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REGULAR ARTICLE

An eco-friendly synthesis of 2-pyrazoline derivatives catalysed by $CeCl_3 \cdot 7H_2O$

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Abstract. 1,3,5-triaryl-2-pyrazoline derivatives were synthesised by a condensation reaction between chalcones and phenyl hydrazine using cerium chloride heptahydrate as a catalyst. All these reactions were carried out in ethyl lactate (70%) as a green solvent. Easy and efficient work up, recyclability of solvent and catalyst are the key merits of this protocol.

Keywords. Cerium chloride heptahydrate; ethyl lactate; green solvent; chalcones; 1, 3, 5-Triaryl-2-pyrazoline.

1. Introduction

Pyrazolines are a well-known class of five-membered nitrogen heterocycles. Pyrazoline derivatives are attracting a lot of interest amongst researchers in the field of medicinal chemistry because of their bioactivity.[1] They have been shown to possess a broad range of physiological activities such as antimicrobial,[2] antiamoebic,[3] antinociceptive,[4] anticancer,[5] antidepressant,[6] and anti-inflammatory.[7] Pyrazolines have also shown promise as a new type of highly active insecticide towards coleopteran and lepidopteran insects.[8] The bioassay of some of these compounds have exhibited fungicidal and plant growth regulatory activities.[9] Further, these compounds have been used in conjugated fluorescent dyes that emit blue fluorescence with high quantum[10] and electroluminescence yields.[11]

In literature, 2-pyrazoline derivatives seem to be frequently studied and a large number of methods are reported for their synthesis. In their pioneering work in the late 19th century, Fischer and Knoevenagel synthesised 2-pyrazolines by the reaction of α, β-unsaturated aldehydes and ketones (chalcones) with hydrazine.[12] This remains one of the most commonly used methods for the synthesis of these compounds. Some of the catalysts used for the synthesis include glacial acetic acid under heating or ultrasound irradiation,[13] K_2CO_3 – mediated microwave irradiation[14] $H_3PW_{12}O_{40}$,[15] Amberlyst 15 in refluxing toluene,[16] hot propionic acid,[17] triethanolamine,[18] pyridine in refluxing ethanol[19] and ethanolic sodium hydroxide[20]/sodium acetate.[21]

Chalcones are aromatic α, β-unsaturated carbonyl compounds that form the central core of a variety of important naturally occurring compounds like flavonoids, isoflavonoids and their derivatives.[22] These compounds have been receiving increased attention due to numerous potential biological and pharmacological activities.[23] While the chalcone backbone itself has physiological properties, the highly electrophilic three

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carbon α, β-unsaturated carbonyl system in them has assumed further significance due to their utility in the synthesis of many heterocyclic compounds. which are biologically active.[24] Thus, chalcones are useful synthons for the synthesis of a large number of bioactive molecules, primarily the nitrogen containing heterocyclics.[25]

Solvents are an important constituent of any organic synthesis and often account for the maximum amount of waste that is generated.[26] The conventional solvents like benzene, DMSO, *etc*., have detrimental environmental impacts.[27] Hence, the use of green solvents in organic synthesis is an area of extensive research and several green solvents like water, ionic liquids, polyethylene glycol and some biomass-based solvents in organic synthesis have been reported in the literature.[28] Ethyl lactate is a versatile green solvent which can be easily obtained from carbohydrate feedstock; it is cheap, non-toxic and biodegradable and addition of a co-solvent like water alters its polarity and the yields of the products.[29]

In the last few years, there has been substantial interest in the organic reactions promoted by cerium chloride.[30] Unlike common Lewis acids, trivalent lanthanide salts are stable in aqueous solutions. Cerium chloride heptahydrate ($CeCl_3 \cdot 7H_2O$), the most common commercially available source of Ce^{+3}, finds useful application as a catalyst in heterocyclic synthesis.[31] It is a mild Lewis acid which has low toxicity and is relatively inexpensive. Hence, it is a good candidate for green organic transformations.[32] Our studies have demonstrated the effective use of $CeCl_3 \cdot 7H_2O$ as a catalyst in the synthesis of imines[33] as well as in reductive amination reactions.[34] Further, we have synthesised 3-methyl isoxazolone derivatives catalysed by $CeCl_3 \cdot 7H_2O$ using ethyl lactate (70%) as a solvent.[35] Recently we have reported the use of low melting mixtures of sugars, urea and $CeCl_3 \cdot 7H_2O$ as efficient green solvents for the synthesis of 1,4-dihydropyridines.[36]

