



LDA Conjugate Addition to a Morita-Baylis-Hillman Ester: Experimental and DFT-based Theoretical Observations

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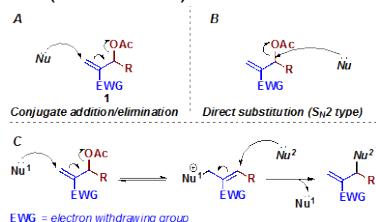
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INTRODUCTION

The Morita-Baylis-Hillman (MBH) reaction is well known for providing valuable building blocks in organic synthesis. In the last few years it has been demonstrated that not only the MBH adducts itself can be useful intermediates, but also, its derivatives. The corresponding esters of MBH adducts (acetates, in most cases) have been extensively described in the literature due to its particular reactivity towards the attack of different nucleophiles¹ (Scheme 1).

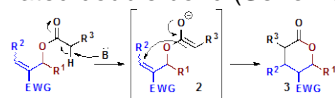


Scheme 1. The reactivity of MBH acetates towards the attack of different nucleophiles.

the use of lithium amides is a very frequent strategy for synthetic chemists in order to produce reactive anionic intermediates. In the case of a MBH ester, the usual chemistry of lithium amides may not be absolute as already observed in different situations². Herein we present an example of LDA conjugate addition to a MBH ester, also providing a Density Functional Theory (DFT)-based description of the reaction pathway, supporting the experimental unexpected results.

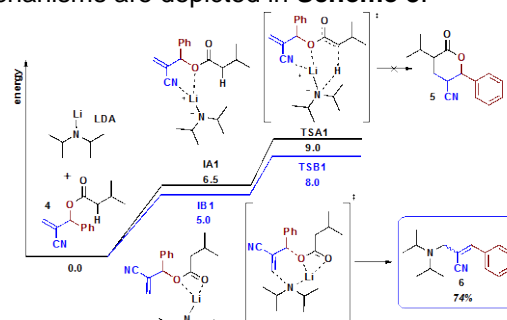
RESULTS AND DISCUSSION

During some studies on MBH esters transformations we have decided investigate the possibility of a 6-exo-trig type cyclization of these esters to produce six-membered lactones (3). This proposition was based on the formation of an enolate (2) by means of a strong base for further conjugate addition to the terminal activated double bond (Scheme 2).



Scheme 2. Initial proposition for the lactonization reaction of MBH esters.

Compound 4 was treated with LDA in order to promote its enolization aiming to generate the lactone 5. Instead, the lactone, compound 6 was isolated in 74 % yield. Theoretical calculations based on DFT were conducted in order to provide reliability to the experimental observation that LDA can actually act as a nucleophile rather than a base. The energy profile for the competing reaction mechanisms are depicted in Scheme 3.



Scheme 3. The computational data were obtained by means of the B3LYP functional and Pople bases (6-31G+(d) for every atom.

CONCLUSION

We have provided experimental and theoretical data for a non-expected conjugate addition of LDA to a MBH ester. We have also calculated the whole reaction profile for both competing reactions, showing that despite the acidity of α -carboxyl protons, this kind of MBH ester cyclization cannot be achieved.

ACKNOWLEDGEMENTS

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