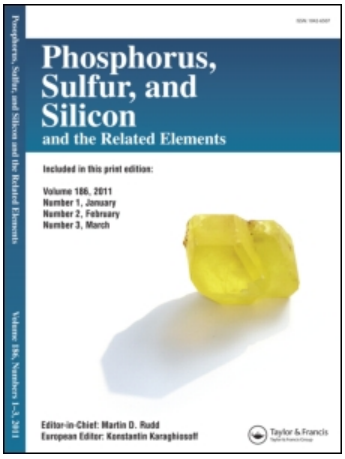

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REACTION OF POLYMERIZATION-RESISTANT 1,2-DITHIOLANES WITH SULFONIUM YLIDES

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Reaction of the polymerization resistant 1,2-dithiolane **1** with sulfonium ylides **2** was examined in relation to coenzyme lipoic acid. The strained cyclic disulfide **1** was highly reactive towards stabilized carbanions **2** to give the corresponding ring-opened products, which further reacted to give the 1,3-dithiane **4** and the 1,3-dithianyl sulfide **5**. The 1,3-dithiane formation was nearly quantitative when the ylide from benzyldimethylsulfonium was used.

Key words: 1,2-Dithiolane, nucleophilic S—S bond cleavage, sulfonium ylide, methylene insertion of cyclic disulfides, 1,3-dithianes.

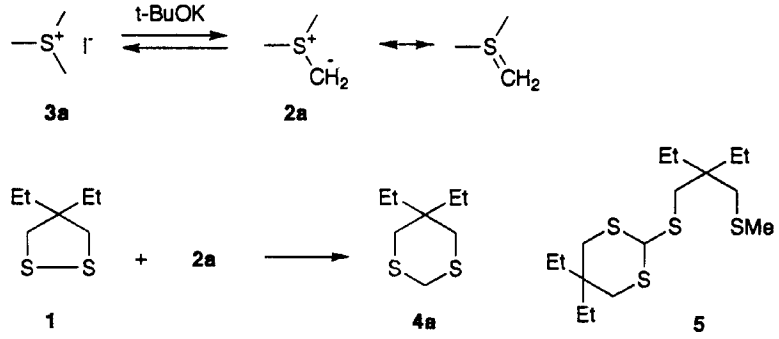
INTRODUCTION

The nucleophilic S—S cleavage of enzyme bound lipoic acid with hydroxyethylidenethiamine diphosphate (HET) was proposed for the reductive acetylation occurring in pyruvate dehydrogenase complex in the Krebs cycle.[1] The HET is a carbanion resonance-stabilized by a thiazolium moiety. Rastetter *et al.* reported that a model compound of HET generated *in situ* by deprotonation of 3-benzyl-2-(1-hydroxyethyl)-4-methylthiazolium salt was unexpectedly unreactive towards a lipoyl derivative.[2] The reason is not well understood.

On the other hand, we found that 4,4-diethyl-1,2-dithiolane **1** is resistant to ring-opening polymerization and highly reactive to non-stabilized carbon nucleophiles such as Grignard reagents and thienyllithiums.[3] The polymerization resistant 1,2-dithiolane is a suitable model for the enzyme-bound lipoic acid, and its behavior towards a stabilized carbanion is interesting. In this study, sulfonium ylides[4] were chosen as the stabilized carbanion, and their reaction with **1** was examined to estimate the intrinsic reactivity of the enzyme-bound lipoic acid.

RESULTS AND DISCUSSION

Reaction of 4,4-diethyl-1,2-dithiolane **1** with dimethylsulfonium methylide **2a** was carried out under various conditions in which the sulfonium ylide **2a** was generated *in situ* by deprotonation of trimethylsulfonium iodide **3a** with appropriate base in appropriate solvent (Scheme I). Reaction using *tert*-butoxide base in *t*-butyl alcohol gave the methylene insertion product **4a** and the dithianylsulfide **5** (Table I, entries 1–4). The importance of the deprotonation of trimethylsulfonium salt **3a** was shown by the fact that ethoxide and DBU are too weak as bases to promote the reaction (entry 6 and 7).



