



Comparative Analysis of Synthesis of A Few Novel 2-Pyrazoline Derivatives

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ABSTRACT

A popular group of nitrogen containing heterocyclic compounds, pyrazoles and pyrazolines [dihydropyrazoles] have been extensively studied. These compounds are easy to synthesize and moreover different moieties can be introduced in the hetero system with suitable reaction conditions. The biological activity that has been investigated include antibacterial, antimicrobial, antimalarial, antifungal, antitumor and anticancer amongst several others. Among all the pyrazolines, 2-pyrazoline have gained maximum attraction and is the most frequently studied one. Pyrazolines, synthesized from chalcones, have also been studied extensively for cytotoxicity. In the present work some novel 2-pyrazoline derivatives have been synthesized and characterized. For the synthesis conventional as well as non-conventional methods has been adopted and a comparative analysis has been studied.

Keywords: Pyrazolines, synthesis, conventional method, non-conventional method, characterization.

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INTRODUCTION

Many of the therapeutically useful compounds such as phenylbutazone, oxyphenbutazone, celecoxib, belonging to pyrazole class of compounds, a 2 Nitrogen containing 5-membered aromatic ring, exhibited antipyretic, anti-inflammatory and analgesic properties¹. Closely related to structure and properties are the pyrazoline derivatives, also recognized as 4, 5-dihydro-1-H-pyrazole derivatives. These derivatives also constitute an interesting class of organic compounds with diverse pharmacological activities. Some of the pharmacological activities reported are antibacterial², anti-inflammatory³, analgesic⁴, antidepressant⁵ and antitumor⁶. Fischer and Knoevenagel in the late 19th century⁷ were the first to discover pyrazolines, after which the reaction between α , β -unsaturated aldehydes and ketones with hydrazine and substituted hydrazines became one of the most popular method for the preparation of 2-pyrazolines⁸⁻¹⁰. Chalcones are prepared by condensation of aromatic aldehydes and acetophenone derivatives which undergo subsequent reactions with hydrazine yielding 2- pyrazolines¹¹.

Hydrazone derivatives are formed as intermediate compounds which are generally not isolated but readily cyclize to 2-pyrazolines in the presence of a suitable cyclizing reagent like acetic acid. Based on the spectrum of activity of pyrazolines, in the present study attempts have been done to synthesize a few 1, 3, 5-triarylsubstituted 2-pyrazolines. The novel compounds are prepared by condensation of a few selected aromatic aldehydes and acetophenone derivatives to form chalcones, which on reaction with phenyl hydrazine or its derivative are converted to 1,3,5-triaryl-4,5-dihydro-1-phenylpyrazoles or popularly known as 1,3,5-triaryl-2-pyrazoline derivatives. The conventional method involves refluxing the reactants with acetic acid for several hours with satisfactory yields of the product. An attempt has been made to enhance the quality and quantity of the pyrazoline derivatives by using non conventional methods.

Several successful reactions with a variety of modifications has been reported in literature, particularly with respect to solvent system¹² and energy source. 2-pyrazoline derivatives have also been synthesized using sonochemical methods¹³. Ultra sound irradiation has been reported as an efficient method of synthesis by several researchers^{14, 15} using different media successfully by reporting excellent yields and implementing green technology.

Recent reports of using microwave irradiation has proved to be an efficient method of synthesis¹⁶, which has given a platform to synthesize several derivatives with greater ease and efficiency. The method selected for investigation is microwave irradiation. The reaction progress has been

monitored by TLC to get optimum results. The synthesized compounds have been characterized and the structures have been confirmed by IR and ¹H NMR analysis.

MATERIALS AND METHOD

Determination of melting point

The melting points are recorded in open capillary tubes and are uncorrected.

Determination of purity

The purity of the compounds has been checked by TLC using ethyl acetate: methanol (2:8) as the mobile phase.

Spectral analysis of the compound

IR spectra (KBr) were recorded on Vertex 70 FT-IR Spectrometer and ¹H NMR spectra recorded on Varian USA, Mercury Plus 300 MHz NMR spectrometer using CDCl₃ as solvent and TMS as the internal standard.

