SYNTHESIS AND CHARACTERIZATION OF SOME NEW PYRAZOLINE DERIVATIVES

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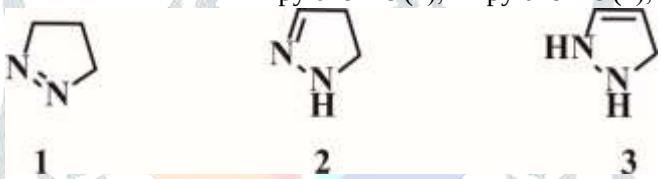
Abstract: Chalcones (**3a-f**) were synthesized by treating acetophenone with substituted benzaldehyde **(2a-f)** using ethanolic alkali as solvent**.** The synthesis of pyrazoline derivative **(5a-f)** were carried out by cyclization of the chalcones**(3a-f)** with hydrazine hydrate in the presence of the formic acid. To synthesize these new pyrazoline derivatives the prediction of activity spectra for substances (PASS) were used. Finally all the synthesized compounds were characterized by elemental analysis and spectral analysis.

Keywords: *Pyrazole, Chalcone, acetophenone, hydrazine hydrate.*

INTRODUCTION

Appreciable number of five membered heterocycles containing nitrogen atoms has turned out to be potential chemotherapeutic and pharmacotherapeutic agents. They exist in numerous natural products, displaying a wide range of biological and pharmaceutical activities[1].

Pyrazole is considered as a unique heterocyclic compounds 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]



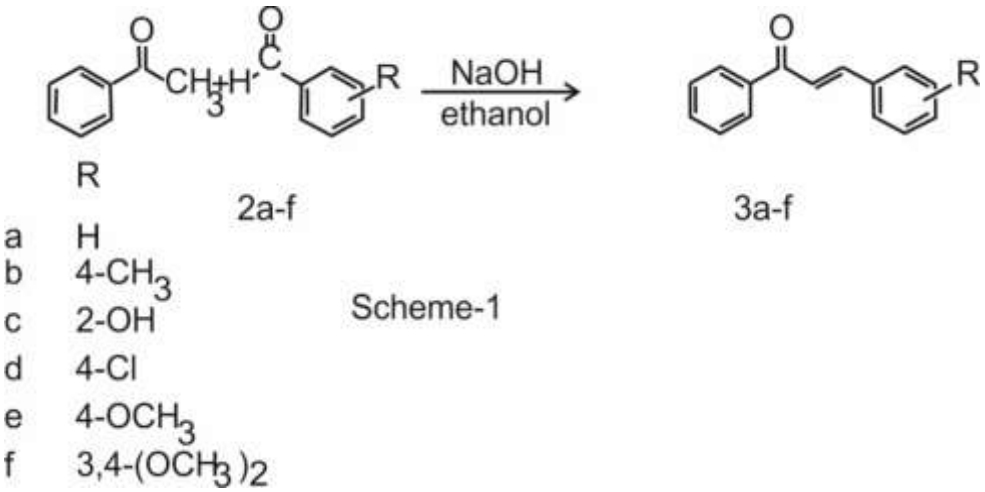
This temptate attracts attention because of its usefulness in drugs designing. Pyrazoline and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity[2], such as anti-inflammatory, antipyretic, analgesic[2], antimicrobial[3], anticancer[4], antiviral[5], anti-hypertensive[6], antiglaucoma[7], antioxidant[8], antidepressant, anxiolytic, neuroprotective[9] and antidiabetic[10] activity .Due to presence of many 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), it became the matter of attraction of attention to design useful drugs. Allopurinol). 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.

EXPERIMENTAL

Melting points of compounds were taken in open glass capillary tube and are uncorrected. The H NMR spectra of compounds were recorded in $CDCl_3$ on Bruker AVANCE II 400 MHz spectrometer, using TMS as an internal standard. Chemical shifts are expressed in δ ppm . All reagent were purchased from commercial source.

