

Synthesis of Thieno[2,3-d]-1,3-dithiol-2-thiones from Thieno[2,3-d]-1,2,3-thiadiazoles: *Matryoshka*-type autoclave for high-temperature, high-pressure thermolysis microscale reactions[†]

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Abstract: Thieno[2,3-d]-1,2,3-thiadiazoles (**1**) react with carbon disulfide in a "Matryoshka-type" double compartment autoclave [1] to yield thieno[2,3-d]-1,3-dithiol-2-thiones (**2**). With BH₃/Me₂S the cyclic trithiocarbonate (**2d**) is cleaved and the product characterized after methylation as **4b**. Compounds **7a** and **7b** are prepared via the thieno[2,3-d]-1,3-dithiolium salts (**6**) followed by NaBH₄-reduction.

Keywords: 1,3-dipolar cycloaddition, high pressure reaction.

Introduction

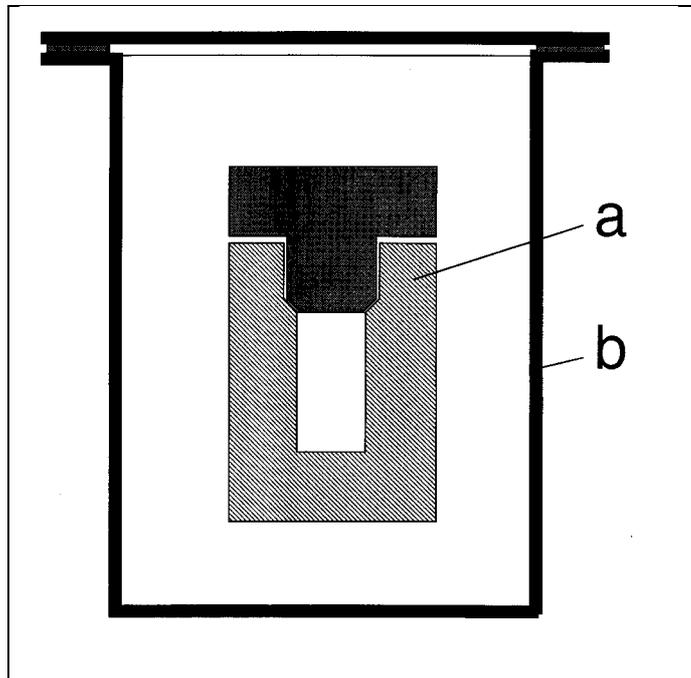
Condensed 1,3-dithiole-2-thiones are valuable intermediates in the preparation of tetrathiafulvalene (TTF) - type organic metals [2]. Some of these compounds also exhibit antifungal activities [3]. Known methods of preparing thieno[2,3-d]-1,3-dithiole-2-thiones include either the annelation of the thiophene ring onto suitably substituted 1,3-dithiole-2-thiones [4,5] or the cyclization of thiophene thiole derivatives [6,7,8]. Thieno[2,3-d]-1,3-dithiole-2-thione has been synthesized by treatment of

O-ethyl-S-(2-oxotetrahydrofuran-3-yl)dithiocarbonate with phosphorous sulfide or sulfur dehydrogenation of 4,5-dihydrothieno[2,3-d]-1,3-dithiole-2-thione [9a]. The formation of **2c** via a thio-Claisen rearrangement has been described [9b]. The isomeric thieno[3,4-d]-1,3-dithiole-2-thione is formed as a side product by thermolysis of 4,6-dihydrothieno[3,4-d]-1,2,3-thiadiazole in the presence of an excess of carbon disulfide (6h, 170°C) [10].

Results and Discussion

In continuation of our previous work on the synthesis of 1,3-benzodithiole-2-thiones [11] we have investigated the reaction of thieno[2,3-d]-1,2,3-thiadiazoles [12] with carbon disulfide. The carbon disulfide thermolysis reactions were performed using a micro-scale, Teflon-autoclave within a 2L steel autoclave (Figures 1a and 1b). By filling both the inner and outer autoclaves with the carbon disulfide solvent, one could reasonably expect that upon heating only a relatively small pressure difference would exist between the inside and outside of the Teflon autoclave, while the pressure within the steel autoclave was between 23 and 35 bar. Indeed, by using this procedure, reactions on a 140-840 mg scale could be performed routinely in this Matryoshka-autoclave, with the added advantage that contamination of the product by impurities (due to reaction of the autoclave with carbon disulfide) is avoided.

