ORGANIC LETTERS

2004
Vol. 6, No. 12
2063−2066

Using Stereoelectronic Effects to Explain Selective Reactions of 4-Substituted Five-Membered Ring Oxocarbenium Ions

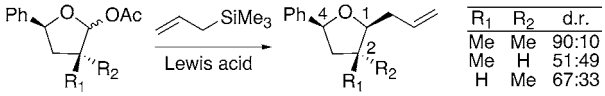
Deborah M. Smith and K. A. Woerpel*

Department of Chemistry, University of California−Irvine, Irvine, California 92697-2025

kwoerpel@uci.edu

Received April 21, 2004

ABSTRACT



The utility of the inside attack model to predict and analyze the stereoselectivities of nucleophilic additions to complex five-membered ring oxocarbenium ions is demonstrated in a systematic study of C-4-substituted acetals.

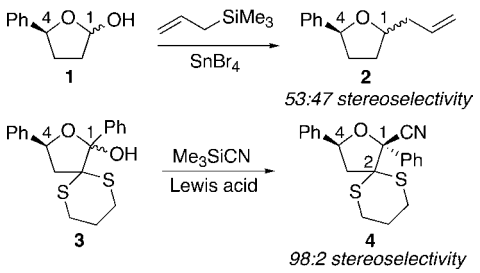
Stereoselective nucleophilic addition reactions to substituted five-membered ring oxocarbenium ions continue to be important transformations in bioorganic and synthetic organic chemistry.[1−5] Our laboratory recently developed a model to explain the stereochemical outcomes resulting from these transformations and, in particular, the strong dependence on the substitution pattern at C-3 for high selectivity.[6,7] This model stipulates that a stereoelectronic preference directs the nucleophile to attack the five-membered ring oxocarbenium ion from the inside face of the envelope conformer, providing the low-energy staggered product.[8,9] Establishing that the stereoelectronic principles of this model tolerate substrate complexity would broaden its application toward highly substituted molecules encountered in synthetic applications and biological systems.[10−13]

Seemingly contradictory selectivities associated with substituted five-membered ring oxocarbenium ions suggest that further efforts to understand the reactivities of these intermediates are required.[14,15] Reissig[16] and others[6,17] demonstrated that the presence of a substituent at the C-4 position of an oxocarbenium ion is not sufficient to obtain selectivity in nucleophilic substitution reactions (Scheme 1). In a separate account, the addition of Me_3SiCN to acetal **3** in the presence of a Lewis acid afforded the contrasteric 1,4-cis product **4** with high selectivity.[18] Because acetal **3** featured

(1) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998−999.
(2) Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374−2375.
(3) Cipolla, L.; Forni, E.; Jiménez-Barbero, J.; Nicotra, F. *Chem. Eur. J.* **2002**, *8*, 3976−3983.
(4) Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, *2*, 763−766.
(5) Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512−15520.
(6) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.
(7) Numbering used in this paper considers the carbocationic carbon as C-1.
(8) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149−14152.
(9) Other five-membered ring cations are believed to undergo nucleophilic addition through similar low-energy staggered transition structures: (a) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221−3242. (b) Bach, T.; Brummerhop, H.; Harms, K. *Chem. Eur. J.* **2000**, *6*, 3838−3848.
(10) Tanaka, K. S. E.; Chen, X.-Y.; Ichikawa, Y.; Tyler, P. C.; Furneaux, R. H.; Schramm, V. L. *Biochemistry* **2001**, *40*, 6845−6851.
(11) Chen, X.-Y.; Berti, P. J.; Schramm, V. L. *J. Am. Chem. Soc.* **2000**, *122*, 1609−1617.
(12) Jiang, Y. L.; Ichikawa, Y.; Song, F.; Stivers, J. T. *Biochemistry* **2003**, *42*, 1922−1929.
(13) Houseknecht, J. B.; Lowary, T. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 677−682.
(14) Figadère, B.; Peyrat, J.-F.; Cavé, A. *J. Org. Chem.* **1997**, *62*, 3428−3429.
(15) Hanessian, S.; Grillo, T. A. *J. Org. Chem.* **1998**, *63*, 1049−1057.
(16) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893−3901.
(17) Franck, X.; Hocquemiller, R.; Figadère, B. *Chem. Commun.* **2002**, 160−161.
(18) Nishiyama, Y.; Katoh, T.; Deguchi, K.; Morimoto, Y.; Itoh, K. *J. Org. Chem.* **1997**, *62*, 9339−9341.

