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IBX-mediated one-pot synthesis of benzimidazoles from primary alcohols and arylmethyl bromides

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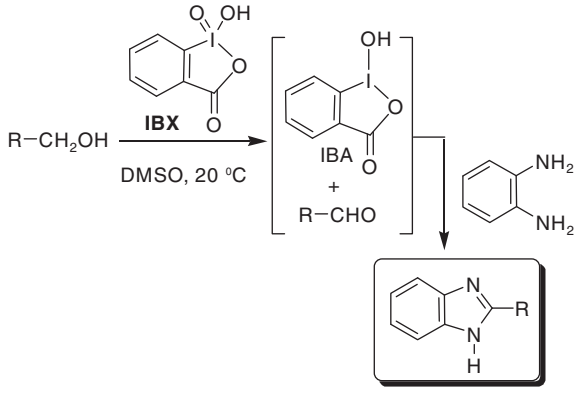
ABSTRACT

A variety of primary alcohols are shown to be converted to the corresponding benzimidazoles in one pot by employing IBX and *o*-phenylenediamine in DMSO at room temperature. *o*-Iodobenzoic acid is the end product of IBX, which is employed in 1.0 equiv. Arylmethyl bromides are also shown to be converted likewise to benzimidazoles in moderate yields in one pot, albeit at slightly elevated temperatures.

IBX has assumed a lot of prominence as an excellent organic reagent in the contemporary oxidation chemistry because of its ease of preparation, cost effectiveness, non-toxic as well as environmentally-benign attributes and moisture stability.[1] The remarkably mild nature and astounding reactivity continue to be exploited for a myriad of organic transformations.[1] There have been successful applications of IBX already in accomplishing multistep transformations in one pot.[2] For example, IBX has been employed for the preparation of α,β-unsaturated carbonyl compounds from benzylic/allylic/propargylic alcohols in one pot.[2b] In a similar manner, facile oxidation of phenols leading to catechols has been exploited for the synthesis of catechol estrogens and other catechol compounds in one pot.[2c]

In our laboratories, we have been concerned with understanding the reactivity of IBX and unraveling new reactions mediated by it.[3] In continuation of these studies, we envisaged the possibility of converting aldehydes, generated in situ from alcohols at rt, to benzimidazoles in one pot based on the reported oxidative dehydrogenation of polycycles by IBX, Scheme 1[4]; it was also surmised that arylmethyl bromides, which have been shown to be converted to aldehydes by us[3b] at relatively higher temperatures, should also be possible to be converted to benzimidazoles likewise. Given that the latter are privileged structural motifs in pharmaceuticals,[5] natural products,[6] functional organic materials,[7] polymers,[8] etc., their preparation directly from alcohols and activated arylmethyl bromides was deemed impressive. A variety of synthetic methodologies are indeed known for the synthesis of benzimidazoles starting from the precursor benzaldehydes or benzoic acids.[9] By contrast, very few synthetic protocols are reported for directly accessing benzimidazoles from benzyl alcohols and virtually none from benzyl bromides in one pot. The reported procedures rely on the use of difficult-to-access and expensive metal catalysts, such as Au deposited on CeO_2,[10a] Pd supported on MgO,[10a] $RuCl_2(PPh_3)_3$,[10b]



Scheme 1.

$Ru(PPh_3)_3(CO)H_2$,[10c] supported $Ru(OH)_x/TiO_2$,[10d] MoO_3–SiO_2,[10e] etc. Herein, we report a convenient and facile one-pot IBX-mediated conversion of primary alcohols to benzimidazoles with IBX in respectable isolated yields. It is shown that 1.1 equiv of IBX suffices for a consecutive reaction involving two steps, namely oxidation of alcohols and dehydrogenation of dihydrobenzimidazoles.

In a typical protocol, benzyl alcohol was initially subjected to oxidation with 1.1 equiv of IBX in DMSO at 20 °C, and the resultant aldehyde was subsequently transformed into the corresponding benzimidazole by adding 1.1 equiv of 1,2-phenylenediamine to the same pot. Preliminary experiments were conducted by introducing molecular sieves before the addition of 1,2-phenylenediamine to facilitate imine formation between aldehyde and 1,2-phenylenediamine, which is a crucial step for the benzimidazole formation (Scheme 2). However, the reaction was observed to proceed smoothly without the addition of molecular sieves. Product formation was also observed when the aldehydes were directly reacted with *o*-phenylenediamine in the presence of IBA

