RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2015, **5**, 51012

Received 4th May 2015
Accepted 28th May 2015

DOI: 10.1039/c5ra08183a

www.rsc.org/advances

Grindstone chemistry: protic ionic liquid-substrate tuned green synthesis of 1,2-disubstituted and 2-substituted benzimidazoles with outstanding selectivity†

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An environmentally benign and highly catalyst-substrate controlled synthesis of 1,2-disubstituted and 2-substituted benzimidazoles with outstanding selectivity has been developed through grinding a mixture of *o*-phenylenediamines, suitable aldehydes and an imidazolium trifluoroacetate protic ionic liquid catalyst. The newly developed metal-free catalysis approach produced 1,2-disubstituted benzimidazoles from aromatic aldehydes bearing electron donating group, whereas aromatic aldehydes possessing electron withdrawing groups and aldehydes with 2-alkoxy substitution selectively furnished 2-substituted benzimidazoles and their chiral analogues. Low energy consumption, short reaction time and solvent-free synthesis make this methodology green, providing a useful contribution to the existing procedures available for the synthesis of benzimidazole derivatives.

Due to growing public sentiment in support of the environment, the focus of academia and industry has shifted to reduce or eliminate the use of volatile organic solvents during manufacturing and processing. The scope of green chemistry considers the environmental, health and safety problems associated with modern chemical manufacturing processes and legal instruments. It also considers some of the underlying principles and concepts that should underpin chemistry and chemical manufacturing in the future. To meet such demands, present day organic synthesis has been driven to reduce or eliminate the toxic and volatile organic solvents that are widely used in huge quantity in organic synthesis because they pose serious threats to the environment. Therefore, to keep the environment clean and sustainable for future generations, the development of efficient and environmentally benign synthetic strategies is the prime task of organic chemists of academic and industrial settings. Thus, over the last few decades tremendous efforts have been devoted towards the exploration of eco-friendly methodology both in academia and industry. Volatile, toxic and hazardous organic and inorganic reagents are continuously being replaced by either the use of solvent-free techniques,[1] ionic liquids,[2] water media,[3] phase transfer catalysts,[4] microwave irradiation[5] or ball-milling processes.[6] Consequently solvent-free as well as metal-free catalytic reactions have tremendous potential and received considerable attention in the area of green synthesis. Thus use of grindstone chemistry[7] is desirable for the synthesis of desired functional molecules through simple mixing of the precursors and nonmetallic catalyst with much faster reaction rates and selectivity under benign reaction conditions. In recent times much attention has been focussed on organic transformations promoted by ionic liquids at ambient temperature because of their potential advantages to operate under environmentally benign conditions. We and others have reported several strategies for organic synthesis catalyzed by protic ionic liquids (PILs) with high performance.[8]

Heterocycles are predominant among all types of pharmaceuticals, agrochemicals, veterinary products, sensors and materials.[9] For instance benzimidazole is one of the fundamental structural units of the pharmaceutical, agricultural, electronic, polymer science and technology industries.[10] Owing to the immense importance and wide range of bioactivities of compounds bearing a benzimidazole motif, efforts have been made to synthesize libraries of compounds and to screen the compounds for potential pharmaceutical properties. Thus benzimidazole has been considered as one of the most important and privileged structures in medicinal chemistry, encompassing a plethora of useful biological activities.[11] Benzimidazoles play a unique role in drug discovery programs because of their wide spectrum of bioactivities, such as anticancer, antihypertensive, anthelmintic, antiprotozoal, antimicrobial, antioxidant, antiinflammatory and analgesic activity.[12] Benzimidazole ring containing molecules also exhibit

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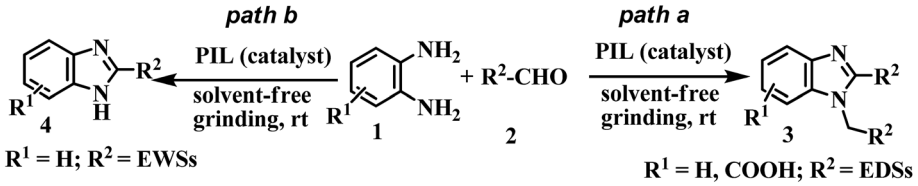
† Electronic supplementary information (ESI) available. CCDC 1062843. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra08183a



Scheme 1 PIL catalysed selective synthesis of benzimidazoles with varied precursors.

