The Synthesis of Cyclic Enol Ethers via Molybdenum Alkylidene-Catalyzed Ring-Closing Metathesis†

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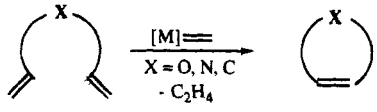
Summary: An efficient method for the construction of five- and six-membered cyclic vinyl ethers from unsaturated esters using stoichiometric titanium reagents to convert the esters to acyclic olefinic enol ethers which are then transformed to the desired products by catalytic ring-closing olefin metathesis with a molybdenum alkylidene complex is described.

Since cyclic enol ethers are often found in a number of bioactive compounds,[1] the development of efficient methods for their construction has been an important goal of organic synthesis. We recently reported the synthesis of carbocycles and heterocycles by ring-closing metathesis of functionalized dienes catalyzed by well-defined transition metal alkylidenes (eq 1)[2] as well as the stoichiometric



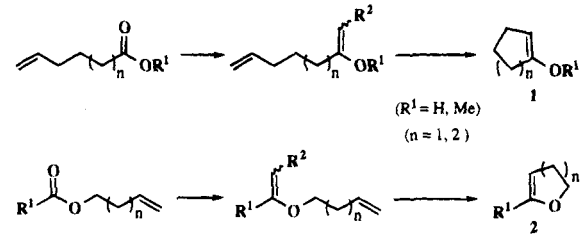
(1)

ring closure of olefinic esters to cyclic enol ethers.[2c,3]

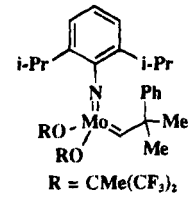
In this paper we report that acyclic olefinic enol ethers easily derived from olefinic esters can be cyclized by catalytic ring-closing metathesis to a variety of cyclic enol ethers. As shown in Scheme 1, the first step is the transformation of readily available olefinic esters into acyclic olefinic enol ethers followed by the cyclization via ring-closing olefin metathesis to give the desired cyclic enol ethers (carbocyclic **1** and heterocyclic **2**).

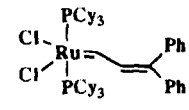
Since there are several known methods which transform esters into enol ethers,[4] we focused on the ring-closing olefin metathesis reaction. Because enol ethers are very sensitive to acid,[5] the well-defined transition

Scheme 1



metal alkylidene catalysts such as **3**[6,7] and **4**[8] which show low Lewis acidity were used in these studies.





Treatment of acyclic olefinic enol ethers with a catalytic amount of **3** (5–12 mol %) cleanly afforded the corresponding cyclic enol ethers (Table 1),[9] five- and six-membered carbocycles (entries 1–3), and oxygen heterocycles (entries 4, 5). The 2-substituted benzofurans[10] which are commonly found in natural products (entries 6, 7) could also be prepared by this procedure.[11] Ruthenium complex **4** did not catalyze the ring-closing me-

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(1) For leading references, see: (a) *Comprehensive Heterocyclic Chemistry*; Meth-Cohn, O., Ed.; Pergamon: New York, 1984. (b) *Carbocycle Construction in Terpene Synthesis*; Ho, T.-L., Ed.; VCH: New York, 1988.

(2) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5462. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3880. (d) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

(3) Preliminary studies in our group on the synthesis of cyclic enol ethers from acyclic olefinic esters were carried out using the tungsten alkylidene complex [W(CHCMe$_3$)(NAr)(OCMe(CF$_3$)$_2$)$_2$, Ar = 2,6-(iPr)$_2$C$_6$H$_3$]. This process required the use of stoichiometric amounts of the expensive and hard to synthesize tungsten alkylidene. The molybdenum alkylidene **3** is relatively easier to prepare.

(4) (a) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. (c) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(5) The high Lewis acidity of classical catalysts (e.g., WCl$_6$ + EtAlCl$_2$) prohibits their use in this reaction.

(6) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378. (c) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.

(7) Catalyst **3** is both air and moisture sensitive. The less reactive *tert*-butoxy analog is commercially available from Strem Chemicals, Inc., 7 Mulliken Way, Newburyport, MA.

(8) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.