Procedure for Synthesis of compounds

Step I: Preparation of 1-(substituted phenyl)-3-substitutedphenyl-2-propen-1-one (chalcones A-H)

A 10% ethanolic solution of KOH was added slowly with continuous stirring at 0 to 5 ° C to a mixture of 0.01 mol of the aromatic aldehyde and 0.01 mol of the acetophenone derivative in ethanol. The reaction mixture was stirred at 30 ° C for 24 hours and then poured into crushed ice and acidified with acetic acid. The solid that separated out was filtered, washed thoroughly with cold water, dried and crystallized from methanol.

Step II:Preparation of 3-(substituted phenyl)-5-substitutedphenyl-4,5-dihydro-1-phenyl pyrazole (pyrazoline derivatives P1 -P16)

Conventional method

A mixture of 0.01 mole of the chalcone and 0.01 mole of phenyl hydrazine or substituted phenylhydrazine in glacial acetic acid was refluxed for the specified reaction time at 110 ° C. The reaction mixture was cooled and poured into excess crushed ice. The solid that separated out was filtered, washed thoroughly with cold water till neutral to litmus, dried and crystallized from ethanol.

Non-conventional method

A mixture of 0.01 mole of the selected chalcone and 0.01 mole of phenylhydrazine or substituted phenylhydrazine in a small amount of glacial acetic acid was taken in a large flask fitted with a loose glass stopper and irradiated in a domestic microwave oven at 350 W for the required time

P5: R ¹ =OH,R ² ,R ⁵ =H, R ³ = HNCOCH ₃ , R ⁴ = Cl,R ⁶ ,R ₆ =NO ₂	P6: R ¹ =OH,R ² ,R ³ ,R ⁴ ,R ⁵ , R ⁶ ,R ₆ =H.
P7: R ¹ =OH,R ² ,R ³ ,R ⁵ , R ⁶ ,R ₆ =H, R ⁴ =Cl	P8: R ¹ =OH,R ² ,R ³ ,R ⁴ , R ₆ =H, R ⁵ = NO ₂ ,R ⁶ =NO ₂
P9: R ¹ =OH,R ² ,R ³ ,R ⁵ , R ₆ =H, R ⁴ =Cl,R ⁶ =NO ₂	P10: R ¹ =OH,R ² ,R ³ ,R ⁴ , R ⁵ =H, R ⁶ ,R ₆ = NO ₂ .
P11: R ¹ =OH,R ² ,R ³ ,R ⁴ =H, R ⁵ , R ⁶ ,R ₆ = NO ₂	P12: R ¹ =OH,R ² ,R ³ ,R ⁵ , =H, R ⁴ = Cl, R ⁶ ,R ₆ =NO ₂
P13: R ² =CH ₃ ,R ¹ ,R ³ ,R ⁵ , R ⁶ ,R ₆ =H, R ⁴ =Cl	P14: R ² =CH ₃ ,R ¹ ,R ³ ,R ⁵ , R ₆ =H, R ⁴ = Cl, R ⁶ =NO ₂ .
P15: R ² =CH ₃ ,R ¹ ,R ³ ,R ⁴ =H, R ⁵ ,R ⁶ ,R ₆ = NO ₂	P16: R ² =CH ₃ ,R ¹ ,R ³ ,R ⁵ , =H, R ⁴ =Cl, R ⁶ ,R ₆ =NO ₂ .

RESULTS AND DISCUSSION

Synthesis

The chalcones (A-H) were synthesized by Claisen –Schmidt condensation of the different acetophenone derivatives with selected aromatic aldehydes in an alkaline medium. These chalcones were further reacted with phenylhydrazine / 4-nitrophenylhydrazine / 2,4-dinitrophenylhydrazine in the presence of acetic acid to yield the 2- pyrazoline derivatives (P1–P16). The reaction for conventional method was heating at 110 ° C under reflux conditions for specific reaction time. Non conventional method involved irradiation of the reactants and the minimum amount of acetic acid. The mixture was taken in a bigger capacity flask and during the irradiation the flask was fitted with a loose glass stopper. The irradiation was done at 350 W for several cycles of 3 min durations and a break for about 30 secs in between. The progress of the product formation was monitored using TLC with similar solvent system as the conventional method, chloroform: methanol: ethylacetate (90:5:5) as a mobile phase. The pyrazoline derivatives with 2, 4-dinitrophenylhydrazine needed the longest reaction time whereas the phenylhydrazine derivatives obtained were obtained at relatively lower reaction time. The time required for completion of the product formation and the yields obtained are tabulated in Table 1 along with the reaction time and yields of the same products following the conventional reflux method. The physical data of the compounds are recorded in Table 2. The IR and ¹HNMR structural data of chalcones (A-H) and pyrazolines (P1– P16) have been tabulated in Table 3.

