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# Solvent Free Synthesis of Substituted-2-Pyrazolines Using Imidazolium Based Ionic Liquid as a Solvent and Catalyst: A Green Route Approach

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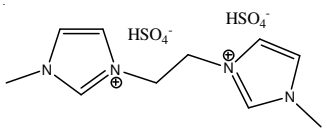
A series of substituted-2-pyrazolines synthesized using imidazolium based ionic liquid, 1,2-[*bis*-(3'-methyl-imidazolium-hydrogen sulphate)]-ethane as a solvent and catalyst, by reacting chalcones react with phenyl hydrazine. The compounds were characterized by means of their $^{1}$H NMR, $^{13}$C NMR spectroscopic data. The product was separated and catalyst was recycled for the next reaction.

**Key Words: Chalcones, 2-Pyrazolines, Ionic liquid.**

## INTRODUCTION

Pyrazoline derivatives have been found to possess a broad spectrum of biological activities such as tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsant, antihypertensive and antidepressant activities[1-6]. Among various pyrazoline derivatives, 2-pyrazolines seem to be the most frequently studied compounds. A variety of methods have been reported for the preparation of this class of compounds. After the pioneering work of Fischer and Knoevenagel in the 19$^{th}$ century, the reaction of α,β-unsaturated aldehydes and ketones with phenyl hydrazine in acetic acid by refluxing became one of the most popular methods for the preparation of 2-pyrazolines[7]. Powers *et al.*[8] reported that the reaction of chalcones and phenyl hydrazine hydrochloride in the presence of sodium hydroxide was carried out in the absolute ethanol at 70 ºC, but there is a disadvantage due to longer the reaction time (8 h). In 2005, the synthesis of 3,5-diaryl-2-pyrazolines by the reaction of chlorochalcones with phenyl hydrazine in acetic acid by refluxing for 3 h was reported by Levai[7], yet the ratio of chlorochalcones and phenyl hydrazine was 1:5. These reaction conditions suffer from economic and environmental concerns. Recently, $K_2CO_3$-mediated microwave irradiation has been shown to be an efficient method for the synthesis of pyrazolines[9]. The recent interest in green chemistry has posed a new challenge for organic synthesis in that new reaction conditions need to be found which reduce the emission of volatile organic solvents and the use of hazardous toxic chemicals. Organic reactions in aqueous media have attracted increasing interest currently because of environmental issues and the understanding of biochemical processes. As a reaction solvent, water offers many practical and economic advantages including low cost, safe handling and environmental compatibility. Recently, many organic reactions in aqueous media have been described in the literature[10].

Ionic liquids have been used in organic synthesis since last three decades. Compared with traditional methods, the procedure is more convenient and can be carried out in higher yields, shorter reaction time or milder conditions in presence of ionic liquids. Continuing our investigations on the application of ionic liquids in organic synthesis, we wish to report an efficient and practical procedure for the synthesis of 3,5-diaryl-2-pyrazolines with chalcones and phenyl hydrazine hydrochloride in presence of imidazolium based ionic liquid (**Scheme-I**).




**Scheme-I**. Ionic liquid used for the synthesis of pyrazolines

## EXPERIMENTAL

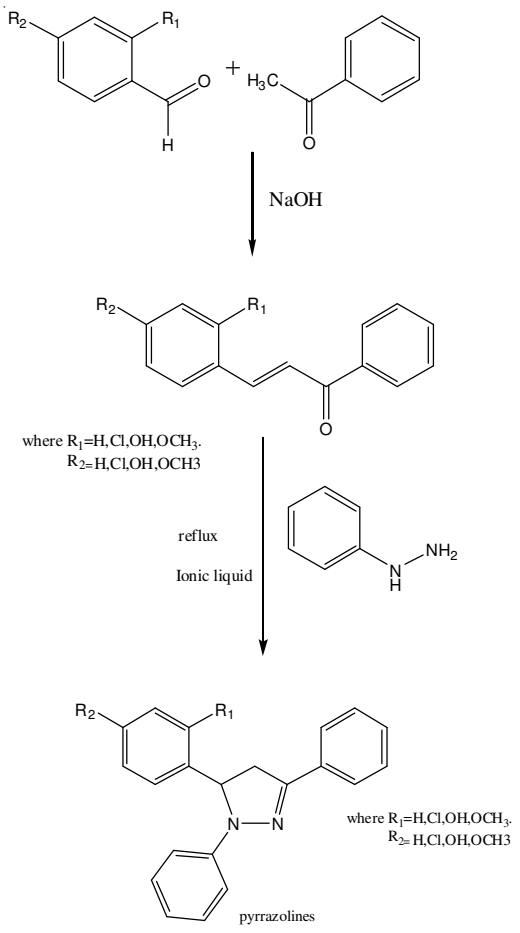
Melting points were determined in open capillary tube and are uncorrected. NMR spectra were recorded using a Bruker spectrometer at a ca. 5-15 % solution in DMSO-$d_6$ (TMS as internal standard). Thin layer chromatography (TLC) was performed on silica gel G for thin layer chromatography (Merck) and spots were visualized by iodine vapours. Physical constants and analytical data of all the compounds reported in this paper are summarized in Table-1. All the chemicals are purchased from Sigma Aldrich.

