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Design, Synthesis, Structure, and Dehydrogenation Reactivity of a Water-Soluble *o*-Iodoxybenzoic Acid Derivative Bearing a Trimethylammonium Group

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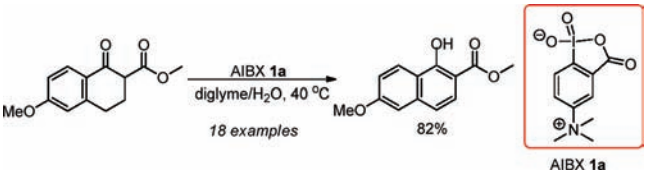
ABSTRACT



5-Trimethylammonio-1,3-dioxo-1,3-dihydro-1λ^5-benzo[*d*][1,2]iodoxol-1-ol anion (AIBX 1a), an *o*-iodoxybenzoic acid (IBX) derivative having the trimethylammonium moiety on its phenyl ring, possesses very good solubility in water and distinct oxidative properties from IBX, which is demonstrated in the oxidation of various β-keto esters to the corresponding dehydrogenated products using water as cosolvent. The regeneration of AIBX 1a can be easily realized from the reaction mixture due to its good water solubility.

IBX (Figure 1), a key representative of organo-pentavalent iodine reagents, has found widespread applications in organic synthesis as a mild and nontoxic oxidizing agent.[1] In most cases, the solvent of IBX mediated reactions is DMSO due to the insolubility of IBX in other common organic solvents, which is a major drawback of IBX to restrict its practical application. IBX has also been reported to be explosive upon impact or excessive heating.[2] To overcome its solubility limitation, a few IBX derivatives have been developed via the functionalization of its phenyl ring.[3] Other approaches involving the replacement of a carboxyl unit by other donor groups have also been developed.[4] However, the majority of IBX derivatives are aimed at improving their solubility in

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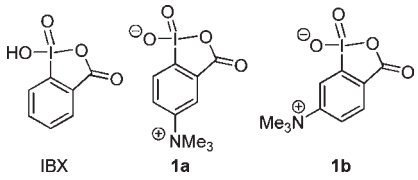
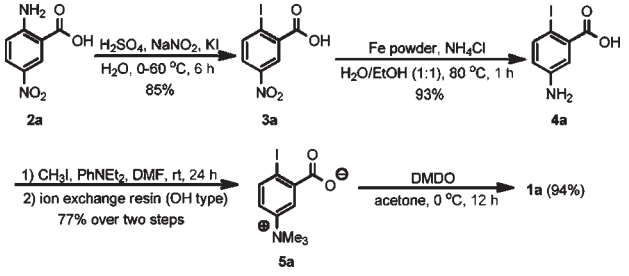


Figure 1. IBX and AIBX **1a** and **1b**.

common organic solvents such as acetone and CH_3CN; very few examples are designed to improve the water solubility of IBX.[3b,3f,4l] Water, being cheap, safe, and environmentally benign, has been recognized as a green solvent and applied in many organic reactions as an ideal medium.[5] As our continuing interest in hypervalent iodine chemistry,[6] we envisaged the development of water-soluble IBX derivatives via the introduction of a trimethylammonium moiety on the phenyl ring. Our design is based on the following rationales: (a) because of good water solubility of the trimethylammonium salt, it would impart better water solubility to IBX when attaching it to the phenyl ring of IBX; (b) the strong electron-withdrawing nature of the trimethylammonium cation would enhance the electrophilicity of the iodine(V) center, thus resulting in an increased reactivity. Herein, we disclose the synthesis, structural characterization, and dehydrogenation reactivity of water-soluble IBX derivatives with the trimethylammonium group being attached directly to the phenyl ring, namely AIBX **1a** and **1b** (Figure 1).

Scheme 1. Synthetic Route of AIBX **1a**



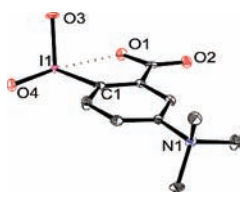


Figure 2. Perspective drawing of **1a** with 50% ellipsoid probability. selected bond distances [Å]: I(1)−O(4) 1.8012(19), I(1)−O(3) 1.8150(19), I(1)−O(1) 2.498.

