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Graphical Abstract

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ABSTRACT

A highly efficient and mild protocol for the synthesis of imidazo-fused polyheterocycles *via* Groebke-Blackburn-Bienaymè reaction under the influence of catalytic amount of lanthanum chloride heptahydrate has been described. A wide range of nitrogen-enriched polyheterocycles are synthesized with high yields under neat conditions.

Multicomponent reactions (MCRs)[1] are known for generating complex, diverse molecules in single step and continuous efforts are going on by scientific community for the development of environmental benign solvent-free MCRs. MCRs occupy a special place in 'diversity oriented synthesis' (DOS)[2] and biology-oriented synthesis (BIOS)[3] design strategies for achieving higher degree of scaffold diversification.

Nowadays, the use of lanthanide (III) compounds as catalysts or promoters in organic synthesis has attracted great attention from scientific community. Literatures reveals that, lanthanide additives or complexes can enhance the reactivity and selectivity of many types of reactions such as, reduction, carbon-carbon bond formation, aldol condensation, cycloaddition, ring-opening and polymerization.[4] Lanthanide ions are considered "hard" Lewis acids and form complexes with substantial ionic character because of poor overlap of the contracted 4f orbitals.[4c] Lanthanides are also able to polarize bonds upon coordination and thus alter the electrophilicity of compounds. Lanthanide (III) compounds are soluble in water, making it easy to isolate from the reaction mixture by aqueous work-up. The lack of orbital interactions combined with the lanthanide contraction allows for easy tuning of the nuclearity and steric environments of the complexes, which have been used to improve the catalytic activity of the lanthanide (III) complexes.[5] Among them, lanthanum complexes are widely used in organic transformations such as, azide-nitrile [3+2] cycloaddition,[6a] benzimidazole synthesis,[6b] Friedlander reaction,[6c] allylation of aldehyde,[6d] chlorination of methane,[6e] guanylation reaction,[6f] Grignard addition[6g] and Biginelli reaction.[6h]

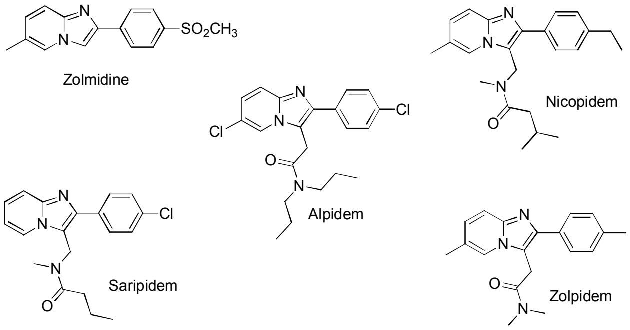

Figure 1: Representative examples of pharmaceutically important molecules having imidazo[1,2-*a*]pyridine as core moiety

Bicyclic pyridines containing ring junction nitrogen are a common structural motif in a wide range of natural products and pharmacologically active molecules. In specific, imidazo-pyridine derivatives are broadly investigated and utilized in the pharmaceutical industry; for example, Zolpidem (treatment of insomnia and some brain disorder),[7] Alpidem (a nonsedative anxiolytic),[8] Saripidem (sedative anxiolytic),[9] Olprinone (cardio tonic agent),[10] Zolimidine (anti-inflammatory),[11] Levamisole (anticancer),[12] and DS-1 (acts as a GABAA receptor agonist).[13] They are also used in bio-imaging probes and molecular recognition because of their structural characters.[14]

Several methods have been reported for the synthesis of these compounds by condensation of an aminoazine, aldehyde and an isocyanide *via* the Groebke-Blackburn-Bienaymè reaction in the presence of Bronsted acids such as AcOH,[15] $HClO_4$,[16] cellulose

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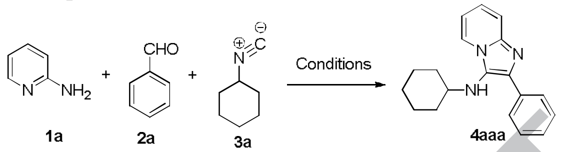
sulphuric acid,[17] p-toluene sulfonic acid[18] or Lewis acids such as $Sc(OTf)_3$,[19] $MgCl_2$,[20] $SnCl_2$,[21] $ZrCl_4$,[22] $ZnCl_2$,[23] $RuCl_3$,[24] and solvent-free protocols like nanoparticle γ-Fe_2O_3@-SiO_2-OSO_3H,[25] montmorilonite K10.[26] However, most of these methods possess several disadvantages such as low yields of products, longer reaction times, harsh reaction conditions, tedious work-ups, and are inconvenient for industrial scale. Hence, development of novel methods to construct a variety of imidazo[1,2-*a*]pyridines is still desirable.