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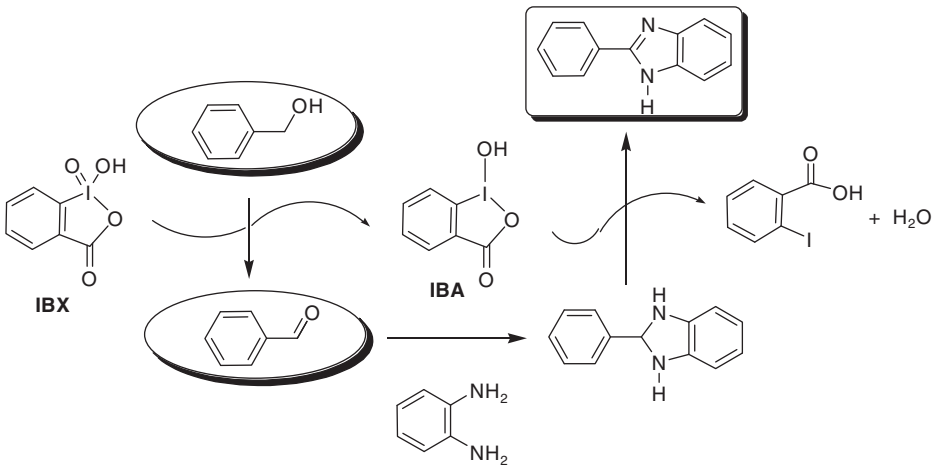
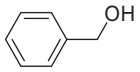
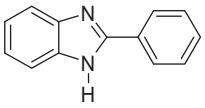
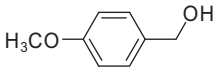
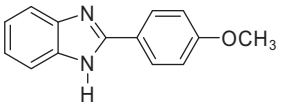
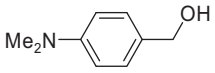
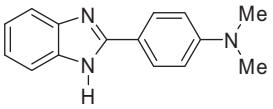
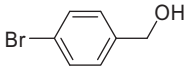
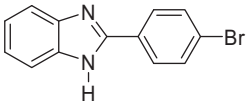
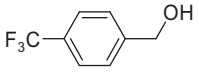
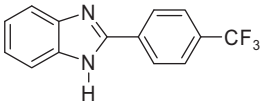
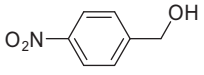
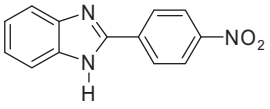
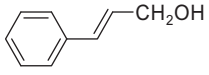
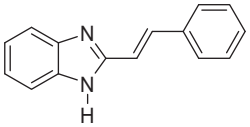
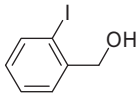
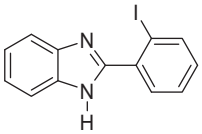
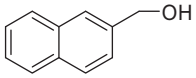
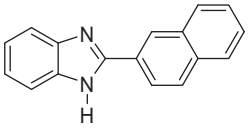


Scheme 2.

Table 1
Results of conversion of benzyl alcohols to the corresponding benzimidazoles with IBX (1.1 equiv) and 1,2-phenylenediamine (1.1 equiv)[a]

Entry	Substrate	Time (h)	Product	Yield (%)
1		5		72
2		3		79
3		5		60
4		8		80
5		3		80
6		9		51
7		6		45
8		8		62
9		7		84

(*continued on next page*)

Table 1 (*continued*)

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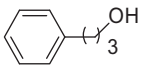
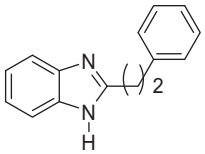
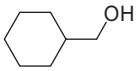
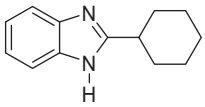
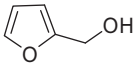
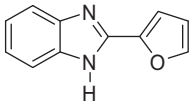
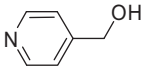
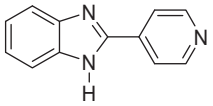
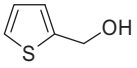
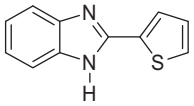
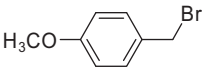
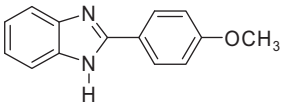
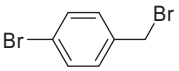
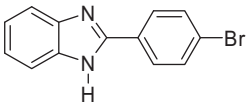
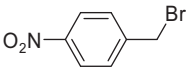
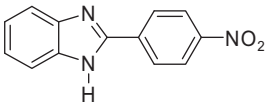
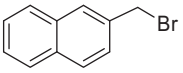
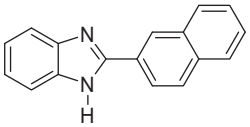
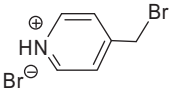
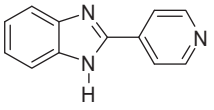
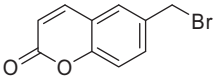
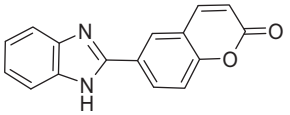
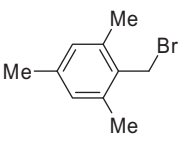
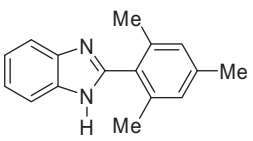
10		6		60
11		5		55
12		12		70
13		16		50
14		8		87

[a] All the reactions were performed on 0.5–1.0 mmol of the aldehyde in DMSO at ca. 25 °C.

