Unusual Reactions of the 1,3-Dithiane Derivative of the Garner Aldehyde and Related Compounds

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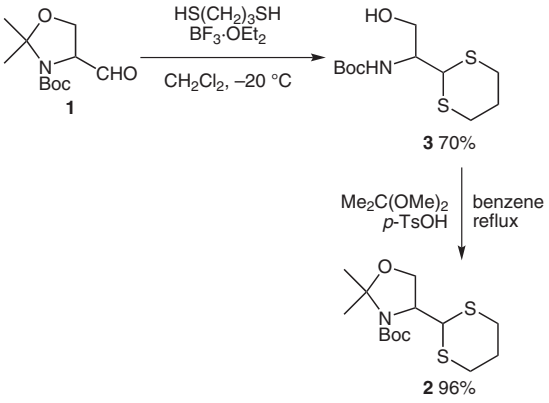
Abstract: Treatment of the 1,3-dithiane derivative of the Garner aldehyde with alkyl halides in the presence of *n*-butyllithium resulted in a ring-opening reaction to give differentially substituted propane-1,3-dithioethers, instead of the expected 2,2-dialkylated 1,3-dithiane products. The corresponding 1,3-dithiolane derivative also reacted in a similar manner. Such ring-opening reactions of dithiane or dithiolane derivatives are rare. A detailed study of this unusual reaction was carried out and a possible mechanism is proposed.

Key words: dithianes, dithiolanes, butyllithium, ring opening, umpolung

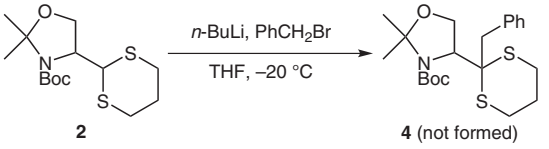
Garner's aldehyde (**1**) and a number of related derivatives have been widely used in the synthesis of various natural and unnatural products. Aldehyde **1** has quite often been used as an efficient chiral starting material for the synthesis of a number of amino acids and carbohydrate derivatives.[1] In connection with our efforts to develop new methods for the synthesis of unnatural amino acids,[2] we postulated that the use of the 1,3-dithiane derivative of **1**, as an umpolung equivalent of the aldehyde function, could be a suitable starting material. Although the chemistry of the Garner aldehyde (**1**) has been widely studied and applied, its 1,3-dithiane derivative has not been reported. We believed that the use of such a derivative could add a new dimension to the chemistry of this versatile synthetic precursor. To our surprise, the 1,3-dithiane derivative **2** synthesized from **1** reacted quite differently to other dithianes and in a completely unpredictable manner. Our observations and the results of related studies toward understanding this rather unusual reactivity are reported here.

The 1,3-dithiane derivative of the Garner aldehyde was synthesized by treatment of **1** with propane-1,3-dithiol ($BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C). The reaction conditions resulted in the opening of the oxazolidine ring, yielding an amino alcohol derivative **3**, which was recyclized with 2,2-dimethoxypropane (*p*-TsOH, benzene, 80 °C) to provide **2** (Scheme 1).

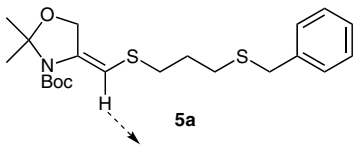
As an initial reaction, we attempted to couple 1,3-dithiane **2** with benzyl bromide, after generating the corresponding anion using *n*-butyllithium (1.5 equiv, THF, –20 °C), and expected to obtain the 2,2-disubstituted 1,3-dithiane derivative **4** (Scheme 2). The reaction proceeded cleanly and only a single product could be isolated; however, the NMR spectra of the product did not match what was expected for **4** and looked very simple, unlike those of many dithiane derivatives. A careful spectroscopic analysis of the product indicated that the dithiane ring had been cleaved under the reaction conditions. The product formed was an unsymmetrical propane-1,3-dithioether, namely **5a** (Figure 1). The ^1H and ^{13}C NMR spectra confirmed the presence of a double bond in the compound. The individual peaks in ^1H NMR spectrum were correlated with the ^{13}C peaks using heteronuclear correlation spectroscopy and the configuration of the double bond was determined from NOE experiments.



