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Expedient synthesis and solvent dependent oxidation behavior of a water-soluble IBX derivative

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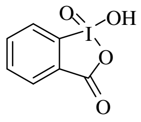
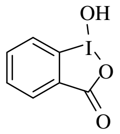
ABSTRACT

IBX derivative **6**, synthesized in two steps from 2-aminoterephthalic acid, **8**, is soluble in both DMF and water. A variety of alcohols are oxidized using **6** in DMF with ease and selectivity identical to that of parent IBX. However, oxidations carried out in water and other aqueous solvent mixtures using **6** exhibit unique selectivities toward different substrates and provide products different from reactions carried out in DMF. A mechanistic rationale is provided for this solvent dependent behavior of **6**.

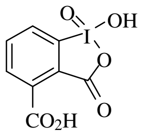
Since the initial report of the use of *o*-iodoxybenzoic acid, IBX, **1** as a mild and selective oxidizing agent for alcohols,[1] IBX has become an important oxidant in synthetic organic chemistry.[2] Several unique and remarkable oxidative transformations have been recently reported using IBX.[3a–f] These transformations are often carried out in DMSO due to the solubility limitations of the reagent in other user-friendly solvents with lower boiling points. Finney and More[4] have, however, reported that the oxidation of alcohols using IBX can be successfully carried out in solvents other than DMSO in which the reagent is only sparingly soluble. Structural modifications on the arene ring of IBX to impart better solubility to the reagent have also been successfully attempted. Recently, Wirth and co-workers reported the synthesis of FIBX **4**[5] a perfluoro derivative of IBX which allows for oxidation reactions using this reagent to be done in acetonitrile and other user-friendly solvent mixtures. Polymer anchored IBX derivatives (e.g., **5**) have also been synthesized and successfully used as oxidants.[6] We reported the water-soluble derivative *m*IBX, **3**, as a selective oxidant for benzylic and allylic alcohols when oxidations are carried out in water or in aqueous THF.[7] A mechanistic rationale for the solvent dependent selectivity of *m*IBX, **3**, toward the oxidation of alcohols was presented in our initial report.[7] In this Letter, we report the synthesis of a second water-soluble IBX derivative **6**, a structural isomer of **3**. Unlike *m*IBX, the water-soluble reagent **6** is prepared in two easy steps from commercially available 2-aminoterephthalic acid, **8**. Oxidation of alcohols using **6** in aqueous solvent mixtures has uncovered synthetically useful and interesting solvent dependent selectivities in its oxidation behavior. We also report these selectivities and provide a mechanistic rationale that also explains the accidentally observed selectivity toward oxidation of allylic and benzylic alcohols using *m*IBX in aqueous THF.



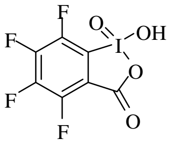
IBX (1)



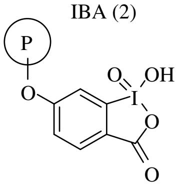
IBA (2)



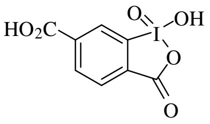
*m*IBX, 3



FIBX, 4



Supported-IBX, 5



6

The synthesis of *m*IBX was achieved in five steps from commercially available 3-nitrophthalic acid, **7**. The multi-step synthesis was necessitated since direct diazotization followed by iodination of **11** to give 2-iodophthalic acid, **12**, the acid precursor for **3**, was unsuccessful owing to the competing aryne formation. 2-Iodoterephthalic acid, **9**, the acid precursor of **6** is a known compound,[8] but to the best of our knowledge a synthesis of **9** from **8** via diazotization followed by iodination has not been reported. Though we were skeptical about the success of this route we decided to carry out the sequence and were pleased when **9** was isolated in 86% yield as a tan colored solid in essentially pure form. Oxidation of **9** to the cyclic iodane **6** was initially attempted using 1.3 equiv of Oxone in water at 70 °C following the procedure reported for the synthesis of IBX.[9] Under these reaction conditions, the insoluble iodoso derivative **10** was isolated in quantitative yield. However, oxidation of **9** with an excess of Oxone (4.0 equiv) in water at reflux produced a clear solution within 2–3 h, indicating the formation of a water-soluble hypervalent iodine reagent. Fortuitously, the isolation of the water-soluble derivative, **6**, was made

