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Synthesis of 1-Substituted-3-(2′-hydroxy-3′-chloro-5′-ethyl phen-1′-yl)-5-aryl-2-pyrazoline

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2′-Hydroxy-3′-chloro-5′-ethyl acetophenone chalcones (**1**) reacted with hydrazine hydrate in ethanol to give 1-H-3-(2′-hydroxy-3′-chloro-5′-ethyl phen-1′-yl)-5-aryl-2-pyrazolines (**2**), 1-benzoyl pyrazolines (**3**) and 1-nitroso pyrazolines (**4**) were prepared from pyrazolines (**2**) by reacting with benzoyl chloride in pyridine and sodium nitrite in HCl respectively. Structural elucidations were done on the basis of elemental and spectral analysis. The antibacterial activity has also been screened.

Key Words: Synthesis, Substituted pyrazoline, Chalcones, Antibacterial activity.

INTRODUCTION

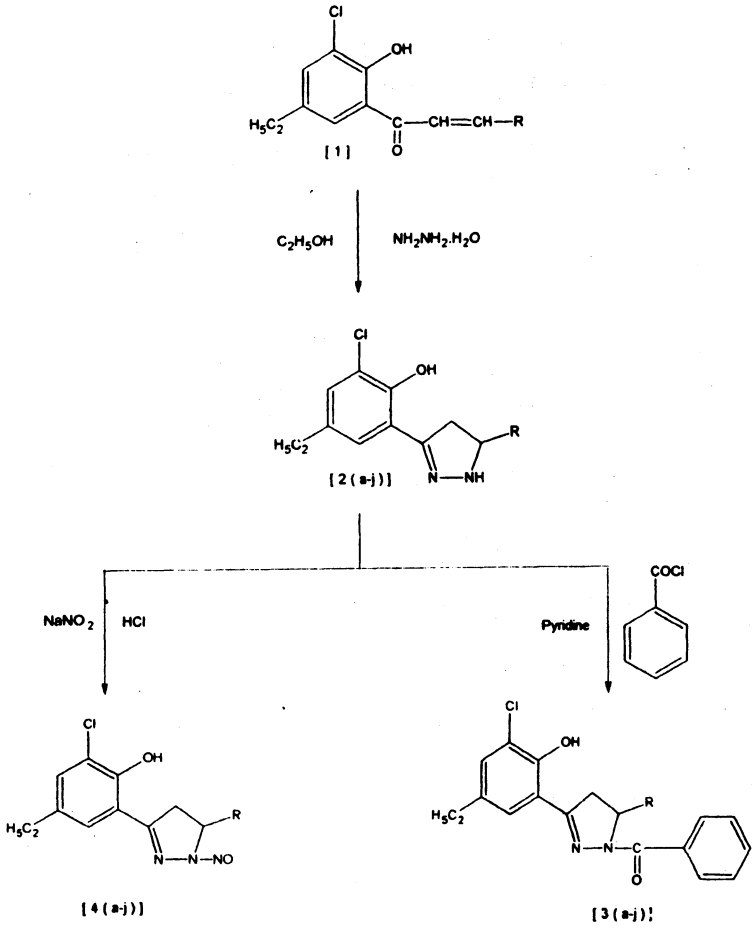
Pyrazoline is a dihydro form of pyrazole which is a five-membered ring containing adjacent nitrogen atoms. Several pyrazoline derivatives possess anti-inflammatory[1], anti-fertility[2], anti-implantantion[3] and insecticidal[4] activity. Pyrazolines were also found as effective chemical bleaching agents, luminescent and fluorescent agents[5, 6].

The most common method for the synthesis of pyrazolines[7–9] is the reaction of hydrazine or substituted hydrazines on α,β-unsaturated carbonyl compounds like chalcones in different solvents like DMSO, acetic acid, ethanol containing a small amount of HCl.

In the present work, 2′-hydroxy-3′-chloro-5′-ethyl acetophenone chalcones[10] (**1**) reacted with hydrazine hydrate in ethanol to give 1-H-3-(2′-hydroxy-3′-chloro-5′-ethyl phen-1′-yl)-5-aryl-2-pyrazolines (**2**). The reaction of (**2**) with benzoyl chloride gave 1-benzoyl-3-(2′-hydroxy-3′-chloro-5′-ethyl phen-1′-yl)-5-aryl-2-pyrazolines. The pyrazolines further reacted with sodium nitrite to give 1-nitroso-3-(2′-hydroxy-3′-chloro-5′-ethyl phen-1′-yl)-5-aryl-2-pyrazolines.

