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# Solvent–free Multicomponent Synthesis of Biologically–active Fused–imidazo Heterocycles Catalyzed by Reusable $Yb(OTf)_3$ Under Microwave Irradiation

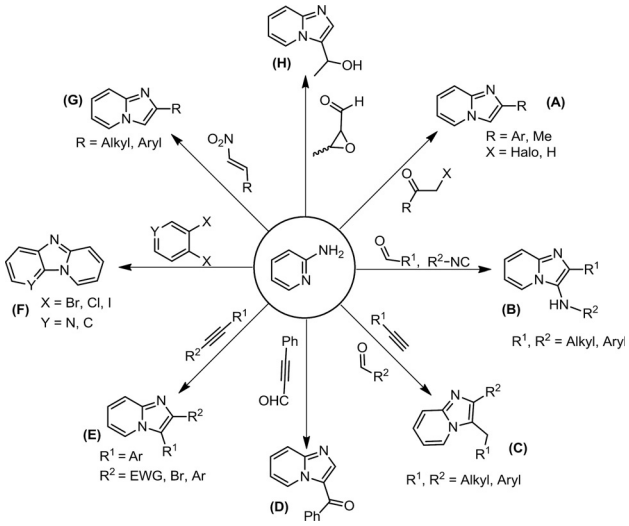
Arshad J. Ansari,[a] Shivani Sharma,[b] Ramdas S. Pathare,[b] Kandasamy Gopal,*[b] Devesh M. Sawant,*[a] and R. T. Pardasani*[b]

A rapid, efficient and solvent-free – green – protocol for Groebke–Bienaymé–Blackburn reaction (G–B-B reaction) for the synthesis of fused-imidazo heterocycles has been developed. The methodology reported here involves multi-component reaction (MCR) catalyzed by reusable $Yb(OTf)_3$ (a mild and water-compatible Lewis acid) under microwave irradiation which allows fast and efficient preparation of the title compounds in excellent yield. The salient features of our protocol are solvent-free, low catalyst loading (2.5–0.1 mol%) with good turnover number (TON: 890) and turnover frequency (TOF: 178/min), less reaction time (5 min), no dependency over specialized purification (by either column chromatography or recrystallization) and very high isolated yield (95–99%) with excellent green chemistry metrics (E-factor: 0.071 and Mass Intensity: 1.071). The water compatibility of the catalyst $Yb(OTf)_3$ has been exploited for its efficient recovery through water washings. In addition, the other exciting milestones of the protocol are catalyst and workup solvent recycling, excellent conversion with notorious substrates such as enolizable aldehyde or isonitrile bearing reactive substituent, very efficient at higher scale (50 mmol) and easy to couple with other methods (one-pot two-step cyclization: G–B-B reaction and Ullmann-type coupling).

## Introduction

Fused-imidazo heterocycles have increasingly become popular among medicinal and organic chemists as they exhibit wide spectrum of pharmacological and biological activity such as antibacterial[1a,b] kinase inhibitor,[1c] antineoplastic,[1d–f] CDK2 inhibitor,[1g] anti-tubercular,[1h] anti-inflammatory,[1i] analgesic[1i] and antiviral activity.[1j–k] It is evident from the fact that many drugs having fused-imidazo heterocycles based on the imidazo [1,2a]pyridine moiety have been developed and are available commercially in the market as anxiolytic (Alpidem),[2a] hypnotic (Zolapidem),[2b] anti-ulcer (Zolimidine),[2c] anti-osteoporetic (Minodronic acid), sedative (Saripidem & Necopidem),[2d] anti-HIV drugs (GSK812397)[2e] and PDE3 inhibitor (Olprinone).[2f] The wide spectrum of biological activity associated with imidazo [1,2-a]pyridine derivatives suggest that this heterocycle has innate affinity for many functional domains of protein targets in drug discovery. Accordingly, any methodology that generate diversified imidazo[1,2-a]pyridine would be desirable and can be considered as biology-oriented synthetic strategies (BIOS).[3]

