A Convenient Synthesis of Nitro-Substituted 1,2-Benzisothiazol-3(2*H*)-one 1,1-Dioxides (Nitrosaccharins)

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Nitro-substituted 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxides (nitrosaccharins) have been synthesized by amminolysis of nitro 2-chlorosulfonylbenzoate esters. This method appears to have advantages over the original procedure of oxidation of an *ortho*-toluenesulfonamide.

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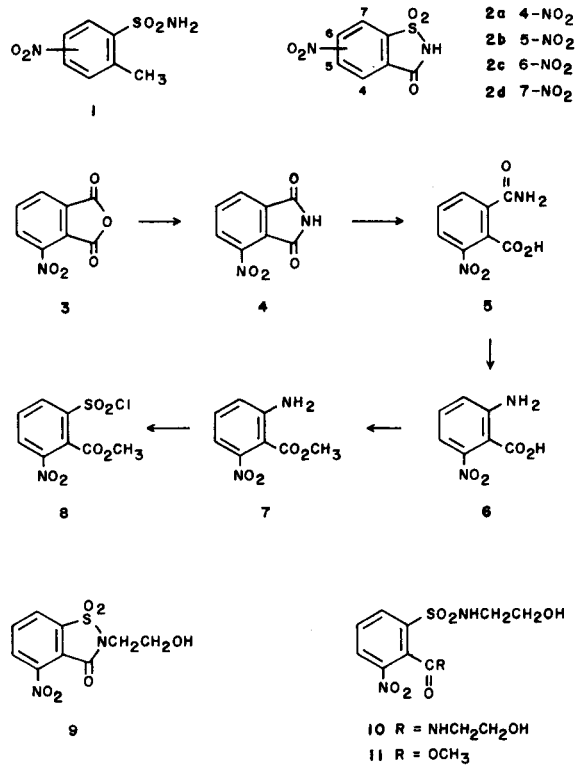
Although syntheses of the four possible mononitro aromatic derivatives **2a-d** of 1,2-benzoisothiazol-3(2*H*)-one 1,1-dioxide (saccharin) have been described [1,5], several groups [6-9] have reported difficulties or failures in repeating the critical permanganate oxidation step, **1** to **2**, of this sequence. Acidic chromic acid oxidation appears to offer some advantages over the original basic oxidation procedure and has been used successfully for preparation of the 5-nitro [6] and 6-nitro [6, 7, 9, 10] derivatives. However we, as well as others [6], have encountered difficulties in controlling this oxidation step on a large scale. In addition, the 4-nitro derivative **2a** could not be prepared by chromic acid-sulfuric acid oxidation of 2-methyl-3-nitrobenzenesulfonamide presumably due to rapid decarboxylation of the intermediate carboxylic acid.

This report describes an alternative synthesis of nitrosaccharins which circumvents the troublesome oxidation step. In this approach, starting materials are used in which that carbon atom is at the same oxidation level as in the final saccharin derivative [11].

6-Nitroanthranilic acid [14], **6**, was prepared in 61% overall yield from 3-nitrophthalic anhydride by modfication of previously published procedures. Methylation of the triethylamine salt of **6** with dimethylsulfate in dimethylformamide afforded a 66% yield of methyl ester **7** which was diazotized and converted to sulfonyl chloride **8**. Reaction of **8** with ammonia led to 4-nitrosaccharin, **2a**, in 89% yield from aminoester **7**.

Similarly, diazotization of readily available methyl 5-nitroanthranilate [15], conversion to the corresponding sulfonyl chloride and amminolysis afforded 5-nitrosaccharin, **2b**, in 74% yield.

