ORGANIC LETTERS

2013
Vol. 15, No. 23
5974–5977

# 2-Methylenetetrahydropyrans: Efficient Partners in the Carbonyl Ene Reaction

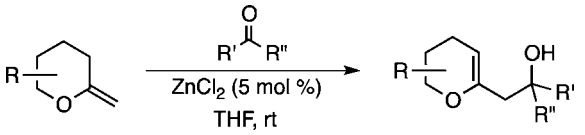
**Guohua Liang, Dakin T. Sharum, Troy Lam, and Nancy I. Totah***

*Department of Chemistry, Syracuse University, Syracuse, New York 13244, United States*

*ntotah@syr.edu*

**Received October 2, 2013**

## ABSTRACT




**The carbonyl ene reaction of 2-methylenetetrahydropyrans provides a rapid, high yielding route for the preparation of $\beta$-hydroxydihydropyrans under mild conditions. This process provides a new entry for the synthesis of 2-substituted tetrahydropyrans and for the direct introduction of oxygen heterocycles into molecular frameworks.**

Exocyclic enol ethers are useful intermediates in organic synthesis. Much effort has been concentrated on the functionalization of the native double bond by the addition of electrophilic reagents, by reduction, and by the addition of heteroatom nucleophiles to the anomeric position.[1] The use of these substrates in carbon−carbon bond forming processes has largely focused on their use in hydroboration/*B*-alkyl Suzuki sequences[2] and cycloaddition reactions.[3] Less well developed is the direct use of exocyclic enol ethers in carbon−carbon bond forming reactions that extend the carbon chain from the olefin terminus. While this alkene has been used as both a radical acceptor[4] and as a nucleophile,[5] such reactions typically proceed in low yields, show very specific substrate requirements, and/or are otherwise limited in scope.

The development of methods that capitalize on the inherent reactivity of these substrates provides a mechanism for the direct incorporation of oxygen heterocycles into complex molecular frameworks. Along these lines, our interest in the synthesis of tetrahydropyran containing natural products led us to consider the carbonyl ene reactions of 2-methylenetetrahydropyrans. These compounds are readily available *via* methylenation of the corresponding lactone[6] or by dehydrohalogenation of a suitably functionalized tetrahydropyran.[7] While acyclic enol ethers have been used effectively in carbonyl-ene processes,[8] prior use of exocyclic enol ethers in ene reactions

(1) For general reviews, see: (a) Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263. (b) C.-H. Lin, C.-H.; Lin, H.-C.; Yang, W.-B. *Curr. Top. Med. Chem.* **2005**, *5*, 1431.

(2) (a) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856. (b) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027. (c) Sasaki, M.; Fuwa, H. *Synlett* **2004**, 1851 and references therein. (d) Ciblat, S.; Kim, J.; Stewart, C. A.; Wang, J.; Forgione, P.; Clyne, D.; Paquette, L. A. *Org. Lett.* **2007**, *9*, 719.

(3) For selected examples, see: Hetero Diels−Alder: (a) Ireland, R. E.; Haebich, D. *Chem. Ber.* **1981**, *114*, 1418. (b) Hayes, P.; Maignan, C. *Synlett* **1994**, 409. (c) Tietza, L. F.; Schneider, G.; Wolfling, J.; Nobel, T.; Wulff, C.; Christian, I.; Rubeling, I. *Angew. Chem., Int. Ed.* **1998**, *37*, 2469. (d) Gallos, J. K.; Sarli, V. C.; Stathakis, C. I.; Koftis, T. V.; Nachmia, V. R.; Coutouli-Argyropoulou, E. *Tetrahedron* **2002**, *58*, 9351. (e) Zhou, G.; Zheng, D.; Da, S.; Xie, Z.; Li, Y. *Tetrahedron Lett.* **2006**, *47*, 3349. Intramolecular Diels−Alder: (f) Wender, P. A.; Keenan, R. M.; Lee, H. Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390. 1,3-Dipolar cycloaddition: (g) Gallos, J. K.; Koftis, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 415. (h) Colinas, P. A.; Jager, V.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2003**, *44*, 1071. (i) Li, X.; Takahashi, H.; Hideyo, O.; Ikegami, S. *Tetrahedron Lett.* **2004**, *45*, 4123. (j) Enderlin, G.; Taillefumier, C.; Didierjean, C.; Chapleur, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 2459. (k) Zhang, P.-Z.; Li, X.-L.; Chen, H.; Li, Y.-N.; Wang, R. *Tetrahedron Lett.* **2007**, *48*, 7813. [3 + 2] Cycloaddition: (l) Mellor, J. M.; Mohammed, S. *Tetrahedron Lett.* **1991**, *32*, 7107. (m) Lindsey, C. C.; Wu, K. L.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2385.

