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NOVEL SYNTHESIS OF A 2H-1,2-BENZOTHIAZINE -1,1-DIOXIDE DERIVATIVE

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Abstract: We report a novel synthesis of 4-chloro-2-cyclohexyl-6,7-dimethoxy-2H-1,2-benzothiazine-1,1-dioxide **6** from 3,4-dimethoxychalcone **1**. Chloro-sulfonation of **1** followed by amination, then epoxidation under basic conditions with immediate elimination of the benzoyl group and electrophilic chlorination resulted in **6**. A mechanism is suggested.

In recent years there has been a rapid growth in the number of literature references to the 1,2-benzothiazine-1,1-dioxide ring system.[1-3] Much of the literature pertains to the discovery that 3-carboxamides of 2-alkyl-4-hydroxy-2H-1,2-benzothiazine-1,1-dioxides are anti-inflammatory agents, which includes the

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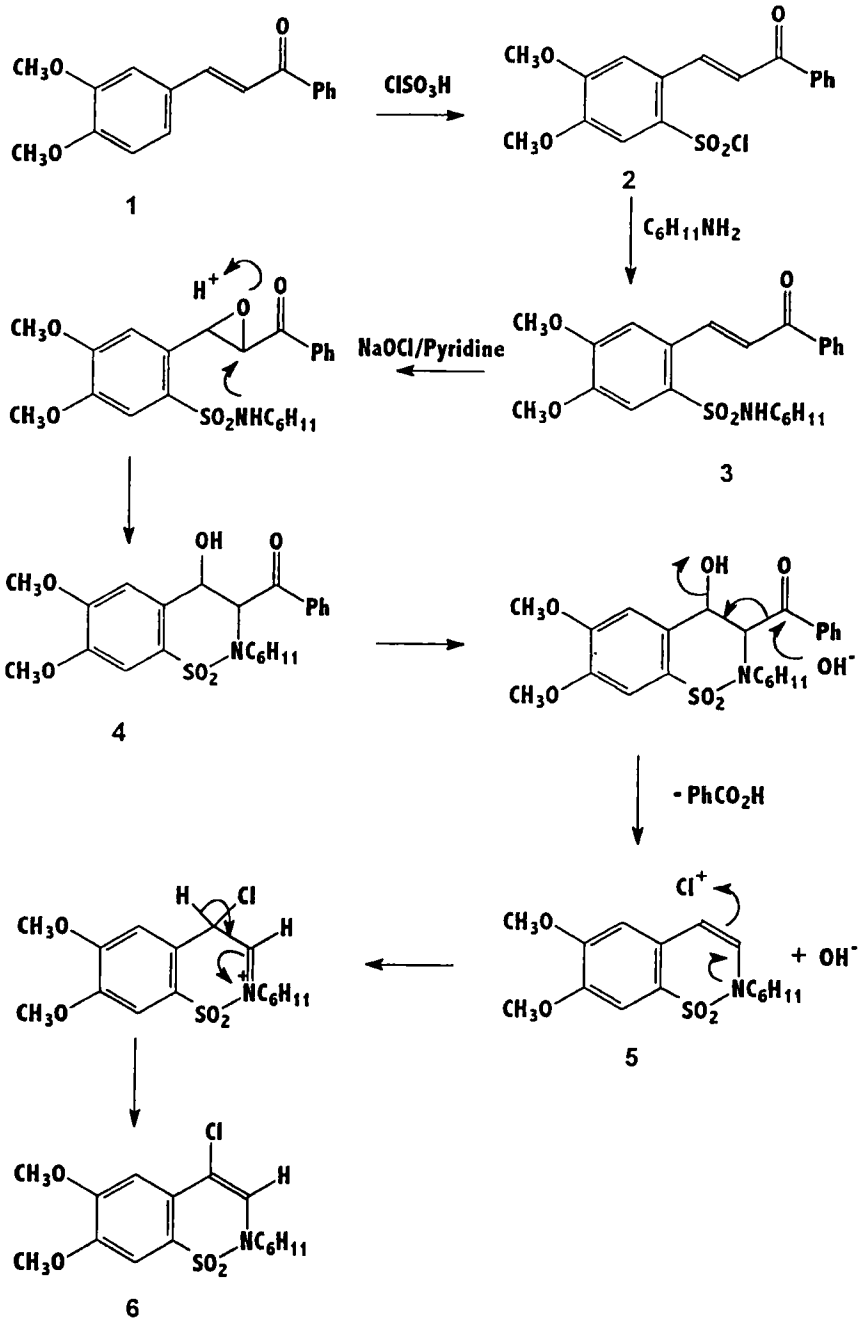
drug piroxicam.[4] The most common route to these types of compounds is *via* the alkoxide rearrangement of saccharin derivatives followed by N-alkylation[5-7]. There are various synthetic routes to the 1,2-benzothiazine-1,1-dioxides, but the starting compounds are not readily available.[8] In our current work on the syntheses of sulfonyl derivatives of α,β-unsaturated carbonyl compounds,[9,10] we now report a novel route to 1,2-benzothiazine derivative from a readily available sulfonamide.