In continuation with our previous work on the use of Cerium chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) as a mild, low cost and high performance catalyst in the green synthesis of heterocyclic compounds, we now report a facile synthesis of a number of 1,3,5-trisubstituted -2-pyrazolines from chalcones and phenyl hydrazine using $CeCl_3 \cdot 7H_2O$ as catalyst and ethyl lactate (70%) as a solvent. To the best of our knowledge, the use of these conditions for the synthesis of pyrazolines is not reported in the literature.

2. Experimental

All the reagents were purchased from SD Fine Chem Limited (India) and Thomas Baker (India) and were used directly without any further purification. The characterization of the products was done by comparing their physical constants with the literature values and by recording spectra. All the melting points were recorded on Veego digital melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured at ambient temperatures using $CDCl_3$ as the solvent on a 500 MHz MHz BRUKER AVANCE DRX-500 instrument.

2.1 *Synthesis of chalcones*

All the chalcones were synthesised using a reported procedure.[37]

2.2 *General procedure for synthesis of 1,3,5-trisubstituted-2-pyrazolines*

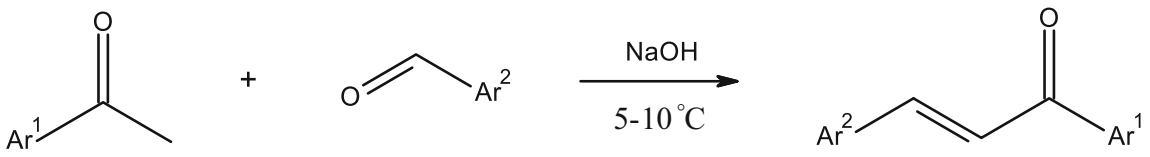
A mixture of phenyl hydrazine **4** (2.0 mmol, 0.20 mL), $CeCl_3 \cdot 7H_2O$ (20 mol%) and chalcone **3** (1.0 mmol) was refluxed in ethyl lactate (70%) for 5 h. The progress of the reaction was monitored by thin layer chromatography (TLC) using n-hexane:ethyl acetate (7:3) as the solvent system. The solid precipitate formed during the reaction was filtered and washed with cold water. In most of the cases, the product obtained was pure, and when impure it was recrystallized using ethanol.

2.2a *Spectral data for 5-(4-methylphenyl)-1,3-diphenyl-2-pyrazoline* ***(5a)***: Colour: light yellow; Time: 300 min; Yield: 82%; M.p.: 128–129 °C; ^1H NMR (500 MHz, Chloroform-d, δ, ppm): 2.30 (s, 3H, CH_3), 3.08 (dd, J = 16.5 Hz, 12.0 Hz, 1H), 3.77 (dd, J = 16.5 Hz, 8.5 Hz 1H), 5.20 (dd, J = 12.0 Hz, 8.5 Hz, 1H), 7.71–6.74 (m, 14H, Ar-H).

^{13}C NMR (125 MHz, Chloroform-d, δ, ppm): 21.1, 43.6, 64.3, 113.4, 119.0, 125.7, 125.8, 128.5, 128.9, 129.8, 132.8, 137.2, 139.7, 144.9, 146.7.

