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Studies on oxidations with IBX: oxidation of alcohols and aldehydes under solvent-free conditions

Jarugu Narasimha Moorthy,* Nidhi Singhal and P. Venkatakrishnan

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

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Abstract—A variety of allylic and benzylic alcohols are oxidized to their respective carbonyl compounds with IBX under solvent-free conditions at ca. 60–70 °C. It has also been found that some of the aromatic aldehydes also undergo oxidation when heated with IBX at 90 °C under solvent-free conditions; notably, this transformation does not occur under the otherwise identical but heterogeneous conditions.

1. Introduction

Oxidation of alcohols to carbonyl compounds constitutes one of the fundamental transformations in organic synthesis. Despite the availability of a variety of methods, there is a growing need for green methodologies that obviate the use of copious amounts of heavy metal oxidants and environmentally unfriendly halogenated solvents.[1] From this point of view, readily available iodine (V) reagents are highly attractive.[2] In particular, *o*-iodoxybenzoic acid (referred to as IBX), a precursor of the well-known DMP (Dess–Martin periodinane reagent), has become a very popular and convenient oxidizing agent due to its nontoxic nature and ease of preparation.[2] The major drawback, however, is its virtual insolubility in common organic solvents. It is precisely this property, which precluded its applications in organic oxidation reactions for almost a century.[3] The recent demonstration by Frigerio and co-workers[4] of the utility of IBX in DMSO for oxidation of alcohols has sparked a revival of interest in IBX-mediated reactions due to its cheap availability and the ease with which the oxidation reactions may be conducted.[2] In recent years, Nicolaou and co-workers,[2,5] and others[6] have uncovered a variety of very useful transformations accomplished by IBX. Considerable effort has also been focused toward the synthesis of modified IBX reagents that permit better solubility and hence application in more common organic solvents.[7] Other efforts aimed at exploiting the potential of IBX in organic oxidations include its application in ionic liquids[8] and in the presence of container molecules such as cyclodextrins,[9] which modify the solubility. Quite remarkably, More and Finney have very recently shown that the limited solubility of IBX in most of the organic solvents at elevated temperatures is substantial enough to achieve oxidation of primary and secondary alcohols to aldehydes and ketones, respectively.[10] We drew inspiration from this report to accomplish the oxidation of highly insoluble and difficultly oxidizable lactols, derived from benzocyclobutenols, to lactones under modified conditions.[11] During these studies, we discovered that IBX works wonderfully as an oxidizing agent under solvent-free conditions. Herein, we wish to document this hitherto unknown facet of IBX to oxidize alcohols to the corresponding carbonyl compounds without the use of any solvent. Further, we also wish to unravel the distinct reactivity of IBX in oxidizing selectively some aldehydes to the corresponding acids, while the same transformation does not occur under the otherwise identical but heterogeneous conditions.[10]

2. Oxidation of primary alcohols

The oxidation of primary allylic and benzylic alcohols occurs in a facile manner on heating with IBX under solvent-free conditions for the durations shown in Table 1 (**CAUTION!** IBX has been reported to explode on

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Keywords: IBX; Oxidations; Solvent-free; Alcohols.

* Corresponding author. Tel.: +91-512-2597438; fax: +91-512-2597436; e-mail: moorthy@iitk.ac.in

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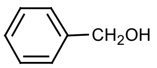
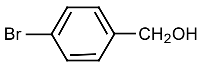
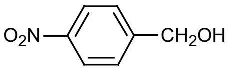
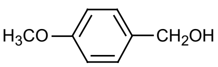
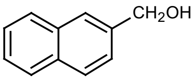
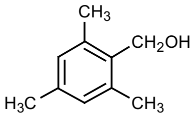
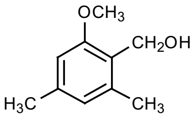
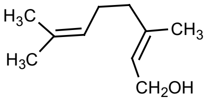
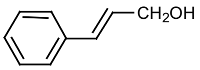
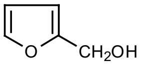
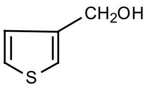
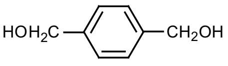
Table 1. Results of the oxidation of primary alcohols with IBX[a]