10.1021/ol0492647 CCC: $27.50
Published on Web 05/08/2004

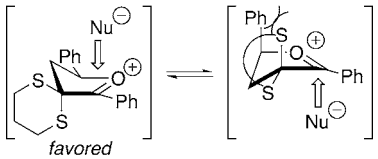
Scheme 1



a single stereocenter at C-4, the selective formation of **4** contradicted the results observed for the nucleophilic substitution of acetal **1**. The counterintuitive stereochemical outcome for acetal **3** was attributed to the steric bias imparted by Lewis acid coordination to the oxonium oxygen and the C-2 heteroatom.[18,19]

While the unselective reaction of the C-4 phenyl acetal **1** is consistent with Reissig's[16] model and our model,[6,8] the correlation between substrates **1** and **3** remains unresolved. We surmised that the sulfur substituents might not participate in a chelated transition structure but would instead influence the conformational preference of the oxocarbenium ion intermediate. According to that hypothesis and the stereoelectronic model,[6,8] the contrasteric 1,4-cis product **4** would arise from inside attack of the nucleophile to the lower energy diequatorial oxocarbenium ion **5** (Scheme 2). This reaction pathway would provide a lower energy transition structure relative to inside attack of the nucleophile on the diaxial conformer **6** (vide infra).[20,21]

Scheme 2



To prove this hypothesis of inside attack and to elucidate the factors that contribute to the selective reaction of acetal **3**, alkyl analogues (R_1, R_2 = Me, Figure 1) with various

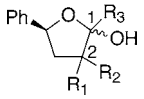


Figure 1. Substitution pattern of the alkyl analogue.

substitution patterns at C-1 and C-2 were investigated. Experiments with alkyl substituents at C-2, in place of the sulfur heteroatoms, eliminate the viability of a chelation-controlled selectivity and reveal the significance of geminal substitution.[22] Perturbation of the C-1 substituent of the oxocarbenium ion intermediate has little effect on reaction stereoselectivity, and analysis of this observation lends additional support for stereoelectronically preferred inside attack of the nucleophile. Our results demonstrate that selective formation of the 1,4-cis product **4** does not require a chelated transition structure, reinforcing the utility of the inside attack model to analyze the reactivity of complex five-membered ring oxocarbenium ion intermediates.

Nucleophilic Substitution Reactions. Prior to the discussion of the nucleophilic substitution reactions, details of the experimental design deserve mention. Anomeric mixtures of the desired acetals were prepared and employed as oxocarbenium ion precursors.[23] Allyltrimethylsilane[24,25] was utilized as the nucleophile in the majority of the addition reactions to obviate product epimerization that may occur with Me_3SiCN.[26−28] The stereochemistry of the substitution products was assigned by analysis of NOE measurements on the products or their derivatives.

Nucleophilic substitution reactions of acetates **7** and **9** indicate that a single substituent at C-2 is not the origin of stereoselectivity for acetal **3** (Scheme 1). Treatment of the trans acetate **7** with allyltrimethylsilane in the presence of $SnBr_4$ provided the 1,4-cis product **8** with 67:33 stereoselectivity (Scheme 3).[29,30] The reaction of the related cis acetate **9** also afforded a mixture of diastereomers.[29,31]

Both the conformational preference of the oxocarbenium ion intermediate and steric interactions that arise in the transition structure for nucleophilic attack influence the stereochemical outcomes observed with acetates **7** and **9**. While the two ground state conformers of the cation derived from trans acetate **7**, namely, **11** and **12**, are comparable in energy, developing steric interactions between the approaching nucleophile and the pseudoequatorial methyl of intermediate **12** slightly disfavor the formation of the 1,4-trans

(19) An oxocarbenium ion intermediate with a Lewis acid blocking one face has been invoked to account for the facial selectivity of a nucleophile: Mukaiyama, T.; Shimpuku, T.; Takashima, T.; Kobayashi, S. *Chem. Lett.* **1989**, 145−148.

(20) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111−128.

(21) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.

(22) Geminal substitution influenced the selectivity in other oxocarbenium ion systems: Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1999**, *55*, 8747−8756.

(23) Acetals **7**, **9**, **15**, **24**, and **26** were prepared from the corresponding known lactones. Details of these experiments are provided as Supporting Information.

(24) Bear, T. J.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **2002**, *67*, 2056−2064.

(25) Burfeindt, J.; Patz, M.; Müller, M.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 3629−3634.

(26) Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; García-López, M. T. *J. Org. Chem.* **1990**, *55*, 2232−2234.

(27) Herranz, R.; Suárez-Gea, M. L.; Vinuesa, S.; García-López, M. T. *J. Org. Chem.* **1993**, *58*, 5186−5191.