3. Results and Discussion

In our earlier work,[35] we reported the synthesis of isoxazole derivatives by the reaction of hydroxylamine hydrochloride with substituted aldehydes and ethyl acetoacetate using $CeCl_3 \cdot 7H_2O$ as catalyst and ethyl lactate (70%) as a solvent. To further our quest for isoxazoles, we first synthesised a series of chalcones. These chalcones were then reacted with hydroxylamine hydrochloride using the standardised procedure. While this reaction did not go to completion and resulted in a mixture which consisted of unreacted chalcone and the desired isoxazole (as demonstrated by GC-MS results), it encouraged us to explore the reaction of the chalcones with phenyl hydrazine.



1 **2** **3**

Scheme 1. Reaction of substituted acetophenones and benzaldehydes to form chalcones.

Table 1. Synthesis of different chalcones using substituted acetophenones and benzaldehydes.

Entry	Ar^1	Ar^2	Melting point (°C)		Yield (%)
			Found	Reported[38–40]	
3a	C_6H_5	$4-CH_3C_6H_4$	94 – 95	94 – 96	86
3b	C_6H_5	$4-ClC_6H_4$	112 – 113	111 – 113	86
3c	C_6H_5	$4-(CH_3)_2NC_6H_4$	113 – 114	112 – 114	80
3d	C_6H_5	$4-MeOC_6H_4$	72 – 73	69 – 71	94
3e	C_6H_5	$4-NO_2C_6H_4$	156 – 158	157	79
3f	C_6H_5	$3-NO_2C_6H_4$	133 – 135	133	87
3g	$4-CH_3C_6H_4$	$4-CH_3C_6H_4$	126 – 127	126 – 127	95
3h	$4-CH_3C_6H_4$	$4-ClC_6H_4$	143 – 144	145 – 147	73
3i	$4-CH_3C_6H_4$	$4-(CH_3)_2NC_6H_4$	128 – 129	129	77
3j	$4-CH_3C_6H_4$	$4-MeOC_6H_4$	95 – 96	94 – 96	94
3k	$4-CH_3C_6H_4$	$4-NO_2C_6H_4$	155 – 156	155 – 157	82
3l	$4-CH_3C_6H_4$	$3-NO_2C_6H_4$	146 – 147	148	93
3m	$4-CH_3C_6H_4$	C_6H_5	46 – 47	42 – 47	74
3n	$4-CH_3C_6H_4$	$2-ClC_6H_4$	112 – 113	115	78
3o	$4-CH_3C_6H_4$	$3,4-diMeOC_6H_3$	135 – 136	135 – 136	98
3p	$4-MeOC_6H_4$	$4-CH_3C_6H_4$	126 – 127	127	98
3q	$4-MeOC_6H_4$	$4-ClC_6H_4$	124 – 125	126 – 128	95
3r	$4-MeOC_6H_4$	$4-(CH_3)_2NC_6H_4$	80 – 81	80	99
3s	$4-MeOC_6H_4$	$4-MeOC_6H_4$	100 – 101	100 – 101	95
3t	$4-MeOC_6H_4$	$4-NO_2C_6H_4$	158 – 159	158	93
3u	$4-MeOC_6H_4$	$3-NO_2C_6H_4$	156 – 157	158	95
3v	$4-MeOC_6H_4$	C_6H_5	105 – 106	104 – 105	99
3w	$4-MeOC_6H_4$	$2-ClC_6H_4$	126 – 128	127	91

Reaction conditions: acetophenone derivative (25 mmol), substituted benzaldehyde (25 mmol), dissolved in 10 mL ethanol, added NaOH (1.0 g in 2–3 mL water), stirred and kept overnight in the freezer**.**

4. Synthesis of chalcones

The synthesis of a series of chalcones was carried out by using a reported procedure from literature.[37] (Scheme 1).

