

# Regioselective Reactions of 1-Alkylidene-2-oxyallyl Cations with Furan: Control of [4 + 3] Cycloaddition, [3 + 2] Cycloaddition, and Electrophilic Substitution

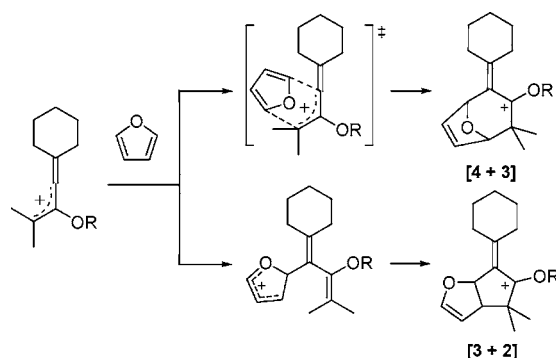
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## ABSTRACT



The ring opening of alkylidenecyclopropanone acetal under acidic conditions produces the 1-alkylidene-2-oxyallyl cation as an intermediate, which reacts with furan to give the [3 + 2] and [4 + 3] cycloadducts as well as an electrophilic substitution product. The product distribution is controlled by the oxy substituents of the cation and by the solvent employed.

Alkylideneallyl cations contain two electrophilic carbon atoms of  $sp$  and  $sp^2$  hybridizations.<sup>1,2</sup> Hybridization affects the electronic and steric character of these reaction sites toward nucleophilic reagents. The electronic property was deduced from the  $^{13}C$  NMR chemical shifts of the alkylideneallyl cations measured under superacidic conditions.<sup>1,2</sup> The

(1) Apeloig, Y.; Müller, T. In *Dicoordinated Carbocations*; Rappoport, Z., Stang, P. J., Eds.; John Wiley & Sons: Chichester, 1997; Chapter 2. Siehl, H.-U. In *Dicoordinated Carbocations*; Rappoport, Z., Stang, P. J., Eds.; John Wiley & Sons: Chichester, 1997; Chapter 5 and references therein.

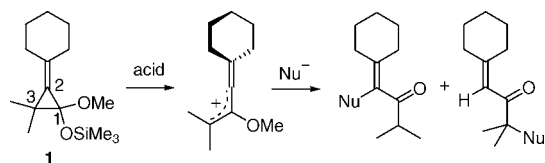
(2) For recent examples, see: Siehl, H.-U.; Brixner, S. *J. Phys. Org. Chem.* **2004**, *17*, 1039–1045. Siehl, H.-U.; Müller, T.; Gauss, J. *J. Phys. Org. Chem.* **2003**, *16*, 577–581.

reactivities of these ambident electrophiles with various nucleophiles are of interest from both mechanistic and synthetic viewpoints. However, few examples have been reported for the reaction of alkylideneallyl cations with nucleophiles: the solvolysis of 2-bromo-1,3-dienes and 2,3-dienyl alcohols took place via an alkylideneallyl cation intermediate that gave a solvolysis product.<sup>2</sup> The Lewis acid-catalyzed reaction of cyclonona-1,2-dien-4-one acetal with dienes gave [4 + 2] cycloadducts.<sup>3</sup>

We have recently found that the ring opening of alkylidenecyclopropanone acetal **1** with a Lewis acid<sup>4a,b</sup> and a Brønsted acid<sup>5ac</sup> generated the 1-alkylidene-2-oxyallyl cation,

which was trapped by chloride ion,<sup>5a,c</sup> methanol,<sup>5a</sup> and silyloxyalkenes<sup>5b</sup> (Scheme 1). The present communication

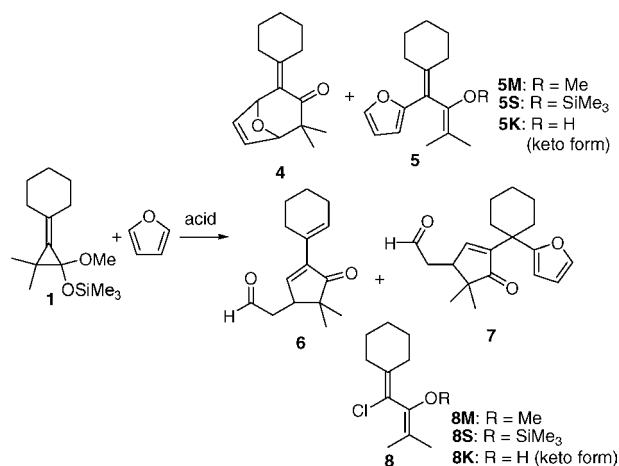
**Scheme 1.** Alkylideneallyl Cation Generated from **1**



shows that the [4 + 3] and [3 + 2] cycloadditions of furan with this cation are controlled by the oxy group of the oxyallyl cation as well as by the reaction conditions including the solvent.<sup>6,7</sup>

