The Reaction of 2-Ethoxy-1,3-dithiolane with Carbonyl Compounds

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The reaction of 2-ethoxy-1,3-dithiolane with carbonyl compounds such as aldehydes and ketones was investigated. The reaction proceeded smoothly in the presence of the $HgCl_2$-catalyst to afford 2-substituted and 2,2-disubstituted 1,3-dithiolanes. The reaction also offers an interesting alternative to the previously reported methods of synthesizing 1,3-dithiolanes which involve the acid-catalyzed reaction of carbonyl compounds with 1,2-ethanedithiol.

Although the chemistry of 1,3-dithiolanes has been extensively studied, together with that of 1,3-dithianes,[1] little is known about the 2-alkoxy derivatives of these compounds, which have been described as five-membered cyclic orthodithioformates. This is mostly because the derivatives are sensitive to acidic reagents, especially to such inorganic acids as hydrochloric and sulfuric acids. For example, the addition of a trace amount of concd hydrochloric acid to 2-ethoxy-1,3-dithiolane resulted in an exothermic reaction leading to 2,2′-[1,2-ethanediylbis(thio)]bis-1,3-dithiolane.[2] A recent report[3] from this laboratory has described a new method for the introduction of the 1,3-dithiolan-2-yl group into some active methylene compounds. The reaction using 2-ethoxy-1,3-dithiolane proceeded smoothly without a solvent under the catalytic action of a metal halide, such as $ZnCl_2$ or $FeCl_3$, and 1,3-dithiolan-2-yl derivatives of the active methylene compounds could be isolated in moderately good yields. As a broadening of the synthetic scope of 2-ethoxy-1,3-dithiolane, we had chosen to react it with such carbonyl compounds as aldehydes and ketones. To date there has been no information on any reaction between one of the so-called cyclic orthodithioformates and carbonyl compounds.

Results and Discussion

It has been observed that the reaction of 2-ethoxy-1,3-dithiolane with aldehydes or ketones proceeds smoothly in the presence of a Lewis-acid catalyst to afford either 2-substituted or 2,2-disubstituted 1,3-dithiolane respectively. Thus, the successful utilization of the readily available 2-ethoxy-1,3-dithiolane in the synthetic reaction has been demonstrated. The first attempt was directed toward establishing the most effective Lewis-acid catalyst in the reaction. When 2-ethoxy-1,3-dithiolane was allowed to react with acetone in dichloromethane at room temperature for 16 h, in the presence of a Lewis-acid catalyst, the major product was 2,2-dimethyl-1,3-dithiolane (**1a**), accompanied by a comparatively small amount of 1-(1,3-dithiolan-2-yl)-2-propanone (**2a**). The results of the reaction with some different Lewis-acid catalysts are shown in Table 1.

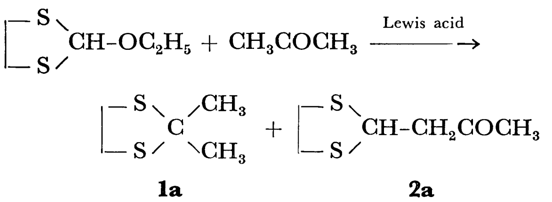
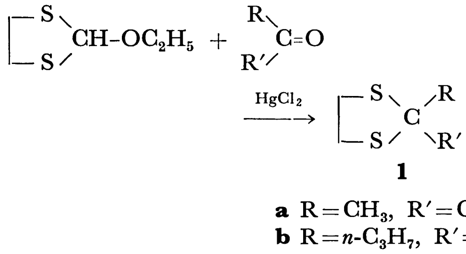