SCHEME I

TABLE I

Reaction of dimethylsulfonium methylide **2a** and 1,2-dithiolane **1**[a]

entry	1 mmol	3a mmol	Base mmol	Solvent, ml	Yield / % 4a	5
1	0.5	1.1	t-BuOK, 1.1	t-BuOH-THF(2:1), 6	24	67
2	1.0	1.2	1.2	t-BuOH-THF(2:1), 6	21	72
3	1.6	1.1	1.2	t-BuOH-THF(2:1), 6	12	87
4	2.1	1.0	1.3	t-BuOH-THF(2:1), 6	8	86
5	0.5	1.3[b]	1.1	t-BuOH-THF(2:1), 6	32	43
6	0.5	1.1	EtONa, 1.2	t-BuOH-THF(2:1), 6	-	-
7	0.5	1.1	DBU, 1.1	t-BuOH-THF(2:1), 6	-	-
8[c]	0.5	1.1	t-BuOK, 1.1	t-BuOH-DMF(2:1), 6	6	91
9[c]	0.5	1.1	1.1	t-BuOH-DMF(1:20), 42	12	69
10[c]	1.0	3.3	1.1	t-BuOH-DMF(1:5), 12	10	89
11	1.1	1.0	t-BuOK, 1.3	THF, 4	6	36[d]

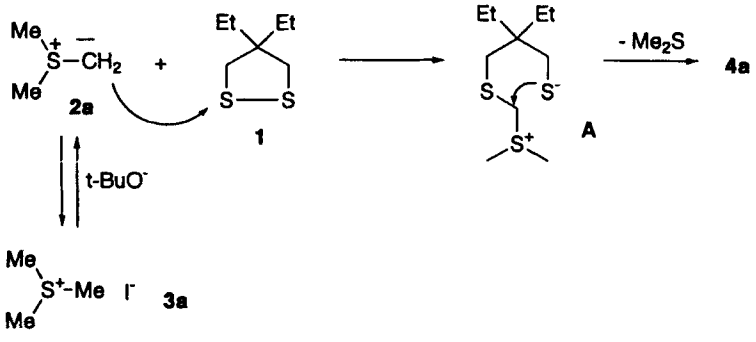
a) Reaction described in Scheme I under argon at room temperature for 12 h unless otherwise noted.
b) Tetrahydro-1-methylthiophenium iodide **3c** was used instead of **3a**.
c) Reaction for 0.5 h.
d) Two additional by-products were suggested during separation.

Field and Chu reported that reaction of a linear disulfide RSSR with dimethylsulfonium methylide **2a** did not give the methylene insertion product $CH_2(SR)_2$, but gave a mixture of tris-sulfide $CH(SR)_3$ and monosulfide CH_3SR.[5] The formation of **5** appears corresponding to the linear disulfide system, since **5** contains mono- and tris-sulfide structures within the molecule in 1:1 ratio. The production of 1,3-dithiane **4a** as the methylene insertion product in this study is different from the linear disulfide system, and this is attributed to the cyclic structure of 1,2-dithiolane. The mechanism for the formation of **4a** is considered as shown in Scheme II. The ring opening reaction of 1,2-dithiolane **1** with dimethylsulfonium methylide **2a** gives the intermediate sulfonium thiolate **A** which degrades to the 1,3-dithiane **4a** and dimethyl sulfide via an intramolecular SN2 reaction. The last step of re-cyclization is favored geometrically in the 1,2-dithiolane system. The corresponding process for a linear disulfide is not favored, since the thiolate nucleophile is lost in the reaction medium before the intermolecular SN2 reaction occurs.

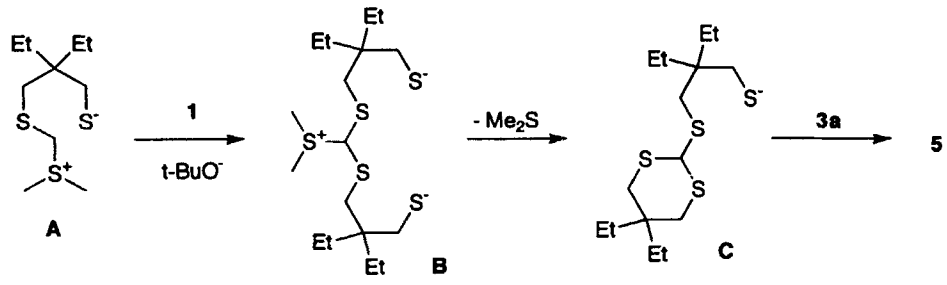
The mechanism for the formation of **5** seemed complicated. Therefore reaction under various conditions was examined and the results are included in Table I. The ratio of **4a** and **5** varied according to the reaction conditions. The sulfonium iodide **3a** is fairly insoluble in *t*-butyl alcohol and thus the reaction in this solvent was performed in the situation [**1**] > [**3a**] >> [**2a**]. The solvent DMF dissolved the salt **3a** completely: This resulted in the rate acceleration and improved yield of **5** (entries 8–10). The total yields of **4a** and **5** are excellent and other (ionic) by-products might not be expected in the products. The reaction in poor solvent THF (entry 11), however, gave a rather complicated mixture in which at least two additional by-products were suggested.