Scheme 1 Synthesis of the 1,3-dithiane derivative **2** of the Garner aldehyde (**1**)



Scheme 2 Expected reaction of **2** with benzyl bromide in the presence of *n*-butyllithium



δ_H = 6.18 ppm (s), no NOE with the CH_2 in the oxazolidine ring

Figure 1 Structure of **5a** formed from the reaction between **2** and benzyl bromide

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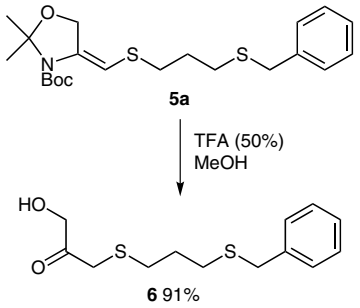
In order to further confirm the structure of the product formed in this reaction, the oxazolidine ring of **5a** was opened and the Boc group was removed by treatment with trifluoroacetic acid (50% in MeOH). As expected, the ketone derivative **6** was isolated, in 91% yield (Scheme 3), confirming the structure of **5a** as that shown in Figure 1.

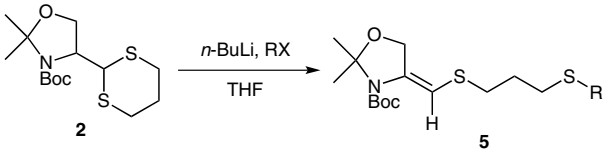


Scheme 3 Acidolysis of **5a**

The formation of **5a** as the only isolable product was surprising, and we could not isolate even traces of the expected product **4**. Products similar to **5a**, formed via opening of the dithiane ring, have very rarely been observed. The only other report of such a reaction was in the case of a dithian-2-yl derivative of diethyl malonate, which underwent a ring-opening reaction on treatment with sodium hydride and iodomethane.[3] It has also been shown that S-alkylation of dithianes can be exploited to achieve ring opening of dithianes.[4] However, since then, cleavage of the dithiane ring as a side reaction during umpolung reactions has not been reported. This prompted us to study this reaction further to comprehend our observation of this unusual reactivity. We performed the reaction of 1,3-dithiane **2** with three other alkyl halides, and the results are listed in Table 1. All of the alkyl halides studied reacted with **2** in the same way as benzyl bromide, and the yields were generally good. Alkyl iodides and bromides reacted in the same manner, and varying the temperature of the reaction did not have any effect on the nature of the product formed (see entries 4 and 5).

We attempted the reaction of 1,3-dithiane **2** with other electrophiles, such as 4-nitrobenzaldehyde and ethyl acrylate. These compounds did not react with **2** to give any isolable products; however, unreacted **2** could not be isolated from the reaction mixture. After the addition of *n*-butyllithium, the 1,3-dithiane **2** disappeared completely by TLC, indicating that it decomposes in the absence of an alkyl halide to react with. In order to confirm this observation and also to understand the exact nature of the deprotonation of **2** with *n*-butyllithium, we tried to quench the anion with D_2O and CD_3OD. When one or more equivalents of *n*-butyllithium were used and the reaction was quenched with deuterated solvents, we could not isolate any amount of deuterated **2**. TLC showed complete disappearance of the starting material and formation of a mixture of polar products, none of which could be isolated and characterized. When the reaction was carried out with

Table 1 Reaction of 1,3-Dithiane **2** with Alkyl Halides

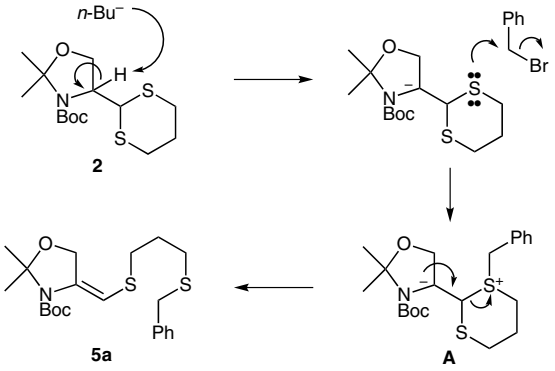


Entry	RX	Temp (°C)	5	Yield[a] (%)
1	$PhCH_2Br$	–20	**5a**	52
2	$H_2C{=}CHCH_2Br$	–20	**5b**	47
3	*i*-PrBr	–20	**5c**	50
4	MeI	–20	**5d**	54
5	MeI	–78	**5d**	51

[a] Isolated yield.