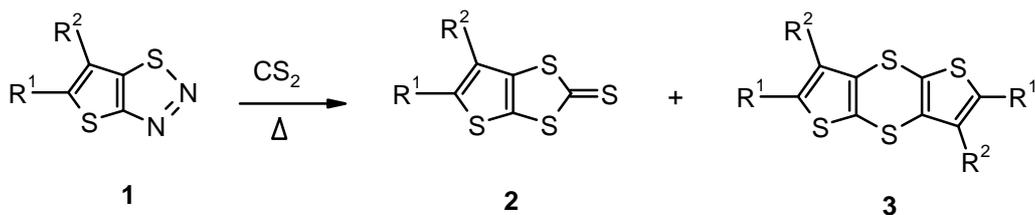
Figure 1a: *Matryoshka* Dolls and *Matryoshka*-Type Autoclave



a: inner TEFLON autoclave
b: outer steel autoclave

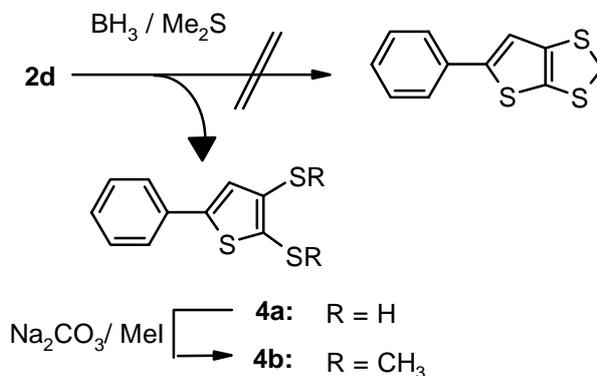
Figure 1b: Autoclaves used in the experiments

The reaction temperature plays a critical role. The optimal temperature for the conversion of benzo-1,2,3-thiadiazole to 1,3-benzodithiole-2-thione was found to be $235 \pm 5^\circ\text{C}$ [13] with a 67% yield of **2a** formed, whereas below 220°C , **1a** was mostly unreacted. Under similar reaction conditions the cyanide derivative **1f** gave, in addition to the thieno[2,3-d]-1,3-dithiole-2-thione (**2f**), the 1,4,5,8-tetrathia-s-indacene (**3f**). The formation of the products **3d** and **3f** can be explained *via* head-to-tail dimerization of the 1,3-dipolar intermediate [14] (Scheme 1).

Scheme 1

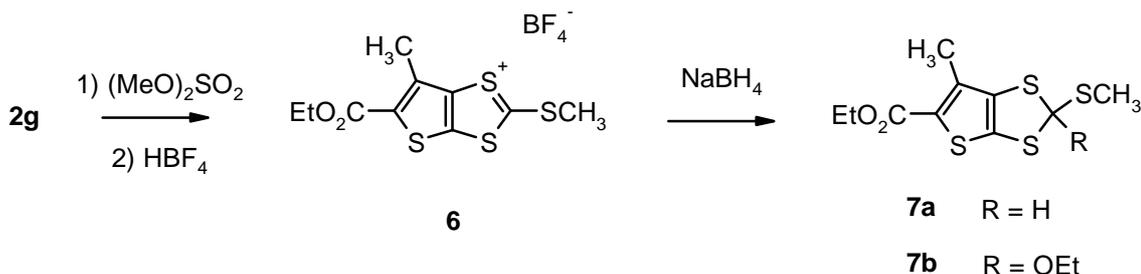
5-Phenylthieno[2,3-d]-1,3-dithiole was not detected upon reduction of **2d** using the boron hydride/dimethyl sulfide complex. Instead, the ring-cleaved dithiole **4a** was formed and characterized as the dimethylated compound **4b** (Scheme 2).

