Exchange reactions of 1,3-bis(nitroarylthio)propanes with propane-1,3-dithiols

A. V. Miroshnichenko, D. V. Demchuk, and G. I. Nikishin*

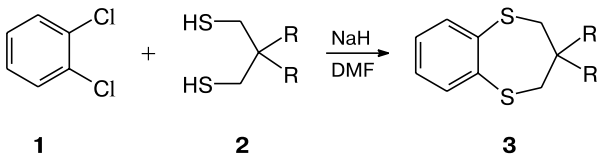
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (495) 135 5328. E-mail: demchuk@ioc.ac.ru

Base-catalyzed reactions of propane-1,3-dithiols with 2-chloronitrobenzene, 3,4-dichloronitrobenzene, and 2-chloro-3-nitropyridine afforded 1,3-bis(nitroarylthio)propanes, whose thiolate—thiolate exchange with propane-1,3-dithiols gave dihydrobenzodithiepines.

Key words: 1-chloro-2-nitrobenzene, propane-1,3-dithiols, dihydrobenzodithiepines, nucleophilic aromatic substitution, thiolate—thiolate exchange reaction.

Earlier,[1] we have synthesized cyclic sulfides, namely, dihydrobenzodithiepines (**3**), by substitution of the thiolate anions from propane-1,3-dithiols (**2**) for the Cl atoms in 1,2-dichlorobenzene (**1**) (Scheme 1).

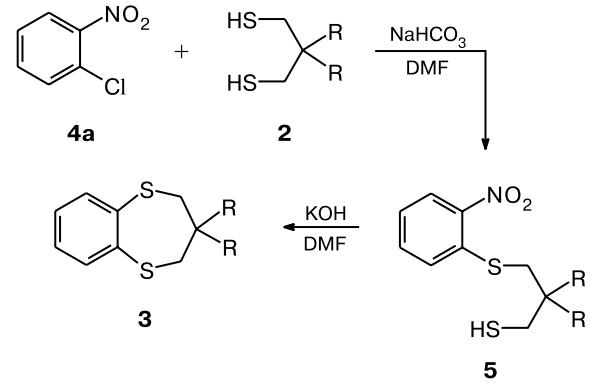
Scheme 1



1 **2** **3**

With more reactive 1-chloro-2-nitrobenzene (**4a**) instead of dichlorobenzene (**1**), the yield of the target product **3** decreased, probably because of polycondensation as a side process. Nevertheless, the *one-pot* reactions between compounds **2** and **4a** in the ratio 1 : 1 also yielded dithiepines **3** in two steps (Scheme 2).

Scheme 2

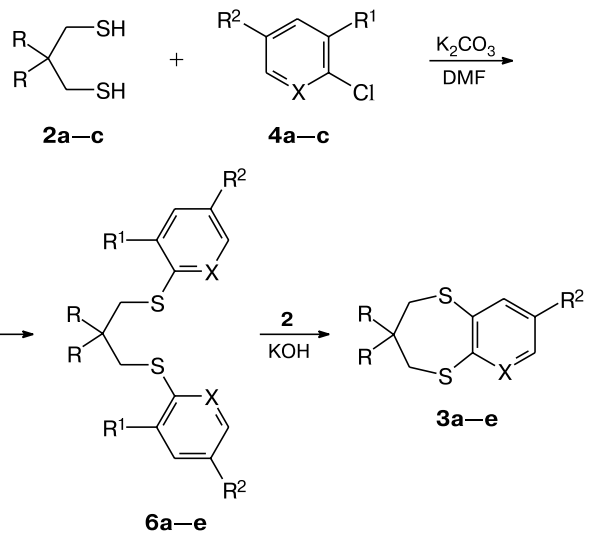


4a **2** **3** **5**

At the first step, the Cl atom was replaced by the thiolate residue of dithiol **2** in the presence of $NaHCO_3$ to give thiol **5**. The second step involved intramolecular substitution of the thiolate anion for the nitro group in thiol **5** under the action of KOH.

Based on those results and available data on the different reactivities of the Cl atom and the nitro group in the aromatic ring toward nucleophilic reagents[2] (including cyclization reactions[3]), here we synthesized 1,3-bis(nitroarylthio)propanes (**6**) and dihydrobenzodithiepines (**3**) (Scheme 3).

