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Synthesis, characterization and antimicrobial activity of some novel pyrazolines

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ABSTRACT

A series of chlorosubstituted 4-Aroylpyrazolines have been synthesized by the interaction of Chlorosubstituted-3-Aroylfluvanones with phenyl hydrazine hydrochloride refluxing in ethanol medium with 0.5 ml of piperidine for two hours. Initially chlorosubstituted-3-Aroylflavanenes have been prepared by the interaction of different aldehydes with 1(2-hydroxy-3,5-dichloropheny)-3-phenyl-1,3-propendione constitution of synthesized compounds have been confirmed on the basis of elemental analysis, Molecular weight determination, UV-visible, I.R. and ^{1}H-NMR spectral studies. The titled compounds were evaluated for their antimicrobial activity.

KEY WORDS: Synthesis, chlorosubstituted, Aroyl, flavanones, pyrazolines.

INTRODUCTION

Heterocyclic compounds [1] promote the life on earth as they are widely distributed in nature and essential for the sustains of life. Any of the groups of heterocyclic compound containing three carbon atoms i.e. two adjacent nitrogen atom and one double bound in the ring is pyrazolines. Pyrazolines derivatives have been found to possess a board spectrum of biological activities. Such as anti-inflamatory [2], insecticidal [3], anti-tubercular [4], anti-tumor [5], tranquilizing [6], immunosuppressive [7], diuretic [8], anticonvulsant [9], Antifungal [10], Antidepressant activities [11] antibacterial activity [12], molluscidal [13].

Synthesis, structural properties and bacterial activities of various 4-Aroylpyrazoline have been reported earlier. Here a method for synthesis of chlorosubstituted 4-aryolypyrazolines has been reported.

MATERIALS AND METHODS

The melting points of all synthesized compounds were recorded using hat paraffin bath and are uncorrected. Chemicals used were of A. R. Grade. ^{1}H NMR spectra using $COCl_3$. I.R. spectra were recorded on Perkin-Elmer spectrophotometer in the range 4000 – 400 Cm^{-1} in nujol mull and as KBr pellets. UV-Vis spectrums were recorded in nujol.

*** Synthesis of 2-benzouloxy-3-S-dichloroacetophenone (3a)**

2-Hydroxy-3, 5-dichloroacetophenone (2a) 0.04M and Bezoyl chlorides (0.05 Mol) were dissolved in 10% NaOH (30 ml). The reaction mixture was shaked for about half hour. The products thus separated was filtered washed wit water followed by Sodium bicarbonate (10%) washing and then again with water. The solid product thus separated was crystallized from ethanol.

*** Synthesis of 1-(-2-hydroxy-3, 5-dichlorophenyl)-3-phenyl-1, 3-propendione (4a)**

2-Benzoyloxy-3, 5-dichloroacetophenone (3a) 0.05 M was dissolved in dry pyridine (40 ml). The solution was warm up to 60°C and pulverized KOH (15 gm) was added slowly with constant stirring. The reaction mixture was kept for overnight and then acidified by adding ice cold HCl (20%). The brownish yellow solid product thus separates was filtered, washed with sodium bicarbonate solution (10%) and finally again with water. It was then crystallized from ethanol to get the compound 4a.

*** Synthesis of 3-benzoyl-2-(4-Nitrophenyl-)-6, 8-dichloroflavonone (5a)**

A mixture of 1-(2-hydroxy-3, 5-dichlorophenyl)-3-phenyl-1, 3-propendione (4a) 0.01 M and P-nitrobenzaldehyde (0.02M) was refluxed in ethanol (25 ml) containing 0.5 ml piperidine for 15 – 20 min. After cooling the reaction mixture was acidified with dil. HCl (20%). The product thus separate was crystallized from ethanol to get the compound (5a).

Similarly other chlorosubstituted flavanones (5b and 5c) were synthesized from 4a by using P-chlorobenzaldehyde and valeraldehyde respectively.

*** Synthesis of 3-(-2-hydroxy-3, 5-dichlorophenyl)-4-benzoly-5-(4-Nitrophenyl)-1-phenyl Δ^2 pyrazoline (6a)**

A mixture of 3-benzoyl-2-(4-Nitrophenyl)-6,8-dichloroflavanone (5a) 0.01 M and phenyl hydrazine hydrochloride 0.02 M was refluxed in ethanol (20 ml) containing 0.5 ml piperidine for two hours. After cooling the reaction mixture was diluted with water. The product thus separated was filtered crystallized from ethanol.

