

Ring cleavage and successive aldol reaction of 3-[(Trialkylsilyl)methyl] cyclobutanones

メタデータ	言語: eng 出版者: 公開日: 2017-10-04 キーワード (Ja): キーワード (En): 作成者: メールアドレス: 所属:
URL	http://hdl.handle.net/2297/30141

Ring Cleavage and Successive Aldol Reaction of 3-[(Trialkylsilyl)methyl]cyclobutanones

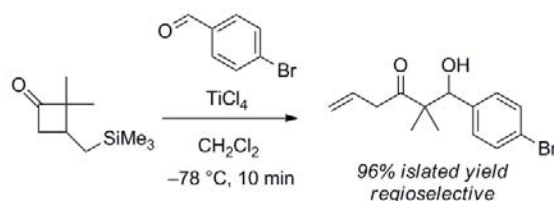
Jun-ichi Matsuo,* Kosuke Harada, Mizuki Kawano, Ryosuke Okuno, and Hiroyuki Ishibashi

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

jimatsuo@p.kanazawa-u.ac.jp

Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



3-[(Trialkylsilyl)methyl]cyclobutanones reacted with aldehydes by activation with titanium(IV) chloride to give acyclic β,γ -unsaturated β' -hydroxy ketones.

Cyclobutanones are interesting building blocks for organic synthesis,¹ and we have reported on the synthetic utility of 3-ethoxycyclobutanones for formal [4+2] cycloaddition reactions with aldehydes,² ketones,² *N*-Ts imines,³ allylsilanes,⁴ and silyl enol ethers⁵ to give the corresponding six-membered ring compounds.^{6,7,8} For

example, 3-ethoxycyclobutanone **1** reacted with benzaldehyde to give tetrahydropyrone **2** under the catalysis of Lewis acid (eq 1).² In the course of these studies, it was also found that substitution with a (trialkylsilyl)methyl group at the 2-position of cyclobutanone facilitated ring cleavage of the cyclobutanone ring.⁹ We then tried to investigate the effect of (trialkylsilyl)methyl group at the 3-position of the cyclobutanone, and found that a reaction between 3-[(trimethylsilyl)methyl]cyclobutanone **3** and an aldehyde gave an acyclic aldol product **4** bearing a β,γ -unsaturated group, which would be difficult to prepare by the regioselective aldol reaction of β,γ -unsaturated ketone **5** (Scheme 1).¹⁰ We would like to describe here this

(1) (a) Conia, J. M.; Robson, M. J. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 473. (b) Belluš, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797. (c) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (d) Namyso, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.

(2) Matsuo, J.; Sasaki, S.; Tanaka, H.; Ishibashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 11600.

(3) Matsuo, J.; Okado, R.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 3266.

(4) Matsuo, J.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3822.

(5) Matsuo, J.; Negishi, S.; Ishibashi, H. *Tetrahedron Lett.* **2009**, *50*, 5831.

(6) Matsuo, J.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Chem. Comm.* **2010**, *46*, 934.

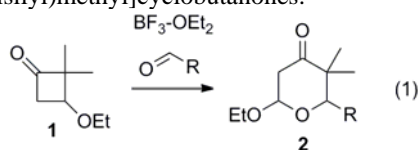
(7) Reaction of donor-acceptor cyclobutanones: (a) Allart, E. A.; Christie, S. D. R.; Pritchard, G. J.; Elsegood, M. R. *J. Chem. Comm.* **2009**, 7339. (b) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202. (c) Moustafa, M. M. A.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4732. (d) Moustafa, M. M. A.; Stevens, A. C.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4736. (e) Stevens, A. C.; Palmer, C.; Pagenkopf, B. L. *Org. Lett.* **2011**, *13*, 1528.

(8) Related reaction: Shan, G.; Liu, P. F.; Rao, Y. *Org. Lett.* **2011**, *13*, 1746.