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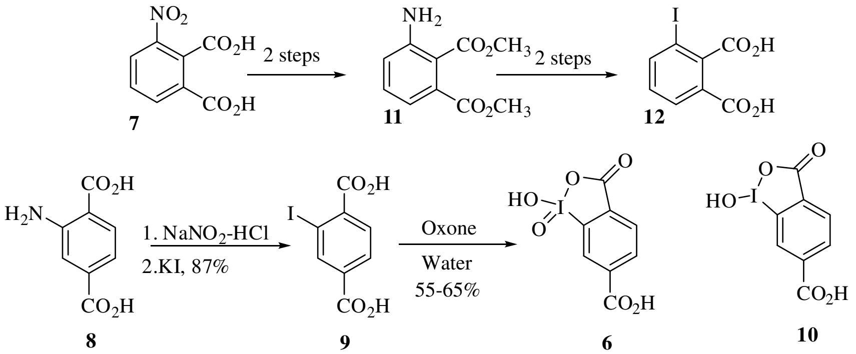


Figure 1. Synthesis of **6**.

easy by the selective precipitation of the cream colored solid upon cooling the reaction mixture. The first crop of crystals was essentially pure λ^5-iodane **6** (^1H NMR, ^{13}C NMR and elemental analysis). The yield of **6** obtained from this reaction varied between 55% and 65% depending on the scale and the amount of the first crop of crystals obtained upon cooling the reaction mixture (Fig. 1).

The ready solubility of **6** in both DMF and water prompted us to evaluate the oxidation of various substrates in these two solvents. It was gratifying to note that a diverse group of alcohols are smoothly and rapidly oxidized by **6** to the corresponding carbonyl compounds either at rt (12 h) or at 55–60 °C (4 h) in DMF, a favored solvent than DMSO from a practical point of view. Table 1 lists the results from the oxidations carried out at 55–60 °C using 1.2 equiv of **6**. Oxidation of benzylic and allylic alcohols (entries 1–4, 11 and 12) are complete within 1 h; progress of the reaction as monitored by ^1H NMR. Though over oxidation of aldehydes to carboxylic acids is not observed in DMF, formation of α,β-unsaturated carbonyl compounds was observed with varying yields depending on the molar ratio of the reagent to substrate used in the reaction. It was particularly remarkable to note that oxidation of 3-phenyl-1-propanol, **22** (entry 9) when carried out in DMF at rt with 2.2 equiv of **6** provided 80% yield of a product mixture comprising dihydrocinnamaldehyde, **35**, and cinnamaldehyde, **29**, in a 3:2 ratio. Similarly, oxidation of 4-phenylcyclohexanol **20** (entry 7) with 2.5 equiv of **6** in water–acetonitrile (vide infra) for 12 h at 55–60 °C gave a 60% yield of **40** along with 15% of the ketone, **33**. We believe that the mild conditions that we present here for the introduction of α,β-unsaturation in aldehydes and ketones is a practical improvement over the reaction conditions reported by Nicolaou for the introduction of α,β-unsaturation using IBX in DMSO or DMSO–PhF at 80 °C.[3a] The oxidation of **24** (entry 11) using 1.2 equiv of the reagent in DMF gave a mixture of the mono-aldehyde **37** and the di-aldehyde **41** in 70% and 16% yield, respectively. The use of 2.2 equiv of the reagent readily oxidizes **24** to give 94% yield of the dialdehyde **41** in 2 h at 55–60 °C, clearly demonstrating that **6** does not exhibit any selectivity for benzylic alcohols over non-benzylic alcohols when the oxidation is carried out in DMF. However, selectivity for benzylic alcohol oxidation and other unique selectivities were observed when reactions were carried out in water or predominantly aqueous solvent mixtures.