EXPERIMENTAL

All the melting points were determined on a PMP-DM Scientific melting point apparatus and are uncorrected. The purity of compounds was checked by TLC on silica gel-G coated glass plates. IR spectra were recorded with KBr on Perkin-Elmer-377 spectrophotometer, ^{1}H NMR spectra on a Brucker DRX-300 in $CDCl_3$ at 200 MHz using TMS as an internal standard.



Scheme-1

Preparation of 1-H-3-[2′-hydroxy-3′-chloro-5′-ethyl phen-1′-yl]-5-aryl-2-pyrazolines [3(a–j)]

A mixture of 2′-hydroxy-3′-chloro-5′-ethyl acetophenone chalcones (0.01 mol) and 99% hydrazine hydrate (0.015 mol) in ethanol (50 mL) was refluxed on a water bath (70–80°C) for 4 h. The mixture was concentrated and allowed to cool. The resulting solid was washed with ethanol and crystallized from ethanol to obtain pyrazolines **(2).**

Following the same procedure, all the compounds of this series were prepared. Their characterization data are recorded in Table-1.

Preparation of 1-benzoyl-3-[2′-hydroxy-3′-chloro-5′-ethyl phen-1′-yl]-5-aryl-2-pyrazolines [3(a–j)]

A mixture of **(2)** (0.001 mol) and benzoyl chloride (0.011 mol) was dissolved in dry pyridine (10 mL) and stirred at room temperature for 1 h. It was then treated with hydrochloric acid (2 N). The solid obtained was filtered, washed with water

and cold NaOH (2%), dried and crystallized from glacial acetic acid to yield benzoyl pyrazolines **(3).**

Following the same procedure, all the compounds of this series were prepared. Their characterization data are recorded in Table-2.

Preparation of 1-nitroso-3-[2′-hydroxy-3′-chloro-5′-ethyl-phen-1′-yl-5-aryl-2-pyrazolines [4(a–j)]

Compound **(2)** (0.002 mol) was dissolved in 1 : 1 hydrochloric acid (2 mL) and then cooled in an ice-bath. Cold solution of sodium nitrite (6 mol) was added dropwise to the mixture with continuous stirring. The mixture was stirred for a further 30 min at room temperature. The solid residue was filtered, washed with distilled water, dried and crystallized from ethanol to give nitroso pyrazolines **(4).**

Following the same procedure, all the compounds of this series were prepared. Their characterization data are recorded in Table-3.

TABLE-1
CHARACTERIZATION DATA OF COMPOUNDS [2(a–j)]

Compd.	R	m.p. (°C)	Yield (%)	m.f. (m.w.)	Found (Calcd.) (%)		
					C	H	N
2a	phenyl	165	63	$C_{17}H_{17}N_2OCl$ (300.78)	67.88 (67.82)	5.70 (5.75)	9.31 (9.36)
2b	4-chloro phenyl	173	65	$C_{17}H_{16}N_2OCl_2$ (335.22)	60.91 (60.97)	4.81 (4.86)	8.36 (8.39)
2c	2,4-dichloro phenyl	196	55	$C_{17}H_{15}N_2OCl_3$ (369.67)	55.23 (55.27)	4.09 (4.07)	7.58 (7.52)
2d	2-hydroxy phenyl	184	57	$C_{17}H_{17}N_2O_2Cl$ (316.78)	64.46 (64.41)	5.41 (5.39)	8.84 (8.88)
2e	4-hydroxy phenyl	177	62	$C_{17}H_{17}N_2O_2Cl$ (316.78)	64.46 (64.50)	5.41 (5.56)	8.84 (8.81)
2f	4-methyl phenyl	188	64	$C_{18}H_{19}N_2OCl$ (314.80)	68.67 (68.62)	6.08 (6.05)	8.90 (8.95)
2g	3-nitro phenyl	245	68	$C_{17}H_{16}N_3O_3Cl$ (345.78)	59.05 (59.09)	4.66 (4.64)	12.15 (12.19)
2h	2-methoxy phenyl	181	59	$C_{18}H_{19}N_2O_2Cl$ (330.80)	65.35 (65.40)	5.79 (5.75)	8.47 (850)
2i	4-methoxy phenyl	198	63	$C_{18}H_{19}N_2O_2Cl$ (330.80)	65.35 (65.31)	5.79 (5.73)	8.47 (8.41)
2j	4-N,N-dimethyl amino phenyl	228	54	$C_{19}H_{22}N_3OCl$ (343.85)	66.37 (66.33)	6.45 (6.42)	12.22 (12.28)

