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In Situ Generation of *o*-Iodoxybenzoic Acid (IBX) and the Catalytic Use of It in Oxidation Reactions in the Presence of Oxone as a Co-oxidant

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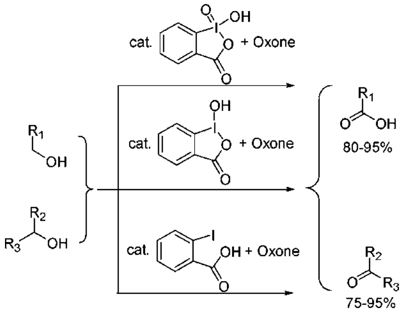
ABSTRACT



Catalytic use of *o*-iodoxybenzoic acid (IBX) in the presence of Oxone as a co-oxidant is demonstrated for the oxidation of primary and secondary alcohols in user- and eco-friendly solvent mixtures. Also demonstrated is the in situ (re)oxidation of 2-iodosobenzoic acid (IBA) and even commercially available 2-iodobenzoic acid (2IBAcid) by Oxone to IBX allowing one to use these less hazardous reagents, in place of potentially explosive IBX, as catalytic oxidants.

Within the past decade, *o*-iodoxybenzoic acid (IBX) has emerged as a powerful yet selective oxidant that effects a plethora of oxidative transformations in synthetic organic chemistry. The synthetic use of IBX as an oxidizing agent was initially demonstrated by Frigerio and Santagostino for the selective transformation of alcohols to carbonyl compounds in 1994.[1] The past few years have seen an explosive growth in the demonstration and use of IBX as a selective reagent for unique oxidative transformations including oxidation of benzylic carbons,[2a] oxidation of amines,[2b] dehydrogenation of ketones and aldehydes to the corresponding α,β-unsaturated analogues,[2a] dehydrogenation of *N*-heterocycles to heteroaromatics,[2b] oxidative cleavage of dithioacetals and dithioketals,[2b] and selective deprotection of triethylsilyl ethers in the presence of *tert*-butyldimethylsilyl (TBDMS) ethers,[3] in addition to the more conventional oxidation of alcohols to carbonyl compounds.[4] These transformations using IBX, a potentially shock-sensitive explosive oxidant,[5] are carried out in DMSO, the only solvent in which the reagent readily dissolves. The practical difficulty in using DMSO as the solvent of choice for IBX reactions has prompted many researchers to structurally modify IBX to produce efficient and user-friendly derivatives that do not possess the deleterious explosive property of IBX and can be used in solvents other than DMSO. The syntheses of solid-phase-anchored

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(1) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022.

(2) (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258. (b) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192−5201.

(3) Wu, Y.; Huang, J.-H.; Hu, Q.; Tang, C.-J.; Li, L. *Org. Lett.* **2002**, *4*, 2141−2144.

(4) (a) De Munari, S.; Frigerio, M.; Sanatgostino, M. *J. Org. Chem.* **1996**, *61*, 9272−9279. (b) Frigerio, M.; Santagostino, M.; Sputore, S. J. *J. Org. Chem.* **1999**, *64*, 4537−4538.

(5) IBX is reported to be a shock-sensitive explosive. See: Plumb, J. B.; Harper, D. *J. Chem. Eng. News* **1990**, *68* (29), 3.

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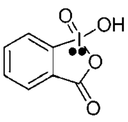
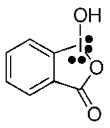
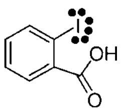
derivatives of IBX[6] and a stabilized formulation of IBX are noteworthy examples in this area.[7] A contribution from this laboratory has also described the synthesis of a water-soluble derivative of IBX as a selective oxidant for allylic and benzylic alcohols.[8] Moreover, a report from Finney Laboratories describes the use of IBX in common organic solvents, such as acetonitrile, acetone, ethyl acetate and toluene at elevated temperatures, thus enhancing the popularity of the reagent.[9]

