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THE SYNTHESIS OF SUBSTITUTED SACCHARINS THROUGH THE o-LITHIATIVE SULFONAMIDATION OF *N,N*-DIETHYLBENZAMIDES

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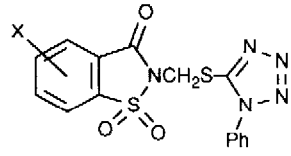
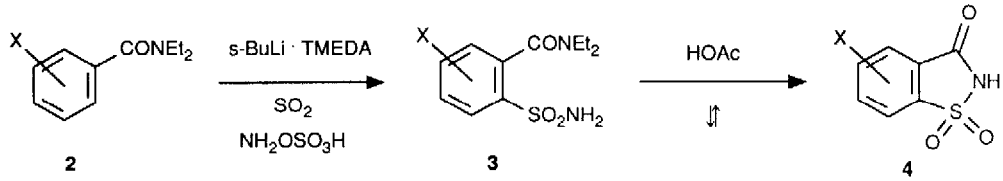
The readily available N,N-diethylbenzamides **2** *are converted in two reaction steps to a variety of substituted saccharins* **4** *in good overall yields.*

In conjunction with our program to discover inhibitors of human leukocyte elastase for potential use in the treatment of emphysema, we have discovered a novel class of mechanism-based inhibitors **1**.[1] To prepare analogs of our lead compound **1** (X=H) we needed general and efficient synthetic methods to prepare the saccharin intermediates **4**.



1

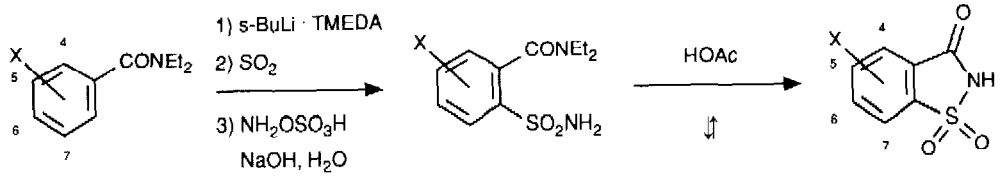
Many syntheses of substituted saccharins are cited in the literature,[2] however, general and high yielding methods were not available. Lombardino[3] prepared substituted saccharins through the *ortho*-lithiation and carbonation of sulfonamides. The overall yields were low and properly substituted sulfonamide starting materials were not readily available. We have developed a method for the synthesis of a variety of substituted saccharins in good overall yields in a two step process from readily available *N,N*-diethylbenzamides **2**.



2 **3** **4**

The 2-alkyl-benzamide starting materials **2a** and **2g** were prepared following the method of Beak and coworkers,[4] the benzamides **2b**, **2c**, and **2f** were prepared from commercially available acid chlorides, and the amides **2d** and **2e** were prepared by O-alkylation of *N,N*-diethylsalicylamide.

SYNTHESIS OF SUBSTITUTED SACCHARINS



2 **3** **4**

Cmpd	X = [a]	% Yield of **3** [b]	mp (°C)	% Yield of **4** [b]	mp (°C)
a	4-$CHCH_3$ (TMS)	41	oil	85	123-125 [c]
	4-CH_2CH_3	--	--	72 [d]	183-185
b	7-Cl	53 [e]	184-189	93 [f]	260-262
c	4-OCH_3	49 [e]	190-194.5	75	162-165 [c]
d	4-OCH_2CH_3	82	172-173	94	190-191 [c]
e	4-$OCH(CH_3)_2$	80	141-142	96	132-133 [c]
f	4,5-$(OCH_3)_2$	82	158-161	86	135-137 [c]
g	4-CH_2CH_3-5,7-$(OCH_3)_2$	70	198-199	96	241-243

[a] Saccharin numbering is used for simplicity. [b] Yields given are for isolated products having satisfactory NMR, IR, MS, and elemental composition. [c] Isolated as the diethylamine salt. [d] Prepared by desilylation of **4a** with CsF in DMF/H_2O.[8] [e] Sodium acetate was used in place of sodium hydroxide. Variable yields of **3c** were obtained (19-49%). [f] *Prepared by cyclization of* **3b** *in 6N HCl/dioxane (1:1) at reflux for 1 h.*

The utility in organic synthesis of *N,N*-diethylbenzamides in *ortho*-lithiation reactions has been widely demonstrated by Beak, Snieckus, and others.[5] We have found that sulfonation of the *ortho*-lithiated benzamides **2**, followed by oxidative amination of the intermediate lithium sulfinate with hydroxylamine-O-sulfonic acid, affords in good yields the sulfonamides **3**. We have modified the oxidative

amination procedure of Graham and Scholtz.[6] Higher and more reproducible yields of **3** were obtained when hydroxylamine-O-sulfonic acid was neutralized with one equivalent of sodium hydroxide prior to addition to the lithium sulfinate intermediate instead of buffering the reaction with sodium acetate. For example, when sodium acetate was used a 38% yield of **3f** was obtained in contrast to the 82% yield obtained with prior neutralization with sodium hydroxide. Also, variable yields (19-49%) of **3c** were obtained with the sodium acetate method.