(4) (a) Motherwell, W. B.; Ross, B. C.; Tozer, M. J. *Synlett* **1989**, 68. (b) Myers, A. G.; Gin, D. Y.; Widdowson, K. L. *J. Am. Chem. Soc.* **1991**, *113*, 9661. (c) Cipolla, L.; Liguori, L.; Nicotra, F.; Torri, G.; Vismara, E. *Chem. Commun.* **1996**, 1253. (d) Dang, H.-S.; Elsegood, M. R. J.; Kim, K.-M.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2061. (e) Vauzeilles, B.; Sinay, P. *Tetrahedron Lett.* **2001**, *42*, 7269.

(5) (a) Lay, L.; Nicota, F.; Panza, L.; Russo, G.; Caneva, E. *J. Org. Chem.* **1992**, *57*, 1304. (b) Liu, H.; Smoliakova, I. P.; Koikov, L. N. *Org. Lett.* **2002**, *4*, 3895. (c) Liang, G.; Bateman, L. J.; Totah, N. I. *Chem. Commun.* **2009**, 6457.

(6) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392. (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393.

(7) See, for example: (a) Prugh, J. D.; Stanley, C. S.; Deana, A. A.; Ramjit, H. G. *Tetrahedron Lett.* **1985**, *26*, 2947. (b) Prandi, J.; Beau, J. M. *Tetrahedron Lett.* **1989**, *30*, 4517. (c) Taillefumier, C.; Chapleur, Y. *Can. J. Chem.* **2000**, *78*, 708.

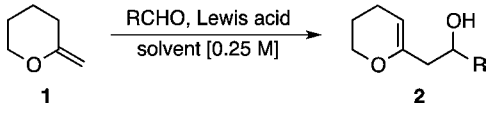
(8) (a) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. (b) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882. (c) Ruck, R. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 4771.

10.1021/ol402843s 
**Published on Web 11/11/2013**

are rare. Miles has reported the ene reaction of 2-methylene-2,3-dihydrofuran,[9] and Rizzacasa has observed the formation of an ene byproduct in the Lewis acid catalyzed Diels–Alder reaction of a functionalized exo glycal.[10]

Our goal in this endeavor was to develop an efficient, catalytic process that could be broadly applied. Central to this objective was the need to identify a Lewis acid that could effectively activate the aldehyde without premature isomerization of the exocyclic double bond. Toward this end, a variety of Lewis acids ($TiCl_4$, $AlCl_3$, $EtAlCl_2$, $SnCl_4$, $BF_3 \cdot OEt_2$, $ZnCl_2$) were screened in the carbonyl ene reaction of 2-methylenetetrahydropyran[11] (Scheme 1). These studies revealed that $ZnCl_2$ was best suited to this transformation with the desired ene adduct obtained cleanly in the presence of 1 equiv of $ZnCl_2$ in THF at room temperature.[12] Under these conditions, reaction of enol ether **1** with *p*-nitrobenzaldehyde gave the dihydropyran **2** (R = *p*-$NO_2C_6H_4$-) in 75% yield. Similar results were obtained when only 5 mol % of $ZnCl_2$ was used. No reaction occurred when the reaction was run in dichloromethane, likely due to the poor solubility of $ZnCl_2$ in this solvent.

**Scheme 1.** Ene Reaction of 2-Methylenetetrahydropyran




Further optimization was effected in the reactions of both 2-methylenetetrahydropyran **1** and 5,6-benzo-2-methylenetetrahydropyran **3** with ethyl glyoxylate (Table 1). Best results were obtained at concentrations of 0.5 M (entries 3, 5, 6) and upon minimization of reaction time (entries 3, 6).

