Synthesis of 5-bromo-4-dibromoamino-3-phenylisothiazole and its light-induced conversion into 3,7-diphenylbisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine

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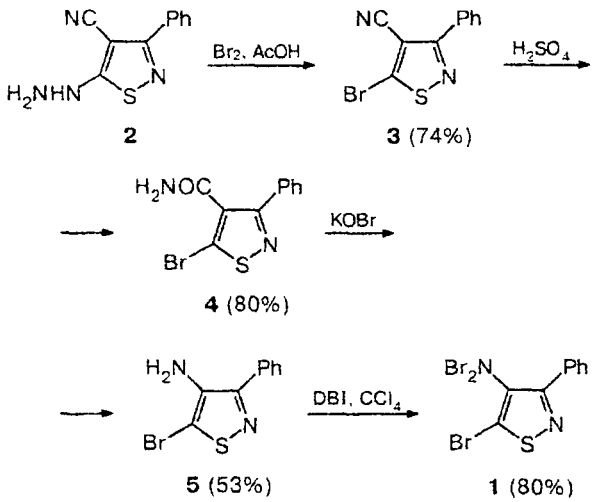
When irradiated with UV light, 5-bromo-4-dibromoamino-3-phenylisothiazole is converted into 3,7-diphenylbisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine and *N*,*N*′-bis(5-bromo-3-phenylisothiazol-4-yl)diazene.

Key words: bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine, dibromoamine, dibromoisocyanuric acid.

Previously, we have reported the formation of 3,7-dichloro- and 3,7-dimethylbisisothiazolo-[4,5-*b*:4′,5′-*e*]pyrazines, which are the first representatives of a new heterocyclic system, from the corresponding 3-substituted 5-halogeno-4-dibromoaminoisothiazoles under the action of the copper—collidine system[1] or UV light.[2] The proposed reaction mechanism involves generation of halogenoaminyl radicals and substitution of the latter for the halogen atom at position 5 of isothiazole ring.[2] With the aim of examining the scope of this reaction and exploring the possibility of synthesis of the previously unknown 3,7-diarylbisisothiazolo-[4,5-*b*:4′,5′-*e*]pyrazines by this reaction, we studied the behavior of 5-bromo-4-dibromoamino-3-phenylisothiazole (**1**) under the above-mentioned conditions.

The starting compound **1** was synthesized according to Scheme 1, which involves oxidative halogenation of readily available[3] 4-cyano-5-hydrazino-3-phenylisothiazole (**2**) under the action of bromine in an acidic medium to form the corresponding 5-bromoisothiazole **3**, hydrolysis of the cyano group of bromide **3** in concentrated H_2SO_4 yielding the amide group, rearrangement of 5-bromo-4-carbamoyl-3-phenylisothiazole (**4**) into the amino derivative **5** under the action of potassium hypobromite (the Hofmann rearrangement), and bromination of the amino group in compound **5** with dibromoisocyanuric acid (DBI) to form the dibromoamino group. The overall yield of isothiazole **1** with respect to the initial hydrazine **2** was 26%.

Scheme 1



Compound **1**, like 3-chloro- and 3-methyl-substituted 5-bromo-4-dibromoaminoisothiazoles synthesized previously,[1,2] exhibits stability anomalous for *N*,*N*-dibromoamines of the aromatic and heteroaromatic series. Thus a solution of isothiazole **1** in CCl_4 can be stored without decomposition at room temperature for several days.

It appeared that isothiazole **1** reacted with the copper—collidine system in CCl_4 to form a mixture of products that did not contain the desired 3,7-diphenylbisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (**6**). UV irradiation of a solution of compound **1** in CCl_4 using a mercury lamp also afforded a mixture of products from which pyrazine **6** and *N*,*N*′-bis(5-bromo-3-phenylisothiazol-4-yl)diazene (**7**) were isolated by TLC (silica gel, a 1 : 1 benzene—hexane mixture as the eluent) (Scheme 2).

Probably, the low selectivity of the reaction (29%) compared to the analogous conversions of 3-methyl- and 3-chloro-4-dibromoamino-5-halogenoisothiazoles (94 and 89%, respectively)[1,2] is attributable to side homolytic processes with the participation of the hydrogen atoms of the aromatic ring as well as to steric hindrances that appear when the transition state of the reaction is realized.