A careful literature survey reveals that imidazo[1,2-a]pyridine based heterocycles can be synthesized by various methods as summarized in Scheme 1. Condensation reaction of 2-aminopyridine with α-haloketones[4] (Scheme 1, A, X = halo), isonitrile based MCR with 2-aminopyridine and aldehyde, which are generally termed as Groebke–Bienaymé–Blackburn reaction (G–B-B reaction)[5] (Scheme 1, B) and cyclization reactions involving alkynes[6] (Scheme 1, C–E) are the most general and fre-




**Scheme 1.** Synthesis of imidazo[1,2a]pyridine derivatives by condensation of 2-aminopyridine and various electrophilic partners.

[a] *A. J. Ansari, Dr. D. M. Sawant*
Department of Pharmacy, Central University of Rajasthan, Bandarsindri, Kishangarh, Ajmer – 305 817, Rajasthan, India
E-mail: dms@curaj.ac.in
[b] *S. Sharma, R. S. Pathare, Dr. K. Gopal, Prof. R. T. Pardasani*
Department of Chemistry, Central University of Rajasthan, Bandarsindri, Kishangarh, Ajmer – 305 817, Rajasthan, India
E-mail: gopalk@curaj.ac.in
rtpardasani@curaj.ac.in

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quently used methods for the synthesis of imidazo[1,2-a]pyridine derivatives. Recently, many new routes have been unearthed, where the conventional electrophilic partners were replaced by modified ones such as 1,2-dihaloaryls[7] (Scheme 1, F), nitroalkenes[8] (Scheme 1, G), methylketones[9] (Scheme 1, A, X = H) and epoxyaldehydes[10] (Scheme 1, H). Among these protocols, isonitrile-based MCR, the G–B-B reaction, that generates imidazo[1,2-a]pyridine derivatives with maximum diversity is widely applicable in the field of drug discovery[5] and can be classified as BIOS.

Several synthetic strategies for the G–B-B reaction (MCR) have been reported to date. For instance, reagents such as Brønsted acids[6e,11] ($HClO_4$, TsOH, AcOH, TFA, BDMS and HCl), solid supported reagents[12] (silica-sulfuric acid, cellulose-sulfuric acid, $Fe_2O_3$@$SiO_2$-$OSO_3H$, zeolite HY, MWCNTs-$OSO_3H$, montmorillonite K 10), Lewis acids[8b,9c,13] ($Sc(OTf)_3$, $ZnCl_2$, $InCl_3$, $ZrCl_4$, $RuCl_3$, $BiCl_3$, $SnCl_2$, $Ga(OTf)_3$, $Fe(NO_3)_3$, CuI), ionic liquids,[14] organic bases such as piperidine,[15] inorganic salts[1h,16] ($NH_4Cl$, $MgCl_2$) and TMSCl[17] have been used as catalyst for the G–B-B reaction (MCR). However, most of these methods are associated with many disadvantages such as longer reaction time, use of expensive catalysts and solvents, poor yield, challenging reaction conditions and tedious work-up that make them inconvenient to scale-up at industrial level. Also, very few protocols have been qualified for greener methodologies,[18] hence it is still essential to develop new sustainable methods to construct diverse fused-imidazo heterocycles. In continuation of our efforts to generate inventive methodologies for the synthesis of biologically active heterocycles,[19] herein we report a simple solvent-free reactions catalyzed by the Lewis acid $Yb(OTf)_3$ under microwave irradiation. Generally, most of the Lewis acids are unstable in aqueous conditions and such Lewis acid catalyzed reactions must be performed under strictly anhydrous conditions. Hence its recovery and reusability are extremely challenging. However, in recent times, rare-earth metal triflates (such as $Sc(OTf)_3$, $Yb(OTf)_3$, *etc.*) was found that can be used as Lewis acid catalysts in water or water-involving reactions (as in the present instance where water is the side-product) and regarded as water-compatible Lewis acids.[20] Owing to this property, rare-earth metal triflates can be certainly recovered after the reactions (through water) and reused without loss of any catalytic activity.[20f] Among the water-compatible Lewis acid catalysts, $Sc(OTf)_3$ is commonly observed as the best Lewis acid for catalysis.[20a–e] However, in the current context, the outstanding catalytic performance by the $Yb(OTf)_3$ is categorized as cost effective,[21] mild and water-compatible Lewis acid catalyst. Furthermore, to the best of our knowledge, this is the first report of the G–B-B reaction (MCR) catalyzed by the combination of both Lanthanide-series Lewis acid ($Yb(OTf)_3$) and microwave irradiation.

