Synthesis of 7-Substituted Saccharins and 8-Substituted Oxicams, and a Novel Saccharin to Oxicam Transformation

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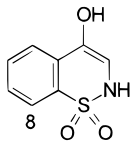
The 4-hydroxy-1,2-benzothiazine 1,1-dioxide (oxicam) ring system **1** is a common substructure of certain pharmaceutically important antiinflammatory agents.[1] It can conveniently be derived from the 1,2-benzoisothiazol-3(2*H*)-one-1,1-dioxide (saccharin) system **2** by ring expansion,[2] and when we recently required a general access to 8-substituted oxicams we logically looked to 7-substituted saccharins[3] as precursors. In particular we were interested in the previously undescribed iodo compounds which, by palladium-catalyzed cross coupling reactions,[4] should function as convenient precursors to a variety of derivatives.



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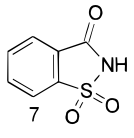

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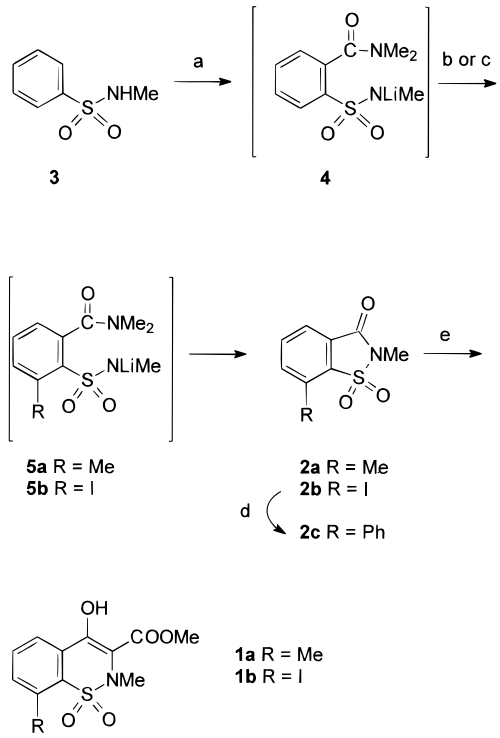
The carboxylation of *o*-lithiobenzenesulfonamides is a convenient method for preparing 2-carboxybenzenesulfonamides that function as standard intermediates for the synthesis of saccharins.[5] Introduction of a dimethylcarbamoyl group rather than a carboxyl group allows this approach to be applied to the synthesis of 7-substituted saccharins as shown in Scheme 1. The dimethylcarbamoyl group in **4** is stable to ortho lithiation conditions and is less effective than the sulfonamide as an ortho-directing group.[6] Lithiation occurs adjacent to the sulfonamide group, and reaction with iodomethane or iodine gives the methyl (**5a**) or iodo (**5b**) derivative which closes to the 7-substituted saccharin **2a** (62%) or **2b** (44%) after workup. The mass balance in general consists of intractable polar material, although on occasion *N*-methyl-2-(*N*,*N*-dimethylcarbamoyl)benzenesulfonamide (corresponding to intermediate **4**) has been isolated. The sequence

Scheme 1[a]



[a] *n*-BuLi, THF, Me_2NCOCl; (b) *n*-BuLi, MeI, 62%; (c) *n*-BuLi, I_2, 44%; (d) $Pd(Ph_3P)_2Cl_2$, $PhBu_3Sn$, NMP, 120 °C, 16 h, 69%; (e) NaHMDS, DMSO/THF, methyl chloroacetate, 60 °C, 35% for **1a**, 36% for **1b**.

constitutes a one-pot conversion of the unsubstituted benzenesulfonamide **3** to the 7-substituted saccharins.

The 7-iodosaccharin **2b** reacts with phenyltributyltin under palladium catalysis[4] to generate the 7-phenylsaccharin **2c** (69%). The 7-methyl and 7-iodosaccharin derivatives **2a** and **2b** are transformed by the procedure of Weeks *et al.*[2c] into the oxicams **1a** (35%) and **1b** (36%).

