxazolines.

INTRODUCTION

Among a wide variety of heterocycles that have been explored for developing pharmaceutically important molecules, isoxazolines is one of them. Literature reveals that number of isoxazoline derivatives have been found to possess antimicrobial[1], anti-inflammatory[2], antidiabeties [3] and antifungal[4] activity. Isoxazolines have been reported to be prepared usually by the action of hydroxylamine hydrochloride on chalcones [5-6] or flavanones [7-8] in pyridine solvent. A series of 3-[3-(2,4-dichloro-5-fluorophenyl)-5-(2-furyl)-4,5-dihydro-1H-pyrazol-1-yl]-5-(substitutedphenyl/2-thienyl)isoxazoline[9] synthesized and reported to posses the antibacterial activity. It has been reported the synthesis of 3-(Naphtho[2,1-b]fur-2yl)-5-aryl-2-isoxazolines in ethanol medium by the condensation of 1-(Naphtho[2,1-b]fur-2yl)-3-aryl-2-propen-1-ones with hydroxylamine hydrochloride[10].

Substituted 3-bromoflavanone is obtained from α,β-dibromochalcone in Acetic acid as a solvent[11]. The bromo and dichloro substituted 3-aroyl flavanones reported by condensation of diketone with aromatic aldehydes by employing the classical Bekar-Venkatraman synthesis [12-13]. This on cyclization with hydroxylamine hydrochloride in alkaline medium gives the corresponding isoxazolines derivatives. Also reported that 4', 5, 7-trihydroxy-3'-prenylflavanones[14] have antimicrobial activities which is prepared by 2'-hydroxy-4, 4', 6'-tris (methoxymethyloxy)-3-prenylchalcone in MeOH containing 10% HCl. 3-Substituted flavanones and flavones have been found to be versatile starting materials for the synthesis of heterocyclic compounds containing oxygen and/or, nitrogen hetero atoms [15-16]. Various analogs of flavanone were reported by oxidative cyclization of Chalcones [17]. With this background, the present communication deals with the synthesis of some novel bromo nitro substituted flavanones and 3, 5 diaryl-4-aroyl isoxazolines derivatives.

