Titanium-Mediated Cyclizations of β-Keto Esters with Acetals: A Convenient Route to 2-Carbalkoxycycloalkenones

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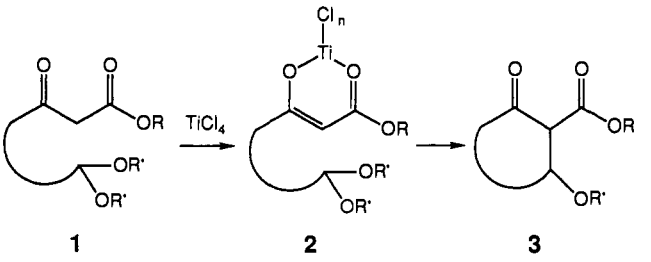
The preparation of both carbocycles and heterocycles by Lewis acid-mediated cyclization reactions of acetals[1] has become a well-documented synthetic strategy following the pioneering investigations of Johnson, who showed that acetals with appropriately positioned olefinic bonds undergo facile closure to mono- or polycyclic products.[2] More recently, extension of the Mukaiyama cross-aldol reaction ($TiCl_4$-promoted condensation of trimethylsilyl enol ethers with acetals)[3] to the intramolecular variant has been proven to be a viable method for the preparation of medium and large ring compounds.[4] It has not been determined whether these cyclizations take place simply by rapid capture of an oxonium ion by the nucleophilic silyl enol ether or via initial formation of a titanium enolate which undergoes subsequent closure, perhaps benefiting from chelation with the acetal functionality.[5,6]

Consequently, we decided to investigate terminating groups more prone to titanation which, in principle, could take advantage of the putative template effect. In view of the fact that Lehnert had shown that the titanium enolates of 1,3-dicarbonyl compounds undergo facile Knovenagel condensations with aldehydes,[7] we decided to examine the $TiCl_4$-promoted cyclizations of the readily available β-keto ester, acetals **1** (Scheme I).[8] Thus, we speculated that complexation of the β-keto ester functionality[9] of **1** by $TiCl_4$ would be competitive with respect to complexation to the acetal moiety. Subsequent enolization and attack of the Ti enolate at the acetal carbon (either complexed or in the form of an oxonium ion) would produce the cyclized β-keto ester **3**. Facile elimination of alcohol from **3** will then afford the corresponding 2-carbalkoxycycloalkenones. We report herein that this transformation is successful for a variety of carbocyclic and heterocyclic ring systems, including eight-membered rings.

Scheme I



The various substrates required for this investigation (Table I) were readily assembled by exploiting the numerous procedures available for the synthesis of β-keto esters, a noteworthy feature of this methodology.[10] For example, the substrates in entries **a–d** were prepared by alkylation of the dianion of ethyl acetoacetate with the corresponding ω-halo acetal according to the Weiler protocol.[10a] Substrates in entries **f** and **g** were prepared by interception of acetylketene with the respective hydroxy or amino acetal,[10b] while substrates in entries **h** and **i** were prepared by methoxycarbonylation of the corresponding keto acetals.[10c]

The cyclizations enumerated in Table I were performed by addition of $TiCl_4$ (1 equiv in CH_2Cl_2, 1.0 M) to a –40 °C solution of the β-keto ester in CH_2Cl_2 (0.5 M). The reactions were typically complete after 1 h, and the products were isolated by silica gel chromatography following an aqueous NH_4Cl quench.[11] Addition of amine bases (pyridine, NEt_3) following addition of the $TiCl_4$ to the reaction mixture gave no appreciable increase in yields. However, $SnCl_4$ proved to be a superior Lewis acid for the cyclization of the β-keto ester of entry **a**.[12]

Several comments are in order. The successful cyclization of the C(2)-substituted β-keto ester of entry **d** suggests that elimination of the alcohol from **3** is not a necessary driving force for these potentially reversible acid-catalyzed cyclizations. Interestingly, only a single diasteromer is obtained, whereas a 7:1 mixture of stereoisomers is produced using the analogous dimethyl acetal.[13] Although we have not examined the intermolecular variant of this reaction in as much detail, the double-Knovenagel

(1) For reviews, see: (a) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043. (b) Fleming, I. Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57.

