Facile Synthesis of 1, 2-Benzisothiazole-3-one-1,1-dioxide Methylsulfonyl Derivatives

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An improved and general synthesis of saccharin methylthio and methylsulfone derivatives from chloro-substituted saccharins is presented. A large-scale procedure for preparation of chloro-substituted saccharins was developed. Treatment of the saccharin chlorides with sodium thiomethoxide and *t*-BuOK in DMF gave the saccharin methyl sulfides, which upon chromium(VI) oxide catalyzed oxidation with periodic acid afforded the corresponding saccharin methylsulfones in high yields.

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1,2-Benzisothiazole-3-one-1,1-dioxides (saccharin derivatives) have found numerous potential as pharmaceuticals and agricultural agents, such as bactericides[1], fungicides[2], herbicides[3,4], α1c adrenergic receptor antagonists [5], matrix-degrading metalloproteinase inhibitors [6], blood platelet aggregation inhibitors [7], aldehyde dehydrogenase inhibitors [8], proteolytic enzyme inhibitors [9], human leukocyte elastase inhibitors [10] and inhibitors of serine protease, trypsin, chymotrypsin, cathepsin G and elastase [11]. In addition, the methylsulfonyl moiety has been found to be an important functional group in a number of biologically active compounds [12]. It was envisaged that the saccharin methylsulfone moiety when incorporated into biologically active molecules may lead to compounds with novel pharmacological profiles. Therefore it was of interest to develop a general synthesis of saccharin methylsulfones.

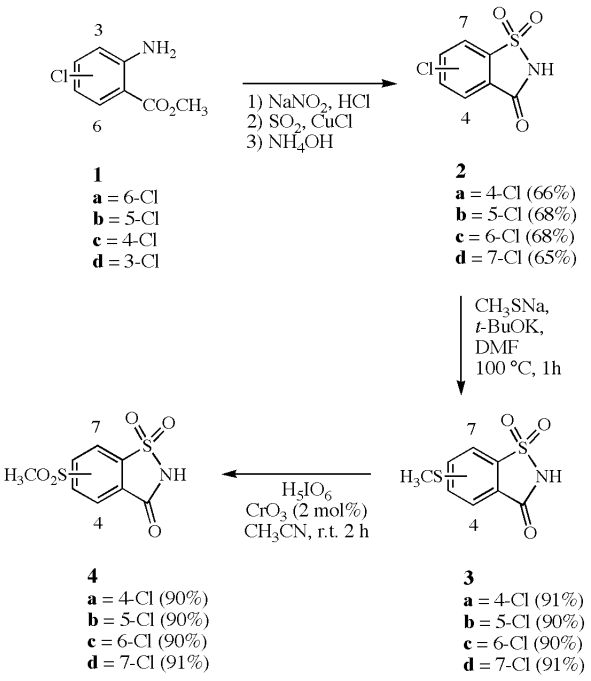
A search of the literature revealed that 6-methyl sulfonyl saccharin has been previously prepared from 6-amino saccharin using diazotization/oxidation chemistry [13]. However, attempts to employ this method resulted in poor overall yields of the desired saccharin derivatives (<14%). In addition, this approach required the synthesis of the corresponding amino substituted saccharin, which was tedious and often low yielding. This prompted an investigation to develop an improved method for the general synthesis of saccharin methylsulfone derivatives.

As illustrated in Scheme 1, the commercially and readily available methyl chloroanthranilates **1a-d** [14,15] were identified as starting materials for the preparation of the corresponding saccharin methylsulfones. Many syntheses of chloro-substituted saccharins are cited in the literature [13,16-19], however, an efficient large-scale procedure is currently unavailable. To this end it was necessary to modify the existing methods and developed a general large-scale procedure for preparation of chloro-substituted saccharins. Diazotization of the methyl chloroanthranilates **1a-d** was achieved with sodium nitrite in hydrochloric acid solution. The resulting diazonium salts were decomposed with excess sulfur dioxide in the presence of 25 mol% of copper (I) chloride at 0 °C. The crude sulfonyl chlorides were treated with ammonium hydroxide to afford the corresponding chloro-substituted saccharins **2a-d** in 65-68% yields.

Treatment of the saccharin chlorides **2a-d** with sodium thiomethoxide and *t*-BuOK in dry *N, N*-dimethylformamide at 100 °C for 1 hour furnished the saccharin methyl sulfides **3a-d** in excellent yields (>90%). Similar results were obtained in dry dimethylsulfoxide or *N*-methyl pyrrolidinone. As expected, the nucleophilic aromatic substitution reaction occurred much more easily at 4- or 7-position of the saccharin ring [shorter reaction times (40 minutes) and lower reaction temperatures (60 °C)] than at the 5- or 6-position. Lower yields of **3a-d** were obtained when the reactions were performed in aqueous alkaline solutions.

