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REACTION OF DITHIOLACTONES WITH BENZYNE: A NOVEL SYNTHESIS OF BENZO-1,3-DITHIOLES

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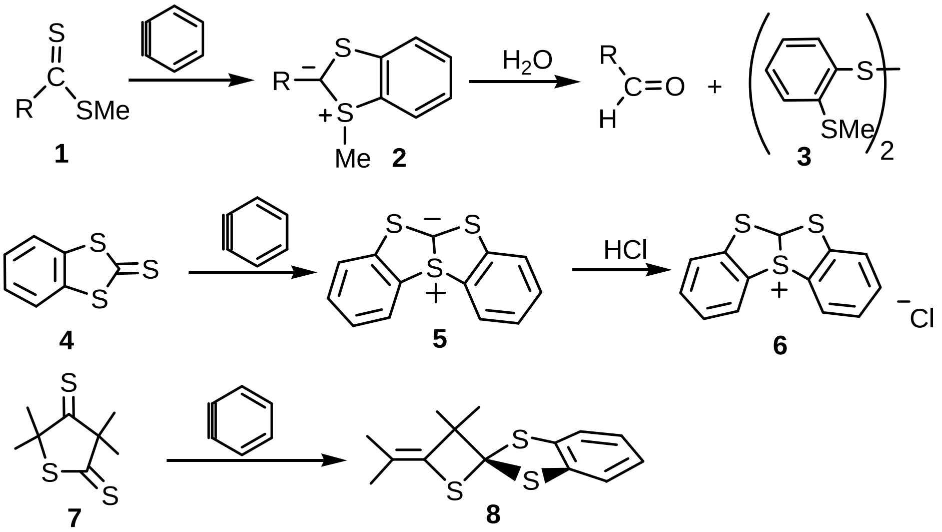
Abstract - The reaction of benzyne with several kinds of dithiolactones, such as β-dithiolactone (**9**), benzothiophene-1-thione (**13**), 1,2-dithiolane-3-thione (**20**), and 3,3,5,5-tetramethyl-4-thioxothiolane-2-thione (**7**), afforded benzo-1,3-dithioles in moderate to good yields, whereas the reaction of benzyne with γ-thionolactone (**16**) gave γ-lactone and diphenyl disulfide.

INTRODUCTION

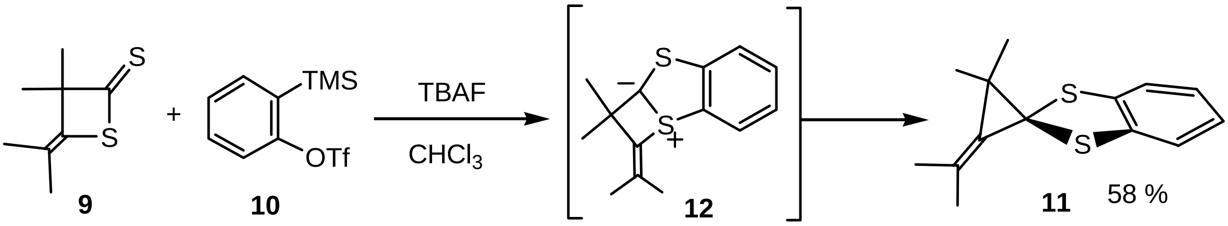
The chemistry of thiones has been studied extensively in recent years because of their unique and interesting properties.[1] Benzyne is a reactive intermediate that reacts with many dienes to afford corresponding cycloadducts.[2] Our ongoing interest in the exploration of reactive benzyne for the synthesis of functionalized S-heterocycles has led to our investigation of the synthesis of benzothietes and benzothianes.[3] The reaction of dithioesters (**1**) with benzyne was reported by Paquer et al. In that reaction, initially formed sulfur ylide (**2**) reacted with water to give thioacetal, which finally yielded aldehydes and *o*-methylthiophenyl disulfide (**3**).[4] A similar type of reaction that involved benzo-1,3-dithiole-2-thione (**4**) and benzyne was reported by Nakayama et al. In this case, sulfonium ylide intermediate (**5**) further reacted with HCl to give sulfonium chloride (**6**).[5] However, to our knowledge, there is no report on the reaction of cyclic dithioesters (dithiolactones) with benzyne. Previously, we have communicated the reaction of 3,3,5,5-tetramethyl-4-thioxothiolane-2-thione (**7**) with benzyne, which resulted in the formation of spirocyclic four-membered cyclic benzo-1,3-dithioles (**8**) (Scheme 1).[6] These results prompted us to investigate the reactivity of dithiolactones with benzyne. We report herein details of the reaction of dithiolactones with benzyne.



