



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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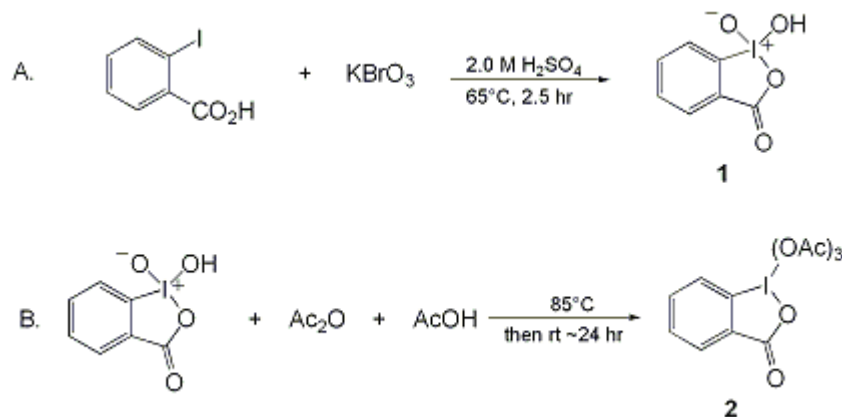
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 10, p.696 (2004); Vol. 77, p.141 (2000).

THE DESS-MARTIN PERIODINANE: 1,1,1-TRIACETOXY-1,1-DIHYDRO-1,2-BENZIODOXOL-3(1H)-ONE

[1,2-Benziodoxol-3(1H)-one, 1,1,1-tris(acetyloxy)-1,1-dihydro-]



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Checked by Kevin P. Minbiolo and Amos B. Smith, III.

1. Procedure

Caution: Compounds **1** and **2** are heat- and shock-sensitive compounds, showing exotherms when heated (>130°C). All operations should be conducted behind an explosion shield.

A. 1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (1). A 2-L, three-necked, round-bottomed flask, fitted with a mechanical stirrer, condenser, and an immersion thermometer is charged with 80.0 g (0.48 mol) of potassium bromate (KBrO₃) and 750 mL of 2.0 M sulfuric acid (Note 1), (Note 2), (Note 3). The resulting clear solution is heated to 60°C in an oil bath and 80.0 g of finely powdered 2-iodobenzoic acid (0.323 mol) is added in ~10-g portions over 40 min (Note 4), (Note 5). The solution becomes red-orange, bromine vapor is evolved, and a white solid begins to separate (Note 6). After the addition is complete, the temperature is maintained at an internal temperature of 65°C for 2.5 hr (Note 3).

The reaction mixture is cooled to 2-3°C in an ice-water bath, and the resulting solids are collected by vacuum filtration (Note 7), (Note 8). The filter cake is thoroughly washed successively with 500 mL of cold deionized water, 2 × 80 mL of absolute ethanol, and 500 mL of cold deionized water affording 88.2 g (98% of theoretical) of moist solid iodine oxide **1** (Note 9), (Note 10).

B. 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (2). A 1-L, three-necked, round-bottomed flask, equipped for magnetic stirring and fitted with an immersion thermometer, is charged with 88.2 g of the moist solid iodine oxide **1**, 150 mL of glacial acetic acid, and 300 mL of acetic anhydride (Note 11). The flask is flushed with dry argon, and maintained under a dry argon atmosphere. Magnetic stirring is commenced, and the mixture is heated to 85°C (internal temperature) over 30 min by means of an oil bath, and kept at this temperature until all the solids dissolve (~20 min) to afford a colorless to clear yellow solution (Note 12). Heating and stirring are discontinued and the reaction mixture is allowed to cool slowly to room temperature in the oil bath for 24 hr. A large quantity of colorless crystals separate during this time (Note 13). The resulting crystalline solids are isolated by careful vacuum filtration in the reaction vessel under argon using a fritted adapter followed by washing the solids with three 80-mL portions of anhydrous ether and subsequent vacuum filtration in the reaction vessel as above (Note 14), (Note 15). Residual solvent is removed under vacuum affording 101.0 g (74% yield over 2 steps) of periodinane **2** as a white, free-flowing crystalline solid that is largely or

completely soluble (slightly cloudy to clear solution) in [chloroform](#) and [methylene chloride](#) and is sufficiently pure (~95%) to be suitable for use in oxidations ([Note 16](#)),([Note 17](#)),([Note 18](#)),([Note 19](#)).

