Heteroatom Chemistry
Volume 9, Number 3, 1998

Reactions of Polymerization-Resistant 1,2-Dithiolanes with Lithiated Oxygen Heterocycles

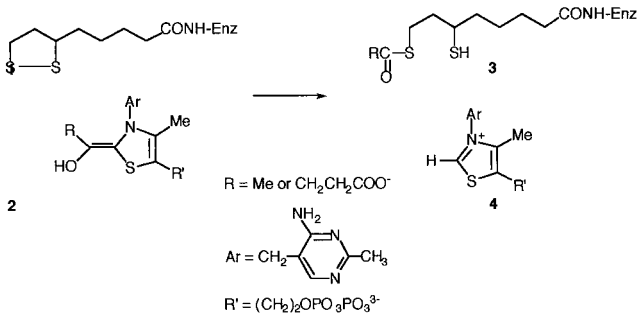
Masato Tazaki,[1] Toshihiko Hieda,[1] Hironori Maeda,[1] Shizuo Nagahama,[1] and Akinori Jyo[2]

[1]*Department of Industrial Chemistry, Kumamoto Institute of Technology, Ikeda 4-22-1, Kumamoto 860, Japan*

[2]*Department of Applied Chemistry and Biochemistry, Faculty of Engineering, Kumamoto University, Kurokami 2-40-1, Kumamoto 860, Japan*

Received 28 March 1997; revised 2 May 1997

ABSTRACT: *Lithiated furans have been found to cleave the S–S bond of polymerization-resistant 1,2-dithiolanes to give the ring opened products in good yields. In the case of lithiated benzofuran, the excess reagent reacted with the normal product to give a mixture. Lithiated dihydrofuran and dihydropyran gave the corresponding ring-opened products that rearranged to spiro-1,3-dithianes during acidic workup. The reaction was applied to the selective synthesis of substrates for intramolecular Diels-Alder reactions.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:281–287, 1998



SCHEME 1

INTRODUCTION

Coenzyme lipoic acid **1** is bound covalently to pyruvate and 2-oxoglutarate dehydrogenase complexes in the Krebs' cycle and is reductively acylated by the active aldehydes **2** bound to thiamine diphosphate **4** (Scheme 1) [1]. This acylation is a reduction of the cyclic disulfides **1** to the 1,3-propanedithiols **3** and a concomitant introduction of acyl groups on one of the thiol groups, ensuring the exclusive formation of the mono-*S*-functionalized 1,3-propanedithiol derivatives **3.** The mechanism of this enzymic reaction is controversial [2]. We are interested in the carbanion mechanism [3] since the related ring opening of 1,2-dithiolanes with carbanions has intrinsic chemoselectivity with regard to formation of mono-*S*-substituted 1,3-propanedithiol derivatives.

We have examined the related ring opening by using some polymerization-resistant 1,2-dithiolanes **5.** For example, we have found that simple Grignard reagents [5] and thienyllithiums [6] react with the dithiolanes **5** to give the corresponding 1,3-propanedithio derivatives in a quantitative manner. The rate enhancement caused by the ring strain of 1,2-dithiolanes **5** was also observed in the reaction with Grignard reagents [7] that showed no reactivity toward lipoic acid itself [8]. On the other hand, sulfonium and oxosulfonium ylides do not give the correspond-

Correspondence to: Masato Tazaki
 CCC 1042-7163/98/030281-07

ing ring-opened products, but give carbene-insertion products under certain conditions [9]. Acetylides give the corresponding ring-opened products that isomerize to vinylene-insertion products in a protic medium [10]. Picolyllithiums show an intermediate property, i.e., they give the corresponding ring-opened products selectively, but by-products, 2-pyridyl-1,3-dithianes, could not be excluded from the reaction mixture [11]. The variety of the reactions led us to examine the reaction of polymerization-resistant 1,2-dithiolanes with lithiated furans and related compounds as described herein.

RESULTS AND DISCUSSION

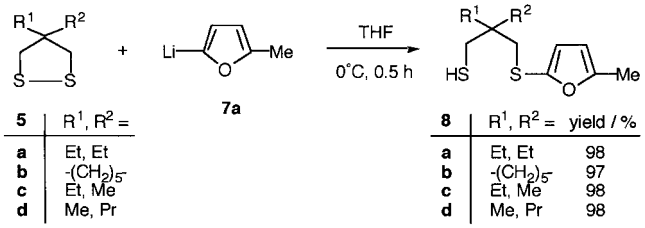
2-Methylfuran **6a** (1.7 mmol) was lithiated with BuLi (1.5 mmol) in THF (5 mL) at 0°C for 30 minutes and reacted with nonpolymerizable 4,4-diethyl-1,2-dithiolane **5a** (1 mmol) at 0°C for 30 minutes. After usual workup, the product **8a** was isolated by kugelrohr distillation in high yield (98%) and high purity (98%, see Scheme 2). The structure of **8a** was confirmed by the following evidence: The expected parent peak in the MS spectra (m/z = 244) was observed. The triplet at δ 1.09 and doublet at 2.55 with ^3J 9.0 Hz in the ^{1}H NMR spectra showed the presence of the CH_2SH group. The vicinal coupling of furan protons, ^3J 3.0 Hz, showed that the furan was 2,5-disubstituted. All other spectral data are consistent with the structure **8a.**

The exclusive formation of mono-*S*-substituted 1,3-propanedithiol **8a** was readily confirmed by the direct GLC analysis of the acidified mixture, showing that neither 2,2-diethyl-1,3-propanedithiol nor 1,3-bis(5-methylfuran-2-ylthio)-2,2-diethylpropane was present in the product.

