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Synthesis of Some Nitrosubstituted Flavanones, Pyrazolines and Their Derivatives

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2-Hydroxy-3-nitro-5-methyl acetophenone (**Ia**) condenses with 3,4-substituted benzaldehyde (**IIa–d**) in ethanol medium in presence of aqueous NaOH to give chalcones (**IIIa–d**). Chalcones (**IIIa–d**) refluxed with 80% ethanol and concentrated sulphuric acid to give flavanones (**IVa–d**). Chalcones (**IIIa–d**) reacted with hydrazine hydrate in ethanol to give pyrazolines (**Va–d**). Chalcones (**IIIa–d**) or flavanones (**IVa–d**) refluxed with hydrazine hydrate, piperidine and ethanol to give same pyrazolines (**Va–d**). Pyrazolines (**Va–b**) reacted with acetic acid to form 1-acetyl pyrazolines (**VIa–b**). Pyrazolines (**Va–b**) or 1-acetyl pyrazolines (**VIa-b**) reacted with acetic anhydride and a pinch of anhydrous sodium acetate to give 1-acetyl-2-acetoxy pyrazolines (**VIIa–b**). Pyrazolines (**Va–b**) were condensed with benzoyl chloride in pyridine medium to give 1-benzoyl pyrazolines (**VIIIa–b**). The structures of all compounds were established on the basis of spectral data (UV, IR, PMR), elemental analysis and chemical properties.

Key Words: Synthesis, Chalcones, Flavanones, Pyrazolines, Pyrazoline derivatives.

INTRODUCTION

Flavanones, pyrazolines and its pyrazolines are known to have bactericidal, fungicidal and insecticidal properties. Flavanones are also reported to have antifungal activities in relation to degree of hydroxylation, methoxylation and glycosidation. Flavanones are antioxidants, preventing heart disease. Therefore they are used as potential cancer chemopreventive agents[1–3]. Some pyrazolines are also reported to have antiinflammatory, antidiabetic and analgesic properties. Pyrazolines and substituted pyrazolines have been reported as antibacterial and antimicrobial agents and have biological activities[4–11].

Chalcones and flavanones[12–18] are interconvertible by acid or alkali catalyzed ring chain tautomerism. Chalcones reacted with hydrazine hydrate in ethanol to give 1-H pyrazolines[19–28] as the same compound which was synthesized pre-

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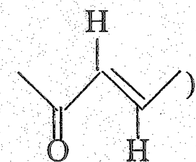
viously from flavanones or chalcones by using EtOH, hydrazine hydrate and piperidine as the reaction medium.

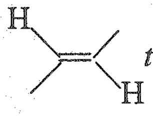
The present work deals with the synthesis of flavanones from chalcones in acidic medium, synthesis of pyrazolines from chalcones and flavonones in alkaline medium and synthesis of some derivatives of pyrazolines. All these compounds have been established on the basis of chemical properties, elemental analysis, spectral analysis (UV, IR, PMR).

EXPERIMENTAL

Purity of compounds was checked by TLC on silica gel-G layers. The melting point were reported on "Tempo" melting point apparatus as well as observed in Thiel's melting point tube containing open capillary tube and are uncorrected. IR spectra were recorded on PE-983/PE-781 IR spectrophotometer, UV on Varian Cary 2390 UV spectrophotometer and PMR on DSX-300 Hz solid state FTNMR spectrophotometer.