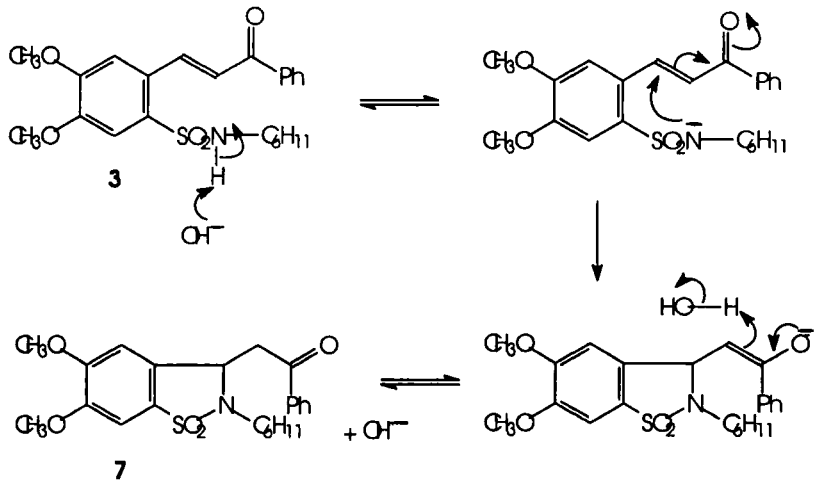
Reaction of 3,4-dimethoxychalcone **1** with chlorosulfonic acid afforded the sulfonyl chloride **2** in a good yield. The sulfonyl chloride **2** was condensed with cyclohexylamine to give the sulfonamide **3**. Chalcones are known to undergo epoxidation with hydrogen peroxide in a basic medium[11] and by the use of sodium hypochlorite in pyridine.[12] We investigated the reaction of **3** with sodium hypochlorite in pyridine and anticipated that epoxidation followed by cyclization should have led to the substituted 1,2-benzothiazine-1,1-dioxide **4**. The reaction under these conditions, instead of providing 1,2-benzothiazine-1,1-dioxide **4**, resulted in the formation of 4-chloro-6,7-dimethoxy-2H-1,2-benzothiazine-1,1-dioxide **6** (Scheme 1).

The structure of **6** was characterized by spectral and analytical data. The ^{1}H spectrum of **6** showed only two singlets at δ 7.6 and δ 7.4 for the aromatic protons and a singlet at δ 6.7 for the vinylic proton. The ^{13}C and IR spectra confirmed the absence of the carbonyl group indicative of the elimination of the benzoyl group.



Scheme 1

The structure of **6** was further confirmed by the mass spectrum, which showed a molecular ion at m/z 357/359 (M^+ ion) and fragmentation ion at m/z 274/276 (M^+-C_6H_{11}) consistent with the structure.



Scheme 2

Reaction of the sulfonamide **3** with hydrogen peroxide in a basic medium was also investigated. It was presumed that this should lead to either the 1,2-benzothiazine **4** or the 1,2-benzothiazine **5**, with no possibility of chlorination occurring. However, under these conditions none of the 1,2-benzothiazines **4** or **5** were isolated, instead 2-cyclohexyl-5,6-dimethoxy-3-phenacyl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide **7** was obtained, presumably *via* hydroxide catalyzed intramolecular Michael addition as shown in Scheme 2.

A series of primary aliphatic amines reacted with the sulfonyl chloride **2** in the absence of hydrogen peroxide all underwent this facile Michael addition to give

1,2-benzisothiazole-1,1-dioxide derivatives analogous to **7**. Thus we were unable to obtain any sulfonamides to attempt further reaction with sodium hypochlorite. In an attempt to overcome this problem we reacted the sulfonyl chloride **2** with sodium hypochlorite in pyridine in the hope of obtaining the epoxide, however, this only gave complex intractable mixtures. Currently we are investigating the versatility of this reaction with other α,β-unsaturated carbonyl compounds and these results will be reported in due course.

Experimental

Melting points were determined using a Gallenkamp electric apparatus and are uncorrected. The NMR spectra were recorded with a Brucker AC250 spectrometer using tetramethylsilane as internal standard and deuterodimethyl sulfoxide as solvent unless otherwise stated. Infrared spectra were recorded with a Nicolet 360 FTIR spectrophotometer. Mass spectra were obtained with a VG 70-250 mass spectrometer operating at 70 eV.

3,4-Dimethoxychalcone **1** was prepared according to the literature method.[12]

3,4-Dimethoxychalcone-6-sulfonyl chloride **2**.

