Tetrahedron Letters,Vol.29,No.41,pp 5241-5244,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# SILICA GEL-CATALYZED CYCLIZATIONS OF MIXED KETENE ACETALS

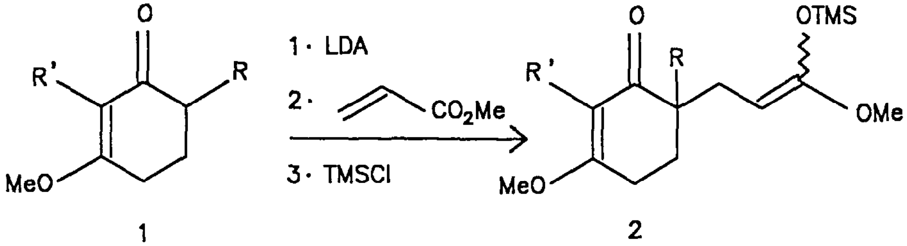
Dieter Schinzer*, Markus Kalesse, and Jazid Kabbara

Institut für Organische Chemie der Universität Hannover, Schneiderberg 1B,
D-3000 Hannover 1, W-Germany

Summary: Mixed ketene acetals of type 2 undergo smooth cyclization upon treatment with silica gel yielding diastereoselectively bicyclo[2.2.2]octanones of type 3. Alternatively, the same result was obtained by exposure of the substrates to $TiCl_4$ at low temperature.

In connection with our studies of Lewis acid-induced cyclizations of allylic and propargylic silanes[1-6] we examined mixed ketene acetals as potential new terminating groups for such cyclization reactions. During these studies we discovered a new cyclization mode yielding highly functionalized bicyclo[2.2.2]octanones.

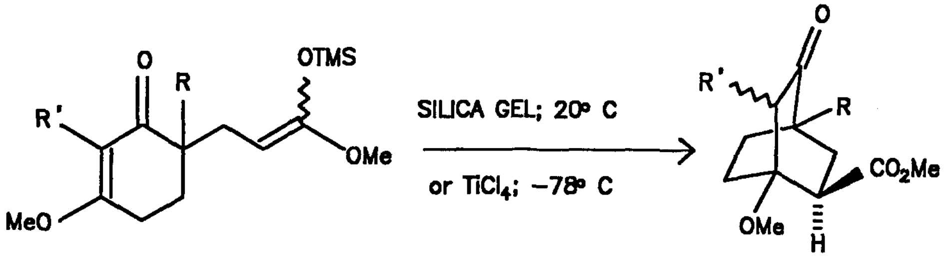
Vinylogous esters of type 1 can be deprotonated with LDA at low temperature. Addition of acrylic ester, and in situ silylation with trimethylsilyl chloride yielded the desired mixed ketene acetals 2. No trace of double Michael addition was detected[7-9].



1 2

R = H, Me
R' = H, Me

Compounds of type 2 are quite stable and can be purified by distillation. Exposure of compounds 2 to a short column of silica gel led in almost quantitative yield to compounds 3[10]. The products obtained are diastereomeric pure containing the exo-configuration at the ester group, which is easily shown by a W-coupling in the 400 MHz $^1$H-NMR spectra.



2

3

R = H, Me

R' = H, Me

The same result was obtained by treatment of compounds 2 with $TiCl_4$ at low temperature.

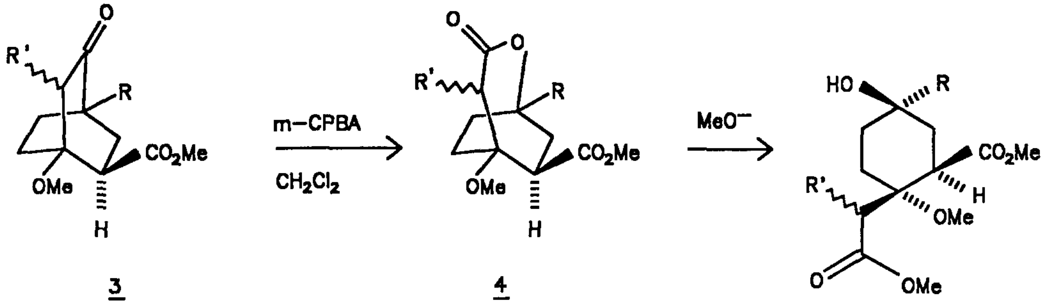
**TABLE I**

| Conversion of 2 → 3 with $TiCl_4$ at -78°C; | | Yield |
|---|---|---|
| 2 R= H; R'=H | 3 R= H; R'= H | 72% |
| 2 R= Me; R'= H | 3 R= Me; R'= H | 83% |
| 2 R= Me; R'= Me | 3 R= Me; R'= Me | 54% |

| Conversion of 2 → 3 with silica gel at 20°C; | | Yield |
|---|---|---|
| 2 R= H; R'= H | 3 R= H; R'= H | >98% |
| 2 R= Me R'= H | 3 R= Me; R'= H | >98% |
| 2 R= Me R'= Me | 3 R= Me; R'= Me | >98% |

| Conversion of 1 → 3 with silica gel at 20°C; | | Yield |
|---|---|---|
| 1 R= H; R'= H | 3 R= H; R'= H | 22% |
| 1 R= Me; R'= H | 3 R= Me; R'= H | 63% |
| 1 R= Me; R'= Me | 3 R= Me; R'= Me | 54% |

Compounds of type 3 are of general interest because they can easily be transformed into monocyclic species as shown by a regioselective Baeyer-Villiger oxidation to a single lactone 4, and subsequent ring opening to compound 5 with three defined configurations, with two of them quaternary.



