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Synthesis of 2-Amino-5(6)-(4-aminophenyl)benzimidazole Derivatives: II. Reaction of 2-Nitro-4-thiocyanatoaniline with 4-Nitrochlorobenzene

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Abstract—The reaction of 2-nitro-4-thiocyanatoaniline with 4-nitrochlorobenzene in aqueous alkaline medium in the presence of phase-transfer catalyst at 95–100°C was studied with a view to obtain 4-amino-3,4'-dinitrodiphenyl sulfide. Optimal conditions for the synthesis and isolation of the product were found.

4-Amino-3,4'-dinitrodiphenyl sulfide (**I**) is a starting material for the synthesis of numerous antihelminthic compounds of the 5(6)-(4-aminophenyl)-2-aminobenzimidazole series [1]. There are published data on the preparation of alkyl aryl sulfides by reaction of aryl thiocyanates with alkyl halides or alcohols in the presence of stoichiometric amounts of metal hydroxides or other bases in the temperature range from 0 to 250°C [2–6]. We previously developed a procedure for the synthesis of sulfide **I** by treatment of 4-chloronitrobenzene with sodium sulfide, acylation of the resulting 4-amino-4'-nitrodiphenyl sulfide with acetic anhydride, nitration of 4-acetylamino-4'-nitrodiphenyl sulfide to 4-acetylamino-3,4'-dinitrodiphenyl sulfide, and removal of the acetyl protection by reaction with aqueous alkali [7]. An alternative route to 4-amino-3,4'-dinitrodiphenyl sulfide (**I**) via reaction of 2-nitro-4-thiocyanatoaniline (**II**) with 4-chloronitrobenzene (**III**) attracts a certain interest. In this case, the number of chemical steps is reduced from four [7] to two. Moreover, 2-nitroaniline and 4-nitrochlorobenzene are large-scale chemicals, and thiocyanation of 2-nitroaniline to 2-nitro-4-thio-

cyanatoaniline was studied by us in detail and was reported in the preceding communication of this series.

In the present work we examined the reaction of thiocyanate **II** with chloronitrobenzene **III**, which leads to formation of the target sulfide **I**. The reaction was carried out in aqueous alkali at 95–100°C in the presence of phase-transfer catalyst (PEG-400 or catamine AB). The process includes two stages. In the first stage, 2-nitro-4-thiocyanatoaniline is converted into sodium 4-amino-3-nitrobenzenethiolate (**IV**). In the second stage, salt **IV** reacts with chloronitrobenzene **III** to give disulfide **I**. Taking into account that sodium cyanate formed in the first stage undergoes hydrolysis to ammonia, the overall process may be represented by Scheme 1.

The reaction of thiocyanate **II** with chloronitrobenzene **III** can also be accompanied by side processes. For example, sodium thiolate **IV** formed in the first stage readily reacts with the second molecule of thiocyanate **II**, leading to formation of bis(4-amino-3-nitrophenyl) disulfide (**V**) (Scheme 2). This side reaction increases consumption of initial compound **II** and sodium hydroxide and favors accumulation of

