Synthesis of Substituted Pyrimidine Derivatives by using $InCl_3$ Catalyst via One Pot Multi-component Reaction

P. CHAVAN[1]*, A. GHOTI[1], S. JADHAV[2], M. RAI[2],
[1] Department of Chemistry, Doshi Vakil College, Goregaon-Raigad (MS), India.
[2]Department of Chemistry, Dr. Rafiq Zakaria College for Women, Aurangabad (MS), India.
*Corresponding Author Email: chemistryp141286@gmail.com

Abstract

*A synthesis of substituted pyrimidine derivatives (4-amino-2-(R)-1,2-dihydroxybenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile)(**4a-j**) through one flask containing three component mixture- benzamidazole (**1**), aromatic aldehyde (**2a-j**), malononitrile (**3**) by using $InCl_3$ (Lewis acid) catalyst under methanol solvent and reflux at 110^oC. This method provides good to excellent yield and simple work procedure.*

Keywords: One pot multi-component reaction, aromatic aldehyde, substituted pyrimidine derivatives and reflux.

INTRODUCTION

A one flask containing multi-component reaction method has been extensively used for the synthesis of natural products [1-4]. Nitrogen containing heterocyclic compounds is very important role play in the medicinal field [5] like antimicrobial, antifungal, etc. properties [6-7]. Recently, number of methods has been discovered for the synthesis of Nitrogen containing heterocyclic compounds [8-9]. However, some of the methods suffer from limitations such as multi-component reaction, wastage of product, long reaction time, and satisfactory yields. A literature survey revealed that, one pot multi-component reactions rarely explored through Lewis acid catalyst.

By considering above fact, we have focused on synthesis of 4-amino-2-(R)-1,2-dihydroxybenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives(**4a-j**) by using Lewis acid catalyzed one pot containing three component like benzamidazole (**1**), aromatic aldehyde (**2a-j**), malononitrile (**3**) in methanol solvent under refluxing condition.

EXPERIMENTAL SECTION

General experimental information: The melting points were recorded manually (incorrect). 1H NMR and 13C NMR spectra were recorded at (Bruker) 400 MHz and 100 MHz in DMSO solvent using TMS internal standard. IR spectra were determined by Perkin-Elmer FT-IR Spectrometer. All AR grade reagents were used for synthesis.

General procedure for synthesis of 4-amino-2-(R)-1,2-dihydroxybenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile derivatives (4) **:** A 100 ml Round Bottom flask were charged with benzamidazole (**1**) (0.1 mol), aromatic aldehyde **(2a-j)** (0.1 mol), malononitrile (**3**) (0.1 mol), and $InCl_3$ (10 mol %) catalyst in 6 ml methanol. The mixture was reflux in water bath using 110^oC and reaction progress was assessed on TLC plate by using ethyl acetate and cyclohexane (5:5) as TLC solvent. After the completion of reaction, round bottom flask containing mixture (filtered through G1 sintered crucible and crude product) were purified by recrystallization from ethanol to afford the pure products (**4a-j**).

4-amino-2-(4-hydroxyphenyl)-1,2-dihydroxybenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile(4a)
Brownish crystals, m.p. 210-213^oC. FTIR (KBr cm^{-1}): 3250, 2922, 2180, 1153, ^1H NMR 400 MHz, DMSO) δ 9.18 (s, 2H, D_2O exchangeable NH_2), 7.69 (m, 2H,Ar), 7.35 (m, 2H,Ar), 7.03-7.17 (m, 2H, Ar),

6.45-6.64, (m, 2H, Ar), 5.40 (s, OH,), 5.26 (s, NH,), 3.2(s,1H), ^{13}C NMR (100 MHz, DMSO): 157.04, 150.11, 142.17, 141.64, 140.97, 129.80, 122.93, 122.85, 120.10, 119.82, 114.99, 115.38, 113.17, 112.25, 62.86, 53.57.