The precursor **5a** of **1a** can be readily prepared from the commercially available compound **2a** by diazotization followed by iodination, the reduction of nitro to an amino group, the methylation of the amino group, and the ion exchange to remove the iodide (Scheme 1). Oxidation with excess DMDO (dimethyldioxirane) afforded AIBX **1a** in an excellent yield after simple filtration workup. Following the same procedure, **1b** was obtained in an overall yield of 21%. On the other hand, when using Oxone as an oxidant in place of DMDO, AIBXs were always contaminated with inorganic impurities due to their high water solubility. Compounds **1a** and **1b** were analyzed by their NMR spectra, IR, high resolution mass spectroscopy (ESI), and the single crystal X-ray analysis of **1a**. The characteristic signals of C-IO_2 *ipso*-carbon were found at ~148 ppm in ^{13}C NMR spectra, which are similar to that of IBX (147 ppm). In the IR spectra of both AIBXs, two strong absorptions of IO_2 were observed at ca. 790 and 760 cm^{-1}. AIBX **1a** and **1b** have very good solubility in water, the concentrations of **1a** and **1b** in water are up to 0.38 and 0.3 M at rt, respectively.

The single crystal of zwitterionic **1a** was grown from water (Figure 2).[7] Comparison with IBX showed the absence of the carboxylic H-atom results in the bond distances I(1)−O(3) and I(1)−O(4) being almost equal. Moreover, the endocyclic I(1)−O(1) bond length (2.498 Å) is slightly longer than that in IBX (2.263(2) Å[8]) but similar to that in sodium 2-iodyl-4-nitrobenzoic acid dihydrate (2.481(3) Å[9]). Generally, IBX derivatives with an I−O distance in the range of 2.20−2.50 Å can be classified as cyclic iodyl compounds.[10] The endocyclic I−O contact of AIBX **1a** is included in this range, allowing us to consider **1a** as a heterocyclic iodine(V) reagent (the packing structure of **1a** is shown in the Supporting Information).

With these two water-soluble AIBXs in hand, we next investigated their oxidative reactivity. It should be mentioned that the oxidative property of most reported IBX derivatives was demonstrated in the alcohol and/or sulfide oxidation.[1i] In the course of our study on the oxidative property of AIBXs, we found that the compound **6a** can be oxidized by AIBX **1a** to the methyl 1-hydroxy-2-naphthoate

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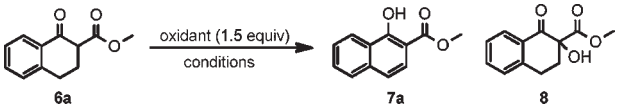
Table 1. Optimization of the Reaction Conditions[a]

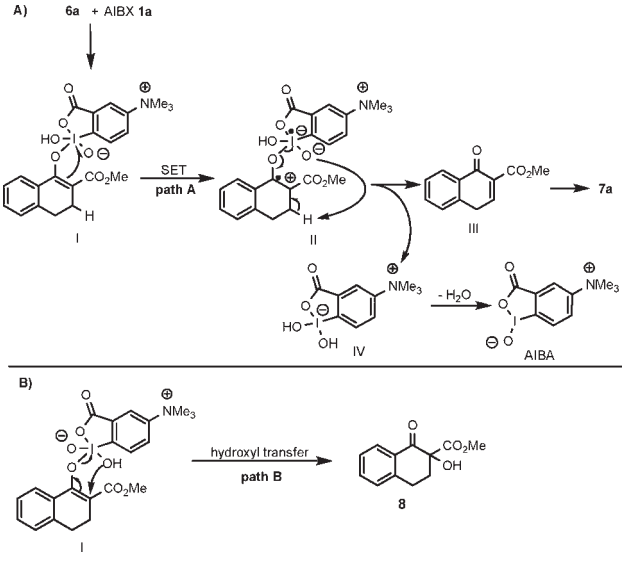


entry	oxidant	sovlent v/v = 1/3	time (h)	conv (%)[b]	yield (%)[b]
1	**1a**	diglyme/H_2O	24	100	74(9)
2	IBX	diglyme/H_2O	3	100	0(91)
3	**1b**	diglyme/H_2O	24	100	66(14)
4	**1a**	CH_3CN/H_2O	24	75	33(26)
5	**1a**	DMSO/H_2O	24	65	35(17)
6	**1a**	1,4-dioxane/H_2O	24	84	58(16)
7	**1a**	PEG-400/H_2O	24	95	65(14)
8	**1a**	$CHCl_3/H_2O$	24	18	7(trace)
9[c]	**1a**	diglyme/H_2O	7.5	100	55(6)

[a] The reactions were run on a 0.15 mmol scale in 2 mL of the solvent. [b] Isolated yields; the numbers in the parentheses are the yields of compound **8**. [c] The reaction was run at 60 °C.