Scheme 1.
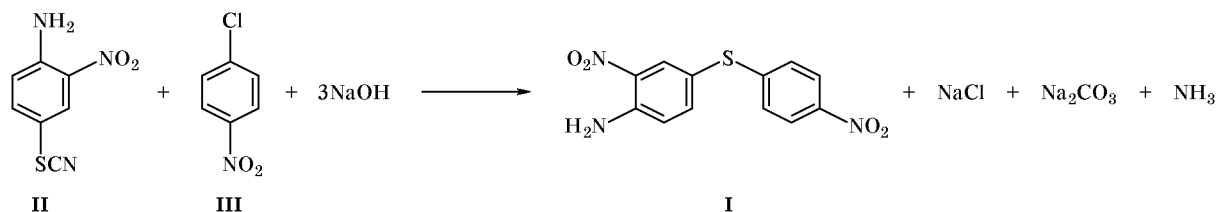
Scheme 2.
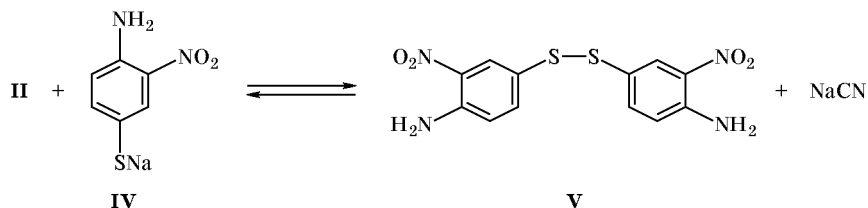
by-products. On the other hand, the formation of disulfide **V** is reversible. By the action of sodium cyanide, compound **V** can be converted back into initial thiocyanate **II** and salt **IV**. Therefore, the formation of **V** from **II** and **IV** can be suppressed by the use of excess sodium cyanide. Also, diphenyl disulfide **V** is readily formed as a result of oxidation processes in the presence of atmospheric oxygen. To avoid these, it is advisable to perform the second stage under nitrogen.

In addition, it is possible that salt **IV**, which is necessary for the synthesis of target product **I**, is partially formed by hydrolysis of thiocyanate **II** through the corresponding thiocarbamate **VI** [8–10] (Scheme 3).
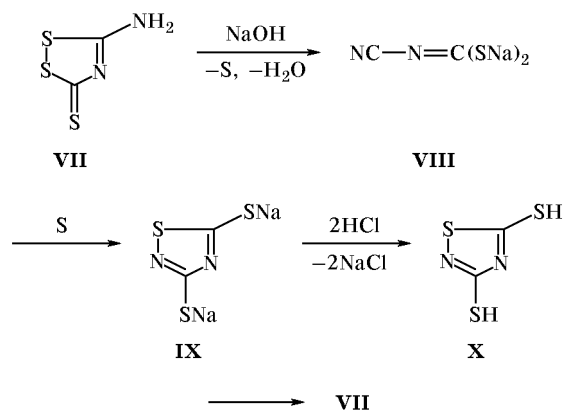
Scheme 3.
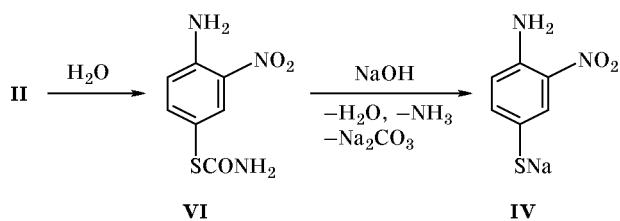
We made an attempt to determine the ways of hydrolysis of thiocyanate **II** to salt **IV**. Analysis of the reaction mixtures showed that the hydrolysis of 1 mol of compound **II** in alkaline medium gave 0.013 mol of sodium carbonate, 0.039 mol of sodium cyanate, and 0.051 mol of sodium cyanide. These data indicate that the amount of sodium cyanide almost coincides with the overall amount of sodium cyanate and sodium carbonate. We also isolated and analyzed insoluble organic by-products formed by transformation of thiocyanate **II**. Taking into account that accumulation of sodium cyanide in the reaction mixture promotes its further consumption for the reverse reaction (decomposition of disulfide **V** according to Scheme 2), we can state with certainty that the major part of salt **IV** is formed through disulfide **V**. Table 1 gives the compositions of products **A** and **B** which were isolated, respectively, from the reaction mixture and the filtrate after hydrolysis of thiocyanate **II**.

These data suggest a complex character of the process which gives rise to a number of various products. Most of the products are unstable and hence are difficult to identify.