The lithiofuran **7a** reacted similarly with another nonpolymerizing 4,4-pentamethylene-1,2-dithiolane **5b** to give the corresponding ring-opened product **8b** in an excellent yield. Fairly readily polymerizable 4-ethyl-4-methyl- and 4-methyl-4-propyl-1,2-dithiolanes **5c** and **5d,** respectively, also reacted with the lithium reagent **7a** to give the corresponding ring-opened products **8c** and **8d** in good yields, if the oligomeric, viscous 1,2-dithiolanes were distilled just before use. Depolymerization of polymeric 1,2-dithiolanes during their distillation has been well documented [12]. Therefore, this result shows that fairly readily polymerizable 1,2-dithiolane **5c,d** could be reacted with lithiofurans similarly to the behavior of the nonpolymerizable 1,2-dithiolanes **5a,b,** if the monomeric dithiolane was introduced into the reaction medium. On the other hand, highly polymerizable lipoic acid did not give the simple products, even if the acid was added to the reaction mixture as a THF solution of the monomer. This suggested that ring-opening polymerization (initiated by thiolate anion) was competing with the simple ring opening in the case of the highly polymerizable lipoic acid.

Unsubstituted furan **6b** was lithiated to give 2-lithiofuran **7b** and reacted with **5a** to give the ring-opened product **9** in good yield (see Scheme 3). These lithium reagents **7a** and **7b** could be used in excess amount in reaction with 1,2-dithiolanes **5,** to assure the complete reaction; i.e., the excess lithium reagents do not interact with the ring-opened products.

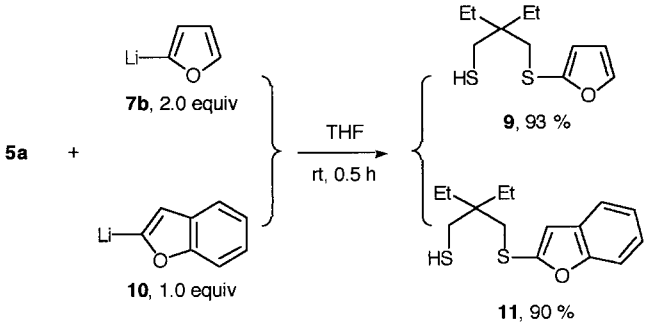
In the case of 2-lithiobenzo[*b*]furan **10,** however, the excess reagent decomposed the ring-opened product (see Scheme 4). For example, 1.5 equivalents of lithiobenzofuran **10** were reacted with 1.0 equivalent of 4,4-diethyl-1,2-dithiolane **5a** in THF, and, after decomposition of excess lithium reagent **10** by addition of methanol, the mixture was further methylated with methyl iodide to give the ring-opened product **12** (41%), accompanied by the furan-collapsed products **13** (18%) and **14** (6%). When equimolar amounts of 1,2-dithiolane **5a** and lithiobenzofuran **10** were reacted, the ring-opened product was obtained without any decomposition (see Scheme 3). This shows that the second decomposition is substantially slower than the first ring opening.



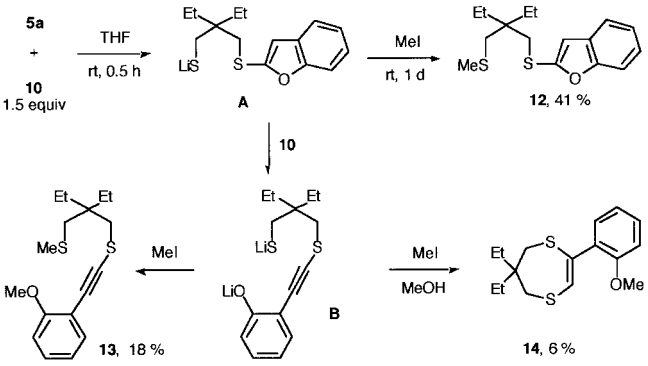
5	R^1, R^2 =
a	Et, Et
b	-$(CH_2)_5$-
c	Et, Me
d	Me, Pr

8	R^1, R^2 =	yield / %
a	Et, Et	98
b	-$(CH_2)_5$-	97
c	Et, Me	98
d	Me, Pr	98

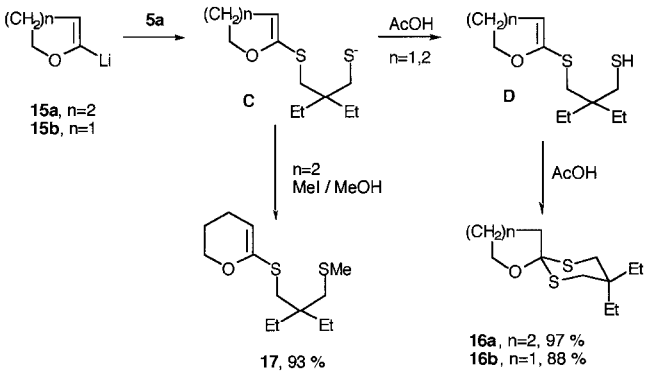
SCHEME 2



SCHEME 3



SCHEME 4



SCHEME 5

The structure of **13** was confirmed by the following evidence: **13** showed the characteristic MeS (δ 2.13) and MeO (δ 3.85) signals in its ^{1}H NMR spectrum, two acetylenic carbon signals (δ 84.74 and 87.54), a weak acetylenic absorption at 2172 cm^{-1} in its spectrum, and a parent peak in the MS spectrum. The structure of **14** was also confirmed by the following evidence: **14** showed the characteristic MeO (δ 3.808) and vinyl proton (δ 5.930) signals in its ^{1}H NMR IR spectrum, and its ^{13}C NMR spectrum is fully consistent with the proposed structure.

The mechanism of the decomposition is considered to be as depicted in Scheme 4. The reaction of the dithiolane **5a** with lithiobenzofuran **10** gives the ring-opened product **A,** which is deprotonated at H-3 by excess **10** and isomerizes to the *o*-alkynylphenolate **B,** this being methylated to give the isolated product **13.** The intermediate **B** cyclizes to a dihydro-1,4-dithiepin under protic conditions, giving **14** after methylation. Similar ring opening of 3-lithiobenzo[*b*]furan to 2-alkynylphenolate has previously been well recognized [13]. The dithiepin formation from such an intermediate **B** was also detected in the reaction of dithiolane with phenylacetylide, in a protic medium [10].