Our interest in the area of developing green and sustainable methods,[27] has provoked us to investigate an alternate milder method for the synthesis of imidazo[1,2-*a*]pyridines. Herein, we wish to report a green protocol for the synthesis of imidazo[1,2-*a*]pyridines under solvent-free conditions by using cheap and readily available hydrated lanthanum chloride as catalyst under milder reaction conditions. So far to the best of our knowledge, there are no reports on solvent-free lanthanum chloride catalyzed synthesis of imidazo[1,2-*a*]pyridine derivatives *via* Groebke-Blackburn-Bienaymè reaction.

In our investigation, initially we have selected 2-aminopyridine (**1a**, 1.06 mmol), benzaldehyde (**2a**, 1.06 mmol) and cyclohexyl isocyanide (**3a**, 1.06 mmol) in ethanol (2ml) as a test reaction for optimum reaction conditions and the results are listed in Table 1. No reaction occured in the absence of catalyst at room temperature. However, when $LaCl_3.7H_2O$ (2 mol%) was added at room temperature, the corresponding imidazo[1,2-*a*]pyridine (**4aaa**) was obtained in 60% yield (Table1, entry 2). The effect of different mol% of lanthanum chloride at various temperatures on the reaction was examined. After successfully obtaining the maximum yield with 10 mol% of lanthanum chloride at 60 °C, we next examined the reaction under solvent-free conditions, which to our delight gave the desired product **4aaa** in excellent yield (95%) in 20 min (Table 1, entry 8). The solvents like methanol and water did not give satisfactory yields. Hence, we choose 10 mol% lanthanum chloride under solvent-free conditions at 60 °C as the optimized condition for further study.

With the optimal condition established, we explored the generality of the reaction by extending the methodology to the aliphatic, aromatic as well as heteroaromatic aldehydes resulting in wide range of imidazo[1,2-*a*]pyridine derivatives in excellent yields as shown in Table 2. In addition, the scope of aldehydes was examined by introducing metal containing aldehyde, e.g., ferrocene-2-carboxaldehyde, which gave **4aja** in 96% yield with short reaction time.

Table1 Optimization of reaction conditions [a]

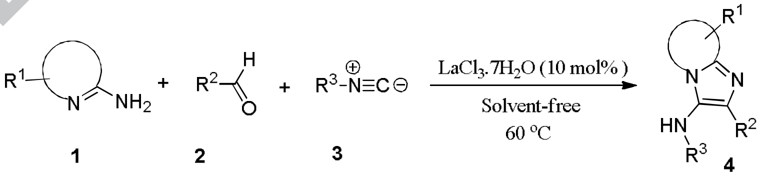


Entry	Solvent	$LaCl_3.7H_2O$ (mol %)	Temperature (°C)	Time (min.)	Yield (%)[b]
1	Ethanol	-[c]	RT	90	-
2	Ethanol	2	RT	90	60
3	Ethanol	2	35	80	65
4	Ethanol	2	60	80	79
5	Ethanol	5	60	60	85
6	Ethanol	10	RT	90	70
7	Ethanol	10	60	60	95
8	-[d]	**10**	**60**	**20**	**95**
9	-[d]	5	60	40	85
10	MeOH	10	60	120	70
11	H_2O	10	60	120	65

[a] Reaction conditions: **1a** (1.06 mmol), **2a** (1.06 mmol) and **3a** (1.06 mmol) [b] Isolated yield after filtration through short pad of silica column. [c] No catalyst used. [d] Solvent-free condition.; For compound **4aaa** first letter refers to 2-aminopyridine part **1a**, second letter refers to benzaldehyde part **2a** and third letter refers to part coming from cyclohexylisocyanide **3a**.

