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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis of 4-Amino-4'-nitrodiphenyl Sulfide

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Abstract—The possibility of preparing 4-amino-4'-nitrodiphenyl sulfide by reaction of chlorobenzene with sodium sulfide in a two-phase system composed of water and organic solvent in the presence of a phase-transfer catalyst under continuous hydroacoustic treatment was examined.

4-Amino-4'-nitrodiphenyl sulfide **I** is an intermediate in production of 3,4,4'-triaminodiphenyl sulfide, the synthetic precursor of antihelminth agents of the 5(6)-(4'-aminophenylthio)-2-aminobenzimidazole series [1].

Thioethers (sulfides) are prepared by condensation of alkyl halides or nitro-substituted aryl halides with sodium sulfide [2–4].

Synthesis of thioethers by reaction of thiocyanates with alcohols under heating in the presence of stoichiometric amounts of alkali or alkaline-earth metal hydroxides or alcoholates or those of tertiary amines is described in a patent [5].

Dialkyl sulfides can also be prepared by reaction of alkyl chlorides with an aqueous or aqueous-alcoholic solution of alkali metal sulfide in an autoclave at high pressure [6]; diaryl sulfides are synthesized by reaction of appropriate nitrochlorobenzenes in dimethylformamide (DMF) with an aqueous solution of sodium sulfide in the presence of finely divided sulfur [7] or in refluxing alcohol with fine powder of a preliminarily fused mixture of sodium sulfide and sulfur [8].

There are numerous procedures for reducing nitro compounds to the corresponding amines [9]; in some cases, it is possible to selectively reduce one of the nitro groups of polynitro compounds with a calculated amount of sodium (or ammnonium) sulfide (or hydrosulfide) [9].

A procedure has been developed for preparing 4,4'-diaminodiphenyl sulfide **I** by reaction of 4-nitrochlorobenzene **II** with sodium sulfide in DMF, followed by reduction of the resulting 4,4'-dinitrodiphenyl sulfide with iron powder in aqueous alcohol in the presence of ammonium chloride under heating [10].

Hodson and Wilson [11] prepared diphenyl sulfide **I** as follows. A solution of **II** in absolute ethanol is heated almost to reflux, and an aqueous solution of sodium sulfide is added in small portions. The resulting mixture is refluxed with stirring for 10 h. Yield of **I** is about 20% (mp 138–142°C).

According to Radulova and Tapalova's procedure [12], a mixture of **II** with water and sodium sulfide is heated, an additional portion of **II** is added, and, after prolonged heating, toluene is added; the yield of **I** is about 68% (mp 143–144°C).

Zasosov and Gal'chenko prepared sulfide **I** by adding a portion of **II** to a boiling aqueous solution of sodium sulfide. After stirring for a certain time, the next portion of **II** is added, and the mixture is refluxed with stirring. Then an additional small amount of aqueous sodium sulfide solution is introduced, and the mixture is refluxed with stirring. The resulting mixture is steam-distilled to remove unchanged **II**; yield of **I** 77–80% (mp 145–147°C, from toluene).

Raiziss *et al.* [14] refluxed a mixture of Na_2S, water, and a part of the required amount of **II**, after which they added the remaining part of **II**, with the refluxing continued. The resulting mixture was steam-distilled; yield of **I** 80% (mp 141–413°C, from ethanol).

Aminonitrodiphenyl sulfides can also be prepared by reaction of alkaline solutions of substituted aminothiophenols with alcoholic solutions of halonitrobensenes [15–20].

All the above procedures for preparing sulfides **I** are time- and labor-consuming; the yield and quality of the target product are poor. The procedures involve

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Table 1. Variation with time of the concentrations of *p*-nitrochlorobenzene **II**, c_{II}, and *p*-chloroaniline **V**, c_V, in the organic phase in the course of synthesis of **I**

Sampling time (from the reaction start) τ, h	c_{II}	c_V
	M	
0	3.16	–
0.5*	2.10	0.10
1.0	1.66	0.12
1.5**	1.56	0.11
2.0	1.50	0.12
2.5	1.50	0.11
3.0	1.46	0.12
3.5	1.06	0.12
4.0	0.67	0.12
5.0	0.42	0.12
6.0	0.23	0.12
7.0	0.08	0.12
8.0	0.01	0.12

