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

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

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.^{6–8} 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

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



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

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Scheme 1. Regioselective Formation of Aldol Adduct 4 from Cyclobutanone 3



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 *tert*butyldimethylsilyl and triisopropylsilyl 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 afforded pure 7i in good yield (Scheme 2).

 Table 1. Preparation of 3-[(Trialkylsilyl)mthyl]cyclobutanones

 7a-h



entry	7	\mathbb{R}^1	\mathbb{R}^2	SiR_3	yield (%)
1	7a	Me	Me	$SiMe_3$	77
2	7 b	\mathbf{Et}	\mathbf{Et}	$SiMe_3$	75
3	7 c	$-(CH_2)_4-$		$SiMe_3$	85
4	7d	-(CH ₂) ₅ -		$SiMe_3$	88
5	7 e	Me	Η	$SiMe_3$	77^a
6	7f	CH_2Ph	Η	$SiMe_3$	64^a
7	7g	Me	Me	$SiMe_2t$ -Bu	85
8	7h	Me	Me	${ m Si}(i{ m -}{ m Pr})_3$	75

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





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 **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



Next, the scope and limitations of the reaction of 3-[(trialkylsilyl)methyl]cyclobutanones and aldehydes were studied using titanium(IV) chloride as a Lewis acid. Benzaldehyde derivatives with methyl, methoxy, or halogens at the para positions of the 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 (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 isobutyl aldehyde, isopropyl aldehyde, and tert-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 addol products 10 isomerized to the corresponding α_{β} -unsaturated ones. The reaction with ketones such as acetophenone did not proceed.

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⁽¹²⁾ Other regioisomers were not obtained.

Table 3. TiCl₄-Promoted Reaction between 7a and VariousAldehydes^a



entry	R	10	yield (%)
1	$4-FC_6H_4$	10a	86
2	$4-ClC_6H_4$	10b	93
3	$4\text{-BrC}_6\text{H}_4$	10c	96
4	$4 - MeC_6H_4$	10d	80
5	$4 - MeOC_6H_4$	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	101	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 vields (Table 4, entries 1-3). The reaction of 2-monoalkylcyclobutanones 7e,f required a slightly elevated temperature $(-45 \,^{\circ}\text{C})$, 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 trialkylsily 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.

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 the 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 ity was preserved during the reaction. The aldol reaction of 14 with aldehyde proceeded to give 15.

The synthetic utility of the β , γ -unsaturated aldol adducts was exemplified by transformation of **8** to the **Table 4.** TiCl₄-Promoted Reaction of Various 3-(Silylmethyl)cyclobutanones 7b-i with Benzaldehyde^{*a*}



entry			conditions ^a	yield (%)
1	o Et Et SiMe₃ 7b	O OH Et Et 11a	–78 °C, 30 min	59
2	o SiMe ₃	O OH Ph 11b	–78 °C, 15 min	91
3	o SiMe ₃ 7d	Ph	–78 °C, 30 min	92
4	SiMe ₃	O OH Ph 11d	-45 °C, 24 h	87 ^b
5	Ph SiMe ₃	O OH Ph Ph	–45 °C, 24 h	67 ^c
6 ^d	°, SiMe₃ 7i	Ile O OH Ph 11f	–20 °C, 30 min	82
7	O TBS 7g	NO OH Ph 8	–78 °C, 15 min	86
8		O OH Ph	–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 equiv) and TiCl₄ (2.1 equiv) were employed.

Scheme 3. Plausible Reaction Mechanism



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Scheme 4. An Example of Transformation of 8



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.

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.

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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.