Intermediates related to **4** in Scheme 1 can also be generated by reaction of a saccharin with dimethylamine as shown by the conversion of *N*-allylsaccharin **2d**[7] to the sulfonamide **4a** (85%) in Scheme 2. Lithiation and iodination of **4a** followed by cyclization generates *N*-allyl-7-iodosaccharin **2e** (68%) in a sequence that constitutes a formal substitution of the saccharin at the 7-position. *N*-allyl-7-iodosaccharin **2e** can also be obtained (47%) from *N*-allylbenzenesulfonamide **3a** in a process analogous to that shown in Scheme 1.

Scheme 2 also illustrates an alternative saccharin to oxicam transformation that is based on the intramolecular Heck reaction of 1-(2′-bromobenzenesulfonyl)-2,5-dihydropyrrole described by Grigg *et al.*[8] Hydrolysis of **2e** with potassium hydroxide in DMSO and reaction with excess iodomethane give the 2,6-disubstituted *N*-allylsulfonamide **6** (89%). Under palladium catalysis and *via* an intramolecular Heck reaction, a 6-exo cyclization of **6** furnishes the bicyclic compound **7** as the major product (61%). We identified as minor components of this reaction the regioisomer **8** and **9**, the product of a 7-endo ring closure. The formation of **9** was not surprising since

(1) Lombardino, J. G.; Wiseman, E. H. *Med. Res. Rev.* **1982**, *2*, 127−152.

(2) (a) Catsoulacos, P.; Camoutsis, C. *J. Heterocycl. Chem.* **1979**, *16*, 1503−1524. (b) Lombardino, J. G.; Kuhla, D. E. *Adv. Heterocycl. Chem.* **1982**, *28*, 73−125. (c) Weeks, P. D.; Vinick, F. J.; Breitenbach, R.; Jung, S. *J. Org. Chem.* **1983**, *48*, 3601−3603.

(3) Some 7-substituted saccharins have been described, but with the exception of a concise approach to the 7-chloro derivative the syntheses are rather lengthy. (a) For 7-methoxysaccharin see: Haworth, R. D.; Lapworth, A. *J. Chem. Soc.* **1924**, *125*, 1299−1307. (b) For 7-chlorosaccharin see: Hlasta, D. J.; Court, J. J.; Desai, R. C. *Tetrahedron Lett.* **1991**, 32, 7179−7182. (c) For 7-nitro and 7-aminosaccharin see: Hamour, G. H. *J. Pharm. Sci.* **1965**, *52*, 603−604. (d) For 7-methylsaccharin see: Milstein, D. US Patent 5034534.

(4) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.

(5) (a) Watanabe, H.; Gay, R. L.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 900−903. (b) Lombardino, J. G. *J. Org. Chem.* **1971**, *36*, 1843.

(6) Brandsma, L.; Verkruijsse, H. *Preparative Polar Organometallic Chemistry 1*; Springer-Verlag: Berlin, 1987; 208−209.

(7) Rice, H. L.; Pettit, G. R. *J. Am. Chem. Soc.* **1954**, *76*, 302−303.

(8) Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Teasdale, A.; Thornton-Pett, M.; Worakun, T. *Tetrahedron* **1991**, *47*, 9703−9720.

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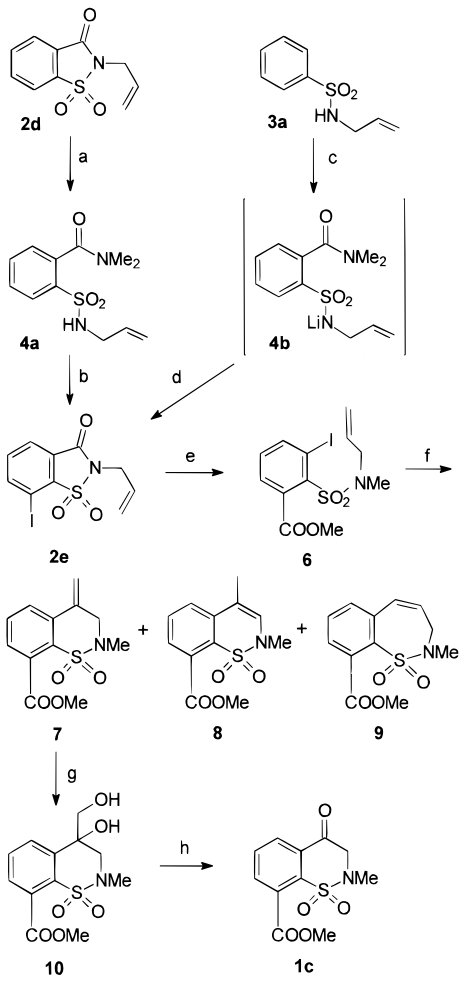
Scheme 2[a]



