ISSN 1070-3632, Russian Journal of General Chemistry, 2008, Vol. 78, No. 3, pp. 446–450. © Pleiades Publishing, Ltd., 2008.
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Synthesis and Fungicidal Activity of Bis(2-arylcarbonylamino-1*H*-benzimidazol-5-yl) Sulfones

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Received April 26, 2007

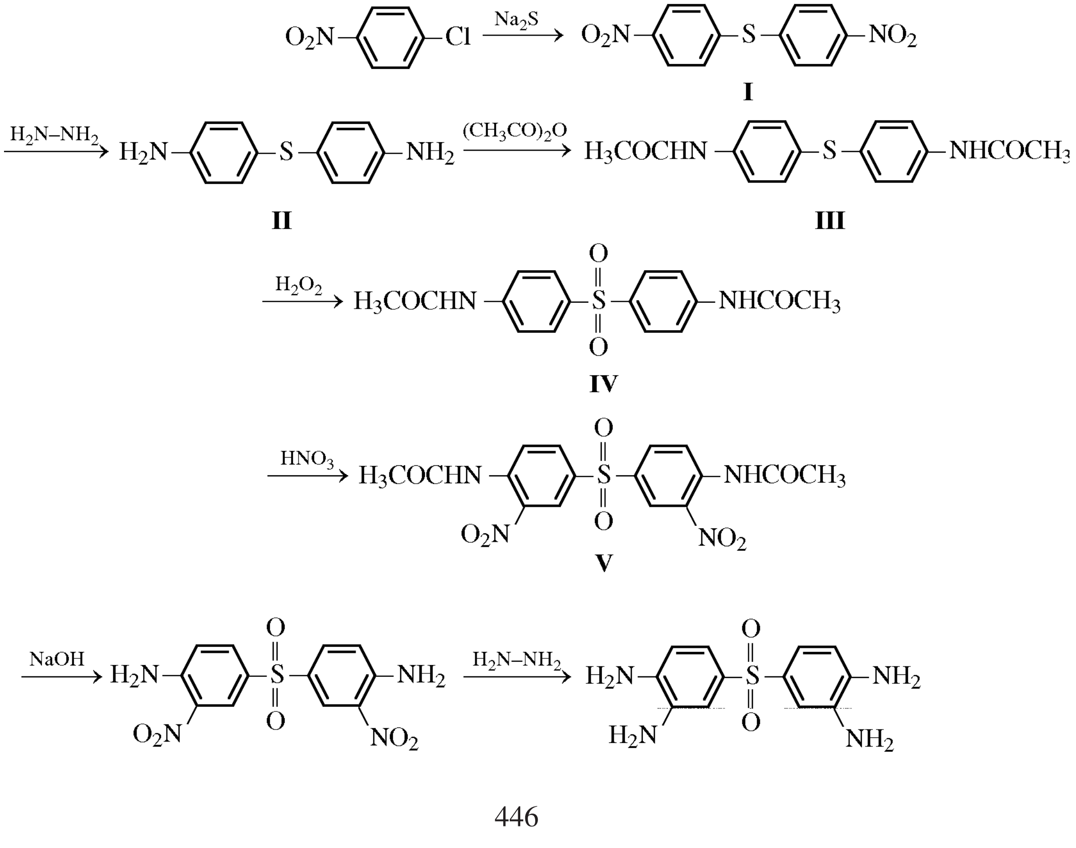
Abstract—A procedure has been developed for the synthesis of bis(2-arylcarbonylamino-1*H*-benzimidazol-5-yl) sulfones by reaction of the corresponding substituted benzoyl chloride with sodium cyanamide and subsequent treatment of the *N*-cyanobenzamide thus formed with 3,3′,4,4′-tetraaminodiphenyl sulfone in acid medium. The products were tested for fungicidal activity.

DOI: 10.1134/S1070363208030195

While continuing search for new biologically active substances (fungicides, antihelminthic agents, etc.) in the series of 2-aminobenzimidazole derivatives [1–4], we have synthesized compounds where, unlike those reported previously [3, 4], two benzimidazole fragments are linked through a sulfinyl bridge.