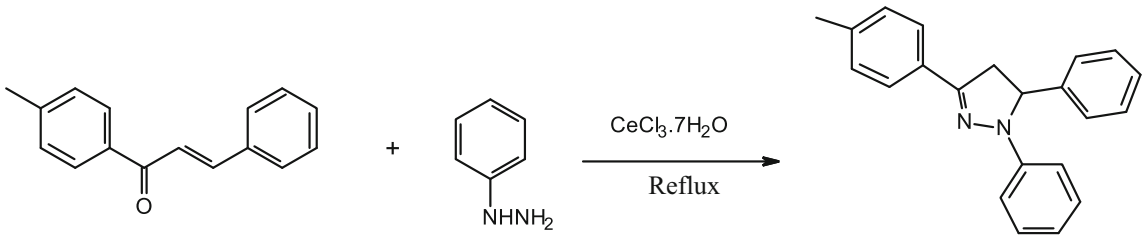
The reaction of substituted acetophenones (**1**) with the substituted benzaldehydes (**2**) occurred in a facile manner to give the chalcones **3**. Good yields of the chalcones were obtained and their formation was confirmed by comparison of their melting points with that reported in the literature. The results are listed in Table 1.

4.1 *Synthesis of 1,3,5-trisubstituted-2-pyrazolines*

An examination of the available literature revealed that the condensation of chalcones and phenyl hydrazine worked best when the latter was in excess. So, we fixed the stoichiometry of chalcone to phenyl hydrazine to be 1:2. To further establish the optimal conditions, a model reaction of chalcone, **3m** with phenyl hydrazine **4** in the ratio 1:2 was chosen (Scheme 2).

For this heterocyclisation reaction, a series of experiments were carried out by varying the solvent, the amount of catalyst and the temperature to arrive at the optimum conditions. The results are summarised in Table 2.

The reaction did not proceed in water and this could be because phenyl hydrazine is insoluble in water (Table 2, entries 1–3). In ethanol, the reaction mixture was faintly turbid and the reaction failed to occur. (Table 2, entries 4, 5). However, no explanation can be attributed to this experimental observation. Only trace amount of the product was obtained in 70% ethyl lactate at R.T.



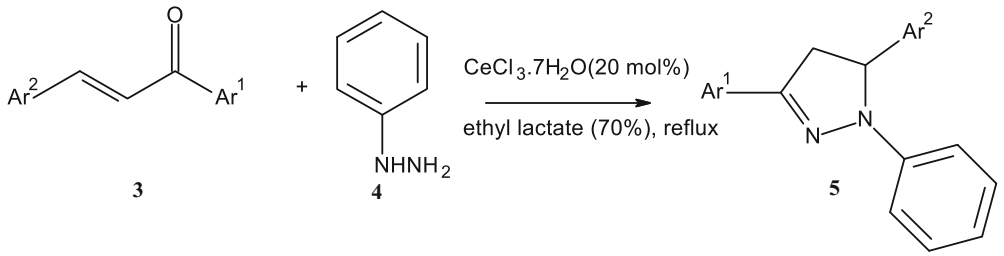
3m **4** **5m**

Scheme 2. Model reaction for the optimisation of reaction conditions.

Table 2. Optimisation of reaction conditions for the synthesis of **5m**.

No.	Solvent	Catalyst (mol%)	Temperature	Time (h)	Yield (%)
1	Water	–	R.T.	24	No product
2	Water	20	R.T.	24	No product
3	Water	20	Reflux	5	No product
4	Ethanol	15	Reflux	5	No product
5	Ethanol	20	Reflux	5	No product
6	Ethyl lactate (70%)	–	R.T.	24	Trace
7	Ethyl lactate (70%)	20	R.T.	24	Trace
8	Ethyl lactate (70%)	5	Reflux	5	Trace
9	Ethyl lactate (70%)	10	Reflux	5	66
10	Ethyl lactate (70%)	15	Reflux	5	69
11	Ethyl lactate (70%)	20	Reflux	5	87
12	Ethyl lactate (80%)	20	Reflux	5	72
13	Ethyl lactate (100%)	20	Reflux	5	Trace

Reaction conditions: chalcone **3m** (1.0 mmol), phenyl hydrazine **4** (2.0 mmol).



