Oxidation of Alcohols

IBX Amides: A New Family of Hypervalent Iodine Reagents**

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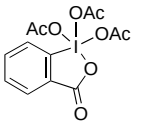
Organic derivatives of pentavalent iodine have found wide application as oxidizing reagents in the synthesis of biologically important complex organic molecules.[1] The most important representatives of this class of compounds, Dess–Martin periodinane (DMP, **1**) and its precursor 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one-1-oxide (**2a**), have emerged as the reagents of choice for the oxidation of alcohols to carbonyl compounds and for other synthetically useful oxidative transformations.[1,2] Reagent **2a** is commonly referred to as 2-iodoxybenzoic acid (IBX, **2b**), although the tautomeric form **2a** is the best representation of the actual structure of this compound. This has been confirmed by X-ray crystallographic analysis, which also indicated that IBX has a polymeric structure formed through an extended linkage of intermolecular secondary I···O bonding interactions.[3] The polymeric structure of IBX renders it essentially insoluble in all nonreactive media. Its low solubility and potentially explosive nature restrict the practical application of this reagent. Herein we report the preparation and structure of novel derivatives of 2-iodoxybenzoic acid, namely 2-iodoxybenzamides **4**, which are stable, soluble reagents with oxidizing properties similar to IBX and DMP. These synthetically valuable characteristics of compounds **4** are best explained by their pseudocyclic structure in which intramolecular secondary I···O bonds partially replace the intermolecular I···O secondary bonds that give rise to the polymeric structures of other reported iodylarenes.



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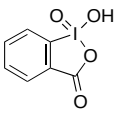
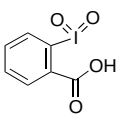
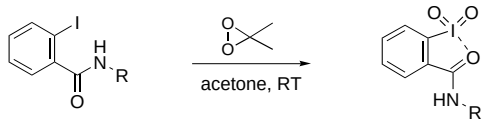


2a



2b

The new 2-iodoxybenzamides **4a–g** were prepared by dioxirane oxidation of the readily available 2-iodobenzamides **3** (Scheme 1) and isolated in the form of stable, white, microcrystalline solids. This procedure allows the preparation of compounds **4** derived from numerous types of amino compounds, such as esters of natural α-amino acids (**4a, 4c**, and **4d**) and non-natural amino acids (**4b**), β-amino acids (**4e** and **4f**), and (*R*)-1-phenylethylamine (**4g**). Optical rotation measurements showed substantially greater $[\alpha]_D$ values for the chiral products **4** relative to the respective amino acids, and, as expected, the values for oxidants **4a** and **4b**, derived from L- and D-alanine, respectively, were opposite in sign and nearly equal in magnitude.[4] It is interesting to note that the dioxirane oxidation of ester derivatives **3a–d** does not result in the formation of cyclic benziodazoles, as has been observed in the oxidation of 2-iodobenzamides derived from α-amino acids[5a] and some other precursors.[5b–d]



3a-g → **4a-g** (45-73%)

a: R = (*S*)-CH(CH$_3$)CO$_2$CH$_3$
b: R = (*R*)-CH(CH$_3$)CO$_2$CH$_3$
c: R = (*S*)-CH(CH$_2$Ph)CO$_2$CH$_3$
d: R = (*S*)-CH(*i*-Bu)CO$_2$CH$_3$
e: R = CH$_2$CH$_2$CO$_2$H
f: R = CH(CH$_3$)CH$_2$CO$_2$H
g: R = (*R*)-CH(Ph)CH$_3$

Scheme 1. Preparation of 2-iodoxybenzamides **4a–g**.

Products **4** were characterized by elemental and spectroscopic analysis, as well as single-crystal X-ray analysis in the case of **4c**.[6,7] IR spectra of all compounds showed an N-H absorption at about $\tilde{\nu} = 3300\ cm^{-1}$, a carbonyl stretch at $\tilde{\nu} =$

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1610–1620 cm^{-1}, and an I=O absorption at $\tilde{\nu} = 780–740\ cm^{-1}$. The signals of the N-H protons in the ^1H NMR spectra of compounds **4** were observed as a characteristic doublet (broad singlet for **4e**) centered at about $\delta = 9.6$ ppm. The most characteristic signals in the ^{13}C NMR spectra of compounds **4** were those of the carbon atom of the amide carbonyl group at $\delta = 165–166$ ppm and C-IO_2 at $\delta =$ ca. 149 ppm. All products **4** have moderate solubility in common organic solvents, such as chloroform, dichloromethane, and acetonitrile.

