Accepted Manuscript

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PII: S0040-4039(14)01556-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.09.055
Reference: TETL 45149

To appear in: *Tetrahedron Letters*

Received Date: 3 July 2014
Revised Date: 6 September 2014
Accepted Date: 8 September 2014

Please cite this article as: Waseem, M.A., Shireen, Srivastava, A., Srivastava, A., Rahila, Siddiqui, I.R., [bmIm]OH: An efficient basic catalyst for the synthesis of 4H-benzo[d][1,3-]oxazin-4-one derivatives in solvent -free conditions, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.09.055

Tetrahedron Letters
journal homepage: www.elsevier.com

[bmIm]OH: An efficient basic catalyst for the synthesis of 4H-benzo[d][1,3-]oxazin-4-one derivatives in solvent -free conditions.

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Green protocol
[bmIm]OH
intermolecular heterocyclization
benzo-oxazin-4-one
iodobenzoic acid

ABSTRACT

Reusable [bmIm]OH was found to be a highly efficient renewable homogenous catalyst for the rapid and convenient synthesis of benzo-oxazin-4-one derivatives from o-iodobenzoic-acid and benzonitrile at 75°C in moderate to good yield. This methodology provides a facile and straightforward path to construct other related heterocycles in eco-compatible fashion.

As part of eco-compatible organic transformations, ionic liquids (ILs) have received substantial attention from the synthetic community[5,6] owing to their properties like negligible vapour pressure, lack of flammability, wide solvating ability and high stability.. Today, ionic liquids offer their potential in controlling a reaction as a catalyst as well as playing a role in rate enhancement of a reaction[7].The association of reactant molecules in solvent cavities due to the internal pressure created by ionic environment of the ionic liquid is probably responsible for the rate enhancement[8-10]. Basic ionic liquids have attracted huge interest for a longtime by virtue of their catalytic efficiency, easy recovery and reuse as compared to the combination of a base and IL in a base-catalyzed process[11]. A basic ionic liquid [BMIM]OH (1-butyl-3-methylimidazolium hydroxide) has been successfully employed as a catalyst for Michael addition[12], Knoevenagel condensation [13], Markovnikov addition, and a number of other reactions [14,15] .It has very successfully replaced conventional bases as it is flexible, non-volatile and non-corrosive.

4H-3,1-Benzoxazin-4-ones are ubiquitous building blocks in medicinal chemistry and are of great interest to organic chemists owing to their diverse biological activities.[16,17] Some of the 2-substituted 4H-3,1-benzoxan-4-ones act as chymotrypsin inactivator[18], HSV(1), protease inhibitors (II),[19] inhibitors of human leucocyte elastase (III),[20] compound(IV) lower level of plasma cholesterol and triglyceride.[21] In addition, cetilistat (V), a novel lipase inhibitor, showed promising anti-obesity remedies[22] (**Figure 1**). Therefore, its synthesis has received intensive attention in medicinal chemistry research. A number of synthetic routes have been reported for the synthesis of benzo-oxazin-4-ones [24,27]. Numerous elegant protocols for the synthesis of this scaffold involving various types of catalysts have been reported. Despite these advances, there are still some potential limitations including unsatisfactory yield, long reaction time, limited substrate tolerance, use of expensive catalyst, toxic organic solvents and cumbersome experimental procedure. All these drawbacks prompted us to develop a more efficient, convenient and eco-friendly methodology [28-32] for the synthesis of this aesthetically appealing molecular architecture.

The processes that involve the incorporation of fragments from different starting components and construction of multiple chemical bonds allows a high level of complexity and diversity to built into pharmaceutically important products and drug like small molecules.