It is worth to mention here that, the protocol would serve to make further ferrocene-based heterocycles, which may have renewed interest due to their well-documented medicinal properties, attractiveness as redox-active biomolecular probes and structural models for peptides.[28] The protocol was also successfully extended to various hetero amino azines, thus resulting in corresponding bicyclic (**4dbc-4dfc**, Table 3) and tricyclic imidazo-fused heterocycles (**4eaa-4eab**, Table 3). Further, scope of the reaction was extended to aromatic isocyanides, which provided the products in high yields (**4alb** and **4eab**). All the products were purified by filtration through short pad of silica column. The products were confirmed by FT-IR, NMR spectroscopic techniques and mass spectrometry.

Table 2 The synthesis of 3-aminoimidazo[1,2-*a*]pyridines **4** *via* Groebke-Blackburn-Bienaymè reaction [a]



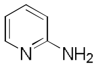
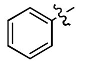
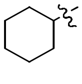
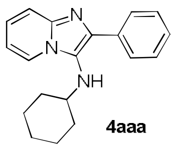
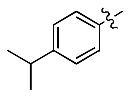
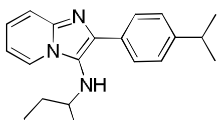
Entry	R^1	R^2	R^3	Product [b]	Time (min)	Yield (%)[c]
1	 **1a**	 **2a**	 **3a**	 **4aaa**	20	95
2	**1a**	 **2b**	**3a**	 **4aba**	60	90

Table 2 *(Continued)*

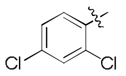
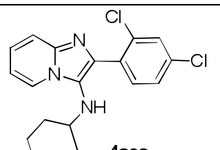
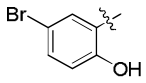
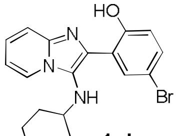
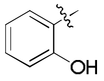
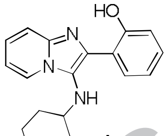
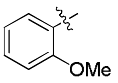
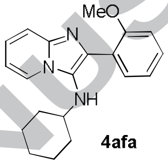
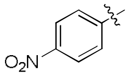
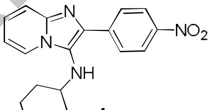
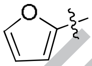
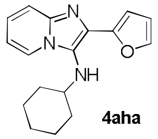
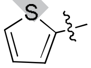
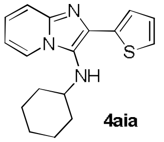
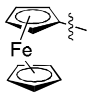
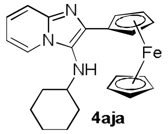
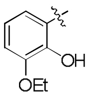
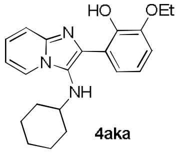
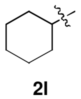
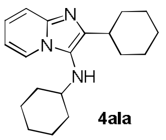
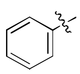
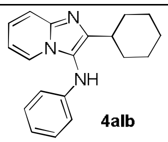
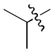
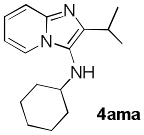
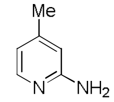
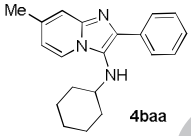
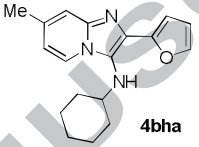
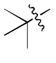
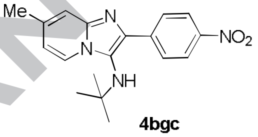
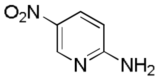
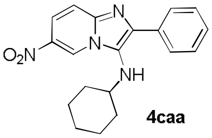
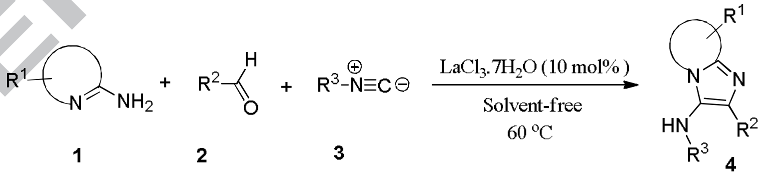
Entry	R^1	R^2	R^3	Product [b]	Time (min)	Yield (%)[c]
3	**1a**	 **2c**	**3a**	 **4aca**	40	96
4	**1a**	 **2d**	**3a**	 **4ada**	55	90
5	**1a**	 **2e**	**3a**	 **4aea**	70	89
6	**1a**	 **2f**	**3a**	 **4afa**	65	86
7	**1a**	 **2g**	**3a**	 **4aga**	40	96
8	**1a**	 **2h**	**3a**	 **4aha**	40	93
9	**1a**	 **2i**	**3a**	 **4aia**	75	83
10	**1a**	 **2j**	**3a**	 **4aja**	45	96
11	**1a**	 **2k**	**3a**	 **4aka**	50	92
12	**1a**	 **2l**	**3a**	 **4ala**	20	90

