Tetrahedron Letters Vol. 21, pp 4301 - 4304
©Pergamon Press Ltd. 1980. Printed in Great Britain

0040-4039/80/1101-4301$02.00/0

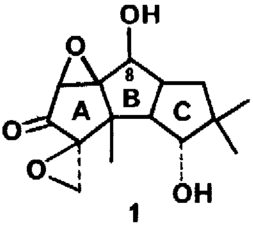
RING EXPANSION OF KETONES TO 1,2-KETO-THIOKETALS

Spencer Knapp*, Adrea F. Trope, and Raphael M. Ornaf

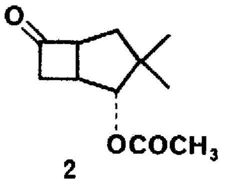
Department of Chemistry
Rutgers University
New Brunswick, New Jersey 08903, USA

Summary: Treatment of cyclic ketones with $(MeS)_3C\text{-}Li$, then $CuClO_4 \cdot 4CH_3CN$, gives the corresponding ring expanded 1,2-keto-thioketals.

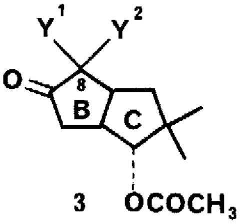
During our studies on the total synthesis of coriolin (1)[1] we needed a ring expansion procedure for preparation of the B ring (2 → 3). This would require the regiospecific insertion of a CY^1Y^2 unit next to the carbonyl carbon. We envisioned a two step process, whereby the reagent $^-CXY^1Y^2$ is first added to the carbonyl group. In a second step, loss of X^- with bond migration leads to the ring expanded ketone. Reagents which fit this general description have been used recently for ring expansion,[2,3,4] but none of them is entirely suitable for the purpose at hand. A potentially useful reagent has $Y^1 = Y^2 = SPh$, so that the resulting thioketal 3 blocks ketone alkylation at carbon 8 (coriolin numbering) and can eventually be converted to the C-8 hydroxyl of 1.



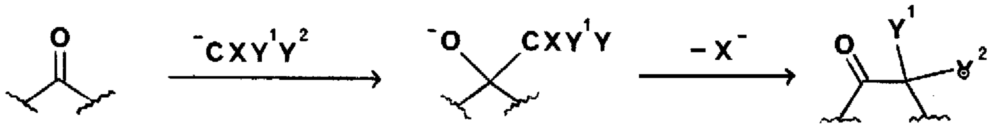
1



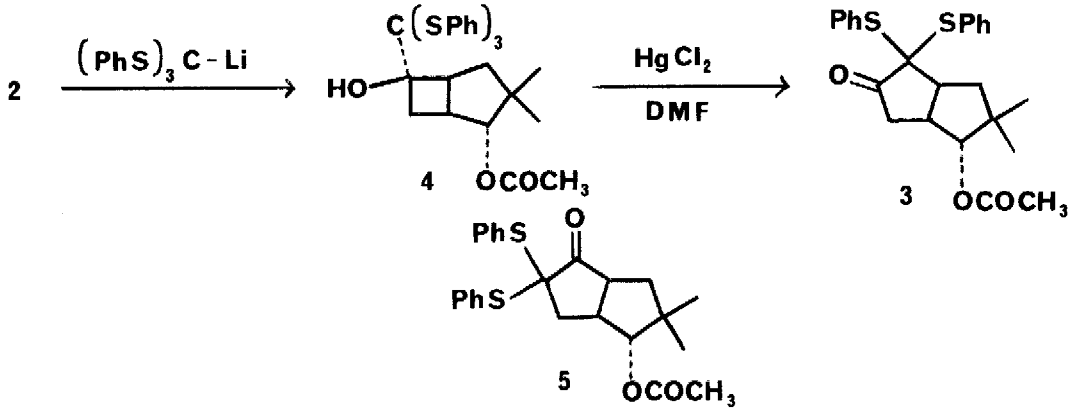
2



3



The successful transformation of 2 to 3 ($Y^1 = Y^2 = SPh$) is shown below. Treatment of 2[5] with tris(phenylthio)methyllithium[6] in tetrahydrofuran solution at -78° gave the adduct 4. Only one isomer is produced, presumably the one from attack on the convex face of 2. Treatment of 4 with 1.1 equiv each of mercuric chloride and diisopropylethylamine in dimethylformamide solution at -40° resulted in the removal of one phenylthio group and ring expansion to give the cyclopentanone 3 in 74% yield (mp 109-111°). Very little if any of the alternate ring expanded ketone 5 was formed. This is quite good selectivity for migration to electron deficient carbon.[7] The feasibility of regiospecific insertion of the $C(SPh)_2$ unit has therefore been established.



The ring expansion method has been extended to other cyclic ketones. Addition of $(PhS)_3C-Li$ to many ketones fails because of competing proton transfer.[6] However, a related reagent, $(MeS)_3C-Li$[8], added smoothly to a variety of substrates (6, Table). The resulting adducts 7 were converted to the ring expanded ketones 8 by the following procedure.