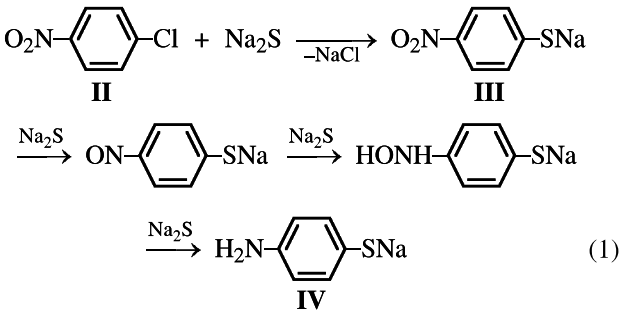
* Completion of loading Na_2S.

** Addition of PEG-400.

numerous auxiliary operations or require difficultly available chemicals. Therefore, none of these procedures has been introduced on the commercial or semicommercial scale.

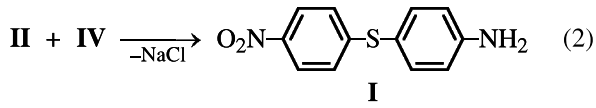
In this study, we developed an improved procedure for preparing sulfide **I**, based on the reaction of nitrochlorobenzene **II** with sodium sulfide in a two-phase system constituted by water and organic solvent (chlorobenzene, toluene, chloroform, etc.) under heating in the presence of a phase-transfer catalyst (PTC: quaternary alkylammonium salts, polyethylene glycol PEG-400, etc.), with simultaneous hydroacoustic treatment of the reaction mixture.

Reaction of **II** with sodium sulfide involves a number of steps: formation of sodium 4-nitrothiophenolate **III** and its successive reduction with sodium sulfide to the nitroso, hydroxylamino, and finally, amino derivatives. Sodium 4-aminothiophenolate **IV** mainly accumulates in the aqueous phase.



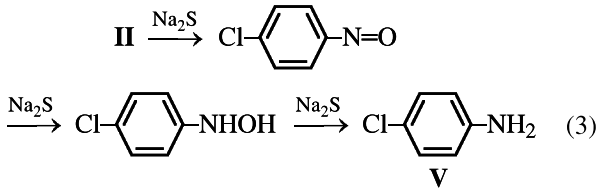
(1)

Sulfide **I** is formed by the reaction of **IV** with the remaining part of **II**:



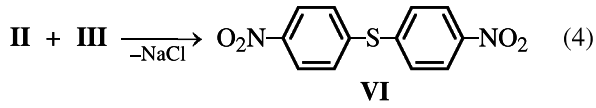
(2)

An impurity of *p*-chloroaniline **V** is formed by reduction of the nitro group via a series of intermediates:



(3)

An impurity of 4,4'-dinitrodiphenyl sulfide **VI** is formed by the reaction of **III** with **II**:



(4)

Thiophenolate **III** and products of its sequential reduction to **IV** are water-soluble and, when formed, pass to the aqueous phase. The compounds mainly occurring in the organic phase are sulfide **I**, chloronitrobenzene **II**, chloroaniline **V**, and also dinitrodiphenyl sulfide **VI** formed in small amounts.

The optimal parameters of sulfide **I** preparation (temperature, reaction time before adding phase-transfer catalyst, water : organic solvent and **II** : Na_2S ratios) are those at which, before adding the phase-transfer catalyst, the amount of **V** is the smallest, compound **VI** is virtually absent, approximately half of **II** is converted to salt **IV** and passes to the aqueous phase, and the other half remains in the organic phase (Table 1).

When a phase-transfer catalyst (PEG-400 etc.) is added at this instant of time to the reaction mixture and the mixture is subjected to intense hydroacoustic treat ment, the transfer of salt **IV** from the aqueous to organic phase and its reaction with chloronitrobenzene **II** in the organic phase to form sulfide **I**, also dissolving in the organic phase, are sharply accelerated. In most cases, in synthesis of **I**, chlorobenzene (Table 2) or toluene (Table 3) is used as organic solvent.

