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Synthesis and characterization of Pyrazoline derivatives

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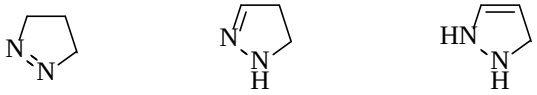
ABSTRACT

In the present study the synthesis of pyrazoline derivatives were carried out by cyclization of the chalcone with hydrazine hydrate in the presence of the formic acid. The synthesized pyrazoline derivatives were synthesized on the basis of prediction of activity spectra for substances (PASS). All the synthesized compounds were characterized by spectral analysis (^{1}H NMR).

Keywords: Pyrazole, Chalcone, Anti-Inflammatory, Analgesic, Antipyretic

INTRODUCTION

Among heterocyclic compounds, pyrazole is considered as a unique scaffold possessing nitrogen atom in the five membered ring. Pyrazoline or dihydropyrazole has three possible tautomeric forms: Δ^1-pyrazoline (**1**), Δ^2-pyrazoline (**2**), Δ^3-pyrazoline (3).[1]



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This template attracts attention because of its usefulness in drugs designing. Pyrazole displays various different pharmacological activities such as anti-inflammatory, antipyretic, analgesic[2], antimicrobial3, anticancer[4], antiviral[5], antihypertensive[6], antiglaucoma[7], antioxidant[8], antidepressant, anxiolytic, neuroprotective[9] and antidiabetic[10] activity There are some well-established pyrazoline nucleus containing drugs in market like Aminopyrine(Analgesic and antipyretic), Dipyrone (Analgesic), Antipyrine(antipyretic and anti-rheumatic), Phenylbutazone (NSAIDS), Zeleplon (Hypnotics and sedatives), Celecoxib (Osteoarthritis and rheumatoid arthritis inhibitors), Allopurinol (Treatment of goat),[5,7] dinitro indazole (Anti- bacterial), 7-amino 5- nitro indazole (Anti-bacterial), Muzolimine (Diuretics). Therefore there is always demand for new molecules, methodologies and improved protocols for synthesis. The present study deals with the synthesis of pyrazoline derivatives by cyclization of the chalchone with hydrazine hydrate in the presence of the formic acid.

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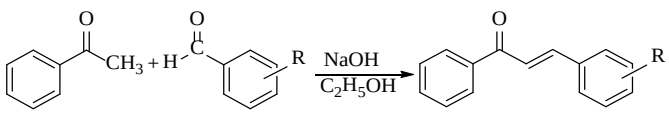
EXPERIMENTAL PROTOCOLS

2.1. Materials and methods

All reagents were purchased from commercial sources and were used without purification. Melting points of compounds were taken on melting apparatus andare uncorrected. The ^{1}H NMR spectra of compounds were recorded in $CDCl_3$ on Bruker AVANCE II 400 MHz spectrometer, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in δ ppm.

2.1.1. Synthesis of Substituted chalcone(3a-g)

2.1.1.1. General Procedure for synthesis of chalcones: Acetophenone (**1**, 1.86 g, 10 mmol) was treated with substituted benzaldehyde (**2a**, 1.08 ml,10 mmol) using ethanolic alkali (20 ml) as a solvent and stirred for15hrs at room temperature. The reaction mixture was kept overnight at 0^{o}C. The reaction mixture then poured into ice water and neutralized with dil HCl to give substituted chalcones **3a** in good yields.[11]



1 **2a-g** **3a-g**

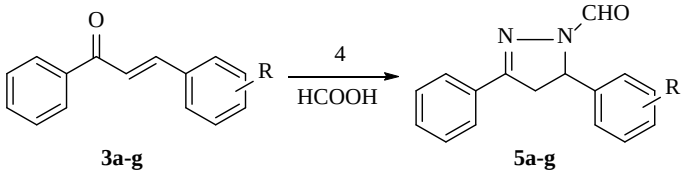
Scheme 1: Synthesis of Substituted chalcone (**3a-g**) from acetophenone (1) and substituted benzaldehydes (**2a-g).**

Similar procedure was adopted for synthesis of other derivatives (**3b-g**). The products were characterised by ^{1}H NMR. Table-1 lists M.P. and % yields of compounds **3a-g**.

