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

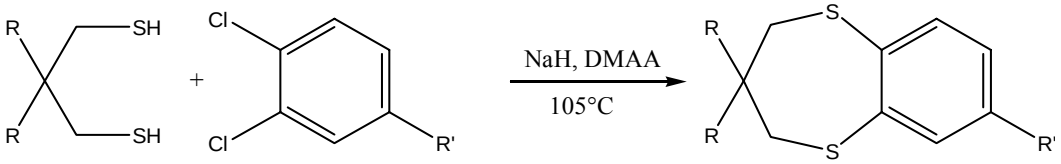
There are several examples of nucleophilic substitution of halogen in aryl halogenides by thiolate groups.[1] The reactivity of non-activated phenyl halogenides decreases in the order PhI>PhF>PhBr>PhCl.[2] A different order has been observed for 1-halogen-2,4-dinitrobenzenes.[3] Compared to substitutions 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**



1a-c **2a,b** **3a-f**

1a R=Me
1b R=Et
1c R+R=$(CH_2)_5$

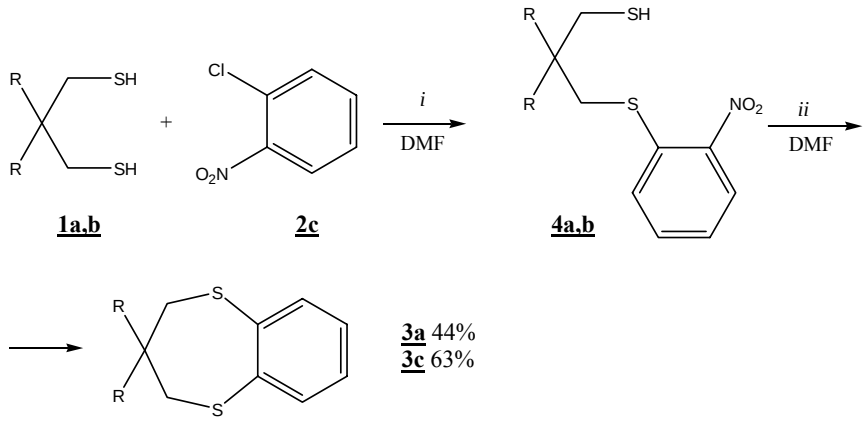
2a R'=H
2b R'=CF_3

3a R=Me, R'=H
3b R=Me, R'=CF_3
3c R=Et, R'=H
3d R=Et, R'=CF_3
3e R+R=$(CH_2)_5$, R'=H
3f R+R=$(CH_2)_5$, R'=CF_3

1a–c	**2a,b**	Reaction time, h	**3a–f**	Isolated yield, %
1a	**2a**	9	**3a**	48
1a	**2b**	6	**3b**	50
1b	**2a**	8	**3c**	69
1b	**2b**	1.5	**3d**	75
1c	**2a**	7	**3e**	88
1c	**2b**	2	**3f**	99

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

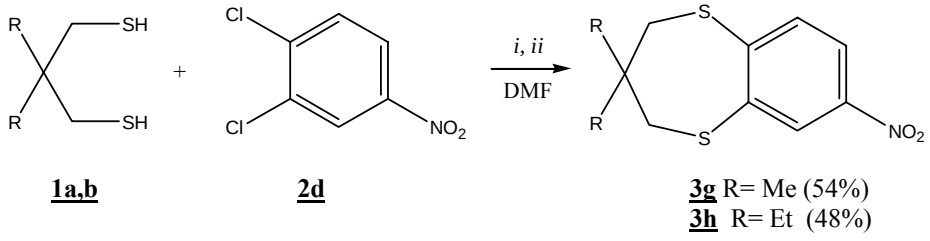
2a along with 1-chloro-2-nitrobenzene, **2c**. However, this variant was inappropriate under the conditions presented in Table 1 because of the low yield of the target products and side reactions. The selectivity of the reaction was enhanced using the one-pot synthesis in two steps. In the first step, the thiolate anion substituted only the chlorine atom in **2c** under the action of the weak base $NaHCO_3$. 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.



Reaction conditions: *i* $NaHCO_3$, **1a** 50°C, 7h; $NaHCO_3$, **1b** 60°C 7h.
ii KOH, **1a** 50°C, 1h; **1b** 60°C, 1,5.

Scheme 1

The reaction of the dithiols **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.



Reaction conditions: *i* $NaHCO_3$, **1a** 60°C, 7h; $NaHCO_3$, **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 $MgSO_4$, the solvent evaporated, and the product isolated by column chromatography (SiO_2 / petroleum).

3,3-Dimethyl-3,4-dihydro-2H-1,5-benzodithiepine (3a). The dithiol **1a** (204 mg) and dichlorobenzene 2a (265 mg) gave **3a**[8] (152 mg, 48%) as a colorless oil. ^{1}H 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. ^{1}H 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); ^{13}C 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 $C_{12}H_{13}F_3S_2$ (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. ^{1}H 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) ^{13}C NMR (75.47 MHz) 7.7, 26.8, 37.9, 41.1, 120.7, 126.8, 132.2; m/z 238 $[M]^+$; Anal. Calcd. for $C_{13}H_{18}S_2$ (238.41): C 65.49, H 7.61, S 26.90, found: C 65.59, H 7.54, S 26.67%.

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. ^{1}H NMR (250 MHz) δ0.85 (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) ^{13}C 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 $C_{14}H_{17}F_3S_2$ (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** (330 mg, 88.0%) as a colorless oil. ^{1}H 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), ^{13}C 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 $C_{14}H_{18}S_2$ (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-dihidro-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. ^{1}H 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) ^{13}C 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 $C_{15}H_{17}F_3S_2$ (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-butanethiol (4b). $NaHCO_3$ (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

$MgSO_4$, evaporated, and the product isolated by column chromatography (SiO_2 / toluene–petroleum, 1:1). Compound **4b** was obtained in 70% yield (164 mg) as yellow crystals; m.p. 52.7¯54.9°C. ^{1}H 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). ^{13}C 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 $C_{13}H_{19}NO_2S_2$ (285.43): C 54.70, H 6.71, S 2.25, found: C 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)

$NaHCO_3$ (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 $MgSO_4$, the solvent evaporated, and the product isolated by column chromatography (SiO_2). 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. ^{1}H NMR (250 MHz) 1.42 (s, 6H), 3.1 (s, 4H), 7.36 (d, J 8.53), 8.05 (dd, J_1 8.53, J_2 2.63, 1H), 8.10 (d, J 2.63, 1H). ^{13}C NMR (50.32 MHz) 27.25, 36.30, 43.30, 121.91, 124.32, 125.88, 132.36, 144.95, 146.27. Anal. Calcd. for $C_{11}H_{13}NO_2S_2$ (255.36): C 51.74, H 5.13, 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. ^{1}H 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 8.82, J_2 1.47, 1H, H_3), 7.60 (dd, J_1 8.82, J_2 1.47, 2H, H_2), 8.10 (d, J 1.47, 1H, H-1). ^{13}C NMR (50.32 MHz) 7.88, 26,33, 40.20, 39.98, 40.43, 120.62, 126.13, 131.19, 137.36, 144.95, 145.57. Anal. Calcd. for $C_{13}H_{17}NO_2S_2$ (283.41): C 55.09, H 6.04, S 22.63, found: C 55.21, H 6.10, S 22.46%.

Acknowledgments

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