Scheme 2



This behavior is in contrast to the analogous conversion of 1,3-benzodithiole-2-thione to benzo-1,3-dithiole, which was produced routinely with yields of 88-92% in our laboratory [15]. On the other hand, 5-ethoxycarbonyl-6-methylthieno[2,3-d]dithiole-2-thione (**2g**) behaved analogously to benzo-1,3-dithiole-2-thione upon treatment with dimethyl sulfate followed by tetrafluoroboric acid. The crystalline salt **6** was then reduced to **7a** using sodium borohydride in $\text{CH}_3\text{CN}/\text{THF}$. When ethanol was used for the reduction as described for similar reactions [16] a mixture of **7a** and **7b** was formed (Scheme 3):

Scheme 3



2-Methylthio-thieno[2,3-d]-1,3-dithiolium salts (e.g. **6**) could serve as starting materials for a host of synthetically useful reactions [17].

Conclusions

We have presented a facile route for the formation of thieno[2,3-d]-1,3-dithiol-2-thiones and developed a nested-type autoclave that allows to the use of Teflon autoclaves even under high pressure.

Experimental

General

Melting points were measured on a Kofler melting point apparatus. ^1H - and ^{13}C -NMR-spectra were recorded on a Bruker AC-200 (200 MHz) pulse Fourier-transform NMR spectrometer using tetramethylsilane as an internal standard and, unless otherwise noted, CDCl_3 as solvent. Thin layer chromatography (TLC) was performed on Merck TLC aluminum sheets silica 60 F_{254} . Visualization was by UV light or spray reagents (molybdophosphoric acid or ninhydrin and heating). Column chromatography was performed using silica gel (Baker). MPLC (medium pressure liquid chromatography) was performed using a LC-8A pump (Shimadzu), a SPD-6AV UV-detector (Shimadzu) and Büchi preparative glass columns. All reactions were magnetically stirred under an argon atmosphere.

4-Cyano-3-methyl-but-3-enoic acid ethyl ester [18,19]. A mixture of ethyl acetoacetate (130.0 g, 1.0 mol), toluene (150 mL), cyanoacetic acid (90.0 g, 1.06 mol), ammonium acetate (16.0 g, 0.2 mol) and acetic acid (30 mL) was refluxed until azeotropic water removal ceased (8 h). Volatiles were removed *in vacuo* and the residue was partitioned between water and methylene chloride (400 mL). The organic phase was dried (Na_2SO_4), evaporated, and the crude product fractionated using a 30 cm Vigreux column to yield 106.5g (69.6%) of the product with b.p.₁₀ 110-118°C (Ref. 14a: b.p.₁₁ 114°C). According to ^1H -NMR, the eluted product fraction also contained isomeric 4-cyano-3-methyl-but-2-enoic acid ethyl ester. This product fraction was used for the preparation of **1a** [20] *via* ethyl 2-amino-4-methyl-thiophene-5-carboxylate hydrochloride [21].

General procedure for the conversion of thieno[2,3-d]-1,2,3-thiadiazoles (1) to thieno[2,3-d]-1,3-dithiol-2-thiones (2) using the Matryoshka-autoclave. A 50-mL Teflon autoclave was charged with **1** (140-840 mg) and carbon sulfide (30 mL). This Teflon autoclave was inserted into a 2L steel autoclave and 100-200 mL carbon sulfide was added. The closed steel autoclave was heated for the time and temperature indicated in Table 1, developing a pressure of 35-40 bar. The reaction temperature was measured inside the steel autoclave using a thermocouple attached to a digital voltmeter as well as a strip chart recorder *via* an analog/digital interface. Following the prescribed reaction time, the cooled autoclaves were opened, the contents of the Teflon autoclave were evaporated to dryness with recovery of the carbon sulfide. The residue was purified by flash column chromatography using methylene chloride/petroleum ether (b.p. 40-60°C) 1:1 as eluant.

Table 1: Thermolysis of Thieno[2,3-d]-1,2,3-thiadiazoles

Run	Starting Mat.	R ¹	R ²	Scale (mg)	Temp. (°C)	Time (h)	Product (yield, %)	m.p. (°C)
1	1a	H	H	750	210-220	7	2a (37)	127-130 (toluene)
2	1a	H	H	240	230-240	8	2a (67)	127-130
3	1b	Cl	H	140	260-270	9	2b (10) ^a	210-215 (LC)
4	1c	CH ₃	H	140	235-245	9	2c (77) ^b	–
5	1d	C ₆ H ₅	H	150	240-267	9	3d (35)	223-224
6	1d	C ₆ H ₅	H	150	210-220	7	2d (80)	175-177
7	1d	C ₆ H ₅	H	840	210-230	6	2d (80)	175-177
8	1e	4-F-C ₆ H ₄	H	140	230-240	9	2e (10)	156-158
9	1f	C ₆ H ₅	CN	610	210-220	9	2f (18); 3f (36)	191-192 302-305
10	1g	COOC ₂ H ₅	CH ₃	8550	207-218	7	2g (29) ^c	169-170
11	1g	COOC ₂ H ₅	CH ₃	3500	225-232	6	2g (54)	169-170