Dihydropyran and dihydrofuran are cyclic vinyl ethers lithiated at the sp^2 carbon adjacent to the oxygen. With this structural similarity in mind, we examined the reaction of these lithiated cyclic vinyl ethers **15a,b** with the 1,2-dithiolane **5a** (see Scheme 5). The lithiation of dihydropyran by BuLi in THF was sluggish, and unreacted BuLi frequently produced, as a by-product, the monobutylated 1,3-propanedithiol derivative. Addition of TMEDA solved this problem. When the dihydropyran (2.5 mmol) was lithiated with BuLi (2.0 mmol)/TMEDA (2.2 mmol) in THF (5 mL), α-lithiation was complete within 2 hours at room temperature. The reagent **15a** was reacted with 4,4-diethyl-1,2-dithiolane **5a** (1.0 mmol) at RT for 2 hours. The excess lithium reagent was destroyed with methanol (12 mmol), and the products were methylated with excess methyl iodide (5 mmol) at RT during 12 hours. The usual workup gave the methylated, ring-opened product **17** in excellent yield. Attempts to obtain the ring-opened product without the subsequent methylation failed, but the thioacetal **16a** was obtained in excellent yield. The thioacetal **16b** was also obtained by the action of lithiated dihydrofuran **15b** in good yield, but the lithiation at a lower temperature was essential to minimize the side reaction. These results showed that ring opening of 1,2-dithiolane **5** with lithiated vinyl ethers **15** proceeds as expected to produce the ring-opened products **C,** but the products are labile and isomerize to the cyclic thioacetal **16** via a β-protonation of the vinyl ethers during the acidic workup.

As shown above, with no exception, a number of lithiated oxygen heterocycles cleaved the S–S bond of 1,2-dithiolane, and these results are in line with the carbanion mechanism [3] proposed for the enzymic, reductive acylation of lipoic acid.

In many cases, ring-opened products were obtained in excellent yields. These ring-opened products are good ligands for transition metals containing oxygen and two sulfurs as the donating atoms. The expected complex would have fused four- and six-membered chelate rings, and specific metal binding properties would be expected from the distorted coordination sphere. Therefore, the ring opening of 1,2-dithiolane with lithiated furans provides a facile, selective synthesis of such ligands.

The best applications of the ring opening to organic syntheses is, however, in the chemoselectivity of formation of the monosubstituted propanedithiols. The furan ring in the products would be ex-

pected to be a good diene in Diels-Alder (D-A) reactions. Thus, some appropriate dienophiles were introduced at the free SH group, leading to substrates for an intramolecular D-A reaction [14].

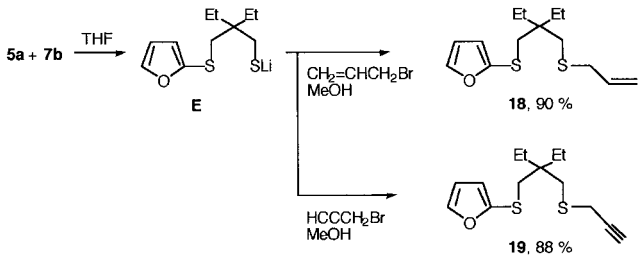
The ring-opened product **E** was prepared in situ and was reacted with allyl and propargyl bromides after destruction of excess lithium reagents in the mixture by the addition of methanol (Scheme 6). Chromatographic separation gave the D-A substrates **18** and **19** in a one-pot manner in good yields. These substrates **18** and **19** are resistant to the intramolecular D-A reaction at elevated temperatures, probably due to the steric hindrance between the divalent sulfurs. But the ring opening is proved to be useful for the facile, selective synthesis of the substrates for possible intramolecular condensation reactions.

EXPERIMENTAL

General Method. ^{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° pulses were employed to determine the number of proton(s) attached to 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. Gas chromatography was performed, to determine the purity of the distilled products, on a Shimadzu GC-8A equipment mounted with a 1.0 m × 2.6 mm i.d. glass column fitted with 2% Silicone OV-17 on Gas chrom Q. The chromatogram from the FID was analyzed by a Shimadzu Chromatopac C-R3A.

Tetrahydrofuran (THF) was distilled under argon from blue benzophenone ketyl just before use. Butyllithium in hexane was titrated in dry tetrahydrofuran with 1-butanol using 1,10-phenanthroline as an indicator [15]. All of the dithiolanes **5a–d** were prepared from the corresponding 1,3-propanediols according to the reported method [16] and distilled by Kugelrohr just before use.

Reaction of 1,2-Dithiolanes **5** *with Lithiated 2-Methylfuran* **7a.** 2-Methylfuran **6a** (140 mg, 1.70 mmol) was lithiated with BuLi (1.44 M hexane solution 1.04 mL, 1.50 mmol) in THF (5 mL) at 0°C during 30 minutes. 4,4-Diethyl-1,2-dithiolane **5a** (156.1 mg, 0.96 mmol) was added to the solution, and the mixture was stirred for 30 minutes at 0°C. After addition of acetic acid (2 mL) and water (10 mL), the mixture was extracted with dichloromethane (10 mL). The organic layer was concentrated and distilled by kugelrohr to give **8a** (229.8 mg, 98%).



