Preparation of Alkylidenecyclobutanes and Their Transformation to 2,2-Disubstituted Cyclopentanones

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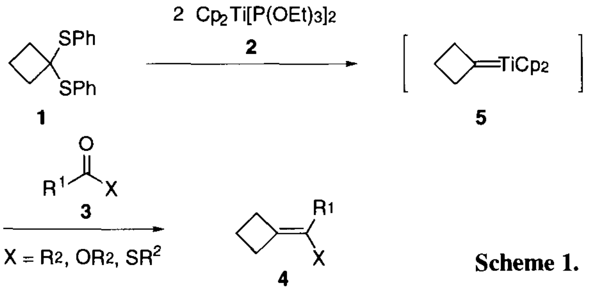
The reaction of ketones with the titanocene reagent prepared by the treatment of 1,1-bis(phenylthio)cyclobutane with the low valent titanium species $Cp_2Ti[P(OEt)_3]_2$ produced the corresponding alkylidenecyclobutanes. These compounds were successfully transformed into 2,2-disubstituted cyclopentanones by the epoxidation and subsequent ring enlargement. The similar reactions of the carbene complexes with carboxylic esters and thiolesters also proceeded to afford (1-alkoxy- and alkylthio-alkylidene)cyclobutanes, respectively, in good yields.

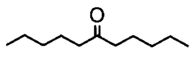
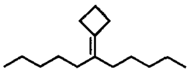
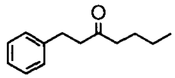
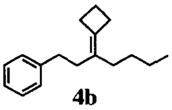
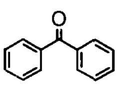
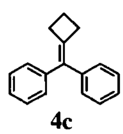
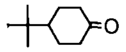
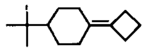
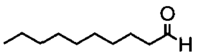
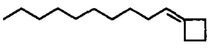
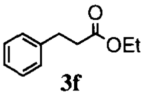
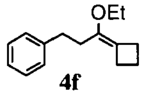
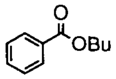
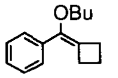
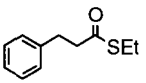
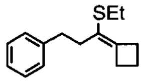
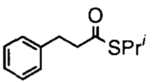
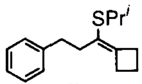
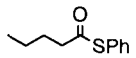
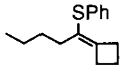
The preparation and reactions of small ring compounds have been well investigated. Although cyclobutanes undergo characteristic reactions using their strain release,[1] the synthetic application of these reactions is sometimes restricted for lack of adequate methods for the preparation of starting materials. Recently we found a new method for the olefination of carbonyl compounds using thioacetals and a low-valent titanium reagent.[2] We have studied the use of this new synthetic tool for the preparation of cyclobutane derivatives and found that the olefination of various carbonyl compounds **3** with the titanium species formed from 1,1-bis(phenylthio)cyclobutane (**1**) proceeded to afford alkylidenecyclobutanes **4** (Scheme 1). We assume that the intermediate of this reaction is cyclobutylidenetitanocene (**5**).



Scheme 1.

The thioacetal **1** was prepared by the reaction of lithium salt of 1,1-bis(phenylthio)methane with 1-bromo-3-chloropropane (1.15 equiv, 0 °C / 10 min and then room temperature / 1.5 h) followed by the treatment with butyllithium (1.5 equiv, -40 °C / 10 min and then room temperature / 2 h) in 79% yield, similarly to the preparation of 5,9-dithiaspiro[3.5]nonane.[3] The successive treatment of **1** (1.5 equiv) with the titanocene(II) species $Cp_2Ti[P(OEt)_3]_2$ (**2**) (3.75 equiv) for 15 min and 1-phenylheptan-3-one (**3b**) at room temperature for 1 h produced the corresponding alkylidenecyclobutane **4b** in 68% yield. The similar reaction of **1** with benzophenone (**3c**) gave the cyclobutane **4c** in 59% yield. When the reaction of organotitanium species **5** with **3c** was performed in refluxing THF, **4c** was obtained in better yield (Entry 3, Table 1). The yield of **4b** also increased slightly by using a higher reaction temperature (Entry 2). Under the same reaction conditions, carboxylic esters and thiolesters were also transformed into the corresponding heteroatom-substituted alkylidenecyclobutanes in good yields.[5]

Table 1. Preparation of alkylidenecyclobutanes **4**[a]

Entry	Carbonyl Compound 3	Product 4	Yield / %[b]
1	 **3a**	 **4a**	73
2	 **3b**	 **4b**	71
3	 **3c**	 **4c**	76
4	 **3d**	 **4d**	64
5	 **3e**	 **4e**	38
6	 **3f**	 **4f**	80
7	 **3g**	 **4g**	74[c]
8	 **3h**	 **4h**	78
9	 **3i**	 **4i**	76
10	 **3j**	 **4j**	66

[a] All reactions were performed with a similar procedure as described in the text. [b] Isolated yield based on the carbonyl compound used. [c] The NMR spectrum showed some unidentified signals.