[a] Me_2NH, dioxane, rt, 85%; (b) *n*-BuLi, THF, −30 °C, I_2, workup and then rt 3 days, 68%; (c) *n*-BuLi, THF, −30 °C, Me_2NCOCl; (d) *n*-BuLi, THF, −50 °C, I_2, rt 5 days, 47%; (e) KOH, DMSO, MeI, 89%; (f) $Pd(Ph_3P)_2Cl_2$, DMF, Et_3N, 55−60 °C, 5 h, 61% of **7**; (g) OsO_4, NMO, dioxane/water, 86%; (h) $NaIO_4$, dioxane/water, 94%.

7-endo cyclization has been reported in related systems.[8,9] A two-step oxidation of the exo-methylene group of **7** completes the transformation (80% over the two steps) to **1c**, an 8-substituted oxicam derivative.

This sequence also proves the regiochemistry of iodination of **3a** and, by analogy, of **3**. If iodination of the intermediate 2-(*N*,*N*-dimethylcarbamoyl)benzenesulfonamide **4b** had occurred ortho to the carboxamide group, the subsequent reactions would have given an isomer of **6** with the iodo substituent ortho to the ester group. This compound could not have participated in the intramolecular Heck reaction or furnished any of the products **7**−**9**.

We have described a straightforward and convenient method for the synthesis of 7-substituted saccharins using benzenesulfonamides or saccharins as starting materials.[10] These 7-substituted saccharins can be transformed into 8-substituted oxicams by a standard ring expansion methodology providing a short and efficient synthesis of these materials. In addition, a new route to the oxicam nucleus via an intramolecular Heck reaction on *N*-allyl-2-iodobenzenesulfonamides is described.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AC-270 spectrometer operating at 270 MHz. Elemental analyses were determined at Midwest Laboratories, Indianapolis, IN. THF, dioxane, and DMSO anhydrous grade solvents were purchased from Aldrich Chemical Co. and used without further purification

7-Iodo-2-methyl-1,2-benzoisothiazol-3(2*H*)-one 1,1-Dioxide (2b) (2-methyl-7-iodosaccharin). To a solution of **3** (8.61 g, 50.3 mmol) in THF (100 mL) cooled below −30 °C was added *n*-BuLi (2 M in cyclohexane, 53 mL) at such a rate that the temperature remained below −30 °C. The mixture was stirred at −30 °C to −40 °C for 45 min. Dimethylcarbamyl chloride (5.0 mL, 54 mmol) was added all at once. The temperature rose to 0 °C, and a precipitate formed. Further THF (200 mL) was added to redissolve the precipitate, and the mixture was cooled to −40 °C. *n*-BuLi (2 M in cyclohexane, 27 mL) was added below −40 °C, and the mixture was stirred for 40 min. Iodine (12.7 g, 50 mmol) in THF (100 mL) was added rapidly, and the mixture was allowed to warm to rt. The mixture was diluted with EtOAc and washed with water (300 mL) and 3% aqueous KOH (100 mL). The combined aqueous phase was acidified (AcOH) and extracted with EtOAc. The combined organic phase was dried, filtered, and evaporated. The residue was warmed on a rotary evaporator at 60 °C for 3 h to effect cyclization to the saccharin. The solid residue was washed with methanol and collected by filtration giving **2b** (5.31 g). The supernatant was fractionated over silica (eluent, hexane/CH_2Cl_2 to CH_2Cl_2/EtOAc gradient) to give further **2b** (1.92 g) (total yield, 7.23 g, 22.4 mmol, 44%): mp 155−157 °C; ^1H NMR ($CDCl_3$) δ 8.18 (1H, dd, J = 1, 8), 8.03 (1H, dd, J = 1, 8), 7.49 (1H, apparent t, J = 8), 3.29 (3H, s); MS(CI) 324 MH^+. Anal. Calcd for $C_8H_6NO_3SI$: C, 29.74; H, 1.87; N, 4.34. Found: C, 30.05; H, 1.86; N, 4.21.