Even more complex mixtures of products were obtained in the presence of the second component, 4-chloronitrobenzene (**III**), necessary for the formation of the target compound (Table 2). Table 2 gives the compositions of solid products which separated from the mother liquor on acidification with hydrochloric acid. Product mixture **C** was isolated from the filtrate obtained after separation of sulfide **I** in a laboratory setup, and product **D** was isolated in a similar way in a pilot setup. The compositions of products **C** and **D** are fairly similar. They consist of 3–4 major components most of which are products of side reactions.

Insofar as most of the above by-products are poorly soluble in water at pH ≈ 7 but readily soluble in alkaline solution, it is reasonable to wash the precipitate of sulfide **I** (after squeezing) first with an aqueous–alkaline solution and then with distilled water (or steam condensate). As a result, the amount of impurities in the final product considerably decreases. For example, acid **VII**, which is present in initial compound **II**, in aqueous sodium hydroxide decomposes into sulfur and disodium salt **VIII** which is readily soluble in water. Salt **VIII** reacts with

Scheme 4.

liberated sulfur to give disodium salt **IX**. The latter is stable in alkaline medium, but its treatment with an acid leads to unstable water-soluble acid **X** which is rapidly converted into insoluble acid **VII** [8, 11] (Scheme 4). Direct reaction of disodium salt **VIII** with hydrochloric acid gives yellow polymer **XI** of unknown structure. By treatment with an aqueous solution of sodium hydroxide, polymer **XI** is converted back into disodium salt **VIII** [12] (Scheme 5).

Scheme 5.
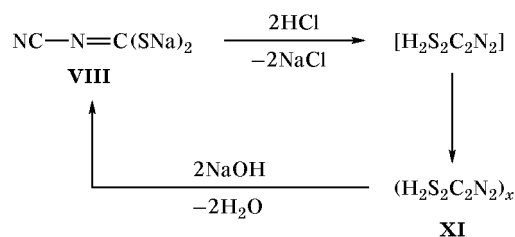
Analogous behavior is typical of some other impurities present in starting compound **II**. Therefore, during the synthesis of disulfide **I**, concomitant by-products can be removed as water-soluble compounds by treatment of the crude solid product with aqueous alkali. They can be isolated from the filtrate and washings by acidification and subsequent filtration.

The ability of sodium hydroxide to convert acid **VII** and polymer **XI** into water-soluble compounds was studied by a special series of experiments. The results are summarized in Table 3. It is seen that compounds **VII** and **XI** are completely converted into water-soluble compounds on heating in an aqueous–alkaline medium (Table 3, run nos. 1, 2). Heating of acid **VII** and polymer **XI** in the presence of chloronitrobenzene **III** leads to accumulation of products insoluble in aqueous alkali (Table 3, run nos. 3, 4). Presumably, the rate of the reaction of chloronitrobenzene **III** with the above compounds is considerably lower than the rate of its reaction with thiocyanate **II**. Thus, after heating of chloronitrobenzene **III** with acid **VII** for 5-h at 95°C (run no. 3), the reaction mixture contained 60% of unchanged compound **III**, about 22% of **III** was consumed for the formation of insoluble (in aqueous alkali) compounds, and the remaining part was converted into soluble products (including losses). On the other hand, the reaction of thiocyanatoaniline **II** with chloronitrobenzene **III** under analogous conditions is complete in 40–60 min (see below).

Chloronitrobenzene **III** reacts with decomposition products of polymer **XI** at a higher rate. After the same period, the precipitate contains only 7% of **III**

Table 1. Compositions (wt %) of products isolated in the hydrolysis of thiocyanate **II** in aqueous–alkaline medium

Component	Initial compound	**A**[a]	**B**[b]
Thiocyanate **II**	97.5	1.57	0.67
2-Nitroaniline	0.91	0.26	1.61
4-Bromo-2-nitroaniline	1.12	0.68	1.40
Disulfide **V**	–	96.01	77.63
Unidentified products X_1–X_7	0.47	1.48	18.69

[a] Solid product isolated by filtration of the reaction mixture after hydrolysis.
[b] Solid product isolated from the filtrate after acidification.