2. Notes

1. Although no problems with explosion of **1** or **2** have been encountered in the use of this procedure, prudence dictates that all operations should be conducted behind an explosion shield.^{2,3 4 5 6 7,8}
2. [Potassium bromate](#) (>99.5%) was used as received from Fluka Chemical Co.
3. Use of higher concentration [sulfuric acid](#) (~2.0 M) than traditionally employed is crucial to allow complete conversion of the [2-iodobenzoic acid](#) to **1**.² In the submitters hands, use of lower concentrations (~0.5 M) of [sulfuric acid](#) at 60°C led to exclusive formation of 1-hydroxy-1,2-benziodoxol-3(1H)-one. When lower concentrations of [sulfuric acid](#) are employed, higher temperatures are required to effect oxidation, as judged by the initiation of [bromine](#) evolution. One of the factors leading to the lack of reproducibility in the preparation of **2** results from incomplete conversion to **1**.
4. [2-Iodobenzoic acid](#) (Aldrich Chemical Company, Inc.) was recrystallized from [toluene](#) (100 g/500 mL).
5. The [bromine](#) vapors are vented by inverting a funnel over the open condenser (allowing a small gap between the funnel and the condenser top) with the stem attached to a gas washing bottle containing saturated aqueous [sodium thiosulfate](#) solution, which is in turn, connected to a water aspirator.
6. Addition of the [2-iodobenzoic acid](#) to the bromate-aqueous acid mixture results in an easily controlled, smooth reaction and an easily stirred reaction mixture. The stirring rate should be regulated such that splashing is minimized and solids do not accumulate on the walls or roof of the reaction vessel. Any solids which adhere to the sides or roof of the reaction vessel above the level of the liquid should be washed back into the reaction mixture with the minimum amount of 2M [sulfuric acid](#). Addition of the bromate to the mixture of [iodobenzoic acid](#) and [sulfuric acid](#) as originally described,² led to a thick precipitate that was difficult to stir, and the accumulation of solid on the walls of the reaction vessel. Given the thermal sensitivity of **1**, the present procedure appears much safer ([Note 1](#)).^{8,9}
7. The reaction mixture is thoroughly cooled prior to filtration and cold water is employed for washing because of the low but appreciable solubility of **1** in water (~0.3 g/100 mL).
8. Use of a ceramic Büchner funnel with coarse filter paper is recommended to avoid scraping a glass frit during removal of **1**. A rubber spatula is recommended for stirring and manipulation of the filter cake. The filter cake can be conveniently removed from the funnel by applying a small amount of air pressure to the stem.
9. All washes were conducted by slurrying the solids on the filter bed with a rubber spatula followed by application of the vacuum. In view of the sensitivity ([Note 10](#)) of this intermediate and/or the periodinane **2**,^{3 4 5 6 7} care should be taken to avoid thorough drying of the solid oxide **1**. The use of the [ethanol](#) washes appears essential to reduce further the explosion hazard. These washes presumably destroy any unreacted bromate present in the solids. The submitters have observed that another of the factors leading to the lack of reproducibility in the preparation of the periodinane is associated with the incomplete removal of [ethanol](#) after the washing in an effort to avoid drying the oxide **1**. The presence of [ethanol](#) in the oxide results in destruction of the periodinane **2** as it is formed in the next transformation. The use of a final aqueous wash serves to remove the [ethanol](#) and keep the oxide moist. This moisture is not detrimental in the next reaction. Small samples of moist solid **1** were also washed successively with reagent grade [acetone](#) and anhydrous [ether](#), and residual solvent was removed under vacuum. Identical overall yields of **2** were obtained by both procedures.
10. Recently, the ¹H NMR of **1** in d₆ DMSO has been reported.⁹ The ¹H NMR spectrum of **1** prepared as described above was identical to that reported: ¹H NMR (400 MHz in d₆ DMSO) δ as follows: 7.84 (t, 1 H, J = 14.8), 7.99 (t, 1 H, J = 7.9), 8.02 (d, 1 H, J = 14.8), 8.15 (d, 1 H, J = 7.9) . Incomplete conversion results in impurity peaks at δ 7.71 (t or m, 1 H) from 1-hydroxy-1,2-benziodoxol-3(1H)-one or from both 1-hydroxy-1,2-benziodoxol-3(1H)-one and [2-iodobenzoic acid](#) (if both are present), and δ 7.48 (t, 1 H) and 7.25 (t, 1 H) from [2-iodobenzoic acid](#) (if present). Conversion to **1** can also be conveniently assayed by reduction of a weighed sample of **1** with excess aqueous [sodium iodide](#) and titration of the resulting [iodine](#) with standardized 1N [sodium thiosulfate](#) solution to a colorless endpoint (1 mmol of thiosulfate per mmol of **1** required). The physical properties of authentic **1** are also diagnostic. From the present procedure, **1** is obtained as a somewhat granular, easily-filtered solid. 1-Hydroxy-1,2-benziodoxol-3(1H)-one or impure samples of **1** containing significant amounts of 1-hydroxy-1,2-

