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Synthesis and Characterization of Some Nitrosubstituted 3,5-Diaryl Isoxazolines, Thioisoxazolines and their Derivatives

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Chalcones (**IIIa-d**) or flavanones (**IVa-d**) were reacted with ethanol, hydroxylamine hydrochloride and aqueous KOH to give isoxazoline (**Va-d**). Isoxazoline (**Va-d**) and P_2S_5 was refluxed with pyridine to give thioisoxazoline (**VIa-d**). Isoxazoline (**Va-d**) was reacted with acetic anhydride and a pinch of anhydrous sodium acetate to give 3-(2-acetoxy)-isoxazoline (**VIIa-d**). Thioisoxazoline (**VIa-d**) was reacted with acetic anhydride in presence of anhydrous sodium acetate to give 3-(2-acetoxy)-thioisoxazoline (**VIIIa-d**).

Key Words: Synthesis, Isoxazolines, Thioisoxazolines, Related isoxazolines and thioisoxazolines.

INTRODUCTION

Chalcones and its substituted derivatives are reported to have antibacterial[1], antifungal, antiparasitic, antitubercular, antiinflammatory and insect repellent propeties[2,3]. Isoxazolines have been reported to be prepared usually by the action of hydroxylamine hydrochloride on chalcones[4,5] or flavanones[6,7] in pyridine solvent. Isomeric trisubstituted isoxazolines were reported from 3-aroyl flavanones[8] in pyridine medium. 3-5-Diaryl isoxazolines also synthesized from chalcones and hydroxylamine hydrochloride in DMSO, pyridine and ethanol solvent[9-12]. Synthesis of 3-5 diaryl isoxazolines[13-22] can be carried out from chalcones or flavanones by the action of hydroxylamine hydrochloride and KOH or piperidine in pyridine, ethylene diamine, ethanol, methanol medium. Recently isoxazolines have been synthesized by the action of hydroxylamine hydrochloride on flavanone in DMF medium containing piperidine[23,24]. Nitrogen heterocyclic compounds like isoxazolines thioisoxazolines and their derivatives have received considerable attention in recent years due to their biological and physiological activities. Some derivatives of isoxazolines have been reported for their bacteriostatic, herbicidal, antiinflammatory and analgesic activities. 2,4-Dimethyl-5-sulphanilamido isoxazolines[25] (gastrin) is known as therapeutically active drug. Literature

survey indicates that, title compounds have not been synthesized from 2-hyroxy-3-nitro-5-methylphenyl-3-substituted chalcones and flavanones. Hence it was thought of interest to prepare some new nitrosubstituted 3,5-diaryl isoxazolines, thioisoxazolines and their derivatives from chalcones and flavanones. Chalcones and flavanones are prepared by known method[26,27].

EXPERIMENTAL

All the synthesized compounds have been established on the basis of chemical properties, elemental analysis and spectral analysis from one series. Purity of compounds were checked by TLC on silica get-G layers. The melting point were reported on "Tempo" melting point apparatus as well as observed in Thiel's m.p. appratus using open capillary tube and are uncorrected. IR spectra were recorded on PE-983/PE-781 IR spectrophotometer. UV-Vis on systronics 119 UV-Vis spectrophotometer and PMR on DSX-300 Hz solid state FT-NMR spectrophotometer. The carbon and hydrogen analysis was carried out on "Carlo Erba 1106" analyser. The nitrogen estimaton was done on "colman-N-analyser 29".

Synthesis of 3-(2-hydroxy-3-nitro-5-methylphenyl)-5-(4-methoxy phenyl) isoxazoline (Vb)

A mixture of 1-(2-hydroxy-3-nitro-5-methylphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (**IIIb**) or 2-(4-methoxyphenyl)-6-methyl-8-nitro flavanone (**IVb**) (0.01 mol) was refluxed in ethanol (50 mL) containing hydroxylamine hydrochloride (0.02 mol) and aqueous KOH (0.3 g in 2 mL water) for about 3 h. The reaction mixture was allowed to cool and acidified with HCl (50%). The solid crude product obtained was filtered and crystalized from ethanol-acetic acid mixture (80:20) yellow crystaline solid. Elemental analysis % found (calcd.) for $C_{17}H_{16}N_2O_5$: C 61.87 (62.19), H 4.61 (4.88), N 8.35 (8.54). Yield 75% m.p. 215ºC, R_f (0.63). IR (Nujol, cm^{-1}) : 3520 ν(O-H); 1610 ν(C = N *str.* in isoxazoline), 1180 ν(C-O *str.* in phenol); 1050 ν(C-O *str.* in ethanol); 1540 and 1370 ν(C-NO_2 *str.*); 1250 ν(Ar-H *str.*); UV-Vis ($CHCl_3$) : λ_{max} 372 and 351 nm, PMR ($CDCl_3$; δ) : 2.25 (s, 3H, Ar-CH_3); 3.80 (s, 3H, O-CH_3); 2.92 (dd, 1H, >CHH_A); 3.50 (dd, 1H, >CHH_B); 5.17 (dd, 1H, >CH_X); 6.8-7.8 (m, 7H, Ar-H). (Va) m.p. 159ºC, yield 80%. (Vc) m.p. 231ºC, yield 78%, (Vd) m.p. 217ºC, yield 85%.