Synthesis of Substituted chalcone (3a-f)

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°C. The reaction mixture then poured into ice water and neutralized with dil HCl to give substituted chalcones **3a** in good yields.[11]



Scheme-1

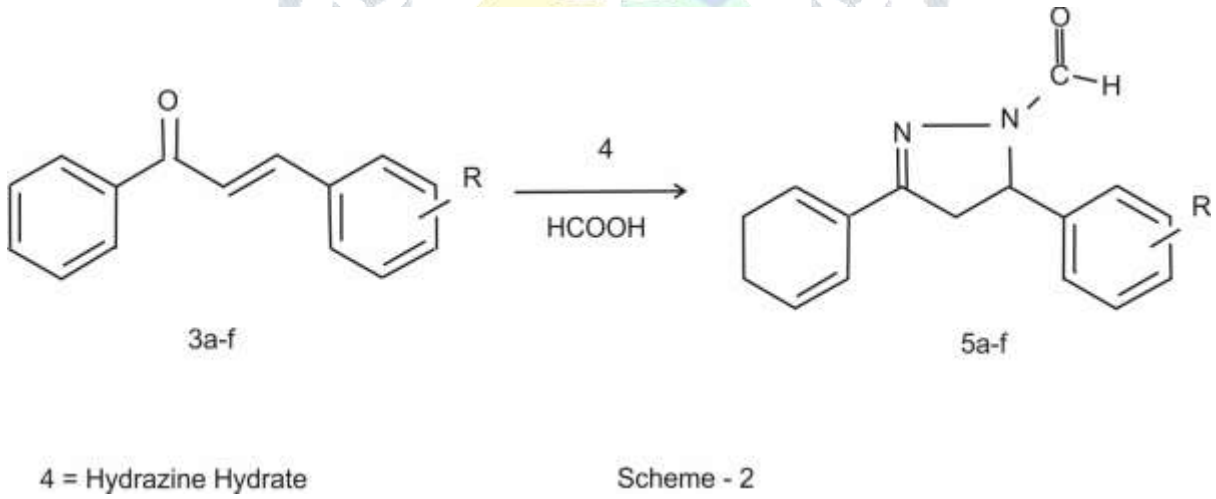
Scheme 1: **Synthesis of Substituted chalcone (3a-f) from acetophenone (1) and substituted benzaldehydes (2a-f).**

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

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

R	**Product**	**M.P. (℃)**	**Yields (%)**
H	3a	56-57	83
4- CH_3	3b	89-90	91
2- OH	3c	148-149	58
4 – Cl	3d	111-112	71
4- OCH_3	3e	75-76	89
3,4 –$(OCH_3)_2$	3f	78-79	88

Synthesis of Pyrazoline Derivative (**5a-f**)



Scheme - 2

Scheme-2 Synthesis of pyrazoline derivative (5a-f) from substituted chalcones(3a-f)

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 : Ethyl acetate (7:3) . 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-f**). All products satisfy the ^{1}H NMR spectroscopic data. M.P. and % yields of products **5a-f** are given in **Table-2.**

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

R	Product	M.P (℃)	Yields(%)
H	5a	144-145	95
4 –CH_3	5b	110-111	93
2– OH	5c	140-142	63
4–Cl	5d	105-107	85
4 –OCH_3	5e	121-123	90
3,4 – $(OCH_3)_2$	5f	116-117	88

RESULT AND DISCUSSION

The condensation of acetophenone **1** with substituted aldehydes(**2a-f)** in ethanolic alkali yielded substituted chalcone (**3a-f)** 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-f)** were synthesized by reacting chalcones (**3a-f)** 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.

^{1}H NMR data of all synthesized compounds

(E)-Chalcone (3a):mp 56 -57°C, (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−8.04 (m, 2H), 7.81 (d, J = 15.7 Hz,1H), 7.48−7.67 (m, 6H), 7.40−7.44 (m, 3H),

4-Methylchalcone (3b):mp 89−90 °C (91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.01−8.03 (m, 2H); 7.81 (d, J =15.6 Hz, 1H), 7.49−7.62 (m, 6H), 7.24 (d, J =7.8Hz, 2H), 3.08 (s, 3H),

2-hydroxychalcone{3-(2-hydroxyphenyl)-1-phenylprop- 2-en-1-one}(3c):mp148-149°C, (58%);^{1}HNMR (400 MHz,$CDCl_3$):*δ* (ppm):8.16(d,1H,J=16.40Hz),8.02–8.04(m,2H),7.72(d,1H,J=16.40Hz),7.55–7.59(m, 2H),7.48–7.52(m,2H),7.29(d,1H,J=8.01Hz),6.93(t,1H, J = 8.01 Hz), 6.92 (d, 1H, J = 8.01 Hz),6.58 (bs, 1H, OH),

