ORGANIC LETTERS

2005
Vol. 7, No. 3
515−517

A Cyclopropane Fragmentation Approach to Heterocycle Assembly: A Convergent Synthesis of Oxepanes

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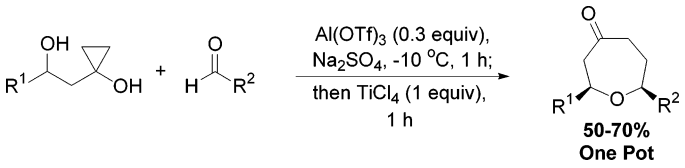
Received December 15, 2004

ABSTRACT

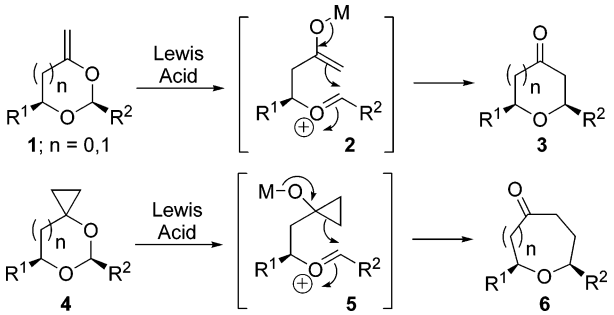


A cyclopropanol fragmentation approach to the synthesis of oxepanes has been developed. This convergent strategy condenses cyclopropyl diols with aldehydes to form an acetal, which is subsequently rearranged to furnish a keto-oxepane. The reaction has been developed as a one-pot procedure, utilizing sequential addition of $Al(OTf)_3$ and $TiCl_4$. Yields range from 50 to 70% for the sequence. A Zimmerman−Traxler transition state disposing substituents in equatorial positions is consistent with the observed formation of strictly cis products.

Cyclopropanes and their hydroxy-substituted analogues are among the most reactive and versatile of hydrocarbon frameworks.[1] The use of cyclopropanols in synthetic methodology has increased since the advent of the Kulinkovich reaction,[2] which converts an ester directly to a cyclopropanol. When exposed to a suitable electrophile, the cyclopropanol substructure reacts as a homoenol, which has led to a host of synthetic applications. Although the fragmentation of cyclopropanols in ring formation events is well precedented,[1] their use in heterocycle formation has not been explored to our knowledge. Herein, we disclose a route to the synthesis of oxepanes via a cyclopropanol fragmentation strategy, forging a new bond to an in situ-generated oxocarbenium species.

The work herein employs cyclopropanols to extend the Petasis−Ferrier rearrangement, developed by Petasis in 1995[3] and later updated by Smith[4] (**1** → **3**, Scheme 1), to provide stereocontrolled access to medium-sized rings. Accordingly, homologation of alkene **1** to cyclopropane **4** promises to furnish a heterocycle of larger ring size such as **6**. The proposed transition state for the cyclization of **5** would mimic **2**, which has led to high levels of stereoselectivity.[3,4] As in

Scheme 1. Petasis−Ferrier Rearrangement (**1** → **3**) and Proposed Rearrangement (**4** → **6**)



(1) (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

(2) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A.; Prityts kaya, T. S. *J. Org. Chem. USSR (Engl. Transl.)* **1989**, *25*, 2027. (b) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789.

(3) (a) Petasis, N. A.; Lu, S.-P. *J. Am. Chem. Soc.* **1995**, *117*, 6394. (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141.

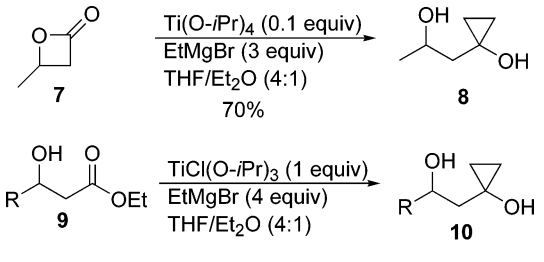
(4) (a) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913. (c) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942.

10.1021/ol047426t CCC: $30.25
Published on Web 01/13/2005

the Petasis−Ferrier reaction, ideally the conversion of **4** to **6** would not be limited in terms of ring size or heteroatom.

