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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-substituited benzimidazoles with outstanding selectivity has been developed through grinding a mixture of o-phenylenediamines, suitable aldehydes and catalyst imidazolium trifluoroacetate protic ionic liquid. 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 bearing 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 and provide useful contribution to the existing procedures available for the synthesis of benzimidazole derivatives.

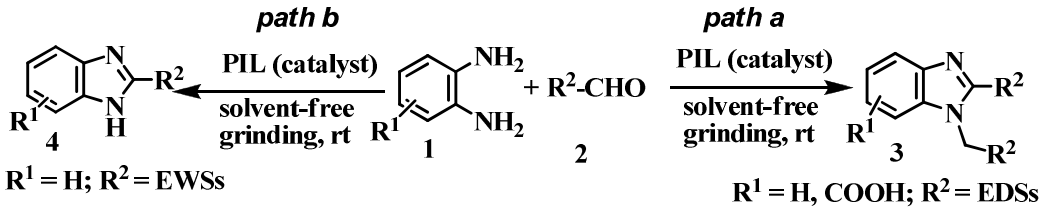
The growing public sentiment in support of our environment, the focus of the academy and industry has shifted to reduce or eliminate the use of volatile organic solvents during manufacturing and processing. The scope of green chemistry considers the environmental, health and safety problems associated with modern chemical manufacturing processes and legal instruments. It also considers some of the underlined principles and concepts that should underpin chemistry and chemical manufacturing in the future. To meet such demands at 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 are posed serious threat to the environment. Therefore, to keep our mother nature clean and sustainable for future generation, the development of efficient and environmentally benign synthetic strategies is the prime task to the 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 either the use of solvent-free techniques,[1] ionic liquids,[2] water media,[3] phase transfer catalysts,[4] microwave irradiations[5] or ball-milling process.[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 synthesis of desired functional molecules through simple mixing of the

precursors and nonmetallic catalyst with much faster reaction rate and selectivity under benign reaction conditions. In recent times much attention has been focussed on organic transformation 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 pharmaceutical industry, agricultural, electronic, polymer science and technology.[10] Owing to the immense importance and wide range of bioactivities of compounds-bearing benzimidazole motif, efforts have been made to synthesize libraries of compounds and screened them for potential pharmaceutical properties. Thus benzimidazole has been considered as one of the most important and privileged structure 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, anthelmenthic, antiprotozoal, antimicrobial, antioxidant, antiinflammatory and analgesic activity.[12] The benzimidazole ring containing molecules are also exhibited significant activity against several viruses[13] such as HIV, influenza and human cytomegalovirus. In addition they are important intermediates in many organic reactions[9] and acts as ligand to transition metals for modeling biological systems.[14] 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. An attractive metal-free strategy is desirable to design and develop that can also simplify reaction procedure, product purification, improves synthetic efficiency, and reduces 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. 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]BF4,[17b] but these reactions work at high temperature with large amount of ionic liquid (2 mL/mmol of substrate!), which was difficult to recycled. Moreover preparation of tetrafluoroborate based protic ionic liquid is difficult since HBF_4 is available only as 40-50% aqueous solution that creates problems in isolation and purification process. Ranu et al. showed[17b] that small differences in the structure of ionic liquids have great influence in 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 strategy for organic synthesis, [8a-d] we were interested to observe the effect of PILs as catalyst for synthesis of both the 1,2-disubstituted (**3**, ***path a***, Scheme 1) and 2-substituted benzimidazoles (**4**, ***path b***, Scheme 1) with high selectivity. Herein direct syntheses of the two classes of benzimidazoles were investigated by the reaction of *o*-phenylenediamines and suitable aldehydes in presence of imidazolium trifluoroacetate PIL catalysts (2-10 mol%) under solvent-free grindstone approach.



Scheme1: PIL catalysed selective synthesis of benzimidazoles with varied precursors

We have synthesized three PILs namely 1-butylimidazolium trifluroacetate (**I**), 1-butyl-2-methyl limidazolium trifluroacetate (**II**) and 1-butyl benzimidazolium trifluoroacetate (**III**) by adding trifluoroacetic acid to the corresponding *N*-butylated imidazole/benzimidazole derivative[8d,20] in dichloromethane (Figure 1) for investigating the selective cyclocondensation catalysis. The potential catalysts were dried under vacuum in order to remove any traces of trifluoroacetic acid present in it and 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.

