ORGANIC
LETTERS

2005
Vol. 7, No. 12
2421−2423

# A One-Step Synthesis of 2,3-Dihydro-4*H*-pyran-4-ones from 3-Ethoxy α,*β*-Unsaturated Lactones

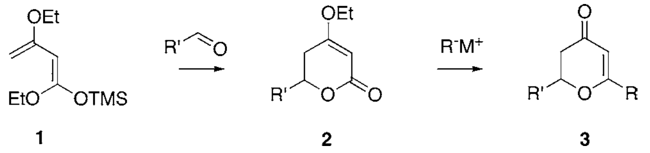
**Jeffrey D. Winkler* and Kyungsoo Oh**

*Department of Chemistry, The University of Pennsylvania,*
*Philadelphia, Pennsylvania 19104*

*winkler@sas.upenn.edu*

Received April 1, 2005

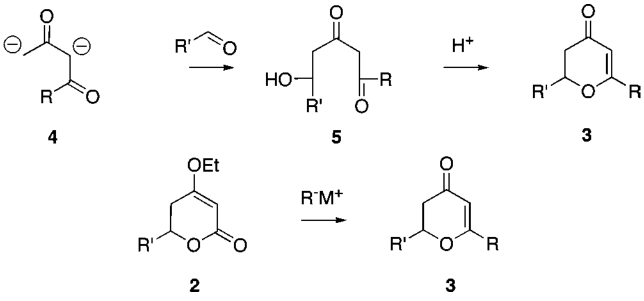
## ABSTRACT



**Addition of diverse nucleophiles to the unsaturated lactone 2 that results from hetero Diels−Alder reaction of Brassard's diene 1 with aldehydes leads to an efficient and general approach to the synthesis of 2,3-dihydro-4*H*-pyran-4-ones 3.**

Dihydropyranones are ubiquitous functionalities in molecules of Nature. They also represent important intermediates in the synthesis of a variety of different structures, many of biological and medicinal significance.[1] While several groups have examined the preparation of the dihydropyranone ring via aldol reaction of the dianion derived from a *β*-diketone with an aldehyde,[2] followed by cyclization of the resulting hydroxydiketone to the dihydropyranone, we have developed an alternative protocol for the synthesis of this ring system as outlined in Scheme 1. Addition of a series of nucleophiles to **2**, the product of hetero Diels−Alder reaction of Brassard's diene with an aldehyde, leads to the formation of dihydropyranone **3**. This approach allows for considerable flexibility in the nature of both the aldehyde R group and the nucleophile, facilitating the preparation of a diverse array of dihydropyranones.

**Scheme 1**



The reaction of Brassard's diene with aldehydes was first reported by Midland,[3] although it was recently reported that the cycloaddition is more efficient with a polymer-bound diene moiety.[4] We have examined the reaction of a series of Lewis acids with the ethyl analogue **1** of Brassard's diene as outlined in Scheme 1. With 1 equiv of diene, the cycloaddition reaction proceeds efficiently using 100 mol % diethylaluminum chloride or 5 mol % yitterbium triflate to give **2a** in 56 and 48% yield, respectively.

These results were then applied to a series of aldehydes and to cyclohexanone (entry **2f**) as outlined in Table 2. Under

---

[1] Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. Danishefsky, S. J.; Biolodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

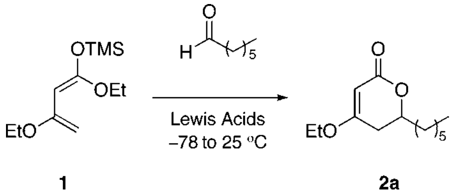
[2] Voight, E. A.; Roethle, P. A.; Burke, S. D. *J. Org. Chem.* **2004**, *69*, 4534. Henryon, V.; Liu, L. W.; Lopez, R.; Prunet, J.; Ferezou, J.-P. *Synthesis* **2001**, 2401. Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830. Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688. For oxidative cyclization of the *β*-hydroxyeneone, see: Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91.

[3] Midland, M. M.; Graham, R. S. *J. Am. Chem. Soc.* **1984**, *106*, 4294.

[4] Pierres, C.; George, P.; Hijfte, L.; Ducep, J.-B.; Hilbert, M.; Mann, A. *Tetrahedron Lett.* **2003**, *44*, 3645.

10.1021/ol050702z CCC: $30.25

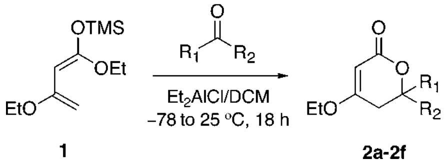
**Table 1.** Hetero Diels−Alder Reactions of Brassard's Diene **1** with *n*-Heptaldehyde in the Presence of a Lewis Acid



| entry | Lewis acid (mol %) | reaction time (h) | yield (%) |
|---|---|---|---|
| 1 | $Ti(i\text{-}PrO)_4$ (100) | 18 | 2 |
| 2 | $BF_3{\cdot}OEt_2$ (100) | 18 | 7 |
| 3 | $ZnCl_2$ (100) | 18 | 11 |
| 4 | $Et_2AlCl$ (100) | 18 | 56 |
| 5 | $Yb(OTf)_3$ (5) | 48 | 48 |
| 6 | $Sc(OTf)_3$ (5) | 48 | 3 |
| 7 | $In(OTf)_3$ (5) | 48 | 8 |

our optimized conditions, 2.5 equiv of the diene **1** was necessary to give the cycloadducts, **2a**−**f**, in good to excellent yields. These results indicate that diethylaluminum chloride efficiently mediates the cycloaddition of carbonyl dienophiles with Brassard's diene **1**.

