ORGANIC LETTERS

1999
Vol. 1, No. 3
487−489

# Highly Diastereoselective Intramolecular Diels–Alder Reactions of Furan-Tethered 1-Alkenesulfinic Acid Esters

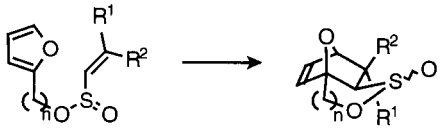
**Adrian L. Schwan,*,† Jennifer L. Snelgrove,† Mark L. Kalin,† Robert D. J. Froese,[1,‡] and Keiji Morokuma*,‡,§**

*Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry, Department of Chemistry and Biochemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1, and Cherry L. Emerson Center for Scientific Computation and Department of Chemistry, Emory University, Atlanta, Georgia 30322*

*schwan@chembio.uoguelph.ca*

**Received May 18, 1999**

## ABSTRACT



n = 1,2; $R^1$, $R^2$ = H, $CO_2Me$

**The capture of selected 1-alkenesulfinyl chlorides with furan-tethered alcohols leads to the formation of diene-tethered 1-alkenesulfinate esters. The esters can spontaneously or with Lewis acid treatment undergo an IMDA reaction to form exo adducts with very high diastereoselectivity. Computational predictions using density functional theory indicate the preferred transition state for cyclization and find little preference for the sulfinyl configuration in the products.**

The intramolecular Diels−Alder (IMDA) reaction is a powerful method for the rapid construction of polycyclic organic skeletons.[2] Elements of reactivity and stereo- and regiochemistry are often superior to those of the bimolecular Diels−Alder reaction. While the tether that connects the diene and dienophile reactive partners may be composed of a number of different atoms,[2] only recently have sulfur acid derivatives been utilized,[3−7] mostly by the Metz group who studied IMDA reactions of dienes tethered to ethenesulfonic acid derivatives.[3,4]

The synthetic versatility of the sulfonate and sulfonamide tethered IMDA adducts discovered to this point and our disclosure of the first preparation of 1-alkenesulfinyl chlorides[8] prompted us to probe the IMDA reaction of dienes tethered with a *sulfinate* linkage. The sulfinate functionality constitutes an additional stereogenic atom and has the potential to show useful responsiveness to Lewis acids. Moreover, a number of 2-substituted ethenesulfinyl chlorides are available for participation in this chemistry and hence

† University of Guelph.
‡ Emory University.
§ morokuma@emory.edu.

(1) Present address: Union Carbide Corporation, P.O. Box 8361, South Charleston, WV, 25303.

(2) (a) Taber, D. F. *Intramolecular Diels−Alder and Alder Ene Reactions*; Springer-Verlag: New York, 1984. (b) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289. (c) Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873.

(3) (a) Bovenschulte, E.; Metz, P.; Henkel, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 202. (b) Metz, P.; Fleischer, M. *Synlett* **1993**, 399. (c) Metz, P.; Seng, D.; Fröhlich, R.; Wibbeling, B. *Synlett* **1996**, 741.

(4) (a) Metz, P.; Fleischer, M.; Fröhlich, R. *Synlett* **1992**, 985. (b) Metz, P.; Fleischer, M.; Fröhlich, R. *Tetrahedron* **1995**, *51*, 711. (c) Metz, P.; Cramer, E. *Tetrahedron Lett.* **1993**, *34*, 6371. (c) Metz, P.; Seng, D.; Plietker, B. *Tetrahedron Lett.* **1996**, *37*, 3841. (d) Metz, P.; Stölting, J,; Läge, M.; Krebs, B. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2195. (e) Metz, P.; Meiners, U.; Fröhlich, R.; Grehl, M. *J. Org. Chem.* **1994**, *59*, 3687. (g) Meiners, U.; Cramer, E.; Fröhlich, R.; Wibbeling, B.; Metz, P. *Eur. J. Org. Chem.* **1998**, 2073.

(5) Galley, G.; Pätzel, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2297.

(6) Doye, S.; Hotopp, T.; Winterfeldt, E. *Chem. Commun.* **1997**, 1491.

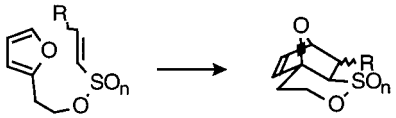
(7) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700.

(8) Schwan, A. L.; Strickler, R. R.; Lear, Y.; Kalin, M. L.; Rietveld, T. E.; Xiang, T.-J.: Brillon, D. *J. Org. Chem.* **1998**, *63*, 7825.

10.1021/ol990674i CCC: $18.00 
**Published on Web 06/22/1999**

our proposed study holds promise for the creation of cycloadducts similar to those of Metz,[2] but retaining two additional chiral centers, Scheme 1. Herein we report our inaugural experiments employing a furan unit as the attached diene and some theoretical calculations pertaining to one of our systems.

