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Synthesis and Characterization of 3,4,5-Trisubstituted Isoxazolines and Isoxazoles

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3-Aroyl flavanone (**IIIa–d**) has been prepared by the condensation of dibenzoyl methane (**IIa–b**) with aromatic aldehyde in ethanol containing few drops of piperidine. 3-Aroyl flavanone (**IIIa–d**) on oxidation with DMSO-I_2 system gives 3-aroyl flavone (**IVa–d**). The compounds (**IIIa–d**) and (**IVa–d**) on refluxing with NH_2OH·HCl in DMF containing small amount of piperidine give 4-aroyl substituted isoxazolines (**Va–d**) and 4-aroyl substituted isoxazole (**VIa–d**) respectively. 4-Aroyl substituted isoxazole (**VIa–d**) have also been synthesized by reaction with 4-aroyl substituted isoxazoline (**Va–d**) with DMSO-I_2-H_2SO_4 system.

Key Words: 3,4,5-Trisubstituted isoxazolines, Isoxazoles.

INTRODUCTION

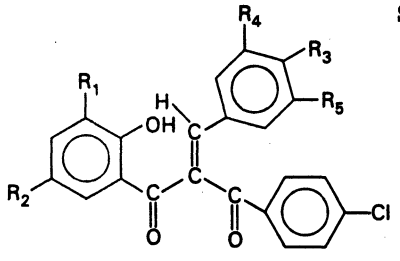
Isoxazole derivatives are important as potential antibacterial[1], antitubercular[2] and antiviral[3] agents. Recently isoxazolines and isoxazoles have been synthesized[4–6] respectively by reaction with hydroxylamine hydrochloride in pyridine. The present work describes the synthesis of some new 3,5-diaryl-4-aroyl substituted isoxazolines (**Va–d**). The isoxazoline when refluxed in DMSO in presence of catalytic amount of I_2 and 2–3 drops of concentrated H_2SO_4 gives 4-aroyl isoxazole (**VIa–d**) and have also been prepared by known method[5].

The dibenzoyl methane was prepared by known method[7] (**IIa–b**). 3-Aroyl flavanones were obtained by condensation of dibenzoyl methane (**IIa–b**) with aromatic aldehydes. The structure of (**IIIa**) was confirmed on the basis of chemical and spectral data. Flavanone on oxidation with DMSO-I_2, H_2SO_4 system and DMSO-I_2 system affords flavone[7]. Hence, 3-aroyl flavanone in DMSO in presence of catalytic amount of I_2 gives 3-aroyl flavone (**IVa–d**). It was interesting to prepare some new substituted 3,5-diaryl-4-aroyl-isoxazoline and 3,5-diaryl-4-aroyl-isoxazoles.

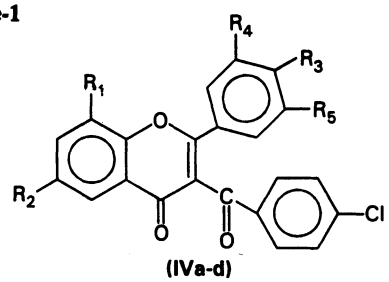
TABLE-1
PHYSICAL DATA OF 4-AROYL SUBSTITUTED PYRAZOLINE AND 4-AROYL SUBSTITUTED PYRAZOLE

