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A mild and novel synthesis of functionalized fused imidazole analogues under environmentally benign reaction media

B. Madhu Babu, G. Santosh Kumar, Pramod B. Thakur, Vikas M. Bangade, H. M. Meshram *

Medicinal Chemistry and Pharmacology Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

A mild and novel approach is described for the synthesis of functionalized fused imidazole analogues in solvent-free and catalyst-free condition in ionic liquid. The short reaction time, good isolated yields, generality and environmentally benign reaction media are the significant features of this protocol.

Fused imidazo-heterocycles containing ring-junction nitrogen atoms play an important role in the area of medicinal chemistry.[1] Particularly, five membered nitrogen containing imidazo[1,2-*a*]pyridine scaffolds has been shown to possess a wide range of biological activities such as anti-inflammatory,[2] antiprotozoal,[3] antiviral,[1c,4] antiulcer,[5] antibacterial[6] and antifungal agents.[7a] Moreover, this framework is a core structure of many commercially available drugs such as zolimidine (antiulcer),[7b] alpidem (anxiolytic),[7c] zolpidem (hypnotic),[8] olprinone (to treat heart failure),[9a] necopidem (sedative) and saripidem (anxiolytic)[9b] (Fig. 1). In addition to this, fused imidazothiazole and imidazobenzothiazole analogues also serve as antibacterial,[10] antifungal,[11] antihelmintic[12] and antitumor agents.[13] Due to such prominence and prevalence of fused imidazole frameworks in the arena of medicinal chemistry, development of efficient protocol for the synthesis of this motif is desirable.

Numerous methods have been reported for the synthesis of fused imidazo-heterocycle framework under different reaction conditions.[14] The classical approach includes, the reaction of heteroamine such as 2-aminopyridine with α-halocarbonyl compounds,[15] and three-component reaction of aromatic amidines with isocyanide and aromatic aldehydes.[16] Other classical methods have been developed by using acid catalysts,[1a,17] solid supported *p*-toluenesulfonic acid,[18a] glyoxalic acid,[18b] Montmorillonite clay K10,[18c] $Sc(OTf)_3$,[18d] $ZnCl_2$,[19] in polar solvents,[19,20a,b] as well as ionic liquid.[20c] One example of catalyst-free[20d] synthesis of fused imidazole framework is also reported. However, most of the methods rely on the use of α-halocarbonyl compound or isocyanide which are difficult to handle and require an excess amount of expensive catalyst.[16f,h] Additionally, a few of the methods require longer reaction time,[1a,16f,h,20d] harsh reaction conditions and cumbersome work-up procedure.[18c,d] Although some of the protocols are satisfactory, still there is a scope to develop general and convenient protocols for the synthesis of a new diversely functionalized fused imidazoles under environmentally benign reaction media.

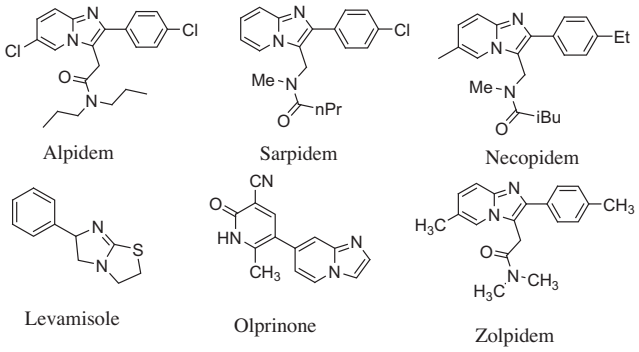

Figure 1. Representative examples of bioactive molecules containing fused imidazole structural framework.

In recent years development of eco-friendly synthetic protocols for the assembly of new chemical entities is gaining great

* Corresponding author. Tel.: +91 40 27191643; fax: +91 40 27193275.
E-mail address: hmmeshram@yahoo.com (H.M. Meshram).

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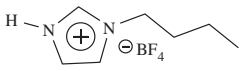
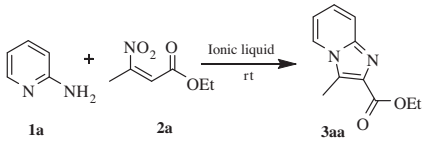


Figure 2. Chemical structure of representative ionic liquid 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4.

importance.[21] In this context, ionic liquids (ILs, Fig. 2) have attracted more attention as benign reaction media in organic synthesis because of their special and unique properties like non-volatility, high thermal stability, negligible flammability and recyclability.[22] The main advantage of ionic liquid is to eliminate the use of hazardous, volatile and toxic solvents,[23a] which satisfy the requirements of modern green chemistry.[23b] Moreover, some of the ionic liquids also promote the organic transformations without the use of any additional catalyst or solvent,[24] because of their high polarity and the ability to solubilize both inorganic and organic compounds, which can accelerate the rate of reactions.