Dilution of the reaction decreased the yield of **5** (entry 9). The production of **5** was preferred, as the concentration of 1,2-dithiolane **1** was increased (entries 1–4). The methyl group on the precursor sulfonium salt appears essential for the production of **5**, since tetrahydro-1-methylthiophenium iodide **3c** gave **5** (entry 5), but 1-ethyl- and 1-isopropyltetrahydrothiophenium bromides produced no products related to **5** structurally (data not presented in this paper).

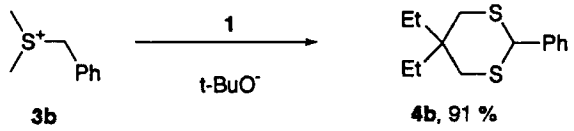
The mechanism for the formation of **5** is speculated to be as shown in Scheme III, according to a part of the evidence described above. The intermediate **A** is further reacted with 1,2-dithiolane **1** to produce 1:2 adduct **B** which re-cyclizes to



SCHEME II



SCHEME III



SCHEME IV

produce 1,3-dithiane intermediate **C** leading to **5** via methylation. In this mechanism, the sulfonium salt **3a** acts as a precursor of sulfonium ylide and a methylating reagent for thiolate: the concentration effect of **1** is well explained.

In summary, these processes proceed via common intermediate **A**, indicating that the polymerization resistant 1,2-dithiolane is highly reactive towards stabilized carbanion **2a** to give the ring-opened product **A**, in line with the carbanion mechanism proposed for the enzyme-bound lipoic acid.[1]

The reaction of benzyldimethylsulfonium salt **3b** gave 2-phenyl-1,3-dithiane **4b** (91% yield). This is important in organic synthesis, since the 1,3-dithiane can function as an acyl anion equivalent in C—C bond forming reactions.[6] A variety of synthetic methods for 2-aryl-1,3-dithianes is available under acidic to neutral conditions using benzaldehydes as starting material; the method under basic conditions is rare. The benzylsulfonium salt is ordinary prepared from benzyl halides. Thus the 1,3-dithiane formation using 1,2-dithiolane is a transformation of benzyl halide to aryl substituted 1,3-dithiane: the dithiane synthesis is quite different in the starting materials and in reaction conditions.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL EX-90 instrument operating at 89.5 and 22.5 MHz, respectively. DEPT methods using 90 and 135 degree pulses were employed to determine the number of proton(s) attached to the carbon. MS spectra were taken at 70 eV on a JEOL AX500 equipment. IR spectra were obtained by using a JASCO FT/IR-7000 spectrometer on KBr pellets of liquid samples.

Dithiolane **1** was prepared from the corresponding 1,3-propanediol according to the reported method.[7] Trimethylsulfonium iodide **3a** was commercially available. Benzyldimethylsulfonium tetraphenylborate **3b** was precipitated by mixing an aqueous solution of $NaBPh_4$ and a methanolic solution of benzyldimethylsulfonium bromide (hygroscopic crystal) which, in turn, was prepared from benzyl bromide and dimethyl sulfide in acetone; **3b** mp 185–186.5°C (from acetone). IR (KBr) ν 3056 (m), 3010 (m), 2986 (m), 1481 (m), 1429 (m), 746 (s), 710 (s), and 605 cm^{-1} (m). ^{1}H NMR (DMSO-d_6) δ 2.6 (6H, s, $2CH_3$), 4.4 (2H, s, CH_2), and 6.4–7.2 ppm (25H, m, 5Ph). Tetrahydro-1-methylthiophenium iodide **3c** was prepared from tetrahydrothiophene and methyl iodide and recrystallized from methanol-ether. mp 198–

9°C. IR (KBr) ν 2994 (s), 2942 (s), 1427 (s), 1406 (m), and 994 cm^{-1} (s). ^1H NMR (DMSO-d_6) δ 2.24–2.35 (4H, m, $2CH_2$), 2.906 (3H, s, CH_3), and 3.34–3.67 ppm (4H, m, $2CH_2$).