Table 1: Comparative Analysis between Conventional and Non Conventional Methods

Compd.	Molecular Formula	Conventional		Microwave	
		Yield	Time hrs	Yield %	Time min
P1	C ₂₃ H ₂₁ O ₂ N ₃	72	8	88	10
P2	C ₂₃ H ₂₀ O ₄ N ₄	65	8	94	10
P3	C ₂₃ H ₂₀ O ₂ N ₃ Cl	60	8	80	10
P4	C ₂₃ H ₁₉ O ₆ N ₅	72	10	75	15
P5	C ₂₃ H ₁₈ O ₆ N ₅ Cl	90	12	95	15
P6	C ₂₁ H ₁₈ ON ₂	67	8	76	8
P7	C ₂₁ H ₁₇ ON ₂ Cl	70	8	85	8
P8	C ₂₁ H ₁₆ O ₅ N ₄	78	10	88	10

P9	C ₂₁ H ₁₆ O ₃ N ₃ Cl	80	10	90	10
P10	C ₂₁ H ₁₆ O ₅ N ₄	60	12	70	15
P11	C ₂₁ H ₁₅ O ₇ N ₅	57	12	75	15
P12	C ₂₁ H ₁₅ O ₅ N ₄ Cl	80	12	85	15
P13	C ₂₁ H ₁₉ N ₂ Cl	65	8	85	8
P14	C ₂₂ H ₁₈ O ₂ N ₃ Cl	80	10	90	10
P15	C ₂₂ H ₁₇ O ₆ N ₅	68	12	85	15
P16	C ₂₂ H ₁₇ O ₄ N ₄ Cl	70	12	80	15

Table 2: Physical Data of chalcones and pyrazoline derivatives

Compd.	Molecular formula	Molecular Weight	Melting point °C	Yield %
A	C ₁₇ H ₁₅ O ₃ N	281	95	56
B	C ₁₇ H ₁₄ O ₅ N ₂	326	170	55
C	C ₁₇ H ₁₃ O ₃ NCl ₂	350	160	62
D	C ₁₅ H ₁₂ O ₂	224.25	162	66
E	C ₁₅ H ₁₁ O ₄ N	269.25	155	55
F	C ₁₅ H ₁₁ O ₂ Cl	258.70	135	90
G	C ₁₆ H ₁₃ O ₃ N	267.28	120	40
H	C ₁₆ H ₁₃ OCl	256.73	115	70
P1	C ₂₃ H ₂₁ O ₂ N ₃	371.40	102	72
P2	C ₂₃ H ₂₀ O ₄ N ₄	416.40	200	65
P3	C ₂₃ H ₂₀ O ₂ N ₃ Cl	405.80	130	60
P4	C ₂₃ H ₁₉ O ₆ N ₅	461.42	140	72
P5	C ₂₃ H ₁₈ O ₆ N ₅ Cl	485.87	165	90
P6	C ₂₁ H ₁₈ ON ₂	314	125	67
P7	C ₂₁ H ₁₇ ON ₂ Cl	348.5	140	70
P8	C ₂₁ H ₁₆ O ₅ N ₄	404	142	78
P9	C ₂₁ H ₁₆ O ₃ N ₃ Cl	393.55	130	80
P10	C ₂₁ H ₁₆ O ₅ N ₄	404.37	140	60
P11	C ₂₁ H ₁₅ O ₇ N ₅	449.37	145	57
P12	C ₂₁ H ₁₅ O ₅ N ₄ Cl	438.82	150	80
P13	C ₂₁ H ₁₉ N ₂ Cl	346.55	105	65
P14	C ₂₂ H ₁₈ O ₂ N ₃ Cl	391.55	185	80
P15	C ₂₂ H ₁₇ O ₆ N ₅	447	175	68
P16	C ₂₂ H ₁₇ O ₄ N ₄ Cl	436.55	185	70