Entry	Alcohol	Equiv	Time (h)	Yield[b] (%)	Product distribution[c]	
					Aldehyde	Acid
1		1.25 2.00	1.0 3.0[d]	>95 70	100 43	 57
2		1.25	1.0	89	100	
3		1.25	1.5	88	100	
4		1.25	1.0	95	100	
5		1.25	3.0	84	100	
6		1.25	2.0[e]	84	60	40
7		2.00 3.00	2.0 4.0[d]	90 91	100 100	
8		1.25	0.75[b]	72	100	
9		1.25 2.50	0.5 1.5	89 86	100 36	 64
10		1.25	0.5	75[f]	100	
11		1.25	1.5	90	100	
12		2.50	2.0	71	100	
13	Cetyl alcohol	2.0	3.0[e,g]			

[a] Under solvent-free conditions, the temperature was 60 °C unless otherwise mentioned, see text.

[b] Isolated yields. The conversion was ⩾95% except for entry 8 (72%).

[c] Relative distribution normalized to 100%.

[d] Temperature = 60–90 °C.

[e] Temperature = 70 °C.

[f] The remaining material was unidentifiable.

[g] No oxidation was observed.

heating).[12] All of the benzylic and allylic alcohols including the heteroaromatic analogues yielded the corresponding aldehydes in respectable isolated yields (72–95%), when the oxidation was conducted with 1.25 equiv (entries 1–6, 8–11). Indeed, the benzylic diol (entry 12) was oxidized to terephthalaldehyde in 71% isolated yield with excess reagent. However, the aliphatic cetyl alcohol could not be oxidized even with 2.0 molar equiv of IBX (entry 13). In contrast, the sterically-hindered benzylic alcohols (entries 6 and 7) underwent clean oxidation in yields higher than 84%; interestingly the formation of mesitoic acid was observed in significant amounts even for 1.25 molar equiv of IBX (entry 6). When IBX was used in excess, over-oxidation to acids (entries 1, 6, and 9) was observed in appreciable yields (vide infra). Importantly, the durations for the conversion of alcohols to aldehydes were found to be comparable to those for oxidation in DMSO (1/2–5 h)[4] and under heterogeneous conditions (ca. 1/2–3 h).[10]

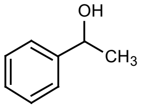
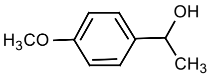
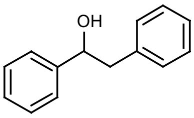
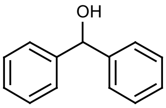
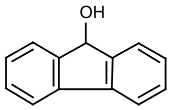
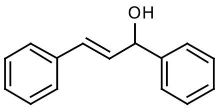
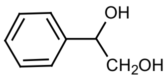
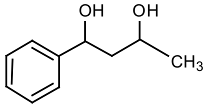
3. Oxidation of secondary alcohols

In a similar vein, the oxidation of secondary allylic and benzylic alcohols also proceeded smoothly to the respective ketones in good yields (Table 2, entries 1–6).[12] The vicinal diol did not afford the glyoxal, but underwent selective benzylic oxidation as revealed by ^{1}H NMR spectroscopy (entry 7); cleavage of the 1,2-diol was not observed. The 1,3-diol, however, underwent oxidation to the diketone when treated with excess IBX (entry 8). It is noteworthy that monooxidation was not observed regardless of whether more or less molar equivalent of IBX were employed. Again, oxidation was ineffective with aliphatic substrates such as cholesterol and menthol (entries 9 and 10).

