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Research Article

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Synthesis of Highly Functionalized Pyrazoles Using $AlCl_3$ as Catalyst

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ABSTRACT

An easy and simple three-component one-pot process for the synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives using aldehyde, phenylhydrazine and malononitrile has been developed. The method gave 79 to 89% yields in a maximum of 30 minutes using $AlCl_3$ as catalyst in aqueous ethanol (1:1 v/v).

Keywords: Pyrazole; One-pot; Multi-component; $AlCl_3$; Lewis acid; Ethanol; Water

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INTRODUCTION

Pyrazole moiety is an important template for many biologically active compounds. The 1-pyrazolyl alanine was the first natural pyrazole which was isolated from the seeds of watermelon in 1959 [1]. The derivatives of pyrazole molecule possess wide range of biological activities such as anticancer [2], anti-inflammatory [3], ACE inhibitor [4], MAO inhibitor [5], cholecystokinin-1 receptor antagonist [6], estrogen receptor (ER) ligand activity [7], anti-microbial [8], anti-fungal [8], antitubercular [9], anti-convulsant [10] etc. One-pot multi-component reaction (MCR) is the most efficient route for the synthesis of heterocyclic molecules [11-14]. It provides a rapid and powerful tool for the synthesis of versatile heterocycles having C-O and C-N bonds [15,16]. Recently MCR have also been viewed in the field of green chemistry [17], because by using this strategy several step transformations can be implemented in single step, thereby reducing the number of workup process, minimizing the extraction and purification process as well as reduction in waste generation. It also saves energy and manpower which are directly linked with the goal of green and sustainable chemistry [18]. Several methods have been reported in the literature for the synthesis of substituted pyrazole by using different catalyst such as urea [19], trisodium citrate dehydrate [20-26], $ZnCl_2$ and $NaCNBH_3$ [27], dodecylbenzenesulphonic acid [28], ZrO_2 nanoparticles [29], cesium fluoride [30], L-Proline [31], molecular I_2 [32], ionic liquid [33], maltose [34]. We have developed; $AlCl_3$ catalyzed three-component one-pot synthesis of highly functionalized pyrazoles by using substituted aldehyde, phenylhydrazine and malononitrile in aqueous ethanol [35-37].

EXPERIMENTAL SECTION

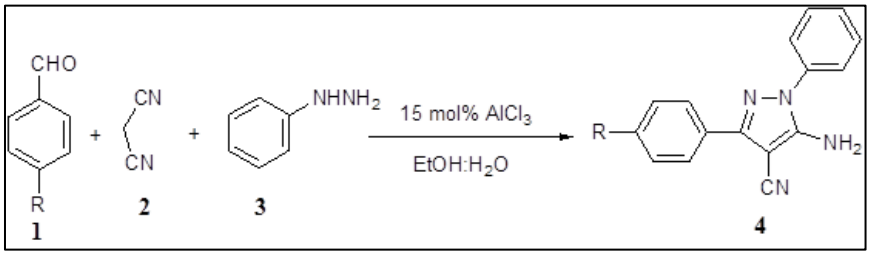
All commercially available solvents and reagents were purchased from reputed company and were used without further purifications. Melting points were determined on a scientific melting point apparatus and are uncorrected. Thin-layer chromatography was performed on aluminium-coated silica plates purchased from Merck.

General Procedure for Synthesis of Substituted 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (4)
A solution of aldehyde (1 mmol), malononitrile (1 mmol) and $AlCl_3$ were taken in 30 mL solution of ethanol:water (1:1, v/v) in 100 mL round bottom flask. The reaction mixture was stirred at 80^oC, till white precipitate was obtained. Once the precipitate was obtained, phenylhydrazine (1 mmol) was added to this mixture and further heated

the reaction mixture for appropriate time (Table 2). The progress of reaction was monitored by TLC (hexane: ethyl acetate, 7:3). After completion of reaction, the reaction mixture was diluted with ice cold water. The solid crude product was obtained which were collected by filtration, washed with water and dried under reduced pressure. The product were further recrystalize by absolute ethanol to afford the pure product.