0.5 equivalents of *n*-butyllithium and the reaction mixture was quenched with D_2O, almost half of compound **2** could be recovered; however, an NMR analysis of **2** isolated from the reaction mixture did not indicate the presence of deuterium. The experiment suggests that deprotonation of 1,3-dithiane **2** leads to its decomposition, unless a very reactive electrophile such as an alkyl halide is present.

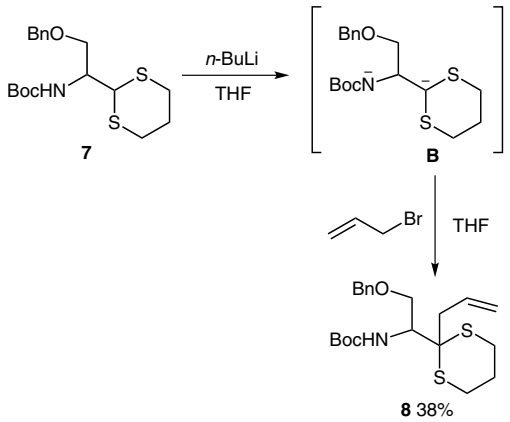
It is known that protons in the α-position to a *N*-Boc group are reasonably acidic.[5] Hence, it is justified to assume that in compound **2** the C–H adjacent to the *N*-Boc group is more acidic than the 2-H in the 1,3-dithiane, and thus deprotonated upon treatment with *n*-butyllithium. We propose the following mechanism for the unusual reaction of **2** with alkyl halides in the light of these assumptions (Scheme 4). It is most likely that the cleavage of the 1,3-dithiane ring happens only as a result of the formation of the sulfonium ion **A**. If a sulfide anion was formed prior to the reaction of the sulfur atom with benzyl bromide, the same anion could have reacted with ethyl acrylate, but it does not. Any stable anionic species formed as an intermediate in the above reaction could have given an isolable product on treatment with D_2O. The absence of any isolable deuterated product even after repeated attempts indicates the possible formation of **A** which, when not



Scheme 4 Proposed mechanism for the formation of **5a** from **2**

possible in the absence of an alkyl halide, results in complete decomposition of the anion formed.

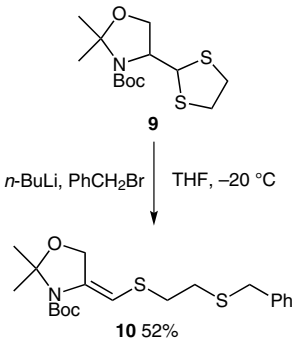
If the C–H adjacent to the *N*-Boc group was rendered less acidic, the reaction of **2** could have proceeded as expected. To substantiate this argument, we prepared the *O*-benzyl derivative **7** of the amino alcohol **3**, and treated it with allyl bromide in the presence of excess *n*-butyllithium. The reaction yielded the 2-allyl-1,3-dithiane derivative **8**, albeit in moderate yield (Scheme 5). The reaction may have proceeded with deprotonation of the NHBoc group, thereby reducing the acidity of the adjacent C–H.[6] Excess *n*-butyllithium deprotonates the 1,3-dithiane at the 2-position, generating the dithianyl anion **B**, which reacts with allyl bromide to give derivative **8**, as expected.



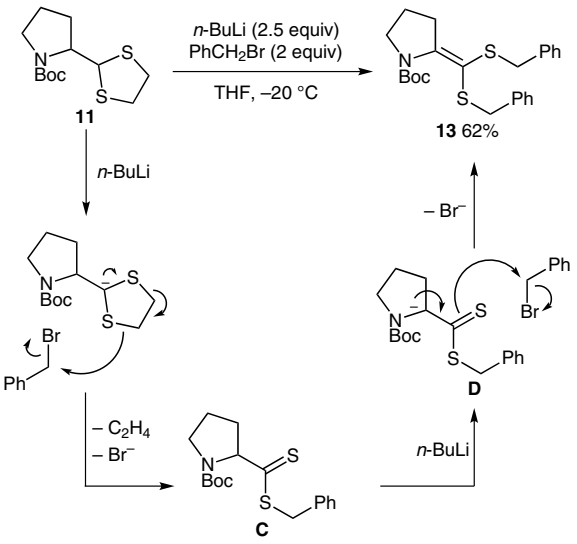
Scheme 5 Reaction of the 1,3-dithiane derivative **7** with allyl bromide

