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Regioselective ring opening of alkylidenecyclopropanone silyl acetals

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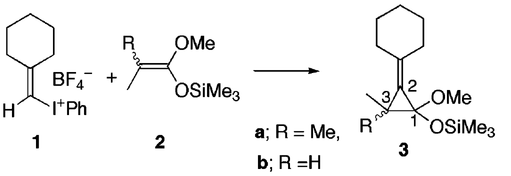
Abstract—Alkylidenecyclopropanone silyl acetals are readily available from the reaction of an alkylidenemethyliodonium salt and ketene silyl acetals in the presence of triethylamine. The three different C–C bonds of the cyclopropane ring can be selectively cleaved with HCl, Lewis acid, or fluoride. The alkylideneallyl cation formed via the cleavage of C2–C3 bond with Lewis acids shows further selectivity in reacting with a nucleophile.

Alkylidenecyclopropanes[1] undergo ring-opening reactions promoted by Brønsted[2,3] and Lewis acids[4,5] as well as by transition metal complexes,[1a,6] and are employed as synthetic building blocks. Reactivity is controlled by a functional substituent on the cyclopropane ring. For example, 1,1-dialkoxy-2-methylenecyclopropanes are in equilibrium with the trimethylenemethane forms, and undergo [3+2] cycloaddition to olefins.[7] Regioselectivity of the bond cleavage of the cyclopropane ring is also an attractive point of interest in these reactions.[5b,6f]

The present communication describes regioselective ring-opening reactions of alkylidenecyclopropanone silyl acetals. The cyclopropane ring contains three different carbon–carbon bonds, and each of these bonds can be cleaved selectively with an appropriate reagent.

Reaction of the alkylidenemethyliodonium salt **1**[8] (10 mM) with triethylamine (16 mM) in chloroform containing ketene silyl acetal **2a** (100 mM) at ambient temperature gave alkylidenecyclopropanone silyl acetal **3a** in 43% yield (Scheme 1). A diastereomeric mixture (3:1) of **3b** was obtained in 31% yield from an *E*/*Z* (3/1) mixture of **2b**.[9] The alkylidenemethyliodonium salt **1** readily gives the corresponding alkylidenecarbene[10] in the presence of amine in an aprotic solvent owing to the high acidity of the α-hydrogen[11,12] and the excellent nucleofugality[13] of the positive iodonio group. The unsaturated carbene[10] must be a key intermediate in the cyclopropanation of the ketene silyl acetal.



Scheme 1. Preparation of alkylidenecyclopropanone silyl acetals.

The reactions of **3a** and **3b** with anhydrous hydrogen chloride (20 mM) in dichloromethane at 0 °C immediately gave allylcarboxylates **4a** and **4b** in 95% and 78% yield, respectively (top of Scheme 2). Yields of the products were determined by GC[14] and the structures were determined by NMR and MS of the isolated products. We propose that cleavage of the C1–C2 bond of the cyclopropane ring of **3** occurs in this reaction, initiated by protonation of the olefinic moiety of **3**, to give $\mathbf{I_1}$, the positive charge of which is stabilized by the α-cyclopropyl group. In the ring-opening reaction of $\mathbf{I_1}$, C1–C2 cleavage is preferred to C2–C3 cleavage because of stabilization of the positive charge by the α-oxy groups in the resulting cation $\mathbf{I}'_1$. Similar regioselective bond cleavage is observed in the ring-opening reactions of 1-alkoxy-2-cyclohexylidenecyclopropanes.[2] The

