

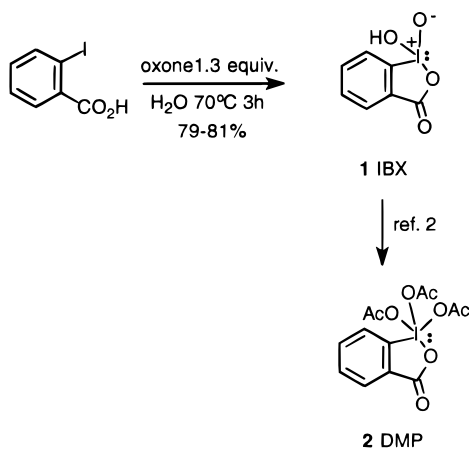
## A User-Friendly Entry to 2-Iodoxybenzoic Acid (IBX)

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IBX, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (2-iodoxybenzoic acid **1**), has been known for more than a century, although its presence on the scene of organic synthesis has remained limited primarily due to its remarkable insolubility in most organic solvents.<sup>1,2b,3a</sup>



In 1983, Dess and Martin reported that IBX could be transformed into the far more soluble periodinane **2**, 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, by warming **1** in an acetic anhydride–acetic acid mixture.<sup>2</sup> Since then, the Dess–Martin periodinane has met with remarkable success for the smooth and selective transformation of alcohols into carbonyl compounds.<sup>2b</sup>

Besides its use as the Dess–Martin periodinane precursor, IBX itself functions as a valuable oxidant of functionalized alcohols when dissolved in DMSO or suspended in other solvents.<sup>3</sup> A number of applications of the reagent have emphasized its generality as a mild oxidizing agent<sup>4</sup> as well as its ability to perform delicate transformations. In particular, IBX oxidizes *vic*-diols without cleaving the glycol C–C bond<sup>3a,5</sup> and allows the

selective oxidation of 1,4-diols to  $\gamma$ -lactols<sup>6</sup> and the oxidative ring closure of amino alcohols to amins.<sup>7</sup> A more recent protocol reports the easy regeneration of carbonyl compounds from oximes or tosylhydrazones by IBX.<sup>8</sup>

Although numerous syntheses of IBX from 2-iodo<sup>9a,b</sup> or 2-iodosobenzoic<sup>9c,d</sup> acid have been described over the years; in most cases, the reported procedures deliver a reagent of poor quality that requires tedious purification. In this light, the Greenbaum procedure<sup>10a</sup> and subsequent modifications<sup>2a,10b,c</sup> stand as significant improvements, giving optimal yields and somewhat better purity, and represent the state-of-the-art procedure for IBX synthesis. However, these KBrO<sub>3</sub>-based oxidation methods are unappealing for the user in that the reaction is performed in hot aqueous sulfuric acid (0.73 M), KBrO<sub>3</sub> is classified as a carcinogen (R-45) in the international classification of substance toxicity, and obnoxious bromine vapors are copiously evolved (62 g/mol of IBX) from the reaction mixture, with personal and environmental contamination risk. Still, incomplete oxidation of 2-iodobenzoic acid is not totally avoided and recovered IBX is contaminated with variable amounts of less-oxidized precursors.<sup>11</sup>

We have now found that the use of Oxone (2KHSO<sub>5</sub>–KHSO<sub>4</sub>–K<sub>2</sub>SO<sub>4</sub>) provides a practical entry to IBX. The oxidation was complete in 3 h in water at 70–75 °C,<sup>12</sup> with 1.3 equiv of oxone (using a 0.44 M solution). IBX was recovered easily from the reaction mixture in high yields (79–81%) and good purity ( $\geq 95\%$ ) by cooling, filtering, and washing the crystals with water and acetone. Moreover, by using a greater dilution and excess oxone (3 equiv), a clear solution was obtained after 1 h at 70 °C from which IBX crystallized upon cooling, free from any reduced contaminant in 77% yield. This new procedure offers distinct advantages over the previous ones: (i) experimental convenience, since it uses a nontoxic reagent and water as solvent, (ii) environmentally safe sulfate salts as the only byproducts, and (iii) easy adaptation of the method to produce analytically pure ( $\geq 99\%$ , NMR) samples of IBX.

The experimental procedure detailed below has been performed several times, by different operators, to pro-

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(8) Bose, D. S.; Srinivas, P. *Synlett* **1998**, 977.

(9) (a) Cl<sub>2</sub>/NaOCl: Bell, R.; Morgan, K. J. *J. Chem. Soc.* **1960**, 1209. (b) Cl<sub>2</sub>: Katritzky, A. R.; Duell, B. L.; Gallos, J. K. *Org. Magn. Reson.* **1989**, *27*, 1007. (c) KMnO<sub>4</sub>: ref 1. (d) Cl<sub>2</sub>: Hartman, C.; Meyer, V. *Chem. Ber.* **1894**, *27*, 1600.

(10) (a) Greenbaum, F. R. *Am. J. Pharm.* **1936**, *108*, 17. (b) Banerjee, A.; Banerjee, G. C.; Bhattacharya, S.; Banerjee, S.; Samaddar, H. *J. Ind. Chem. Soc.* **1981**, *58*, 605. (c) An improved procedure for the preparation of IBX and the Dess–Martin periodinane, which is a modification of the classic KBrO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub> procedure, is in press (Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.*).

