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Reaction of 2-Nitro-4-thiocyanatoaniline with 4-Nitrochlorobenzene

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Abstract—A method for preparing 4-amino-3,4'-dinitrodiphenyl sulfide is developed, based on the reaction of 2-nitro-4-thiocyanatoaniline with 4-nitrochlorobenzene in aqueous-alkaline medium in the presence of a phase-transfer catalyst (PEG 400 or Katamin AB).

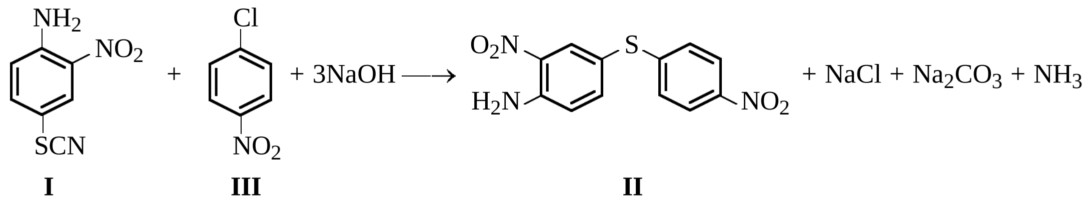
There have been information in the literature on the direct synthesis of alkyl aryl sulfides from aryl thiocyanates by addition of 25% aqueous sodium cyanide to a boiling mixture of methylene chloride, 2-nitro-4-thiocyanatoaniline (**I**), 1-propanol, propyl bromide, and tributyl(methyl)ammonium chloride and subsequent boiling of the reaction mixture for 4 h [1, 2] or by addition of alkyl halide to ethanolic solution of potassium hydroxide and thiocyanate **I** and subsequent keeping of the reaction mixture at a temperature of no higher than 20°C for 20 h [3, 4]. The synthesis of thioethers by reactions of thiocyanates with primary or secondary saturated or unsaturated alcohols at 0–250°C in the presence of stoichiometric amounts of hydroxides or alkali and alkaline-earth metal hydroxides or alkoxides, or tertiary amines has also been reported [5].

We earlier proposed a synthesis of 4-amino-3,4'-dinitrodiphenyl sulfide (**II**) by reaction of 4-nitrochlorobenzene (**III**) with sodium sulfide, acylation of the amino group in the resulting 4-amino-4'-nitrodiphenyl sulfide with acetic anhydride to form 4-acetylamino-4'-nitrodiphenyl sulfide, followed by nitration of the latter to 4-acetylamino-3,4'-dinitrodiphenyl sulfide, and, finally, removal of the acetyl protection in aqueous-alcoholic medium [6].

We suggested that sulfide **II** can better be produced by reaction of thiocyanate **I** with nitro compound **III**. This synthesis involves two steps instead of four [6]. Moreover, 2-nitroaniline and nitro compound **III** are commercial products, and the thiocyanation of 2-nitroaniline, providing thiocyanate **I**, has been studied in detail in [7].

It the present work we studied the reaction of thiocyanate **I** with nitro compound **III**, leading to sulfide **II**, in aqueous-alkaline medium at 95–100°C in the presence of a phase-transfer catalyst (PEG 400 or Katamin-AB).

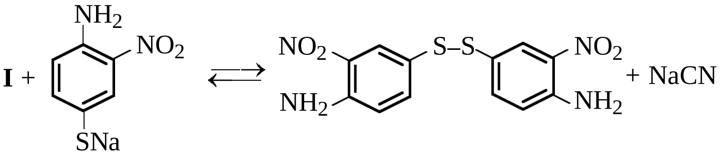
The reaction occurs in two stages. In the first stage, thiocyanate **I** reacts with sodium hydroxide to form sodium 4-amino-3-nitrothiophonolate (**IV**). The second stage involves the reaction of salt **IV** with nitro compound **III,** yielding sulfide **II**. In view of the fact that the sodium cyanide formed in the first stage further hydrolyzes to ammonia, the synthesis of sulfide **I** can be represented by scheme (1).



(1)

I **III** **II**

Along with the above reactions, many other reactions can occur, leading both to the target product and to a number of by-products. Thus, salt **IV** formed in the first stage reacts with a further thiocyanate **I** molecule to give bis(4-amino-3-nitrophenyl) sulfide (**V**) by scheme (2).