Table 2. Composition (wt %) of products isolated from the filtrate obtained in the stage of synthesis of sulfide **I**

Component	Products	
	C	**D**
Sulfide **I**	0.51	21.57
4-Nitrochlorobenzene (**III**)	–	0.73
Disulfide **V**	73.53	39.31
Unidentified products X_1–X_{13}	25.96	38.39

(Table 3, run no. 4), 63% of **III** is consumed for formation of insoluble products, and about 30% is converted into soluble compounds (including losses).

Using IR and ^{13}C NMR spectroscopy and high-performance liquid chromatography, among the isolated solid products we detected 4,4′-dinitrodiphenyl sulfide (**XII**) and 4-amino-4′-nitrodiphenyl sulfide (**XIII**). Their fractions were 59–83 and 8–24%, respectively (the residual amount of **III** was not taken into account). The other components were not identified. Dinitrodiphenyl sulfide **XII** is likely to be formed by reaction of chloronitrobenzene **III** with sulfides present in the reaction mixture. Presumably, compound **XII** is then partially reduced to aminonitrodiphenyl sulfide **XIII** with those sulfides.

Under analogous conditions we performed syntheses of sulfide **I** from thiocyanate **II** contaminated with various amounts (0 to 27.5%) of water-insoluble impurities (Table 4). In run no. 1 (Table 4) we used thiocyanate **II** which was prepared in a laboratory setup and purified by recrystallization from acetone. Runs nos. 2 and 3 were performed with compound **II**

Table 3. Reactivity of impurities present in technical-grade thiocyanatoaniline **II** (amounts of reactans: water, 120 ml; NaOH, 16.8 g; PEG-400, 2 ml; temperature 93–95°C; reaction time 5 h)

Run no.	Amounts of reactants, g			Amount of solid product, g	Product composition, wt %						
	VII	**XI**	**III**		X_1	X_2	**III**	**XIII**	X_3	X_4	**XII**
1	22	–			–						
2	–	22			–						
3	28	–	15.5	12.0	–	–	–75.7	1.9	2.2		20.2
4	–	22	15.5	11.0	0.36	1.66	9.98	21.5	0.80	12.5	53.2

Table 4. Amounts of impurities in initial thiocyanatoaniline **II** and composition of sulfide **I** obtained therefrom (molar ratio **II**:**III**:NaOH:PEG-400:H$_2$O = 1.0:0.9:4.0:0.04:45; temperature 95°C, reaction time 5 h)

Run no.	Composition of **II**, wt %		Composition of **I**, wt %			
	main substance	insoluble impurities	main substance	**XIII**	**XII**	other impurities
1	100	–	99.5	–	–	0.50
2	95.0	5.0	97.1	0.25	1.20	1.45
3	93.0	7.0	97.0	0.30	1.20	1.50
4	72.5	27.5	91.86	0.75	3.39	4.00

which was synthesized in a laboratory setup and was not subjected to additional purification, and the substrate in run no. 4 was a nonstandard sample of **II** obtained in a pilot setup. The results show that during the synthesis of sulfide **I** a considerable part of impurities present in initial compound **II** is converted into soluble compounds which are removed by washing of the target product. However, it is clearly seen that the concentration of impurities in the final product increases as the amount of impurities in the initial compound increases. Despite the presence of

Table 5. Composition of 4-amino-3,4′-dinitrodiphenyl sulfide (**I**) after heating for 15 h at 100°C in water and 5% aqueous sodium hydroxide (40 ml)

Component	Composition, wt %		
	initial	water	5% NaOH
Sulfide **I**	97.23	94.97	86.85
Chloronitrobenzene **III**	1.08	0.48	0.30
Unidentified impurities X_1–X_7	1.69	4.55	12.85

20 to 34 wt % of impurities in thiocyanate **II**, in a large-scale synthesis we succeeded in obtaining sulfide **I** containing no less than 91% of the main substance. Nevertheless, the product contained impurities insoluble in aqueous–alkaline medium. Some of these, e.g., 2-nitro- and 4-bromo-2-nitroanilines, come to the reaction mixture together with initial compound **II** and are then transferred to the target product.