(2) Johnson, W. S.; Kinnel, R. B. *J. Am. Chem. Soc.* **1966**, *88*, 3861.

(3) (a) Hayashi, M.; Mukaiyama, T. *Chem. Lett.* **1974**, 15. For a review, see: (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 263.

(4) (a) Alexakis, A.; Chapdelaine, M. J.; Posner, G. H.; Runquist, A. W. *Tetrahedron Lett.* **1978**, 4205. (b) Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219. (c) Issac, K.; Kocienski, P. *J. Chem. Soc., Chem. Commun.* **1982**, 460. (d) Cockerill, G. S.; Kocienski, P. *Ibid.* **1983**, 705. (e) Cockerill, G. S.; Kocienski, P.; Treadgold, R. *J. J. Chem. Soc., Perkin Trans. I* **1985**, 2101. (f) Kuwajima, I.; Furukawa, T.; Horiguchi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8277. (g) Kuwajima, I.; Horiguchi, Y.; Morihira, K.; Furukawa, T. *Tetrahedron* **1992**, *48*, 6975. (h) Linderman, R. J.; Viviani, F. G.; Kwochka, W. R. *Tetrahedron Lett.* **1992**, *33*, 3571.

(5) It should be noted, however, that the metathesis reaction of silyl enol ethers with $TiCl_4$ is slow at low temperatures (–80 °C), and therefore cyclization reactions performed at these temperatures most likely proceed via the oxonium ion pathway, see: (a) Kuwajima, I.; Horiguchi, Y.; Shimada, J.-I.; Nakamura, E. *Tetrahedron Lett.* **1983**, *24*, 3341. (b) Denmark, S. E.; Almstead, N. G. *Tetrahedron* **1992**, *48*, 5565.

(6) Recent work by other groups argues against the *necessity* of a template effect for efficient medium ring closure. For example, Trost has reported the preparation of an eight-membered carbocyclic ring in good yield by trimethylsilyl triflate-promoted cyclization of a substrate wherein a vinylcyclopropanol (protected as the silyl ether) is employed as the cyclization terminator, see: Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556. Moreover, Overman has shown that eight-membered cyclic ethers are obtained from $SnCl_4$-mediated cyclizations in moderate yields if a terminating group incapable of chelation (vinyl silane) is present, see: (a) Overman, L. E.; Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.

(7) (a) Lehnert, W. *Tetrahedron Lett.* **1970**, 4723. (b) Lehnert, W. *Tetrahedron* **1972**, *23*, 663. (c) Lehnert, W. *Ibid.* **1973**, *29*, 635. (d) Lehnert, W. *Synthesis* **1974**, 667. (e) Beckman, J. C.; Campaigne, E. *Ibid.* **1978**, 385.

(8) Part of this work has been reported previously: Funk, R. L.; Daily, W. J.; Olmstead, T. A.; Jellison, K. M. International Chemical Congress of Pacific Basis Societies, Honolulu, HI, Dec, 1989; Division of Organic Chemistry, Abstract 0010. During the course of this investigation, two papers of relevance to this work have appeared. Intermolecular titanium-mediated condensations of β-keto esters with cyclic acetals: Williams, R. M.; Esslinger, C. S. *Tetrahedron Lett.* **1991**, *32*, 3635. Generation of amide and ketone enolates by a modified Lehnert protocol ($TiCl_4$/amine) and subsequent reactions with ortho esters and acetals: Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

(9) For the X-ray crystallographic analyses of stable 1:1 complexes of $TiCl_4$ with 1,3-dicarbonyl compounds, see: (a) Maier, G.; Seipp, U.; Boese, R. *Tetrahedron Lett.* **1987**, *28*, 4515. (b) Viard, B.; Poulain, M.; Grandjean, D.; Amaudrut, J. *J. Chem. Res. Synop.* **1983**, *84*.