benziodoxol-3(1H)-one and possibly 2-iodobenzoic acid are obtained as sticky precipitates which are difficult to filter and wash, and which retain substantial amounts of solvent. *Samples of the moist oxide 1 were found to exhibit impact sensitivity and were found to exhibit exotherms upon heating (> 130°C) characteristic of an explosive material upon examination by differential scanning calorimetry.*^{2,3,4}

^{5,6,7,8}

11. Glacial acetic acid and acetic anhydride were used as received from J. T. Baker Chemical Co. The checkers used glacial acetic acid as received from Fisher Scientific and acetic anhydride (99%) as received from Aldrich Chemical Company, Inc.

12. Monitoring the reaction by NMR immediately upon dissolution of **1** indicated that the major product was the desired **2** accompanied by a minor amount of what is likely the I(V) monoacetate and a small amount (<5%) of 1-acetoxy-1,2-benziodoxol-3(1H)-one possibly resulting from incomplete oxidation to **1** (see (Note 17) for chemical shift values). Heating the reaction mixture for 3 hr at 110°C results in complete conversion to 1-acetoxy-1,2-benziodoxol-3(1H)-one; thus prolonged heating should be avoided.

13. Slow cooling affords better product crystallinity and easier handling during isolation of **2**.

14. Ether was dried and deoxygenated by distillation from sodium benzophenone ketyl under nitrogen just prior to use. Experience has shown that the quality of reagent **2** is most directly affected by 1) failure to control conversion to the triacetate and 2) exposure to moisture during filtration and other manipulations performed during isolation of the periodinane. Extensive hydrolysis of **2** was observed when washing with ether was conducted in a humid environment.

15. Vacuum filtration was accomplished with a water aspirator fitted with a drying tube. A gas inlet tube with a Teflon stopcock and a medium to coarse porosity glass fritted disc sealed in the bottom of the joint was employed for filtration in the flask. The outlet of the fritted adapter is connected to a filter flask that is attached to a water aspirator, and argon is introduced to equalize pressure in the flask during filtration. The fritted outlet adapter can be purchased from Ace Glass Co., Vineland, NJ (Cat. No. 5295-16-SP). The checkers used a similar adapter from United Glass Technologies. A glove bag or Schlenk filtration is also suitable to effect filtration under an inert atmosphere when the humidity is high.



16. The submitters reported a two-step yield of 111.0 g (80%).

17. The purity of the Dess-Martin periodinane (**2**) was assayed by treatment of **2** (1 equiv) with an excess of benzyl alcohol (2 equiv) in methylene chloride (CH₂Cl₂) followed by analysis of the reaction mixture for benzaldehyde by capillary vapor phase chromatography (15-m fused silica capillary column, Durawax DX3 stationary phase, 120°C). After correction for response factors, the purity was established to be ≥95%.

18. The Dess-Martin periodinane (**2**) had ¹H NMR (300 MHz in CDCl₃) δ as follows: 1.99 (s, 6 H), 2.32 (s, 3 H), 7.91 (t, 1 H, J = 7.4), 8.09 (t, 1 H, J = 8.1), 8.29 (d, 2 H, J = 8.1). Minor impurity peaks were observed at δ 8.39 (d), 8.21 (d), 8.00 (d), 7.27 (s), and 2.08 (s) (possibly the mono acetate); ¹³C NMR (75 MHz in CDCl₃) δ: 20.2, 20.4, 125.9, 126.5, 131.7, 133.8, 135.8, 142.2, 166.1, 174.0, 175.7. The checkers note that a freshly opened bottle of deuteriochloroform (CDCl₃) was required to dissolve **2** and that drying of older CDCl₃ by running the solvent through potassium carbonate (K₂CO₃) did not facilitate dissolution. The submitters observed the same phenomenon and believe that traces of acid in the fresh CDCl₃ may be responsible for this observation.

