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Basic ionic liquid promoted heterocyclization to access fused imidazopyridines

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ABSTRACT

A single step access to fused imidazopyridine involving [bmIm]OH promoted click cyclocondensation of *N*-methylisatin with 2-aminopyridine has been achieved. The title heterocyclic scaffolds were obtained in excellent yield with high purity. [bmIm]OH was found to be more attractive as it plays the role of solvent, base, and catalyst.

Nitrogen-containing heteroaromatics and their analogous are pharmaceutically attractive scaffolds and are broadly present in naturally occurring and synthetic biologically active molecules. Fused imidazo[1,2-*a*]heterocycles such as benzimidazo[2,1-*a*]isoquinolines (**I**)[1] and pyrido[1,2-*c*]purines (**II**) are anticancer agents[2], pyridino[1,2-*a*]imidazo[5,4-*b*]indol (**III**)(Fig. 1) and dimeric analogues of 2 aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole, are potent antihypertensive compounds.[3,4] They possibly interact with DNA and display biological and pharmaceutical activity.[5] Moreover, drugs like zolpidem which is clinically used for the treatment of insomnia, olprinone which is used for the treatment of acute heart failure, minodronic acid for the treatment of osteoporosis, and zolimidine as an anti-ulcer agent (Fig. 2) have imidazo[1,2-*a*]pyridine as the core structure.[6]

A number of synthetic routes have been reported for the synthesis of imidazo[1,2-*a*]pyridine.[7] The synthesis of imidazopyridines containing pyrrole as an auxiliary group also suffered limitations like scope, generality, substrate availability, hazardous catalysts, carcinogenic VOLs (volatile organic liquids), and unavoidable need of bases. Furthermore these synthetic protocols involved time consuming sequential multistep processes with harsh reaction conditions. Because of strong requirement of fused imidazo[1,2-*a*]pyridine scaffolds in medicament, there is a demand for developing a straightforward, simple, high yielding, and convenient facile methodology for the synthesis of imidazo[1,2-*a*]pyridine from simple and readily available precursors.

The pressing need is the use of alternative reaction medium that circumvents the problems associated with many traditional organic solvents. Operations resulting in the construction of highly functionalized heterocycles remain a great scientific challenge. This has prompted us to utilize [bmIm]OH in intermolecular cyclization to facilitate the synthesis of fused imidazopyridine. Buoyed from the green credentials of task specific basic ionic liquids (TSBIL)[8–10] as well as part of our ongoing endeavors for the development of simple, efficient, and versatile synthetic methodologies for the synthesis of biodynamic heterocyclic scaffolds,[11–16] we report herein a single step methodology using 2-aminopyridine and *N*-methyl isatin as reactants catalyzed by [bmIm]OH (1-butyl-3-methylimidazolium hydroxide) to furnish fused imidazopyridine scaffolds (Scheme 1).[17]

We have successfully developed an efficient method to prepare a number of fused imidazopyridine derivatives via basic ionic liquid promoted cyclocondensation of *N*-methylisatin and 2-aminopyridine at room temperature. The selection of base, catalyst, and solvent system is a main issue as per importance of environmental purity. However, in the previously reported work, catalysts like Cu, Pd, Rh, solvents such as DMF, ethanol, toluene, and bases like NaOH have already been used in standard reaction conditions. We have replaced toxic catalysts, hazardous bases, and carcinogenic volatile organic solvents with recyclable and non hazardous [bmIm]OH and achieved better yield of the product (89%).

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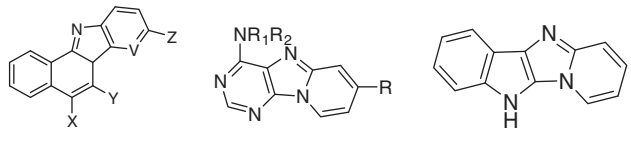
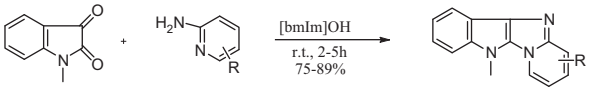
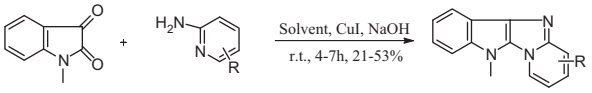


Figure 1.