Notes: ^aYield based on 64 mg starting material recovered; ^b Yield of crude product; ^cYield based on 3.4 g starting material recovered.

Table 2: Physical Properties of Compounds **2** and **3**

Product	Anal.	MS (<i>m/z</i>)	Remarks, NMR
2a	Calcd for C ₅ H ₂ S ₄ : C, 31.55; H, 1.06; Found: C, 31.70; H, 1.32.	190 (M ⁺)	¹ H-NMR: δ 6.85 (d, 1H, 4-H), 7.45 (d, 1H, H-6). ¹³ C-NMR δ 119.9 (C-6), 130.8 (C-5), 132.5 (C-6a), 138.0 (C-3a), 215.2 (C=S).
2b	Calcd for C ₅ HClS ₄ : C, 26.72; H, 0.05. Found: C, 26.74; H, 0.30.	224 (M ⁺ , 100), 180, 150, 148, 113, 104, 69.	¹³ C-NMR (CDCl ₃ /d ₆ -DMSO) δ 119.5 (C-6), 130.0, 136.1, 134.8 (C-3a, C-5, C-6a), 215.2 (C=S).
2c		204 (M ⁺ , 100), 169, 160, 140, 128, 113, 99, 85, 84, 71, 59, 57.	The crude product contained unreacted 1c and sulfur. A sample for MS was purified by flash-LC on silica using 7:3 petroleum ether/CH ₂ Cl ₂ . ¹ H-NMR δ 2.58 (s, 3H, CH ₃), 6.6 (s, 1H, C-H).

2d	Calcd for C ₁₁ H ₆ S ₄ : C, 49.59; H, 2.27. Found: C, 49.35; H, 2.18.	266 (M ⁺ , 100), 222, 190, 165, 146, 133, 121, 106, 102.	
2e	Calcd for C ₁₁ H ₅ FS ₄ : C, 46.45; H, 1.77. Found: C, 46.48; H, 1.87.	284 (M ⁺ , 100), 240, 208, 164, 139, 120.	¹ H-NMR δ 7.10 (s, 1H, H-6), 7.10-7.20 (m, 2H, arom.), 7.40-7.60 (m, 2H, arom.). ¹³ C-NMR δ 115.5 (C-6), 116.2 (C-o ArF), 127.5 (C-m ArF), 128.0 and 132.0 (C-3a and C-6a), 138.5 (C-p ArF), 145.5 (C-5), 164.0 (C-ipso ArF), 214.5 (C=S).
2f	Calcd for C ₁₂ H ₅ NS ₄ : C, 49.46; H, 1.73; N, 4.81. Found: C, 49.22; H, 1.90; N, 4.47.	291 (M ⁺ , 100), 247, 227, 215, 171, 121.	
2g	Calcd for C ₉ H ₈ O ₂ S ₄ : C, 39.11; H, 2.92; S, 46.40. Found: C, 38.98; H, 2.67; S, 47.33.	276 (M ⁺ , 100)	¹ H-NMR δ 1.45 (t, 3H, CH ₃ CH ₂), 2.57 (s, 3H, CH ₃), 4.38 (q, 2H, OCH ₂).
3d	Calcd for C ₂₀ H ₁₂ S ₄ : C, 63.12; H, 3.18. Found: C, 63.05; H, 3.31.	380 (M ⁺ , 100), 348, 303, 259, 190.	¹ H-NMR δ 7.05 (s, 2H, 3H and 6-H), 7.25-7.50 (m, 10H, arom.). ¹³ C-NMR δ 128.3, 128.5, 131.4, 131.5, 131.9, 132.0, 132.2, 133.6.
3f	Calcd for C ₂₂ H ₁₀ N ₂ S ₄ : C, 61.37; H, 2.34; N, 6.51. Found: C, 60.81; H, 2.09; N, 6.11.	430 (M ⁺ , 100), 398, 215, 121.	