Reaction of 4,4-diethyl-1,2-dithiolane **1** *with dimethylsulfonium methylide* **2a** *in t-BuOH-THF (2:1)*: Potassium *tert*-butoxide (127 mg, 1.13 mmol), trimethylsulfonium iodide **3a** (217 mg, 1.06 mmol), *tert*-butyl alcohol (4 ml) and THF (2 ml) were mixed under argon; most of the trimethylsulfonium iodide was insoluble. 4,4-Diethyl-1,2-dithiolane **1** (74.7 mg, 0.46 mmol) was added to the suspension, and the mixture was stirred at room temperature for 12 h. After being acidified with acetic acid (1 ml, 17 mmol) and water (40 ml), the mixture was extracted with dichloromethane (30 ml). The organic layer was concentrated under reduced pressure and the residue was distilled by kugelrohr to give 5,5-diethyl-1,3-dithiane **4a** 19.2 mg (24% based on **1**), colorless liquid, ot (oven temp.) 100–140°C/20 mmHg. Found: C, 54.76; H, 9.00%. Calcd for $C_8H_{16}S_2$: C, 54.49; H, 9.14%. IR (KBr) ν 2968 (s), 1452 (m), 1381 (m), 1189 (m), 980 (m), 756 (m), and 717 cm^{-1} (m). ^1H NMR ($CDCl_3$) δ 0.80 (6H, t, J = 7.4 Hz, $2CH_3$), 1.62 (4H, q, J = 7.4 Hz, $2CH_2$), 2.24 (4H, s, $2SCH_2$), and 3.62 ppm (2H, s). ^{13}C NMR ($CDCl_3$) δ 6.92 ($2CH_3$), 21.28 (C), 27.46 ($2CH_2$), 31.80 (CH_2), and 38.80 ppm ($2CH_2$).

The residue was almost pure **5**; yield 54.7 mg (67% based on **1**). Found: C, 54.12; H, 8.88%. Calcd for $C_{16}H_{32}S_4$: C, 54.49; H, 9.14%. IR (KBr) ν 2968 (s), 2918 (s), 2880 (s), 1452 (m), 1425 (s), 1379 (m), 1267 (m), 975 (m), 795 (m), and 723 cm^{-1} (m). ^1H NMR ($CDCl_3$) δ 0.700–1.012 (12H, m, $4CH_3$), 1.292–1.876 (8H, m, $4CH_2$), 2.118 (3H, s, CH_3S), 2.326 (2H, d, J = 14.0 Hz, 2CHS), 2.558 (2H, s, CH_2S), 2.698 (2H, s, CH_2S), 3.060 (2H, d, J = 14.0 Hz, 2CHS), and 4.818 ppm (1H, s). ^{13}C NMR ($CDCl_3$) δ 6.98 (CH_3), 7.14 (CH_3), 7.72 ($2CH_3$), 17.36 (CH_3S), 24.22 (CH_2), 27.72 ($2CH_2$), 30.06 (CH_2), 30.78 (C), 34.72 ($2CH_2$), 40.54 (CH_2), 41.12 (C), 42.10 (CH_2), and 47.88 ppm (CH). MS m/z (%) 177 (base), 175 (82), 162 (13), 129 (20), 97 (18), and 55 (83).

Results in entries 2–4 in Table I were obtained similarly.

Reaction of 4,4-diethyl-1,2-dithiolane **1** *with dimethysulfonium methylide* **2a** *in DMF-t-BuOH (2:1)*: Sulfonium salt **3a** (217 mg, 1.05 mmol) and 4,4-diethyl-1,2-dithiolane **1** (78.5 mg, 0.485 mmol) were dissolved in DMF (4 ml), mixed with *t*-BuOK (127 mg, 1.13 mmol) in *t*-BuOH (2 ml), and stirred for 0.5 h at room temperature. After work-up described above, **4a** 5.7 mg (6%) and **5** 77.7 mg (91%) were obtained.