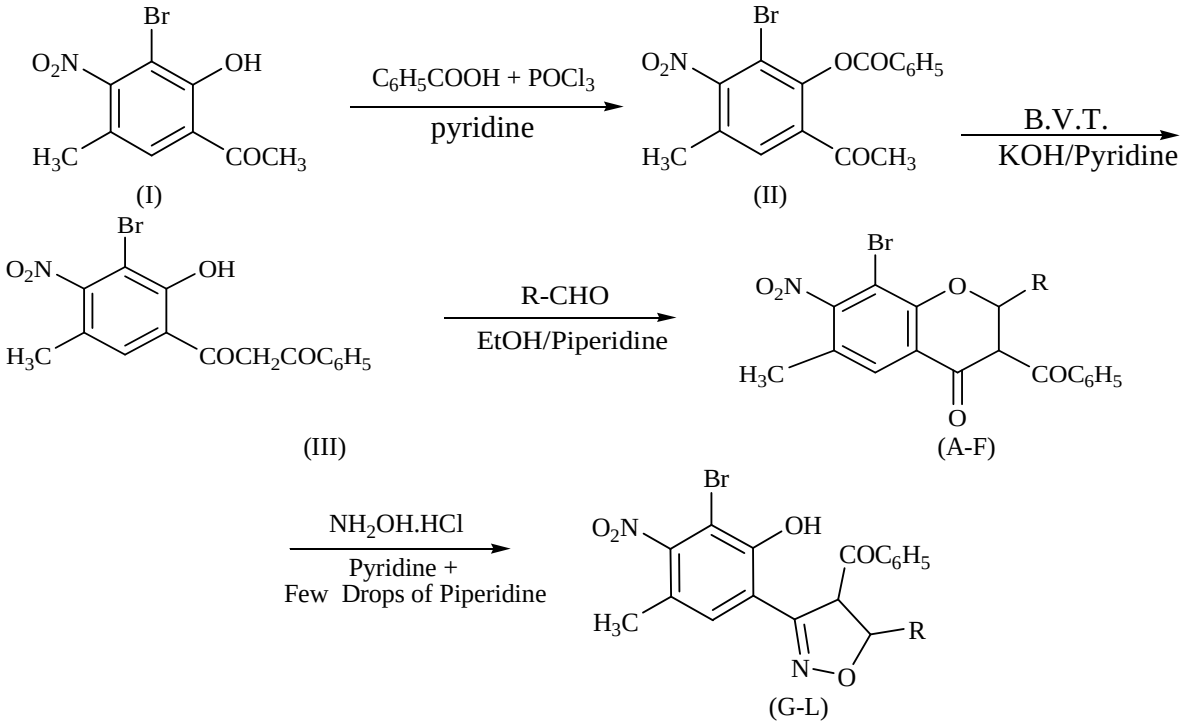
MATERIALS AND METHODS

The purity of synthesized compounds were checked by the thin layer chromatography using silica G. Melting points of all synthesized compounds were determined in open capillary tube M.P. apparatus expressed in ^{0}C and are uncorrected. Chemicals and solvents were of highest purity commercially available. ^{1}H NMR spectra were recorded in the indicated solvent on Bruker AVANCE II 400 NMR spectrometer with TMS as internal standard. I.R. were recorded on Perkin-Elmer-841 spectrometer in KBr disc.

Synthesis of 2-hydroxy-3-bromo-4-nitro-5-methyl acetophenone (I)
p-cresyl acetate was prepared by known method. Then by fries migration 2-hydroxy-5-methyl acetophenone was obtained. This on bromination gives 2-hydroxy-3-bromo-5-methyl acetophenone. Which further on nitration gives starting compound i.e. 2-hydroxy-3-bromo-4-nitro-5-methyl acetophenone (I).

Synthesis of 2-benzyloxy-3-bromo-4-nitro-5-methyl acetophenone (II)
2-hydroxy-3-bromo-4-nitro-5-methyl acetophenone (I) 0.04M and benzoic acid (0.05 mol) were dissolved in pyridine and $POCl_3$ is added with constant stirring, maintain the temperature below 10^{0}C. The reaction mixture was kept overnight at RT. The reaction mixture was decomposed by ice cold 10% HCl. The products thus separated was filtered washed with water followed by Sodium bicarbonate (10%) and then again with water. The solid product thus separated was crystallized from ethanol to get the compound m.p. 108^{0}C.

Scheme:-I



The groups **R** are given in table.

TABLE 1: CHEMICAL DATA OF THE COMPOUNDS (A-F)

Compound No.	R	Molecular Formula	Melting Point (°C)	Yield (%)
(A)	-4-OH-phenyl	$C_{23}H_{16}BrNO_6$	108	78
(B)	-4-Cl-phenyl	$C_{23}H_{15}BrClNO_5$	113	76
(C)	-3,4-$(OCH_3)_2$-phenyl	$C_{25}H_{20}BrNO_7$	116	75
(D)	-3-OCH_3-4-OH-Phenyl	$C_{24}H_{18}Br\ NO_7$	125	80
(E)	-3-NO_2-Phenyl	$C_{23}H_{15}Br\ N_2O_7$	122	74
(F)	-2-OH-phenyl	$C_{23}H_{16}BrNO_6$	135	71

Synthesis of 1-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-3-phenyl-1, 3-propanedione (By Baker-Venkatraman transformation) (III):-

2-benzyloxy-3-bromo-4-nitro-5-methyl acetophenone (II) (0.05 M) was dissolved in dry pyridine (40 ml). The solution was warm up to 60^0C and pulverized KOH (15 gm) was added slowly with constant stirring. The reaction mixture was kept for 6-8 hours and then acidified by adding ice cold HCl (1:1). The brownish yellow solid product thus separate was filtered, washed with Sodium bicarbonate (10%) and finally again with water. It was then crystallized from ethanol to get the compound (III) m.p. 94^0C.

Synthesis of 3-benzoyl-2-(substitutedphenyl)-6-methyl-7-nitro-8-bromoflavanone (A-F):

A mixture of 1-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-3-phenyl-1, 3-propanedione (III) 0.01 M and substituted benzaldehyde 0.01 M was refluxed in ethanol (30 ml) containing 0.5 ml piperidine for 30 min. After cooling reaction mixture was acidified with dil. HCl. The product thus separate was crystallized from ethanol to get the following compounds,

(A) 3-benzoyl-2-(4'-hydroxyphenyl)-6-methyl-7-nitro-8-bromoflavanone;
(B):- 3-benzoyl-2-(4'-chlorophenyl)-6-methyl-7-nitro-8-bromoflavanone;
(C):- 3-benzoyl-2-(3',4'-dimethoxyphenyl)-6-methyl-7-nitro-8-bromoflavanone;
(D):- 3-benzoyl-2-(4'-hydroxy-3'-methoxyphenyl)-6-methyl-7-nitro-8-bromoflavanone;
(E):- 3-benzoyl-2-(3'-nitrophenyl)-6-methyl-7-nitro-8-bromoflavanone;
(F):- 3-benzoyl-2-(2'-hydroxyphenyl)-6-methyl-7-nitro-8-bromoflavanone; were synthesized separately from (III) by using 4-hydroxybenzaldehyde; p-chlorobenzaldehyde; Vertraldehyde; Vanillin; 3-nitrobenzaldehyde and Salicyladehydes respectively.

