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Synthesis of 5(6)-(4-Aminophenythio)-2-aminobenzimidazole Derivatives: III. Preparation Procedure for 3,4,4'-Triaminodiphenyl Sulfide

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Abstract—A procedure for preparation of 3,4,4'-triaminodiphenyl sulfide by reduction of 4-amino-3,4'-dinitrodiphenyl sulfide with hydrazine hydrate in butanol catalyzed by a mixture of iron(III) chloride and activated carbon was developed providing the product in no less than 80% yield with the main compound content no less than 93%.

The reduction of nitro compounds is known [1, 2] to be effected by different means: with sulfides, with tin in hydrochloric acid or by solution of tin(II) chloride in the concn. hydrochloric acid, with iron powder in water in the presence of hydrochloric or acetic acid, with zinc powder in alkali, and with hydrazine in the presence of palladium on carbon.

Frequently the reduction of nitro-substituted diaryl sufides into the corresponding amines is performed by catalytic hydrogenation on Raney nickel, platinum, palladium etc. under pressure [3–7].

We formerly developed procedures of synthesis of 3,4,4'-triaminodiphenyl sulfide, a semiproduct in production of a number of helminthicidic preparations [8], by electrochemical reduction of 4-amino-3,4'-dinitrodiphenyl sulfide. Our attempts to perform the reduction with sodium sulfide under various conditions failed for only one nitro group was then reduced.

In the present study we investigated reduction of 4-amino-3,4'-dinitrodiphenyl sulfide (**I**) to 3,4,4'-tri-aminodiphenyl sulfide (**II**) using 64–67% hydrazine hydrate. As reduction catalysts iron(III) chloride and activated carbon were applied. The reduction was carried out in a mixture of ethylene glycol and 1,4-dioxane or in butanol at 95–105°C within 12–14 h.

The results of dinitrodiphenyl sulfide **I** reduction with hydrazine hydrate at 100–102°C in the mixture of ethylene glycol and 1,4-dioxane in the presence of iron(III) chloride and activated carbon are presented in Table 1.

In the study of dinitrodiphenyl sulfide **I** reduction we adjusted the molar ratio of reagents (Table 2) required for complete reduction, and also the time of optimal addition of hydrazine hydrate and duration of the process.

As seen from Table 2, the performance of reduction providing amine **II** of good quality should occur at molar ratio dinitrophenyl sulfide **I** : hydrazine equal to 1 : (10–13), time of hydrazine hydrate addition should be about 8 h, and the reaction should be carried on for 6 h after the end of hydrazine hydrate addition.

At lower amount of hydrazine hydrate or shorter duration of the process the accumulated intermediate reduction products have not enough time to transform completely into the final product. The variation of reduction products composition as a function of the reaction time is given in Table 3.

We carried out 10 runs of dinitrodiphenyl sulfide **I** reduction on a pilot installation in a reactor of 100 l capacity in the mixture of ethylene glycol and 1,4
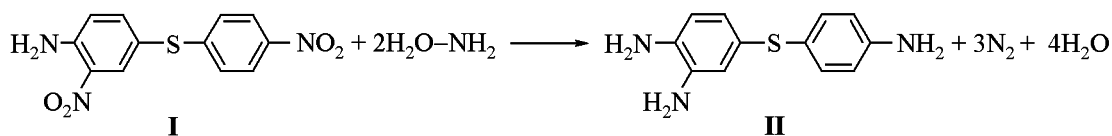

$$H_2N-\text{⟨⟩}-S-\text{⟨⟩}-NO_2 + 2H_2O{-}NH_2 \longrightarrow H_2N-\text{⟨⟩}-S-\text{⟨⟩}-NH_2 + 3N_2 + 4H_2O$$

I   **II**

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Table 1. Results of dinitrodiphenyl sulfide **I** reduction in a mixture ethylene glycol–1,4-dioxane (volume ratio 1 : 4) in the presence of iron(III) chloride and activated carbon at 100–102°C