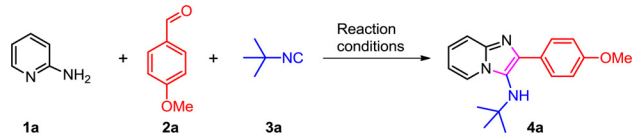
## Results and Discussion

We embarked our studies on the preparation of imidazo[1,2a] pyridine derivative **4a** by reacting 2-aminopyridine **1a** (1.0 mmol), 4-methoxybenzaldehyde **2a** (1.0 mmol) and *tert*-butylisonitrile **3a** (1.0 mmol) in the presence of various Brønsted or Lewis acids as catalyst under either conventional or microwave heating (Table 1). No product was furnished when the reaction was carried out at room temperature in the absence of catalyst. Either heating alone or in presence of the catalyst at room temperature (for prolonged time) triggered the cyclization with moderate conversion (Table 1, entries 1–5). Intriguingly, the rapid microwave-based heating protocols produced good results than the conventional heating. Nonetheless, inclusion of catalyst in to the microwave heating protocols produced best results with minimal reaction time and maximal product yields (Table 1, entries 14–28). Lewis acids were found to be more efficient in catalyzing the G–B-B reaction than the Brønsted acids, such as $NH_4Cl$ which are in good agreement with the literature reports.[13] Ethereal solvents (THF, $Et_2O$, DME, diglime) and chlorinated solvents (DCM, $CHCl_3$, DCE) produced the desired product in low to moderate yield; whereas hydrocarbons (*n*-pentane and *n*-hexane) failed to initiate the reaction, even in the presence of catalyst. Under polar and protic solvent conditions produced the desired product with quantitative conversion (Table 1, entries 2, 4, 8–11). Interestingly, solvent-free (neat) reactions under heating (both conventional and microwave) had offered best results with good conversion (Table 1, entries 5–7, 12–28).

Overall, among the catalysts tested, $Yb(OTf)_3$ was found to be the best with complete conversion in 5 min and minimal catalyst loading (2.5 mol%, Table 1, entry 19). Interestingly, even with the very low catalytic loading (1 and 0.1 mol%) produced the desired product **4a** in quantitative yield (Table 1, entries 20–21). In order to understand the efficacy of the catalyst, its turnover number (TON) and turnover frequency (TOF) were calculated[22] for the reactions with catalyst loading of 2.5 mol% (TON: 39; TOF: 8/min), 1 mol% (TON: 93; TOF: 19/min) and 0.1 mol% (TON: 890; TOF: 178/min). It indicates that the catalyst $Yb(OTf)_3$ is extremely efficient and highly active in many catalytic cycles for the conversion of as many substrates into products. Consequently, heating the mixture of **1a**, **2a** and **3a** under microwave at 160 °C (at 40 W) in the presence of $Yb(OTf)_3$ (2.5 mol%) produced the crude product. The reaction mixture obtained was first triturated with *n*-pentane followed by washing with deionized water (to remove the water soluble Yb $(OTf)_3$) yields the title compound **4a** in excellent isolated yield (98%) and no further purification by either column chromatography or recrystallization was required as evident by $^1$H NMR experiment (as the product obtained so exhibited ⩾99% purity). It is important to note that the solvent used for workup (*n*-pentane) and the catalyst ($Yb(OTf)_3$) were recovered, purified and recycled continuously (see Experimental Section in the Supporting Information).[20f] On each occasion of the catalyst recycling experiments, the catalyst was found to retain its activity (even after five cycles) and furnished the desired product **4a** with identical isolated yield (98, 97, 98, 97, 97 and 97%).

