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Short Communication

CuI/[bmim]OAc in [bmim]PF_6: A highly efficient and readily recyclable catalytic system for the synthesis of 2,3-disubstituted benzo[*b*]furans

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ABSTRACT

A combination of CuI (10 mol%) and [bmim]OAc (20 mol%) in [bmim]PF_6 was found to be a highly efficient and readily recyclable catalytic system for the synthesis of 2,3-disubstituted benzo[*b*]furans *via* three-component tandem reactions of 2-hydroxybenzaldehydes, amines and alkynes. Remarkable advantages of this new strategy include high efficiency, convenient recovery and efficient reuse of the catalytic system.

1. Introduction

The benzo[*b*]furan framework has attracted much attention due to its broad existence in natural products and frequent utilization in organic synthesis [1,2]. As a result, the development of methods for the construction of benzo[*b*]furan scaffold continues to be of interest [3–13]. In this aspect, a newly emerged three-component tandem reaction of 2-hydroxybenzaldehyde, alkyne and amine is a reliable pathway toward 2,3-disubstituted benzo[*b*]furans. Firstly, Li et al. reported that Cu(I)-catalyzed coupling of salicylaldehydes, amines, and alkynes afforded 2,3-disubstitued benzo[*b*]furans with good efficiency [14]. However, the alkynes employed therein were limited to those aliphatic alkynes bearing a heteroatom, such as propargyl alcohols or propargyl amines. Secondly, Sakai et al. reported that this tandem reaction could be realized under the catalysis of a combination of Cu(I) and Cu(II) in the presence of DMAP, but the alkyne substrates were limited to alkynylsilanes [15]. More recently, Li et al. presented an improved, more general procedure starting from inactivated alkynes in the presence of CuI, K_2CO_3 and Bu_4NBr [16]. While the aforesaid methods enriched approaches to benzo[*b*]furan derivatives, their utility and applicability are often compromised by loss of catalysts, limited substrate scope and adverse environmental impact due to the use of volatile and toxic organic solvents. Therefore, there is an urgent need to develop an economically more efficient and environmentally more sustainable protocol for the preparation of 2,3-disubstituted benzo[*b*]furans.

On the other hand, the use of non-volatile solvents and recyclable catalysts is very promising. In this regard, increasing expectations have been built up on ionic liquids (ILs) due to their negligible volatility, nonflammability and reusability [17–20]. In addition to being broadly utilized as alternative reaction media for sustainable chemistry, ionic liquids have also been studied as efficient immobilizing agents to facilitate catalyst recycling. Moreover, many elaborately designed task-specific ionic liquids (TSILs) have been successfully used as highly efficient catalysts for various organic transformations [21–23].

As a continuation of our research in developing new synthetic methods by using ionic liquids as both reaction media and catalysts [24–26], we developed an efficient and recyclable catalytic system consisting of CuI and [bmim]OAc (1-butyl-3-methylimidazolium acetate) in [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate). With this catalytic system, a series of 2,3-disubstituted benzo[*b*]furan were prepared with high efficiency and in an economically and environmentally sustainable manner. Herein, we report our preliminary results in this regard.

2. Experimental

2.1. General

Melting points were measured by a Kofler micromelting point apparatus and were uncorrected. Flash chromatographic purification of products was performed on silica gel (200–300 mesh). Thin-layer chromatography was visualized with UV light (254 and 365 nm). ^1H

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and ^{13}C NMR spectra were determined on a Bruker AC 400 spectrometer as $CDCl_3$ solutions. Chemical shifts were expressed in parts per million (δ) downfield from the internal standard tetramethylsilane and were reported as s (singlet), d (doublet), t (triplet), m (multiplet) and coupling constants *J* were given in Hz. Mass spectra were obtained in API mode using a Waters Acquity SQ HPLC-mass spectrometer. The HRMS (High-Resolution Mass Spectra) were performed on a JEOL HX 110A spectrometer.