2-Methyl-7-phenyl-1,2-benzoisothiazol-3(2*H*)-one 1,1-Dioxide (2c) (2-methyl-7-phenylsaccharin). A solution of **2b** (0.323 g, 1.00 mmol), phenyltributyltin (0.460 g, 1.25 mmol), and $Pd(Ph_3P)_2Cl_2$ (0.035 g, 0.050 mmol) in NMP (2.5 mL) was heated at 120 °C under nitrogen in a sealed tube for 16 h. The mixture was cooled, TBAF (1 M in THF, 2 mL) was added, and the mixture was stirred at rt for 2 h. The mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. The residue was fractionated over silica (EtOAc/hexane/CH_2Cl_2) to give **2c** (0.189 g, 69%): mp 154−156 °C; ^1H NMR ($CDCl_3$) δ 8.06 (1H, dd, J = 1, 8), 7.85 (1H, apparent t, J = 8), 7.79 (1H, dd, J = 1, 8), 7.73−7.70 (2H, m), 7.56−7.52 (3H, m), 3.26 (3H, s); MS(CI) 291 M + NH_4^+. Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.12. Found: C, 61.42; H, 4.18; N, 5.08.

4-Hydroxy-8-iodo-3-(methoxycarbonyl)-2-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide 1b. To a solution of **2b** (4.37 g, 13.5 mmol) and methyl chloroacetate (2.5 mL, 29 mmol) in DMSO (20 mL) was added NaHMDS (1 M in THF, 28 mL) dropwise over 10 min. The mixture was stirred at rt for 1.5 h and then warmed at 60 °C for 1 h. Further methyl chloroacetate (2.5 mL) and NaHMDS (14 mL) were added, and stirrring was continued at 60 °C for 2 h. The mixture was diluted with EtOAc and washed with water and 2% aqueous KOH. The organic phase was dried filtered and evaporated to give recovered **2b** (2.33 g, 53%). The combined aqueous phase was acidified with AcOH and extracted with EtOAc. This organic phase was washed with 2% aqueous AcOH, dried, filtered, and evaporated. Chromatography over silica gel gave **1b** (1.90 g, 4.81 mmol, 36%): mp 194−198 °C (EtOAc); ^1H NMR ($CDCl_3$) δ 11.92 (1H, s), 8.23 (1H, dd, J = 1, 8), 8.05 (1H, dd, J = 1, 8), 7.33 (1H, apparent t, J = 8), 3.96 (3H, s), 3.02 (3H, s); MS(CI) 396 MH^+. Anal. Calcd for $C_{11}H_{10}NO_5SI$: C, 33.43; H, 2.55; N, 3.54. Found: C, 33.57; H, 2.53; N, 3.45.

2,7-Dimethyl-1,2-benzoisothiazol-3(2*H*)-one 1,1-Dioxide (2a) (2,7-dimethylsaccharin). To a solution of *N*-methylbenzenesulfonamide (4.63 g, 27.0 mmol) in THF (100 mL) cooled to −40 °C under argon was added *n*-BuLi (2 M in hexanes, 26 mL) at

(9) (a) Beckwith, A. L. J.; Meijs, G. F. *J. Org. Chem.* **1987**, *52*, 1922−1930. (b) Brown, C. D. S.; Dishington, A. P.; Shishkin, O.; Simpkins, N. *Synlett*. **1995**, 943−944. (c) Gibson, S. E.; Middleton, R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1743−1744. (d) Ma, S.; Negishi, E.-I. *J. Am. Chem. Soc.* **1995**, *117*, 6345−6357.