With optimal reaction conditions in hand, we next explored the generality of the reaction with diverse aldehydes as shown in the Scheme 2. It is noteworthy that benzaldehydes with both electron donating and withdrawing substituents, aliphatic and heteroaromatic aldehydes and sterically demanding aldehydes (*ortho*-substituted benzaldehydes) produced the desired prod-

**Table 1.** Optimization of the reaction conditions.




1a 2a 3a 4a

| Entry | Method[a] | Catalyst (mol%) | Solvent | Temp (°C) | Time | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1. | A | $NH_4Cl$ (100) | - | rt | 24 h | 65 |
| 2. | A | $NH_4Cl$ (100) | MeOH | rt | 24 h | 50[c] |
| 3. | A | $Yb(OTf)_3$ (5) | - | rt | 24 h | 70[c] |
| 4. | B | - | MeOH | 65 | 16 h | 60[c] |
| 5. | B | - | - | 160 | 5 min | trace |
| 6. | B | $NH_4Cl$ (100) | - | 120 | 4 h | 78 |
| 7. | B | $Yb(OTf)_3$ (5) | - | 160 | 4 h | 79[c] |
| 8. | B | $NH_4Cl$ (100) | MeOH | 65 | 4 h | 60[c] |
| 9. | B | $NH_4Cl$ (100) | Dioxane | 110 | 5 h | 60[c] |
| 10. | B | $Yb(OTf)_3$ (2.5) | MeOH | 65 | 2.5 h | 80 |
| 11. | B | $Yb(OTf)_3$ (5) | DMF | 160 | 45 h | 80 |
| 12. | C | - | - | 160 | 5 min | trace |
| 13. | C | - | - | 160 | 45 min | 30 |
| 14. | C | $NH_4Cl$ (100) | - | 160 | 5 min | 60 |
| 15. | C | $NH_4Cl$ (100) | - | 160 | 15 min | 75 |
| 16. | C | $NH_4Cl$ (100) | - | 160 | 45 min | 85 |
| 17. | C | $Yb(OTf)_3$ (2.5) | - | 120 | 5 min | 85[c] |
| 18. | C | $Yb(OTf)_3$ (2.5) | - | 140 | 5 min | 92[c] |
| **19.** | **C** | **$Yb(OTf)_3$ (2.5)** | **-** | **160** | **5 min** | **98[d]** |
| 20. | C | $Yb(OTf)_3$ (1) | - | 160 | 5 min | 93[c,e] |
| 21. | C | $Yb(OTf)_3$ (0.1) | - | 160 | 5 min | 89[c,f] |
| 22. | C | $Sc(OTf)_3$ (5) | - | 160 | 5 min | 81 |
| 23. | C | $NiCl_2$ (5) | - | 160 | 5 min | 83 |
| 24. | C | $CuCl_2$ (5) | - | 160 | 5 min | 75 |
| 25. | C | $ZnCl_2$ (5) | - | 160 | 5 min | 83 |
| 26. | C | $CdCl_2$ (5) | - | 160 | 5 min | 80 |
| 27. | C | $BiCl_3$ (5) | - | 160 | 5 min | 85 |
| 28. | C | $SnCl_2$ (5) | - | 160 | 5 min | 81 |

[a] Method A: room temperature (rt, 33 °C) stirring; Method B: conventional heating; Method C: microwave heating (MW, 40 W); [b] Isolated yield; [c] Starting materials were recovered; [d] Best conversion was obtained under microwave heating at 40 W; catalyst TON: 39 and TOF: 8/min; [e] Catalyst TON: 93 and TOF: 19/min; [f] Catalyst TON: 890 and TOF: 178/min.

