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A Facile Construction of 4-Hydroxymethylbenzisothiazolone-1,1-dioxide

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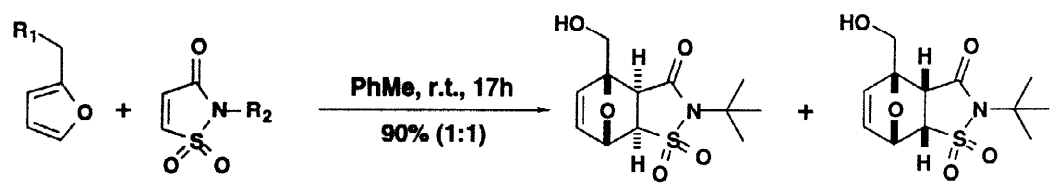
Abstract: 4-Hydroxymethylbenzisothiazolone-1,1-dioxide could be facilely synthesised *via* a highly regioselective Diels-Alder cycloaddition between furfuryl alcohol and 2-(*tert*-butyl)-isothiazolone-1,1-dioxide, followed by aromatization of the adduct under basic conditions. A secondary effect from intramolecular hydrogen bonding is found also to influence the regioselectivity of the cycloaddition. Unequivocal proof of the regiochemistry of the Diels-Alder reaction is provided by X-ray crystallography and *ab initio* calculations showed electronic and steric effects on transition structure asynchronicity.

Benzisothiazolone-1,1-dioxide is a heterocycle of pharmaceutical importance. It is the key structural element in the CNS-active drugs like Ipsapirone and Supidimide. Compounds containing the benzisothiazolone-1,1-dioxide nucleus have also been explored for use as therapeutic agents for treating a variety of diseases.[1] A survey of the existing literature showed that substituted benzisothiazolone-1,1-dioxides are mostly limited to alkyl and alkoxy derivatives.[2] Methods to prepare substituents, functionalized at the benzylic carbon with heteroatoms, that can serve as the side chains of hydrophilic amino acids (*e.g.* those of arginine, serine, threonine, cysteine) are lacking. Herein, we report a simple and rapid construction of 4-hydroxymethylbenzisothiazolone-1,1-dioxide *via* the Diels-Alder reaction between furfuryl alcohol **1** and 2-(*tert*-butyl)-isothiazolone-1,1-dioxide **2**.[3]

Furfuryl alcohol (1.3 equiv.) reacted smoothly with 2-(*tert*-butyl)-isothiazolone-1,1-dioxide **2**[4] in toluene at ambient temperature to give a ~1:1 mixture[5] of the C-4[6] exo product **3** and its endo isomer **4** in 90% combined yield after separation by flash column chromatography (10% → 50% EtOAc/hexane)[7] (**Scheme 1**). No C-7



1 R_1 = HO **2** R_2 = ^{t}Bu
5 R_1 = H **6** R_2 = H

3 **4**

Scheme 1

isomers could be identified by 300 MHz ^{1}H NMR analysis on the crude reaction mixture. Unlike previous examples, we found that the adducts are very stable at ambient temperature, and no fragmentation and extrusion of SO_2 was detected.[8] The confirmation of the structure and the regiochemistry was performed by X-ray crystallography on the exo isomer **3** (**Figure 1**).[9]

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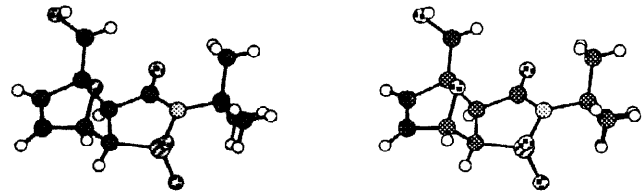
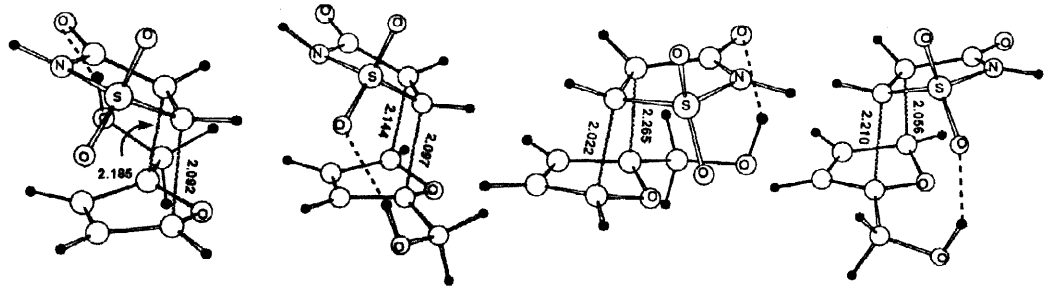