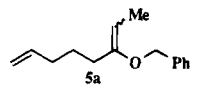
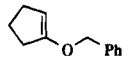
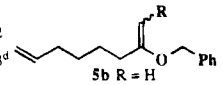
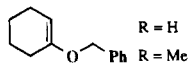
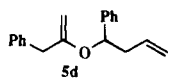
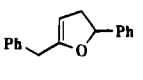
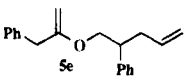
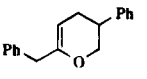
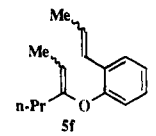
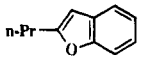
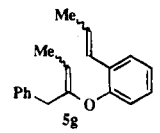
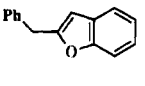
(9) Typical experimental procedure (Table 1, entry 5): The acyclic olefinic enol ether (69 mg, 0.25 mmol) was added to a homogeneous yellow solution of **3** (23 mg, 0.03 mmol) in 5 mL of dry *n*-pentane under argon. The resulting mixture was stirred at 20 °C for 3.5 h, at which time TLC showed the reaction to be complete. The reaction mixture was opened to the air and stirred for 15 min before it was concentrated. Flash chromatography (basic alumina, activity III, hexane/Et$_3$N = 100/1) yielded 52 mg (84%) of the cyclic enol ether as a colorless oil. Note: The presence of impurities in the starting reaction mixture inhibits the reaction.

(10) In the case of the benzofuran synthesis, *n*-hexane was used as the solvent since a higher temperature was required for complete reaction. Silica gel was used for purification.

(11) For example, see the following: (a) *The Chemistry of Heterocyclic Compounds Vol. 29, Benzofurans*; Mustafa, A., Ed.; John Wiley & Sons: New York, 1974. (b) *The Chemistry of Natural Products*; Thomson, R. H., Blackie: London, 1985.

0022-3263/94/1959-4029$04.50/0

Table 1. Catalytic Ring-Closing Metathesis of Acyclic Olefinic Enol Ethers[a]

entry	substrate	product	time (h)	Yield[b] (%)
1[c]	 5a		3.5	88
2	 5b R = H	 R = H	3.0	80
3[d]	5c R = Me	R = Me	4.0	84
4	 5d		2.0	81
5	 5e		3.5	84
6[e]	 5f		2.0	87
7[e]	 5g		7.0	87

[a] 12–13 mol % of **3**, *n*-pentane, 20 °C. [b] Isolated yield. [c] 6.0 mol % of **3** was used. [d] 5.6 mol % of **3** was used. [e] This reaction was run at 60 °C, *n*-hexane as solvent.

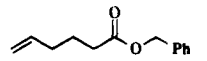
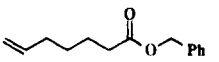
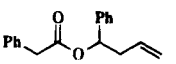
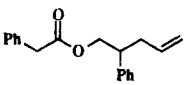
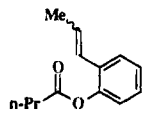
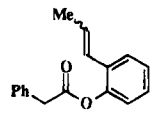
tathesis of acyclic enol ethers but slowly catalyzed the dimerization of the starting material.[12]

Acyclic olefinic enol ethers **5a–g** are synthesized in moderate to good yield from the corresponding olefinic esters by stoichiometric use of the titanium-based olefination reagents, such as the Utimoto–Takai protocol[4a] or Tebbe's reagent.[4b,13] These results are shown in Table 2.

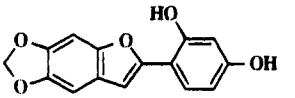
Combination of these two processes (ring-closing metathesis and olefination of ester carbonyls) provides a new synthetic strategy for the construction of cyclic enol ethers that uses easy to prepare complexes to carry out the stoichiometric conversion of the ester to an acyclic enol ether and saves the more difficult to prepare complex for the catalytic reaction. This procedure also provides an efficient method for the synthesis of a variety of 2-substituted benzofurans, since the required starting materials (2-propenylphenols) are also easily prepared from the appropriate phenols in three steps: allylation, Claisen rearrangement,[14] and olefin isomerization.[15]

In order to demonstrate an application of this process, we chose the naturally occurring benzofuran 2-(2′,4′-dihydroxyphenyl)-5,6-(methylenedioxy)benzofuran (**6**) (*Sophora* compound I), the antifungul phytoalexine isolated from aerial part of *Sophora tomentosa* L.[16] as a synthetic target.