Table 2
Results of conversion of benzyl bromides to the corresponding benzimidazoles with IBX (1.5–1.6 equiv) and 1,2-phenylenediamine (1.5–1.6 equiv)[a]

Entry	Substrate	Time (h)	Product	Yield[b] (%)
1		8		53
2		12		50
3		16		45
4		10		80
5		6		50
6		8		50
7		8		30

[a] All reactions were conducted on 0.5–1.0 mmol of the benzyl bromide in DMSO, see text.
[b] Isolated yields.

as well as IBX. No product formation was observed when the reaction was carried out between aldehyde and 1,2-phenylenediamine in the absence of IBA or IBX. Longer reaction durations did not influence the isolated yields appreciably. As for the work-up of the reactions, DMSO was first distilled out in vacuo at ca. 60–65 °C, and the reaction mixture was treated with $NaHCO_3$ solution to remove the iodo acid formed in the reaction mixture.[11]

Generality of the methodology was examined for a series of benzyl alcohols bearing both electron-donating as well as electron-withdrawing groups. As shown in Table 1, the yields of benzimidazoles isolated are impressive, and range from 45% to 87%. Lower yields were isolated for highly electron-rich 4-*N*,*N*-dimethylaminobenzyl alcohol and electron-poor *p*-nitrobenzyl alcohol (entries 3 and 6). Otherwise, all aliphatic, allylic, and benzylic alcohols were found to undergo reactions smoothly to afford the corresponding benzimidazoles in moderate to excellent isolated yields. To probe the reaction mechanism, progress of the reaction of *p*-methoxybenzyl alcohol was monitored by 400 MHz ^{1}H NMR spectroscopy, cf. Supplementary data. Following the addition of 1,2-phenylenediamine to the aldehyde formed subsequent to oxidation of benzyl alcohol with IBX in DMSO, disappearance progressively of the aldehyde signal with concomitant appearance of the signal corresponding to the benzimidazole product was observed. The other noteworthy feature is the formation of *o*-iodobenzoic acid as the end product of IBX. Clearly, IBA—the I(III) species derived from IBX via oxidation of alcohols—is further reduced to *o*-iodobenzoic acid (Scheme 2). Thus, IBX undergoes overall 4e reduction. In other words, IBA is involved in the formation of the benzimidazole. Indeed, we established, in an independent experiment, that the reaction of *p*-methoxybenzaldehyde and 1,2-phenylenediamine leads to the corresponding benzimidazole in the presence of a molar equiv of IBA. Of course, *o*-iodobenzoic acid was observed as the reduction product. Overall, a sequence of reactions entailing the oxidation of alcohol with IBX, formation of Schiff base with 1,2-phenylenediamine and subsequent cyclization and IBA-mediated dehydrogenation lead to benzimidazoles. The one-pot procedure should prove highly advantageous for labile aldehydes in particular.

Benzimidazoles were also accessed from arylmethyl bromides in one pot by treatment of the latter with 1.5–1.6 equiv of IBX in DMSO at 65–70 °C; as mentioned at the outset, we have previously shown that benzyl bromides are converted to benzaldehydes at slightly elevated temperatures in DMSO. Thus, after conversion of arylmethyl bromide to the corresponding aldehyde with IBX in DMSO at 65–70 °C as monitored by TLC analysis, the reaction mixture was brought to room temperature, and 1.5–1.6 equiv of 1,2-phenylenediamine was introduced. Subsequently, the reaction mixture was stirred until the disappearance of the aldehyde. Regular work-up led to isolation of benzimidazole.[11] As shown in Table 2, yields of the isolated benzimidazoles are moderate (45–80%) with the exception of mesityl bromide (entry 7).

In conclusion, a convenient and effective one-pot synthetic strategy has been uncovered for benzimidazoles starting from primary alcohols and arylmethyl bromides using IBX as the reagent. It is shown that 1.1 equiv of IBX suffices for two consecutive oxidative transformations involving an overall 4e-redox process that leads to *o*-iodobenzoic acid as the end product of IBX. Given that IBX is a mild and non-toxic reagent, the one-pot protocol described herein for the benzimidazoles—the end products of a consecutive reaction—clearly attests to a new dimension in the applications of IBX, which we continue to explore.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.047.

References and notes

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11. *General procedure for the one-pot conversion of alcohols to benzimidazoles*: In a typical experiment, the primary alcohol (0.5–0.6 mmol) and IBX (1.1 equiv) were stirred in DMSO at ca. 20 °C. Once the oxidation of alcohol to aldehyde was complete, as judged from TLC analysis, *o*-phenylenediamine (1.1 equiv) was introduced into the reaction mixture and the reaction mixture was allowed to stir at room temperature until the aldehyde disappeared. At the end of the reaction, DMSO was removed under high vacuum, and the residue was treated with 1.0 M $NaHCO_3$ solution until the pH was 8–9. The organic matter was extracted with ethyl acetate. Regular work-up followed by silica-gel column chromatography led to pure benzimidazoles, which were characterized spectroscopically.
For conversion of benzyl bromides to benzimidazoles, the same procedure as above was followed except that the initial conversion to aldehydes was conducted at 70 °C. Once the halide was completely converted to the corresponding aldehyde, the reaction temperature was lowered to rt and *o*-phenylenediamine was introduced.