However, under these conditions, reaction of sulfonyl chloride **8** with excess ethanolamine did not yield the expected *N*-hydroxyethyl derivative **9**, but instead gave amide **10**. Apparently **9** is formed in this reaction but undergoes facile ring opening with ethanolamine to form **10**. Ring opening was not observed in the case of the unsubstituted imides **2a** and **2b** since these acidic imides are stabilized as the anion. An authentic sample of **9**, prepared by alkylation of **2a** with ethylene oxide, did react with ethanolamine under comparable conditions to give a 91% yield of **10**.



In another approach to synthesis of **9**, ester **11** was prepared in 89% yield by reaction of sulfonyl chloride **8** with ethanolamine under less strenuous conditions. However, cyclization of **11** to **9** thermally or with base catalysis proved to be surprisingly difficult. Although **9** was not formed in refluxing toluene, the cyclized product was obtained in 15% yield by heating **11** at 200° for 1 hour.

Amminolysis of 2-chlorosulfonylbenzoate esters appears to be an improved method for the synthesis of certain nitro-substituted saccharin derivatives. In addition, this procedure may be useful for the preparation of other saccharin derivatives.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus using open capillaries and are uncorrected. The ^{1}H nmr spectra were recorded for all intermediates and final products on either a Varian XL-300 or a GE NT-360 instrument using tetramethylsilane as an internal standard and are consistent with assigned structures. E. Merck silica gel, 230-400 mesh, was used for the flash chromatographies.

Methyl 2-Amino-6-nitrobenzoate (**7**).

A mixture of 2-amino-6-nitrobenzoic acid [14] (30.0 g, 0.165 mole), dimethylsulfate (15.6 ml, 0.165 mole) and triethylamine (23 ml, 0.165 mole), DMF (350 ml) was stirred at room temperature for 18 hours. After concentrating at 50° and 0.2 mm, the residue was partitioned between ethyl acetate and a saturated aqueous solution of sodium chloride. The ethyl acetate extract was then washed with a saturated sodium bicarbonate solution, saturated sodium chloride solution and dried to give 28.8 g of crude product. Recrystallization from *n*-butylchloride-hexane gave 18.5 g (57 %) of **7**, mp 105-107°. An additional 2.7 g (8.4%) of pure ester was obtained upon flash chromatography of the filtrate material over silica gel and elution with 50% toluene-50% chloroform. An analytical sample, mp 107-109° (reported [16] mp 108-110°) was obtained upon recrystallization from ethyl acetate-hexane; ^{1}H nmr (deuteriochloroform): δ 3.8 (s, CH_3), 5.3 (br s, NH_2), 6.9 (d,d, aromatic CH), 7.0 (d,d, aromatic CH), 7.3 (t, aromatic CH).

Anal. Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.26; H, 4.15; N, 14.23.

Methyl 2-Chlorosulfonyl-6-nitrobenzoate (**8**).

A solution of sodium nitrite (2.86 g, 41.4 mmoles) in water (11.2 ml) was added slowly to a well stirred suspension of methyl 2-amino-6-nitrobenzoate (7.6 g, 38.7 mmoles) in glacial acetic acid (37 ml) and concentrated hydrochloric acid (67 ml), cooled to −5°. After addition was complete, the mixture was stirred at −5° to 0° for an additional 30 minutes and then added, in portions, to a cold solution of cupric chloride dihydrate (2.45 g) and sulfur dioxide (25 g, 0.39 moles) in glacial acetic acid (50 ml) and water (8.5 ml). The reaction mixture was stirred in an ice bath for 3 hours, stirred at room temperature for 18 hours and then poured onto ice (500 g). The precipitated tan solid was removed by filtration and dried to give sulfonyl chloride **8** (9.1 g, 84%), mp 152-154°.

Anal. Calcd. for $C_8H_6ClNO_6S$: C, 34.36; H, 2.16; N, 5.01. Found: C, 34.57; H, 2.15; N, 5.09.

Methyl 2-[*N*-(2-Hydroxyethyl)aminosulfonyl]-6-nitrobenzoate (**11**).

