ORGANIC
LETTERS

2003
Vol. 5, No. 9
1583−1586

Synthesis and Structure of Amino Acid-Derived Benziodazoles: New Hypervalent Iodine Heterocycles

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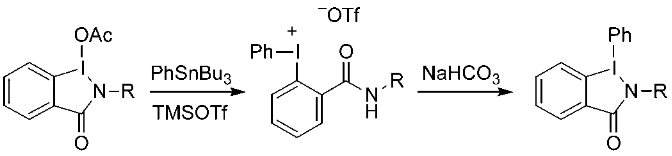
Received March 14, 2003

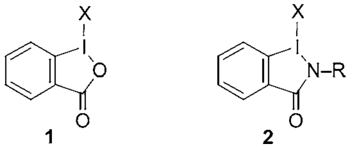
ABSTRACT



R = (S)-CH(CH$_3$)CO$_2$CH$_3$, (S)-CH(i-Pr)CO$_2$CH$_3$

New N-functionalized benziodazoles were prepared by the peracetic oxidation of 2-iodobenzamides derived from alanine or valine. X-ray crystal structural analysis of two benziodazole-based phenyliodonium derivatives provides insight into facile interchange between benziodazoles and iminium benziodoxoles under acidic or basic conditions.

Over the past decade, there has been considerable interest and research activity focused on the chemistry of five-membered iodine(III) heterocycles, derivatives of benziodoxole **1** (Figure 1).[1] The most important and best investigated heterocyclic iodane is 1-hydroxy-1,2-benziodoxol-3(1H)-one, the cyclic tautomer of 2-iodosylbenzoic acid. Other iodine-substituted benziodoxoles **1**, such as the peroxide,[2a] azide,[2b] cyanide,[2b] amides,[2b] and tosylate,[2b,c] can be prepared by ligand exchange on iodine upon treatment of 1-hydroxy-1,2-benziodoxol-3(1H)-one with the appropriate nucleophile. These various benziodoxole derivatives have found practical application as the reagents for oxidative functionalization of organic substrates.[1c,2] In contrast to benziodoxoles **1**, the analogous five-membered iodine−nitrogen heterocycles, benziodazoles **2**, have received much less attention and, moreover, their structural assignment in some cases was not reliable.[3,4] The most important and readily available derivative of benziodazole, acetoxybenzi-



1 **2**

Figure 1. Benziodoxoles **1** and benziodazoles **2**.

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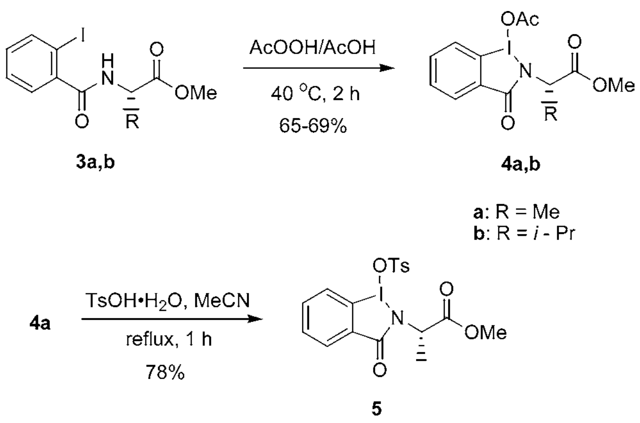
10.1021/ol0344523 CCC: $25.00

Scheme 1. Preparation of Acetoxybenziodazoles **4** and Tosyloxybenziodazole **5**



odazole (**2**, X = OAc, R = H), was first prepared in 1965 by the peracetic oxidation of 2-iodobenzamide.[3a] Recently, we reported the X-ray crystal structure of this compound and the preparation of azido- and tosyloxybenziodazoles (**2**, X = N_3 or OTs, R = H), which are potentially useful reagents with a reactivity similar to benziodoxoles **1**.[4] Only few examples of the N-substituted benziodazole derivatives were previously reported in the literature.[3,5] In particular, the dioxirane oxidation of 2-iodobenzamides derived from α-amino acids resulted in the formation of novel benziodazole-based macrocycles, which were found to be useful ligands for selective binding of metal cations.[5]

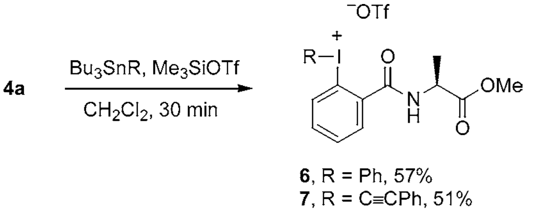
In the present paper, we report the preparation of a new class of N-functionalized benziodazoles derived from natural amino acids. Compared to the nonsubstituted benziodazoles (**2**, R = H), these compounds have improved stability and solubility, which is important for the development of potentially useful benziodazole-based reagents. In addition, we report two X-ray crystal structures of the first benziodazole-derived iodonium salts, which provide insight into the relationship between benziodazoles and iminium benziodoxoles under acidic conditions.

