Synthesis of Exocyclic Allenes by Double Reduction with Lithium Aluminum Hydride

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ABSTRACT

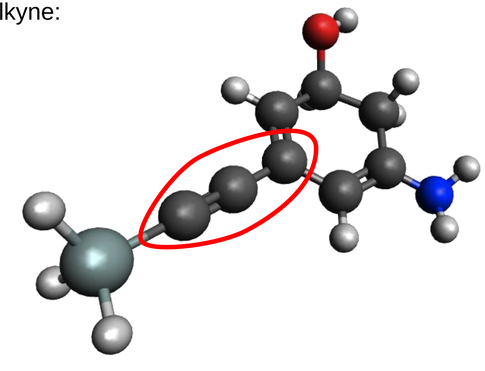
Exocyclic allenes are well represented among allene-containing natural products, such as the grasshopper ketone. Allenes have been demonstrated in certain circumstances to embody similar properties to alkynes, and consequently have shown potential as alternative functional groups to be utilized as molecular scaffolds for pharmaceutical development. Commonly syntheses of exocyclic allenes rely on extended conjugate additions, or S_N2-like alkylations and reductions of alkynyl epoxides.[1] We report rapid synthesis of exocyclic allenes with 2 molar equivalents of lithium aluminum hydride in reduction of a vinylogously propargylic intermediate alcoholate with an attached trimethylsilyl group,[2,3] thus providing a new, potentially general, method for their preparation.

INTRODUCTION

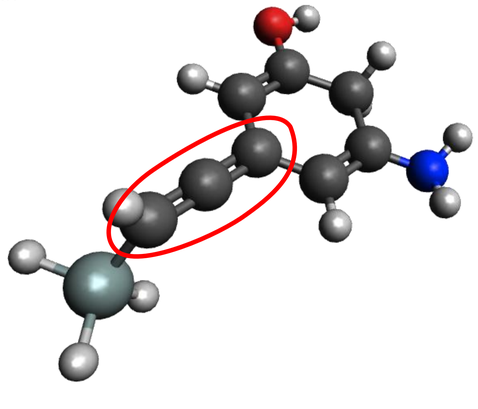
One of the less researched functional groups in organic chemistry is the allene group. They are rare in nature, and there are relatively few methods to synthesize them in a laboratory. As this functional group remains largely unexplored, many of its uses are potentially being missed.

Allenes have potential for use in pharmaceutical development. They have been demonstrated in some circumstances to embody similar properties to alkynes, and they have shown potential as alternative functional groups to be utilized as molecular scaffolds in pharmaceutical development.[4] Notice the similarities between the two molecules below at the point of the functional group, one of which contains an alkyne, and the other of which contains an allene.

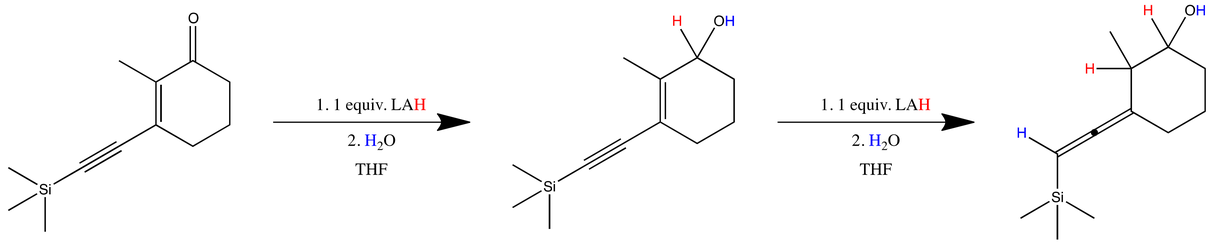
Alkyne:



Allene:

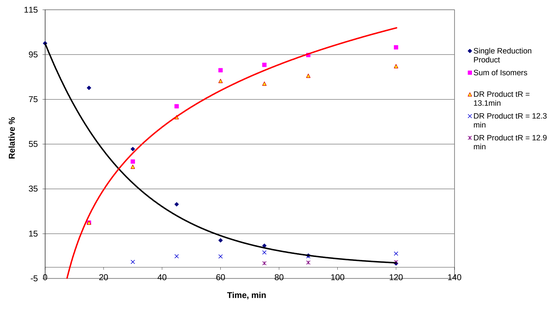


REACTION

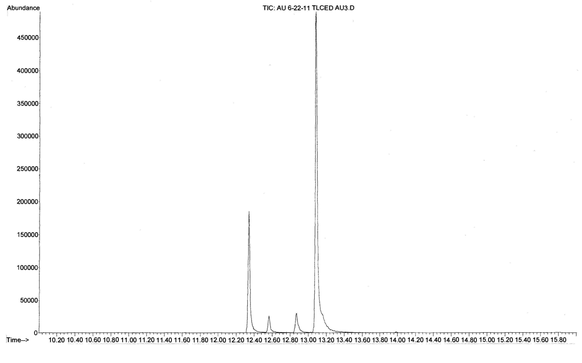


REACTION KINETICS

We studied the rate of this reaction by following its progress with gas chromatography. An aliquot was taken from the reaction flask immediately after the LAH was added, and every 15 minutes thereafter until 120 minutes had passed. The aliquots were quenched by injecting into water, and the organic layer was taken for GC injection. We compared the area of the peak represented by the starting material to the peaks representing the multiple allene product stereoisomers. The reaction appears to be 1st order, and the results are graphed below:



From this evidence it becomes clear that the reaction takes place in a sufficiently short amount of time to make it viable as an industrial synthesis. Additionally, we observed that the single reduction product is generated before the double reduction (allene group) product, leading us to believe that the single reduction product is an intermediate. We confirmed this by running the reaction starting with the single reduction product, which still resulted in the generation of the double reduction product.