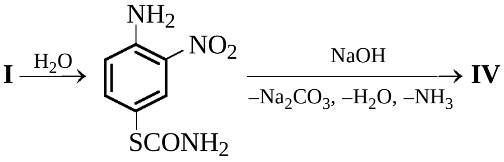
IV **V**

(2)

As a result, more thiocyanate **I** and sodium hydroxide are consumed and by-products are accumulated. However, the process is equilibrium. Under the action of sodium cyanide, disulfide **V** can convert to the starting compounds **I** and **IV**. Therefore, by adding to the reaction mixture considerable amounts of sodium cyanide one can suppress the undesirable reaction.

Disulfide **V** is readily formed by oxidative processes induced by atmospheric oxygen. For suppression of these processes, an inert atmosphere is required.

Finally, it must not be ruled out that part of salt **IV** necessary for the synthesis of sulfide **II** is formed by hydrolysis of thiocyanate **I** via thiocarbamate **VI** [scheme (3)].



VI

(3)

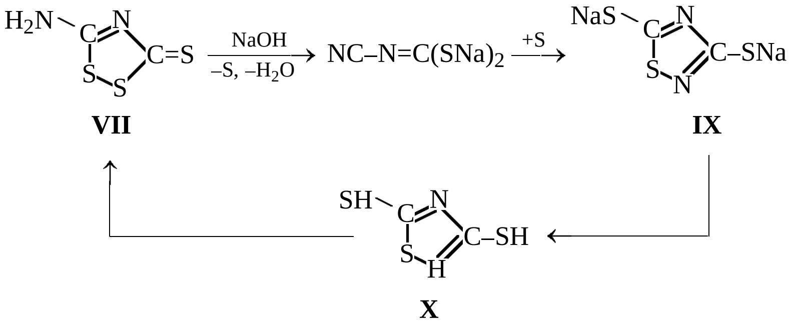
We attempted to gain a deeper insight into the scheme of the hydrolysis of thiocyanate **I**, yielding salt **IV**.

Analysis of the reaction mixtures showed that alkaline hydrolysis of 1 mol of thiocyanate **I** gives 13 mmol of sodium carbonate, 39 mmol of sodium cyanate, and 51 mmol of sodium cyanide, i.e. the amount of sodium cyanide is almost equal to the total amount of sodium cyanate and carbonate. We also isolated and analyzed insoluble organic products of hydrolysis of thiocyanate **I**. To this end, the reaction product undissolved in the aqueous-alkaline solution was filtered off, washed with water to neutral washings, dried, and analyzed on a liquid chromatograph (product **A**). The filtrate combined with the washings was made acidic with hydrochloric acid, the precipitate that formed was washed with water, dried, and analyzed (product **B**). It was found that if the contents of thiocyanate **I** and 2-nitroaniline in the starting compound and the hydrolysis products **A** and **B** are 98, 0.9, 1.6, 0.3, 0.7, and 1.6 wt%, respectively, then their disulfide **V** contents are 0.96 and 78 wt%, respectively. Taking into account that, as sodium cyanide is accumulated, disulfide **V** begins to be consumed by scheme (2), we can state with assurance that salt **IV** is mostly formed via disulfide **V**. The total contents of unidentified admixtures (7 components) in the starting compound **I** and the hydrolysis products **A** and **B** are 0.5, 1.5, and 19 wt%, respectively.

The above data show that the hydrolysis of thiocyanate **I** is an intricate process involving a great number of different compounds. Many of them are unstable and thus difficult to identify.

Still more complex mixtures are formed in the presence of nitro compound **III** required for the synthesis of the target product **II**. By analysis of the precipitates dropping from the mother liquor after its acidification with hydrochloric acid in the synthesis of sulfide **II** in laboratory conditions (precipitate **D**) or in a pilot device (precipitate **E**) we found up to 13 unidentified compounds with total contents in precipitates **D** and **E** of 26 and 38 wt%, respectively. The contents of sufide **II** and disulfide **V** in these precipitates are 0.5, 74, 22, and 39 wt%. Precipitates **D** and **E** are close to each other in composition. The most abundant are 3–4 components, while the contents of the others are low. Part of them is introduced with the starting materials, but the most part is formed by side processes.