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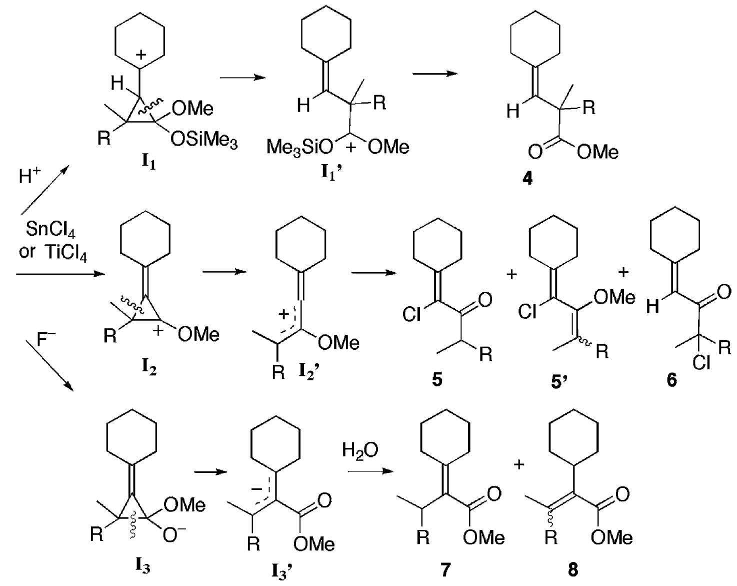
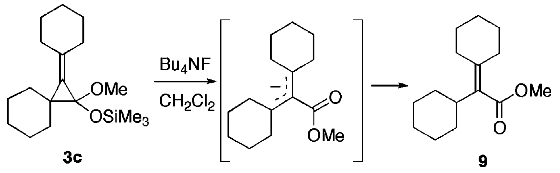


Scheme 2. Regioselective cleavage of the cyclopropane ring of **3**.

ring-opening reaction initiated by protonation at the carbon–carbon double bond is well known for the acid-mediated ring opening of simple alkylidenecyclopropanes.[3]

When Lewis acids $TiCl_4$ or $SnCl_4$ were employed for the reaction of **3**, two isomeric products, **5** and **6**, were obtained plus **5**′, the enol ether related to **5** (middle of Scheme 2).[15] The yields determined by GC are summarized in Table 1. The C2–C3 bond in **3** is selectively cleaved in these reactions, although the regioselectivity of chloride substitution (**5**/**6**) depends on the reaction conditions. These products can be rationalized by a reaction pathway involving the alkylideneallyl cation[16] intermediate $\mathbf{I}'_2$ formed via silyloxide elimination.[17]

Yet another type of ring-opening reaction was observed in the reaction of **3a** with Bu_4NF (76mM) in CH_2Cl_2 at ambient temperature to give a 1:1 mixture of esters **7a** and **8a** in 93% yield in 5min.[18] Ring cleavage occurs at the C1–C3 bond (bottom of Scheme 2). Reaction of **3a** with fluoride ion must be initiated by elimination of the silyl group to give the anion $\mathbf{I}_3$. Cleavage of the C1–C3 bond of this first-formed anion then opens the ring selectively to give the allylically stabilized anion $\mathbf{I}'_3$, which is protonated to yield a mixture of vinylcarboxylates, **7a** and **8a**. The fluoride initiated ring-opening reaction of the spiro substrate **3c** gave a single product **9** in 95% yield as expected because of the symmetrical structure of the allylic anion intermediate (Scheme 3).



Scheme 3. Reaction via a symmetrical allylic anion.

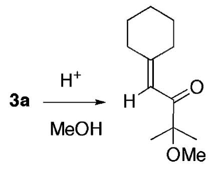
Among these three regioselective ring-opening reactions of **3**, further consideration is warranted of the Lewis-acid-mediated reaction involving the alkylideneallyl cation intermediate $\mathbf{I}'_2$, which has two electrophilic centers, the sp and sp^2 carbons. The product ratio of (**5**+**5**′):**6** depends on the reaction conditions. Exclusive formation of **5** (**5**′) is observed in the reaction of **3a** with $SnCl_4$ (entries 3 and 4), but the $TiCl_4$-induced reaction also gives **6**

Table 1. Reaction of **3** with Lewis acid in CH_2Cl_2

Entry	Subst.[a]	Acid (concn, mM)	Temp (°C)	Time (min)	Yield (%)		
					5	**5**′	**6**
1	**3a**	$TiCl_4$ (9)	0	2	16	51	29
2	**3a**	$TiCl_4$ (6)	−78	5	0	82	6
3	**3a**	$SnCl_4$ (7)	0	5	0	85	0
4	**3a**	$SnCl_4$ (6)	−78	10	0	98	0
5	**3b**	$TiCl_4$ (5)	0	3	32	[b]	63
6	**3b**	$TiCl_4$ (4)	−78	3	49	[b]	27
7	**3b**	$SnCl_4$ (5)	0	5	65	[b]	35
8	**3b**	$SnCl_4$ (4)	−78	5	70	[b]	10

[a] Concentration of **3a** was 2.5–4.6mM, and that of **3b** was 1.2–1.5mM.