Our investigations began with the requisite cyclopropyl diol preparations. Exploiting the Kulinkovich protocol (Scheme 2) permitted access to cyclopropyl diol **8**[5] via β-butyrolactone **7**. For convenience, additional cyclopropyl diol substrates **10a** and **10b** were prepared from readily available β-hydroxy esters **9a** (R = isopropyl) and **9b** (R = propyl)[6] without hydroxyl protection. This is possible employing a modified cyclopropanation procedure developed by Cha, utilizing $TiCl(O\text{-}iPr)_3$.[7]

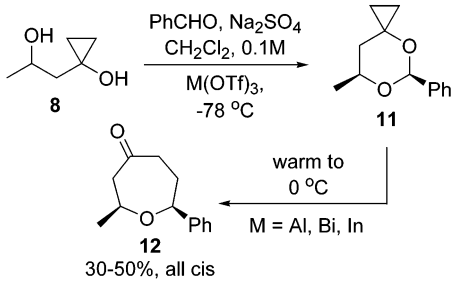
Scheme 2. Cyclopropyl Diol Preparation



R	Yield
$CH(CH_3)_2$ (**10a**)	51%
$(CH_2)_2CH_3$ (**10b**)	51%

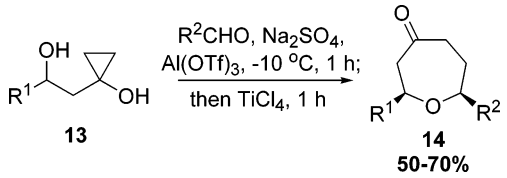
To explore the intended cyclization, cyclopropyl diol **8** was exposed to benzaldehyde in the presence of a Lewis acid and a drying agent (Scheme 3). To our delight, a variety of metal triflates [$Al(OTf)_3$, $Bi(OTf)_3$, $In(OTf)_3$] effected sequential formation of acetal **11**, as indicated by TLC, and then the rearranged product (**12**, 0 °C, 6 h).[8] Although the yields were modest with these conditions (30−50%), strictly the cis-fused isomer of **12** was observed.[9]

Scheme 3. Single Lewis Acid Promotion of Rearrangement



While successful with benzaldehyde, our initial conditions failed to effect rearrangement of aliphatic aldehydes. However, exposure of the preformed acetal to $TiCl_4$ did effect rapid, clean heterocycle formation with a number of aldehydes. This has led us to an improved procedure, in which acetal formation is first catalyzed by $Al(OTf)_3$, and then $TiCl_4$ (0.9−1.0 equiv) is added to the reaction to furnish the rearranged heterocycle (Scheme 4). No adverse effect was noted from the presence of two Lewis acids, as compared to isolation of the acetal and reexposure to $TiCl_4$. Although $Al(OTf)_3$ effects acetal formation in catalytic quantities (0.3 equiv), using similar amounts of $TiCl_4$ results in a lower yield of oxepanes. To date, this convenient protocol has led to yields in the 50−70% range for the entire condensation/rearrangement sequence. It is important to note that only the *cis*-oxepane is observed under these conditions.[10,11]

Scheme 4. Sequential Lewis Acid Promotion of Rearrangement



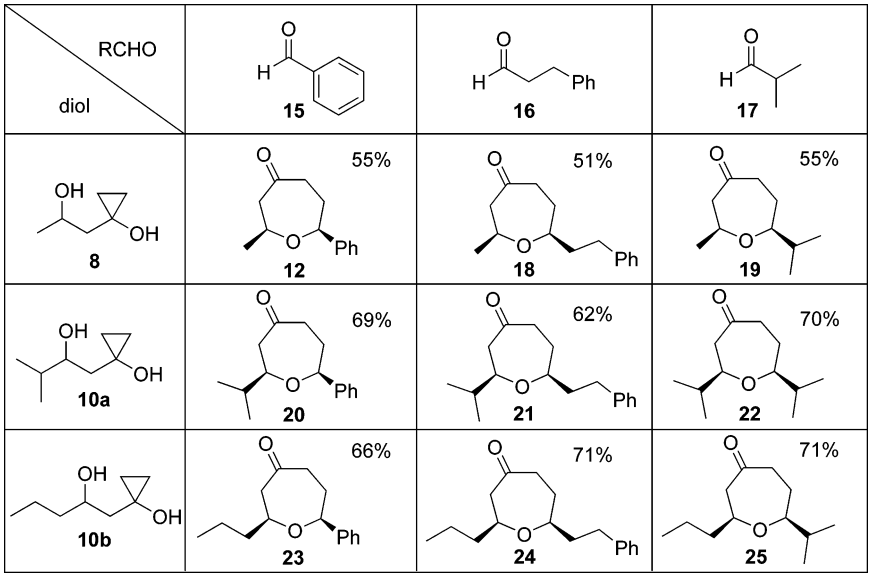
Examples of this reaction are shown in Scheme 5, illustrating combinations of aldehyde and diol, as well as the resulting heterocycle.

