

Synthesis and reactions of amino acid-derived benziodazole oxides: new chiral oxidizing reagents

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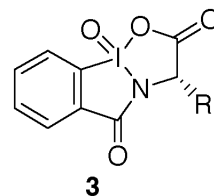
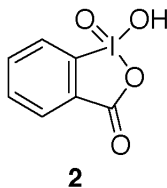
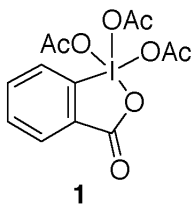
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Abstract

The novel benziodazole oxides (**3**) can be prepared by oxidation of the readily available 2-iodobenzamides (**5** or **6**) with potassium bromate. Benziodazole oxides can find practical application as selective oxidizing reagents analogous to the widely used Dess–Martin periodinane (**1**) and benziodoxole oxide (**2**). Preliminary results indicate that reagents **3** can oxidize primary alcohols to aldehydes, while non-symmetric sulfides are oxidized to chiral sulfoxides with moderate enantioselectivity. © 2000 Published by Elsevier Science Ltd.

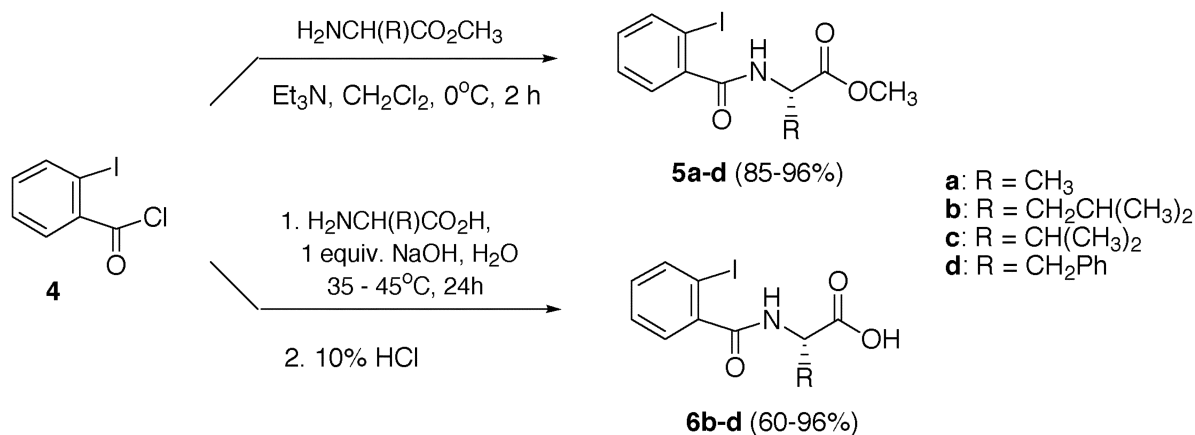
The Dess–Martin periodinane (**1**) as well as its precursor, benziodoxole oxide **2**, have found wide practical application in organic synthesis as reagents for oxidation of alcohols to carbonyl compounds.¹ Dess–Martin reagent **1** is particularly useful in natural product synthesis as a mild, selective oxidizer soluble in dichloromethane, chloroform or acetonitrile. Reagent **2** is a cheaper alternative to Dess–Martin reagent; however, its practical application is limited due to the potentially explosive nature and insolubility in common solvents.¹ Despite these limitations, benziodoxole oxide **2** was shown to be particularly useful as the reagent for a highly selective oxidation of alcohols to carbonyl compounds in DMSO.²



We wish to report the preparation, structure, and chemistry of novel cyclic derivatives of penta-valent iodine, benziodazole oxides **3**. In contrast to the analogous benziodoxole oxide **2**, compounds **3** are non-explosive and are soluble in dichloromethane and other common non-polar organic

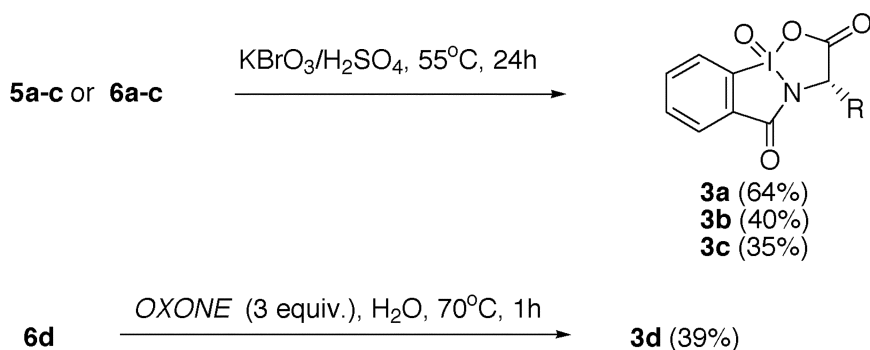
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solvents. These new benziodazole oxides (**3**) can be conveniently prepared by oxidation of the readily available 2-iodobenzamides (**5** or **6**) with potassium bromate or OXONE[®] (2KHSO₅/KHSO₄/K₂SO₄). The starting materials, 2-iodobenzamides **5** and **6**, are prepared in high yield from the commercially available 2-iodobenzoyl chloride **4** and natural amino acids or their methyl esters (Scheme 1).³



Scheme 1.