**Scheme 1**




sulfonate: n=2, R=H
sulfinate: n=1, R=H, alkyl, Ar, ester

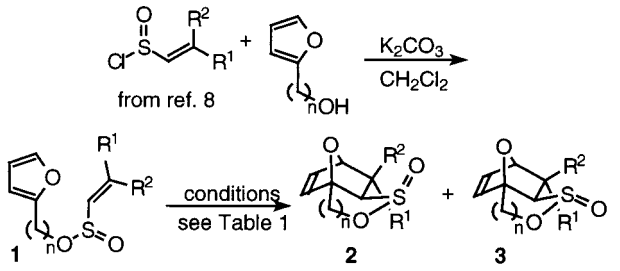
Our initial studies were carried out by synthesizing sulfinate ester **1a**, which originates from 2-(2-furyl)ethanol and ethenesulfinyl chloride.[8] Sulfinate **1a** demonstrates a sluggish propensity toward cycloaddition but can be converted to cycloadduct only after prolonged heating or Lewis acid treatment. Under either of those conditions, the increased cycloaddition rate was accompanied by some decomposition of the solution constituents. Thermal activation afforded two diastereomeric cycloadducts, while the most useful Lewis acids, $ZnBr_2$ and $Et_2AlCl$, at room temperature gave a single diastereomer (Table 1).[9] That single isomer was assigned the structure **3a** with exo attachment of sulfur and an equatorial oxygen on that sulfur. While the oxygen configuration was ascertained by $^1$H NMR spectroscopy,[10] the exo configuration was established by oxidation to the sulfonate and crystal structure analysis.[11] It was confirmed through other oxidation experiments that the accompanying isomer was the epimer **2a**, possessing an axial oxygen (Scheme 2).[12]

**Table 1.** IMDA Cyclizations of Furan-Tethered 1-Alkenesulfinate Esters

| no. | **1**[a] | conditions | products (yields)[b]/[l.r.][c] |
|---|---|---|---|
| 1 | **1a** | 68 °C, toluene, 24 d, 0.1 equiv of BHT | **2a**, **3a** (54)[d,e]/[**1a**] |
| 2 | **1a** | 62 °C, toluene, 7 h, 1.2 equiv of $Et_2AlCl$ | **3a** (53)[d]/[**1a**] |
| 3 | **1a** | rt, $CH_2Cl_2$, 2 d, 1.2 equiv of $Et_2AlCl$ | **3a** (37)/[**1a**] |
| 4 | **1a** | rt, toluene, 5 d, 2 equiv of $ZnBr_2$ | **3a** (30)/[**1a**] |
| 5 | **1b** | −30 °C, $CH_2Cl_2$, 19 h,[f] 0.1 equiv of BHT | **2b** (42), **3b** (5)/[2-(2-furyl)-EtOH][g] |
| 6 | **1b** | rt, $CH_2Cl_2$, 3.5 h, 1.2 equiv of $ZnBr_2$ | **2b** (63), **3b** (15)/[**1b**] |
| 7 | **1d** | −30 °C, $CH_2Cl_2$, 19 h,[f] 0.1 equiv of BHT | **2d** (71), **3d** (12)/[furfuryl-OH][g] |
| 8 | **1d** | −77 °C, $CH_2Cl_2$, 9 h,[f] 0.1 equiv of BHT | **2d** (77)/[furfuryl-OH][g] |
| 9 | **1e** | −50 °C, $CH_2Cl_2$, 19 h[f] | **2e** (47)[h]/[furfuryl-OH][g] |

[a] Sulfinate **1a** originates from the oxidative fragmentation of diphenylmethyl vinyl sulfoxide, while other sulfinates **1** arise from *p*-methoxybenzyl sulfoxides. [b] Yields are of chromatographically pure material. [c] Identity of limiting regent for yield determination. [d] Yield calculation on the basis of % unconsumed starting sulfinate (always <10%). [e] Compounds **2a** and **3a** were formed in ca. a 1:1 ratio ($^1$H NMR). [f] Reaction may have been completed in a shorter period of time. [g] Yield is based on one-pot, three-step transformation. [h] Higher yields of **2e** (up to 80%) have been obtained but not on a consistent basis.

**Scheme 2**




**a** n=2; $R^1$=$R^2$=H
**b** n=2; $R^1$=$CO_2$Me; $R^2$=H
**c** n=2; $R^1$=H; $R^2$=$CO_2$Me
**d** n=1; $R^1$=$CO_2$Me; $R^2$=H
**e** n=1; $R^1$=H; $R^2$=$CO_2$Me
**f** n=1; $R^1$=$R^2$=H

Structural adaptations were made to the original system through the addition of a methyl ester to the 2-position of the double bond and/or shortening of the tether. Thus, sulfinates **1b**−**e** were prepared by reaction of 2-(2-furyl)-ethanol or furfuryl alcohol with (*E*)- and/or (*Z*)-2-carbomethoxyethenesulfinyl chloride.[13] The structural revisions accelerated the cyclization considerably, and selected data are presented in Table 1. In some cases the IMDA reaction proceeded without isolation of the furylalkyl 1-alkenesulfinate, and hence the yield reported is actually for the one-pot, three-step sequence of 1-alkenesulfinyl chloride formation, alcohol capture, and cycloaddition.