Scheme 3



2a—c **4a—c** **6a—e** **3a—e**

We assumed that 1,3-bis(arylthio)propanes **6** and related compounds could serve as convenient units for design of more complex cyclic structures such as crown

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Table 1. Synthesis of 1,3-bis(nitroarylthio)propanes (**6**) and dihydrobenzodithiepines (**3**)

Starting reagent	R	R^1	R^2	X	Yields (%) of the products	
					6	**3**
2a, **4a**	H	NO_2	H	CH	78 (**a**)	56 (**a**)
2b, **4a**	Me	NO_2	H	CH	77 (**b**)	58 (**b**)
2c, **4a**	Et	NO_2	H	CH	88 (**c**)	55 (**c**)
2c, **4b**	Et	Cl	NO_2	CH	78 (**d**)	56 (**d**)
2c, **4c**	Et	NO_2	H	N	95 (**e**)	93 (**e**)

sulfides. This could be possible in the case of plausible 1+1 intermolecular replacement of the nitro group in compounds **6** by the thiolate anions of dithiols **2** (Scheme 4, pathway *b*). In addition, the formation of both dithiepines **3** (as the result of nucleophilic transthiylation) and oligomeric linear sulfides containing the fragments of constituent structures **2** and **6** could not be ruled out. To verify these assumptions, we synthesized dinitro derivatives **6** and carried out their reactions with dithiols **2** in the presence of KOH.

For the ratio **2** : **4** = 1 : 2.2, the yields of compounds **6** were 77—95%. According to the data obtained, the reactions of equivalent amounts of compounds **2** and **6** followed the mechanism of thiolate—thiolate exchange followed by intramolecular cyclization of nitro thiol **5**. The resulting compounds **3** containing a seven-membered ring were isolated in 55—93% yields, the starting reagents being completely consumed (see Table 1 and Scheme 4). In the synthesis of diarylated adducts **6** and their subsequent cyclization into dithiepines **3**, the same dithiol **2** was used; otherwise, the formation of a mixture of two dithiepines could be expected.

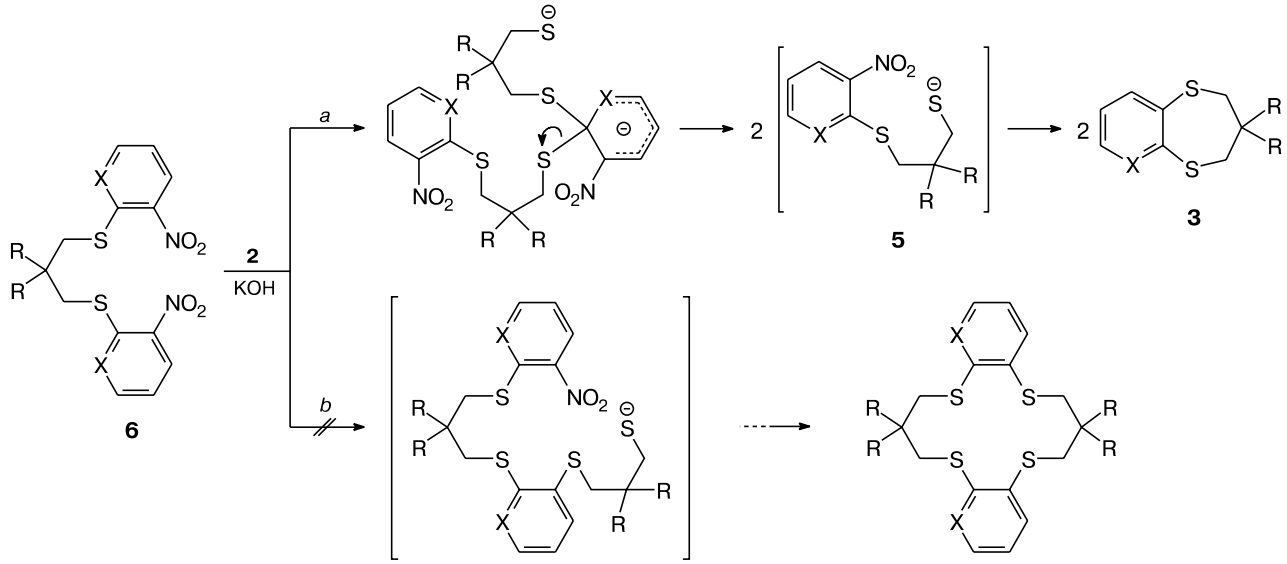
The reaction mechanism (see Scheme 4, pathway *a*) includes generation of a thiolate anion from dithiol **2** in alkaline medium, addition of the thiolate anion to the aromatic ring at the C atom bound to the S atom, splitting of the adduct anion into two thiolate anions **5**, and cyclization of the latter into dihydrobenzodithiepines **3**.