2.2. Chemicals

[Bmim]OAc was prepared based on a literature procedure [27]. Other reagents are commercially available and used without further purification.

2.3. General procedure for the synthesis of 2,3-disubstituted benzo[b]furans

To a solution of 2-hydroxybenzaldehyde (**1**, 1 mmol), alkyne (**2**, 1.5 mmol) and amine (**3**, 1.2 mmol) in [bmim]PF_6 (1.5 g) were added [bmim]OAc (0.2 mmol) and CuI (0.1 mmol). The mixture was stirred at 80 °C. Upon completion as indicated by TLC analysis, the reaction mixture was cooled to room temperature and extracted with diethyl ether (4 mL×3). The combined ether phases were concentrated *in vacuo* and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (30:1) as eluent to give 2,3-disubstituted benzo[*b*]furans (**4**).

2.4. Recovery of the catalytic system

Upon completion, the reaction mixture was extracted with diethyl ether (4 mL×3) to remove product and possible by-products. The residual containing CuI, [bmim]OAc and [bmim]PF_6 was concentrated and dried under reduced pressure at 80 °C overnight to recover the catalytic system for reuse.

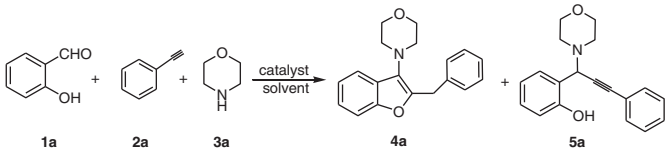
3. Results and discussion

3.1. Optimization of reaction conditions

Initially, the reaction of 2-hydroxybenzaldehyde (**1a**), phenylacetylene (**2a**) and morpholine (**3a**) proceeded smoothly in [bmim]BF_4 under the catalysis of CuI (20 mol%) and afforded propargylamine **5a** in a yield of 83% (Table 1, entry 1). However, it failed to give benzo[*b*]furan (**4a**). When the same reaction was run in the presence of 1 equiv of [bmim]OAc, to our delight, it gave **4a** in a yield of 81% (Table 1, entry 2). In further screening, the yield of **4a** increased to 87% by using [bmim]PF_6 instead of [bmim]BF_4 as the reaction medium (Table1, entry 4). This increase is most likely attributed to the hydrophobic activation activity of [bmim]PF_6, which may help to extrude water out of the ionic liquid phase and thus push the equilibrium forward and result in a higher conversion.

Different cuprous salts were then tested as catalysts. Among them, CuCl, CuBr and CuCN were found to be inferior to CuI (Table 1, entries 4–7). With $AgNO_3$ or AgOAc, only trace amount of **4a** was formed as indicated by TLC analysis (Table 1, entries 8 and 9). It was also demonstrated that the reaction rate increased with increasing amount of CuI. However, when the amount of CuI was higher than 10 mol%, it did not improve the reaction further obviously (Table 1, entries 4, 10–13). Consequently, 10 mol% of CuI was used for further optimization. The effect of reaction temperature was then studied. It turned out that while the reaction was accelerated with increased temperature, the optimum yield was obtained at 80 °C (Table 1, entries 11, 14–16). As a further aspect, the influence of the quantity of [bmim]OAc was studied. Surprisingly, [bmim]OAc in less than 1 equiv resulted in good or even better yields (Table 1, entries 11, 17–20). For example, the yield of **4a** amounted to 89% when 20 mol% of [bmim]OAc were used (Table 1, entry 18). To our knowledge, this is the first example in which 20 mol% of base together with 10 mol% of CuI were used for the formation of benzo[*b*]furans from **1**, **2** and **3**. In precedent procedures,

