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Synthesis of γ-Acylmethylenetetronates from Squaric Acid

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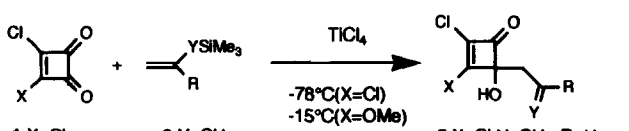
Abstract: Adducts obtained from the addition reaction of squaric acid ester chloride with a silyl enol ether were converted thermally to the title compounds *via* consecutive ring opening, recyclization and dehydrochlorination.

A wide variety of compounds containing the 5-ylidene-2(5*H*)-furanone moiety are found in nature,[1,2] and some of these display useful biological properties (*e.g.* protoanemonin,[3a] fimbrolide,[3b] basidalin,[3c] agglomerin,[3d] and rubrolide[3e]). Thus, synthetic methods to construct this ring system have drawn much attention.[2,4,5,6] Recently, the ring-opening reaction of cyclobutenones has emerged as a useful method for elaboration of complex ring systems.[7] Thermal electrocyclic ring-opening takes place with high torquoselectivity (*e.g.* outward rotation for an electron-donating 4-substituents)[8] to form a vinylketene, which then leads to the products by a successive ring closure process. In the case of thermal reactions of 4-hydroxycyclobutenones, the selective ring-opening suitably arranges 4-alkenyl (alkynyl) and allyl substituents in a cis-relationship with a ketene group, which then allows further electrocyclization to phenols (quinone)[7,9] and [2+2]cycloaddition to bicyclo[3.2.0]heptenones[10], respectively. We now wish to report another ring transformation of the 4-hydroxycyclobutenone derivative with a 4-acylmethyl substituent leading to the title compounds.

The required structure is most easily accessible from squaric acid. Recently we reported the Lewis acid-catalyzed addition reaction of squaric acid dichloride **1** and ester chloride **2** with unsaturated organosilanes **3** and **4** to give 4-hydroxycyclobutenones **5-8** (Scheme 1).[11] These products are promising for the ring-transformation as described above.



1 X=Cl
2 X=OMe

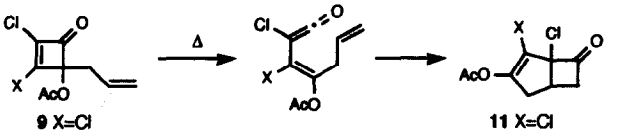
3 Y=CH_2
4 Y=O

5 X=Cl, Y=CH_2, R=H
6 X=OMe, Y=CH_2, R=H
7 X=Cl, Y=O, R=Ph
8 X=OMe, Y=O

Scheme 1

Moore demonstrated that the vinylketenes derived from 4-allylated squarates undergo facile intramolecular [2+2]cycladdition to give bicyclo[3.2.0]heptenones.[10] In fact, our allylsilane-squaric acid chloride adducts followed this type of reaction to afford the expected cycloadduct in a high yield, provided the 4-hydroxyl group was protected by acetylation (Scheme 2). In this regard, the 4-acetoxycyclobutenone **9** derived from dichloride **2** was heated to reflux in xylene for 1 h to give **11** in 91% yield. Similarly, **10** derived from the ester chloride **3**

underwent the same rearrangement to **12** at relatively lower temperature (reflux in toluene).[12] The structures were assigned on the basis of spectral data.[13] This reaction failed for the 4-hydroxy derivatives, *i.e.* **5** and **6**.

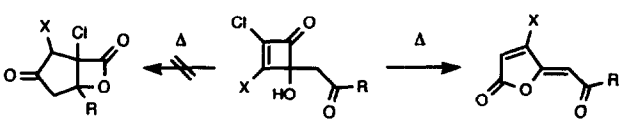


9 X=Cl
10 X=OMe

11 X=Cl
12 X=OMe

Scheme 2

On the analogy of the conversion of **9** to **11**, 4-acylmethyl-substituted cyclobutenones **7** and **8** derived from the reaction of **1** and **2** with a silyl enol ether **4** were expected to give a cyclopentane-fused β-lactone **13** (or its decarboxylated product).[14] Interestingly, the reaction took a different course. The rearrangement of 4-phenacyl-substituted cyclobutenone **7** occurred smoothly at reflux temperature in benzene for 2 h, and the product was separated by silica gel column chromatography in 37% yield. On the basis of its spectral data, the strucure was assigned as γ-phenacylidenefuranone **14** rather than a β-lactone (Scheme 3). The mass spectral and elemental analyses indicated loss of HCl from the molecule, and the IR absorptions at 1795 and 1661 cm^{-1} suggested the existence of a furanone moiety. ^{13}C NMR signals appeared all at lower field (δ_C 106.3, 128.7, 129.3, 132.0, 134.3, 136.6, 138.1, 157.8, 163.4 and 189.3), showing all the carbons to be sp^2 hybridized. Particularly the ^1H NMR spectrum revealed that two vinylic protons (δ_H 7.03 and 8.36) had a long-range coupling of J=0.6 Hz. The observed spectral patterns were closely related to those reported for a γ-methylenefuranone and supported *Z*-geometry of a benzoyl group by the long-range coupling.[15] In the same manner the methoxy-substituted analog **8a** produced γ-phenacylidenetetronate **15a** upon heating in xylene for 2 h. Again the spectral data of the product were consistent with the tetronate structure.[16] In this case the yield was low (15%), probably because the liberated HCl damaged the product. To this end, the reaction was carried out in the presence of a base; pyridine was more effective than 4-dimethylaminopyridine, triethylamine and *N,N*-diethylaniline and the yield was raised to 64%. The other γ-acylmethylenetetronate **15b-15f** were thus obtained in 54-63% yield under these conditions from 1,2-addition products **8b-f** starting from ester chloride **3** and silyl enol ethers of alkyl, alkenyl and aryl ketones **4b-4f** (Table). This ring transformation was also applicable to a ketene silyl acetal **4g** (entry 7).