4. Oxidation of aromatic aldehydes

The formation of acids from some of the alcohols (Table 1) when IBX was used in excess amounts prompted us to examine the oxidation of aldehydes. The prototypical aromatic aldehyde, viz., benzaldehyde, was found to undergo oxidation at 60 °C, albeit in low yields. The oxidation was found to be more facile at slightly higher temperatures, ca. 90 °C. Accordingly, we subjected rather less-volatile aldehydes to oxidation at 90 °C (Table 3). Whereas *p*-bromobenzaldehyde underwent oxidation to the acid in 63% isolated yield in 3 h (Table 3, entry 1), *p*-nitro, and *p*-methoxy aldehydes were found to react sluggishly with the former undergoing no oxidation at all (entries 2 and 3). Rather inexplicably,

Table 2. Results of the oxidation of the secondary alcohols to ketones[a]

Entry	Alcohol	Equiv	Time (h)	Conv. (%)	Yield[b] (%)
1		1.25 2.00	3.0 2.0	100 100	83 81
2		2.00	2.0	100	93
3		1.25 2.00	3.0 2.0	100 100	92 87
4		2.00	3.0	100	94
5		2.00 2.00	3.0 6.0	60 60	84 84
6		1.50	1.0	95	70[c]
7		2.50	2.0		[d]
8		2.50	4.0	89	62[e]
9	Cholesterol	2.00	5.0[f]		
10	(−)-Menthol	2.00	3.0[f]		

[a] Under solvent-free conditions, temperature = 70 °C, see text.

[b] Isolated yields based on conversion.

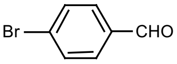
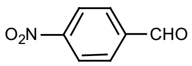
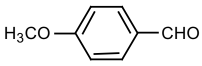
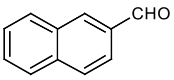
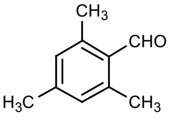
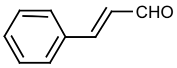
[c] The remaining material was unidentifiable.

[d] From ^{1}H NMR analysis of the crude reaction mixture, only benzylic oxidation was found to occur with the formation of glyoxal being negligible, yields were not determined.

[e] Oxidation of both of the groups was found to occur simultaneously regardless of the molar equivalent of IBX employed.

[f] No oxidation was observed.

Table 3. Results of the oxidation of aldehydes to acids[a]

Entry	Aldehyde	Equiv/temp (°C)/time (h)	Conv. (%)	Yield[b] (%)
1		1.25/90/3	70	63
2		2.0/90/10	[c]	
3		1.25/90/5	14	50
4		2.0/90/10	14	50
5		1.25/90/4.5	75	80
6		1.25/90/4.0	73	86

[a] Mass balance in all the cases was >90%, except for entry 1 (63%).
[b] Isolated yields based on conversion.
[c] No acid was detected.

mesitaldehyde underwent smooth oxidation, while naphthalene-2-carboxaldehyde reacted only sluggishly (entries 4 and 5). Cinnamaldehyde underwent facile oxidation to the acid in an excellent isolated yield (entry 6). In contrast, the oxidation of *p*-bromobenzaldehyde and mesitaldehyde with 3.0 equiv of IBX as a suspended material in ethyl acetate at reflux for 3 h under heterogeneous conditions[10] did not lead to the corresponding acids. This signifies the unique reactivity that appears to be especially associated with IBX under solvent-free conditions.

5. Direct oxidation of alcohols to acids and mechanistic rationalizations

Encouraged by the oxidation of aldehydes, we examined the direct conversion of alcohols to acids. The progress of the reaction of *p*-bromobenzyl alcohol, a representative case, was directly monitored by ^{1}H NMR spectroscopy. Thus, the alcohol and IBX (2.5 equiv) were ground together with a mortar and pestle, and the reaction of the solid mixture on heating was analyzed by ^{1}H NMR spectroscopy in MeOH-d_4 at regular time intervals. As can be seen from Figure 1, the formation of aldehyde in small amounts was observed upon mere grinding. On heating the mixture at 60 °C for 1 h in a Kugelrohr (Buchi glass oven),[12] complete conversion to the aldehyde occurred (spectrum b). Continued heating at 90 °C for 2 h led to the acid almost quantitatively, see traces c and d. Although IBX and its reduction product remained as suspended solid materials, the signals due to some solubility in this solvent are clearly evident in the region around ca. δ 8.0 in all of the spectra. Clearly, the oxidation of alcohols to acids proceeds via two steps.