In the case of 3,4-dichloronitrobenzene **4b**, the reaction of 2,2-diethylpropane-1,3-dithiol (**2c**) with two equivalents of compound **4b** gave, through replacement of the activated Cl atom in the latter, diarylation product **6d**. At the second step, thiolate—thiolate exchange between compound **6d** and dithiol **2c** followed by intramolecular replacement of the other Cl atom in the aromatic residue yielded nitrobenzodithiepine **3d**. Along with benzene derivatives **4a** and **4b**, we used 2-chloro-3-nitropyridine **4c** for the synthesis of compounds **6** and **3** according to Schemes 3 and 4, which afforded products **6e** and **3e** with higher selectivity.

The chemical literature contains no systematic data on nucleophilic replacement of alkylthio groups in the aromatic ring by other alkylthio groups. However, thiolate—thiolate exchange has been found in reactions of aliphatic thiols with 2-isopropylthio- and 5-*tert*-butylthio-6-nitroquinoline in the presence of K_2CO_3[4] and in the reaction of sodium ethanethiolate with 1,4-diisopropylthio-2-nitrobenzene, in which the isopropyl group in position 1 is replaced by the ethylthio group.[5] In these compounds, as in compounds **6**, the exchanged alkylthio groups are activated by the *o*-nitro group.

Thus, we demonstrated that the thiolate—thiolate exchange in reactions of bis(2-nitrophenylthio)propanes

Scheme 4



with propane-1,3-dithiols in the presence of KOH gives rise to dihydrobenzodithiepines.

Experimental

NMR spectra were recorded on Bruker AC-200, Bruker WM-250, and Bruker AM-300 spectrometers in $CDCl_3$. Chemical shifts were measured relative to the signals for the solvent (δ 7.25 and 77.0 for ^1H and ^{13}C, respectively). Melting points were determined on a Kofler hot stage. TLC analysis was carried out on Sorbfil UV-254 plates. Silica gel 60 (0.063—0.200 mm, Merck) was used for column chromatography. Mass spectra were recorded on a Kratos-MS30 instrument.

The starting reagents propane-1,3-dithiol (**2a**), 2,2-dimethylpropane-1,3-dithiol (**2b**), and 2,2-diethylpropane-1,3-dithiol (**2c**) were prepared as described earlier.[6] Commercial compounds 1-chloro-2-nitrobenzene (**4a**), 1,2-dichloro-4-nitrobenzene (**4b**), and 2-chloro-3-nitropyridine (**4c**) were used without additional purification.