Synthesis of 3-(2-hydroxy-3-nitro-5methylphenyl)-5-(4-methoxyphenyl)thioisoxazoline (VIb)

A mixture of 3-(2-hydroxy-3-nitro-5methylphenyl)-5-(4-methoxyphenyl) isoxazoline (**Vb**) (0.01 mol) and P_2S_5 (0.01 mol) was refluxed in pyridine (20 mL) for about 3 h. The reaction mixture was allowed to cool and acidified with HCl (50%). The solid product thus sepa-

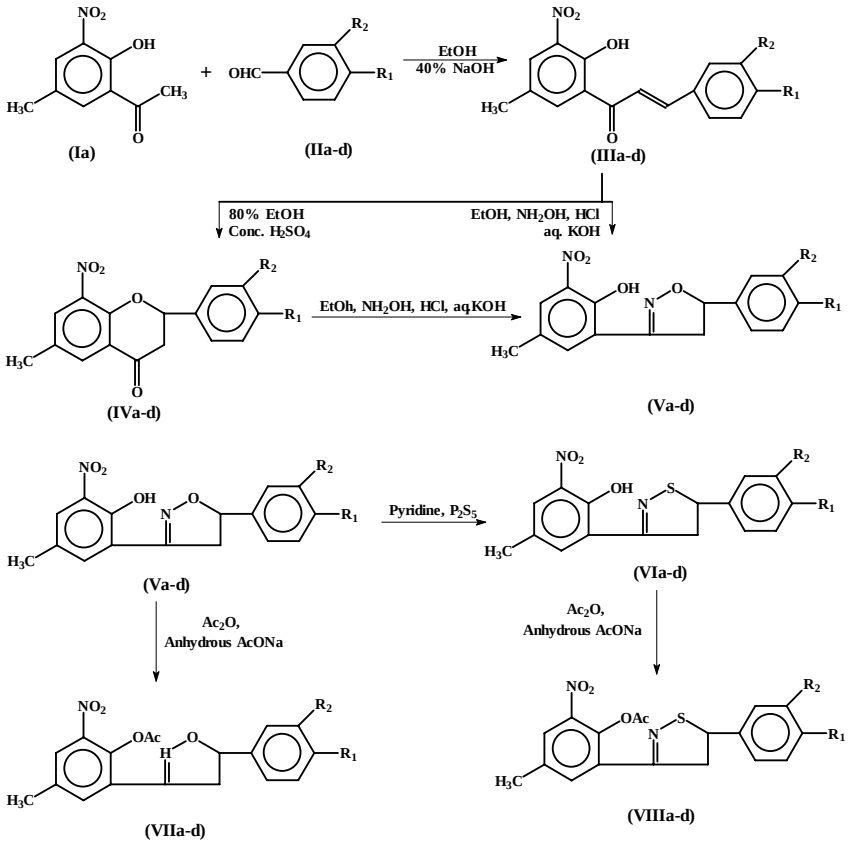
rated was filtered, washed with sodium bicarbonate solution (2%) and then with water. The solid crude product obtained was crystallized from ethanol + acetic acid mixture (80:20) to get the compound, (VIb) m.p. 163ºC; yield 80%, IR (Nujol, cm^{-1}): 3490 ν(O-H str.); 1590 ν(C=N *str.* in thioisoxazoline), 1190 ν(C-O *str.* in phenol), 1060 ν(C-O *str.* in ether); 1550 and 1390 ν(C-NO_2 *str.*); 1230 ν(Ar-H *str.*); 690 ν(C-S *str.* in thioisoxazoline); UV-Vis ($CHCl_3$) : λ_{max} 374 and 354 nm; PMR ($CDCl_3$; δ) : 2.20 (s, 3H, Ar-H); 3.70 (s, 3H, Ar-OCH_3); 2.85 (dd, 1H, >CHH_A); 3.40 (dd, 1H, >CHH_B); 5.25 (dd, 1H, >CH_X); 6.8 - 7.4 (m, 7H, Ar-H); (VIa) m.p. 178ºC; yield 75%, (VIc) m.p. 117ºC; yield 72%, (VId) m.p. 129ºC; yield 70%.