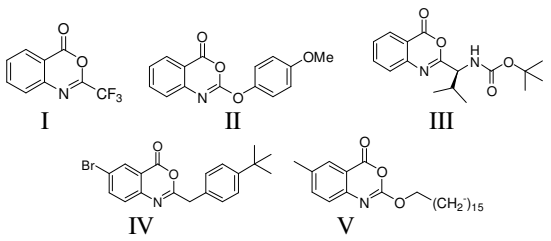
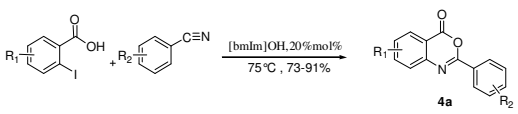


Figure 1: Medicinally recognized compounds with benzooxazine-4-one as a core structure.

In view of above consideration, here in we wish to report a more practical and expedient synthesis of 4H-benzo[d][1,3-]oxazin-4-one derivatives by using iodobenzoic acid and benzonitrile in basic ionic liquid ([bmIm]OH) at 75°C (Scheme 1)

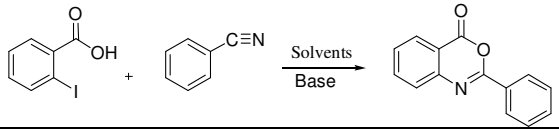


Scheme 1: [bmIm]OH promoted synthesis of benzo-oxazin-4-one and its derivatives

This synthetic protocol is efficient, convergent and allows easy placement of various types of substituents around the periphery of the heterocyclic ring system. Our careful literature survey revealed that there is no report on the use of [bmIm]OH as a catalyst for the synthesis of benzo-oxazine derivatives.

In our preliminary experiments we attempted to investigate the optimization of the reaction conditions regarding the solvent, base, time and yield. For this, 2-iodobenzoic acid and benzonitrile were selected as model substrates. In order to find optimum reaction condition equimolar amounts of model substrates were used in the absence of catalyst but no desired product were formed (Table 1, entry 1).However, when the reaction was carried out in presence of organic bases like NEt_3, DBU, pyridine, product was obtained but the reaction took long time for completion with low yield .(Table 1 Entry 2, 3, 4).

Table 1 Screening of base, solvent, tempature for the synthesis of benzooxazine-4-one derivatives[a] **4a**



Entry	Solvent	Base	Mol%	Temp75°C	Time(h)	Yield[b]%
1	EtOH	-	-	Reflux	12	-
2	EtOH	NEt_3	5	Reflux	11	23
3	EtOH	DBU	7	Reflux	11	21
4	EtOH	Pyridine	5	Reflux	10	19
5	DCM	NaOH,	10	100	11	27
6	THF	KOH	5	110	12	23
7	CH_2Cl_2	K_2CO_3	5	75	12	21
8		[bmIm]OH	35	75	7	91

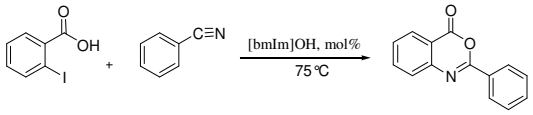
[a]Reaction conditions: Benzonitrile (2.0 mmol) and o-iodobenzoic acid (2.0 mmol) , Solvents, Bases, Basic [bmIm]OH.

[b]Isolated yields

Replacing organic bases by inorganic bases, NaOH, KOH, K_2CO_3 in different solvents like DCM, THF, CH_2Cl_2 in sealed vessels, no progress in reaction time and product yield were observed (Table1 entries 5,6,7, We then planned to exploit [bmIm]OH as a basic catalyst. To our delight the reaction resulted in the formation of desirable products (4a) in good yield with appreciable reaction time, as monitored by TLC (Table 1 entry 8). With [bmIm]OH as good activator in hand, we next intended to investigate the reaction by using different amounts of [bmIm]OH.