Knowing that most by-products found in the precipitates are poorly soluble in water at pH ~7 and fairly readily soluble in aqueous-alkaline solutions, in the synthesis of sulfide **II** one should wash the precipitate first with aqueous-alkaline solution and only then with condensate or distilled water. This allows the amount of admixtures in the reaction product to be reduced considerably. Thus, isoperthiocyanic acid (**VII**) which is present in the starting thiocyanate **I** decomposes in aqueous sodium hydroxide into sulfur and a readily water-soluble disodium salt **VIII**. The latter reacts with the sulfur precipitated to form a water-soluble disodium perthiocyanate (**IX**) which is stable in alkaline media. On acidification, an unstable, water-soluble perthiocyanic acid (**X**) precipitates and



(4)

quickly converts to an insoluble acid **VII** [8, 9] [scheme (4)].

When directly treated with hydrochloric acid, disodium salt **VIII** polymerizes and precipitates as a yellow polymer **XI** which could not be identified. Treatment of the latter with aqueous sodium hydroxide gives the starting disodium salt **VIII** [scheme (5)].

$$\begin{tikzcd}
 & {[H_2S_2C_2N_2]} \arrow[dr] & \\
\underset{\textbf{VIII}}{NC\text{–}N{=}C(SNa)_2} \arrow[ur, "HCl", "-2NaCl"'] & & \underset{\textbf{XI}}{(H_2S_2C_2N_2)_x} \arrow[ll, "2NaOH", "-2H_2O"']
\end{tikzcd} \qquad (5)$$

Some other admixtures in the starting commercial thiocyanate **I** produced by thiocyanation of 2-nitroaniline [7] behave similarly. Thus, the above procedure make possible these admixtures to be removed in the course of the synthesis of sulfide **II** as water-soluble compounds by treatment of the filtered precipitate of crude product **II** with aqueous alkali. The admixtures can be isolated from the filtrate and washings by acidification followed by filtration.

We studied the ability of sodium hydroxide to convert acid **VII** and polymer **XI** into water-soluble compounds in a special series of experiments. When heated in aqueous-alkaline medium in the presence of PEG-400 at 95°C for 5 h, the precipitates of acid **VII** or polymer **XI** dissolve completely, and their subsequent transformations involve no precipitate formation.

Heating of acid **VII** or polymer **XI** in the presence of nitro compound **III** gives rise to compounds insoluble in aqueous-alkaline media. The rates of these two reactions appear to be much lower than the rate of reaction of compound **III** with thiocyanate **I**. Thus, after 5-h heating of nitro compound **III** with acid **VII** we found in the reaction mixture 60% of unreacred nitro derivative **III**. Therewith, ~22% of the latter had been consumed for formation of compounds insoluble in aqueous-alkaline medium, and the rest, for formation of soluble compounds and losses. The reaction of thiocyanate **I** with nitro compound **III** under the same conditions, as will be shown below, is complete within 40–60 min.

With products of decomposition of polymer **XI** in aqueous-alkaline media, nitro compound **III** reacts slightly faster. Thus, after the same period of time, as little as 7% of nitro compound **III** was found in the precipitate, while 63% of it had been consumed for formation of insoluble compounds and ~30%, for formation of soluble compounds and losses.

By ^{13}C NMR spectroscopy and HPLC we found in the isolated precipitates 4,4'-dinitrodiphenyl disulfide and 4-amino-4'-nitrodiphenyl sulfide (20, 53, 2, and 22 wt%, respectively). The contents of nitro compound **III** in these precipitates were 76 and 10 wt%, respectively. Moreover, the precipitates contained by 4 unidentified compounds. 4,4'-Dinitrodiphenyl sulfide probably results from reactions of nitro compound **III** with sulfides formed in the solution and then partially reduced by the sulfides to 4-amino-4'-nitrodiphenyl sulfide.

When an individual thiocyanate **I** is used as the starting material in the synthesis of sulfide **II**, the crude product contains 99.5 wt% of compound **II** and 0.5 wt% of admixtures. When the starting material contains 95 wt% of thiocyanate **I** and 5 wt% of the acid **VII** and polymer **XI** admixtures insoluble in aqueous-organic media, the crude product contains 97% of sulfide **II**. With thiocyanate **I** containing a total 28% of acid **VII** and polymer **XI**, the crude product contains 92% of sulfide **II**.

Our results show that the content of admixtures in the resulting sulfide **II** may also increase in the course of the synthesis, since the product is rather unstable thermally. When this sample is heated at 100°C for 15 h in water or in a 5% aqueous solution of sodium hydroxide, the content of sulfide **II** in it decreases from 97 to 95 and 87%, respectively, and 3–4 new admixtures appear.