1,3-Bis(2-nitrophenylthio)propane (6a). Potassium carbonate (414 mg, 3.0 mmol) and a solution of 1-chloro-2-nitrobenzene (**4a**) (347 mg, 2.2 mmol) in DMF (4 mL) were added under argon to a stirred solution of 90% propane-1,3-dithiol (**2a**) (120 mg, 1.0 mmol) in anhydrous DMF (10 mL). The reaction mixture was heated at 50 °C for 8 h, cooled, and poured into water (150 mL) acidified with conc. HCl (2 mL, 22 mmol). The product was extracted with ethyl acetate (3×10 mL). The organic layer was washed with water (2×20 mL), dried with $MgSO_4$, and concentrated. The residue was dried *in vacuo* and chromatographed on SiO_2 with toluene as the eluent (R_f 0.50). Recrystallization from toluene (3 mL) gave compound **6a** (273 mg, 78%) as yellow crystals, m.p. 140.5—143.0 °C (*cf.* Ref. 7: m.p. 140 °C). Found (%): C, 51.33; H, 3.87; N, 7.56; S, 18.69. $C_{15}H_{14}N_2O_4S_2$. Calculated (%): C, 51.41; H, 4.03; N, 7.99; S, 18.30. ^1H NMR (300 MHz), δ: 2.16 (m, 2 H, CH_2, J = 7.0 Hz); 3.16 (t, 4 H, CH_2S, J = 7.0 Hz); 7.27 (td, 2 H, H(4), J = 7.7 Hz, J = 1.5 Hz); 7.41 (dd, 2 H, H(6), J = 8.1 Hz, J = 1.5 Hz); 7.53 (td, 2 H, H(5), J = 7.7 Hz, J = 1.5 Hz); 8.17 (dd, 2 H, H(3), J = 8.1 Hz, J = 1.5 Hz). ^{13}C NMR (50 MHz), δ: 26.0 ($\underline{C}H_2$); 31.0 ($\underline{C}H_2S$); 124.8, 126.2, 126.7, 133.6, 136.7 ($\underline{C}$(1)); 146.4 ($\underline{C}$(2)).

Compounds **6b**, **6c**, **6d**, and **6e** were obtained analogously from compounds **2b** and **4a**, **2c** and **4a**, **2c** and **4b**, and **2c** and **4c**, respectively.

2,2-Dimethyl-1,3-bis(2-nitrophenylthio)propane (6b). The yield was 77%, yellow crystals, m.p. 91.0—92.1 °C. Found (%): C, 53.80; H, 4.66; N, 7.14; S, 17.31. $C_{17}H_{18}N_2O_4S_2$. Calculated (%): C, 53.95; H, 4.79; N, 7.40; S, 16.95. ^1H NMR (300 MHz), δ: 1.28 (s, 6 H, CH_3); 3.09 (s, 4 H, CH_2S); 7.21 (td, 2 H, H(4), J = 7.7 Hz, J = 1.5 Hz); 7.48 (m, 4 H, H(5), H(6)); 8.05 (dd, 2 H, H(3), J = 8.1 Hz, J = 1.5 Hz). ^{13}C NMR (50 MHz), δ: 27.5 ($\underline{C}H_3$); 36.0 ($\underline{C}$); 43.7 ($\underline{C}H_2S$); 124.7, 125.7, 127.7, 133.3, 136.9 ($\underline{C}$(1)); 146.8 ($\underline{C}$(2)).

2,2-Diethyl-1,3-bis(2-nitrophenylthio)propane (6c). The yield was 88%, yellow crystals, m.p. 84.6—86.5 °C. Found (%): C, 56.05; H, 5.39; N, 6.72; S, 16.13. $C_{19}H_{22}N_2O_4S_2$. Calculated (%): C, 56.14; H, 5.45; N, 6.89; S, 15.78. ^1H NMR (300 MHz), δ: 0.90 (t, 6 H, Me, J = 7.5 Hz); 1.64 (q, 4 H, CH_2, J = 7.5 Hz); 3.04 (s, 4 H, CH_2S); 7.19 (m, 2 H, H(4)); 7.48 (m, 4 H, H(5), H(6)); 8.03 (dd, 2 H, H(3), J = 8.0 Hz, J = 1.5 Hz). ^{13}C NMR (50 MHz), δ: 7.5 ($\underline{C}H_3$); 27.8 ($\underline{C}H_2$); 39.0 ($\underline{C}H_2S$); 41.0 ($\underline{C}$); 124.7, 125.6, 127.8, 133.3, 136.9 ($\underline{C}$(1)); 146.8 ($\underline{C}$(2)). MS, m/z 406 $[M]^+$.