Table 3: IR and ¹H NMR Spectral Data

Compd.	Analytical Data
A	<p>1-(5-acetamido-2-hydroxyphenyl)-3-phenyl-2-propen-1-one IR cm⁻¹: 3048 (OH), 2742 (NH), 1638 (C=O), 1570 (C=C), 1152 (aromatic H), 738 (p-subst.), 694 (o-subst). ¹H NMR δ ppm: 2.5(s, H, C=C), 3.3 (s, H, CH₃), 7.90 (m, H, aromatic), 12.5 (s, H, OH). Mass Spectrum: Molecular Ion Peak 282.3, a base peak at 240.3 and several fragmentation peaks at 264.3, 223.5, 204.3 and 162.2.</p>
B	<p>1-(5'-acetamido-2'-hydroxyphenyl)-3-(4-nitrophenyl)-2-propen-1-one IR cm⁻¹: 3283 (OH), 3106 (NH), 1702 (C=O), 1651 (C=C), 1514 (N-H), 1488 (N-O, asym), 1343 (N-O, sym), 834 (p-subst), 688 (o-subst).</p>

	¹ HNMR δ ppm: 2.5 (s,H,C=CH ₃), 3.4 (s,H, CH ₃) , 7.8 (m,H,aromatic), 10.0 (s,H,OH).
C	1-(5'-acetamido-2'-hydroxyphenyl)-3-(2-chlorophenyl)-2-propen-1-one IR cm ⁻¹ : 3290(OH), 2958(NH), 1641(C=O), 1513 (NH), 828 (p-subst.), 684 (o-subst.). Mass Spectrum: Molecular ion Peak 315.4, Base Peak 196.3.
D	3-(2-hydroxyphenyl)-1-phenyl-2-propen-1-one IR cm ⁻¹ : 3047 (OH), 1689 (C=O), 1638 (C=O), 1570 (C=C), 1485(aromatic H), 1202(aromatic H), 754 (o-subst.).
E	3-(2'-hydroxyphenyl)-1-(4-nitrophenyl)-2-propen-1-one IR cm ⁻¹ : 3378 (OH), 3079 (OH), 1701 (C=O), 1599 (C=C), 1517, 1345 (N=O), 1211 (C-O), 1107 (aromatic H), 852 (p-subst), 753 (o-subst.)
F	3-(2'-hydroxyphenyl)-1-(2-chlorophenyl)-2-propen-1-one IR cm ⁻¹ : 3358 (OH), 2924 (C=C), 1668 (CO), 1532 (C=C), 1485 (aromatic H), 740 (o-subst.), 673 (C-Cl). ¹ HNMR δ ppm: 2.5 (s,H,CH), 3.4 (s,H, CH) , 7.5 (m,H,aromatic), 12.2 (s,H,OH).
G	3-(4'-methylphenyl)-1-(4-nitrophenyl)-2-propen-1-one IR cm ⁻¹ : 3060 (C=C), 1594 (C=O), 1502,1455 (CH ₃), 1137 (aromatic H), 1073 (C=C), 821 (p-subst.)
H	3-(4'-methylphenyl)-1-(2-chlorophenyl)-2-propen-1-one IR cm ⁻¹ : 2921 (C=C), 1667 (C=O), 1605 (C=O), 1473, 1441(CH ₃), 1333 (C=O), 1035 (C=C), 825 (p-subst.), 751,728 (o- subst). ¹ HNMR δ ppm: 2.5 (s,H,CH), 3.2 (s,H,CH) , 7.0(m, H, aromatic).
