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PAPER

IBX Works Efficiently under Solvent Free Condition in Ball milling†

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

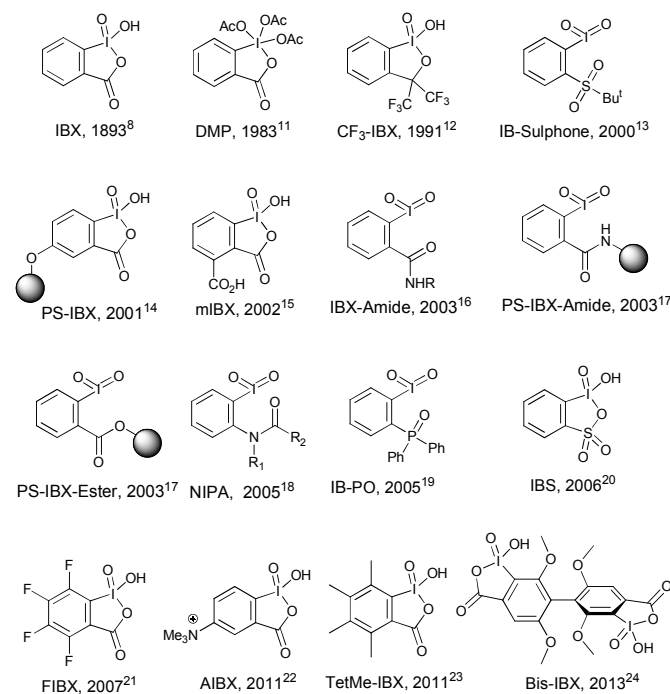
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IBX (2-iodoxybenzoic acid), discovered in 1893, is an oxidant in synthetic chemistry whose extensive use is impeded by its explosiveness at high temperature and poor solubility in common organic solvents except DMSO. Since the discovery of Dess-Martin Periodinane in 1983, several modified IBX systems have been reported. However, under ball milling condition, IBX works efficiently with various organic functionalities at ambient temperature under solvent free conditions. Also, the waste IBA (2-iodosobenzoic acid) produced from the reactions was in situ oxidized to IBX in following step using oxone and thus reused for multiple cycles by conserving its efficiency (only ~6% loss after 15 cycles). This work describes an overview of a highly economical synthetic methodology which overcomes the problem of using IBX, efficiently in gram scale and non-explosive way.

Introduction

With rising public concern over alternative energy¹ and global warming, it is important to trim down the usage of chemicals in routine chemical synthesis. In addition, eliminating waste and developing recyclable methodology is an essential aspect for doing reaction in greener fashion.² Similarly, the metal free reagents are very popular in pharmaceutical industries to avoid toxic metal contamination in drugs.³ 2-Iodoxybenzoic acid (IBX) is a mild, environmental benign and easily available hypervalent iodine(V) reagent has been preferred for metal free oxidative transformations in organic synthesis.⁴⁻⁷ Although journey of IBX started in 1893 by Hartmann and Meyer⁸ but its industrial/laboratory scale use was restricted due to explosiveness at higher temperature⁹ and poor solubility in common organic solvents except DMSO.¹⁰ In solvent DMSO, the large scale (gram quantities) syntheses using IBX have practical difficulties in isolation and purification. The limited solubility and explosive nature of IBX has encouraged many investigators to develop modified-IBX. After the first report on modified IBX i.e., Dess-Martin Periodinane¹¹ in 1983 (DMP, Figure 1), several modified IBX¹²⁻²⁴ and solid-supported IBX²⁵ are reported in literature to overcome the constraint of using IBX as utile oxidant. Recently, several research groups like Nicolaou,^{9, 26-29} Zhdankin,³⁰ Ishihara,^{5, 31, 32} Moorthy,^{23, 24} Wirth^{21, 33-35} and others^{7, 36, 37} have thoroughly explored the potential use of hypervalent iodine reagent (DMP, IBX etc.) in organic synthesis.^{30, 37-41} Nowadays, the hypervalent iodine

reagents are gaining popularity in organic syntheses because of their application in electron transfer chemistry.^{42, 43}



IB = Iodyl-Benzene; PS = Polymer Supported; PO = Phosphine Oxide

Fig 1 Selected and updated information on modified-IBX from 1893 and the abbreviated names are from the references shown as superscript.