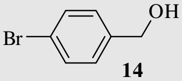
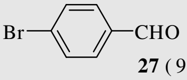
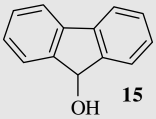
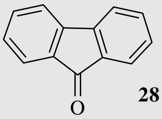
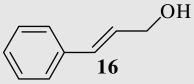
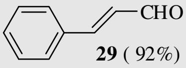
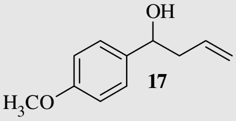
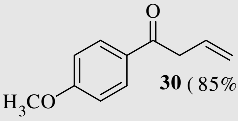
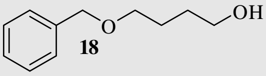
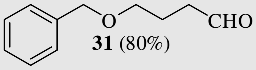
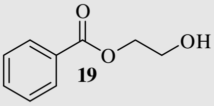
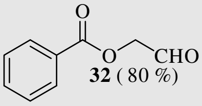
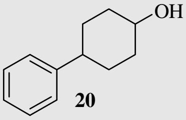
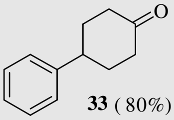
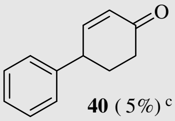
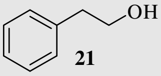
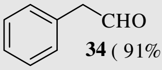
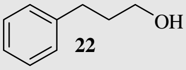
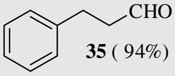
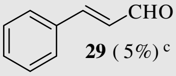
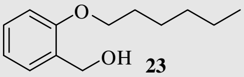
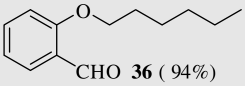
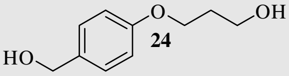
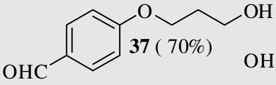
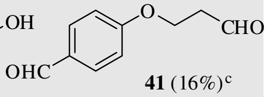
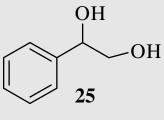
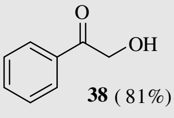
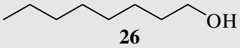
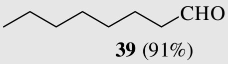
Realizing that only a select group of substrates will be completely soluble in water, we first set out to identify useful co-solvents that can be used with water. Diol **24**, which contains both benzylic and non-benzylic alcohols, was chosen as a prototypical substrate for this co-solvent optimization study. The oxidation of **24** in various solvent mixtures was carried out either at rt or at 65 °C; several general trends are readily discernable from the results shown in Table 2. The reactivity difference between the benzylic and non-benzylic alcohol groups toward oxidation by **6** is much more pronounced in aqueous solvent mixtures than in DMF (vide supra). Benzaldehyde derivative **37** is obtained in higher than 90% yield from reactions carried out at rt or at 65 °C for 3 h. Longer reaction time (18 h) at 65 °C or use of a larger substrate to **6** ratio increases the amount of dialdehyde, **41** formed. A comparison of the relative rates of oxidation of **24** to di-aldehyde **41** in DMF and in aqueous solvent systems clearly indicates that the non-benzylic alcohol is only sluggishly oxidized in aqueous solvent mixtures, unlike in DMF (vide supra). While oxidation of **24** using 2.2 equiv of **6** in water–THF (4:1) gave a 98% yield of **37**, attempted oxidation in a water–acetone mixture under identical conditions failed.