Molar ratio (**I**) : hydrazine	Ratio of weight parts (**I**) : ethylene glycol	Ratio of weight parts (**I**) : FeCl$_3$: activated carbon	Yield of crude triamine **II**, wt%	Triamine **II** content in the crude product, wt%
1.00 : 2.08	1.00 : 2.77	50.4 : 1.0 : 6.25	52.0	53.7
1.00 : 2.98	1.00 : 2.77	50.4 : 1.0 : 6.25	54.9	65.5
1.00 : 3.12	1.00 : 2.77	50.4 : 1.0 : 6.25	57.4	69.5
1.00 : 3.34	1.00 : 2.77	50.4 : 1.0 : 6.25	67.9	72.4
1.00 : 3.65	1.00 : 2.77	50.4 : 1.0 : 6.25	66.0	73.7
1.00 : 4.86	1.00 : 1.17	100.0 : 1.0 : 10.5	55.8	68.3
1.00 : 4.86	1.00 : 1.17	100.0 : 1.0 : 10.5	55.7	68.1
1.00 : 4.86	1.00 : 1.21	100.0 : 1.0 : 12.7	52.1	69.5
1.00 : 4.86	1.00 : 1.21	100.0 : 1.0 : 12.7	51.7	69.2
1.00 : 6.09	1.00 : 2.80	49.9 : 1.0 : 6.25	47.0	78.4
1.00 : 6.44	1.00 : 1.20	93.1 : 1.0 : 12.7	45.0	79.3
1.00 : 6.44	1.00 : 1.20	93.1 : 1.0 : 12.7	44.9	79.0
1.00 : 7.24	1.00 : 1.20	93.1 : 1.0 : 12.7	44.7	87.1
1.00 : 8.05	1.00 : 1.20	93.1 : 1.0 : 12.7	43.9	89.6
1.00 : 9.30	1.00 : 2.77	50.4 : 1.0 : 6.25	76.0	90.1
1.00 : 11.0	1.00 : 2.77	50.4 : 1.0 : 6.25	79.7	93.7
1.00 : 13.0	1.00 : 2.77	50.4 : 1.0 : 6.25	82.0	94.6

Table 2. Dependence of the produced triamine **II** quality on reaction time and molar ratio hydrazine : dinitrodiphenyl sulfide **I** (temperature 100–102°C, catalyst activated carbon and iron(III) chloride)

Molar ratio hydrazine : (**I**)	Time of hydrazine addition, h	Time of keeping, h	Content in the crude product, wt%	
			triamine **II**	disulfide **I**
5.5	4	9	59.08	3.73
7.4	4	9	77.85	3.14
9.3	4	9	90.12	3.16
11.0	4	9	93.60	0.60
13.0	4	9	94.10	0.40
15.0	4	9	94.20	0.38
11.0	4	4	78.44	2.60
11.0	4	4	76.75	2.68
11.0	4	5	88.61	2.38
11.0	4	6	89.67	1.57
11.0	4	8	90.30	1.23
11.0[a]	4	4	88.94	0.88
11.0	5	6	90.92	0.68
11.0	6	6	92.10	0.36
11.0	6	8	92.70	0.28
11.0	8	2	90.54	0.47
11.0	8	3	91.87	0.27
11.0	8	5	93.09	–
11.0	8	6	94.73	–
11.0	8	8	94.80	–
11.0	8	13	95.49	–
9.0	8	8	91.93	–
10.0	8	8	94.60	–

[a] After the end of hydrazine hydrate addition iron(III) chloride was again charged into the reactor.