In the last few years, β-nitroacrylates have been emerged as a versatile class of electron-poor alkenes[26] in chemical synthesis.[27,28] Although β-nitroacrylates are less readily available compared to 2-halocarbonyl compounds, they display a significantly higher reactivity and efficiency towards aminopyridine compared to the halocarbonyl compounds. Due to this β-nitroacrylates have been explored in the synthesis of a variety of heterocycles[29] by replacing highly toxic and lachrymatory 2-halocarbonyl compounds. In this context, recently we have explored β-nitroacrylates in the synthesis of thiazol-2-imine derivatives using ionic liquid under solvent-free and catalyst-free condition.[25a] In continuation of our ongoing interest in the application of ionic liquids[25] in the synthesis of biologically active molecules, we envisaged the possible utilization of β-nitroacrylates in the synthesis of fused imidazole frame work using suitable ionic liquid. To the best of our knowledge, there is no report on utilization of β-nitroacrylates in the synthesis of fused imidazole molecular framework by the reaction of amidines with β-nitroacrylates. Herein we wish to report a catalyst-free, solvent-free, efficient and general method for the preparation of diversely functionalized fused imidazo-heterocycles by the reaction of β-nitroacrylates with amidine in the presence of ionic liquid as a reusable reaction media.

Initially, we attempted the reaction of 2-aminopyridine **1a** (1 mmol) and β-nitroacrylate, ((*Z*)-ethyl 3-nitrobut-2-enoate) **2a** (1 mmol) in 5 mL ionic liquid [Hbim]BF_4 (Scheme 1) at room temperature and progress of the reaction was monitored continuously



Scheme 1. Optimization of the reaction conditions.

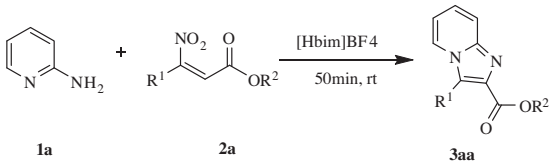
Table 1
Screening of reaction media[a]

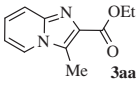
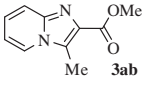
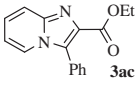
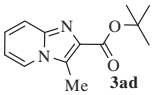
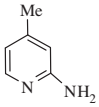
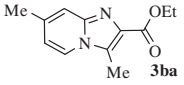
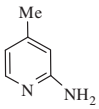
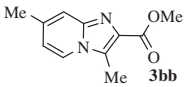
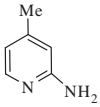
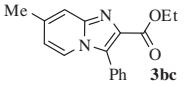
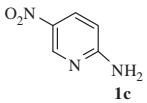
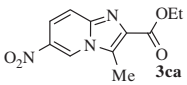
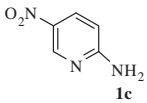
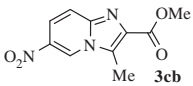
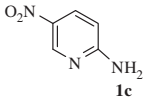
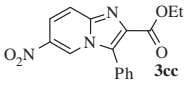
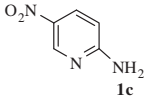
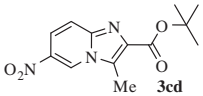
Entry	Reaction media	Time (min)	Yield[b] (%)
1	[Hbim]BF_4	50	74
2	[bim]BF_4	50	59
3	[bim]PF_6	50	61
4	[emim]BF_4	50	65
5	—	24 h	Trace[c]

[a] Reaction condition: 2-aminopyridine **1a** (1 mmol), β-nitroacrylate, (*Z*)-ethyl 3-nitrobut-2-enoate **2a** (1 mmol) in 5 mL ionic liquid.
[b] Isolated yield.
[c] Under neat reaction condition.

by TLC. After completion of the reaction (50 min) the reaction mixture was extracted from ionic liquid using diethyl ether to get crude reaction mass and subjected to ^{1}H NMR analysis. On analysis of ^{1}H NMR spectrum of crude mass, it was observed that the reaction of 2-amino pyridine **1a** with β-nitroacrylate ((*Z*)-ethyl 3-nitrobut-2-enoate) **2a** in ionic liquid affords only regioselective product ethyl 3-methyl *H*-imidazo[1,2-*a*]pyridine-2-carboxylate (**3aa**) (Table 2, entry 1). As a part of the study, the scope of the reaction

Table 2
Synthesis of fused imidazole derivatives[a]



Entry	Amino pyridine	R^1	R^2	Product	Yield[b] (%)
1	 **1a**	Me	Et	 **3aa**	74
2	 **1a**	Me	Me	 **3ab**	75
3	 **1a**	Ph	Et	 **3ac**	71
4	 **1a**	Me	^{t}Bu	 **3ad**	73
5	 **1b**	Me	Et	 **3ba**	86
6	 **1b**	Me	Me	 **3bb**	84
7	 **1b**	Ph	Et	 **3bc**	83
8	 **1c**	Me	Et	 **3ca**	71
9	 **1c**	Me	Me	 **3cb**	74
10	 **1c**	Ph	Et	 **3cc**	70
11	 **1c**	Me	^{t}Bu	 **3cd**	72

[a] All products exhibited physical and spectral (NMR, Mass, HRMS and IR) properties in accordance with the assigned structure.
[b] Isolated yield.