Oxidation of methyl esters **5** by potassium bromate in aqueous sulfuric acid affords products **3** in moderate yields along with benziodoxole oxide **2** as the by-product due to hydrolysis of amides **3** (Scheme 2).⁴ To minimize the formation of by-product **2**, we used milder reaction conditions compared to the originally reported conditions for the bromate oxidation.⁵ Amides **6** can be oxidized to products **3** under similar conditions (Scheme 2), but the yields are generally lower. The structure of products **3** was elucidated from spectral data in comparison with the previously reported benziodazoles.⁶ In addition, the structure of product **3a** was theoretically investigated by ab initio molecular orbital calculations (Fig. 1).⁷ According to the calculations, the molecule is planar with the alkyl group **R** and the oxygen atom of $\text{I}=\text{O}$ out of plane. The geometry around the iodine atom resembles a typical see-saw structure derived from a trigonal bipyramidal electron pair geometry.



Scheme 2.

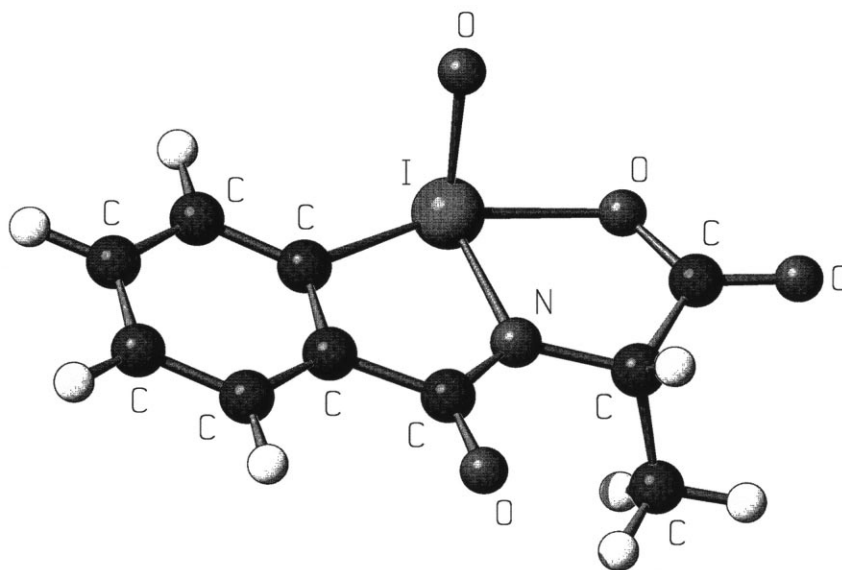
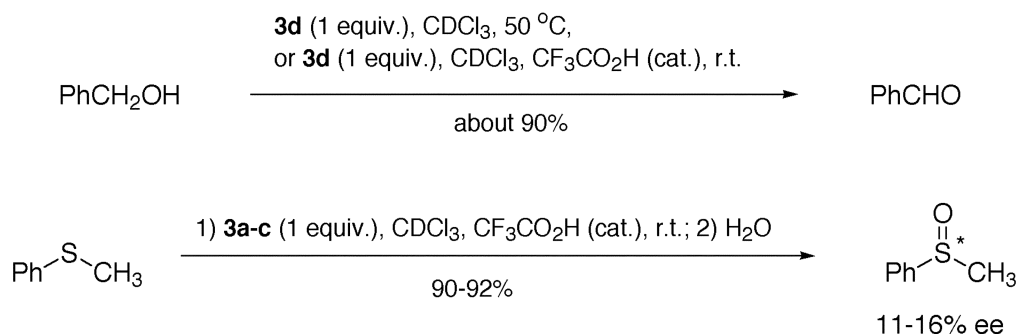


Figure 1. Calculated structure of benziodazole oxide **3a** at the HF/LANL2DZ level of theory. Selected bond lengths and angles: I–N 2.02 Å, I–C 2.13 Å, I–O 2.13 Å; C–I–O 155.1°

Derivatives of phenylalanine (**5d** and **6d**) form only products of decomposition under bromate oxidation reaction conditions. We have found, however, that **6d** can be oxidized by the commercially available oxidizer OXONE[®] instead of potassium bromate. Oxidation of 2-iodobenzamide **6d** by OXONE[®] in distilled water affords benziodazole oxide **3d** in a moderate yield (Scheme 2).⁸

