Tetrahedron Letters No. 8, pp 577 - 580, 1973. Pergamon Press. Printed in Great Britain.

A NEW APPROACH TO THE SYNTHESIS OF DIHYDRO-γ-PYRONES AND 3-FURANONES

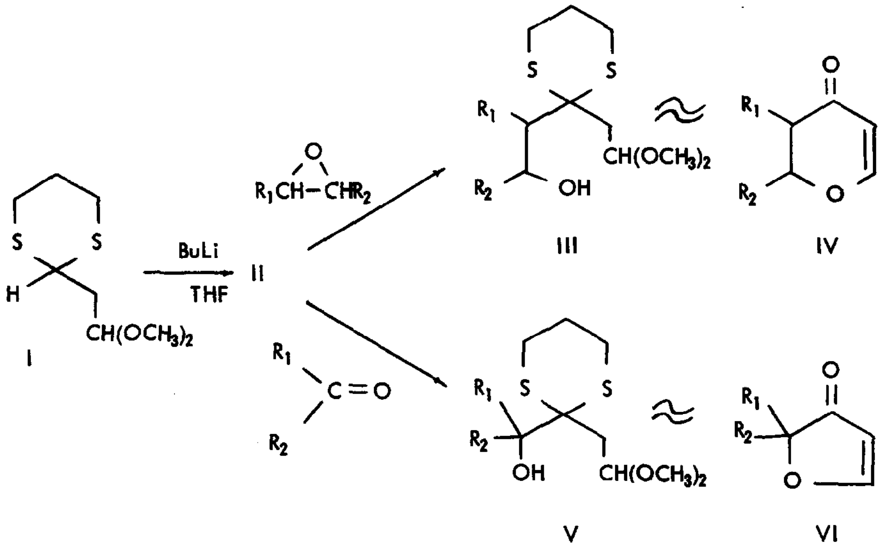
Frank Sher, John L. Isidor, Hans R. Taneja and Robert M. Carlson

Department of Chemistry, University of Minnesota, Duluth, Minnesota 55812

(Received in USA 24 October 1972; received in UK for publication 13 January 1973)

We would like to report the development of a method for the synthesis of compounds oxygenated in a 1,3,5 or 1,3,4 relationship by way of the readily available 2,2-dimethoxymethyl-1,3-dithiane.[1,2] The technique was illustrated by the synthesis of a number of dihydro- γ -pyrones and 3-furanones,[3] compounds valued as synthetic intermediates and as perfume components.

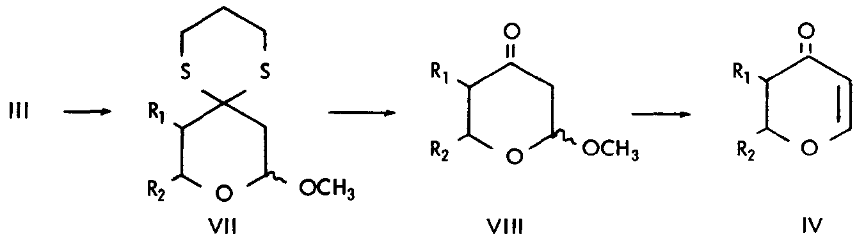
The addition of the lithium derivative of I,[1] 2-lithio-2-(2,2-dimethoxyethyl)-1,3-dithiane (II), to epoxides generated a compound (III) inherently possessing all of the structural features of the dihydro- γ -pyrone system (IV, eqn. 1). In similar fashion, the addition of II to ketones produced the homologous, masked 3-furanones(V, eqn. 2). The addition reaction of II with both epoxides and ketones proceeded in a nearly quantitative fashion, and in the case of epoxides, substitution occurred at the less hindered carbon.



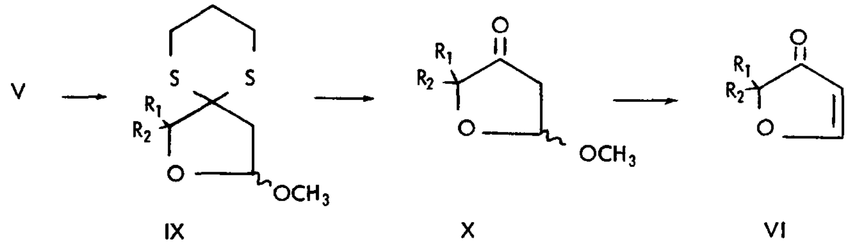
(1)

(2)

The ultimate conversion to IV and VI was accomplished by the following general sequence of reactions: II, prepared by the low temperature (-30°) addition of *n*-butyl lithium to a solution of I in THF, was treated with the appropriate epoxide or ketone to give III or V respectively. Conversion of III or V to the corresponding cyclic acetals (VII or IX) was accomplished with *p*-toluenesulfonic acid (*p*-TSA) in refluxing benzene or THF. The desired dihydro-γ-pyrone or 3-furanone was then generated (eqn. 3 or 4 respectively) by sequentially removing the thioacetal grouping to give the ketone (VIII or X) and subsequently eliminating methanol with *p*-TSA in refluxing aqueous THF to produce the vinylogous lactone structure common to IV and VI.