The advantage of chlorobenzene is that, in contrast to toluene, this solvent (and solution of **I** in it) can be subsequently used for preparing 4-amino-3,4'-dinitrodiphenyl sulfide. Furthermore, as follows from

Table 2. Synthesis of sulfide **I** in chlorobenzene under various conditions and at various reactant ratios (phase-transfer catalyst PEG-400,* reaction time before adding PEG-400 1 h**)

II : Na_2S molar ratio	Water–chlorobenzene volume ratio	**II** : chlorobenzene weight ratio	Amount of PEG-400 relative to **II**, %	*T*, °C	τ (h) after adding PEG-400	Yield of crude product, %	Content of **I** in crude product, wt %
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	3.125	98	6	93	91
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	3.125	95	7	93	90
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	3.125	104	6	93	94
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	3.125	90	7	70	72
1.00 : 1.74	Water	1.00 : 0.00	3.125	100	7	76	85
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	No	102	8	52	74
1.00 : 1.74[a]	2.50 : 1.00	1.00 : 0.56	3.125	98	6	75	86
1.00 : 1.74[b]	2.50 : 1.00	1.00 : 0.56	3.125	98	6	90	91
1.00 : 1.74[c]	2.50 : 1.00	1.00 : 0.56	2.50	102	6	92	93
1.00 : 1.74[d]	2.50 : 1.00	1.00 : 0.56	3.125	100	6	90	91
1.00 : 1.74	2.00 : 1.00	1.00 : 0.69	3.125	98	6	91	95
1.00 : 1.74	3.00 : 1.00	1.00 : 0.46	3.125	100	6	93	93
1.00 : 1.74	6.00 : 1.00	1.00 : 0.23	3.125	100	6	79	94
1.00 : 1.74	1.50 : 1.00	1.00 : 0.93	3.125	100	6	92	93
1.00 : 1.74	1.00 : 1.00	1.00 : 1.38	3.125	100	6	81	93
1.00 : 1.74	2.50 : 1.00	1.00 : 0.48	3.125	102	6	93	93
1.00 : 1.74	2.50 : 1.00	1.00 : 0.69	3.125	100	6	92	93
1.00 : 1.74	2.50 : 1.00	1.00 : 1.01	3.125	102	6	91	93
1.00 : 1.74	2.50 : 1.00	1.00 : 1.37	3.125	102	6	77	91
1.00 : 1.74	2.50 : 1.00	1.00 : 0.29	3.125	100	6	71	94
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	2.500	102	6	92	93
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	2.000	100	6	92	93
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	1.000	100	7	92	92
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	0.520	100	6	78	88
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	4.000	100	6	93	92
1.00 : 1.74	2.50 : 1.00	1.00 : 0.56	5.200	100	6	95	68
1.00 : 1.74	2.79 : 1.00	1.00 : 0.50	2.600	102	6	93	93
1.00 : 1.74[e]	2.79 : 1.00	1.00 : 0.50	2.600	102	6	82	85
1.00 : 1.74[f]	2.79 : 1.00	1.00 : 0.50	2.600	102	7	94	71
1.00 : 1.74	2.79 : 1.00	1.00 : 0.50	2.600	102	5	87	78
1.00 : 1.40	2.79 : 1.00	1.00 : 0.50	2.600	102	6	92	93
1.00 : 1.03	2.79 : 1.00	1.00 : 0.50	2.600	102	6	81	78
1.00 : 2.00	2.79 : 1.00	1.00 : 0.50	2.600	102	6	92	93
1.00 : 2.50	2.79 : 1.00	1.00 : 0.50	2.600	102	6	84	85
1.00 : 1.74	2.79 : 1.00	1.00 : 0.50	2.600	102	8	93	93
1.00 : 1.74	2.79 : 1.00	1.00 : 0.50	2.600	102	9	92	93

* Specific features of particular experiments: [a] a mixture of water, chlorobenzene, and sodium sulfide was charged, after which compound **II** was added; [b] Katamin AB used instead of PEG-400; [c] Tetraethylammonium iodide used instead of PEG-400; [d] toluene used instead of chlorobenzene.

