Research Paper

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# A Novel And Green Route for Synthesis of Pyrazoline Derivatives in an Aqueous Media By Using Ionic Liquid at Reflux Condition

Chemistry

KEYWORDS : pyrazoline, chalcones, ionic liquid, reflux.

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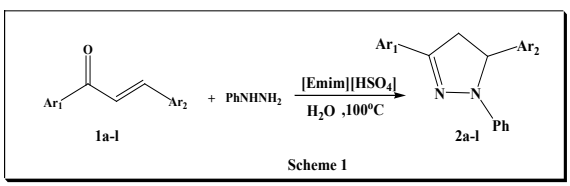
## ABSTRACT

*A novel and green route was develop for the synthesis of 1,3,5-trisubstituted pyrazoline derivatives from phenyl hydrazine and substituted chalcones in an aqueous media by using 1-ethyl-3-methylimidazolium hydrogen sulfate ionic liquid as a catalyst at reflux condition. The reaction protocol gave 1, 3, 5-trisubstituted-2-pyrazolines in good to high yields via a one-pot addition–cyclocondensation between chalcones and arylhydrazines. The catalyst can be reused without much loss in the catalytic activity. The structures of the synthesized compounds were confirmed by their spectral data analysis.*



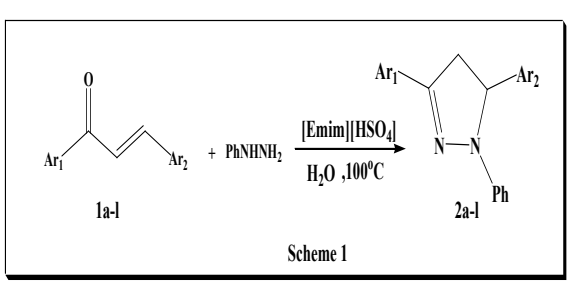

Scheme 1

## INTRODUCTION

Pyrazoline derivatives differ considerably in their properties from those of pyrazole, owing to their much lower stability. Pyrazoline and its homologues are weak bases. In general they only dissolve in concentrated acids, forming unstable salts which dissociate on the addition of water. Among the five membered heterocyclics containing two hetero atoms in its ring structure, pyrazole is one of the most important one as large variety of biological activities have been reported for various pyrazole derivatives such as antitumor[1], immunosuppressive[2], antibacterial[3], anti-inflammatory[4], anticancer[5], antidiabetic[6] and antidepressant[7].

Literature survey shows that there are numerous procedures have been developed for the synthesis of 1,3,5-trisubstituted-2-pyrazoline moieties[8-22]. Most of the existing methods for the preparation of 1,3,5-trisubstituted-2-pyrazoline moieties suffers from drawbacks such as low yield, long reaction time, expensive and occurrence of side products.

Thus, the green synthesis of the 1,3,5-trisubstituted 2-pyrazolines moiety is always a great challenge. To overcome this problem we have developed the green synthesis of pyrazoline by using ionic liquids in an aqueous media as an alternative to synthesis of pyrazoline derivatives **(Scheme 1).**




Scheme 1

## EXPERIMENTAL

### Material and methods

Melting points were measured in open glass capillaries on a Veego melting-point apparatus and were uncorrected. $^1$H NMR was recorded at room temperature on a BrukerAvance II 400MHz Spectrometer (SAIF, Punjab University, Chandigarh) in CDCl using TMS as internal standard. IR spectra (using KBr pellets) were obtained with a Perkin Elmer Spec-trum RX FTIR (SAIF, Punjab University, Chandigarh) instru-ment. The reactions were monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography were distilled before use. The products were also characterized by comparison of their melting point with literature values.

### Experimental procedure for chalcone derivative synthesis

A mixture ofbenzaldehyde derivatives (10 mol) and acetophenone derivatives (10 mol) was dissolved in 100 ml rectified spirit in a 250 round-bottomed flask equipped with a magnetic stirrer. Then 10% NaOH solution was added drop wise to the reaction mixture on vigorous stirring for 30 minutes when solution became turbid. The reaction temperature was maintained between20-25˚C using a cold water bath on the magnetic stirrer. After vigorous stirring for 4-5 hours the reaction mixture was neutralized by 0.1-0.2N HCl whereby the precipitation occurred. On filtering off, the crude chalcones were dried in air and recrystallized by rectified spirit.

### General procedure for synthesis of 1,3,5-substituted pyrazoles derivatives

Chalcone (1.0 mmol), arylhydrazine hydrochloride (2 mmol) and [EMIM][$HSO_4$] (0.2 mmol, 20 mol%) were added to a 50 ml round bottom flask containing distilled water (10 ml). The reaction mixture was reflux at 100°C with stirring for appropriate time asshown in **Table 3.** After completion of the reaction as indicated by TLC, the reaction mixture was filtered and washed with water and dried over vacuum. The crude solid product was recrystallized with ethanol to obtain the pure product.