Table 2 *(Continued)*

Entry	R^1	R^2	R^3	Product ^{b}	Time (min)	Yield (%)^c
13	**1a**	**2l**	 **3b**	 **4alb**	25	90
14	**1a**	 **2m**	**3a**	 **4ama**	45	85
15	 **1b**	**2a**	**3a**	 **4baa**	60	90
16	**1b**	**2h**	**3a**	 **4bha**	50	92
17	**1b**	**2g**	 **3c**	 **4bgc**	45	92
18	 **1c**	**2a**	**3a**	 **4caa**	90	73

[a] Reaction conditions: Aminoazines **1** (1.06 mmol), aldehyde **2** (1.06 mmol), isocyanide **3** (1.06 mmol). [b] Product was confirmed by ^{1}H NMR, ^{13}C NMR and mass spectral analyses. [c] Isolated yield after filtration through short pad of silica column. For compound **4** first letter refers to aminoazines part **1a**-**1e**, second letter refers to aldehydes part **2a**-**2o** and third letter refers to part coming from isocyanides **3a**-**3c**.

Table 3 The synthesis of 3-aminoimidazo-fused hetero substituted tricyclic and bicyclic scaffolds **4** *via* Groebke-Blackburn-Bienaymè reaction^a



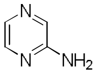
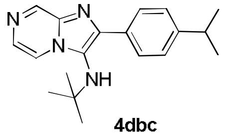
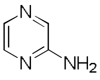
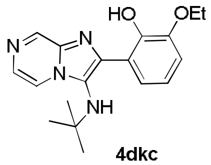
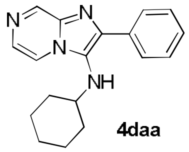
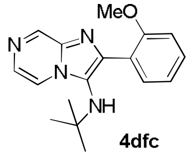
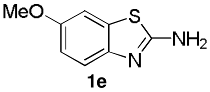
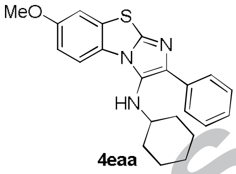
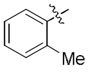
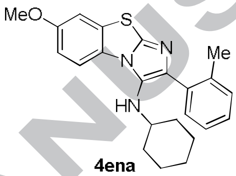
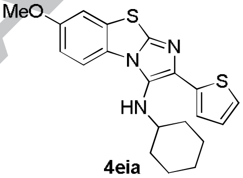
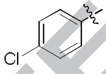
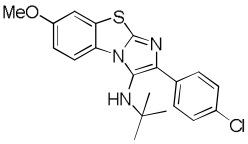
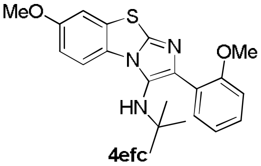
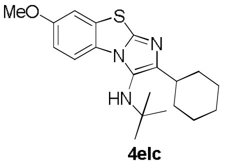
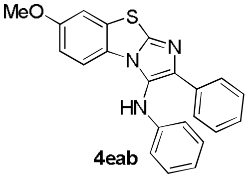
Entry	R^1	R^2	R^3	Product ^{b}	Time (min)	Yield (%)^c
1	 **1d**	**2b**	**3c**	 **4dbc**	45	90
2	 **1d**	**2k**	**3c**	 **4dkc**	55	85

