The Synthesis of 2-Carbonyl-1,3-dithiolanes from the Reaction of 1,2-Disulfenyl Chlorides with Aldehydes and Active Methylene Compounds

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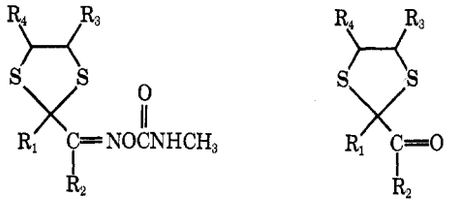
A new reaction of 1,2-disulfenyl chlorides with aldehydes to give substituted 1,3-dithiolanes is reported. Treatment of 1,2-ethane- or 1,2-propanedisulfenyl chloride with propionaldehyde, butyraldehyde, isovaleraldehyde, and phenylacetaldehyde provided 2-substituted 1,3-dithiolone-2-carboxaldehydes **4a–h**. Ethyl acetoacetate and the disulfenyl chlorides gave keto ester dithiolanes **5a** and **6a**, which afforded 2-acetyl-1,3-dithiolanes **5b** and **6b** on hydrolysis and decarboxylation.

As part of our continued interest in 2-substituted 1,3-dithiolane-2-carboxyaldehyde *O*-(methylcarbamoyl)oximes of structure **1** as potential insecticides and nematicides,[2] a convenient method for the preparation of dithiolane aldehyde and ketone precursors **2** was necessary.



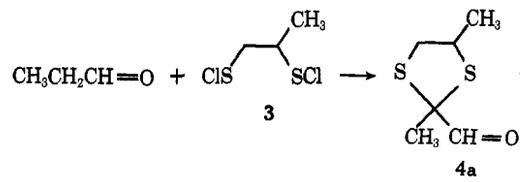
1 **2**

Presently, compounds of type **2** in which $R_1 = R_2 = CH_3$ (**2a**) and $R_1 = CH_3$, $R_2 = H$ (**2b**) are readily prepared from the reaction of 2,3-butanedione or of aqueous pyruvaldehyde with a variety of vicinal dithiols.[3]

Additional examples in which R_1 is a group other than methyl have not been readily available by this method, however, either owing to inaccessibility of the starting α-dicarbonyl compounds or to the complex mixture of products obtained from the reactions.

As a possible alternative route to such compounds of interest, the reaction of vicinal disulfenyl chlorides with suitable carbonyl compounds was investigated. Some precedence in the literature gave an indication of the feasibility of such a scheme. For example, the reaction of certain aryl sulfenyl chlorides with ketones to provide β-keto sulfides is well documented;[4] however, only one example of a similar reaction of simple aliphatic sulfenyl chlorides with an active methylene compound has been reported.[5]

Initial attempts to prepare 2,4-dimethyl-1,3-dithiolane-2-carboxaldehyde (**4a**) from 1,2-propanedisulfenyl chloride (**3**) and propionaldehyde in benzene solution were unsuccessful, resulting in extensive tar formation and no detectable amount of desired material. However, in methylene chloride solution, a 30% yield of **4a** was obtained. A variety of other solvents and reaction conditions were tested, with best results being realized in cold (0°), dilute ethyl acetate solution, which provided the dithiolane aldehyde **4a** in 50–55% yields.

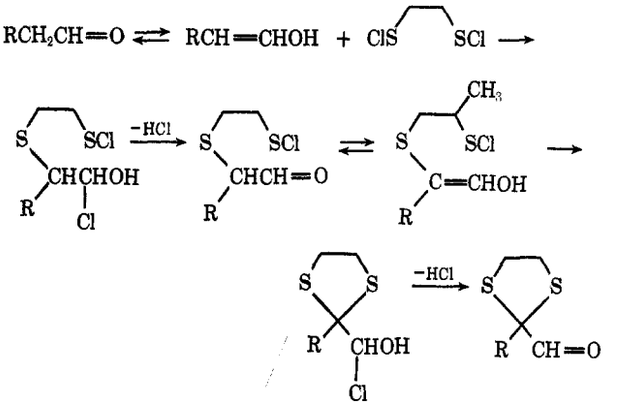


3 **4a**

Several other 2-substituted 1,3-dithiolane-2-carboxaldehydes were prepared in this manner from various aldehydes and disulfenyl chlorides, and results are listed in Table I. In these experiments, no attempts were made to determine optimum conditions.