Support for an ene-type mechanism comes from the reaction of 2-methylenetetrahydropyran **1** and *p*-nitrobenzaldehyde in the presence of excess $Et_3SiH$ (3 equiv). When a mixture of these components was treated with $ZnCl_2$ (1 equiv), only the ene adduct **2** was isolated (Scheme 2). None of the corresponding tetrahydropyran **6**, expected upon the intermediacy of an oxonium species, was observed. The dihydropyran **2** can be readily reduced to **6** in situ upon addition of catalytic $BF_3 \cdot OEt_2$. The same product **6** can be obtained after isolation of **2** and treatment with $BF_3 \cdot OEt_2$ in the presence of $Et_3SiH$.

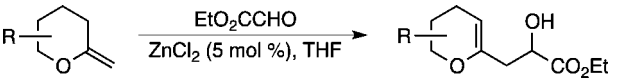
(9) In this case, developing aromaticity helps to drive the reaction forward. See: Miles, W. H.; Dethoff, E. A.; Tuson, H. H.; Ulas, G. *J. Org. Chem.* **2005**, *70*, 2862.

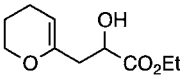
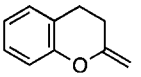
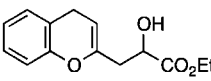
(10) (a) El Sous, M.; Ganame, D.; Tregloan, P. A.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 3001. (b) El Sous, M.; Ganame, D.; Tregloan, P.; Rizzacasa, M. A. *Synthesis* **2010**, 3954.

(11) Neokosmidi, A.; Ragoussis, V.; Evangelatos, G. *J. Agric. Food Chem.* **2004**, *52*, 4368.

(12) When stronger Lewis acids were utilized, complex reaction mixtures, competing isomerization of the exocyclic enol ether, and elimination of the alcohol in the β-hydroxydihydropyran product were observed.

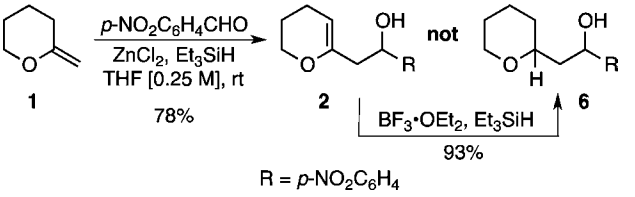
**Table 1.** Reaction of 2-Methylenetetrahydropyrans with Ethyl Glyoxylate[a]




| entry | enol ether | [M] | time | product | yield |
|---|---|---|---|---|---|
| 1 |  | 0.25 | 3 h |  | 79% |
| 2 | | 0.25 | 2 h | | 87% |
| 3 | **1** | 0.5 | 2 h | **4** | 92% |
| 4 |  | 0.1 | 24 h |  | 59% |
| 5 | | 0.5 | 24 h | | 74% |
| 6 | **3** | 0.5 | 1 h | **5** | 91% |

[a] A 1:1.2 ratio of enol ether to ethyl glyoxylate was used.

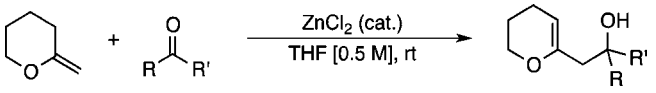
**Scheme 2.** Attempted Oxonium Ion Trap

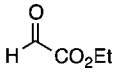
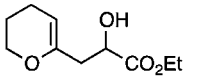
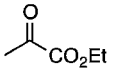
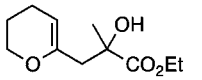
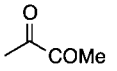
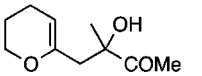
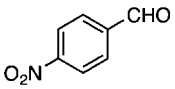
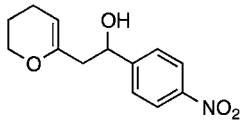
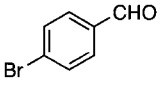
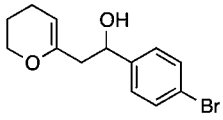
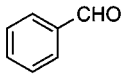
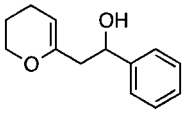
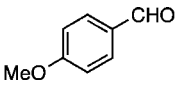
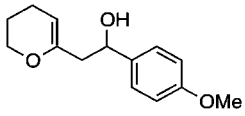
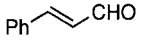
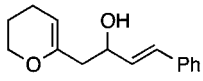
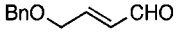
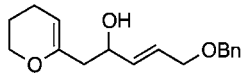
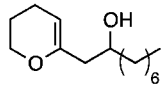
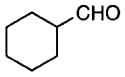
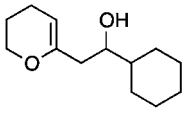
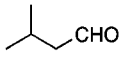
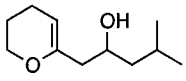