Among the different protocols to prepare sulfones, the oxidation of sulfides has become the most popular and straightforward method in organic synthesis and many oxidants have been used for this transformation [20]. However, most of the commonly used reagents were not suitable for the preparation of the saccharin methylsulfones. Oxidation with *m*-chloroperoxybenzoic acid[21-23] gave low yields of the desired saccharin methylsulfones due to contamination of the by-product *m*-chlorobenzoic acid. Attempted oxidation of **3a-d** with OXONE® [24,25] or H_2O_2 [26] conducted in aqueous acidic solution gave low yields due to low solubility of the saccharin methyl sulfides. The facile oxidation of the saccharin methyl sulfides **3a-d** to the corresponding **4a-d** saccharin methylsulfones was achieved with periodic acid (4 equivalents) and catalyzed by chromium (VI) oxide (2 mol%) in acetonitrile at room temperature to give the corresponding sulfones in high yields (90-91%)[20].

Scheme 1



1
a = 6-Cl
b = 5-Cl
c = 4-Cl
d = 3-Cl

2
a = 4-Cl (66%)
b = 5-Cl (68%)
c = 6-Cl (68%)
d = 7-Cl (65%)

3
a = 4-Cl (91%)
b = 5-Cl (90%)
c = 6-Cl (90%)
d = 7-Cl (91%)

4
a = 4-Cl (90%)
b = 5-Cl (90%)
c = 6-Cl (90%)
d = 7-Cl (91%)

In conclusion, an improved and general synthesis of saccharin methylsulfone derivatives has been developed from readily available methyl chloro anthranilates. The saccharin methylsulfone derivatives **4a-d** were prepared on multigram scale with good overall yields of 52-55%.

EXPERIMENTAL

All new compounds were characterized by ir, ^{1}H and ^{13}C nmr, elemental analysis (C, H, N). ^{1}H and ^{13}C nmr spectra were recorded on a Varien-400 MHz spectrometer at ambient temperature in deuteriodimethylsulfoxide-d_6 (Cambridge Isotope Laboratories, Inc.). Elemental analyses were determined by Atlantic Microlabs, Inc., Norcross, GA. Melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected.

General Procedure for the Preparation of Chloro-1, 2-benzisothiazole-3-one-1,1-dioxides (**2a-d**).

A solution of the corresponding methyl chloro-2-amino benzoate **1a-d** (22 g, 0.12 mol) in 20% hydrochloric acid (78 ml) was warmed until all solids were dissolved. The solution was cooled to 0 °C with stirring to precipitate the hydrochloride salt. To this suspension, a solution of sodium nitrite (8.3 g, 0.12 mol) in water (20 ml) was added dropwise at such a rate that the internal reaction temperature did not exceed 5 °C. After the addition was completed the mixture was stirred at 0 °C for 45 minutes to afford a clear solution. Sulfur dioxide (61.5 g, 0.96 mol) was bubbled into a mixture of acetic acid (96 ml) and water (10 ml) at 0 °C. Copper (I) chloride (3.0 g, 0.03 mol) was then added to the sulfur dioxide solution. The resulting blue-green mixture was then cooled to 0 °C. To this mixture was added the diazonium salt solution portionwise with vigorous stirring over a period of 30 minutes. After the addition was completed the reaction mixture was stirred at 0 °C for 1 hour and then the ice bath was removed and the mixture was allowed to warm to room temperature. The green mixture was stirred at room temperature until the evolution of nitrogen ceased (1-2 hour). The mixture was poured into ice water (500 g) and extracted with dichloromethane (3 × 100 ml). The combined extracts were washed with saturated aqueous sodium bicarbonate until effervescence ceased, then brine, and then dried over magnesium sulfate. The solvent was removed *in vacuo* to afford the crude sulfonyl chloride (27.5 g) as an orange oil.

The crude sulfonyl chloride was dissolved in tetrahydrofuran (90 ml) and the solution was cooled to 0 °C. Precooled (0 °C) concentrated (28%) ammonium hydroxide (50 ml) was added portion-wise at such a rate that the internal reaction temperature was maintained below 10 °C. After the addition was completed, the mixture was allowed to warm to room temperature and stirred for 1 hour. The solvent was removed *in vacuo* and the residue was dissolved in saturated aqueous sodium bicarbonate (60 ml) and extracted with diethyl ether (80 ml). The aqueous layer was acidified with concentrated hydrochloric acid to pH 1. The resulting precipitate was collected by filtration and dried under vacuum.

4-Chloro-1,2-benzisothiazole-3-one-1,1-dioxides (**2a**).

