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AN INSIGHT IN TO GENERAL FEATURES OF IBX (2-IODOXYBENZOIC ACID)

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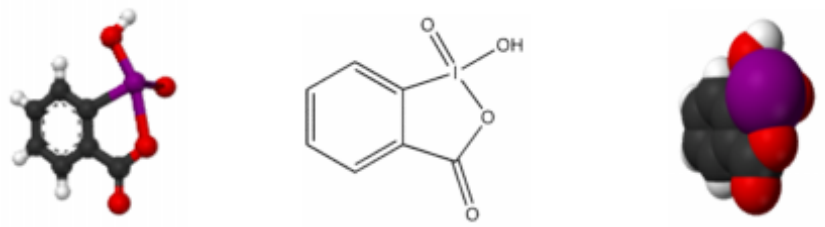
ABSTRACT

IBX acid or 2-iodoxybenzoic acid is an organic compound used in organic synthesis as an oxidizing agent. This Periodinane is especially suited to oxidize alcohols to aldehydes. The IBX acid is prepared from 2-iodobenzoic acid, potassium bromate and sulfuric acid[1]. Frigerio and co-workers have also demonstrated, in 1999 that potassium bromate may be replaced by commercially available Oxone[2]. One of the main drawbacks of IBX is its limited solubility; IBX is insoluble in many common organic solvents. In the past, it was believed that IBX was shock sensitive, but it was later proposed that samples of IBX were shock sensitive due to the residual potassium bromate left from its preparation.[3,4] Commercial IBX is stabilized by carboxylic acids such as benzoic acid and isophthalic acid.



Structure of IBX

Key words: IBX (2-Iodoxybenzoic acid), Oxidizing agent, Shock sensitive.

INTRODUCTION

The reaction mechanism for an oxidation of an alcohol to an aldehyde according the so-called hypervalent twisting mechanism[6] involves a ligand exchange reaction replacing the hydroxyl group by the alcohol followed by a twist and a elimination reaction. The twist is a requirement because the iodine to oxygen double bond is oriented out of plane with the alkoxy group and the concerted elimination would not be able to take place. This twist reaction is a rearrangement in which the oxygen atom is moved into a proper plane for a 5 membered cyclic transition state in the elimination reaction and is calculated by Computational chemistry to be the rate-determining step in the oxidation. The twist mechanism also explains why oxidation is faster for larger alcohols than for small alcohols. The twist is driven forward by the steric hindrance that exists between the ortho hydrogen atom and the protons from the alkoxy group and larger alkoxy groups

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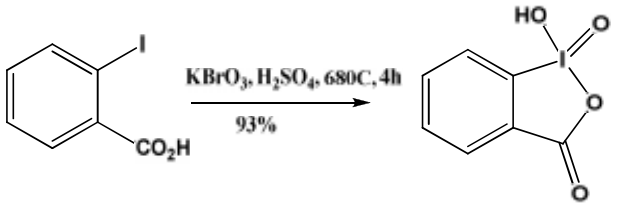
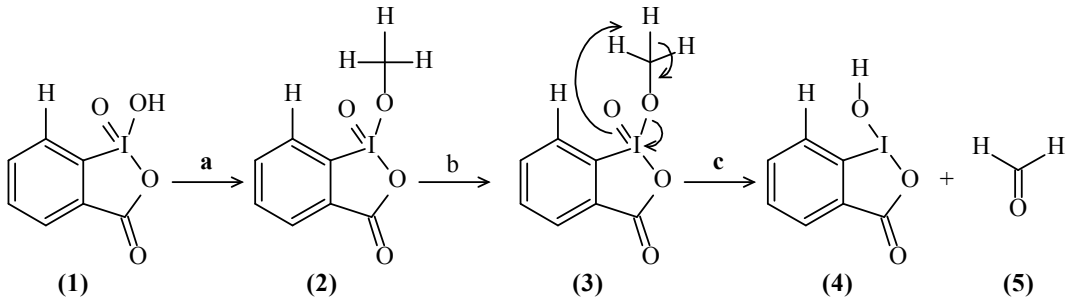
create larger steric repulsion. The same computation predicts a much faster reacting IBX derivative with a 100 fold reaction rate when this ortho hydrogen atom is replaced by a methylgroup thus facilitating the twist until the elimination reaction takes prevalence as the rate determining step.

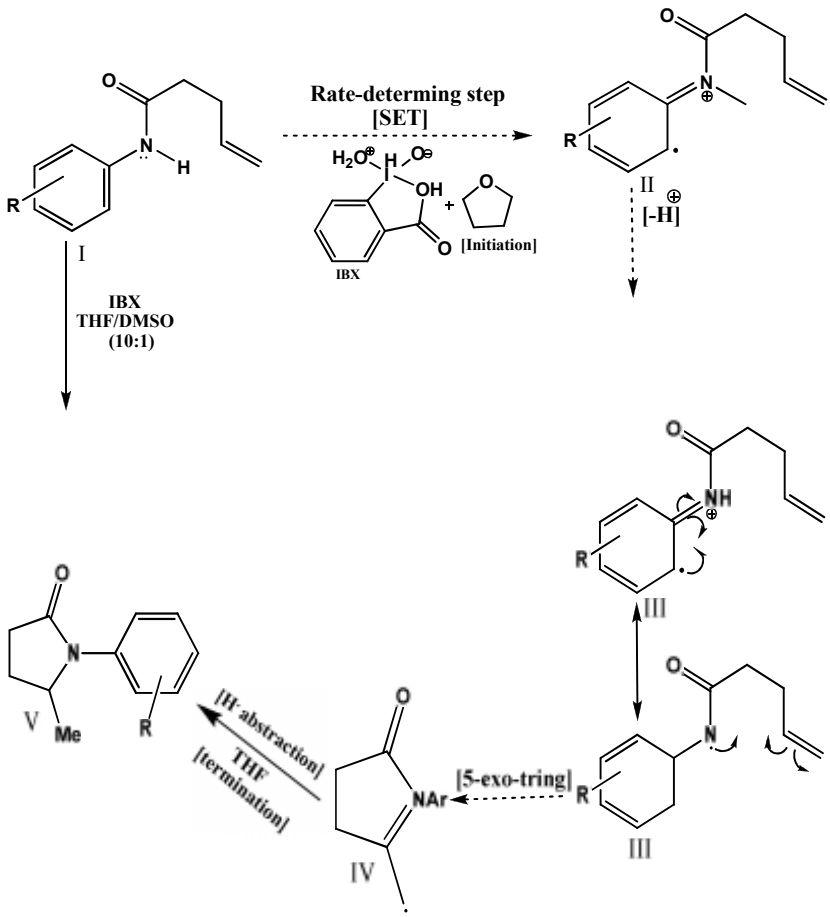
Preparation of IBX[5]



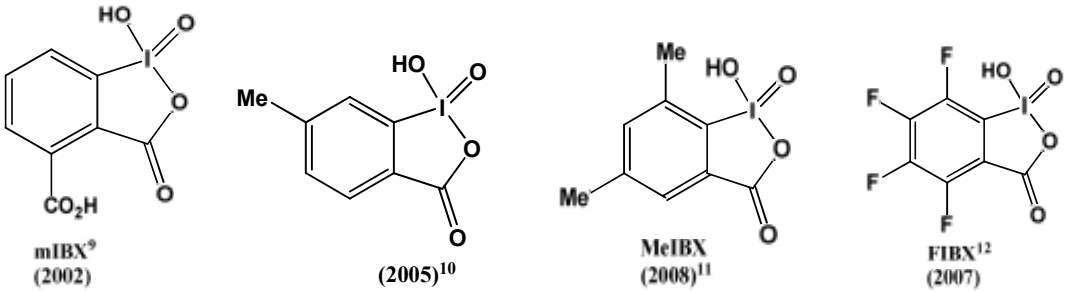
Reaction mechanism



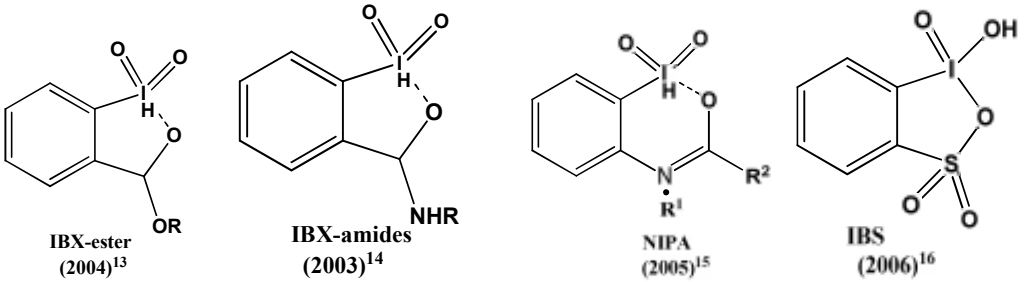
Mechanism of IBX Cyclization[7,8]



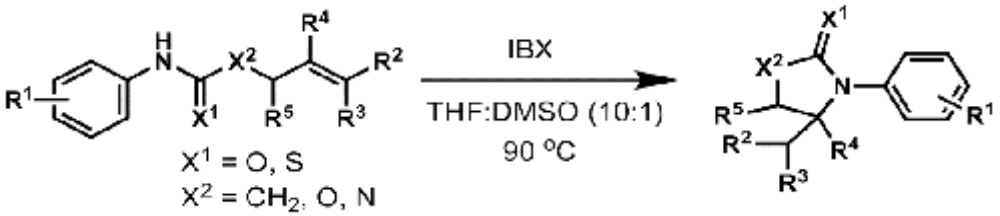
Arene-modified IBX Analogs[9-12]



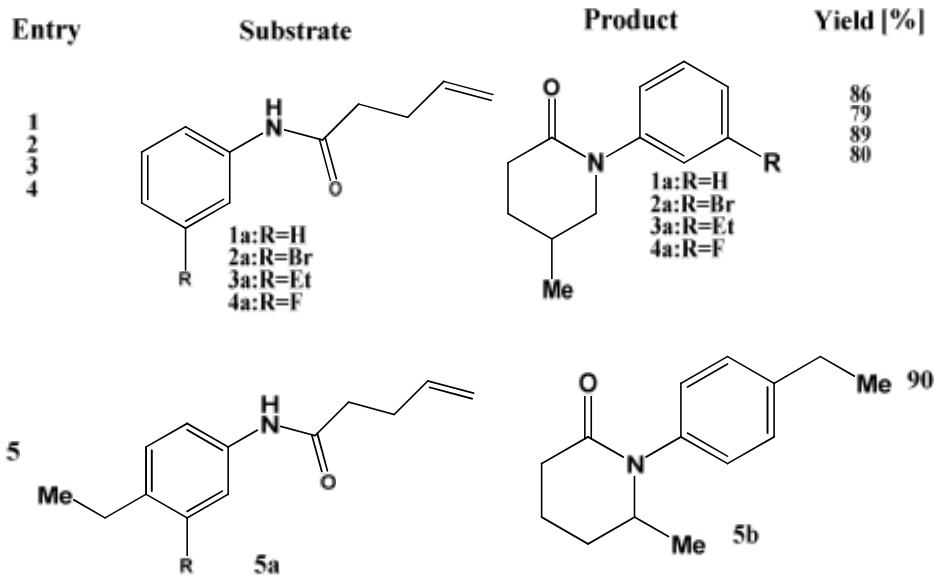
Ortho-group-modified IBX Analogs[13-16]