4-amino-2-(4-cyanophenyl)-1,2-dihydroxybenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile(4c)
Light yellow crystals, m.p. 223-225^{o}C. FTIR (KBr cm^{-1}): 3244, 2922,2189, 1157, ^{1}H NMR 400 MHz, DMSO) δ 9.22 (s, 2H, D_2O exchangeable NH_2), 7.84 (m, 2H,Ar), 7.55-7.57 (m, 2H,Ar), 7.03-7.18 (m, 2H, Ar), 6.30-6.95, (m, 2H, Ar), 5.06 (s, NH,), 3.9(s,1H), ^{13}C NMR (100 MHz, DMSO): 157.94, 152.13, 149.37, 144.34, 143.97, 129.80, 123.63, 123.65, 120.15, 119.37, 116.99, 116.57, 115.38, 113.17, 112.25, 62.90, 53.97.

4-amino-2-(3-hydroxy-4-methoxyphenyl)-1,2-dihydroxybenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile(4d)
Dark yellow crystals, m.p. 230-233^{o}C. FTIR (KBr cm^{-1}): 3425, 3322, 2924, 1162, 1149, ^{1}H NMR 400 MHz, DMSO) δ 9.13 (s, 2H, D_2O exchangeable NH_2), 7.69 (m, 2H,Ar), 7.7.33 (m, 2H,Ar), 6.85-7.13 (m, 2H, Ar), 6.56, (m, 1H, Ar), 5.42 (s, 1H), 5.24 (s, NH,), 3.41 (s, 3H), 3.0(s,1H), ^{13}C NMR (100 MHz, DMSO): 157.51, 150.01, 141.00, 141.02, 140.23, 127.90, 123.03, 121.95, 118.79, 118.73, 115.10, 115.09, 113.17, 111.89, 61.96,56.20, 53.41.

4-amino-2-(4-methoxyphenyl)-1,2-dihydroxybenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile(4f)
White crystals m.p. 200-203^{o}C. FTIR (KBr cm^{-1}): 3240, 2912, 2182, 1169, 1154, ^{1}H NMR 400 MHz, DMSO) δ 9.15 (s, 2H, D_2O exchangeable NH_2), 7.71 (m, 2H,Ar), 7.32 (m, 2H,Ar), 7.03-7.15 (m, 2H, Ar), 6.38-6.68, (m, 2H, Ar), 5.27 (s, NH,), 3.46 (s, 3H), 3.2(s,1H), ^{13}C NMR (100 MHz, DMSO): 157.54, 149.91, 141.10, 141.02, 140.67, 128.80, 123.03, 122.95, 119.92, 119.82, 115.00, 115.09, 113.07, 112.25, 62.85,56.20, 53.51.

4-amino-2-(4-chlorophenyl)-1,2-dihydroxybenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile(4h)
Creamy white crystals, m.p. 210-212 ^{o}C. FTIR (KBr cm^{-1}): 3252, 2933,2189, 1154, ^{1}H NMR 400 MHz, DMSO) δ 9.24(s, 2H, D_2O exchangeable NH_2), 7.88 (m, 2H,Ar), 7.57-7.59 (m, 2H,Ar), 7.07-7.18 (m, 2H, Ar), 6.31-6.98, (m, 2H, Ar), 5.07 (s, NH,), 3.8(s,1H), ^{13}C NMR (100 MHz, DMSO): 157.92, 152.03, 148.97, 143.94, 143.37, 129.00, 123.26, 123.55, 120.05, 118.37, 118.57, 115.61, 114.00, 111.95, 62.98, 53.95.

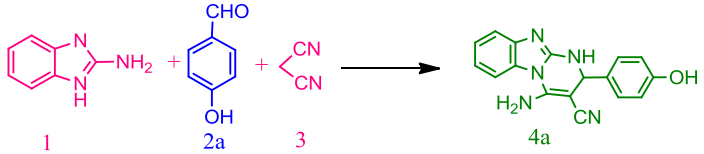
3. Result and Discussions

One flask multi-component reaction is one of the highly efficient strategies for the construction carbon-carbon bond and carbon-nitrogen bonds.

