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SYNTHESIS OF BENZO[d]BENZO[2,3][1,4]DIAZEPINO[1,7-b]ISOTHIAZOLE, A NEW HETEROCYCLIC RING SYSTEM

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Abstract: A facile synthesis of benzo[d]benzo[2,3][1,4]diazepino[1,7-b] isothiazole, a new heterocyclic ring system is reported.

The benzodiazepine nucleus an important pharmacophore has stimulated research resulting in a considerable number of papers and patents in the literature.[1-3] It has been demonstrated that different heterocyclic rings annelated to the 1,4- and 1,5-benzodiazepine systems enhance the biological activity of these compounds.[4-7]

In recent years tetracyclic benzodiazepines have received a great deal of attention due to the psychotropic properties of such compounds as aptazepine and bretazenil.[8] A recent review[9] comprehensively covers the most common route to 1,5-benzodiazepines; reaction of o-phenylenediamines with 3-ketoaldehydes, 1,3-diketones, α,β-unsaturated aldehydes, α,β-unsaturated ketones and β-ketoesters. To our knowledge there are no reports of a 1,2-benzisothiazole-1,1-dioxide moiety

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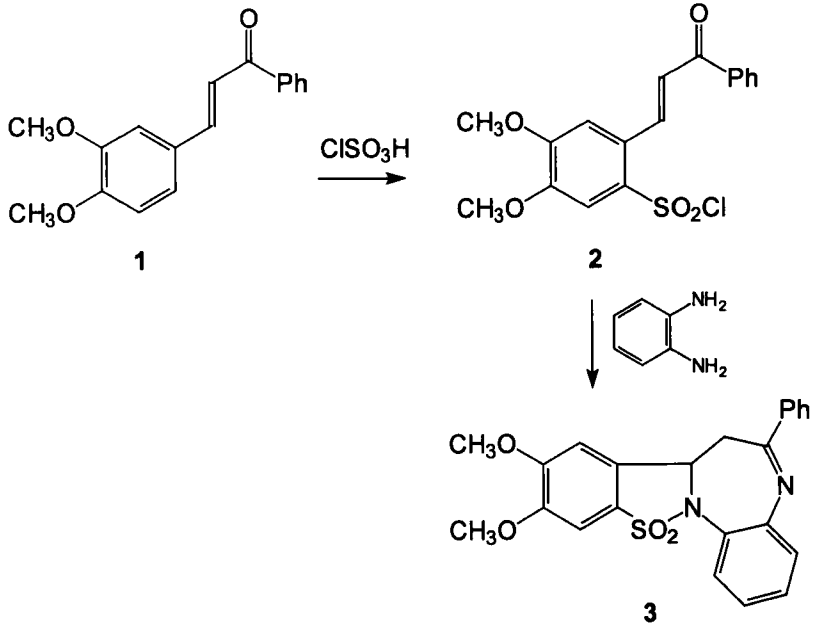
fused to the "a" face of 1,5-benzodiazepine. In connection with our general research program concerned with the synthesis and biological properties of sulfonyl derivatives,[10-12] we now report the synthesis of the heterocyclic ring system benzo[d]benzo[2,3][1,4]diazepino[1,7-b]isothiazole by a simple synthetic route.

Reaction of 3,4-dimethoxychalcone **1** with chlorosulfonic acid afforded the sulfonyl chloride **2** as previously reported.[13] The crude sulfonyl chloride **2** was reacted with *ortho*-phenylenediamine to yield 13,14-dihydro-2,3-dimethoxy-12-phenyl benzo[d]benzo[2,3][1,4]diazepino[1,7-b]isothiazole-5,5-dioxide **3**, a novel tetracyclic ring of potential medicinal interest (Scheme 1).



1 **2** **3**

Scheme 1

Spectroscopic evidence was consistent with the structure of **3**. The infrared and ^{13}C spectra showed no evidence for the presence of the carbonyl group. The ^{1}H-nmr spectrum of **3** showed a multiplet for the aromatic protons and exhibited an AMX system for the chiral (doublet of doublet) and diasterotopic (two doublet of doublets) protons. The mass spectrum showed the expected molecular ion.

Reaction of **2** and other chalcone sulfonyl chlorides with various diamines is under investigation. The behaviour of the C=N moiety in 1,5-benzodiazepines as a dipolarophile in cycloaddition reactions, a reported procedure[14], is also being investigated and these results will be reported in future communications

Experimental

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

3,4-Dimethoxychalcone was prepared according to the literature method.[15]

13,14-Dihydro-2,3-dimethoxy-12-phenyl-benzo[d]benzo[2,3][1,4]diazepino[1,7-b] isothiazole *-5,5-dioxide* **3.**

3,4-Dimethoxychalcone **1** (5.0g, 0.0186 mol) was added portionwise to stirred chlorosulfonic acid (17.3g, 0.15 mol) in an ice bath. The mixture was allowed to come to room temperature and then stirred for 24 hours. The dark red solution was added cautiously to ice-water and the resulting greenish-yellow precipitate was collected by suction filtration, washed with water and dried in a vacuum desiccator, 5.5g (80%) of the crude sulfonyl chloride **2**. *ortho*-Phenylenediamine (2 mol. equivalent) dissolved in acetone (20 ml) was added dropwise to a stirred

solution of **2** dissolved in acetone (200 ml) at room temperature. Upon completion of the addition, the mixture was warmed on a water bath for 30 minutes; allowed to stand at room temperature overnight, then poured onto crushed ice. After acidification with 2M sulfuric acid the suspension of gummy precipitate was stirred vigorously for several hours until the precipitate became granular. Filtration yielded 4.5g (79 %) of crude **3**. This was first recrystallized from acetonitrile and then aqueous acetone to give a white solid, mp 249-250°C; IR (KBr) ν_{max} 1606 cm^{-1} (C=N), 1599 cm^{-1} (C=C), 1304, 1149 cm^{-1} (SO_2); ^1H NMR (DMSO-D) δ7.82-7.21 (multiplet,11H, aromatic), δ5.79-5.77 (dd, 1H), δ3.89-3.83 (dd,1H), δ3.83(singlet, 3H, OCH_3), δ3.75(singlet, 3H, OCH_3), δ3.22-3.14(dd, 1H); MS m/z 420 M^+, 355(M^+-SO_2): Elemental analysis: Calc.: C,65.7; H,4.8; N,6.7 Found: C,65.9; H,5.0;N,6.6.

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