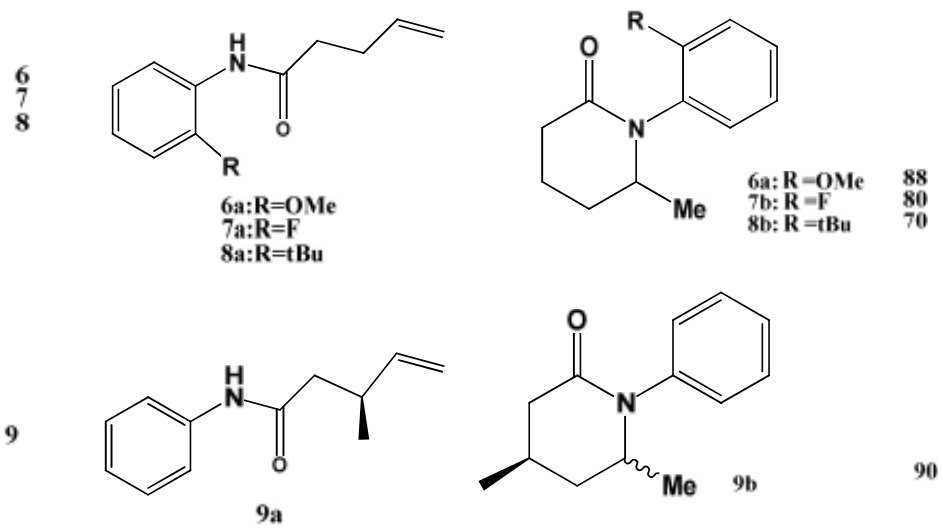


IBX Mediated formation of heterocycles[17]

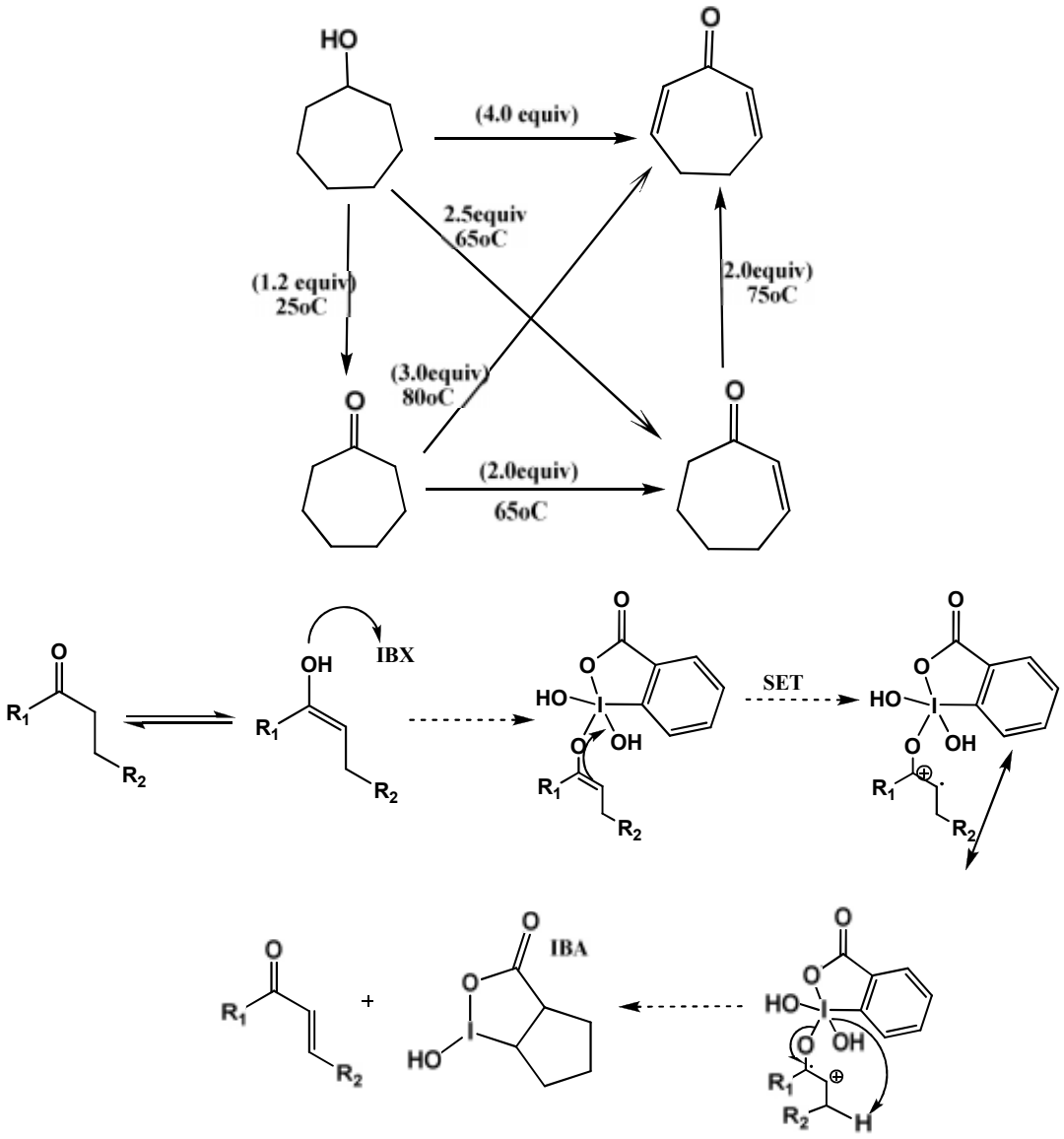


IBX Mediated formation of heterocycles[18]

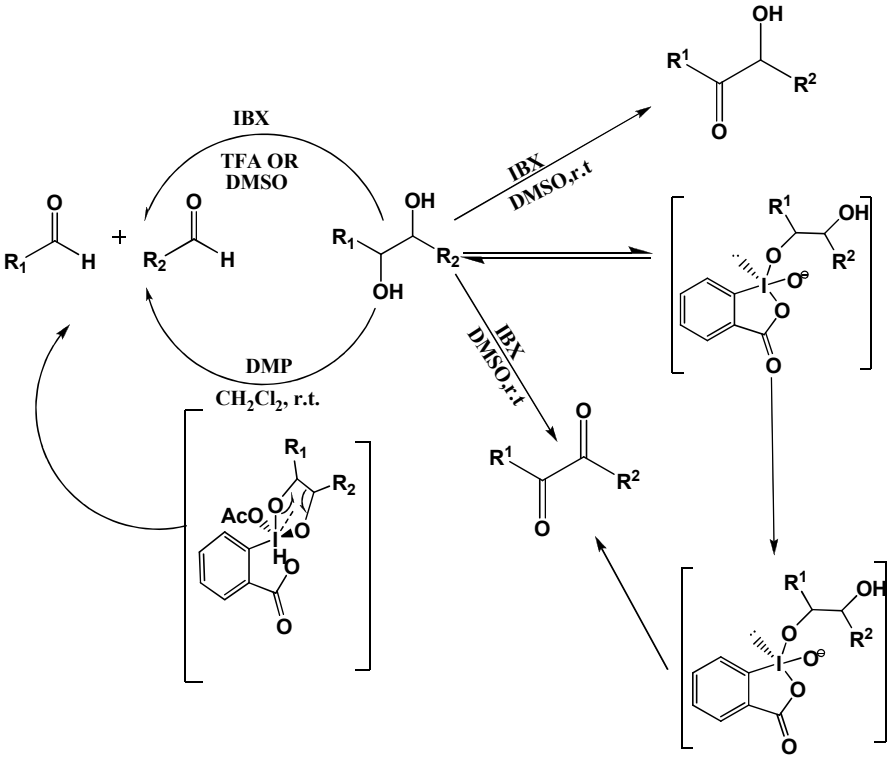




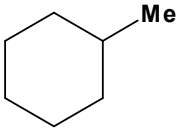
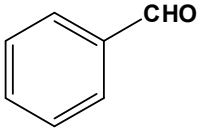
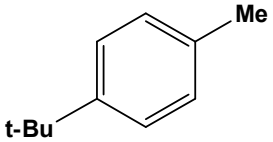
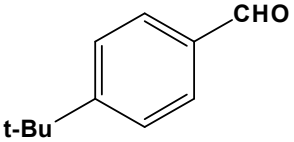
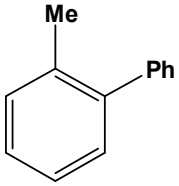
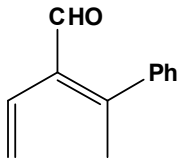
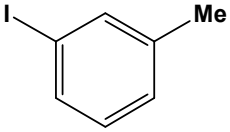
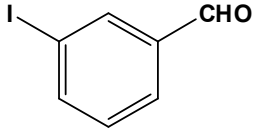
Synthetic applications of IBX α.β-unsaturated), IBX in DMS[19]

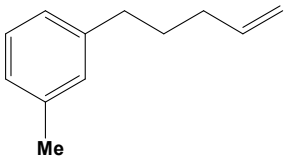
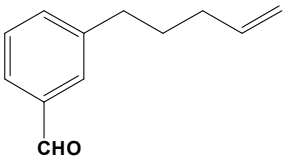
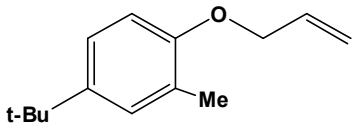
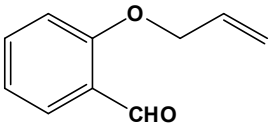
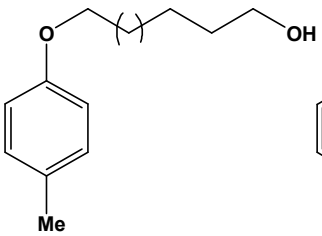
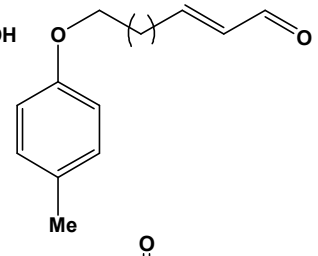
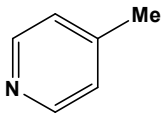
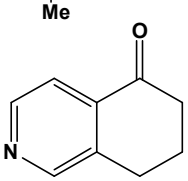