Scheme 1

RESULTS AND DISCUSSION

The reaction of 3-hydroxy-2,2,4-trimethylpent-3-enoic acid dithiolactone (**9**)[7] with *o*-trimethylsilylphenyl triflate (**10**)[8] in the presence of tetrabutylammonium fluoride (TBAF) gave colorless crystals (**11**). The ^{1}H NMR spectrum of **11** displayed signals at δ 1.27, 1.80, and 1.95 ppm for three methyl protons (2:1:1 ratio) and 7.01 and 7.19 ppm for A_2B_2-type aromatic protons. The ^{13}C NMR spectrum of **11** showed three methyl, two quaternary, two olefinic, and three aromatic carbons. Thus, the structure was proposed to be spiro[benzo-1,3-dithiol-2,2'-[3',3']dimethyl-[2']-(propan-[2"]-ylidene)cyclopropane] **11**, which was finally confirmed by X-ray crystallographic analysis (Scheme 2). The ORTEP drawing of **11** is shown in Figure 1.



Scheme 2

The reaction of benzyne with β-dithiolactone **9** should produce sulfonium ylide intermediate by analogy with the reactions of dithioesters **1** and benzo-1,3-dithiole-2-thione **4**.[4,5] Thus, the reaction might proceed as follows: 1,3-cycloaddition afforded sulfonium ylide intermediate (**12**), which further rearranged to afford novel cyclic 3-membered spiro-benzo-1,3-dithiole **11**. The difference in reactivity between **4** and **9** might be due to the stability of sulfonium ylides. The fused 4- and 5-membered exomethylene ring of **12** is less stable than the fused 5-membered ring of **5**. Compound **11** is a novel type of dithiamethylenecyclopropane. The synthesis and reaction of spirocyclic methylenecyclopropanes have been reported by many researchers.[9] In particular, Yamago *et al.* synthesized dioxamethylenecyclopropanes by [3+2] cycloaddition via the reversible generation of trimethylenemethane derivative.[10] This is the first example of dithiamethylenecyclopropane.

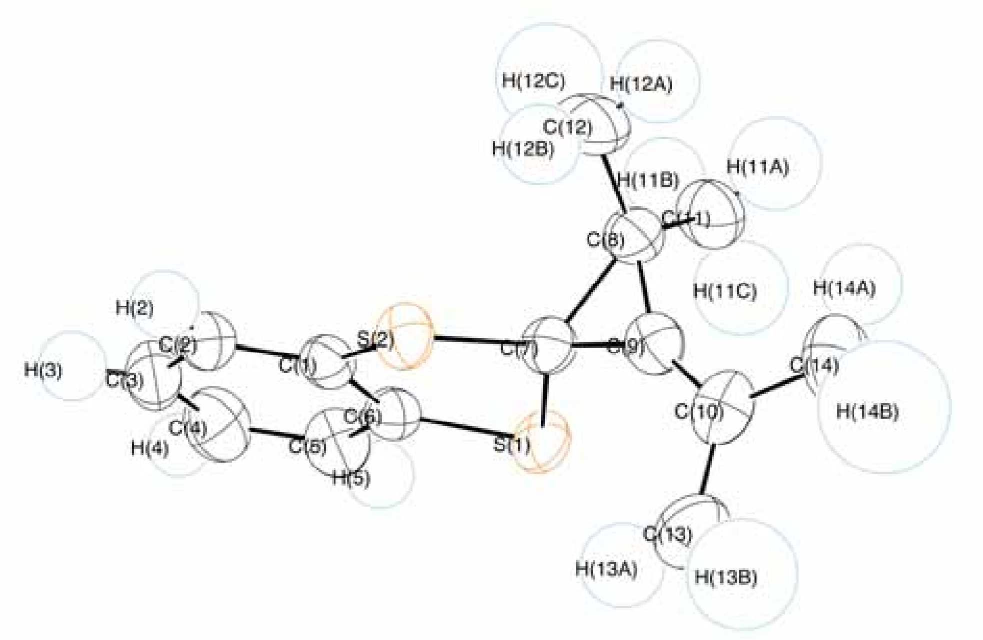
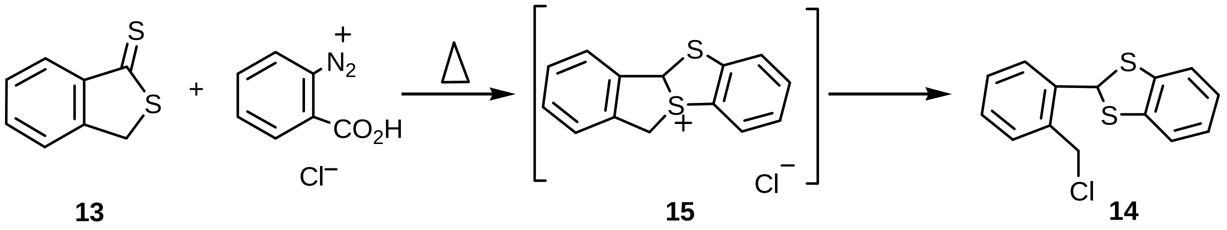