Acetoxybenziodazoles **4** were prepared by the peracetic oxidation of the readily available 2-iodobenzamides **3**[6] (Scheme 1) and isolated in the form of stable, white, microcrystalline solids.[7] Acetoxybenziodazole **4a** was further converted to the tosylate **5** by a procedure analogous to that previously reported for the preparation of tosyloxybenziodoxole.[2c]

Products **4** and **5** were characterized by spectroscopic data and elemental analysis. In particular, the ^{1}H NMR spectra displayed the typical signals of the benziodazole moiety[4] as well as the respective signals of the amino acid fragment and the tosyloxy group (for **5**). The IR spectra of all compounds showed two different carbonyl stretches at 1710−1730 (carboxylic C=O) and 1610−1640 (benziodazole C=O). In contrast to the analogous parent benziodazoles (**2**, R = H), products **4** and **5** have an excellent solubility in nonpolar solvents. For example, solutions of compound **4a** up to 0.44 M can be obtained in CH_2Cl_2.

Considering the importance of iodonium salts in organic synthesis[1,8] and aiming at further structural investigation of the benziodazole moiety, we explored the possibility for the preparation of the previously unknown benziodazole-derived phenyl- and alkynyliodonium salts. The most common approach to the preparation of iodonium salts involves a reaction of electrophilic hypervalent iodine reagents with arenes or alkynes or their trimethylsilyl derivatives.[8] We investigated reactions of compounds **4** and **5** with several unsaturated precursors and found that arenes, alkynes, or their trimethylsilyl derivatives were not reactive toward these benziodazoles even in the presence of trimethylsilyl triflate. However, the tributyltin-substituted substrates were much more reactive in these reactions. Thus, acetoxybenziodazole **4a** in the presence of trimethylsilyl triflate cleanly reacted with tributylphenyltin or tributylphenylethynyltin at room temperature with the formation of iodonium salts **6** or **7**, respectively (Scheme 2).

Scheme 2. Reaction of Acetoxybenziodazole **4a** with Tributylphenyltin and Tributylphenylethynyltin



Products **6** and **7** were characterized by spectroscopic data and elemental analysis. In particular, the IR spectrum of product **7** showed the triple bond absorption at 2159 cm^{-1}, while the ^{13}C NMR of this product displayed the typical alkynyliodonium salt[8c] signals of the acetylenic carbons at 113 (*C*≡CI) and 51 (C≡*C*I) ppm. The structure of iodonium triflate **6** was unambiguously established by single-crystal X-ray analysis.[9] The molecular structure of phenyliodonium triflate **6** (one of the two crystallographically independent molecules) is shown in Figure 2.

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(5) Zhdankin, V. V.; Koposov, A. E.; Smart, J. T.; Tykwinski, R. R.; McDonald, R.; Morales-Izquierdo, A. *J. Am. Chem. Soc.* **2001**, *123*, 4095.

(6) Zhdankin, V. V.; Smart, J. T.; Zhao, P.; Kiprof, P. *Tetrahedron Lett.* **2000**, *41*, 5299.

(7) **Representative Procedure.** 2-Iodobenzamide **3a** (1.79 g, 5.4 mmol) was added to a freshly prepared 20% solution of peracetic acid in acetic acid (5 mL) at room temperature. The reaction mixture was stirred at 40 °C for 2 h, cooled to room temperature, and diluted with 10 mL of cold water. The resulting white precipitate was collected by filtration, washed with water and cold ether, and dried in a vacuum to afford 1.46 g (69%) of product **4a**: mp 149−150 °C; $[\alpha]^{25}_{D} = +121.2$ ($c = 0.0067$, CH_2Cl_2); IR (KBr) 3100, 2989, 2356, 1712, 1633, 1565, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (m, 2H), 7.77 (td, 1H), 7.65 (td, 1H), 5.12 (q, 1H), 3.87 (s, 3H), 2.18 (s, 3H), 1.51 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 173.19, 170.85, 162.37, 129.79, 128.28, 126.43, 125.97, 125.52, 113.19, 48.93, 48.71, 17.23, 15.26. Anal. Calcd for $C_{13}H_{14}INO_5$: C, 39.92; H, 3.61; N, 3.58; I, 32.44. Found: C, 39.91; H, 3.50; N, 3.60; I, 32.21. Additional synthetic and characterization details are provided as Supporting Information.