Synthetic applications of IBX (1, 2-diols)[20]



Benzylic oxidation of IBX[21,22]

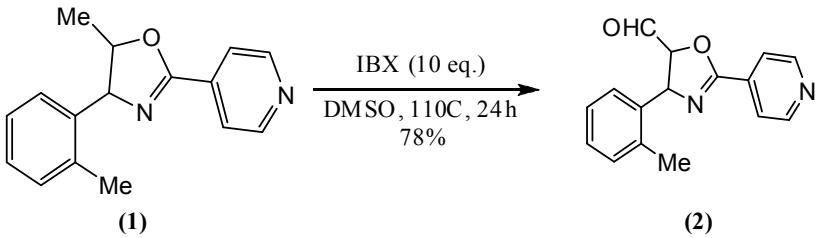
Entry	Substrate	Product	Condition	Yield %
1			IBX (3 eq) 85^{0}C, 12h	85
2			IBX (3 eq) 85^{0}C, 8h	95
3			IBX (3 eq) 85^{0}C, 8h H_2O (100 eq)	90
4			IBX (4 eq) 85^{0}C, 16h	78

Entry	Substrate	Product	Condition	Yield %
1			IBX (3 eq.) 80^{0}C, 8 h	88
2			IBX (3 eq.) 80^{0}C, 12 h	80
3			IBX (3 eq.) 65^{0}C, 8 h	75
4			IBX (4 eq.) 85^{0}C, 12 h	70

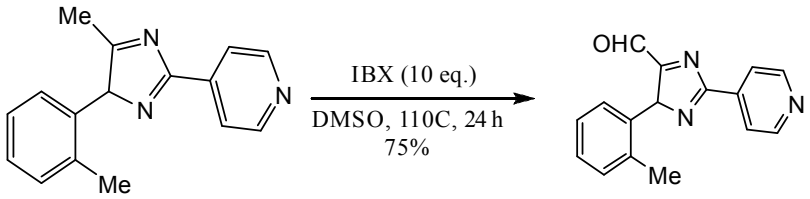
Types of oxidation with IBX

1. Selective oxidation of substituted oxazoles with IBX

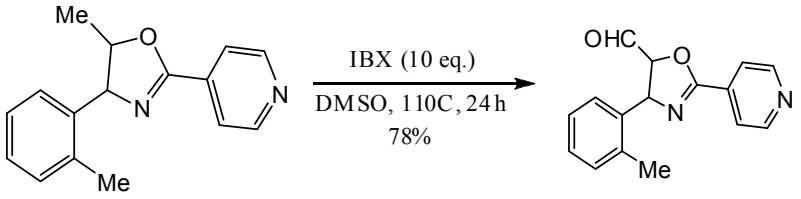
The bis-methyl substituted pyridyl oxazoles 1-3 were chosen for their resistance to undergo oxidation at either methyl group with a variety of known oxidants[23]. In the event, compounds 1-3 were oxidized at 110°C employing 10 equiv of IBX in DMSO, furnishing aldehydes 4-6 in 75-78% isolated yield.



(1) **(2)**



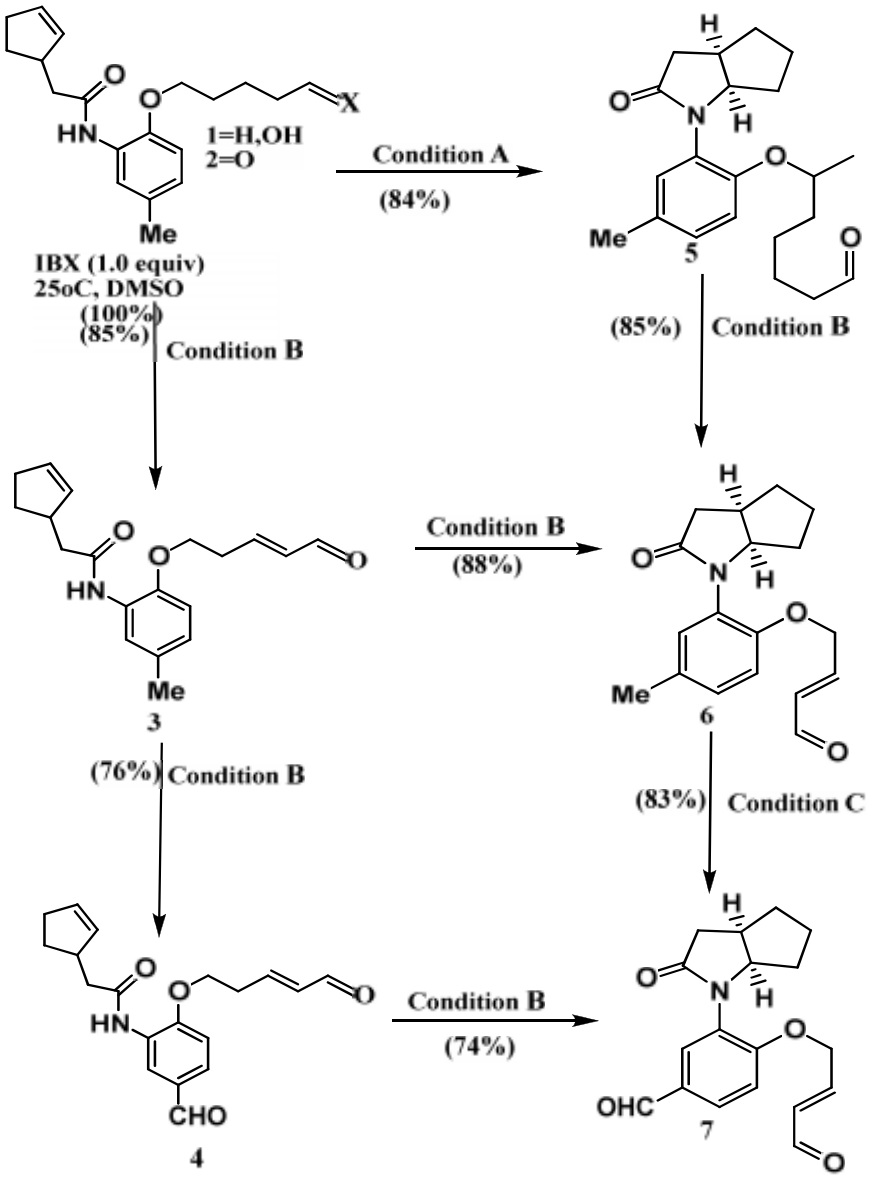
(3) **(4)**



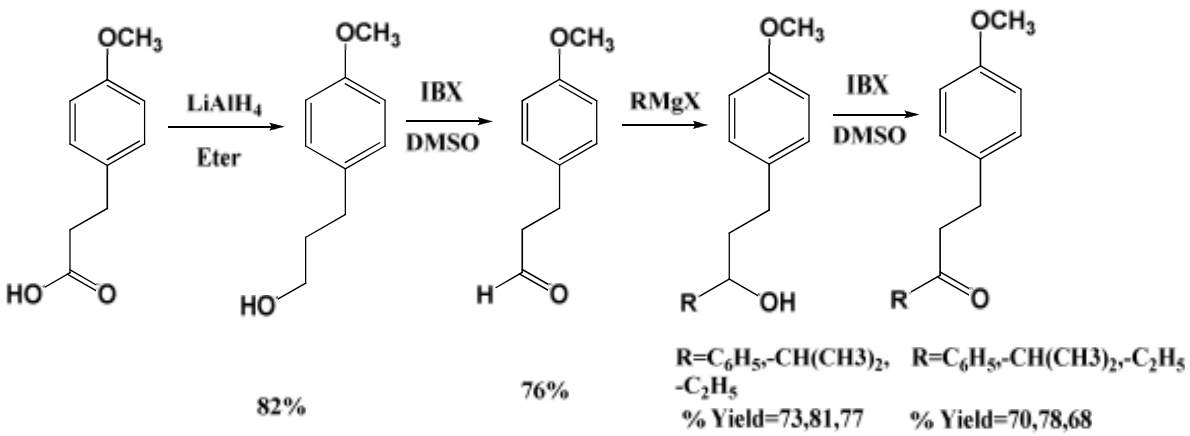
(5) **(6)**

2. Selective chemical transformations with IBX

Finally, to probe the selectivity and controllability of the recently discovered IBX-based oxidations, we designed and synthesized compound **1** to be used as a substrate. Using only three standard conditions, 1 could be easily converted into **2-7**. Thus, treatment of **1** with 2.0 equiv of IBX at 65°C in fluorobenzene/DMSO (2:1) in the presence of catalytic amounts of TsOH (conditions B, Scheme 4) led to R unsaturated aldehyde **3** in 85% isolated yield. Further oxidation of **3** with 3.0 equiv of IBX in DMSO at 90°C (conditions C) furnished fully oxidized compound 4 in 76% isolated yield. Compounds **1-4** could be converted to **5-7** simply by employing IBX and THF/DMSO as the solvent system (conditions A). Alternatively, **5** could also be cleanly converted to **6** by conditions B, which, in turn, was smoothly transformed to **7** by conditions C[24].



Methoxy phenyl propionic acid and some derivatives are converted to ketones using a new method. All classical methods to obtain ketones from carboxylic acids via acid halide consistently gave very low yields and regularly generated intermolecular cyclisation products or polymeric materials. However, high ketones yields are obtained by using the new IBX method[25].



This new method depends on the reduction and oxidation of the carbonyl groups. In these reactions, oxidation is carried out with the new oxidation reagent, IBX (o-iodoxybenzoic acid), which has recently been found to be a good oxidation agent. Cheap and non-toxic, IBX, a selective oxidation reagent, is therefore very suitable for oxidising alcohols to aldehyde or ketones. Firstly reduced the acids to alcohols with $LiAlH_4$[26-30] and then oxidised them with IBX to form aldehyde. After the mono alkylation of aldehydes with the Grignard reagent (RMgX), the obtained alcohols were re-oxidised with IBX to the ketones. High ketone yields are the result.

Among oxidizing agents, 2-iodoxybenzoic acid (IBX) stands out for being mild, selective, and environmentally friendly, as it contains no toxic or expensive heavy metals, and variants exist that operate in aqueous solution. IBX effects oxidations of functionality beyond simple alcohols[31,32].

A modification of IBX predicted to increase its oxidizing power while preserving its selectivity, based on a new mechanism in which the rate-limiting step is hypervalent twisting. Our mechanism, derived from density functional quantum mechanics (QM) calculations[33], also explains the native alcohol size selectivity of unmodified IBX.

Hypervalent twisting is a coordinated motion of ligands driven by the necessity of generating a stable, planar form of the byproduct IBA 4 from an IBX-alcohol intermediate 3 (Figure 1). The proposed modification, substitution of IBX at the ortho position, lowers the barrier of this step. Since the rate-accelerating ortho position is near the site of substrate binding, it offers a possible route to an oxidant capable of chiral discrimination[34].