RESULTS AND DISCUSSION

The reaction of benzaldehyde, phenylhydrazine and malononitrile gave 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (4a) in 85% yield using 15 mol% $AlCl_3$ in aqueous ethanol (1:1, v/v) (Scheme 1, Table 1 entry 9, Table 2 entry 4a). A number of reactions were performed to optimize the reaction condition. The optimum result was obtained using 15 mol% $AlCl_3$ as catalyst in ethanol-water (1:1, v/v) solvent system (Table 1). The optimization of catalyst in different solvent systems is given in Table 1. We tried other Lewis acids such as BF_3-OEt_2 and $ZnCl_2$ (Table 1, entry 11-14) also for the reaction which gave yield less than $AlCl_3$.



Scheme 1: Synthesis of substituted 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile

To optimize the reaction time, the reaction was performed for 1 hour with evaluation at 30 min and 45 min for the completion of reaction and yield. The yield remains constant after 30 minutes of the reaction. The reaction was performed in sequential manner. This is because; using all the reactants at one time did not give product more than 40% in all the cases. For this we first dissolve benzaldehyde (1 mmol) in ethanol-water (30 mL) and then added 15 mol% of $AlCl_3$ followed by malononitrile (1 mmol). The reaction mixture was stirred till white precipitate was obtained. To this white precipitate in the same reaction vessel, added phenylhydrazine (1 mmol) with constant stirring. After addition of all phenylhydrazine the reaction mixture was stirred at 80^{o}C for 30 min and the progress of reaction was monitored by TLC.

Table 1: Synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (4a) under different reaction conditions

Entry	Solvent	Catalyst	Time (h)	% Yield
1	CH_3CN	15 mol% $AlCl_3$	1	46
2	CH_2Cl_2	15 mol% $AlCl_3$	1	43
3	THF	15 mol% $AlCl_3$	1	36
4	H_2O	15 mol% $AlCl_3$	1	74
5	EtOH	10 mol% $AlCl_3$	1	62
6	EtOH	15 mol% $AlCl_3$	1	75
7	EtOH	20 mol% $AlCl_3$	1	75
8	EtOH:H_2O	10 mol% $AlCl_3$	1	64
9	EtOH:H_2O	15 mol% $AlCl_3$	1	85
10	EtOH:H_2O	20 mol% $AlCl_3$	1	85
11	EtOH	15 mol% BF_3-OEt_2	1	68
12	EtOH:H_2O	15 mol% BF_3-OEt_2	1	72
13	EtOH	15 mol% $ZnCl_2$	1	74
14	EtOH:H_2O	15 mol% $ZnCl_2$	1	75

CONCLUSION

In the present work, we have developed a simple and easy method for the one-pot synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives using $AlCl_3$ as catalyst in environmental friendly solvent ethanol-water. The method gave 79 to 89% yields in maximum of 30 minutes. This method ensures the wide substrate scope with excellent yields and the products were isolated and purified by recrystallization.

Table 2: Derivatives of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (4) synthesized

S. No.	Ar-CHO	Time (min)	%Yield	Melting point (°C)	
				Found	Lit[ref]
4a	C_6H_5	30	85	161	159-160 [33]
4b	4-ClC_6H_4	20	88	129	128–130 [32]
4c	4-CH_3C6H_4	30	84	120	117–118 [35]
4d	4-$OCH_3C_6H_4$	30	83	110	106–108 [33]
4e	4-$NO_2C_6H_4$	15	80	163	164–166 [32]
4f	3-$NO_2C_6H_4$	15	79	130-131	128–130 [32]
4g	2-$OCH_3C_6H_4$	25	85	130	130–132 [33]
4h	3-CNC_6H_4	20	83	156	158–160 [32]
4i	2-$OHC6H_4$	30	89	159	160–162 [32]
4j	3,4-di$OCH_3C_6H_3$	30	84	120-122	120–123 [32]

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