1,3-Bis(2-chloro-4-nitrophenylthio)-2,2-diethylpropane (6d). The yield was 78%, yellow crystals, m.p. 170.5—171.2 °C (toluene). Found (%): C, 48.37; H, 4.45; Cl, 14.45; N, 5.64; S, 13.06. $C_{19}H_{20}Cl_2N_2O_4S_2$. Calculated (%): C, 48.00; H, 4.24; Cl, 14.91; N, 5.89; S, 13.49. ^1H NMR (300 MHz), δ: 0.93 (t, 6 H, Me, J = 7.4 Hz); 1.66 (q, 4 H, CH_2, J = 7.4 Hz); 3.08 (s, 4 H, CH_2S); 7.33 (d, 2 H, H(6), J = 8.8 Hz); 8.02 (dd, 2 H, H(5), J = 8.8 Hz, J = 2.2 Hz); 8.12 (d, 2 H, H(3), J = 2.2 Hz). ^{13}C NMR (50 MHz), δ: 7.6 ($\underline{C}H_3$); 27.9 ($\underline{C}H_2$); 38.7 ($\underline{C}H_2S$); 41.1 ($\underline{C}$); 121.9 ($\underline{C}$(5)H); 124.2 ($\underline{C}$(3)H); 126.1 (C(2)); 132.4 ($\underline{C}$(6)H); 144.9 ($\underline{C}$(1)); 146.3 ($\underline{C}$(4)).

2,2-Diethyl-1,3-bis(3-nitro-2-pyridylthio)propane (6e). The yield was 95%, yellow crystals, m.p. 76.0—77.0 °C. Found (%): C, 49.67; H, 5.31; N, 13.49; S, 15.64. $C_{17}H_{20}N_4O_4S_2$. Calculated (%): C, 49.98; H, 4.93; N, 13.72; S, 15.70. ^1H NMR (250 MHz), δ: 0.91 (t, 6 H, Me, J = 7.6 Hz); 1.63 (q, 4 H, CH_2, J = 7.6 Hz); 3.47 (s, 4 H, CH_2S); 7.13 (dd, 2 H, H(5), J = 8.3 Hz, J = 4.6 Hz); 8.40 (dd, 2 H, H(4), J = 8.3 Hz, J = 1.8 Hz); 8.63 (dd, 2 H, H(6), J = 4.6 Hz, J = 1.8 Hz). ^{13}C NMR (75 MHz), δ: 7.9 ($\underline{C}H_3$); 28.3 ($\underline{C}H_2$); 36.1 ($\underline{C}H_2S$); 40.2 ($\underline{C}$); 118.4 ($\underline{C}$(5)H); 133.6 ($\underline{C}$(3), $\underline{C}$(4)); 152.7 ($\underline{C}$(6)H); 158.0 ($\underline{C}$(2)).

3,4-Dihydro-2*H*-1,5-benzodithiepine (3a). Potassium hydroxide (100 mg, 1.5 mmol) and a solution of compound **6a** (80 mg, 0.21 mmol) in anhydrous DMF (3 mL) were added under argon to a stirred solution of 90% propane-1,3-dithiol (**2a**) (40 mg, 0.21 mmol) in anhydrous DMF (8 mL). The reaction mixture was stirred at room temperature for 2 h and poured into water (150 mL) acidified with conc. HCl (2 mL, 22 mmol). The product was extracted with light petroleum (3×10 mL). The organic layer was washed with water (2×20 mL), dried with $MgSO_4$, and concentrated. The residue was dried *in vacuo* and chromatographed on SiO_2 with light petroleum as the eluent (R_f 0.23). The yield of compound **3a** was 43 mg (56%), colorless crystals, m.p. 62.5—63.9 °C (*cf.* Refs 8 and 9: m.p. 59.5—60.5 and 60—61 °C, respectively). ^1H NMR (250 MHz), δ:[9] 2.30 (m, 2 H, CH_2); 2.86 (m, 4 H, CH_2S); 7.15 (m, 2 H, H(7), H(8)); 7.62 (m, 2 H, H(6), H(9)). ^{13}C NMR (62.90 MHz), δ:[10] 33.0 ($\underline{C}H_2$); 33.4 ($\underline{C}H_2S$); 127.8 ($\underline{C}$(6)H, $\underline{C}$(7)H, $\underline{C}$(8)H, $\underline{C}$(9)H); 134.0 ($\underline{C}$(5a), $\underline{C}$(9a)).

Compounds **3b**, **3c**, **3d**, and **3e** were obtained analogously from compounds **2b** and **6b**, **2c** and **6c**, **2c** and **6d**, and **2c** and **6e**, respectively.