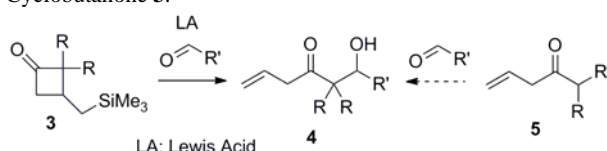
(9) Matsuo, J.; Kawano, M.; Okuno, R.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 3960.

(10) (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (b) Mahrwald, R. *Modern Aldol Reaction*; Wiley-VCH: Weinheim, 2004. (c) Trost, B. M.; Fleming, I.; Semmelhack, M. F. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.4-1.9. (d) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

unique ring cleavage and aldol reaction of 3-[(trialkylsilyl)methyl]cyclobutanones.

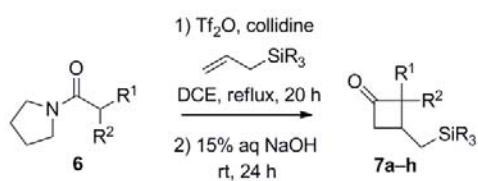


Scheme 1. Regioselective Formation of Aldol Adduct **4** From Cyclobutanone **3**.



The 3-[(trialkylsilyl)methyl]cyclobutanones **7a–h** employed in this study were prepared by a [2+2] cycloaddition reaction between allylsilane and a keteneiminium salt which was generated from the corresponding pyrrolidine amide **6** (Table 1).¹¹ 2,2-Dialkyl- and 2-monoalkyl-substituted 3-[(trimethylsilyl)methyl]cyclobutanones **7a–f** were prepared in good yields. Cyclobutanones having *t*-butyldimethylsilyl and trisopropylsilyl groups **7g,h** were prepared by the same method. Attempted preparation of cyclobutanone **7i** which had no substituents at its 2-position gave an inseparable mixture of **7i** and byproducts by this procedure. Therefore, **7i** was prepared by another route: [2+2] cycloaddition between dichloroketene and allyltrimethylsilane followed by dechlorination, pure **7i** was obtained in good yield (Scheme 2).

Table 1. Preparation of 3-[(Trialkylsilyl)methyl]cyclobutanones **7a–h**



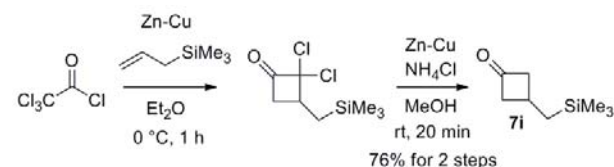
entry	7	R ¹	R ²	SiR ₃	yield (%)
1	7a	Me	Me	SiMe ₃	77
2	7b	Et	Et	SiMe ₃	75
3	7c	-(CH ₂) ₄ -		SiMe ₃	85
4	7d	-(CH ₂) ₅ -		SiMe ₃	88
5	7e	Me	H	SiMe ₃	77 ^a
6	7f	CH ₂ Ph	H	SiMe ₃	64 ^a

(11) (a) Hogue, C.; Frisque-Hesbain, A. M.; Mockel, A.; Ghosez, L.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 2920. (b) Marko, I.; Ronsmans, B.; Hesbain-Frisque, A. M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192.

7	7g	Me	Me	SiMe ₂ <i>t</i> -Bu	85
8	7h	Me	Me	Si(<i>i</i> -Pr) ₃	75

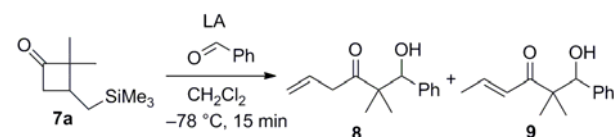
^a Mixture of diastereomers: **7e** (84:16), **7f** (93:7).

Scheme 2. Preparation of Cyclobutanone **7i**.



First, we screened Lewis acids which promoted the reaction between cyclobutanone **7a** and benzaldehyde (Table 2). It was found that the use of titanium(IV) chloride gave β,γ-unsaturated aldol product **8** in 93% yield, while the use of titanium(IV) bromide gave α,β-unsaturated one **9** in 34% yield (entries 1 and 2).¹² It was assumed that enone **9** was formed by isomerization of the initially formed product **8**. Catalysis of tin(IV) chloride gave **8** in only 4% yield (entry 3). Even ring cleavage of **7a** was not observed in the case of other Lewis acids such as BF₃·OEt₂ and Sc(OTf)₃.