SCHEME 6

2-(2-Ethyl-(2-mercaptomethyl)butyl)thio-5-methylfuran **8a,** yield 230 mg (98%), purity 98% (gc), oven temperature (OT) 52–125°C/0.4 mmHg. ^{1}H NMR ($CDCl_3$, 89.5 MHz) δ 0.752 (6H, t, J = 7.4 Hz, $2CH_3$), 1.092 (1H, t, J = 9.0 Hz, $\underline{H}SCH_2$), 1.396 (4H, q, J = 7.4 Hz, $2CH_2$), 2.286 (3H, dd, J = 0.8 and 0.4 Hz, CH_3), 2.552 (2H, d, J = 9.0 Hz, $C\underline{H_2}SH$), 2.820 (2H, s, SCH_2), 5.936 (1H, dq, J = 3.0 and 1.0 Hz, H-4 in furan), and 6.366 ppm (1H, dq, J = 3.0, 0.4 Hz, H-3 in furan). ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 7.52 ($2CH_3$), 13.94 (CH_3), 26.04 ($2CH_2$), 30.18 (CH_2), 40.86 (C), 42.34 (CH_2), 107.64 (CH), 117.66 (CH), 144.02 (C), and 155.10 ppm (C). IR (KBr) ν 2968 (s, C-H), 2928 (m, C-H), 2882 (m, C-H), 2584 (vw, S-H), 1454 (m), 1019 (m), and 785 cm^{-1} (m). MS *m/z* (%) 244 (32, M^+), 131 (14, M-SC_4H_2OMe), 114 (base, Me-furan-SH^+), 113 (35, Me-furan-S^+), 97 (26), 86 (11), 85 (16), 82 (10). Found: C, 58.90; H, 8.17%. Calcd for $C_{12}H_{20}OS_2$: C, 58.97; H, 8.25%.

4,4-Pentamethylene-1,2-dithiolane **5b** reacted with 5-methyl-2-furanyllithium **7a** similarly to give **8b.** 2-(1-Mercaptomethylcyclohexyl)methylthio-5-methylfuran **8b,** yield 220 mg, 97% (from **5b** 155 mg, 0.89 mmol) purity 99% (gc). Pale yellow oil, OT 76–129°C/0.4 mmHg. ^{1}H NMR ($CDCl_3$) δ 1.098 (1H, t, J = 9.0 Hz, $\underline{H}SCH_2$), 1.414 (10H, s, $5CH_2$), 2.286 (3H, d, J = 1.0 Hz, CH_3), 2.668 (2H, d, J = 9.0 Hz, $C\underline{H_2}SH$), 2.942 (2H, s, SCH_2), 5.942 (1H, dq, J = 3.0, 1.0 Hz, H-4 in furan), and 6.368 ppm (1H, d, J = 3.0 Hz, H-3 in furan). IR (KBr) ν 2928 (s, C-H), 2856 (m), 2576 (vw, S-H), 1454 (m), 1019 (m), and 785 cm^{-1} (m). Found: C, 60.82; H, 7.80%. Calcd for $C_{13}H_{20}OS_2$: C, 60.89; H, 7.86%.

Fairly polymerizable 4-ethyl-4-methyl- and 4-methyl-4-propyl-1,2-dithiolanes **5c,d** were distilled by kugelrohr just before use and reacted with 1.5 equiv of 5-methyl-2-furanyllithium **7a** in THF to give the corresponding ring-opened products **8c** and **8d,** respectively, in high yields.

2-(2-Mercaptomethyl-2-methylbutyl)thio-5-methylfuran **8c,** pale yellow oil, OT 46–102°C/0.3 mmHg. Yield 213 mg, 98% (from **5c** 139.8 mg, 0.94 mmol), purity 99% (gc). ^{1}H NMR ($CDCl_3$) δ 0.796 (3H, t, J = 8.0 Hz, CH_3), 1.230 (1H, t, J = 9.0 Hz, $\underline{H}SCH_2$), 1.432 (2H, q, J = 8.0 Hz, CH_2), 2.286 (3H, d, J = 1.0 Hz,

CH_3), 2.568 (2H, d, J = 9.0 Hz, $C\underline{H}_2SH$), 2.842 (2H, s, SCH_2), 5.950 (1H, dq, J = 3.0, 1.0 Hz, H-4 in furan), and 6.368 ppm (1H, d, J = 3.0 Hz, H-3 in furan). IR (KBr) ν 2968 (s, C-H), 2880 (m), 2576 (vw, S-H), 1454 (m), 1019 (m), and 785 cm^{-1} (m). Found: C, 57.35; H, 7.86%. Calcd for $C_{11}H_{18}OS_2$: C, 57.34; H, 7.87%.

2-(2-Mercaptomethyl-2-methylpentyl)thio-5-methylfuran **8d,** pale yellow oil, OT 52–107°C/0.1 mmHg, yield 227.9 mg, 98% (from **5d** 154.9 mg, 0.95 mmol), purity 99% (gc). ^1H NMR ($CDCl_3$) δ 0.892–1.290 (11H, m, Pr, Me, and SH), 2.286 (3H, d, J = 1.0 Hz, CH_3), 2.574 (2H, d, J = 9.0 Hz, $C\underline{H}_2SH$), 2.844 (2H, s, SCH_2), 5.950 (1H, dq, J = 3.0 and 1.0 Hz, H-4 in furan), and 6.366 ppm (1H, d, J = 3.0 Hz, H-3 in furan). IR (KBr) ν 2962 (s, C-H), 2930 (m), 2874 (m), 2576 (vw, S-H), 1458 (m), 1019 (m), and 785 cm^{-1} (m). Found: C, 58.91; H, 8.25%. Calcd for $C_{12}H_{20}OS_2$: C, 58.97; H, 8.25%.

Reaction of 4,4-Diethyl-1,2-dithiolane **5a** *with 2-Lithiofuran* **7b.** A hexane solution of *n*-BuLi (2.00 mmol) was added to a THF solution (5 mL) of freshly distilled furan (150 mg, 2.20 mmol) with stirring under argon at 0°C. After the mixture had been stirred for 30 minutes, 4,4-diethyl-1,2-dithiolane **5a** (170 mg, 1.05 mmol) was added by means of a gas-tight syringe, and the mixture was stirred at room temperature for 30 minutes. The mixture was acidified with acetic acid (2 mL), diluted with water (10 mL), and extracted with dichloromethane (5 mL). The organic layer was concentrated under reduced pressure and distilled by kugelrohr.