Similarly other compounds 6b – 6c were synthesized form 5b – 5c respectively.

The compound (5a): yield 75%, M.P. 90°C (Found C = 59.68, H = 2.86, O = 18.00, Cl = 15.96, N = 3.10. Calculated for $C_{22}H_{13}O_5NCl_2$ C = 59.72, H = 2.94, O = 18.09, Cl = 16.06, N = 3.16%) λmax – 364 nm (n → π*) νmax 3050.5 (C-H streaching in Ar) 1611.4 (C=O), 1473.9 (C-NO_2), 1278 (-C-O), 1182.6 (-C-O) 717.7 cm^{-1} (-C-Cl). δ($CDCl_3$ solvent) 6.75 (1H, d, -C**H**-CH) 6.9 (1H, d, -CH-C**H**), 6.875 – 8.712 (11H, m, Ar-H)[13-14].

The compound (5b): yield 80%, M.P. 120°C (Found C = 61.10, H = 2.96, O = 11.00, Cl = 24.18,. Calculated for $C_{22}H_{13}O_3Cl_3$ C = 61.18, H = 3.01, O = 11.12, Cl = 24.68 %) λmax – 319 nm (n → π*) νmax 2928.6 (C-H streaching in Ar) 1612.6 (C=O), 1427.7 (C-H in Ar), 1086.5 (C-O), 764.6 cm^{-1} (-C-Cl). δ($CDCl_3$ solvent) 6.76 (1H, d, -C**H**-CH) 6.79 (1H, d, -CH-C**H**), 6.926– 8.315 (11H, m, Ar-H).

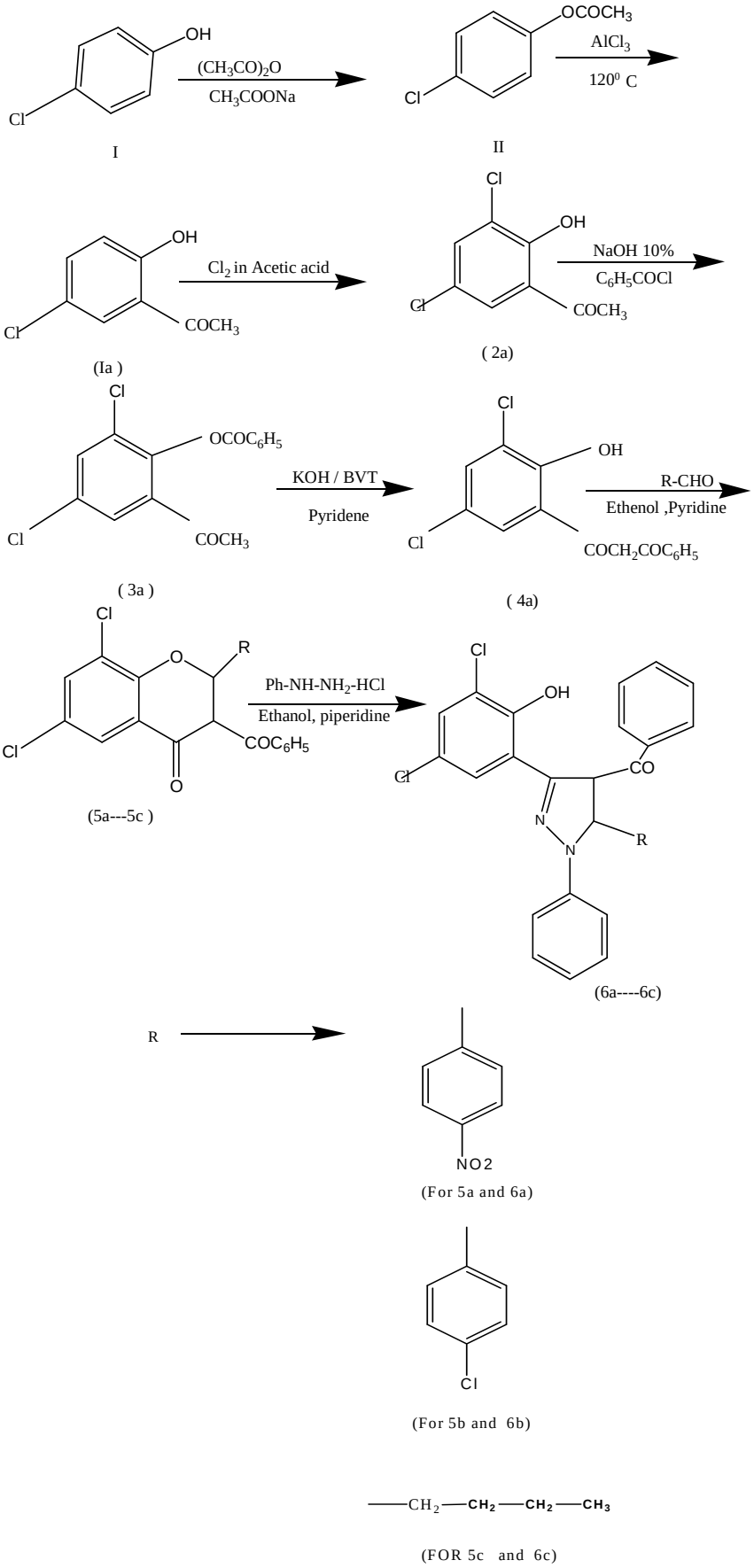
The compound (5c) : yield 80%, M.P. 192°C (Found C = 63.54, H = 4.50, O = 12.68, Cl = 18.75, Calculated for $C_{20}H_{18}O_3Cl_2$ C = 63.66, H = 4.77, O = 12.73, Cl = 18.83 %) λ max – 363 nm (n → π*) νmax 3068.7 (C-H stretching in Ar) 2866.4 (C-H stretching in Ar), 2866.4 (C-H in –$(CH_2)_3$-), 1689.5 (C=O), 1605.8 (C- H stretching in Ar) 1457.7 (-CH_3 Bending), 1286.3 (C – O in ether), 705.4 cm^{-1} (-C-Cl). δ($CDCl_3$ solvent) 0.90 (3H, t, $(CH_2)_3$-C**H**$_3$) 1.25 (2H, m $(CH_2)_2$-C**H**$_2$ – CH_3) 1.50 (2H, t, -CH_2-C**H**$_2$-CH_2-CH_3) 2.65 (2H, t, C**H**$_2$-$(CH_2)_2$-CH_3) 6.88 (1H, d, C-H), 6.93 (1H, d, C-H) 7.00 – 8.225 (7H, ,m, Ar-H).