A research objective of an ongoing project in our laboratory is to develop user- and eco-friendly protocols for oxidation of alcohols and other substrates using environmentally safe reagents and solvents. As such, the benign environmental character of IBX and other hypervalent iodine reagents attracted our attention. The recently demonstrated use of IBX as an oxidant in water-miscible organic solvents[9] and the fact that Oxone,[10] an environmentally safe reagent, oxidizes organoiodo compounds in aqueous solvent systems to their hypervalent state prompted us to investigate the oxidation of alcohols using catalytic amounts of IBX in the presence of Oxone as a co-oxidant.[11] Our planned strategy is the in situ reoxidation of the reduced form of IBX, namely, iodosobenzoic acid (IBA), back to the active I (V) state using Oxone. We were also aware of the fact that should our strategy be successful then we could potentially use the nonexplosive IBA as a precursor to catalytic IBX. Better yet, we could use commercially available 2-iodobenzoic acid (2IBAcid), the ultimate precursor for IBX and IBA, as our catalytic reagent. Preliminary results of these successful strategies are reported herein.


IBX


IBA


2IBAcid

Our initial effort was directed at identifying a suitable aqueous solvent system in which the organic substrate could be oxidized using IBX and in which the reduced form of IBX could be reoxidized to its active state using Oxone. 3-Phenyl-1-propanol was chosen as a protypical substrate for this optimization, as well as other optimization studies reported in this paper. Oxidation reactions were attempted in aqueous mixtures of THF and acetonitrile. Aqueous mixtures of acetone were not included in this study for fear of complications from in situ generated dioxirane as an alternate and potential oxidant in the reaction medium.[12] Reactions carried out in aqueous THF provided only trace amounts of the oxidized substrate along with substantial amounts of γ-butyrolactone, an oxidized product of THF. This solvent system was thus deemed inappropriate for our study. Though reactions carried out in both 1:1 and 2:1 v/v mixtures of acetonitrile and water yielded oxidized products, significant differences in the yields of the products in the two solvent system were not noted. For example, oxidation of 3-phenyl-1-propanol using 0.3 equiv of IBX and 0.5 equiv of Oxone as the co-oxidant gave 3-phenylpropanoic acid in 51% and 58%, respectively. The yield of the acid product was, however, above 90% in both solvent systems when the amount of Oxone was increased to 1.5 equiv. These results from our initial but limited solvent optimization studies were encouraging and significant for the following reasons. The product from the four attempts were the corresponding carboxylic acid and not the aldehyde, the usual oxidation product of primary alcohols using IBX.[4a,b] Recently reported easy oxidation of aldehydes to the corresponding acids using Oxone clearly offers an explanation for the formation of acid products from these reactions.[13] Control oxidation reactions carried out using Oxone and 3-phenyl-1-propanol returned the starting alcohol, confirming the inability of Oxone to oxidize alcohols to carbonyl compounds efficiently. The formation of 3-phenylpropanoic acid in yields more than 30%, which would have been the maximum yield obtained if IBX was not being regenerated in the reaction medium, was gratifying and indicative of a ready reoxidation of IBA back to IBX during the reaction. At this juncture we realized that the implications of this observation go beyond the simple regeneration of IBX but also allude to the possibility of using the less hazardous IBA or even commercially available 2IBAcid as precursors to catalytic amounts of IBX needed for oxidation reactions.

Our attention was then turned to identify the optimum molar ratios of IBX (or IBA or 2IBAcid) and Oxone required to effect quantitative conversion of primary alcohols to the corresponding carboxylic acids. Table 1 lists our optimization results from such an investigation. We reasoned that potassium persulfate present in Oxone[10] is the active oxidant responsible for the (re)oxidation of IBA and 2IBAcid to IBX, as well as for the oxidation of the initially formed aldehyde to carboxylic acid. The theoretical yield of carboxylic acid, calculated on the basis of the total availability of oxidants and its consumption in each reaction, is given in parantheses in the yield column in Table 1. A cursory evaluation of the summarized results reveals that the two instances where appreciable amounts of aldehyde product is observed is when the molar amount of Oxone present is less than the amount of IBX present in the reaction mixture. Though we have not investigated this optimization study in greater detail and at the rigorous exclusion of oxygen, these preliminary results are an indication that the Oxone-facilitated reoxidation of IBA back to IBX is likely faster than the oxidation of aldehyde to carboxylic acid by the same reagent. This

