Synthesis of dihydrobenzodithiepines by the reactions of 1,2-dichloro- and 1-chloro-2-nitrobenzenes with 1,3-dithiols

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Dedicated to Professor B. A. Trofimov on his 65th birthday
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Abstract
The reactions of nucleophilic substitution of the chlorine atoms and the nitro group in 1,2-dichloro- and 1-chloro-2-nitrobenzenes 2 by the thiolate anions generated from 2,2-disubstituted 1,3-propanedithiols 1 under the action of bases afford dihydrobenzodithiepines 3.

Keywords: 1,3-Propanedithiol, 1,2-dichlorobenzene, 1-chloro-2-nitrobenzene, aromatic nucleophilic substitution, dihydrobenzodithiepines

Introduction
There are several examples of nucleophilic substitution of halogen in aryl halogenides by thiolate groups.1 The reactivity of non-activated phenyl halogenides decreases in the order PhI>PhF>PhBr>PhCl.2 A different order has been observed for 1-halogen-2,4-dinitrobenzenes.3 Compared to substitutions with mono-thiolates, reactions between aliphatic or aromatic dithiolates and mono- or dihalogenoarenes have been poorly substituted. Examples of known reactions are the formation of benzodithianes from 1,2-di-iodobenzene and 1,2-ethanethiol,4 and of 1,1’-dinaphthyl-2,2’-ethanedithiol and 4,5-dichloro-1,2-dicyanobenzene,5 while condensation of 1,2-dimercaptobenzene with 1,2,3,4-tetra- and hexa-fluorobenzenes afforded benzodithianes with two or three dithiane rings.6

In the present work, which is aimed at synthesizing macrocyclic sulfides and thia-crown ethers, we report the first results of our study of nucleophilic substitution of the halogen atoms and the nitro group in the aromatic cycle by thiolate anions.

Results and Discussion
We first optimized the conditions for synthesis of the benzodithiepine 3c using the reaction of 1b with 2a. The results presented in Table 1 were obtained under the optimal conditions. The thiylation of the dichlorobenzene 2a with the dithiols 1a–c occurred under the action of sodium hydride in dimethylacetamide (DMA) solution at reactant concentrations of ~0.1 M. The complete conversion of dithiols 1a–c (GLC monitoring) at 105°C took 6–9 h (Table 1). The trifluoromethyl group in the benzene ring activates the chlorine atoms, and the reaction of dichlorobenzene, 2b, with dithiols 1b,c occurred much more rapidly, and its selectivity was higher. The yield of dithiepines 1a–f varies from 48 to 99%, depending on the substituents in reactants 1 and 2. The bulkier substituents in the dithiols 1a–c provide a higher yield of the target products. For example, the reaction of 1c with dichlorobenzene 2b affords the benzodithiepine 3f in ~100% yield.

Table 1. Reaction of 1,2-dichloro– and 1,2-dichloro–4–trifluoromethylbenzenes 2a,b with 1,3-propanedithiols 1a–c

<table>
<thead>
<tr>
<th>1a–c</th>
<th>2a,b</th>
<th>Reaction time, h</th>
<th>3a–f</th>
<th>Isolated yield, %</th>
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<td>9</td>
<td>3a</td>
<td>48</td>
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<tr>
<td>1a</td>
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<td>2a</td>
<td>8</td>
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<td>2b</td>
<td>2</td>
<td>3f</td>
<td>99</td>
</tr>
</tbody>
</table>

Like the substituted dithiols 1a–c, unsubstituted 1,3-propanedithiol reacted readily with 2a. However, in this case, only resin-like substances, probably polycondensation products, were formed. In order to extend the range of starting reactants in the synthesis of 3a and 3c, we used...
2a along with 1-chloro-2-nitrobenzene, 2c. However, this variant was inappropriate under the conditions presented in Table 1 because of the low yield of the target products and side reactions. The selectivity of the reaction was enhanced using the one-pot synthesis in two steps. In the first step, the thiolate anion substituted only the chlorine atom in 2c under the action of the weak base NaHCO₃. This resulted in the formation of intermediate thiol 4 (Scheme 1), which was isolated and identified (4b, R=Et) in one of the experiments. In the second step, KOH was introduced into the reaction mixture without isolating the thiol 4, and the process formed the dithiepines 3a,c by intramolecular substitution of the nitro group by the thiolate anion.

![Scheme 1](image)

Reaction conditions: i NaHCO₃, 1a 50°C, 7h; NaHCO₃, 1b 60°C 7h.  
ii KOH, 1a 50°C, 1h; 1b 60°C, 1.5.

