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Graphical Abstract

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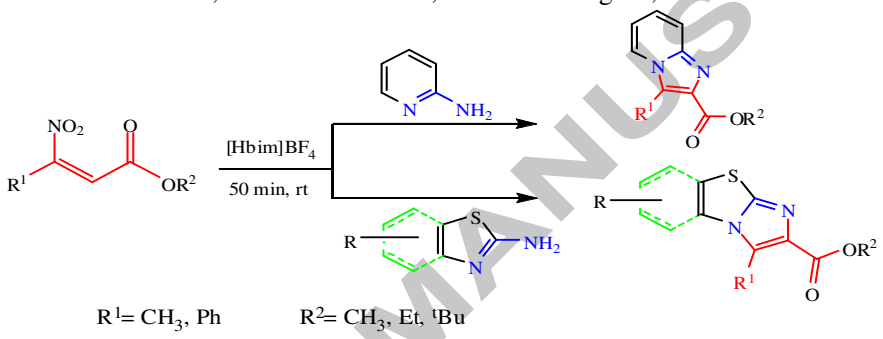


R^1= CH_3, Ph R^2= CH_3, Et, ^{t}Bu

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

Tel.: +91-40-27191643, Fax: +91-40-27193275, E-mail address- hmmeshram@yahoo.com

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.

Keywords: β-Nitroacrylate, 2-Aminopyridine, Fused heterocycles, Ionic liquid, Green synthesis.

Fused imidazo-heterocycles containing ring-junction nitrogen atoms plays an important role in the area of medicinal chemistry.[1] Particularly, five membered nitrogen containing imidazo[1,2-a]pyridine scaffolds have been shown to possess a wide range of biological activity 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.

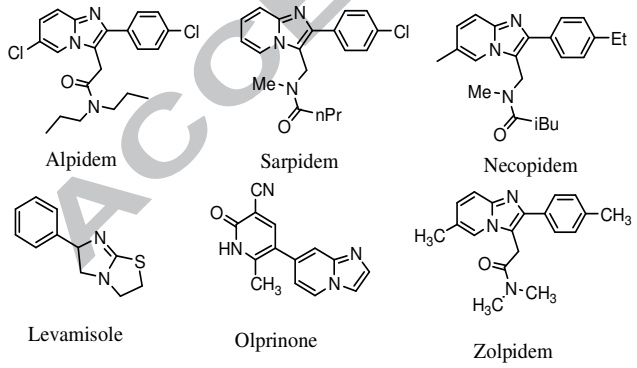


Fig. 1: Representative examples of bioactive molecules containing fused imidazole structural framework.

Numerous methods have been reported for the synthesis of fused imidazo-heterocycles 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,20b] 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,16h] Additionally, a few of the methods require longer reaction time,[1a,16f,16h,20d] harsh reaction conditions and cumbersome work-up procedure.[18c,18d] 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.

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

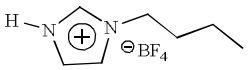
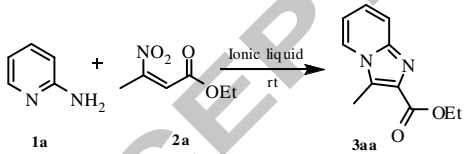


Fig. 2: Chemical structure of representative ionic liquid 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4.

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 ulitization 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



Scheme 1: Optimization of the reaction conditions.

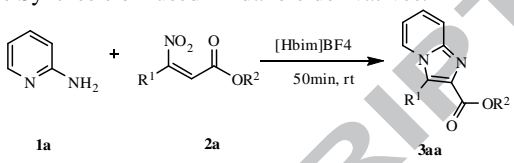
Table 1: Screening of reaction media[a]

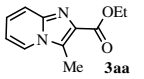
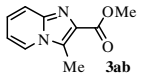
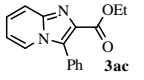
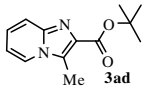
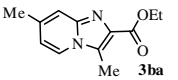
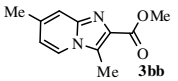
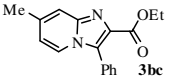
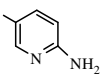
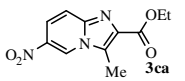
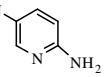
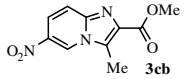
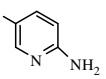
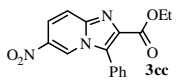
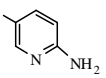
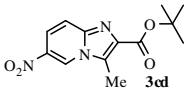
Entry	Reaction media	Time (min)	Yield[b](%)
1	[Hbim]BF_4	50	74
2	[bmim]BF_4	50	59
3	[bmim]PF_6	50	61
4	[emim]BF_4	50	65
5	-	24 h	trace[c]

[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.

temperature and progress of the reaction was monitored continuously 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

Table 2: Synthesis of fused imidazole derivatives.[a]