Figure 1. ORTEP Drawing of Benzo-1,3-dithiole **11.** Selected bond lengths: S(1)-C(6) 1.747(8) Å, S(1)-C(7) 1.793(8) Å, S(2)-C(1) 1.751(5) Å, S(2)-C(7) 1.801(10) Å, C(1)-C(6) 1.390(9) Å, C(7)-C(8) 1.5739 Å, C(7)-C(9) 1.4571 Å, C(8)-C(9) 1.4778 Å, C(9)-C(10) 1.3126 Å. Selected bond angles: C(6)-S(1)-C(7) 94.9(5)°, C(1)-S(2)-C(7) 94.7(3)°, C(6)-C(1)-S(2) 115.7(3)°, C(1)-C(6)-S(1) 116.4(4)°, S(1)-C(7)-S(2) 109.1(4)°, C(9)-C(8)-C(7) 56.9°, C(8)-C(7)-C(9) 58.2°, C(7)-C(9)-C(8) 64.9°.

Since compound **9** is the only reported β-dithiolactone, we attempted to use γ-dithiolactone in the reaction. When the reaction of benzothiophene-1-thione (**13**) with carboxybenzenediazonium chloride as benzyne precursor was carried out, the product was another type of 2-[(*o*-chloromethyl)phenyl]benzo-1,3-dithiole (**14**) in 38% yield. Presumably, sulfonium ion intermediate (**15**) further reacted with chloride anion to give **14**（Scheme 3）. Since this compound gave single crystals, X-ray crystallographic analysis was carried out. The ORTEP drawing of **14** is shown in Figure 2.



Scheme 3

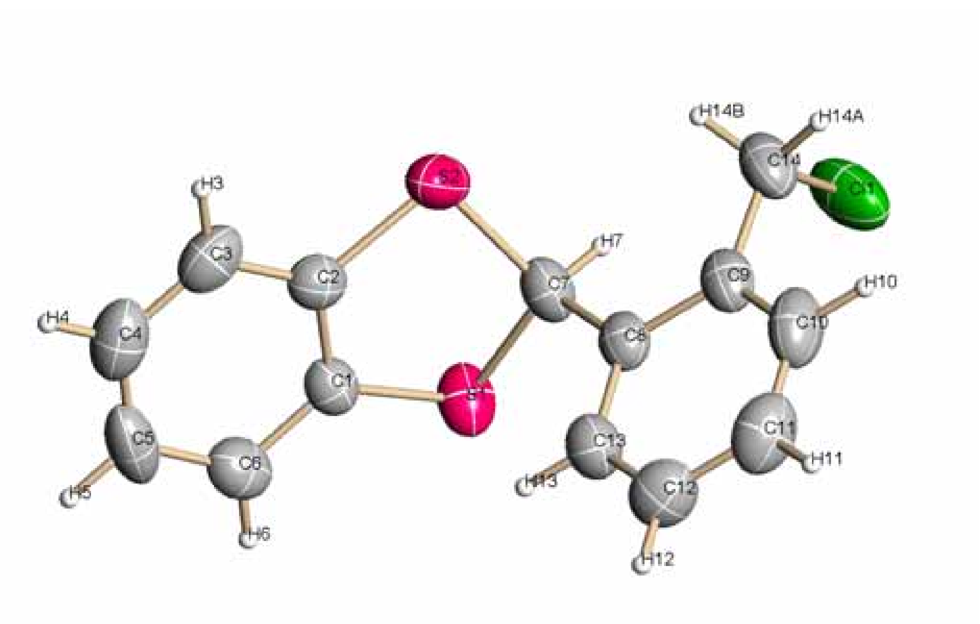
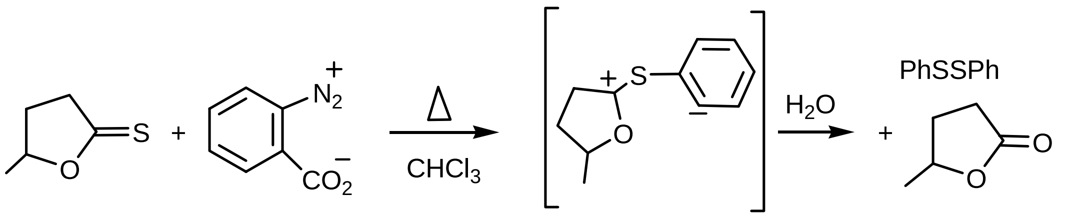