The reaction of dithianes with a base is quite different to that of the corresponding dithiolanes. Dithiolanyl anions are known to dissociate into dithiocarboxylates and ethylene.[7] We assumed that if a dithiolane equivalent of **2** could be prepared, its reaction with *n*-butyllithium would confirm the position of initial deprotonation. If the deprotonation occurs at the 2-position of the dithiolane the product would be a dithiocarboxylate derivative, whereas deprotonation of the C–H adjacent to the *N*-Boc group would result in a product similar to **5**. The 1,3-dithiolane derivative **9** was prepared from the Garner aldehyde (**1**) using a procedure similar to that used for the preparation of 1,3-dithiane **2**. When **9** was treated with benzyl bromide and *n*-butyllithium, the dithioether **10** was obtained (Scheme 6), confirming the proposed mechanism for the reaction of **2**.

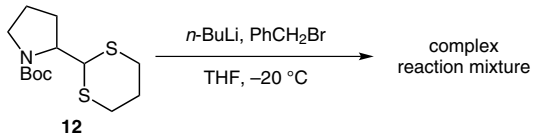
Based on the above observations, a similar reactivity profile could be anticipated for the 1,3-dithiane and 1,3-dithiolane derivatives of N-protected prolinals. We synthesized the 1,3-dithiolane **11** and 1,3-dithiane **12** derivatives of Boc-prolinal following the procedure used for the synthesis of derivatives **9** and **2**. When the 1,3-dithiolane derivative **11** was treated with *n*-butyllithium (1.5 equiv) and benzyl bromide (1 equiv), the only isolable product was the dithio derivative **13**, in low yield. On performing the reaction with 2.5 equivalents of *n*-butyllithium and 2 equivalents of benzyl bromide, product **13** could be isolated in 62% yield (Scheme 7). The formation of **13** gives a new insight into these reactions. The 2-H in the 1,3-dithiolane is the first proton to be removed in this reaction, which results in the elimination of ethylene and formation of the benzyl dithiocarboxylate derivative **C**; however, the proton adjacent to the *N*-Boc group becomes more acidic after the formation of derivative **C**, and is deprotonated. The formation of thioenolate **D** from **C** results in a subsequent reaction with one more equivalent of benzyl bromide, giving the product **13** (Scheme 7). This is a clear indication that the acidity of the 2-alkyl-2-dithiolanyl proton, and possibly that of 2-alkyl-2-dithianyl protons, lies between the acidity of the C–H adjacent to the *N*-Boc group in **9** and that of the adjacent C–H in **11**. Unfortunately, the reaction of the corresponding 1,3-dithiane **12** with *n*-butyllithium and benzyl bromide was quite complex and we could not isolate any products from the reaction, even after repeated efforts at different temperatures (Scheme 8).



Scheme 6 Reaction of the 1,3-dithiolane **9** with benzyl bromide



Scheme 7 Reaction of 1,3-dithiolane **11** with benzyl bromide



Scheme 8 Reaction of 1,3-dithiane **12** with benzyl bromide

In conclusion, our studies clearly suggest that dithianes and dithiolanes react in an unusual manner if an acidic β-hydrogen is present in the molecule. Ideally, a base-induced reaction, such as those with dithianes, should not have any other acidic protons in the substrate. However, a clear definition of how much acidity could be accommodated in such a reaction is not trivial. Our studies shed more light on defining such a limit for reactions involving dithianes and dithiolanes, and also provide a very curious reactivity profile for compounds with an acidic β-hydrogen. The ring-opening reaction is facilitated if the β-carbon is sterically hindered, as in the case of the Garner aldehyde or prolinal derivatives. From our studies, it is safe to say that the acidity of the 2-CH of 2-alkyl-1,3-dithianes and -dithiolanes is between that of the 2-CH of a *N*-Boc-protected pyrrolidine and the 4-CH of a *N*-Boc-protected oxazolidine.