2-(2-Ethyl-(2-mercaptomethyl)butyl)thiofuran **9,** yield 225.6 mg (93%), purity 92% by glc, OT 130–190/20 mmHg. ^1H NMR ($CDCl_3$) δ 0.750 (6H, t, J = 7.4 Hz, $2CH_3$), 1.088 (1H, t, J = 8.8 Hz, $H\underline{S}CH_2$), 1.396 (4H, q, J = 7.4 Hz, $2CH_2$), 2.548 (2H, d, J = 8.8 Hz, $C\underline{H}_2SH$), 2.860 (2H, s, SCH_2), 6.354 (1H, dd, J = 3.2 and 2.0 Hz, H-4 in furan), 6.468 (1H, dd, J = 3.2 and 0.8 Hz, H-3 in furan), and 7.468 ppm (1H, dd, J = 2.0 and 0.8 Hz, H-5 in furan). ^{13}C NMR ($CDCl_3$) δ 7.50 ($2CH_3$), 26.06 ($2CH_2$), 30.20 (CH_2), 40.88 (C), 41.82 (CH_2), 111.60 (CH), 116.02 (CH), 145.02 (CH), and 146.60 ppm (C). IR (KBr) ν 2968 (s, C-H), 2936 (m, C-H), 2880 (m, C-H), 2584 (vw, S-H), 1456 (m), 1152 (m), 1006 (m), 907 (m), and 741 cm^{-1} (m). MS m/z (%) 230 (66, M^+), 131 (72, M − SC_4H_3O), 100 (70), 99 (34, $C_4H_3OS^+$), 97 (100), 75 (32), 69 (44), 61 (26).

Reaction of **5a** *with 2-Lithiobenzo[b]furan* **10:** *Equimolar Reaction.* Benzo[*b*]furan 124 mg (1.05 mmol) was treated with 1.3 M BuLi 0.75 mL (1.0 mmol) in THF (5 mL) at room temperature for 30 minutes. Dithiolane **5a** 167 mg (1.03 mmol) was added to the solution by means of a gas-tight syringe, and the mixture was stirred for 30 minutes at room temperature. The mixture was acidified with acetic acid (2 mL) and water (20 mL) and extracted with hexane (10 mL). The organic layer was filtered, concentrated under reduced pressure, and distilled by kugelrohr.

2-(2-Ethyl-2-(mercaptomethyl)butyl)thiobenzo[*b*]furan **11,** yield 261 mg (90%). Purity 99% (gc). OT 137–165°C/0.8 mmHg. ^1H NMR ($CDCl_3$) δ 0.756 (6H, t, J = 7.4 Hz, 2 CH_3), 1.140 (1H, t, J = 8.8 Hz, $H\underline{S}CH_2$), 1.408 (4H, q, J = 7.4 Hz, $2CH_2$), 2.546 (2H, d, J = 8.8 Hz, $C\underline{H}_2SH$), 3.022 (2H, s, CH_2S), 6.740 (1H, d, J = 0.9 Hz, H-3 in benzofuran), 7.124–7.294 (2H, m, H-arom), and 7.364–7.494 ppm (2H, m, H-arom). ^{13}C NMR ($CDCl_3$) δ 7.52 ($2CH_3$), 26.18, ($2CH_2$), 30.24 (CH_2), 40.42 (CH_2), 40.76 (C), 110.18 (CH), 110.80 (CH), 120.24 (CH), 122.84 (CH), 124.24 (CH), 128.64 (C), 151.06 (C), and 156.12 ppm (C). IR (KBr) ν 2968 (s, C-H), 2584 (vw, S-H), 1446 (s), 1255 (m), 1160 (m), and 748 cm^{-1} (m).

Reaction with Excess Reagent **10** *and Further Methylation.* A THF solution (5 mL) of 2-lithiobenzo[*b*]furan (1.51 mmol) was prepared as described above. 4,4-Diethyl-1,2-dithiolane **5a** 167 mg (1.03 mmol) was added to the solution by means of a gas-tight syringe, and the mixture was stirred at room temperature for 30 minutes. After methanol (3 mL) and iodomethane 650 mg (4.6 mmol) had been added, the mixture was stirred at room temperature for 1 day. The mixture was diluted with dichloromethane (10 mL) and washed with water (20 mL). The organic layer was concentrated, and the residue was chromatographed on Wako-gel C-300. Hexane-CH_2Cl_2 (3:1) eluted the ring-opened product **12,** and its isomerized products **14** and **13** in that order of elution.

2-(2-Ethyl-2-(methylthiomethyl)butyl)thiobenzo[*b*]furan **12,** yield 124.2 mg (41%), colorless oil. ^1H NMR ($CDCl_3$) δ 0.786 (6H, t, J = 7.4 Hz, $2CH_3$), 1.450 (4H, q, J = 7.4 Hz, $2CH_2$), 2.070 (3H, s, CH_3S), 2.576 (2H, s, CH_2S), 3.072 (2H, s, CH_2S), 6.738 (1H, d, J = 0.9 Hz, H-3 in benzofuran), and 7.12–7.48 ppm (4H, m, H-arom). ^{13}C NMR ($CDCl_3$) δ 7.56 ($2CH_3$), 17.30 (CH_3), 27.25 ($2CH_2$), 41.28 (CH_2), 41.35 (C), 41.55 (CH_2), 109.80 (CH), 110.78 (CH), 120.18 (CH), 122.80 (CH), 124.10 (CH), 128.74 (C), 151.54 (C), and 156.10 ppm (C). IR (KBr) ν 2968 (s, C-H), 2920 (m), 1446 (s), 1255 (m), and 748 cm^{-1} (m). MS m/z (%) 294 (26, M), 150 (13), 149 (20), 145 (82, M-SC_8H_5O), 121 (11), 97 (32), 61 (100, $MeSCH_2^+$). Found: C, 65.23; H, 7.56%. Calcd for $C_{16}H_{22}OS_2$: C, 65.26; H, 7.53%.