Synthesis of 1-(2-hydroxy-3-nitro-5-methylphenyl)-3-(3-nitrophenyl)-2-propen-1-one (IIIa–d)

2-Hydroxy-3-nitro-5-methyl acetophenone **(Ia)** (0.01 mol) was dissolved in ethanol (100 mL) followed by the addition of 3-nitrobenzaldehyde **(IIa)** (0.01 mol) solution and the solution was heated to near boiling. To this hot solution, aqueous NaOH (40%, 30 mL) was added dropwise with vigorous stirring. After some time, a coloured solid was obtained which was kept overnight and acidified by 10% HCl, washed by 10% $NaHCO_3$ followed by water and crystallized from ethanol to give yellow crystals of chalcone **(IIIa),** m.p. 225°C, yield 75%, m.f. $C_{16}H_{12}O_6N_2$, m.w. 328. IR (Nujol, cm^{-1}): 3100 ν(typical of orthohydroxy acetophenone, O—H str., H bonded), 1650 ν(C═O str., cross conjugated diene), 1580 ν(C═C str., conjugated with C═O), 1525 and 1350 ν(C—NO_2 str.), 1440 and 1460 ν(asym. str. in 

), 1275 ν(

trans), 1170 and 1210 ν(C—O str. in phenol), 980 ν(C—H, out-of-plane) 960 and 900 ν(1, 2, 3, 5 arom. substitution, out-of-plane). UV-Vis (MeOH): λ_{max} 374 nm corresponding to n-π^* transition. PMR ($CDCl_3$, δ) : 2.34 (S, 3H, Ar-CH_3); 6.7 (d, 1H, ═CH—); 7.10 (d. 1H, ═CH—); 7.2–8.3 (m, 6H, Ar—H); 13.7 (S, 1H, Ar—OH);

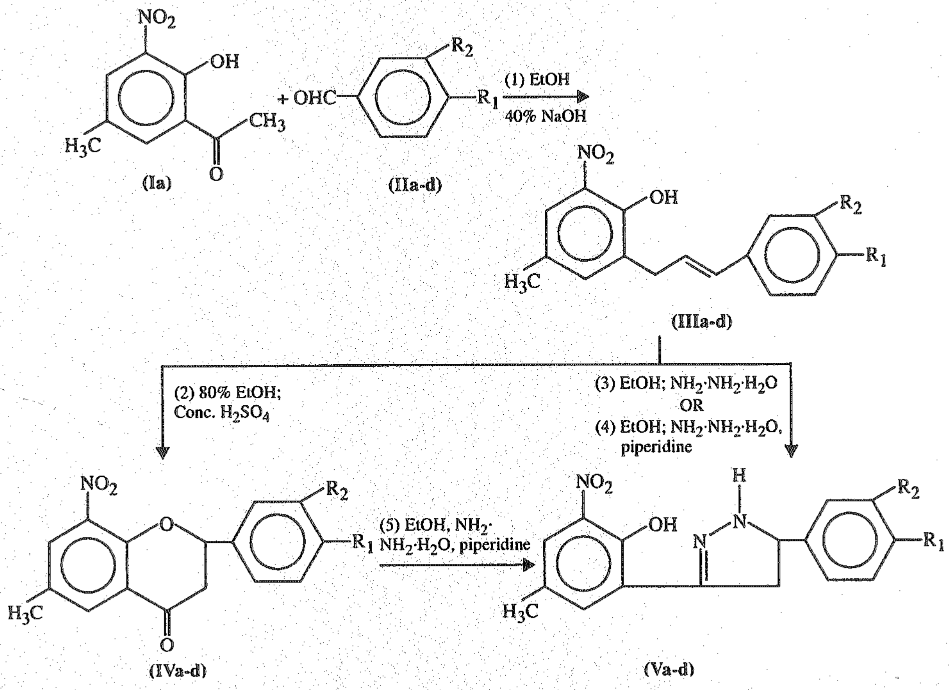
Synthesis of 3-nitro-6-methyl-8-nitroflavanone (IVa–d)

1-(2-Hydorxy-3-nitro-5-methylphenyl)-3-(3-nitrophenyl)-2-propen-1-one **(IIIa)** (0.01 mol) was refluxed in ethanol (80%, 100 mL) containing concentrated sulphuric acid (1 mL) for about 24 h. The crystals obtained were filtered off, dried, washed with 5% $NaHCO_3$ solution followed by water. The product was recrystallized from ethanol-acetic acid mixture (80 : 20) to obtain pale yellow crystals of flavanone **(IVa)**, m.p. 177°C, yield 80%, m.f. $C_{16}H_{12}O_6N_2$, m.w. 328.