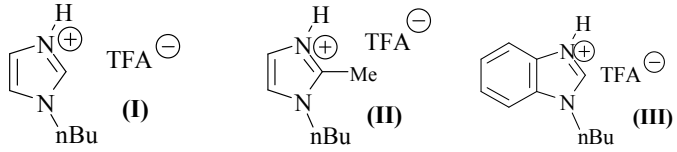
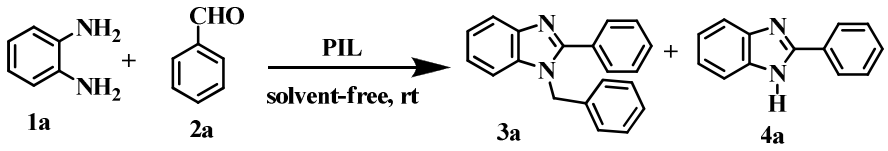


Figure 1: Synthesized protic ionic liquids for catalysis

Initially one experiment was conducted in absence of PIL using OPD and benzaldehyde of one mmol each at ambient temperature under 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 in thin layer chromatography (TLC). The column chromatographic separation of the mass has shown formation of none of the desired products (**3a**, **4a**, Table 1). Next the reaction was carried out with 10 mol% of PIL-**I** taken in a mortar 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*-phenylediamine (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 ^{o}C). Surprisingly it was found that there is no influence of molecular oxygen on the cyclocondensation process because it smoothly produced desired product in presence or absence of oxygen (entries 3, 4). On use of the PIL-**II** and PIL-**III** (Figure 1) under the similar reaction conditions the heterocycle **3a** (entries 5, 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 the PIL-**II** producing the 1,2-disubstituted product **3a** with 85% yield (entry 9).

Table 1: Comparison of reaction results using different PIL



1a 2a 3a 4a

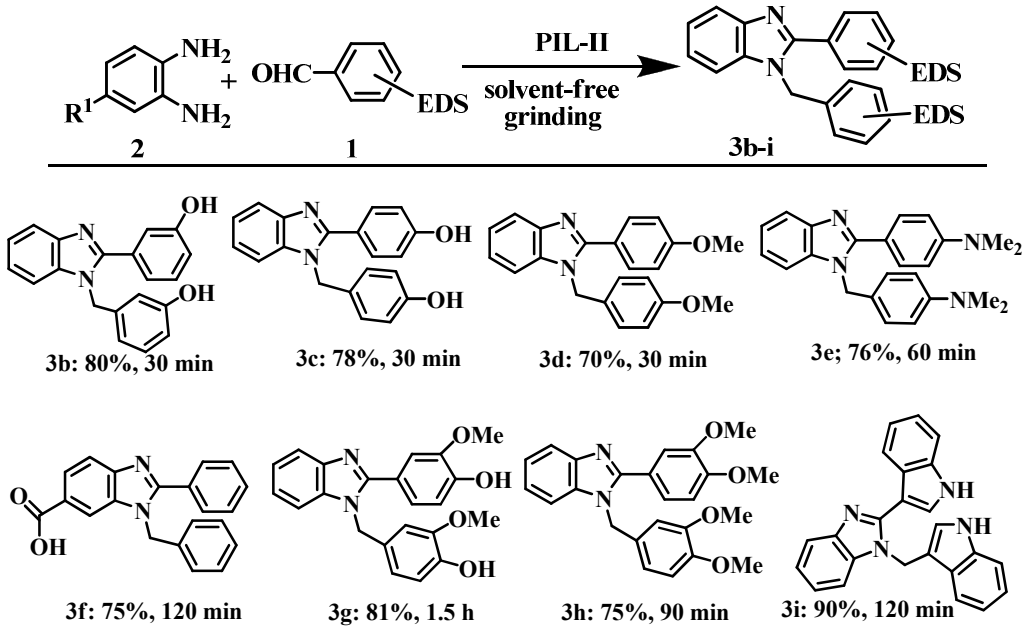
Entry	OPD : PhCHO (mmol)	PIL catalyst (mol%)	Time (h)	Conversion (%)	Yield (%)[a] (**3a**)
1	1:1	Nil	48	75	Mixture[c]
2	1:1	**I** (10)	2	100	41[b,c]
3	1:2.2	**I** (10)	2	100	83[c]
4	1:2.2	**I** (10)	2	100	83[d]
5	1:2.2	**II** (10)	2	100	87[c]
6	1:2.2	**III** (10)	2	100	80[c]
7	1:2.2	**II** (5)	2	100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

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 yield (70-90%) and fast reaction rate (0.5-2.0 h). The OPD possessing –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 strongly electron withdrawing 4-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-disubstitute 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 formation of the other possible product 2-arylbenzimidazoles (**4**, Table 2, entries1-5) 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 corresponding 2-substituted benzimidazoles were furnished in 77% and 65% yield respectively (**4f**, **g**, entries 6, 7). Surprisingly no 1,2-disubstituted benzimidazoles were detected in both the cases. Herein alkoxy substituents present at β-position might play a vital role along with the catalyst PIL-**II** for controlling selectivity towards construction of the outcome. Thus we have synthesized different alkoxy aldehydes using salicylaldehyde through alkylation under basic conditions and successfully used for synthesis of the 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**.