This compound was obtained as white crystals (17.3 g, 66%), mp 244-246 °C (lit. [13] 245-246 °C); ir (nujol): 1744, 1459, 1376 cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 8.11 (m, 1H), 7.90 (m, 2H); ^{13}C nmr (DMSO-d_6): δ 159, 141.7, 136.6, 136.1, 131.6, 123.7, 120.1.

5-Chloro-1,2-benzisothiazole-3-one-1,1-dioxide (**2b**).

This compound was obtained as an orange solid (17.8 g, 68%), mp 213-215 °C (lit. [16] 212-215 °C); ir: (nujol): 1717, 1458, 1376 cm^{-1}; ^{1}H nmr (DMSO- d_6): δ 8.23 (d, J = 7.6 Hz, 1H), 8.05 - 8.07 (m, 2H); ^{13}C nmr (DMSO-d_6): δ 159.7, 139.5, 137.9, 135.2, 129.8, 124.6, 123.0.

6-Chloro-1,2-benzisothiazole-3-one-1,1-dioxides (**2c**).

This compound was obtained as white crystals (17.8 g, 68%, mp 220-222 °C (lit. [18] 216-218 °C); ir (nujol): 1718, 1457, 1375 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.43 (s, 1H), 7.98 (s, 2H); ^{13}C nmr (DMSO-d_6): δ 160.9, 141.7, 141.2, 135.5, 127.29, 127.25, 122.4.

7-Chloro-1,2-benzisothiazole-3-one-1,1-dioxides (**2d**).

This compound was obtained as white crystals (17 g, 65%), mp 260-262 °C (lit. [17] 260-262 °C); ir (nujol): 1715, 1457, 1376 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.04 (d, J = 7.6 Hz, 1H), 7.95 (m, 2H); ^{13}C nmr (DMSO-d_6): δ 160, 136.7, 136.4, 135.4, 130.5, 126.6, 123.5.

General Procedure for the Preparation of Methylthio-1,2-benzisothiazole-3-one-1,1-dioxides (**3a-d**).

The corresponding chloro-1,2-benzisothiazole-3-one-1,1-dioxide **2a-d** (8.7 g, 0.04 mol) was dissolved in dry *N,N*-dimethylformamide (120 ml) under an argon atmosphere and the solution was cooled to 0 °C. To this solution was added potassium *tert*-butoxide (4.5 g, 0.04 mol) followed by sodium thiomethoxide (2.8 g, 0.04 mol). The reaction mixture was stirred at 0 °C for 15 minutes and then heated to 100 °C for 1 hour. The mixture was then cooled, poured into ice water (240 g) and acidified with concentrated hydrochloric acid to pH 1. The resulting

precipitate was collected by filtration and dried under vacuum (0.1 mm Hg) at 80 °C.

4-Methylthio-1,2-benzisothiazole-3-one-1,1-dioxides (**3a**).

This compound was obtained as white crystals (8.34 g, 91%), mp 287-289 °C; ir (nujol): 1711, 1459, 1376 cm^{-1}. ^1H nmr (DMSO-d_6): δ 7.91 (t, J = 7.6 Hz, 1H), 7.85(d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 2.58 (s, 3H). ^{13}C nmr (DMSO-d_6): δ 160.6, 142.4, 140.5, 135.3, 129.1, 121.1, 115.8, 13.6.

Anal. Calcd. for $C_8H_7NO_3S_2$: C, 41.91; H, 3.08; N, 6.11. Found: C, 41.95; H, 3.01; N, 6.01.

5-Methylthio-1,2-benzisothiazole-3-one-1,1-dioxides (**3b**).

This compound was obtained as white crystals (8.24 g, 90%), mp 198-200 °C; ir (nujol): 1717, 1456, 1375 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.13 (d, J = 8.4 Hz, 1H), 7.87(d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 2.71 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 160.4, 148.1, 134.7, 131.2, 128.3, 121.1, 119.7, 14.1.

Anal. Calcd. for $C_8H_7NO_3S_2$: C, 41.91; H, 3.08; N, 6.11. Found: C, 41.87; H, 3.09; N, 6.08.

6-Methylthio-1,2-benzisothiazole-3-one-1,1-dioxides (**3c**).

This compound was obtained as white crystals (8.44 g, 90%), mp 264-266 °C (lit. [4], 232-234 °C); ir (nujol): 1714, 1459, 1376 cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.0 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 2.65 (s 3H) ^{13}C nmr (DMSO-d_6): δ 161.6, 150.8, 141.3, 131.7, 125.8, 124.3, 117.7, 15.4.

Anal. Calcd. for $C_8H_7NO_3S_2$: C, 41.91; H, 3.08; N, 6.11. Found: C, 41.83; H, 3.10; N, 6.04.