6,6-Diethyl-2-(2-methoxyphenyl)-6,7-dihydro-5*H*-1,4-dithiepin, **14,** yield 53.1 mg (18%), colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.798 (6H, t, J = 7.2 Hz, $2CH_3$), 1.550 (4H, q, J = 7.2 Hz, $2CH_2$), 3.234 (4H, s, CH_2S), 3.808 (3H, s, OCH_3), 5.930 (1H, s, H-vinyl), 6.78–6.94 (2H, m, H-arom), and 7.12–7.30 ppm (2H, m, H-arom). ^{13}C NMR ($CDCl_3$) δ 7.95 ($2CH_3$), 26.48 ($2CH_2$), 39.48 (CH_2), 40.10 (C), 41.82 (CH_2), 55.86 (CH_3O), 111.50 (CH), 118.80 (CH), 120.42 (CH), 128.88 (CH), 130.10 (CH), 130.88 (C), and 156.52 ppm (C).

2-[2-Ethyl-2-(methylthiomethyl)butyl]thioethynyl-1-methoxybenzene, **13,** yield 18.7 mg (6%), pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.852 (6H, t, J = 7.2 Hz, $2CH_3$), 1.474 (4H, q, J = 7.2 Hz, $2CH_2$), 2.130 (3H, s, CH_3S), 2.615 (2H, s, CH_2S), 2.990 (2H, s, CH_2S), 3.850 (3H, s, CH_3O), 6.78–6.94 (2H, m, H-arom), and 7.14–7.42 ppm (2H, m, H-arom). ^{13}C NMR ($CDCl_3$) δ 7.68 ($2CH_3$), 17.40 (CH_3), 27.15 ($2CH_2$), 41.52 (CH_2), 41.65 (C), 43.35 (CH_2), 55.68 (CH_3O), 84.74 (C), 87.54 (C), 110.58 (CH), 112.90 (C), 120.36 (CH), 129.28 (CH), 133.32 (CH), and 160.05 ppm (C). IR (KBr) ν 2968 (m, C–H), 1446 (s), 2172 (w, CC acetylenic), 1493 (m), 1464 (m), 1435 (m), 1259 (s, C–O), and 752 cm^{-1} (m). MS *m/z* (%) 308 (12, M), 261 (2, M-SMe), 145 (64, M-SCCPhOMe), 119 (15), 97 (29), 91 (33), 89 (19), 69 (12), 61 (100, $MeSCH_2^+$).

Reaction of 1,2-Dithiolane **5a** *with 5-Lithio-2,3-dihydrofuran* **15a.** Freshly distilled 2,3-dihydrofuran, 152.3 mg (2.17 mmol), was lithiated in THF (5 mL) with 1.44 M BuLi (1.05 mL, 1.51 mmol) over a Dry Ice–acetone bath for 0.5 hours. 4,4-Diethyl-1,2-dithiolane **5a** 155.3 mg (0.96 mmol) was added to the THF solution of **15a** at 0°C, and the mixture was stirred for 30 minutes at room temperature. The mixture was acidified with acetic acid (3 mL), diluted with water (20 mL), and extracted with dichloromethane. The organic layer was concentrated under reduced pressure and distilled by Kugelrohr to give **16a** 195.5 mg (88%), purity 95% by GLC.

8,8-Diethyl-1-oxa-6,10-dithiaspiro[4.5]decane, **16a,** colorless oil, OT 82–143°C/0.4 mm Hg. ^{1}H NMR ($CDCl_3$) δ 0.796 (3H, J = 7.4 Hz, CH_3), 0.858 (3H, J = 6.8 Hz, CH_3), 1.356 (2H, q, J = 7.4 Hz, CH_2), 1.830 (2H, q, J = 7.4 Hz, CH_2), 1.96–2.16 (4H, m, CH_2), 2.402 (2H, d, J = 14.0 Hz, 2CHS), 3.132 (2H, d, J = 14.0 Hz, 2CHS), and 3.984 ppm (2H, t, J = 6.8 Hz, CH_2O). ^{13}C NMR ($CDCl_3$) δ 7.40 (CH_3), 7.48 (CH_3), 22.62 (CH_2), 24.82 (CH_2), 30.24 (C), 30.84 (CH_2), 37.14 ($2CH_2$), 40.64 (CH_2), 68.06 (CH_2), and 91.18 ppm (C). MS *m/z* (%) 232 (32, M^+), 201 (15), 134 (19), 130 (35), 103 (100), 102 (58), 101 (24), 97 (22), 82 (87), 69 (38). IR (KBr) ν 2968 (m, C–H), 1696 (w), 1452 (m), 1035 (s), 988 (m), and 919 cm^{-1} (w). Found: C, 56.93; H, 8.71%. Calcd for $C_{11}H_{20}OS_2$: C, 56.84; H, 8.67%.

Reaction of 4,4-Diethyl-1,2-dithiolane **5a** *with 6-Lithio-3,4-dihydro-2H-pyran* **15b.** To a solution of 3,4-dihydro-2*H*-pyran 208 mg (2.5 mmol) and TMEDA, 254 mg (2.2 mmol), in THF (5 mL), BuLi (2.0 mmol, hexane solution) was added, and the mixture was stirred at room temperature for 2 hours. Then, 4,4-diethyl-1,2-dithiolane **5a,** 164 mg (1.01 mmol), was added to the mixture and allowed to react under stirring for 2 hours at room temperature. The mixture was acidified with acetic acid (6 mL), diluted with water (20 mL), and extracted with hexane (8 mL). The organic layer was concentrated and the residue distilled under reduced pressure by kugelrohr.