The proposed mechanism for oxidation (Fig. 2) explains the differences in the rate of oxidation of the two alcohols in aqueous solvent systems, the observed selectivity for benzylic alcohol oxidation in presence of THF, and the lack of oxidation in aqueous acetone. The established mechanism[10] of oxidation of alcohols by IBX in polar aprotic solvents is the ligand exchange mechanism shown on the top of Figure 2. It is evident from this mechanism that water plays a significant role as the reversible ligation of alcohol on the iodine center is dependent on water concentration and thus not a feasible step in aqueous mixtures. We believe that the mechanism in aqueous media involves an H atom abstraction from a C–H bond of the CH_2OH group followed by a single electron transfer (SET) to the highly oxygenated iodine site[11,12] as the two crucial steps. To confirm the radical nature of the reaction, as required by the postulated mechanism, an inhibition study was carried out in presence of the radical scavenger, galvinoxyl.[13] A complete inhibition of the oxidation occurred when 1.2 equiv of the radical scavenger galvinoxyl was added to the reaction mixture during the oxidation of **22** (Table 1, entry 9).

The ease of oxidation of the benzylic alcohol over the non-benzylic alcohol is explained by the BDE difference[14] of the two relevant C–H bonds and the stability of the resulting benzylic radical after the H-abstraction. Moreover, the (accidental) selectivity for benzylic alcohol oxidation in aqueous THF is explained as follows. Though the BDEs of the α C–H bonds in THF (α to ring O) and non-benzylic alcohols (α to OH) are similar[14] the stereoelectronically favored H-atom abstraction in THF[15] results in the preferential oxidation of THF over non-benzylic alcohols. The complete lack of oxidation in aqueous acetone is presumed to be caused by the abstraction of the allylic H atom from the enol tautomer of acetone by **6**.

Some of the unique and unexpected product distributions and additional selectivities observed from oxidations carried out in aqueous solvent mixtures are shown in Figure 3. These examples lend further credence to the proposed H-abstraction reaction mechanism. Oxidation of homoallylic alcohol **17** in H_2O–CH_3CN (1:1) gave a mixture of **30** (70%) and the isomer **42** (6%). The

Table 1
Substrate scope[a]

Entry	Substrate	Product(s)[b]
1	 **14**	 **27** (94%)
2	 **15**	 **28** (88%)
3	 **16**	 **29** (92%)
4	 **17**	 **30** (85%)
5	 **18**	 **31** (80%)
6	 **19**	 **32** (80 %)
7	 **20**	 **33** (80%)  **40** (5%)[c]
8	 **21**	 **34** (91%)
9	 **22**	 **35** (94%)  **29** (5%)[c]
10	 **23**	 **36** (94%)
11	 **24**	 **37** (70%)  **41** (16%)[c]
12	 **25**	 **38** (81%)
13	 **26**	 **39** (91%)

[a] Reactions were carried out on 0.2–0.4 mmol scale with 1.2 equiv of **6** in DMF at 55–60 °C for 4 h.

[b] Reported yields are for chromatographically and spectroscopically pure compounds, except for **38** and **40**, the yield of which was determined by NMR methods.

[c] Higher yields of these over-oxidized products were obtained with a larger molar ratio of **6** in the reaction.

Table 2
Solvent optimization studies

Solvent	Equiv **6**	Temp (°C), time (h)	Yield[a,b] (%) (**37**:**41**)
H_2O	3.0	rt, 18	98:Trace
H_2O/CH_3CN (4:1)[c]	2.2	rt, 18	92:8
H_2O/CH_3CN (9:1)	3.0	65, 3	100:0
H_2O	2.2	65, 18	76:24
H_2O/CH_3CN (1:1)	2.2	65, 18	66:34
H_2O/CH_3CN (1:1)	4.0	65, 4	73:27
H_2O/THF (4:1)	2.2	65, 18	98:Trace[d]
H_2O/acetone (1:1)	2.2	65, 18	No oxidation

[a] Product ratio estimated by NMR methods.
[b] Presence starting alcohol, **24** was not detected in any of the product mixtures.
[c] Ratio of solvents are reported in v/v.
[d] Oxidation of THF to γ-butyrolactone was detected by GC–MS.