Table 1: Physical data of synthesized compounds(**3a-g**)

R	Product	Mp (^{o}C)	Yields (%)
H	**3a**	56	82
4-CH_3	**3b**	89	92
4-OCH_3	**3c**	75	89
3,4-$(OCH_3)_2$	**3d**	78	88
2-OH	**3e**	148	57
4-Cl	**3f**	110	72
3-NO_2	**3g**	140	88

2.1.2. Synthesis of pyrazoline derivative (**5a-g**)



3a-g **5a-g**

Scheme 2: Synthesis of pyrazoline derivative (**5a-g**) from substituted chalcones(**3a-g**)

2.1.2.1. Procedure for synthesis of pyrazoline (**5a**). A mixture of Chalcone (**3**, 10.0mmol), hydrazine hydrate (**4**, 50.0mmol) and formic acid (40ml) were refluxed for 26 hours continuously. Reaction was monitored by TLC continuously using solvent system Petroleum ether:Ethylacetate (7:3)[12]. On completion of reaction (TLC monitoring) the resulting solution was poured into ice cold water and allowed to stand overnight. Precipitate formed were filtered and washed with cold water. The product was recrystallized with ethanol.

Similar procedure was adopted for synthesis of other derivatives(**5b-g**). All products satisfy the ^{1}H NMR spectroscopic data. M.P. and % yields of products **5a-g** are given in Table-2.

Table 2: Physical data of synthesized compounds (5a-5g)

R	Product	Mp (^{o}C)	Yields (%)
H	**5a**	145-146	94
4-CH_3	**5b**	110-111	92
4-OCH_3	**5c**	121-122	90
3,4-$(OCH_3)_2$	**5d**	115-116	88
2-OH	**5e**	140-141	63
4-Cl	**5f**	105-106	85
3-NO_2	**5g**	160–162	87

RESULT AND DISCUSSION

The condensation of acetophenone **1** with substituted aldehydes **2a-g** in ethanolic alkali yielded substituted chalcone **3a-g** which were purified by recrystallization in ethanol. All products were characterized by proton NMR spectroscopy. M.P. of these chalcones were recorded (uncorrected) and have been summarized in Table-1. Coupling constant values in ^{1}H NMR indicate trans geometry of carbon-carbon double bond. Pyrazoline derivatives **5a-g** were synthesized by reacting chalcones **3a-g** with hydrazine hydrate in formic acid. The products were recrystallized with ethanol. M. P. (Table-2) were recorded and ^{1}H NMR spectroscopic data satisfies the structure. N-formylation occurred *in situ*. Formyl group can be replaced by other groups by replacing formic acid with other acids.

2.3: ^{1}H NMR data of all synthesized compounds

(E)-Chalcone (**3a**): mp 56 -57°C, (82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−8.04 (m, 2H), 7.82 (d, J = 15.6 Hz, 1H), 7.49−7.66 (m, 6H), 7.40−7.44 (m, 3H),

4-Methylchalcone (**3b**): mp 89−90 °C (92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00−8.04 (m, 2H); 7.80 (d, J = 15.6 Hz, 1H), 7.48−7.61 (m, 6H), 7.23 (d, J =7.8 Hz, 2H), 3.08 (s, 3H),

4-Methoxychalcone (**3c**): mp 75-76 °C, (89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00−8.02 (m, 2H), 7.79 (d, J =16.0 Hz, 1H), 7.48−7.62 (m, 5H), 7.42 (d, J = 15.6 Hz, 1H), 6.92−6.95 (m, 2H), 3.86 (s, 3H)

2-hydroxychalcone{3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one} (**3e**): mp 148-149 °C, (57%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.17 (d, 1H, J = 16.40 Hz), 8.01–8.03 (m, 2H), 7.71 (d, 1H,J = 16.40 Hz), 7.55–7.59 (m, 2H), 7.47–7.51 (m, 2H), 7.28 (d, 1H, J = 8.00 Hz), 6.94 (t, 1H, J = 8.00 Hz), 6.90 (d, 1H, J = 8.00 Hz),6.58 (bs, 1H, OH),

4-Chlorochalcone (**3f**): mp 110−111 °C (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00−8.03 (m, 2H), 7.76 (d, J = 15.6 Hz, 1H), 7.56−7.62 (m, 3H), 7.55 (d, J = 15.6 Hz, 1H), 7.48−7.53 (m, 2H), 7.38−7.40 (m, 2H),