TABLE 1. REACTION OF 2-ETHOXY-1,3-DITHIOLANE WITH ACETONE IN THE PEESENCE OF SEVERAL DIFFERENT LEWIS-ACID CATALYSTS

Run[a)]	Catalyst (mmol)	Yield/%[b)] **1a**	Yield/%[b)] **2a**[c)]
1	$HgCl_2(6)$	60	0
2	$ZnCl_2(30)$	44	17
3	$BF_3\cdot Et_2O(15)$	52	12
4	$FeCl_3(6)$	60	3
5	$AlCl_3(6)$	45	21

a) In all the reaction runs, 30 mmol of 2-ethoxy-1,3-dithiolane, 30 mmol of acetone, and 40—50 ml of dichloromethane were employed. Reaction conditions: room temperature, 16 h. b) Determined by gas-chromatographic analysis. c) Bp 100—101 °C/2 Torr (lit,[4]) 143—145 °C/10 Torr), ^1H-NMR, δ (ppm from TMS, in $CDCl_3$), 4.77 (t, 1H, CH), 3.20 (s, 4H, SCH_2CH_2S), 3.00 (d, 2H, CH_2), 2.13 (s, 3H, CH_3). Found: C, 44.20; H, 5.99%. Calcd for $C_6H_{10}OS_2$: C, 44.41; H, 6.21%.

As is evident from Table 1, the reaction using $HgCl_2$ as the catalyst resulted in the formation of **1a** in a 60% yield, while no **2a** was produced. Thus, we have studied the $HgCl_2$-catalyzed reaction of 2-ethoxy-1,3-dithiolane with a number of different aldehydes and ketones in the hope that the desired 2-substituted and 2,2-disubstituted 1,3-dithiolanes (**1**) could be exclusively made by the reaction with $HgCl_2$. The results are summarized in Table 2.



a $R=CH_3$, $R'=CH_3$
b $R=n\text{-}C_3H_7$, $R'=H$
c $R=C_6H_5$, $R'=CH_3$
d $R=C_6H_5$, $R'=H$
e $R=p\text{-}ClC_6H_4$, $R'=H$
f $R=p\text{-}CH_3OC_6H_4$, $R'=H$
g $R=p\text{-}NO_2C_6H_4$, $R'=H$
h $R=p\text{-}(CH_3)_2NC_6H_4$, $R'=H$
i $R=p\text{-}CHOC_6H_4$, $R'=H$
j $R=C_6H_5CH{=}CH$, $R'=H$
k $R=CH_3CH{=}CH$, $R'=H$
l $\overset{R}{\underset{R'}{}}\!\!>C\!<\;=(CH_2)_5C\!<$

TABLE 2. REACTION OF 2-ETHOXY-1,3-DITHIOLANE WITH ALDEHYDES OR KETONES(RCOR′) UNDER THE CATALYTIC ACTION OF $HgCl_2$

Run	R	R′	Products	
			Abbreviation	Yield/%[a)]
1[b)]	CH_3	CH_3	**1a**	78
2[b)]	*n*-C_3H_7	H	**1b**	82
3[b)]	C_6H_5	CH_3	**1c**	64
4[b)]	C_6H_5	H	**1d**	82
5[b)]	*p*-ClC_6H_4	H	**1e**	87
6[b)]	*p*-$CH_3OC_6H_4$	H	**1f**	79
7[c)]	*p*-$NO_2C_6H_4$	H	**1g**	91
8[b)]	*p*-$(CH_3)_2NC_6H_4$	H	**1h**	52
9[c)]	*p*-$CHOC_6H_4$	H	**1i**	27
10[c)]	$C_6H_5CH{=}CH$	H	**1j**	89
11[c)]	$CH_3CH{=}CH$	H	**1k**	56
12[c)]	-$(CH_2)_5$-		**1l**	91

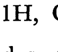
a) All yields refer to isolated products. Some starting 2-ethoxy-1,3-dithiolane was recovered in all runs. b) Carried out without any solvent. c) Carried out in a dichloromethane solvent.

As was originally anticipated, 2-substituted or 2,2-disubstituted 1,3-dithiolane (**1**), which is well known as a carbonyl-protective group,[5)] was the sole product in the $HgCl_2$-catalyzed reaction. It was recognized by thin-layer chromatography that, even in the run involving a low yield of the product, the residue consists of the starting materials containing a small amount of an indefinite by-product. It should also be noted that the procedure is simple to carry out and applicable to a wide range of aldehydes and ketones.