All the chemicals were purchased from commercial sources and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded either on a 400 MHz (100 MHz for ^{13}C) or on a 500 MHz (125 MHz for ^{13}C) JEOL-Lambda NMR spectrometer at 25 °C. The ^{1}H NMR signals are referenced to TMS (δ = 0.00 ppm) and the ^{13}C NMR peaks are referenced to the residual $CHCl_3$ signal (δ = 77.0 ppm). The chemical shifts are reported in parts per million and coupling constants in Hz. The multiplicities are assigned as s (singlet), d (doublet), t (triplet), qu (quintet), br s (broad singlet), dd (double doublet) and m (multiplet). High-resolution mass spectra were obtained using a Waters Q/Tof Premier micromass HAB 213 spectrometer with an ESI source. IR spectra were recorded on a Bruker Vector 22 FTIR instrument and melting points were recorded on a DBK Automatic Programmable digital instrument. Column chromatography was performed using 100–200 mesh silica gel, and appropriate mixtures of petroleum ether (PE) and EtOAc were used as eluent.

1,3-Dithiane Derivatives of the Garner Aldehyde and Boc-Prolinal

A soln of the Garner aldehyde (**1**; 1.145 g, 5 mmol) or Boc-prolinal (0.995 g, 5 mmol) in CH_2Cl_2 was cooled to –20 °C, and propane-1,3-dithiol (0.500 mL, 0.540 g, 5 mmol) was added under nitrogen. The solution was stirred at –20 °C and $BF_3{\cdot}OEt_2$ (0.001 mL) was added. The reaction mixture was allowed to attain r.t. (30 °C) and the stirring was continued until complete disappearance of the starting material (by TLC). The reaction was quenched by adding H_2O (10 mL) and the mixture was diluted with CH_2Cl_2 (50 mL) and then transferred into a separating funnel. The organic layer was separated and washed with a 10% soln of KOH (15 mL) and with brine (15 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography. Although the expected 1,3-dithiane derivative **12** was obtained from Boc-prolinal, the product obtained from the Garner aldehyde was the amino alcohol derivative **3**, which was cyclized to provide the 1,3-dithiane derivative **2** in a subsequent step.

The amino alcohol derivative **3** (0.837 g, 3 mmol) was suspended in benzene (10 mL), and 2,2-dimethoxypropane (0.734 mL, 0.624 g, 6 mmol) and *p*-TsOH (0.010 g, 0.06 mmol) were added. The reaction mixture was refluxed for 2.5 h, quenched with sat. Na_2CO_3 soln (10 mL) and extracted with Et_2O (2 × 30 mL). The crude solution was dried over anhyd Na_2SO_4 and concentrated, and the 1,3-dithiane **2** was purified by column chromatography.

***N*-Boc-Protected 2-Amino-2-(1,3-dithian-2-yl)ethanol (3)**

Yield: 976 mg (70%); oily liquid; R_f = 0.45 (PE–EtOAc, 7:3).

IR (thin film): 3418, 1694 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.18–5.22 (m, 1 H), 4.29 (d, *J* = 5.0 Hz, 1 H), 3.99 (br s, 1 H), 3.91 (dd, *J* = 11.2, 3.7 Hz, 1 H), 3.74 (dd, *J* = 11.5, 4.6 Hz, 1 H), 2.79–2.93 (m, 4 H), 1.86–2.07 (m, 2 H), 1.43 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 80.0, 63.0, 54.9, 48.6, 29.6, 28.3, 25.7.

HRMS (ESI): *m*/*z* [M + Na$^+$] calcd for $C_{11}H_{21}NO_3S_2$: 302.0861; found: 302.0754.

***N*-Boc-Protected 4-(1,3-Dithian-2-yl)-2,2-dimethyloxazolidine (2)**

Yield: 918 mg (96%); white crystalline solid; mp 71–73 °C; R_f = 0.50 (PE–EtOAc, 15:1).

IR (KBr): 1698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.45–4.49 (m, 1 H), 4.12–4.19 (m, 2 H), 3.88–3.91 (m, 1 H), 2.72–2.85 (m, 4 H), 1.79–2.05 (m, 2 H), 1.41–1.57 (m, 15 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (mixture of rotamers) = 152.7, 151.8, 94.7, 94.1, 80.6, 80.4, 65.2, 65.0, 60.3, 60.1, 51.3, 49.1, 30.4, 30.1, 28.6, 28.5, 26.1, 25.9, 24.3.

HRMS (ESI): *m*/*z* [M + Na$^+$] calcd for $C_{14}H_{25}NO_3S_2$: 342.1174; found: 342.1171.