Cyclohexylidene-cyclopropanone bis(trimethylsilyl)acetal **2** and the dimethylacetal **3** as well as the mixed acetal **1** were treated with TiCl<sub>4</sub> at -78 °C in dichloromethane in the presence of furan to give adducts of furan, **4** and **5**, in addition to a small amount of chloride **8**, which was the major product in the absence of furan<sup>5a,c</sup> (condition A of Tables 1–3). All the products are the result of the C2–C3 bond cleavage of **1–3** and are rationalized by a reaction

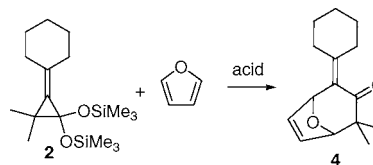
**Table 1.** Acid-Mediated Reactions of **1** with Furan



condition <sup>a</sup>	[furan] (mM)	yield (%) <sup>b</sup>				
		<b>4</b>	<b>5(5M/5S/5K)</b>	<b>6</b>	<b>7</b>	<b>8(8M/8S/8K)</b>
A	30	5	44(93/7/0)	<1	<1	5(100/0/0)
A	200	11	49(90/10/0)	<1	<1	10(100/0/0)
B	6	4	6(0/0/100)	26	<1	42(0/0/100)
B	15	5	13(0/0/100)	<1	43	4(0/0/100)
B	100	<1	<1	<1	44	<1
B <sup>c</sup>	100	<1	10(0/0/100)	<1	55	4(0/0/100)
B <sup>d</sup>	100	<1	66(0/0/100)	<1	<1	7(0/0/100)

<sup>a</sup> Under the condition A, reaction of **1** (7 mM) was carried out at -78 °C for 30 min in dichloromethane containing furan and TiCl<sub>4</sub> (14 mM). Under the condition B, reaction of **1** (7 mM) was carried out at 0 °C for 5 min in HFIP containing furan and HCl (20 mM). <sup>b</sup> Yields were determined by GC. <sup>c</sup> In the presence of H<sub>2</sub>O (1% v/v). <sup>d</sup> In the presence of THF (10% v/v).

**Table 2.** Acid-Mediated Reactions of **2** with Furan



condition <sup>a</sup>	[furan] (mM)	yield (%) <sup>b</sup>				
		<b>4</b>	<b>5(5S/5K)</b>	<b>6</b>	<b>7</b>	<b>8K</b>
A	13	44	7(0/100)	<1	<1	3
A	100	52	7(0/100)	<1	<1	<1
A <sup>c</sup>	100	70	4(24/76)	<1	<1	<1
B	15	76	<1	<1	<1	<1
B	100	67	<1	<1	<1	<1
B <sup>d</sup>	100	79	3(0/100)	<1	<1	5

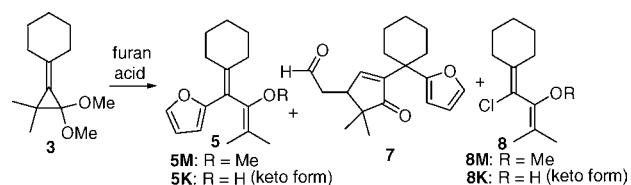
<sup>a</sup> See footnote a for Table 1. <sup>b</sup> Yields were determined by GC. <sup>c</sup> SnCl<sub>4</sub> was employed instead of TiCl<sub>4</sub>. <sup>d</sup> In the presence of H<sub>2</sub>O (2% v/v).

mechanism that proceeds via the alkylideneallyl cation intermediate. The reactions of **1** and **3** preferentially gave a furanyl product **5** in contrast to the preferential formation of the [4 + 3] cycloadduct **4** in the reaction of the disilyl acetal substrate **2**. The reaction also took place using SnCl<sub>4</sub>.

