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1,3-Di-*n*-butylimidazolium tribromide [BBim]Br_3: An efficient recyclable catalyst mediated synthesis of *N*-substituted azepines and their biological evaluation-interaction study with human serum albumin

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ABSTRACT

A majority of previously reported methods suffer from insufficient yields as well as more complicated experimental procedures, a smaller amount of isolated yields involving time-consuming and tiresome work-up with the use of metal catalyst and restricted scope of substrates. To overcome these issues, an environmentally benign, ionic liquid endorsed multi-component protocol to *N*-substituted azepines has been exploited by means of coupling aromatic amines, dimethyl/diethyl acetylene dicarboxylate, 2,5-dimethoxytetrahydrofuran using 1,3-Di-*n*-butylimidazolium tribromide [BBim]Br_3. The catalyst can be recycled and reused for subsequent reactions. The reactivated ionic liquid could be further reused twice as an accelerator All the synthesized compounds were further screened for their antimicrobial properties against three gram positive, four gram negative, and five fungal strains with chloromycin, norflaxacin, and fluconazole as reference drugs. Most of the tested compounds presented significant potency, especially, compound **4e** displayed significant antibacterial activity (MIC = 1–16 μg/mL) whereas compound **4k** showed momentous antifungal efficacy (MIC = 2–32 μg/mL). In addition binding behavior of compound **4e** was investigated by binding study between calf thymus DNA and compound **4e** by UV–Visible absorption spectroscopy and further research about HSA interactions were carried out. The observed wavelength showed a constancy thus revealing the occurrence of non-covalent π-π stacking interactions of compound **4e** and HSA.

1. Introduction

In the recent times, multi-component reactions (MCRs) have been employed as a proficient means in the synthesis of biologically active compounds [1–2]. Multi-component reactions (MCRs) are becoming increasingly prevalent due to their improved efficiency, simplicity, atom economy, reduced waste, and rapid access for the synthesis of biologically active compounds [3–5]. The current scenario highlights the need for the discovery and development of new drugs. However, multi-component reactions (MCRs) are powerful tools employed in the production of combinatorial libraries for drug discovery [6–8]. Consequently, MCRs are exceptionally convergent, producing a high molecular complexity in a single step process [9].

Azepines and its derivatives are unsaturated heterocyclic seven membered ring structures with nitrogen replacing a carbon at one position. These azepine derivatives are principal structural motifs of various natural and synthetic compounds which hold an elevated activity profile owing to their extensive range of biological/medicinal activities that include anti-inflammatory [10], anticonvulsant [11], antitumor [12], antiarrhythmic [13], anti-HIV [14], fungicidal activity [15], anti-malarial [16–17], stomach disorders [18] and other pharmaceutical applications [19,20]. In the current years, azepine derivatives have become an attractive research in the vicinity of medicinal chemistry. Some of the marketed available drug motifs are shown in Fig. 1.

Accordingly, the synthesis of azepine structure is of immense pharmacological significance and a variety of synthetic approaches were used for instance intramolecular Heck reaction [21], cyclization of diene, conjugated nitrile ylides prepared by the base catalyzed dehalogenation of the corresponding imidoyl chlorides, thermolysis of azides and [4 + 2] cycloaddition reactions [22]. In addition, transition metal catalyzed aza [5 + 2] cycloaddition, *N*-arylazepines via inter molecular annulations between propargyl ester and *N*-phenylimine [23] and *N*-substituted azepines by transition metal catalyzed aza-

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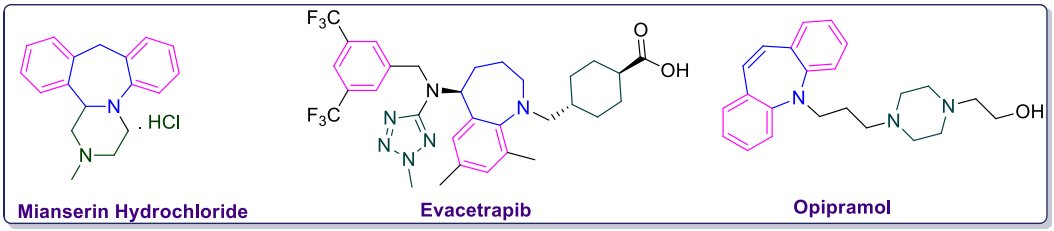


Fig. 1. Some of the biologically active drug motifs.

[5 + 2] cycloaddition of various imines have also been reported [24]. Recently, *N*-substituted azepines are prepared by using amines, DMAD/DEAD, and 2,-5 dimethoxy tetrahydrofuran mediated by *β*-cyclodextrin under aqueous medium at 50–60 °C [25] poly ethylene glycol (PEG-400) under 100–110 °C [26] and CsI under aqueous medium at ambient temperature [27]. On the other hand, a majority of these methods endure from inadequate yields, complicate experimental procedures, less isolated yields, along with time-consuming tiresome work-up, the use of metal catalyst, and restricted scope of substrates.

