Remarkable influence of substituent in ionic liquid in control of reaction: simple, efficient and hazardous organic solvent free procedure for the synthesis of 2-aryl benzimidazoles promoted by ionic liquid, [pmim]BF_4†

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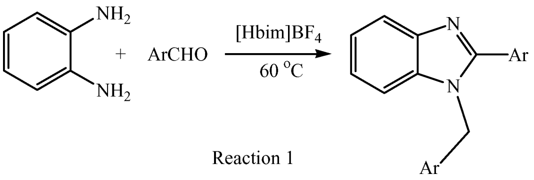
A simple and efficient procedure for the synthesis of 2-substituted benzimidazoles has been developed by a one-pot reaction of *o*-phenylenediamine with aromatic aldehydes in the presence of an ionic liquid, 1-methyl-3-pentylimidazolium tetrafluoroborate, [pmim]BF_4 at room temperature in open air without any organic solvent. The ionic liquid is recycled. A remarkable influence of the substituent on the imidazolium unit of the ionic liquid on the outcome of the reaction is observed.

1 Introduction

The benzimidazoles have received considerable attention in recent times because of their applications as antiulcers, antihypertensives, antivirals, antifungals, anticancers and antihistamines among others.[1] In addition, they are important intermediates in many organic reactions[2] and act as ligands to transition metals for modeling biological systems.[3] This has led to the development of several methods for the synthesis of benzimidazoles during the last few years. Two protocols are usually followed. One of them is the coupling of *o*-phenylenediamines with carboxylic acids or their derivatives[4] and the second route involves condensation of *o*-phenylenediamine and aldehydes followed by oxidative cyclo-dehydrogenation.[5] However, the second approach has become more popular probably because of the ease of accessibility of a variety of substituted aldehydes. The reported procedures for this protocol involved a wide spectrum of reagents including (bromodimethyl) sulfonium bromide/MeCN,[6a] iodobenzene diacetate/1,4-dioxane,[6b] H_2O_2/HCl in MeCN,[6c] chlorotrimethylsilane/DMF,[6d] I_2/KI/K_2CO_3/H_2O,[6e] air/dioxane,[6f] ytterbium triflate in neat,[6g] *p*-TsOH/DMF,[6h] $Na_2S_2O_5$ in neat under microwave irradiation,[6i] [$(NH_4)H_2PW_{12}O_{14}$] in dichloroethane,[6j] H_2O_2/CAN,[6k] [Hbim]BF_4,[6l] proline,[6m] *p*-TsOH/graphite,[6n] sodium hydrogen sulfite,[6o] *p*-TsOH/silica gel[6p] and ytterbium(III) perfluorooctanesulfonate.[6q] Although these methods are quite satisfactory, many of them employed considerable amounts of hazardous organic solvents either for carrying out the reactions or for extraction and purifications (column chromatography) or for both, which are not environmentally friendly. Moreover, several of these reactions were carried out at higher temperatures and using costly reagents.

The use of large volumes of volatile hazardous organic solvents in industrial processes posed a serious threat to the environment. Thus, procedures involving alternative benign solvents in reaction, isolation and purification are of high priority in industry. The room temperature ionic liquids have been the subject of considerable interest in the context of green chemistry because of their relatively benign character, very low volatility, thermal stability, efficiency as a catalyst and promoter and reusability.[7] As a part of our continued activities in this area,[8] we became interested to investigate this condensation reaction using ionic liquid. From a literature search we found a recent report by Wang *et al.*[6l] describing a reaction of *o*-phenylenediamine and aromatic aldehydes using an ionic liquid, [Hbim]BF_4 to produce 2-aryl-1-arylmethyl-benzimidazoles (Reaction 1). It was also reported that their efforts to synthesize 2-aryl benzimidazoles using this IL failed.[6l]



Reaction 1

Very interestingly, we discovered that a change of substituent, specifically a replacement of *N*-H by *N*-alkyl on the imidazolium unit of the ionic liquid, dramatically influences the course of the reaction. The same condensation of *o*-phenylenediamine and aromatic aldehydes when mediated by the ionic liquid, 1-methyl-3-pentylimidazolium tetrafluoroborate [pmim]BF_4 under organic solvent-free conditions produced exclusively 2-aryl benzimidazoles (Scheme 1) in contrast to 2-aryl-1-arylmethyl-benzimidazole as reported by Wang *et al.*[6l] using [Hbim]BF_4 and the results are reported here.

