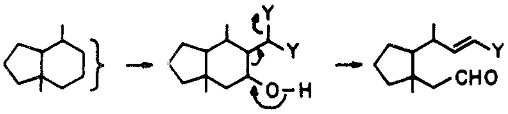
Grob-Type Fragmentation of Five- and Six-Membered Rings Promoted by Cuprous Ion

Summary: Copper(I) salts, especially the triflate and trifluoroacetate, promote efficient cleavage of 1-hydroxy-2-[bis(phenylthio)methyl]cyclohexane and cyclopentane; a cyclic intermediate is unlikely, as complete reaction requires more than 2 mol equiv of copper(I); the product contains aldehyde and latent aldehyde units.

Sir: During studies directed toward the synthesis of natural sesquiterpene α-methyl-γ-lactones,[1] we required a mild technique to convert the readily accessible perhydroindan skeleton (e.g., 1) into the open-chain homologue (e.g., 2) with a free aldehyde and a latent aldehyde for further elaboration. An obvious sequence is nucleophilic addition of $LiCHY_2$ to some appropriate derivative of 1, followed by Grob-type fragmentation[2] of 3. The unit Y must stabilize the reagent $LiCHY_2$ and also readily depart as Y^- during the fragmentation. We have employed the anion of bis(phenylthio)methane[3] and wish to report preliminary results which suggest a particularly mild and efficient fragmentation procedure.



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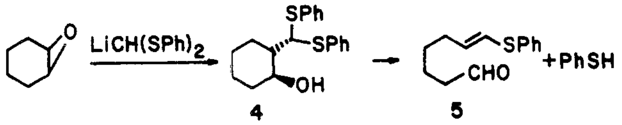
The reaction of lithio bis(phenylthio)methide with 1,2-epoxycyclohexane produces the alcohol 4 in 73% yield. While this compound is set up well for the Grob-fragmentation mechanism, the usual conditions required for parallel examples[4,5] are not mild. For example treatment of 4 with potassium *tert*-butoxide or sodium hydride (THF, 55 °C, 14 h) led to recovery of 4 (largely) accompanied by decomposition products (Table I, entries 1 and 2). None of the desired aldehyde (5) was obtained. Monoxidation (*m*-chloroperbenzoic acid) produced the corresponding sulfoxide (6), but led to no improvement in the ease and efficiency of fragmentation (5 not detectable; NaH/THF, 65 °C, 24 h).



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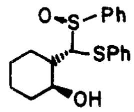

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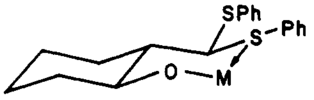

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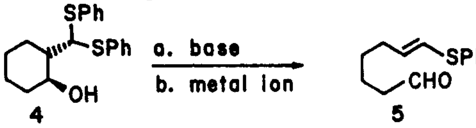
Metal-promoted ionization of the carbon–sulfur bond was considered, with the possibility of a cyclic intermediate (e.g., 7) during fragmentation.[6] Treatment of 4 with *n*-butyllithium (to generate the alkoxide) followed by salts of mercury, silver, and copper produced positive results only in the case of copper (Table I). Cuprous triflate[7] and cuprous trifluoroacetate (crude reagent) were most successful; optimum conditions promoted fragmentation at 25 °C in high yields.

Cuprous triflate has been used to bring about ionization and overall elimination from bis(phenylthio) acetals[7] (e.g., 4) and this is the primary reaction of 4 with cuprous triflate in the absence of added strong base (entry 5), but initial treatment with *n*-butyllithium followed by 4 mol equiv of cuprous triflate led to smooth fragmentation (entry 8). The cyclic intermediate is not likely, considering the fact that 1 mol equiv of cuprous triflate does not promote fragmentation at 20 °C. Presumably, the usual stereoelectronic control of the Grob fragmentation is important, with at least one cuprous ion to coordinate with the alkoxide unit and another cuprous ion to associate with the departing (anti) phenylthio unit (as depicted in 8).[6]

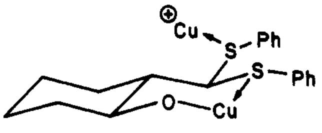
Table I. Fragmentation of Cyclohexanol 4



4 5

Entry	Conditions[a]	Metal ion (mol equiv)	Yield, %[b] (conversion, %)
1	NaH/THF, 55, 14	None	0 (0)
2	KOBu/DMSO, 90, 48	None	0 (90)
3	BuLi/THF, 20, 24	$HgCl_2$ (1)	0 (0)
4	BuLi/THF, 20, 3	$AgOT_f$ (4)[c,d]	0 (>80)
5	C_6H_6, 20° 3	$CuOT_f$ (2)[d,e]	0 (100)
6	BuLi/THF, 20, 3.5	$CuOT_f$ (1)[c,d]	0 (0)
7	BuLi/THF, 20, 3.5	$CuOT_f$ (2)[c,d]	30 (30)
8	BuLi/THF, 20, 3.5	$CuOT_f$ (4)[c,d]	92 (100)
9	BuLi/THF, 20, 72	CuOAc (8)	25 (50)
10	BuLi/THF, 20, 3	CuOTFA (4)[f]	90 (100)
11	BuLi/THF, 20, 3	CuOTFA (4)[g]	25 (40)