Table 2. Effect of Lewis Acid on Reaction Between **7a** and Benzaldehyde.



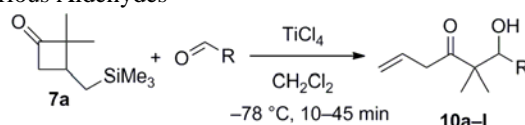
entry	Lewis acid	8 (% yield)	9 (% yield)
1	TiCl ₄	93	-
2	TiBr ₄	-	34
3	SnCl ₄	4	-

Next, the scope and limitations of the reaction of 3-[(trialkylsilyl)methyl]cyclobutanones and aldehydes were studied using titanium(IV) chloride as Lewis acid. Benzaldehyde derivatives with methyl, methoxy, or halogens at the para positions of benzene ring were employed first. It was found that substitution with halogens gave high yields of the desired products **10a–c** (Table 3, entries 1–3) whereas reactions of methyl or methoxy-substituted benzaldehyde gave the desired compounds **10d,e** in 80 and 54% yields, respectively

(12) Other regioisomers were not obtained.

(entries 4 and 5). Therefore, the electrophilicity of the aldehydes affected the efficiency of this reaction. The reaction with 1-naphthyl aldehyde proceeded sluggishly to afford **10f** in 55% yield, but that of 2-naphthyl aldehyde gave the corresponding product **10g** in 88% yield (entries 6 and 7). Notable differences were observed in the reaction with 1- and 2-naphthyl aldehydes suggesting that this reaction was influenced easily by steric effects. Aliphatic aldehydes such as octanal and 3-phenylpropanal gave the desired products **10h,i** in high yields (entries 8 and 9), while increased steric hindrance in aldehydes such as *i*-butyl aldehyde, *i*-propyl aldehyde, and *t*-butyl aldehyde caused decreased yields of the desired products **10j-l** (entries 10–12). When the reactions were carried out at higher reaction temperatures, the β,γ -unsaturated aldol products **10** isomerized to the corresponding α,β -unsaturated ones. The reaction with ketones such as acetophenone did not proceed.

Table 3. TiCl₄-Promoted Reaction Between **7a** and Various Aldehydes^a

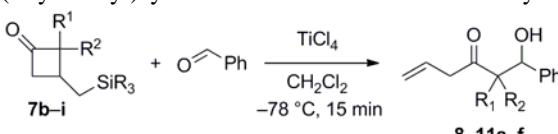


entry	R	10	yield (%)
1	4-FC ₆ H ₄	10a	86
2	4-ClC ₆ H ₄	10b	93
3	4-BrC ₆ H ₄	10c	96
4	4-MeC ₆ H ₄	10d	80
5	4-MeOC ₆ H ₄	10e	54
6 ^b	1-Naph	10f	55
7	2-Naph	10g	88
8	CH ₃ (CH ₂) ₆	10h	93
9	Ph(CH ₂) ₂	10i	83
10	<i>i</i> -PrCH ₂	10j	49
11	<i>i</i> -Pr	10k	17
12	<i>t</i> -Bu	10l	0

^a Cyclobutanone **7a** (1.4 equiv), Aldehyde (1.0 equiv), and TiCl₄ (1.4 equiv) were employed. ^b Reaction temperature: –78 to –18 °C, 3 h.

The reaction of other 2,2-dialkylcyclobutanones such as diethylcyclobutanone **7b** and spirocyclobutanones **7c,d** with benzaldehyde proceeded smoothly at –78 °C to afford β,γ -unsaturated aldol products **11a–c** in good to high yields (Table 4, entries 1–3). The reaction of 2-monoalkylcyclobutanones **7e,f** required slightly elevated temperature (–45 °C), and that of 2-nonsubstituted cyclobutanone **7i** needed to be carried out at –20 °C for efficient conversion (entries 4–6). More substituted cyclobutanones reacted at lower temperatures. Moderate *syn* selectivities were observed in the products **11d,e** (entries 4 and 5). It was noted that cyclobutanones bearing other trialkylsilyl groups such as TBS and TIPS groups **7g,h** gave the aldol product **8** (entries 7 and 8). These results suggested that even sterically hindered trialkylsilyl groups reacted in this reaction.