***N*-Boc-Protected 2-(1,3-Dithian-2-yl)pyrrolidine (12)**

Yield: 1.29 g (89%); solid; mp 66–68 °C; R_f = 0.50 (PE–EtOAc, 97:3).

IR (KBr): 1684 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (mixture of rotamers) = 4.79 (br s), 4.60 (br s), 4.07 (br s), 3.98 (br s), 3.70 (br s), 3.49 (br s), 3.22–3.27 (m), 2.74–2.89 (m), 2.57–2.61 (m), 2.06–2.08 (br s), 1.92–1.93 (br s), 1.42–1.45 (m).

^{13}C NMR (125 MHz, $CDCl_3$): δ (mixture of rotamers) = 154.7, 154.2, 79.9, 79.6, 61.3, 60.2, 53.8, 52.1, 47.6, 47.1, 33.5, 33.4, 31.4, 30.7, 30.1, 28.6, 27.7, 27.4, 26.4, 24.5, 24.4, 23.8, 23.5, 23.3.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{13}H_{23}NO_2S_2$: 290.1248; found: 290.1248.

1,3-Dithiolane Derivatives of the Garner Aldehyde and Boc-Prolinal

The 1,3-dithiolane derivatives **9** and **11** of the Garner aldehyde and Boc-prolinal, respectively, were prepared using a similar procedure to that used for the 1,3-dithiane derivatives.

***N*-Boc-Protected 4-(1,3-Dithiolan-2-yl)-2,2-dimethyloxazolidine (9)**

Yield: 960 mg (63%); white crystalline solid; mp 70–72 °C; R_f = 0.50 (PE–EtOAc, 15:1).

IR (KBr): 1703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (mixture of rotamers) = 5.07, 4.92 (1 H), 4.20, 4.06 (1 H), 3.96–4.00 (m, 2 H), 3.19–3.25 (m, 4 H), 1.45–1.61 (m, 15 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (mixture of rotamers) = 152.9, 152.0, 95.3, 94.7, 80.6, 80.4, 65.7, 65.3, 61.1, 60.9, 55.7, 55.2, 38.9, 38.9, 38.7, 38.5, 28.5, 28.4.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{13}H_{23}NO_3S_2$: 306.1198; found: 306.1194.

***N*-Boc-Protected 2-(1,3-Dithiolan-2-yl)pyrrolidine (11)**
Yield: 963 mg (70%); gummy solid; R_f = 0.50 (PE–EtOAc, 97:3).

IR (KBr): 1686 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.08 (s, 1 H), 3.51 (s, 1 H), 3.29–3.34 (m, 2 H), 3.16–3.23 (m, 4 H), 1.72–2.03 (m, 4 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 79.8, 61.7, 56.3, 47.6, 38.9, 38.8, 29.8, 28.6.

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{12}H_{21}NO_2S_2$: 276.1092; found: 276.1095.

Reaction of 1,3-Dithianes and 1,3-Dithiolanes with Alkyl Halides; General Procedure
The 1,3-dithiane or 1,3-dithiolane (1 mmol) was dissolved in THF (10 mL) under nitrogen atmosphere; the solution was cooled to –20 °C and 1.6 M *n*-BuLi in hexane (0.950 mL, 1.5 mmol) was added dropwise. The mixture was stirred for 30 min, then a soln of the alkyl halide (1 mmol) in THF (3 mL) was added dropwise over a period of 10 min. The stirring was continued for 30 min, then the reaction mixture was brought to r.t. and quenched with sat. NH_4Cl soln (3 mL). The solution was partitioned between H_2O (30 mL) and EtOAc (30 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (30 mL). The organic layers were combined, dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography.

***N*-Boc-Protected (*E*)-4-((3-(Benzylthio)propylthio)methylene)-2,2-dimethyloxazolidine (5a)**
Yield: 213 mg (52%); oily liquid; R_f = 0.70 (PE–EtOAc, 97:3).

IR (thin film): 1705 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.30 (m, 5 H), 6.18 (s, 1 H), 4.58 (d, *J* = 2.0 Hz, 2 H), 3.69 (s, 2 H), 2.63 (t, *J* = 7.2 Hz, 2 H), 2.50 (t, *J* = 7.2 Hz, 2 H), 1.84 (qu, *J* = 7.2 Hz, 2 H), 1.56 (s, 6 H), 1.52 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.7, 138.5, 138.1, 128.9, 128.6, 127.1, 98.1, 96.4, 81.9, 77.5, 77.1, 76.9, 66.9, 36.3, 33.9, 30.0, 29.2, 28.4, 25.6.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{21}H_{31}NO_3S_2$: 432.1643; found: 432.1645.