Figure 1: Stereoview of the C-4 exo product **3**

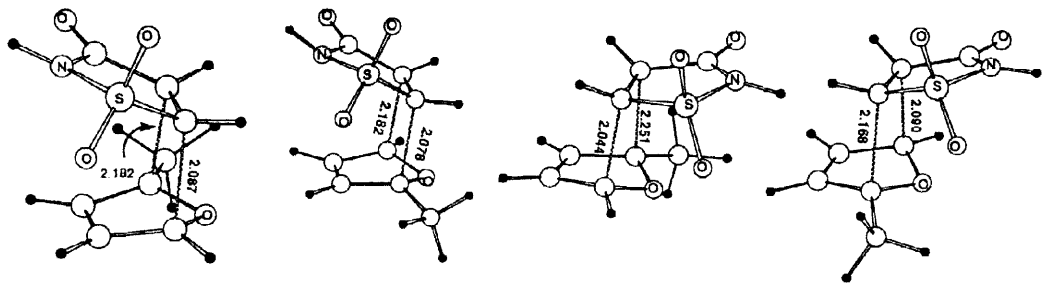
The observed regioselectivity was predicted by *ab initio* molecular calculations on the transition structures of the Diels-Alder reaction between furfuryl alcohol **1** and isothiazolone-1,1-dioxide **6**. Transition structures located at the MP2/6-31G* level of theory[10] predicted that those for the C-7 regioisomers (**8** and **10**) were about 2 kcal/mol higher in energy than the ones for the C-4 regioisomers (**7** and **9**) (**Scheme 2**).



7 (0.0) **8 (1.78)** **9 (3.20)** **10 (5.56)**

Scheme 2: MP2/6-31G* Transition Structures and Energies (kcal/mol) for the Cycloaddition between **1** and **6**.

It was anticipated that differential intramolecular hydrogen bonding by the hydroxyl group of furfuryl alcohol may play a role in enhancing the desired regioselectivity, although, intramolecular hydrogen bonding is not evident in the solid state structure of **3** in which the hydroxyl group is hydrogen bonded intermolecularly. Calculations on the reaction between 2-methylfuran **5** and **6**, where intramolecular hydrogen bond is absent, showed a much decreased level of regioselectiviy in favor of the C-4 regioisomers (**Scheme 3**). Experimentally, 300 MHz ^{1}H NMR analysis on the crude reaction mixture of the cycloaddition reaction between **5** and **2** under identical conditions (PhMe, r.t.) showed one major exo isomer and two endo isomers in a ratio of 4:2:1. It is thus reasonable to assume that the regioselectivity of the Diels-Alder reaction involving the unsymmertrical dienophile can be influenced by intramolecular hydrogen bonding.

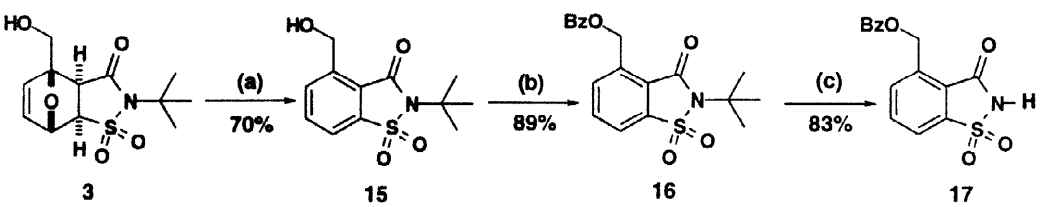


11 (0.0) **12 (0.1)** **13 (0.8)** **14 (3.5)**

Scheme 3: MP2/6-31G* Transition Structures and Energies (kcal/mol) for the Cycloaddition between **5** and **6**.