Bis(2-arylcarbonylamino-1*H*-benzimidazol-5-yl) sulfones were synthesized according to Schemes 1 and 2. In the first step, 4-nitrochlorobenzene was treated with sodium sulfide to obtain 4,4'-dinitrodiphenyl sulfide (**I**) which was reduced to 4,4'-diaminodiphenyl

Scheme 1.



sulfide (**II**) with hydrazine hydrate. Acylation of diamine **II** at both amino groups with acetic anhydride afforded 4,4′-bis(acetylamino)diphenyl sulfide (**III**), and the latter was oxidized with hydrogen peroxide to 4,4′-bis(acetylamino)diphenyl sulfone (**IV**). Diphenyl sulfone **IV** was converted into 4,4′-bis(acetylamino)-3,3′-dinitrodiphenyl sulfone (**V**) by nitration with nitric acid, and the acetyl protection was removed by treatment with alkali. 4,4′-Diamino-3,3′-dinitrodiphenyl sulfone (**VI**) thus obtained was reduced to 3,3′,4,4′-tetraaminodiphenyl sulfone (**VII**) by the action of hydrazine hydrate.

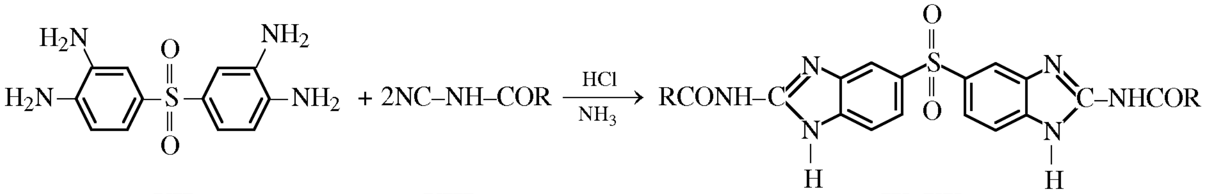
Substituted *N*-cyanobenzamide or *N*-cyanobenzenesulfonamide sodium salt (prepared by reaction of the corresponding substituted benzoyl chloride or benzenesulfonyl chloride with an aqueous suspension of sodium cyanamide) was acidified with hydrochloric acid, and neutral *N*-cyano amides **VIII** reacted with 3,3′,4,4′-tetraaminodiphenyl sulfone (**VII**) to give the target bis(2-arylcarbonylamino-1*H*-benzimidazol-5-yl) sulfones **IX**–**XX** (Scheme 2).

The structure of intermediate nitro- and amino-substituted diphenyl sulfides and sulfones **I**–**VII** was established using high-performance liquid chromatography (HPLC) and ^{13}C NMR spectroscopy (Table 1). The carbon signals were assigned by analysis of the chemical shifts, coupling constants, signal multiplicities, and intensity ratios. While interpreting the ^{13}C NMR spectra of **I**–**VII**, we used the corresponding data for model compounds such as diphenyl sulfide, diphenyl sulfoxide, and diphenyl sulfone [6] and the calculated shielding constants of carbon nuclei in the aromatic rings having various substituents [5, 7–9].

The progress of reactions of 3,3′,4,4′-tetraaminodiphenyl sulfone (**VII**) with *N*-cyanobenzamides and of the cyclization processes leading to structures **IX**–**XX** was monitored by HPLC and ^{13}C NMR.

Fungicidal activity of compounds **IX**–**XX** at a concentration of 0.003% was estimated on the basis of growth inhibition of pathogenic fungi *Fusarium culmorum* and *Helminthosporium sativum* using pure cultures (Table 2). Primary results of laboratory tests showed that the synthesized compounds are less toxic than 2-aminobezimidazole derivatives reported previously [5] against *Fusarium culmorum* and *Helminthosporium sativum*.

Scheme 2.



VII **VIII** **IX**–**XX**

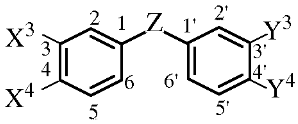
IX, R = 2-HO-5-ClC_6H_3CO; **X**, R = 4-$O_2NC_6H_4$CO; **XI**, R = 4-ClC_6H_4CO; **XII**, R = 2-Cl-5-$O_2NC_6H_3$CO; **XIII**, R = 2-BrC_6H_4CO; **XIV**, R = PhSO_2; **XV**, R = PhCO; **XVI**, R = 2-MeO-5-ClC_6H_3CO; **XVII**, R = 2,5-$Cl_2C_6H_3$CO; **XVIII**, R = 3-IC_6H_4CO; **XIX**, R = 2-MeO-3,5-$Cl_2C_6H_2$CO; **XX**, R = 2-MeOC_6H_4CO.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Bruker CXP-100 spectrometer with Fourier transform at a frequency of 22.63 MHz both with complete decoupling from protons and without it. Dimethyl sulfoxide was used as solvent, and the chemical shifts were measured relative to hexamethyldisiloxane.

