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Solvent-dependent regioselectivity of hydrogen chloride-mediated ring opening of alkylidenecyclopropanone acetal

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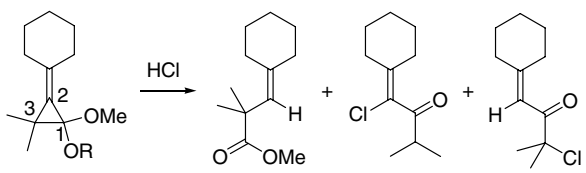
Abstract—Ring opening reactions of 2-cyclohexylidene-3,3-dimethylcyclopropanone acetal (**1**) are readily induced by treatment of hydrogen chloride in various solvents. Bond cleavage takes place at the C1–C2 or C2–C3 bond, and the ratio of C1–C2/C2–C3 cleavages changes from >99/1 to <1/99 depending on the solvent. The two modes of bond cleavage must be initiated by protonations at the carbon–carbon double bond and the acetal oxygen, respectively. The regioselectivity can be rationalized by the rate-determining protonation at carbon and the equilibrium protonation at oxygen.

Ring opening reactions of alkylidenecyclopropanes[1] have been achieved by using transition metal complex,[1–4] Lewis acid,[5,6] and also Brønsted acid,[7,8] and the reactions have been utilized for synthetic and mechanistic studies. Regioselectivity of the ring opening is one of the attractive issues in exploring this field of chemistry, and the selectivity was controlled by selection of metal reagents (catalyzes) and/or the structure of the cyclopropane substrate.[3,4]

We have recently found that regioselective cleavage of the three different carbon–carbon bonds of the cyclopropane ring of alkylidenecyclopropanone silyl acetals takes place depending on the reagents employed.[9] Lewis acids induced the C2–C3 bond cleavage, while hydrogen chloride did the C1–C2 bond cleavage in dichloromethane. The present communication describes that the regioselectivity of the ring opening with hydrogen chloride can be controlled only by changing the solvent. The solvent effects are discussed on the basis of the mechanisms of acid catalysis.

The reaction of cyclohexylidenecyclopropanone acetal **1** with hydrogen chloride was carried out at rt in various solvents, including dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, DMF, and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP). The ring opening of **1a** and **1b** readily proceeded to give an ester **2** and chloride substitution products **3** and **4**, as shown in Scheme 1. No siloxy products were observed for **1a**. Yields of the products are dependent on the solvent used, as summarized in Tables 1 and 2. Ester **2** is the result of cleavage of the C1–C2 bond of **1**, while the chloride products **3** and **4** are the result of cleavage of the C2–C3 bond. Formation of **2** was observed for the reaction of **1b** in dichloromethane, as observed for **1a**.[9a] In contrast, the ring opening reaction in HFIP took place at the C2–C3 to give only **3** both for **1a** and **1b**. For **1a**, the regioselectivity **2**/(**3**+**4**) was gradually changed with the solvent employed; the content of **2** seems to decrease with the increasing polarity of the solvent. The reaction of **1b** prefers the formation of **2**, and the C1–C2 cleavage selectively took place even in DMF and aqueous acetonitrile. The regioselectivity of the reaction of **1a** is also affected by the water content in aqueous acetonitrile solutions; the fraction of **2** became lower with the



Scheme 1. Ring opening of **1** with hydrogen chloride.

Keywords: Cyclopropane; Brønsted acid; Regioselectivity; Ring opening.
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Table 1. Reaction of **1a** with hydrogen chloride[a]

Solvent	Yield (%)			**2**/(**3**+**4**)	**3**/**4**
	2	**3**	**4**		
CH_2Cl_2	82	<1	<1	>99/1	
Et_2O	59	19	2	73/27	89/11
THF	47	20	3	67/33	87/13
MeCN	37	22	9	55/45	71/29
99% MeCN/H_2O	35	48	14	36/64	77/23
99% MeCN/D_2O[b]	18	44	11	24/76	80/20
97% MeCN/H_2O	21	53	17	23/77	76/24
95% MeCN/H_2O	16	53	21	18/82	71/29
90% MeCN/H_2O	8	41	22	11/89	65/35
DMF	18	48	3	26/74	95/5
HFIP	<1	77	<1	<1/99	>99/1

[a] Reaction was carried out at rt for 1 h in the presence of **1a** (5 mM) and HCl (0.1 M).
[b] Deuterium chloride (0.1 M) was employed.

Table 2. Reaction of **1b** with hydrogen chloride[a]