The compound (6a) : yield 75%, M.P. 160°C (Found C = 63.10, H = 3.50, O = 12.00, N = 7.80, Cl = 13.25, Calculated for $C_{28}H_{19}O_4N_3Cl_2$ C = 63.15, H = 3.57, O = 12.03, N = 7.89, Cl = 13.34 %) λmax – 341 nm (n → π*) νmax 3438.6 (Strong intermolecular H-bended O-H streaching) 3071.8 (C-H streaching in Ar), 1598.2 (C=O), 1528 (C = N), 1348.2 (C – NO_2) 1260.3 (-C-O), 751.4 cm^{-1} (-C-Cl). δ($CDCl_3$ solvent) 6.5 (1H, d, -C**H**-CH-) , 6.7 (1 H, d, -CH-C**H**-) 6.80 – 8.98 (16 H, m, Ar–CH) 10.20 (1H, s, Ar-OH)

The compound (6b) : yield 80%, M.P. 155°C (Found C = 64.38, H = 3.60, O = 6.08, N = 5.30, Cl = 20.35, Calculated for $C_{28}H_{19}O_2N_2Cl_3$ C = 64.42, H = 3.64, O = 6.13, N = 5.36, Cl = 20.42 %) λmax – 320 nm (n → π*) νmax 3287 (O-H) 1597 (C=O), 1248 (-C-O), 768.3 cm^{-1} (-C-Cl). δ($CDCl_3$ solvent) 5.10 (1H, d, -C**H**-CH-) , 5.90 (1 H, d, -CH-C**H**-) 6.24 – 8.20 (16 H, m, Ar–CH) 9.98 (1H, s, Ar-OH)

The compound (6c) : yield 85%, M.P. 180°C (Found C = 66.74, H = 5.08, O = 6.80, N = 5.90, Cl = 15.10, Calculated for $C_{26}H_{24}O_2N_2Cl_2$ C = 66.80, H = 5.13, O = 6.85, N = 5.90, Cl = 15.20 %) λmax – 324 nm (n → π*) νmax 3421.3 (Ar O-H) 3060.1 (Ar - CH), 2924.4 (CH in alkane) 1764.2 (C=O), 1602.5 (-C = N), 1456.8 (CH_2-bending) 1188.6 (C-O) 764.9 cm^{-1} (-C-Cl). δ($CDCl_3$ solvent) 0.9 to 2.989 (9H, m, -$(CH_2)_3$-CH_3) 6.59 – 8.465 (15 H, m, Ar–H).

