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Rapid and High yielding One Pot Efficient Protocol for the Synthesis of Pyrazoline Derivative

Patki A. S.[1], Wakhradakar M. G.[2], Pande P. R[3]., Phulwale S. P. [4], Kendre T. U.[5], Walle M. R.[6], Muley D. B*.

[1]Department of Chemistry, Shivaji Mahavidyalaya, Renapur, Maharashtra, India

[2]Department of Chemistry, Hutatma Jaywantrao Patil Mahavidyalaya, Himayatnagar, Maharashtra, India

[3]Department of Chemistry, Nutan Mahavidyalaya, Selu, Maharashtra, India

[4]Department of Chemistry, K. N. Bhise Arts, Commerce and Vinayakrao Patil Science College Vidyanagar, Bhosare, Kurduwadi, Maharashtra, India

[5]Department of Chemistry, Toshniwal ACS College Sengaon, Maharashtra, India

[6]Department of Chemistry, Sundarrao More ACS College Poladpur, Maharashtra, India

[*]Department of Chemistry, Shivaji Mahavidyalaya, Udgir, Maharashtra, India

Abstract:

A facile route was developed for the synthesis of 1,3,5-trisubstituted pyrazoline derivatives from Aromatic aldehyde, aromatic ketone and phenyl hydrazine in an aqueous media by using $CoFe_2(C_4H_4O_6)_3.6H_2O$ as a catalyst at reflux condition. The reaction protocol generate 1,3,5-trisubstituted-2-pyrazolines in good to excellent yields via a one-pot addition–cyclocondensation between aromatic aldehyde, acetophenone and aryl hydrazines. The catalyst can be reused without much loss in the catalytic activity. The structures of the synthesized compounds were confirmed by analytical techniques.

Keyword: Pyrazoline, reflux, $CoFe_2(C_4H_4O_6)_3.6H_2O$, aromatic aldehyde.

Introduction:

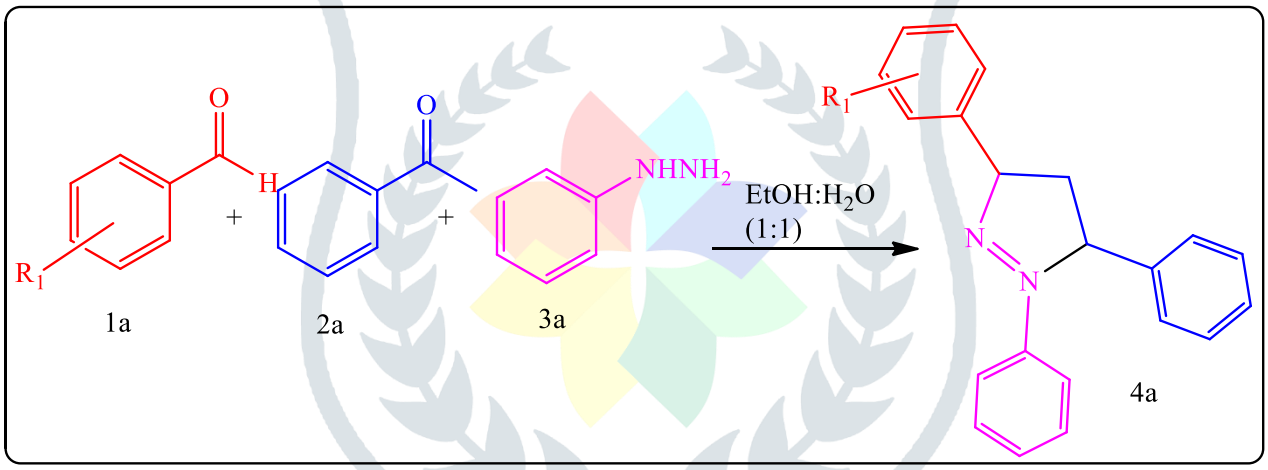
In Recent era Considerable interest has been concentrated on the pyrazole structure, which has been recognized to possess a wide range of biological activities such as tranquillizing, psycho analeptic, anticonvulsant and antihypotensive activities [1-2]. Pyrazoline derivatives are attracting many researchers, not only in biological concern of their bioactivity but also several pyrazoline derivatives possess important pharmacological activities and therefore they find wide application in drugs synthesis. Pyrazolines are biologically active moiety with a diversified biological activities like and anti-HIV [3], antimicrobial [4], antitubercular [5], antiinflammatory [6], antitumor [7], anticancer [8], anticonvulsant [9], Some of the pyrazoline derivatives are also reported to possess anti-inflammatory [10], antidiabetic [11] and antibacterial properties [12].

Experimental:

Chemicals were procured from sigma aldrich and were used without further purification. Melting points of compounds were determined by in an open capillary method and are uncorrected. The product confirmation was done by TLC plate method. IR spectra were recorded (in KBr pallets) on Bruker spectrophotometer. ^{1}H NMR spectra were recorded (in DMSO-d6) on Avance-300 MHz spectrometer using TMS as an internal standard.