4,4′-Dinitrodiphenyl sulfide (I). A three-neck flask equipped with a stirrer, dropping funnel and reflux condenser was charged with 25 g of 4-nitrochlorobenzene in 20 ml of dimethylformamide (DMF). The mixture was heated to the boiling point, and a solution of 28.5 g of sodium sulfide in 20 ml of water was added dropwise from a dropping funnel.

Table 1. ^{13}C NMR spectra of some substituted diaryl sulfides, diaryl sulfoxides, and diaryl sulfones of the general formula



Z	X^3	X^4	Y^3	Y^4	δ_C, ppm													
					C^1	C^2	C^3	C^4	C^5	C^6	$C^{1'}$	$C^{2'}$	$C^{3'}$	$C^{4'}$	$C^{5'}$	$C^{6'}$	CO	CH_3
S	H	NO_2	H	H	148.4	126.5	123.9	145.2	123.9	126.6	130.3	134.6	130.0	129.6	130.0	134.6		
S	H	NO_2	H	NO_2	142.7	131.6	124.6	147.4	124.6	131.6	142.7	131.6	124.6	147.4	124.6	131.6		
S	H	NO_2	H	NH_2	144.6	125.6	124.1	151.0	124.1	125.6	112.4	137.4	115.6	151.6	115.6	137.4		
S	H	NH_2	H	NH_2	121.9	133.2	115.2	148.7	115.2	133.2	121.9	133.2	115.2	148.7	115.2	133.2		
S	H	NO_2	H	NHAc	141.6	124.6	126.7	149.2	126.7	124.6	122.8	136.4	122.1	145.4	122.1	136.4		
S	H	NH_2	NH_2	NH_2	121.9	133.2	115.2	148.7	115.2	133.2	134.6	128.3	131.1	140.8	95.0	137.9	168.5	
S	H	NH_3	NH_3	NH_3	146.6	103.8	154.0	114.6	114.6	129.8	138.3	134.4	132.3	126.2	150.3	125.3	168.0	
S	H	NO_2	NO_2	NHAc	139.7	128.5	124.8	146.2	124.8	128.5	124.8	142.5	130.4	146.2	139.7	125.8	166.1	24.7
S	H	NO_2	NO_2	NH_2	147.3	126.1	124.3	149.3	124.3	126.1	115.0	131.5	141.8	145.5	121.5	133.8		
S	H	NHAc	H	NHAc	129.2	131.9	120.5	139.2	120.5	131.9	129.2	131.9	120.5	139.2	120.5	131.9	168.9	24.5
SO	H	H	H	H	145.1	126.7	128.2	131.7	128.2	126.7	145.1	126.7	128.2	131.7	128.2	126.7		
SO	H	NO_2	H	NHAc	149.3	126.4	120.2	152.1	120.2	126.4	138.4	125.8	120.0	143.0	120.0	125.8	169.5	24.6
SO	H	NHAc	H	NHAc	140.0	126.0	120.1	142.3	120.1	126.0	140.0	126.0	120.1	142.3	126.0	120.1	169.5	24.6
SO_2	H	H	H	H	141.6	127.6	129.3	133.2	129.3	127.6	141.6	127.6	129.3	133.2	129.3	127.6		
SO_2	NH_2	NH_2	NH_2	NH_2	130.5	112.5	135.0	140.1	117.7	113.2	130.5	112.5	135.0	140.1	117.7	113.2		
SO_2	H	NO_2	H	NHAc	147.6	125.5	129.8	150.7	129.8	125.5	133.4	129.3	119.9	145.1	119.9	129.3	170.2	24.6
SO_2	H	NO_2	NO_2	NHAc	135.4	126.5	137.0	141.6	125.8	133.5	146.0	125.7	130.0	151.2	130.0	125.7	170.1	24.2
SO_2	H	NHAc	H	NHAc	142.7	125.4	119.3	146.0	119.3	125.4	142.7	125.4	119.3	146.0	119.3	125.4	170.0	24.7
SO_2	NO_2	NHAc	NO_2	NHAc	142.8	126.7	134.6	141.6	121.9	130.6	142.8	126.7	134.6	141.6	121.9	130.1	169.5	24.1