The exo ring junction and (pseudo)axial sulfinyl oxygens of structures **2b** and **2d** were ascertained through single-crystal X-ray analysis.[14] The identities of the other products were determined by comparison of their $^1$H NMR data to those of **2b** and **2d**. Clearly the addition of an ester functionality to the double bond of the sulfinate offers a

(9) All new compounds were characterized either as mixtures of isomers or as pure entities by $^1$H and $^{13}$C NMR, IR, MS, and elemental analysis. See Supporting Information.

(10) Harpp, D. N.; Gleason, J. G. *J. Org. Chem.* **1971**, *36*, 1314.

(11) Ferguson, G.; Schwan, A. L.; Kalin, M. L.; Snelgrove, J. L. *Acta Crystallogr.* **1997**, *C53*, #IUC 9700009.

(12) Control experiments were performed on some of the cycloadducts to ensure that our observations were not being corrupted by reversibility of the cyclization reactions. At this stage, the cycloadducts appear to be both the thermodynamic and kinetic products.

(13) Cyclizations of sulfinate **1c** both with and without Lewis acids were unsuccessful. Our group has found that some (*Z*)-carbomethoxyethenesulfinate esters exhibit instability.

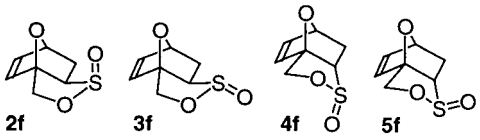
(14) ORTEP diagrams and a summary of crystal data, data collection, structure solution, and refinement details for **2b** and **2d** are presented in the Supporting Information. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-112630 and 112631. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44)1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

substantial rate increasing effect without sacrificing stereoselection: a single isomer can be obtained for **1d** and **1e**, in the very vessel in which those sulfinates are generated (Table 1, entries 8 and 9). Moreover, the presence of the ester unit contributes one more diastereomeric center and increased synthetic diversity of the cycloadducts.

The origin of the exo preference of the sulfur during six-membered sultone formation through cycloaddition has been studied by Metz.[2a] Herein we have demonstrated that a similar preference is present not only for six-membered sultine formation but also for five-membered sultines. To further pursue the preferences of the five-membered sultines, we have located transition states and products and found activation and reaction energies for the four possible diastereomeric IMDA products of model compound **1f**.[15] Calculations were performed with the GAUSSIAN94 program.[16] Geometries were optimized at the hybrid density functional theory level, B3LYP, with the 6-31G and 6-31G-(d) basis sets.

The computational predictions for the various routes for the IMDA cyclization were determined and are presented in Table 2. The data corroborate our lack of evidence of any endo isomers, as the transition state and product energies are significantly higher than the exo analogues. The theoretical data predict that the cycloadduct energies of exo isomers **2f** and **3f** are essentially equivalent, suggesting minimal preference for oxygen configuration. However, the transition state leading to **2f**, the isomer possessing the pseudoaxial sulfinyl oxygen, is predicted to be slightly favored, and this slim preference would appear to be borne out in our practical results. Additional structural information is available in the Supporting Information.

**Table 2.** Relative Energies for Various IMDA Cyclization Modes of Sulfinate **1f** Optimized Using Density Functional Theory




| IMDA product | transition state energy (kcal mol$^{-1}$)[a] | product energy (kcal mol$^{-1}$)[a] |
|---|---|---|
| **2f** (exo, p-ax. O) | 22.7 | −4.1 |
| **3f** (exo, p-eq. O) | 24.5 | −4.1 |
| **4f** (endo, p-ax. O) | 29.8 | 6.2 |
| **5f** (endo, p-eq. O) | 34.9 | 8.8 |

[a] Energies are conveyed in relation to a minimized conformation of **1f**.

Our experiments indicate that 1-alkenesulfinate esters bearing tethered furans can undergo highly diastereoselective IMDA reactions when exposed to the proper conditions. Future work involves experimentation with other tethered dienes, synthetic adaptations of the cycloadducts, and the determination of the reasons behind the conflicting axial/equatorial preferences of S═O bond of six-membered sultines **3a** and **3b**.

**Acknowledgment.** This work was supported by a grant from the Petroleum Research Fund, administered through the American Chemical Society (to A.L.S.), and by the National Science Foundation (to K.M.). R.D.J.F. thanks NSERC of Canada for a Postdoctoral Fellowship. The authors thank Prof. George Ferguson for the X-ray structure determinations.

**Supporting Information Available:** Experimental procedures and spectral data for new compounds, details of the crystallographic analyses including ORTEP diagrams and Cartesian coordinates for the optimized structures of compounds **2f**−**5f**, and their transition states for formation and for two conformations of reactant **1f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990674I

(15) IMDA cyclizations of **1f** could not be achieved. Furfuryl chloride was the compound isolated from preparation targeting sulfinate **1f**.

(16) Gaussian 94, Revision E.3. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.