Synthesis of Highly Substituted Cyclohexenes via Mixed Lewis Acid-Catalyzed Diels–Alder Reactions of Highly Substituted Dienes and Dienophiles

Michael E. Jung,* David Ho, and Hiufung V. Chu

Department of Chemistry and Biochemistry, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, California 90095

Received February 19, 2005

ABSTRACT

A high-yielding method is described for the rapid synthesis of very hindered cyclohexenes by the Diels–Alder reaction of hindered silyloxy dienes and dienophiles using the mixed Lewis acid catalyst system (AlBr₃/AlMe₃). Thus, reaction of the hindered diene 4 with various substituted enones gave good yields of the expected cycloadducts even though both partners are quite sterically hindered.

The Diels–Alder reaction has been a mainstay of synthetic organic chemistry for more than 70 years due to its predictable reactivity and control of the regio- and stereochemistry in the formation of the two new σ bonds in the intermolecular combination of a diene and dienophile. However, despite its well-deserved reputation in synthesis, problems still exist in the application of these cycloadditions to certain cases. In particular, the use of Diels–Alder reactions to prepare highly substituted cyclohexene systems has generally met with failure owing to severe problems with steric hindrance. Recently, we reported two examples of the preparation of a 6,6,5-tricyclic system, using the mixed Lewis acid system, AlBr₃/AlMe₃, via both the cycloaddition of hindered dienophiles with 2-silyloxydienes and the inverse-electron-demand Diels–Alder reaction of a hindered silyl enol ether with a 2-acyldiene. We now report an examination of the scope of this process which demonstrates that it is quite general for the production of highly substituted cyclohexenes.

The cycloaddition of the silyloxydiene 1 with 1-acetyl-2-methylcyclopentene 2 using a 10:1 mixture of AlBr₃/AlMe₃ at 0 °C for 4 h in toluene/dichloromethane solvent afforded an 88% yield of a 2.6:1 mixture of the stereoisomers 3x and 3n, favoring the exo product (Scheme 1). Since the cycloaddition is most likely a stepwise process (a Mukaiyama–Michael followed by an intramolecular Michael-like process) and the two bonds are not formed simultaneously, the normal Alder endo transition state rules would not be in effect (no substantial secondary orbital overlap) and the stereochernistry would probably be controlled by steric hin-
drance. In this case, the trimethylene bridge is less sterically demanding than the methyl and acetyl groups on the dienophile and thus the exo isomer $3x$ is the major product as shown in Figure 1.

More highly substituted dienes can also be used in this process. For example, the silyl enol ether $4$ prepared from mesityl oxide was reacted with $2$ using a 5:1 mixture of AlBr$_3$/AlMe$_3$ at $-5 \, ^\circ C$ for 48 h to produce a 5:1 mixture of the desired cycloadduct $5$ and the byproduct $6$ in 78% yield (Scheme 2). Although these two compounds could not be separated, treatment of the mixture with DIBAL at $-78 \, ^\circ C$ reduced the byproduct $6$ and allowed the isolation, after silyl enol ether methanolysis, of the dione $7$ in 95% yield (based on $5$). This ketone is an extremely congested molecule possessing three contiguous quaternary centers. We propose that the byproduct arises via the following pathway: since the desired cycloaddition is quite slow under these conditions, the electron-rich silyl enol ether can react with the Lewis acid to produce the zwitterion $I$, which is a very activated dienophile and can add to the diene $4$ to give $6$. The structure of $6$ was proven by its preparation from $4$ and mesityl oxide and its conversion to the dione $8$, which was identified by its high symmetry.

Since 1-acylcyclohexenes are generally less reactive than 1-acylcyclopentenes in cycloadditions, we wanted to test the reactivity of the higher homologue. Reaction of the substituted diene $4$ with 1-acyt-2-methylcyclohexene $9$ in the presence of 5:1 AlBr$_3$/AlMe$_3$ at $-5 \, ^\circ C$ for 48 h gave a 5:1 mixture of the desired cycloadduct $10$ and the byproduct $6$ in 75% yield (Scheme 3). Reduction and methanolysis afforded the dione $11$ in 99% yield (based on $10$), which is also a very sterically encumbered molecule with three contiguous quaternary centers.