2 Results and discussion

The experimental procedure is very simple. A mixture of *o*-phenylenediamine and an aromatic aldehyde was stirred at room temperature in air in the presence of an ionic liquid, [pmim]BF_4 for the required period of time (TLC). The solid

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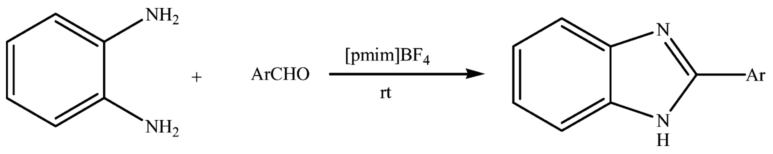
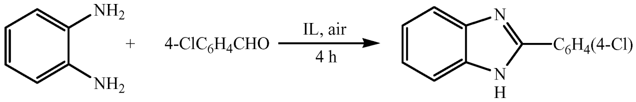
† Electronic supplementary information (ESI) available: Copies of ^1H NMR, ^{13}C NMR and HRMS spectra of all the products listed in Table 2, copies of ^1H NMR spectra of ionic liquid, [pmim]BF_4 of the fresh and recovered (after reaction) samples and copies of ^1H NMR and HRMS spectra of compounds obtained as products listed in entries 8 and 10, Table 3. See DOI: 10.1039/b823543k



Scheme 1 Synthesis of 2-aryl benzimidazole.

Table 1 Standardisation of reaction conditions



Entry	IL	Temp./°C	Yield[a] (%)
1	[pmim]BF$_4$	80	85
2	**[pmim]BF$_4$**	**25**	**92**
3	[bmim]BF$_4$	25	82
4	[pmim]Br	25	88

[a] Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR).

product was isolated by filtration and purified by crystallization from ethanol. The ionic liquid, [pmim]BF$_4$ was found to give best results at room temperature (25 °C) in comparison to other imidazolium based ionic liquids such as [pmim]Br and [bmim]BF$_4$ as illustrated in Table 1.

The remaining ionic liquid, [pmim]BF$_4$ after isolation of product, was recycled for the first two subsequent reactions without any significant loss of efficiency, while the next two reactions showed some loss of efficiency in terms of yields of products (Fig. 1). To find out any change of the recovered ionic liquid from the fresh one the ^{1}H NMR of the two samples were checked. Both were found to be basically same except two additional spikes in the region of 2–4 ppm in the spectrum of the recovered one, probably due to contamination of trace impurities from the reaction.

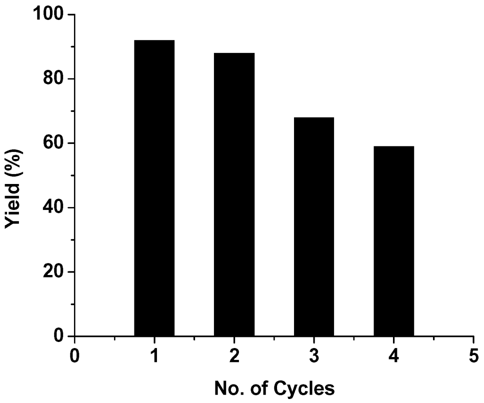
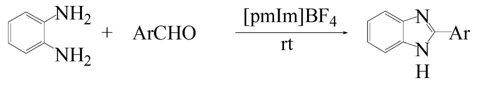
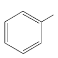
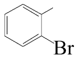
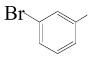
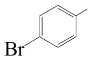
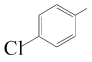
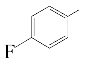
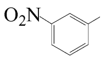
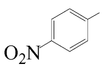
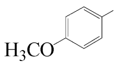
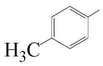
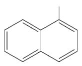
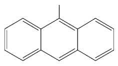
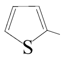


Fig. 1 Recyclability diagram for the reaction of *o*-phenylenediamine and *p*-tolualdehyde.