A solution of ethanolamine (2.4 g, 39.3 mmoles) in dry tetrahydrofuran (20 ml) was added over 1 hour to a stirred, cooled solution of methyl 2-chlorosulfonyl-6-nitrobenzoate (5.0 g, 17.9 mmoles) in tetrahydrofuran (200 ml). After addition was complete, the reaction mixture was stirred for 1 hour more in the ice bath, quenched with 1*N* hydrochloric acid (7 ml) and concentrated under reduced pressure. The oily residue was dissolved in ethyl acetate, washed with saturated sodium chloride solution, dried and concentrated. Recrystallization from ethyl acetate-hexane afforded **11** (4.58 g, 89%), mp 113-115°; ^{1}H nmr (DMSO-d_6): δ 2.9 (t, CH_2), 3.4 (q, CH_2), 3.9 (s, OCH_3), 4.8 (t, OH), 8.0 (t, aromatic CH), 8.3 (d,d, aromatic CH), 8.5 (d,d, aromatic CH).

Anal. Calcd. for $C_{10}H_{12}N_2O_7S$: C, 39.47; H, 3.98; N, 9.21. Found: C, 39.49; H, 3.86; N, 9.28.

4-Nitro-2*H*-1,2-benzisothiazol-3-one 1,1-Dioxide (**2a**).

A solution of sodium nitrite (4.6 g, 67 mmoles) in water (17 ml) was added slowly to a well stirred suspension of methyl 2-amino-6-nitrobenzoate (12.3 g, 63 mmoles) in acetic acid (60 ml) and concentrated hydrochloric acid (110 ml), cooled to −5°. After addition was complete, the mixture was stirred at −5° to 0° for an additional 30 minutes and then added, in portions, to a cold solution of cupric chloride dihydrate (5.04 g) and sulfur dioxide (40 g) in acetic acid (80 ml) and water (11 ml). The reaction mixture was allowed to warm to room temperature over 3 hours and then poured onto ice (1.5 kg). The precipitated sulfonyl chloride was removed by suction filtration and sucked dry for 30 minutes. The sulfonyl chloride was added to cold, concentrated ammonium hydroxide (400 ml) and stirred at room temperature for 18 hours. Cooling and acidfying to *p*H 1 with concentrated hydrochloric acid gave 12.8 g (89%) of pure 4-nitrosaccharin, homogeneous tlc (20% methanol-80% chloroform) R^f = 0.22. Recrystallization from 2-propanol-hexane gave 9.4 g (65%) of product, mp 230-232° (reported [3], 236-238°).

Anal. Calcd. for $C_7H_4N_2O_5S$: C, 36.85; H, 1.77; N, 12.28. Found: C, 37.02; H, 1.67; N, 12.08.

5-Nitro-2*H*-1,2-benzisothiazol-3-one 1,1-Dioxide (**2b**).

Diazotization of methyl 2-amino-5-nitrobenzoate [15] (3.0 g, 15.3 mmoles) and reaction with ammonia by the same procedure used to prepare the 4-nitro isomer **2a** afforded 2.59 g (74%) of 5-nitrosaccharin, mp 217-219° (reported 212-214° [7], 210-213° [8]). An analytical sample (1.93 g, 55%) with the same mp was obtained upon recrystallization from ethyl acetate-hexane.

Anal. Calcd. for $C_7H_4N_2O_5S$: C, 36.85; H, 1.77; N, 12.28. Found: C, 36.89; H, 1.74; N, 12.43.

N-(2-Hydroxyethyl) 2-(2-Hydroxyethylamino)sulfonyl-6-nitrobenzamide (**10**).

From Methyl 2-Chlorosulfonyl-6-nitrobenzoate (**8**).