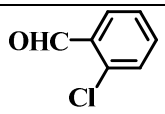
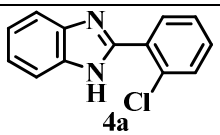
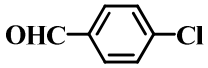
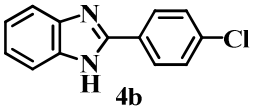
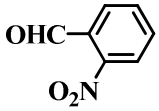
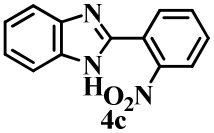
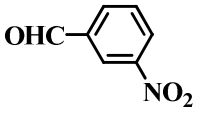
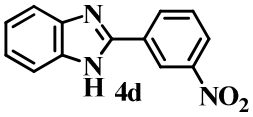
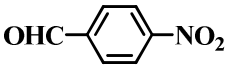
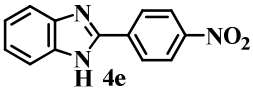
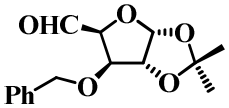
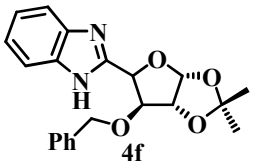
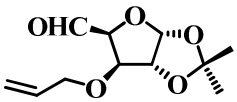
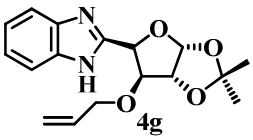
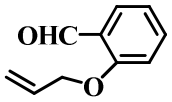
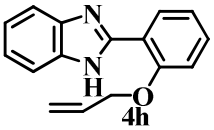
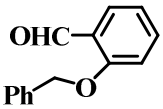
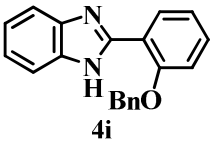
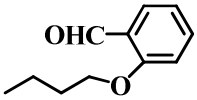
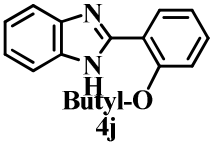


Scheme 2: Highly selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles

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

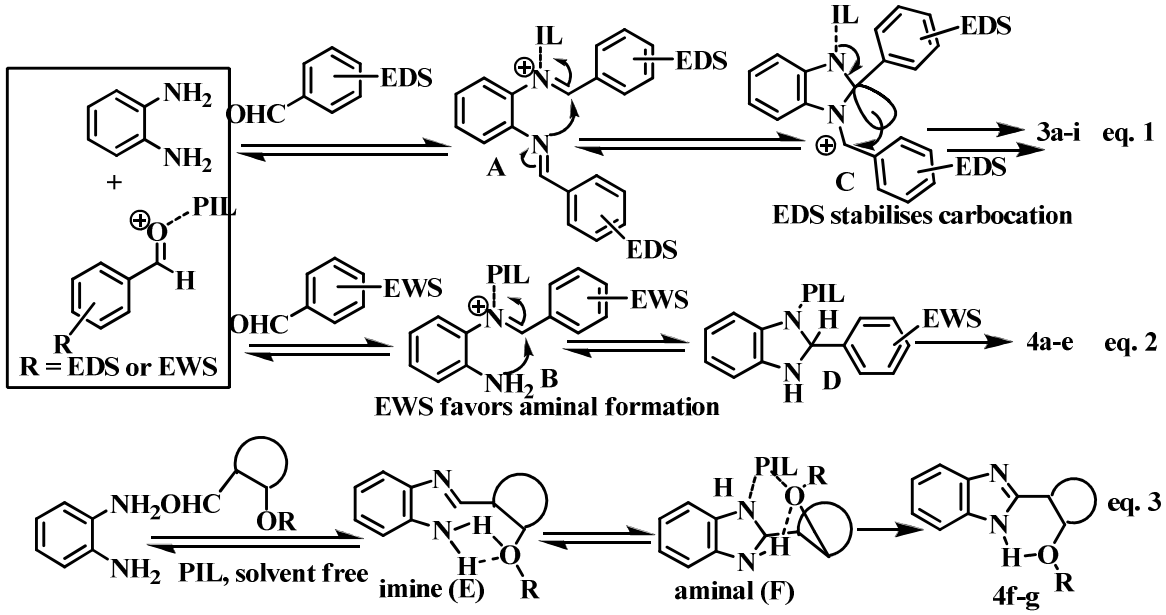
dibenzimidine **A**, which on cyclisation generates intermediate **C**, and subsequent 1,3-hydride shift produces 1,2-disubstituted benzimidazoles. In our experiments PIL-**II** is expected to activate aldehyde first and rapidly performs condensation with one of the $-NH_2$ groups of OPD to form **A**, which on ring

