

Ionic Liquid Promoted One-pot Synthesis of Benzo[b][1,4]oxazines

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Abstract—benzo[b][1,4]oxazines have been synthesized in good to excellent yields in the presence of the ionic liquid 1-butyl-3-methylimidazolium bromide [bmim]Br under relatively mild conditions without any added catalyst, the reaction workup is simple and the ionic liquid can be easily separated from the product and reused.

Keywords—Isocyanide, Benzo[b][1,4]oxazines, Multi-component reactions, [bmim]Br, Ionic Liquid.

I. INTRODUCTION

HETEROCYCLIC skeletons serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs [1]. This is especially true for six-member ring heterocyclic compounds, which are core components of a large number of substances that possess a wide range of interesting biological activities [2]. In this respect, the utility of the benzo[b][1,4]oxazin scaffold as a privileged structure for the generation of drug like libraries in drug-discovery programs has been amply demonstrated. The benzo[b][1,4]oxazin derivatives have been used as the basic framework for substances of interest in numerous therapeutic areas, such as anti-candida albicans [3], antifungals [4], and kinase inhibitors [5].

Multi-component reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion [6]. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis [7]. As such processes avoid time-consuming and costly purification processes, as well as protection-deprotection steps, they are inherently more environmentally benign and atom-economic [8]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [9]. MCRs that involve isocyanides are by far the most versatile reactions in terms of scaffolds and number of accessible compounds [10].

II. EXPERIMENTAL

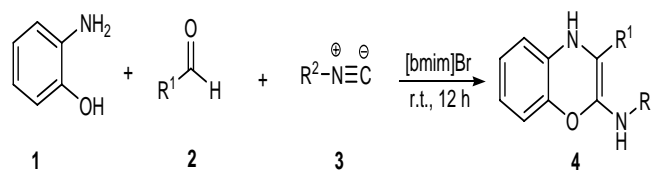
In recent years, studies of low waste routes and reusable reaction media for enhanced selectivity and energy

minimization are the key interests of synthetic organic chemists world over [11]. In this context, in recent times, the use of room-temperature ionic liquids as green solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapor pressure, and easy recyclability [12]. We have recently shown that they can also promote and catalyze isocyanide-based MCRs under ambient conditions without the need for any added catalyst or ligand [13].

Proceeding on the same lines, we chose to evolve an efficient and ecofriendly process for the preparation of benzo[b][1,4]oxazines by the three-component condensation of 2-aminophenol 1, an aldehyde 2, and isocyanide 3 in the presence of 1-butyl-3-methylimidazolium bromide ([bmim]Br) as reaction media as well as promoters in the absence of any added catalyst at ambient temperature (scheme 1).

As indicated in Table 1, the reaction of aldehydes with 2-aminophenol and isocyanides afforded benzo[b][1,4]oxazines in [bmim]Br as a promoter in very high yields.

In order to optimize the reaction conditions, we conducted the condensation of benzaldehyde (1 mmol), 2-aminophenol (1 mmol) and cyclohexyl isocyanide (1mmol) with stirring at room temperature in various ionic liquids (1 mmol) after 12 h. The results showed that the efficiency and the yield of the reaction in [bmim]Br was higher than those obtained in other ionic liquids. Also to illustrate the need for [bmim]Br, the reaction was studied in the absence of [bmim]Br, no product was produced at room temperature after 12 h. Obviously, [bmim]Br is an important component of the reaction (Table 2).



Scheme 1 the preparation of benzo[b][1,4]oxazines

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TABLE I SYNTHESIS OF BENZO[B][1,4]OXAZINES IN [BMIM]Br

Entry	R ¹	R ²	Product	Yield (%)
1	Ph	Cyclohexyl	4a	94
2	4-ClC ₆ H ₄	Cyclohexyl	4b	98
3	3-NO ₂ C ₆ H ₄	Cyclohexyl	4c	97
4	4-NO ₂ C ₆ H ₄	Cyclohexyl	4d	99
5	4-CH ₃ C ₆ H ₄	Cyclohexyl	4e	96
6	4-CH ₃ OC ₆ H ₄	Cyclohexyl	4f	95
7	4-HOC ₆ H ₄	Cyclohexyl	4g	95
8	Ph	<i>tert</i> -Butyl	4h	91
9	4-NO ₂ C ₆ H ₄	<i>tert</i> -Butyl	4i	94
10	4-CH ₃ OC ₆ H ₄	<i>tert</i> -Butyl	4j	91
11	4-NO ₂ C ₆ H ₄	1,1,3,3-tetramethyl-butyl	4k	98

3155. MS, *m/z* (%): 381 (25), 268 (100), 253 (40), 57 (50).

One of the advantages of ionic liquids is their ability to function as a recyclable reaction medium. We were able to separate [bmim]Br from the reaction medium easily by washing with water and evaporating the solvent under vacuum, and reuse it for subsequent reactions.

TABLE II SYNTHESIS OF BENZO[B][1,4]OXAZINES IN THE PRESENCE VARIOUS IONIC LIQUIDS

Ionic liquid	Yield (%)
Tetrabutylammonium bromide	50
Tetrabutylphosphonium bromide	60
Tetrabutylphosphonium chloride	75
benzyltributylammonium chloride	trace
1-butyl-3-methylimidazolium bromide ([bmim]Br)	99
Without ionic liquid	trace

III. CONCLUSION

In conclusion, we have introduced an efficient and environmentally friendly approach for the synthesis of benzo[b][1,4]oxazines via condensation of an aldehyde, 2-aminophenol and an isocyanide using [bmim]Br in good to excellent yields at room temperature. The method offers easy experimental work-up procedure and reuse ionic liquid.

All products (except 4k) are known compounds, which were characterized by IR and ¹H NMR spectral data, and their melting points were compared with literature reports [14].

Typical procedure: To a solution of 2-aminophenol (1 mmol), aldehyde (1.1 mmol) and isocyanide (1.1 mmol) was added [bmim]Br (0.3 g, 1.4 mmol). The resulting mixture was stirred for 12 h at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 2:1), the reaction mixture was washed with water (2×10 ml) and the solid residue was crystallized from ethanol to give pure product.

N-(2,4,4-trimethylpentan-2-yl)-3-(4-nitrophenyl)-4H benzo[b][1,4]oxazin-2-amine (4k) yellow crystals (0.37 g, yield 98%); mp 185-187 °C. IR (KBr) (*v*_{max} /cm⁻¹): 3165,

¹H NMR (200 MHz, CDCl₃): δ_H (ppm) 1.01 (9H, s, C(CH₃)₃), 1.41 (6H, s, C(CH₃)₂), 1.71 (2H, s, CH₂), 5.50 (2H, brs, 2NH), 6.96-8.87 (8H, m, H-Ar). ¹³C NMR (75 MHz, CDCl₃): δ_C (ppm) 31.1 (C(CH₃)₂), 31.4 (CH₂), 53.3 (C(CH₃)₃), 53.2 (C(CH₃)₂), 118.2, 124.3, 125.8, 127.8, 128.4, 130.3, 131.0, 132.4, 141.7, 147.9, 149.5, 159.1 (C-Ar and NH-C=C-NH). Anal. Calcd for C₂₂H₂₇N₃O₃: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.34; H, 7.01; N, 11.12.

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