Scheme 1. Basic ionic liquid catalyzed synthesis of fused imidazo-pyridine.

Table 1
Influence of various solvents on the synthesis of **4a** using NaOH as base and CuI as catalyst[a]



Entry	Solvent	Base (10%)	Catalyst (10%)	Time (h)	Yield[b] (%)
1	H_2O	NaOH	CuI	7	21
2	Ethanol	NaOH	CuI	5	37
3	DCM	NaOH	CuI	4	53
4	THF	NaOH	CuI	5	43
5	DMF	NaOH	CuI	6	48

[a] Reaction conditions: *N*-methylisatin (2.0 mmol), 2-aminopyridine (2.0 mmol).
[b] Isolated yields.

In order to explore the generality and feasibility of the strategy we attempted to investigate the optimization of reaction conditions using 2-aminopyridine and *N*-methyl isatin as model reactants. Various solvents were used in the presence of NaOH as a base and CuI as a catalyst to afford desirable products and the results are summarized in Table 1.

It was inferred from Table 1 that the best solvent in terms of product yield and reaction time was DCM (Table 1, entry 3**)** while ethanol, THF, CH_2Cl_2, and H_2O proved less effective as lower yield of product was obtained and longer reaction time was needed (Table 1, entries 2, 4, and 5). To achieve high product conversion the reaction was carried out in DCM with different catalysts like CuI, CuBr, $ZnCl_2$, and $InCl_3$ and it was found that CuI turns out to be the best catalyst for the transformation of reactants into products (Table 2, entry 1).

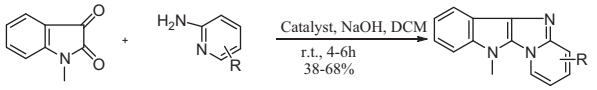
Reports regarding heterocyclization reactions in ionic liquid encouraged us to perform the reaction in this versatile reaction medium which in most of the cases acted also as a promoter and additionally sometimes as base. So this reaction involving model reactants was carried using ionic liquids [bmIm]OH and [bmIm]Br without inorganic base, organic solvent, and metal halide as catalyst and the results are summarized in Table 3. From Table 3 [bmIm]OH was found to be the most efficient as there was no need to use additional catalyst and base. Further the suitable work-up process for the reaction is an additional advantage of the protocol.

The effect of mol % of [bmIm]OH on product yield and reaction time was also optimized for the synthesis of fused imidazopyridine by using different mol % of the ionic liquid **(**Table 4**).** From the results shown in Table 4, entry 1 it was inferred that 20 mol % of [bmIm]OH proved to be the optimum catalyst loading for intermolecular heterocyclization with the product yield of 86%. By decreasing the amount of catalyst to 15 from 20 mol % relative to substrate, the yield of product **4a** decreased (Table 4, entry 2) but by increasing the amount of catalyst from 20 to 25 mol %, no appreciable change in the yield of product was observed (Table 4, entry 3). It was also observed that when [bmIm]OH was used as solvent and catalyst, at higher reaction temperature no appreciable effect on the yield was observed (Table 4, entry 6).

The task specific basic ionic liquid was synthesized according to a reported procedure.[18] Ionic liquid [bmIm]OH was recovered completely and recycled twice for the synthesis with no appreciable decrease in the efficiency of the process (Fig. 3). The procedure for the synthesis of [bmIm]OH, and procedure for its recycling are given in the experimental section (Fig. 3).[17]

The formation of **4a** may be rationalized by the condensation of the carbonyl group of *N*-methyl isatin with 2-aminopyridine which on cyclization gives imidazopyridine intermediate **3**. This intermediate undergoes tautomerization and dehydration under the reac-