The new compounds were characterized by the data of ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.

In summary, we synthesized the first representative of 3,7-diarylbisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines (Ph as the aryl group). Since compound **6** was obtained in low yield, it is worthwhile to search for alternative ap-

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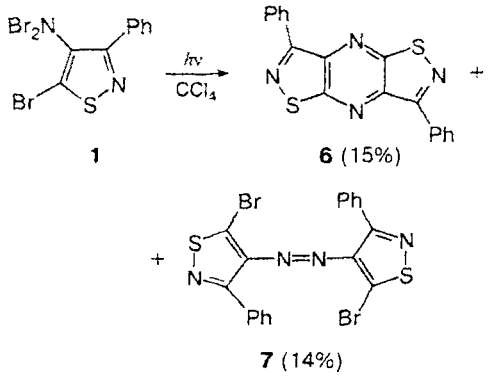
Scheme 2



proaches to the synthesis of the structures of this series. Owing to the planar structures, compounds of this type may be of use in the design of new DNA intercalators.[4]

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (operating at 300.13 and 62.9 MHz for ^1H and ^{13}C, respectively) in DMSO-d_6 and in a CCl_4—$CDCl_3$ mixture. The chemical shifts δ_H and δ_C were measured relative to DMSO-d_6 (2.50 and 39.5 ppm, respectively) and $CDCl_3$ (7.27 and 76.9 ppm, respectively). The TLC analysis was carried out on Silpearl UV-250 silica gel using benzene as the eluent. 4-Cyano-5-hydrazino-3-phenylisothiazole (**2**) was prepared according to a procedure reported previously.[3] A mercury-quartz OKN-11 emitter equipped with a DRT-220 mercury lamp (850 W) without a filter was used as the radiation source. The reactions were carried out in glass vessels with the lower transmission cut-off of 280 nm.

5-Bromo-4-cyano-3-phenylisothiazole (3). Bromine (0.07 mL, 1.38 mmol) was added to a solution prepared from Na_2CO_3 (0.07 g, 0.68 mmol), isothiazole **2** (0.10 g, 0.46 mmol), and AcOH (2 mL), at 15 °C. The reaction mixture was stirred at 15 °C for 2 h, poured into water (20 mL), and extracted with ether (2×8 mL). The extract was washed with a 5% solution of sodium thiosulfate (5 mL), dried over $CaCl_2$, and concentrated *in vacuo*. The residue was crystallized from hexane. Bromide **3** was obtained in a yield of 0.08 g (74%), m.p. 82—85 °C, R_f 0.85. ^1H NMR ($CDCl_3$), δ: 7.78 (br.s, 2 H, *o*-H); 7.50 (br.s, 3 H, *m*-H, *p*-H). Found (%): C, 44.86; H, 1.91; Br, 30.25; N, 10.44; S, 12.31. $C_{10}H_5BrN_2S$. Calculated (%): C, 45.30; H, 1.90; Br, 30.14; N, 10.57; S, 12.09.

5-Bromo-4-carbamoyl-3-phenylisothiazole (4). A mixture of bromoisothiazole **3** (0.70 g, 2.60 mmol) and H_2SO_4 (3.50 mL, d = 1.8 g cm^{-3}) was kept at 80 °C for 2 h and then poured into water (20 mL). The precipitate that formed was filtered off. Amide **4** was obtained in a yield of 0.59 g (80%), m.p. 215—217 °C. ^1H NMR ($CDCl_3$), δ: 8.20 (br.s, 1 H, NH); 7.90 (br.s, 1 H, NH); 7.78 (br.s, 2 H, *o*-H); 7.50 (br.s, 3 H, *m*-H, *p*-H). Found (%): C, 42.95; H, 2.39; Br, 28.95; N, 10.11; S, 11.53. $C_{10}H_7BrN_2OS$. Calculated (%): C, 42.42; H, 2.49; Br, 28.22; N, 9.89; S, 11.32.

