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

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***Abstract*—** In continuation of earlier work, the simple and efficient protocol was adopted to synthesize bromo-pyrazoline derivatives. The synthetic protocol instigates with acetylation of properly substituted phenol **1a**, subsequently, Fries migration was performed to afford substituted acetophenone **2a**. The product **2a** was then treated with appropriately substituted aromatic aldehyde to afford the corresponding chalcone **3a**. The chalcone **3a** was then reacted with hydrazine hydrate to provide 1H-pyrazoline **4a** and its derivatives **4b-d** using 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- *Bromo substituted Chalcone, Pyrazoline, synthesis, IR, PMR*

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I. INTRODUCTION *(HEADING 1)*

The chemistry of heterocyclic molecules is integral part of modern organic chemistry. The knowledge and applications of heterocyclic molecules have been widely accepted and continued in the field of catalysis, reagents, medicines, dyes, polymers, etc. [1-4]. Heterocyclic molecules encompassing multiple heteroatoms are important compounds in pharmaceutical, agronomy and other fields for synthesis of a range of compounds with various applications and preferred activity. Nirogen heterocycles viz. pyrazoles, imidazoles, etc. have expanded the horizons of heterocyclic chemistry and are at prime consideration and high regard of researchers due to their therapeutic properties like anti-cancer, anti-HIV, 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 bromo substituted chalcones have never been employed for the synthesis of respective pyrazolines using simple reported method. Therefore, in the present work, the synthesis of pyrazolines has been accomplished following a simple yet very efficient route, reported earlier. The emphasis in the present work is on expanding the utility of earlier synthetic protocol for easily scalable and competent route for bromo derivatives of pyrazolines.

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 bromobenzaldehyde (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 $NaHCO_3$ (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-bromophenyl)prop-2-en-1-one **3a**. Yield: 80%, m.p.: 142°C. FT-IR (cm^{-1}): 3432 (presence of free –OH group), 1644 (-CO- in conjugation with -C=C-), 1584 (-C=C- moiety), 1051 and 1071 (aromatic C-Cl and C-Br stretch), 815, 795 and 737 (presence of substituted benzene ring). PMR (δ): 12.46 (phenolic -O**H**), 2.35 and 2.54 (-C**H** = C**H**-), 6.91-8.28 (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.: 200°C. FT-IR (cm^{-1}): 3300 (broad –OH and -NH (2^o amine)), 3062 (aromatic C-H stretch), 1609 (-C=N- of pyrazoline), 1589 (aromatic C=C), 1437 (-CH_2- of pyrazoline ring), 1063 and 1071 (aromatic C-Cl and C-Br stretch), 820, 791, and 735 (substituted benzene ring). PMR (δ): 11.80 (phenolic –O**H**), 1.08 (-C**H**$_3$), 2.31 (-C**H**$_2$), 4.80 (-N**H**) and 6.86-8.31 (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.: 280°C.

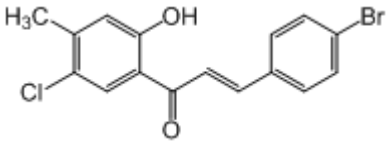
Synthesis of 4c: An equimolar mixture of **4a** (0.01 mol) and benzoyl chloride was dissolved in dry pyridine (10 ml) and stirred at room temperature for 1 hr. The reaction mixture was treated with cold dil HCl (2N). The resulting solid was filtered, washed with water, cold NaOH (2N) and again with water. The crude solid was crystallized from ethanol to give brownish-yellow solid. Yield: 75%, m.p.: 180°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.: 268°C.

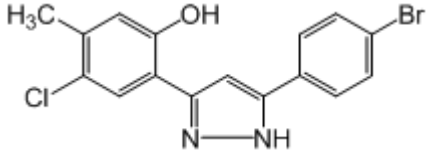
Results and discussion: The synthesis of targeted pyrazolines **4a-d** commenced with the acetylation of appropriately substituted phenol **1a**, followed by Fries migration employing the literature method to afford substituted acetophenone **2a**. The next step comprises reaction of **2a** with substituted benzaldehyde in the presence of NaOH in ethanol as solvent to provide corresponding substituted chalcone **3a**. In the further step, the chalcone **3a** was condensed 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 3432 indicating the presence of free –OH group. The signal at 1644 could be assigned to -CO- in conjugation with -C=C-. The presence of -C=C- moiety is indicated by the signal at 1584. The signal at 1071 indicates the presence of aromatic C-Br stretch. The peaks at 815, 795 and 737 point the presence of substituted benzene ring. The PMR spectrum of **3a** is with a peak at 12.46 indicating the presence of phenolic –O**H**. The peaks at 2.35 and 2.54 were correlated with -C**H** = C**H**-. The multiplet at 6.91-8.28 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. On the basis of elemental analysis, chemical reactivity and spectral data (FT-IR and PMR), the compound **3a** was assigned the following structure:



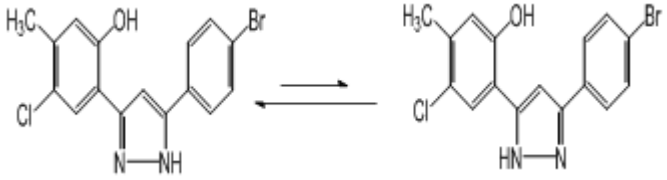
3a

The FT-IR of **4a** showed a broad absorption signal at 3300 specifying the presence of –OH and -NH (2° amine) groups. The peak at 3062 is due to the aromatic C-H stretch. The presence of -C=N- moiety of pyrazoline is indicated by the signal at 1609. The 1437 peak indicates the presence of $-CH_2-$ moiety present in the pyrazoline ring. The signals at 1071 and 1009 arose due to the aromatic C-Br and C-Cl stretch, respectively. The peaks at 820, 791, and 735 point the presence of substituted benzene ring. The PMR spectrum of **4a** is with a peak at 11.80 indicating the presence of phenolic –O**H**. The peak at 1.08 is indicative of $-CH_3$. The peaks at 2.31 can be assigned to $-CH_2$. The -N**H** proton gave peak at 4.80. The multiplet at 6.86-8.31 indicates the presence of aromatic C**H**. In addition, **4a** gave red colour with $FeCl_3$, thus it contains phenolic –OH group. On the basis of elemental analyses, chemical reactivity and spectral data (FT-IR and PMR), the compound **4a** was assigned the following structure:



4a

Interestingly, the PMR of **4a** revealed additional peaks, which might have arose due to the plausible tautomerism as depicted below:



Sr.No.	*Compound*	*Percent yield (%)*	*Melting point(°C)*
1	3a	80	142°C
2	4a	80	200°C
3	4b	75	280°C
4	4c	75	180°C
5	4d	75	268°C

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

II. CONCLUSION

In conclusion, the earlier reported procedure is very efficient synthetic protocol for the synthesis of bromo-chalcone and bromo-pyrazoline involving use of effortlessly available starting materials and reaction conditions. The reaction provides good yields and scalable, also.

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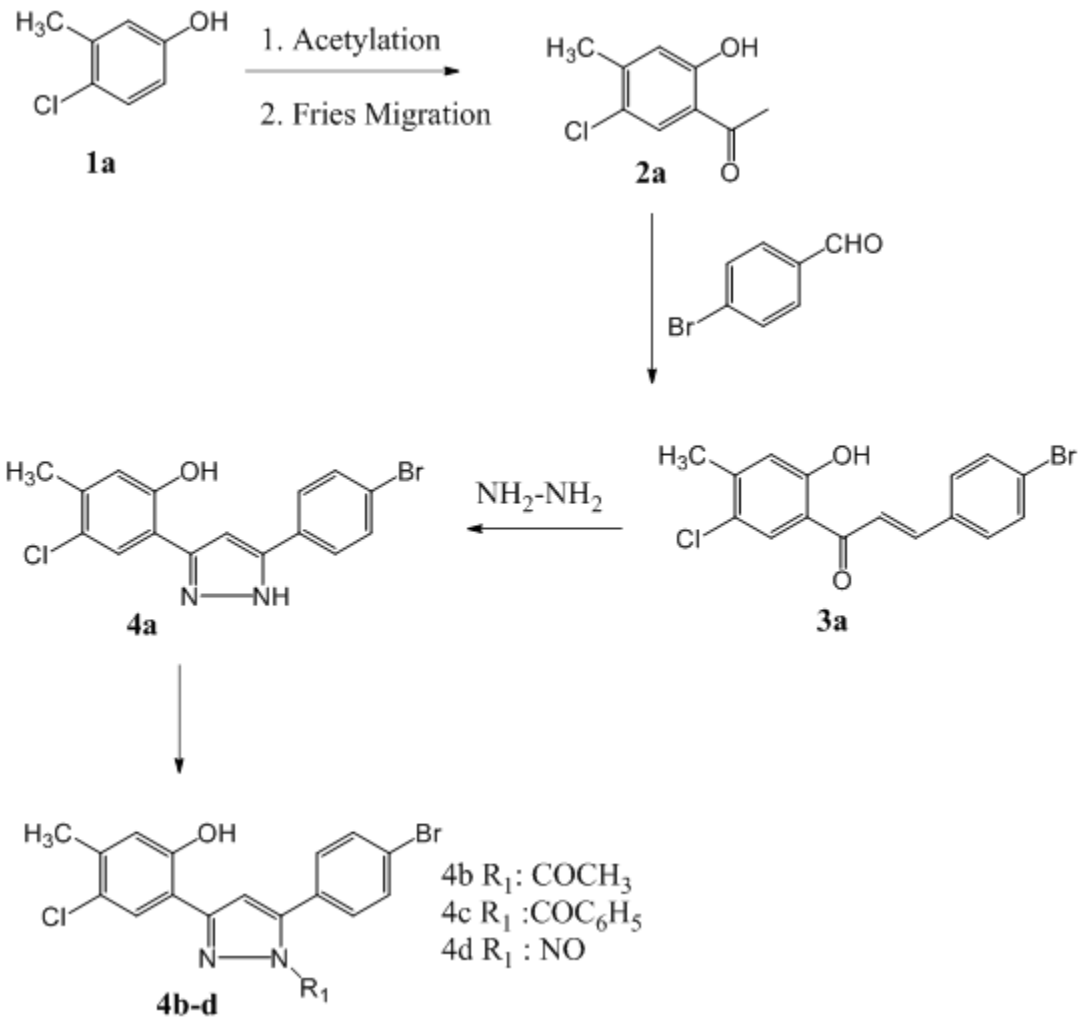

Figure 1. Synthetic scheme used in the present work for the synthesis of bromo substituted pyrazolines