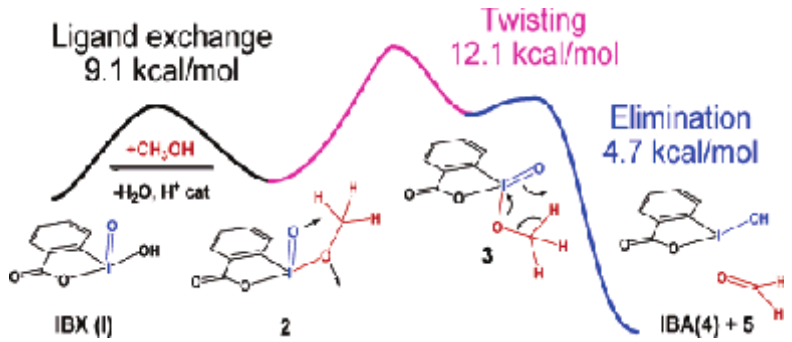
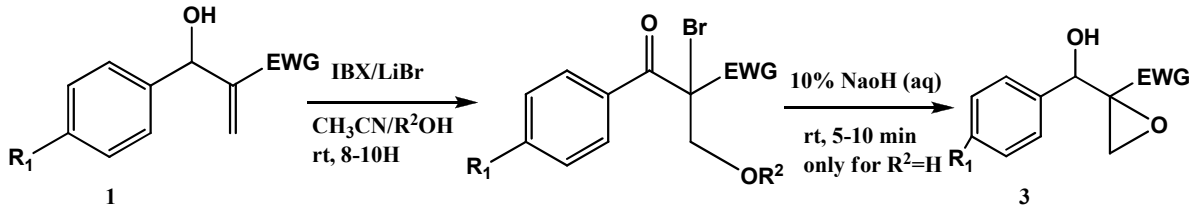


Fig. 1: Hypervalent twist (HT) mechanism showing the reaction path and associated barriers for oxidation of alcohols by IBX (barriers relative to reactants at each step). The coordinated motion that converts intermediate 2 to 3 is the rate-limiting step of the reaction

Comparative study of IBX, $NaIO_4$, and CAN

Amongst various hypervalent iodine reagents, 2-iodoxybenzoic acid (IBX) has become the reagent of choice due to easy handling, ready availability, tolerance of moisture[35] mild reaction conditions and zero toxic waste generation. IBX selectively oxidizes alcohols in the presence of olefins, thioethers and amino groups[36].

The first example of IBX/LiBr-promoted one-pot oxidative bromohydroxylation and bromoalkoxylation of BH adducts **1**, which opens up a new aspect of the synthetic utility of BH adducts. In order to optimize reaction conditions, we carried out bromohydroxylation[37] of the representative BH adduct **1** using KBr, NaBr, or LiBr as the bromine source and $NaIO_4$, CAN, or IBX as the oxidant. Among these, LiBr and IBX gave the best results in terms of the yield of bromohydrin 2 (86%) under the reaction conditions[38].

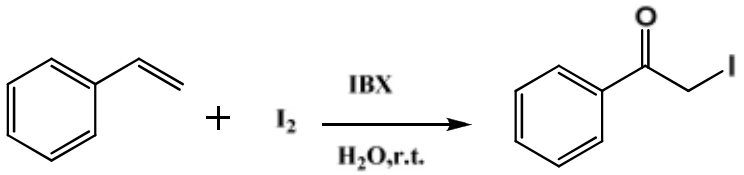


1 **2,** R^2**=H, Yield 81-89%** **3**

EWG=CN, COOMe **4,** R^2**=Me, Et, Yield 78-87%** **84-94%**

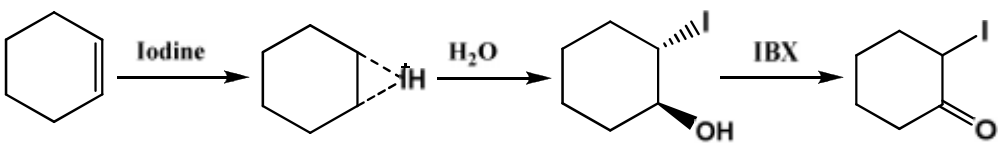
IBX/LiBr-promoted oxidative bromohydroxylation and bromoalkoxylation of BH olefins 1

Thus, the overall yield of 2 (86%) is significantly higher in the case of IBX than in the case of $NaIO_4$ (51%) or CAN (42%). The first direct and metal catalyst-free oxidation of alkenes and alkynes using the IBX/I_2 reagent system to produce a-iodoketones under mild conditions. Initially, we examined the oxidation of styrene **1** using 1.2 equiv of IBX and 1.0 equiv of iodine **2** in water. The reaction proceeded smoothly at room temperature and the desired product, 2-iodo-1-phenylethanone 3 was obtained in 86% yield.



1 **2** **3**

Mechanistically, it is possible that iodine interacts with the alkene to generate cyclic iodonium ion, which reacts simultaneously with water to form an iodohydrin. The in situ formed iodohydrin reacts immediately with IBX to produce the a-iodoketone as shown in.

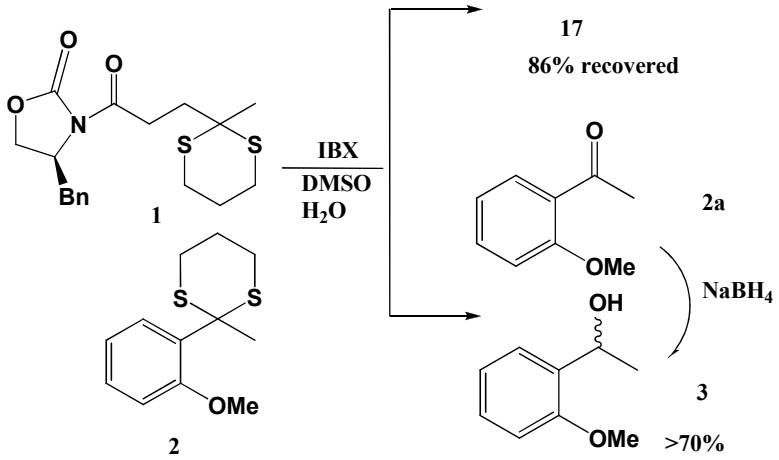


A plausible reaction mechanism

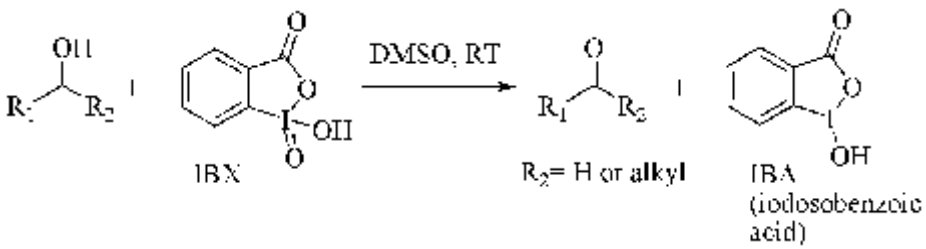
In conclusion, IBX/I_2 has proved to be an effective reagent system for the preparation of a-iodoketones from alkenes and alkynes under mild conditions. The combination of IBX and water makes this method simple, convenient and user-friendly[39].

Our deprotection of 'activated' dithianes/ditholanes (e.g. those at benzylic and allylic positions) was realized by treatment of the substrate with *o*-iodoxybenzoic acid[40,41] (IBX) in DMSO containing traces of added water.

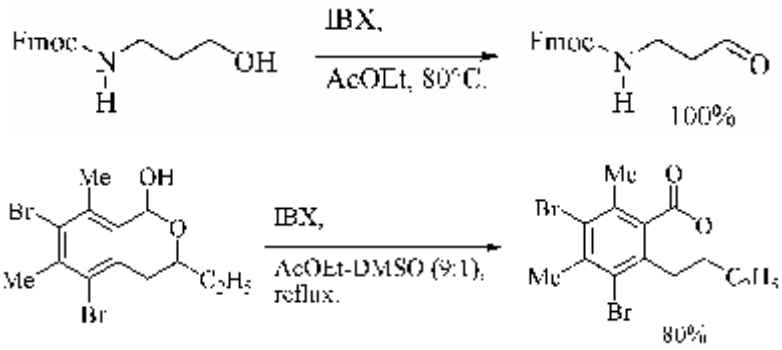
To have a closer comparison of the selectivity between the activated and non-activated substrates we carried out competition tests. Thus, an equimolar mixture of **1** and **2** was treated with 1.5 molar equiv. of IBX at 22–26°C (ambient temperature)[42] for 9 h. The resulting reaction mixture was worked up and further treated with NaBH to reduce the resulting aromatic ketone (because **2a** had the same *R*4 as that of **2** on TLC) into the corresponding alcohol **3**. Column chromatographic separation gave **3** and theunreacted starting **2** in 70% and 86% yields (with some loss of material during the work-up), respectively.



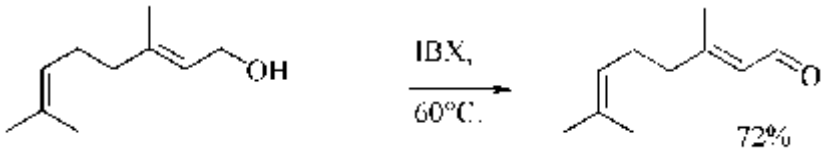
Frigerio and Santagostino[43] reported in 1994 the first successful oxidation of a variety of alcohols with IBX in DMSO, the only solvent in which its solubility is appreciable. IBX is easily accessible, non-toxic and insensitive to the presence of air or moisture[44]. IBX is commercially available but could be prepared by oxidation of 2-iodoxybenzoicacid (2IBX Acid) with oxone[45]. Unfortunately, DMP and IBX decompose violently under impact and/or heating (>200°C), clearly limiting industrial applications[46]. However, as we will see, SIMAFEX a French company developed and patented a non-explosive white-powder formulation of IBX composed of a mixture of IBX itself (49%), isophthalic acid (29%) and benzoic acid (22%)[47].



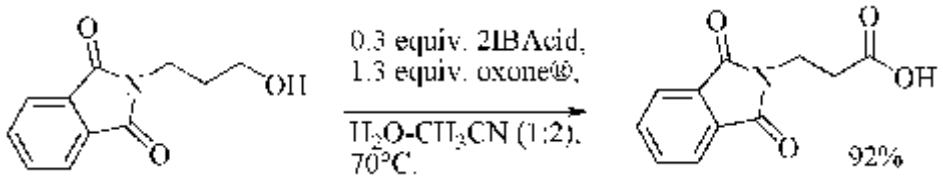
At elevated temperature, IBX is soluble in most solvents to carry on oxidation of alcohols[48,49]. Best results were obtained with EtOAc or DCE as solvent: byproducts are insoluble at RT and therefore removed by simple filtration. It should be pointed out that in these conditions, toluene (vide infra) and THF used as solvent are oxidized in benzaldehyde and butyrolactone, respectively.