Reactions in entries 9 and 10 in Table I were carried out similarly.

Reaction of 4,4-diethyl-1,2-dithiolane **1** *with dimethylsulfonium methylide* **2a** *in THF*: Sulfonium salt **3a** (212 mg, 1.0 mmol) and *t*-BuOK (144 mg, 1.29 mmol) were suspended in THF (4 ml), and stirred with 1,2-dithiolane **1** (170 mg, 1.05 mmol) for 12 h. After the usual work-up, 1,3-dithiane **4a** (6%) was separated by kugelrohr distillation. The residue was rather complicated and chromatographed on silica-gel (eluent: hexane) to afford **5** (65 mg, 36%). At least two unidentifiable by-products were suggested during the chromatography.

Reaction with tetrahydrothiophenium methylide **2c**. *t*-BuOK (123 mg, 1.10 mmol), tetrahydro-1-methylthiophenium iodide **3c** (228 mg, 1.25 mmol) and 4,4-diethyl-1,2-dithiolane **1** (79.2 mg, 0.49 mmol) were mixed in *t*-BuOH-THF (2:1) 6 ml and stirred at room temperature for 12 h. After addition of acetic acid (1 ml) and water (30 ml), the mixture was extracted with dichloromethane (30 ml). The organic layer was concentrated and the residue distilled by kugelrohr to give **4a** 25.1 mg (32%), ot 90–140°C/20 mmHg. The residue (55.0 mg) contained 67% of **5** as estimated from glc that corresponded to 43% yield of **5**.

Reaction with benzyldimethylsulfonium tetraphenylborate **3b**: A mixture of *t*-BuOK (443 mg, 3.96 mmol), the sulfonium salt **3b** (470 mg, 1.00 mmol), *t*-butyl alcohol (4 ml), THF (2 ml) and dithiolane **1** (204 mg, 1.26 mmol) was stirred under argon at room temperature for 12 h. The mixture was added with water (40 ml) and saturated aq. NH_4Cl (10 ml), and extracted with dichloromethane (30 ml). The organic layer was concentrated under reduced pressure, and the residue was distilled by kugelrohr. After recovery of excess **1** (41.8 mg, ot 90–100°C/20 mmHg), 5,5-diethyl-3-phenyl-1,3-dithiane **4b** was obtained; yield 228 mg (91%), ot 140–170°C/0.5 mmHg; colorless crystal, mp 87–88°C. Found: C, 66.59; H, 7.85%. Calcd for $C_{14}H_{20}S_2$: C, 66.61; H, 7.99%. IR (KBr) ν 2966 (s), 2842 (s), 2896 (s), 2880 (s), 1464 (m), 1452 (s), 1381 (m), 1265 (m), 1178 (m), 743 (m), 717 (s), and 696 cm^{-1} (s). ^1H NMR ($CDCl_3$) δ 0.796 (3H, t, J = 7.4 Hz, CH_3), 0.844 (3H, t, J = 7.4 Hz, CH_3), 1.330 (2H, q, J = 7.4 Hz, CH_2), 1.964 (2H, q, J = 7.4 Hz, CH_2), 2.596 (2H, d, J = 13.8 Hz, 2SCH), 2.834 (2H, d, J = 13.8 Hz, 2SCH), 5.036 (1H, s), and 7.21–7.57 ppm (5H, m, Ph). ^{13}C NMR ($CDCl_3$) δ 6.92 (CH_3), 7.32 (CH_3), 22.72 (CH_2), 29.92 (C), 31.38 (CH_2), 40.88 ($2CH_2$), 51.60 (CH), 127.78 (2CH), 128.30 (CH), 128.58 (2CH), and 138.82 ppm (C). MS m/z (%) 252 (M, 80), 122 (58), 121 (51), 83 (84), and 82 (100).

The benzyldimethylsulfonium salt **3b** decomposes slowly to 1-methyl-2-(methylthio)methylbenzene under the conditions, and thus the use of slight excess 1,2-dithiolane **1** as described above was essential for the selective production of 2-phenyl-1,3-dithiane **4b**.

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