formation of **42** is believed to occur via the intermediate **42**–**I**, which in turn is formed by a facile abstraction of the allylic H atom in **30**. There is no evidence of formation of **42** when **17** was oxidized in DMF. Oxidation of 3-phenyl-1-propanol **22** with 2.5 equiv of **6** in $H_2O–CH_3CN$ (4:1) gave a mixture of products including 3-phenylpropanoic acid **43** in 20% yield. The initially formed 3-phenylpropanal, **35**, is likely to be hydrated under these reaction conditions and is further oxidized via a facile H atom abstraction from the hydrate as schematically shown in Figure 3. Aromatic aldehydes and α,β-unsaturated aldehydes which have K_{eq} less than unity[16] for hydration are not oxidized under these conditions. Conspicuously absent from the oxidation of **22** was *trans*-cinnamic acid, **44**. Oxidation of 1-octanol with 1.2 equiv of **6** gave a 50% yield of octanoic acid, **43** along with 8% of **39** and 40% of alcohol was recovered from the reaction. This product distribution clearly shows the ease of H-atom abstraction from the hydrate of an aldehyde. It is also to be noted that oxidation of 1-octanol by **6** in DMF (Table 1, entry 13) gave only octanal as the product. We believe that the selective oxidation of aliphatic aldehydes over aromatic/alkenyl aldehydes in aqueous solvent systems is a unique and a desirable trait of **6**. Finally, 2-phenylethanol is not oxidized to **34** even with 3.0 equiv of reagent in aqueous solvent mixtures. The only identifiable product (by GC–MS) from the reaction is **38** in trace amounts. We believe that the failure to oxidize **21** in aqueous solvent systems is due to the lower BDE of the benzylic C–H bond than the C–H bond of the CH_2OH group in **21**. This BDE difference is likely to cause a permanent presence of a radical center β to the OH group (see **38**–**I**) thus preventing the abstraction of the H-atom needed for the oxidation to occur. Trace amounts of **38** could be accounted by the further oxidation of **38**–**I**.

In summary a two-step synthesis of **6**, a user-friendly derivative of IBX, from commercially available 2-aminoterephthalic acid, **8**, is reported. The solubility of **6** in DMF allows for its use as a convenient substitute for IBX to carry out selective oxidation of a variety of alcohols and other substrates. Oxidation reactions using **6** in aqueous solvent mixtures have uncovered unique selectivities in its oxidation behavior. The established change in mechanism of oxidation in the two solvent systems and the observed change in product distribution makes **6** a practically convenient solvent–dependent hypervalent iodine oxidant.

Acknowledgments

Authors gratefully acknowledge the National Science Foundation (CHE-0412614) for support of this research. The authors also thank the University Research Council of Western Illinois University for providing a SEED grant to initiate this investigation.

Supplementary data

Supplementary data (experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra of compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.017.