On the contrary, these modified IBXs are most often complicated due to involvement of tedious synthetic procedure in non-economical way.²⁴ Therefore the modification approach has not been converged and is still in demand for better methods via recyclable methodology.⁴⁴ We envisioned that ball milling methodology^{45, 46} may possibly be used to make IBX compatible with various organic functionalities without introducing any modification. Herein we are investigating the potential use of IBX⁴⁷ under solvent free, milling condition at room temperature to the following reactions: mainly oxidation of primary/secondary alcohols to corresponding carbonyl compounds,³² amine to imine,⁹ conversion of olefins to α -bromo/iodoketones,⁴⁸ sulfide to sulfoxide,⁴⁹ dithianes deprotection⁹ and synthesis of benzimidazoles from primary alcohols⁵⁰ etc (*vide infra*). Advantageously, this methodology has been established for long-range working window e.g., 10 mg to 2.5 grams.⁵¹ Also, the waste 2-iodosobenzoic acid (IBA) was recyclable to multiple cycles by in situ oxidative regeneration of IBX.⁵² This methodology does not require any aqueous workup, avoids chromatographic purification and found to be highly cost effective to be successfully used in pharmaceutical/chemical industry.

In Figure 1, selective examples of modified IBXs are shown. Now, we are highlighting few shortcomings of these modified systems. The Dess-Martin Periodinane is soluble in common organic solvents but requires anhydrous condition for storing the reagent.¹¹ Besides, CF₃-IBX¹² undergoes rapid ligand exchange with water-acetonitrile solution, water soluble mIBX¹⁵ is non-reactive towards non-allylic/benzylic alcohols, and FIBX²¹ have influence on acid sensitive reactions. In addition, AIBX,²² TetMe-IBX²³ and Bis-IBX²⁴ are synthetically challenging. Polymer supported IBX²⁵ which can work under heterogeneous media, easily separable by filtration, are generally expensive.¹⁴ IBX is also known to work in ionic liquids,⁵³ in aqueous medium with β -cyclodextrin (β -CD) through formation of host-guest complexes⁵⁴ and in solid state at elevated temperature (70-90 °C) which associated with explosiveness, uncontrollable over-oxidation of primary alcohols to acids.⁵⁵

Results and Discussion

We have tested our methodology on oxidation of alcohols to carbonyls⁵ and the results are depicted in Figure 2. The oxidized products of primary, secondary and aliphatic alcohols were obtained in very good to excellent yield in relatively smaller time. Now we are comparing our method with few literature known systems. For example, **2e** (Figure 2) was prepared in 45 min using IBX under ball-milling than 8 h using IBX-CH₃CN-AcOH (traditional) method.⁵ The synthesis of **2w** (Figure 2) using Bis-IBX (Figure 1) is reported for 11.5 h in MeCN/H₂O²⁴ rather than 1 h under ball-milling. In continuation, the supramolecular system like cucurbit[8]uril catalyzed oxidation of alkyl alcohols **2p** to corresponding aldehyde with IBX in aqueous solvent is known to be < 5%,⁵⁶

however our methods resulted the same in 77% yield. Thus, primary alcohols are efficiently converted to the corresponding aldehydes and no over oxidation to acids were found. The results shown in Figure 2 are obtained by ball-milling process and this clearly establishes that the disadvantages associated with poor solubility of IBX are now overcome.