7a in a yield of 74% with a small amount of hydroxylated product **8** in the homogeneous solution of water and diglyme at 40 °C (Table 1, entry 1).[11] On the contrary, when using IBX as the oxidant under the otherwise same reaction conditions, the hydroxylated product **8** was isolated as the only product (entry 2).[12] It was believed that such a difference is a result of the incorporation of the trimethylammonium group. The control experiment showed that **7a** cannot be formed via the direct dehydration of **8** under the reaction conditions for entry 1 (93% recovery of **8**). As shown in Scheme 2, the strong electron-withdrawing nature of the trimethylammonium group made the adduct **I**, generated from AIBX **1a** and the enol form of **6a**, prefer the SET pathway (path **A**) to form the radical cation species **II**.[13] The collapse of **II** gave intermediate **IV** and the thermally unstable enone **III** which could rapidly aromatize to the desired product **7a** under the thermal conditions.[14] Then, the dehydration of intermediate **IV** provided AIBA. The competitive path **B** involving an intramolecular hydroxyl transfer in the intermediate **I** can be used to explain the formation of byproduct **8**. We speculated that IBX could also form a similar intermediate to the adduct **I** with the enol form of **6a**. However, due to the relatively weak electrophilicity of IBX compared with that of AIBX **1a**, the reaction only proceeded through path **B** to afford the hydroxylated product.

Scheme 2. Proposed Mechanism for Dehydrogenation Reaction Mediated by AIBX **1a**



This interesting finding prompted us to further optimize the reaction conditions, and the results are summarized in Table 1. AIBX **1b** was also employed in this transformation, giving the desired product **7a** in a relatively lower yield of 66% (Table 1, entry 3). The solvent screening study indicated that diglyme was still the best one for this transformation among the tested solvents (entries 4–8 and Table S1 and S2 in the Supporting Information). Elevating the reaction temperature to 60 °C resulted in a decreased chemical yield of **7a** (entry 9). Accordingly, the optimal conditions that were established are shown as entry 1 and used in the following study.

To test the generality of this dehydrogenation reaction, a variety of β-keto esters and a β-diketone were tried and the results are listed in Scheme 3. Like **7a**, **7b** and **7c** were obtained in high yields. It should be noted that the benzyl group, which can be oxidized by IBX at elevated temperature,[15,13c] can be well tolerated under the present conditions. Those β-keto esters containing varied electron-donating (OMe, NMe_2) and electron-withdrawing functionalities (Br, Cl, F) can be transformed to the corresponding products **7d**–**h** in moderate to high yields. It was observed that the location of the methyl group at the cyclohexanone ring had a significant influence on the dehydrogenation reaction. For compounds with the methyl located at the benzylic position, the reactions worked well, yielding **7i** and **7j** in respective 83% and 71% yields. However, the oxidation of β-keto ester with a methyl group attached at the β-position relative to the carbonyl moiety failed to give **7k**, which was presumably due to the steric hindrance of the methyl group on the proton transfer to form the enone **III** from intermediate **II** (Scheme 2). β-Diketone proved to be a good substrate for

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(13) For radical cation intermediates, see: (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993–996. (b) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996–1000. (c) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.