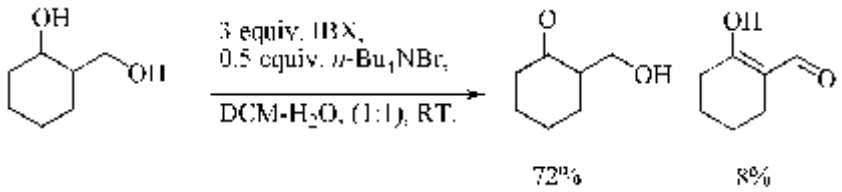
Oxidation of allylic and benzylic alcohols to corresponding carbonyl compounds have been efficiently achieved under solvent-free conditions at elevated temperature, as well as oxidation of aromatic aldehydes to[50].



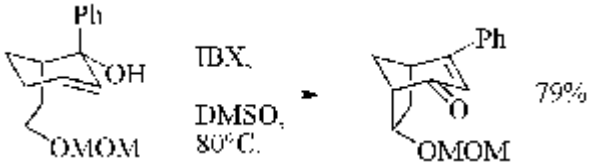
An efficient protocol for oxidation of alcohols by in situ generation of IBX from catalytic amounts of 2IBA acid in the presence of oxone as co-oxidant is published very recently[51]. In these conditions, oxone oxidizes not only IBA (the reduced formed of IBX), but also the aldehyde intermediates into acids.



A good chemo selective oxidation of secondary alcohol to ketone in the presence of primary alcohol was observed with 1 IBX and n-Bu_4 NBr as a phase transfer catalyst in the DCM-water mixture[52].

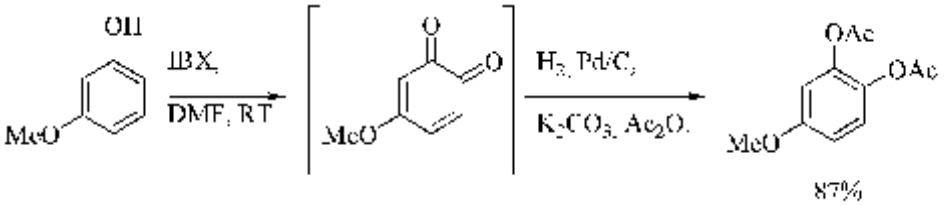


Oxidative rearrangement of five- and six-membered cyclic tertiary allylic alcohols was performed with IBX[53].

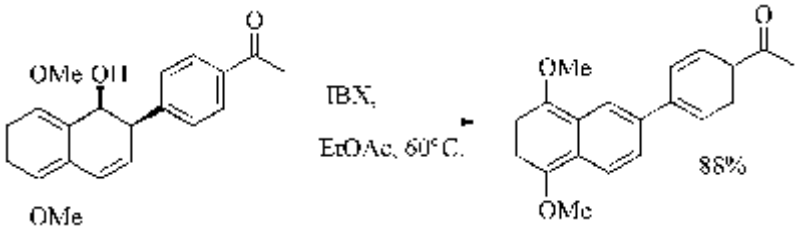


Oxidation of various phenolic compounds to o-quinone intermediates were reported with IBX. In DMF at RT, phenols containing at least one electron-donating group led regioselectively to o-quinones, which were reduced in situ to the corresponding catechols[54]. In a CHCl /MeOH mixture at low temperature,

the phenolic oxidation was found to be less regioselective but could be expanded to phenol itself[55]. Synthesis of o-benzothiophenquinones has been also reported using IBX[56].



2-Substituted cis-1, 2-dihydronaphthols were oxidized to their corresponding naphthols with IBX in EtOAc or acetone as outlined in this transformation was examined without success with numerous oxidants[57].



Biologically important process of oxidation of amidoximes has been investigated using IBX (*o*iodoxybenzoic acid) and combination of IBX with TEAB (tetraethylammonium bromide).The reaction proceeds with high % conversion leading to selective formation of amide and nitrile depending upon the combination of reagents**.**

Oxidations with IBX

Investigations were initiated with IBX as oxidant using benzamidoxime **1a** as the substrate (Table 1). Reactions were performed in acetonitrile-water mixture at room temperature with equimolar ratio of IBX and benzamidoxime **1a** and formation of both amide **2a** and nitrile **3a** was observed with some amount of starting material remaining unreacted (Table 1, entry 1). Upon increasing the reagent/substrate mole ratios, formation of nitrile **3a** increases.

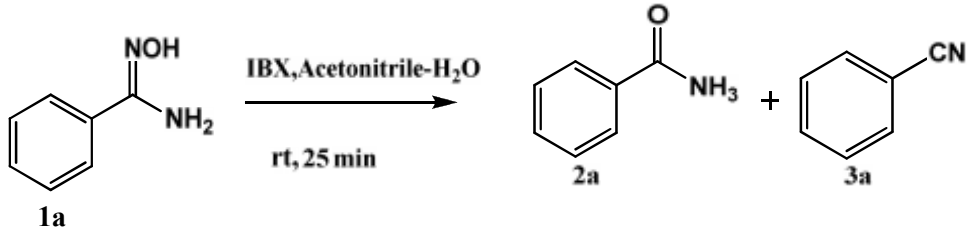
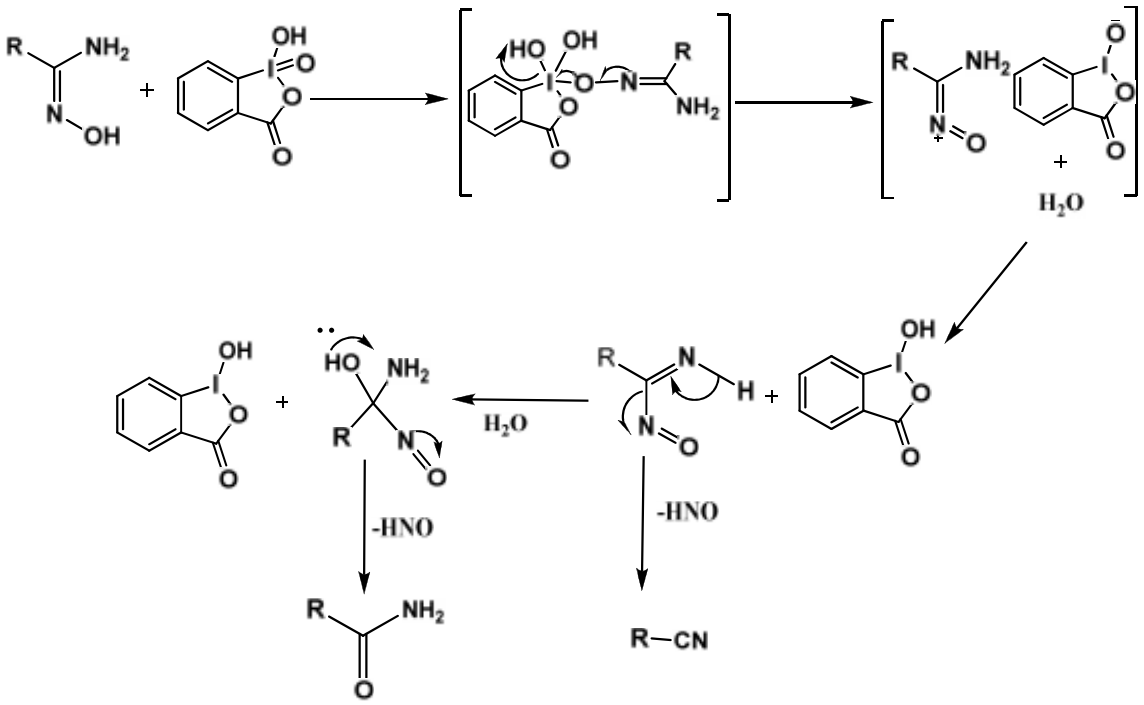


Table 1: Reaction of benzamidoxime 1a with IBX

Entry	Mole (IBX) ratio	Products	Yields (3a)	Unreacted 1a
1	1	76	7	15
2	1.5	83	10	-
3	2	69	20	-
4	2.5	52	40	-

IBX-mediated oxidations have been explained invoking both ionic as well SET mechanisms[58]. In the present case formation of amide as major product and in presence of water strongly suggest that the reaction might be proceeding predominantly by ionic mechanism as shown below.



Plausible mechanism of formation of amide and nitrile with IBX

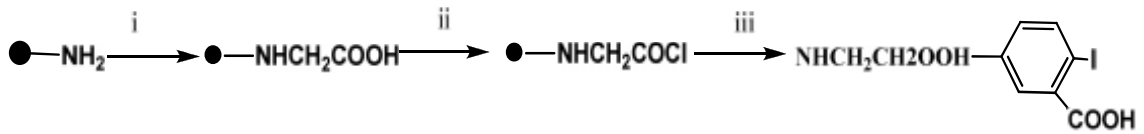
A mild, efficient, and environmentally friendly procedure for the oxidation of alcohols with polymer-supported IBX in the presence of N $(CH_2CH_3)_3$ in CH_2Cl_2 has been developed. This reagent has advantages over traditionally supported IBX reagents because of simplified preparation method and a high oxidation activity of 1.5 mmol/g.

Much effort has been devoted to the synthesis and applications of polymer-supported IBX reagents for the oxidation of alcohols in recent years[59–63].

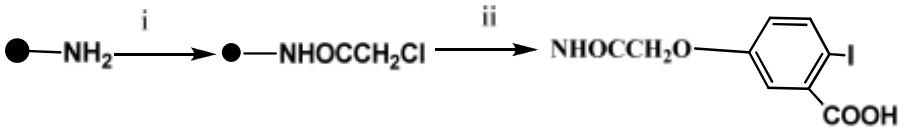
The oxidation of alcohols using supported-IBX as the oxidant prepared in the presence of the organic base $N(CH_2CH_3)_3$. This new oxidation system has all the advantages of using the solid-phase and also yielded high active component loadings of 1.5 mmol/g.

In order to evaluate the active component loadings of the polymers, excessive benzyl alcohol was treated with polymer-supported IBX in CH_2Cl_2 and the reaction mixture was analyzed by GC/MS after completion of the oxidation reaction.

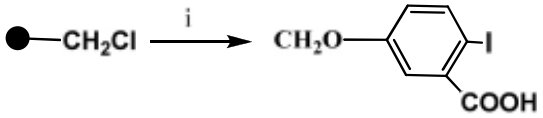
In this way, the active component loadings of the polymer-supported oxidant were determined and the results are shown in Table 2.