As part of our interest in research field, we have synthesized 4-amino-2-(R)-1,2-dihydroxybenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives (**4)** via MCR.

Initially, the three component reaction of benzamidazole (**1**), 4-hydroxy benzaldehyde (**2a**), malononitrile (**3**) and catalytic amount of $InCl_3$, a simple skeleton was discovered to establish the feasibility of strategy and to optimize the reaction conditions (**scheme-1**).

Scheme-1.



The effect of solvents and catalysts evaluated for this reaction scheme (**Table-1**).

Table-1. Optimization of reaction conditions-

Entry	Solvent	Temp.	Catalyst	Time (h)	Isolated yields %
1	MeOH	Rt	$InCl_3$ (10 mol %)	08	-
2	EtOH	Rt	$InCl_3$ (10 mol %)	08	-
3	ACN	Rt	$InCl_3$ (10 mol %)	08	-
4	DCM	Rt	$InCl_3$ (10 mol %)	08	-
5	DCE	Rt	$InCl_3$ (10 mol %)	08	-
6	THF	Rt	$InCl_3$ (10 mol %)	08	-
7	MeOH	110 ^oC	$InCl_3$ (10 mol %)	1.05	85
8	EtOH	110 ^oC	$InCl_3$ (10 mol %)	1.30	69
9	ACN	110 ^oC	$InCl_3$ (10 mol %)	2.00	45
10	DCM	110 ^oC	$InCl_3$ (10 mol %)	2.00	38
11	DCE	110 ^oC	$InCl_3$ (10 mol %)	2.30	35
12	THF	110 ^oC	$InCl_3$ (10 mol %)	3.00	-
13	MeOH	110 ^oC	$AlCl_3$ (10 mol %)	2.00	65
14	MeOH	110 ^oC	$FeCl_3$ (10 mol %)	2.30	59

(**Reaction conditions**- benzamidazole(**1**) (0.1 mol), 4-hydroxy benzaldehyde **(2a)** (0.1 mol), malononitrile (**3**) (0.1 mol), and in 6 ml different solvents and temperature).

Initially, model reaction containing mixture was stirred at room temperature using MeOH, EtOH, ACN, DCM, DCE and THF as solvents using $InCl_3$ Lewis acid catalyst, product (**4a**) was not found (Table-**1**, entries **1-6**). Further, we changed temperature from room temperature to 110 ^oC for same reaction model, product(**4a**) (85%, 69%, 45%, 38% and 35% using MeOH, EtOH, ACN, DCM and DCE) were found(Table-**1**, entries **7-10**). But 0% product (**4a**) was observed by using THF (Table-**1**, entry **11**). Thus we observed effect of temperature on reaction using same solvents.

We tried to use other catalyst such as $AlCl_3$ and $FeCl_3$ at 110^oC using methanol solvent on model reaction, product(**4a**) was found but in less amount are compared to $InCl_3$ catalyst (Table-**1**, entries **13-14**).

We turned to test the effect of amount of optimized catalyst ($InCl_3$). Optimizing the catalyst loading (5, 10, 15, 20 and 25 mol %) (Table-**2**, entries **1-5**). A 10 mol % loading of the $InCl_3$ was better pushing the reaction forward within time (Table-**2**, entry **2**). 5 mol % was not enough (Table-**2**, entry **1**) and higher amount of $InCl_3$ did not lead to significant changes in the reaction yields under the optimized conditions.

Table-2. Effect of amount of $InCl_3$ catalyst via (MCRs) model reaction-

Entry	Catalyst (mol %)	Time (h)	Isolated yields %
1.	5	1.30	75
2.	10	1.05	85
3.	15	1.05	82
4.	20	1.05	83
5.	25	1.05	83

(**Reaction conditions**- benzamidazole(**1**) (0.1 mol), 4-hydroxy benzaldehyde **(2a)** (0.1 mol), malononitrile (**3**) (0.1 mol) and in 6 ml methanol at 110^oC).