The stability of sulfide **II** under the synthesis conditions was studied in special experiments. To this end, after the synthesis of compound **II** had been complete, and the reaction mixture had been brought up to the required state, the reactor content was stirred at 100°C, and its samples were periodically taken. The samples were washed by the conventional procedure to remove water-soluble admixtures and then analyzed. The time of the first sampling was taken as the reference point. In this case, too, the content of the main substance decreases with time. Thus, after 4 h the content of sulfide **II** in the sample decreases from 95 to 94 and after 10 h, to 90 wt%.

The time of the synthesis of sulfide **II** (40–60 min) was determined in laboratory conditions. A longer reaction time has no effect on the content of the main substance in the product (95%), while after 5 h the content of admixtures in it increases from 5 do 7 wt%. The data obtained on a laboratory scale were then confirmed by experiments on a pilot device.

We also studied the effect of the temperature (80–100°C) on the quality of the resulting product. It was found that as the temperature is decreased from 100 to 80°C, the content of nitro compound **III** in the product increases to 4–7 wt%.

Based on the above results, we produced sulfide **II** on a pilot device in a 400-l reactor. The results obtained on a larger scale proved to be nicely consistent with those obtained on a laboratory scale. The content of the main substance in the crude product varied within 92–97 wt% and was strongly dependent on the quality of the starting thiocyanate **I** and the synthesis time and temperature. The average yield of sulfide **II** with respect to nitro compound **III** was 90%.

EXPERIMENTAL

Laboratory experiments were performed using a glass jacketed reactor equipped with an anchor stirrer, a reflux condenser, a thermometer, and a dropping funnel. In the synthesis of sulfide **II**, the reactor was charged with water and heated to 65–70°C, after which PEG 400, nitro compound **III**, and thiocyanate **I** were added in succession with stirring. The mixture was heated with stirring to 75–80°C, and 40–44% alkali was gradually added over the course of 25–30 min. The reaction mixture was then heated to 95–100°C and stirred at that temperature for the required time. Samples were periodically taken in the course of the synthesis. If the reaction mixture after 1–1.5 h contained appreciable amounts of nitro compound **III**, additional portions of thiocyanate **I** and sodium hydroxide were added, and the process was continued. If only traces of nitro compound **III** were found, the reaction mixture was cooled to room temperature, filtered, the precipitate on the filter was thoroughly washed first with aqueous-alkaline solution and then with water or condensate, dried, and analyzed.

When studying hydrolysis of thiocyanate **I**, to 200 ml of CO_2-free alkali (*c* 2 M) we added 0.1 mol of thiocyanate **I**, and the mixture was heated to 100°C and stirred for 1 h at that temperature.

When studying the ability of sodium hydroxide to convert acid **VII** and polymer **XI** to water-soluble compounds, the reactor was charged with 120 ml of water, 16.8 g of sodium hydroxide, 2 ml of PEG-400, and 22 g of acid **VII** or polymer **XI**. The mixture was heated for 5 h at 95–100°C, cooled to room temperature, and filtered through a glass frit. The precipitate on the filter was dried at room temperature, weighed, and analyzed.

Acid **VII** was prepared by the procedure described in [8]. Polymer **XI** was prepared by adding bromine dropwise at room temperature to an excess of a solution of potassium thiocyanate in acetic acid. Polymer **XI** that precipitated was filtered off, washed with water, and dried at room temperature.

When studying the thermal stability of sulfide **II**, we took two 4-g samples of the latter and added to them by 2–3 drops of PEG 400. The first sample was then treated with 40 ml of distilled water and the second, with 40 ml of 5% aqueous sodium hydroxide. Both samples were then heated for 15 h under reflux, cooled, and analyzed by HPLC.

The time of the synthesis of sulfide **II** was determined in laboratory conditions. To this end, a 250-ml glass reactor was charged with 100 ml of distilled water and then 1–3 g of PEG-400, 0.4 mol of sodium hydroxide, 0.1 mol of thiocyanate **I**, and 0.1 mol of nitro compound **III** were added with stirring. The reaction mixture was quickly heated to 100°C, and sampling was initiated.

The reaction progress was followed by TLC, HPLC, and chemical analysis.

Certain samples were analyzed by ^{13}C NMR and IR spectroscopy, and gas chromatography–mass spectrometry. Analysis of the starting thiocyanate **I** and crude sulfide **II** was performed by HPLC on an Altex chromatograph (UV detector, λ_{max} 254 nm) on an Ul'trasfer–oktil column in the system acetonitrile–water (45:55, by volume) plus 5 % of dimethyl sulfoxide. The chromatograms were treated by the internal calibration technique.

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