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A New Route to Silyl-substituted Cyclobutenones and Silylketenes

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Abstract

2-Silyl-cyclobutene(di)ones are obtained by an addition/substitution approach on dimethyl squarate using silyl anions. The acetal and in particular the thioacetal derivatives readily undergo electrocyclic ring opening to reactive silyl(vinyl)ketenes.

Keywords

Silyl anions; Cyclobutenones; Silylketenes; Cyclopentenones; Cycloaddition Reactions

Introduction

1-Alkenyl(silyl)ketenes (“silyl(vinyl)ketenes”) \textsuperscript{1} show remarkable stability, but are sufficiently reactive especially in cycloaddition chemistry to make them attractive synthetic building-blocks.\textsuperscript{2-4} including in applications such as natural product synthesis.\textsuperscript{5} Four main routes have been described for their synthesis which, however, suffer from certain drawbacks (Scheme 1). Thus, the dehydrohalogenation of appropriately substituted acyl chlorides \textsuperscript{2} is limited to produce vinylketenes in which \textit{R}\textsuperscript{2} = H in order to avoid regiochemical ambiguity.\textsuperscript{6} Similarly, the Wolff rearrangement of \textit{α,β}-unsaturated \textit{α'}-diazoketones \textsuperscript{3} works best for purely aliphatic 1-alkenyl substitution.\textsuperscript{2} The outcome of the reaction of silyl-substituted alkynes \textsuperscript{4} with Fischer carbene complexes \textsuperscript{5} depends on the size of the silyl substituent and is limited to the preparation of vinylketenes in which \textit{R}\textsuperscript{3} is an alkoxy group.\textsuperscript{5,7,8} Finally, the [2+2] cycloaddition of aryl(silyl)acetylenes \textsuperscript{4} (\textit{R}\textsuperscript{2} = aryl) with dichloroketene and subsequent dehalogenation gives 2-silyl-cyclobutenones and from there the corresponding silylketenes, but the regioselectivity in the cycloaddition step can only be secured when \textit{R}\textsuperscript{2} is an aryl substituent.\textsuperscript{5} So it appeared attractive to develop an independent method for regiospecific introduction of a silyl substituent into the cyclobutenone ring.
Results and discussion

Dialkyl squarates 7 are excellent starting materials for the synthesis of cyclobutene(di)ones. 9,10 In a convenient one-pot reaction sequence, carbanions are first added to 7, the resulting alkoide is trifluoroacetylated to 8, and then a nucleophile is introduced in an SN2' process to give intermediate 9 (Scheme 2).11–13 Thus, with water as nucleophile cyclobutenediones are formed via the hemiacetal, the use of alcohols as nucleophile leads to acetals, and the addition of amines produces cyclobutenimines.14 We reasoned that this approach might be amenable to the introduction of a silyl residue if a silyl anion is used as attacking nucleophile in the 1,2 addition step (R2 = silyl). In fact, silyl anions 10a–c turned out to give a smooth addition to squarate 7 (R1 = Me) and, depending on the method of work-up, provide dienes of type 7 (one silyl instead of MeO) or acetals 11a–c (Scheme 3).16 Isolated yields are good for 11a and 11b, but probably due to steric reasons, 11c is formed only in trace amounts (Table 1). Products 11 are stable at room temperature and show no apparent tendency to undergo ring opening to silylketenes.

Interestingly, the remaining methoxy group in methoxycyclobutenone 11a can be exchanged for a methyl or phenyl group following the addition/substitution approach outlined in Scheme 2. Thus, with methyl or phenyllithium and after aqueous work-up, cyclobutenones 13a (57%) and 13b (77%) are formed (Scheme 4).

In a further modification, the acetal group in acetals 11a,b and 13a,b can be transformed into a thioacetal group which, if a dithiolane is formed, can be considered as a latent thione unit (Scheme 5).17 As in earlier studies, zirconium tetrachloride turned out to be the most efficient Lewis acid catalyst for this transformation. However, yields remain relatively low as in contrast to acetals 11, 13, thioacetals 14 show, even at room temperature, a pronounced tendency to undergo electrocyclic ring opening to give silylketenes which display variable stability. Thus, immediately after chromatographic purification, products 14 already show the characteristic ketene vibration at 2100 cm⁻¹ in the IR spectra. The best yield is obtained for thioacetal 14c, followed by 14d, while the methoxy-substituted derivative 14a is isolated in lower yield and 14b only in trace amounts (Table 1). For 14c, complete conversion into silylketene 15b20 is achieved by heating to 90 °C in toluene for 30 min. However, due to the limited stability of ketenes 15 and the corresponding species derived from acetals 13 it is advantageous to use precursors 12–14 in reactions and generate the silylketene in situ.

