ORGANIC LETTERS

2007
Vol. 9, No. 16
3065−3068

An Epoxide Intermediate in Nucleophilic Acylations by Thiazolium Precursors

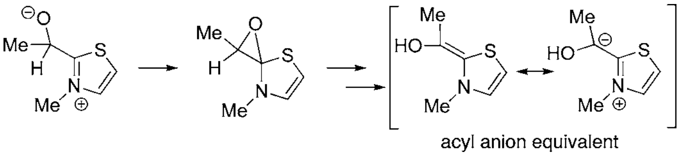
Scott Gronert*

Department of Chemistry, Virginia Commonwealth University, 1001 West Main Street, Richmond, Virginia 23284

sgronert@vcu.edu

Received May 16, 2007

ABSTRACT



Computational work at the MP2/6-31+G(d,p) level is used to explore the nucleophilic species derived from the fluoride activation of O-silylated thiazolium carbinols. These species recently have been shown by Scheidt to be useful acyl anion synthons, but the mechanism of their formation has been an open question. The data point to an unusual spiroepoxide intermediate that rearranges via acid/base chemistry to give the active nucleophile. The addition of the nucleophile to nitroethene is also examined.

Recently, Scheidt and co-workers have shown that the treatment of O-silylated thiazolium carbinols with fluoride produces a nucleophilic species that cleanly undergoes conjugate additions to nitroalkenes and *o*-quinone methides.[1,2] The process is promising and involves the equivalent of an acyl anion intermediate. As noted by Scheidt, this intermediate is closely related to the intermediate implicated by Breslow[3,4] in the thiazolium-catalyzed benzoin condensation as well as other processes catalyzed by N-heterocyclic carbenes.[5−12] However, there are open questions with respect to the mechanism of forming the nucleophilic intermediate from the O-silylated thiazolium carbinol, particularly the need for a 1,2-proton shift. Here, we use ab initio calculations to propose a likely reaction mechanism and identify an unusual intermediate on the reaction surface.[13−15]

When an O-silylated thiazolium carbinol is treated with a fluoride source, it produces a nucleophilic species that behaves like an acyl anion equivalent. Scheidt suggested that the initially formed alkoxide zwitterion, **1**, undergoes some

---

(1) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932.

(2) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 4508.

(3) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241.

(4) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

(5) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715.

(6) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326.

(7) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632.

(8) de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284.

(9) Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 14675.

(10) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558.

(11) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639.

(12) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

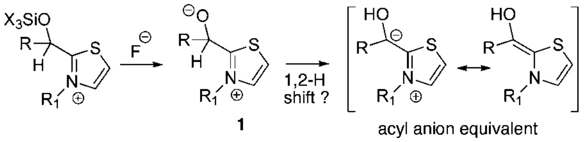
(13) Calculations were completed at the MP2/6-31+G(d,p) level. When there was a possibility of multiple rotamers, preliminary calculations at lower levels were used to identify the most stable one for the higher-level calculations. Reported energies include zero-point vibrational energy corrections from HF/6-31+G(d,p) calculations scaled by 0.9135 (see ref 15). All species exhibited the proper number of imaginary frequencies. Energies do not contain thermal corrections.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(15) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

10.1021/ol0711467 CCC: $37.00

type of 1,2-proton shift to produce a species that can be viewed as an α-hydroxy carbanion or an enol (eq 1).[1] A direct 1,2-proton shift is unexpected (formally forbidden by orbital symmetry rules), and Scheidt included a question mark in the equation to suggest that a more complicated process might be involved. Calculations at the MP2/6-31+G(d,p) level confirm that a direct 1,2-proton shift is not viable. Using a model system with R and R_1 = CH_3, the transition state, **2**, is computed to be 33 kcal/mol above the energy of the alkoxide zwitterion (Figure 1) and therefore would not be accessible at −40 °C. It is true that the calculations are for a gas-phase process; however, the reaction occurs in a relatively nonpolar solvent (CH_2Cl_2), and solvation effects will be moderate.



