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Preparation of 4-Alkylthio-Δ^4-1,3-Oxathianes, Novel Endocyclic Ketene Dithioacetals, via an Acetalization of β-Hydroxydithioesters

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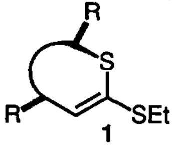
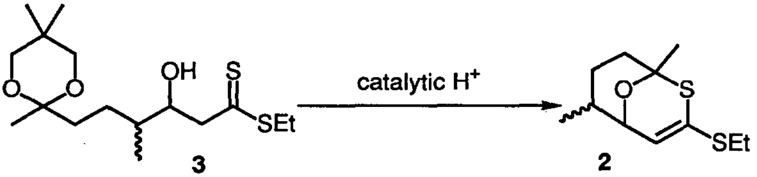
Abstract: *The treatment of β-hydroxydithioesters with dimethyl or diethyl acetals in the presence of an acid catalyst resulted in the formation of the six-membered endocyclic ketene dithioacetals, 4-alkylthio-Δ^4-1,3-oxathianes, via transacetalization.*

In association with our ongoing interest in the synthesis and reactions of enol ethers having novel dispositions of attached groups,[1] we have embarked upon studies of ketene dithioacetals in which both of the doubly bonded carbons and one of the sulfur atoms are part of a ring. Such so-called endocyclic ketene dithioacetals (general structure 1) are rare,[2] and little is known about their chemistry. Acyclic and exocyclic ketene dithioacetals (the latter having the double bond disposed exocyclic to a ring which encompasses the two sulfur atoms) are well-known, and their synthetic value as recipients of nucleophiles or electrophiles has been demonstrated.[3] It would seem that the extra structural rigidity and stereochemical definition imposed upon a ketene dithioacetal group when it is "tied up" in a stereodefined substituted ring (as in 1) will impart unusual reactivity to it and, possibly, stereoselectivity in its reactions.



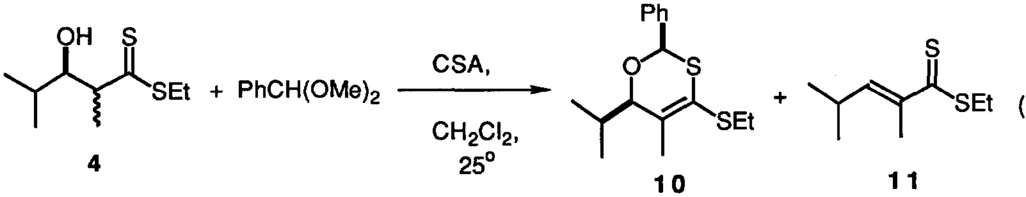
1

In 1985, Meyers and Walkup reported, during the course of an unrelated study, an unexpected formation of the 4-alkylthio-Δ^4-1,3-oxathiane 2 by the intramolecular transketalization of the β-hydroxydithioester 3 under acidic conditions (equation 1).[4] We have examined the intermolecular variant of this transformation, namely the transacetalization of acetals by β-hydroxydithioesters. In this missive, we report that a novel class of stereodefined six-membered endocyclic ketene dithioacetals, 4-alkylthio-Δ^4-1,3-oxathianes, are readily available by this general synthetic route.



3 2 (1)

The general form of the reaction and our results for a variety of 4-alkylthio-Δ^4-1,3-oxathianes are summarized in the Table. The β-hydroxydithioester starting materials **4** - **9** were readily available from the aldol reactions between the lithium enolate derivatives of dithioesters and aldehydes.[4,5] For initial studies, we examined the reaction between the dithiopentanoate **4** and benzaldehyde dimethyl acetal. As expected, simple stirring of these two reactants in the presence of an acid catalyst (d-10-camphorsulfonic acid, CSA) resulted in the formation of the 4-alkylthio-Δ^4-1,3-oxathiane **10** (equation 2 and Table, entry 1). However, a significant amount (40%) of the dehydration byproduct, the α,β-unsaturated dithioester **11**, was also obtained. It turns out that such α,β-unsaturated dithioester byproducts are always produced during the course of this synthesis of 4-alkylthio-Δ^4-1,3-oxathianes. However, one can keep their formation to a minimum (<10% of the product mixture) by avoiding aryl acetals or aryl substituents on the β carbon (what would become C_6 of the oxathiane ring) [entries 7 and 8, Table] and by using the milder Lewis acid, palladium(II) chloride, as a catalyst for the transacetalization [compare yields for entries 1 and 2, Table]. In systems which introduce only alkyl groups into the 4-alkylthio-Δ^4-1,3-oxathiane, CSA is a suitable catalyst for the transacetalization reaction [compare yields for entries 3 and 4, Table].