S. No.	Comp.	R_1	R_2	R_3	R_4	R_5	m.p. (°C)	Yield (%)	R_f
1	**IIIa**	H	Cl	$N(CH_3)_2$	H	H	121–122	60	0.90
2	**IIIb**	H	Cl	OH	$-OCH_3$	$-OCH_3$	125	70	0.35
3	**IIIc**	NO_2	CH_3	$N(CH_3)_2$	H	H	138	72	0.41
4	**IIId**	NO_2	CH_3	OH	$-OCH_3$	$-OCH_3$	143	74	0.60
5	**IVa**	H	Cl	$N(CH_3)_2$	H	H	132	80	0.42
6	**IVb**	H	Cl	OH	$-OCH_3$	$-OCH_3$	155	78	0.15
7	**IVc**	NO_2	CH_3	$N(CH_3)_2$	H	H	180	75	0.21
8	**IVd**	NO_2	CH_3	OH	$-OCH_3$	$-OCH_3$	195	77	0.36
9	**Va**	H	Cl	$N(CH_3)_2$	H	H	198	72	0.51
10	**Vb**	H	Cl	OH	$-OCH_3$	$-OCH_3$	188	70	0.46
11	**Vc**	NO_2	CH_3	$N(CH_3)_2$	H	H	195	75	0.42
12	**Vd**	NO_2	CH_3	OH	$-OCH_3$	$-OCH_3$	190	74	0.28
13	**VIa**	H	Cl	$N(CH_3)_2$	H	H	208	70	0,46
14	**VIb**	H	Cl	OH	$-OCH_3$	$-OCH_3$	206	68	0.46
15	**VIc**	NO_2	CH_3	$N(CH_3)_2$	H	H	199	65	0.42
16	**VId**	NO_2	CH_3	OH	$-OCH_3$	$-OCH_3$	191	67	0.28

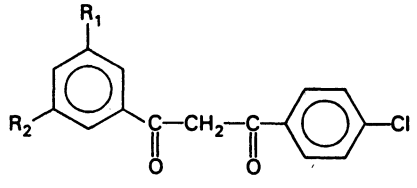
Scheme-1



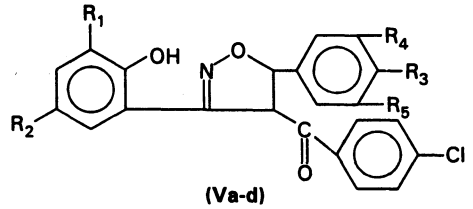
(Ia-d)



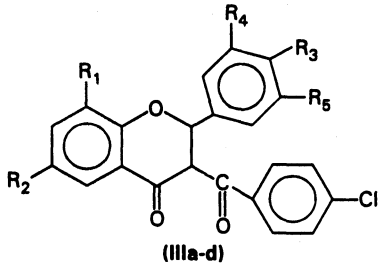
(IVa-d)



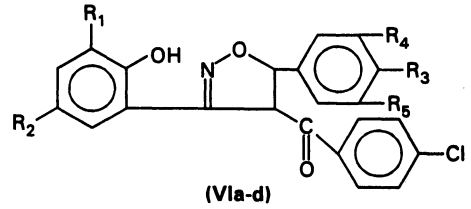
(IIa-b)



(Va-d)



(IIIa-d)



(VIa-d)

EXPERIMENTAL

Synthesis of 4′-(N,N′-dimethylamino)-3-(4′-chloro benzoyl)-6-chloro flavanone (IIIa)

1-(2′-Hydroxy-5′-chlorophenyl)-3-(4′-chlorophenyl)-1,3-propanedione **(IIa)** (0.01 mol) and 4-(N,N-dimethyl) amino benzaldehyde (0.012 mol) was refluxed in ethanol containing few drops of piperidine (0.5 mL) for 1 h. The reaction mixture on cooling gave white needles, filtered and crystallized from ethanol-acetic acid mixture to give IIIa; yield: 60%., m.p.: 121–122°C; IR (Nujol): 1658 ν(C═O), 1610 ν(C═O), 109 ν(C—O—C) and 781 cm^{-1} ν(C—Cl); ^1H NMR ($CDCl_3$): 2.85δ (s, 6H, —$N(CH_3)_2$), 5.38δ (d, 1H, —CH of methine), 6.04δ (d, 1H, —CH of methine) and 6.5–7.83δ (m, 11H, Ar—H).

The other flavanones **(IIIb–d)** were prepared and characterized by same method.