(1)

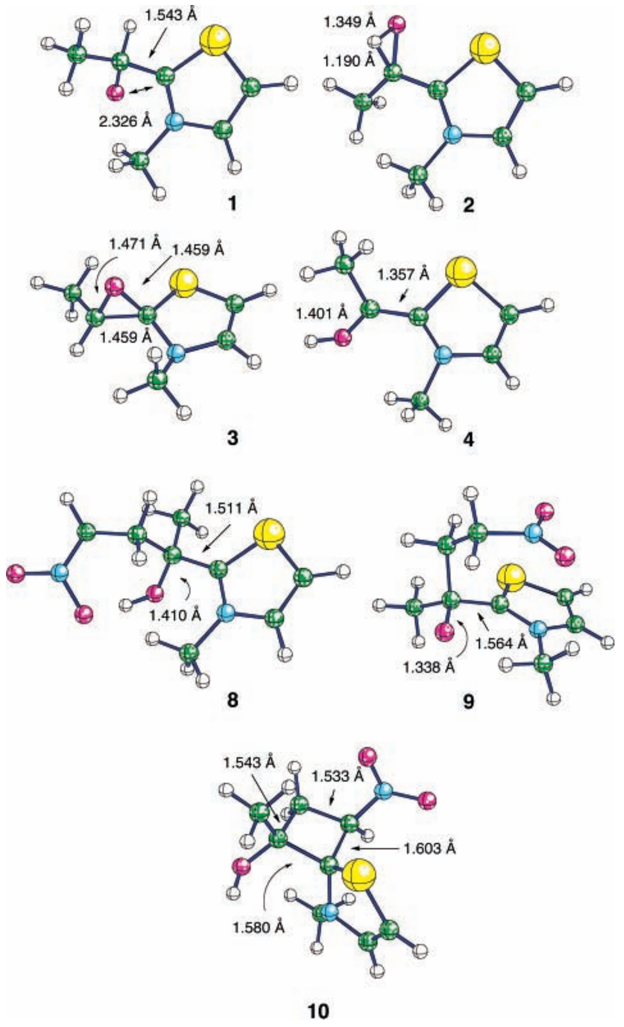
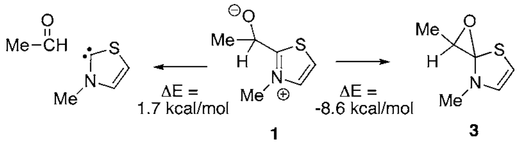


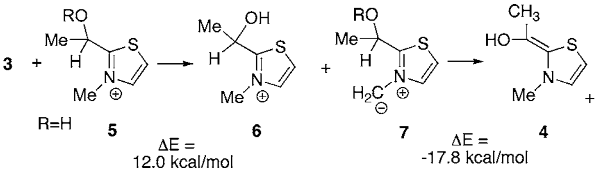
Figure 1. Structures of key intermediates and transition states (MP2/6-31+G(d,p)). Color key: carbon (green), hydrogen (white), oxygen (red), nitrogen (blue), and sulfur (yellow).

While searching for alternative pathways, it became clear that the alkoxide zwitterion, **1**, is marginally stable and collapses with little or no barrier to a spiroepoxide, **3** (eq 2). Although a transition state can be found at the HF level, it disappears at the MP2 level suggesting that the only barrier to cyclization is rotation around the C−C bond to give a conformation appropriate for cyclization. Formation of the epoxide is calculated to be favored by nearly 9 kcal/mol relative to **1**.[16,17] This is an unusual structure, and there do not appear to be other reports of related thiazole spiro-epoxides. Nonetheless, it is a reasonably stable species on the potential energy surface and helps explain why the system does not undergo immediate C−C cleavage to give an aldehyde and a thiazole carbene (eq 2). Although the loss of acetaldehyde from **1** is nearly thermoneutral and favored by entropy, the loss of acetaldehyde from **3** is significantly endothermic, and therefore it should be stable with respect to dissociation. The problem then becomes the rearrangement of **3** to the nucleophilic species, **4** (eq 3). The reaction is computed to be exothermic by 5.9 kcal/mol from the epoxide, **3**, but as noted above cannot occur directly via transition state **2**. Formation of the *Z* isomer of **4** is less exothermic by 0.4 kcal/mol.