Table 2 Synthesis of benzimidazoles



Entry	Ar	Time/h	Yield[a] (%)	Mp/°C (Lit M.P.)	Ref.
1		5	85	288 (289–291)	6*b*
2		6	88	242 (243–244)	9
3		6	90	264 (264–266)	6*b*
4		4	92	298 (299–300)	6*b*
5[b]		4	92	290 (292–294)	6*b*
6		7	80	250 (250–251)	6*b*
7		5	90	207 (209)	10
8		4	94	328 (327)	10
9		6	88	224 (224–226)	6*b*
10[c]		5	92	276–277 (277)	6*e*
11		6	80	270 (272–274)	11
12		7	82	261–263	
13		7	90	332 (330)	6*e*

[a] Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR). [b] The reaction when performed in 10 mmol scale under identical reaction conditions, the corresponding product was formed in 88% yield. [c] The reaction when performed in 10 mmol scale under identical reaction conditions, the corresponding product was formed in 90% yield.

Several substituted aromatic aldehydes underwent condensations with *o*-phenylenediamine by this procedure to produce the corresponding 2-substituted benzimidazoles. The results were summarized in Table 2. The aldehydes with electron donating (entries 9 and 10, Table 2) as well as with electron withdrawing groups (entries 2–8, Table 2) participated in this reaction uniformly. Apparently, the nature and position of substitution on the aryl ring did not make much difference in reactivity (entries 2, 3, 4 Table 2). The sensitive molecule like thiophen-2-aldehyde (entry 13, Table 2) produced the corresponding benzimidazole without any difficulty. The sterically hindered 9-anthraldehyde (entry 12, Table 2) also underwent reaction by this procedure. The reactions of sterically hindered aldehydes were not addressed by many of the existing methods. Significantly, when the reaction of 9-anthraldehyde and *o*-phenylenediamine was carried out using conventional reagents such as $I_2/KI/K_2CO_3/H_2O$,[6e] O_2/dioxane[6f] and H_2O_2/HCl[6c] no appreciable product was isolated by us.

The reactions, in general are high yielding. No hazardous organic solvent was used in this process. In several reactions, dialdimines were formed in small amounts (2–8%) which were separated during crystallization. Several functional groups such as Cl, Br, NO_2, OMe and sensitive molecules like thiophene-2-carboxaldehyde are compatible with the reaction conditions. A comparison of results of reactions with a few substrates using ionic liquid, [pmim]BF_4 with those reported by Wang *et al.*[6l] using [Hbim]BF_4 reveals that minor variations of substituents in core imidazolium ionic liquid and reaction conditions (room temperature from 60 °C) change the outcome of the reaction producing 2-aryl benzimidazole **I** by [pmim]BF_4 against 2-aryl-1-arylmethyl benzimidazole **II** by [Hbim]BF_4 without any exception. These results are summarized in Table 3. The outcome of the reaction with one substrate using a mixture of our ionic liquid, [pmim]BF_4 with [Hbim]BF_4 (Wang *et al.*[6l]) in varying proportions has also been investigated and the results are included in entries 11–13, Table 3. Significantly, 1 : 1 and 1 : 3 mixture of these two ionic liquids led exclusively to Wang *et al.*'s product, **II**, while 3 : 1 mixture of the same ionic liquids produced 22% of our product, **I**. These results clearly indicate a general tendency towards formation of 2-aryl-1-arylmethyl benzimidazole **II** and our ionic liquid, [pmim]BF_4 is powerful enough to change the usual course of the reaction leading to **I**. This dramatic influence of ionic liquid, although very surprising, is not unprecedented.[12]

The ionic liquid (75 mol%) works here as catalyst as well as reaction medium. Presumably, [pmim]BF_4 activates the aldehyde towards nucleophilic attack by *o*-phenylenediamine forming a monoaldimine **1** which on cyclization followed by oxidative dehydrogenation by air[6f] leads to benzimidazole (Scheme 2).

To check the role of O_2 (air) in this process two simultaneous reactions were run with 4-clorobenzaldehyde in air and in argon. In the presence of air the intermediate **A** undergoes oxidation to provide the product **I**, while in the presence of argon condensation of **A** with another molecule of aldehyde is facilitated leading to product **II** (Wang *et al.*'s compound[6l]) as outlined in Scheme 3.