Table 2. Transformation of Olefinic Esters into Olefinic Enol Ethers[a]

entry	substrate	product	method	time (h)	Yield[b] (%)
1		5a[c]	A	11	55
2		5b	A	11	80
			B	0.8	81
3		5c[c]	A	12	68
4		5d	A	13	71
			B	2	61
5		5e	B	1.5	78
6		5f[d]	A	5	88
7		5g[d]	A	5	79

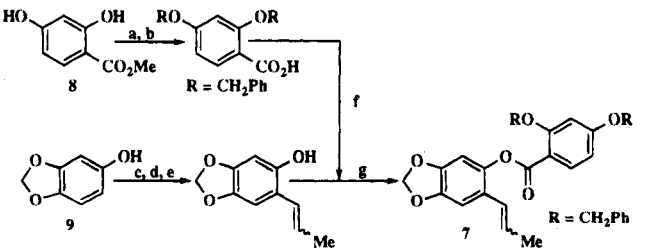
[a] Method A: $RCHBr_2$ (R = H, Me), $TiCl_4$, Zn, TMEDA, cat. $PbCl_2$, THF, 20 °C. Method B: $CpTiClAlMe_2$, toluene–THF, 60 °C. [b] Isolated yield. [c] *Z*/*E* mixture. [d] Mixture of 4 isomers.



6

The ester **7** was synthesized from commercially available methyl 2,4-dihydroxybenzoate **8** and sesamol **9** in several steps as shown in Scheme 2.

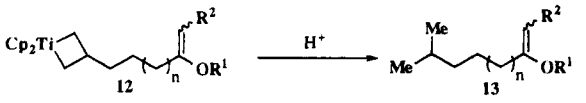
Scheme 2[a]



[a] Key: (a) $PhCH_2Br$, K_2CO_3/DMF, 60 °C, 20 h, quant; (b) KOH/MeOH–H_2O, 50 °C, 18 h, 90%; (c) allyl bromide, K_2CO_3/acetone, reflux, 15 h, 93%; (d) Δ/*N*,*N*-dimethylaniline, 190 °C, 2.5 h, 82%; (e) KOH/*n*-BuOH, reflux, 2 h, 85%, *E*/*Z* = 67/33; (f) $SOCl_2$, 60 °C, 45 min, quant; (g) Cat. *n*-Bu_4NHSO_4, NaOH/dioxane, rt 17 h + 60 °C 2 h, 70%.[17]

(12) Fujimura, O. Unpublished results. The ruthenium carbene formed by the reaction with the terminal olefin does not react with the vinyl ether. This may be due to steric hindrance at the enol ether or to unfavorable relative polarization of the carbene and vinyl ether.

(13) A higher temperature (60 °C) was required to avoid the formation of byproducts **13** which results from metallacycle **12**. **12** is relatively stable at lower temperature as described in the original paper.



12 **13**

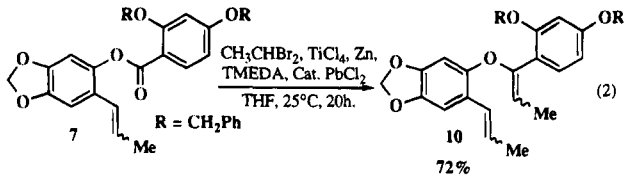
(14) Claisen rearrangement, see: Maruoka, K.; Sato, J.; Banno, H.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 377 and references cited therein.

(15) Base-promoted olefin isomerization, see: Hubert, A. J.; Reimlinger, H. *Synthesis* **1969**, 97.

(16) (a) McKittrick, B. A.; Scannell, R. T.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 3017. The overall yield of **6** was 8.0% from **8** and 7.7% from **9**. (b) Komatsu, M.; Yokoe, I.; Shirataki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 1274.

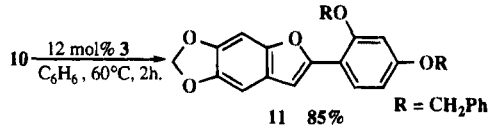
(17) Illi, V. O. *Tetrahedron Lett.* **1979**, 2431.

Olefination of the ester carbonyl gave the acyclic enol ether **10** (eq 2). Ring-closing metathesis of **10** yielded

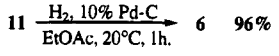


(2)

benzofuran **11**, a protected precursor for the *Sophora* compound I, in high yield (eq 3). Deprotection of **11** gavethe desired product **6** in high yield (eq 4). The overall yield from **8** is 33% and from **9** 29%.[16a]



(3)



(4)

Catalytic ring-closing metathesis of acyclic olefinic enol ethers combined with the olefination of ester carbonyls provides an efficient and versatile route to carbocyclic enol ethers and heterocycles including benzofurans. The application of metathesis to the synthesis of other natural products including asymmetric cyclization and improvements in the catalytic efficiency for this transformation are currently under investigation.

Acknowledgment. Support has been provided by the National Institutes of Health. Fellowship support for O.F. by the Ube Industries, Ltd., is gratefully acknowledged. O.F. thanks Dr. Z. Wu for helpful discussions.

Supplementary Material Available: Characterization data for all reaction products (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.