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FACILE PREPARATION OF 1-HYDROXY-1,2-BENZIODOXOL-3(1*H*)-ONE 1-OXIDE (IBX) AND DESS–MARTIN REAGENT USING SODIUM HYPOCHLORITE UNDER CARBON DIOXIDE

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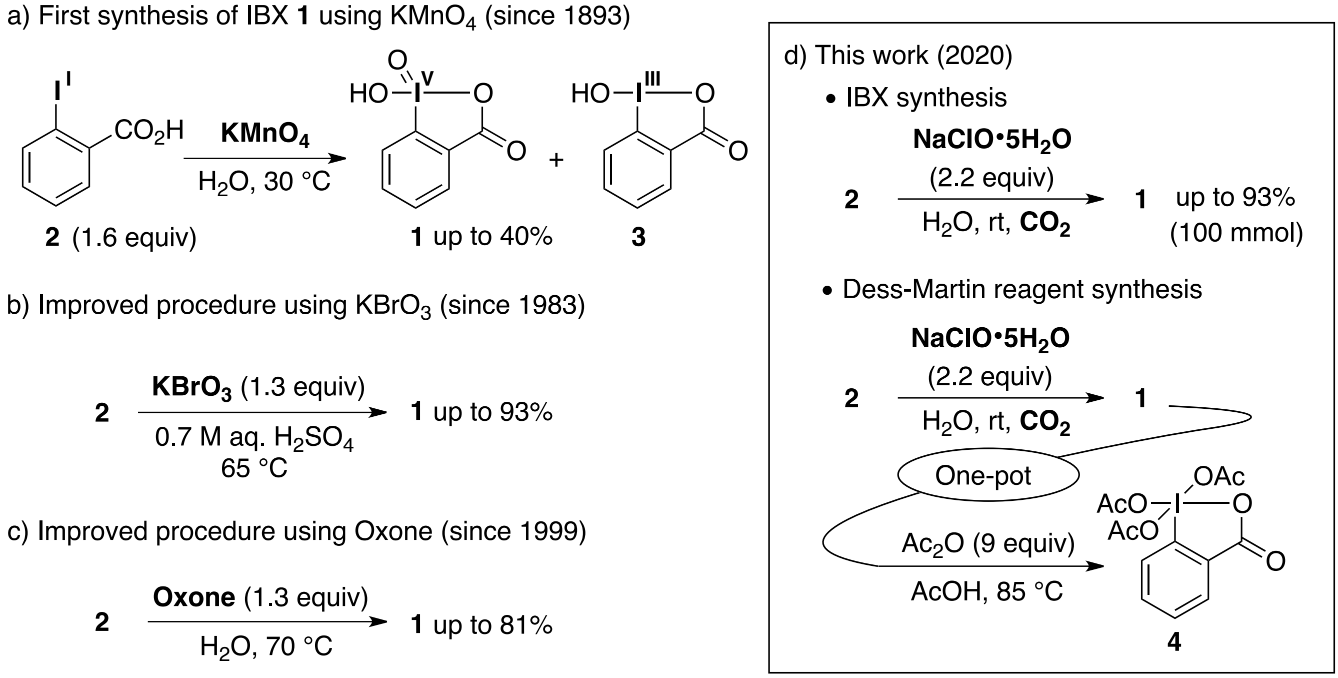
Abstract – We have developed a safe, convenient, and inexpensive method for preparation of the widely used oxidizing agent 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX), by treatment of 2-iodobenzoic acid with aqueous sodium hypochlorite under CO_2 at room temperature. As the only by-product is NaCl, this reaction can be utilized for one-pot synthesis of 1,1,1-triacetoxy-1,2-benziodoxol-3(1*H*)-one (Dess-Martin reagent) in excellent yield.

