

THIOACETAL-HEMITHIOACETAL-ACETAL INTERCHANGE UNDER MILD CONDITIONS

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The interchange of thioacetal, hemithioacetal, and acetal groups (or the corresponding changes in the ketal series) can be of considerable value in synthesis. Such direct interchange processes may provide any or a combination of the following advantages:

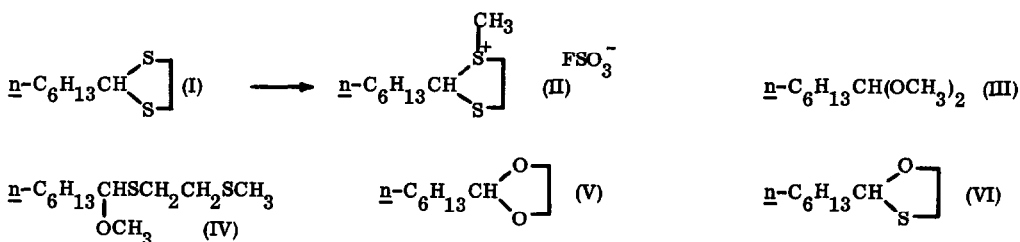
1) remove interference by the original protecting group to a subsequent synthetic step; e.g., replacement of thioacetal by acetal could permit oxidation or hydrogenation processes not possible in the presence of a sulfur-containing group.¹

2) allow a change in protecting group without going through the free carbonyl compound, a very important consideration in dealing with β, γ -unsaturated- or β -hydroxy aldehyde derivatives.

3) permit unmasking of the aldehyde or ketone under conditions which do not affect the molecule elsewhere. Hemithioacetal groups, for example, may be cleaved rapidly under neutral conditions (THF--water--CaCO₃--HgCl₂ at 0°) and are more useful for acid-sensitive intermediates than dithioacetal or acetal groups.

We describe herein some novel and mild procedures for acetal interchange starting from dithioacetals. These procedures are illustrated for a single aldehyde, *n*-heptanal. However, they have been used successfully in our laboratories for substantially more complex substrates.

Treatment of the ethylenedithioacetal of heptanal (I) with methyl fluorosulfonate (MFS, "Magic Methyl") in methylene chloride at 0° for 10 min and then at 23° for 2 hr resulted in a solution of the sulfonium derivative II² which could be used directly without isolation for the preparation of the interchanged derivatives III, IV, V, and VI using the conditions indicated (yields refer to products purified by distillation or by silica gel column chromatography).³



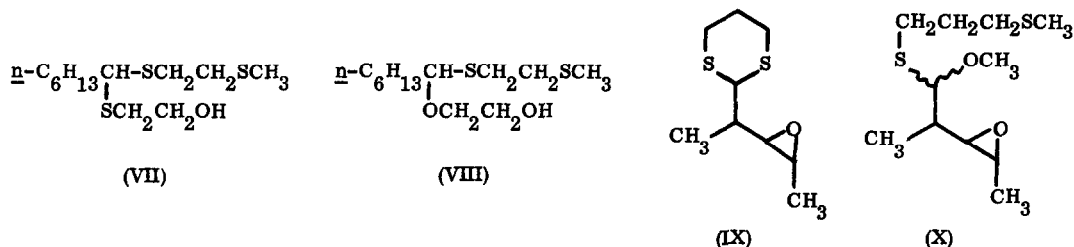
III: CH₃OH in CH₂Cl₂, 18 hr 23° (87% yield).

IV: CH₃OH in CH₂Cl₂, 2 hr 23° (72% yield).

V: HOCH₂CH₂OH in CH₂Cl₂, 18 hr 23° (82% yield).

VI: HOCH₂CH₂SH in CH₂Cl₂, 18 hr 23° (80% yield).

If the reaction of II with mercaptoethanol was carried out under milder conditions (at 0° for 2 hr), the intermediate VII could be isolated (70%), and similarly, II could be converted to VIII (79%) by reaction with ethylene glycol at 0° for 2 hr.⁴



Exactly parallel transformations were carried out with the trimethylenedithioacetal of heptanal. These acetal interchange processes are especially useful in the 1,3-dithiane series, since such intermediates are both common and important in current synthetic practice.⁵ An example of the operation of the acetal exchange method in an acid-sensitive system is provided by the dithioacetal IX which was converted into hemithioacetal X (88%) essentially as described above, except that dry triethylamine was added to the reaction mixture at 0° prior to reaction with methanol. Application of acetal exchange to the synthesis of complex natural products will be described in due course.⁶

References

1. For an example of such a case, see E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, **90**, 3245 (1968).
2. See (a) M. Fetizon and M. Jurion, *Chem. Commun.*, 382 (1972); (b) T. Oishi, K. Kamemoto, and Y. Ban, *Tetrahedron Lett.*, 1085 (1972); (c) T-L. Ho and C. M. Wong, *Synthesis*, 561 (1972).
3. All reactions monitored by thin layer chromatography. A small amount of potassium carbonate was added to the distillation charge to prevent the possibility of acid-catalyzed decomposition.
4. The structures assigned to IV and VII-X were confirmed by infrared, proton magnetic resonance, and mass spectral data. Compounds III, V, and VI were compared with authentic samples.
5. See D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
6. This work was assisted financially by a grant from the U. S. National Institutes of Health and a Fellowship to T. H. from the Fulbright-Hays Program.