13

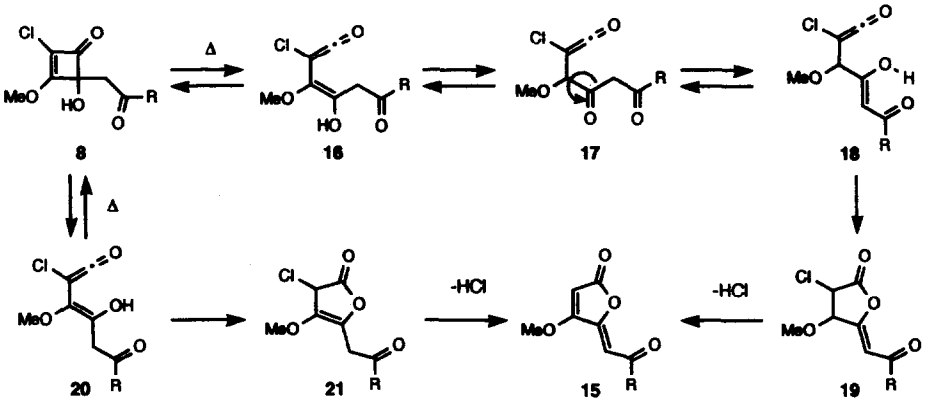
7 X=Cl,R=Ph
8 X=OMe

14 X=Cl,R=Ph
15 X=OMe

Scheme 3

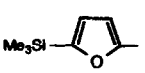
Scheme 4 illustrates the plausible mechanism for the stereospecific formation of the tetronates **15**. The 1,2-addition product **8** undergoes thermally allowed electrocylic ring-opening to give an enol ketene **16**. Although the hydroxyl group may be oriented outwardly as a result of the torquoselective ring-opening, favorable isomerization of the enol moiety can occur *via* a 1,3-diketone **17** and recyclization to a γ-lactone **19**. Subsequent dehydrochlorination affords the tetronate **15**. The observed *Z*-geometry of the γ-methylene group of **15** is attributable to the hydrogen-bonded enol form **18** of the 1,3-diketone **17**. Thermolysis of trimethlsilyl-protected

derivative of **8a** resulted in only decomposition of the starting materials, probably because of fixation of the enol form. The other mechanism involves the opposite way of ring-opening; the hydroxyl group may be oriented inwardly with a less favored but kinetically competitive process. The following lactonization and stereospecific dehydrochlorination leads to thermodynamically more stable *Z*-isomer (**8** → **20** → **21** → **15**).



Scheme 4

Table Formation of Tetronate **15** from Ester Chloride **2** and Silyl Enol Ether **4**

entry	R	4	8 (Yield %)[a]	15 (Yield %)[b]	mp (°C)
1	Ph	**4a**	**8a** (80)	**15a** (64)	159-162
2	CH_3	**4b**	**8b** (72)	**15b** (56)	80-83
3	$CH_3(CH_2)_4$-	**4c**	**8c** (61)	**15c** (63)	oil
4		**4d**	**8d** (45)	**15d** (61)	74-78
5		**4e**	**8e**(73)	**15e** (61)	77-80
6		**4f**	**8f**(82)	**15f** (54)	131-133
7	PhO	**4g**	**8g**(83)	**15g** (37)	136-139

a) General Procedure: The reaction was carried out at -15°C in the same manner as described in ref. 11b.
b) General Procedure: A solution of **8** (0.03 M) and pyridine (1.1 eq.) in dry xylene was refluxed for 2 h. The solvent was evaporated and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 3:1) to give the tetronate **15**.

In conclusion, a novel transformation of squaric acid ester chlorides to γ-acylmethylenetetronates was developed in which an acyl group was introduced stereospecifically (*Z*-geometry). This merit of preparation overcomes the non-stereoselective condensation reaction of maleic anhydride with an ylide.[6a-f] The present method seems to be potentially useful for the synthesis of bioactive compounds having a butenolide structure.

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12. The corresponding amide chloride (**5**, X=NEt_2) resisted to udergo the ring-opening even by heating in mesitylene for 3 h. This fact was indicative of dependency of the ring-opening reactivity on C_3- as well as C_4-substituents (ref. 8a).
13. For **12**, IR (neat) 1792, 1769, 1682, 1198 cm^{-1}; ^1H NMR δ 2.20 (3 H, s), 2.55 (1 H, d, *J* =16.4 Hz), 2.80 (1 H, m), 3.11 (1 H, dd, *J* =16.4, 7.4 Hz), 3.12 (1 H, dd, *J* =18.2, 6.8 Hz), 3.46 (1 H, dd, *J* =18.2, 9.6 Hz), 3.77 (3 H, s); ^{13}C NMR δ 20.7, 32.7, 33.3, 50.6, 58.6, 82.6, 131.8, 137.4, 168.4, 197.7; MS m/e (rel intensity) 230 (M^+, 2), 187 (60), 160 (80), 146 (100).
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16. For **15a**, IR (KBr) 1803, 1680, 1624, 961, 833 cm^{-1}; ^1H NMR δ 4.03 (3 H, s), 5.44 (1 H, d, *J* =0.6 Hz), 6.55 (1 H, d, *J*=0.6 Hz), 7.44-8.00 (5 H, m); ^{13}C NMR δ 59.9, 91.4, 100.2, 128.9, 129.0, 133.8, 138.0, 151.0, 167.6, 171.0, 188.5; MS m/e (rel intensity) 230 (M^+, 10), 170 (36), 105 (100).

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