An Expedient Synthesis of 2,3-Dihydro-5,6-dimethoxy-3-methylsulfonamido-1,2-benzisothiazole-1,1-dioxide *via* Intramolecular Sulfamoyl Michael Addition

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A simple method of introducing a sulfamoylmethyl group on carbon-3 in 1,2-benzisothiazole-1,1-dioxide is described.

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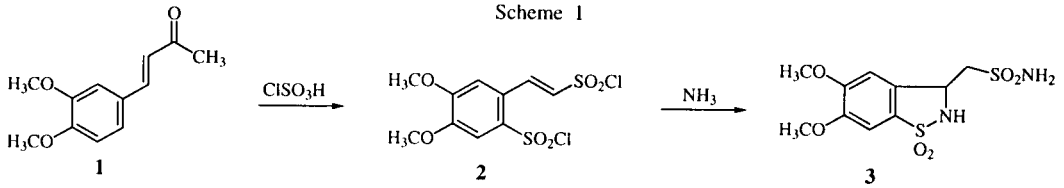
3-Substituted 1,2-benzisothiazole 1,1-dioxides are an important class of heterocycles with a broad range of biological activity. Compounds of this structural type have found numerous applications as pharmaceutical [1,2] and agrochemical [3] agents. Over the years various different synthetic routes have been developed for these types of compounds [4-7].

Uno and Kurokawa reported [8] the synthesis of 3-methylsulfonamido-1,2-benzisothiazole from the chlorosulfonation and amination of 1,2-benzisothiazol-3-acetic acid in a low yield (14%). In our previous studies [9,10] the reaction of benzylideneacetone and 2-thienylideneacetone with chlorosulfonic acid was investigated under mild conditions, resulting in the formation of styrene-4,β-disulfonyl dichloride and 2-thienylidene-5,β-disulfonyl dichloride, respectively. A reaction mechanism was suggested in which ω-chlorosulfonation was proposed as the first step, as was reported with acetophone [11], followed by migration of the sulfonyl group with subsequent elimination of the acetyl group. Since the position *para* to one of the methoxy groups in 3,4-dimethoxybenzylideneacetone **1** is activated, we investigated the reaction of **1** with chlorosulfonic acid under mild conditions in the hope of obtaining the *ortho*-chlorosulfonyl α,β-unsaturated sulfonyl chloride. The reaction of **1** with chlorosulfonic acid gave the disulfonyl dichloride **2** which was, without purification, treated with excess ammonium hydroxide to afforded 2,3-dihydro-5,6-dimethoxy-3-methylsulfonamido-1,2-benzisothiazole-1,1-dioxide **3** (Scheme 1) in a satisfactory yield (55%). The formation of **2** probably proceeds in a similar mechanism to benzylideneacetone and 2-thienylideneacetone, in forming the α,β-unsaturated sulfonyl chloride moiety with additional chlorosulfonation *para* to the methoxy group. Through this route we were able to construct the α,β-unsaturated sulfonyl chloride and to introduce the chlorosulfonyl group in the same one-pot reaction.

Structure of 2,3-dihydro-5,6-dimethoxy-3-methylsulfonamido-1,2-benzisothiazole-1,1-dioxide **3** is based on spectral evidence. The ir spectrum of **3** showed the characteristic symmetric (1145 cm^{-1}) and anti-symmetric (1340 cm^{-1}) S=O vibrations of the 1,1-dioxide. The ^1H nmr exhibited two singlets for the aromatic protons and the benzisothiazole NH signal was observed as an exchangeable singlet at δ 7.93. It also exhibited, besides the methoxy (two singlets at δ3.91 and δ3.90) protons, an AMX system for the methine proton attached to the stereogenic carbon (doublet of doublets) and diastereotopic (two doublet of doublets) protons. Further confirmation was obtained from the ^{13}C nmr of **3**, which showed the presence of ten resonances with distinct chemical shifts. Four of these were due to the quaternary carbon atoms, three were due to tertiary carbon atoms and the remainder were assigned to the methoxy and methylene carbon atoms, on the basis of off-resonance decoupling and signal intensity. The mass spectra showed the expected molecular ion for **3**.