To a stirred solution of chlorosulfonic acid (17.3g, 0.15 mole) at 0°C 3,4-dimethoxychalcone (5g, 0.019 mole) was added. The dark red solution was stirred

at room temperature for 3 hours, and added to iced-water. The resulting precipitate was filtered, washed with water and dried in a vacuum desiccator. This was recrystallized from acetronitrile to give **2** (5.5g, 80%): m.p. 172-73°C. IR (KBr) ν_{max} 1645 (C=O), 1325,1140 (SO_2 stretch) cm^{-1}; ^1H NMR (DMSO-d) δ8.5-7.24 (multiplet, 9H, aromatic), δ4.0 (singlet, 3H, OCH_3) and δ3.9 (singlet, 3H, OCH_3); ^{13}C NMR δ190, 154,149,138, 137, 135, 133, 128.9, 128.8, 128.6, 127, 111, 110, 56.6 and 56.5; MS m/z 366/368 M^+, 331 (M^+-Cl), 267 (M^+-SO_2Cl),

Anal. Calcd. For $C_{17}H_{15}ClO_5S$: C, 55.7; H, 4.1

Found C, 55.5; H, 4.2

3,4-Dimethoxychalcone-6-cyclohexyl sulfonamide **3**.

3,4-Dimethoxychalcone-6-sulfonyl chloride **2** (2g, 0.0055 mole) was reacted with excess cyclohexylamine in acetone (100 ml). The mixture was initially kept at 0°C and left at room temperature for one hour. The mixture was poured onto crushed ice (100 ml), the precipitate was collected, washed with water and dried to give **3**, 1.85g (79%). The crude sulfonamide was purified by recrystallization from ethanol, m.p. 199-200°C. IR (KBr) ν_{max} 1665 (C=O), 1316,1137 (SO_2 stretch) cm^{-1}; ^1H NMR (DMSO-d) δ8.5-7.24 (multiplet, 9H, aromatic and 1H, NH), δ4.0 (singlet, 3H, OCH_3) and δ3.9 (singlet, 3H, OCH_3), δ2.15-1.2 (multiplet, 11H, cyclohexyl); MS m/z 429 (M^+), 365 (M^+-SO_2), 346 (M^+-C_6H_{11})

Anal. Calcd. For $C_{23}H_{27}NO_5S$: C, 64.33; H, 6.3; N, 3.3

Found C, 64.44; H, 6.2; N, 3.4

4-Chloro-2-cyclohexyl-6,7-dimethoxy-2H-1,2-benzothiazine-1,1-dioxide **6**

To a stirred solution of the sulfonamide **3** (1g, 0.0023 mole) dissolved in pyridine (20 ml) was added excess sodium hypochlorite solution (10 ml) at room temperature. The mixture was stirred at this temperature for 30 minutes and poured onto crushed ice. The resulting precipitate was filtered, washed with water and dried to give 0.85g (72%) of **6** as a white solid. Crude **6** was recrystallized from acetonitrile and ethanol, m.p. 205-206°C. IR (KBr) ν_{max} 1605 (C=C), 1325,1145 (SO_2 stretch) cm^{-1}; ^1H NMR (DMSO-d) δ7.6 (singlet, 1H, aromatic), δ7.4 (singlet, 1H, aromatic), δ6.7 (singlet, 1H, vinylic), δ3.87 (singlet, 3H, OCH_3), δ3.86 (singlet, 3H, OCH_3), δ2.18-1.1 (multiplet, 11H, cyclohexyl); ^{13}C NMR δ153, 151, 130, 122.9, 122.8, 103, 101, 93, 57, 56.3, 56.3, 29, 25, 24.9; MS m/z 357/359 M^+, 274/276 (M^+- C_6H_{11}), 210/212 (M^+- $SO_2C_6H_{11}$)

Anal. Calcd. For $C_{16}H_{20}ClNO_4S$: C, 53.7; H, 5.6; N, 3.9

Found C, 53.5; H, 5.6; N, 3.8

2-Cyclohexyl-5,6-dimethoxy-3-phenacyl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide **7**.

To a stirred solution of sulfonamide **3** (1g, 0.0023 mole) dissolved in THF (20 ml) 30% hydrogen peroxide (10 ml) was added. The mixture was stirred at room temperature and 1M sodium hydroxide (10 ml) was added drop-wise over a period of time. The resultant orange solution was stirred at room temperature for one hour and then poured onto crushed ice. The resulting solid was filtered, dried and

recrystallized from acetonitrile to give 0.95g (95%) of **7**, m.p. 194-95°C. IR (KBr) ν_{max} 1695 (C=O), 1600 (C=C), 1340,1150 (SO_2 stretch) cm^{-1}; ^1H NMR (DMSO-d) δ7.91-6.95 (multiplet, 7H, aromatic), δ5.92-5.82 (dd, 1H), δ4.09-4.80 (dd, 1H), δ3.85 (2 singlets, 6H, OCH_3), δ3.70-3.40 (dd, 1H), δ2.20-1.19 (multiplet, 11H, cyclohexyl); MS m/z 429 (M^+), 365 (M^+-SO_2), 346 (M^+-C_6H_{11})

Anal. Calcd. For $C_{23}H_{27}NO_5S$: C, 64.33; H, 6.3; N, 3.3

Found C, 64.46; H, 6.3; N, 3.2

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