(1)

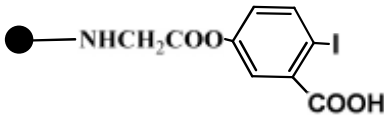
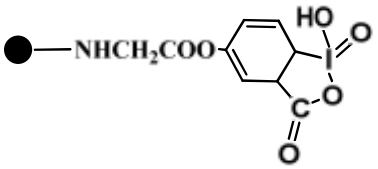
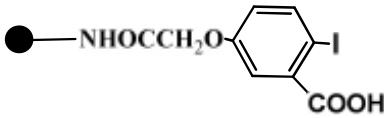
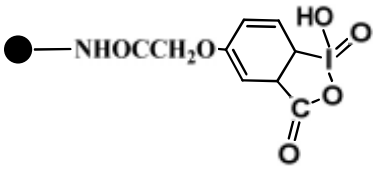
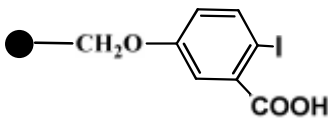
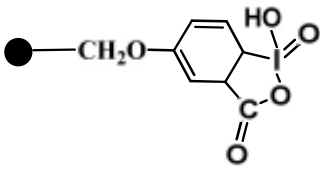
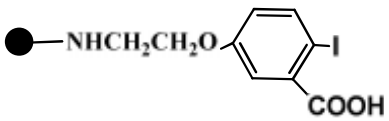
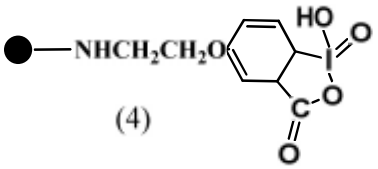


(2)



(3)

Table 2: The effect of different linkers on the loading of supported IBX

Supported 2-iodo-5-hydroxy benzoic acid supported IBX		Loading of supported IBX (mmol/g)
		**0.3**
		**0.6**
		**0.4**
	 (4)	**0.8**

The IBX is known to convert ketones into enones[64-66]. through a mechanism involving single electron transfer. When the ketone **1** was reacted with IBX in dimethylsulfoxide (DMSO) no desired enone **2** was formed; instead the diketone **4** was isolated in 70% yield. Although Nicolaou has reported that thioacetals are cleaved with IBX[67-69].

We were surprised to find that ketals also react with IBX to form ketones (Table 1). Treatment of the silyl enol ether **8** with IBX in DMSO gave a mixture of the diketone **4** and the enone **9** showing that deprotection of the ketal moiety together with oxidation of the silyl enol ether had taken place.

Of interest to note is that the bromide **13** does not react with IBX in DMSO. This would seem to suggest that the bromine atom present in **13** could inhibit single electron transfer; this antioxidant activity would hence prevent the ketal cleavage. In contrast to this, the a-chloroenone **6** deprotects to diketone **7**

under same conditions with excellent yield (81%). Similarly, the vinyl chloride **10** showed deprotection to ketone **11** followed by intramolecular hemiacetal formation to a ord **12** with acceptable yield (overall 69%).

The presence of **2** singlet carbons at 220.7 (C=O in 16) and 98.5 ppm (hemiketal C in 17) in broadband and other nmr-assignments clearly indicated the presence of both isomers **11** and **12** in an unequal ratio. It is also interesting to note that the enol ether **8** reacts with IBX to form the diketone **4** together with the enone **1** which results from the oxidation of the enol ether moiety present. It is believed on the basis of observations that evidence exists for the cleavage of ketals by single electron transfer. Further support for the mechanism outlined below has been obtained by experimentation. When the dibromide **13** was added to ketone **1**, followed by the addition of IBX, no ketal cleavage was observed. The dibromide **13** is thus an inhibitor of the oxidative ketal cleavage.

Cleavage of acetals with IBX in DMSO

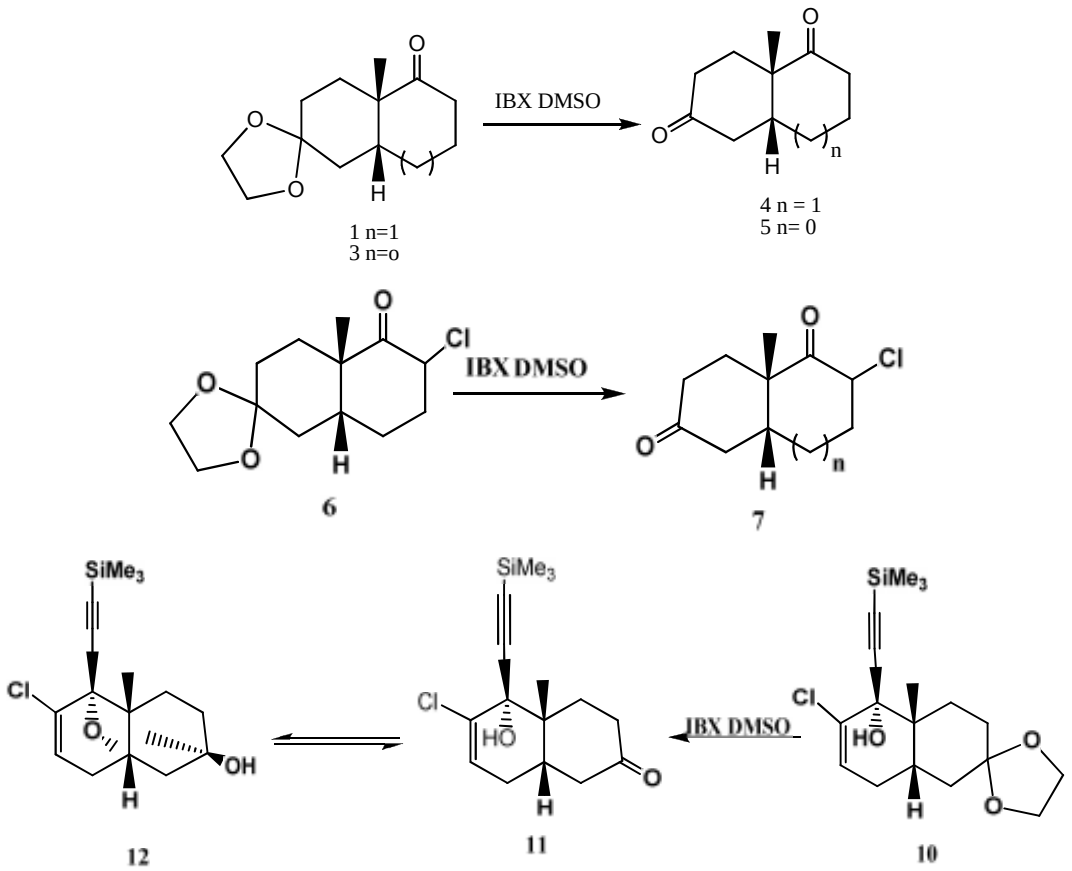
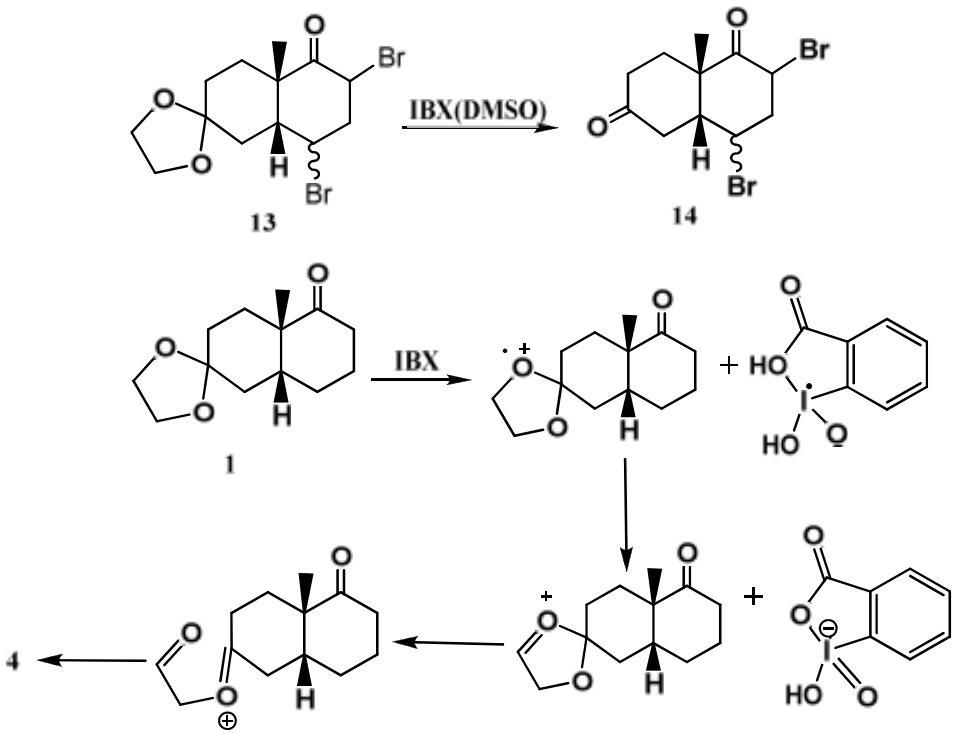


Table 3:

Entry	Compound	Temp. (^{o}C)	Time (hr.)	Products	Yield (%)
1	1	70	42	9	30
2	3	70	20	10	70
3	6	80	24	12	81
4	8	80	24	9 & 14	49, 39
5	10	80	22	16 & 17	69



IBX and analogous reagents

IBX and its analogs have attracted increasing interest as mild and selective oxidizing reagents. Solutions of IBX in DMSO are useful for the clean oxidation of alcohols to carbonyl compounds even in the presence of other functional groups. Specifically, the allylic alcohols **1** are selectively oxidized by IBX to ketones **2** in high yield[70].

The oxidation of alcohols **1** under similar conditions selectively affords 5-monosubstituted 3-acyl-4-*O*-methyl tetronates **4**, which are structurally similar to the tetrodecamycin antibiotics[71].

The IBX oxidation of diol **90** was applied in the synthesis of the functionalized hexahydroanthracene dione **7** a model for the D rings of taxoids[72].

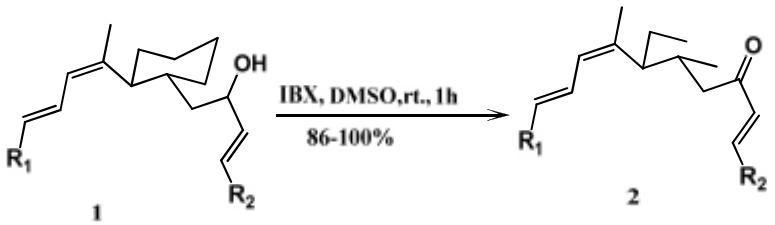
Likewise, the oxidation of diol **8** affords hemiacetal **9** a key precursor to the antifungal agent GM222712[73].

The IBX oxidation of carbohydrate **10** was used in the synthetic studies of moenomycin A disaccharide analogs[74].