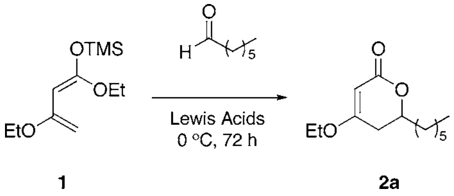
**Table 2.** Hetero Diels−Alder Reactions of Brassard's Diene **1** with Carbonyl Dienophiles



| entry | R¹ | R² | yield (%) |
|---|---|---|---|
| **2a** | H | $(CH_2)_5CH_3$ | 68 |
| **2b** | H | Ph | 79 |
| **2c** | H | *c*-Hexyl | 83 |
| **2d** | H | *t*-Bu | 96 |
| **2e** | H | $CH_2CH_2OBn(CH_2)_5CH_3$ | 33 |
| **2f** | $-CH_2(CH_2)_3CH_2-$ | | 97 |

Feng and Zhang recently reported the reaction of Brassard's diene **1** with aldehydes to give dihydropyranones mediated by the use of a tridentate titanium catalyst with high enantioselectivities.[5] We examined a series of chiral catalysts for the cycloaddition as shown in Table 3. While Feng's catalyst gives very high enantiomeric excess with aromatic aldehydes as reported, the analogous reaction of aliphatic aldehydes proceeds in low yield with poor enantiocontrol (entry 1). We have also found that the Jacobsen catalyst, which mediates the reaction of furan nucleophiles with aldehydes with very high enantioselectivity,[6] leads to modest selectivity in this system. Similarly, the use of lanthanide catalysts (entry 2) proved to be unsuccessful. The control of the absolute stereochemistry of the reaction remains an unsolved problem.

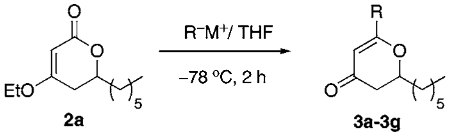
**Table 3.** Hetero Diels−Alder Reactions of Brassard Diene **1** with *n*-Heptaldehyde in the Presence of Chiral Lewis Acids

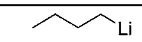
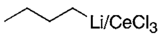
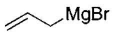
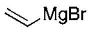
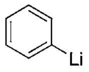
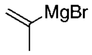
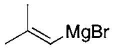
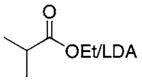


| entry | Lewis acid (mol %) | yield (%) | ee (%) |
|---|---|---|---|
| 1 | Feng's catalyst (10) | 14 | 8.0 |
| 2 | (+)-Eu$(hfc)_3$ (5) | 39 | 6.5 |
| 3 | Jacobsen's catalyst (1.5) | 14 | 4.5 |

Stork has described the utility of vinylogous esters for the synthesis of β-substituted cyclohexenones via nucleophilic addition and acid rearrangement.[7] We reasoned that the analogous reaction of vinylogous carbonate **2a** could lead to a general approach to the synthesis of dihydropyranones **3a**−**g**. In contrast to the results of Anand[8] and Firth[9], who reported that reactions of vinylogous carbonates with excess of Grignard reagents lead to ring opened double addition products, we find that, at low temperature, the monoaddition of diverse nucleophiles occurs to generate the requisite dihydropyranones (Table 4).

**Table 4.** Preparation of 2,3-Dihydro-4*H*-pyran-4-ones from Nucleophilic Addition to 3-Ethoxy α,β-Unsaturated Lactone



| entry | R⁻M⁺ | yield(%) |
|---|---|---|
| 3a |  | 52 |
| 3a |  | 63 |
| 3b |  | 78 |
| 3c |  | 41 |
| 3d |  | 80 |
| 3e |  | 52 |
| 3f |  | 52 |
| 3g |  | 92 |

We have now demonstrated that coupling the hetero Diels−Alder reaction of Brassard's diene and aldehydes with nucleophilic addition to the resulting vinylogous carbonate

---

[5] Fan, Q.; Lin, L.; Liu, J.; Huang, Y.; Feng, X.; Zhang, G. *Org. Lett.* **2004**, *6*, 2185.

leads to a general approach to the synthesis of dihydropyranones. The application of this methodology to the synthesis of dihydropyranone-containing natural products is currently underway in our laboratory, and our results will be reported in due course.

**Acknowledgment.** We would like to thank the National Institutes of Health (GM065941), GlaxoSmithKline, and Amgen for their generous support of this program.

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

OL050702Z

---

(6) Winkler, J. D.; Oh, K.; Asselin, S. M. *Org. Lett.* **2005**, *7*, 387. Also see Supporting Information.

(7) Stork, G.; Danheiser, R. *J. Org. Chem.* **1973**, *38*, 1775.

(8) Anand, R. C.; Ranjan, H. *Indian J. Chem., Sect. B* **1985**, *24B*, 560.

(9) Firth, J. W.; Livingstone, R. *J. Chem. Res., Miniprint*. **2000**, *7*, 308.