In previous studies, silylketenes have been shown to be useful substrates for reaction with C1 transfer reagents to give cyclopentenones in a [4+1] approach.21–23 A particularly smooth reaction had been observed for (trimethylsilyl)diazomethane21 and this is now confirmed for the reaction with the novel silylcyclobutenones / silylketenes 11–14/15 (Scheme 6).24 Generally good yields (50–74%)25 are obtained both from acetals 11 and 13 and from thioacetals 14 implying that at temperatures above 90 °C ketene intermediates of type 15 are also formed from acetals 11, 13 which at room temperature are stable compounds with no apparent tendency to undergo electrocyclic ring opening. However, only trace amounts of cyclopentenone products 16c,f are formed from silylcyclobutenones 13a and 14b where the corresponding ketene intermediates 15 are apparently quite labile and preferably undergo decomposition.

The inherent 4π system in vinylketenes 15 invites the use of precursors 11, 13, and 14 as dienes in Diels-Alder chemistry.2 Here we had little success with olefinic reaction partners. Only tetracyanoethylene gives a smooth reaction with thioacetals 14c,d, but no cycloadduct 17 with 3-methoxy-cyclobutenone 14a (Scheme 7). The alternative 2-alkenyl-cyclobutanone
structure for 17 can be ruled out because of a carbonyl vibration at relatively low wavenumber around 1700 cm\(^{-1}\).

[2+2] Cycloadditions of cyclobutenones 14 with C=N systems turned out to be more successful. In particular, 14d undergoes a smooth reaction with N-methyl-4-nitrobenzaldimine to give β-lactam 18 in two diasteromeric forms with a characteristic carbonyl absorption at 1740 cm\(^{-1}\) (Scheme 7). Under the reaction conditions, ketene 15a from cyclobutenone 14a apparently decomposes and 14c/15c gives no reaction. In contrast, N-silylimines and silylketene precursors 14c,d give δ-lactams 19a-d,\(^{26}\) but to obtain the indicated yields of 16–72% catalysis by zinc triflate is required; the aqueous work-up leads to N-desilylation.

**Conclusion**

The addition/substitution method (Scheme 2) offers convenient access to silylcyclobutenones. Acetals 11 show no spontaneous electrocyclic ring opening to silylketenes 12, but the ketene species is apparently formed on heating with silyldiazomethane and trapped to give cyclopentenones 16a–d. Thioacetals 14a–d are in equilibrium with silylketenes 15, which can be trapped to 16–19, but decomposition of 15 sometimes interferes.

**Acknowledgments**

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**References and notes**

16. Cyclobutenone 11a. Typical Procedure: Me\(_2\)PhSiLi (70 mL, 0.5 M in THF, 35.0 mmol) was added dropwise to 7 (R\(^1\) = Me; 4.886 g, 34.4 mmol) in dry THF (500 mL) at −78 °C. After 20 min, TFAA (5.5 mL, 34.4 mmol) was added and after another 20 min dry MeOH (40 mL). The mixture was allowed to warm to rt over 30 min with stirring and aq. NaHCO\(_3\) (20%, 250 mL) added. The product was extracted with ether (2 × 250 mL), the ethereal solution washed with brine (2 × 150 mL), dried (MgSO\(_4\)) and concentrated in vacuo. Purification by flash chromatography (SiO\(_2\)).
petroleum ether / EtOAc = 101) yielded cyclobutenone 11a (8.212 g, 46 %). Yellow oil; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.56 (m, 2 H), 7.38 (m, 3 H), 3.95 (s, 3 H), 3.53 (s, 6 H), 0.42 (s, 6 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 193.5, 192.1, 136.9, 133.7, 131.5, 129.5, 128.0, 115.0, 60.2, 53.5, −2.5 ppm. IR (film): $\nu$ = 1750 cm$^{-1}$. HRMS (ESI): [M+Na]$^+$ found 315.1023, calcd. 315.1023.