The chiral rhenium complexes of allylic and propargylic alcohols **12** are selectively oxidized by IBX to the respective carbonyl derivatives **13** in good yields under mild conditions[75].

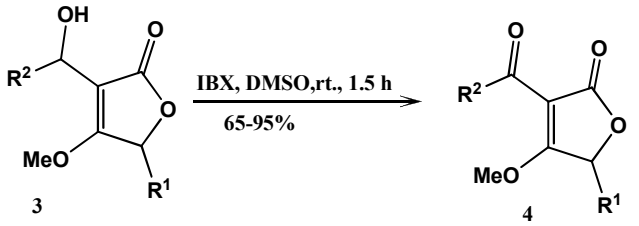
Benzylic, allylic, and propargylic alcohols, as well as diols, can be oxidized with IBX in the presence of the stabilized Wittig ylide **15** to generate α, β□-unsaturated esters **16** in one pot[76]. this is a useful procedure when the intermediate aldehydes are unstable and difficult to isolate.

The oxidation of alcohols with IBX in DMSO was also used in the development of a new silyl ether linker for solidphase organic synthesis[77], in the kinetic study of organic reactions on polystyrene grafted microtubes[78] and in the total synthesis of a cyclic depsipeptide somamide[79].



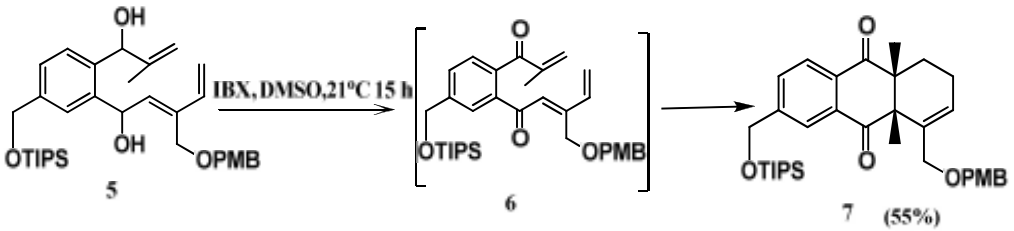
1 2

R^1=H, SPH; R^2 H, SO_2Ph, CO_2Me, Ts

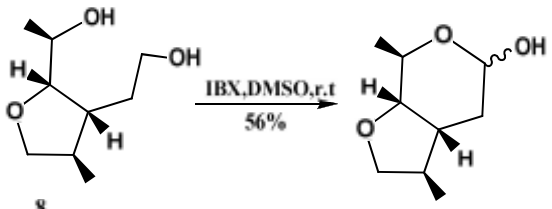


3 4

R^1=H,Me, R^2= i-Bu, Pr, Ph, $(CH_2)_2CH_2OTBDMS$

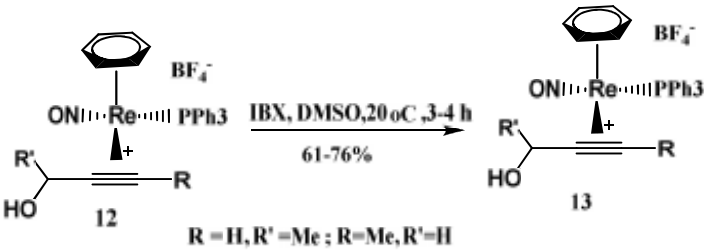


5 6 7 (55%)



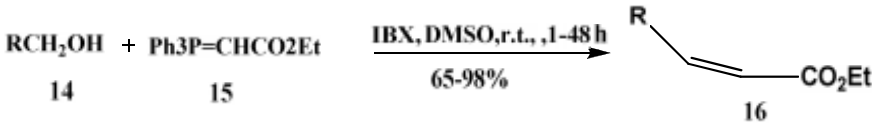
8 9

10 11



12 13

R = H, R' =Me ; R=Me, R'=H



14 15 16

R=Ph, PhCH, Me_2C=$CHCH_2CH_2$(Me)C=CH, HC≡C, C_5H_{11}C≡C,etc

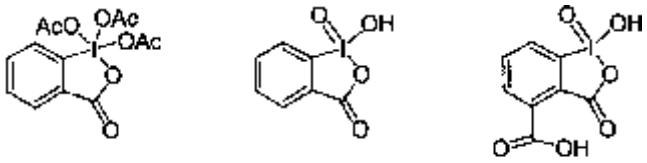
Hypervalent iodine reagents, due to their low toxicity and ready availability, have attracted considerable attention recently as mild and selective oxidizing agents[80].

While oxidation reactions using both DMP and IBX tolerate the presence of moisture in the reaction medium[80f, 81c], The presence of large amounts of water, when used as a solvent or co-solvent, is detrimental to the outcome of the oxidation reactions using these reagents. This is due to the fact that the mechanisms of oxidation with both the oxidizing agents involve reactive intermediates formed in an equilibrium step that is disfavored with increasing concentrations of water[80f,g].

A series of elegant papers from Nicolaou Laboratories have recently identified several new oxidative transformations, including a selective oxidation of benzylic carbons using IBX[82].

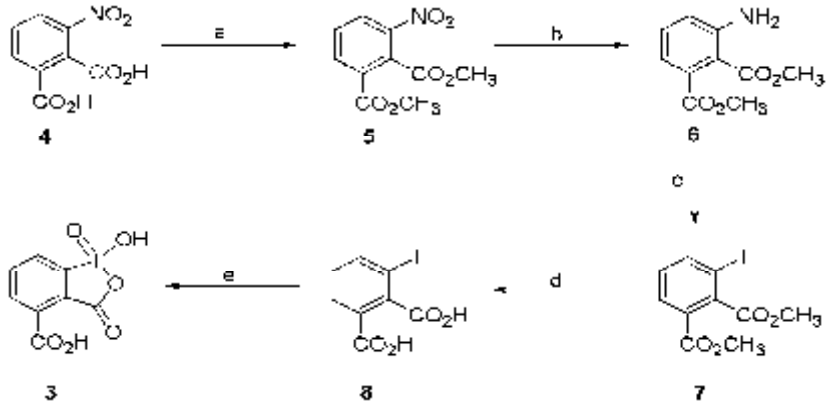
These reactions were carried out either in DMSO or fluorobenzene/DMSO mixtures. Single electron transfer (SET) reaction pathways have been proposed for these synthetic technologies[82c,d,f].

The ever-growing demand for eco-conscious chemical processes 83 and our interest in green-chemistry prompted us to synthesize a water-soluble derivative of IBX that could potentially behave as a green-oxidant capable of oxidizing alcohols in water, possibly via a SET mechanism (vide infra), similar to the one proposed by Nicolaou. In this paper we describe the synthesis of **3**, a water-soluble derivative of IBX, which we call modified IBX (mIBX), and oxidation of allylic and benzylic alcohols using **3** in water and other ecofriendly solvents.



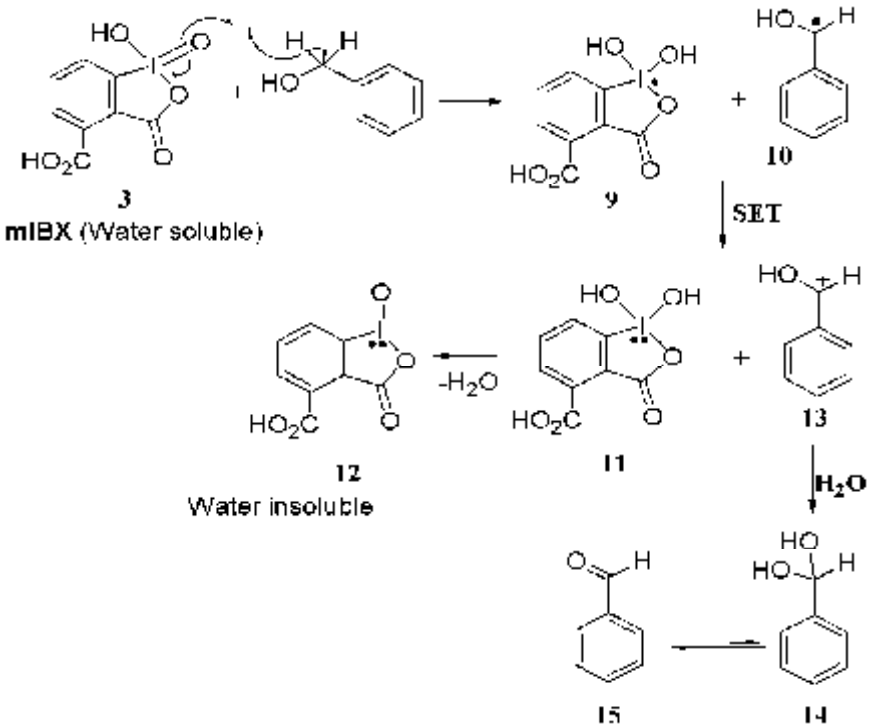
Synthesis of mIBX

The synthesis of mIBX, **3**, is readily accomplished from commercially available 3-nitrophthalic acid (**4**) as follows: esterification of **4** via the corresponding acid chloride gave nitrodiester, **5** (100%), which upon catalytic hydrogenation provided the aminodiester, **6** (100%). Diazotization followed by iodination of **6** provided dimethyl 3-iodophthalate (**7**) in 91% yield. Saponification followed by acidification of **7** yielded 3-iodophthalic acids (**8**) in 93% yield. Oxidation of **8** to the water-soluble mIBX, **3**, was carried out using $KBrO_3$ 84a .The 70% yield reported for the conversion of **8** to **3** is the isolated yield of **3**, with the actual conversion near quantitative as evident from monitoring the oxidation of **8** to **3** by 1H NMR spectroscopy. Water-soluble mIBX, **3**, was isolated as an analytically pure white solid, mp: 258-260°C[84,b,c].



