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Lewis Acid-Catalyzed [4 + 3] Cycloaddition of 2-(Trimethyl Silyloxy)acrolein with Furan. Insight on the Nature of the Mechanism from a DFT Analysis

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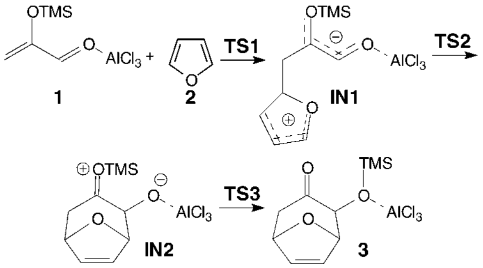
ABSTRACT



The mechanism for the Lewis acid-catalyzed [4 + 3] cycloaddition of 2-(trimethylsilyloxy)acrolein 1 with furan 2 has been studied at the B3LYP/6-31G* level. This reaction is a three-step process that is initialized by the nucleophilic attack of 2 to the *β*-conjugated position of 1 to give a zwitterionic intermediate IN1. The key step on the formation of the seven-membered ring is the electrophilic attack of the furan residue to the electrophilically activated carbonyl carbon at this intermediate.

The direct construction of seven-membered rings via [4 + 3] cycloadditions is the most attractive strategy for preparing this frequently observed natural product substructure.[1] Therefore, a great amount of effort has been focused on methods to synthesize the less accessible three-atom component of these reactions. Oxyallyl cations are the most employed intermediates in generation of this moiety.[2]

Alternatively, the use of 2-(silyloxy)acroleins and related compounds in the presence of a Lewis acid (LA) catalyst as dienophiles in the [4 + 3] cycloadditions has received much interest in the last years. Sasaki et al.[3] demonstrated that treatment of 2-(trimethylsilyloxy)acrolein **4** with 1 equiv of $SnCl_4$ in the presence of a slight excess of cyclopentadiene afforded, after acidic workup, the α-hydroxycycloheptenone **5** in 72% yield as a 2.7:1 mixture of endo and exo isomers, respectively (Scheme 1).

The use of 2-(triisopropylsilyloxy)acrolein as the three-atom component of a [4 + 3] cycloaddition has been recently reported by Harmata and Sharma.[4] This dienophile reacts with selected dienes in the presence of catalytic amounts of scandium triflate to give the products that are formal [4 +

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[1] (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163−344. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1−19. (c) Hosomi, A.; Tominaga, Y. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 593−615. (d) Rigby, J. *J. Org. React.* **1997**, *51*, 351. (e) Harmata, M. *Terahedron* **1997**, *53*, 6453−6280.

[2] (a) Mann, J. *Tetrahedron* **1986**, *42*, 4611−4659. (b) Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217−232. (c) Harmata, M.; Jones, D. E.; Kahraman, M.; Sharma, U.; Barnes, C. L. *Tetrahedron Lett.* **1999**, *40*, 1831−1834. (d) Sarhan, A. A. O. *Curr. Org. Chem.* **2001**, *5*, 827−844. (e) Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59−61.

[3] Sasaki, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1693−1696.

[4] Harmata, M.; Sharma, U. *Org. Lett.* **2001**, *2*, 2703−2705.

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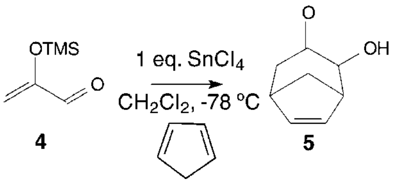
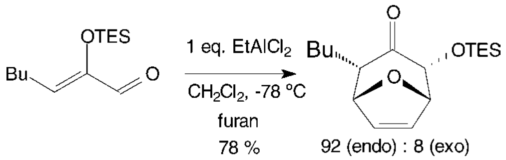
Scheme 1



3] cycloadducts. An exception was in the case of butadiene, where only the [4 + 2] cycloadduct was observed.

More recently, Aungst and Funk[5] reported the LA-catalyzed [4 + 3] cycloadditions of 2-(trialkylsililoxy)-2-enales with a series of dienes. In many instances the [4 + 3] cycloadditions occur with excellent regio- and/or stereoselectivity (Scheme 2). Several observations were obtained from these experiments. In all cases, the silyl group is cleanly transferred to the aldehyde oxygen. The endo cycloadducts are uniformly preferred over the exo counterparts, and the stereoselectivity is better for smaller silyl substituents. The endo/exo ratio can also be significantly improved by the choice of the LA catalyst.