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

closing followed by hydride shift furnished **3** as the sole product (eq. 1, Scheme 3). Indeed we have recorded FTIR spectrum of an equimolar mixture of *p*-methoxy benzaldehyde and PIL-**II**, immediate lowering of carbonyl stretching frequencies (~21cm^{-1}) was observed. It supports our hypothesis regarding first role of PIL-**II** as an activator to the carbonyl functionality of aldehydes.

Under the reaction conditions bis-imine (**A**, eq. 1) formation with aromatic aldehydes possessing electron with-drawing group might be disrupted by the powerful PIL-**II** catalyst and the second amino group of monoimine (**B**, eq. 2) is allowed for ring closing to construct dihydrobenzimidazole-PIL-**II** intermediate (**D**).[23] Subsequent release of PIL-**II**.H leading 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 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 eq. 3 (Scheme 3). Presumably, -NH_2 group of OPD attack PIL-**II** activated aldehyde forming 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**).



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

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

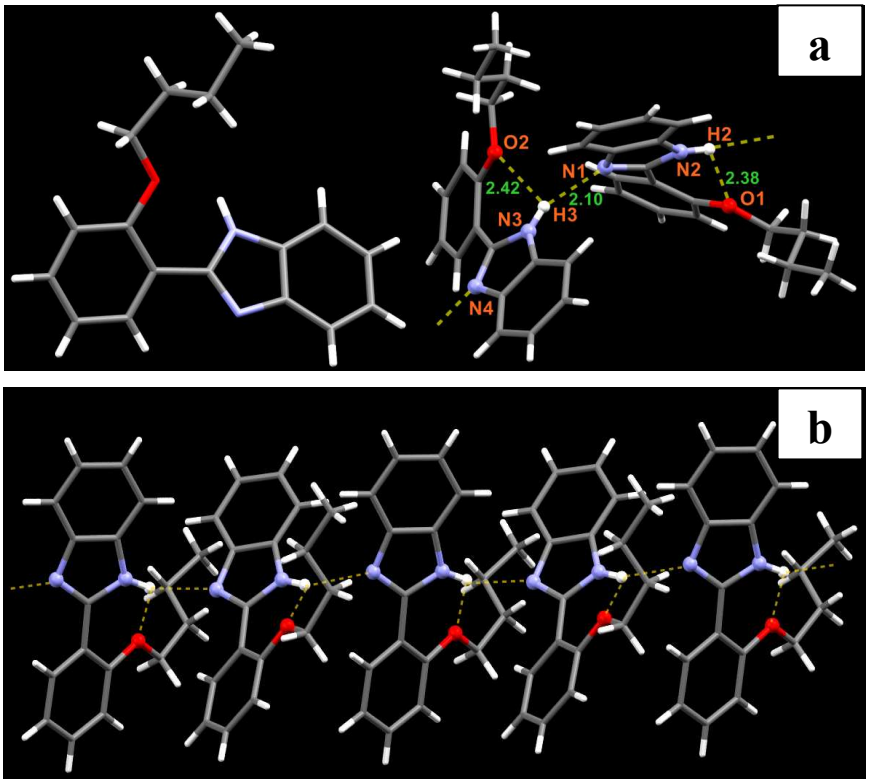


Figure 2: Single crystal structure and crystal packing of **4j**

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 chemistrythe towards 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 benzidazoles whereas aromatic aldehydes

with 'electron withdrawing substituents' or 2-alkoxy aldehydes favour 2-substituted benzimidazoles . Easy accessibility of 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 grinded 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 washed thoroughly with water. The product was re-crystallized from ethanol-water to obtain the pure product. For the products displayed in Table 2, 1.2 mmols 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, ^{1}H and ^{13}C NMR and HRMS spectral data (ESI).

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