(11) We have prepared several 5–200 g batches of IBX (75–85% yield) according to the Dess–Martin procedure.<sup>2b</sup> The purity of the reagent varied between 90 and 95%, the major contaminants being 2-iodobenzoic acid (1–3%) and 2-iodosobenzoic acid (5–10%).

(12) Working at higher temperature (95–100 °C) is not advisable since IBX is consistently reduced to 2-iodosobenzoic acid under these conditions; for the same reason, recrystallization from pure water (at 75 °C, 1.0 g of IBX 98% in 60 mL) is unapplicable since the procedure yields a product (56% yield) of decreased purity (90% of IBX, 7% and 3% of 2-iodoso and 2-iodobenzoic acid, respectively).

(1) Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727.  
(2) (a) Dess, B. D.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, B. D.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277 and references therein. Improved protocols for the preparation of **2** from **1** have been reported: (c) Ireland, R. E.; Liu, L. J. *J. Org. Chem.* **1993**, *58*, 2899. (d) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.  
(3) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (b) Frigerio, M.; Santagostino, M.; Sputore S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (c) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272.  
(4) For some recent examples, see: Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 3149. Varadarajan, S.; Mohapatra, D. K.; Datta, A. *Tetrahedron Lett.* **1998**, *39*, 1075. Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, *38*, 8245. Pearson, W. H.; Clark, R. B. *Tetrahedron Lett.* **1997**, *38*, 7669. Andrus, M. B.; Shih, T.-L. *J. Org. Chem.* **1996**, *61*, 8780. Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498.  
(5) Frigerio, M.; Santagostino, M.; Sputore, S. *Synlett* **1997**, 833. Hegde, S. G.; Myles D. C. *Tetrahedron Lett.* **1997**, *38*, 4329.

vide 45–50 g batches of IBX with reproducible yields and purity.

### Experimental Section

**CAUTION!** IBX is explosive under impact or heating to >200 °C.<sup>13</sup> Sporadically, IBX did not decompose explosively at 233 °C, but melted with browning. However, this *cannot be taken as an indication of absence of explosivity since the same batch showed inconsistent results*. An analytically pure sample (≥99%) was subjected to explosibility tests, which confirmed the earlier observations by Plumb and Harper.<sup>13</sup>

Reagents were commercially available and were used without further purification. Reactions were conducted in an open flask. Elemental analyses and water (Karl Fisher) determination were carried out by Redox, Cologno Monzese (Milano, Italy).

**IBX, 1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-Oxide (1)** (≥95% Purity). 2-Iodobenzoic acid (50.0 g, 0.20 mol) was added all at once to a solution of Oxone (181.0 g, 0.29 mol, 1.3 equiv) in deionized water (650 mL, 0.45 M) in a 2 L flask. The reaction mixture was warmed to 70–73 °C over 20 min and mechanically stirred at this temperature for 3 h. The aspect of the mixture varies consistently during the reaction. The initial thick slurry coating the walls of the flask eventually becomes a finely dispersed, easy to stir suspension of a small amount of solid that sedimented easily upon stopping the stirring. The suspension was then cooled to 5 °C and left at this temperature for 1.5 h with slow stirring. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly

rinsed with water (6 × 100 mL) and acetone (2 × 100 mL). The white, crystalline solid was left to dry at rt for 16 h and weighed 44.8–45.7 g (79–81%).

Mother and washing liquors were oxidizing and acidic. They were treated with solid Na<sub>2</sub>SO<sub>3</sub> (70 g, 0.55 mol) and neutralized with NaOH (1 M) before disposal. The internal temperature rose to 30 °C.

The purity of IBX obtained by this method was ≥95% (<sup>1</sup>H NMR, elemental analysis). The remainder was 2-iodosobenzoic (4%) and 2-iodobenzoic (~0.5%) acids, as judged by integration of the triplets at 7.70 and 7.47 ppm, respectively, in the <sup>1</sup>H NMR spectrum (ca. 5 mg in 0.5 mL of DMSO-*d*<sub>6</sub>).

Mp: 233 °C dec (lit.<sup>2b</sup> mp 232–233 °C). Anal. Calcd for C<sub>7</sub>H<sub>5</sub>IO<sub>4</sub>: C, 30.03; H, 1.80; I, 45.32. Found: C, 30.16; H, 1.82; I, 45.32. H<sub>2</sub>O <0.1% (K.F.). <sup>1</sup>H NMR, <sup>13</sup>C NMR, and IR spectra all agree with those previously reported.<sup>3a</sup>

IBX (≥99% purity, <sup>1</sup>H NMR, elemental analysis) was similarly prepared by adding 2-iodobenzoic acid (5.0 g, 0.020 mol) to an Oxone solution in deionized water (37.2 g, 0.061 mol, 3 equiv in 200 mL) in a 0.5 L flask. The suspension was set to 70 °C; after 1 h at this temperature a clear solution was obtained that delivered analytical grade IBX upon cooling the solution to 0–5 °C for 0.5 h and filtering and washing the crystals as described before (4.4 g, 77%).

Mp: 233 °C dec. Anal. Found: C, 30.02; H, 1.77; I, 45.09. H<sub>2</sub>O <0.1% (K.F.).

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