In order to assess the scope of carbonyl substrates, the ene reaction of 2-methylenetetrahydropyran **1** was further evaluated (Table 2). Reactions were carried out in THF at room temperature using a slight excess of the carbonyl derivative in the presence of catalytic $ZnCl_2$. As shown, both ethyl glyoxylate **7** and ethyl pyruvate **8** react readily under these conditions providing excellent yields of the corresponding ene adducts (entries 1–2). Despite a similar electronic advantage, the reaction of 2,3-butanedione **9** proceeded in a slightly lower yield, 59%, perhaps due to competing polymerization of the diketone over the longer reaction time.[13] Best results were obtained in the presence of 0.2 equiv of $ZnCl_2$ (entry 3). No added benefit in yield was observed with increasing concentration or upon extending the reaction time further. With aromatic substrates, the electronic nature of the aldehyde had a significant influence on the rate of the reaction, with electron poor substrates reacting more readily than those that were electron rich (entries 4–7). In cases where less highly activated aldehydes were used (entries 6–7), yields could be enhanced by increasing the amount of $ZnCl_2$ to 20 mol %. For example, dihydropyran **23** is formed in 84% yield when 5 mol % $ZnCl_2$ is used, but in 93%

(13) (a) Shapiro, R.; Hachmann, J.; Wahl, R. *J. Org. Chem.* **1966**, *31*, 2710. (b) Baldenius, K.; Dallman, P.; Hudec, J. *Tetrahedron Lett.* **1993**, *34*, 1517.

**Table 2.** Reaction of 2-Methylenetetrahydropyran with Aldehydes and Ketones

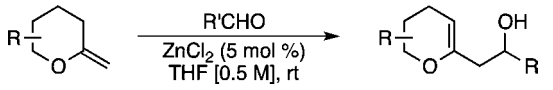


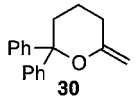
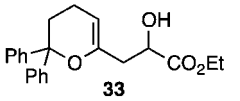
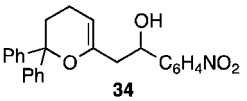
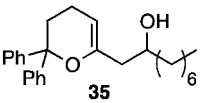
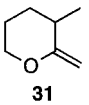
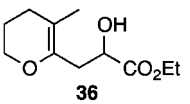
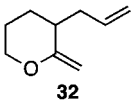
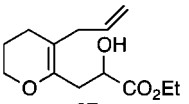
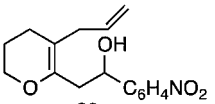
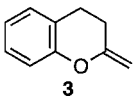
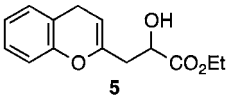

| entry | carbonyl compound | | time | $ZnCl_2$ | product | | yield |
|---|---|---|---|---|---|---|---|
| 1 |  | **7** | 2 h | 5 mol % |  | **4** | 92% |
| 2 |  | **8** | 15 h | 5 mol % |  | **19** | 90% |
| 3 |  | **9** | 8 h | 20 mol % |  | **20** | 69% |
| 4 |  | **10** | 2 h | 5 mol % |  | **21** | 90% |
| 5 |  | **11** | 10 h | 5 mol % |  | **22** | 94% |
| 6 |  | **12** | 24 h | 20 mol % |  | **23** | 93% |
| 7 |  | **13** | 24 h | 20 mol % |  | **24** | 95% |
| 8 |  | **14** | 24 h | 20 mol % |  | **25** | 75% |
| 9 |  | **15** | 24 h | 20 mol % |  | **26** | 76% |
| 10 |  | **16** | 12 h | 5 mol % |  | **27** | 93% |
| 11 |  | **17** | 24 h | 5 mol % |  | **28** | 85% |
| 12 |  | **18** | 18 h | 20 mol % |  | **29** | 81% |