P1	3-(5'-acetamido-2'-hydroxyphenyl)-1,5-diphenyl-4,5-dihydropyrazole IR cm ⁻¹ : 3282 (OH), 2922 (NH), 1660 (C-O of NCOCH ₃), 1597 (C=N), 1561 (aromatic H), 1371 (CH ₂ of pyrazoline ring), 1252 (OH), 1114 (C-N), 827 (p-subst.), 749, 691(o-subst.) . ¹ HNMR δ ppm: 2.0 (s,H,CH) ,2.5 (s,H,CH ₂), 3.5 (s,H ,CH ₃) , 7.50 (m, H, aromatic), 10.0 (s,H,NH), 11.9 (s,H,OH). Mass Spectrum: Molecular Ion peak 371.4, Base Peak 328.4.
P2	3-(5'-acetamido-2'-hydroxyphenyl) - 5-(4''-nitrophenyl)-4,5-dihydro-1-phenylpyrazole IR cm ⁻¹ : 3266 (OH), 3061(NH), 1666 (C-O of NCOCH ₃), 1597 (C=N), 1515 (NO ₂), 1487 (aromatic H), 1371 (CH ₂ of pyrazoline ring), 1249(OH), 1175 (C-N), 829 (p-subst.), 692 (o-subst.).
P3	3-(5'-acetamido-2'-hydroxyphenyl) - 5-(2''-chlorophenyl)-4,5-dihydro-1-phenylpyrazole IR cm ⁻¹ : 3265 (OH), 3064 (NH), 1652 (C-O of NCOCH ₃), 1595 (C=N), 1495 (aromatic H), 1370 (CH ₂ of pyrazoline ring), 1255 (OH), 1140 (C-N), 828 (p-subst.), 744 , 689 (o-subst.). ¹ HNMR δ ppm: 2.0 (s,H,C=C),2.5 (s,H,CH ₂), 3.3 (s,H ,CH ₃) , 7.3 (m, H, aromatic), 9.8 (s,H,NH), 10.1 (s,H,OH).
P4	3-(5'-acetamido-2'-hydroxyphenyl)-1-(2,4-dinitrophenyl)-5-phenyl-4,5-dihydropyrazole IR cm ⁻¹ : 3565 (OH), 3078 (NH), 1671 (C-O of NCOCH ₃), 1614 (C=N), 1584(aromatic H), 1523, 1339 (NO ₂), 1365 (CH ₂ of pyrazoline ring), 1240 (OH), 1145 (C-N), 833 (p-subst.), 742 (o-subst.). ¹ HNMR δ ppm: 2.0 (s,H,CH ₂),2.5 (d,H,C=C), 3.3 (s,H ,CH ₃) , 7.8 (m, H, aromatic), 9.9 (s,H,NH), 11.7 (s,H,OH).
P5	3-(5'-acetamido-2'-hydroxyphenyl)- 5-(2''-chlorophenyl)-1-(2,4-dinitrophenyl)-4,5-dihydropyrazole IR cm ⁻¹ : 3358 (OH), 2924 (NH), 1695 (C-O of NCOCH ₃), 1616 (C=N), 1579 (aromatic H), 1532, 1356 (NO ₂), 1411 (CH ₂ of pyrazoline ring), 1262 (OH), 1187 (C-N), 855 (p-subst.), 740 (o-subst.).
P6	3-(2-hydroxyphenyl)-1,5-diphenyl-4,5-dihydropyrazole