A single crystal of **4c** suitable for X-ray crystallographic analysis was obtained through the slow evaporation of an acetonitrile solution and was analyzed as the respective solvate. The unit cell consists of four crystallographically independent molecules that are pseudocentrosymmetrically arranged in a tetrameric structure (Figure 1). Strong secondary I···O bonding interactions between neighboring molecules of this tetramer (e.g., I1–O42 2.690(5) Å, I1–O32(5) 2.594 Å, shown as dashed lines) enforce this arrangement. Hydrogen bonding (shown as dotted lines) between the amide proton of molecules 1 and 3 and an oxygen atom of molecules 2 and 4 link adjacent tetramers together. An additional intramolecular close contact of the hypervalent iodine center with the oxygen atom of the amide group (e.g., I1–O13 2.571(6) Å) within each molecule enforces a planar geometry on the resulting five-membered ring, a geometry that is analogous to that observed for IBX and other benziodoxoles.[3,8]

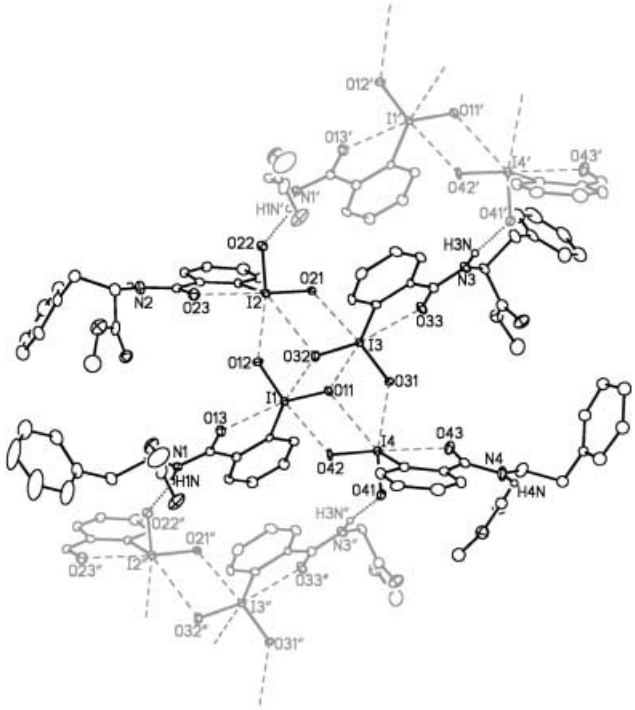
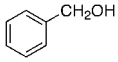


Figure 1. Perspective view of the four crystallographically independent molecules of **4c**·CH_3CN (shown in black, CH_3CN removed for clarity) and extended lattice (shown in gray). Selected distances [Å] and angles [°]: I1–O11 1.823(5), I1–O12 1.807(5), I1–O13 2.571(6), I1–O32 2.594(5), I1–O42 2.690(5), I1–C1 2.114(8); O11–I1–C1 92.4(3), O12–I1–C1 98.4(3), O13–I1–C1 71.0(3).

The solid-state structure suggests that the partial replacement of intermolecular I···O bonds with intramolecular I···O bonds through the introduction of an *ortho* substituent is crucial for stabilization and improved solubility.[9,10] Furthermore, intermolecular I···O interactions in other iodyl benzene derivatives afford structures best described as polymeric, which accounts for their more limited solubility in comparison to **4c**, with its discrete tetrameric structure. The significance of secondary I···O bonding interactions in previously reported iodylbenzene derivatives,[9] including a 2-sulfonyl-substituted iodylbenzene, has recently been discussed by Protasiewicz and co-workers.[10a]

Preliminary experiments demonstrate that 2-iodoxybenzamides show aspects of reactivity similar to both IBX and DMP, but consistent with neither. As outlined in Table 1, a range of alcohols were oxidized to the respective carbonyl compounds under mild conditions. For example, the reaction of benzyl alcohol with **4c** gave benzaldehyde cleanly, as the only product detected by ^1H NMR spectroscopy (Table 1, entry 1). A variety of secondary alcohols were converted into the corresponding ketones in good yields with **4a–c** (Table 1, entries 2, 3, and 5), although reaction times varied as a function of the reagent used. The oxidative kinetic resolution of racemic *sec*-phenethyl alcohol was also investigated with reagents **4a–c**. The reaction mixture containing 0.5 equivalents of the respective oxidant was analyzed by gas chromatography (GC) on a chiral stationary phase. Whereas analysis of the reactions with **4a** and **4b** indicated no enantiomeric enrichment of the alcohol remaining in the product mixture (Table 1, entries 5 and 6), in the reaction with **4c** the alcohol starting material was enriched to a very modest 9% *ee* (Table 1, entry 7). Reagent **4b**, in contrast with DMP, effected

Table 1: Reaction of IBX amides **4a–c** with alcohols.[a]

Entry	Alcohol	Reagent (equiv)	*t* [h]	Yield [%]
1		**4c** (1.02)	2	100
2		**4c** (1.04)	18	98
3		**4c** (1.03)	18	89
4		**4b** (0.50)	24	26[b,c]
5		**4b** (0.50)	72	94[b,c]
6		**4a** (0.51)	72	100[b,c]
7		**4c** (0.46)	18	96[b,d]
8		**4c** (1.00)	48	309[e]

[a] Reactions were carried out in $CDCl_3$ at room temperature. [b] Yield of ketone based on oxidant. [c] Remaining alcohol is racemic, as determined by GC. [d] Remaining alcohol shows 9% *ee*, as determined by GC. [e] Yield of 1,6-hexanedial.

oxidative cleavage of *cis*-1,2-cyclohexanediol to give hexanedial in 30% yield (Table 1, entry 8). It should be emphasized that, according to literature data,[1] iodylbenzene ($PhIO_2$) and other noncyclic iodylarenes do not react with alcohols in the absence of acid catalysis. In agreement with their structural features, the oxidizing reactivity of 2-iodoxybenzamides **4** is closer to that of the benziodoxole-based pentavalent iodine reagents.

