Titanocene(II)-Promoted Cyclization of Unsaturated Thioacetals

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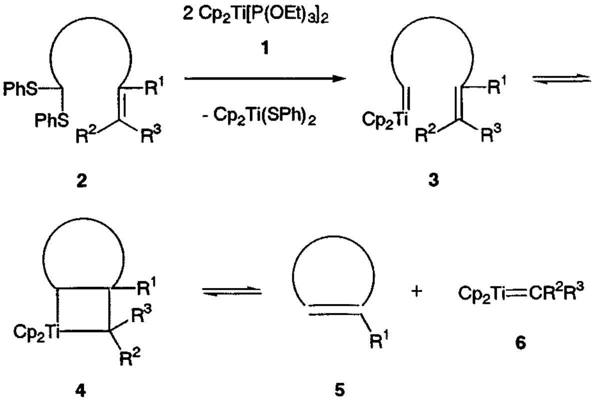
Abstract: The low-valent titanium species-promoted transformation of unsaturated thioacetals to cyclic compounds was studied. The cyclization of thioacetals having an olefin moiety proceeded with the loss of terminal olefin carbon to produce the corresponding five-, six-, and seven-membered cycloalkenes when they were treated with the low-valent titanium species $Cp_2Ti[P(OEt)_3]_2$ in refluxing THF. The similar reactions of 1-[3,3-bis(phenylthio)propoxy]-2-(prop-1- and prop-2-enyl)benzenes gave the seven- and eight-membered unsaturated cyclic ethers, respectively.

Key words: titanocene(II), thioacetal, cyclization, ring-closing metathesis

Construction of cyclic molecules is of fundamental importance in organic synthesis, and many carbon-carbon bond forming reactions have been employed for this purpose. The transition metal catalyzed ring-closing metathesis (RCM) of dienes is a useful method for the preparation of various cyclic compounds.[1] Molybdenum,[2] tungsten,[3] and rhenium[4] complexes have been employed as catalysts for such transformations. Since the discovery of Grubbs' catalysts,[5] syntheses of complex molecules by the ruthenium alkylidene-catalyzed RCM of dienes have been extensively studied.[6] As for the titanium methylidene-promoted RCM, Nicolaou et al. recently reported the preparation of cyclic ethers from unsaturated esters using the Tebbe or Petasis reagent, in which the alkylidenetitanium having a terminal vinyl ether moiety was suggested as an intermediate.[7]

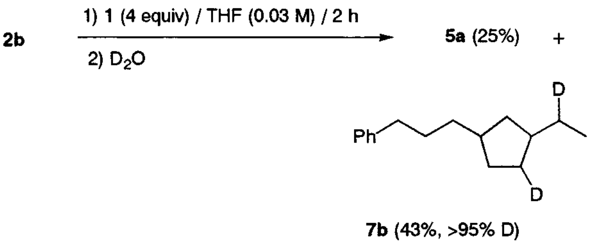
Recently we found that alkylidenetitanocenes or their equivalents are easily formed by the desulfurization of thioacetals with a low-valent titanium reagent **1**. These active species react with organic molecules having a carbon-oxygen[8] or carbon-carbon multiple bond.[9] For example, their reaction with trialkylallylsilanes affords the metathesis products, γ-substituted allylsilanes, along with the homoallylsilanes which would be formed by the β-hydride elimination from the intermediary titanacycle.[9c] Since these findings clearly showed the potential synthetic utility of thioacetals as starting materials for RCM, we have studied the preparation of cycloalkenes from thioacetals having an olefin moiety. Our new process consists of the formation of titanium carbene complex **3** by the treatment of unsaturated thioacetal **2** with the low-valent titanium **1**, its intramolecular reaction with the double bond to form titanacyclobutane **4**, and the subsequent elimination of the alkylidenetitanocene **6** (Scheme 1). We also describe in this paper the application of this method for the construction of unsaturated oxygen heterocycles.



Scheme 1

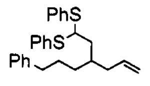
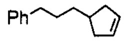
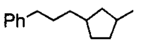
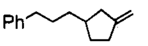
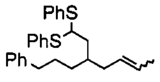
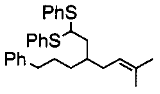
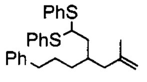
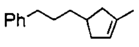
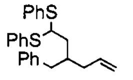
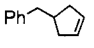
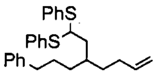
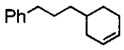
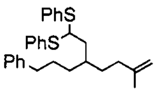
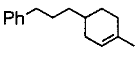
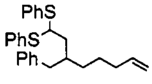
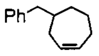
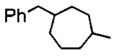
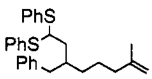
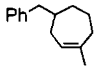
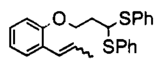
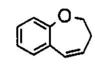
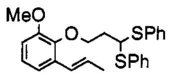
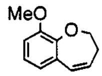
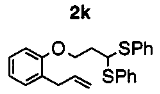
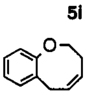
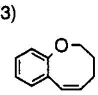
The treatment of unsaturated thioacetal **2a** with the titanocene(II) species **1** (4 equiv) in THF at room temperature for 17 h afforded the cyclopentene **5a** in 14% yield along with the methylcyclopentane **7a** and methylenecyclopentane **8** (entry 1, Table 1). Unlike the intermolecular reaction,[9c] the metathesis proceeded selectively to produce cyclopentene **5a** in 71% yield as the sole product when the reaction mixture was refluxed for 1 h after the treatment of **2a** with **1** at room temperature for 2 h (entry 2). Under similar reaction conditions, the cyclization of the methyl group substituted homologues of **2a** was studied. The unsaturated thioacetals having a 1,2-disubstituted olefin moiety **2b** also produced the cyclopentene **5a** in comparable yield (entry 3). In contrast to these results, only 8% of **5a** was produced from the thioacetal having a trisubstituted double bond **2c**. On the other hand, the reaction by which a trisubstituted olefin was formed proceeded smoothly giving the cyclopentene **5b** in high yield (entry 5).[10]