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR THE SYNTHESIS OF PYRAZOLINES

| S. No. | Solvent | Temp. (ºC) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | Ethanol | 75 | 5 | 81 |
| 2 | Methanol | 60 | 5 | 78 |
| 3 | Pyridine | 75 | 5 | 85 |
| 4 | Acetonitrile | 75 | 5 | 77 |
| 5 | No solvent | 75 | 5 | 30 |
| 6 | No solvent | 85 | 5 | 43 |
| 7 | No solvent | 95 | 5 | 45 |
| 8 | No solvent | 100 | 5 | 49 |
| 9 | **No solvent[a]** | **100** | **3** | **84** |
| 10 | No solvent[a] | 100 | 2.5 | 78 |
| 11 | No solvent[a] | 100 | 2 | 70 |

[a]Reaction conditions: 10 mmol chalcone, 10 mmol phenyl hydrazine, 0.1 mmol IL.

**General procedure for the synthesis of chalcones:** In a 100 mL conical flask 3 g of NaOH is dissolved in 10 mL water.To it 8 mL of ethanol was added and swirled the flask to mix thoroughly. Flask was cooled until the solution reaches to 20 ºC 0.1 mol of acetophenone and 0.1 mol of aldehydes were added and swirled the flask to mix the solution thoroughly, reaction mixture was stirred for 2 h. Reaction mixture was kept in the refrigerator overnight. Solid precipitate was washed with cold water and cold ethanol in order to remove the excess NaOH till neutral pH. The compound was dried and recrystallized with ethanol. Melting point was determined. Yield 88 % **Scheme-II**.




**Scheme-II.** Synthesis of 1,3,5-triaryl-2-pyrazolines

**General procedure for the synthesis of 2-pyrazoline:** 0.005 mol of the chalcone was taken and 0.005 mol of phenyl hydrazine was added in the round bottomed flask and ionic liquid (1 %) was mixed well by shaking the flask. and the reaction mixture was refluxed for about 5 h. The reaction mixture was cooled to room temperature and quenched in ice cold water, separated and recrystallized in ethanol. The water from the aqueous layer was removed by vacuum distillation to get ionic liquid. It was used without further purification for the next cycle. The products were summarized in the Table-2.

TABLE-2
PREPARATION OF PYRAZOLINES DERIVATIVES USING OPTIMIZED CONDITIONS

| $R_1$ | $R_2$ | Pyrazoline | Yield (%) | m.p. ºC [L*] |
|---|---|---|---|---|
| H | H | I | 84 | 110-112 [108] |
| $OCH_3$ | H | II | 85 | 101-102 [101] |
| H | $OCH_3$ | III | 77 | 102-105 [108] |
| Cl | H | IV | 80 | 104-105 [102] |
| H | Cl | V | 74 | 105-108 [108-110] |

Reaction condition: 10 mmol chalcone, 10 mmol phenyl hydrazine, 0.1 mmol IL catalyst, reflux in absence of solvent; L*- the melting points are comparable with the literature values

### Spectral data of the pyrazoline

**$^1$H NMR (400 MHz, DMSO-$d_6$):** 3.10 (dd, $J$ = 17.4, 6 Hz, 1H); 3.92 (dd, $J$ = 17.4, 12.4 Hz, 1H); 5.48 (dd, $J$ = 12.4, 6.4 Hz, 1H); 6.695-7.761 (15-Ar-H). $^{13}$C NMR spectrum (DMSO-$d_6$, ppm), δ: 42.96, 63.12, 112.92, 118.58, 125.67, 125.83, 127.38, 128.63, 128.68, 128.84, 128.98, 132.25, 142.54, 144.22, 147.16.

## RESULTS AND DISCUSSION

Initially, the synthesis of pyrazoline was carried out at different temperature in the various molecular solvents in absence of ionic liquid catalyst (Table-1, entry 1-4).The same reaction was carried out in absence of any solvent and ionic liquid which gave poor conversion of the product inspite of increasing the temperature of the reaction mixture. It showed that ionic liquid was necessary for conversion of chalcone to pyrazolines. (Table-1, entry 5-8) Subsequently the reaction was carried out in presence of ionic liquid gave good yield of the product in short duration (Table-1, entry 9). The percentage yield decrease when the duration of the reaction was decreased from 3 to 2 h. (Table-1, entry 10-11).

Having an optimized conditions the derivatives of pyrazolines were synthesized and summarized in the Table-2.

### Conclusion

In summary, we have described solvent free, a practical and convenient procedure for the synthesis of 3,5-diaryl-2-pyrazolines in presence of imidazolium based ionic liquid. This proves to be an environmental friendly method avoiding use of solvent during the course of reaction. The catalyst can be recycled for next cycle without loosing its activity.

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