	IR cm⁻¹ : 3162, 3060 (OH), 1594 (C=N), 1492 (C=C,Aromatic), 1258 (-CO of phenol), 1329 (CH ₂ of pyrazoline ring), 1137 (C-N), 756,738 (o-subst.).
P7	3-(2-hydroxyphenyl)-5-(2'-chlorophenyl)-4,5-dihydro-1-phenylpyrazole IR cm⁻¹ : 3059 (OH), 1598 (C=N), 1491 (C=C,Aromatic), 1374 (CH ₂ of pyrazoline ring),1253 (-CO of phenol), 1114 (C-N), 746,691(o-subst.). ¹ HNMR δ ppm : 2.5 (s,H,CH),3.3 (s,H,CH ₂), 7.0 (m, H, aromatic), 10.4 (s,H,OH).
P8	3-(2'-hydroxyphenyl)-5-(4''-nitrophenyl)-4,5-dihydro-1-(4-nitro phenyl) pyrazole IR cm⁻¹ : 3344 (OH), 1507,1305 (NO ₂), 1597 (C=N), 1462 (C=C,Aromatic), 1334 (CH ₂ of pyrazoline ring), 1255 (-CO of phenol) ,1112 (C-N), 851 (p-subst.), 752 (o-subst.).
P9	5-(2-chloro phenyl)-3-(2'-hydroxyphenyl)-4,5-dihydro-1-(4-nitro phenyl)pyrazole IR cm⁻¹ : 3277, 2919 (OH), 1681, 1441 (NO ₂), 1565 (C=N), 1486 (C=C,Aromatic), 1334 (CH ₂ of pyrazoline ring), 1264 (-CO of phenol),1156 (C-N), 849 (p-subst.),749 (o-subst.).
P10	3-(2'-hydroxyphenyl)-5-phenyl-4,5-dihydro-1-(2,4-dinitrophenyl)pyrazole IR cm⁻¹ : 3344, 2925 (OH), 1678,1304 (NO ₂), 1596 (C=N), 1486 (C=C,Aromatic), 1332 (CH ₂ of pyrazoline ring), 1256 (-CO of phenol) ,1180 (C-N), 852,824 (m-subst.), 753 (o-subst.).
P11	3-(2'-hydroxyphenyl)-5-(4''-nitrophenyl)-4,5-dihydro-1-(2,4-dinitro phenyl)pyrazole IR cm⁻¹ : 3347 (OH), 1598 (C=N), 1515,1425 (NO ₂), 1462 (C=C, aromatic), 1342 (CH ₂ of pyrazoline ring), 1106 (C-N), 852 (m-disubst.), 753 (o-subst.).
P12	5-(2''-chlorophenyl)-3-(2'-hydroxyphenyl)-4,5-dihydro-1-(2,4-dinitro phenyl)pyrazole IR cm⁻¹ : 3351 (OH), 1516,1462 (NO ₂), 1598 (C=N), 1342 (CH ₂ of pyrazoline ring), 1108 (C-N), 853 (m-disubst.), 753 (o-subst.).
P13	5-(2'-chlorophenyl)-3-(4-methylphenyl)-1-phenyl-4,5-dihydropyrazole IR cm⁻¹ : 1670 (C=C,Aromatic), 1498 (C=N), 1368 (CH ₂ of pyrazoline ring),1180 (C-N), 821 (p-subst.), 692 (o-subst.). ¹ HNMR δ ppm : 1.8 (s,H,CH), 2.4 (s,H,CH ₂), 3.5 (s,H ,CH ₃) , 7.0 (m, H, aromatic).
P14	5-(2''-chlorophenyl)-3-(4'-methylphenyl)-1-(4-nitro phenyl)-4,5-dihydropyrazole IR cm⁻¹ : 1678 (C=C,Aromatic), 1563 (C=N), 1503, 1405 (NO ₂), 1373 (CH ₂ of pyrazoline ring), 1180 (C-N), 849(p-subst.),751(o-Cl).
P15	5-(4''-nitrophenyl)-3-(4'-methylphenyl)-1-(2,4-dinitro phenyl)-4,5-dihydropyrazole IR cm-1 : 2853 (C=C,Aromatic), 1596, 1324 (C=O), 1495 (C=N), 1385 (CH ₂ of pyrazoline ring), 1157 (C-N), 873 (p-subst.), 743 (m-disubst.).
P16	5-(2''-chlorophenyl)-3-(4'-methylphenyl)-1-(2,4-dinitro phenyl)-4,5-dihydropyrazole IR cm⁻¹ : 2922 1678 (C=C, Aromatic), 1563, 1332 (NO ₂) ,1503 (C=N), 1373 (CH ₂ of pyrazoline ring), 1180 (C-N), 849 (p-subst.), 751(m-subst.), 688 (o-subst.).

CONCLUSION

The spectral analysis of the compounds synthesized is given in Table 3. Some of the significant features of the spectral analysis that confirm the formation of the chalcone derivatives are; the IR spectrum showed bands around 3048 cm⁻¹, 2742 cm⁻¹, 1638 cm⁻¹ and 1570 cm⁻¹ which are characteristic of the phenolic -OH group, -NH group in N-acetyl, carbonyl group and C=C respectively. Additionally ¹HNMR and Mass spectrum wherever taken confirm the structures of the chalcone as well as the pyrazoline derivatives, as predicted in the scheme. It is also evident from the results that have been tabulated that microwave irradiation, a technique that promotes green chemistry, does enhance the yields considerably as well as the quality of the product as

compared to conventional reflux method. The isolation of the product is also more efficient. A significant advantage in using microwave irradiation is the short reaction time.

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