20. Selected data of compounds: Ketene 15b: slightly yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.26): $\delta$ = 7.60 (m, 2 H), 7.39 (m, 1 H), 7.29−7.17 (m, 3 H), 3.38 (m, 4 H, SCH$_2$), 1.77 (s, 3 H), 0.49 (s, 6 H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 198.6, 137.1, 133.8, 129.6, 85.3, 38.8, 38.1, 24.8, 0.9, −1.6. IR (film): $\nu$ = 2958, 2086, 1589, 1428, 1252, 1115, 982, 813, 734, 701 cm$^{-1}$.


25. Cyclopentenone 16a: waxy solid, mp 74 °C. $^1$H NMR (200 MHz, CDCl$_3$ = 7.26): $\delta$ = 7.37 (m, 1 H), 7.21 (m, 4 H), 3.47 (s, 3 H), 3.28 (s, 3 H), 3.14 (s, 3 H), 2.41 (s, 1 H), 0.06 (s, 3 H), 0.04 (s, 3 H), 0.00 (s, 9 H). $^{13}$C NMR (125 MHz, CDCl$_3$ = 77.4): $\delta$ = 206.7, 188.8, 140.6, 134.5, 130.0, 128.9, 116.0, 107.9, 62.4, 52.4, 52.3, 51.1, 0.1, 0.0. IR (film): $\nu$ = 2950, 2899, 2834, 1678, 1619, 1458, 1428, 1308, 1246, 1147, 1110, 1045, 970, 841, 816, 777, 734, 701, 650 cm$^{-1}$. HRMS (TOF-MS ES): [M + Na]$^+$ found 401.1591, calcd. 401.1584.

26. $\delta$-Lactam 19c: colorless crystals, mp 205 °C. $^1$H NMR (200 MHz, CDCl$_3$ = 7.26): $\delta$ = 7.91 (m, 2 H), 7.56 (m, 2 H), 7.24 (m, 11 H), 6.42 (broad s, 1 H), 5.29 (s, 3 H), 2.97 (m, 4 H), 0.45 (s, 3 H), 0.16 (s, 3 H). $^{13}$C NMR (125 MHz, CDCl$_3$ = 77.4): $\delta$ = 177.4, 139.3, 137.0, 136.9, 133.0, 130.5, 129.5, 129.7, 129.5, 128.9, 128.5, 67.7, 48.2, 39.2, 38.4, 1.5, 0.0. IR (KBr): $\nu$ = 3166, 3056, 1676, 1491, 1445, 1427, 1374, 1348, 1303, 1246, 1111, 1018, 835, 818, 775, 730, 701, 652, 610, 544 cm$^{-1}$. HRMS (TOF-MS ES): [M + Na]$^+$ found 496.1207, calcd. 496.1201.
Scheme 1.
Routes to silyl(vinyl)ketenes.
Scheme 2.
Introduction of a substituent $R^2$ into a squarate
Scheme 3.
Synthesis of silyl-substituted cyclobutenones (for yields see Table 1)
Scheme 4.
Methoxy substitution in methoxy-cyclobuteneone 11a.

13a: $R^3 = \text{Me}$ (58%)
13b: $R^3 = \text{Ph}$ (77%)
Scheme 5.
Formation of thioacetals 14 and electrocyclic ring opening to ketenes 15 (for yields see Table 1).
Scheme 6.
2,5-Bis-silylated cyclopentenones 16 from acetals 11, 13 or thioacetals 14.
Scheme 7.
Formal Diels-Alder reactions of silylketene precursors 14. (a) TCNE, toluene, 110 °C, 12 h (for 14c,d). (b) N-Methyl-4-nitrobenzaldimine, toluene, 110 °C, 24 h (for 14d). (c) TMS-N=CH-Ph or TMS-N=CH-CH=CH-Ph, cat. Zn(OTf)₂, THF, rt, 24 h (for 14c,d); aq. work-up.
Table 1
Starting materials, products, and yields in the reactions of Schemes 3, 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 (R¹ = Me)</td>
<td>11a</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>7 (R¹ = Me)</td>
<td>11b</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>7 (R¹ = Me)</td>
<td>11c</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>11a</td>
<td>14a</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>11b</td>
<td>14b</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
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</tr>
<tr>
<td>9</td>
<td>13b</td>
<td>14d</td>
<td>32</td>
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