Table 3 *(Continued)*

Entry	R^1	R^2	R^3	Product [b]	Time (min)	Yield (%)[c]
3	**1d**	**2a**	**3a**	 **4daa**	25	99
4	**1d**	**2f**	**3c**	 **4dfc**	60	93
5	 **1e**	**2a**	**3a**	 **4eaa**	80	75
6	**1e**	 **2n**	**3a**	 **4ena**	90	83
7	**1e**	**2i**	**3a**	 **4eia**	80	76
8	**1e**	 **2o**	**3c**	 **4eoc**	120	79
9	**1e**	**2f**	**3c**	 **4efc**	90	81
10	**1e**	**2l**	**3c**	 **4elc**	90	80
11	**1e**	**2a**	**3b**	 **4eab**	30	85

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[a] Reaction conditions: Aminoazines **1** (1.06 mmol), aldehyde **2** (1.06 mmol), isocyanide **3** (1.06 mmol). [b] Product was confirmed by ^{1}H NMR, ^{13}C NMR and mass spectral analyses. [c] Isolated yield after filtration through short pad of silica column; For compound **4** first letter refers to aminoazines part **1a**-**1e**, second letter refers to aldehydes part **2a**-**2o** and third letter refers to part coming from isocyanides **3a**-**3c**.

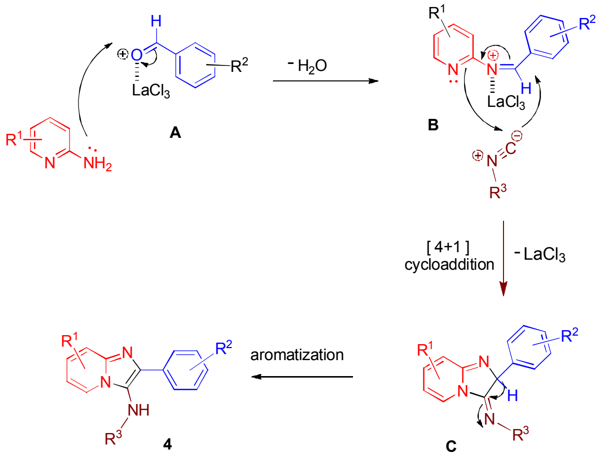

Figure 2. Plausible reaction mechanism for the synthesis of imidazo[1,2-*a*]pyridine **4**.

A tentative mechanism is proposed (Figure 2). Initially the aldehyde oxygen gets coordinated with the lanthanum chloride, which increases the carbonyl electrophilicity. Then the aminopyridine condenses with the aldehyde leading to imine, which is further activated by lanthanum chloride to form Schiff base **B**[29] and subsequent attack of isocyanide on electrophilic imine carbon followed by [4+1] cycloaddition[30] to form cyclic adduct **C**. Finally, the intermediate adduct **C** undergoes aromatization *via* 1,3-H shift to furnish the desired product **4**.[31]

In summary, we have successfully developed a highly efficient lanthanum chloride heptahydrate promoted protocol *via* one-pot three component Groebke-Blackburn-Bienaymè reaction to synthesize medicinally and biologically relevant imidazo-fused polyheterocycles. There are several advantages associated with this method (i) high yields (ii) easy accessibility of imidazo[1,2-*a*]pyridines (iii) wide substrate scope (iv) minimal energy requirement and (v) short reaction time. This methodology might prove as a better alternative to the existing literature methods.

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Supplementary Material

Supplementary material associated with this manuscript can be found in online version as separate electronic file.

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29. (a) Our attempts to isolate pure imine from the reaction mixture failed, however, we have confirmed the imine formation by mass spectral analysis and also by TLC of reaction mixture with reference imine (separately prepared); (b) When we have performed the reaction of reference imine (prepared separately) with isocyanide **3** in presence of lanthanum chloride as catalyst gave the product **4** in excellent yield (90%), supporting the proposed plausible mechanism.
30. For similar kind of cycloaddition see: Umkehrer, M; Ross, G.; Jager, N.; Burdack, C.; Kolb, J.; Hu, H.; Alvim-Gastonb, M.; Hulme, C. *Tetrahedron Lett.* **2007**, *48*, 2213.
31. The proposed plausible mechanism is well known mechanism proposed in the isocyanide-based multicomponent reactions,[13-24] which also proposes the intermediate imine formation and further its transformation to product **4** through similar kind of reaction mechanism.