Supporting Information for

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

Viktor V. Zhdankin,*[,†] Alexey Y. Koposov,[†] Liansheng Su,[†] Vyacheslav V. Boyarskikh,[†] Brian C. Netzel,[†] and Victor G. Young Jr.[‡]

Department of Chemistry, University of Minnesota Duluth, Duluth, Minnesota 55812, and X-Ray Crystallographic Laboratory, Chemistry Department, University of Minnesota, Minneapolis, MN 55455

vzhdanki@d.umn.edu

Contents:

1. Synthetic and characterization data for all new compounds (PDF file)

2. X-ray crystallographic details for compounds **6** and **9** (CIF file).

EXPERIMENTAL SECTION

General. All melting points were determined in an open capillary tube with a Mel–temp II melting point apparatus and are uncorrected. Infrared spectra were recorded as a KBr pellet on a Perkin–Elmer 1600 series FT–IR spectrophotometer. NMR spectra were recorded on a Varian UNITY INOVA 300 MHz NMR spectrometer at 300 MHz (^{1}H NMR), and 75.5 MHz (^{13}C NMR). Chemical shifts are reported in parts per million (ppm). ^{1}H and ^{13}C chemical shifts are referenced relative to the residual nondeuteriated solvent. Microanalyses were carried out by Atlantic Microlab, Inc., Norcross, Georgia.

Materials. All commercial reagents were ACS reagent grade and used without further purification. Methylene chloride and acetonitrile were distilled from CaH_2 immediately prior to use. Diethyl ether was distilled from Na/benzophenone. Amino acid-derived 2-iodobenzamides **3** were prepared by a known method (Zhdankin, V. V.; Smart, J. T.; Zhao, P.; Kiprof, P. *Tetrahedron Lett.* **2000**, *41*, 5299) from commercially available (Aldrich) 2-iodobenzoyl chloride and methyl esters of alanine and valine. Reaction flasks were oven–dried at 200 ˚C, flame–dried and flushed with dry nitrogen prior to use.

Oxidation of *N*-(2-Iodobenzoyl) Amino Acid Esters 3 with Peracetic Acid (General Procedure).

The appropriate amino acid derivative **3** (1 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 40^0 C for additional 2 hrs, then cooled to room temperature. Then the reaction mixture was diluted with 10 ml of cold water. The white precipitate formed after dilution was filtered and washed with water and cold ether and dried in vacuum to afford analytically pure product **4**.

Oxidation of *N*-(2-iodobenzoyl) alanine methyl ester **3a** (1.79 g, 5.4 mmol) according to the general procedure afforded 1.46 g (69%) of product **4a**, mp 149-150 °C (with decomposition); $[a]^{25}_D$ = +121.2° (c = 0.0067, CH_2Cl_2); IR (KBr): 3100, 2989, 2356, 1712, 1633, 1565, 1254, cm^{-1}; ^{1}H NMR ($CDCl_3$): d 8.20 (m, 2H), 7.77 (td, J_1=7.8 Hz, J_2=1.8 Hz, 1H), 7.65 (td, J_1=7.4 Hz, J_2=1.8 Hz, 1H), 5.12 (q, J=6.9 Hz, 1H), 3.87 (s, 3H), 2.18 (s, 3H), 1.51 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): d 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.

Oxidation of *N*-(2-iodobenzoyl) valine methyl ester **3b** (1.0 g, 2.77 mmol) according to the general procedure afforded 0.75 g (65%) of product **4b**, mp 145-146 °C (with decomposition). IR (KBr): 3100, 2956, 1709, 1642, 1580, 1363, 1263, cm^{-1}; ^{1}H NMR ($CDCl_3$): d 8.20 (m, 2H), 7.77 (td, J_1=7.7 Hz, J_2=1.7 Hz, 1H), 7.65 (td, J_1=7.5 Hz, J_2=1.0 Hz, 1H), 4.98 (d, J=6.8 Hz, 1H), 3.85 (s, 3H), 2.28 (s, 1H), 2.17 (s, 3H), 1.01 (t, J=6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$): d 173.08, 169.52, 162.45, 129.82, 128.24, 126.71, 125.98, 125.44, 112.89, 57.65, 48.37, 29.38, 17.18, 15.05, 14.15. Anal. Calcd. for $C_{15}H_{18}INO_5$: C, 42.98; H, 4.33; N, 3.34; I, 30.27. Found: C, 42.77; H, 4.25; N, 3.24; I, 30.12.