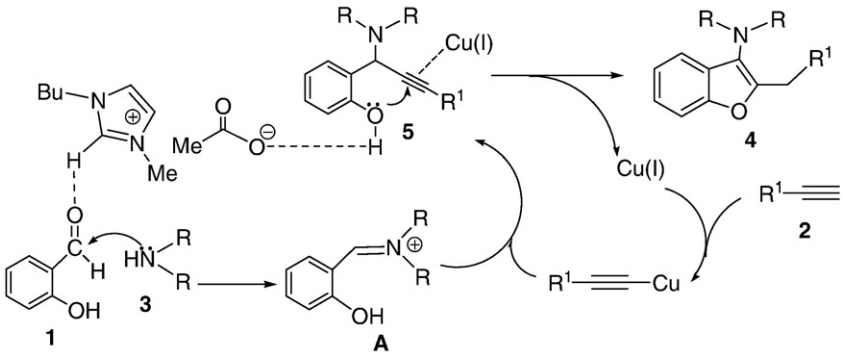
Table 1
Optimization of the reaction conditions.[a]



1a 2a 3a 4a 5a

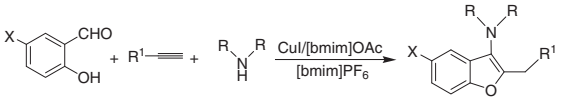
Entry	Solvent	Catalyst (mol%)	[bmim]OAc (eq.)	Temp. (°C)	Time (h)	**4a** (%) [b]	**5a** (%) [b]
1	[bmim]BF_4	CuI (20)	–	80	3	–	83
2	[bmim]BF_4	CuI (20)	1	80	5	81	–
3	[bmim]PF_6	CuI (20)	–	80	3	–	88
4	[bmim]PF_6	CuI (20)	1	80	5	87	–
5	[bmim]PF_6	CuCl (20)	1	80	5	66	–
6	[bmim]PF_6	CuBr (20)	1	80	5	78	–
7	[bmim]PF_6	CuCN (20)	1	80	5	74	–
8	[bmim]PF_6	$AgNO_3$ (20)	1	80	15	trace	–
9	[bmim]PF_6	AgOAc (20)	1	80	15	trace	–
10	[bmim]PF_6	CuI (5)	1	80	8	71	–
11	[bmim]PF_6	CuI (10)	1	80	6	83	–
12	[bmim]PF_6	CuI (15)	1	80	5	82	–
13	[bmim]PF_6	CuI (30)	1	80	5	84	–
14	[bmim]PF_6	CuI (10)	1	60	10	62	–
15	[bmim]PF_6	CuI (10)	1	100	5	79	–
16	[bmim]PF_6	CuI (10)	1	120	4	57	–
17	[bmim]PF_6	CuI (10)	0.1	80	10	70	–
18	[bmim]PF_6	CuI (10)	0.2	80	6	89	–
19	[bmim]PF_6	CuI (10)	0.5	80	6	84	–
20	[bmim]PF_6	CuI (10)	1.5	80	6	75	–
21	[bmim]PF_6	CuI (10)	1[c]	80	6	–	85
22	[bmim]PF_6	$Cu(OAc)_2$ (100)	–	80	6	–	72

[a]Reaction conditions: **1a**, 1 mmol; **2a**, 1.5 mmol; **3a**, 1.2 mmol; [bmim]BF_4 or [bmim]PF_6, 1.5 g.
[b]Isolated yield. [c]1 mmol of NaOAc instead of [bmim]OAc.

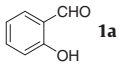
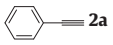
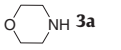
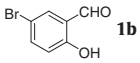
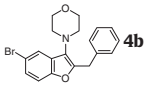
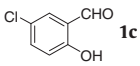
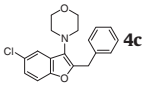
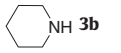
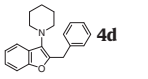
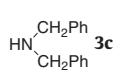
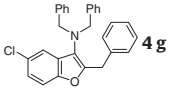
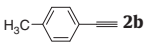
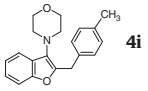
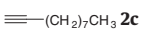
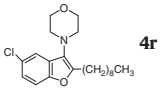
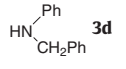
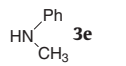


Scheme 1. Plausible pathway of the catalytic tandem process.