(10) (a) Weiler, L.; Huckin, S. N. *Can. J. Chem.* **1974**, *52*, 2157. (b) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431. (c) Kraus, G. A.; Hon, Y.-S.; Sy, J. *J. Org. Chem.* **1986**, *51*, 5625. For two new methods for the preparation of β-keto esters and a tabulation of other methods therein, see: (d) Roskamp, E. J.; Holmquist, C. R. *J. Org. Chem.* **1989**, *54*, 3258. (e) Turner, J. A.; Jacks, W. S. *Ibid.* **1989**, *54*, 4229.

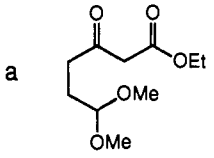
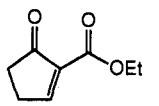
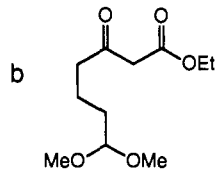
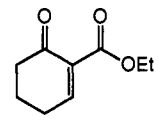
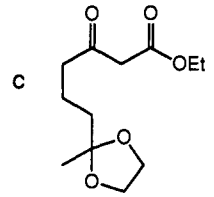
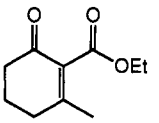
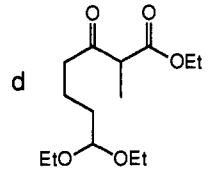
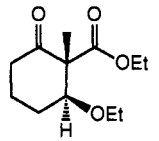
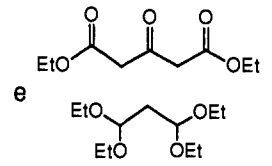
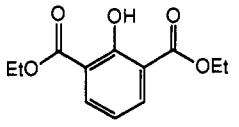
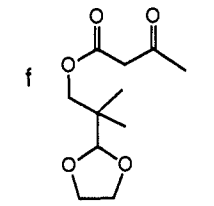
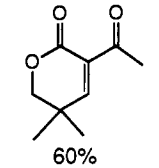
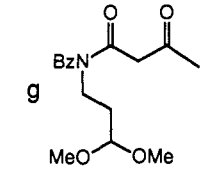
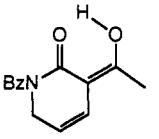
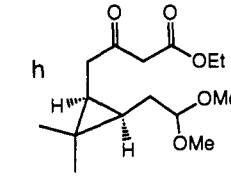
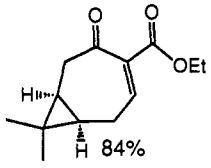
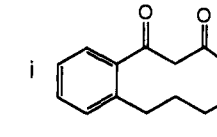
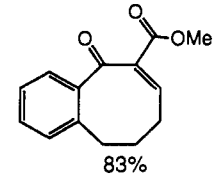
(11) All new cyclization products reported herein exhibit satisfactory spectral (IR, NMR) and high-resolution mass spectral characteristics.

(12) This compound could not be completely purified and readily polymerized. For similar difficulties see: Marx, J. N.; Minaskanian, G. *J. Org. Chem.* **1982**, *47*, 3306.

(13) The stereochemical assignment is tentative and is based on the diagnostic ethoxymethine resonance at δ 4.03 (200 MHz, dd, J = 5.3, 2.0 Hz) in comparison to the analogous resonance in the minor isomer produced from the cyclization of the dimethylacetal at δ 3.36 (dd, J = 10.0, 3.1 Hz).