Synthesis of 4′-(N,N′-dimethylamino)-3-(4′-chlorobenzoyl)-6-chloro flavone (IVa)

A solution of 4′-(N,N′-dimethylamino)-3-(4′-chlorobenzoyl)-6-chloro flavanone **(IIIa)** (0.01 mole) in (20 mL) DMSO and crystals of iodine was refluxed for 1 h. The resultant product was washed with sodium thiosulphate (10%) (to remove unreacted iodine), washed several times with water and crystallised from acetic-acid ethanol mixture to get **IVa**; yield: 80%; m.p.: 131°C; IR (Nujol): 1639 ν(C═O), 1608 ν(C═C), 1559 ν(C—O—C) and 646 cm^{-1} ν(C—Cl). No absorption above 3000 cm^{-1} but many absorption bands below 3000 cm^{-1} indicate C—$N(CH_3)_2$ stretching; ^1H NMR ($CDCl_3$): 2.85 (S, 6H, —$N(CH_3)_2$), 6.77–8.16δ (m, 11H, Ar—H).

The other flavones **(IVb–d)** were prepared and characterized by the same method.

Synthesis of 3-(2′-hydroxy-5′-chlorophenyl)-4-(4′-chlorobenzoyl)-5-(4′-N,N-dimethyl aminophenyl) isoxazoline (Va)

A mixture of **IIIa** (0.01 mole) and hydroxylamine hydrochloride (0.02 mol) in DMF (20 mL) and few drops of piperidine (0.5 mL) was refluxed for 1.3 h. The reaction mixture was cooled, acidified with (1 : 1) HCl, washed with $NaHCO_3$ (2%) solution and washed with water and crystallized from ethanol-acetic acid mixture to give **Va**; yield: 72%; m.p.: 198°C; IR (Nujol): 3448 ν(—OH), 1745 ν(C═O), 1569 ν(C═N), 1461 ν(C═C), 1286ν (C—N), 1238 ν(C—O stretching in phenol), 1190–1112 ν(C—O), 970 ν(C═N—O) and 819 cm^{-1} ν(C—Cl); ^1H NMR ($CDCl_3$): 2.85δ (s, 6H, —$N(CH_3)_2$), 4.9δ (d, 1H, —CH), 5.3δ (d, 1H, —CH), 6.95–8.33δ (m, 11H, Ar—H) and 11.99δ (s, 1H, —OH).

The other isoxazolines **(Vb–d)** were prepared and characterized by same method.

Synthesis of 3-(2′-hydroxy-5′-chlorophenyl)-4-(4′-chlorobenzoyl)-5-(4′-N,N-dimethyl aminophenyl) isoxazole (VIa)

A mixture of **(IVa)** (0.01 mol) and hydroxylamine hydrochloride (0.02 mol)

in DMF (20 mL) and few drops of piperidine (0.5 mL) was refluxed for 1–2 h. The reaction mixture was cooled, acidified with HCl (1 : 1), wash with $NaHCO_3$ (2%) solution and finally washed with water, filtered and crystallized from ethanol-acetic acid mixture to give compound **VIa**; yield: 70%; m.p.: 208°C; IR (Nujol): 3448 ν(O—H), 1751–1612 ν(C=O), 1569 ν(C=N), 1612–1569 ν(C=N—O), 1461–1569 ν(C=C), 1377 ν(C—O stretching in phenol), and 609 cm^{-1} ν(C—Cl); ^1H NMR ($CDCl_3$): 2.85δ (s, 6H, —$N(CH_3)_2$), 6.7–8.16δ (m, 11H, Ar—H) and 11.92δ (s, 1H, Ar—OH).

The other isoxazoles **(VIb–d)** were prepared and characterized by the same procedure.

2nd Method: Compound **(Va–d)** was dissolved in DMSO and catalytic amount of I_2 added to the solution in presence of 2–3 drops of H_2SO_4. The mixture was refluxed for 1 h, diluted with cold water, filtered and crystallized from ethanol to give 3,5-diaryl-4-aroyl isoxazoles **(VIa–d).**

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