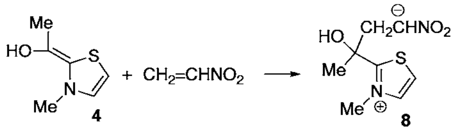
(2)

As Breslow[4] suggested for the benzoin rearrangement, the 1,2-proton migration is more likely driven by acid/base chemistry via a protonation/deprotonation route, with the solvent acting as the proton donor/acceptor in protic solutions. However, the present reaction can be completed under anhydrous conditions in CH_2Cl_2. It is possible that an adventitious proton donor catalyzes the rearrangement to **4**, but the starting material could provide a viable acid/base catalyst for the rearrangement. The *N*-methyl group of the thiazolium is a reasonable acid and is capable of transferring a proton to intermediate **3**. The process in eq 3 is computed to be endothermic by 12 kcal/mol. Deprotonation of **6** (equivalent to **5**) to give **4** is exothermic by 17.8 kcal/mol. Because the thiazolium, **5**, only needs to catalyze the rearrangement from **3** to **4** (i.e., escort the proton from C to O), the barrier is probably considerably less than the 12 kcal/mol required for complete transfer and separation.[18] It must be stressed that this pathway probably would not be competitive if a competent proton donor/acceptor is available in the solution.[19]



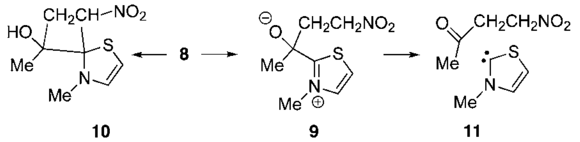
(3)

To probe the nucleophilic behavior of **4**, its reaction with nitroethene was examined. Scheidt and co-workers have shown that nucleophiles like **4** readily add to nitroalkenes, even heavily substituted ones, to eventually yield β-nitro ketones.[1] The first intermediate in the process is a zwitterionic thiazolium/nitrocarbanion, **8** (eq 4). The barrier to forming it is negligible (much less than the complexation energy of **4** with nitroethene), and the addition is exothermic by 15.8 kcal/mol.



(4)

The zwitterion is capable of a five-center, intramolecular proton transfer, resulting in a new zwitterionic species, **9**, whose ionic structure is equivalent to **1** (eq 5). Structure **9** can cyclize to another spiroepoxide, **12** (not shown), or directly dissociate to give the 4-nitro-2-butanone product and a thiazole carbene. Alternatively, the nitrocarbanion in **8** could attack the thiazolium to produce a spirocyclobutane structure, **10**. The cyclization has no barrier and is exothermic by 12.3 kcal/mol, and **10** is preferred in the gas phase by 2.0 kcal/mol over the proton-transfer product, **9**. It is the low point on the potential energy surface. To reach the observed products, the system must pass through **9** on the way to a complex of 4-nitro-2-butanone and the thiazole carbene. The dissociation process to give **11** has only a minor barrier (8.2 kcal/mol relative to **9**) and is nearly thermoneutral. The product complex is 2.2 kcal/mol less stable than **10**.



(5)

A plot of the reaction surface is given in Figure 2. Starting from **1**, the system closes to give spiroepoxide **3** as a stable intermediate. Conversion to the active nucleophile bypasses transition state **2** and instead proceeds via acid/base chemistry, potentially catalyzed by a thiazolium via intermediates **6** and **7**. This process has the highest barrier on the path and is 12 kcal/mol above **3**. Addition of nitroethene to **4** has nearly no barrier and results in nitrocarbanion **8**, which can cyclize to **10** or undergo a proton transfer to give **9**, which can dissociate to products. Each of these steps involves modest barriers and should occur readily. In contrast to species **3**, none of the bicyclic products (**9** or **10**) are significantly more stable than the dissociation product, **11**.