The reaction of **1** with furan also proceeds in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) containing hydrogen chloride at 0 °C to yield a cyclopentenone product **7** as well as the products obtained in the reaction with Lewis acids, **4**, **5**, and **8** (condition B). The formation of the cyclopentenone product **7** was not apparent with a deficient amount (less than 1 equiv) of furan, but a simple cyclopentenone product **6** was obtained. The addition of THF also retarded the formation of **7** for the reaction in HFIP with the increasing yield of **5**. The preferential formation of the [4 + 3] cycloadduct **4** was observed without the formation of **7** for the reaction of **2** in HFIP as was observed with the Lewis acid in dichloromethane (Table 2). The reaction of **3** in HFIP gave **7** (Table 3) with a product distribution similar to that of **1** in HFIP.

The product distribution for the reaction of **1–3** with furan depends on the reaction conditions as well as on the oxy

**Table 3.** Acid-Mediated Reactions of **3** with Furan

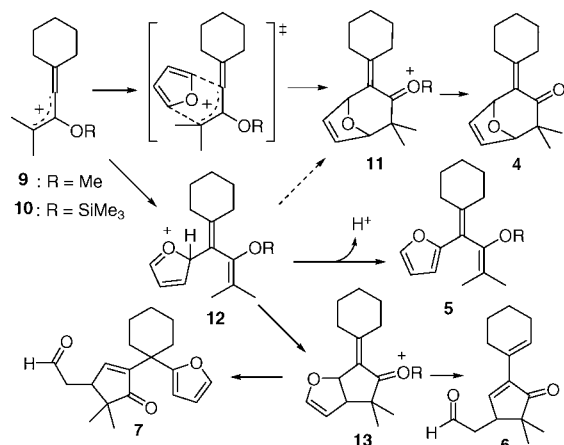


condition <sup>a</sup>	[furan] (mM)	yield (%) <sup>b</sup>				
		<b>4</b>	<b>5(5M/5K)</b>	<b>6</b>	<b>7</b>	<b>8(8M/8K)</b>
A	14	<1	56(81/19)	<1	<1	20(89/11)
B	100	<1	<1	<1	75	<1

<sup>a</sup> See footnote a for Table 1. <sup>b</sup> Yields were determined by GC.

group of the acetal substrates **1–3**. The diverse products of the reaction of **1–3** with furan are rationalized by the reaction pathways illustrated in Scheme 2. All the products are

**Scheme 2.** Possible Pathways for the Reaction of **9** (**10**) with Furan



provided by the nucleophilic addition of furan to the alkydeneallyl cation intermediate **9** (**10**), which is generated by the acid-mediated ring opening of cyclopropanone acetals **1–3**. The [4 + 3] cycloadduct **4** is simply formed via **11**, and the furanyl product **5** is formed by the deprotonation of **12**. The cyclopentenone structure of **6** and **7** may be formed via **13** that is a result of the [3 + 2] cycloaddition of **9** (**10**) with furan. The [4 + 3] cycloaddition must be concerted, whereas the [3 + 2] reaction should occur in a stepwise manner. Transformation from the dihydrofuran of **13** to the carbaldehyde of **6** and **7** is rationalized by the acid-mediated ring opening of the dihydrofuran via the carbon protonation (see below).

The reaction of **2** preferentially gave the [4 + 3] cycloadduct **4** in both HFIP and dichloromethane solvents, whereas only a small amount of **4** was obtained in the reactions of **1** and **3**, in which the product distribution depended upon the reaction conditions including the solvent. The contrasting tendency of the product distribution may be

(3) (a) Grob, C. A.; Spaar, R. *Helv. Chim. Acta* **1970**, *53*, 2119–2129. (b) Olsson, L.-I.; Claesson, A.; Bogentoft, C. *Acta Chem. Scand.* **1973**, *27*, 1629–1636. (c) Gelin, R.; Gelin, S.; Albrand, M. *Bull. Soc. Chim. Fr.* **1972**, 720–723.

(4) Gassman, P. G.; Lottes, A. C. *Tetrahedron Lett.* **1991**, *32*, 6473–6476.

(5) (a) Fujita, M.; Fujiwara, K.; Mouri, H.; Kazekami, Y.; Okuyama, T. *Tetrahedron Lett.* **2004**, *45*, 8023–8026. (b) Fujita, M.; Fujiwara, K.; Okuyama, T. *Chem. Lett.* **2006**, *35*, 382–383. (c) Fujita, M.; Hanagiri, S.; Okuyama, T. *Tetrahedron Lett.* **2006**, *47*, 4145–4148.