Table 2. Fungicidal activity of 2-aminobenzimidazole derivatives at a concentration of 0.003% against pure fungal cultures

Comp. no.	Inhibition of growth of pathogenic fungi, %	
	Fusarium culmorum	*Helminthosporium sativum*
IX	8.6	41.6
X	6.8	28.1
XI	7.6	38.4
XII	9.3	24.1
XV	16.9; 19.4	32.3; 31.3
XVIII	6.0	25.0
XIX	18.6	30.3
XX	34.0	17.6

When the addition of sodium sulfide was complete, the mixture was stirred for 1 h at heating and poured into water. The yellow precipitate of 4,4′-dinitrodiphenyl sulfide (**I**) was filtered off, dried, and recrystallized from acetic acid, mp 154–155°C. Yield 95%. The product contained no less than 90% of the main substance.

4,4′-Thiodianiline (II). A 1-l three-neck flask equipped with a reflux condenser, Dean–Stark trap, thermometer, and dropping funnel was charged with 83 g of 4,4′-dinitrodiphenyl sulfide (**I**), 320 ml of butanol, 2 g of iron(III) chloride, and 15–20 g of activated charcoal. The mixture was slowly heated to 30–35°C, and 120 ml of 60% hydrazine hydrate was added dropwise, while continuing to heat the mixture to the boiling point (95–105°C). The addition of hydrazine hydrate required about 4 h. Simultaneously, azeotropic mixture consisting of water, hydrazine, and butanol distilled off, and the boiling point of the mixture increased from 95 do 105°C as water was removed therefrom. The reduction process was assumed to be complete when water no longer separated and a white foam appeared on the surface of the reaction mixture. The overall time of the reduction of 4,4′-dinitrodiphenyl sulfide (**I**) was 15–16 h. The mixture was filtered while hot to remove charcoal, the filtrate was cooled, and the colorless crystals were filtered off and dried. The mother liquor containing some amount of 4,4′-diaminodiphenyl sulfide (**II**) was used as solvent for the reduction of another portion of dinitrodiphenyl sulfide **I**. The yield of 4,4′-diaminodiphenyl sulfide (**II**) in the first run was about 40%, and it increased in the subsequent runs.

***N*,*N*′-[4,4′-Thiobis(4,1-phenylene)]diacetamide (III).** A 500-ml flask was placed into a water bath and charged with 50 g of sulfide **II**, 150–200 ml of chlorobenzene, and a few drops of sulfuric acid. The mixture was heated to 28–30°C, and ~50 ml of acetic anhydride was added over a period of 15–20 min under stirring. During the addition, the mixture turned thick and colorless. When the addition was complete, the mixture was stirred for 2 h at 70–75°C, cooled to 35–40°C, and filtered. The precipitate was washed with a small amount of alcohol, taking into account that compound **III** is soluble therein. Yield ~100%.

***N*,*N*′-[4,4′-Sufinylbis(4,1-phenylene)]diacetamide (IV).** A 500-ml flask was charged with 60 g of sulfide **III**, and 300 ml of concentrated sulfuric acid was added. The mixture warmed up. It was cooled under stirring to 15–20°C, and 28 ml of 30% hydrogen peroxide was added dropwise very slowly (over a period of 2.0–2.5 h), maintaining the temperature not below 28–30°C. The mixture was stirred for 3 h at 30–35°C (it turned thick and more transparent) and poured into a beaker charged with crushed ice. A solid immediately separated; its color varied from light pink to lilac–gray. The mixture was left overnight, and the precipitate was filtered off, stirred with a large volume of water (to remove impurities), and dried. Yield 60–70%.

***N*,*N*′-[4,4′-Sufinylbis(2-nitro-4,1-phenylene)] diacetamide (V).** A 250-ml flask was placed into a cooling bath, and 70 ml of concentrated nitric acid (5-fold weight amount with respect to sulfone **IV**) was placed therein and cooled under stirring to –6 to –8°C. Sulfone **IV** was added in small portions under stirring, maintaining the temperature below –5°C. The time of addition of sulfone **IV** was about 1 h. The mixture was then stirred for 3 h at –6 to –10°C and poured into a beaker containing crushed ice. Light yellow solid separated. The mixture was left to stand overnight, and the bright yellow precipitate was filtered off, washed with water, and dried. Yield 75–85%.