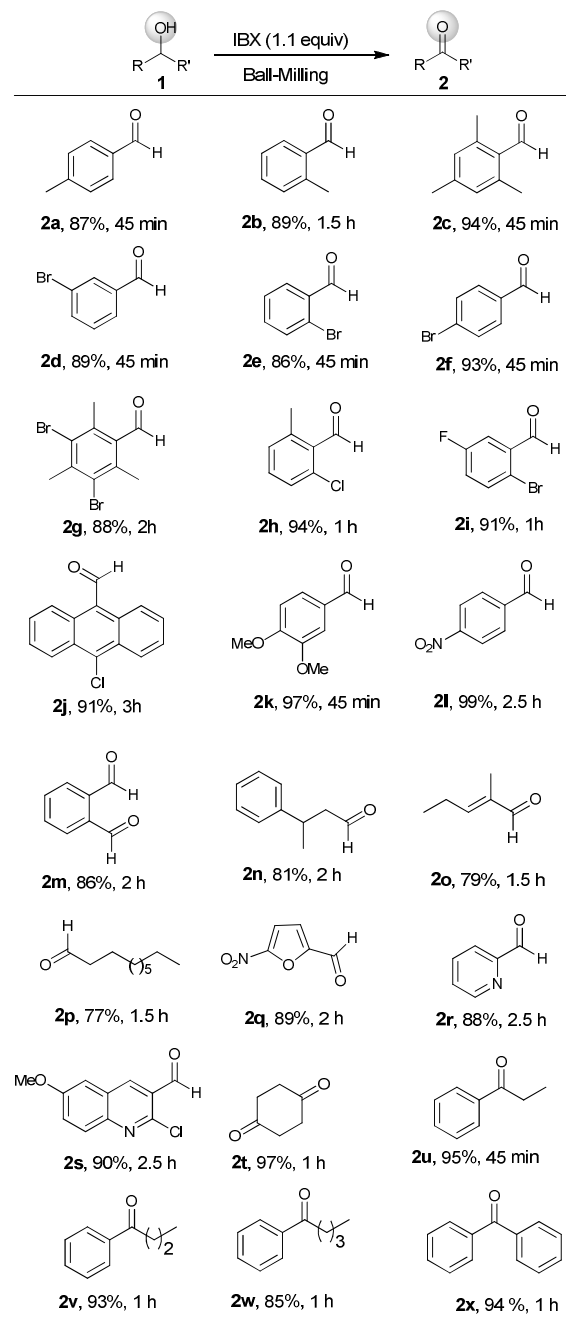


Fig 2 Oxidation of alcohols to carbonyls; also shown compounds number, isolated yields and reaction times.