A solution of methyl 2-chlorosulfonyl-6-nitrobenzoate (0.50 g, 1.79 mmoles) and ethanolamine (2.2 g, 36 mmoles) in water (25 ml) was stirred at room temperature for 18 hours. After removing unreacted sulfonyl chloride (60 mg) by filtration, the filtrate was cooled and acidified to *p*H 1 with concentrated hydrochloric acid. The precipitate was filtered off and dried to give 0.25 g (42%) of hydroxyethyl amide **10**, mp 175.5-176.5°, identical with that prepared from reaction of **9** with ethanolamine; ^{1}H nmr (DMSO-d_6): δ 2.9 (q, CH_2), 3.2 (q, CH_2), 3.4 (q, CH_2), 3.5 (q, CH_2), 4.8 (q, 2-OH, exchangeable), 7.3 (t, NH, exchangeable), 7.9 (t, aromatic CH), 8.2 (d,d, aromatic CH), 8.3 (d,d, aromatic CH), 8.8 (t, NH).

Anal. Calcd. for $C_{11}H_{15}N_3O_7S$: C, 39.64; H, 4.54; N, 12.61. Found: C, 39.87; H, 4.51; N, 12.84.

From 2-(2-Hydroxyethyl)-4-nitro-2*H*-1,2-benzisothiazol-3-one 1,1-Dioxide (**9**).

A solution of 2-(2-hydroxyethyl)-4-nitro-2*H*-1,2-benzisothiazol-3-one 1,1-dioxide (100 mg, 0.37 mmole) and ethanolamine (24 mg, 0.40 mmole) in THF (5 ml) was stirred at room temperature for 3 days. After concentrating under reduced pressure, the residue was recrystallized from methanol-ethyl acetate-hexane to give hydroxyethyl amide **10** (112 mg, 91%), mp 176.5-177.5°.

Anal. Calcd. for $C_{11}H_{15}N_3O_7S$: C, 39.64; H, 4.54; N, 12.61. Found: C, 39.84; H, 4.66; N, 12.67.

2-(2-Hydroxyethyl)-4-nitro-2*H*-1,2-benzisothiazol-3-one 1,1-Dioxide (**9**).

From 4-Nitro-1,2-benzisothiazol-3-one 1,1-Dioxide (**2a**).

A suspension of 4-nitro-2*H*-1,2-benzisothiazol-3-one 1,1-dioxide (2.0 g, 8.8 mmoles) in water (140 ml) was added to ethylene oxide (approximately 2 ml) cooled in an ice bath. After stirring at ice bath temperature for 1 hour, the mixture was allowed to stir at room temperature for 18 hours. Water was removed under reduced pressure and the residue flash chromatographed over silica gel. Elution with 2% isopropanol-98% methylene chloride and recrystallization from ethyl acetate-hexane gave the *N*-(2-hydroxyethyl) derivative **9** (0.39 g, 16%), mp 140-142°; ^{1}H nmr (DMSO-d_6): δ 3.7 (q, CH_2), 3.8 (t, CH_2), 5.0 (t, OH), 8.3 (t, aromatic CH), 8.4 (d, aromatic CH), 8.6 (d, aromatic CH).

Anal. Calcd. for $C_9H_8N_2O_6S$: C, 39.71; H, 2.96; N, 10.29. Found: C, 40.06; H, 2.93; N, 9.92.

From Methyl 2-[*N*-(2-Hydroxyethyl)aminosulfonyl]-6-nitrobenzoate (**11**).

Methyl ester **11** (300 mg) was heated neat at 200° for 1 hour. After cooling and dissolving in ethyl acetate, the organic extract was washed with water, dried and concentrated. The residue was flash chromatographed over silica gel, eluted with 2% methanol-98% chloroform and recrystallized form ethyl acetate-hexane to give 41 mg (15%) of product, mp 136-139°. This product was confirmed to be the *N*-(2-hydroxyethyl) derivative **9** by mmp, ^{1}H nmr and tlc comparison with the product obtained from alkylation of 4-nitro-2*H*-1,2-benzisothiazol-3-one 1,1-dioxide with ethylene oxide.

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