Synthesis of 3-(2-acetoxy-3-nitro-5-methylphenyl)-5-(4-methoxyphenyl) isoxazoline (VIIb)

A mixture of 3-(2-hydroxy-3-nitro-5-methylphenyl)-5-(4-methoxyphenyl) isoxazoline (**Vb**); (1 g) acetic anhydride (5 mL) and fused sodium acetate (0.5 g) was refluxed for about 45 min. After cooling the reaction mixture was diluted with water. The solid separated was filtered and crystallized from ethanol to get the compound (VIIb) m.p. 135ºC; yield 75%, IR (Nujol, cm^{-1}) : 1690 ν(C=O stretching in ester); 1180 ν(C-O stretching in ester), 1610 ν(C=N stretching in isoxazoline); 1530 and 1460 ν(C-NO_2 stretching); 1230 ν(Ar-H stretching); 1060 ν(C-O stretching in ether); UV-Vis ($CHCl_3$) : λ_{max} 345 nm corresponding to n → π* transition; PMR ($CDCl_3$; δ) : 2.2 (s, 3H, Ar-CH_3); 2.30 (s, 3H-Co-CH_3); 3.70 (s, 3H-OCH_3); 3.20 (dd, 1H >CHH_A); 3.64 (dd, 1H >CHH_B); 5.38 (dd, 1H > CH_X); 6.7 - 7.5 (m, 6H, Ar-H), (VIIa) m.p. 119ºC; yield 74%, (VIIc) m.p. 147ºC; yield 79%, (VIId) m.p. 153ºC; yield 85%.

Synthesis of 3-(2-acetoxy-3-nitro-5-methylphenyl)-5-(4-methoxyphenyl)thioisoxazoline (VIIIb)

A mixture of 3-(2-hydroxy-3-nitro-5-methylphenyl)-5-(4-methoxyphenyl) thioisoxazoline (**VIb**); (1 g) acetic anhydride (5 mL) and fused sodium acetate (0.5 g) was refluxed for about 45 min. After cooling the reaction mixture was diluted with water. The solid separated was filtered and crystallized from ethanol to get the compound (VIIIb) m.p. 191ºC; yield 85%, IR (Nujol, cm^{-1}) : 1710 ν(C=O stretching in ester); 1190 ν(C-O stretching in ester), 1630 ν(C=N stretching in thioisoxazoline); 1550 and 1430 ν(C-NO_2 stretching); 1240 ν(Ar-H stretching); 670 ν(C-S stretching in thioisoxazoline); 1070 ν(C-O stretching in ether), UV-Vis ($CHCl_3$) : λ_{max} 338 nm, corresponding to n → π* transition; PMR ($CDCl_3$; δ) : 2.20 (s, 3H, Ar-CH_3); 2.35 (s, 3H-$COCH_3$); 3.65 (s, 3H-OCH_3); 3.30 (dd, 1H >CHH_A); 3.60 (dd, 1H > CHH_B); 5.30 (dd, 1H >CH_X); 6.9 - 7.3 (m, 6H,Ar-H), (VIIIa) m.p. 121ºC; yield 80%, (VIIIc) m.p. 161ºC; yield 75%, (VIIId) m.p. 139ºC; yield 78%.



Scheme-1

Synthesis of chalones, flavanones, isoxazolines, thioisoxazolines, acetyl isoxazolines and acetyl thioisoxazolines

TABLE
PHYSICAL CHARACTERIZATION DATA OF SYNTHESIZED COMPOUND

Sr. No.	Comp.	Substituents		m.f.	m.w.	'N' (%)		m.p. (ºC)	Yield (%)
		R_1	R_2			Obs.	Calcd.		
1	Va	H	H	$C_{16}H_{14}N_2O_4$	298	9.10	9.39	159	80
2	Vb	OCH_3	H	$C_{17}H_{16}N_2O_5$	328	8.35	8.54	215	75
3	Vc	H	NO_2	$C_{16}H_{13}N_3O_6$	343	11.97	12.24	231	78
4	Vd	O, O	CH_2	$C_{17}H_{14}N_2O_6$	342	7.90	8.19	217	85
5	VIa	H	H	$C_{16}H_{13}N_2O_3S$	314	8.75	8.91	178	75
6	VIb	OCH_3	H	$C_{17}H_{16}N_2O_4S$	344	8.05	8.14	163	80
7	VIc	H	NO_2	$C_{16}H_{13}N_3O_5S$	369	11.15	11.38	117	72
8	VId	O, O	CH_2	$C_{17}H_{14}N_2O_5S$	368	7.51	7.61	129	70
9	VIIa	H	H	$C_{18}H_{16}N_2O_5$	340	8.10	8.23	119	74

Sr. No.	Comp.	Substituents		m.f.	m.w.	'N' (%)		m.p. (ºC)	Yield (%)
		R_1	R_2			Obs.	Calcd.		
10	VIIb	OCH_3	H	$C_{19}H_{18}N_2O_6$	370	7.35	7.57	135	75
11	VIIc	H	NO_2	$C_{18}H_{15}N_3O_7$	385	10.70	10.91	147	79
12	VIId	O O	CH_2	$C_{19}H_{16}N_2O_7$	384	7.11	7.29	153	85
13	VIIIa	H	H	$C_{18}H_{16}N_2O_4S$	356	7.67	7.86	191	80
14	VIIIb	OCH_3	H	$C_{19}H_{18}N_2O_5S$	386	7.01	7.25	121	85
15	VIIIc	H	NO_2	$C_{18}H_{15}N_3O_6S$	401	10.23	10.47	161	75
16	VIIId	O O	CH_2	$C_{19}H_{16}N_2O_6S$	400	6.79	7.00	139	78

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