Since its first discovery in 1893[1a] and later re-evaluation by Frigerio and Santagostino *et al.* in 1994,[1b] 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (commonly known as IBX) (**1**) has been developed as an efficient reagent for the oxidation of a variety of functional groups, including alcohols, phenols, amines, sulfide, carbonyl compounds, *etc.* under mild conditions.[2a] Indeed, because of its remarkably high chemo-/regio-/stereoselectivity and its environment- and user-friendly character, **1** is considered a uniquely effective reagent for a broad range of organic synthesis.[2b-d] The first synthesis of **1** by Hartman and Mayer involved the oxidation of 2-iodobenzoic acid (**2**) with potassium permanganate in water at 30 °C, but this process suffered from a low yield of **1** (30–40%) and the by-products of incomplete oxidation include 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (**3**), so that tedious work-up is required (Figure 1a).[1a] Ninety years later, Dess and Martin developed a greatly improved protocol by modifying Greenbaum's method,[3a] in which potassium bromate ($KBrO_3$) was introduced as an oxidant in hot aqueous H_2SO_4 (0.73 M) (Figure 1b).[3b] This method provides **1** in high yield (>90%) after a simple work-up, but there are several safety concerns: for example, 1) carcinogenicity of $KBrO_3$, 2) generation of toxic Br_2, and 3) formation of bromate-related impurities with the potential to undergo violent decomposition upon impact and/or heating.[3c,4] In 1999, these concerns were dispelled by the development of an alternative method using less toxic and safer Oxone ($2KHSO_5$-$KHSO_4$-K_2SO_4) in water.[5] This procedure substantially reduced the amount of explosive impurities and is now considered a standard method for the synthesis of **1** (Figure 1c). However, we have discovered a safer, less expensive and highly reliable alternative method for the preparation of **1** simply by using sodium hypochlorite (NaClO) and carbon dioxide (CO_2) in water. Furthermore, as the only by-product is NaCl, this reaction can be utilized for one-pot synthesis of 1,1,1-triacetoxy-1,2-benziodoxol-3(1*H*)-one (Dess-Martin reagent)[3a] (**4**) in excellent yield (Figure 1d).


a) First synthesis of IBX **1** using $KMnO_4$ (since 1893)

b) Improved procedure using $KBrO_3$ (since 1983)

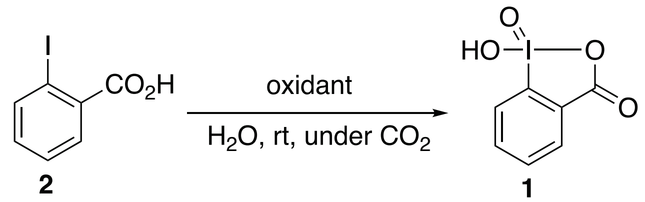
c) Improved procedure using Oxone (since 1999)

d) This work (2020)

Figure 1. Milestones in the synthesis of IBX 1, and the present work

We have recently demonstrated that the activation of $NaClO•5H_2O$[6] with acetic acid is effective for the oxidation of iodoarenes to trivalent (diacetoxyiodo)arenes.[7] Unfortunately, this method was not applicable to the preparation of **1**, since trivalent **3** was produced as a major product. In 2005, Zhdankin and co-workers reported an excellent preparation method for pentavalent alkyl 2-iodylbenzoate using 4% aqueous sodium hypochlorite (NaClO) in the presence of an excess amount of dry ice.[8] Inspired by this result and a report that the disproportionation of NaClO to sodium chlorate ($NaClO_3$) and sodium chloride is significantly accelerated by CO_2,[9] we decided to examine the oxidation of 2-iodobenzoic acid **2** with $NaClO•5H_2O$ under carbon dioxide (1 atm). Exposure of iodoarene **2** to 2.2 equivalents of $NaClO•5H_2O$ in water at room temperature under CO_2 resulted in the slow evolution of foam during the initial ca. 30 minutes, and after 3 hours, IBX **1** was obtained in good yield (Table 1, entry 1). Prolonging the reaction time slightly increased the yield (entry 2). In sharp contrast, the reaction in air (ca. 0.04% CO_2) or in air containing ca. 4% CO_2 did not or scarcely promoted this oxidation (entry 3). Scalability of the synthesis of **1** was demonstrated in the range of 10–100 mmol (entry 4). We did not experience any dangerous events (rapid gas evolution or temperature rise) in the large-scale operations, but we found that the yield was improved when the reaction was started at 0 °C, especially at 100 mmol scale. Use of commercially available 13% aq. NaClO instead of $NaClO•5H_2O$ gave a comparable yield of **1**, whereas 4% aq. NaClO or $Ca(ClO)_2•3H_2O$ afforded only moderate to low yield of **1** (entries 5–7). Solvent-free and highly concentrated conditions (3 M) were less effective, probably because of the reduced stirring efficiency of the magnetic stirrer bar under these conditions (entries 8 and 9).