**Scheme 1**

The reaction of the di thiols 1a,b with 1,2-dichloro-4-nitrobenzene 2d (Scheme 2) was performed similarly. In the two-step variant, we succeeded in decreasing the probability of substitution of the nitro group in 2d by the thiolate anion. The benzodithiepines 3g,h containing the nitro group in the aromatic ring were prepared in satisfactory yields.

![Scheme 2](image)

Reaction conditions: i NaHCO₃, 1a 60°C, 7h; NaHCO₃, 1b 50°C 7h.  
ii KOH, 1a 60°C, 1h; 1b 50°C, 1.5.

**Scheme 2**
The structures of compounds 3a–h were proved by \(^1\)H- and \(^{13}\)C- NMR spectra, elemental analysis, and mass spectra.

**Summary**

The simple and convenient one-pot synthesis of new benzodithiepines 3a–h was developed on the basis of aromatic nucleophilic reactions of 2-substituted 1,3-propanedithiols 1 with easily accessible 1,2-dichloro- and 1-chloro-2-nitrobenzenes. The reaction occurred under the action of bases at a ratio of reactants close to stoichiometric. The yields of dihydrobenzodithiepines 3 ranged from 48\% to ~100\%, depending on the character of substituents in the starting reactants. In the synthesis of 3 we also used 1,2-dichloro-4-trifluoromethyl and 1,2-dichloro-4-nitrobenzene.

**Experimental Section**

**General Procedures.** GLC analysis was carried out on a Chrom 5 chromatograph with a flame-ionization detector and a column 3m×3mm using Chromaton N-super (0.160–0.200 mm) as the sorbent with the SE-Superphase (5\%) liquid phase. NMR spectra of solutions in CDCl\(_3\) were recorded on Bruker AC-200, Bruker WM-250, and Bruker AM300 spectrometers. Coupling constants (J) were reported in Hz. NMR chemical shifts, δ were expressed in ppm, and were related to the internal solvent peak. Mass spectra were obtained on a Kratos-MS30 instrument.

Silica gel 60 (0.063–0.200 mm) Merck was used in column chromatography. TLC analysis was carried out on Sorbfil plates. Melting points were determined on a Kofler hot-stage apparatus.

**Starting reactants**
1,2-Dichlorobenzene, 1-chloro-2-nitrobenzene, 1,2-dichloro-4-nitrobenzene, and 1,2-dichloro-4-trifluoromethylbenzene were commercial compounds, used without further purification. 2,2-Dimethyl-1,3-propanedithiol, 2,2-diethyl-1,3-propanedithiol, and 2,2-pentamethylene-1,3-propanedithiol were prepared according to known procedures.\(^7\)

**Reaction of propanedithiols 1a–c with dichlorobenzenes, 2a,b, Preparation of compounds 3a–3f**

**General procedure 1 (Table 1)**

95\% NaH (96 mg, 3.8 mmol) was added with stirring to the dithiol 1 (1.5 mmol) in DMA (20 ml), under argon. The reaction mixture was heated to 105°C, a solution of 1,2-dichlorobenzene 2 (1.8 mmol) in DMA (5 ml) was added, and the mixture kept at this temperature to the end of the reaction, (monitored by GLC of the content of dithiol 1). The reaction mixture was cooled, poured into water (250 ml), acidified (conc. HCl, 0.5 ml, 5.5 mmol), and extracted with
petroleum (4×10 ml). The extract was washed with water (2×15 ml), dried with MgSO₄, the solvent evaporated, and the product isolated by column chromatography (SiO₂ / petroleum).

3,3-Dimethyl-3,4-dihydro-2H-1,5-benzodithiepine (3a). The dithiol 1a (204 mg) and dichlorobenzene 2a (265 mg) gave 3a (152 mg, 48%) as a colorless oil. ¹H NMR (250 MHz) 1.17 (s, 6H), 2.80 (s, 4H), 7.08 (m, 2H), 7.44 (m, 2H).