19. The Dess-Martin periodinane (**2**) can be stored in a dark bottle under argon at ~ -20°C in a freezer.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

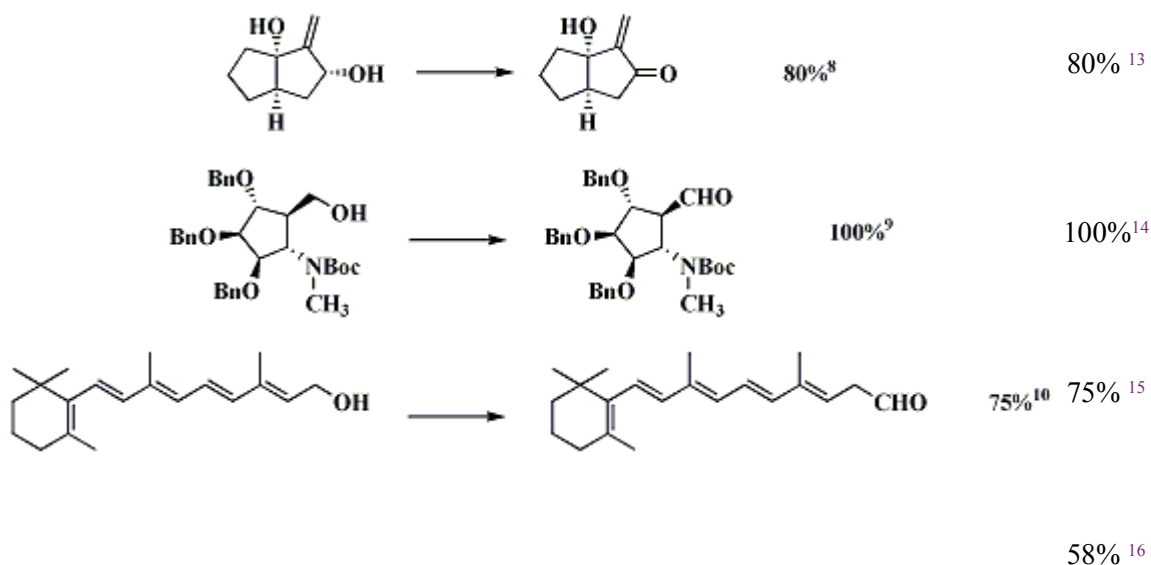
3. Discussion

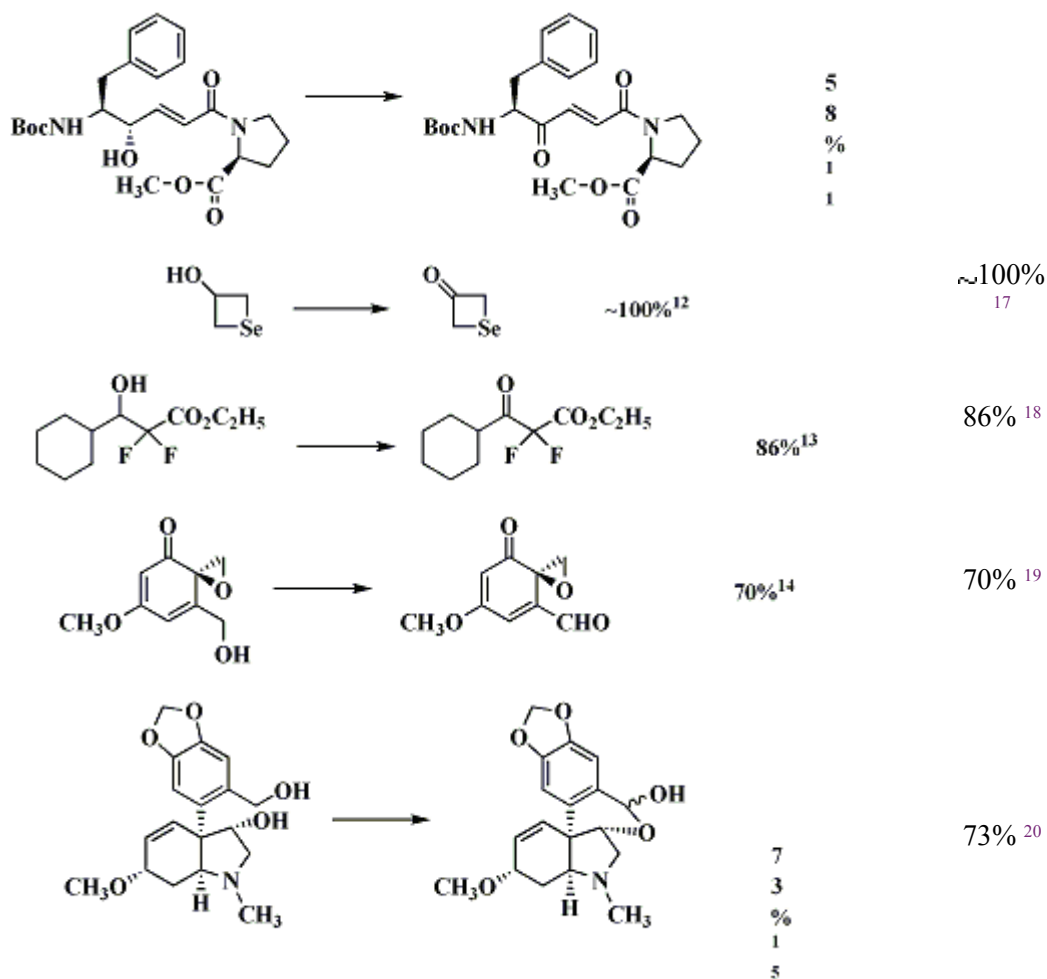
The Dess-Martin periodinane [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (**2**)] is one of several 12-I-5 periodinane species developed by J. C. Martin and co-workers, and has found wide acceptance and utility for the selective oxidation of primary and secondary alcohols to carbonyl compounds.^{2,10} The present procedure is a variation of the Martin procedure and is based heavily upon it.² Modified preparations have been reported by Ireland and Schreiber.^{11 12} The reported explosiveness of samples of impure **2**^{3 4 5 6 7} has prompted a more thorough examination of the properties of **2**.² Possible impurities that could be responsible for rendering the samples explosive are **1** and/or the monoacetate derivatives of **1** and **2** that could arise by incomplete oxidation to **1** or hydrolysis of **2** on storage. Samples of **2** that indicate the presence of significant quantities of **1** or the monoacetate derivatives of **1** and **2** as judged by ¹H NMR should be handled with caution. *Although these investigations were inconclusive as to the precise nature of the impurity/ies that rendered the impure samples of **2** explosive, fresh samples of crude moist **1** were found to be both impact and heat sensitive, decomposing explosively under confinement. Pure **2** is significantly less temperature and impact sensitive; nevertheless, it should be handled with appropriate caution as a potentially explosive material.*⁸