TABLE-2
CHARACTERIZATION DATA OF COMPOUNDS [3(a–j)]

Compd.	R	m.p. (°C)	Yield (%)	m.f. (m.w.)	Found (Calcd.) (%)		
					C	H	N
3a	phenyl	151	65	$C_{24}H_{21}N_2O_2Cl$ (404.88)	71.19 (71.15)	5.23 (5.27)	6.92 (6.97)
3b	4-chloro phenyl	154	60	$C_{24}H_{20}N_2O_2Cl_2$ (439.33)	65.61 (65.66)	4.59 (4.51)	6.38 (6.41)
3c	2,4-dichloro phenyl	172	62	$C_{24}H_{19}N_2O_2Cl_3$ (473.77)	60.84 (60.87)	4.04 (4.10)	5.91 (5.67)
3d	2-hydroxy phenyl	168	60	$C_{24}H_{21}N_2O_3Cl$ (420.88)	68.49 (68.45)	5.03 (5.08)	6.66 (6.61)
3e	4-hydroxy phenyl	146	60	$C_{24}H_{21}N_2O_3Cl$ (420.88)	68.49 (68.44)	5.03 (5.06)	6.66 (6.62)
3f	4-methyl phenyl	162	62	$C_{25}H_{23}N_2O_2Cl$ (418.91)	71.68 (71.62)	5.53 (5.57)	6.69 (6.64)
3g	3-nitro phenyl	202	65	$C_{24}H_{20}N_3O_4Cl$ (449.88)	64.07 (64.02)	4.48 (4.42)	9.34 (9.39)
3h	2-methoxy phenyl	163	58	$C_{25}H_{23}N_2O_3Cl$ (434.91)	69.04 (69.08)	5.33 (5.38)	6.44 (6.41)
3i	4-methoxy phenyl	177	55	$C_{25}H_{23}N_2O_3Cl$ (434.91)	69.04 (69.02)	5.33 (5.37)	6.44 (6.49)
3j	4-N,N-dimethyl amino phenyl	198	65	$C_{26}H_{26}N_3O_2Cl$ (447.95)	69.71 (69.76)	5.85 (5.82)	9.38 (9.35)

TABLE-3
CHARACTERIZATION DATA OF COMPOUNDS [4(a–j)]

Compd.	R	m.p. (°C)	Yield (%)	m.f. (m.w.)	Found (Calcd.) (%)		
					C	H	N
4a	phenyl	140	62	$C_{17}H_{16}N_3O_2Cl$ (329.78)	61.91 (61.96)	4.89 (4.84)	12.74 (12.79)
4b	4-chloro phenyl	142	68	$C_{17}H_{15}N_3O_2Cl_2$ (364.22)	56.06 (56.09)	4.15 (4.19)	11.54 (11.56)
4c	2,4-dichloro phenyl	159	70	$C_{17}H_{14}N_3O_2Cl_3$ (398.67)	51.22 (51.28)	3.54 (3.59)	10.54 (10.59)
4d	2-hydroxy phenyl	153	59	$C_{17}H_{16}N_3O_3Cl$ (345.78)	59.05 (59.09)	4.66 (4.61)	12.15 (12.19)
4e	4-hydroxy phenyl	132	65	$C_{17}H_{16}N_3O_3Cl$ (345.78)	59.05 (59.01)	4.66 (4.63)	12.15 (12.11)
4f	4-methyl phenyl	151	67	$C_{18}H_{18}N_3O_2Cl$ (343.80)	62.88 (62.84)	5.28 (5.24)	12.22 (12.26)
4g	3-nitro phenyl	168	65	$C_{17}H_{15}N_4O_4Cl$ (374.77)	54.48 (54.44)	4.03 (4.07)	14.95 (14.99)
4h	2-methoxy phenyl	153	60	$C_{18}H_{18}N_3O_3Cl$ (359.80)	60.09 (60.04)	5.04 (5.09)	11.68 (11.64)
4i	4-methoxy phenyl	168	60	$C_{18}H_{18}N_3O_3Cl$ (359.80)	60.09 (60.07)	5.04 (5.01)	11.68 (11.63)
4j	4-N,N-dimethyl amino phenyl	165	62	$C_{19}H_{21}N_4O_2Cl$ (372.84)	61.21 (61.26)	5.68 (5.64)	15.03 (15.08)