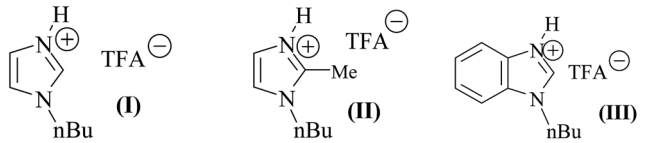
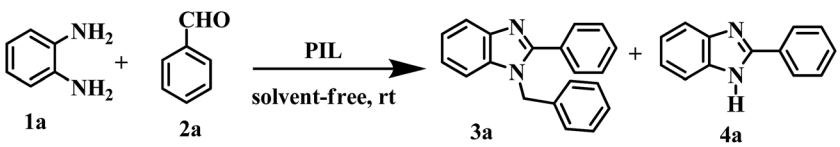


Fig. 1 Synthesized protic ionic liquids for catalysis.

significant activity against several viruses[13] such as HIV, influenza and human cytomegalo virus. In addition they are important intermediates in many organic reactions[9] and act as ligands to transition metals for modeling biological systems.[14,15] These impressive biological and physical properties of the privileged benzimidazole nucleus has prompted us to develop a new selective approach for preparing these important compounds. Presently the design, development, and utilization of efficient and environmentally benign synthetic processes have become the conscientious choice of synthetic chemists due to tight legislation and environmental issues. It is desirable to design and develop an attractive metal-free strategy that can also simplify the reaction procedure, product purification, improve synthetic efficiency, and reduce consumption of toxic solvents as well as their disposal. Consequently the potential harmful impact of various chemicals and metals on the environment is minimized and sustainability is improved.

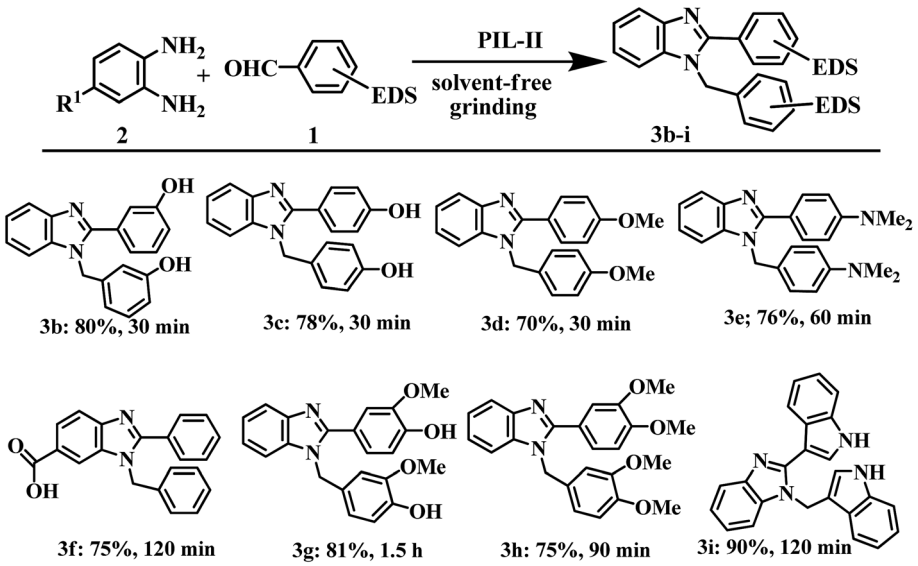
Usually two protocols for the synthesis of benzimidazoles are commonly used: one of them is the coupling of *o*-phenylenediamines (OPDs) with carboxylic acids or their activated derivatives[16] and the second route involves the oxidative cyclocondensation of *o*-phenylenediamine with aldehydes.[17] In addition, 1,2-disubstituted benzimidazoles can also be accessed by direct one-step condensation of OPDs with aldehydes under the influence of different acid catalysts.[18] Although some of these methods are quite satisfactory, many of these processes suffer from serious limitations, such as drastic reaction conditions, low yields, tedious work up and co-occurrence of several side-reactions and disposal issues. Moreover, several of these reactions were carried out with high energy consumption and employed costly reagents. A recent synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles was developed by the condensation of aromatic aldehydes and OPDs using 1-butyl-imidazolium tetrafluoroborate as promoter[19] and 2-aryl-1*H*-benzimidazole using 1-methyl-3-pentylimidazolium tetrafluoroborate, [pmim]BF_4,[17b] but these reactions work at high temperature with a large amount of ionic liquid (2 mL $mmol^{-1}$ of substrate!), which was difficult to recycle. Moreover preparation of tetrafluoroborate based protic ionic liquid is difficult since HBF_4 is available only