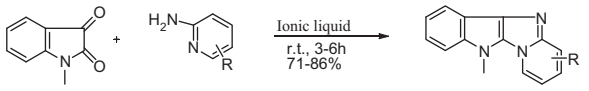
Table 2
Influence of catalyst on the synthesis of **4a**[a]



Entry	Catalyst (10%)	Solvent	Catalyst (10%)	Time (h)	Yield[b] (%)
1	CuI	DCM	NaOH	4	63
2	CuBr	DCM	NaOH	5	45
3	$ZnCl_2$	DCM	NaOH	6	38
4	$InCl_3$	DCM	NaOH	5	46

[a] Reaction conditions: *N*-methylisatin (2.0 mmol), 2-aminopyridine (2.0 mmol).
[b] Isolated yields.

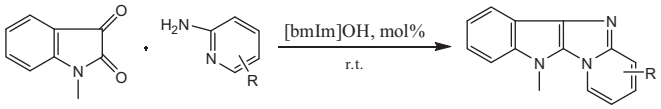
Table 3
Influence of Ionic liquid on the synthesis of **4a**[a]



Entry	Ionic liquid	Time (h)	Yield[b] (%)
1	[bmIm]OH	3	86
2	[bmIm]Br	6	71

[a] Reaction conditions: *N*-methylisatin (2.0 mmol), 2-aminopyridine (2.0 mmol).
[b] Isolated yields.

Table 4
Influence of different mol (%) of [bmIm]OH on **4a**[a]



Entry	[bmIm]OH (mol %)	Time (h)	Temp (°C)	Yield[b] (%)
1	20	3	rt	86
2	15	3	rt	71
3	25	3	rt	86
4	20	4	rt	86
5	20	2	rt	78
6	20	3	60	86

[a] Reaction conditions: *N*-methylisatin (2.0 mmol), 2-aminopyridine (2.0 mmol).
[b] Isolated yields.

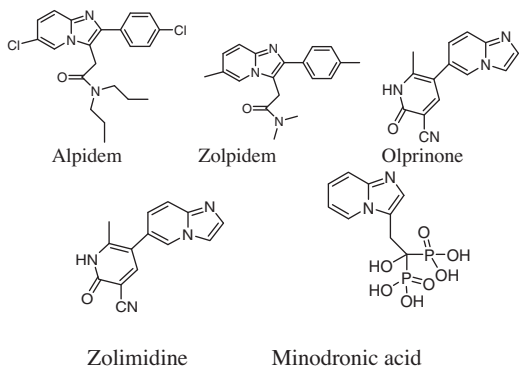


Figure 2.

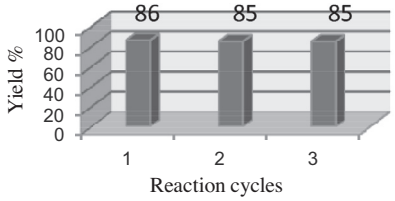
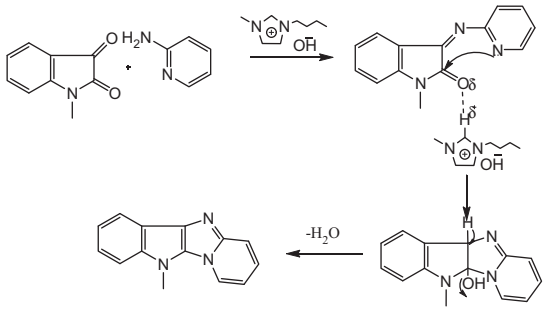


Figure 3. Recycling of [bmIm]OH.



Scheme 2. Plausible mechanism for fused imidazopyridine promoted by [bmIm]OH.

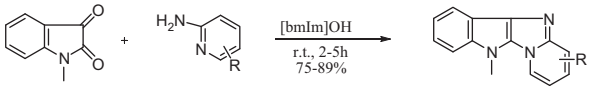
tion conditions to afford 5-methyl-5*H*-4*a*,5,10-triaza-indeno [2,1-*a*]indene derivatives (Scheme 2).