[a] Reactants, temperature (°C), time (hours). In cases where BuLi is indicated, *n*-butyllithium (1.0 mol equiv) was added to 4 in THF at −78 °C to generate the alkoxide. [b] The yield is based on isolated 5, not corrected for recovered 4. [c] A solution of the metal salt in benzene or toluene was added to the alkoxide in THF. [d] A small molar excess of 2,6-dimethylpyridine was present. [e] Strong base was not present. [f] Cuprous trifluoroacetate prepared in toluene solution and used without purefication. [g] The cuprous trifluoroacetate was purified by crystallization; see ref 12.



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Consistent with this picture of the intermediate is predominant formation of (*E*)-vinyl sulfide (5)[8] from the fragmentation reaction.

Other cuprous salts also bring about the fragmentation; the results of a number of experiments are summarized in Table I (entries 9–11). Anhydrous cuprous acetate has limited solubility in a variety of polar aprotic solvents and induces fragmentation more slowly and less efficiently that cuprous triflate. Cuprous trifluoroacetate, prepared by reaction of cuprous oxide and trifluoroacetic anhydride in toluene and used without purification as a solution in toluene, gave essentially the same results as cuprous triflate (entry 10). However, purified cuprous trifluoroacetate[10] gave slower cleavage, resulting in only 40% conversion under conditions where cuprous triflate gives complete reaction. The reason for the different reactivity of the crude and purified cuprous trifluoroacetate is not yet understood.

The five-membered-ring analogue (9) was prepared in the same way, and found to undergo fragmentation efficiently using the standard conditions for 4 (*n*-BuLi/THF/$CuOT_f$, 20 °C, 3 h, 93% yield). However, the mono(phenylthio) derivative 10 is inert to these conditions and does not fragment smoothly even at higher temperature.

Further questions of ring size and stereochemical requirements, versatility in the unit Y in 3 and application in more complex systems are under consideration.[11,12]

References and Notes

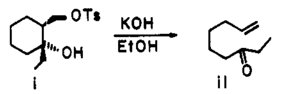
(1) For an earlier paper in this series, see M. F. Semmelhack and E. S. C. Wu, *J. Am. Chem. Soc.*, **98**, 3384 (1976). A simple target molecule is confertin.

For a recent synthesis, see J. A. Marshall and R. H. Ellison, *ibid.*, **98,** 4312 (1976).

(2) (a) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6,** 1 (1967); (b) C. A. Grob in "Theoretical Organic Chemistry; the Kekule Symposium", Butterworth, London, 1959, p 114.

(3) E. J. Corey and D. Seebach, *J. Org. Chem.*, **31,** 4097 (1966).

(4) For example, basic solvolysis of the simple six-membered ring in i proceeded at reflux temperatures, and produced ii in only 20% yield: Y. M. Portnyagin and V. V. Sova, *J. Org. Chem. USSR*, **4,** 1515 (1968).



i ii

(5) For example, an aldehyde is produced in a favorable bicyclic system after 30 min at reflux with potassium *tert*-butoxide in *tert*-butyl alcohol: J. A. Marshall and C. J. V. Scanio, *J. Org. Chem.*, **30,** 3019 (1965).

(6) The stereoelectronic factors in the general Grob fragmentation favor an anti transition state as depicted in iii.[2a]

iii

(7) (a) T. Cohen, K. Kuhn, and J. R. Falck, *J. Am. Chem. Soc.*, **97,** 4749 (1975); (b) T. Cohen, G. Herman, J. R. Falck, and A. J. Mura, *J. Org. Chem.*, **40,** 812 (1975).

(8) A sample 7-(phenylthio)hept-6-en-1-al (**5**, mixture of *E* and *Z* isomers) was prepared by reaction of 6,6-dimethoxyhexanol with (phenylthio)(trimethylsilyl)methyllithium[9] followed by hydrolysis of the acetal unit. This material was homogeneous by TLC analysis, with R_f identical with that of **5** prepared by fragmentation. The *E* stereochemistry follows from analysis of the ^{1}H NMR chemical shifts and coupling constants.[9]

(9) F. A. Carey and A. S. Count, *J. Org. Chem.*, **37,** 939 (1972).

(10) M. B. Kines, *Inorg. Chem.*, **11,** 2949 (1972).

(11) Acceptable combustion analyses and spectral data (^{1}H NMR, IR, mass spectroscopy) have been obtained for compounds **4, 5, 9,** and **10.**

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