Table 1 Comparison of reaction results using different PIL



Entry	OPD : PhCHO (mmol)	PIL catalyst (mol%)	Time (h)	Conversion (%)	Yield[a] (%) (**3a**)
1	1 : 1	Nil	48	75	Mixture[c]
2	1 : 1	**I** (10)	2	100	41[b,c]
3	1 : 2.2	**I** (10)	2	100	83[c]
4	1 :'2.2	**I** (10)	2	100	83[d]
5	1 : 2.2	**II** (10)	2	100	87[c]
6	1': 2.2	**III** (10)	2	100	80[c]
7	1 : 2.2	**II** (5)	2	100	87[c]
8	1 : 2.2	**II** (3)	2	100	86[c]
9	**1 : 2.2**	**II** (2)	**4**	**100**	**85**[c]
10	1 : 2.2	**II** (1)	24	90	75[c]

[a] Yield was calculated on the basis of isolated pure product. [b] Reaction was performed in open air using mortar and pestle. [c] 33% starting material recovered. [d] Stirring carried out under inert argon atmosphere.



Scheme 2 Highly selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles.

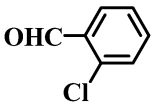
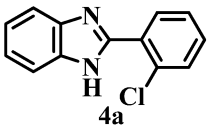
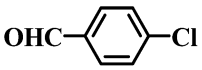
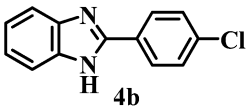
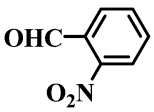
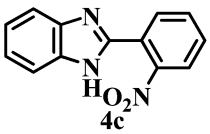
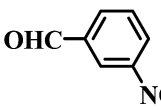
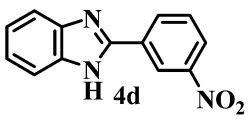
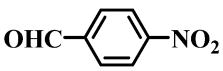
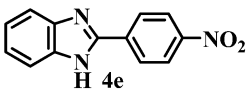
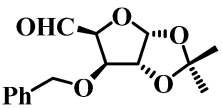
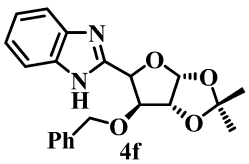
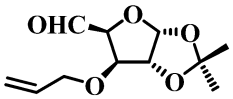
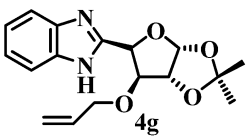
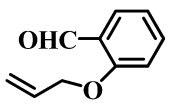
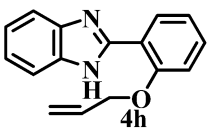
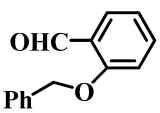
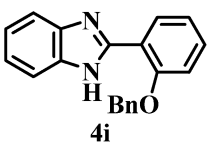
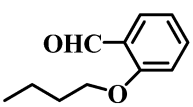
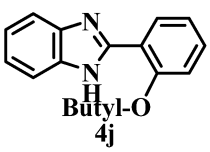
as 40–50% aqueous solution that creates problems in isolation and the purification process. Ranu *et al.* showed[17b] that small differences in the structures of ionic liquids have a great influence on the outcome of the selectivity of the reaction.[17b] As a part of our ongoing programme to design and develop solvent-free and metal-free strategies for organic synthesis,[8a–d] we were interested to observe the effect of PILs as catalysts for the synthesis of both 1,2-disubstituted (**3**, path a, Scheme 1) and 2-substituted benzimidazoles (**4**, path b, Scheme 1) with high selectivity. Herein the direct syntheses of the two classes of benzimidazoles were investigated by the reaction of *o*-phenylenediamines and suitable aldehydes in the presence of imidazolium trifluoroacetate PIL catalysts (2–10 mol%) under a solvent-free grindstone approach.