Figure 2. ORTEP Drawing of Compound 14. Selected bond lengths: S(1)-C(1) 1.752(4) Å, S(1)-C(7) 1.823(4) Å, S(2)-C(2) 1.753(4) Å, S(2)-C(7) 1.829(4) Å, C(1)-C(2) 1.396(5) Å.
Selected bond angles: C(1)-S(1)-C(7) 95.67(17)°, C(2)-S(2)-C(7) 96.02(17)°, C(2)-C(1)-S(2) 116.4(3)°, C(1)-C(2)-S(2) 115.6(3)°, S(1)-C(7)-S(2) 106.87(18)°.

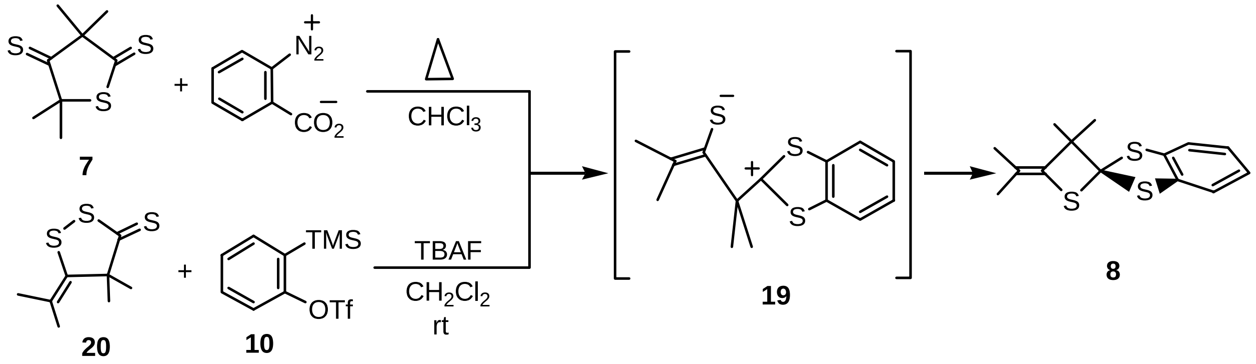
In order to compare the reactivity between dithiolactones (**9**, **13**) and thionolactone toward benzyne, we performed the reaction with γ-thionolactone (4-hydroxypentanoic acid thiolactone **16**). When **16** was reacted with benzenediazonium carboxylate in refluxing chloroform, diphenyl disulfide and γ-lactone (**17**) were obtained. Probably, the less nucleophilic ether oxygen did not attack betaine intermediate (**18**) to give sulfonium ylide, while betaine intermediate **18** was further attacked by water to give thioacetal, which dissociated to afford γ-lactone **17** and benzenethiol (Scheme 4). Thus, the thioether sulfur of dithiolactone plays an important role in the formation of benzo-1,3-dithioles.