Reagents and conditions: (a) (i) $SOCl_2$ heat, (ii) CH_3OH, heat, 100%; (b) H_2 (55 psi), Pd-C, CH_3OH, 100%; (c) (i) $NaNO_2$, HCl, 0–5°C, (ii) KI, 91%; (d) (i) NaOH, THF–H_2O (3:1v/v), (ii) aq. HCl, 93%; (e) $KBrO_3$, 0.73 M H ,55°C, 3 h,70%

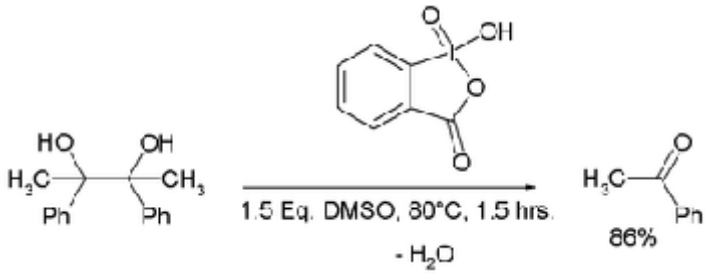
Mechanism of oxidation of benzylic/allylic alcohols in water using mIBX



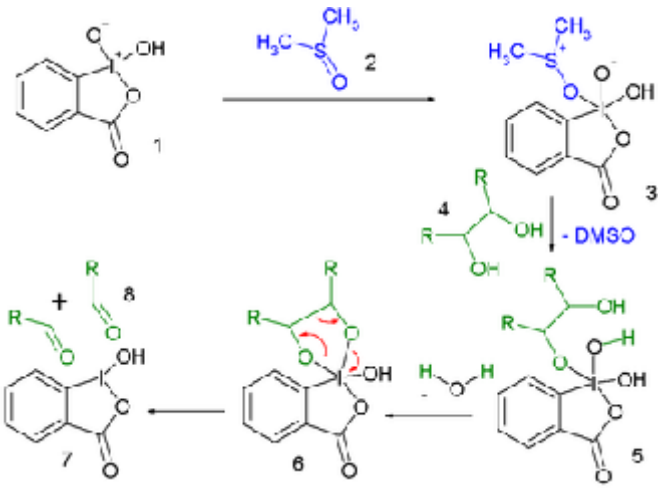
Application of IBX

1. Application IBX acid is replaced by Dess-Martin periodinane, which is more soluble in common organic solvents. A sample reaction is a IBX oxidation used in the total synthesis of eicosanoid[84].

2. IBX is notable for oxidizing vicinal diols (or glycols) to diketones without cleavage of the carbon-carbon bond[85], but oxidative cleavage of glycols to dialdehydes or diketones can occur when modified conditions are used (elevated temperatures or trifluoroacetic acid solvent)[86].

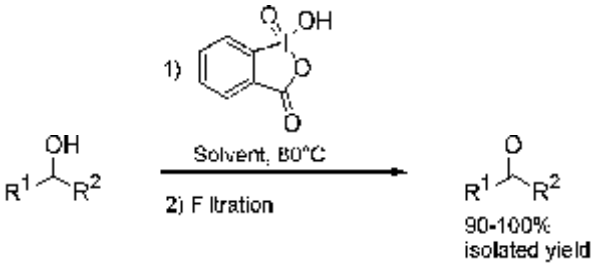


The reaction mechanism for this glycol cleavage is based on initial formation of an adduct between IBX and DMSO to an intermediate **3** in which DMSO acts as a leaving group for incoming alcohol **4** to intermediate **5**. One equivalent of water is split off forming spirobicyclic periodinane **6** setting the stage for fragmentation to **7** with hydroxyl alpha protons presents oxidation to the acyloin competes. Trifluoroacetic acid is found to facilitate the overall reaction.

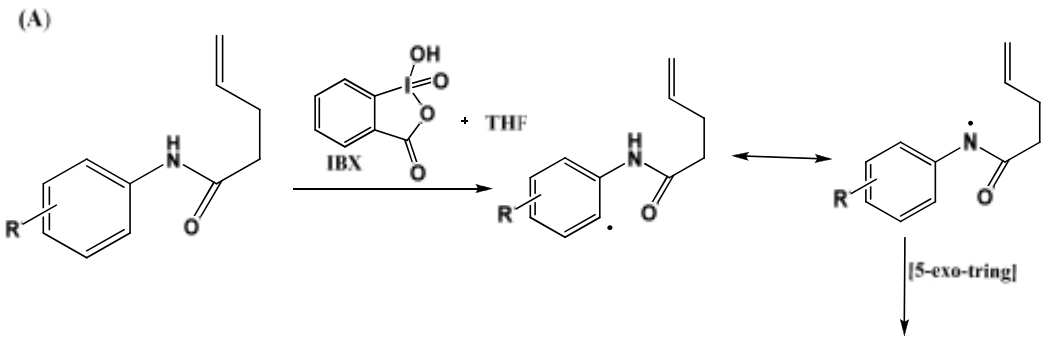


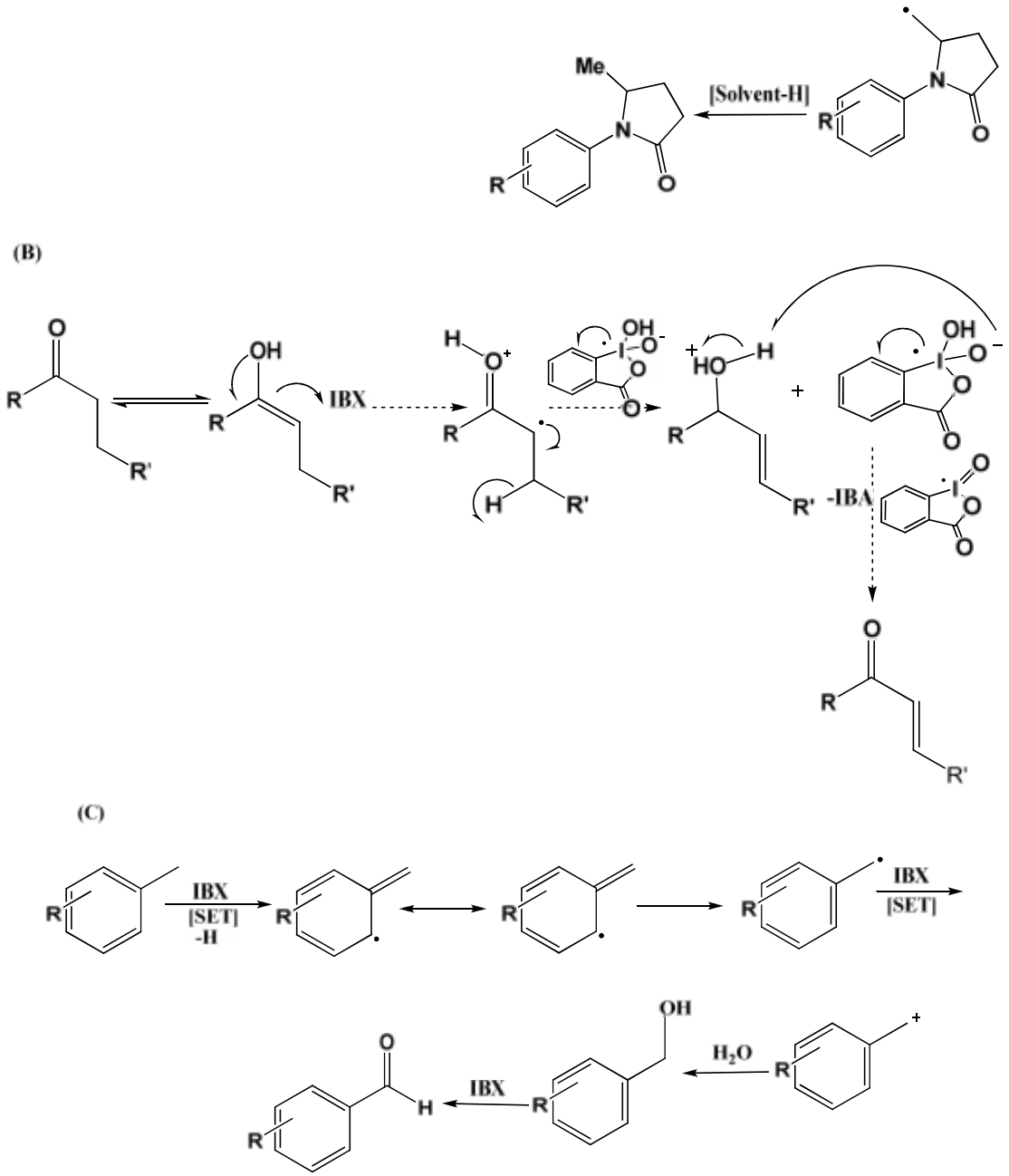
IBX (o-iodoxybenzoic acid) has gained great popularity as a mild oxidant for the conversion of alcohols to aldehydes or ketones[87,89] IBX is virtually insoluble in most organic solvents, and the perception that solubility is a prerequisite for reactivity accounts for the great length of time between the discovery of IBX and the first practical applications of it in DMSO (the only solvent in which it does dissolve) [90,91].

A solution of the alcohol in the presence of suspended IBX followed by filtration and removal of the solvent gives excellent yields of the corresponding carbonyl compounds. IBX is an effective heterogeneous oxidant in most organic solvents. Indeed, the limited solubility of IBX makes it a defacto solid-phase reagent, with all of the commensurate benefits[92].



A number of new synthetic technologies based on the reactivity of the periodinane reagents DMP and IBX have recently been reported from these laboratories[93]. These reactions include the IBX induced cyclization of unsaturated anilides (Fig. A)[94b], whose single-electron transfer (SET) mechanism was recently elucidated[95(a,b)], and the introduction of unsaturation next to carbonyl groups[94d], now also believed to proceed, by analogy, via a SET mechanism (Fig. B). On the basis of these mechanistic rationales, we hypothesized that benzylic positions could be oxidized by IBX via a SET mechanism as postulated in (Fig. C).





Summary

The potential use of IBA, IBX, and several derivatives as catalysts for the hydrolytic cleavage of organic phosphates was examined in detail when aiming to develop reagents for the decontamination of chemical warfare agents[97].

In studies conducted during the early 20th century both IBA and IBX were found to possess bactericidal activity. This observation is not overly surprising considering their known oxidizing properties[98].

In numerous animal experiments that may appear rather bizarre from today's perspective, aqueous solutions of IBX and its salts were injected into rabbits and dogs to probe the influence of these substances on respiratory function and the immune system[98].

Moreover, in the first half of the 20th century, a number of authors even recommended the medicinal use of IBX and its salts for the treatment of arthritic diseases[99].

In fact, both the ammonium and calcium salts of IBX were temporarily marketed as drugs under the trade names "Amiodoxyl" or "Oxoate"[100]. Their therapeutic usefulness, however, was soon cast into doubt, and severe side effects were reported[101]. To the best of our knowledge, the last reports on such treatments were in 1950, when a clinical trial showed that these preparations based on IBX are no more effective than aspirin[102]. afterwards, the "iodoxybenzoates" fell into oblivion for about 30 years.

For more than a decade now, IBX has enjoyed great popularity as an oxidant in organic synthesis. A huge amount of methodological studies as well as an ever increasing number of applications in the total synthesis of complex natural products bear testimony to the great reliability put on this reagent. IBX has now become one of the most important tools in the synthetic chemists' repertoire for the mild oxidation of alcohols. The power of attraction of IBX also keeps steadily growing because of its ability to make many further oxidative processes possible that are currently not feasible through the use of alternative reagents. Hence, IBX has emerged as an almost universally applicable oxidizing agent that permits the dehydrogenation of various functional groups as well as the transfer of oxygen atoms to phenols,

Benzylic sites and the a positions of carbonyl groups. Furthermore, IBX is capable of inducing one-electron-transfer processes that result in the generation of radical species, the full synthetic potential of which seems still to be underexploited.

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