Scheme 2



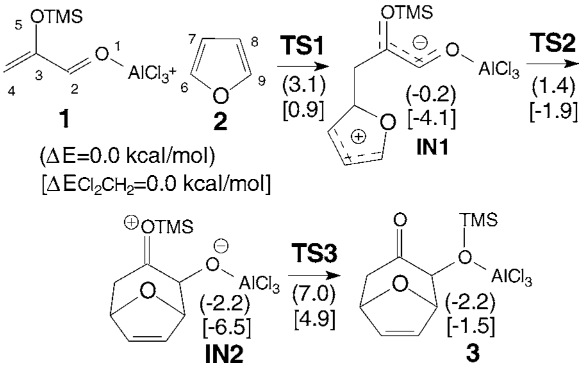
The mechanism of these formal [4 + 3] cycloadditions is not absolutely clear. Harmata and Sharma[4] proposed that these cycloadditions with high levels of simple diastereoselectivity might be regarded as concerted processes. On the other hand, the occurrence of stereoisomers or the production of mixtures of [4 + 2] and [4 + 3] cycloadducts with 2,3-dimethylbutadiene suggests the possibility of an intermediate that can afford both [4 + 2] and [4 + 3] cycloadducts or [4 + 3] cycloadducts with eroded diastereoselectivity.[5]

The computational approach is very appealing in this field, given the diversity and the difficulties of the experimental elucidation of the corresponding synthetic routes. The mechanism of the [4 + 3] cycloaddition reaction between hydroxyallyl cations and butadiene has been recently studied from a theoretical point of view by Cramer and Barrow.[6] This reaction takes place through a stepwise mechanism, and the first step is the electrophilic attack of the hydroxyallyl cation on the diene to give a cation intermediate, which by a subsequent ring-closure process affords the final [4 + 3] cycloadduct. For the intramolecular [4 + 3] cycloadditions between hydroxyallyl cations and furan, a stepwise-like mechanism has been predicted by Harmata and Schreiner,[7] while the endo/exo preferences involving the cyclopentenyl cation have been explained through a concerted process.[8]

The 2-hydroxyallyl cation has an electrophilicity index[9] of $\omega = 21.5$ eV. This very high value indicates that the hydroxyallyl cations will participate as a very strong electrophile in reactions with a large ionic character. The transition structure (TS) associated with the electrophilic attack of the 2-hydroxyallyl cation to 1,3-butadiene is located −8.9 kcal/mol (MP2/6-31G*) lower than reactants.[6a] On the other hand, the 2-silyloxyacrolein has an electrophilicity of $\omega = 2.57$ eV. This value is slightly larger than that for acrolein, $\omega = 1.84$ eV.[10] As a consequence, it is expected that the reactivity pattern of 2-silyloxyacrolein will be more like that for acrolein than that for the hydroxyallyl cations. However, the presence of the donor group on the 2-silyloxyacrolein is responsible for the formation of the formal [4 + 3] cycloadduct instead of the [4 + 2] cycloadduct.

The mechanism of the reaction of 2-(trialkylsilyloxy)-2-alkenals as the three-atom component in these [4 + 3] cycloadditions has not yet been theoretically studied. Now, the reaction between 2-(trimethylsilyloxy)acrolein **1** and furan **2** in the presence of $AlCl_3$ as LA catalyst is studied as a computational model of these [4 + 3] cycloadditions (Scheme 3).

Scheme 3



The electrophilicity analysis indicates that the LA-catalyzed reaction of 2-silyloxyacroleins with dienes should be like that for the LA-catalyzed reaction of acrolein, which has been extensively studied at the B3LYP level.[11] Therefore, the B3LYP[12] exchange-correlation functional, together with the standard 6-31G* basis set,[13] have been used for the study

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(5) Aungst, R. A., Jr.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3553−3555.

(6) (a) Cramer, C. J.; Barrow, S. E. *J. Org. Chem.* **1998**, *63*, 5523−5532. (b) Cramer, C. J.; Barrow, S. E. *J. Phys. Org. Chem.* **2000**, *13*, 176−186.

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(8) Cramer, C. J.; Harmata, M.; Rashatasakhon, P. *J. Org. Chem.* **2001**, *66*, 5641−5644.

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(10) Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417−4423.

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(12) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

of this [4 + 3] cycloaddition. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[14] Solvent effects have been considered by B3LYP/6-31G* single-point calculations on the gas-phase optimized geometries using a self-consistent reaction field (SCRF)[15] based on the polarizable continuum model (PCM) of Tomasi's group.[16] All calculations were carried out with the Gaussian 98 suite of programs.[17]

The [4 + 3] cycloaddition between 2-(trialkylsilyloxy) acroleins and furan can take place along two stereoisomeric channels, the endo and exo, with mainly the endo cycloadduct being formed;[4,5] therefore, the endo channel was chosen to investigate the mechanism. An analysis of the results indicates that the reaction between the LA-coordinated 2-(trimethylsilyloxy)acrolein **1** and furan **2** to give the formal [4 + 3] cycloadduct **3** takes place along a three-step process (see Scheme 3). The first step is the nucleophilic attack of **2** to the C4 carbon, at the β-conjugated position, of **1** to yield the zwitterionic intermediate **IN1**. This step presents a very low barrier, 3.1 kcal/mol; the formation of the zwitterionic intermediate **IN1** is slightly exothermic, −0.2 kcal/mol. The second step is the ring-closure process at this intermediate to construct the oxabicyclo[3.2.1]octane skeleton present in **3**. This process, which involves the electrophilic attack of the C9 carbon of the furan framework on the electrophilically activated carbonyl C2 carbon of **1**, has a very low barrier, 1.6 kcal/mol. Finally, the migration of the trimethylsilyl group from the O5 oxygen to the carbonyl O1 oxygen affords the formal [4 + 3] cycloadduct **3**. The barrier associated with this process is 9.2 kcal/mol; as a consequence, the silyl migration is the rate-determining step of this LA-activated [4 + 3] cycloaddition. The optimized geometries of the TSs, together with the lengths of the forming bonds involved in the [4 + 3] cycloaddition, are given in Figure 1.