***N*-Boc-Protected (*E*)-4-((3-(Allylthio)propylthio)methylene)-2,2-dimethyloxazolidine (5b)**
Yield: 169 mg (47%); oily liquid; R_f = 0.70 (PE–EtOAc, 97:3).

IR (thin film): 1706 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.17 (s, 1 H), 5.71–5.79 (m, 1 H), 5.05–5.09 (m, 2 H), 4.57–4.58 (m, 2 H), 3.09 (d, *J* = 7.1 Hz, 2 H), 2.64 (t, *J* = 7.1 Hz, 2 H), 2.51 (t, *J* = 7.0 Hz, 2 H), 1.83 (qu, *J* = 7.3 Hz, 2 H), 1.56 (s, 6 H), 1.49 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.7, 138.1, 134.4, 117.1, 98.1, 96.4, 81.9, 66.9, 34.8, 33.9, 29.3, 29.2, 28.4, 25.5.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{17}H_{29}NO_3S_2$: 382.1487; found: 382.1489.

***N*-Boc-Protected (*E*)-4-((3-(Isopropylthio)propylthio)methylene)-2,2-dimethyloxazolidine (5c)**
Yield: 181 mg (50%); oily liquid; R_f = 0.70 (PE–EtOAc, 97:3).

IR (thin film): 1701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.16 (s, 1 H), 4.57 (d, *J* = 2.0 Hz, 2 H), 2.86–2.87 (m, 1 H), 2.65 (t, *J* = 6.9 Hz, 2 H), 2.58 (t, *J* = 6.9 Hz, 2 H), 1.83–1.86 (m, 2 H), 1.53 (s, 6 H), 1.46 (s, 9 H), 1.23 (s, 3 H), 1.21 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.7, 138.0, 128.7, 98.1, 96.5, 81.9, 66.9, 34.9, 34.1, 29.8, 29.2, 28.3, 25.7, 23.5.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{17}H_{31}NO_3S_2$: 384.1643; found: 384.1647.

***N*-Boc-Protected (*E*)-2,2-Dimethyl-4-((3-(methylthio)propylthio)methylene)oxazolidine (5d)**
Yield: 170 mg (51%); oily liquid; R_f = 0.70 (PE–EtOAc, 97:3).

IR (thin film): 1706 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.14 (s, 1 H), 4.55 (d, *J* = 2.2 Hz, 2 H), 2.67 (t, *J* = 7.1 Hz, 2 H), 2.57 (t, *J* = 7.1 Hz, 2 H), 2.03 (s, 3 H), 1.85–1.89 (m, 2 H), 1.55 (s, 6 H), 1.51 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.7, 138.1, 128.7, 98.1, 96.4, 81.9, 66.9, 33.8, 32.8, 28.2, 25.5, 15.5.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{15}H_{27}NO_3S_2$: 356.1330; found: 356.1331.

***O*-Benzyl-*N*-Boc-Protected 2-(2-Allyl-1,3-dithian-2-yl)-2-aminoethanol (8)**
n-BuLi (3 equiv) was used for this reaction.

Yield: 155 mg (38%); oily liquid; R_f = 0.70 (PE–EtOAc, 97:3).

IR (thin film): 3065, 1714 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.27 (m, 5 H), 5.91–6.01 (m, 1 H), 4.99–5.08 (m, 2 H), 4.41–4.52 (m, 2 H), 3.81 (m, 2 H), 3.07 (m, 1 H), 2.84 (m, 1 H), 2.57–2.66 (m, 4 H), 1.78–1.92 (m, 2 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 138.1, 133.4, 128.4, 127.7, 127.7, 118.5, 79.6, 73.1, 69.5, 56.4, 53.5, 41.3, 28.5, 26.5, 26.2, 24.7.

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{21}H_{31}NO_3S_2$: 410.1824; found: 410.1811.

***N*-Boc-Protected (*E*)-4-((2-(Benzylthio)ethylthio)methylene)-2,2-dimethyloxazolidine (10)**
Yield: 205 mg (52%); oily liquid; R_f = 0.70 (PE–EtOAc, 97:3).