3-Nitrochalcone{3-(3-nitrophenyl)-1-phenylprop-2-en-1-one} (**3g**): mp 140−141 °C (88%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.23–8.51 (m, 2H), 8.02–8.05 (m, 2H), 7.92 (d, 1H, J = 7.60 Hz), 7.84 (d, 1H, J = 16.00 Hz), 7.67 (d, 1H, J = 16.00 Hz), 7.51–7.60 (m, 4H)

3,5-Diphenyl-4,5-dihydropyrazole-1-carbaldehyde (**5a**). Yield: 94%; mp: 145–147 C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.97 (s, 1H),7.75–7.73 (m, 2H), 7.45–7.42 (m, 3H), 7.36–7.28 (m, 5H), 5.54 (dd, J = 4.5,12.0 Hz, 1H), 3.82 (dd, J=12.0, 16.0 Hz, 1H), 3.22 (dd, J= 4.5, 16.0 Hz, 1H);

5-(4-Methylphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (**5b**). Yield: 92%; mp: 110–112 ºC; ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm):8.95 (s, 1H), 7.75-7.72 (m, 2H), 7.46–7.41 (m, 3H), 7.14(s,4H) , 5.51 (dd, J=4.92, 11.8 Hz, 1H), 3.79 (dd, J=11.8, 17.7, Hz, 1H), 3.23 (dd, J=4.92, 17.76 Hz,1H) 2.31 (s,3H)

5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (**5c**). Yield: 90%; mp: 121–123 ºC; ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm):8.94 (s, 1H), 7.75-7.73 (m, 2H), 7.45–7.43 (m, 3H), 7.19 (J=6.64 Hz, 2H), 6.86 (d, J=6.64 Hz, 2H), 5.50 (dd, J=4.8, 11.7 Hz, 1H), 3.78 (dd, J=11.7, 17.7, Hz, 1H), 3.21 (dd, J=4.6, 17.76 Hz,1H)

5-(3,4-Dimethoxyphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (**5d**). Yield: 88%; mp: 115–117 ºC; ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm):8.97 (s, 1H), 7.76-7.73 (m, 2H), 7.46–7.42 (m, 3H), 6.82-6.81 (d, 2H), 6.76 (s,1H), 5.50 (dd, J=4.9, 11.7 Hz, 1H), 3.85 (s, 3H), 3.84(s,3H), 3.80 (dd, J=11.7, 17.76 Hz,1H), 3.21 (dd, J=4.9, 17.7 Hz, 1H)

5-(2-Hydroxyphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (**5e**) Yield: 63%; 140–142 ºC; ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm):8.82 (s, 1H), 7.99-7.80 (m, 2H), 7.52–7.49 (m, 3H), 7.18-7.14 (m, 1H), 7.01-6.99 (m, 1H), 6.91-6.83 (m, 2H), 5.85 (dd, J=3.7, 11.4 Hz, 1H), 3.77 (dd, J=11.4, 18.04 Hz,1H), 3.21 (dd, J=3.7, 18.04 Hz, 1H)

5-(4-Chlorophenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (**5f**). Yield: 85%; mp: 105–107 ºC; ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm):8.98 (s, 1H), 7.75 (m, 2H), 7.47–7.42 (m, 3H), 7.33–7.30 (m, 2H), 7.21-7.18 (m, 2H), 5.52 (dd, J=4.9, 11.88 Hz, 1H), 3.81 (dd, J=11.8, 17.7 Hz,1H), 3.20 (dd, J=4.9, 17.7 Hz, 1H)

5-(3-Nitrophenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (**5g**). Yield: 87%; mp: 160–162 ºC; ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm):8.98 (s, 1H), 8.17-8.12 (m, 2H), 7.76–7.74 (m, 2H), 7.61 (d, 1H J=6.6), 7.54 (t, 1H J=7.8), 7.48-7.43 (m, 3H), 5.6 (dd, J=5.2, 11.9 Hz, 1H), 3.91 (dd, J=11.9, 17.8 Hz,1H), 3.21 (dd, J=5.2, 17.8 Hz, 1H)

CONCLUSION

In conclusion, we have synthesized a number of various pyrazoline derivative (**5a-g**). The reaction conditions were established and found to be reproducible. These derivatives may exhibit various pharmacological activities as indicated by PASS.[13]

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