The concentration of impurities in crude sulfide **I** may increase during the synthesis as a result of its thermal decomposition (Table 5). Reduction of the concentration of the main substance becomes appreciable even after prolonged heating in water. In this case, 3–4 new compounds are formed. In alkaline medium, the concentration of the main substance decreases more rapidly, due mainly to considerable increase in the concentration of one by-product (X_1). The stability of sulfide **I** under the conditions of its synthesis was studied by special experiments. For this purpose, when the synthesis of **I** was complete, the reaction mixture was further stirred at 100°C, and samples were withdrawn, washed to remove water-soluble impurities, and analyzed. The time of withdrawal of the first sample was assumed to be the initial moment. The results are given in Table 6. The concentration of the main substance decreases mainly

at the expense of increase in the amount of two unidentified products X_1 and X_2. However, in this case, by-products can be formed not only by decomposition of the main substance but also as a result of other chemical processes.

The time necessary to complete the synthesis of sulfide **I** was determined using a laboratory setup (Table 7). As a rule, 40–60 min is sufficient. Increase of the reaction time does not result in increased concentration of the main substance in the crude product, but the amount of impurities rises. The data obtained in a laboratory setup were then confirmed in enlarged syntheses in a pilot setup. The latter was also used to examine the effect of the reaction temperature on the purity of the target product. Reduction of the temperature from 100 to 80°C leads to increased concentration of chloronitrobenzene **III** in the product (up to 4–7 wt %).

Taking into account the above data, we performed enlarged synthesis of sulfide **I** in a pilot setup using a 400-l reactor. The results were consistent with those obtained in a laboratory setup. The concentration of the main substance in the crude product (without additional purification) was within 92–97 wt %, and it strongly depended on the purity of initial compound **II**, reaction time, and temperature. The average yield of 4-amino-3,4′-dinitrodiphenyl sulfide **I**, calculated on 4-nitrochlorobenzene (**III**), was 90.5%.

EXPERIMENTAL

The progress of reactions was monitored by thin-layer and high-performance liquid chromatography, as well as by chemical analysis. Some products were identified by IR and ^{13}C NMR spectroscopy. The IR spectra were recorded on a Jasco 810-IR spectrometer from samples dissolved in CCl_4 or dispersed in mineral oil. The ^{13}C NMR spectra were obtained on Bruker CXP-100 instrument (22.63 MHz), both with and without decoupling from protons; DMSO-d_6 was used as solvent, and HMDS, as internal reference. The signals were assigned by analysis of the chemical shifts, coupling constants, multiplicities, and intensity ratios.

Initial compound **II** and crude disulfide **I** were analyzed by HPLC using an Altex chromatograph; 25-cm × 4.6-mm stainless steel column was packed with Ultraspher-C_8 reversed phase; eluent acetonitrile–water (45 : 55) with addition of 5% of DMSO (relative to the overall amount of acetonitrile and water); UV detector, λ = 254 nm. The components were quantitated by the internal normalization technique with respect to peak area using correction coefficients.

Table 6. Stability of 4-amino-3,4′-dinitrodiphenyl sulfide (**I**) during its synthesis (temperature 100°C)

Component	Product composition, wt %		
	initial	after 4 h	after 10 h
Sulfide **I**	95.01	94.37	90.37
Thiocyanatoaniline **II**	0.37	0.34	0.31
2-Nitroaniline	0.25	0.27	0.24
4-Bromo-2-nitro-aniline	1.02	1.10	1.10
Nitrochlorobenzene **III**	2.09	1.94	1.15
Unidentified impurities X_1–X_3	1.26	1.98	8.93

