Synthesis of 3-(2-hydroxyethyl)-2(5H)-furanone

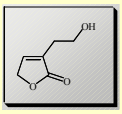
Markus Rugen and Dieter E. Kaufmann*

Institute of Organic Chemistry, Technical University of Clausthal,

Leibnizstrasse 6, D-38678 Clausthal - Zellerfeld, Germany

Introduction

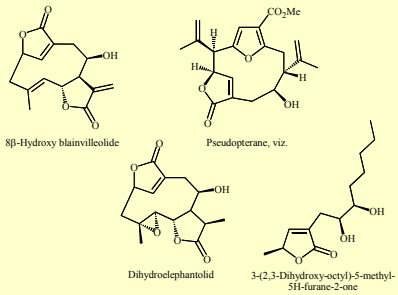
Many natural and *non*-natural products have a 3-(2-hydroxyethyl)-2(5*H*)-furanone subunit.



target structure

For this molecule *Paquette et al.* have described a ten step synthesis [1]. The possibility of a substitution reaction on the 2-(5*H*)furanone ring system (position 5) and the possibility of a carbon-carbon bond formation on the side chain (position 7), for example by oxidation of the hydroxy group and subsequent *Grignard* reaction, could make the target molecule to an important key compound in organic synthesis. The aim was to find a simple, short and efficient reaction pathway for the preparation of the target compound.

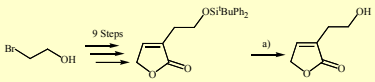
3-(2-hydroxyethyl)-2(5*H*)-furanone as subunit in natural and *non*-natural products



Literature

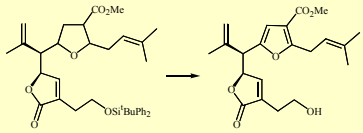
Paquette et al. have published the synthesis of 3-(2-hydroxyethyl)-2(5*H*)-furanone in 1992. They have used this compound as a model-system for a very problematical deprotection step in the synthesis of furanocembranolides.

In the paper the cleavage of the O-Si bond succeeded by using various sources of the fluoride ion, but in general it did not work. Curiously, the only exception was benzyltrimethyl-ammonium fluoride in cold acetonitrile.



a) $PhCH_2N^+Me_3F^-$, CH_3CN, 0 °C, 92 %

The adaption of these conditions to the desilylation step in the described synthesis did furnish the desired product, but in low yield.

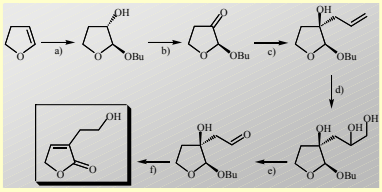


a) $PhCH_2N^+Me_3F^-$, CH_3CN, 0 °C, 10 %.

Approach

The preparation of 3-(2-hydroxyethyl)-2(5*H*)-furanone is a seven step synthesis with 20 % overall yield. *Lallemand et al.* described the first three reaction steps without giving any experimental details [2]. The opening reaction of the epoxide with 1-butanol in the first step leads to two diastereomers of the desired product (a) in 70 % yield (in the following reactions we will focus on one diastereomer, only). We carried out a *Swern* oxidation (>90 %) instead of an oxidation with PDC (b), following by a *Grignard* reaction (75 %), (c).

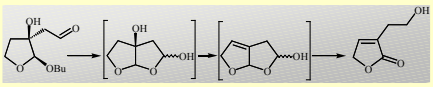
The diol was synthesized by using OsO_4/NMO (90 %); the reaction with $KMnO_4$ did not work (d). The procedure of the carbon-carbon bond cleavage was carried out by using $NaIO_4$ in 92 % yield (e). The final reaction of the sequence was an acid catalyzed reaction (2 M HCl, 51 %), (f). This reaction did not work in the presence of organic acids like *p*-TsOH monohydrate.



a) *m*-CPBA, 1-BuOH, 0 °C – rt, 15 h, 70 %; b) Oxalylchloride, DMSO, NEt_3, DCM, -60 °C – rt, 8 h, >90 %; c) Allylmagnesiumbromide, OEt_2, 0 °C – rt, 4 h, 75 %; d) OsO_4, NMO, THF/H_2O, rt, 12 h, 90 %; e) $NaIO_4$, EtOH/H_2O, rt, 1 h, 92 %; f) 2 M HCl, 90 °C, 1.5 h, 51 %.

Mechanism of the key step

The postulated mechanism is formally a two step synthesis.



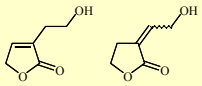
The first step is the formation of the described bicyclic *semi*-acetal. Elimination of water is presumable the second step.Therefore the equilibrium (monomeric effect) between the *semi*-acetal and the desired product leads to the target molecule.

Ab initio calculations (B3LYP/6-311+g**//B3LYP/6-31g*) are in good agreement with the prediction of the equilibrium. The result is that the monocyclic system is more stable than the bicyclic acetal (ca. 28 kcal/mol).

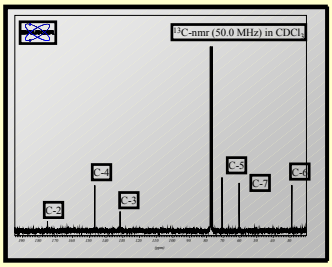
Spectroscopy and *ab initio* nmr calculations

Paquette et al. described the target compound and many spectroscopic data; unfortunately, the carbon nmr-spectrum is missing.

The carbon nmr values were calculated by using *ab initio* methods because in our reaction pathway the formation of the *E* and *Z* *exo*-olefins is possible. The correct identification of the *endo*-olefin is difficult because the spectra of all possible olefins were predicted to be very similar. The identification was made by using literature data and *ab initio* calculations. The carbon nmr spectrum is shown in the next scheme.



endo- *exo-*



carbon	calculated [ppm]	experimental [ppm]	difference
3	135.0	131.4	+3.6
4	145.8	146.7	-0.9
5	67.5	70.5	-3.0
2	172.8	174.9	-2.1
6	30.9	28.8	+2.1
7	61.7	60.3	+1.4

Calculated nmr shifts with B3LYP/6-311+G(2d,p); calculated standard was TMS (177.2).

The calculated values of the *endo*-olefin are in good agreement with the experimental data. Therefore, the calculation (B3LYP/6-311+g** / / B3LYP/6-31g*) of the energy of the isomers has shown that the *endo*-isomer is more stable than the two *exo*-(*E*, *Z*) isomers (ca. 5.1 kcal/mol).

References

[1] L.A. Paquette, A.M. Doherty, C.M. Rayner, *J. Am. Chem. Soc.* **1992**, *114*, 3910-3926.

[2] M. Jalali-Naini, J.Y. Lallemand, *Tetrahedron Letters* **1986**, *27*, 4, 497-500.

Calculations

All structures presented here were completley optimised at the DFT level by using B3LYP hybrid functional proposed by Becke as implement in the Gaussian 98 set of programs.