The reaction most likely proceeds by the stepwise addition of the disulfenyl chloride to the enol form of the aldehyde, possibly as outlined in Scheme I.[6]

SCHEME I



Under the highly acidic conditions encountered during the course of this reaction, it is very likely that a major competing reaction involves the aldol condensation of the aldehydes. The usual products in this event (aldols, α,β-unsaturated aldehydes, and water) can all serve to destroy the highly reactive disulfenyl chlorides.[7] Attempts to minimize these undesirable reactions through the use of dilute solutions and by keeping the temperatures low were only partially successful, as evidenced by the often rather low yields of dithiolanes obtained, especially in those cases using ethanedisulfenyl chloride (Table I). Nevertheless, the simplicity of the method and ready availability of the starting materials make the route an attractive one, since most

(1) Contribution No. 643.

(2) T. L. Fridinger, E. L. Mutsch, J. W. Bushong, and J. W. Matteson, *J. Agr. Food Chem.*, **19**, 422 (1971).

(3) T. L. Fridinger and K. R. Henery-Logan, *J. Hetrocycl. Chem.*, **8**, 469 (1971).

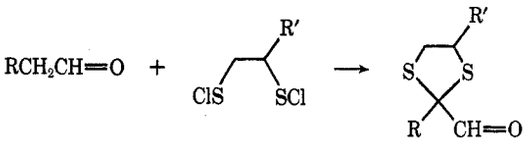
(4) C. Rappe and R. Gustafsson, *Acta Chem. Scand.*, **22**, 2927 (1968), and references cited therein.

(5) I. F. Kay, D. J. Lovejoy, and S. Glue, *J. Chem. Soc. C*, 445 (1970).

(6) (a) N. Kharasch in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, Oxford, 1961, p 375; (b) R. Gustafsson, C. Rappe, and J. O. Levin, *Acta Chem. Scand.*, **23**, 1843 (1969).

(7) M. L. Kee and I. B. Douglass, *Org. Prep. Proced.*, **2**, 235 (1970), and references cited therein.

TABLE I
DITHIOLANE ALDEHYDES

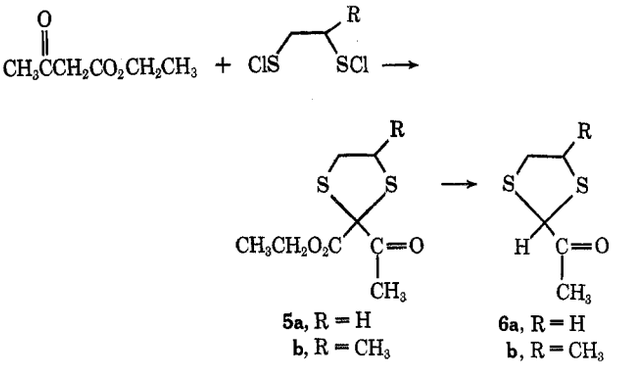


Compd	R	R′	Yield, %	Bp, °C (mm)	Ir (neat), cm⁻¹ (-CH=O)	Nmr ($CDCl_3$), δ	Calcd, % C	Calcd, % H	Found, % C	Found, % H
4a	CH_3	CH_3	55[a]	70–73 (0.1)	1725	1.50 (m, 3, >CHCH₃) 1.78 (s, 3, -CCH₃) 3.30 (m, 2, -CH₂CH<) 4.05 (m, 1, -CH₂CH<) 9.55 (d, 1, -CH=O)[e]	44.5	6.2	44.5	6.1
4b	CH_3CH_2	CH_3	47[b]	89–95 (0.1)	1720	1.15 (t, 3, J = 7.45 Hz) 1.44 (d, 3) 2.16 (q, 2, J = 7.45 Hz) 3.24 (m, 2) 4.00 (m, 1) 9.25 (d, 1)	47.7	6.8	47.9	6.9
4c	$(CH_3)_2CH$	CH_3	60[a,c]	90–95 (0.2)	1725	1.15 (m, 6) 1.43 (d, 3) 2.38 (m, 1) 3.00 (m, 2) 3.80 (m, 1) 9.45 (d, 1)	50.5	7.4	50.4	7.1
4d	C_6H_5	CH_3	49[a,d]	137–140 (0.1)	1725	1.48 (d, 3) 3.20 (m, 2) 9.98 (m, 1) 7.42 (m, 5) 9.40 (s, 1)	58.9	5.4	59.1	5.4
4e	CH_3	H	19[a]	71–84 (0.4)	1715	1.85 (s, 3, -CCH₃) 3.38 (s, 4, -CH₂CH₂-) 9.42 (s, 1, -CH=O)	40.5	5.4	40.5	5.5
4f	CH_3CH_2	H	30[b]	71–75 (0.1)	1720	1.11 (t, 3, J = 7.45 Hz) 2.10 (q, 2, J = 7.45 Hz) 3.34 (s, 4) 9.50 (s, 1)	44.5	6.2	44.7	6.2
4g	$(CH_3)_2CH$	H	29[a]	62–70 (0.1)	1730	1.16 (d, 6) 2.50 (m, 1) 3.30 (s, 4) 9.60 (s, 1)	47.7	6.8	47.3	6.5
4h	C_6H_5	H	25[a]	150–160 (0.5)	1730	3.32 (m, 4) 7.37 (m, 5) 9.58 (s, 1)	57.2	4.8	57.5	4.8