TABLE-4
IR, ^{1}H NMR SPECTRAL DATA OF COMPOUNDS **2, 3 AND 4**

Compd.	IR (cm^{-1}) (KBr)	^{1}H NMR ($CDCl_3$) (δ ppm)
2a	850 (—C—Cl), 3046 (—OH), 1641 (C=N), 3362 (—NH)	5.46 (1H, s, —NH), 4.66 (4H, s, —CH_2), 9.1 (1H, s, —OH), 1.95 (3H, s, —CH_3), 7.00–7.23 (7H, m, Ar—H)
2c	842 (—C—Cl), 3041 (—OH), 1647 (C=N), 3368 (—NH),	5.44 (1H, s, —NH), 4.68 (4H, s, —CH_2), 9.3 (1H, s, —OH), 1.91 (3H, s, —CH_3), 7.10–7.28 (5H, m, Ar—H)
3e	835 (—C—Cl), 3053 (—OH), 1652 (C=N), 1352 (—C—N), 1706 (—C=O)	4.69 (4H, s, —CH_2), 9.7 (2H, s, —OH), 1.98 (3H, s, —CH_3), 7.15–7.32 (11H, m, Ar—H)
3f	853 (—C—Cl), 3050 (—OH), 1655 (C=N), 1345 (—C—N), 1716 (—C=O), 1312 (—CH_3)	4.65 (4H, s, —CH_2), 9.4 (2H, s, —OH), 1.92 (6H, s, —CH_3), 7.20–7.38 (10H, m, Ar—H)
4i	845 (—C—Cl), 3048 (—OH), 1655 (C=N), 1350 (—C—N), 1545 (—NO), 2830 (—OCH_3)	4.60 (4H, s, —CH_2), 9.2 (2H, s, —OH), 1.94 (3H, s, —CH_3), 7.09–7.41 (6H, m, Ar—H), 2.71 (3H, s, —OCH_3)
4j	850 (—C—Cl), 3046 (—OH), 1652 (C=N), 1348 (—C—N), 1556 (—NO), 1310 (—N(CH_3)2)	4.48 (4H, s, —CH_2), 9.3 (2H, s, —OH), 1.91 (3H, s, —CH_3), 7.11–7.32 (6H, m, Ar—H), 1.45 (6H, s, —N(CH_3)$_2$)

Antibacterial activity

The compounds were screened for antibacterial activity. Micro-organisms employed were gram-positive bacteria, *i.e.*, *Staphylococcus aureus* and gram-negative *Escherichia coli.* The cup-plate method was used for this process. The compounds were tested at the concentration of 50μg/mL in DMF for antibacterial activity. The results were compared against tetracycline and gentamycine at the same concentration. All compounds show the activity mild to moderate.

TABLE-5
ZONE OF INHIBITION OF COMPOUNDS **2, 3 AND 4** (mm)

No.	*S. aureus*	*E. coli*	No.	*S. aureus*	*E. coli*	No.	*S. aureus*	*E. coli*
2a	+++	++++	**3a**	+++	+++	**4a**	+++	+++
2b	+++	++++	**3b**	++	+++	**4b**	+++	+++
2c	++++	++++	**3c**	+++	++++	**4c**	+++	+++
2d	++	++	**3d**	++	+++	**4d**	+++	++++
2e	++	+++	**3e**	+++	+++	**4e**	++	+++
2f	+++	+++	**3f**	+++	++++	**4f**	+++	++++
2g	+++	++++	**3g**	+++	++++	**4g**	++	++++
2h	++	+++	**3h**	++	+++	**4h**	++	+++
2i	+++	++++	**3i**	+++	++++	**4i**	+++	+++
2j	+++	+++	**3j**	+++	++++	**4j**	+++	++++

ZONE OF INHIBITION OF STANDARD DRUGS (mm)		
Tetracycline	+++++	–
Gentamycine	–	+++++

Here, ++ = 5 to 7 mm, +++ = 8 to 10 mm, ++++ = 11 to 13 m, +++++ = 18 to 21 mm

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