(8) (a) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers: New York, 1992. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (c) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927.

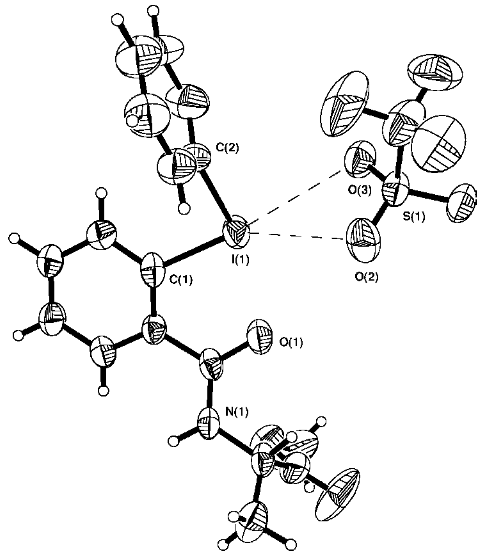


Figure 2. Perspective view of one of two crystallographically independent molecules of iodonium triflate **6**. Selected distances (Å) and angles (deg): I(1)−C(1) 2.118, I(1)−C(2) 2.093, I(1)−O(1) 2.558, C(1)−I(1)−C(2) 95.1.

The structural data revealed a typical geometry of an iodonium salt with the C1−I−C2 bond angle of 95.1° and the triflate anion weakly associated with the iodine atom (the distance between the iodine atom and the nearest oxygen of the triflate anion, I···OTf, is 3.008 Å). The closest contacts between the triflate anion and the organic cation are through moderately strong hydrogen bonds with the amido hydrogen and an oxygen atom of each triflate anion. Within each molecule, an additional intramolecular close contact of the hypervalent iodine center with the oxygen atom of the amido group (e.g., I−O1 2.558 Å) enforces a planar array for the resulting five-membered ring, a geometry that is analogous to iminium benziodoxoles **8** (Figure 3), which were isolated from the reactions of the parent benziodazoles (**2**, R = H) with alcohols or amides under acidic conditions.[4] With consideration of this I···O interaction, the actual structure of **6** can be best presented as a hybrid of two canonical forms **6a** and **6b** (Figure 3).

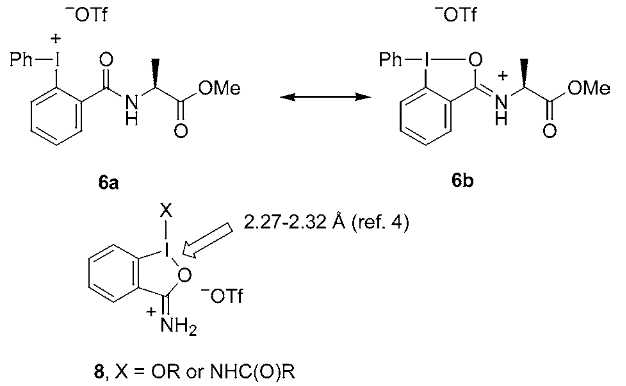
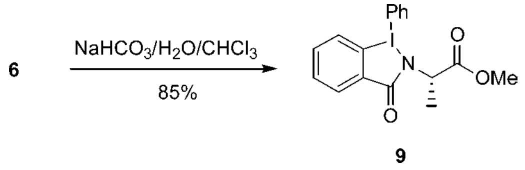


Figure 3. Structural relationship between iodonium salt **6** and iminium benziodoxoles **8**.

The treatment of iodonium triflate **6** with an aqueous sodium bicarbonate resulted in a restoration of the benziodazole ring with the formation of a novel phenylbenziodazole **9** (Scheme 3).