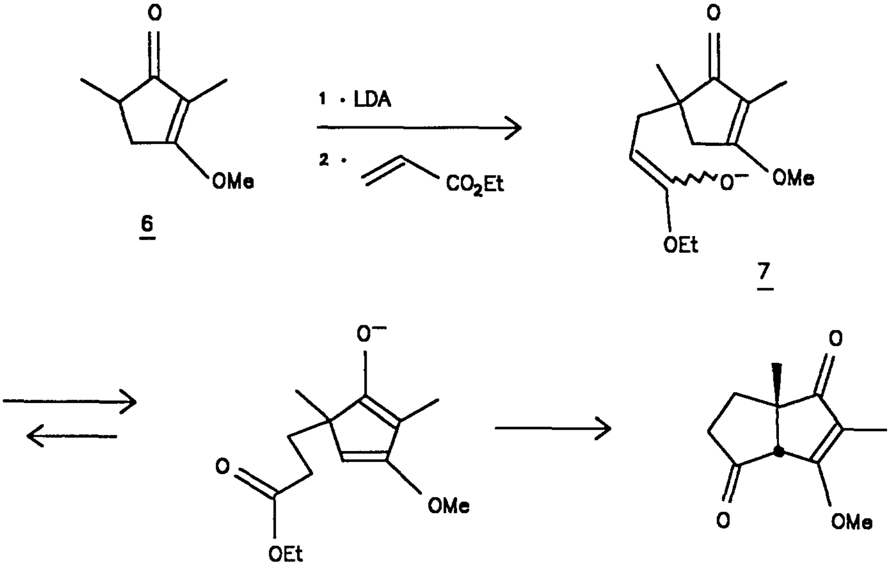
3

4

R = Me
R' = H

5

A completely different reaction was obtained with compound 6. We were unable to isolate a mixed ketene acetal, but instead the bicyclo[3.3.0]octanone[11] 9 was obtained in 25% yield. The product can be explained by an addition-transprotonation sequence followed by cyclization. The primary adduct probably suffers proton transfer to the intermediate 8, followed by an intramolecular ester condensation:



6

7

8

9

In conclusion, we have shown that highly functionalized compounds of type **3** can be obtained by a very simple one-pot purification-cyclization procedure starting with vinylogous esters. Further investigations of these new reactions are in progress.

**Acknowledgement:** This work was supported by the Deutsche Forschungsgemeinschaft (DFG) (Heisenberg-fellowship to D.S.), and the Fonds der Chemischen Industrie.

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10. **Typical procedure:** To a freshly prepared solution of LDA (4.4 ml of diisopropylamine, 10 ml of butyl lithium) in 20 ml of THF is added at -78° C 2.37g (16.7 mmol) of vinylogous ester **1** (R= Me; R'= H). The reaction mixture is stirred for 20 min at the same temperature, and 1.42 ml (16.7 mmol) of acrylic ester is added. After stirring overnight at room temperature 2.5 ml (14.7 mmol) of TMSCl is added in one portion at -78° C. The mixture is poured into a solution of 20ml of saturated NaHCO$_3$, extracted twice with 20ml of ether, washed with 30ml of brine, and dried over MgSO$_4$. The crude solution is passed through a short path of silica gel, and the solvent is removed under reduced pressure to obtain 2.0g (9.0 mmol) (63%) of pure **3** (R= Me; R'= H). IR(Film): 2960; 2870; 2840; 1725; 1650; 1610; 1455; 1435; 1170; 1110; 910 cm$^{-1}$. $^1$H-NMR(CDCl$_3$): 0.99 (s, 3H); 1.7 (m, 4H); 2.1 (m, 2H); 2.4 (m, 2H); 3.0 (m, 2H); 3.28 (s, sH); 3.75 (s, 3H). $^{13}$C-NMR(CDCl$_3$): 211.45 (s); 174.25 (s); 76.17 (s); 51.83 (q); 49.88 (q); 44.56 (d); 43.90 (t); 42.20 (s); 34.55 (t); 29.64 (t); 28.11 (t); 18.81 (q).
11. Compound **2** was obtained as a single isomer, and the structure is in full agreement with spectroscopic data.

(Received in Germany 6 July 1988)