[a] Ethyl acetate as solvent. [b] Methylene chloride as solvent. [c] 0.2 mol scale. [d] 0.1 mol scale. [e] In most cases in which R′ = CH_3 the product is an isomeric mixture, which is reflected in the appearance of the aldehyde proton as a doublet.

of the compounds are not available by any other means.[8]

Attempts to prepare compounds of type **2** in which $R_1 = R_2 = H$ from the reaction of disulfenyl chlorides with acetaldehyde were unsuccessful, with only polymeric materials being obtained. In addition, acetone and acetophenone gave no detectable amounts of dithiolane ketones under the conditions investigated. However, compounds of type **2** where $R_1 = H$ and $R_2 = CH_3$ could be prepared by a convenient two-step procedure. Ethyl acetoacetate and 1,2-ethanedisulfenyl chloride gave 2-carbethoxy-2-acetyl-1,3-dithiolane (**5a**). Hydrolysis and decarboxylation of the material provided 2-acetyl-1,3-dithiolane (**6a**). The 4-methyl derivatives **5b** and **6b** were prepared similarly from



ethyl acetoacetate and 1,2-propanedisulfenyl chloride (**3**).

(8) A very brief attempt to prepare 2,4-dimethyl-1,3-dithiolane-2-carboxaldehyde (**4a**) by a modification of the method of Corey and Seebach[9] starting with 2,4-dimethyl-1,3-dithiolane and *n*-butyllithium failed completely, probably because the resulting dithiolane carbanion was much more unstable than the corresponding 1,3-dithiane carbanions more commonly employed.

(9) (a) D. Seebach, *Synthesis*, **1**, 17 (1969); (b) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075, 1077 (1966).

Experimental Section

Boiling points are uncorrected. Vapor phase chromatographic (vpc) analyses were performed on a Varian Aerograph 1720 instrument using a 5-ft 20% SE-30 on Chrom W column. The following spectrometers were used: nmr, Varian A-60D (TMS as internal standard); ir, Perkin-Elmer Model 137B. Microanalyses were performed by Paul Olson and the microanalytical group of these laboratories. The starting aldehydes (used to prepare the compounds listed in parentheses) were freshly distilled prior to use: propionaldehyde (**4a** and **4e**), butyraldehyde (**4b** and **4f**), isovaleraldehyde (**4c** and **4g**), and phenylacetaldehyde (**4d** and **4h**). The preparations were run on a 0.5-mol scale, unless otherwise noted.[10]

Dithiolane Aldehydes. General Procedure.—To a solution of 0.5 mol of 1,2-dithiol in 500 ml of either ethyl acetate or methylene chloride[10] cooled to −20 to −10° was added dropwise with mechanical stirring 135.0 g (1.0 mol) of sulfuryl chloride over a 0.5-hr period. A white precipitate of polymeric disulfide[11] which formed initially slowly dissolved to give a red solution of disulfenyl chloride.[12] The solution was allowed to warm to 0° and stirred at this temperature for 0.5 hr. The aldehyde (0.52 mol) dissolved in 50 ml of the appropriate solvent was added dropwise with stirring at 0° over a 1-hr period from a dropping funnel equipped with a pressure-equalizing side arm. A slow stream of dry nitrogen was passed through the funnel into the vented reaction vessel to prevent the resulting HCl fumes from contacting the acid-labile aldehyde. After addition was complete, the reaction was stirred at 0° for 4–8 hr, and then allowed to warm to room temperature overnight. The black solution was filtered if necessary and washed with water and saturated sodium bicarbonate solution until neutral, the organic phase was dried ($MgSO_4$), and the solvent was evaporated to give a black oil which was distilled under high vacuum. During the distillation, especially of the higher-boiling aldehydes, impurities present in the mixture often decomposed as the pot temperature reached ~100°, giving off HCl fumes which made maintaining a good vacuum difficult during this brief period. Nevertheless, after the decomposition was completed, high vacuum was regained and examination by vpc of the products obtained revealed them to be consistently of 97–99% purity.