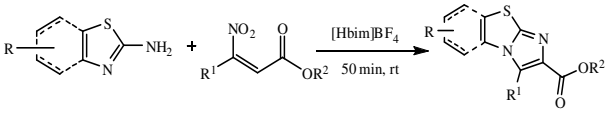


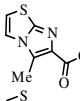
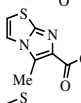
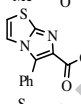
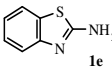
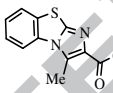
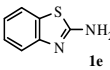
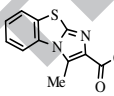
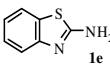
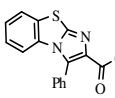
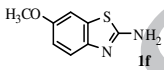
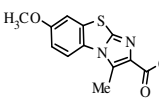
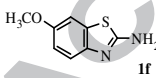
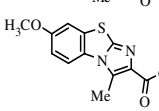
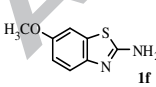
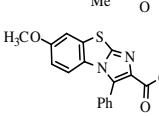
Entry	Amino pyridine	R^1	R^2	Product	Yield[b](%)
1	 **1a**	Me	Et	 **3aa**	74
2	 **1a**	Me	Me	 **3ab**	75
3	 **1a**	Ph	Et	 **3ac**	71
4	 **1a**	Me	^{t}Bu	 **3ad**	73
5	 **1b**	Me	Et	 **3ba**	86
6	 **1b**	Me	Me	 **3bb**	84
7	 **1b**	Ph	Et	 **3bc**	83
8	 **1c**	Me	Et	 **3ca**	71
9	 **1c**	Me	Me	 **3cb**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

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 was also tested in different ionic liquids such as, 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4, 1-butyl-3-methylimidazolium hexafluoro phosphate [bmim]PF_6, 1-ethyl-3-methylimidazolium tetrafluoroborate [emim]BF_4. After screening results, we found that ionic liquid [Hbim]BF_4 as a most suitable reaction media for optimum conversion in terms of reaction time and isolated yield (Table 1, entry 1). The results evaluating the merits of various ionic liquids are presented in Table 1.

Table 3: Synthesis of fused imidazothiazole derivatives.[a]

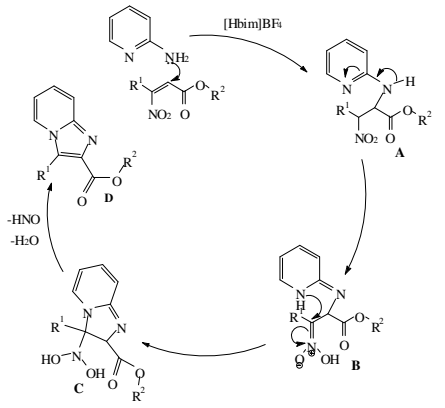


Entry	Thiazole	R^1	R^2	Product	Yield[b](%)
1	 **1d**	Me	Et	 **3da**	78
2	 **1d**	Me	Me	 **3db**	74
3	 **1d**	Ph	Et	 **3dc**	71
4	 **1e**	Me	Et	 **3ea**	76
5	 **1e**	Me	Me	 **3eb**	80
6	 **1e**	Ph	Et	 **3ec**	72
7	 **1f**	Me	Et	 **3fa**	76
8	 **1f**	Me	Me	 **3fb**	79
9	 **1f**	Ph	Et	 **3fc**	73

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

Further to determine the scope of this reaction, we planned to examine the reaction of various β-nitroacrylates with substituted 2-aminopyridines under optimized condition. In this context, we screened 2-aminopyridine with various β-nitroacrylates which reacted smoothly in the standard reaction condition to furnish the expected product in very good yield (Table 2, entries 1-4). Further the scope was tested with substituted 2-aminopyridine like 4-methyl 2-aminopyridine and 5-nitro 2-aminopyridine. We were delighted to observe that, the reaction of 5-nitro 2-aminopyridine led to excellent yields of the desired products (Table 2, entries 8-11). The reaction of 4-methyl 2-aminopyridine with β-nitroacrylates also afforded the corresponding products in good to moderate yields (Table 2, entries 5-7).

The efficiency of the reaction was further strengthened by the participation of 2-aminothiazole with β-nitroacrylates. For example the reaction of 2-aminothiazole **1d** with β-nitroacrylates proceeded efficiently and afforded corresponding products **3da, 3db, 3dc** in good yield (Table 3, entries 1-3). To further extend the substrate scope of the reaction, we intended to study the reaction of fused ring heteroamines with β-nitroacrylates. In this regard, we treated aminobenzothiazoles with β-nitroacrylates in the presence of [Hbim]BF_4. It is worthy to mention that, aminobenzothiazoles also reacted with β-nitroacrylates in similar fashion to afford the respective product in good yield (Table 3, entries 4-6). Other substituted aminobenzothiazoles like 6-methoxyaminobenzothiazoles also participated effectively under same reaction conditions to furnish corresponding products in good to moderate yields (Table 3, entries 4-9).



Scheme 2: Plausible mechanistic pathway for the formation of substituted imidazo[1,2-a]pyridine in the presence of [Hbim]BF_4.

Keeping the green chemistry criteria in mind, we have tested the reusability of ionic liquid. After completion of reaction, the product was isolated from reaction mixture simply by extraction with ether (3x15 mL). Then the residual [Hbim]BF_4 was dried under vacuum and used for subsequent three cycles without any appreciable loss in the catalytic activity. It was noticed that the yield of the product **3aa** gradually decreased from first to third cycle (74%, 73% and 70%), respectively.

The plausible mechanism for the formation of desired product was given in Scheme 2. Initially, the Michael addition of 2-aminopyridine occurs on to β-nitroacrylate to form Michael adduct **A.** Then the adduct **A** tautomerizes into the reactive species **B** (aci-nitro tautomer),[25a] which is promptly attacked by the nitrogen atom of pyridine ring, with the formation of the five membered ring **C**. Finally, elimination of water and nitroxyl molecules, lead to the formation of the target imidazo[1,2-a]pyridine **D**.

In conclusion, we have demonstrated novel and efficient synthesis of new diversely functionalized fused imidazole analogues. The developed protocol is operationally simple, mild and provide direct access for regioselective synthesis of fused imidazo-heterocyclics. Moreover, reusable reaction media and generality of the procedure are the important features of present protocol.

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