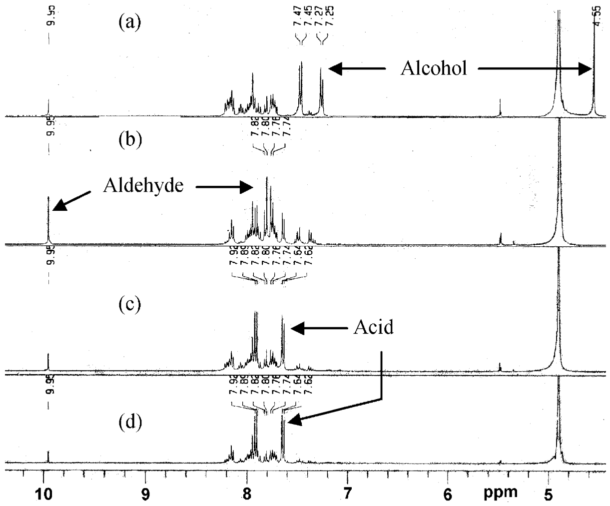
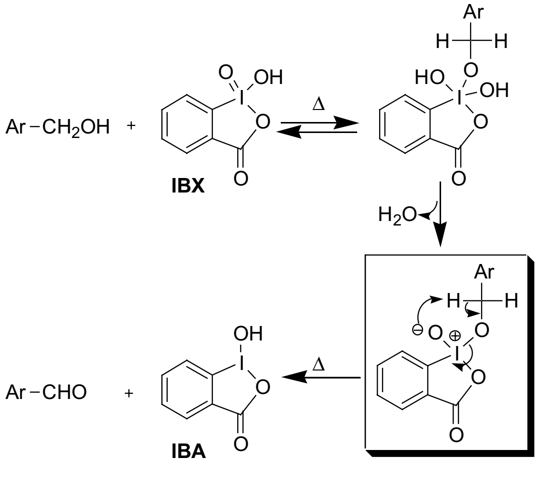


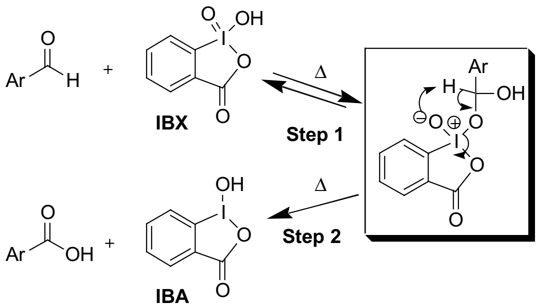
Figure 1. ^{1}H NMR (400 MHz, MeOH-d_4) spectral monitoring of the solid-state reaction of *p*-bromobenzyl alcohol with 2.5 molar equiv of IBX: (a) alcohol and IBX mixture after grinding in a mortar and pestle for 5–10 min; (b) after heating at 60 °C for 1 h; (c) after 2 h, temp = 90 °C; (d) after 3 h, temp = 90 °C.

The oxidation of alcohols to aldehydes is known to occur by the mechanism shown in Scheme 1.[2a,c] Removal of the water formed at the reaction temperature (60–70 °C) (see Ref. 12 for the procedure) may facilitate the forward process.[13]

The IBX-mediated oxidation of aldehydes to acids is heretofore unknown and is a difficult procedure to rationalize. We propose that the addition intermediate of the type shown in Scheme 2 may form via initial protonation of the aldehyde by IBX followed by attack of its conjugate base; it should be noted that IBX has been reported to be a mild acid.[14] The reason as to why only some aldehydes react to afford the acids (Table 3) should be traceable to the subtle electronic factors operative in steps 1 and 2 of the proposed mechanism.