16 **18** **17**

Scheme 4

Previously, we have synthesized 3,3,5,5-tetramethyl-4-thioxothiolane-2-thione **7**, a kind of dithiolactone, by sulfurization of 2,2,4,4-tetramethyl-1,3-cyclobutanedione at elevated temperature.[11] Thus, the reaction of dithiolactone **7** with benzyne was carried out. Treatment of **7** with benzenediazonium carboxylate in refluxing chloroform resulted in the formation of spiro[1,3-benzodithiol-2,2'-[3',3'] dimethyl-[2']-(propan-[2'']-ylidene)thietane] **8** in 78% yield. The structure of **8** was confirmed by spectroscopic analysis. The ^{1}H NMR spectrum of **8** displayed signals at δ 1.41, 1.66, and 1.73 for three methyl protons (1:2:1 ratio), and 7.05 and 7.18 for aromatic protons. The ^{13}C NMR spectrum of **8** showed three methyl, two quaternary, two olefinic, and three aromatic carbons. The structure was finally determined by X-ray crystallographic analysis.[6] Thus, compound **7** could react with benzyne to afford betaine intermediate (**19**) and finally **8**. We recently reported the synthesis of 1,2-dithiolane-3-thione (**20**) by basic sulfurization of β-dithiolactone **9**, an isomer of 4-thioxothiolane-2-thione **7**.[6] If the above mechanism is operative, the same betaine intermediate **19** would be formed by the reaction of **20** with benzyne. Actually, treatment of dithiolane-3-thione **20** with **10**, followed by the addition of TBAF, resulted in the formation of the same product **8** in 85% yield (Scheme 5). Using benzenediazonium carboxylate as a benzyne precursor, the same compound **8** was obtained in 81% yield.



Scheme 5

We have succeeded in the synthesis of many types of benzo-1,3-dithioles (**11**, **14**, and **8**) by the reaction of dithiolactones (**9**, **13**, **7**, and **20**) with benzyne. γ-Thionolactone **16**, in contrast, gave diphenyl disulfide and γ-lactone, indicating that the sulfide group of dithiolactones plays an important role in the formation of the 1,3-dithiole ring.

EXPERIMENTAL

All chemicals were obtained from commercial suppliers and were used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and flash column chromatography was performed with silica gel (Merck, 70-230 mesh). NMR spectra (^{1}H at 400 MHz; ^{13}C at 100 MHz) were recorded in CDCl$_3$, and chemical shifts are expressed in ppm relative to internal

TMS for ^{1}H- and ^{13}C-NMR. Melting points were uncorrected.

Materials

β-Dithiolactone **9**,[7] *o*-trimethylsilylphenyl triflate **10**,[8] γ–thionolactone **16**,[12] 1,2-dithiolane-3-thione **20**,[6] and thioxothiolane **7**[11] were synthesized according to the reported methods.

Reaction of β-Dithiolactone with *o*-Trimethylsilylphenyl Triflate in the Presence of Tetrabutylammonium Fluoride.

To a solution of *o*-trimethylsilylphenyl triflate **10** (358 mg, 1.2 mmol) and β-dithiolactone **9** (172 mg, 1.0 mmol) in $CHCl_3$ (4 mL) was added dropwise a solution of TBAF (1.0 M solution in THF, 2 mL, 2 mmol) at rt. After stirring for 1 h, the reaction mixture was evaporated and extracted with hexane (3 X 10 mL). The hexane solution was evaporated to give a pale brown oil, which was chromatographed over silica gel by elution with hexane to give yellow crystals of 1,3-dithiole **11** (162 mg , 0.58 mmol). Compound **11**: yellow crystals: mp 90-91 °C. ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 6H, CH_3), 1.80 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 6.68-7.04 (m, 2H, Ar), 7.10-7.23 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.1 (CH_3), 21.9 (CH_3), 22.1 (CH_3), 30.0 (q-C), 46.4 (S-C-S), 122.2, 125.3, 138.5 (Ar). Anal. Calcd for $C_{14}H_{16}S_2$: C, 67.69%; H, 6.49%. Found: C, 67.33%; H, 6.47%.

X-Ray crystallographic data of **11**: Formula $C_{14}H_{16}S_2$, FW 248.410, Monoclinic, space group = C2/c, a = 25.68 (10), b = 6.07 (5), c = 21.40 (6) Å, α = 90.00°, β = 126.0 (4)°, γ = 90.00 °, V = 270.(3) x 10^1 Å^3, Z = 8, D_x = 1.222 Mg m^{-3}, μ (Mo *K*α)= 0.366 mm^{-1}, T = 298 K. Final R and wR were 0.0673 and 0.2239, respectively, using 2670 reflections.