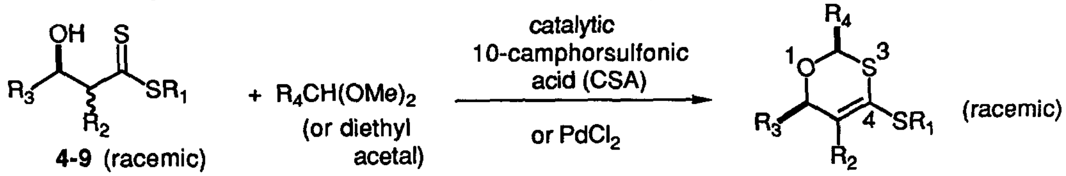


(2)

As indicated in the Table, a wide variety of 4-alkylthio-Δ^4-1,3-oxathianes can be synthesized by this method. The transformations were clean; according to spectroscopic analysis of the crude reaction mixtures, only the oxathianes and (usually) small amounts of the corresponding α,β-unsaturated dithioesters were formed.[6] The low isolated yields reported for some of the cases indicated in the Table are attributed to partial decomposition of the products during chromatography and evaporative losses during solvent removal *in vacuo*.

It should be noted that every 4-alkylthio-Δ^4-1,3-oxathiane that we synthesized was produced as a single diastereomer according to HPLC and NMR analyses of the reaction mixtures from the transacetalization reactions. Based on a puckering of the otherwise planar ring at the oxygen atom to produce pseudoaxial/pseudoequatorial dispositions at carbons 2 and 6 of the ring --- a conformation which is indicated to be the lowest energy one by an AM1 calculation for the unsubstituted Δ^4-1,3-oxathiane[7] --- it seems reasonable that the single diastereomers formed are the *cis* isomers, which would have the groups attached to C_2 and C_6 in a diequatorial arrangement. Attempts to verify this assignment by measuring nuclear Overhauser effects between hydrogens on C_2, C_6, and on groups attached to C_2 and C_6 were inconclusive. Future structural studies are necessary to rigorously prove the assigned stereochemistry.

Table. **4-Alkylthio-Δ^4-1,3-Oxathianes from β-Hydroxydithioesters.**



4-9 (racemic)

10,12-19

Entry	R_1	R_2	R_3	R_4	β-Hydroxy Dithio-ester	4-Alkyl-thio-Δ^4-1,3-Oxa-thiane	Catalyst, Time[a]	Yield of Oxa-thiane[b]
1	CH_3CH_2	CH_3	$(CH_3)_2CH$	C_6H_5	**4**	**10**	CSA, 1 day	40%[c]
2	CH_3CH_2	CH_3	$(CH_3)_2CH$	C_6H_5	**4**	**10**	$PdCl_2$, 4 hr.	66%
3	CH_3CH_2	CH_3	$(CH_3)_2CH$	CH_3CH_2	**4**	**12**	$PdCl_2$, 2 days	65%
4	CH_3CH_2	CH_3	$(CH_3)_2CH$	CH_3CH_2	**4**	**12**	CSA, 2 days	70%
5	CH_3CH_2	CH_3	$(CH_3)_2CH$	$PhCH_2$	**4**	**13**	$PdCl_2$, 4 days	32%[d]
6	CH_3CH_2	CH_3	$(CH_3)_2CH$	$CH_2{=}CH$	**4**	**14**	$PdCl_2$, 1 day	67%
7	CH_3CH_2	CH_3	C_6H_5	CH_3CH_2	**5**	**15**	CSA, 3 days	47%[d]
8	CH_3CH_2	H	$(CH_3)_2CH$	C_6H_5	**6**	**16**	$PdCl_2$, 1 hr.	37%[d]
9	$CH_2{=}CHCH_2$	CH_3	$(CH_3)_2CH$	CH_3CH_2	**7**	**17**	CSA, 3 days	60%
10	CH_3CH_2	$CH_2{=}CH(CH_2)_2$	$(CH_3)_2CH$	CH_3CH_2	**8**	**18**	CSA, 5 days	50%
11	CH_3CH_2	CH_3	CH_3CH_2	CH_3CH_2	**9**	**19**	CSA, 2 days	55%

[a] In all cases, the reaction involved stirring 0.025 M solutions of the β-hydroxydithioester in the presence of 5-10 mole % of the catalyst in dry CH_2Cl_2 under a $CaCl_2$ drying tube, at 25° C. The indicated times represent the time required for a complete disappearance of the starting material to be observed, according to TLC analysis. [b] Yield of oxathiane after purification by silica gel chromatography (230-400 mesh; hexanes eluent). [c] 40% of the α,β-unsaturated dithioester **11** was also isolated. [d] >20% of the α,β-unsaturated dithioester was formed during the reaction.