9,9-Diethyl-1-oxa-7,11-dithiaspiro[5.5]undecane, **16b,** yield 241 mg (97%), purity 99% (GLC), OT 117–128°C/0.6 mmHg. ^{1}H NMR ($CDCl_3$) δ 0.780 (3H, t, J = 7.4 Hz, CH_3), 0.844 (3H, t, J = 6.8 Hz, CH_3), 1.318 (2H, q, J = 7.4 Hz, CH_2), 1.53–1.95 (8H, m), 2.278 (2H, d, J = 14.0 Hz, 2CHS), 2.990 (2H, d, J = 13.8 Hz, 2CHS), and 3.858 ppm (2H, t, J = 5.2 Hz, CH_2O). ^{13}C NMR ($CDCl_3$) δ 7.36 (CH_3), 7.40 (CH_3), 19.36 (CH_2), 22.30 (CH_2), 25.10 (CH_2), 30.82 (C), 31.20 (CH_2), 34.96 ($2CH_2$), 37.02 (CH_2), 62.98 (CH_2), and 86.74 ppm (C). IR (KBr) ν 2966 (m, C–H), 1462 (w), 1064 (w), 1038 (w), 1017 (s), 870 (w), and 787 cm^{-1} (w). Found: C, 58.71; H, 9.06%. Calcd for $C_{12}H_{22}OS_2$: C, 58.49; H, 9.00%.

Reaction of 4,4-Diethyl-1,2-Dithiolane **5a** *with* **15b** *and Further Methylation.* Dihydropyran, 204 mg (2.4 mmol), was lithiated with BuLi (2.0 mmol) in the presence of TMEDA (2.1 mmol) in THF (5 mL) at room temperature for 2 hours and reacted with 1,2-dithiolane **5a** 166 mg (1.0 mmol) at room temperature for 2 hours as described above. The excess lithium reagent was destroyed by addition of methanol 1 mL (12 mmol), and the mixture was stirred with MeI 693 mg (4.9 mmol) at room temperature for 12 hours. After dilution with water, the mixture was extracted with hexane and distilled by kugelrohr under reduced pressure to give **17** as a sole product.

6-(2-Ethyl-2-(methylthiomethyl)butylthio)-3,4-dihydro-2*H*-pyran, **17,** yield 248 mg (93%), purity 99% (GLC). OT 109–121°C/0.5 mmHg. ^{1}H NMR ($CDCl_3$) δ 0.796 (6H, t, J = 7.2 Hz, $2CH_3$), 1.382 (4H, q, J = 7.2 Hz, $2CH_2$), 1.75–2.11 (4H, m, $2CH_2$), 2.104 (3H, s, CH_3S), 2.530 (2H, s, CH_2S), 2.752 (2H, s, CH_2S), 4.062 (2H, t, J = 5.0 Hz, CH_2O), and 5.042 ppm (1H, t, J = 3.6 Hz, CH=). ^{13}C NMR ($CDCl_3$) δ 7.66 ($2CH_3$), 17.36 (CH_3), 21.88 (CH_2), 22.18 (CH_2),

27.22 ($2CH_2$), 37.24 (CH_2), 41.30 (C), 41.62 (CH_2), 67.90 (CH_2), 103.38 (CH), and 148.94 ppm (C). MS *m/z* (%) 260 (M^+, 20), 145 (39), 144 (42), 117 (40), 115 (100), 97 (33), 83 (42).

Reaction of 4,4-Diethyl-1,2-dithiolane **5a** *with Lithiated Furan* **7b** *and further Allylation with Allyl Bromide.* Freshly distilled furan, 172 mg (2.5 mmol), in THF (5 mL) was lithiated with BuLi (2.0 mmol, 1.6M hexane solution) at 0°C and reacted with 4,4-diethyl-1,2-dithiolane **5a,** 183.6 mg (1.13 mmol), at room temperature for 1.5 hours. After addition of methanol, 390 mg (12 mmol), the mixture was further reacted with allyl bromide, 710 mg (5.9 mmol), at room temperature for 0.5 days. The mixture was diluted with CH_2Cl_2, 10 mL, and washed with dilute aqueous acetic acid solution. The organic layer was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, eluent: hexane) to give **18** 275 mg (90%).

2-(2-Ethyl-2-(2-propenylthiomethyl)butylthio)-furan, **18.** ^{1}H NMR ($CDCl_3$) δ 0.760 (6H, t, J = 7.4 Hz, $C\underline{H}_3CH_2$), 1.420 (4H, q, J = 7.4 Hz, $CH_3C\underline{H}_2$) 2.494 (2H, s, CH_2S), 2.888 (2H, s, CH_2S), 3.110 (2H, dt, J = 7.0 and 1.0 Hz, $SC\underline{H}_2CH=$), 4.988–5.228 (2H, m, $CH_2=$), 5.804 (1H, ddt, J = 17.2, 9.4, and 7.0 Hz, $SCH_2C\underline{H}=$), 6.350 (1H, dd, J = 3.2 and 2.0 Hz, H-4 in furan), 6.452 (1H, dd, J = 3.2 and 0.8 Hz, H-3 in furan), and 7.460 ppm (1H, dd, J = 2.0 and 0.8 Hz, H-5 in furan). ^{13}C NMR ($CDCl_3$) δ 7.54 ($2CH_3$), 27.26 ($2CH_2$), 36.20 (CH_2), 37.64 (CH_2), 41.02 (C), 42.76 (CH_2), 111.52 (CH), 115.68 (CH), 116.84 (CH_2), 134.74 (CH), 144.86 (CH), and 146.92 ppm (C). IR (KBr) ν 2970 (s, C-H), 2926 (m, C-H), 2882 (m, C-H), 1636 (w, C=C) , 1462 (m), 1152 (m), 1006 (m), 907 (m), and 739 cm^{-1} (m). MS *m/z* (%) 270 (8, M), 229 (base, M-$CH_2CH=CH_2$), 171 (12, M-C_4H_3OS), 131 (24), 129 (84), 99 (58, $C_4H_3OS^+$), 87 (68, $CH_2SCH_2CH=CH_2^+$), 73 (22), 71 (48), 69 (30).