The Dess-Martin periodinane (**2**) has found wide utility as a selective oxidant in sensitive, highly functionalized intermediates commonly encountered in the synthesis of natural products and related complex molecules.² The Dess-Martin periodinane (**2**) has several advantages over other commonly employed oxidizing agents such as chromium(VI)-based reagents and dimethyl sulfoxide (DMSO)-based oxidations including nearly ideal stoichiometry, mild non-acidic or mildly acidic reaction conditions, shorter reaction times, relative ease in the preparation and storage of the reagent, simplified workups with easy removal of the by-products of oxidation, the ease of safe disposal of residues, and the lower toxicity of the reagents and by-products [relative to chromium(VI) reagents in particular].²

A selection of cases in which **2** has been found to be particularly efficacious is given in the Table. Additional examples are cited in references ¹ and ⁹. Particularly noteworthy examples include the oxidation of acid- and base-sensitive systems, systems containing sulfur and selenium, and 1,3-diols to 1,3-dicarbonyl compounds. Use of chromium reagents in these latter cases often leads to fragmentation products.

TABLE





References and Notes

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- Differential scanning calorimetry and impact studies on **1** and **2** were performed by the courtesy of Dr. David Coffen and his colleagues of Hoffmann La-Roche Inc., and Dr. Ichiro Shinkai and his colleagues of Merck Co. Both moist and partially dried samples of **1** were found to exhibit impact sensitivity and large exotherms characteristic of potentially explosive deflagration were observed beginning at temperatures above 140°C. Samples of pure **2** appeared somewhat less impact sensitive, and had smaller exotherms beginning at ~170°C, but prudence dictates that **2** be handled with appropriate precautions as well.
- Recently, an alternative preparation of **1** employing oxone as the oxidant has been reported: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

1,1,1-Triacetoxo-1,1-dihydro-1,2-benziodoxol-3(1H)-one:
1,2-Benziodoxol-3(1H)-one, 1,1,1-tris(acetyloxy)-1,1-dihydro- (11); (87413-09-0)

1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide:
1,2-Benziodoxol-3(1H)-one, 1-hydroxy-, 1-oxide (10); (61717-82-6)

Potassium bromate:
Bromic acid, potassium salt (8,9); (7758-01-2)

2-Iodobenzoic acid:
Benzoic acid, o-iodo- (8);
Benzoic acid, 2-iodo- (9); (88-67-5)

Bromine (8,9); (7726-95-6)

Glacial acetic acid:
Acetic acid (8,9); (64-19-7)

Acetic anhydride (8);
Acetic acid anhydride (9); (108-24-7)