N,N-Diethylbenzamides are notoriously resistant to nucleophilic attack.[5,7] Nevertheless, the sulfonamides **3** cyclized in refluxing glacial acetic acid over 6 to 24 h to give the substituted saccharins **4** in excellent yields. The ease of cyclization may be explained by the intramolecular nature of the acid catalyzed addition of the sulfonamide to the amide carbonyl. The 7-chlorosaccharin **4b** was prepared by cyclization of the sulfonamide **3b** in a 1:1 mixture of 6N hydrochloric acid and dioxane at reflux for 1 h. However, under these conditions the cyclization of **3c** and **3f** required prolonged reaction times (3 days) and only a 40% yield of 4-methoxysaccharin **4c** was obtained, while a complex mixture resulted with the 4,5-dimethoxy derivative **3f**. These results contrast with the excellent yields of **4c** and **4f** obtained with the acetic acid method. Hydrolysis in these examples appears to compete with the cyclization, since refluxing **3c** in a 1:2 mixture of 6N hydrochloric acid and acetic acid for 19 h gave as the only isolable product 2-methoxy-6-sulfobenzoic acid in 30% yield as a diethylamine salt.

To expand the generality of this method and provide for the preparation of 4-*n*-alkyl-saccharins, the silyl derivative **4a** was desilylated with cesium fluoride in *N,N*-dimethylformamide-water at room temperature for 8 h to afford 4-ethylsaccharin in 72% yield. A similar strategy was developed by Snieckus and coworkers[8] to block benzylic sites in tolylamides thereby obtaining products resulting from *ortho*-lithiation. *N,N*-Diethyl-2-ethylbenzamide could not be used directly for the preparation of 4-ethylsaccharin, since lithiation with *s*-BuLi · TMEDA takes place predominately at the benzylic site[4] and treatment of this anion with trimethylsilylchloride gave **2a** in 68% yield. In contrast, the benzylic site of the benzamide **2g** was not lithiated with *s*-BuLi · TMEDA, instead only the *ortho*-lithiated product **3g** was obtained upon subjection of **2g** to our typical reaction procedure. The ethyl substituent of **2g** apparently can not adopt the necessary conformation for deprotonation of the benzylic proton due to steric crowding by the adjacent methoxy group.

The efficient two step process described in this letter has enabled us to prepare saccharins with dissimilar substituents and thereby to examine the structure-activity relationships in a series of novel human leukocyte elastase inhibitors **1**.[1]

Typical *o*-Lithiative Sulfonamidation Procedure. To a solution of *sec*-butyllithium (27.8 mL, 25 mmol of a 0.9 M solution in cyclohexane) and *N,N,N',N'*-tetramethylethylenediamine (3.4 mL, 23 mmol) in 100 mL of tetrahydrofuran at -78 °C and under nitrogen was added dropwise over 15 min a solution of *N,N*-diethyl-2-ethoxybenzamide (5.0 g, 22.6 mmol) in 60 mL of tetrahydrofuran. After completion of addition, the reaction mixture was stirred at -78 °C for 90 min. Condensed sulfur dioxide (20 mL) was added cautiously to the mixture and stirring was continued overnight (16 h), while allowing the reaction to come to

room temperature. The intermediate lithium sulfinate precipitated from the reaction. The reaction mixture was concentrated to dryness, and the residue was dissolved in 250 mL of water and cooled in an ice-water bath. To an ice cold solution of sodium hydroxide (2.7 g, 68 mmol) in 40 mL of water was added an ice cold solution of hydroxylamine-O-sulfonic acid (7.66 g, 67.8 mmol) in 40 mL of water. This solution was added to the lithium sulfinate solution, and the mixture was stirred at room temperature for 6h. A precipitate formed and was filtered off, washed with water, and dried under vacuum to give 5.59 g (82%) of **3d** as white crystals; mp 172-173 °C.

Typical Cyclization Procedure. A solution of **3d** (4.59 g, 15.3 mmol) in 50 mL of glacial acetic acid was refluxed for 15 h, the solvent evaporated, toluene was added, and the solvent partially evaporated to remove residual acetic acid. The mixture was filtered to give 4.33 g (94%) of **4d** diethylamine salt as a tan solid; mp 180-186 °C. An analytical sample was obtained by recrystallization from methanol-hexanes to give white crystals; mp 190-191 °C.

Footnotes and References:

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