IR (thin film): 1714 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.30 (m, 5 H), 6.18 (s, 1 H), 4.59 (s, 2 H), 3.71–3.74 (m, 2 H), 2.68–2.71 (m, 2 H), 2.60–2.63 (m, 2 H), 1.56 (s, 6 H), 1.53 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (mixture of rotamers) = 150.7, 139.6, 138.3, 128.9, 128.3, 127.0, 126.8, 98.3, 95.4, 82.1, 67.0, 66.5, 36.4, 36.3, 34.8, 31.4, 31.1, 28.3, 25.6.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{20}H_{29}NO_3S_2$: 418.1487; found: 418.1486.

***N*-Boc-Protected 2-(Bis(benzylthio)methylene)pyrrolidine (13)**
n-BuLi (2.5 equiv) and BnBr (2 equiv) were used for this reaction.

Yield: 252 mg (62%); oily liquid; R_f = 0.70 (PE–EtOAc, 97:3).

IR (thin film): 1701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.33 (m, 10 H), 3.99 (s, 2 H), 3.90 (s, 2 H), 3.39 (t, *J* = 7.0 Hz, 2 H), 2.13 (t, *J* = 7.6 Hz, 2 H), 1.56 (s, 9 H), 1.39–1.45 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.6, 151.5, 138.9, 138.8, 129.2, 128.3, 128.1, 126.6, 110.7, 81.2, 49.7, 39.1, 37.9, 32.3, 29.8, 28.5, 20.6, 14.3.

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{24}H_{29}NO_2S_2$: 428.1718; found: 428.1809.

1-(3-(Benzylthio)propylthio)-3-hydroxypropan-2-one (6)
The disulfide derivative **5a** (0.410 g, 1 mmol) was dissolved in MeOH (3 mL), and TFA (3 mL) was added to this solution at 0 °C. After 30 min, the volatiles were removed under reduced pressure and the crude product was filtered through a silica gel column.

Yield: 245 mg (91%); oily liquid; R_f = 0.40 (PE–EtOAc, 4:1).

IR (thin film): 3428, 1715 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.32 (m, 5 H), 4.44 (s, 2 H), 3.69 (s, 2 H), 3.46 (s, 1 H), 3.21 (s, 2 H), 2.57 (t, *J* = 7.1 Hz, 2 H), 2.47 (t, *J* = 7.1 Hz, 2 H), 1.78 (qu, *J* = 7.1 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.2, 138.3, 128.9, 128.6, 127.1, 66.5, 36.6, 36.3, 31.1, 29.9, 28.2.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{13}H_{18}O_2S_2$: 293.0646; found: 293.0647.

_O_-Benzyl-_N_-Boc-Protected 2-Amino-2-(1,3-dithian-2-yl)ethanol (7)

The amino alcohol derivative **3** (0.280 g, 1 mmol) dissolved in THF (2 mL) was added to a suspension of NaH (0.026 mg, 1 mmol) in THF (5 mL) at 0 °C. After 15 min, a soln of BnBr (0.171 mg, 0.118 mL, 1 mmol) in THF (1 mL) was added dropwise to the above solution with constant stirring, and the stirring was continued at r.t. for 16 h. The reaction was quenched with MeOH (1 mL), the volatiles were removed under reduced pressure and the residue was dissolved in Et_2O (50 mL), which was then washed with sat. NH_4Cl soln (20 mL). The ether solution was dried over anhyd Na_2SO_4 and concentrated under reduced pressure, and the benzyl derivative **7** was isolated by column chromatography.

Yield: 100 mg (27%); oily liquid; R_f = 0.50 (PE–EtOAc, 97:3).

IR (thin film): 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.34 (m, 5 H), 5.04 (d, *J* = 8.9 Hz, 1 H), 4.52 (s, 2 H), 4.17–4.24 (m, 1 H), 3.59–3.86 (m, 2 H), 2.72–3.01 (m, 4 H), 1.88–2.06 (m, 2 H), 1.44 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6, 138.0, 128.4, 127.8, 127.7, 79.7, 73.3, 69.3, 52.8, 47.9, 28.7, 25.8.

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{18}H_{27}NO_3S_2$: 370.1511; found: 370.1531.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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