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Synthesis of (E)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(4-nitrophenyl)prop-2-en-1-one and 4-chloro-5-methyl-2-(5-(4-nitrophenyl)-4,5-dihydro-1h-pyrazol-3-yl)phenol and its derivatives

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Abstract— In the present work, a simple and efficient protocol was followed to synthesize pyrazoline derivatives. The synthetic protocol commences with acetylation of appropriately substituted phenol **1a**, followed by Fries migration to afford substituted acetophenone **2a**. The product **2a** was then condensed with properly substituted benzaldehyde to provide corresponding chalcone **3a**. The chalcone **3a** was then subjected to treatment with hydrazine hydrate to furnish 1H-pyrazoline **4a** and its derivatives **4b-d** following acetylation, benzoylation and nitrosoation in moderate to high yields. The structures of the intermediate **1a**, **2a**, **3a, and** pyrazolines **4a-d** were established using chemical reactivity, elemental and spectral analyses.

Keywords- *nitro-Chalcone, Pyrazoline, synthesis, IR, PMR*

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I. INTRODUCTION

The synthesis of heterocyclic molecules has enriched the understanding and knowledge of reactivity and chemistry of catalysts, reagents, reaction intermediates, medicines and toxicants [1-4]. Heterocyclic molecules bearing two or more heteroatoms are key compounds in medicinal, agriculture and other fields for synthesis of variety of compounds with diverse applications and desired toxicity/activity. Nirogen heterocycles viz. pyrazoles, imidazoles, etc. have gained the prime attention and reverence of researchers due to their therapeutic properties like anti-bacterial, anti-fungal, anti-inflammatory, etc., a few to mention [5-12, 14]. Recently, Bandgar *etal* highlighted the various methods of synthesis and applications of pyrazoline derivatives as anti-inflammatory and anti-oxidants [13].

From the literature survey [1-7], it has been found that nitro substituted chalcones have never been employed for the synthesis of respective pyrazolines using reported method. Therefore, in the present work, the synthesis of pyrazolines has been accomplished following a simple yet very efficient route. The emphasis in the present work is on developing synthetic protocol for easily scalable and competent route for pyrazolines.

II. EXPERIMENTAL SECTION

All the chemicals were of analytical grade and used as supplied. The m.p. were recorded in an open capillary and are uncorrected. The FT-IR spectra were recorded on Agilent Spectrophotometer and reported in cm^{-1}. The PMR were recorded in DMSO-d6 using TMS as an internal standard and reported in ppm.

Synthesis of chalcone 3a [1-8]**:** Appropriately substituted acetophenone 2a (0.01 mol) and nitrobenzaldehyde (0.012 mol) were dissolved in ethanol (20 ml), then the mixture was brought to boiling. To this hot solution, NaOH (0.03 mol) was added with constant stirring and solution was kept overnight. The sodium salt obtained was decomposed by aq. HCl (1:1) in cold condition. The yellow solid obtained was filtered, washed with NaHCO3 (2%) and then with water. The product was crystallized from ethanol to get yellow crystal of (E)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(4-nitrophenyl)prop-2-en-1-one **3a**. Yield: 80%, m.p.: 250^{o}C. FT-IR (cm^{-1}): 3750.21 (presence of free –OH group), 1642.64 (-CO- in conjugation with -C=C-), 1574.25 (-C=C- moiety), 1514.23 and 1340.40 (asymmetric and symmetric stretch for aromatic -NO_2), 1050.29 (aromatic C-Cl stretch), 841.41, 788.23 and 731.47 (presence of substituted benzene ring). PMR (δ): 12.37 (phenolic -O**H**), 1.23 (-C**H**$_3$), 2.53 and 2.38 (-C**H** = C**H**-), 6.93-8.35 (multiplet, aromatic C**H**)

Synthesis of pyrazoline 4a [1-8]**:** The chalcone **3a** (0.01 mol) and hydrazine hydrate (0.012 mol) in 20 ml ethanol was refluxed for 2 hr, and the mixture was then concentrated. On cooling, the resulting solid was filtered, and crystallized from ethanol. Yield: 80%, m.p.: 220-225^{o}C. FT-IR (cm^{-1}): 3753.20 (free –OH group), 3330.27 (-NH (2^{o} amine)), 3078.79 (aromatic C-H stretch), 1594.24 (-C=N- of pyrazoline), 1514.53 and 1340.86 (aromatic -NO_2), 1442.21 (-CH_2- of pyrazoline ring), 1067. 31 (aromatic C-Cl stretch), 849.83, 753.46, and 729.16 (substituted benzene ring). PMR (δ): 10.93 (phenolic –O**H**), 2.29 (-C**H**$_3$), 2.53 (-C**H**$_2$), 6.86 (-N**H**) 7.21-8.23 (multiplet, aromatic C**H**).