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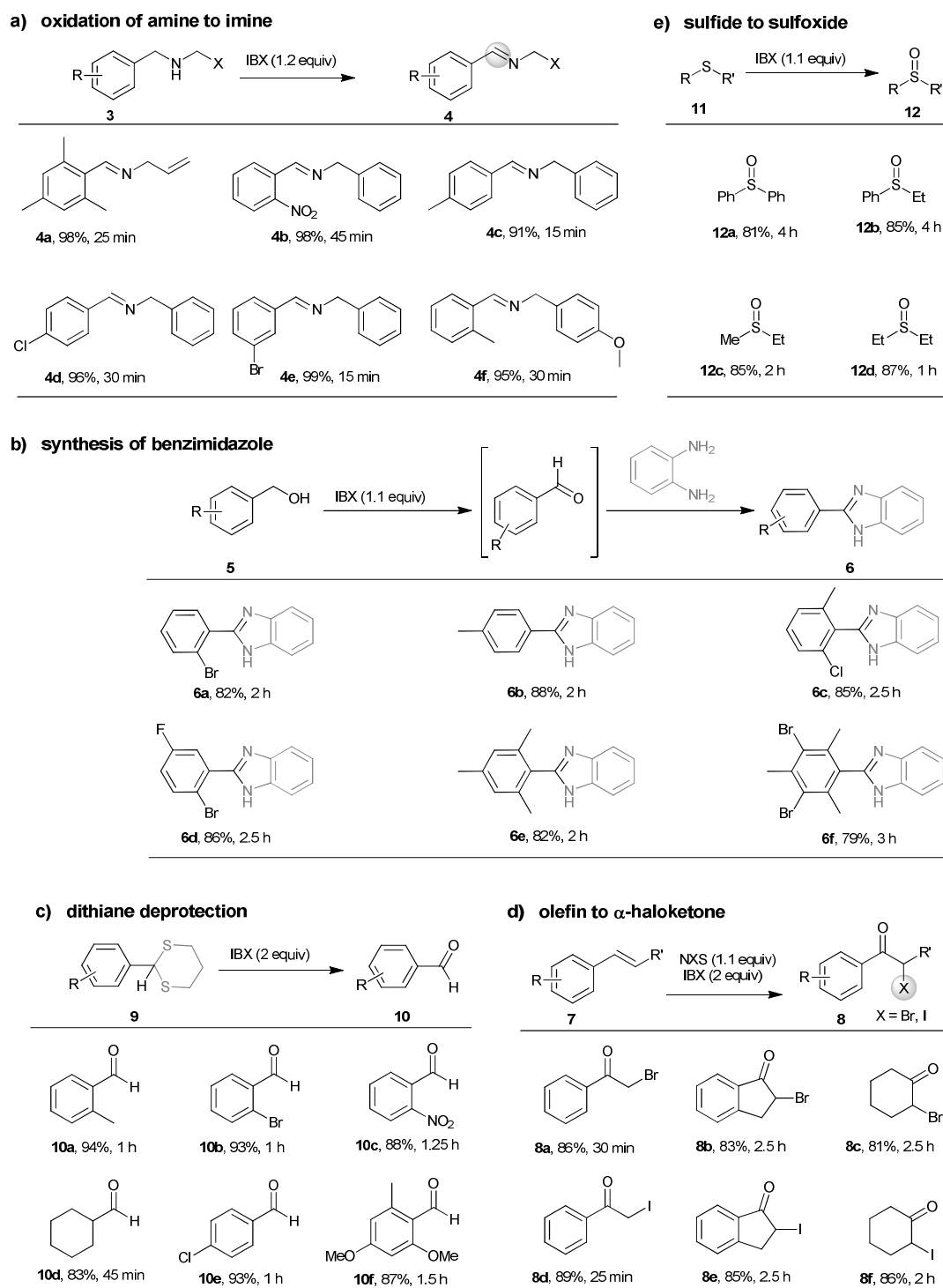


Fig 3 a)-e) Methods tested on different reaction Schemes; only isolated yields are shown.

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The efficiency and convenience of this methodology on alcohol oxidations have also encouraged us to further explore the scope to verify other IBX-mediated literature reported reaction systems. As described in Figure 3, these literature known examples are amine to imine,⁹ conversion of olefins to α -bromo/iodoketones,⁴⁸ sulfide to sulfoxide,⁴⁹ dithianes deprotection⁹ and synthesis of benzimidazoles from primary alcohols⁵⁰ etc.

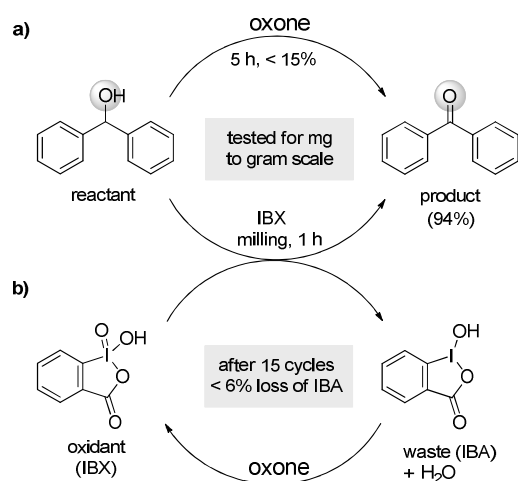
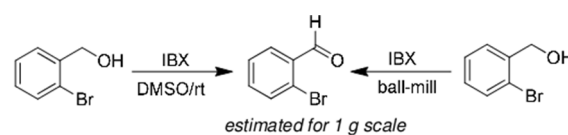


Fig 4. a) Efficiency: the methodology is efficient for the transformation of benzhydrol to benzophenone, up to 1 g substrate was successfully oxidized in 1 h. b) Overview of recycling performance conducted on the following step using waste IBA and oxone.