Reaction of 4,4-Diethyl-1,2-dithiolane **5a** *with Lithiated Furan* **7b** *and Further Reaction with Propargyl Bromide.* Furan, 141.4 mg (2.08 mmol), was lithiated with BuLi (2.00 mmol) in THF (5 mL) and reacted with 4,4-diethyl-1,2-dithiolane **5a,** 173.2 mg (1.07 mmol), as described earlier for **18.** After addition of methanol, 252 mg (7.87 mmol), the mixture was further reacted with propargyl bromide, 779.5 mg (6.55 mmol). Usual workup including column chromatography (silica gel-hexane) gave **19,** 252.3 mg (88%), as a pale yellow oil.

2-[2-Ethyl-2-(2-propynylthiomethyl)butylthio]-furan, **19.** ^{1}H NMR ($CDCl_3$) δ 0.788 (6H, t, J = 7.4 Hz, $C\underline{H}_3CH_2$), 1.438 (4H, q, J = 7.4 Hz, $CH_3C\underline{H}_2$), 2.232 (1H, t, J = 2.6 Hz, HC ≡ C), 2.742 (2H, s, CH_2S), 2.890 (2H, s, CH_2S), 3.226 (2H, d, J = 2.6 Hz, $SCH_2C\equiv$), 6.350 (1H, dd, J = 3.2 and 2.0 Hz, H-4 in furan), 6.462 (1H, dd, J = 3.2 and 0.8, Hz, H-3 in furan), and 7.462 ppm (1H, dd, J = 2.0 and 0.8 Hz, H-5 in furan). ^{13}C NMR ($CDCl_3$) δ 7.50 ($2CH_3$), 20.66 (CH_2), 27.30 ($2CH_2$), 38.42 (CH_2), 41.16 (C), 42.74 (CH_2), 70.92 (CH), 80.34 (C), 111.54 (CH), 115.84 (CH), 144.94 (CH), and 146.72 ppm (C). IR (KBr) ν 3298 (m, ≡ C-H), 2970 (s, C-H), 2928 (*m,* C-H), 2882 (m, C-H), 1462 (m), 1152 (m), 1006 (m), 907 (m), and 741 cm^{-1} (m). MS *m/z* (%) 268 (10, M), 229 (98, M-$CH_2C\equiv CH$), 169 (16, M-SC_4H_3O), 129 (base), 99 (70, $SC_4H_3O^+$), 85 (89, $CH_2SCH_2C\equiv CH^+$), 71 (63).

REFERENCES

[1] Y. H. Kim: Biochemistry of Disulfides, in S. Oae and T. Okuyama (eds): *Organosulfur Chemistry: Biochemical Aspects,* CRC Press, Tokyo (1992); L. Teuber, *Sulfur Rep., 9,* 1990, 257; L. J. Reed, *Acc. Chem. Res., 7,* 1973, 40; N. Isenberg, M. Grdinic, *J. Chem. Educ., 49,* 1972, 392; U. Schmidt, P. Grafen, K. Altland, H. W. Goedde, *Adv. Enzymol. Relat. Areas Mol. Biol., 32,* 1969, 423.

[2] Carbanion mechanisms [3] and redox mechanism [4] have been proposed.

[3] R. Breslow, *Ann. N.Y. Acad. Sci., 98,* 1962, 445; F. G. White, L. L. Ingraham, *J. Am. Chem. Soc., 84,* 1962, 3109.

[4] M. L. Das, M. Koike, L. J. Reed, *Proc. Natl. Acad. Sci. USA, 47,* 1961, 753; P. A. Frey, D. S. Flournoy, K. Gruys, Y.-S. Yang, *Ann. N.Y. Acad. Sci., 573,* 1989, 21.

[5] M. Tazaki, S. Nagahama, M. Takagi, *Chem. Lett.,* 1988, 1339.

[6] M. Tazaki, H. Tanabe, T. Hieda, S. Nagahama, K. Inoue, M. Takagi, *Phosphorus, Sulfur and Silicon, 88,* 1994, 189.

[7] M. Tazaki, H. Tanabe, S. Nagahama, M. Takagi, *J. Chem. Soc., Chem. Commun.,* 1994, 291.

[8] E. H. Smith, *J. Chem. Soc., Perkin Trans., 1,* 1984, 523.

[9] M. Tazaki, M. Kumakura, S. Nagahama, M. Takagi, *Phosphorus, Sulfur and Silicon, 106,* 1995, 227; M. Tazaki, M. Yamada, *Phosphorus, Sulfur and Silicon, 116,* 1996, 253.

[10] M. Tazaki, M. Kumakura, S. Nagahama, M. Takagi, *J. Chem. Soc., Chem. Commun.,* 1995, 1763.

[11] M. Tazaki, S. Okai, T. Hieda, S. Nagahama, M. Takagi, *Phosphorus, Sulfur and Silicon, 112,* 1996, 101.

[12] L. J. Reed: Lipoic Acid, in N. Kharasch (ed): *Organosulfur Compounds,* Vol. 1, Pergamon Press, New York (1961).

[13] H. Gilman, D. S. Melstrom, *J. Am. Chem. Soc., 70,* 1948, 1655; T. Gilchrist, *Adv. Heterocycl. Chem., 41,* 1987, 41.

[14] E. Ciganek, *Organic Reactions, 32,* 1984, 1.

[15] S. C. Watson, J. F. Eastham, *J. Organomet. Chem., 9,* 1967, 165.

[16] G. Bergson, A. Biezais, *Arkiv Kemi, 22,* 1964, 475.