3,3-Dimethyl-3,4-dihydro-2*H*-1,5-benzodithiepine (3b). The yield was 58%, a colorless oil (R_f 0.35, light petroleum). ^1H NMR (300 MHz), δ:[10] 1.16 (s, 6 H, CH_3); 2.79 (s, 4 H, CH_2S); 7.08 (m, 2 H, H(7), H(8)); 7.45 (m, 2 H, H(6), H(9)).

3,3-Diethyl-3,4-dihydro-2*H*-1,5-benzodithiepine (3c). The yield was 55%, a colorless oil, R_f 0.33 (light petroleum) (*cf.* Ref. 1: m.p. 43.5—44.5 °C). ^1H NMR (250 MHz), δ: 0.85 (t, 6 H, Me, J = 7.3 Hz); 1.60 (q, 7.3, 4 H, CH_2); 2.87 (s, 4 H, CH_2S); 7.05 (m, 2 H, H(7), H(8)); 7.40 (m, 2 H, H(6), H(9)). ^{13}C NMR (62.9 MHz), δ: 7.6 ($\underline{C}H_3$); 26.2 (vbr, $\underline{C}H_2$); 41.1 ($\underline{C}H_2S$); 126.8 (br.s, $\underline{C}$(6)H, $\underline{C}$(7)H, $\underline{C}$(8)H, $\underline{C}$(9)H); 132.1 (br.s, $\underline{C}$(5a), $\underline{C}$(9a)). MS, m/z 238 $[M]^+$.

3,3-Diethyl-7-nitro-3,4-dihydro-2*H*-1,5-benzodithiepine (3d). The yield was 56%, yellow crystals, m.p. 109.0—110.2 °C (*cf.* Ref. 1: m.p. 82.0—83.4 °C). ^1H NMR (300 MHz), δ: 0.84 (t,

6 H, CH_3, J = 7.4 Hz); 1.57 (q, 4 H, CH_2, J = 7.4 Hz); 3.06 (s, 2 H, CH_2S); 3.11 (s, 2 H, CH_2S); 7.33 (d, 1 H, H(9), J = 8.4 Hz); 7.78 (dd, 1 H, H(8), J = 8.4 Hz, J = 2.3 Hz); 8.09 (d, 1 H, H(6), J = 2.3 Hz). ^{13}C NMR (62.9 MHz), δ: 7.8 ($\underline{C}H_3$); 26.2 ($\underline{C}H_2$); 39.9 ($\underline{C}H_2S$); 40.3 ($\underline{C}H_2S$); 120.6 ($\underline{C}$(8)H); 126.1 ($\underline{C}$(6)H); 131.1 ($\underline{C}$(9)).

3,3-Diethyl-3,4-dihydro-2*H*-[1,4]dithiepino[2,3-*b*]pyridine (3e). The yield was 93%, yellowish crystals, m.p. 95.1—96.0 °C. Found (%): C, 60.29; H, 7.41; N, 5.95; S, 26.55. $C_{12}H_{17}NS_2$. Calculated (%): C, 60.20; H, 7.16; N, 5.85; S, 26.79. ^{1}H NMR (250 MHz), d: 0.83 (t, 6 H, Me, J = 7.5 Hz); 1.55 (q, 4 H, CH_2, J = 7.5 Hz); 3.09 (s, 2 H, CH_2S); 3.17 (s, 2 H, CH_2S); 6.85 (dd, 1 H, C(7), J = 7.9 Hz, J = 4.6 Hz); 7.43 (dd, 1 H, H(6), J = 7.9 Hz, J = 1.6 Hz); 8.15 (dd, 1 H, C(8), J = 4.6 Hz, J = 1.6 Hz). ^{13}C NMR (75 MHz), d: 7.9 ($\underline{C}H_3$); 26.1 ($\underline{C}H_2$); 38.9 ($\underline{C}H_2S$); 39.6 ($\underline{C}H_2S$); 40.3 ($\underline{C}$); 119.7 ($\underline{C}$(7)H); 132.0 ($\underline{C}$(5a)H); 138.4 ($\underline{C}$(6)H); 146.2 ($\underline{C}$(8)H); 157.1 ($\underline{C}$(9a)). MS, m/z 239 $[M]^+$.

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