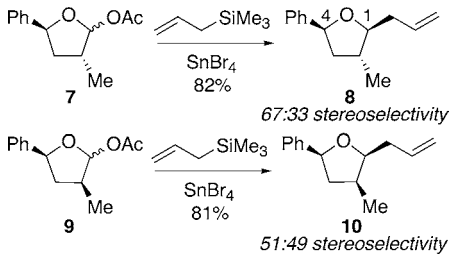
(28) Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *Synthesis* **1996**, 123−132.

(29) Use of $BF_3{\cdot}OEt_2$ and Me_3SiOTf as the Lewis acid provided similar selectivities.

(30) For all experiments, stereoselectivities were determined by GC and/or ^1H NMR spectroscopic analysis of unpurified reaction mixtures. The reported yields are based upon purified products (details of these experiments are provided as Supporting Information).

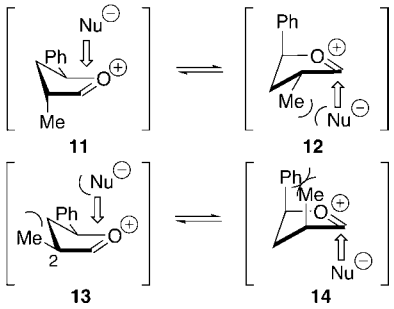
(31) Low selectivity with C-2- and C-4-cis-substituted five-membered ring oxocarbenium ions has been observed: see ref 22.

Scheme 3



product (Scheme 4). The low selectivity obtained from the reaction of cis acetate **9** indicates that the difference in

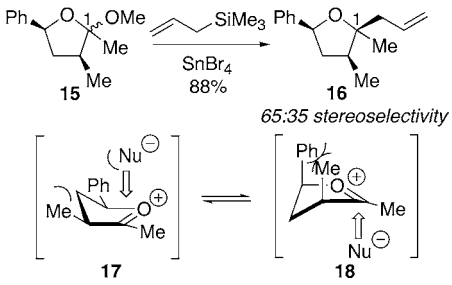
Scheme 4



transition state energies ($\Delta\Delta G^{\ddagger}$) is negligible. Inside attack of the nucleophile to the two ground state conformers **13** and **14** each involve destabilized transition structures. The transition structure for inside attack on the lower energy conformer **13** develops a destabilizing gauche-butane interaction between the nucleophile and the pseudoequatorial C-2 methyl substituent.[31,32] While inside attack on conformer **14** circumvents an unfavorable interaction with the nucleophile, the steric interactions between the methyl and phenyl groups destabilize the transition structure leading to product.[21,33]

The origin of the contrasting selectivities exhibited by acetal **1**[16] and acetal **3**[18] is not attributable to the presence of an alkyl substituent at the acetal carbon (C-1). Treatment of acetal **15** with allyltrimethylsilane in the presence of $SnBr_4$ afforded tetrahydrofuran **16** with 65:35 stereoselectivity (Scheme 5).[34,35] The C-1 substituent exerts minimal influence on the equilibrium of the ground-state conformers **17** and **18** and the respective transition state structures for inside

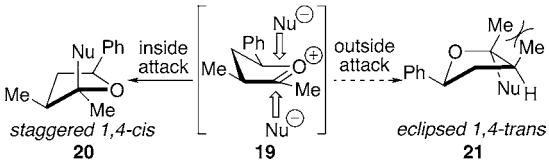
Scheme 5



attack, resulting in a similar selectivity for the reaction of the C-1-unsubstituted substrate **9** (Scheme 3).

The selectivities for the reactions of acetate **9** and acetal **15** provide experimental support for stereoelectronically preferred inside attack on five-membered ring oxocarbenium ions, confirming the importance of torsional angle effects in addition reactions.[6,8,36] A potential reaction pathway leading to the minor 1,4-trans product obtained with acetal **9** could involve outside attack of the nucleophile to the lower energy conformer **13**. The reaction of acetate **15** resolves this ambiguity because formation of the 1,4-trans product **21** via outside attack on conformer **19** would be disfavored due to a more severe eclipsing interaction (Me↔Me and a Me↔H) that develops in the transition structure (Scheme 6).[37] If outside attack occurred, acetal **15** should have shown

Scheme 6



considerably higher selectivity for the staggered 1,4-cis product **20**. The selectivity for the nucleophilic substitution reaction of methyl-substituted acetal **15** confirms that the minor product obtained with acetate **9** is the result of inside attack on the higher energy conformer of the cation and not outside attack on the lower energy conformer.[38]

Because the C-4-substituted acetals in this study exhibit low selectivity as was observed for acetal **1**[16] (Scheme 1), the unique feature of acetal **3**[18] that contributes to high

(32) For a study on the developing steric interactions between C-2 substituents and the incoming nucleophile in six-membered ring oxocarbenim ion intermediates, see: Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521−15528.