Table 2
Preparation of various 2,3-disubstituted benzo[*b*]furans.[a]



1 2 3 4

Entry	Aldehyde (**1**)	Alkyne (**2**)	Amine (**3**)	Product (**4**)	Time (h)	Yield (%) [b]
1	 **1a**	 **2a**	 **3a**	**4a**	6	89
2	 **1b**	**2a**	**3a**	 **4b**	6	92
3	 **1c**	**2a**	**3a**	 **4c**	6	83
4	**1a**	**2a**	 **3b**	 **4d**	7	85
5	**1b**	**2a**	**3b**	**4e**	7	82
6	**1c**	**2a**	**3b**	**4f**	7	73
7	**1c**	**2a**	 **3c**	 **4 g**	9	75
8	**1b**	**2a**	**3c**	**4 h**	8	81
9	**1a**	 **2b**	**3a**	 **4i**	6	85
10	**1c**	**2b**	**3a**	**4j**	6	81
11	**1b**	**2b**	**3a**	**4 k**	6	90
12	**1a**	**2b**	**3c**	**4 l**	8	83
13	**1c**	**2b**	**3c**	**4 m**	9	81
14	**1b**	**2b**	**3c**	**4n**	9	89
15	**1a**	**2b**	**3b**	**4o**	7	87
16	**1c**	**2b**	**3b**	**4p**	7	80
17	**1b**	**2b**	**3b**	**4q**	7	81
18	**1c**	 **2c**	**3a**	 **4r**	7	52
19	**1c**	**2a**	 **3d**	–	9	–
20	**1c**	**2a**	 **3e**	–	9	–
21	**1c**	**2a**	$PhNH_2$	–	9	–

[a] **1**, 1 mmol; **2**, 1.5 mmol; **3**, 1.2 mmol; CuI, 0.1 mmol; [bmim]OAc, 0.2 mmol; [bmim]PF_6, 1.5 g; 80 °C. [b] Isolated yield.

stoichiometric organic [15] or inorganic base [16] was provided to get reasonable yields.

To better understand the roles played by [bmim]OAc in this tandem reaction, 10 mol% of CuI together with 1 equiv of NaOAc in [bmim]PF_6 were used. It turned out that no **4a** but **5a** was obtained after the mixture being stirred for 6 h (Table 1, entry 21). Then, 1 equiv of $Cu(OAc)_2$ in [bmim]PF_6 were tried as both catalyst and base for the same reaction, but **4a** was not obtained either(Table 1, entry 22). Further investigations are still underway to explore the reasons behind the superiority of CuI/[bmim]OAc over CuI/NaOAc and $Cu(OAc)_2$ in promoting this tandem reaction.

3.2. Plausible pathway of the catalytic reaction

Based on the above observations, a plausible pathway for the formation of 2,3-disubstituted benzo[*b*]furan is proposed in Scheme 1. Firstly, the condensation between 2-hydroxybenzaldehyde (**1**) with amine (**3**) gives an active iminium intermediate **A**. At the same time, CuI reacts with terminal alkyne (**2**) to form a Cu–alkynyl complex. The resulting cuprous acetylide intermediate reacts with **A** to form propargylamine **5**. At this stage, the OAc anion of [bmim]OAc plays its role as a base to promote the polarization of the O—H bond in **5** and thus increase the nucleophilicity of oxygen and facilitate the *intramolecular* hydroaryloxylation of the C—C triple bond coordinated with Cu(I) to give 2,3-disubstituted benzo[*b*]furan (**4**) as the final product. It is noted that along with the formation of **4**, both Cu(I) and OAc anion are released from the intermediates and ready for the next catalytic cycle. In this procedure, the activation effect of [bmim]PF_6 or [bmim]OAc on the condensation of **1** and **3** *via* hydrogen bond formation between H on the 2-position of imidazolium cation in [bmim]PF_6 or [bmim]OAc and O of the carbonyl of aldehyde cannot be excluded.