The Diels-Alder transition structures were found to be asynchronous[11] in terms of the two forming C-C σ-bonds. The C-C forming bond involving the dienophile carbon attached to sulfonyl was more advanced than that involving the dienophile carbon attached to carbonyl, except in the case of unfavorable **10**. The resonance effects of the carbonyl group dominate polarization and orbital interactions of the dienophile with the diene. The intrinsic orbital perturbations by the carbonyl group resulted in asynchronous bond formations of a longer C--C(C=O) bond than C--C(SO_2) bond. Steric gauche repulsion between SO_2 and CH_2OH in **10** elongated C--C(SO_2) bond, which is accompanied by a shortening of the C--C(C=O) bond to compensate the overall extend of bond formation in the transition structure. The gauche interactions are much less significant in the endo transition structure **8**, where S-C--CC torsional angle is 84° as compared to that of 40° in **10**.

The dehydration of the exo adduct **3** and its endo isomer **4** to the aromatic saccharin nucleus in **15**[7] was then examined separately under various reaction conditions. The dehydration of **3** under acidic conditions (TFA, HCl, conc. H_2SO_4) proved to be ineffective and led either to a retro Diels-Alder reaction, decomposition or no reaction. Basic conditions were explored despite of the fact that the arylsulfonamide carbonyl group is susceptible to nucleophile attack. It was found that dehydration of exo adduct **3** using LHMDS in the presence of TMSCl (**Scheme 4**) provided 4-hydroxymethylbenisothiazolone-1,1-dioxide **15** in 70% yield[12] after purification by flash



Scheme 4: (a) LHMDS, TMSCl, THF/CH_2Cl_2, –78°C (b) Bz_2O, DMAP, CH_2Cl_2, r.t. (c) TFA, 85°C (83%) or conc. H_2SO_4/AcOH, r.t. (69%)

column chromatography. Interestingly, the dehydration performed on the endo isomer **4** under identical conditions only led to retro Diels-Alder reaction with the dieneophile **2** isolated in 81% yield.[13] More conveniently, upon completion of the Diels-Alder reaction, the solvent was removed *in vacuo* and the crude mixture of adducts was dehydrated to give the hydroxymethylsaccharin **15** in 76% theoretical yield (38% overall yield), together with the recovered dienophile **2** which could be recycled. After protection of the benzylic hydroxyl group in **15** as a benzoate ester, the *N-tert*-butyl group of compound **16** could be conveniently removed under acidic conditions to give the saccharin derivative **17** in high yields (**Scheme 4**).

In summary, 4-hydroxymethylbenisothiazolone-1,1-dioxide could be readily prepared from inexpensive and readily available materials in two steps. Different ester analogues of **17** could be easily prepared by this sequence. These compounds should serve as useful synthetic intermediates for further functionalization to provide benzisothiazolone-1,1-dioxides with interesting biological activities.

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(1) For example: (a) Lombardino, J. G; Wiseman, E. H.; Mclamore, W. M. *J. Med. Chem.* **1971**, *14*, 1171. (b) Choi, S.-Y.; Lee, S.-G.; Yoon, Y.-J.; Kim, K.-W. *J. Heterocyclic Chem.* **1989**, *26*, 1073. (c) Sunkel, C. E.;

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(2) (a) Dunlap, R. P.; Boaz, N. W.; Mura, A. J.; Kumar, V.; Subramanyam, C.; Desai, R. C.; Hlasta, D. J.; Saindane, M. T.; Bell, M. R.; Court, J. J.; Farrell, R. P. *Patent*, US 5,512,589 (Apr. 30, **1996**). (b) For nitro derivatives see Saari, W. S.; Schwering, J. E. *J. Heterocyclic Chem.* **1986**, *23*, 1253.

(3) Related studies: (a) Weiler, E. D.; Brennan, J. J. *J. Heterocyclic Chem.* **1978**, *15*, 1299. (b) Abou-Gharbia, M.; Moyer, J. A.; Patel, U.; Webb, M.; Schiehser, G.; Andree, T.; Haskins, J. K. *J. Med. Chem.* **1989**, *32*, 1024. (c) Pelter, A.; Singaram, B. *Tetrahedron Lett.* **1982**, *23*, 245. (d) Burri, K. *F. Helv. Chim. Acta* **1990**, *73*, 69. (e) For related system using α,β-unsaturated hydrazones as dienes see (i) Waldner, A. *Helv. Chim. Acta* **1989**, *72*, 1435. (ii) Waldner, A. *Tetrahedron Lett.* **1989**, *30*, 3061.