In order to probe the intermediary of this reaction, the unsaturated thioacetal **2b** was treated with **1** for 2 h at room temperature and then the reaction was quenched with D_2O (Scheme 2). The formation of dideuterio compound **7b** suggests that the present reaction proceeds via the titanacyclobutane intermediate **4**. Taking into account the reaction pathway depicted in Scheme 1, the substituent effect of methyl groups observed in the above reactions of **2a**, **b**, and **d** is explained by the extent of the retrograde reaction between the cycloalkene **5** and the alkylidenetitanocene **6**. In the case of **2c**, the steric repulsion between the two terminal methyl substituents of **2c** and Cp rings on titanium makes the formation of titanacycle **4** unfavorable.



Scheme 2

Table 1. Cyclization of Unsaturated Thioacetals 2[a]

Entry	Unsaturated Thioacetal 2	Titanocene(II) 1 (equiv) / Concentration of 2 (M)	Product (Yield / %)
1[b]	 2a	4 / 0.03	 5a (14)  7a (17)  8 (13)
2	2a	3 / 0.03	5a (71)
3[c]	 2b (*E* : *Z* = 82 : 18)	3 / 0.1	5a (67)
4[c]	 2c	3 / 0.1	5a (8)
5	 2d	3 / 0.03	 5b (87)
6[d]	 2e	4 / 0.03	 5c (74)
7[c]	 2f	3 / 0.1	 5d (50)
8	 2g	3 / 0.03	 5e (87)
9[d]	 2h	3 / 0.03	 5f (58)  7c (9)
10	 2i	4 / 0.015	 5g (81)[e]
11[c]	 2j (*E* : *Z* = 96 : 4)	4 / 0.03	 5h (75)
12[c]	 2k	3 / 0.03	 5i (73)
13	 2l	3 / 0.015	 +  5j 8 (61) (98 : 2)
14[d]	2l	4 / 0.015	5j + 8 (70) (82 : 18)

[a] All reactions were performed with a similar procedure as described in ref. 10, unless otherwise noted. All products had satisfactory elemental analysis and the spectral data were consistent with the postulated structures. [b] Carried out at room temperature for 17 h. [c] Carried out at room temperature for 1 h and then for 1 h under reflux. [d] Carried out at room temperature for 2 h and then for 3 h under reflux. [e] Contaminated with 6-benzyl-2-methyloct-1-ene (3%). The yield was corrected for the contaminant.

Next we examined the reactions of the unsaturated thioacetals having a longer carbon chain **2f-g** and found that the corresponding six- and seven-membered rings were also obtained in good yields. Similarly to the preparation of cyclopentenes, the trisubstituted olefins **5e** and **g** were produced in better yields than their unsubstituted congeners (entries 8 and 10).

Since a diphenyl thioacetal moiety is easily introduced to organic molecules by alkylation of bis(phenylthio)methane or treatment of carbonyls with thiophenol, it is clear that the low-valent titanium reagent promoted cyclization of unsaturated thioacetals is a strong synthetic tool for the construction of a variety of cyclic compounds including heterocycles. This idea was substantiated when the 2-allyl- and 2-(prop-1-enyl)phenyl ethers **2j-l** were treated with the titanocene(II) species **1**. As shown in Table 1, the seven- and eight-membered unsaturated cyclic ethers **5h-j** were obtained in good yields. In the case of the allylbenzene derivative **2l**, the initial product **5j** partially isomerized to the conjugated olefin **8** when a large excess of **1** was used (see entries 13 and 14).

In summary, we have developed an intramolecular metathesis of titanium carbene complexes formed from unsaturated thioacetals. The further application of this new methodology to the preparation of various types of carbo- and hetero-cycles is now under investigation.

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(10) Typical experimental procedure (Table 1, entry 5): Finely powdered molecular sieves 4A (150 mg), magnesium turnings (40 mg, 1.65 mmol; purchased from Nakarai Tesque Inc. Kyoto, Japan), and Cp_2TiCl_2 (374 mg, 1.5 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure (2-3 mmHg). Care was taken not to sublime titanocene dichloride. After cooling, THF (6.7 mL) and $P(OEt)_3$ (0.52 mL, 3 mmol) were added successively with stirring at room temperature under argon. Within 15 min, the reaction mixture turned dark green and then dark brown with slight evolution of heat. After 3 h, the unsaturated thioacetal **2d** (216 mg, 0.5 mmol) in THF (10 mL) was added to the reaction mixture, which was further stirred for 2 h. Then the reaction mixture was refluxed for 1 h. After cooling, the reaction was quenched with 1M NaOH (10 mL) and vigorously stirred for 20 min. The insoluble materials were filtered off through celite and washed with ether (50 mL). The organic phase was separated and dried over Na_2SO_4. After removal of solvent, the residue was purified by PTLC (hexane) to yield 87 mg (87%) of the cyclopentene **5b**.