2,3-Bis-methylthio-5-phenyl-thiophene (4b). Borane-dimethylsulfide (200 mg, 26 mol) was added to a solution of **2d** (160 mg, 6.0 mmol) in dry toluene (20 mL), and the reaction kept at 80-90°C until TLC showed complete consumption of the starting material (30 min). The cooled reaction mixture was hydrolyzed with dry MeOH and evaporated to dryness. The addition of MeOH and evaporation was repeated 3 times until the flame test for boron was negative. The crude product did not show any ¹H-NMR signals in the region of 4.5 ppm, indicative of the S-CH₂-S moiety of the expected dithioacetal **5**. Alkylation using an excess of MeI and 20% N₂CO₃ gave, after extraction and Kugelrohr-distillation (0.2 mbar/110°C), 126 mg (72%) of **4b** as a oil that solidified on standing, m.p. 36-68°C. ¹H-NMR δ 2.43 (s, 1H, SCH₃), 2.49 (s, 1H, SCH₃), 7.10 (s, 1H, H-4), 7.25-7.60 (m, 5H, arom.); MS *m/z* 252 (M⁺, 92), 237, 203, 173, 160, 145, 121, 102, 91, 77.

Ethyl 2-Methylthio-6-methylthieno[2,3-d]-1,3-dithiole-5-carboxylate (7a) and ethyl 2-ethoxy-2-methylthio-6-methylthieno[2,3-d]-1,3-dithiole-5-carboxylate (7b). Compound **1g** [21](0.32 g, 1.16 mol) was stirred with freshly distilled dimethyl sulfate (4 mL) at 90-100°C under N₂ until it was dissolved (30 min.). To the cooled solution tetrafluoroboric acid (54%, 0.4 mL) was added, followed by ether (20 mL) to give 0.41g (93%) of crude **6**. The yellow salt was dissolved in a 1:1 mixture of

THF and MeCN (20 mL). NaBH₄ (0.2 g, 5.3 mol) was added, resulting in a colorless solution that was stirred for 1 h. The solvents were evaporated and the residue was partitioned between CH₂Cl₂/H₂O. The organic layer was dried (Na₂SO₄) and evaporated to yield **7a** (0.25 g, 74%) as colorless crystals, m.p. 71-74°C (from petroleum ether/EtOAc). ¹H-NMR: δ 1.35 (3H, t, O-CH₂CH₃), 2.26 (s, 3H, C-CH₃), 2.47 (s, 3H, S-CH₃), 4.30 (q, 2H, O-CH₂), 6.50 (s, 1H, H-2). Anal. for C₁₀H₁₂O₂S₂: Calcd: C, 41.07; H, 4.14; S, 343.85. Found: C, 41.27; H, 3.86; S, 43.64. Using EtOH instead of THF/MeCN as the solvent [10] gave, after work-up and column chromatography on silica using 99:1 petroleum ether (b.p. 40-60°C)/t-BuOMe, a mixture of **7a** and **7b**. **7b** eluted first and was characterized by its ¹H-NMR: δ 1.32 (3H, t, O-CH₂CH₃), 1.41 (3H, t, O-CH₂CH₃), 2.43 (s, 3H, C-CH₃), 2.47 (s, 3H, S-CH₃), 3.75 (q, 2H, O-CH₂), 4.30 (q, 2H, O-CH₂). The second fraction was identical with **7a** prepared using THF/MeCN by ¹H-NMR and HPLC.

References and Notes

1. Matryoshkas (=Matriushka, Matrushka) nesting dolls were introduced at the end of the 19th century by the Russian artist Sergei Maliutin who painted a wooden doll as a peasant girl with a rooster. Inside of this hollow doll there were seven more dolls all painted differently (Figure 1a).
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Sample Availability: Compounds **2c-d**, **3d** and **4b** are available from MDPI.

Appendix: Information on Matryoshkas

Many links to information about Matryoshkas can be found in the Web by using the 3 most common transliterations in search engines.

Figure 2: Examples of matryoshkas*:



* I thank my friends Victoria & Peter H. for allowing me to take photographs of their impressive collection of matryoshkas.

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