Scheme 3. Preparation of 1-Phenylbenziodazole **9**



Product **9** was characterized by elemental analysis, spectroscopic data, and single-crystal X-ray analysis.[10] X-ray crystallographic analysis of **9** (Figure 4) shows that the benziodoxole ring system is essentially planar and has a relatively long I−N bond of 2.445 Å. This value is significantly larger than that of the analogous I−N bond in

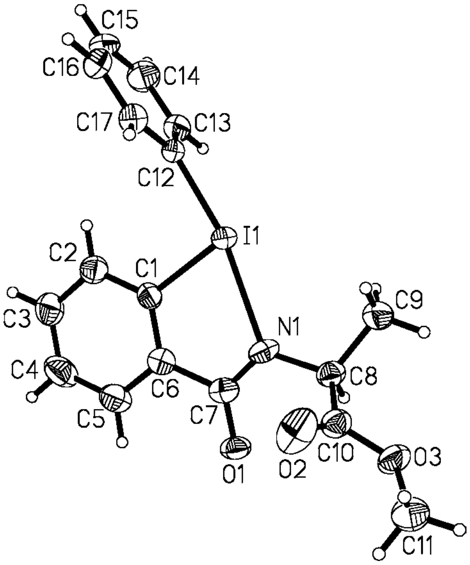


Figure 4. X-ray crystal structure of phenylbenziodazole **9**. Selected distances (Å) and angles (deg): I(1)−C(1) 2.112, I(1)−C(12) 2.133, I(1)−N(1) 2.445, C(1)−I(1)−C(12) 92.9.

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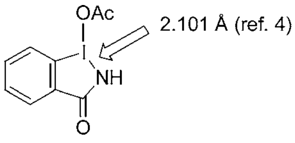
(9) Compound **6** ($C_{18}H_{17}F_3INO_6S$; formula weight 559.29): monoclinic, space group $P2_1$ with $a = 10.1570(16)$ Å, $b = 16.733(3)$ Å, $c = 13.165(2)$ Å; $\beta = 104.326(3)°$, $V = 2167.8(6)$ Å^3, $Z = 4$; $R = 0.0411$ for 7700 independent observed reflections ($I > 2\sigma(I)$); wR2 = 0.1060 (F^2, all data). Full details on the crystal structure of **6** are available in the Supporting Information.

(10) Compound **9** ($C_{17}H_{16}INO_3$; formula weight 409.21): tetragonal, space group $P4_1$ with $a = 9.0611(8)$ Å, $b = 9.0611(8)$ Å, $c = 20.066(3)$ Å; $V = 1647.5(3)$ Å^3, $Z = 4$; $R = 0.0474$ for 3904 independent observed reflections ($I > 2\sigma(I)$); wR2 = 0.0841 (F^2, all data). Full details on crystal structure of **9** are available in the Supporting Information.



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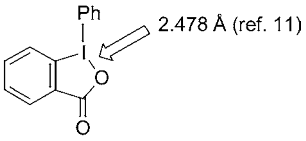

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Figure 5. Structures **10** and **11**.

acetoxybenziodazole **10** (Figure 5),[4] which is indicative of a substantial ionic character of the I−N interaction in **9**.

Overall, the geometry of **9** is similar to that observed for the reported structure of phenylbenziodoxole **11** (Figure 5).[11] The I−C1 and I−C12 bond lengths at 2.121 and 2.133 Å, respectively, and the C1−I−C12 angle of 92.9° in structure **9** are close to the analogous parameters of phenylbenziodoxole **11**. The solid-state packing of **9** demonstrates the significance of secondary bonding interactions, which link individual molecules of **9** into infinite chains via interactions between a carbonyl oxygen of one molecule with the $\mathrm{I^{III}}$ center of its neighbor. This secondary bonding also affords an approximately square planar configuration about iodine, with an intermolecular I···O interaction of 2.78 Å.

In conclusion, we report the preparation and structure of new N-functionalized benziodazoles derived from natural amino acids. Phenylbenziodazole **9** represents a new structural type of λ^3-iodanes with two carbon ligands and one nitrogen ligand attached to the iodine atom. Structural features of benziodazole-derived iodonium salts **6** and **9** demonstrate close relationship and facile interchange between benziodazoles and iminium benziodoxoles under acidic or basic conditions.

Acknowledgment. This work was supported by a research grant from the National Science Foundation.

Supporting Information Available: Synthetic and characterization data for all new compounds and X-ray crystallographic details for compounds **6** and **9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Batchelor, R. J.; Birchall, T.; Sawyer, J. F. *Inorg. Chem.* **1986**, *25*, 1415.