(a) IR (Nujol, cm^{-1}): 1700–1550 ν(C—O str. cyclic ketone), 1310–1215 ν(—ArO str. arom. ether), 1090–1070 ν(asym. C—O—C str. cyclic 6-membered ether), 1545 ν(Ar—NO_2, asym. N—O str.), 1320 ν(Ar—NO_2 sym. N—O str.), 845 ν(Ar—NO, C—N str.). In addition to these peaks, other peaks characteristic of aromatic compounds were also observed. UV-Vis (MeOH): λ_{max} 270 nm and 339 nm corresponds to n-π* transition. PMR ($CDCl_3$, δ): 2.32 (S, 3H, Ar—CH_3); 2.90 (dd, 1H, —CHH_A); 3.15 (dd, 1H, —CHH_B); 5.57 (dd, 1H, —CH_X); 7.2–8.1 (m, 6H, Ar—H).

Synthesis of 3-(2-hydroxy-3-nitro-5-methylphenyl-1-H-5-(3-nitrophenyl)-Δ^2-pyrazolines (Va–d)

A mixture of 1-(2-hydroxy-3-nitro-5-methylphenyl) (3-nitrophenyl)-2-propen-1-one **(IIIa)** (0.01 mol) or 3-nitro-6-methyl-8-nitroflavanone **(IVa)** (0.01 mol) was refluxed in ethanol (50 mL) containing hydrazine hydrate (0.02 mol) and piperidine (1 mol) for about 2 h. After cooling, the reaction mixture was diluted with water and acidified with 50% HCl. The product separated was filtered and crystallized from ethanol-acetic acid mixture (80 : 20) to afford the same pale yellow coloured crystals of pyrazoline **(Va)** from both substrates **(IIIa)** and **(IVa)**, m.p. 190°C, yield 80%, m.f. $C_{16}H_{14}N_4O_5$, m.w. 342. IR (Nujol, cm^{-1}): 3860 ν(N—H str.); 3290 ν(O—H str.); 1695 ν(C═N of pyrazoline); 1344 ν(N—H str.); 1590 ν(C—NO_2 Str.); 1440 ν(C—NO_2 str.). UV-Vis (MeOH): λ_{max} 220 nm and 225 nm corresponding to n-π* transition. PMR ($CDCl_3$, δ): 2.15 (S, 3H, Ar—CH_3); 3.10 (dd, 1H, —CHH_A); 3.41 (dd, 1H, —CHH_B); 4.75 (dd, 1H, —CH_X); 5.8 (S, 1H, N—H) 6.45–7.45 (m, 6H, Ar—H); 11.75 (S, 1H, —OH).



Scheme-1

Synthesis of 3-(2-hydroxy-3-nitro-5-methyl phenyl)-1-acetyl-5-(3-nitrophenyl)-Δ^2- pyrazolines (VIa–d)

A mixture of 3-(2-hydroxy-3-nitro-5-methyl phenyl)-1-H-5-(3-nitrophenyl)-

Δ^2-pyrazolines **(Va)** (1 g) acetic acid (10 mL) was refluxed for about 2 h. The reaction mixture was then concentrated and allowed to cool. The solid product was filtered, washed with water and crystallized from ethanol to obtain greenish yellow crystals of 1-acetyl pyrazoline **(VIa)**, m.p. 163°C, yield 70%, m.f. $C_{18}H_{16}O_6N_4$, m.w. 384. IR (Nujol, cm^{-1}): 3340–3290 ν(O—H str.); 1650 ν($\text{—N—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}CH_3$); 1610 ν(C═N of pyrazoline); 1560 ν(C—NO_2 str.); 1470 ν(C—NO_2 str.); 1170 ν(C—O str. in phenolic compound); 1220 ν(C—N str.). UV-Vis (MeOH): λ_{max} 210 nm, 250 nm and 330 nm corresponding to n-π* transition. PMR ($CDCl_3$, δ): 2.22 (S, 3H, Ar—CH_3); 230 (S, 3H, —$COCH_3$); 3.20 (dd, 1H, —CHH_A); 3.62 (dd, 1H, —CHH_B); 5.35 (dd, 1H, —CH_X); 6.8–7.5 (m, 7H, Ar—H)