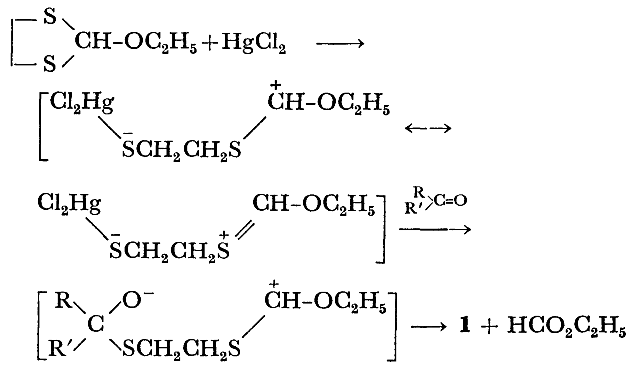
It is obvious that an exclusive C–S bond fission occurred in the $HgCl_2$-catalyzed reaction of 2-ethoxy-1,3-dithiolane. Therefore, the first necessary step in the reaction would seem to be the coordination of $HgCl_2$ with one of the S atoms of the ring. Thus, a mechanism for the reaction was proposed involving, first, the formation of a resonance-stabilized sulfocarbonium ion, which would then combine with carbonyl carbon.

This seems probable on the basis of the information on the symbiotic effect on the HSAB principle presented by Pearson and Songstad.[6)] In previous work on the reduction of 1,3-oxathiolanes with a mixture of $LiAlH_4$ and $AlCl_3$ in ether solution, Leggetter and

TABLE 3. PHYSICAL PROPERTIES AND ANALYTICAL DATA OF 2-SUBSTITUTED AND 2,2-DISUBSTITUTED 1,3-DITHIOLANES (**1**)

Compound	Mp (°C) or Bp (°C/Torr)	^{1}H-NMR δ(ppm from TMS, in $CDCl_3$)	Found (Calcd) (%)		
			C	H	N
1a[a)]	68—71/28 Lit,[10)] 171/760	3.32(s, 4H, SCH_2CH_2S), 1.77(s, 6H, CH_3)	44.36 (44.73)	7.66 (7.51)	
1b[a)]	109—110/26	4.40(t, 1H, CH), 3.18(s, 4H, SCH_2CH_2S), 2.0—1.2(m, 4H, CH_2CH_2), 1.1—0.8(m, 3H, CH_3)	48.80 (48.60)	8.21 (8.16)	
1c[a)]	116—121/2 Lit,[11)] 131/3	7.7—7.1(m, 5H, ArH), 3.36(broad s, 4H, SCH_2CH_2S), 2.09(s, 3H, CH_3)	61.66 (61.18)	6.25 (6.16)	
1d[a)]	176—177/20 Lit,[10)] mp 29 °C	7.6—7.1(m, 5H, ArH), 5.60(s, 1H, CH), 3.7—3.0(m, 4H, SCH_2CH_2S)	59.15 (59.30)	5.31 (5.53)	
1e[b)]	59—60 Lit,[12)] 62	7.5—7.1(m, 4H, ArH), 5.53(s, 1H, CH), 3.5—3.2(m, 4H, SCH_2CH_2S)	49.64 (49.87)	4.48 (4.18)	
1f[c)]	60—61 Lit,[10)] 64—65	7.5—7.3(m, 2H, ArH), 6.9—6.7(m, 2H, ArH), 5.61(s, 1H, CH), 3.78(s, 3H, OCH_3), 3.7—3.2 (m, 4H, SCH_2CH_2S)	56.38 (56.57)	5.74 (5.70)	
1g[b)]	67—69	8.3—8.1(m, 2H, ArH), 7.7—7.5(m, 2H, ArH), 5.67(s, 1H, CH), 3.7—3.2(m, 4H, SCH_2CH_2S)	47.35 (47.56)	4.06 (3.99)	6.29 (6.16)
1h[d)]	100—101 Lit,[13)] 105	7.5—7.3(m, 2H, ArH), 6.7—6.5(m, 2H, ArH), 5.62(s, 1H, CH), 3.5—3.1(m, 4H, SCH_2CH_2S), 2.90(s, 6H, CH_3)	58.89 (58.62)	6.82 (6.71)	5.97 (6.22)
1i[e)]	148—152/3	10.00(s, 1H, CHO), 7.9—7.6(m, 4H, ArH), 5.64(s, 1H, CH), 3.6—3.3(m, 4H, SCH_2CH_2S)	56.95 (57.11)	4.95 (4.79)	
1j[b)]	59—59.5	7.30(m, 5H, ArH), 6.53(d, 1H, ArCH), 6.14(dd, 1H, CH- ), 5.18(d, 1H, CH), 3.28(broad s, 4H, SCH_2CH_2S)	63.35 (63.42)	5.78 (5.81)	
1k[a)]	60—61/2	5.7—5.2(m, 2H, CH=CH), 5.1—4.9(m, 1H, CH), 3.23(broad s, 4H, SCH_2CH_2S), 1.66(d, 3H, CH_3)	49.22 (49.27)	7.12 (6.89)	
1l[a)]	147—148/30 Lit,[14)] 114—115/6	3.27(s, 4H, SCH_2CH_2S), 2.1—1.2[m, 10H, $(CH_2)_5$]	55.04 (55.12)	8.26 (8.09)	