3 **4** **5**

Scheme 3. Synthesis of 1,3,5-trisubstituted-2-pyrazoline derivatives.

in the presence and absence of a catalyst. (Table 2, entries 6, 7). As per the above results, the best yield was obtained when the reaction was carried out in ethyl lactate (70%) at reflux using $CeCl_3 \cdot 7H_2O$ (20 mol%) (Table 2, entry 11). Higher concentrations of ethyl lactate reduced the yield considerably (Table 2, entries 12, 13). On the basis of the above results, several 1,3,5-triaryl pyrazoline derivatives were synthesised using $CeCl_3 \cdot 7H_2O$ (20 mol%) in the presence of ethyl lactate (70%) as a solvent at reflux temperature (Scheme 3).

The reactions proceeded well for several substrates, but those with electron donating substituent generally gave higher yields than those with electron withdrawing substituent. However, in the case of chalcones **3b, 3d, 3e, 3f, 3k, 3r, 3t, 3u** and **3w** no product was obtained even after prolonged heating. Table 3 gives the yields and melting points of the pyrazoline derivatives synthesised.

All the products were characterised by comparison of their melting points with those available in literature and by spectral analysis. The IR spectrum of all the synthesised 2-pyrazoline derivatives showed characteristic peaks in the following ranges *viz.* 1590 – 1620 cm^{-1}(C=N stretch of the pyrazoline ring), 1495 – 1520 cm^{-1}(C=C stretch of aromatic ring) and 1120 – 1220 cm^{-1} (C-N stretch of pyrazoline ring). All these values match well with the reported values for these functional groups.

Table 3. Synthesis of 1,3,5-trisubstituted-2-pyrazoline derivatives.

Entry	Ar_1	Ar_2	Yield %	Melting point (°C)	
				Found	Reported
5a	C_6H_5	$4-CH_3C_6H_4$	82	128 – 129	128 – 130[41]
5b	C_6H_5	$4-ClC_6H_4$	No product	–	–
5c	C_6H_5	$4-(CH_3)_2NC_6H_4$	70	120 – 121	120[42]
5d	C_6H_5	$4-MeOC_6H_4$	No product	–	–
5e	C_6H_5	$4-NO_2C_6H_4$	No product	–	–
5f	C_6H_5	$3-NO_2C_6H_4$	No product	–	–
5g	$4-CH_3C_6H_4$	$4-CH_3C_6H_4$	62	139 – 140	141 – 142[43]
5h	$4-CH_3C_6H_4$	$4-ClC_6H_4$	71	152 – 153	155 – 156[44]
5i	$4-CH_3C_6H_4$	$4-(CH_3)_2NC_6H_4$	72	141 – 142	140[42]
5j	$4-CH_3C_6H_4$	$4-MeOC_6H_4$	73	138 – 139	140 – 142[45]
5k	$4-CH_3C_6H_4$	$4-NO_2C_6H_4$	No product	–	–
5l	$4-CH_3C_6H_4$	$3-NO_2C_6H_4$	38	143 – 144	144 – 146[46]
5m	$4-CH_3C_6H_4$	C_6H_5	86	155 – 156	155 – 157[47]
5n	$4-CH_3C_6H_4$	$2-ClC_6H_4$	74	121 – 122	123 – 124[46]
5o	$4-CH_3C_6H_4$	$3,4-diMeOC_6H_3$	68	119 – 120	118 – 119[48]
5p	$4-MeOC_6H_4$	$4-CH_3C_6H_4$	75	135 – 136	136 – 137[41]
5q	$4-MeOC_6H_4$	$4-ClC_6H_4$	52	158 – 159	160 – 161[14]
5r	$4-MeOC_6H_4$	$4-(CH_3)_2NC_6H_4$	No product	–	–
5s	$4-MeOC_6H_4$	$4-MeOC_6H_4$	87	145 – 146	147 – 148[49]
5t	$4-MeOC_6H_4$	$4-NO_2C_6H_4$	No product	–	–
5u	$4-MeOC_6H_4$	$3-NO_2C_6H_4$	No product	–	–
5v	$4-MeOC_6H_4$	C_6H_5	66	113 – 114	110 – 112[46]
5w	$4-MeOC_6H_4$	$2-ClC_6H_4$	No product	–	–

Reaction conditions: chalcone **3** (1.0 mmol), phenyl hydrazine **4** (2.0 mmol), $CeCl_3 \cdot 7H_2O$ (20 mol%). Refluxed in ethyl lactate (70%) for 5 h.