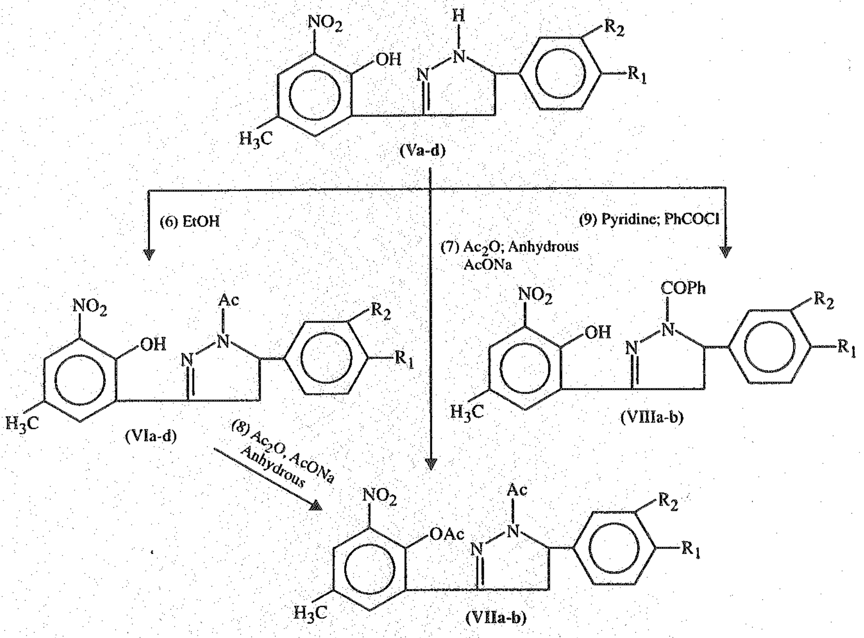
Synthesis of 3-(2-acetoxy-3-nitro-5-methylphenyl)-1-acetyl-5-(3-nitrophenyl)-Δ^2-pyrazolines (VIIa)

A mixture of 3-(2-hydroxy-3-nitro-5-methylphenyl)-1-H-5-(3-nitrophenyl)-Δ^2- pyrazolines **(Va)** (1 g) or 3-(2-hydroxy-3-nitro-5-methylphenyl)-1-acetyl-5-(3-nitrophenyl)-Δ^2-pyrazolines **(VIa)** (1 g), acetic anhydride (10 mL) and a pinch of fused sodium acetate was refluxed for about 45 min. After cooling, the reaction mixture was diluted with water. The solid product separated was filtered and crystallized from ethanol to obtain pale green crystals of 1-acetyl-2-acetoxy pyrazoline **(VIIa)**, m.p. 146°C, yield 75%, m.f. $C_{20}H_{18}O_7N_4$, m.w. 425. IR (Nujol; cm^{-1}): 3340–3290 ν(O—H str.); 1680 ν(C═O str. in esters); 1640 ν($\text{—}\overset{|}{N}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}CH_3$); 1610 ν(C═N of pyrazoline); 1560 ν(C—NO_2 stretch); 1470 ν(C—NO_2 str.); 1180 ν(C—O in ester). UV-Vis (MeOH): λ_{max} 225 nm and 290 nm corresponding to n-π* transition. PMR ($CDCl_3$, δ): 2.22 (S, 3H, Ar—CH_3); 2.30 (S, 6H, —$2COCH_3$); 3.06 (dd, 1H, —CHH_A); 3.68 (dd, 1H, —CHH_B); 5.38 (dd, 1H, —CH_X); 6.7–7.5 (m, 6H, Ar—H).