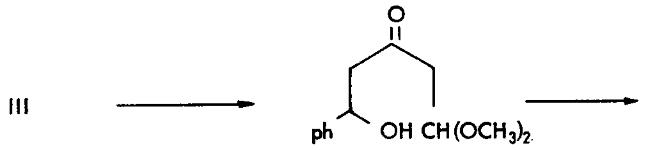
(3)



(4)

As can be seen from Table I, the overall yields through 4 steps were moderate. In all cases, the limiting factor in this synthetic scheme was the low yield consistently encountered in the removal of the thioacetal function. The examination of established hydrolytic methods[4] produced such complications as increasing stability of the mercuric complex with increasing molecular weight and low reactivity of these specific dithianes towards alkyl halides. In some cases improvement was noted when one of two new procedures were utilized: 1) the addition of N-bromosuccinimide (NBS) to a mixture of the acetal and freshly prepared silver carbonate in aqueous acetonitrile and, 2) the addition of NBS to a solution of the acetal in absolute alcohol for an initial high yield conversion to the O-acetal.[5]

Several attempts were made to hydrolyze the thioacetal group at an earlier stage (from III or V), but only in one case (R_1 = H, R_2 = ph, eqn. 5) was the overall yield of the final product[6] comparable to that obtained earlier (eqn. 3 or 4).



(5)

Acknowledgement: Support of this work was provided in part through a National Institute of Health Research Grant No. AI-1D597-01.

REFERENCES

1. D. Seebach, Synthesis, 17 (1969).

2. A convenient preparation of I consists of the treatment of excess malondialdehyde bis-dimethyl acetal (4 equiv.) with I equivalent of 1,3-propanedithiol in a manner similar to that used for the synthesis of 1,3-dithiane: E. J. Corey and D. Seebach, Organic Synthesis, 50, 72 (1970).

3. Some currently available synthetic methods are described in the following references; dihydro- γ -pyrones: S. Gelin and R. Gelin, Bull. Soc. Chim. Fr., 4091 (1969); G. Casnati, A. Quilico, A. Ricca and P. V. Finzi, Tetrahedron Lett., 233 (1969); T. M. Harris, S. Boatman, and C. R. Hauser, J. Amer. Chem. Soc., 87, 3186 (1965). 3-Furanones: P. Margaretha, Tetrahedron Lett. 4891 (1971); B. K. Carpenter, K. E. Clemens, E. A. Schmidt, H. M. R. Hoffman, J. Amer. Chem. Soc. 94, 6213 (1972); and references cited therein.

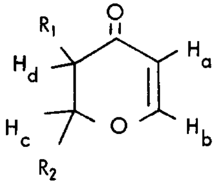
4. M. Fetizon and M. Jurion, J. Chem. Soc., Chem. Commun., 382 (1972); T. Oishi, K. Kamemoto, and Y. Ban, Tetrahedron Lett., 1085 (1972); E. Vedejs and P. L. Fuchs, J. Org. Chem., 36, 366 (1971); H. W. Chang, Tetrahedron Lett., 1989 (1972); and references cited therein.

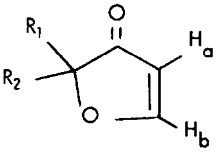
5. Addition of 4-6 equivalents of N-bromosuccinimide to a cooled (-10°C) solution of the dithiane in an excess of the desired alcohol gave nearly quantitative yields of O-acetal. Subsequent hydrolysis proceeded in low yield.

6. Samples for analysis were obtained by preparative-layer chromatography on silica gel with a subsequent short-path distillation.

TABLE I

DIHYDRO-γ-PYRONES



Compound		%Overall Yield	ir(cm^{-1}, C=O)	nmr data(ppm, m=multiplet, d=doublet, CCl$_4$/TMS)			
R$_1$	R$_2$			Ha	Hb	Hc	Hd
H	Ph	19^b	1660	5.33, m	7.31, m	(2.6, m)	
H	C_2H_5	15^b	1685	5.16, d ^{f}	7.33, d	4.3, m	2.3, m
H	n-C_6H_{13}	14^b	1680	5.20, d ^{f}	7.22, d	4.3, m	2.3, m
CH_3	$CH(OC_2H_5)_2$	13^b	1680	5.21, d ^{f}	7.25, d	3.5, m	2.4, m
3-FURANONES							
Ph	Ph	20^c	1700	9.0, d ^{g}	5.72, d	---	---
C_2H_5	C_2H_5	34^d	1710	8.18, d ^{g}	5.5, d	---	---
-(CH_2)-$_4$		25^d	1700	8.25, d ^{g}	5.55, d	---	---
CH_3	CH_3	60^e	1710	8.25, d ^{g}	5.65, d	---	---

a. Satisfactory elemental analyses were obtained.

b. The thioacetal group was removed in aqueous acetonitrile using 6 equivalents each of N-bromosuccinimide, sodium carbonate, and silver nitrate.

c. The thioacetal was converted to the dimethyl-O-acetal with N-bromosuccinimide in methanol and then hydrolyzed with p-toluenesulfonic acid in aqueous THF.

d. Thioacetal removal was affected with mercuric chloride-mecuric oxide in refluxing aqueous acetonitrile.

e. Mercuric oxide - boron trifluoride etherate in aqueous THF was used for thioacetal hydrolysis.

f. J=6Hz

g. J=2.5Hz