Table 1. Oxidation of 2-iodobenzoic acid 2 with NaClO in water[a]

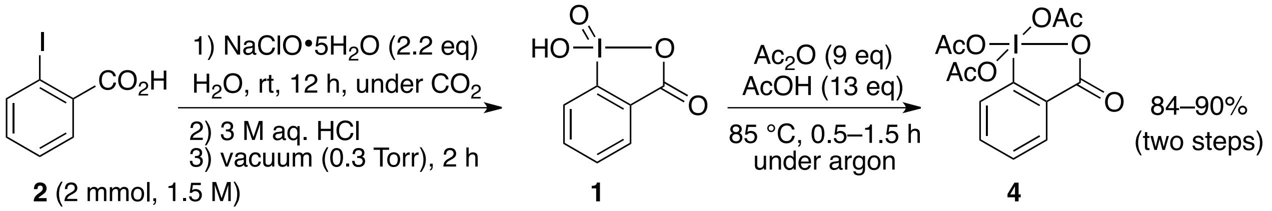


entry	oxidant (equiv)	time (h)	yield (%)[b]
1	$NaClO•5H_2O$ (2.2)	3	74
2	$NaClO•5H_2O$ (2.2)	12	88
3	$NaClO•5H_2O$ (2.2)	24	46[c], 65[d]
4	$NaClO•5H_2O$ (2.2)	12	80[e], 93[f,g]
5	13% aq. NaClO (2.2)[h]	12	80

6	4% aq. NaClO (2.2)[h]	12	68
7	$Ca(ClO)_2$•$3H_2O$ (1.1)	12	12
8[i]	NaClO•$5H_2O$ (2.2)	12	54
9[j]	NaClO•$5H_2O$ (2.2)	12	75

[a]Unless otherwise noted, 2 mmol of **2** was dispersed in water (1.5 M). [b]Isolated yields. [c]In air. [d]In air containing ca. 4% CO_2. [e]10 mmol (2.5 g) scale. [f]100 mmol (25 g) scale. [g]The reaction was started at 0 °C. [h]Commercially available aqueous NaClO was used. [i]Under solvent-free conditions. [j]Run with **2** (3 M).

To our delight, the new strategy could be employed for one-pot direct preparation of Dess-Martin reagent **4**, as the only by-product is NaCl. After reaction of **2** under the optimized conditions (Table 1 entry 2), the reaction mixture was neutralized, washed with water, and dried. In the same flask, **1** was then acetylated with acetic anhydride (9 equiv) in acetic acid at 85 °C to give analytically pure **4** in 90% yield (Scheme 1).[3a] In contrast, an attempt at direct synthesis of **4** with Oxone instead of NaClO•$5H_2O$ was unsuccessful,[5] partly because of the formation of large amounts of inorganic acidic by-products, such as $KHSO_4$.



Scheme 1

In conclusion, our results demonstrate that oxidation of 2-iodobenzoic acid with NaClO•$5H_2O$ under CO_2 is an efficient, convenient and safe method for the synthesis of IBX and Dess-Martin reagent. Key advantages include: 1) easy work-up – filtration of the reaction mixture, followed by washing of the cake with water and acetone on a glass filter was sufficient to afford analytically pure **1**; 2) no formation of harmful/toxic waste – environmentally safe NaCl is a sole by-product; 3) safety – all of the batches of **1** obtained by our procedure were inert when hit with a steel hammer or scraped intensively with a stainless steel spatula.[4] Further studies on the reaction mechanism and applications are in progress.

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SUPPORTING INFORMATION

Supplementary data (representative experimental procedures and analytical data for reaction products) associated with this article can be found, in the online version, at URL: https: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27083/103/2

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