3,3-Dimethyl-7-trifluoromethyl-3,4-dihydro-2H-1,5-benzodithiepine (3b). The dithiol 1a (204 mg) and 1,2-dichloro-4-trifluoromethylbenzene 2b (387 mg) gave 3b (209 mg, 50%) as colorless crystals, m.p. 67.5–68.3°C. ¹H NMR (250 MHz) δ 1.21 (s, 6H), 2.97 (s, 4H), 7.28 (d, J 2.63 Hz, 1H) 7.46 (d, J 7.88 Hz, 1H), 7.62 (s, 1H); ¹³C NMR (75.47 MHz) δ 26.7, 35.4, 44.2, 123.3, 128.9, 132.2, 129.0, 124.00 (q, J 180); m/z 278 [M]+; Anal. Calcd. for C₁₂H₁₃F₃S₂ (278.36): C 51.73, H 4.67, found: C 51.74, H 4.59%.

3,3-Diethyl-3,4-dihydro-2H-1,5-benzodithiepine (3c). The dithiol 1b (247 mg) and dichlorobenzene 2a (265 mg) gave 3c (246 mg, 69%) as colorless crystals; m.p. 43.5–44.5°C. ¹H NMR (250 MHz) 0.83 (t, J 7.72, 6H), 1.58 (q, J 7.72, 4H), 2.87 (s, 4H), 7.02–7.13 (m, 2H) 7.35–7.43 (m, 2H).

3,3-Diethyl-7-trifluoromethyl-3,4-dihydro-2H-1,5-benzodithiepine (3d). The dithiol 1b (247 mg) and 3,4-dichloro-1-trifluoromethylbenzene 2b (387 mg) gave 3d (345 mg, 75%) as colorless crystals, m.p. 78.7–80.4°C. ¹H NMR (250 MHz) δ 0.85 (t, J 7.50, 6H), 1.56 (q, J 7.50, 4H), 3.00 (s, 4H), 7.25 (d, J 8.46, 2H) 7.40 (d, J 8.46, 2H) 7.43 (s, 1H); ¹³C NMR (75.47 MHz) 24.4, 37.9, 38.3, 38.5, 120.7, 126.3, 115.2–129.0 (q, J 180) 129.6, 126.4; m/z 306 [M]+; Anal. Calcd. for C₁₄H₁₇F₃S₂ (306.41): C 54.90, H 5.56, found: C 55.15, H 5.76%.

3-Spirocyclohexane-3,4-dihydro-2H-benzo-1,5-dithiepine (3e). The dithiol 1c (264 mg) and dichlorobenzene 2a (265 mg) gave 3e (265 mg, 69%) as a colorless oil. ¹H NMR (250 MHz) δ 0.97 (m, 5H), 2.37 (m, 5H), 2.93 (s, 4H), 7.27,7.21,7.24 (m, 2H), 7.66–7.73 (m, 2H), 13C NMR (75.47 MHz) 22.1, 24.3, 26.6, 35.2, 42.6, 129.0, 127.1, 132.6; m/z 250 [M]+; Anal. Calcd. for C₁₄H₁₈S₂ (250.43): C 67.15, H 7.24, S 25.61, found: C 67.27, H 7.19, S 25.67%.

7-Trifluoromethyl-3-spirocyclohexane-3,4-dihydro-2H-benzo-1,5-dithiepine (3f). The dithiol 1c (264 mg) and 3,4-dichloro-1-trifluoromethylbenzene 2b (387 mg) gave 3f (473 mg, 99.0%) as colorless crystals; m.p. 81.0–82.5°C. ¹H NMR (250 MHz) 1.45–1.58 (m, 10H), 3.07 (s, 4H), 7.22 (d, J 8.09, 2H) 7.37 (d, J 8.09, 1H) 7.53 (s, 1H); ¹³C NMR (75.47 MHz) 21.8, 26.1, 26.1, 34.7, 37.2, 41.5, 41.7, 122.9, 119.0–130.0 (q, J 180) 131.8; m/z 318 [M]+. Anal. Calcd. for C₁₅H₁₇F₃S₂ (318.42): C 56.58, H 5.48, found: C 56.45, H 5.40%.