The ^{1}H NMR spectrum of product **5m** shows a multiplet in the region 6.77–7.72 ppm integrating for 14 protons which is due to the protons of three phenyl rings, one of which is monosubstituted with a methyl group in the *para* position. A doublet of a doublet at 5.22 ppm is attributed to the single proton at position 5 of the pyrazoline ring (Figure 1). The two protons in position 4 of this ring are diastereotopic and they appear as two doublets of doublet at 3.11 ppm and 3.80 ppm. The two geminally coupled protons have large coupling constant (J = 12.5 Hz) which are very characteristic. The methyl group on one of the phenyl rings appears as a singlet at 1.55 ppm. These values are in good agreement with literature values for this compound.[47] The ^{1}H NMR spectra of all the products were analysed and found to show the expected peaks corresponding to the above structural features.

The ^{13}CNMR shows the characteristic peaks for the aromatic carbons. The quaternary carbon at C-3 appears in the range 140–145 ppm. Peaks in the range 40–45 ppm and 60–64 ppm, which are attributed to the secondary and tertiary carbons at C-4 and C-5, respectively, were observed for all the compounds. Thus, the structures of all the products were unambiguously established.

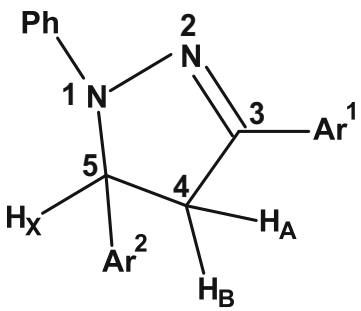
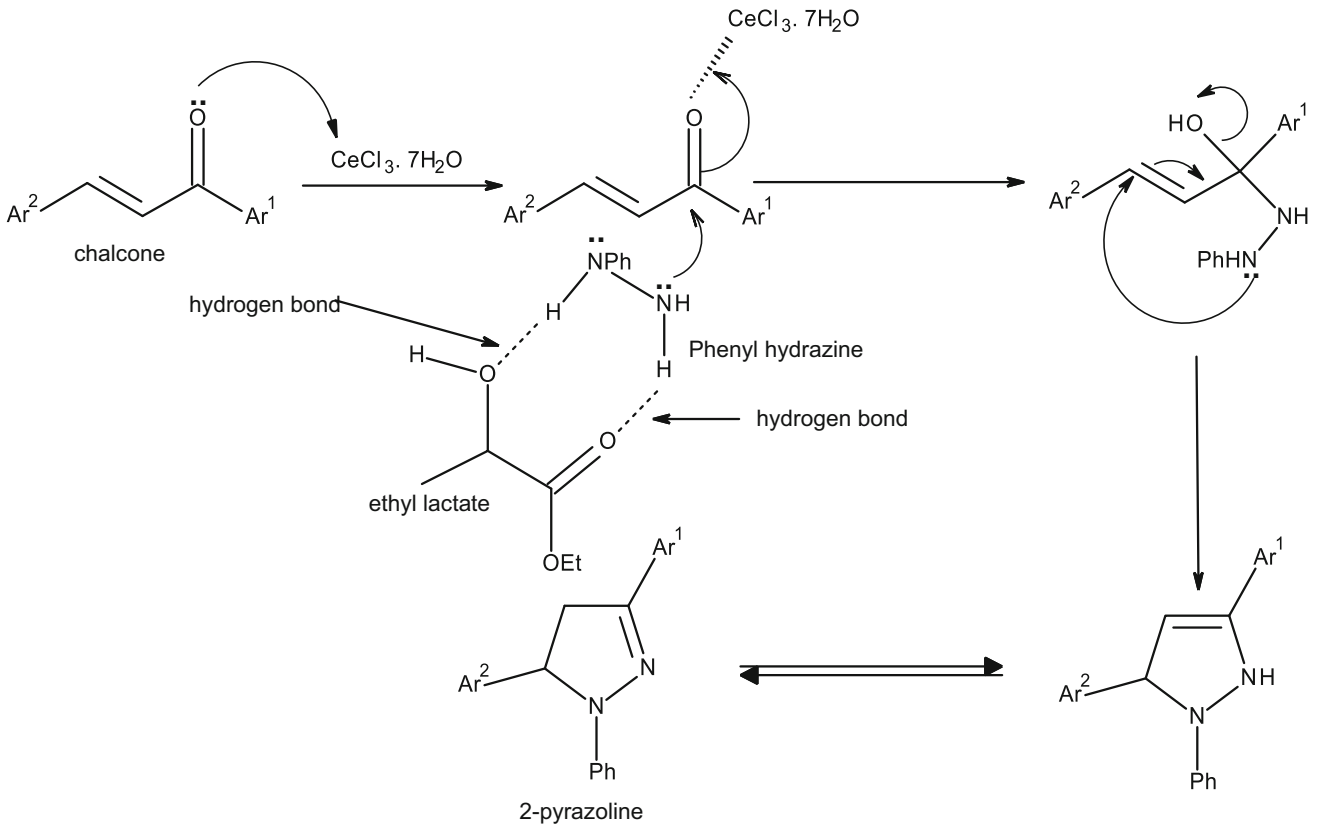