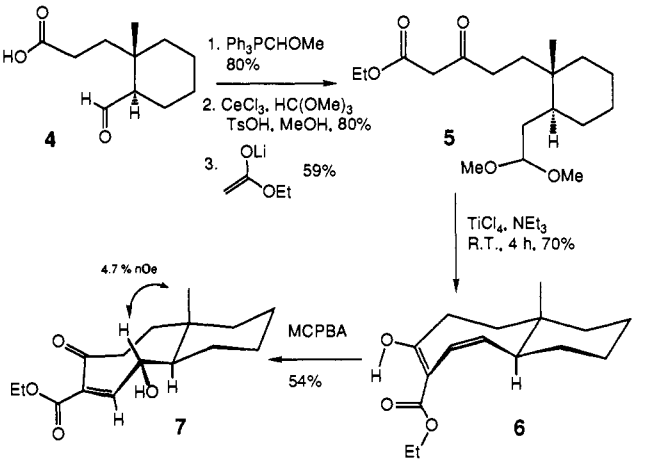
0002-7863/93/1515-8849$04.00/0

Table I. Titanium-Mediated Cyclizations of β-Keto Esters

entry	β-keto ester	carbalkoxycycloalkenone yield (%)
a		 78%
b		 98%
c		 81%
d		 72%
e		 58%
f		 60%
g		 87%
h		 84%
i		 83%

condensation of entry **e** attests to its potential in this regard.[14] The products of the cyclizations shown in entries **f** and **g** signify that this method is equally suitable for the preparation of heterocycles. The enolization shown in entry **g** could not be suppressed and reflects the superior hydrogen-bonding capability of amides. Finally, the successful cyclization reactions of the albeit somewhat conformationally biased β-keto esters of entries **h** and **i** suggest that this method may be of service in the preparation of natural products which embody medium-sized rings.

Scheme II



To that end, we have examined the cyclization reaction shown in Scheme II in the context of a projected successive annelation-based (C → CB → CBA) taxane synthesis.[15] Thus, the readily available aldehyde **4**[16] was homologated to the corresponding ester acetal and subjected to a Claisen condensation reaction with the lithium enolate of ethyl acetate to afford the cyclization substrate **5**. Following sequential addition of $TiCl_4$ (1 equiv) and triethylamine (1 equiv) at −70 °C to the β-keto ester **5** in CH_2Cl_2, a slow but efficient cyclization took place (4 h, room temperature, 70%) to provide the annelated product as the dienol ester **6**. Epoxidation of dienol **6** with MCPBA and concomitant ring opening afforded alcohol **7** as a single diastereomer (54%) accompanied by a structurally isomeric tertiary allylic alcohol (27%).[17]

In summation, β-keto esters serve as excellent terminating groups for Lewis acid-promoted cyclization reactions with acetals. This strategy constitutes one of the most convenient methods for the preparation of 2-carbalkoxycycloalkenones, whose reactivity in conjugate addition or cycloaddition reactions is exemplary.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health to Raymond L. Funk (Grant No. GM28663).

Supplementary Material Available: Experimental procedures for cyclizations and spectral data for all cyclization products (5 pages). Ordering information is given on any current masthead page.

(14) For somewhat related $TiCl_4$-mediated syntheses of aromatic compounds, see: (a) Chan, T. H.; Stossel, D. *J. Org. Chem.* **1988**, *53*, 4901. (b) Declercq, G.; Moutardier, G.; Mastagli, P. *C. R. Hebd. Seances Acad. Sci.* **1975**, *286*, 279.

(15) Kuwajima has exploited an internal vinylogous Mukaiyama reaction in a C → CA → CBA taxane synthesis, see ref 4g.

(16) Jenkins, P. R.; Brown, P. A.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1984**, 253.

(17) It is anticipated that a nucleophilic hydroxyl equivalent will add to the reactive Michael acceptor **7** with the implicit facial selectivity and permit the stereoselective introduction of the C(1) hydroxyl substituent of taxol. Consequently, the preparation of a ketal analogous to **5** which bears a methallyl substituent on the ketal carbon required for the anticipated aldol-based elaboration of the A-ring is underway.