** Unless otherwise indicated ([e], 2 h; [f], 0.67 h).

Table 3. Synthesis of sulfide **I** in toluene (molar ratio **II** : Na_2S = 1.0 : 1.7, volume ratio water : toluene = 2.5 : 1.0, weight ratio **II** : toluene = 1.17 : 1.00, phase-transfer catalyst PEG-400)

Amount of PEG-400 relative to **II**, %	Reaction time after completion of adding Na_2S, h		Yield of crude product, %	Content of **I** in crude product, wt %
	before adding PEG-400	after adding PEG-400		
3.00	1.00	6	91	90
3.12	1.00	6	90	91
2.15	1.00	7	89	90
1.50	1.50	7	90	90
4.00	1.50	6	89	90
3.12	1.5	6	89	90
3.12	1.0	7	90	90

Tables 2 and 3, chlorobenzene, compared to toluene, ensures higher yield and quality of **I**.

Laboratory experiments on development of a procedure for preparing **I** (Table 2) show that the best synthesis conditions are as follows. Temperature schedule: 80–85°C in the stage of adding Na_2S, keeping for 0.5 h at 80–85°C after adding the whole amount of Na_2S; heating to 96–102°C for 0.5–1.0 h before adding phase-transfer catalyst (PEG-400); addition of PEG-400 and subsequent reaction at 96–102°C. Ratios: water : chlorobenzene (by volume) 2.5 : 1.0, chlorobenzene : **II** (by weight) 1.00 : 1.17, **II** : Na_2S (molar) 1.0 : 1.7, and **II** : PEG-400 (by weight) 1.000 : (0.014–0.017). Under these optimal conditions, sulfide **I** is prepared relatively simply in a yield of no less than 92%, with the main substance content of no less than 93 wt %. The process was developed on a semicommercial scale (160-l reactor with immersed device for hydroacoustic treatment [21]).

EXPERIMENTAL

The reaction mixtures and crude products in the stage of preparation of **I** were analyzed qualitatively by TLC and quantitatively by HPLC, and identified by IR and ^{13}C NMR spectroscopy.

The IR spectra were recorded with a Jasco 810-IR spectrometer in the 4000–400 cm^{-1} range using CCl_4 solutions or mulls in mineral oil. The ^{13}C NMR spectra were measured on a Bruker CXP-100 spectrometer at a working frequency of 22.63 MHz under conditions of total proton decoupling or without it; solvent DMSO, internal reference HMDS. The signal assignment was based on the chemical shifts, coupling constants, multiplicities, and relative intensities; data for related model compounds and results of calculation of magnetic shielding in an aromatic ring were also taken into account.

The TLC analysis was performed on Silufol plates; the development involved reduction with an $SnCl_2$ solution, diazotization of the resulting anilines, and azo coupling with 1-naphthol; eluent C_6H_6 : C_2H_5OH, 10 : 1 by volume.

Quantitative HPLC analysis was performed with an Altex model 330 liquid isocratic chromatograph equipped with a model 110 pump, a model 153 detector, model 210 20-μl loop dosing units, and 30-, 50-, and 100-μl SNR Hamilton microsyringes. Separation and analysis of a mixture of nitrobenzene **II**, sulfide **I**, dinitro sulfide **VI**, and chloroaniline **V** were performed on a stainless steel column (25 cm × 4.6 mm i.d.) packed with Ultraspher ODS phase (grain size 5 μm). The products were analyzed and identified using water–acetonitrile (20 : 80 to 30 : 70 by volume) eluent and diphenyl as internal reference.

A glass reactor equipped with a reflux condenser was charged with the required amounts of water and organic solvent (chlorobenzene, toluene, chloroform, etc.), after which crystalline chloronitrobenzene **II** was added. The mixture was vigorously stirred with a hydroacoustic device mounted on the reactor lid and heated to 65–70°C; in so doing, chloronitrobenzene **II** gradually dissolved in the organic phase. Then crystalline $Na_2S \cdot 9H_2O$ (or its aqueous solution prepared in advance) was added in small portions so as to keep the reaction temperature within 80–85°C. When solid sodium sulfide was added, the temperature first noticeably decreased owing to endothermic dissolution of Na_2S and then sharply increased owing to fast exothermic reaction (with the Na_2S solution prepared in advance, the temperature variations are weaker). Therefore, Na_2S should be added carefully, since overheating of the reaction mixture (above 80–85°C) causes side reactions.