Synthesis of 3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(substituted phenyl)-isoxazoline (G-L):

A mixture of 3-benzoyl-2-(substituted phenyl)-6-methyl-7-nitro-8-bromoflavanone 0.01 M and hydroxylaminehydrochloride 0.02 M was refluxed in pyridine (20 ml) containing 0.5 ml piperidine for 2-3 hours. After cooling the reaction mixture was acidified with ice cold HCl (1:1). Thus product separated was filtered crystallized from ethanol to get the following compounds,

(G):- 3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(4-hydroxyphenyl)-isoxazoline;
(H):-3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(4-chlorophenyl)-isoxazoline;
(I):- 3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(3,4-dimethoxyphenyl)-isoxazoline;
(J):-3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(3-methoxy-4-hydroxyphenyl)-isoxazoline;
(K):- 3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(3-nitrophenyl)-isoxazoline;
(L):-3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(2-hydroxyphenyl)-isoxazoline;were synthesized separately from A to F respectively.

TABLE 2: CHEMICAL DATA OF THE COMPOUNDS (G-L)

Compound No.	R	Molecular Formula	Melting Point (^{o}C)	Yield (%)
(G)	-4-OH-phenyl	$C_{23}H_{17}BrN_2O_6$	164	72
(H)	-4-Cl-phenyl	$C_{23}H_{16}BrClN_2O_5$	139	70
(I)	-3,4-$(OCH_3)_2$-phenyl	$C_{25}H_{21}BrN_2O_7$	171	78
(J)	-3-OCH_3-4-OH-Phenyl	$C_{24}H_{19}Br\ N_2O_7$	184	77
(K)	-3-NO_2-Phenyl	$C_{23}H_{16}Br\ N_3O_7$	106	75
(L)	-2-OH-phenyl	$C_{23}H_{17}BrN_2O_6$	153	80

RESULTS AND DISCUSSION

The synthesized Bromo-Nitro-Substituted Flavanones and 3,5-Diaryl-4-aroyl-isoxazolines were screened on the basis of IR, ^{1}H NMR, elemental analysis and Mass spectral analysis.

Characterizations:

1-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-3-phenyl-1, 3-propanedione:

IR (KBr cm^{-1}): 3237 (broad Ar-OH), 2924 (C-H Stretching of Ar-H), 2736 (C-H Stretching of aliphatic H), 1638 and 1613 (C=O stretching of diketone), 1250 (Ar C-O stretching), 1556 & 1370 (-NO_2 stretching), 1442 (-C=C-),

556 (C-Br). **^{1}H NMR ($CDCl_3$)**: - δ 2.27 (S, 3H, Ar-CH_3), 2.68 (S, 2H, -CH_2), 7.46-7.65 (m, 5H, Ar-H), 8.22-8.23 (S, 1H, Ar-H), 12.75 (Ar-OH). **$C_{16}H_{12}BrNO_5$:- (**Calculated C=50.82, H=3.20, N=3.70. and Found C=52.30, H=4.34, N=3.98). **Mass: - m**/z 378.0 (M^+) & 380.0 (M^++2), Base peak 226.9 & 228.9, 362.0, 245.0.

3-benzoyl-2-(4'-chlorophenyl)-6-methyl-7-nitro-8-bromoflavanone:
IR (KBr cm^{-1}): 3366 (C-H Stretching of Ar-H), 2924 (C-H Stretching of aliphatic H), 1640 and 1612 (C=O stretching of diketone), 1244 (Ar C-O stretching), 1563 & 1346 (-NO_2 stretching), 1446 (-C=C-), 713 (-C-Cl), 560 (C-Br). **^{1}H NMR (DMSO)**: - δ 2.35 (S, 3H, Ar-CH_3), 5.6 (d, 1H, -CH_A), 5.7 (d, 1H, -CH_B), 7.4-8.0 (m, 10H, Ar-H). **$C_{23}H_{15}BrClNO_5$:- (**Calculated C=55.17, H=3.02, N=2.80. and Found C=54.34, H=4.72, N=2.56). **Mass: - m**/z 496.4 (M^+), Base peak 147.1 & 453.4, 385.0, 387.0, 257.0.