7-Methylthio-1,2-benzisothiazole-3-one-1,1-dioxides (**3d**).

This compound was obtained as white crystals (8.34 g, 91%), mp 250-252 °C; ir (nujol) 1717, 1459, 1376 cm^{-1}. ^1H nmr (DMSO-d_6): δ 7.87 (m, 2H), 7.74 (m, 1H), 2.69 (s, 3H). ^{13}C nmr (DMSO-d_6): δ 160.8, 135.8, 135.6, 135.3, 132.0, 128.8, 120.8, 14.9.

Anal. Calcd. for $C_8H_7NO_3S_2$: C, 41.91; H, 3.08; N, 6.11. Found: C, 41.86; H, 3.12; N, 6.08.

General Procedure for the Preparation of Methylsulfonyl-1,2-benzisothiazole-3-one-1,1-dioxides (**4a-d**).

Periodic acid (9.1 g, 40 mmol) was dissolved in acetonitrile (120 ml) by vigorous stirring at room temperature for 30 minutes. Then chromium (VI) oxide (20 mg, 0.2 mmol, 2 mol%) was added to the solution and the mixture was stirred at room temperature for 5 minutes to give a clear orange solution. To this solution was added the corresponding methylthio-1,2-benzisothiazole-3-one-1,1-dioxide (**3a-d**, 2.3 g, 10 mmol) in one portion. A precipitate formed immediately with an exothermic reaction. The mixture was stirred at room temperature for 2 hours followed by the addition of isopropyl alcohol (15 ml). The reaction mixture was stirred at room temperature for additional 1 hour, filtered and the filtered cake was washed with acetone (30 ml). The filtrate was concentrated *in vacuo* at room temperature. The residue was dissolved in saturated aqueous sodium bicarbonate (40 ml), filtered and the filtrate was acidified with concentrated hydrochloric acid to pH 1. The resulting precipitate was filtered and dried under vacuum (0.1 mm Hg) at 80 °C.

4-Methylsulfonyl-1,2-benzisothiazole-3-one-1,1-dioxides (**4a**).

This compound was obtained as a white solid (2.35 g, 90%), mp >350 °C; ir (nujol): 1748, 1457, 1375 cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.50 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 8.22 (t, J = 8.0 Hz, 1H), 3.60 (s, 3H). ^{13}C nmr (DMSO-d_6): δ 160.2, 143.5, 139.9, 137.1, 134.5, 127.2, 127.0, 43.8.

Anal. Calcd. for $C_8H_7NO_5S_2$: C, 36.78; H, 2.70; N, 5.36. Found: C, 36.90; H, 2.74; N, 5.43.

5-Methylsulfonyl-1,2-benzisothiazole-3-one-1,1-dioxides (**4b**).

This compound was obtained as a white solid (2.34 g, 90%), mp 252-254 °C; ir (nujol): 1729, 1458, 1376 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.31-8.45 (m, 3H), 3.40 (s, 3H). ^{13}C nmr (DMSO-d_6): δ 161.0, 146.5, 144.3, 133.9, 130.3, 123.8, 122.8, 43.5.

Anal. Calcd. for $C_8H_7NO_5S_2$: C, 36.78; H, 2.70; N, 5.36. Found: C, 36.82; H, 2.63; N, 5.34.

6-Methylsulfonyl-1,2-benzisothiazole-3-one-1,1-dioxides (**4c**).

This compound was obtained as a white solid (2.35 g, 90%), mp 277-279 °C; ir (nujol) 1744, 1459, 1376 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.71 (s, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 3.41 (s, 3H). ^{13}C nmr (DMSO-d_6): δ 160.8, 147.0, 141.1, 133.4, 132.7, 126.4, 120.7, 43.2.

Anal. Calcd. for $C_8H_7NO_5S_2$: C, 36.78; H, 2.70; N, 5.36. Found: C, 36.81; H, 2.63; N, 5.33.

7-Methylsulfonyl-1,2-benzisothiazole-3-one-1,1-dioxides (**4d**).

This compound was obtained as a white solid (2.37 g, 91%), mp 264-266 °C; ir (nujol) 1741, 1460, 1376 cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.38 (d, J = 7.2 Hz, 1H), 8.31 (d, J = 7.6 Hz, 1H), 8.16 (t, J = 7.6 Hz, 1H), 3.40 (s, 3H). ^{13}C nmr (DMSO-d_6): δ 161.8, 138.9, 137.0, 136.8, 135.6, 132.1, 130.9, 45.0.

Anal. Calcd. for $C_8H_7NO_5S_2$: C, 36.78; H, 2.70; N, 5.36. Found: C, 36.80; H, 2.78; N, 5.34.

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