We expect that benziodazole oxides and their derivatives can find practical application as selective, chiral oxidizing reagents in organic synthesis. Preliminary results indicate that compounds **3** can selectively oxidize primary alcohols to aldehydes similarly to benziodoxoles **1** and **2**. For example, reagent **3d** slowly reacts with benzyl alcohol in chloroform at 50°C affording benzaldehyde as the only product detected by ¹H NMR. This reaction can be accelerated in the presence of catalytic amount of trifluoroacetic acid. Under similar conditions, reagents **3** oxidize organic sulfides to sulfoxides in almost quantitative yield. Oxidation of non-symmetric sulfides affords chiral sulfoxides with moderate enantioselectivity (Scheme 3).



Scheme 3.

In conclusion, the novel benziodazole oxides (**3**) can be prepared by oxidation of the readily available 2-iodobenzamides (**5** or **6**) with potassium bromate. In contrast to the known benziodoxole oxide (**2**), they are non-explosive and are soluble in dichloromethane and other common non-polar organic solvents. We expect that benziodazole oxides and their derivatives can find practical application as selective, chiral oxidizing reagents in organic synthesis.

Acknowledgements

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- Representative procedure for the preparation of amides 5*: To a stirred, cold (ice-bath) mixture of L-alanine methyl ester hydrochloride (1.396 g, 10 mmol) in CH₂Cl₂ (50 ml), triethylamine (2.78 ml, 20.0 mmol) and 2-iodobenzoyl chloride (2.67 g, 10 mmol) were slowly added. After 2 hours of additional stirring, water (40 ml) was added and organic layer was separated. The organic layer was washed with 10% hydrochloric acid (50 ml), 5% sodium hydroxide (2×25 ml) and dried over anhydrous magnesium sulfate. Solvent was evaporated and resulting yellow solid was recrystallized from ethylacetate–hexane and dried in vacuum to afford 3.3 g (96%) of analytically pure amide **5a**: mp 130–131.5°C; ¹H NMR (CDCl₃): 7.83 (d, 2H), 7.40 (m, 2H), 6.50 (br.d, 1H, NH), 4.80 (m, 1H), 3.80 (s, 3H), 1.58 (d, 3H). Anal. calcd for C₁₁H₁₂INO₃: C, 39.66; H, 3.63; N, 4.20. Found: C, 39.83; H, 3.76; N, 4.25.
- Representative procedure for preparation of benziodazole oxides 3 by bromate oxidation*: To a stirred mixture of **5a** (3.331 g, 10 mmol) in 0.75 M sulfuric acid (150 ml) at 55°C, potassium bromate (2.171 g, 13 mmol) was added over a 0.5 hour period. The mixture was stirred for 24 hours at 55°C. The resulting solution was cooled to 0°C and the precipitate was filtered. The precipitate was washed with water (100 ml), acetone (75 ml), diethyl ether (50 ml), and dried in vacuum to yield 2.141 g (64%) of benziodazole oxide **3a**: mp 151°C (with decomposition); ¹H NMR (CDCl₃): 8.31 (d, 1H), 8.19 (d, 1H), 7.81 (t, 1H), 7.68 (t, 1H), 5.00 (q, 1H), 1.68 (d, 3H). Anal. calcd for C₁₀H₈INO₄: C, 36.06; H, 2.42; N, 4.21. Found: C, 36.18; H, 2.45; N, 4.30.
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- Preparation of benziodazole oxide 3d by OXONE® oxidation*: To a stirred mixture of **6d** (1.186 g, 3 mmol) in 75 ml of distilled water, OXONE® (5.533 g, 9 mmol) was added all at once. The reaction mixture was warmed to 70–75 °C for 20 min and then stirred at this temperature for 1 hour. The finely dispersed suspension was then cooled to 5°C and left at this temperature for 1.5 hours with slow stirring. The white precipitate was then filtered, washed with 100 ml of distilled water, and dried in a vacuum to give 0.158 g (39%) of **3d**: mp 134–135°C; ¹H NMR (CDCl₃): 8.2 (m, 2H), 7.8–7.6 (m, 2H), 7.4–7.0 (m, 5H), 5.0 (d, 1H, CH), 3.40 (m, 2H, CH₂Ph). ¹³C NMR (CDCl₃): 178.4, 167.2, 135.9, 134.3, 131.4, 130.6, 130.1, 129.6, 129.5, 128.7, 128.1, 120.2, 58.6, 53.5. Anal. calcd for C₁₆H₁₂INO₄: C, 46.97; H, 2.96; N, 3.42. Found: C, 46.75; H, 3.03; N, 3.36.