For this, we first examined the synthesis of 4a in the presence of 10mol% of [bmIm]OH. After 8.5h, the desired product 4a was formed in small amounts (Table 2, Entry 1). Use of 20, 25 and 30 mol% of catalyst afforded the desired product with moderate to good yield (Table 2, Entry 2, 3, 4) while using 35mol% of catalyst the yield of product was excellent (Table 2 entry 5).On increasing further mol% of ionic liquid to 40 and 45mol% no enhancement of product yield was observed (Table 2, entry 6, 7). Finally, we noticed that 35mol% of [bmIm]OH was the most appropriate amount of catalyst for achieving the desired conversion .(Table 2,Entry 5)

Table2: Influence of various mol% of [bmIm]OH on benzooxazine-4-one derivatives[a] **4a**



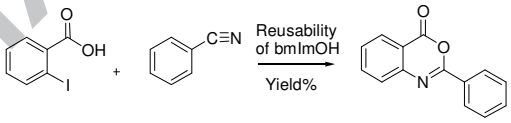
Entry	Catalyst mol%	Time (h)	Yield[b] (%)
1	10	8.5	51
2	20	8	67
3	25	7.5	73
4	30	7.5	80
5	35	7	91
6	40	7	91
7	45	7	91

[a]Reaction conditions: Benzonitrile (2.0 mmol) and o-iodobenzoic acid (2.0 mmol) in [bmIm]OH.

[b]Isolated yields.

Next, a series of catalytic cycles were run to explore the consistancy of the catalyst activity for the synthesis of benzo-oxazine derivatives. After completion of reaction, the product was extracted with ethyl acetate. The catalyst left after extraction was used for the subsequent cycles. The results showed that there was no appreciable loss in yield of product (4a) up to five times of recycling of [bmIm]OH..(Table 3 Entries 1-5).

Table 3 Reusability of catalyst for the synthesis of benzooxazine-4-one derivatives [a] 4a



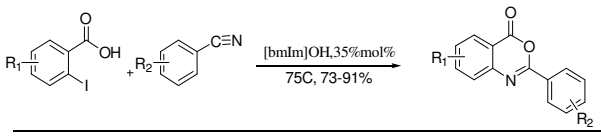
Entry	Time (h)	Yield[b] (%)
1	7	91
2	7	91
3	7	89
4	7.5	89
5	7.5	87

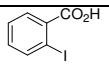
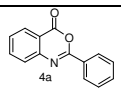
[a]Reaction conditions: Benzonitrile (2.0 mmol) and o-iodobenzoic acid (2.0 mmol) and [bmIm]OH (35mol).

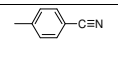
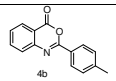
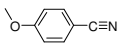
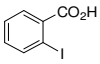
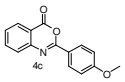
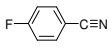
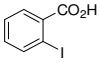
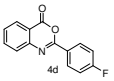
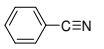
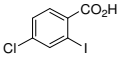
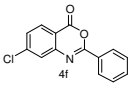
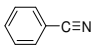
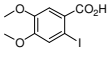
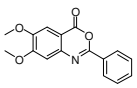
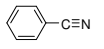
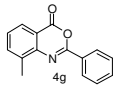
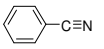
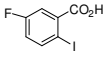
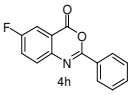
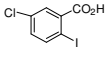
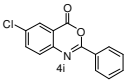
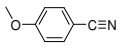
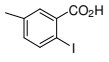
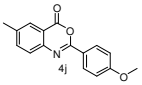
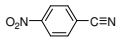
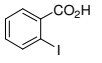
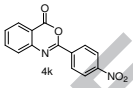
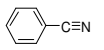
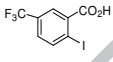
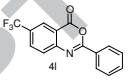
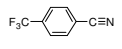
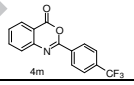
[b]Isolated yields.

Next, to explore the robustness of the methodology, various derivatives of o-halo benzoic acid and benzonitrile were used for the construction of a library of benzo-oxazinone. The corresponding functionalized benzo-oxazinone derivatives were obtained in good yield. The results are summarized in Table 4.