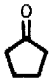
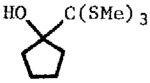
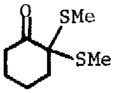
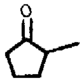
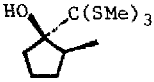
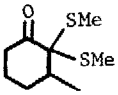
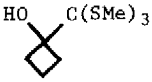
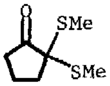
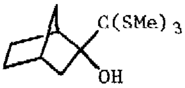
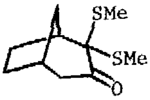
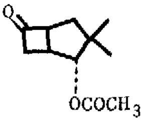
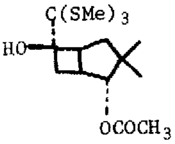
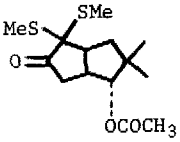
A solution of 1.0 mmol of adduct 7 in 10 ml of toluene was treated with 1.0 mmol of n-butyllithium to convert the alcohol to its lithium salt. Tetrakis(acetonitrile)copper(I) perchlorate[9] (2.0 mmol) was added, and the mixture was heated at 75° for 1-4 h. The reaction mixture was cooled, treated with aqueous ammonium chloride/ammonium hydroxide solution, and filtered through Celite. Extraction with ether followed by column chromatography gave the ketone 8 in the yields indicated (Table).

For the ring expansion step, tetrakis(acetonitrile)copper(I)perchlorate proved superior to copper(I)triflate[3], mercury(II)chloride, and mercury(II)trifluoroacetate. This crystalline reagent is easily prepared and, despite its high reactivity toward divalent sulfur, can be stored and transferred without special precautions.[10]

The ring expansion of 7 to 8 may occur without the accumulation of an epoxide intermediate.[3] When the reaction of 7a was quenched with aqueous sodium bicarbonate after 45 min at 55°, the only methylthio-containing products apparent by NMR analysis were 8a and unreacted 7a. The high regiospecificity of the bond migration process was demonstrated by reductive desulfurization of the crude products 8b and 8d using zinc in acetic acid. The resulting 3-methylcyclohexanone and bicyclo[3.2.1]octan-3-one were contaminated with less than 5% of 2-methylcyclohexanone and 0.5% of bicyclo[3.2.1]octan-2-one, respectively, according to gas chromatographic comparison with authentic samples.

The 1,2-keto-thioketal group of 8 is a useful one for further transformations, such as alkylation, hydrolysis, desulfurization, carbonyl transposition, and ring cleavage.[11] Its preparation by ring expansion gives these transformations added flexibility, a point we plan to demonstrate by elaboration of 3 to the coriolin ring system. These studies are currently under way.

Table. Ring Expansions of Ketones

entry	ketone **6**	adduct **7**	yield (melting point)	ketone **8**	yield (melting point)
a			78%		60% (36-37°)
b			73%		57%
c			72%		75%
d			62%		61%
e			51% (86-87°)		71% (124-125°)

Acknowledgments. This investigation was supported by Grant Number CA-24747, awarded by the National Cancer Institute, DHEW. We wish to thank Professors H.J. Schugar and J.R. Falck for helpful discussions and Rutgers University for a graduate fellowship to A.F.T.

References and Notes

1. For recent synthesis and leading references see S. Danishefsky, R. Zamboni, M. Kahn, and S.J. Etheredge, *J. Amer. Chem. Soc.*, **102**, 2097 (1980).
2. Y^1 = H, Y^2 = CO_2Et; X = N_2: W.L. Mock and M.E. Hartman, *J. Org. Chem.*, **42**, 459 (1977).
3. Y^1 = H; Y^2 = SPh; X = SPh: T. Cohen, D. Kuhn, and J.R. Falck, *J. Amer. Chem. Soc.*, **97**, 4749 (1975).
4. Y^1 = H; Y^2 = SMe; X = OSMe: M. Yamashita *et al.*, ORGN 459, Abstracts of the 177th ACS National Meeting, Honolulu, 1979.
5. Compound **2** was prepared from 6,6-dimethoxy-bicyclo[3.2.0]heptan-2-one[12] by the following sequence: 1) NaH (2.1 equiv), CH_3I, THF, 25°, 21h (98%); 2) Li, NH_3, EtOH, -78°[13] (65%, mp 63-64°); 3) Ac_2O, Et_3N, DMAP[14], CH_2Cl_2, 25°, 5h (85%); 4) 5% aqueous H_2SO_4, Et_2O, 25°, 24h (80%). We are grateful to Mr. J.J. Barchi, Jr. for this synthesis.
6. D. Seebach, *Angew. Chem. Internat. Ed. Eng.*, **6**, 442 (1967).
7. C.D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, 1968. See also references 2 and 3.
8. R.E. Damon and R.H. Schlessinger, *Tetrahedron Lett.*, 1561 (1976). See also O.D. Dailey, and P.L. Fuchs, *J. Org. Chem.*, **45**, 216 (1980).
9. M. Kubota and D.L. Johnson, *J. Inorg. Nucl. Chem.*, **29**, 769 (1967).
10. Tetrakis(acetonitrile)copper(I)perchlorate does not react readily with atmospheric oxygen or water. Reactions of any perchlorate at elevated temperatures should be performed with adequate safety shielding. Tetrakis(acetonitrile)copper(I)tetrafluoroborate may be substituted without affecting yield in large scale reactions.
11. For leading references see D. Seebach and M. Teschner, *Tetrahedron Lett.*, 5113 (1973).
12. E.J. Corey, J.D. Bass, R. LeMahieu, and R.B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964).
13. J.W. Huffman and J.T. Charles, *J. Amer. Chem. Soc.*, **90**, 6486 (1968).
14. W. Steglich and G. Hofle, *Angew. Chem. Internat. Edit. Eng.*, **8**, 981 (1969).

(Received in USA 16 June 1980)