(10) While this work was in progress a conceptually similar di-ortho functionalization of benzenesulfonate esters was reported. Spangler, L. A. *Tetrahedron Lett.* **1996**, *37*, 3639−3642.

such a rate that the internal temperature remained below −30 °C. The mixture was stirred at −40 to −50 °C for 1 h. Dimethylcarbamyl chloride (2.5 mL, 27 mmol) was added, and the mixture was stirred at −30 °C for 20 min. The mixture was cooled to −60 °C, *n*-BuLi (2 M in hexanes, 16 mL) was added, and the mixture was stirred for 40 min. Iodomethane (2.0 mL, 27 mmol) was added all at once, and the mixture was stirred at −50 °C for 30 min. The reaction was quenched by adding AcOH (5 mL) and water (5 mL) and allowed to warm to rt. The mixture was diluted with EtOAc and extracted with aqueous 2% NaOH. The aqueous phase was acidified with HCl and extracted with $CHCl_3$. The organic phase was dried, filtered, evaporated, and left at rt for 3 days to effect cyclization to the saccharin. The crystalline product **2a** was treated with a small amount of cold methanol and collected by filtration (3.64 g, 62%): mp 97−99 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (1H, d, J = 8), 7.68 (1H, apparent t, J = 8), 7.60 (1H, d, J = 8), 3.26 (3H, s), 2.72 (3H, s); MS (CI) 229 M + NH_4^+. Anal. Calcd for $C_9H_9NO_3S$: C, 51.17; H, 4.29; N 6.63. Found: C, 51.08; H, 4.32; N, 6.66.

4-Hydroxy-3-(methoxycarbonyl)-2,8-dimethyl-2*H*-1,2-benzothiazine 1,1-Dioxide (1a). To a solution of **2a** (1.06 g, 5.0 mmol) and methyl chloroacetate (1.0 mL, 12 mmol) in DMSO (10 mL) stirred at rt was added NaHMDS (1 M in THF, 10 mL) dropwise with stirring. The mixture was then stirred at 60 °C for 2.5 h. The mixture was diluted with EtOAc and extracted with aqueous 0.5% KOH (2 × 50 mL). The aqueous phase was acidified with acetic acid and extracted with $CHCl_3$. The organic phase was washed with water, dried, filtered, and evaporated. Trituration of the residue with $Et_2O/CHCl_3$ gave **1a** (0.50 g, 35%) as a solid which was collected by filtration: mp 158−160 °C; ^{1}H NMR ($CDCl_3$) δ 11.96 (1H, s), 7.90 (1H, d, J = 8), 7.58 (1H, apparent t, J = 8), 7.48 (1H, d, J = 8), 3.95 (3H, s), 2.99 (3H, s), 2.72 (3H, s); MS (CI) 301 M + NH_4^+. Anal. Calcd for $C_{12}H_{13}NO_5S$: C, 50.88; H, 4.63; N, 4.94. Found: C, 50.90; H, 4.75; N, 4.73.

***N*-Allyl-2-(*N*,*N*-dimethylcarbamoyl)benzenesulfonamide (4a).** A mixture of **2d**[7] (3.68 g, 16.5 mmol) and dimethylamine (0.81 g) in dioxane (10 mL) was left at rt in a stoppered flask for 31 h. The solvent was evaporated, and the residue was taken up in EtOAc, washed with 0.5% aqueous HCl, dried, filtered, and evaporated. The residue was fractionated over silica gel to give **4a** (3.86 g, 14.1 mmol, 85%) as an oil that crystallized on standing: mp 47−49 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (1H, dd, J = 1, 8), 7.57 (1H, apparent dt, J = 1, 8), 7.52 (1H, apparent dt, J = 1, 7), 7.33 (1H, dd, J = 1, 7) 5.77 - 5.62 (2H, complex, CH + NH), 5.16 (1H, d, J = 1, 7), 5.03 (1H, dd, J = 1, 10) 3.66 (1H, br), 3.42 (1H, br), 3.12 (3H, s), 2.88 (3H, s). Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.97; H, 5.91; N, 10.49.