Scheme


OH
Cl
(CH3CO)2O
CH3COONa
I
OCOCH3
AlCl3
120⁰ C
II
Cl
OH
Cl2 in Acetic acid
COCH3
(Ia)
Cl
OH
NaOH 10%
C6H5COCl
COCH3
(2a)
Cl
OCOC6H5
COCH3
(3a)
KOH / BVT
Pyridene
Cl
OH
R-CHO
Ethenol ,Pyridine
COCH2COC6H5
(4a)
Cl
O
R
COC6H5
O
(5a---5c)
Ph-NH-NH2-HCl
Ethanol, piperidine
Cl
OH
CO
N
N
R
(6a----6c)
R
NO2
(For 5a and 6a)
Cl
(For 5b and 6b)
CH2—CH2—CH2—CH3
(FOR 5c and 6c)

Antifungal Activities:-

The synthesized compound 2a, 3a, 4a, 5a-5c, 6a-6c were screened for their antifungal activity using Cup plate diffusion method [15-17]. The fungi used were *Aspergillus niger, Rhizopus sp., Curvularia eryostides, Drecheslera tetrameda, Fusarium cicerg, Bipolaris sorokenia.* Sensitivity plates were seeded with fungal innoculum of 1 x 10^6 CIU ML^{-1} and each well (diameter 10 mm) was loaded with 0.1 mL of test compound solution 100 µg mL^{-1}. The zone of inhibition was recorded after incubation for 24 hrs at 37°C, using vernier caliper.

S. No.	Test Compound	Zone of inhibition (mm)					
		Aspergillus niger,	*Rhizopus sp.,*	*Curvularia eryostides,*	*Drecheslera tetrameda,*	*Fusarium cicerg,*	*Bipolaris sorokenia*
1	2 a	2	3	3	4	2	5
2	3 a	18	23	22	30	30	20
3	4a	5	12	8	7	6	10
4	5a	14	12	18	26	25	14
5	5b	13	13	15	24	20	16
6	5c	12	11	16	23	27	13
7	6a	10	10	18	30	8	10
8	6b	12	11	16	28	12	12
9	6c	14	10	15	27	16	12

RESULTS AND DISCUSSION

The compound 3a was prepared from 2-Hydroxy-3, 5-dichloroacetophenone (2a) and Bezoyl chloride dissolved in 10% NaOH. The mixture was shaked for about half an hour and product was filtered, washed with water followed by Sodium bicarbonate (10%) and then water. The product was crystallized from ethanol.

Compound 3a was dissolved in dry pyridine (40 ml) and warm up to 60°C then pulverized KOH 15 gm was added slowly with constant stirring. The reaction mixture kept for overnight and then acidified by adding ice cold HCl (20%). Thus product was separate washed with sodium bicarbonate and finally again with water. It was crystallized from ethanol. The synthesized compound was 1-C_2-Hydroxy-3, 5-dichlorophenyl)-3-phenyl-1, 3-propendione (4a).

The compound (4a) was refluxed with P-Nitrobenzaldehyde, P-chlorobenzaldehyde, Valeraldehyde in ethanol containing little (0.5 ml) piperidine for 15 – 20 min. separately. After cooling reaction mixture was acidified with dil. HCl (20%). The product thus separate was crystallized from ethanol to get compound 5a-5c respectively.

The compound 6a – 6c were prepared from 5a – 5c refluxing with Phenyl hydrazine hydrochloride in ethanol (30 ml) containing 0.5 ml piperidine for about two hours respectively. After cooling the reaction mixture was diluted with water. The product thus separated was filtered and crystallized from ethanol.

The synthesized compounds were screened on the basis of elemental analysis, molecular determination, U.V., I.R., N.M.R. spectral date analysis.

The synthesized compounds were screened for their antifungal activity using cup plate diffusion method. The fungi used were *Aspergillus niger, Rhizopus sp., Curvularia eryostides, Drecheslera tetrameda, Fusarium cicerg, Bipolaris sorokenia.* Inhibition zone record of the compounds that were active against all fungi sp. used. Compound 2a was less active, 4a moderately active and compound 3a, 5a, 5b, 5c and 6a, 6b, 6c were highly active.

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