a) Purified by distillation. b) Purified by recrystallization (ethanol). c) Purified by recrystallization (hexane). d) Purified by both column chromatography and recrystallization (ethanol). e) Purified by both colume chromatography and distillation.



Brown[7)] have found that the C–O, but not the C–S, bond is ruptured. This result suggests that the coordination of $AlCl_3$ with the O-atom is more favorable than the similar coordination of $AlCl_3$ with the S-atom. The formation of **2a** in the reaction of 2-ethoxy-1,3-dithiolane with acetone, using $AlCl_3$ as the catalyst, may be explained by a mechanism which involves the initial loss of the exocyclic ethoxyl group to give the 1,3-dithiolan-2-ium ion, and its subsequent attack on acetone. A similar coordination with the O-atom of 2-ethoxy-1,3-dithiolane leading to **2a** occurred in the end, but to a lesser extent, when $ZnCl_2$, $BF_3\cdot Et_2O$, or $FeCl_3$ was used instead of the $AlCl_3$ catalyst. However, the major product formed in the reaction using these Lewis-acid catalysts is not **2a**, but **1a**, suggesting that the C–S bond fission in the starting 2-ethoxy-1,3-dithiolane is predominant. Because the only available evidence is that listed in Table 1, we are presently unable to establish a reasonable pathway to afford **1a** when these Lewis-acid catalysts are used. At least, as to the reaction with $AlCl_3$, which has a poor coordination ability with the S atom, **1a** might also be formed by another path involving the coordination[8)] of $AlCl_3$ with acetone in the initial step of the reaction.

Such compounds as 2-substituted and 2,2-disubstituted 1,3-dithiolanes (**1**) can serve as protected aldehydes and ketones. They are commonly prepared by the acid-catalyzed reaction of carbonyl compounds with 1,2-ethanedithiol.[9)] The present reaction offers an interesting alternative, because the protected carbonyl compounds are formed easily and under nonacidic conditions by the reaction of 2-ethoxy-1,3-dithiolane with carbonyl compounds.

Experimental

Preparation of 2-Substituted and 2,2-Disubstituted 1,3-Dithiolanes (1). *General Procedure*: To a mixture of 2-ethoxy-1,3-dithiolane (30 mmol) and an aldehyde (or ketone) (30 mmol) in dichloromethane (40—50 ml), was added $HgCl_2$ (6 mmol) at 0—5 °C. In some cases (Runs 1, 2, 3, 4, 5, 6, and 8) the dichloromethane solvent was omitted. The mixture was brought to room temperature, stirred for 24 h, and then poured into a mixture of ice water and ether. The ethereal layer was separated, and then it was combined with a dichloromethane extract of the aqueous phase. The organic layer was washed repeatedly with dilute aqueous $NaHCO_3$, and then with water, and dried ($MgSO_4$), a subsequent evaporation of the solvents gave a residue which was further purified by distillation, recrystallization or column chromatography on silica gel, using ether as the eluent.

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