2-Allyl-7-iodo-1,2-benzoisothiazol-3(2*H*)-one 1,1-Dioxide (2e) (2-allyl-7-iodosaccharin). To a solution of **4a** (0.514 g, 1.53 mmol) in THF (5 mL) cooled to −30 °C was added *n*-BuLi (2.5 M in hexanes 1.9 mL) dropwise over 10 min. After 5 min, iodine (0.71 g, 2.8 mmol) in THF (3 mL) was added all at once, and the mixture was allowed to warm to rt. The mixture was diluted with EtOAc, washed with aqueous sodium thiosulfate, dried, filtered, and evaporated. The residue was left standing at rt for 3 days to effect cyclization to the saccharin. Chromatography over silica (EtOAc/hexane) gave **2e** (0.369 g, 1.05 mmol, 68%) as an oil that crystallized on standing: mp 82−83 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 8.18 (1H, dd, J = 1, 8), 8.03 (1H, dd, J = 1, 8), 7.49 (1H, apparent t, J = 8), 5.96 (1H, m), 5.46 (1H, dd, J = 1, 7), 5.33 (1H, dd, J = 1, 10), 4.40 (2H, d, J = 6). Anal. Calcd for $C_{10}H_8NO_3SI$: C, 34.40; H, 2.31; N, 4.01. Found: C, 34.68; H, 2.23; N, 3.94.

2-Allyl-7-iodosaccharin 2e is also obtained from *N*-allylbenzenesulfonamide **3a** as follows. To a solution of **3a** (3.61 g, 18.2 mmol) in THF (30 mL) cooled below −30 °C under argon was added *n*-BuLi (2 M in cyclohexane, 21 mL, 42 mmol). Dimethylcarbamyl chloride (2.2 mL, 24 mmol) was added all at once. The mixture was stirred for 10 min and, after cooling to −50 °C, further *n*-BuLi (2 M in cyclohexane, 10 mL) was added. The mixture was stirred for 30 min, iodine (4.94 g, 19.2 mmol) in THF (15 mL) was added rapidly, and the mixture was allowed to warm to rt. The mixture was diluted with EtOAc, washed with aqueous sodium thiosulfate and water, dried, filtered, and evaporated. The residue was left standing at rt for 5 days to effect cyclization to the saccharin. Fractionation over silica gel (CH_2Cl_2/hexane) gave **2e** (3.06 g, 47%).

***N*-Allyl-*N*-methyl-2-iodo-6-(methoxycarbonyl)benzenesulfonamide (6).** To a solution of **2e** (8.96 g, 25.7 mmol) in DMSO (25 mL) stirred at rt was added crushed KOH (3.54 g, 63.1 mmol). The mixture was stirred at rt for 24 h, and iodomethane (6.0 mL, 97 mmol) was added. After 5 h, the mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. The residue was fractionated over silica (hexane/CH_2Cl_2) to give **6** (8.64 g, 22.8 mmol, 89%) as an oil that crystallized slowly on standing: mp 41-42 °C (^{i}Pr$_2$O); ^{1}H NMR ($CDCl_3$) δ 8.18 (1H, dd, J = 1, 8), 7.39 (1H, dd, J = 1, 8), 7.19 (1H, apparent t, J = 8), 5.79 (1H, m), 5.30−5.22 (2H, m), 3.92 (3H, s), 3.92 (2H, d, J = 6), 2.85 (3H, s). Anal. Calcd for $C_{12}H_{14}NO_4SI$: 36.47; H, 3.57, N, 3.54. Found: C, 36.49, H, 3.51, N, 3.38.