(4) 2-(*tert*-Butyl)-isothiazolone-1,1-dioxide **2** was prepared from 3,3ℵ-dithiodipropanoic acid according to literature procedures: (a) Lewis, S. N.; Millar, G. A.; Hausman, M.; Szamborski, E. C. *J. Heterocyclic Chem.* **1971**, *8*, 571. (b) Lewis, S. N.; Millar, G. A.; Hausman, M.; Szamborski, E. C. *J. Heterocyclic Chem.* **1971**, *8*, 591. (c) Burri, K. *F. Helv. Chim. Acta* **1989**, *72*, 1416.

(5) Presumably, this was a thermodynamic equilibrium mixture of the exo and endo isomers. 300 MHz ^{1}H NMR analysis on the crude reaction mixture indicated a 1.3:1 ratio of exo/endo products. Sometimes, a 2:1 ratio could be obtained. The reaction could not be carried out at high temperature due to the thermal instability of furfuryl alcohol.

(6) For convenience, the numbering of benzisothiazolone-1,1-dioxide is used.

(7) **3:** ^{1}H NMR δ (300 MHz, $CDCl_3$) 6.71 (1H, d, J = 5.7 Hz, C5-H), 6.48 (1H, br dd, J = 5.7, 1.8 Hz, C6-H), 5.55 (1H, d, J = 1.8 Hz, C7-H), 4.07 (1H, dd, J = 12.4, 9.2 Hz, CH_AH_B), 3.99 (1H, dd, J = 12.4, 5.9 Hz, CH_AH_B), 3.63 (1H, d, J = 7.8 Hz, α-CH), 3.28 (1H, d, J = 7.8 Hz, α-CH), 3.17 (1H, dd, J = 9.2, 5.9 Hz, OH), 1.63 (9H, s, ^{t}Bu). **4:** ^{1}H NMR δ (300 MHz, $CDCl_3$) 6.71 (1H, dd, J = 5.8, 1.7 Hz, C6-H), 6.44 (1H, d, J = 5.8 Hz, C5-H), 5.34 (1H, dd, J = 5.1, 1.7 Hz, C7-H), 4.28-4.16 (2H, m, J = 12.4, 9.2 Hz, CH_2), 3.96 (1H, dd, J = 9.3, 5.1 Hz, C8-H), 3.76 (1H, d, J = 9.3 Hz, C9-H), 1.51 (9H, s, ^{t}Bu). **15:** ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.77-7.70 (3H, m, Ar-H), 4.95 (2H, d, J = 7.2 Hz, CH_2), 3.88, (1H, t, J = 7.2 Hz, OH), 1.76 (9H, s, ^{t}Bu).

(8) Ref. 3(d) and Burri, K. F. *Chimia* **1992**, *46*, 335.

(9) **X-ray crystallographic analysis of 3:** A colorless crystal of approximate size 0.15X 0.18 X 0.70 mm grown from methylene chloride was used for X-ray diffraction experiments carried out at room temperature on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Cu *K*α radiation (λ = 1.5418 Å). The crystal is monoclinic, space group *P21/a*, cell constants *a* = 9.8830(3), *b* = 10.6715(5), *c* = 13.5454(3) Å, *β* = 110.335(2)ℑ, *V*=1339.56(9) Å^3 with 4 molecules in the unit cell; calculated crystal density *Dx* = 1.426 g/cm^3; absorption coefficient *μ* = 2.27 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares.[a] Final agreement factors *R(F)*= 0.056, *wR(F)* = 0.079, where *w* = 1/(σ^2+0.02F^2), for 2410 reflections with I | 3σ(I) and 173 variables.[b] (a) Fair, C. K. (1990). *MolEN. An Interactive Intelligent System for Crystal Structure Analysis.* Enraf-Nonius, Delft, The Netherlands. (b) Atomic coordinates, thermal parameters, bond lengths and angles have been deposited with the Cambridge Crystallographic Data Center and can be obtained upon request.

(10) Calculations were performed using Gaussian 94, Revision A.1, Gaussian, Inc., Pittsburgh PA, 1995. For a detailed discussion of this method, see: (a) M♠ller,C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. (b) Hehre, W.J.; Radom, L.; Schleyer, P.V. R.; Pople, J.A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(11) Houk, K. N.; Gonzalez, J.; Li, Y. *Acct. Chem. Res.* **1995**, *28*, 81.

(12) The reaction yield was reduced to 33% in the absence of TMSCl.

(13) Presumably, dehydration of the endo isomer **4** under basic conditions involves unfavorable *syn* elimination, whereas favorable *anti* elimination takes place for the exo isomer **3**.