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(6) (a) Mûlbaier, M.; Giannis, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4393−4394. (b) Sorg, G.; Mengel, A.; Jung, G. *Angew. Chem., Int. Ed.* **2001**, *39*, 4395−4397.

(7) Ozanne, A.; Pouységu, L.; Depernet, D.; François, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903−2906.

(8) Thottumkara, A. P.; Vinod, T. K. *Tetrahedron Lett* **2002**, *43*, 569−572.

(9) Moore, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001−3003.

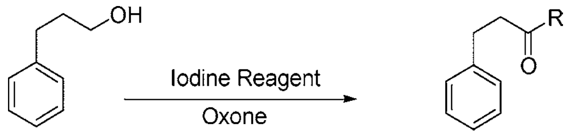
(10) Oxone is commercially available from Aldrich Chemical Co. and is a 2:1:1 molar mixture of $KHSO_5$, $KHSO_4$, and K_2SO_4. For the use of Oxone in the oxidation of 2-iodobenzoic acid to IBX, see: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

(11) Bunton, C. A.; Foroudian, H. J.; Gillitt, N. D. *J. Phys. Org. Chem.* **1999**, *12*, 758−764.

(12) Webb, K. S.; Ruszkay, S. J. *Tetrahedron* **1998**, *54*, 401−410.

(13) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031−1034.

Table 1. Efficiency of Oxone as a Co-oxidant[a]



reagent (equiv)	Oxone (equiv)	yield, % (R = OH)	yield, % (R = H)
IBX, 0.2	0.3	26 (40)[b]	trace
IBX, 0.3	0.65	62 (70)[b]	trace
IBX, 0.3	1.5	93 (100)[b]	trace
IBX, 0.5	0.4	50 (65)[b]	28
IBX, 0.6	0.3	63 (75)[b]	18
IBX, 0.3	0.9	80 (90)[b]	trace
2IBAcid, 0.2	0.8	52 (70)[b]	trace
2IBAcid, 0.3	1.15	92 (100)[b]	trace

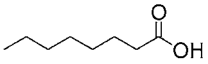
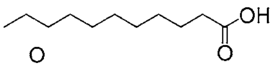
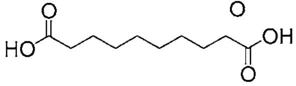
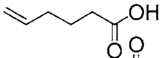
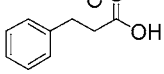
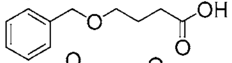
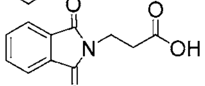
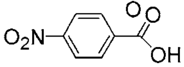
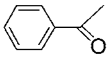
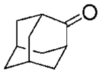
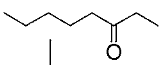
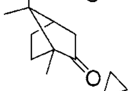
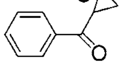
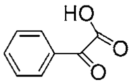
[a] All reactions were carried out at 1.5 mmol scale at 70 °C for 6h. [b] Theoretical yield of acid based on the total consumption of available oxidants are given in parenthesis.

conclusion is based on the fact that the Oxone present in the reaction medium can only effect the oxidation of aldehydes to acids and IBA (or 2IBAcid) to IBX and cannot oxidize primary alcohols to carboxylic acids (vide supra). Therefore, once all of the Oxone present in the reaction medium is consumed, the only oxidation that can occur is the selective oxidation of the primary alcohol to the aldehyde by the regenerated IBX, resulting in the isolation of the aldehyde product. This optimization study clearly indicated to us that commercially available and less expensive 2IBAcid can be successfully used as a precursor for IBX in these oxidation reactions. The scope and viability of using 2IBAcid as a precursor to the required catalytic amount of IBX is demonstrated through efficient oxidation of several primary and secondary alcohols (vide infra).

