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A new route to alkenylcyclobutenes

Shigeki Oishi, Tomohiro Shono, Takehiro Nagasawa, Takafumi Inoue, Akira Tsubouchi, Takeshi Takeda *

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

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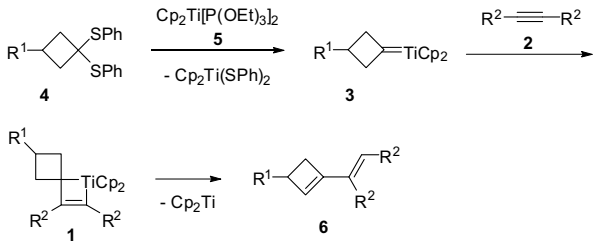
ABSTRACT

Reaction of titanium cyclobutylidene complexes, prepared by the desulfurizative titanation of 1,1-bis(phenylthio)cyclobutanes with $Cp_2Ti[P(OEt)_3]_2$, with alkynes gave 1-(alk-1-enyl)cyclobutenes.

Alkenylcyclobutenes are interesting synthetic intermediates for organic synthesis because of their unique structure and reactivity. Especially, the Diels–Alder reaction using these compounds as dienes has been investigated as a convenient tool for the preparation of benzocyclobutenes.[1] A variety of methods for the preparation of alkenylcyclobutenes have been reported.[1,2] They include, for example, addition of vinylmagnesium bromide to cyclobutanone and subsequent dehydration,[1a,d] Pd(0)-catalyzed coupling between 1-cyclobutenylmetals and alkenyl halides,[2g] decarboxylative dehydration of β,γ-unsaturated δ-hydroxy acids having a cyclobutane substructure,[2e] Pt(II) chloride-catalyzed intramolecular cycloisomerization of allenynes,[2j] and the Grubbs II-catalyzed 1,5-enyne metathesis.[2k] All these reactions, however, suffer serious limitations: they are only applicable to the preparation of specific alkenylcyclobutenes, and the starting materials are not readily accessible.

Recently, we reported the first synthesis of titanacyclobutenes with a spiro-bonded cyclopropane.[3] It is of interest that these strained titanacycles were thermally stable and could be isolated. In connection with this study, we examined the preparation of titanacyclobutenes having a cyclobutane substructure **1** by the reaction of internal alkynes **2** with titanium cyclobutylidene complexes **3**, generated by the reductive titanation of cyclobutanone diphenyl thioacetals **4** with the titanocene(II) reagent $Cp_2Ti[P(OEt)_3]_2$ **5**.[4] Unlike the titanacyclobutenes bearing a cyclopropane ring, the spirocyclic titanacyclobutenes **1** were thermally unstable and readily decomposed to produce alkenylcyclobutenes **6** through the β-hydride elimination[5] (Scheme 1).



Scheme 1.

The treatment of the thioacetal **4a** with **5** at room temperature for 15 min in THF generated the carbene complex **3a,** which was further treated with the alkyne **2a** at reflux for 2 h to produce the alkenylcyclobutene **6a**. The cyclobutene **6a** was found to be unstable under air, and gradually decomposed during workup. The difficulty in isolation was overcome by the use of a trace amount of hydroquinone as a stabilizing agent, and thus **6a** was isolated in 71% yield (Table 1, entry 1). The reaction was completely stereoselective: the substituents (R^2) originated from the alkyne **2a** were found to be cis to each other. Similarly, the symmetrical alkyne **2b** also gave the alkenylcyclobutene **6b** in good yield (entry 2).

Although the alkenylcyclobutene **6c** was obtained by the reaction of the alkyne **2c** having ether linkages, the reaction of the propargyl ether **2d** predominantly gave the vinylvinylidenecyclobutane **7** along with a small amount of the alkenylcyclobutene **6** (entry 4). The formation of **7** is attributable to the preferential elimination of an alkoxy group of the titanacyclobutene intermediate **8** prior to β-hydride elimination as depicted in Scheme 2.

* Corresponding author. Tel./fax: +81 42 388 7034.
E-mail address: takeda-t@cc.tuat.ac.jp (T. Takeda).

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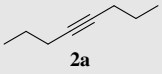
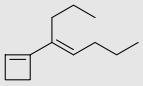
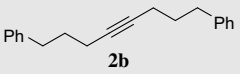
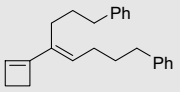
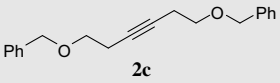
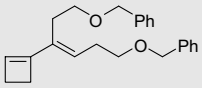
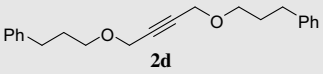
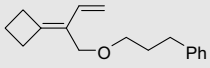
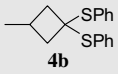
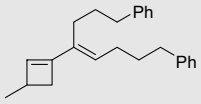
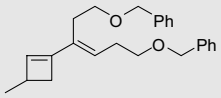
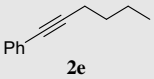
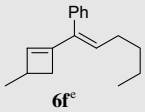
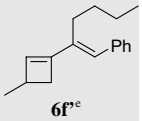
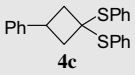
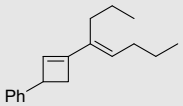
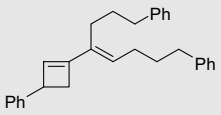
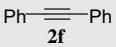
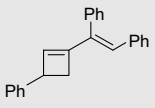
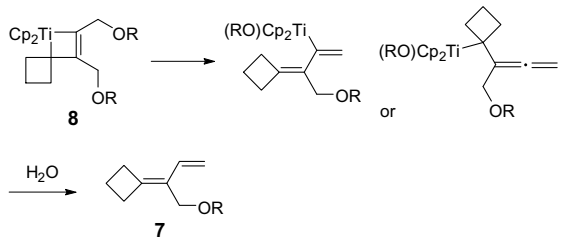
Table 1
Preparation of alkenylcyclobutenes[a]