2-Carbethoxy-2-acetyl-1,3-dithiolane (5a).—The procedure was essentially the same as for the aldehydes above. To a solution of 1,2-ethanedisulfenyl chloride prepared from 47.1 g (0.50 mol) of 1,2-ethanedithiol and 135.0 g (1.0 mol) of sulfuryl chloride in 300 ml of methylene chloride was added 65.1 g (0.50 mol) of ethyl acetoacetate dropwise with stirring at 0–5° over a 1-hr period. After addition was complete, the reaction mixture was stirred for 2 hr at 0–5° and at room temperature for an additional 2 hr. The golden yellow solution was filtered to remove a small amount of white polymer, the solvent was evaporated, and the crude brown oil was distilled under high vacuum. All material distilling from 140–160° (0.1–0.5 mm) (HCl evolution) was collected and redistilled. The fraction boiling at 119–125° (0.1 mm) was collected to give 53.6 g (49%) of **5a** as a light yellow oil: ir (neat) 1720, 1750 cm^{-1}; nmr ($CDCl_3$) δ 1.32 (t, 3, J = 7.45 Hz), 2.40 (s, 3), 3.40 (s, 4), 4.28 (q, 2, J = 7.45 Hz).

Anal. Calcd for $C_8H_{12}O_3S_2$: C, 43.6; H, 5.5. Found: C, 43.4; H, 5.4.

2-Carbethoxy-2-acetyl-4-methyl-1,3-dithiolane (5b).—The procedure was identical with that for the preparation of **5a** except that ethyl acetate was used as solvent and 54.1 g (0.50 mol) of 1,2-propanedithiol was used in place of ethanedithiol. Work-up and distillation provided the crude product, bp 136–156° (0.1–1.0 mm), which was redistilled to afford 42.3 g (36%) of **5b**: bp 118–122° (0.1 mm); ir (neat) 1720, 1750 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (m, 6), 2.38 (s, 3), 3.23 (m, 2), 3.84 (m, 1), 4.26 (q, 2).

Anal. Calcd for $C_9H_{14}O_3S_2$: C, 46.1; H, 6.0. Found: C, 46.0; H, 5.9.

2-Acetyl-1,3-dithiolane (6a).—A mixture of 47.5 g (0.21 mol) of **5a**, 80 ml of water, 10 ml of glacial acetic acid, and 20 ml of concentrated H_2SO_4 was stirred and heated under reflux for 24 hr. A vpc of an aliquot revealed the complete disappearance of the starting material. The mixture was cooled to room temperature and the product was extracted with two 100-ml portions of methylene chloride. The combined extracts were dried ($MgSO_4$) and evaporated to give a brown oil. Distillation afforded 27.5 g (86%) of **6a**: bp 70–73° (0.05 mm); ir (neat) 1740 cm^{-1}; nmr ($CDCl_3$) δ 2.32 (s, 3), 3.35 (s, 4), 4.86 (s, 1).

Anal. Calcd for $C_5H_8OS_2$: C, 40.50 H, 5.4. Found: C, 40.6; H, 5.3.

2-Acetyl-4-methyl-1,3-dithiolane (6b).—The procedure was identical with that for the preparation of **6a** above except that 48 hr were required for complete hydrolysis and decarboxylation of the keto ester. From 41.8 g (0.18 mol) of **5b** there was obtained 24.7 g (84%) of **6b**: bp 63–69° (0.05 mm); ir (neat) 1740 cm^{-1}; nmr ($CDCl_3$) δ 1.45 (m, 3), 2.30 (d, 3), 3.22 (m, 2), 3.90 (m, 1), 4.85 (d, 1).

Anal. Calcd for $C_6H_{10}OS_2$: C, 44.5; H, 6.2. Found: C, 44.4; H, 6.2.

Registry No.—**4a**, 33177-96-7; **4b**, 33406-16-5; **4c**, 33406-17-6; **4d**, 33406-18-7; **4e**, 26419-66-9; **4f**, 33406-20-1; **4g**, 33406-21-2; **4h**, 33406-22-3; **5a**, 33406-23-4; **5b**, 33406-24-5; **6a**, 33406-25-6; **6b**, 33406-26-7.

Acknowledgment.—The author wishes to express his sincere appreciation to Mr. Roy T. Knafla for his competent technical assistance, to Dr. Edward L. Mutsch for his interest and many helpful discussions during the course of this work, and to P. E. Olson and the members of the Analytical Research and Services Laboratory of the 3M Company for microanalytical analyses.

(10) See Table I.

(11) W. H. Mueller and M. Dines, *J. Heterocycl. Chem.*, **6**, 627 (1969).

(12) When 1,2-propanedisulfenyl chloride was prepared in methylene chloride solution, this polymer was evidently soluble, since no precipitate was observed throughout the addition.