Table 4 Scope of substrate for the synthesis of benzooxazine-4-one derivatives[a] **4a**



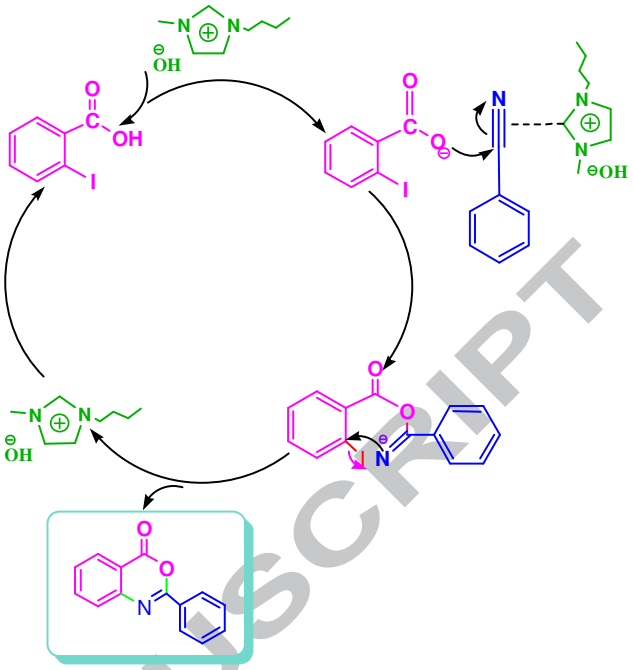
Entry	Benzonitrile	o-Halobenzoic acid	Product (a-m)	Time(h)	Yield[b] (%)
1			 4a	3	87

2				3	91
3				4	89
4				5	85
5				4	80
6				3	85
7				3	83
8				4	75
9				5	80
10				5	83
11				4	76
12				5	73
13				5	81

[a]Reaction conditions: Benzonitrile (2.0 mmol) and o-iodobenzoic acid (2.0 mmol) and [bmIm]OH (35mol) was stirred at room temperature for (3-5) h.

[b]Isolated yields.

When benzonitrile and its derivatives were used under optimized conditions, the compounds with electron-donating group on the benzene furnished the corresponding products in higher yields than the substrates with electron withdrawing substitutents.(**Table 4, entry 1,2,3,4,10,11,13**)..When several derivatives of iodobenzoic acid were used in this reaction, compounds containing electron donating groups gave high yields (**Table 4 entries 6,7**) and componds with electron withdrawng groups furnished the products in low yield (**Table 4 entries 5,8,9,12**).



Scheme 2: Tentative mechanism for 4H-benzo[d][1,3-]oxazin-4-ones

On the basis of above results, a plausible mechanism for the formation benzo-oxazin-4-ones derivatives **4(a-m)** can be tentatively **presented** , (scheme 2.) Presumably the reaction is triggered by proton abstraction from carboxylic group of o-iodobenzoic acid by hydroxyl group of [bmIm]OH. Then nucleophilic attack of generated carboxylate anion on activated nitrile group, followed by intramolecular nucleophilic attack of the $C{=}N^-$ on the I of o-iodobenzoic acid provides the target heterocyclic compounds **4(a-m). Scheme 2**

In summary, we have disclosed a convenient ,efficient and straightforward two -component one-pot approach for the synthesis of 4H-benzo[d][1,3-]oxazin-4-one framework using the environmentally benign catalyst [bmIm]OH under metal-free conditions. In this experimentally simple process two new bonds are formed in a single operation with all reactants efficiently utilized. Further no by-product formation was observed .The short reaction time, excellent yield and more importantly recyclability without losing catalytic activity prove that the protocol is a good alternative to the previously reported methods.

Acknowledgement

The authors gratefully acknowledge UGC, New Delhi for financial grant in the form of junior research fellowship and Department of Chemistry, University of Allahabad, Allahabad. The authors would also like to thank SAIF, Chandigarh for spectral analysis.

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GRAPHICAL ABSTRACT

[bmIm]OH: An efficient basic catalyst for the synthesis of 4H-benzo[d][1,3-]oxazin-4-one derivatives in solvent free condition.

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