Preparation of Tosyloxybenziodazole 5.

p-Toluenesulfonic acid monohydrate (0.19 g, 1 mmol) was added to a stirred solution of acetoxybenziodazole **4a** (0.391 g, 1 mmol) in 30 ml of acetonitrile at room temperature. The reaction mixture was refluxed for 1 hour, then cooled to room temperature. Then the reaction mixture was diluted with 30 ml of cold diethyl ether and cooled in a refrigerator. The white precipitate formed after dilution was filtered and washed with cold ether and dried in vacuum to afford 0.39 g (78%) of product **5**; m.p. 137-138 ^{0}C (with decomposition). IR (KBr): 3017, 2360, 1733, 1611, 1586, 1535, 1456, 1371, 1206, 1146, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$): d 8.36 (d, J=8.5Hz, 1H), 8.18 (dd, J_1= 7.7 Hz, J_2=1.5 Hz, 1H), 7.87, (d, J= 8.5 Hz, 2H), 7.83 (t, J=7.5 Hz, 1H), 7.70 (td, J_1= 7.4 Hz, J_2= 1.0 Hz, 1H), 7.28 (d, J= 8.1 Hz, 2H), 5.15 (q, J= 6.8 Hz, 1H), 3.95 (s, 3H), 2.41 (s, 3H), 1.6 (br. s, H_2O), 1.53 (d, J= 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): d 173.32, 170.92, 146.26, 135.12, 131.36, 127.14, 127.07, 126.74, 125.32, 124.82, 121.91, 113.89, 49.86, 48.72, 17.00, 14.70. Anal. Calcd. for $C_{18}H_{18}INO_6S•H_2O$: C, 41.47; H, 3.87; N, 2.69; I, 24.34; S, 6.15. Found: C, 41.55; H, 3.81; N, 2.74; I, 24.35; S, 6.18.

Preparation of Iodonium Salt 6.

To a stirred mixture of acetoxybenziodoxole **4a** (0.391 g, 1 mmol) in methylene chloride (20 ml), trimethylsilyl triflate (0.258 g, 1 mmol) was added. After 10 minutes of stirring the tributylphenyltin (0.425 g, 1.16 mmol) was added. The reaction mixture was stirred for additional 30 minutes, then the solvent was evaporated to give a colorless oil. The

residue was washed with water (20 ml) and hexane (20 ml). Recrystallization from ethyl acetate/hexane and drying in vacuum afforded 0.318 g (57%) of product **6**, mp 131-132°C (with decomposition); $[\alpha]^{25}_{D}$ = +20.5° (c = 0.0032, CH_2Cl_2); IR (KBr): 3309, 3082, 2352, 1738, 1620, 1261, 1158, cm^{-1}, ^1H NMR ($CDCl_3$): δ 9.09 (d, J=6.9 Hz, 1H), 8.62 (d, J=6.3 Hz, 1H), 8.06 (d, J=7.2 Hz, 1H), 7.82 (t, J=7.8 Hz, 1H), 7.72 (t, J=7.2 Hz, 1H), 7.63 (t, J=7.6 Hz, 2H), 7.53 (t,J=7.8 Hz, 1H), 6.93 (d, J=8.1 Hz, 2H), 4.6 (m, 1H), 3.78 (s, 3H), 1.63 (d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.9, 165.8, 137.8, 135.9, 133.7, 132.5, 131.9, 131.3, 128.8, 127.3, 122.5 (q, J= 319 Hz), 112.6, 110.7, 52.7, 50.3, 16.6. Anal. Calcd. for $C_{18}H_{17}F_3INO_6S$: C, 38.65; H, 3.06; N, 2.50; I, 22.69; S, 5.73. Found: C, 38.50; H, 3.09; N, 2.65; I, 22.60; S, 5.75.

A single crystal of **6** suitable for X–ray crystallographic analysis was obtained via slow evaporation of an ethyl acetate solution. A crystal (approximate dimensions 0.25 x 0.10 x 0.05 mm^3) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Bruker SMART system for a data collection at 173(2) K. A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 150 reflections. The data collection was carried out using MoKα radiation (graphite monochromator) with a frame time of 30 seconds and a detector distance of 4.9 cm. A randomly oriented region of reciprocal space was surveyed to the extent of 1.5 hemispheres and to a resolution of 0.84 Å. Three major sections of frames were collected with 0.30º steps in ω at 3 different φ-settings and a detector position of -28° in 2θ. The intensity data were corrected for absorption and decay (SADABS).[1] Final cell constants

were calculated from 3644 strong reflections from the actual data collection after integration (SAINT 6.01, 1999).[2] The structure was solved using SHELXS-86[3] and refined using SHELXL-97.[3] The space group $P2_1$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters unless stated otherwise. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to R1 = 0.0411 and wR2 = 0.1060 (F^2, all data). Two formula units are found per asymmetric unit. This pair is related by a pseudo a-glide. No glide operation is possible since only one enantiomer is present. The solution simulates the space group P21/a. The remaining difference Fourier peaks are near both iodine atoms. The closest contacts between the triflate anion and the organic cation are in moderately strong hydrogen bonds with the amido proton and an oxygen atom of each triflate anion. For further details on crystal structure of **6** see CIF file.