After adding the whole amount of Na_2S, the mixture was vigorously stirred at 80–85°C with a built-in device for hydroacoustic treatment for an additional 30 min, after which it was heated to 96–102°C and stirred at this temperature for 0.5–1 h. Then, a phase-transfer catalyst (PEG-400 or quaternary alkylammonium salt) was added in the amount of 1–4% relative to the charged chloronitrobenzene **II**, and the mixture was vigorously stirred at 96–102°C with the hydroacoustic treatment for 6–7 h.

After reaction completion and phase separation, the lower aqueous salt solution was separated and discarded, and the organic layer was washed with hot water with vigorous stirring to remove the inorganic salts and organic intermediates more completely. After phase separation, the lower organic layer (a solution of crude sulfide in chlorobenzene, toluene, or chloroform) was poured into a crystallizer and cooled to 0°C. The precipitated crystals of **I** were filtered off, washed with water, and dried at 60–70°C.

CONCLUSION

The reaction of 4-nitrochlorobenzene with sodium sulfide in a two-phase system constituted by water and organic solvent (chlorobenzene, toluene, chloroform, etc.) in the presence of a phase-transfer catalyst (PEG-400, quaternary alkylammonium salts, etc.) added after a definite period of time, under vigorous hydroacoustic treatment and at temperature maintained

in the ranges 80–85 (addition of Na_2S, before adding phase-transfer catalyst) and 96–102°C (phase-transfer step), gives 4-amino-4'-dinitrodiphenyl sulfide in a yield of no less than 92%, with the main substance content of no less than 93%.

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REFERENCES

1. USSR Inventor's Certificate, no. 1246563.
2. Neniţescu, C.D., *Chemie Organica*, Bucharest: Tehnica, 1960, vol. 1.
3. Nesmeyanov, A.N. and Nesmeyanov, N.A., *Nachala organicheskoi khimii* (Fundamentals of Organic Chemistry), Moscow: Khimiya, 1969, book 1.
4. UK Patent 1498410.
5. FRG Patent 1193047.
6. Polish Patent 56199.
7. USSR Inventor's Certificate, no. 230133.
8. Krulikovskaya, E.A., Kirilova, V.G., and Bykova, L.B., *Tr. Tomsk. Univ.*, 1968, vol. 192, pp. 13–19.
9. Fieser, L.F. and Fieser, M., *Advanced Organic Chemistry*, New York: Reinhold, 1962.
10. USSR Inventor's Certificate, no. 491624.
11. Hodson, H.H. and Wilson, J., *J. Chem. Soc.*, 1912, vol. 101, no. 9, pp. 1693–1696.
12. Radulova, S. and Tapalova, E., *Vet. Mid. Nauki* (Sofia), 1965, vol. 2, no. 9, pp. 873–877.
13. Zasosov, V.A. and Gal'chenko, M.I., *Zh. Prikl. Khim.*, 1946, vol. 19, nos. 5–6, pp. 580–584.
14. Raiziss, G.W., Clemence, L.W., Sevarac, M., and Maetsch, J.C., *J. Am. Chem. Soc.*, 1939, vol. 61, no. 12, pp. 2763–2768.
15. Gupta Satya Prokash and Gara Devendra Mohan Lal, *Indian J. Appl. Chem.*, 1966, vol. 29, nos. 2–3, pp. 51–56.
16. Sharma, H.L., Sharma, V.N., and Mital, A.L., *Aust. J. Chem.*, 1968, vol. 21, no. 21, pp. 3081–3084.
17. Sharma, H.L., Sharma, V.N., and Mital, A.L., *Tetrahedron Lett.*, 1967, no. 17, pp. 1657–1662.
18. Davis, F.A. and Wetzel, R.B., *Tetrahedron Lett.*, 1969, no. 51, pp. 4483–4487.
19. Sevbo, D.P. and Ginzburg, O.F., *Zh. Org. Khim.*, 1970, vol. 6, no. 2, pp. 345–348.
20. Jain, S.M., Chandra, D., and Mital, R.L., *Indian J. Chem.*, 1971, vol. 9, no. 11, pp. 1236–1241.
21. USSR Inventor's Certificate, no. 1477458.