The typical experimental procedure: To a dry flask charged with finely powdered molecular sieves 4A (188 mg), magnesium turnings (55 mg, 2.25 mmol), and Cp_2TiCl_2 (467 mg, 1.88 mmol), were added THF (4 ml) and $P(OEt)_3$ (0.64 ml, 3.75

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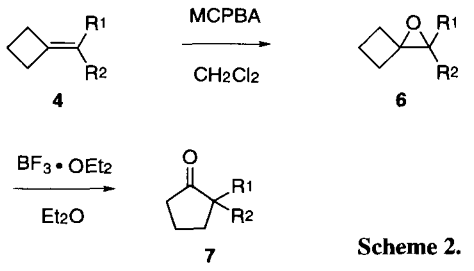
mmol) successively with stirring at room temperature under argon. Within 15 min, the reaction mixture turned dark green and then dark brown with slight evolution of heat.[4] After 3 h, **1** (204 mg, 0.75 mmol) in THF (1 ml) was added to the reaction mixture which was further stirred for 15 min. Then **3b** (93 mg, 0.5 mmol) in THF (1.5 ml) was added dropwise over 10 min, and the reaction mixture was refluxed for 1 h. After being cooled to room temperature, the reaction mixture was diluted with hexane (30 ml) and the insoluble materials were filtered off through Celite. The filtrate was condensed under reduced pressure. The crude product was purified by PTLC (hexane) to afford (1-phenethylpentylidene)cyclobutane (**4b**) (81 mg, 71%).

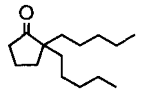
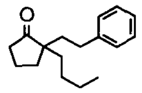
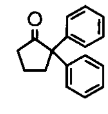
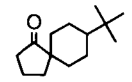
Although Scherer and Lunt reported the synthesis of **4c** by the Wittig reaction of **3c** using the cyclobutylidenephosphorane,[6] the efficiency of this reaction seems to be problematic. The results listed in Table 1 indicate that the present reaction is useful for the preparation of various alkylidenecyclobutanes including the heteroatom-substituted ones.

The synthetic utility of alkylidenecyclobutanes **4** thus obtained is demonstrated in the following synthesis of 2,2-disubstituted cyclopentanones **7** (Scheme 2). The oxidation of **4** having two alkyl substituents with MCPBA (1.5 equiv, CH_2Cl_2 / 0 °C ~ room temperature / 1.5 h) produced the epoxides **6**. Without any purification, the epoxides **6** were treated with BF_3•OEt_2 (1.1 equiv, Et_2O / 0 °C ~ room temperature / overnight) to afford the cyclopentanones **7** in high overall yields (Table 2).[7]



Scheme 2.

Table 2. Preparation of 2,2-disubstituted cyclopentanones **7**

Entry	Cyclobutane **4**	Product **7**	Overall Yield / %
1	**4a**	 **7a**	92
2	**4b**	 **7b**	85
3	**4c**	 **7c**	92
4	**4d**	 **7d** (70 : 30)[a]	91

[a] The ratio of diastereomers determined on the basis of the isolated yields.

The preparation of cyclopentanones from cyclic ketones or a certain methyl ketone has been achieved by the addition of lithium salt of cyclobutyl methyl selenide[7c] or cyclobutyl phenyl sulfoxide[8] followed by several transformations of the adducts including a pinacol-type ring expansion. It should be noted that the present reaction provides an operationally straightforward route to 2,2-dialkyl or diaryl substituted cyclopentanones.

Further study on the synthetic application of the heteroatom substituted alkylidenecyclobutanes is now in progress and will be reported in due course.

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References and Notes

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2 Y. Horikawa, M. Watanabe, T. Fujiwara, and T. Takeda, *J. Am. Chem. Soc.*, **119**, 1127 (1997). T. Takeda, M. Watanabe, N. Nozaki, and T. Fujiwara, *Chem. Lett.*, **1998**, 115. M. A. Rahim, H. Taguchi, M. Watanabe, T. Fujiwara, and T. Takeda, *Tetrahedron Lett.*, **39**, 2153 (1998). T. Takeda, M. Watanabe, M. A. Rahim, and T. Fujiwara, *Tetrahedron Lett.*, in press.

3 D. Seebach and A. K. Beck, *Org. Synth.*, Coll. Vol. VI, 316 (1988).

4 Since water prevents the reduction of Cp_2TiCl_2, the dried reagents should be used for the preparation of titanocene(II) species **2**.

5 In the case of carboxylic acid derivative, the reaction was quenched with 1M NaOH aqueous solution. The enol ethers (**4f** and **g**) were purified by column chromatography [Merck aluminum oxide 90 (Brockmann III)].

6 K. V. Scherer, Jr. and R. S. Lunt, III, *J. Org. Chem.*, **30**, 3215 (1965).

7 Lithium halides have been employed as a catalyst for the ring expansion of 1-oxaspiro[2.3]hexane derivatives to cyclopentanones. For example, Trost and Latimer reported the ring enlargement reaction of the oxaspirohexane derivative bearing two hydrogen atom on the epoxide ring using LiBr-HMPA in refluxing benzene.[b] It was found, however, that the treatment of the tetrasubstituted epoxide **6** with LiBr-HMPA under the same reaction conditions gave the cyclopentanone **7** only in low yield, which would be due to the steric hindrance between substituents on the epoxide ring and the approaching bromide ion. a) M. L. Leriverend and P. Leriverend, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **280**, 791 (1975). b) B. M. Trost and L. H. Latimer, *J. Org. Chem.*, **43**, 1031 (1978). c) S. Halazy and A. Krief, *J. Chem. Soc., Chem. Commun.*, **1982**, 1200.

8 L. Fitjer, W. Schlotmann, and M. Noltemeyer, *Tetrahedron Lett.*, **36**, 4985 (1995).