The use of α,β-unsaturated sulfones as Michael acceptors with a range of nucleophiles has been well documented [12]. Rao and Hamor first reported [13] the Michael reaction where a sulfamoyl ($-SO_2NH_2$) group acts as a donor component to synthesize alkyl esters of 3-carboxymethyl-1,2-benzisothiazole-1,1-dioxides from *ortho*-sulfamoylcinnamates.

Scheme 1



1 2 3

In the presence of excess ammonium hydroxide, first the disulfonyl dichloride **2** is converted to the disulfonamide, which subsequently undergoes intramolecular Michael addition with the SO_2NH anion acting as the donor component and the α,β-unsaturated sulfonamide moiety as the acceptor component.

In conclusion, formation of **3** from **2** *via* a Michael addition provides a facile and convenient route to 3-methylsulfonamido-1,2-benzisothiazole-1,1-dioxide in a satisfactory yield, that would otherwise require more difficult steps. Further reactions of **2** are currently under investigation in order to generate other heterocycles.

Attempts to obtain a methylnitro group in the 3-position of the benzisothiazole-1,1-dioxide moiety from the reaction of 3,4-dimethoxy-β-nitrostyrene with chlorosulfonic acid failed, because of decomposition of 3,4-dimethoxy-β-nitrostyrene.

EXPERIMENTAL

Melting points were determined using a Gallenkamp electric apparatus and are uncorrected. The nmr spectra were recorded with a Bruker AC250 spectrometer using tetramethylsilane as internal standard and deuterodimethyl sulfoxide as solvent. Infrared spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Mass spectra were obtained with a VG 70-250 mass spectrometer operating at 70 eV.

3,4-Dimethoxybenzylideneacetone **1** was prepared according to the literature method [14].

2,3-Dihydro-5,6-dimethoxy-3-methylsulfonamido-1,2-benzisothiazole-1,1-dioxide **3.**

To a stirred solution of chlorosulfonic acid (16g, 0.138 mole) in dry chloroform (25 ml) at 0°C was added 3,4-dimethoxybenzylideneacetone (5g, 0.023 mole) dissolved in dry chloroform (25 ml). The solution was stirred at room temperature for 5 days, and then added to iced-water. After separation of the organic phase, the aqueous layer was re-extracted with chloroform. The combined chloroform layers were washed twice with water, dried over magnesium sulfate and evaporated under reduced pressure. The resulting solid was dissolved in ethanol and treated with ammonium hydroxide solution with stirring overnight at room temperature. The solution was poured onto crushed ice. The precipitate was filtered off under suction, washed with water and recrystallized twice from ethanol to give **3** (55%), mp 217-19°C; ir (KBr) ν_{max} 3150,3345 (SO_2NH_2) 1595 (C=C stretch), 1340, 1145 (SO_2 stretch) cm^{-1}; ^1H nmr (DMSO-d_6) δ 7.93 (exchangeable NH), δ 7.33 (singlet, 1H, aromatic), δ 7.31 (singlet, 1H, aromatic), δ 7.01 (broad singlet, 2H, NH_2), δ 4.95 (dd, 1H), δ 3.9 (2 singlets, 6H, OCH_3), δ 3.84 (dd, 1H), δ 3.17 (dd, 1H); ^{13}C nmr δ 52.2, 56.0, 56.1, 59.3, 102.2, 106.8, 127.1, 131.2, 150.0, 152.9 ppm; ms *m/z* 322 M^+, 241 (M^+ - SO_2NH_2), 228 (M^+ -$CH_2SO_2NH_2$).

Anal. Calcd. for $C_{10}H_{14}N_2O_6S_2$: C, 37.3; H, 4.3; N, 8.7. Found: C, 37.5; H, 4.5; N, 8.6.

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