Reaction of Benzothiophene-1-thione 13 with Carboxybenzenediazonium Chloride

To a solution of benzothiophene-1-thione **13** (106 mg, 1.0 mmol) in $CHCl_3$ (10 mL) was added portionwise carboxybenzenediazonium chloride (553 mg, 3.0 mmol). After refluxing for 2 h, the reaction mixture was evaporated to give a dark brown oil, which was chromatographed over silica gel by elution with hexane-CH_2Cl_2 (5:1) to afford **14** (105 mg, 0.38 mmol). Pale pink prisms: mp 95-96 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 4.68 (s, 2H, CH_2), 6.62 (s, 1H, CH), 7.06-7.35 (m, 7H, Ar) 7.97 (d, 1H, *J* =7.6 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 43.9 (CH_2), 52.0 (CH), 122.3, 126.2, 128.9, 129.2, 130.1, 130.6, 134.0, 137.7, 140.0 (Ar). Anal. Calcd for $C_{14}H_{11}ClS_2$: C, 60.31; H, 3.98%. Found: C, 60.04; H, 4.21%.

X-Ray crystallographic data of **14**: Formula $C_{14}H_{11}ClS_2$, FW 278.80, Monoclinic, space group = P2$_1$/n, a = 12.2818 (16) Å, b = 7.7135 (10) Å, c = 14.6595 (19) Å, α= 90°, β = 117.740 (2)°, γ = 90°, V = 1290.0(3) Å^3, Z = 4, D_x = 1.436 Mg m^{-3}, μ (Mo *K*α)= 0.366 mm^{-1}, T = 296 K. Final R and wR were 0.0510 and 0.1190, respectively, using 3113 reflections.

Reaction of γ-Thionolactone 16 with Benzenediazonium Carboxylate

To a solution of γ-thionolactone **16** (116 mg, 1.0 mmol) in $CHCl_3$ (10 mL) was added portionwise benzenediazonium carboxylate (395 mg, 2.4 mmol). After refluxing for 1 h, the reaction mixture was evaporated to give a dark brown oil, which was chromatographed over silica gel by elution with hexane-CH_2Cl_2 (5:1) to afford diphenyl disulfide (33 mg, 0.15 mmol) and γ-lactone **17** (31 mg, 0.31 mmol). The spectral data of diphenyl disulfide and compound **17** were identical with those of commercial samples.

Reaction of 3,3,5,5-Tetramethyl-4-thioxothiolane-2-thione 7 with Benzenediazonium Carboxylate

A mixture of thioxothiolane **7** (204 mg, 1.0 mmol) and benzenediazonium carboxylate (422 mg, 2.3 mmol) in $CHCl_3$ (10 mL) was refluxed for 1 h. The resulting mixture was evaporated to give brown crystals, which were chromatographed over silica gel by elution with hexane-CH_2Cl_2 (5:1) to afford benzo-1,3-dithiole **8** (218 mg, 0.78 mmol). Compound **8**: colorless prisms: mp 98-99 °C. ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H, CH_3), 1.67 (s, 6H, CH_3), 1.73 (s, 3H, CH_3), 7.00-7.22 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ 20.3 (CH_3), 22.0 (CH_3), 27.5 (CH_3), 61.9 (q), 84.3 (S-C-S), 119.7 (=C), 122.0, 125.9, 129.8 (=C), 136.5 (Ar). Anal. Calcd for $C_{14}H_{16}S_3$: C, 59.95; H, 5.75%. Found: C, 59.66; H, 5.60%.

Reaction of 1,2-Dithiolane-3-thione 20 with *o*-Trimethylsilylphenyl Triflate

To a solution of *o*-trimethylsilylphenyl triflate **10** (358 mg, 1.2 mmol) and dithiolane-3-thione **20** (204 mg, 1.0 mmol) in $CHCl_3$ (4 mL) was added dropwise a solution of TBAF (1.0 M solution in THF, 2 mL, 2 mmol) at rt. After stirring for 1 h, the reaction mixture was evaporated and extracted with hexane (3 X 10 mL). The hexane solution was evaporated to give a pale brown oil, which was chromatographed over silica gel by elution with hexane- CH_2Cl_2 (5:1) to afford benzo-1,3-dithiole **8** (237 mg, 0.85 mmol). mp 98-99 °C.

CCDC-676906 and -676905 for compound **11** and **14** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html.

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