yield at the higher catalyst loading. A similar increase in yield is seen in the reaction of *p*-methoxybenzaldehyde **13**. α,β-Unsaturated aldehydes showed levels of reactivity similar to that of the electron rich aromatic aldehydes (entries 8−9). Aliphatic aldehydes were also found to be suitable partners in this carbonyl ene reaction (entries 10−12). Efficient reaction was observed with both the sterically unencumbered octanal **16** as well as with more hindered aldehydes **17** and **18** that show branching at the α- and β-positions, respectively. The endocyclic enol ethers prepared by this method do not participate further in the ene reaction, nor does ene reaction of the endocyclic isomer of **1** occur. Several additional exocyclic enol ethers were prepared and evaluated for efficacy in the carbonyl ene reaction (Table 3). Under the optimized conditions identified above, reaction of these substrates with aldehydes occurs cleanly and in excellent yield. As shown, both 6,6-disubstituted (entries 1−3) and 3-substituted (entries 4−5) exocyclic enol ethers participate readily in the reaction as does the corresponding dihydrocoumarin derivative **3**.

(14) Ruck, R. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 4771.

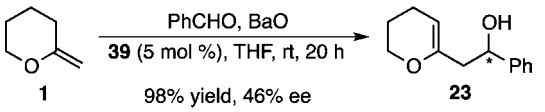
**Table 3.** Ene Reaction of Other 2-Methylenetetrahydropyrans

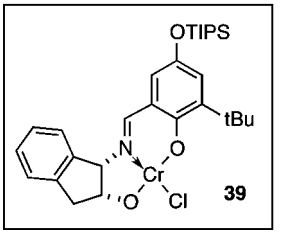



| entry | enol ether | R'CHO | time | product | yield |
|---|---|---|---|---|---|
| 1 |  **30** | **7** | 1 h |  **33** | 90% |
| 2 | **30** | **10** | 6 h |  **34** | 99% |
| 3 | **30** | **16** | 12 h |  **35** | 91% |
| 4 |  **31** | **7** | 1 h |  **36** | 97% |
| 5 |  **32** | **7** | 12 h |  **37** | 93% |
| 6 | **32** | **10** | 24 h |  **38** | 95% |
| 7 |  **3** | **7** | 1 h |  **5** | 91% |

The potential of using a chiral Lewis acid to effect this transformation was also explored. In preliminary investigations, we found that the chromium(III)-salen derivative **39**[14] effectively catalyzes the reaction of 2-methylenetetrahydropyran **1** with benzaldehyde to give the desired ene adduct **23** in excellent yield and with moderate enantioselectivity (Scheme 3). These findings provide impetus for the further optimization of this reaction in the interest of developing an catalytic asymmetric protocol.

**Scheme 3.** Enantioselective Reaction: Preliminary Findings




In conclusion, we have demonstrated the utility of 2-methylenetetrahydropyrans as participants in the carbonyl ene reaction with aldehydes and activated ketones. These reactions proceed in high yield under mild conditions using essentially equimolar amounts of ene and enophile components in the presence of catalytic $ZnCl_2$. Early studies toward the development of an enantioselective protocol show promising results. This methodology expands the scope of the ene reaction for the synthesis of substituted dihydropyrans. The resulting $\beta$-hydroxydihydropyrans will be useful intermediates for the synthesis of functionalized tetrahydropyrans, as both hydroxyl and alkene functions can serve as sites for further manipulation. This method may also facilitate the direct incorporation of these oxygen heterocycles into complex molecular frameworks. Application of this chemistry to natural product synthesis is currently ongoing as are efforts to optimize an enantioselective version of this reaction. The results of these studies will be reported in due course.

**Acknowledgment.** Support from the National Institutes of Health (R01 GM064357) and National Science Foundation (CHE 1112370) is gratefully acknowledged.

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

The authors declare no competing financial interest.