We have synthesized three PILs namely 1-butylimidazolium trifluoroacetate (**I**), 1-butyl-2-methyl imidazolium trifluoroacetate (**II**) and 1-butyl benzimidazolium trifluoroacetate (**III**) by adding trifluoroacetic acid to the corresponding *N*-butylated imidazole/benzimidazole derivative[8d,20] in dichloromethane (Fig. 1) to investigate the selective cyclocondensation catalysis. The potential catalysts were dried under vacuum in order to remove any traces of trifluoroacetic acid present and were fully characterized by spectroscopic techniques. The PILs have shown tremendous ability activating various functional groups[8] including aldehydes for highly selective organic transformations under metal-free conditions.

Initially one experiment was conducted in the absence of PIL using OPD and benzaldehyde of one mmol each at ambient temperature under an inert atmosphere. After 48 h of stirring a thick mass (Table 1, entry 1) was obtained showing a complex mixture of products, which was detected using thin layer chromatography (TLC). The column chromatographic separation of the mass has not shown formation of the desired products (**3a** and **4a**, Table 1). Next the reaction was carried out with 10 mol% of PIL-**I** using a mortar and pestle with occasional grinding. The 1,2-disubstituted product **3a** (1-benzyl-2-phenylbenzimidazole) was obtained in 41% yield along with the unreacted starting material OPD (~33%) after 2 h (entry 2). However the other precursor benzaldehyde was consumed completely (TLC) in this experiment. On treatment of 2.2 mmol of benzaldehyde with 1.0 mmol of *o*-phenylenediamine (OPD) the cyclocondensation reaction was complete in 2 h and the yield was improved to 85% (entry 3). The di-substituted product **3a** was found as a sole product, which is in very good agreement with the results obtained by Wang and colleagues[19] using imidazolium tetrafluoroborate ionic liquid in large excess under heating conditions (70 °C). Surprisingly it was found that there is no influence of molecular oxygen on the cyclocondensation process because it smoothly produced the desired product in the presence or absence of oxygen (entries 3 and 4). On use of PIL-**II** and PIL-**III** (Fig. 1) under similar reaction conditions the heterocycle **3a** (entries 5 and 6) was produced in comparable yields (87% and 80% respectively). We continued optimization of the reaction with the most efficient catalyst PIL-**II**. Gratifyingly the reaction was successfully optimized (entries 7–10) with only 2 mol% of PIL-**II** producing the 1,2-disubstituted product **3a** with 85% yield (entry 9).