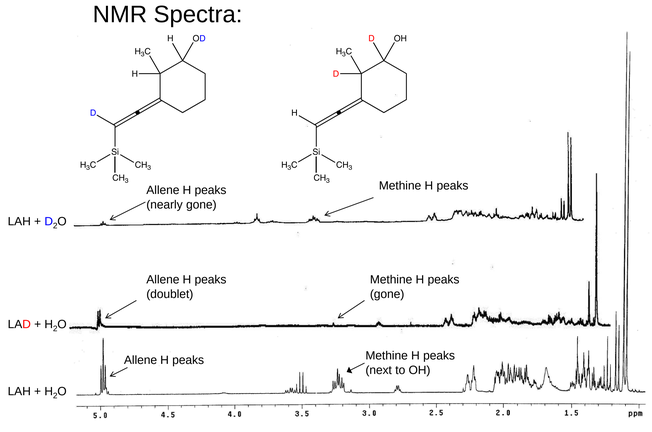


Shown above is an example gas chromatograph of our allene product.

MECHANISM DETERMINATION

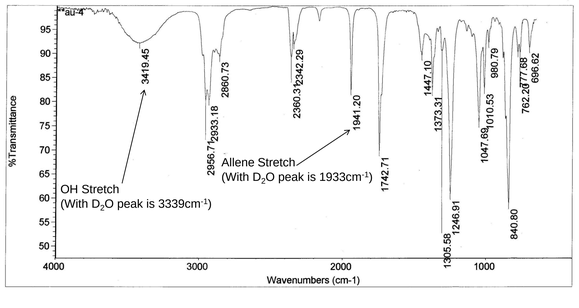
We studied the mechanism by performing two reactions, one using LAD in place of LAH, and one using D_2O instead of H_2O. With the deuterium labeling, one can observe where the hydrogens from each reactant appear in the final product. This can be done by noting the absence of the relevant peaks in ^1H NMR, and the shift of the relevant peaks in IR spectroscopy. The relevant NMR spectra are included below, one from using LAD as a reactant, and one from using D_2O as a reactant.

NMR Spectra:

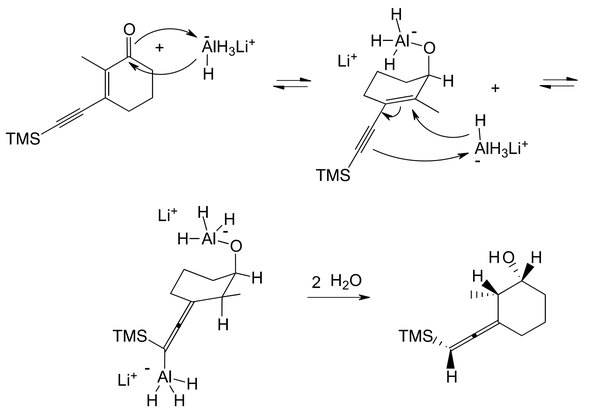


As is shown by the shifts in the following IR spectra of both the allene peak and the alcohol peak, the hydrogens from the H_2O (D_2O) add to those two areas. The IR spectrum for the synthesis utilizing LAD does not appear remarkably different from the spectrum for the synthesis utilizing LAH. This is to be expected, as the addition of two more sp^3 hybridized C-H bonds to the 18 already present should not result in a large shift.

IR Spectra:



POTENTIAL MECHANISM



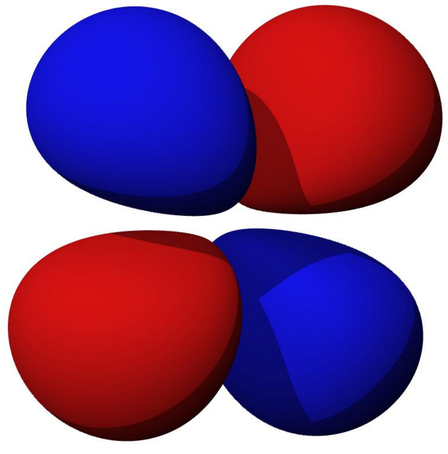
FUTURE WORK

Future work includes:

-Determination of an exact mass

-Removing the TMS group after synthesis

-Using trimethyltin instead of trimethylsilyl



REFERENCES

1. Modern Allene Chemistry, vol 1-2. Krause, N.; Haskimi, S. K., Eds. Wiley-VCH: New York, **2004**. b. Brandsma, L. Synthesis of Acetylenes, Allenes and Cumulenes. Elsevier: Oxford, **2004**.

2. Funk, R.; Vollhardt, K. *Synthesis* **1980**, 2, 118-119.

3. Kita, Y.; Furukawa, A.; Futamura, J; Ueda, K,; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* **2001**, 66, 8779-8786

4. Ban, H.; Onagi, S.; Uno, M.; Nabeyama, W.; Nakamura, H. *ChemMedChem*, **2008**, 3, 1094–1103.