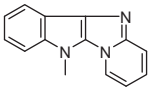
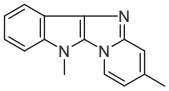
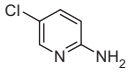
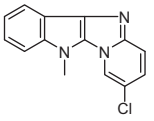
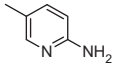
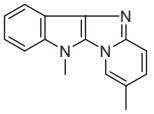
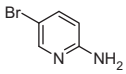
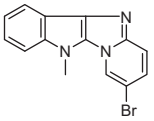
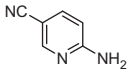
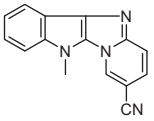
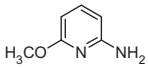
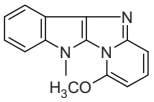
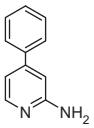
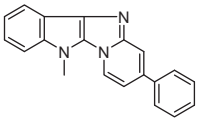
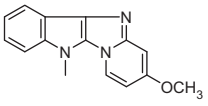
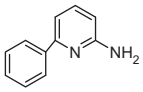
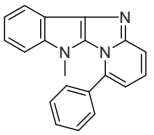
The presence of both electron donating and electron withdrawing groups present in the benzene ring of imidazopyridine has been well studied and they have been found to have pronounced effect on product yield and reaction time. It was observed from Table 5 that fused imidazopyridines bearing electron withdrawing groups were obtained at a faster rate and with better yield, than those containing electron releasing groups.

From Table 5 it was also inferred that reactants bearing electron withdrawing groups on the benzene ring of *o*-alkynylphenol react faster with better yield than those having electron donating groups.

In summary, we have developed a novel [bmIm]OH mediated protocol for the synthesis of 5-methyl-5*H*-4*a*,5,10-triaza-indeno[2,1-*a*]indene derivatives without using VOL as reaction medium, transition metal halide catalyst, and any inorganic base. The strategy could be applied to various available substrates with a one-step synthetic procedure in moderate to good yields. High efficiency, generality, short reaction time, and clean reaction profiles are the advantages of the protocol.

Table 5
Ionic liquid [bmIm]OH promoted synthesis of products **4**(**a**–**j**)[a]



Entry	R	Product	Time (h)	Yield[b] (%)
1			3	86
2			4	76
3			3	81
4			5	75
5			4	86
6			3	89
7			5	83
8			3	78
9			4	85
10			5	77

[a] Reaction conditions: *N*-methylisatin (2.0 mmol), 2-aminopyridine (2.0 mmol).
[b] Isolated yields.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.054.