Figure 4 represents the efficiency and recycling ability of this methodology. Waste IBA i.e., the reduced product of IBX after reaction, was isolated by paper filtration and subsequently *in situ* oxidized to IBX⁵² with inexpensive oxone in following recycling step. Importantly, towards waste management via recycling, in oxidation of benzhydrol to benzophenone (yield 94%, 1 h), after 15 cycles no significant loss ($\sim 6\%$) of IBA was observed. However, oxone in absence of IBA could not efficiently oxidize benzhydrol (conversion $< 15\%$, 5 h) under milling condition. On the other hand, oxidized products were isolated after filtration and purified. Most of the compounds were found to be sufficiently pure and did require chromatographic purification (HPLC analysis) to be used for synthetic applications.

The reaction shown in Figure 5 is truly advantageous in terms of cost effectiveness. Per gram synthesis of 2-bromo benzaldehyde from (2-bromophenyl)methanol using IBX, in a single step using ball-milling, we could save nearly 48% of the

estimated cost (Figure 5, electricity, manpower costs are excluded). However in recycling the same reaction with IBA and oxone, additional 31% could be saved after one recycle (Figure 5).



| methods | traditional | milling |
|--------------|---|------------------------------|
| reagents | IBX (1.5 equiv); 2.3 gm, \$75 | IBX (1.1 equiv) 1.7 gm, \$55 |
| solvents | DMSO (reaction), 50 mL, \$10, DCM (extraction), 300 mL, \$3.5 | -- |
| purification | chromatography pet. ether, 1.2 L, \$11; ethyl acetate, 400 mL, \$4; silica gel, 60 g, \$4.5 | filtration DCM 120 mL \$1.4 |
| time | 2 h | 45 min |
| yield | 82% | 87% |
| total cost | \$108 | \$56.4 |

*in one recycle with IBA and oxone additional \$33.5 was saved

Fig 5. Comparative statement on economic benefit may be obtained from our methodology over traditional one. Using 25 mL of ZrO₂ jar, 2.5 g of (2-bromophenyl)methanol was successfully oxidized

In this work we have demonstrated an outline of a highly economical synthetic methodology which overcomes the problem of using IBX for large scale synthesis. The solubility issue related to using IBX is also addressed carefully. Still, this method has certain limitations e.g., doing any reactions with aniline derivatives and for oxidation of toluenes to benzaldehydes. In both the cases detonation of the reaction mixture was observed. In addition, imines and benzimidazoles have tendency to get decomposed at room temperature and open atmosphere. Similarly, during HPLC analysis (Supporting Information) in polar protic solvent decomposition was also observed for imines and benzimidazoles. However, compounds were stable for longer time (weeks) under inert atmosphere and at low temperature ($-20\text{ }^\circ\text{C}$). We have observed loss of materials while working with volatile compounds like sulfoxides (Figure 4e) and α -haloketones (Figure 4d) and therefore isolated yields were found to be lesser than expected.