3.3. Preparation of various benzofuran derivatives

With the optimized reaction conditions (Table 1, entry 18), the scope and generality of this protocol was evaluated with various 2-hydroxybenzaldehydes, alkynes and amines (Table 2). It was demonstrated that the reaction accommodated various 2-hydroxybenzaldehyde derivatives and generated the corresponding products in good yields. With aliphatic secondary amines including morpholine, dibenzylamine and piperidine, the corresponding benzofuran derivatives were produced in high efficiency. On the other hand, no benzo[*b*]furan product was formed when aromatic secondary amines, such as *N*-benzylaniline or *N*-methylaniline, were used (Table 2, entries 19 and 20). This result was reasonably attributed to the reduced nucleophilicity of the —NH— moiety conjugated to an aromatic ring. Aromatic primary amine such as aniline was also tried, and no benzo[*b*]furan product was obtained (Table 2, entry 21). It was revealed that for the alkyne substrates, aromatic alkynes were more reactive than aliphatic alkyne for this reaction (Table 2, entry 18).

All products were substantially purified by flash chromatography and characterized by m.p., ^{1}H NMR, ^{13}C NMR and MS analysis. Spectra data of **4a** are listed as follows:

4-(2-Benzyl-benzofuran-3-yl)-morpholine (**4a**): m.p. 107–108 °C (lit. [16] 105–108 °C);^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.17 (t, J = 4.8 Hz, 4 H), 3.84 (t, J = 4.8 Hz, 4 H), 4.16 (s, 2 H), 7.15–7.38 (m, 8 H), 7.65–7.67 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 32.26, 52.57, 67.68, 111.67, 119.87, 122.06, 123.44, 126.06, 126.44, 128.48, 128.52, 128.72, 138.15, 150.21, 153.46. MS: *m/z* 294 [M + H].

3.4. Studies on the recovery and reuse of CuI/[bmim]OAc/[bmim]PF_6

The recovery and reuse of CuI/[bmim]OAc in [bmim]PF_6 were studied by using **1a**, **2a** and **3a** as model substrates. Upon completion, the reaction mixture was extracted with diethyl ether to remove the product and possible by-products. The residual containing CuI/[bmim]OAc/[bmim]PF_6 was concentrated and dried under reduced pressure at 80 °C overnight. The recovered CuI/[bmim]OAc/[bmim]PF_6 system was successively reused for 5 times and no obvious loss in its efficiency was observed (Table 3). In these reactions, [bmim]PF_6 not only acted as solvent, but also as an immobilizing agent to facilitate the catalysts recycling. It is worth to be noted herein that with literature protocols toward 2,3-disubstituted benzo[*b*]furan, the precious cuprous catalyst and the volatile and toxic organic solvents were not recycled, which is, in our opinion, neither economically nor environmentally sustainable.

Table 3
Studies on the reuse of CuI/[bmim]OAc in [bmim]PF_6.[a,b]

Round	Time (h)	Temp. (°C)	Yield (%)[c]
1	6	80	89
2	6	80	88
3	6	80	85
4	6	80	85
5	6	80	82
6	6	80	81

[a] **1a**, 1 mmol; **2a**, 1.5 mmol; **3a**, 1.2 mmol for each run.
[b] CuI, 0.1 mmol; [bmim]OAc, 0.2 mmol; [bmim]PF_6, 1.5 g for the first run.
[c] Isolated yield.

4. Conclusion

In summary, a highly practical and efficient synthesis of 2,3-disubstituted benzo[*b*]furans *via* CuI/[bmim]OAc catalyzed tandem reactions in [bmim]PF_6 was developed. Compared with literature methods, notable advantages of this procedure include: 1) low loading of catalyst and base; 2) convenient recovery and efficient reuse of the catalytic system; 3) avoidance of volatile organic solvents, and 4) no aqueous work-up thereby avoiding the generation of toxic wastes. Further studies in searching more applications of this novel catalysis protocol are currently underway and the results will be reported in due course.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.catcom.2011.01.024.

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