3 Experimental section

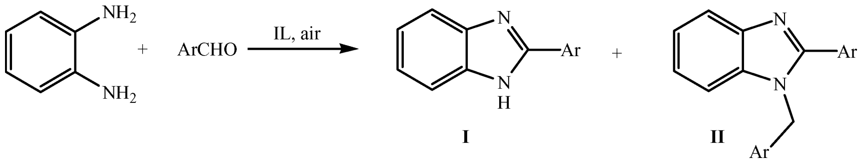
General

The ionic liquid, [pmim]Br was prepared following a reported procedure[13a] and [pmim]BF_4 was then obtained by a metathesis reaction of [pmim]Br with $NaBF_4$ also following a reported procedure.[13b]

General experimental procedure for the synthesis of 2-arylbenzimodazole. Representative procedure for the condensation of *o*-phenylenediamine and *p*-tolualdehyde (entry 10, Table 2)

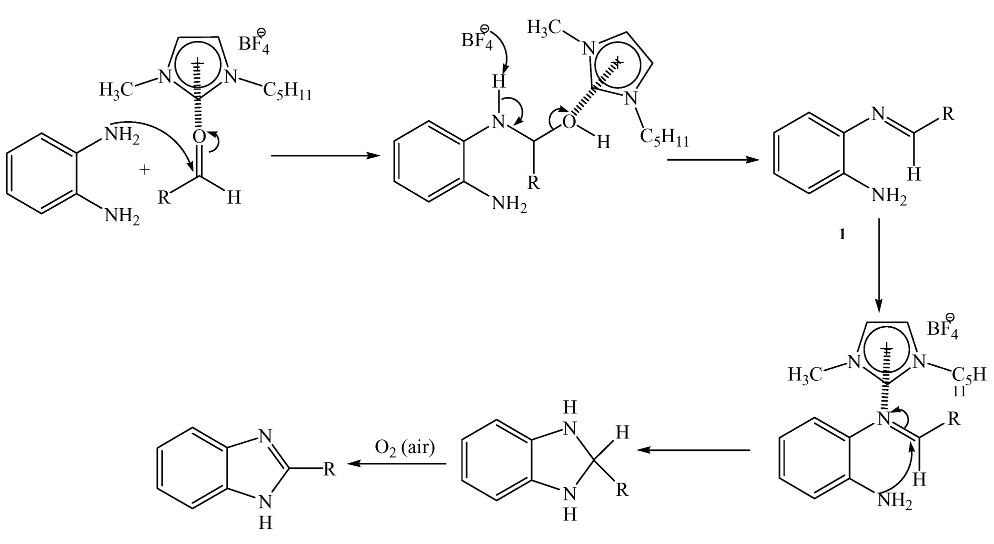
A mixture of *o*-phenylenediamine (108 mg, 1 mmol) and *p*-tolualdehyde (120 mg, 1 mmol) was stirred at room temperature in the presence of [pmim]BF_4 (178 mg, 0.75 mmol) in air for 5 h (monitored by TLC). After the reaction was over, H_2O (10 mL) was added and a solid product appeared. This crude product was collected by filtration and recrystallized from ethanol to afford