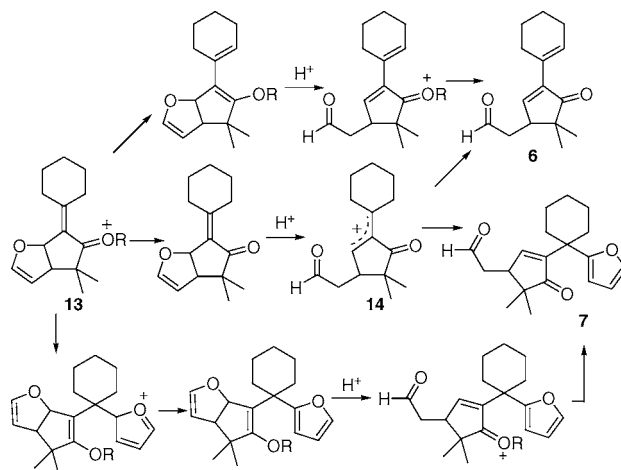
(6) (a) The [3 + 2] cycloaddition reactions of the alkydeneallyl cations have been reported, but the reaction proceeds via a metal complex<sup>6b</sup> and trimethylenemethane<sup>6c</sup> to result in a different regioselectivity. (b) For example: Binger, P.; Schäfer, B. *Tetrahedron Lett.* **1988**, *29*, 4539–4542. Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 4911–4915. (c) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867–877.

(7) (a) Palladium-catalyzed reactions of alkydeneallyl cations with furans gave an electrophilic substitution product at the 2-position of furan.<sup>7b</sup> (b) Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2661–2662. Nakamura, I.; Siriwardana, A. I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3445–3449.

ascribed to the difference in the oxy group of the alkydeneallyl cation intermediate: methyl acetals **1** and **3** give the methoxy cation **9**, and the disilyl acetal **2** produces the siloxy cation **10**. The preferential formation of the methoxy-substituted allylic cation **9** from the unsymmetrical acetal **1** is rationalized by the higher basicity and leaving ability of the trimethylsiloxy vs the methoxy group, and the same tendency has been observed in the reactions with the Lewis and Brønsted acids.<sup>5</sup> It is possible for the [4 + 3] intermediate **11** to form concertedly but also in a stepwise manner via **12**.<sup>8,9</sup> The preferential formation of the [4 + 3] cycloadduct **4** from **2** was independent of the solvent employed for the reaction in comparison with the solvent-dependent product distribution of the reactions of **1** and **3**, which may mainly proceed via **12**. The lack of a solvent effect is reasonable for the concerted pathway of the [4 + 3] cycloaddition of **10** with furan derived from **2**.<sup>10</sup> That is, the competition between the concerted reaction of the siloxy cation **10** and the stepwise one of the methoxy cation **9** may result in the product distribution depending on the oxy groups of the substrates **1–3** and on the reaction conditions including the solvent. Theoretical and stereochemical studies for the cycloadditions of 2-oxyallyl cations with dienes indicate that an electron-donating 2-oxy group decreases the electrophilicity of the cation resulting in a favorable concerted mechanism.<sup>8a,11</sup> The effect of the oxy group of the 2-oxyallyl cations agrees well with the difference between the methoxy- and siloxy-substituted alkydeneallyl cations (**9** and **10**).

The solvent-dependent product distribution for the reactions of **1** and **3** is rationalized by the reaction pathways bifurcated from the cation **12**. The acidic HFIP solvent retards the deprotonation from **12** to result in the promotion of an internal cyclization to give **13**. Tetrahydrofuran acts as a base to promote the deprotonation from **12** to yield **5** in HFIP. An excess amount of furan acts as a nucleophile toward **13** and/or **14** to yield the double addition product **7** as illustrated in Scheme 3 but does not work as a base due to the lower basicity. The use of a smaller amount of furan provides a single addition product **6** instead of the double addition product **7**. The formation of these two products may