**Table 2.** Comparison of green chemistry metrics for the G–B-B reactions under microwave (MW) and conventional heating conditions.[a]

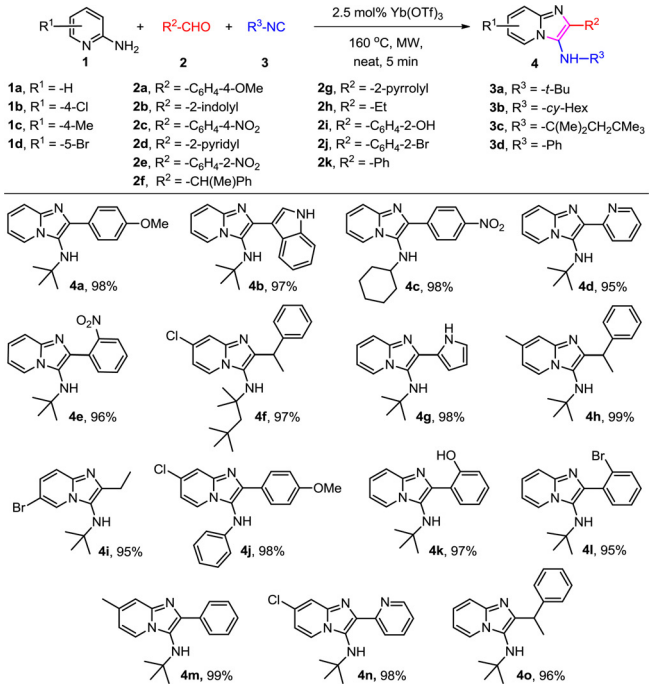
| Entry | Reaction Condition | Time (min) | Yield (%)[b] | E-factor | Mass Intensity |
|---|---|---|---|---|---|
| 1. | $ZnCl_2$ (5 mol%), 1,4-dioxane, MW[13b] | 60 | 60 | 10.54[c] | 11.54 |
| 2. | $Sc(OTf)_3$ (4.3 mol%), MeOH, MW (200 W), 160 °C[13i] | 10 | 93 | 10.33[c] | 11.33 |
| 3. | 4N HCl/1,4-dioxane, dry MeCN, MW (400 W), 110 °C[11f] | 20 | 69 | 7.66[c] | 8.66 |
| 4. | $ZrCl_4$ (10 mol%), PEG-400, 50 °C[13d] | 300 | 95 | 3.63[c] | 4.63 |
| 5. | $\gamma$-$Fe_2O_3$@$SiO_2$-$OSO_3H$ (1 mol%), neat, 35 °C[12b] | 60 | 90 | 0.54[c] | 1.54 |
| 6. | Montmorillonite clay K10, neat, MW (900 W)[12d] | 3 | 84 | 0.50[c] | 1.50 |
| 7. | $RuCl_3$ (5 mol%), neat, 40 °C[13e] | 60 | 87 | 0.36[c] | 1.36 |
| 8. | $BiCl_3$ (5 mol%), neat, 110 °C[13f] | 5 | 94 | 0.19[c] | 1.19 |
| 9. | Neat, 160 °C[18a] | 120 | 95 | 0.13[c] | 1.13 |
| **10.** | **$Yb(OTf)_3$ (2.5 mol%), neat, MW (40 W), 160 °C** | **5** | **99** | **0.071[d]** | **1.071** |

[a] Refer Supporting Information for specific reaction considered; [b] Isolated yield; [c] Excluding workup and purification (typically extraction, column chromatography and/or recrystallization); [d] Including workup/purification.