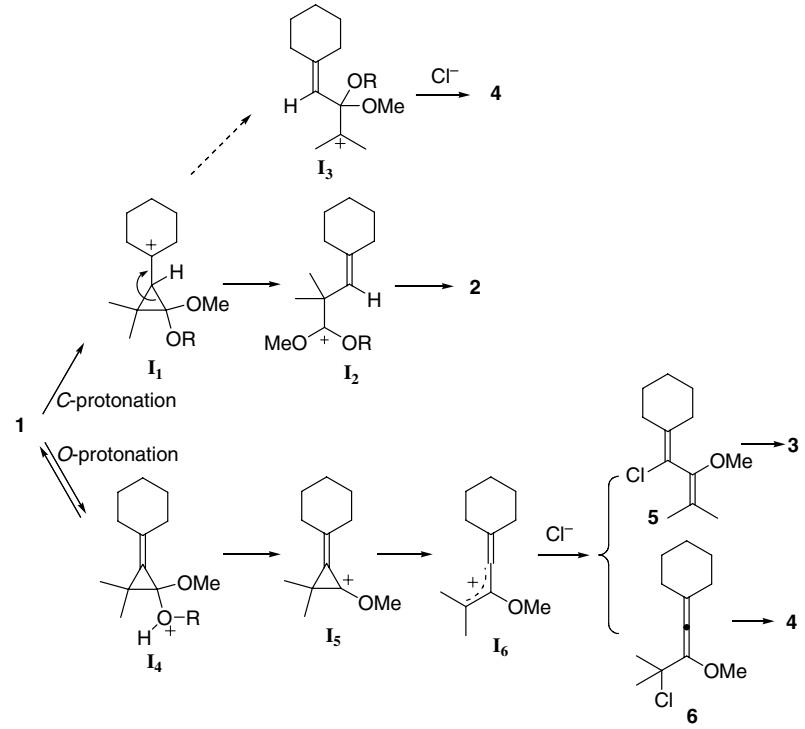
Solvent	Time (h)	Yield (%)			**2**/(**3**+**4**)
		2	**3**	**4**	
CH_2Cl_2	1	98	<1	<1	>99/1
Et_2O	20	60	<1	<1	>99/1
MeCN	1	82	<1	9	90/10
90% MeCN/H_2O	4	94	<1	<1	>99/1
DMF	75	98	<1	<1	>99/1
HFIP	1	<1	69	<1	<1/99

[a] Reaction was carried out at rt in the presence of **1b** (1 mM) and HCl (0.1 M).

increasing amount of water. When deuterium chloride was employed for the reaction of **1a** in aqueous acetonitrile, the ratio of **2**/(**3**+**4**) became smaller than that observed in the reaction with hydrogen chloride.

The acid-mediated ring opening reactions of **1** should be initiated by protonation, and substrate **1** contains two kinds of protonation sites, the acetal oxygen and the olefinic carbon, as illustrated in Scheme 2. Protonation of the olefinic carbon gives the cyclopropyl-stabilized cation $\mathbf{I}_1$, which may lead to the cleavage of the C1–C2 bond to form the dioxy-stabilized carbocation $\mathbf{I}_2$, finally. If the cleavage of the C2–C3 bond of $\mathbf{I}_1$ took place, a dimethylcarbocation $\mathbf{I}_3$ should have been generated and finally given **4**.[10] Judging from the stability of these alternative carbocation intermediates ($\mathbf{I}_2$ and $\mathbf{I}_3$), the C2–C3 bond cleavage via the carbon protonation is unlikely. In contrast, the C2–C3 bond cleavage via the oxygen protonation can reasonably explain the product distribution of **3** and **4**. Protonation of the acetal oxygen should provide the cyclopropyl cation $\mathbf{I}_5$ stabilized by the oxy group, and this is followed by ring opening at the C2–C3 bond to give alkylideneallyl cation $\mathbf{I}_6$.[11] The allylic cation $\mathbf{I}_6$ is trapped by chloride ion to give **5** and **6**, the facile hydrolysis of which results in the identified products **3** and **4**. The alkylideneallyl cation $\mathbf{I}_6$ can be generated by the reaction of **1a** with $TiCl_4$ in dichloromethane to lead to preferential formation of **3** (**5**) over **4**.[9] The ratio of **3**/**4** obtained in hydrogen chloride-mediated reaction agrees with that obtained in the Lewis acid-mediated reaction. Thus, both **3** and **4** may form mainly via the oxygen protonation, and the ratio of **2**/(**3**+**4**) becomes a measure of that of ring opening reactions initiated by the carbon and oxygen protonations.[12]

Protonation of carbon must be followed by rapid ring opening, while the protonation of oxygen must take



Scheme 2. Regioselective ring opening of **1**.

place reversibly and the ensuing acetal cleavage should be rate determining.[13] These mechanisms of carbon and oxygen protonations can be differentiated by the kinetic isotope effect: the rate-determining carbon protonation should be decelerated by deuterium acid while the equilibrium protonation should be facilitated.[14] The reaction with deuterium chloride gave a lower yield of **2** than that observed in the reaction with hydrogen chloride in accord with these considerations. Compared with the dimethyl acetal substrate **1b**, the monosiloxy substrate **1a** has a higher tendency to lead to the C2–C3 bond cleavage via the oxygen protonation. This may be rationalized if the siloxy oxygen is more basic than the methoxy oxygen due to the lower electronegativity of silicon, and the siloxy is the better leaving group.[15] This is also in agreement with the higher reactivity of **1a** than that of **1b**. Effects of the solvent on the regioselectivity are not straightforward. The reactions in a non-basic aprotic solvent CH_2Cl_2 provide solely **2**, the product of the carbon protonation, while those in an acidic protic solvent HFIP exclusively give **3**, the product of the oxygen protonation. The equilibrium protonation may be favored in a protic solvent abundant in available protons. In other basic solvents, the proton donor involved in the reaction should be the conjugate acid of the solvent, and many factors may delicately control the selectivity of the reaction.

In summary, regioselectivity of ring opening of alkylidenecyclopropanone acetal **1** with hydrogen chloride is fully controlled by solvent, and is rationalized by the competition of protonations at the acetal oxygen and the olefinic carbon of **1**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.067.

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