References and notes

1. Deady, L. W.; Loria, P. M.; Rodermann, T. *Aust. J. Chem.* **1998**, *51*, 941–945.
2. Pinguet, F.; Mavel, S.; Galtier, C.; Gueiffier, A. *Pharmazie* **1999**, *54*, 876–878.
3. Adhikary, P. K.; Das, S. K. *J. Med. Chem.* **1976**, *19*, 1352–1354.
4. Birch, D. J.; Guildford, A. J.; Tometzki, M. A.; Turner, R. W. *J. Org. Chem.* **1982**, *47*, 3547–3548.
5. Lee, C. S.; Hashimoto, Y.; Ohta, T.; Shudo, K.; Okamoto, T. *Chem. Pharm. Bull.* **1982**, *30*, 3046–3049.
6. Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888.
7. (a) Katritzky, A. R.; Xu, Y. J.; Tu, H. *J. Org. Chem.* **2003**, *68*, 4935. and references cited therein; (b) Ueno, M.; Nabana, T.; Togo, H. *J. Org. Chem.* **2003**, *68*, 6424; (c) Adib, M.; Mahdavi, M.; Noghani, M. A.; Mirxaei, P. *Tetrahedron Lett.* **2007**, *48*, 7263; (d) Adib, M.; Mahdavi, M.; Abbasi, A.; Jahromi, A. H.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2007**, *48*, 3217; (e) Kumar, S.; Sahu, D. P. *ARKIVOC* **2008**, *15*, 88; (f) Enguehard-Gueiffier, C.; Croix, C.; Hervet, M.; Kazock, J. Y.; Gueiffier, A.; Abarbri, M. *Helv. Chim. Acta* **2007**, *90*, 2349; (g) Parenty, A. D. C.; Cronin, L. *Synthesis* **2008**, *9*, 1479; (h) Zhang, R.; Hu, Y. *Synth. Commun.* **2007**, *37*, 377; (i) Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synthesis* **2009**, *2*, 271; (j) Bakherad, M.; Keivanloo, A.; Hashemi, M. *Synth. Commun.* **2009**, *39*, 1002–1011; (k) Adib, M.; Shebani, E.; Zhu, L.-G.; Mirzaei, P. *Tetrahedron Lett.* **2008**, *49*, 5108; (l) Yadav, J. S.; Reddy, B. V. S.; Rao, Y. G.; Srinivas, M.; Narsaiah, A. V. *Tetrahedron Lett.* **2007**, *48*, 7717.
8. Yadav, L. D. S.; Singh, S.; Rai, V. K. *Tetrahedron Lett.* **2009**, *50*, 2208–2212.
9. Gu, L.; Lib, X. *J. Braz. Chem. Soc.* **2011**, *22*, 2036–2039.
10. Ranu, B. C.; Jana, R.; Sowmiah, S. *J. Org. Chem.* **2007**, *72*, 3152–3154.
11. Siddiqui, I. R.; Singh, P. K.; Singh, J.; Singh, J. *J. Agric. Food Chem.* **2003**, *51*, 7062–7065.
12. Siddiqui, I. R.; Singh, P. K.; Singh, J.; Singh, J. *Chem. Res.* **2004**, *8*, 554–555.
13. Siddiqui, I. R.; Shamim, S.; Kumar, D.; Shireen; Waseem, M. A. *New J. Chem.* **2012**, *36*, 2209–2214.
14. Siddiqui, I. R.; Shireen; Shamim, S.; Abumhdi, A. A. H.; Waseem, M. A.; Srivastava, A.; Rahila; Srivastava, A. *New J. Chem.* **2013**, *37*, 1258–1263.
15. Siddiqui, I. R.; Srivastava, V.; Singh, P. K. *Nucleosides, Nucleotides and Nucleic Acids* **2008**, *27*, 1532–2335.
16. Siddiqui, I. R.; Singh, A.; Shamim, S.; Srivastava, V.; Singh, P. K.; Yadav, S.; Singh, R. K. P. *Synthesis* **2010**, *20*, 1613–1616.
17. *Genereal procedure for synthesis of* ***4a***: A mixture of *N*-methyl-isatin **1** (2.0 mmol), 2-aminopyridine **2a** (2.0 mmol) and [bmIm]OH (0.4 mmol) was stirred at room temperature for 2–5 h. After completion of reaction as indicated by TLC, 20 mL of water was added to the reaction mixture and stirred well. The product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 to afford the crude product and recrystallized from ethanol to obtain analytically pure compound **4** (75–89%). After isolation of the product, the remaining aqueous layer containing the ionic liquid was washed with ether (2 × 10 mL) to remove organic impurities and filtered. The filtrate was extracted with dichloromethane (2 × 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to afford [bmIm]OH, which was recycled twice in subsequent runs without further purification.
4a*: 5-Methyl-5H-4a,5,10-triaza-indeno[2,1-a]indene*: ^{1}H NMR (400 MHz, CDCl3/TMS) δ: 8.09(d, 1H), 7.51(d, 1H), 7.17–7.17(m, 4H), 7.03(m, 1H), 6.65(m, 1H), 3.60(s, 3H, CH3); ^{13}C NMR (100 MHz, CDCl3/TMS) δ: 149.8, 139.1, 136.2, 135.7, 127.9, 127.7, 123.6, 123.6, 121.7, 120.5, 119.6, 111.0, 102.4, 43.6; EIMS: (*m*/*z*):221 (M^+), Anal. Calcd for $C_{14}H_{11}N_3$: C, 76.00; N, 18.99; H, 5.01. Found: C, 76.10; N, 18.84; H, 5.05.
18. Ranu, B. C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049–3052.