The production of a keto-oxepane supports a mechanism analogous to the Petasis−Ferrier reaction, as shown in Scheme 6. Accordingly, condensation of the cyclopropyl diol (**8**) with an aldehyde furnished acetal **26** as a relatively stable intermediate. Subsequent Lewis acid activation of the acetal presumably generates an oxonium species (**28**), which is attacked by the pendant alkoxy cyclopropane, acting as a homoenolate, to furnish the target heterocycle. Acetal **26** has two oxygen atoms available for Lewis acid complexation. However, only one of these sites can lead to productive ring opening and recombination to afford the keto-heterocycle. Complexation at oxygen is expected to be reversible, while the formation of the heterocycle represents an irreversible final step. This mechanism is consistent with our inability to form an oxepane from diol **30**. In this case, oxocarbenium formation can lead to aldehyde loss and formation of benzylic cation **33**. As a result, spiro compound **34** was the major product recovered (69%).[12]

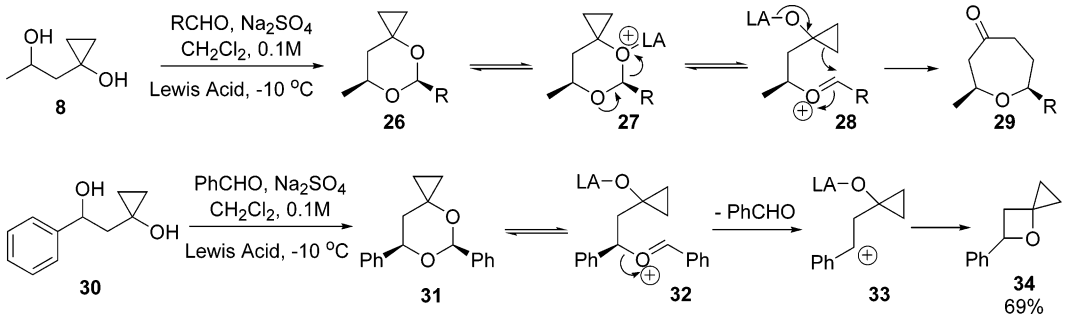
The recovery of a cis-fused oxepane in all cases suggests that, in the transition state of cyclization, a chair conformation was adopted wherein both R groups are disposed in an equatorial fashion (Scheme 7, structure **35**). This conforms

(5) Esposito, A.; Taddei, M. *J. Org. Chem.* **2000**, *65*, 9245.
(6) Ethyl 3-hydroxy hexanoate (**9b**) is commercially available; **9a** was prepared by the reduction of ethyl isobutyryl acetate ($NaBH_4$).
(7) Cho, S. Y.; Cha, J. K. *Org. Lett.* **2000**, *2*, 1337.
(8) A number of softer Lewis acids ($CuSO_4$, $ZnCl_2$, $SnCl_2$) effected formation of acetal **11**, though no further reaction was observed.
(9) Cis relative stereochemistry of both **11** and **12** was confirmed by one-dimensional NOE analysis. In both cases, irradiation of the benzylic proton led to significant enhancement (~10%) of the other carbinol proton resonance.
(10) Excess $TiCl_4$ effected epimerization at the benzylic position when benzaldehyde was employed (R^2 = Ph).
(11) Deliberate addition of triflic acid did not effect condensation or rearrangement.
(12) Spiro compound **34** was not observed in the absence of an aldehyde.
(13) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

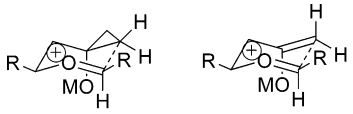
Scheme 5. Yields of Prepared Keto-oxepanes



Scheme 6. Proposed Mechanism of Rearrangement



Scheme 7. Proposed Conformation of Cyclization



with both the Zimmerman−Traxler model[13] as well as the transition state (**36**) invoked by Petasis.[3b]

Overall, we have developed a convergent, one-pot synthesis of oxepanes from readily available cyclopropyl diols and aldehydes. The extension of this reaction to other heteroatoms and ring sizes is currently being pursued.

Acknowledgment. This study was supported by James Madison University and Research Corporation (Cottrell College Science Award, #CC5970). K.E.O. acknowledges a GlaxoSmithKline Undergraduate Summer Research Fellowship Award. Mass spectrometry was performed at the Nebraska Center for Mass Spectrometry.

Supporting Information Available: Experimental procedure and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047426T