Table 3. The variation of reduction products composition in the course of dinitrodiphenyl sulfide **I** reduction in two parallel runs performed under identical conditions (reaction temperature 100–102°C, molar ratio dinitrodiphenyl sulfide (**I**) : hydrazine hydrate 1.0 : 1.0)

Run no.	Time since the start of hydrazine hydrate addition, h	Composition of the crude product formed, wt%									
		triamine (II)	sulfide (I)	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8
1	2	5.22	70.60	2.04	3.05	1.91	1.02	1.02	14.00	0.60	–
	4	27.7	6.60	1.99	3.32	2.04	1.59	1.66	39.50	0.60	Trace
	6	42.3	5.63	0.87	4.47	4.79	0.39	0.89	43.70	0.92	0.50
	8	68.4	2.64	0.64	4.51	6.93	0.38	0.39	15.30	0.29	0.26
	10	89.3	0.82	0.39	2.86	3.06	0.38	0.38	1.93	0.23	Trace
	12	93.9	0.50	0.34	1.49	1.25	0.23	0.26	0.21	–	–
2	4	25.1	18.70	2.39	1.78	4.37	–	1.89	38.80	0.74	0.68
	6	47.8	7.16	0.98	2.89	5.59	1.72	0.97	37.10	0.47	1.40
	8	91.2	1.09	0.64	2.13	4.78	0.90	0.34	4.68	0.27	0.15
	10	93.6	0.59	0.31	1.71	1.38	0.24	0.24	0.91	0.14	–
	12	94.8	0.21	0.14	0.71	0.68	0.13	0.11	0.26	–	–

Table 4. Results of dinitrodiphenyl sulfide **I** reduction with hydrazine

Molar ratio of the charged component to compound **I**					Tempera-ture, °C	Content of main substance, wt%	Yield of crude triamine (**II**), %
Solvent		Catalyst		N_2H_4			
name	ratio	name	ratio				
Ethylene glycol	26.6	$FeCl_3$	0.01	6.63	120–140	66.0	83.8
2-Propanol	12.8	$FeCl_3$	0.01	6.63	80–85	47.8	81.1
Butanol	10.4	$FeCl_3$	0.01	6.63	100–105	87.5	91.7
Butanol	8.7	$FeCl_3$	0.01	5.59	97–100	64.6	91.2
Butanol	10.6	$FeCl_3$	0.01	7.00	100–105	91.1	85.2
Butanol	10.6[a]	$FeCl_3$	0.01	6.50	100–105	93.2	83.8
Butanol	10.6[a]	$FeCl_3$	0.01	6.50	100–105	94.0	83.4
Butanol	10.6[a]	$FeCl_3$	0.01	6.50	100–116	90.0	62.0
Butanol	10.6[a]	$FeCl_3$	0.01	6.50	100–120	89.0	33.0
2-Propanol	12.8	Ni/Si	0.01[b]	14.30	85	Trace	–
Butanol	12.0[a]	Ni/Si	0.125[b]	6.85	100–105	74.1	88.7
Butanol	10.6	Pd/savunite	0.01[b]	7.00	100–105	96.8	73.5

[a] With azeotropic water distillation. [b] Weight fractions.

dioxane. Over 80 kg of crude triamine **II** was obtained in about 80% yield containing no less than 93% of the target product.

In the laboratory the search was carried out for replacement of difficultly available (1,4-dioxane) and difficultly recoverable (ethylene glycol) solvents with more accessible substances. Therefore 2-propanol and butanol were tested, and better results were obtained with butanol. In this case the reduction occurred the most complete if simultaneously with hydrazine hydrate charging into the reactor the water was distilled off as azeotrope butanol–water. The reaction temperature was therewith in the range 95–105°C. Results obtained are listed in Table 4.

The optimum reagents ratios for dinitrodiphenyl sulfide **I** reduction in butanol are as follows: molar

ratio dinitrodiphenyl sulfide I : hydrazine (64–67%) is 1.0 : (6.0–7.0); weight ratio dinitrodiphenyl sulfide I : butanol is 1.0 : (2.7–2.8). Under these conditions the yield of crude diamine was 80–85% with content of the target products in no less than 93%.

Under laboratory conditions we also investigated the possibility of replacing iron(III) chloride with nickel or palladium catalyst (Table 4). As seen from the presented data, the best results were obtained with palladium catalyst.