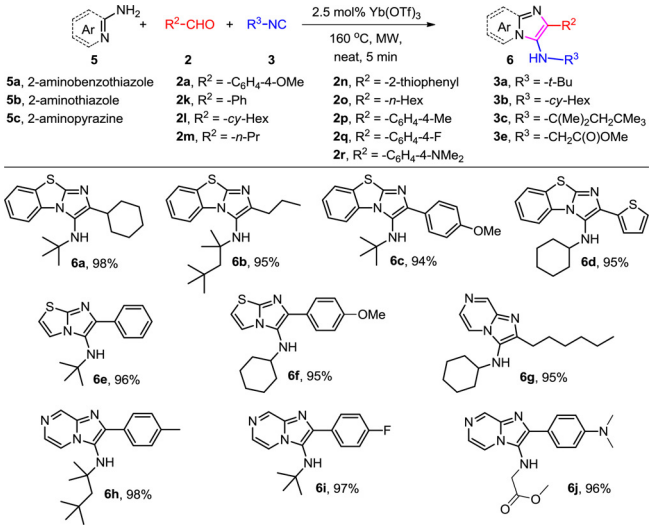
ucts **4a–o** in 5 min reaction time with excellent isolated yields (95–99 %). Thus, the methodology was not influenced by the stereo-electronic factors of the substituents. Indeed, all reactions furnished the desired product in excellent purity after trituration with *n*-pentane and washed with deionized water. Interestingly, even the enolizable aldehyde, Ph-CH(Me)-CHO **2f** furnished the desired products **4f**/**4h**/**4o** with remarkable yield (Scheme 2). In addition, the reaction involving phenylisonitrile **3d** exhibited complete conversion under microwave irradiation (for the synthesis of **4j**) when compared to the analogous conventional heating reactions.[23]

We next explored the hetero-aminoazines diversity (**5**) for the synthesis of fused-imidazo bi- and tricyclic heterocycles and the results are summarized in Scheme 3. All the reactions produced the desired products **6a–j** with exceptional conversion. Similar to enolizable aldehyde **2f**, the isonitrile bearing reactive ester group, MeO(O)C-$CH_2$-NC **3e** also furnished the desired product **6j** with remarkable yield (Scheme 3).

Being faster, easier and no dependency over purification, this protocol qualifies for one of the best greener methods for the G–B-B reaction. To gauge the greenness of the present protocol, we evaluated the green chemistry metrics (such as E-factor and Mass Intensity)[24] in conjunction with the reported protocols based on either conventional or microwave heating (Table 2). The results clearly indicate that our protocol is far better than the literature reports[18a] by exhibiting excellent E-factor which is almost zero and Mass Intensity which is nearly one (entry 10). In comparison with all the methods listed in Table 2 (entries 1–9; were required either column chromatography or recrystallization at the end), the present method (entry 10) doesn't need any type of purification and the solvents (used for workup) and catalyst were recycled incessantly (*vide supra*).




**Scheme 2.** Synthesis of various imidazo[1,2-a]pyridine derivatives (**4**).



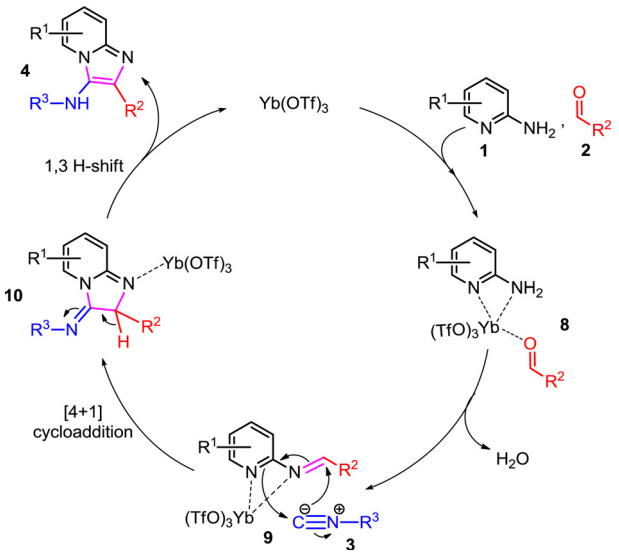

**Scheme 3.** Synthesis of fused-imidazo bi- and tricyclic heterocycles (**6**).

Among all the microwave-based protocols for the G–B-B reactions, our methodology alone could be categorized as best greener method.