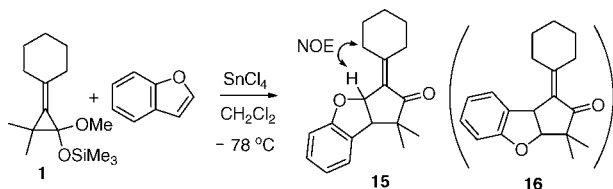
**Scheme 3.** Possible Pathways Leading to **6** and **7**



be a result of the [3 + 2] cycloaddition of **9** with furan, followed by the acid-mediated opening of the furan ring to give the formylmethylcyclopentenone (**6** and **7**).<sup>12</sup>

To obtain further information on the [3 + 2] cycloaddition of the alkylideneallyl cation **9**, the reaction with 2,3-benzofuran was carried out as shown in Scheme 4. The

**Scheme 4.** Reaction of **1** with Benzofuran



reaction of **1** gave a simple [3 + 2] cycloadduct **15** as a single regioisomer in 76% isolated yield. No regioisomer **16** was detected by <sup>1</sup>H NMR measurements. The regioisomeric structure of **15** confirmed by NOE measurements is quite compatible with the cyclic structure of **13**. These results are consistent with the mechanism, in which the

(8) For recent reviews of [4 + 3] cycloaddition, see: (a) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351–478. (b) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371–2395. (c) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595–605. (d) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1–19. (e) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934–1949.

(9) The [4 + 3] cycloaddition via nucleophilic addition at the sp<sup>2</sup> carbon of **9** (**10**) cannot be excluded, but there is no evidence of sp<sup>2</sup> addition products.

(10) (a) Solvent effects on the reaction of the 2-oxyallyl cation with furans have been reported.<sup>10b</sup> (b) Shimizu, N.; Tanaka, M.; Tsuno, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1330–1340.

(11) (a) Cramer, C. J.; Barrows, S. E. *J. Phys. Org. Chem.* **2000**, *13*, 176–186. (b) Cramer, C. J.; Barrows, S. E. *J. Org. Chem.* **1998**, *63*, 5523–5532.

(12) If the carbaldehyde was formed before the internal cyclization of **12**, the cyclopentenones **6** and **7** could not have been obtained.

nucleophilic addition of furan selectively proceeds at the sp carbon of the alkylideneallyl cation **9** to yield **5–7** via **12**.<sup>13</sup> The selective addition of furan at the sp carbon of **9** is in contrast to the sp<sup>2</sup> addition observed for the reaction with siloxyalkenes and methanol. Although reasons for the regioselective addition at the sp carbon are not clear, the frontier orbital interactions between furan and the allyl cation may control the regioselectivity<sup>14</sup> because the sp selectivity is not compatible with the electronic and steric advantages of the sp<sup>2</sup> addition of nucleophiles to **9**.<sup>1,2,5b</sup>

In summary, the 1-alkylidene-2-oxyallyl cations (**9** and **10**) generated from the alkylidenecyclopropanone acetals **1–3** were employed for the reaction with furan. The [4 + 3] cycloaddition effectively takes place for the reaction via the siloxyallyl cation (**10**). The [3 + 2] cycloaddition preferentially proceeds for the reaction of the methoxyallyl cation (**9**) in a nonbasic HFIP solution. Control of the modes of these cycloadditions is rationalized by the concerted and stepwise mechanisms for the reaction of the 1-alkylidene-2-oxyallyl cations with furan.

**Supporting Information Available:** General procedures and characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) (a) If the [3 + 2] cycloaddition was initiated by nucleophilic addition at the sp<sup>2</sup> carbon of **9**, the nucleophilic site of furan should be the 3-position that has a poorer reactivity toward an electrophile than the 2-position. The electrophilic substitution of furan with carbocations proceeds at the 2-position.<sup>13b</sup> (b) For example, see: Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* **2005**, *127*, 9348–9349.

(14) (a) An alternative mechanism for the preferential sp addition may be the formation of **12** by the ring opening of the concertedly formed **11**. A similar ring opening reaction has been reported for the [4 + 3] cycloaddition products of a 2-oxyallyl cation with furan.<sup>14b</sup> However, the same regiochemistry as **13** was observed for the [3 + 2] cycloaddition of 2,3-benzofuran with **9** despite the improbable [4 + 3] cycloaddition with benzofuran. Treatment of **4** with TiCl<sub>4</sub> in dichloromethane at –78 °C gave no **5**. Therefore, **12** may be directly formed from **9** but not via **11**. (b) Mann, J.; Wilde, P. D.; Finch, M. W. *Tetrahedron* **1987**, *43*, 5431–5441.