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A Mild and Efficient Method for Synthesis of Benzimidazoles using Thallium Nitrate or Lanthanum Nitrate Catalysts

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Abstract— A simple and efficient route for synthesizing benzimidazoles from o-Phenylenediamine and aromatic aldehydes using rare earth metal catalyst like Thallium nitrate or Lanthanum nitrate has been proposed. The easy work-up, higher yields and shorter reaction times at room temperature are the advantages over other methods.

Keywords— Aromatic aldehyde, benzimidazole, Lanthanum nitrate, Thallium nitrate

I. INTRODUCTION

Benzimidazole, and its derivatives are found to be used in many natural products as well as a number of biologically active compound such as anti-cancer [1,2], anti-viral [3], anti-inflammatory [4], anti-bacterial [5], anti-protozoal [6], anti-depressant [7], anti-HIV [8], anti-ulcer [9], anti-hypertensive [10], and as kinase inhibitors [11].

There have been various methods developed for the synthesis of substituted benzimidazole based on cyclo-condensation of o-Phenylenediamine with carboxylic acid derivatives [12] and condensation with aldehydes [13]. There are many catalyst promoted methods reported in literature to synthesize the benzimidazole derivatives such as CAN [14], iodine [15], metal halides [16], solid-supported catalysts [17], metal oxides [18], metal triflates[19], proline[20], ionic liquid [21], and microwave-promoted [22] synthesis. Unfortunately many of the above said methods have major drawbacks such as low yields, drastic reaction conditions, higher reaction temperature, tedious workup procedures and some side reactions.

As a result it is important to develop an efficient, simpler and user friendly method for the synthesis of substituted benzimidazoles to overcome these limitations.

II. RELATED WORK

Over the past few years, researchers have made significant efforts to develop rare earth metal salts as catalysts in organic synthesis for their vital role in enhancing the reactivity and selectivity in reactions like carbon-carbon bond formation, cyclo-addition, reduction, aldol condensation[23,24]. The use of Thallium and lanthanide compounds as catalysts or promoters in organic synthesis has attracted great interest, among which the nitrate salts appeal in their catalytic activity due to the greater catalytic activity, stability and easy handling[25][26]. Carbon-hydrogen bond activation can also be triggered in presence of ruthenium and palladium complexes [27].

In this article, we report a simple and convenient method for the synthesis of benzimidazole derivatives from o-phenylenediamine and various aromatic aldehydes using Thallium nitrate $Tl(NO_3)_3$ and Lanthanum nitrate hexahydrate $La(NO_3)_3.6H_2O$ under mild conditions. The structures of the molecules were characterised by physical characteristic and spectral techniques.

III. METHODOLOGY

All the chemicals and reagents were obtained from Sigma-Aldrich. Dry solvents have been used to perform the reactions. Reaction was monitored by Thin Layer Chromatography (TLC). Products were confirmed by Mass Spectra which was recorded on Agilent LCMS (Ion trap method) and melting point measurement using Stuart SMP3 (Bibby Sterlin Ltd., UK) apparatus and was uncorrected. The ^1H NMR spectra were recorded on Bruker 400 MHz NMR spectrometer.

General procedure for synthesis of **3**: To a 50mL round bottom flask was added o-phenylenediamine **1** (1mmol), aromatic aldehydes **2** (1mmol) and dissolved in MeCN (10mL). The mixture was stirred for complete dissolution followed with the addition of $Tl(NO_3)_3$ catalyst (5mol%) or $La(NO_3)_3$ catalyst (10mol%) and stirred at ambient temperature for 2-10h. Reactions were monitored by TLC. Once the reaction was completed, the reaction mixture was poured into cold water, the crude product was obtained as a solid which was filtered and further purified by recrystallization in ethanol to yield benzimidazole **(3a-3k)** as shown in Table 4. The details for the syntheses are shown in Scheme 1 and the corresponding products were identified by spectroscopic and physical data.

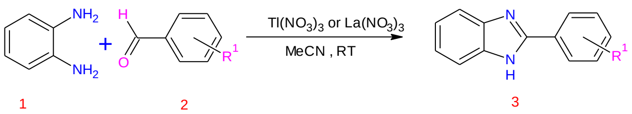


Figure 1. Scheme 1 synthesis.

IV. RESULTS AND DISCUSSION

In the beginning, efforts were made to study the catalytic efficiency of $Tl(NO_3)_3$ and $La(NO_3)_3.6H_2O$ towards the synthesis of benzimidazoles. The reaction of o-Phenylenediamine **(1)** and p-nitro benzaldehyde **(2c)** was performed with different acidic catalysts (10mol%) like $InCl_3$, CuO, $FeCl_3$, I_2, $CuSO_4$, CAN, $Tl(NO_3)_3$ and $La(NO_3)_3.6H_2O$ to get **3c** after the reaction mixture was refluxed for 2-24h in MeCN (table 1).