General Procedure for the synthesis of pyrazoline:

Mixture of aromatic acetophenone (2 mmol), aromatic benzaldehyde (2 mmol), potassium hydroxide (20%, 5 mL) and phenyl hydrazine (4mmol) in Ethanol: Water as a solvent in 1:1 ratio (15 mL), a catalytic amount $CoFe_2(C_4H_4O_6)_3.6H_2O$ of catalyst also added and were allowed to react in round bottom flask under reflux condition. Reaction progress was monitored by using TLC plates after regular interval of timetime. After the completion of reaction, the mixture was poured to crushed ice to yield solid product. The solid compound was filtered and washed and then recrystalized using methanol to yield pyrazoline derivatives.



Catalytic Activity:

Synthesis of 1,3,5 triaryl pyrazoline is carried out by the reaction of aromatic aldehyde, aromatic ketone and phenyl hydrazine under optimized reaction condition. In order to select appropriate solvent the synthesis we carried different trial which were listed in table 1.

As seen from the table no polar benzene media yields 58 % of desired product with elevated time period of 6 hr., the formed was not satisfactory so several other trials were taken in which Acetonitrile, ethyl alcohol and water were used which deliver 66%, 74% and 68 % of product yield with time taken for the reaction 5,5,6 hr respectively. In last attempt and experiment was made by taking EtOH: H_2O as a solvent in 1:1 ratio and surprisingly product yield was raised to 82% with short of reaction time.

Table 1: Optimization of solvent for reaction condition.

Entry	Solvent	Time (hr.)	Yield (%)
1	C_6H_6	6	58
2	CH_3CN	5	66
3	EtOH	5	74
4	H_2O	6	68
5	EtOH:H_2O	4	82

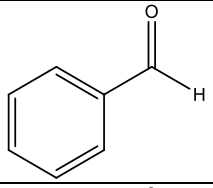
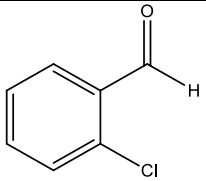
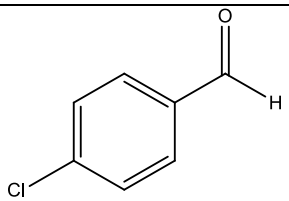
Optimization of Amount of catalyst was confirmed by carrying different set of separate reaction with different amount of catalyst and it was found that synthesis of 1,3,5 triaryl pyrazoline was found to be most feasible with 10 mol% of catalyst.

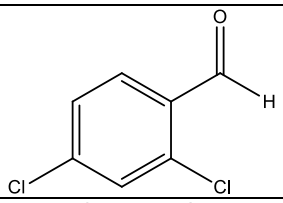
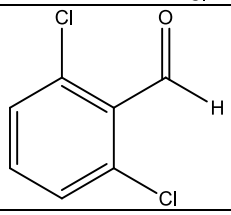
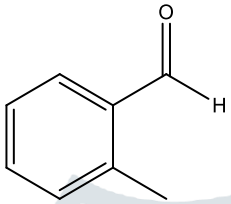
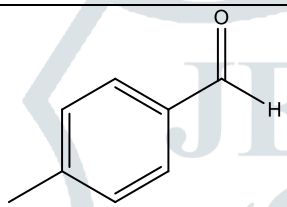
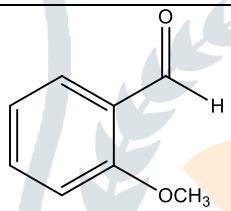
Table 2: Optimization of amount of catalyst for reaction condition.

Entry	Amount (mol%)	Time (hr.)	Yield (%)
1	5	4	78
2	10	4	82
3	15	3.5	86
4	20	3	86

Synthesis of 1,3,5 triaryl pyrazoline by one pot cyclocondensation of substituted benzaldehyde, aromatic ketone and phenyl hydrazine under the $CoFe_2(C_4H_4O_6)_3.6H_2O$ as a catalyst under reflux condition. The reaction was tested with differently substituted electron withdrawing and releasing group. The result was displayed in table 3. As seen from the Table 3 electron withdrawing group dominates the yield of pyrazoline product. Entry 4 clearly shows 90% of pyrazoline was obtained with very short of time 3hr. Table 3 indicates that synthesis of pyrazoline under these optimized redaction condition delivers good to Excellent yield.

Table 3: Optimization of Synthesis of 1,3,5 triaryl pyrazoline from differently substituted aromatic aldehyde

Entry	Aromatic Aldehyde	Product	Time Hr.	Yield[X]
1		**4a**	4	82
2		**4b**	3	88
3		**4c**	3.5	86

4		**4c**	3	90
5		**4d**	3.5	85
6		**4e**	5	71
7		**4f**	4.5	74
8		**4g**	6	68
X represent isolated product				

Conclusion:

Synthesis of 1,3,5 triaryl pyrazoline from aromatic aldehyde, aromatic ketone and phenyl hydrazine under reflux condition by using $CoFe_2(C_4H_4O_6)_3.6H_2O$ catalyst afford good to excellent yield. The major advantage of this protocol is short reaction time, excellent yield and easy recovery of catalyst at the end of reaction. reaction proceeds smoothly and the catalyst used three time for further synthesis.

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