Synthesis of 3-(2-hydroxy-3-nitro-5-methyl phenyl)-1-benzoyl-5-(3-nitrophenyl)-Δ^2- pyrazolines (VIIIa–b)

A mixture of 3-(2-hydroxy-3-nitro-5-methyl phenyl)-1-H-5-(3-nitrophenyl)-Δ^2- pyrazolines **(Va)** (0.01 mol) and benzoyl chloride (0.01 mol) was dissolved in pyridine (10 mL) and stirred at room temperature for 1 h after which the reaction mixture was treated with cold dilute HCl. The resulting solid was filtered, washed successively with water, cold NaOH (2%) and water, and finally crystallized from ethanol to obtain pale yellow crystals of 1-benzoyl pyrazoline **(VIIIa)**, m.p. 187°C, yield 72%, m.f. $C_{23}H_{18}O_6N_4$, m.w. 446 . IR (Nujol; cm^{-1}): 3310–3270 ν(O—H str.); 1690 ν($\text{—}\overset{|}{N}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}$ str.); 1630 ν(C═N of pyrazoline); 1550 ν(C—NO_2 str.); 1370 ν(C—NO_2 str.); 1220 ν(C—H str.); 1160 ν(C—O str. in phenolic compound). UV-Vis (MeOH): λ_{max} 247 nm and 325 nm corresponding to n-π* transition. PMR ($CDCl_3$, δ): 2.15 (S, 3H, Ar—CH_3); 3.30 (dd. 1H,

—CHH_A); 3.65 (dd, 1H, —CHH_B); 5.32 (dd, 1H, —CH_X); 6.5 (S, 5H, $-\underset{\underset{O}{\|}}{C}-C_6H_5$) 7.2–7.9 (m, 7H, Ar—H).



Scheme-2

Similarly all other compounds of this series were prepared and their analytical data are recorded in Table-1.

TABLE-1

PHYSICAL CHARACTERIZATION DATA OF SYNTHESIZED COMPOUNDS

Compound	R_1	R_2	m.f.	m.w.	m.p. (°C)	Elemental analysis (%), N Found	Elemental analysis (%), N Calcd.	Yield (%)
IIIa	H	NO_2	$C_{16}H_{12}N_2O_6$	328	225	8.49	8.53	75
IIIb	—O—CH_2—O—		$C_{17}H_{13}NO_6$	327	257	4.11	4.28	70
IVa	H	NO_2	$C_{16}H_{12}N_2O_6$	328	177	8.41	8.53	80
IVb	—O—CH_2—O—		$C_{17}H_{13}NO_6$	327	198	4.17	4.28	76
IVc	H	H	$C_{16}H_{13}NO_4$	283	115	4.71	4.94	72
IVd	OCH_3	H	$C_{17}H_{15}NO_5$	313	133	4.39	4.47	78
Va	H	NO_2	$C_{16}H_{14}N_4O_5$	342	195	16.25	16.37	80
Vb	—O—CH_2—O—		$C_{17}H_{15}N_3O_5$	341	219	12.18	12.31	72
Vc	H	H	$C_{16}H_{15}N_3O_3$	297	137	13.97	14.14	85
Vd	OCH_3	H	$C_{17}H_{17}N_3O_4$	327	189	12.71	12.84	78
VIa	H	NO_2	$C_{18}H_{16}N_4O_6$	384	163	14.45	14.58	70
VIb	—O—CH_2—O—		$C_{19}H_{17}N_3O_6$	383	207	10.83	10.96	68
VIIa	H	NO_2	$C_{20}H_{18}N_4O_7$	426	146	13.01	13.14	75
VIIb	—O—CH_2—O—		$C_{21}H_{19}N_3O_7$	425	169	9.77	9.88	79
VIIIa	H	NO_2	$C_{23}H_{18}N_4O_6$	446	187	14.29	14.34	72
VIIIb	—O—CH_2—O—		$C_{24}H_{19}N_3O_6$	445	229	9.37	9.43	80

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