In conclusion, we have reported the preparation and structure of novel 2-iodoxybenzamides **4**, which are stable and soluble compounds with unique and synthetically valuable oxidizing properties. X-Ray data on **4c** reveals a pseudobenziodoxole structure in which intramolecular I···O secondary bonds partially replace the intermolecular I···O secondary bonds, thus disrupting the polymeric structure characteristic of $PhIO_2$ and other previously reported iodylarenes. This structural characteristic substantially increases the solubility and stability of these reagents relative to other I^V reagents.

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Keywords: alcohols · hypervalent compounds · iodine · oxidation · synthetic methods

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[4] In addition to the chirality of the amino acid derived moiety, the iodine is also a potential stereogenic center, as is seen in the solid state. As the preferred conformation/configuration about the iodonium center in solution is not known, the enantiomeric/diastereomeric relationship between **4a** and **4b** can not be established.

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[6] Representative procedure: A freshly prepared solution of dimethyldioxirane in acetone (0.1M, 90 mL, 9 mmol) was added to a stirred mixture of **3c** (1.23 g, 3.0 mmol) in dry dichloromethane (15 mL) at 0°C, upon which the solution immediately turned light yellow. The reaction mixture was stirred at room temperature for an additional 8 h, then filtered, and the precipitate collected was washed with diethyl ether and dichloromethane, and dried under vacuum to afford **4c** (0.86 g, 65%) as a white microcrystalline solid. M.p. 156°C (decomp); $[\alpha]_D^{RT} = -34$ ($c = 0.0023$, CH_3CN); ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25°C): $\delta = 9.66$ (d, ^3J(H,H) = 7.8 Hz, 1H; NH), 8.27 (m, 2H; Ar), 7.95 (t, ^3J(H,H) = 7.6 Hz, 1H; Ar), 7.76 (t, ^3J(H,H) = 7.6 Hz, 1H; Ar), 7.27 (m, 5H; Ph), 4.74 (m, 1H; CH), 3.67 (s, 3H; OCH_3), 3.21 ppm (m, 2H; CH_2); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO, 25°C): $\delta = 171.2$, 166.1, 149.1, 137.1, 133.1, 131.3, 128.9, 128.3, 127.9, 127.2, 126.6, 123.1, 54.7, 52.1, 35.8 ppm; IR (KBr): $\tilde{\nu} = 3220$ (NH), 1744 (C=O), 1620 (C=O), 760 cm^{-1} (I=O); elemental analysis: calcd for $C_{17}H_{16}INO_5$: C 46.28, H 3.66, N 3.17, I 28.76; found: C 46.07, H 3.69, N 3.17, I 28.47; MS(CI): m/z (%): 410.0 $[M-MeOH+H]^+$ (78). See Supporting Information for additional synthetic and characterization details.

[7] X-ray diffraction data were collected on a Bruker PLATFORM/SMART 1000 CCD diffractometer with graphite monochromated $Mo_{K\alpha}$ radiation (0.71073 Å). Crystal data for **4c** $C_{68}H_{64}I_4N_4O_{20}\cdot C_7H_{10.50}N_{3.50}$: $M_r = 1908.52$, colorless, $0.46 \times 0.22 \times 0.07$ mm^3, monoclinic, $P2_1$ (No. 4), $a = 11.1810(8)$, $b = 30.221(2)$, $c = 12.0210(9)$ Å, $\beta = 100.468(2)°$, $V = 3994.2(5)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.587$ g cm^{-3}, $\mu = 1.634$ mm^{-1}. Data collection and refinement: ω scans (0.2°; 20 s exposures), $T = -80$°C, 2θ max = 52.80°, total data collected = 25445, independent reflections = 15852 ($R_{int} = 0.0366$). The data were corrected for absorption with a multiscan model by using *SADABS* (transmission factors: 0.8942–0.5203). The structure was solved by direct methods (*SHELXS-86*) and full-matrix least-squares refinement on F^2 of 904 variables (*SHELXL-93*) converged to $R_1 = 0.0451$ (for 13250 observed data with $F_o^2 \geq 2\sigma(F_o^2)$), $wR_2 = 0.1093$, and $S = 1.036$ (all data, $F_o^2 \geq -3\sigma(F_o^2)$); Flack parameter = 0.01(2). Non-hydrogen atoms were refined anisotropically; hydrogen atoms were included in calculated positions using a riding model. Residual electron density = 1.413 and −0.696 e Å^{-3}. CCDC-200547 (**4c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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