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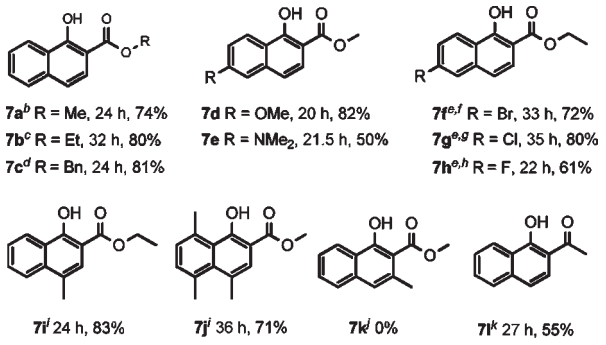
Scheme 3. Dehydrogenation Reactions of Various β-Keto Esters by **1a**[a]

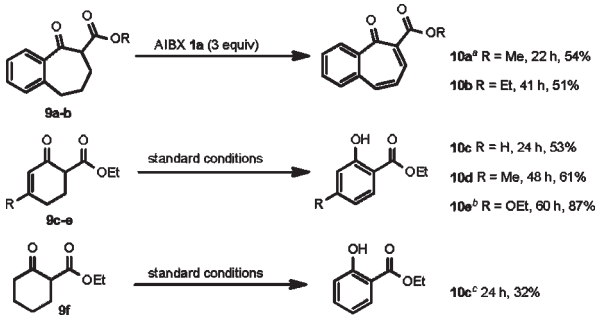


[a] Reactions were run in 0.3 or 0.45 mmol scale and other parameters see entry 1 in Table 1. [b]With 11% of **8**. [c]With 4% of hydroxylated product. [d]The reaction was run at 60 °C in 5 mL of the solvent (v/v = 2/3), and the hydroxylated product was isolated in 5% yield. [e]The reaction was conducted at 60 °C in 5 mL of the solvent (v/v = 2/3) with 2 equiv of **1a**. [f]With 10% of hydroxylated product. [g]With 16% of hydroxylated product. [h]With 6% of hydroxylated product. [i]The reaction was carried out at 60 °C with 2 equiv of **1a**. [j]Recovery of SM: 93%. [k]The reaction was carried out in a mixed solvent of diglyme/PhF/H_2O (v/v/v = 9/1/30), and the hydroxylated product was formed in 2% yield.

this transformation, and its dehydrogenated product **7l** can be obtained in 55% yield. When the β-keto esters derived from 1-benzosuberone were subjected to the oxidation of AIBX **1a**, the benzotropones **10a** and **10b**, double dehydrogenation products, were produced in 54% and 51% yields, respectively (Scheme 4, top reaction).[16] However, DDQ, a powerful dehydrogenation reagent, only afforded **10b** in 14% yield (conditions: DDQ 2.5 equiv; 1,4-dioxane 0.1 M; reflux 9 h). The obtained benzotropone skeleton is present in various bioactive natural products as a core structure, such as epitheaflavic acids[17] and taxamairins.[18]

The success in the oxidation of benzofused β-keto esters inspired us to explore the possibility of replacing the benzene ring with the C−C double bond. Accordingly, the substrates **9c**−**e** were subjected to the standard reaction conditions. The desired salicylate derivatives **10c**−**e** were produced in 53%, 61%, and 87% yields, respectively. The ethyl salicylate **10c** can also be obtained even without the preintroduced C−C double bond (Scheme 4, bottom reaction), whereas IBX only provided the hydroxylated product in 71% yield under the same reaction conditions. Again, this result proved that AIBX **1a** had distinct reactivity from IBX.

Scheme 4. Dehydrogenation Reactions by **1a**[a]



[a] With 6% of hydroxylated product. [b]Conversion: 90%. [c]Recovery of **9f**: 38%.

Due to the good water solubility of AIBX **1a**, the regeneration of **1a** can be easily achieved as exemplified in the oxidation of **6a** in which **1a** could be regenerated in 92% yield. Usually, the recyclability of IBX is realized via the immobilization of it onto a polymeric support.[19]

In summary, we have prepared two water-soluble and stable AIBXs **1a** and **1b** by the incorporation of a trimethylammonium group directly onto the phenyl ring of IBX. The structure of **1a** was established by its single crystal X-ray diffraction. Of particular interest was that **1a** was capable of oxidizing various β-keto esters to their corresponding dehydrogenated products, which was markedly different from IBX. This difference was believed to be the result of the presence of the strong electron-withdrawing trimethylammonium group. Further work on the detailed mechanism study of the present reaction and applications of AIBX in other synthetic transformations is underway.

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Supporting Information Available. The experimental procedures, the characterization of all compounds, and crystallgraphic data for AIBX **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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