Table 1. Synthesis of compound 3c under different catalytic conditions

Sl. No.	Catalyst (10mol%)	Time (h)	Yield^i (%)
	$InCl_3$	20	70
	CuO	15	60
	$FeCl_3$	15	65
	I_2	12	75
	$CuSO_4$	12	75
	CAN	10	96
	$Tl(NO_3)_3$	3	98
	$La(NO_3)_3$	3	95

^{i} - isolated yield, Condition - reflux, MeCN as solvent

After screening for different catalysts the product yield **3c** was found to be greater for CAN, $Tl(NO_3)_3$, and $La(NO_3)_3.6H_2O$ at lesser reaction time. Hence in order to investigate the effect of temperature we further carried out the same reaction at different temperature ranging from room temperature (RT) to reflux conditions (table 2)

Table 2. Optimization of temperature for the synthesis of 3c

Sl. No.	Catalyst (10mol%)	temperature	Time (h)	Yield^i (%)
1.	CAN	RT	24	--
		50	24	43
		75	10	96
		100	8	97
		125	8	95
2.	$Tl(NO_3)_3$	RT	3	98
		50	3	98
		75	1	96
		100	1	97
		125	1	93
3.	$La(NO_3)_3$	RT	3	95
		50	3	96
		75	1	95
		100	1	94
		125	1	92

^{i} -isolated yield, Condition -under different temperature conditions, MeCN as solvent

From the above screened results it was observed that the $Tl(NO_3)_3$ and $La(NO_3)_3.6H_2O$ catalysed reactions yield 98% and 95% of product **3c** respectively within 3h at room temperature whereas the CAN catalysed reaction also yields 96% in 10h under reflux conditions. Due to the low temperature and faster reaction, the former catalysts are found to be efficient and better catalysts. Hence our further studies were focussed to optimise the $Tl(NO_3)_3$ and $La(NO_3)_3.6H_2O$ catalysed reactions. To further investigate the catalytic activity of catalyst, reactions were carried out using different mole percentage of $Tl(NO_3)_3$ and $La(NO_3)_3.6H_2O$ such as 2, 5, 10 ,15 and 20mol% as shown in table 3.

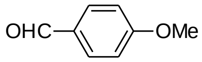
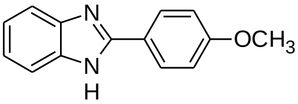
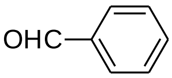
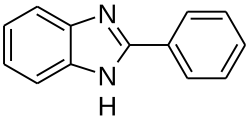
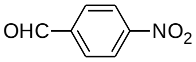
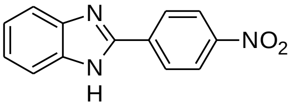
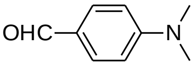
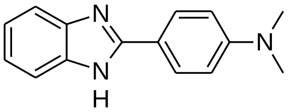
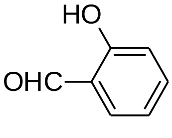
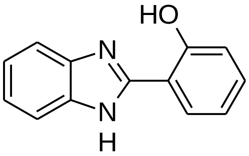
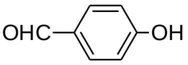
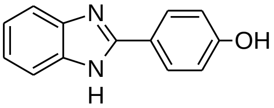
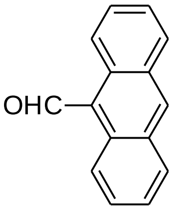
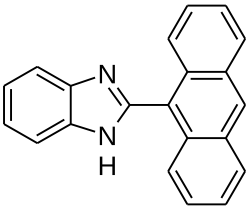
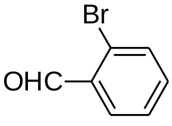
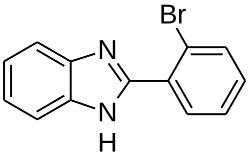
Table 3. Optimization of catalyst ratio for the synthesis 3c

Sl. No.	Catalyst Ratio (mol %)	temperature (°C)	
a.	2	RT	
b.	5		
c.	10		
d.	15		
e.	20		
		Yield^i (%)	
Sl. No.	Time (h)	$Tl(NO_3)_3$	$La(NO_3)_3$
a.	3	82	75
b.		98	88
c.		98	95
d.		97	95
e.		95	93

^{i} – isolated yield

$Tl(NO_3)_3$ and $La(NO_3)_3.6H_2O$ yields maximum at 5 and 10mol % respectively whereas below the optimised catalyst ratio, it shows lesser yield and excess catalyst shows no change in yield and reaction time. We extended above optimised conditions to synthesize benzimidazole derivatives as shown in table 4. It is found that optimised conditions yield maximum at RT for similar derivatives. Hence in this article, we are reporting the use of $Tl(NO_3)_3$ and $La(NO_3)_3.6H_2O$ as mild and efficient catalysts for synthesis of benzimidazoles and their derivatives. The main advantage with the use of above catalysts is the faster reaction at lower temperature in greater yields. The easy work up is an additional advantage; because of their crude purity, the solid precipitates out which is easily filtered and further purity of compound improved by recrystallization techniques. Physical and spectral characterization of the products was confirmed by comparison with available literature data.

Table 4. Details about the synthesised compounds

Entry	Substrate	Product
a.		
b.		
c.		
d.		
e.		
f.		
g.		
h.		
	Time (h)	Yield^{i} (%)
a.	3	94
b.	3	95
c.	2	98
d.	3	97
E.	3	96
f.	3	95
g.	2	98
h.	2	96

V. CONCLUSION AND FUTURE SCOPE

$Tl(NO_3)_3$ and $La(NO_3)_3.6H_2O$ have been employed for the first time as a mild and efficient reagents for the one-pot synthesis of benzimidazoles and their derivatives in high yields. This protocol offers appealing features such as a) employs ambient reaction temperature b) use of cheap, mild catalyst (c) improved yields (d) faster reaction (e) easy work up. Similar studies could be done using nitrates of transition and inner transition metals. Further other salts may be employed to increase the yield of the products.

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