Synthesis of substituted pyrimidine derivatives using (10 mol %) $InCl_3$ catalyst at 110^oC in MeOH solvent under reflux condition evolved an efficient procedure in terms of good to excellent yields. **Scheme-2.**

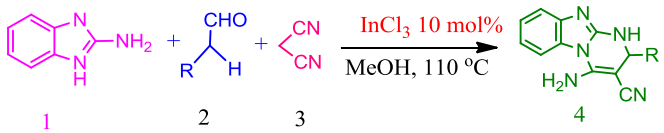
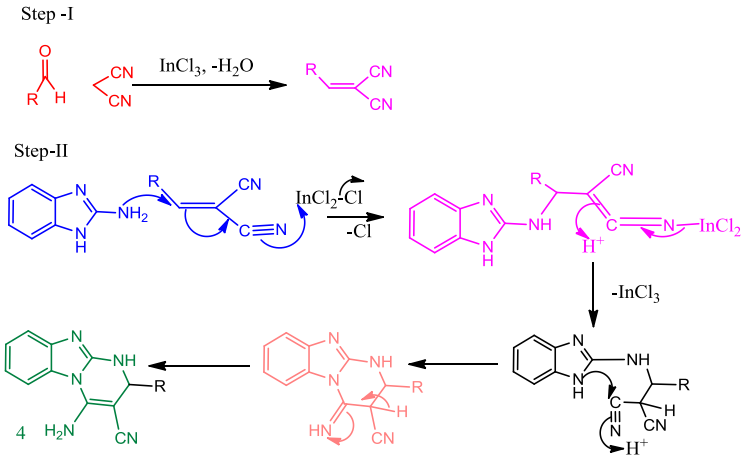


Table-3. Synthesis of 4-amino-2-(R)-1,2-dihydroxybenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile Derivatives(4)

Entry	R	Product	Time (h)	Isolated yields (%)
1	4- HOC_6H_4	4a	1.05	85
2	3- HOC_6H_4	4b	1.50	81
3	4- CNC_6H_4	4c	1.21	79
4	3-MeO-4- HOC_6H_3	4d	1.15	80
5	4- BrC_6H_4	4e	1.04	82
6	4- $MeOC_6H_4$	4f	1.09	84
7	2,5- $(MeO)_2C_6H_3$	4g	2.15	82
8	4- ClC_6H_4	4h	2.08	78
9	2,4- $(Cl)_2C_6H_4$	4i	1.50	80
10	4- FC_6H_4	4j	1.10	81

(**Reaction conditions**- benzamidazole (**1**) (0.1 mol), 4-hydroxy benzaldehyde **(2a-j)** (0.1 mol), malononitrile(**3**) (0.1 mol), $InCl_3$ (10 mol %) catalyst and 6 ml Methanol as solvent at reflux to 110°C).

***Scheme-3.* Proposed mechanism for the synthesis of substituted pyrimidine derivatives (4):**



The result are reported in table-3, the excellent yields of product(**4a,4b, 4f, 4e, 4g, 4i** and **4j)** from **(**entries **1,2,4-7, 9** and **10**) and good yields of product(**4c** and **4g)** from **(**entries **3** and **8**).

The products were recrystallized by ethanol and characterized by FTIR, ^{1}H NMR and ^{13}C NMR spectrometers.

CONCLUSIONS

In conclusion, we have successfully discovered 4-amino-2-(R)-1,2-dihydroxybenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives (**4a-j**) from benzamidazole (**1**), aromatic aldehyde (**2a-j**), malononitrile (**3**) by using $InCl_3$ (Lewis acid) catalyst under methanol. The utilization of this method has several benefits like high percentage of yields and high reaction rate and one time addition of reactant in reaction flasks.

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