Substituted cyclic ketones can also be used as dienophiles in this process. For example, the relatively unhindered 3-methylcyclohex-2-en-1-one $12$ reacted with the substituted diene $4$ in the presence of 5:1 AlBr$_3$/AlMe$_3$ at $-5 \, ^\circ C$ for 48 h to give the desired cycloadduct $13$ in 82% yield (Scheme 4). As in most reactions with relatively unhindered dienophiles, no more than a trace of the byproduct $6$ was observed

(5) Even though this is likely a stepwise process, it should still be considered a Diels–Alder reaction since Diels and Alder only described the reaction of a diene and dienophile to give a cyclohexene without implying any mechanistic detail; thus, this reaction should be considered a Diels–Alder reaction by their definition.

here. Acidic hydrolysis of the silyl enol ether afforded the expected dione, which can exist in two conformations, 14ab. On treatment with acidic methanol, the ring juncture stereochemistry was epimerized to give an 85:15 mixture of the trans and cis diones 15 and 14. This mixture could also be prepared by treatment of 13 directly with excess tosic acid in methanol. Molecular mechanics calculations (MM2) indicate a 1.3 kcal/mol difference in energy favoring 15 over 14b. The fact that one can isomerize the cis ring juncture to the trans opens up the possibility of using this process for the synthesis of the AB ring system of various terpenoid natural products.

The value of a new synthetic method is determined by its ability to work even in difficult cases, and we believe that this new mixed Lewis acid catalyzed process meets this criterion. The very sterically hindered dienophile, 2,3-dimethylcyclohex-2-en-1-one reacted with the dimethyl-substituted diene 4 in the presence of 5:1 AlBr3/AlMe3 at −5 °C for 48 h to give the desired tetramethyl cycloadduct 17 in 79% yield (Scheme 5). Acidic hydrolysis as before gave the dione 18 in 93% yield. However, acidic methanolysis of the silyl enol ether did not afford the expected dione 18 but rather gave a different product which exhibited only a single ketone resonance at 18.219.0 in the 13C NMR and one methoxy singlet at δ 3.2 in the 1H NMR. We have assigned the methoxy twistanone structure 19 to this product. The formation of hydroxy twistanones from diones similar to 18 has been reported previously. Here, the twistanone 19 is the major product of a 3:1:1 mixture along with the dione 18 and another, as yet, unidentified product. Presumably the reaction proceeds via the attack of the enol of the diketone on the α-methoxy carbocation (oxocarbenium ion) in an aldol-type process as shown in II. The mutual steric repulsion of the four methyl groups may well favor the cyclization in a kind of geminal and vicinal polyalkyl effect.

We also decided to explore briefly the generality of the inverse-electron-demand Diels–Alder reaction3 of a hindered silyl enol ether with a 2-acetyldiene that we reported earlier.3.2 In summary, we have demonstrated that highly substituted cyclohexene systems can be prepared directly by a Diels–Alder reaction in either the direct or inverse-electron-demand mode catalyzed by the novel mixed Lewis acid system AlBr3/AlMe3. The preparation of such systems and their use in synthesis is currently under study in our laboratory.

Acknowledgment. We thank the National Science Foundation (CHE0314591) for their financial support. H.V.C. thanks the National Institutes of Health for support via Grant No. GM08496.

Supporting Information Available: Spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050361P

(8) Simple molecular mechanics calculations (MM2) indicate that the driving force for forming the twistanone 19 from the diketone is far greater than that for the formation of the unsubstituted twistanone presumably due to the buttressing steric effect of the four methyl groups. For a review of gem-dialkyl effects, see: Jung, M. E. Synlett 1999, 843–46; Jung, M. E. Synlett 1990, 186–90. Jung, M. E.; Pizzi, G. Chem. Rev. 2005, in press.

(9) As with the previous case, this reaction is presumably stepwise, namely a Mukaiyama–Michael addition followed by an intramolecular aldol condensation onto the very hindered ketone.

(10) (a) Prepared by Stille coupling of ethyl 2-t-butyldimethylstannylacrylate with 1-bromo-2-methylpropene. (b) Prepared by Stille coupling of 2-t-butyldimethylstannyl-1-butene with 1-bromo-2-methylpropene followed by Swern oxidation.