4-Chlorochalcone (3d): mp 111−112 °C (71%); 1H NMR(400 MHz, CDCl3) δ (ppm): 8.01−8.03 (m, 2H), 7.75(d, J =15.6 Hz, 1H), 7.58−7.62(m, 3H), 7.57 (d, J = 15.5 Hz, 1H),7.48−7.55(m, 2H), 7.38−7.42(m, 2H),

4-Methoxychalcone (3e): mp 75-76 °C, (89%); 1H NMR(400 MHz, CDCl3) δ (ppm): 8.01−8.02 (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)

3,5-Diphenyl-4,5-dihydropyrazole-1-carbaldehyde (5a).Yield: 95%; mp: 144–145 C; 1H NMR (CDCl3, 400 MHz) δ(ppm): 8.96 (s, 1H),7.74–7.75 (m, 2H), 7.46–7.42 (m, 3H),7.36–7.29 (m, 5H), 5.53 (dd, J = 4.5,12.0 Hz, 1H), 3.82(dd, J=12.0, 16.0 Hz, 1H), 3.21 (dd, J= 4.5, 16.0 Hz,1H);

5-(4-Methylphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (5b).

Yield: 93%; mp: 110–111 ºC; 1H NMR(CDCl3, 400MHz) δ (ppm):8.94 (s, 1H), 7.75-7.72 (m, 2H),7.45–7.40 (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-(2-Hydroxyphenyl)-3-phenyl-4,5-dihydropyrazole-1- carbaldehyde (5c)

Yield: 63%; 140–142 ºC; ^{1}H NMR ($CDCl_3$,400MHz)δ(ppm):8.81(s,1H),7.99-7.80(m,2H),7.51–7.48(m,3H),7.18-7.14(m,1H),7.01-6.99(m,1H),6.91-6.82(m,2H),5.85(dd,J=3.7,11.4Hz,1H),3.76(dd,J=11.4, 18.04 Hz,1H), 3.21 (dd, J=3.7, 18.03 Hz, 1H)

5-(4-Chlorophenyl)-3-phenyl-4,5-dihydropyrazole-1- carbaldehyde (5d)

Yield: 85%; mp: 105–107 ºC; ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm):8.98 (s, 1H), 7.74 (m, 2H),7.46–7.42 (m,3H),7.34–7.30(m,2H),7.20-7.17(m,2H),5.52(dd, J=4.9, 11.87 Hz, 1H), 3.82 (dd, J=11.8, 17.7 Hz,1H), 3.20 (dd, J=4.9, 17.7 Hz, 1H)

5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (5e).
Yield: 90%; mp: 121–123 ºC; 1H NMR(CDCl3, 400MHz) δ (ppm):8.94 (s, 1H), 7.74-7.72 (m, 2H),7.45–7.43 (m, 3H), 7.18 (J=6.64 Hz, 2H), 6.86 (d, J=6.63Hz, 2H), 5.51 (dd, J=4.8, 11.7 Hz, 1H), 3.78 (dd, J=11.7,17.7, Hz, 1H), 3.22 (dd, J=4.6, 17.76 Hz,1H)

5-(3,4-Dimethoxyphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (5f).
Yield: 88%; mp: 116–117 ºC; 1HNMR (CDCl3, 400MHz) δ (ppm):8.96 (s, 1H), 7.76-7.73 (m,2H), 7.46–7.42 (m, 3H), 6.82-6.82 (d, 2H), 6.76 (s,1H), 5.51 (dd, J=4.9, 11.7 Hz, 1H), 3.86 (s, 3H), 3.84(s,3H), 3.80 (dd, J=10.7, 17.76 Hz,1H), 3.19 (dd, J=4.9, 17.7 Hz, 1H)

CONCLUSION

In conclusion, we have synthesized a number of various pyrazoline derivative (**5a-f**). The reaction conditions were established and found to be reproducible. These derivatives may exhibit various pharmacological activities.

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