Preparation of 2-Ethyl-2-[(2-nitrophenyl)thia[methyl]-1-butaneethiol (4b). NaHCO₃ (129 mg, 0.82 mmol) and then a solution of the chloronitrobenzene 2c (129 mg, 0.82 mmol) in DMF (4 ml) were added with stirring to 90% of the dithiol 1b (150 mg, 0.82 mmol) in absolute DMF (8 ml) under argon. The reaction mixture was kept at 50°C, to the complete conversion of dithiol 1b. After 7 h, the mixture was poured into water (150 ml), acidified (conc. HCl, 2 ml, 22 mmol), and extracted with toluene (3×10 ml). The extract was washed with water (2×20 ml), dried with
MgSO₄, evaporated, and the product isolated by column chromatography (SiO₂ / toluene–petroleum, 1:1). Compound 4b was obtained in 70% yield (164 mg) as yellow crystals; m.p. 52.7–54.9°C. ¹H NMR (250 MHz) 0.86 (t, J 7.80 Hz, 6H), 1.22 (t, J 7.80, 1H), 1.54 (q, J 11.15 Hz, 2H), 2.65 (d, J 11.15, 2H), 2.93 (s, 2H), 7.26 (t, J 6.55, 1H), 7.49–7.52 (m, 2H), 8.18 (d, J 7.50, 1H). ¹³C NMR (63 MHz) 7.56, 26.67, 30.59, 37.9, 40.35, 124.45, 125.95, 127.23, 133.39, 137.90. Anal. Calcd. for C₁₃H₁₉NO₂S₂ (285.43): С 54.70, H 6.71, S 2.25%. Found: С 54.73, H 6.88, S 2.23%.

Reaction of propanedithiols 1a,b with 2-chloronitrobenzene, 2c, and 3,4-dichloronitrobenzene, 2d. Preparation of compounds 3a, 3c, 3g, 3h

**General procedure 2 (Schemes 1,2)**

NaHCO₃ (69 mg, 0.82 mmol) and then a solution of 2c or 2d (0.82 mmol) in DMF (4 ml) were added with stirring to the dithiol 1 (0.82 mmol) in dry DMF (8 ml) under argon. The mixture was stored at 60°C until complete conversion of 1. Then KOH (46 mg, 0.70 mmol) was added, and the mixture stirred at 50°C. The reaction mixture was poured into water (150 ml), acidified (conc. HCl, 2 ml), and extracted with petroleum (3 × 10 ml). The extract was washed with water (2 × 20 ml), dried with MgSO₄, the solvent evaporated, and the product isolated by column chromatography (SiO₂). The fractions containing 3 were collected.

**3,3-Dimethyl-3,4-dihydro-2H-1,5-benzodithiepine (3a).** The dithiol 1a (112 mg) and 2-chloronitrobenzene 2c (129 mg) gave 3a (83 mg, 44%). Petroleum was used as the eluent.

**3,3-Diethyl-3,4-dihydro-2H-1,5-benzodithiepine (3c).** The dithiol 1b (135 mg) and 2-chloronitrobenzene 2c (129 mg) gave 3c (135 mg, 63%); m.p. 43.5–44.5°C. Petroleum was used as the eluent.

**3,3-Dimethyl-7-nitro-3,4-dihydro-2H-1,5-benzodithiepine (3g).** The dithiol 1a (112 mg) and 3,4-dichloronitrobenzene 2d (157 mg) gave 3g (106 mg, 54 %) as yellow crystals, m.p. 151–152.3°C. Toluene–petroleum (1:1) was used as eluent. ¹H NMR (250 MHz) 1.42 (s, 6H), 3.1 (s, 4H), 7.36 (d, J 8.53), 8.05 (dd, J 1.82, J 2.63, 1H), 8.10 (d, J 2.63, 1H). ¹³C NMR (50.32 MHz) 27.25, 36.30, 121.91, 124.32, 125.88, 132.36, 144.95, 146.27. Anal. Calcd. for C₁₁H₁₃NO₂S₂ (255.36): C 51.74, H 5.15, S 25.11, found: C 51.86, H 5.21, S 24.96%.

**3,3-Diethyl-7-nitro-3,4-dihydro-2H-1,5-benzodithiepine (3h).** The dithiol 1b (135 mg) and 3,4-dichloronitrobenzene 2d (157 mg) gave 3h (135 mg, 48%) as yellow crystals; m.p. 82.0–83.4°C. A toluene–petroleum (1:1) mixture was used as eluent. ¹H NMR (250 MHz) 0.85 (t, J 7.35 6H), 1.59 (q, J 7.35 4H), 3.0 (s, 2H), 3.2 (s, 2H), 7.34 (dd, J 1.82, J 2.63, 1H), 7.60 (dd, J 1.82, J 2.63, 2H, H₂), 8.10 (d, J 1.47, 1H, H-1). ¹³C NMR (50.32 MHz) 7.88, 120.62, 126.13, 131.19, 137.36, 144.95, 145.57. Anal. Calcd. for C₁₃H₁₇NO₂S₂ (283.41): C 55.09, H 6.04, S 22.63, found: C 55.21, H 6.10, S 22.46%.

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References