8-(Methoxycarbonyl)-4-methylene-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-Dioxide (7). A mixture of **6** (2.96 g, 7.82 mmol) and $Pd(Ph_3P)_2Cl_2$ (0.125 g, 0.18 mmol) in Et_3N (95 mL) and DMF (10 mL) was degassed under vacuum and covered with argon four times. The mixture was stirred under argon at 55−60 °C for 5 h and then diluted with EtOAc, washed with water, dried, filtered, and evaporated. Trituration of the crude product with ^{i}Pr$_2$O/CH_2Cl_2 gave crystalline **7** (1.13 g) which was collected by filtration. Chromatography of the supernatant over silica gel (eluent, CH_2Cl_2/hexane to CH_2Cl_2 gradient) gave a fraction from which further product (0.15 g) crystallized (total yield, 1.28 g, 4.79 mmol, 61%): mp 150−152 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, dd, J = 1, 8), 7.67 (1H, dd, J = 1, 8), 7.57 (1H, apparent t, J = 8), 5.97 (1H, s), 5.39 (1H, s), 4.49 (2H, s), 3.99 (3H, s), 2.71 (3H, s). Anal. Calcd for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: 53.59; H, 4.93; N, 5.19. The combined residual supernatant from this and two other reactions was fractionated by preparative layer chromatography to give **8-(methoxycarbonyl)-4-methyl-2*H*-1,2-benzothiazine 1,1-dioxide (8)** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.66−7.57 (3H), 6.40 (1H, br s), 4.01 (3H, s), 3.28 (3H, s), 2.20 (3H, d, J = 1); MS (CI) 268 MH^+. Anal. Calcd for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 53.71; H, 5.01; N, 5.17. Also obtained was **9-(methoxycarbonyl)-2*H*-1,2-benzothiazepine 1,1-dioxide (9)**: mp 82−84 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 7.58−7.42 (3H), 6.51 (1H, dt, J =2, 13), 5.94 (1H, dt, J = 3, 13), 4.22 (2H, br), 3.96 (3H, s), 2.67 (3H, s); MS (CI) 285 M + NH_4^+. Anal. Calcd for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 53.80; H, 4.83; N, 5.18.

8-(Methoxycarbonyl)-4-hydroxy-4-(hydroxymethyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-Dioxide (10). A mixture of **7** (1.28 g, 4.80 mmol), *N*-methylmorpholine *N*-oxide (0.605 g, 5.17 mmol), and OsO_4 (4% aqueous solution, 0.1 mL) in dioxane (25 mL) and water (10 mL) was stirred at rt for 40 h. The mixture was diluted with EtOAc and washed with aqueous acetic acid. The aqueous phase was back extracted with EtOAc, and the combined organic phase was dried, filtered, and evaporated. The residue was triturated with EtOAc/Et_2O to give crystalline **10** (1.25 g, 4.15 mmol, 86%) collected by filtration: mp 161−163 °C; ^{1}H NMR (DMSO-d_6) δ 7.88 (1H, dd, J = 1, 8), 7.76 (1H, apparent t, J = 8), 7.65 (1H, dd, J = 1, 8), 5.80 (1H, s, OH), 5.17 (1H, t, J = 6, OH), 4.28 (1H, d, J = 15), 3.82 (3H, s), 3.59−3.37 (3H, complex), 2.76 (3H, s); MS (CI) 302 MH^+. Anal. Calcd for $C_{12}H_{15}NO_6S$: C, 47.83; H, 5.02; N, 4.65. Found: C, 48.25; H, 5.11; N, 4.40.

3,4-Dihydro-8-(methoxycarbonyl)-4-oxo-2*H*-1,2-benzothiazine 1,1-Dioxide (1c). To a solution of **10** (0.300 g, 0.99 mmol) in dioxane (10 mL, warmed to dissolve) was added water (10 mL) followed by $NaIO_4$ (0.225 g, 1.06 mmol) in water (5 mL). The mixture was stirred at rt for 20 min, when TLC showed complete conversion. The mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated to give **1c** (0.253g, 0.94 mmol, 94%): mp 148−150 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (1H, dd, J = 1, 8), 8.03 (1H, dd, J = 1, 8), 7.79 (1H, apparent t, J = 8), 4.45 (2H, s), 4.02 (3H, s), 2.90 (3H, s); MS (CI) 287 M + NH_4^+. Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.11; N, 5.20. Found: C, 48.88; H, 4.07; N, 5.09.

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