Figure 1. General structure of the 2-pyrazoline derivatives.

To evaluate the recyclability of the solvent and catalyst, the filtrate obtained after removal of the product **5m** was reused as such for consecutive reactions. It was confirmed that there is no product and reactant left in the filtrate, with the help of thin layer chromatography (TLC). Three consecutive trials were performed and the yields at the end of each cycle were measured as follows: 86, 83 and 78% in 1st, 2nd and 3rd cycle, respectively. Good yield at the end of the third cycle confirms the recyclability of the solvent – catalyst mixture without appreciable loss in activity.



Scheme 4. Suggested mechanism for the reaction of chalcone with phenyl hydrazine in the presence of $CeCl_3 \cdot 7H_2O$.

A reasonable pathway for the reaction between chalcone and phenyl hydrazine in the presence of $CeCl_3 \cdot 7H_2O$ is proposed based on the results obtained and information in the literature. $CeCl_3 \cdot 7H_2O$ is a mild Lewis acid capable of coordinating with carbonyl oxygen which enhances its reactivity. Liu and Wen have proposed the participation of ethyl lactate in increasing the nucleophilicity of the amino group by hydrogen bond formation.[50] Based on mechanisms proposed by Fazaeli *et al.*, in the synthesis of 2-pyrazolines by tungstophosphoric acid,[46] by Kidwai and Jahan in Mannich reaction catalysed by $CeCl_3 \cdot 7H_2O$,[51] and by Liu and Wen in the synthesis of keto and aldoximes in the presence of ethyl lactate,[50] we propose the following likely mechanism for this reaction (Scheme 4).

5. Conclusions

This paper describes a facile protocol for the synthesis of 1,3,5-triaryl-2-pyrazoline derivatives using cerium chloride heptahydrate in ethyl lactate (70%). This protocol involves easy workup and fulfils some of the principles of green chemistry. It uses ethyl lactate which is a biodegradable solvent and $CeCl_3 \cdot 7H_2O$, which is a water-tolerant Lewis acid. Further, the catalyst and solvent are recyclable up to three times without appreciable loss in activity. The reaction works well for all systems giving good to moderate yields of the desired products. As compared to reported methods, the current methodology provides a cleaner route to the synthesis of the target molecules with the additional advantage of recyclability of solvent and catalyst.

Supplementary Information (SI)

The supplementary information gives the experimental details, physical constants, ^{1}H NMR and ^{13}C NMR data for all the synthesised 1,3,5-trisubstituted 2-pyrazolines. Supplementary Information is available at www.ias.ac.in/chemsci.

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