Conclusions

We anticipate that a broad range of substrates is compatible with this operationally simple organo-oxidant IBX which works under solvent free condition, at room temperature, non-explosive way and also avoids aqueous workup. This methodology adapts in to milder reaction condition and is

highly economical, time saving and reducing waste through smarter recycling. Therefore, this methodology may serve as an important addition not only to the synthetic field but also to industries. Thus, after 120 years of its discovery IBX may quench the thrust of Modified-IBX and has a huge potential in solving a long-standing problem of organic chemistry. Our study will certainly be of interest to other researchers working not only on the development of hypervalent iodine mediated oxidation methodologies but also to chemists looking for better methodologies under the research area of organic mechanochemistry.⁵⁷

Experimental

Procedure for (2-bromophenyl)methanol oxidation under ball-milling

(2-Bromophenyl)methanol (100 mg, 0.53 mmol), IBX (162 mg, 0.58 mmol) and one grinding ball (15 mm diameter, ZrO₂) were placed in a ball milling 10 mL ZrO₂ jar. The progress of the reaction under milling condition was monitored by thin layer chromatography (TLC) and ¹H NMR spectroscopy.⁵⁸ After completion of the reaction, the reaction mixture was then transferred into 30 mL of dichloromethane (DCM), followed by product was isolated by paper filtration and waste IBA as precipitate. The resulting filtrate were concentrated in vacuum to isolate 85 mg (yield 87%) of 2-bromobenzaldehyde (**2e**) as colourless liquid.

Optimization of gram scale reaction under ball-milling with (2-bromophenyl)methanol

(2-Bromophenyl)methanol (2.5 g, 13.4 mmol) and IBX (4.12 g, 14.7 mmol) were transferred to a milling 25 mL ZrO₂ jar containing one 15 mm diameter ZrO₂ grinding ball. After completion of reaction at 1 h, the product 2-bromobenzaldehyde isolated by following the procedure as presented above (2.10 g, yield: 85%).

Data for unknown compounds

N-(2,4,6-Trimethylbenzylidene)prop-2-en-1-amine (4a): Yield 98%; colourless liquid; IR (KBr): 2960, 2921, 2857, 1687, 1609, 1436, 1377, 1207, 1147, 1033 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.61 (s, 1H), 6.88 (s, 2H), 6.17-6.07 (m, 1H), 5.30-5.16 (m, 2H), 4.30-4.29 (m, 2H), 2.42 (s, 6H), 2.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): 162.08, 138.75, 137.49, 136.47, 131.23, 129.38, 115.68, 64.82, 21.18, 20.68; Anal. Calcd for C₁₃H₁₇N: C 83.37, H 9.15, N 7.48; found C 82.98, H 9.32, N 7.71.

(E)-N-(4-Chlorobenzylidene)-1-phenylmethanamine (4d): Yield 96%; colourless liquid; IR (KBr): 3041, 3015, 2794, 1693, 1628, 1572, 1443, 1189 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.38 (s, 1H), 7.79 (d, *J* = 8 Hz, 2H), 7.54-7.24 (m, 7H), 4.89 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 160.45,

139.01, 136.60, 134.55, 129.42, 128.79, 128.49, 127.94, 127.04, 64.84; Anal. Calcd for C₁₄H₁₂ClN: C 73.20, H 5.27, N, 6.10; found C 73.46, H 5.51, N 6.48.

N-(3-Bromobenzylidene)-1-phenylmethanamine (4e): Yield 99%; colourless liquid; IR (KBr): 3061, 3028, 2844, 1700, 1644, 1565, 1453, 1425, 1210, 1065, 783, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.33 (s, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 7.69-7.67 (m, 1H), 7.57-7.55 (m, 1H), 7.41-7.38 (m, 4H), 7.32-7.27 (m, 2H), 4.85 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 160.11, 138.82, 138.06, 133.49, 130.74, 130.01, 128.46, 127.91, 127.03, 126.96, 122.82, 64.85; Anal. Calcd for C₁₄H₁₂BrN: C 61.33, H 4.41, N 5.11; found C 61.56, H 4.70, N 5.49.