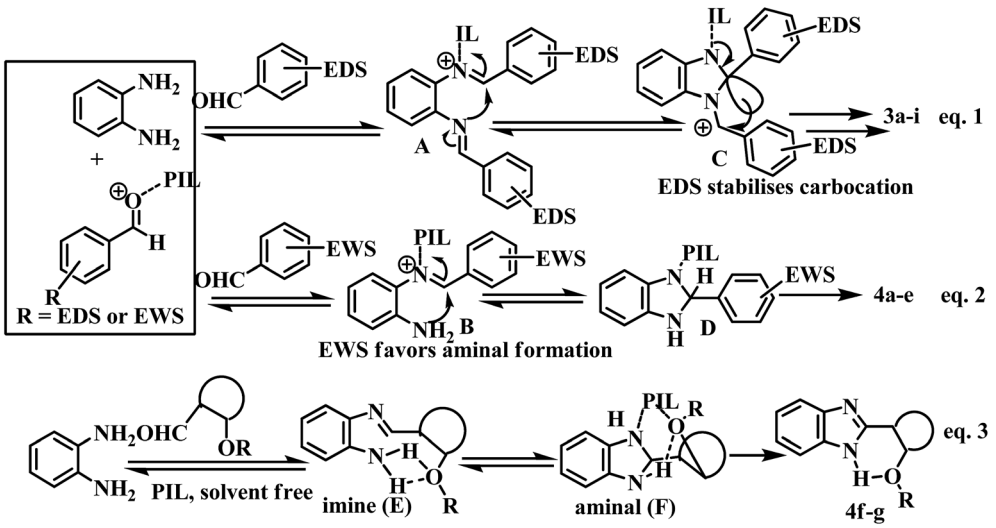
The scope of the cyclization process was successfully investigated by using large varieties of aromatic aldehydes bearing electron releasing and highly sensitive functionalities such as –OH, –OMe, and $-NMe_2$ under solvent-free grindstone conditions (Scheme 2). In all cases the nonmetallic catalyst efficiently furnished 1-arylmethyl-2-aryl substituted benzimidazoles (**3b–i**) as exclusive products at ambient temperature with high yields (70–90%) and fast reaction rates (0.5–2.0 h). The OPD possessing a –COOH (R^1, Scheme 1, path a) functional group also reacted in the same fashion with benzaldehyde to afford corresponding 1,2-disubstituted benzimidazole (**3f**) in 2 h with high yield (75%), whereas the reaction was unsuccessful with *o*-phenylenediamine bearing a strongly electron withdrawing 4-

Table 2 Selective synthesis of 2-substituted benzimidazoles

Entry	Aldehyde	Product	Time (h)	Yield (%)
1		 4a	1	72
2		 4b	0.5	82
3		 4c	2	79
4		 4d	1	81
5		 4e	1	85
6		 4f	6	77
7		 4g	6	65
8		 4h	4	75
9		 4i	5	81
10		 4j	5	71

nitro substituent. The reaction of strongly electron releasing indole-3-carboxaldehyde with OPD is not addressed by most of the existing methods. In our protocol it smoothly produced the desired 1,2-disubstituted benzimidazole **3i** in 90% yield after purification by crystallization from methanol–water.

Surprisingly on use of aldehydes bearing electron withdrawing substituents such as halogen and nitro groups the powerful catalyst guided the reaction towards the formation of other possible 2-arylbenzimidazoles products (**4**, Table 2, entries 1–5) in excellent yield (72–85%). Next we turned our attention to use sugar-based aldehydes for synthesis of valuable chiral benzimidazoles.[21] On treatment of 3-*O*-benzyl-1,2-*O*-isopropylidenexylose-5-carboxaldehyde or *O*-allyl-1,2-*O*-isopropylidenexylose-5-carboxaldehyde only the corresponding



Scheme 3 Mechanistic rationale of PIL-substrate controlled selectivity to benzimidazoles.