In addition, many of those reported methods required longer reaction time (Table 2, entries 2, 3, 6, 7 and 9), which may lead to the decomposition of the product/reactant and or formation of the side products. For instance, the reaction involving enolizable aldehyde **2f** produced the desired product **4o** with 63% isolated yield under conventional heating condition (by following the solvent-free and catalyst-free protocol;[18a] Table 3, Method A). However, the reaction also produces enamine **7** as the side product.[25] On the other hand, analogous reaction involving $BiCl_3$ as catalyst furnished the desired product **4o** with 83% isolated yield (by following the $BiCl_3$ catalyzed protocol[13f]) and no formation of the side product **7** was observed (Table 3, Method B). However, the reactants were not consumed completely and **1a** was recovered after purification by column chromatography. In contrast, corresponding reaction under our methodology produced **4o** with remarkable yield (E-factor: 0.11, Mass Intensity: 1.11) and no formation of the side product **7** was observed (Table 3, Method C). It clearly indicates that expedited synthesis with lower reaction time (5 min) helped to suppress the formation of the side product **7.**

In order to explore the applicability of the current protocol for higher scale reaction, one such scale-up reaction was designed for the synthesis of **4m.** A mixture of **1c** (50 mmol), **2k** (50 mmol), **3a** (50 mmol) and $Yb(OTf)_3$ (1.25 mmol) was heated under microwave by following the current protocol (see Experimental Section in the Supporting Information). After the workup analytically pure **4m** was isolated in 98% yield with excellent E-factor (0.088) and Mass Intensity (1.088) which is in very good agreement with the corresponding micro-scale reaction (Table 2, entry 10; see Supporting Information). At this stage also, the solvent used for workup and catalyst were isolated, purified and recycled (*vide supra*). The catalyst recovered was again employed four successive times for the synthesis of **4m** at higher scale level of experiments and found to retain its activity and furnished the desired product **4m** with identical isolated yield (97%, see Experimental Section in the Supporting Information).

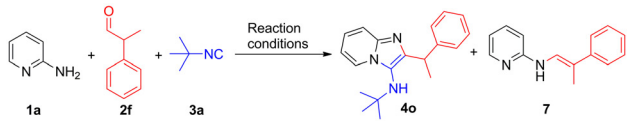
A plausible mechanism for the conversion of fused-imidazo heterocyclic skeleton has been depicted in Scheme 4. In the




**Scheme 4.** Plausible mechanism for the G–B-B reaction (MCR).

first instance, $Yb(OTf)_3$ coordinates with the nitrogens of 2-aminopyridine and oxygen of aldehyde (**8**). This leads to the increase of electrophilicity on the carbonyl carbon of the alde-

**Table 3.** Comparison of methods on the synthesis of **4o.**[a].

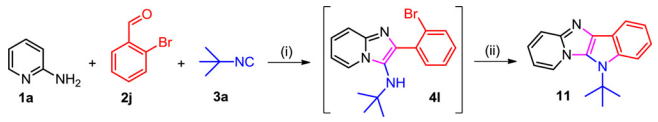



| Method | Reaction Condition | 4o (%)[b] | 7 (%)[b] | E-factor | Mass Intensity |
|---|---|---|---|---|---|
| A | 160 °C, 2 h[18a,25] | 63 | 21 | 0.69 | 1.69 |
| B | $BiCl_3$ (5 mol%), 110 °C, 5 min[13f] | 83[c] | NO[d] | 0.34 | 1.34 |
| **C** | **$Yb(OTf)_3$ (2.5 mol%), MW, 160 °C, 5 min** | **96** | **NO[d]** | **0.11** | **1.11** |

[a] Refer Supporting Information for E-factor and Mass Intensity calculations; [b] Isolated yield; [c] Unreacted **1a** was recovered; [d] NO: not observed through TLC.

hyde which undergoes nucleophilic attack by the amine to form azomethine intermediate **9.**[5,11d] The intermediate **9** undergoes [4+1] cycloaddition with isonitrile to generate cyclized adduct **10.** This cyclization is again facilitated by the coordination of the catalyst. Finally, the cyclized adduct **10** undergoes 1,3-H shift to give the desired product **4** and regenerate the catalyst $Yb(OTf)_3$ to complete the catalytic cycle.