1-(4-Methoxyphenyl)-N-(2-methylbenzylidene)-methanamine (4f): Yield 95%; colourless liquid; IR (KBr): 3406, 3003, 2932, 2835, 1635, 1606, 1512, 1247, 1174, 1034 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.71 (s, 1H), 7.96-7.94 (m, 1H), 7.35-7.20 (m, 5H), 6.94-6.90 (m, 2H), 4.81 (s, 2H), 3.82 (s, 3H), 2.53 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 160.33, 158.74, 137.71, 134.25, 130.87, 130.37, 129.18, 127.71, 126.27, 114.06, 114.00, 65.09, 55.37, 19.43; Anal. Calcd for C₁₆H₁₇NO: C 80.30, H 7.16, N, 5.85; found C 80.07, H 7.27, N 5.76.

2-(2-Chloro-6-methylphenyl)-1H-benzo[d]imidazole (6c): Yield 85%; colourless solid; mp 247-248 °C; IR (KBr): 3417, 2923, 2852, 1632, 1454, 1260, 1013 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.50-7.47 (m, 2H), 7.27-7.11 (m, 4H), 7.11-7.09 (m, 1H), 2.06 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 149.05, 140.94, 138.17, 134.56, 130.75, 129.98, 128.67, 127.03, 122.86, 115.36, 20.32; HRMS (ESI-TOF) Calculated for C₁₄H₁₂ClN₂ (MH⁺) 243.0689, found 243.0672; Anal. Calcd for C₁₄H₁₁ClN₂: C 69.28, H 4.57, N 11.54; found C 70.11, H 4.45, N 11.72.

2-(2-Bromo-5-fluorophenyl)-1H-benzo[d]imidazole (6d): Yield 86%; colourless solid; mp 139-143 °C; IR (KBr): 3438, 2924, 2853, 1633, 1465, 1260, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.08-8.02 (m, 4H), 7.47-7.43 (m, 2H), 7.23-7.18 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 141.97, 139.77, 135.85, 135.03, 133.84, 133.47, 132.04, 129.38, 129.25, 128.13, 127.46; HRMS (ESI-TOF) Calculated for C₁₃H₉BrFN₂ (MH⁺) 290.9933, found 290.9960; Anal. Calcd for C₁₃H₈BrFN₂: C 53.63, H 2.77, N 9.62; found C 53.82, H 2.93, N 9.51.

2-(3,5-Dibromo-2,4,6-trimethylphenyl)-1H-benzo[d]imidazole (6f): Yield 79%; colourless solid; mp 290-292 °C; IR (KBr): 3437, 1633, 668 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.57 (s, 1H), 7.32-7.28 (m, 4H), 2.74 (s, 3H), 2.07 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 150.92, 139.78, 137.29, 130.63, 125.86, 123.15, 26.30, 22.28; HRMS (ESI-TOF) Calculated for C₁₆H₁₅Br₂N₂ (MH⁺) 392.9602, found 392.9604; Anal. Calcd for C₁₆H₁₄Br₂N₂: C 48.76, H 3.58, N 7.11; found C 48.61, H 3.69, N 7.28.

Acknowledgements

We are thankful to DST (New Delhi, India; Grant No INT/FINLAND/P-06 and SR/S1/IC-59/2010) for financial support. TKA and SM are thankful to UGC and CSIR (India), respectively for fellowship. We are also thankful to Dr. C. Giri for his help during manuscript preparation and IMMT Bhubaneswar for elemental analysis.

Notes and references

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†Electronic Supplementary Information (ESI) available: Supporting Information file contains supporting data and NMR spectra for all the literature known compounds. See DOI: 10.1039/b000000x/

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- Using 25 mL of milling jar we could successfully perform the reactions on 2.5 gram scale and scaled down to 10 mg with a smaller jar (10 mL). In all the cases one ball with 15 mm diameter was used and also followed recommended maximum loading 1/3 volume of the jar capacity.
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- The ball-milling apparatus was stopped and small portion of sample was collected from the jar to study either proton NMR/TLC (Thin Layer Chromatography). Followed by, the reaction was started and this operation time was excluded for reporting the reaction timing.