Furthermore, it was reported that ionic liquid has fascinated massive curiosity as benign reaction media in organic synthesis [28] in the recent decades because of their unique properties of non-volatility, non-flammability, recyclability, and the ability to dissolve a wide range of materials. As a consequence of their green credentials and potential to increase reaction rates and selectivity, ionic liquids have been found to have wide applications in organic synthesis, including many MCRs [29].

Based on this prospect, there is an insistent requisite to exploit a universal, resourceful and recyclable-catalyst technique for the synthesis of azepine derivatives. Therefore, the advancement of improved methods for the synthesis of azepine derivatives has attained relevance to recent exploration. As a part of our going research towards the development of novel, efficient, and environmentally benign synthetic methodologies using inexpensive and eco-friendly methods, we have investigated the synthesis of azepines from substituted anilines, DMAD/DEAD and 2,5-dimethoxytetrahydrofuran, mediated by 1,3-Di-*n*-butylimidazolium tribromide ([BBim]Br_3) as a catalyst. Further, we have screened all the synthesized compounds for their antimicrobial activity and the most active derivatives were subjected to various spectroscopic application studies.

2. Experimental Section

2.1. Chemistry

In this study, we have stated an efficient, novel one-pot protocol for the synthesis of azepine derivatives involving aniline **1a**, DMAD/DMED with 2,5-dimethoxytetrahydrofuran using ionic liquid [BBim]Br_3 as a reaction media and catalyst (Scheme 1).

In order to optimize the reaction conditions, we have initially carried out the reaction between aniline, DMAD/DMED with 2,5-dimethoxy-tetrahydrofuran using 10 mol% [BBim]Br_3 in water at room temperature for 5 h. The yield of desired product was very low. Therefore, the same reaction was carried out at 50 °C, the desire product was obtained in moderate yield. Furthermore, the reaction was performed in the presence of different solvents such as CH_3CN, THF, MeOH, EtOAc, DCM, and DMF using a catalytic amount of [BBim]Br_3 as shown in Table 1. Finally, we concluded that the suitable condition was 4 mL of ionic liquid [BBim]Br_3. It was found that the use of IL with dual role as a catalyst also as a solvent dramatically reduces the reaction time with improved product yield in (94%) at 50 °C as shown in the Table 1 The reaction was completed within 4 h (Table 1, entry 8).

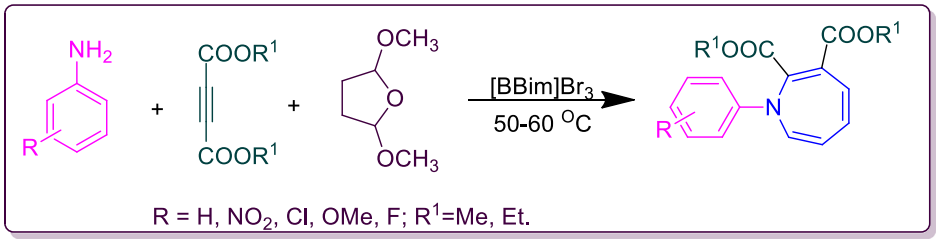
Table 1
Optimization of the reaction conditions for the synthesis of (2E, 4Z, 6Z)-dimethyl 1-phenyl-1H-azepine-2,3-dicarboxylate (**4a**).

Entry	Catalyst (10 mol%)	Solvent	Time (hr)	Yield (%)
1	[BBim]Br_3	CH_3CN	5	76
2	[BBim]Br_3	CH_3OH	6	77
3	[BBim]Br_3	CH_3COOEt	5	58
4	[BBim]Br_3	DMF	5	62
5	[BBim]Br_3	THF	4	65
6	[BBim]Br_3	DCM	5	60
7	[BBim]Br_3	H_2O	6	35
8	–	[BBim]Br_3	4	94

The reaction in ionic liquid is more advantageous, because ionic liquid can be recyclable and reused in subsequent reactions as indicated in Table 1. After the separation of the product by extraction of ionic liquid, it was thoroughly washed with ether and activated at 80 °C under reduced pressure. The reactivated ionic liquid was further reused twice as an accelerator (Table 2).

Encouraged by the result obtained with aniline, we have applied this methodology to a variety of amines such as aromatic and heterocyclic substrates under similar reaction conditions and the results were displayed in Table 3 (Scheme 1). Amines bearing electron donating groups successfully underwent reaction with DMAD/DMED and 2, 5-dimethoxytetrahydrofuran to produce the products in excellent yields, whereas electron with-drawing groups on anilines such as nitro-, chlor-, fluoro-, and bromo- gave the products in moderate yields. Similarly, heterocyclic amines gave good yields.

The plausible mechanism of *N*-substituted azepines in the presence of ionic liquid, by the simple nucleophilic addition of aniline with DMAD substrate to form intermediate [A] which further attacks with 2,5-dimethoxytetrahydrofuran [B], subsequent cyclization followed by elimination to form the title compound [C] which is showed in Scheme 2. All the products were confirmed by their proton nuclear magnetic resonance (^{1}HNMR), infrared (IR), and mass spectroscopy analysis.



Scheme 1. Synthesis of *N*-substituted azepine derivatives.