Besides the single example reported by Meyers,[4] the Δ^4-1,3-oxathiane ring system has been sparsely reported: as a bicyclic 2-imido-4-carboxamide form in some steroidal rhodanine derivatives,[8] as a 6-oxo form in one of several products from the reaction of two cyclopropenones with sulfur,[9] and as a bicyclic 2-carboxamide-6-amido form from the cycloaddition-rearrangement reactions of nitroso compounds and 2H-pyran-2-thiones.[10] Thus the results presented here represent the first truly general synthetic approach to simple alkyl-substituted forms of this heterocyclic ketene dithioacetal.

We conclude that a novel class of heterocycles, 4-alkylthio-Δ^4-1,3-oxathianes, are readily available via a facile transacetalization reaction. Research exploring the reactivity of these novel endocyclic ketene dithioacetals is currently underway. For example, we have found that these compounds undergo selective monooxidation to exocyclic sulfoxide derivatives. These and other investigations of the chemistry of the title heterocycles will be reported in due time.[11]

REFERENCES

1) For accounts of our research on silicon functionalized silyl enol ethers, see Walkup, R.D., Obeyesekere, N.U., and Kane, R.R. *Chem. Lett.* **1990**, 1055, and references therein.

2) Three reports of 2-alkylthio-Δ^2-thianes --- analogues of our system having a carbon in place of the ring oxygen --- have appeared: a) Lawson, K.R., Singleton, A., Whitham, G.H. *J. Chem. Soc. Perkin I* **1984**, 859; b) Lawson, K.R., Singleton, A., Whitham, G.H. *ibid.* **1984**, 865; c) Vedejs, E., Stults, J.S. *J. Org. Chem.* **1988**, *53*, 2226.

3) Kolb, M. in Patai, S. (ed.), *The Chemistry of Ketenes, Allenes, and Related Compounds*, Part 2; NY: John Wiley & Sons; 1980; pp. 669-699.

4) Meyers, A.I. and Walkup, R.D. *Tetrahedron* **1985**, *41*, 5089.

5) The dithioesters used as the precursors to the enolates were prepared according to Meijer, J., Vermeer, P. and Brandsma, L. *Rec. Chem. Pays-Bas* **1973**, *92*, 601.

6) For the general procedure, see footnote a of the Table. Diagnostic ^{1}H-NMR signals for the 4-alkylthio-Δ^4-1,3-oxathianes ($CDCl_3$, TMS standard) include 1) a signal at δ 4.75-5.28 ppm (R_4 = alkyl) or 5.87-6.02 (R_4 = aryl) for the hydrogen at C_2; 2) a signal at δ 4.12-4.39 for the hydrogen at C_6; 3) a signal at δ 1.85-1.90 ppm for the allylic hydrogens of the "R_2" group (δ 5.90-6.00 ppm when R_2 = H); 4) a change in the signals for the alkylthio group ("R_1") to reflect the diastereotopicity of the hydrogens on the carbon attached to the sulfur atom (for R_1 = ethyl, δ 2.61-2.70 and 2.89-2.92 ppm; for R_1 = allyl, δ 3.24 and 3.56 ppm). Diagnostic ^{1}H-NMR signals for the α,β-unsaturated dithioester byproducts include 1) a signal for the vinylic hydrogen on the β carbon, at δ 6.46-6.71 (R_3 = alkyl) and 7.58 ppm (R_3 = aryl); 2) a signal for the allylic hydrogens on "R_2" at δ 2.15-2.25 ppm (or a signal for R_2 = H at δ 6.71 ppm); 3) a signal for the allylic hydrogens on "R_3" at 2.43-2.65 ppm; 4) an absence of diastereotopicity for the alkylthio group signal, at δ 3.22-3.29. All spectroscopic and analytical data were in accordance with the assigned structures.

7) We are grateful to our colleague, professor David M. Birney, for this calculation.

8) Huttenrauch, R., Olthoff, U. *Pharmazie* **1973**, *28*, 523.

9) Behringer, H., Meinetsberger, E. *Liebigs Ann. Chem.* **1982**, 315.

10) Defoin, A., Augelmann, G., Fritz, H., Geffroy, G., Schmidlin, C., Streith, J. *Helv. Chim. Acta* **1985**, *68*, 1998.

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