### Spectral data for some synthesized 1,3,5-substituted pyrazoles derivatives at reflux condition

[1] 5-(2-Chlorophenyl)-1,3-diphenyl-2-pyrazoline (Table 3, Entry 6) - 1H- NMR (δ): 3.10 (1H, dd, J = 4.9, 17.6 Hz, 4-Htrans), 3.90 (1H, dd, J =11.4, 17.6 Hz, 4-Hcis), 5.74 (1H, dd, J = 4.9, 11.4 Hz, 5-H), 6.76–7.74 (m, 14 arom. H); 13CNMR (δ): 41.6, 60.9, 112.1, 118.8, 126.7, 126.3, 126.6, 127.8, 127.6, 127.7, 130.0. 129.8, 131.0,132.8, 140.2, 145.4, 147.2; MASS(m/z) = 332.14

[2] 5-(4-Chlorophenyl)-1,3-diphenyl-2-pyrazoline (Table 3, Entry 4) -1H- NMR (δ): 3.01 (1H, dd, J = 7.4, 17.6 Hz, 4-Htrans), 3.67 (1H, dd, J =11.6, 17.6 Hz, 4-Hcis), 5.77 (1H, dd, J = 7.4, 11.6 Hz, 5-H), 6.70–7.61 (m, 14 arom. H); 13CNMR(δ): 44.4, 62.8, 112.4, 120.4, 126.7, 128.3, 128.5, 128.8, 129.0, 129.3, 130.9, 132.6, 134.3,

142.1, 144.8, 145.7; MASS(m/z) = 332.11

**RESULT AND DISCUSSION**

As a part of our ongoing work on synthesis of heterocyclic compounds by using different catalyst, here we report ionic liquid as a green catalyst for the synthesis of 1,3,5-trisubstituted-2-pyrazoline derivatives in an aqueous media at reflux condition by using arylhydrazines with α,β–unsaturated ketones (Chalcones).

In the standardization experiment, to determine the optimization conditions of the reaction we first take chalcone and phenylhydrazine hydrate chosen as a model reaction for the synthesis of 4,5-dihydro-1,3,5-triphenyl-1H-pyrazole derivatives at reflux condition in an aqueous media. Different solvents were used for the synthesis of 4,5-dihydro-1,3,5-triphenyl-1H-pyrazole derivatives and results are summarized in **Table 1**. From **Table 1**, it was found that water is the best solvent for the synthesis of pyrazoline derivatives in concern with reaction time and yield (**Entry 5, Table 1**).

**Table - 1**

**Optimization of solvent for synthesis of 4,5-dihydro-1,3,5-triphenyl-1H-pyrazole by using [EMIM][$HSO_4$].**

| Entry | Solvent | Time (hr) | Yielda(%) |
|---|---|---|---|
| 1 | No solvent | 4 | 80% |
| 2 | Acetonitrile | 5 | 70% |
| 3 | Chloroform | 5 | 78% |
| 4 | DMF | 5 | 70% |
| 5 | Water | 3 | 96% |

[a]Isolated yields

Further the effect of amount catalyst on yield and time of reaction for the same reaction was investigated (Table 2). It was found that ( from the Table 2) 20 mol % of [EMIM][HSO4] gives excellent yield in shorter reaction time at reflux condition in an aqueous media(Entry 4,Table 2).

**Table-2**

**Optimization of catalyst for synthesis of 4,5-dihydro-1,3,5-triphenyl-1H-pyrazole by using [EMIM][$HSO_4$].**

| Entry | Catalyst amount in mol% | Time (hr) | Yield[a](%) |
|---|---|---|---|
| 1 | 05 | 5 | 77% |
| 2 | 10 | 5 | 81% |
| 3 | 15 | 4 | 88% |
| 4 | 20 | 3 | 96% |
| 5 | 25 | 3 | 96% |

[a]Isolated yields

To explore the synthetic scope and versatility of the protocol, a series of arylhydrazines were reacted with different α,β–carbonyl compounds under the optimal reaction conditions. The results are summarized in **Table 3**. Various functional groups, such as -Br, -Cl, -$OCH_3$, -$CH_3$ on chalcones and arylhydrazines were well tolerated under these conditions, affording corresponding 1,3,5-substituted pyrazoles in high to excellent yields (87–96%).

**CONCLUSION**

1,3,5-trisubstituted pyrazoles are therapeutically important class of heterocyclic compounds. The method used in the present study is one of the best method for introducing substitution at 1,3,5 positions of the pyrazole ring. The reaction protocol exhibited tolerance with different functional groups, generating pyrazoles in good to high yields (87–96%) without any requirement for additional reagents. The catalyst can be reused up to four cycles without much loss in catalytic activity.

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**Table - 3**

**Synthesis of 1,3,5-trisubstituted-2-pyrazoline derivatives by using [EMIM][$HSO_4$] ionic liquid at reflux conditions.**

| Entry | Ar1 | Ar2 | Product | Time (Hr) | Yielda (%) | M.P (0C) |
|---|---|---|---|---|---|---|
| 1 | -C6H5 | -C6H5 | 2a | 3 | 96 | 132-135 |
| 2 | -C6H5 | 4-CH3-C6H4 | 2b | 3 | 92 | 127-130 |
| 3 | -C6H5 | 4-CH3O-C6H4 | 2c | 2.5 | 95 | 110-112 |
| 4 | -C6H5 | 4-Cl-C6H4 | 2d | 4 | 91 | 135-137 |
| 5 | -C6H5 | 3-Br-C6H4 | 2e | 4 | 90 | 142-144 |
| 6 | -C6H5 | 2-Cl-C6H4 | 2f | 3.5 | 91 | 133-135 |
| 7 | -C6H5 | 3-Cl-C6H4 | 2g | 3 | 90 | 134-136 |
| 8 | 2-napthyl | 4-Cl-C6H4 | 2h | 2 | 87 | 129-130 |
| 9 | 2-napthyl | 4-CH3O-C6H4 | 2i | 2 | 89 | 134-136 |
| 10 | 4-CH3-C6H4 | 3-CH3-C6H4 | 2j | 2 | 90 | 124-126 |
| 11 | 4-CH3O-C6H4 | 2-CH3-C6H4 | 2k | 3 | 90 | 88-90 |
| 12 | 4-Cl-C6H4 | -C6H5 | 2l | 2 | 91 | 144-146 |

[a]Isolated yields

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