Table 2 lists a variety of alcohols, both primary and secondary, oxidized by the catalytic use of in situ generated IBX in the presence of Oxone. Several salient features of the protocol are readily apparent. The use of 2IBAcid in catalytic amounts and the use of aqueous mixtures of organic solvents as the reaction medium are both desirable goals of eco-friendly approaches to carrying out chemical transformations. The protocol is widely applicable and tolerates the presence of a wide range of substituents on substrates (entries 4, 6−8, and 13). Oxidation of both primary and secondary alcohols occurs in good to excellent yields. While primary alcohols are cleanly oxidized to the corresponding carboxylic acids, oxidations of secondary alcohols to ketones are not complicated by the undesired accompaniment of Bayer−Villiger oxidation of ketones due to the presence of Oxone in the reaction. Oxidation of vicinal alcohol (entry 14) does not result in the cleavage of the C−C bond, and a sensitive group such as a cyclopropyl moiety survives the reaction conditions (entry 13). Also noteworthy is the fact that the oxidation of 5-hexene-1-ol cleanly provided the corresponding acid without affecting and/or oxidatively transforming the double bond. The oxidation of 1,10-decanediol to sebacic acid in 97% yield was achieved using only 0.4 equiv of 2IBAcid along with 2.8 equiv of Oxone, clearly indicating a promise for achieving an acceptable turnover number for the present catalyst system.

Table 2. Scope of Substrates

$$\text{R-OH} \xrightarrow[\text{Oxone}]{\text{2IBAcid}} \text{Product}$$

entry	product	#eq. 2IBAcid/#eq. Oxone	yield
1		0.3/1.3	93
2		0.3/1.3	95
3		0.4/2.8	97
4		0.2/1.3	94
5		0.4/1.2	93
6		0.4/1.5	87
7		0.3/1.3	92
8		0.3/1.3	90
9		0.3/0.8	74
10		0.3/0.8	80
11		0.2/1.0	90
12		0.3/0.8	94
13		0.3/1.0	89
14		0.2/1.8	94

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(14) **General Procedure for Oxidation of Alcohols.** To a solution of the alcohol substrate (1.5 mmol) in acetonitrile/water (20 mL, 2:1 v/v) was added the required amount of the catalytic oxidant (IBX, IBA, or 2IBAcid) and the required amount of Oxone (see text). The mixture was then maintained at 70 °C for 6 h and subsequently cooled in an ice bath to completely precipitate the insoluble hypervalent iodine byproduct, which was then removed by filtration. The precipitate was successively washed with water (2 × 10 mL) and dichloromethane (2 × 10 mL), and the combined filtrate was subsequently extracted with dichloromethane (2 × 20 mL). The organic extract was then treated as follows depending on whether a primary or secondary alcohol was being oxidized. The organic extract obtained from the workup of a primary alcohol oxidation reaction was dried ($MgSO_4$) and evaporated to yield the carboxylic acid product, sometimes contaminated with ca. 2−5% of 2-iodobenzoic acid derivatives, requiring column chromatographic purification. The organic extract obtained from the oxidation of secondary alcohols was subsequently washed with aqueous sodium bicarbonate (15% solution, 30 mL) to remove the acidic impurities, dried ($MgSO_4$), and evaporated to yield ketones in essentially pure form.

We anticipate that the simplicity and catalytic nature of the system, the recyclability of the catalyst, and the use of aqueous solvent systems as the reaction medium will make the protocol appealing to synthetic chemists, especially to those practicing greener approches to synthetic chemistry.[14]

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Supporting Information Available: Experimental procedures and characterization data and copies of ^{1}H NMR spectra of selected products that are not commercially available. This material is available free of charge via the Internet at http://pubs.acs.org.

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