Entry	Thioacetal **4**	Alkyne **2**	Alkenylcyclobutene **6**[b] (Yield/%)[c]	
1	 **4a**	 **2a**		**6a** (71)
2	**4a**	 **2b**		**6b** (75)
3	**4a**	 **2c**		**6c** (69)
4[d]	**4a**	 **2d**		**7** (53)
5	 **4b**	**2b**		**6d** (89)
6	**4b**	**2c**		**6e** (69)
7	**4b**	 **2e**	 **6f**[e] 79% (**6f** : **6f'** = 55 : 45)	 **6f'**[e]
8	 **4c**	**2a**		**6g** (67)
9	**4c**	**2b**		**6h** (91)
10	**4c**	 **2f**		**6i** (81)

[a] All reactions were performed with a similar procedure as described in the text, unless otherwise noted.
[b] The stereochemistry was determined by NOE experiment.
[c] Isolated yield based on **2**.
[d] The reaction was carried out at 25 °C for 2 h.
[e] The stereochemistry of both isomers was estimated by analogy with the other examples.

The titanium carbene complexes were also generated from the thioacetals of substituted cyclobutanones **4b** and **4c**, and their reactions with alkynes **2** gave the alkenylcyclobutenes **6d**–**i** (entries 5–10).[6] When the unsymmetrical alkyne **2e** was employed, the reaction produced an almost 1:1 mixture of the regioisomers **6f** and **6f'** (entry 7). These cyclobutenes were rather stable as compared with the alkenylcyclobutenes with no alkyl substituent on the cyclobutene ring. In contrast to the above results, no alkenylcyclobutene was obtained when terminal alkynes, such as phenylacetylene, were employed.



Scheme 2.

In conclusion, we have established a new route to 1-(alk-1-enyl)cyclobutenes utilizing diphenyl thioacetals of cyclobutanones and alkynes. Since the starting materials are readily available, this method enables us to prepare various alkenylcyclobutenes. Further study on the unique reactivity of these strained unsaturated compounds is currently underway.

Acknowledgments

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6. *A typical experimental procedure is as follows*: Magnesium turnings (33 mg, 1.4 mmol), finely powdered molecular sieves 4A (113 mg) and Cp_2TiCl_2 (280 mg, 1.1 mmol) were placed in a flask and dried by heating with a heating gun under reduced pressure (2–3 mmHg). After cooling, THF (2.3 ml) and $P(OEt)_3$ (0.39 ml, 2.3 mmol) were added successively with stirring at 25 °C under argon. After 3 h, a THF (1.0 ml) solution of the thioacetal **4c** (157 mg, 0.45 mmol) was added to the mixture and stirring was continued for 15 min. After a THF (2.0 ml) solution of **2f** (53 mg, 0.30 mmol) was added dropwise over 10 min, the reaction mixture was refluxed for 2 h. After cooling to room temperature, a few crystals of hydroquinone were added to the mixture, and the reaction mixture was quenched by the addition of 1 M NaOH. The insoluble materials were filtrated off through Celite and washed with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. After the combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated, the residue was purified by silica gel column chromatography (eluted with hexane/AcOEt (98:2) containing a trace amount of hydroquinone) to give **6i** (75 mg, 81%); mp 126–127 °C. ^{1}H NMR δ 2.65 (dd, J = 12.6, 1.9 Hz, 1H), 3.32 (dd, J = 12.7, 5.0 Hz, 1H), 3.93 (br d, 1H), 5.93 (s, 1H), 6.52 (s, 1H), 6.94–7.05 (m, 2H), 7.05–7.16 (m, 3H), 7.16–7.43 (m, 10H); ^{13}C NMR δ 38.1, 42.2, 126.2, 126.8, 126.99, 127.04, 127.3, 128.0, 128.3, 128.6, 129.2, 129.4, 133.0, 136.4, 137.2, 137.4, 143.8, 149.0; IR (KBr) 3078, 3058, 3023, 2951, 2921, 2903, 1602, 1491, 1444, 1073, 1028, 938, 920, 841, 771, 760, 737, 712, 689 cm^{-1}. Anal. Calcd for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 93.09; H, 6.73.