Scheme 1. Mechanism of the IBX-mediated oxidation of alcohols to aldehydes.



Scheme 2. Mechanism of the IBX-mediated oxidation of aldehydes to acids.

The direct conversion of alcohols to acids with a mild oxidizing agent is an important transformation in organic synthesis. Based on a rational approach that involves the initial conversion of an aldehyde to the corresponding hemiacetal via nucleophilic attack with an additive such as 2-hydroxypyridine/*N*-hydroxysuccinimide followed by oxidation with IBX, Mazitschek et al. have very recently demonstrated the oxidation of alcohols-to-aldehydes-to-acids;[15] the reaction times in DMSO are as long as 16 h. In light of this, the oxidation of aromatic aldehydes observed with IBX under solvent-free conditions is noteworthy.

In summary, we note the following for the solvent-free oxidation of alcohols and aldehydes with IBX:

- Both primary and secondary aliphatic alcohols do not undergo oxidation with the exception of entry 8 in Table 2, whereas the allylic and benzylic alcohols react readily (Tables 1 and 2) without any dependence on the electronic factors. The results suggest the necessity of some unsaturation in the molecules to achieve appropriate orientation with respect to IBX for reaction to ensue in the solvent-free state.
- The oxidation of alcohols to aldehydes occurs with a small excess (1.25–1.50 equiv) of IBX and over-oxidation to acids can be controlled with temperature.
- Intriguingly, the sterically-hindered mesityl alcohol undergoes direct oxidation to the acid, while 2-methoxy-4,6-dimethylbenzyl alcohol yields only the aldehyde (Table 1, entries 6 and 7).
- Some aromatic aldehydes are found to undergo oxidation to the corresponding acids (Table 3), whilst being unreactive under identical but heterogeneous conditions, cf. More and Finney.[10]

Although IBX has been reported to be sensitive to hard impact and high temperatures, we have not had a single instance of any explosion at the temperatures employed at 1–2 mmol scale operations. We admit that the solvent-free oxidation protocol described herein cannot be applied to large-scale operations in view of the explosion hazards. Given that the potential of IBX as an oxidizing agent went unnoticed for well over a century due to its insolubility in a variety of organic solvents, the observed results are indeed a revelation. In view of the importance associated with IBX in terms of eco-friendly advantages and its ease of regeneration with oxone,[16] modified IBX derivatives with enhanced reactivity should constitute very useful reagents for facile oxidation of alcohols and aldehydes at *room temperature* under solvent-free conditions, and we are continuing our investigations toward this goal.

CAUTION! IBX has been reported to detonate upon heavy impact and heating over 190 °C.[17]

Acknowledgements

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12. The typical experimental procedure involved heating the mixture of alcohol/aldehyde and finely powdered IBX in a Kugelrohr (glass oven, Buchi) at 60–70 °C (for alcohols) or at 90 °C (for aldehydes) for the appropriate durations given in Tables 1–3. For liquid substrates, their ether solutions were treated with finely powdered IBX, the

solvent removed and the solid admixture thus formed was heated. In the case of crystalline substrates, IBX and the substrate were ground together with a mortar and pestle, and the admixture was heated in a Kugelrohr oven. Filtration of the reaction mixture over a short-pad of silica gel afforded the aldehydes/acids. The IBX employed for the reactions was prepared by the reported procedure, see: Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* *77*, 141.

13. The exclusion of water may occur either by homolysis involving a single electron transfer mechanism (SET) or by heterolysis. The former has been proposed in the case of oxidation of electron-rich amines, see: Ref. 5b. A similar SET process is unlikely in the case of alcohols.
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