Table 7. Composition of 4-amino-3,4′-dinitrodiphenyl sulfide (**I**) depending on the reaction time

Time, min	Composition, wt %		
	sulfide **I**	nitrochloro-benzene **III**	other impurities
30	92.24	1.55	6.21
40	93.89	1.03	5.08
60	94.75	0.38	4.97
225	93.62	0.32	6.06
240	93.15	0.35	6.50
295	92.17	0.35	7.48

2-Nitro-4-thiocyanatoaniline (**II**) was synthesized by the procedure reported [7]; reagent-grade 4-nitrochlorobenzene (**III**) contained 99.75 wt % of the main substance.

A laboratory setup consisted of a glass reactor equipped with a jacket, anchor stirrer, reflux condenser, thermometer, and dropping funnel. The reactor was charged with a specified amount of water which was heated to 65–70°C, and PEG-400, nitrochlorobenzene **III**, and thiocyanatoaniline **II** were added in succession under stirring. The mixture was heated under stirring to 75–80°C, and a required amount of 40–44% aqueous sodium hydroxide was added over a period of 25–30 min. The mixture was then heated to 95–100°C and was stirred at that temperature for a required time. During the synthesis, samples were withdrawn for analysis. If the reaction mixture contained an appreciable amount of chloronitrobenzene

III after 1.0–1.5 h, additional amounts of thiocyanato-aniline **II** and sodium hydroxide were added, and the process was continued; otherwise, the mixture was cooled to room temperature and filtered, and the precipitate was washed on a filter first with aqueous alkali and then with distilled water or steam condensate, dried, and analyzed.

The hydrolysis of compound **II** was studied as follows. Compound **II**, 0.1 mol, was added to 200 ml of a 2 M solution of carbonate-free alkali, and the mixture was heated for 1 h at 100°C under vigorous stirring (using a hydroacoustic setup). The mixture was cooled to room temperature, and the precipitate was filtered off, washed with water, dried, and analyzed by HPLC (product **A**, Table 1). The filtrate was combined with the washings and acidified with hydrochloric acid. The precipitate was filtered off, washed with water, dried, and analyzed (product **B**, Table 1).

The reaction of NaOH with acid **VII** and polymer **XI** to give water-soluble compounds was performed as follows. The reactor was charged with 120 ml of water, 16.8 g of NaOH, 2 ml of PEG-400, and a specified amount of compound **VII** or **XI** (Table 3). The mixture was kept for 5 h at 95–100°C, cooled to room temperature, and filtered through a glass filter. The precipitate was washed on a filter with water, dried at room temperature, weighed, and analyzed.

Acid **VII** was prepared as described in [8]. Polymer **XI** was synthesized by addition of bromine to a solution of excess potassium thiocyanate in acetic acid at room temperature. The precipitate was filtered off, washed with water, and dried at room temperature.

Thermal stability of sulfide **I** was studied by the following procedure. Two 4-g samples of sulfide **I** were placed in two 50-ml flasks equipped with reflux condenser, 2–3 drops of PEG-400 were added to each flask, 40 ml of distilled water was added to one of the flasks, and 40 ml of a 5% solution of NaOH was added to the other. The mixtures were heated to maintain them slightly boiling, kept for 15 h under these conditions, cooled to room temperature, and filtered. The precipitates were dried and analyzed by HPLC.

The time necessary for the synthesis of sulfide **I** to be complete (in a laboratory setup) was determined as follows. A 250-ml glass reactor was charged with 100 ml of distilled water, and 1–3 g of PEG-400, 0.4 mol of NaOH, 0.1 mol of chloronitrobenzene **III**, and 0.1 mol of thiocyanatoaniline were added under stirring. The mixture was quickly heated to 100°C, and samples were withdrawn for analysis.

The synthesis of sulfide **I** in a pilot setup was performed using a 400-l enameled reactor with a bottom discharge equipped with a jacket, anchor stirrer (65–135 rpm), and reflux condenser.

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