2-substituted benzimidazoles were furnished in 77% and 65% yield respectively (**4f** and **g**, entries 6 and 7). Surprisingly no 1,2-disubstituted benzimidazoles were detected in both cases. Herein alkoxy substituents present at the β-position might play a vital role along with the catalyst PIL-**II** for controlling the outcome of the reaction. Thus we have synthesized different alkoxy aldehydes using salicylaldehyde through alkylation under basic conditions and successfully used them for the synthesis of functionalized benzimidazoles. In each case, 2-substituted benzimidazole derivatives were accomplished exclusively in very good yield even if excess aldehyde is employed (**4h–j**, entries 8–10). There was almost no discrimination in reaction rate and yield using aldehydes possessing 2-allyloxy, 2-benzyloxy and 2-butyloxy substituents using the powerful catalyst PIL-**II**.

A literature search reveals that in a similar reaction the presence or absence of oxygen sometimes makes a difference.[17b,19] Usually the presence of oxygen favours formation of 2-

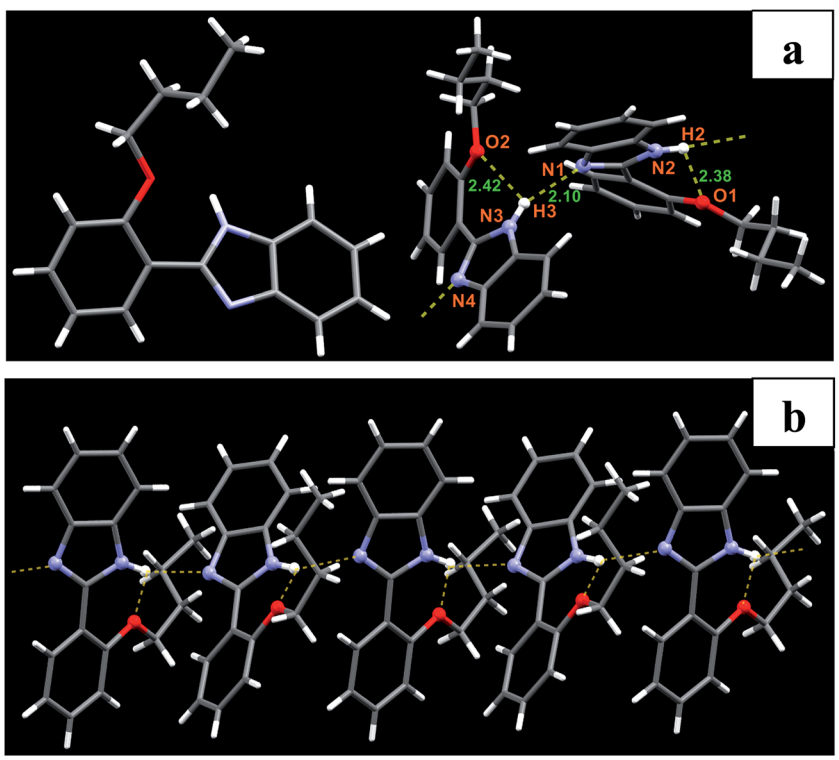


Fig. 2 Single crystal structure and crystal packing of **4j**.

substituted benzimidazole and the absence of oxygen leads to 1,2-disubstituted benzimidazole using excess aldehydes. It was speculated[22] that both the $-NH_2$ groups of OPD react with aldehydes to form dibenzamidine **A**, which on cyclisation generates intermediate **C**, and a subsequent 1,3-hydride shift produces 1,2-disubstituted benzimidazoles. In our experiments PIL-**II** is expected to activate aldehyde first and rapidly perform condensation with one of the $-NH_2$ groups of OPD to form **A**, which on ring closing followed by a hydride shift furnished **3** as the sole product (eqn (1), Scheme 3). Indeed we have recorded the FTIR spectrum of an equimolar mixture of *p*-methoxy benzaldehyde and PIL-**II**; immediate lowering of the carbonyl stretching frequencies ($\sim$21 cm^{-1}) was observed. It supports our hypothesis regarding the first role of PIL-**II** as an activator of the carbonyl functionality of aldehydes.