Synthesis of 4b-d pyrazoline derivatives [4-9]**:**

Synthesis of 4b: A mixture of **4a** (0.01 mol) and acetic acid (10 ml) was refluxed for 2 hr. On cooling, the resulting solid was filtered, and crystallized from ethanol. Pale yellow solid. Yield: 75%, m.p.: 239^{o}C.

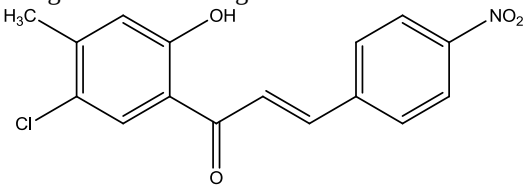
Synthesis of 4c: An equimolar mixture of **4a** (0.01 mol) and benzoyl chloride was dissolved in dry pyridine (10 ml) and stirred at room temperature for 1 hr. The reaction mixture was treated with cold dil HCl (2N). The resulting solid was filtered, washed with water, cold NaOH (2N) and again with

water. The crude solid was crystallized from ethanol to give brownish-yellow solid. Yield: 75%, m.p.: 290°C.

Synthesis of 4d: A mixture of **4a** (0.01 mol) was dissolved in ice cold 2 ml HCl (1:1) and cooled to 0°C and 10% $NaNO_2$(6 ml) was added dropwise with constant stirring. The mixture was stirred for 30 minutes at room temperature. The resulting solid was crystallized from ethanol to afford the yellowish solid. Yield: 75%, m.p.: 106°C.

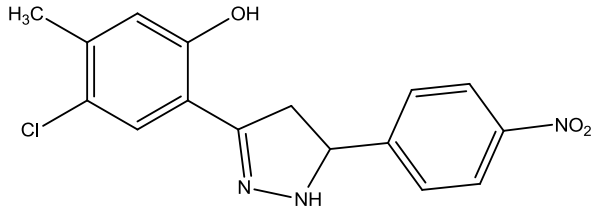
Results and discussion: The synthesis of targeted pyrazolines **4a-d** initiated with the acetylation of properly substituted phenol **1a**, followed by Fries migration using the literature method to provide substituted acetophenone **2a**. Further step involves treatment of **2a** with substituted benzaldehyde in the presence of NaOH in ethanol as solvent to furnish corresponding substituted chalcone **3a**. In the very next step, the chalcone **3a** was treated with hydrazine hydrate to give 1H-pyrazoline **4a**, which was then converted to **4b-d**. The synthesis scheme adopted in the present work has been depicted in figure 1.

The FT-IR of **3a** showed an absorption signal at 3750.21 indicating the presence of free –OH group. The signal at 1642.64 could be assigned to -CO- in conjugation with -C=C-. The presence of -C=C- moiety is indicated by the signal at 1574.25. The two signals of almost same intensity at 1514.23 and 1340.40 have been assigned to asymmetric and symmetric stretch for aromatic -NO_2. The signal at 1050.29 indicates the presence of aromatic C-Cl stretch. The peaks at 841.41, 788.23 and 731.47 point the presence of substituted benzene ring. The PMR spectrum of **3a** is with a peak at 12.37 indicating the presence of phenolic –O**H**. The peak at 1.23 is indicative of -C**H**$_3$. The peaks at 2.53 and 2.38 were correlated with -C**H** = C**H**-. The multiplet at 6.93-8.35 indicates the presence of aromatic C**H**. In addition, **3a** decolorized the bromine water and gave red colour with $FeCl_3$, thus it contains unsaturation and phenolic –OH group. Treatment of **3a** with Fe and HCl, followed by reaction with alkaline solution of β-naphthol gave orange-red dye, thereby, indicating the presence of –NO_2 group. Thus, on the basis of elemental analysis, chemical reactivity and spectral data (FT-IR and PMR) the compound **3a** was assigned the following structure:



3a

The FT-IR of **4a** showed an absorption signal at 3753.20 specifying the presence of free –OH group. The signal at 3330.27 could be assigned to –NH (2° amine) present in a ring. The peak at 3078.79 is due to the aromatic C-H stretch. The presence of -C=N- moiety of pyrazoline is indicated by the signal at 1594.24. The two signals of almost same intensity at 1514.53 and 1340.86 have been assigned to asymmetric and symmetric stretch for aromatic -NO_2. The 1442.21 peak indicates the presence of -CH_2- moiety present in the pyrazoline ring. The signal at 1067. 31 arose due to the aromatic C-Cl stretch. The peaks at 849.83, 753.46, and 729.16 point the presence of substituted benzene ring. The PMR spectrum of **4a** is with a peak at 10.93 indicating the presence of phenolic –O**H**. The peak at 2.29 is indicative of -C**H**$_3$. The peaks at 2.53 can be assigned to –C**H**$_2$. The -N**H** proton gave peak at 6.86. The multiplet at 7.21-8.23 indicates the presence of aromatic C**H**. In addition, **4a** gave red colour with $FeCl_3$, thus it contains phenolic –OH group. The treatment of **4a** with Fe and HCl, followed by reaction with alkaline solution of β-naphthol gave orange-red dye, thereby, indicating the presence of –NO_2 group. Thus, on the basis of elemental analyses, chemical reactivity and spectral data (FT-IR and PMR) the compound **4a** was assigned the following structure:



4a

Sr.No.	*Compound*	*Percent yield (%)*	*Melting point(°C)*
1	3a	80	250
2	4a	80	220-225
3	4b	75	239
4	4c	75	290
5	4d	75	106

Table 1. *List of synthesized compounds, their melting points and percent yield*

Conclusion: In conclusion, a very efficient synthetic protocol has been followed to synthesize the chalcone and pyrazoline synthesis using easily scalable reactions involving use of effortlessly available starting materials and reaction conditions.

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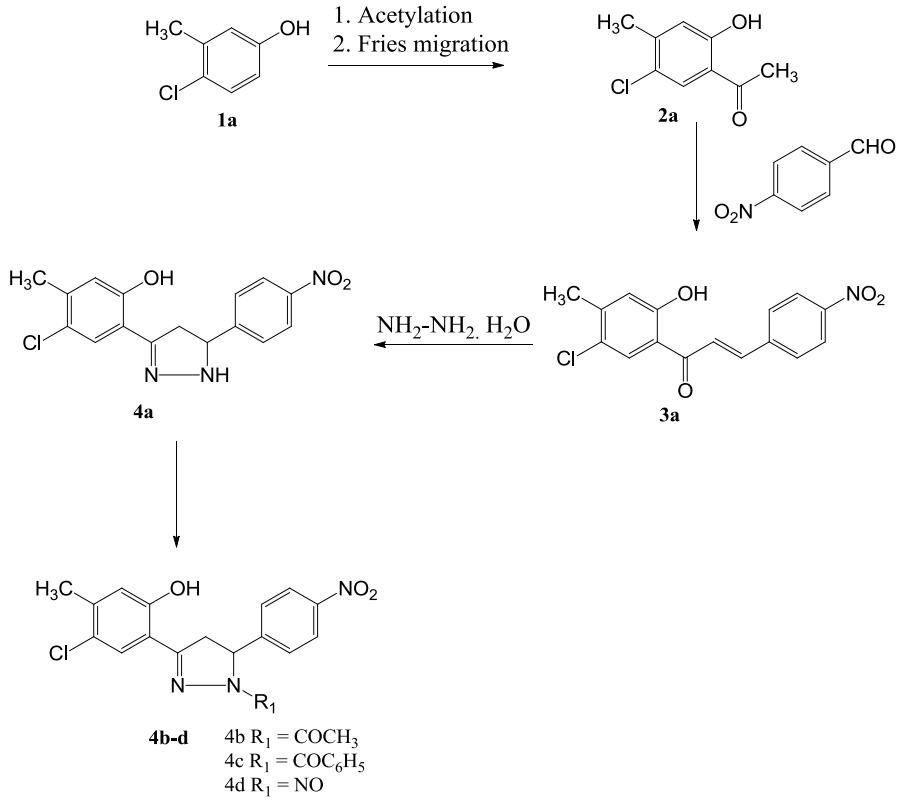

Figure 1. Synthetic scheme used in the present work for the synthesis of substituted pyrazolines