4,4′-Sufinylbis(2-nitrobenzenamine) (VI). A 500-ml flask was placed into a water bath and charged with 100 g of isopropyl alcohol, 25 g of sulfone **V** was added under stirring, and a solution of 7.1 g of sodium hydroxide in 16.6 ml of water was then added over a period of 15–20 min under stirring; simultaneously, the mixture was gradually heated to 80°C. It was stirred for 20–30 min at that temperature and poured into water. A few drops of hydrochloric acid were added to the solution for better crystallization. After several hours, the precipitate was filtered off, thoroughly washed with water on a filter, and dried. Yield ~95%.

4,4′-Sufinylbis(benzene-1,2-diamine) (VII). A 250-ml flask equipped with a reflux condenser, Dean–Stark trap, dropping funnel, and thermometer was charged with 100 ml of butanol, 20 g of sulfone **VI**, 0.3 g of $FeCl_3$, and 3 g of activated charcoal. The mixture was heated to 40°C on a water bath without stirring, and 50 ml of hydrazine hydrate was slowly added in three approximately equal portions. The mixture warmed up to 95°C and began to boil, and water started to separate as azeotrope with butanol. As water was removed, the temperature of the reaction mixture rose to 105°C (~20 h). When water no longer separated, the mixture was heated for an additional 1.5–2.0 h and filtered while hot to remove charcoal. Sulfone **VII** started to crystallize from the filtrate almost immediately. The light beige lustrous precipitate was filtered off and washed with water. An additional amount of product **VII** was isolated by concentration of the mother liquor. Yield 40–50%.

Bis(2-acylamino-1*H*-benzimidazol-5-yl) sulfones

IX–XX (*general procedure*)**.** Finely powdered calcium cyanamide containing 27.5% of the main substance, 24 g, was dispersed in 900 ml of water, and the corresponding substituted benzoyl chloride or benzenesulfonyl chloride (solid benzoyl chlorides were added as solutions in anhydrous acetone), 0.33 mol, was added under vigorous stirring at such a rate that the temperature did not exceed 40–45°C. The mixture was stirred for 1 h at 40–45°C, cooled to room temperature, and filtered from inorganic salts present in the initial calcium cyanamide. The filtrate was adjusted to pH 3 by adding concentrated hydrochloric acid, and the precipitate of RC(O)NHCN·HCl was filtered off and dried in air in a hood. Depending on the initial acyl chloride, the yield of the complex RC(O)NHCN·HCl varied from 7.6 (5-chloro-2-hydroxybenzoyl chloride) to 95% (benzenesulfonyl chloride).

A flask equipped with a mechanical stirrer, reflux condenser, and thermometer was charged with 0.15 mol of sulfone **VII**, 0.45 mol of glacial acetic acid, 300 ml of water, 300 ml of isopropyl alcohol, and 0.3 mol of the isolated complex. The mixture was heated to 75–78°C and stirred for 6–7 h at that temperature; the progress of the reaction being monitored by TLC (following the disappearance of the initial complex). As a rule, a light beige solid separated during the process (except for the benzenesulfonyl derivative). The mixture was cooled to room temperature, and the precipitate was filtered off, washed with water, and dried. The yields of sulfones **IX**–**XX** ranged from 21 to 83%; their melting points were as follows,: **IX**, 96°C; **X**, 269°C; **XI**, 275°C; **XII**, 340°C; **XIII**, 114°C; **XIV**, 231°C; **XV**, 162°C; **XVI**, 89°C; **XVII**, 153°C; **XVIII**, 224°C; **XIX**, 148°C; **XX**, 131°C.

Primary tests of compounds **IX**–**XX** for fungicidal activity were performed by inoculation of phytopathogenic fungi into a dense nutrient medium containing a compound to be tested. All compounds were tested at a concentration of 0.003%. To ensure uniform distribution over the medium, they were dissolved in acetone (1 : 150) or thoroughly powdered. Potato glucose agar was used as substrate. Compounds **IX**–**XX** were applied to the nutrient medium before solidification (at 45–50°C), and it was then poured onto Petri dishes in 15-cm^3 portions. Each Petri dish was inoculated with *Fusarium culmorum* and *Helminthosporium sativum* mycelia simultaneously at three points. In blank experiment, the fungal cultures were inoculated into the same nutrient medium containing no fungicides. The dishes were incubated for 72 h at 25–26°C, and the average diameter of the colonies was measured.

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