Table 4. TiCl₄-Promoted Reaction of Various 3-(Silylmethyl)cyclobutanones **7b–i** with Benzaldehyde.^a



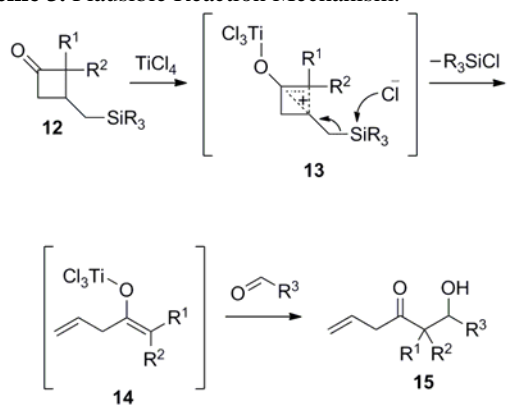
entry	conditions ^a	yield (%)
1	–78 °C, 30 min	59
2	–78 °C, 15 min	91
3	–78 °C, 30 min	92
4	–45 °C, 24 h	87 ^b
5	–45 °C, 24 h	67 ^c
6 ^d	–20 °C, 30 min	82
7	–78 °C, 15 min	86
8	–78 °C, 30 min	88

^a For reaction conditions, see Table 3 unless otherwise noted. ^b *syn/anti* = 80:20. ^c *syn/anti* = 70:30. ^d **7i** (1.4 equivalents) and TiCl₄ (2.1 equivalents) were employed.

A plausible mechanism for the present ring cleavage and aldol reaction of 3-[(trialkylsilyl)methyl]cyclobutanones is shown in Scheme 3. Activation of cyclobutanone **12** with titanium(IV) chloride gave bicyclobutonium ion **13**,¹³ and chloride ion attacked the trialkylsilyl group to form a trichlorotitanium enolate **14**, whose formation was consistent with *syn* selectivity for the aldol reaction of a trichlorotitanium

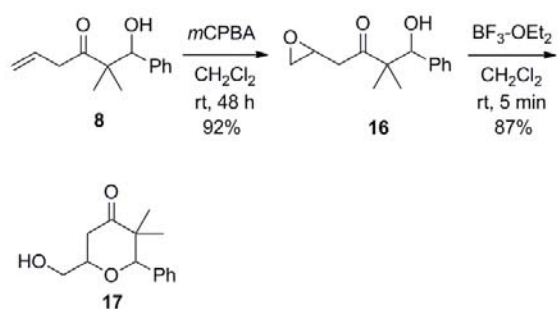
enolate.¹⁴ The regioselectivity for the formation of **14** was controlled by formation of the more substituted bicyclobutonium ion **13**, and the regioselectivity was preserved during the reaction. The aldol reaction of **14** with aldehyde proceeded to give **15**.

Scheme 3. Plausible Reaction Mechanism.



The synthetic utility of the β,γ -unsaturated aldol adducts was exemplified by transformation of **8** to the tetrahydropyrone **17** (Scheme 4). Epoxidation of β,γ -unsaturated aldol adduct **8** with *m*CPBA gave epoxide **16** in 92% yield. Treatment of epoxide **16** with boron trifluoride etherate gave tetrahydropyrone **17** in 87% yield.

Scheme 4. An Example of Transformation of **8**.



In conclusion, 3-[(trialkylsilyl)methyl]cyclobutanones react with aldehydes upon activation with titanium(IV) chloride to afford β,γ -unsaturated aldol adducts. Regioselective formation of a β,γ -unsaturated trichlorotitanium enolate was proposed. The present

method for generation of this unique enolate will likely be applicable to reactions with other electrophiles.

Acknowledgment This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available Detailed experimental procedures and full spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(14) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343.