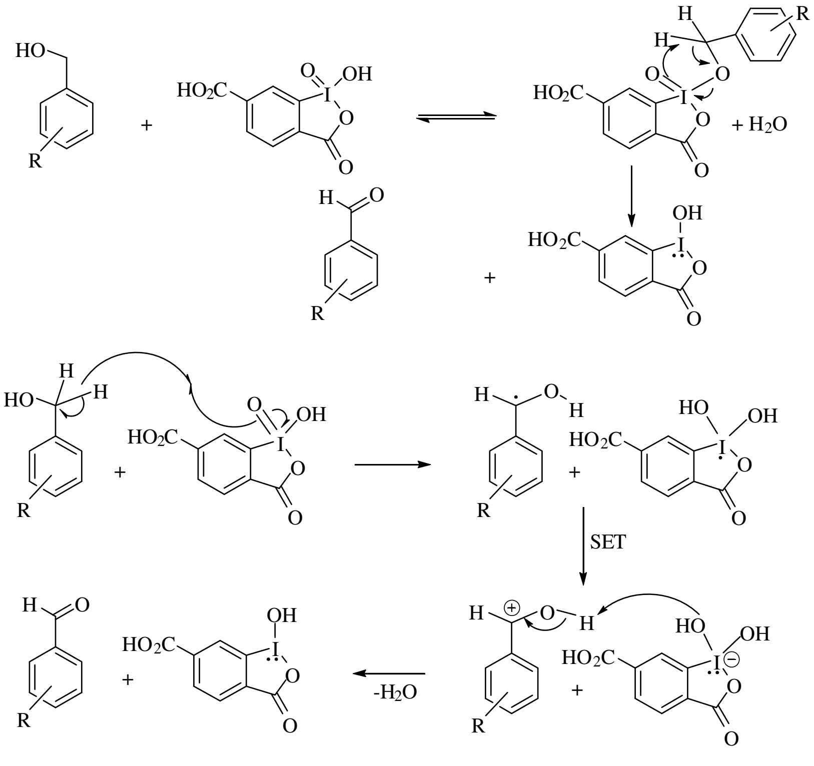


Figure 2. Proposed mechanism of oxidation using **6** in polar aprotic and aqueous solvents.

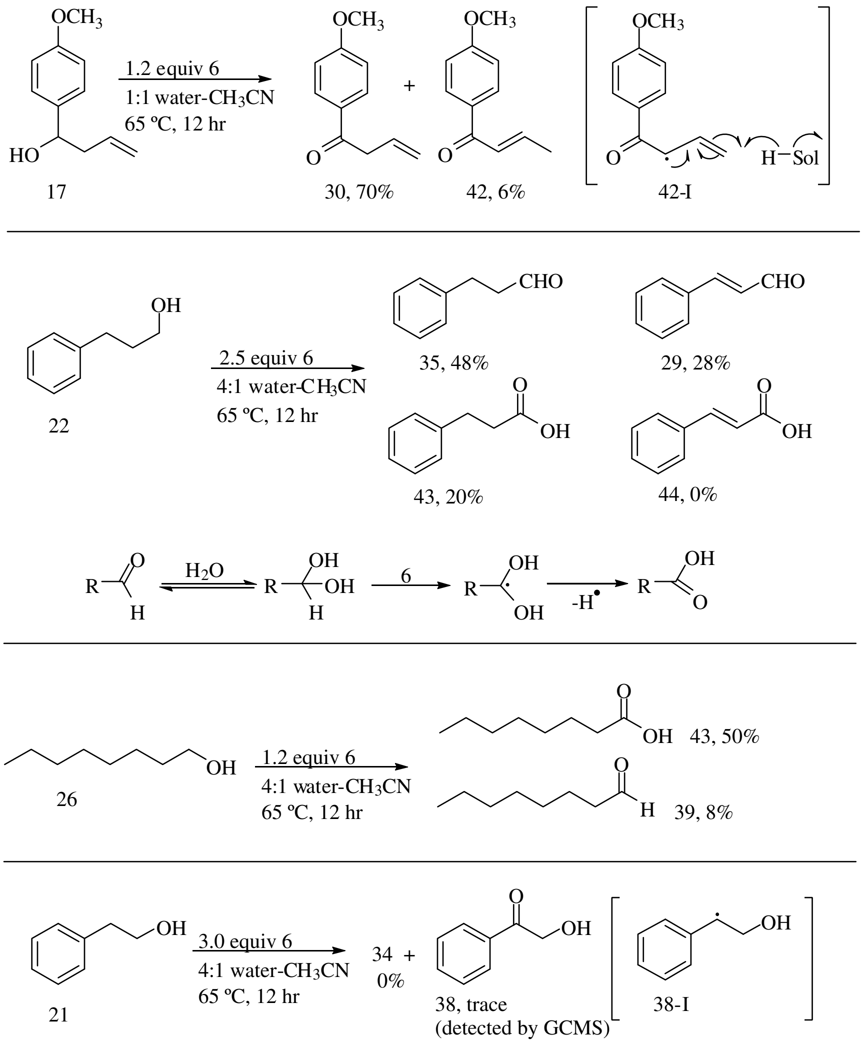


Figure 3. Selectivity of oxidations in aqueous solvent mixtures.

References and notes

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