Inclusion of solvent effects, dichloromethane, leads to a larger stabilization of the TSs and intermediates, between 8 and 10 kcal/mol, than reactants and product, between 1 and 5 kcal/mol, due to the large zwitterionic character of the former. As a consequence, in dichloromethane, while the activation barrier for the first step decreases to 0.9 kcal/mol, the barriers for the ring-closure and silyl migration steps increase to 2.2 and 11.4 kcal/mol, respectively.

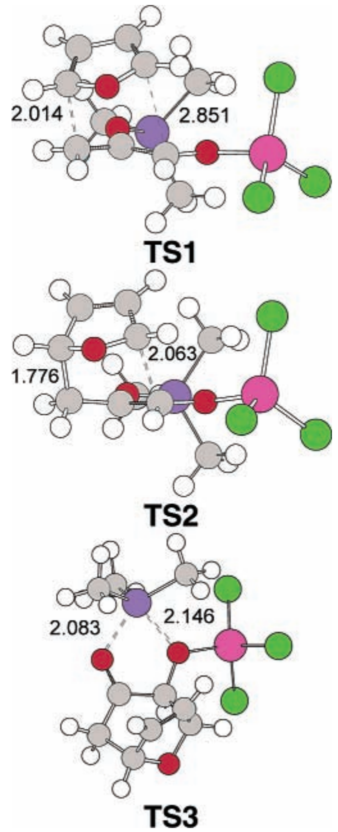

Figure 1. Optimized geometries of the transition structures, **TS1**, **TS2**, and **TS3**, for the three-step [4 + 3] cycloaddition between LA-coordinated 2-(trimethylsilyloxy)acroleine **1** and furan **2**.

The bond order (BO) values[18] of the C4−C6 and C2−C9 forming bonds at the TSs and intermediate involved at this [4 + 3] stepwise cycloaddition are 0.46 and 0.09 at **TS1**, 0.84 and 0.13 at **IN1**, 0.88 and 0.43 at **TS2**, respectively. The C3−O5 BO value at **TS2**, 1.12, indicates a slight π character of the C3−O5 bond as a consequence of the participation of the O5 oxygen atom at the ring-closure step. The BO values between the Si and O1 and the O5 oxygen atoms at **TS3** are 0.26 and 0.27, respectively; therefore, along the silyl migration the Si−O1 forming bond and Si−O5 breaking bond, processes are concerted.

Along the stepwise [4 + 3] cycloaddition, the charge transfer from furan **2**, acting as a donor, to LA-coordinated 2-(trimethylsilyloxy)acrolein **1**, acting as a good acceptor, is −0.32 e (**TS1**), −0.43 e (**IN1**), and −0.31 e (**TS2**). Therefore, there is a large charge transfer along this polar cycloaddition that is characterized by the nucleophilic attack of furan to the β conjugated position of **1** to give a zwitterionic intermediate **IN1**.

The presence of the silyloxy group on the C3 position of acrolein polarizes the HOMO electron density at the inter-

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mediate **IN1**, favoring the subsequent electrophilic attack of the positively charged furan moiety to the carbonyl C2 carbon to give the [4 + 3] cycloadduct instead of the attack to the C3 position to give the [4 + 2] cycloadduct.

The LA-coordinated 2-(trimethylsilyloxy)acrolein **1** presents a large electrophilicity index, 4.09 eV, being classified as a strong electrophile.[10] On the other hand, furan has a very low electrophilicity value, 0.58 eV, being a good nucleophile.[10] The difference of global electrophilicity power between the reagent pair, $\Delta\omega$, has been used to predict the polar character of the cycloaddition processes.[10] The $\Delta\omega$ computed for this [4 + 3] cycloaddition, 3.51 eV, points out the large polar character of this process, in clear agreement with the large charge-transfer found along this stepwise [4 + 3] cycloaddition.[10]

In summary, the LA-catalyzed [4 + 3] cycloaddition between 2-(trimethylsilyloxy)acrolein and furan takes place through a three-step mechanism. The first step corresponds to the nucleophilic attack of furan to the β-conjugated position of acrolein to give a zwitterionic intermediate. The presence of the 2-silyloxy group polarizes the HOMO electron density of this intermediate located mainly in the acrolein moiety, favoring the ring-closure at the carbonyl carbon with formation of the seven-membered ring. Finally, the silyl migration to the carbonyl oxygen allows the formation of the formal [4 + 3] cycloadduct. Investigations are in progress to elucidate the factors controlling the regio- and stereoselectivity of these [4 + 3] processes.

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Supporting Information Available: Cartesian coordinates of all reported structures, as well the total electronic energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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