Under the reaction conditions bis-imine (**A**, eqn (1)) formation with aromatic aldehydes possessing an electron withdrawing group might be disrupted by the powerful PIL-**II** catalyst and the second amino group of monoimine (**B**, eqn (2)) is allowed for ring closing to construct the dihydrobenzimidazole-PIL-**II** intermediate (**D**).[23] Subsequent release of PIL-**II**·H leads to synthesis of 2-substituted benzimidazoles (**4**). We performed another experiment using 2-chlorobenzaldehyde and OPD in the presence of 5 mol% of PIL-**II** under a N_2 atmosphere, we were pleased to observe that only 2-(2-chlorophenyl) benzimidazole (**4a**) was formed after 1 h at room temperature in 72% yield (Table 2, entry 1). A possible mechanism to explain the exclusive formation of the 2-disubstituted benzimidazoles from the reaction between OPD and 2-alkoxy aldehyde is depicted in eqn (3) (Scheme 3). Presumably, the $-NH_2$ group of OPD attacks the PIL-**II** activated aldehyde forming an imine (**E**), which is arrested immediately after its formation *via* hydrogen bonding and immediately undergoes ring closing to dihydrobenzimidazole **F** followed by aromatization to afford 2-substituted benzimidazoles (**4**).

Herein disfavouring to bis-imine formation (like **A**, eqn (1)) due to steric congestion (**E** and **F**, eqn (3)) could not be avoided. Our attempts to capture **E** and/or intermediate **F** failed. However the crystal structure of compound **4j**[24] (entry 10, Table 2) clearly indicated the presence of strong hydrogen bonds between benzimidazole NH and the side chain oxygen atom (panel a, Fig. 2). The reaction of either imine (**E**) or aminal (**F**) with a second molecule of aldehyde is rather impossible due the participation of hydrogen bonding with the alkoxy oxygen at the 2-position. The hydrogen bonding leads to the formation of an assembly of **4j** (panel b), which is an important property of the molecule towards the generation of a valuable self-aggregated organic material.

In conclusion, the present procedure provides a very simple, fast and eco-compatible methodology for cyclocondensation of aromatic-1,2-diamines and suitable aldehydes using grindstone chemistry towards the synthesis of 2-aryl-1-arylmethyl benzimidazoles and 2-aryl benzimidazoles with outstanding selectivity. Herein we have demonstrated that the aromatic aldehydes bearing 'no' or 'electron releasing' substituents favour 1,2-disubstituted benzimidazoles whereas aromatic aldehydes with 'electron withdrawing' substituents or 2-alkoxy aldehydes favour 2-substituted benzimidazoles. The easy accessibility of the protic ionic liquid catalyst (**II**), shorter reaction time, solvent-free medium and high yield of the products makes this method very green. To the best of our knowledge this is the first report for the substrate-PIL controlled highly selective annulation of aldehydes and *o*-phenylenediamines to valuable 1,2-disubstituted and 2-substituted benzimidazoles and their chiral analogues at ambient temperature using grindstone chemistry.

General experimental procedure

A mixture of *o*-phenylenediamine (10 mmol), aromatic aldehyde (22 mmol), and protic ionic liquid (5 mol%) was ground by means of mortar and pastel at room temperature. The reaction was monitored by TLC. After completion of the reaction the residue was poured on crushed ice and the solid was filtered and washed thoroughly with water. The product was recrystallized from ethanol–water to obtain the pure product. For the products displayed in Table 2, 1.2 mmol of aldehyde were used with respect to *o*-phenylenediamine. The structures of the products were confirmed through analysis of FTIR, NMR spectral data and were compared with the melting point reported in literature. All new compounds were fully characterised by FTIR, ^1H and ^{13}C NMR and HRMS spectral data (ESI†).

Acknowledgements

One of the authors M. C. is thankful to the Council of Scientific & Industrial Research (CSIR), Govt. of India for providing fellowship.

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