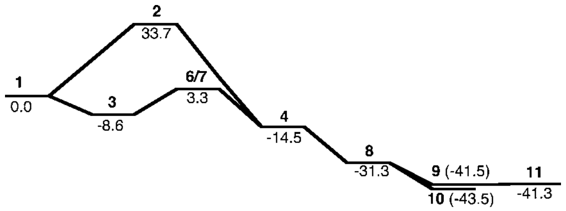


Figure 2. Reaction surface for the formation of **4** and its subsequent reaction with nitroethene. Energies in kcal/mol. Transition states were located, but for clarity, all but **2** are omitted.

To explore the nucleophilic nature of the intermediates, NPA calculations were completed on **1**, **3**, and **4** (Figure 3).

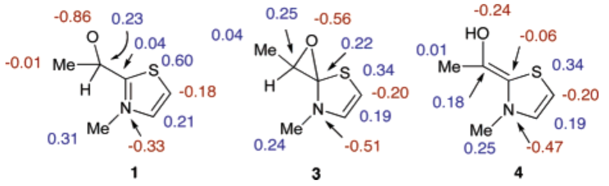


Figure 3. NPA charges at the MP2/6-31*G(d,p) level. Hydrogen charges are added to the adjacent carbon or oxygen.

The charges reveal two interesting points about the electronic structures. First, the sulfur carries the bulk of positive charge in the thiazolium ring, suggesting that a resonance form with a C═S double bond (charged sulfur) and a neutral nitrogen might better represent the structure (Figure 4). This is also consistent with the fact that cyclization to **3** greatly reduces the charge on the sulfur. Second, the nucleophilic carbon in **4** has a positive charge. This suggests that the nucleophilicity of **4** is derived from the ability of the ring nitrogen and sulfur to donate electron density in response to the reaction with an electrophile rather than the presence of high electron

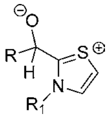


Figure 4. Alternative resonance form for **1**.

---

(16) Solvation will favor **1** because it is a zwitterion with a large dipole moment. To crudely estimate the effect, an aqueous solvation calculation using the SM5 model was completed at the MP2/6-31+G(d) level. The energetic advantage of **3** over **1** is reduced to almost zero in this model of aqueous solution. In a less polar solvent such as dichloromethane, one would expect **3** to dominate.

(17) Aqueous solvation energies were computed in Spartan 02 using Cramer and Truhlar's SM5 approach in conjunction with MP2/6-31+G(d) calculations: Johnson, J. A.; Deppmeir, B. J.; Driessen, A. J.; Hehre, W. J.; Klunzinger, P. B.; Pham, I. N.; Wantanabe, M. *Spartan 02*, 1.0.8; Wavefunction: Irvine, CA, 2002.

(18) Calculations at the HF level indicate that complexation of **6** with **7** provides 8 kcal/mol of stabilization in the gas phase. This is a crude measure of the barrier reduction. At the MP2 level, the complex reverts to **3** and **5** without a barrier.

(19) A unimolecular rearrangement from **1** to **7** to **4** was calculated. The barriers are high (7.5 and 19.3 kcal/mol relative to **1**). See Supporting Information.

density at the nucleophilic center. Although **4** acts like an α-hydroxy carbanion, this is not reflected in its ground-state electron distribution.

In Scheidt's experimental work, thioureas were added to increase the product yield.[1] Scheidt also noted that chiral thiourea additives were capable of asymmetric induction. Although not pursued here computationally, it is likely that the thiourea coordinates with the nitroalkene and facilitates the addition process.

In summary, this computational study indicates that a spiroepoxide is the first key intermediate in the activation of O-silylated thiazolium carbinols. This class of epoxide has not been reported before but is marginally stable and potentially trapped. This would be most likely in a system with a tertiary carbinol that could not rearrange to a nucleophilic species like **4**. The necessary 1,2-proton migration in the mechanism for forming the active nucleophile proceeds via acid/base chemistry, not a direct 1,2-sigmatropic shift.

Acknowledgment. Support from the National Science Foundation (CHE-0348809) is gratefully acknowledged. Computer time from the VCU High-Performance Computer Center is also acknowledged.

Supporting Information Available: The details of the computational work (geometries, electronic energies, and vibrational energies). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0711467