[b] Not determined, but must be small (less than 5% yield).



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Scheme 4. Trapping of alkylideneallyl cation by methanol.

(entries 1 and 2) although the reaction at the lower temperature provided more **5** (**5′**). Thus, the selective nucleophilic reaction at the sp position is more pronounced at lower temperature, and with $SnCl_4$ compared with $TiCl_4$. These tendencies are common to the reactions of **3a** and **3b**, but the monomethyl substrate **3b** yielded more **6** than did **3a**. The positive charge is localized mainly at the sp and sp^2 carbons of the allylic cation $\mathbf{I}_2'$, and the methyl group(s) on $\mathbf{I}_2'$ will stabilize the positive charge at the sp^2 position; consequently, the dimethyl substituted species ($\mathbf{I}_2'\mathbf{a}$) may be expected to lead to more **6** than its monomethyl substituted analogue ($\mathbf{I}_2'\mathbf{b}$).[16,19] However, a smaller amount of the sp^2 substituted product **6** was obtained in the reaction of dimethyl substrate **3a**. This unexpected selectivity cannot be explained by the charge distributions of allylic cations $\mathbf{I}_2'\mathbf{a}$ and $\mathbf{I}_2'\mathbf{b}$.

Although the major reaction of **3** with anhydrous HCl in an aprotic solvent was the olefinic protonation leading to the C1–C2 cleavage, the C2–C3 cleavage can also be induced by HCl in a protic solvent. The reaction of **3a** in methanol containing HCl (0.4 M) at ambient temperature gave **10** in 80% yield in 5 min (Scheme 4). When the reaction was carried out in CD_3OD, deuterium was incorporated at the vinylic position of **10**, and **10** contained the labeled methoxy CD_3O group. This is consistent with a reaction mechanism involving the nucleophilic addition of methanol to $\mathbf{I}_2'\mathbf{a}$ formed by the proton-induced silyloxide elimination.[20] The original methoxy group must be removed during acid-induced cleavage of the initially formed enol ether product.[21] The selective nucleophilic addition at the sp^2 position of $\mathbf{I}_2'\mathbf{a}$ agrees with the charge distribution of $\mathbf{I}_2'\mathbf{a}$,[16,19] but is in contrast to the chloride addition in the Lewis-acid-mediated reaction.

In summary, alkylidenecyclopropanone silyl acetals have been prepared for the first time, and the silyl acetal functional group plays an important role in controlling the regioselective cleavage of the three different C–C bonds of the cyclopropane ring of **3**. Compound **3** is a good precursor of the alkylideneallyl cation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.002.

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14. A solution containing **3** (1–5 mM) and tetradecane (1.4 mM) as an internal standard was employed for the ring-opening reactions of **3**. The products were extracted with ether and washed with water. The yields of the products were determined by GC with the internal standard.
15. (a) The β-monomethyl enol ether **5b**′ and the allene derivative were not detected owing to their high reactivity toward acid hydrolysis to give ketones **5b** and **6**. The β,β-dimethyl enol ether **5a**′ could be isolated due to its resistance to acid hydrolysis;[15b,c] (b) Okuyama, T.; Fueno, T.; Nakatsuji, H.; Furukawa, J. *J. Am. Chem. Soc.* **1967**, *89*, 5826–5831; (c) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228–7233.
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19. (a) Solvolysis of 3-bromo-2,5-dimethyl-2,4-hexadiene in ethanol at 100 °C for 80 min gives 5-ethoxy-2,5-dimethyl-2,3-hexadiene in 100% yield.[19b] This indicates that ethanol selectively nucleophilically attacks the sp^2 carbon of the alkylideneallyl cation intermediate; (b) Grob, C. A.; Spaar, R. *Helv. Chim. Acta* **1970**, *53*, 2119–2129.
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21. Under solvolysis conditions, the methoxy group of $\mathbf{I}'_2$**a** is possibly replaced by the hydroxy or silyloxy group before the methanol addition. See also Ref. 17c.