(33) In accordance with the Curtin−Hammett principle, the relative energies of the transition state structures dictate the stereochemical outcome, not the relative energies of the ground-state structures.

(34) The two anomers of acetal **15** were isolated in various ratios. Control experiments demonstrate that the starting anomer ratio does not affect the stereochemical outcome of the product, consistent with the intermediacy of oxocarbenium ions.

(35) Use of $BF_3{\cdot}OEt_2$ as the Lewis acid afforded a 54:46 ratio of cis:trans isomers for the allylation of **15**.

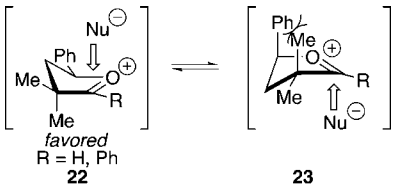
(36) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117.

(37) We estimate the energy difference between a Me↔Me and a Me↔H eclipsing interaction to be 2 kcal/mol. This approximation was extrapolated from the rotational barriers of *n*-butane and *n*-propane. For *n*-butane, see: Allinger, N. L.; Fermann, J. T.; Allen, W. D.; Schaefer, H. F., III. *J. Chem. Phys.* **1997**, *106*, 5143−5150. For *n*-propane, see: Bürgi, H.-B.; Hounshell, W. D.; Nachbar, R. B., Jr.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 1427−1438.

(38) For an investigation of torsional angle effects (eclipsing strain energy) on the reaction selecitivity of hydroxymercuration of substituted cyclohexenes, see: Pasto, D. J.; Gontarz, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 6909−6913.

selectivity may be geminal substitution at C-2. With a pseudoequatorial methyl in both ground state conformers **22** and **23**, steric interactions with the approaching nucleophile would be comparable in both transition structures (Scheme 7). Therefore, the energy difference between the transition

Scheme 7

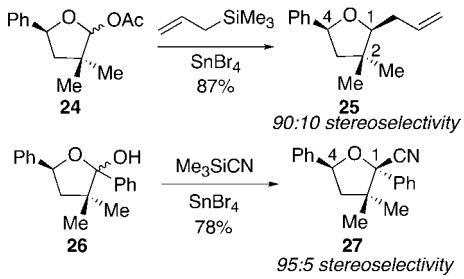


structures of inside attack would reflect the relative energy difference between the ground-state oxocarbenium ion conformers **22** and **23**. Inside attack on the favored diequatorial conformer **22** should afford the 1,4-cis product with high selectivity, consistent with acetal **3**.

Our experiments confirm that geminal substitution at the C-2 position, regardless of the substitution pattern at C-1, is required to obtain high stereoselectivity for this series of substrates. Allylation of geminal dimethyl acetate **24** in the presence of $SnBr_4$ afforded the 1,4-cis product **25** with high selectivity (Scheme 8).[29,39] To mimic the experiments reported for the nucleophilic substitution reaction of dithiane-substituted acetal **3** (Scheme 1), the reaction of C-1 phenyl acetal **26** with Me_3SiCN was studied. In accord with experiments described previously, the substituent at C-1 exerted little influence on the selectivity. The kinetically controlled addition of Me_3SiCN to **26** in the presence of $SnBr_4$ afforded the 1,4-cis product **27** with high selectivity.[29,40]

(39) The solvent employed for these nucleophilic substitution reactions was CH_2Cl_2. With toluene as the solvent, selectivities were optimized to a 96:4 ratio of cis:trans isomers for the reaction of acetate **24**.

Scheme 8



In conclusion, the dissimilar selectivities exhibited by the two related tetrahydrofuran acetals shown in Scheme 1 are not the result of chelation of the Lewis acid. Instead, the substituent at C-4 biases the conformation of the oxocarbenium ion, and inside attack provides the product with high cis selectivity. This study demonstrates the capacity of the model to analyze the stereochemical outcomes of nucleophilic addition reactions to complex five-membered ring oxocarbenium ions.

Acknowledgment. This research was supported by the National Institutes of Health, National Institute of General Medical Science (GM-61066), and by Johnson & Johnson. D.M.S. thanks Johnson & Johnson for a graduate research fellowship. K.A.W. thanks Merck Research Laboratories for an award to support research. We thank Dr. John Greaves and Dr. John Mudd for mass spectrometric data.

Supporting Information Available: Complete experimental procedures, product characterization, stereochemical proofs, and GC and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0492647

(40) Control experiments indicate that this reaction is irreversible at low (−78 °C) reaction temperatures (details of these experiments are provided as Supporting Information).