We also attempted to obtain triamine II by reduction of dinitrodiphenyl sulfide I with hydrogen under pressure of 25–50 at on nickel or palladium catalyst. Here 2-propanol and butanol were used as solvent. Regretfully, the results were poor due to strong tarring in the reaction mixture.

During the scaling of dinitrodiphenyl sulfide I reduction with hydrazine in butanol to the pilot plant scale significant problems often emerged at separation of the target product from the reaction mixture after its filtration from carbon and distilling off the main part of butanol and hydrazine. Sometimes the product did not crystallize in the residual mixture. Besides the crystalline triamine II gradually oxidized at storage.

In this connection we tested the possibility of separation and storage of triamine II in the form of trihydrochloride. To this end after completing the reduction and performing analysis of the reaction mixture by TLC and HPLC to prove that no initial and intermediate compounds were present the reaction mixture should be filtered from carbon, and butanol and hydrazine should be removed under reduced pressure as fully as possible.

The butanol must be completely removed from the reaction mixture for triamine II hydrochloride is notably soluble in the mixture of butanol and hydrochloric acid. Hydrazine dihydrochloride is less soluble than triamine II trihydrochloride in all tested organic solvents and in water. Therefore hydrazine removal from the reaction mixture after the end of reduction is no less important.

To the residue after removal of butanol and hydrazine on cooling to room temperature was gradually added at vigorous stirring the concn. (38%) HCl till molar ratio HCl : triamine II equal to (4.0–5.0) : 1.0. The crystallization of triamine II hydrochloride gradually proceeded within 3–4 h. Then the crystals were filtered off, washed on the filter with a portion of concn. HCl, discharged from the filter, and dried. Yield of the crude triamine II trihydrochloride

was no less than 85%, and it contained no less than 93% of the main substance.

The reduction of dinitrodiphenyl sulfide I in butanol followed by the isolation of triamine II as trihydrochloride was also performed on the pilot installation in the reactor of 100 l capacity. The results obtained were fully consistent with those of the laboratory investigations.

EXPERIMENTAL

The reduction of dinitrodiphenyl sulfide I was studied in a four-neck reactor equipped with a jacket connected to ultrathermostat for maintaining constant reaction temperature, with a stirrer, a thermometer, a dropping funnel, and a reflux condenser with a Dean-Stark trap used in experiments carried out in butanol.

In the reduction with hydrazine hydrate to a solution of 63 g (0.216 mol) of dinitrodiphenyl sulfide I in a mixture of 600 ml of 1,4-dioxane and 150 ml of ethylene glycol was added 1.2 g (0.0045 mol) of iron(III) chloride hexahydrate preliminary ground with 7,5 g of activated carbon. The mixture was heated to 100–102°C for 30 min under a slow stream of nitrogen. Then at this temperature into the reactor within 1–6 h was added dropwise 60 ml of hydrazine hydrate (1.2 mol). Thereafter the reaction mixture was heated to weak boiling without stirring for 6–10 h till completion of the reduction, The first indication of the process end was decoloration of the foam that arose at boiling of the reaction mixture.

After the end of the process from the reaction mixture 1,4-dioxane was distilled off in a vacuum. The residue was poured from the reactor into cold boiled water (200 ml). After stirring and standing from the layer of formed triamine II was decanted the mixture of ethylene glycol and water. Then triamine II was dissolved in a mixture of 300 ml of 2-propanol and 300 mi of water to remove the traces of solvents. At cooling and stirring from the solution slowly precipitated crystals of triamine II that was washed on the filter with cold water and dried.

When butanol was used as solvent in the reduction process the vapors of water, butanol, and hydrazine hydrate were removed from the reactor as azeotrope and were collected in the Dean-Stark trap. There the liquid separated into water and butanol phases. The hydrazine in the trap was distributed between the water layer that time and again was rejected, and the organic layer that was continuously returned into the reactor. The fraction of hydrazine lost with water

removed from the reaction zone was relatively small and equaled to several percent.

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