Table 3 Comparison of reaction results using [pmim]BF_4 and [Hbim]BF_4

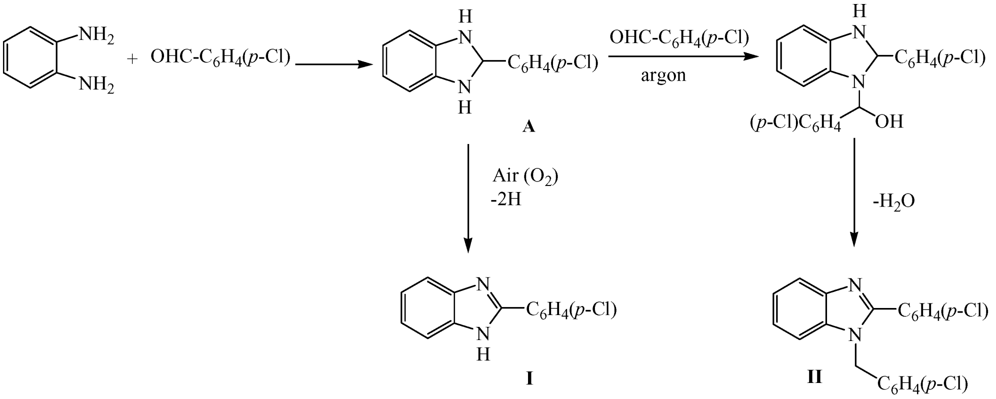


Entry	Ar	IL	Product ratio (I : II)	Yield[a] (%)
1[b]	C_6H_5	[pmim]BF_4	100 : 0	85
2[c]	C_6H_5	[Hbim]BF_4	0 : 100	88
3[b]	4-ClC_6H_4	[pmim]BF_4	100 : 0	92
4[c]	4-ClC_6H_4	[Hbim]BF_4	0 : 100	80
5[b]	4-$H_3CC_6H_4$	[pmim]BF_4	100 : 0	92
6[c]	4-$H_3CC_6H_4$	[Hbim]BF_4	0 : 100	84
7[b]	4-BrC_6H_4	[pmim]BF_4	100 : 0	92
8[d]	4-BrC_6H_4	[Hbim]BF_4	0 : 100	86
9[b]	4-FC_6H_4	[pmim]BF_4	100 : 0	80
10[d]	4-FC_6H_4	[Hbim]BF_4	0 : 100	82
11[e]	4-ClC_6H_4	[pmim]BF_4+[Hbim]BF_4 (1 : 1)	0 : 100	78
12[e]	4-ClC_6H_4	[pmim]BF_4+[Hbim]BF_4(1 : 3)	0 : 100	80
13[e]	4-ClC_6H_4	[pmim]BF_4+[Hbim]BF_4(3 : 1)	22 : 78	75

[a] Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ^1H NMR and ^{13}C NMR). [b] The reaction where performed in 25 °C for the required time period as mentioned in Table 2 in the text. [c] The reaction when performed at 60 °C for the required time period as mentioned in ref. 6*l*. [d] The reactions were performed at 60 °C for 1 h. [e] The reactions were performed at 60 °C for 4 h.



Scheme 2 Plausible mechanism.



Scheme 3 Comparison of plausible reaction pathway in air to that in argon atmosphere.

pure 2-tolylbenzimidazole (192 mg, 92%), mp 276–277 °C (mp 277 °C[6e]). The spectroscopic data (^{1}H and ^{13}C NMR) are in good agreement with those reported for the authentic sample.[6e] The ionic liquid, left in the reaction vessel was dried under vacuum and was reused for subsequent reactions.

This procedure was followed for the synthesis of all the products listed in Table 2. Although the general experimental procedure was based on 1 mmol scale reaction multimol reactions also produced similar results (entries 5 and 10, Table 2). All the products are known compounds except one (entry 12, Table 2). The known compounds were identified by comparison of their spectral data with those reported earlier (see references in Table 2). The new compound, 2-anthracen-9-yl-1H-benzimidazole (entry 12, Table 2), a pale yellow solid, mp 261–263 °C, was characterized by its IR, ^{1}H NMR and ^{13}C NMR and HRMS spectroscopic data: IR (KBr): 3435, 3350, 2956, 2862, 1612, 1595, 1296, 1082 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.32–7.35 (m, 2H), 7.48–7.59 (m, 5H), 7.65–7.74 (m, 4H), 8.19–8.22 (d, J = 8.2 Hz, 2H), 8.86 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 114.9 (2C), 122.0 (2C), 124.8 (2C), 125.1 (2C), 125.3 (2C), 126.6 (2C), 128.2 (2C), 128.7, 130.1 (4C), 130.2, 149.0; HRMS m/z calculated for $C_{21}H_{14}N_2$ [M + H]$^+$ 295.1233; found: 295.1235.

4 Conclusion

In conclusion, the present procedure using an easily available ionic liquid, [pmim]BF_4[13] provides a very simple and efficient methodology for the synthesis of 2-aryl benzimidazoles by condensation of *o*-phenylenediamine and aromatic aldehydes. Besides mild reaction conditions (room temperature), low energy consumption, high yields, and reusability of ionic liquids, this procedure uses no hazardous organic solvents in the entire process including workup and purification. To the best of our knowledge this is the first report of condensation of aldehydes and *o*-phenylenediamine to 2-aryl-benzimidazoles, promoted by an ionic liquid without any other solvent and catalyst. Most significantly, the influence of substituent on the imidazolium unit of the ionic liquid to dictate the outcome of this reaction to produce 2-arylbenzimidazole exclusively, preventing further condensation as reported by Wang *et al.*[6l] using [Hbim]BF_4 is remarkable and induces further investigation for useful applications.

Acknowledgements

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