Preparation of Iodonium Salt 7.

To a stirred mixture of acetoxybenziodoxole **4a** (0.391 g, 1 mmol) in methylene chloride (20 ml), trimethylsilyl triflate (0.333 g, 1.5 mmol) was added. After 10 minutes of stirring the tributylphenylethynyltin (0.735 g, 2 mmol) was added. The reaction mixture was stirred for additional 30 minutes, then the solvent was evaporated to give a

yellow oil. The residue was washed with hexane (20 ml). Recrystallization from ethyl acetate/hexane and drying in vacuum afforded 0.297 g (51%) of product **7**, mp 89-90 °C (with decomposition). IR (KBr): 3279, 3082, 2947, 2159, 1747, 1620, 1244, 1156, cm^{-1}; ^{1}H NMR ($CDCl_3$): d 9.72 (d, J=5.7 Hz, 1H), 8.84 (d, J=6.3 Hz, 1H), 8.29 (d, J=7.5 Hz, 1H), 7.91 (m, 2H), 7.66 (d, J=6.6 Hz, 2H), 7.5 (m, 3H), 4.66 (m, 1H), 3.76 (s, 3H), 1.68 (d, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): d 171.1, 166.6, 137.1, 133.4, 133.0, 131.8, 128.9, 128.8, 128.6, 125.5, 120.5 (q, J=320 Hz), 119.4, 113.3, 111.7, 52.8, 50.9, 39.1, 16.4. Anal. Calcd. for $C_{20}H_{17}F_3INO_6S•H_2O$: C, 39.95; H, 3.18; N, 2.33; I, 21.10; S, 5.33. Found: C, 40.25; H, 3.21; N, 2.51; I, 21.09; S, 5.40.

Preparation of 1-Phenylbenziodazole 9.

To a stirred mixture of iodonium salt **6** (0.279 g, 0.5 mmol) in chloroform (20 ml), an aqueous solution of sodium bicarbonate (20 ml, 1%) was added. The mixture was shaken in separatory funnel for 15 minutes, then the organic layer was separated and dried under Na_2SO_4. The solvent was evaporated and the residue was recrystallized to afford (0.174 g, 85%) of benziodazole **9**, mp 129-130 °C (with decomposition); IR (KBr): 3047, 2947, 1743, 1585, 1544, 1382, 1129, cm^{-1}; ^{1}H NMR ($CDCl_3$): d 8.45 (m, 1H), 7.90 (d, J=6.9 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H), 7.55 (m, 3H), 7.30 (t, J=5.9 Hz, 1H), 6.82 (d, J=8.1 Hz, 2H), 4.93 (m, 1H), 3.76 (s, 3H), 1.52 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): d 177.2, 162.3, 137.4, 135.9, 131.9, 131.4, 131.3, 130.5, 130.3, 126.8, 126.0, 114.7, 53.3, 52.0, 20.4. Anal. Calcd. for $C_{17}H_{16}INO_3$: C, 49.90; H, 3.94; I, 31.01; N, 3.42. Found: C, 49.73; H, 3.46; I, 30.81; N, 3.46.

A single crystal of **9** suitable for X–ray crystallographic analysis was obtained via slow evaporation of an ethyl acetate solution. A crystal (approximate dimensions 0.28 x 0.06 x 0.03 mm^3) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Bruker SMART system for a data collection at 173(2) K. A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 80 reflections. The data collection was carried out using MoKa radiation (graphite monochromator) with a frame time of 30 seconds and a detector distance of 4.9 cm. A randomly oriented region of reciprocal space was surveyed to the extent of 1.5 hemispheres and to a resolution of 0.76 Å. Three major sections of frames were collected with 0.30º steps in w at 3 different f settings and a detector position of -28° in 2q. The intensity data were corrected for absorption and decay (SADABS).[1] Final cell constants were calculated from 2980 strong reflections from the actual data collection after integration (SAINT 6.35A, 1999).[2] The structure was solved and refined using SHELXL-V6.12.[3] The space group $P4_1$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters unless stated otherwise. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative

isotropic displacement parameters. The final full matrix least squares refinement converged to R1 = 0.0474 and wR2 = 0.0841 (F^2, all data). For further details on crystal structure of **9** see CIF file.

References

1. An empirical correction for absorption anisotropy, R. Blessing, Acta Cryst. A51, 33 - 38 (1995).
2. SAINT V6.1, Bruker Analytical X-Ray Systems, Madison, WI.
3. SHELXTL-Plus V5.10, Bruker Analytical X-Ray Systems, Madison, WI.