In order to explore the possibility of coupling our protocol (G–B-B reaction) with other methods such as transition-metal catalyzed post-condensation modification (Ullmann-type coupling), a rigorous one-pot two-step sequential method was developed (Scheme 5). Accordingly, **1a**, **2j** and **3a** were reacted




**Scheme 5.** One-pot two-step cyclization reaction (G–B-B reaction and Ullmann-type coupling). Reaction conditions: (i) 2.5 mol% $Yb(OTf)_3$, neat, 160 °C, MW, 5 min; (ii) CuI, 1,10-phenanthroline, DMF, 120 °C, MW, 10 min.

by following the optimized protocol for the synthesis of **4l** (*vide supra*) at first step. After the reaction, CuI, 1,10-phenanthroline and DMF were added to the same reaction vessel and heated further under microwave irradiation at 120 °C for 10 min (at the second step) to furnish the tetracyclic compound, pyrido[2′,1′:2,3]imidazo[4,5-b]indole (**11**). The one-pot two-step protocol reported here is a rapid and efficient method for the synthesis of **11** with maximum yield (overall 91 %) when compared to the literature reports.[26] Also, it is important to note that our methodology can be easily coupled with transition metal catalyzed post-condensation modifications (one-pot two-step cyclization).

## Conclusions

In summary, we have developed a simple, fast and efficient microwave assisted solvent-free protocol for one-pot synthesis of fused-imidazo heterocycles catalyzed by mild and water-compatible Lewis acid, $Yb(OTf)_3$ under microwave irradiation. The salient features of our protocol are solvent-free, low catalyst loading with good TON and TOF, less reaction time, no specialized purification (by either column chromatography or recrystallization), catalyst and solvent recycling, very high isolated yield and easy to couple with other methods. The demonstration of excellent green chemistry indices qualifies it to be categorized as best green methodology and this is the first report of green method involving microwave-lanthanide catalyzed G–B–B reaction. The current method exhibits high substrate scope and diversity which provides access to diversified *N*-fused bi- and tricyclic heterocycles for the drug discovery. The efficiency of our protocol was unambiguously established by exhibiting excellent conversion and green metrics on the reactions involving enolizable aldehyde and isonitrile bearing reactive ester group where other protocols reported till date failed to produce good results. The solvent and catalyst recyclability feature can be elegantly exploited at higher scale reaction, where it could reduce the overall cost involved in the reaction. Hence, this protocol can be easily applied for the possible synthesis of fused-imidazo heterocycles at industrial scale. Moreover, the method is also amenable to couple with various post-condensation modification protocols reported in the literature as evident by the synthesis of **11** (one-pot two-step cyclization: G–B-B reaction and Ullmann-type coupling). Currently, we are exploring the photo-luminescent properties[27] and biological activity of the title compounds and possibilities of post-condensation modifications thereof to synthesize diversified polyheterocycles.

**Supporting Information** (see footnote on the first page of this article): experimental details and characterization data; calculation of green chemistry metrics; copies of the spectra ($^1H$, $^{13}C$ NMR and EI-MS) of all reported compounds.

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Bruker 500 MHz NMR spectrophotometer facility at the University campus.

**Keywords:** Multi-component reaction (MCR) · $Yb(OTf)_3$ · Microwave-assisted catalysis · Catalyst recycling · Solvent-free reactions · Imidazo[1,2a]pyridine

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