3-benzoyl-2-(3', 4'-dimethoxyphenyl)-6-methyl-7-nitro-8-bromoflavanone:
IR (KBr cm^{-1}):- 3005 (C-H Stretching of Ar-H), 2968 (C-H Stretching of aliphatic H), 1639 and 1608 (C=O stretching), 1264 (Ar C-O stretching), 1524 & 1383 (-NO_2 stretching), 1463 (-C=C-), 1343 (pyrone ring), 575 (C-Br). **^{1}H NMR ($CDCl_3$)**: - δ 2.64 (S, 3H, Ar-CH_3), 3.89-3.91 (S, 6H, Ar-$(OCH_3)_2$), 5.55 (d, 1H, -CH_A), 6.7 (d, 1H, -CH_B), 6.80-7.7 (m, 9H, Ar-H).

3-benzoyl-2-(3'-nitrophenyl)-6-methyl-7-nitro-8-bromoflavanone:
IR (KBr cm^{-1}):- 3068 (C-H Stretching of Ar-H), 2953 (C-H Stretching of aliphatic H), 1635 and 1607 (C=O stretching), 1241 (Ar C-O stretching), 1529 & 1345 (-NO_2 stretching), 1445 (-C=C-), 556 (C-Br). **^{1}H NMR ($CDCl_3$)**: - δ 2.64 (S, 3H, Ar-CH_3), 5.5 (d, 1H, -CH_A), 5.7 (d, 1H, -CH_B), 7.40-8.00 (m, 10H, Ar-H).

3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(4-chlorophenyl)-isoxazoline:
IR (KBr cm^{-1}):- 3396 (Ar-OH), 2920 (C-H Stretching of Ar-H), 2858 (C-H Stretching of aliphatic H), 1632 (C=O stretching), 1261 (Ar C-O stretching), 1561 & 1386 (-NO_2 stretching), 1459 (-C=C-), 1189 (C=N-O-), 1599 (C=N-), 735(-C-Cl), 576 (C-Br). **^{1}H NMR (DMSO)**: - δ 2.35 (S, 3H, Ar-CH_3), 3.5 (d, 1H, -CH_A), 5.2 (d, 1H, -CH_B), 6.7-7.85 (m, 10H, Ar-H), 11.5 (S, 1H, Ar-OH).

3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(3,4-dimethoxyphenyl)-isoxazoline:
IR (KBr cm^{-1}):- 3397 (Ar-OH), 2922 (C-H Stretching of Ar-H), 2832 (C-H Stretching of aliphatic H), 1632 (C=O stretching), 1266 (Ar C-O stretching), 1518 & 1385 (-NO_2 stretching), 1461 (-C=C-), 1596 (C=N-), 575 (C-Br). **^{1}H NMR ($CDCl_3$)**: - δ 2.35 (S, 3H, Ar-CH_3), 3.79-3.96 (S, 6H, Ar-$(OCH_3)_2$), 3.47-3.52 (d, 1H, -CH_A), 5.17-5.21 (d, 1H, -CH_B), 6.86-7.60 (m, 9H, Ar-H), 12.3 (S, 1H, Ar-OH). **Mass: - m**/z 541.2 (M^+), 310.1, 347.10, 349.10 & 215.0.

3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(3-methoxy-4-hydroxyphenyl)-isoxazoline:
IR (KBr cm^{-1}):- 3396 (Ar-OH), 2961 (C-H Stretching of Ar-H), 2922 (C-H Stretching of aliphatic H), 1633 (C=O stretching), 1262 (Ar C-O stretching), 1515 & 1385 (-NO_2 stretching), 1459 (-C=C-), 1615(-C=N-), 574 (C-Br). **^{1}H NMR ($CDCl_3$)**: - δ 2.27-2.31 (S, 3H, Ar-CH_3), 2.36 (S, 3H, Ar-OCH_3), 3.98 (d, 1H, -CH_A), 5.50 (d, 1H, -CH_B), 6.9-7.4 (m, 9H, Ar-H), 8.2-8.4 (S, 1H, Ar-OH), 12.0-12.3 (S, 1H, Ar-OH).

3-(2-hydroxy-3-bromo-4-nitro-5-methylphenyl)-4-benzyol-5-(3-nitrophenyl)-isoxazoline:
IR (KBr cm^{-1}):- 3395 (broad Ar-OH), 2918 (C-H Stretching of Ar-H), 2849 (C-H Stretching of aliphatic H), 1630 (C=O stretching), 1255 (Ar C-O stretching), 1530 & 1348 (-NO_2 stretching), 1460 (-C=C-), 576 (C-Br). **^{1}H NMR ($CDCl_3$)**: - δ 2.4 (S, 3H, Ar-CH_3), 3.56-3.67 (d, 1H, -CH_A), 5.16-5.25 (d, 1H, -CH_B), 7.0-8.29 (m, 10 H, Ar-H), 12.1 (S, 1H, Ar-OH).

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