4-Amino-5-bromo-3-phenylisothiazole (5). Bromine (0.10 mL, 2.16 mmol) was added with stirring to a solution of KOH (0.61 g, 10.81 mmol) in water (15 mL) cooled to 3 °C. After 5 min, amide **4** (0.50 g, 1.83 mmol) was added. The reaction mixture was stirred at 60 °C for 3 h and cooled to 20 °C. Then AcOH was added to pH 5. The reaction mixture was kept at 15 °C for 5 h and then neutralized with a 20% NaOH solution. The precipitate that formed was filtered off and crystallized from hexane. Amine **5** was obtained in a yield of 0.24 g (53%), m.p. 110—112 °C, R_f 0.67. ^1H NMR ($CDCl_3$), δ: 3.75 (br.s, 2 H, NH); 7.78 (d, 2 H, *o*-H, J = 7.5 Hz); 7.48—7.51 (m, 3 H, *m*-H, *p*-H). Found (%): C, 42.95; H, 2.79; Br, 31.40; N, 10.64; S, 12.48. $C_9H_7BrN_2S$. Calculated (%): C, 42.37; H, 2.77; Br, 31.32; N, 10.98; S, 12.57.

5-Bromo-4-dibromoamino-3-phenylisothiazole (1). Dibromoisocyanuric acid (0.60 g, 2.09 mmol) was added to a solution of amine **5** (0.27 g, 1.39 mmol) in anhydrous CCl_4 (5 mL). The reaction mixture was stirred at 15 °C for 1 h. The precipitate of isocyanuric acid was filtered off and washed with CCl_4 (1 mL). TLC analysis demonstrated that the mother liquor contained only product **1**, R_f 0.9. The solvent was removed under reduced pressure. Dibromoamine **1** was obtained as a yellow oil in a yield of 0.45 g (80%). Compound **1** decomposed upon chromatography on silica gel, which did not allow us to obtain reasonable data of elemental analysis. ^1H NMR (CCl_4—$CDCl_3$), δ: 7.75 (br.s, 2 H, *o*-H); 7.50 (br.s, 3 H, *m*-H, *p*-H). ^{13}C NMR (CCl_4—$CDCl_3$), δ: 172.7 (C—Ph); 154.8 (C—NBr_2); 131.6 (C—Br); 130.2 (*m*-C); 130.0 (*o*-C); 120.3 (*p*-C). UV (CCl_4), λ_{max}/nm: 260, 390. A solution of dibromoamine **1** in CCl_4 was subjected to photochemical conversion without additional purification.

3,7-Diphenylbisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (6) and *N*,*N*′-bis(5-bromo-3-phenylisothiazol-4-yl)diazene (7). A solution of isothiazole **1** (0.45 g, 1.11 mmol) in CCl_4 (5 mL) was irradiated with UV light at 30—35 °C for 12 h. After completion of irradiation, the initial compound **1** was virtually absent in the reaction mixture (according to TLC). The solvent was removed *in vacuo* and then hexane (5 mL) was added to the residue. The precipitate that formed was filtered off, washed with hexane (1 mL), and dried under an air stream. The resulting mixture of products was separated by chromatography (a 1 : 1 benzene—hexane mixture as the eluent). Compounds **6** and **7** were isolated. **Pyrazine 6** (0.025 g, 15%), m.p. >360 °C, R_f 0.72. ^1H NMR (DMSO-d_6), δ: 7.75 (br.s, 2 H, *o*-H); 7.50 (br.s, 3 H, *m*-H, *p*-H). ^{13}C NMR (DMSO-d_6), δ: 163.6 (C—S); 156.5 (C—Ph); 142.4 (C(4)); 130.2 (*p*-C); 129.4 (*o*-C); 129.2 (*m*-C). MS, m/z (I_{rel} (%)): 346 [M^+] (100); 243 [M^+ − PhCN] (21), 140 [M^+ −2 PhCN] (34). Found (%): C, 63.01; H, 2.62; N, 16.23; S, 18.46. $C_{18}H_{10}N_4S_2$. Calculated (%): C, 62.41; H, 2.91; N, 16.17; S, 18.51. ***N*,*N*′-Bis(5-bromo-3-phenylisothiazol-4-yl)diazene (7)** (0.04 r, 14%), m.p. 73—76 °C, R_f 0.8. ^1H NMR (DMSO-d_6), δ: 7.8 (br.s, 2 H, *o*-H); 7.55 (br.s, 3 H, *m*-H, *p*-H). ^{13}C NMR (DMSO-d_6), δ: 134.5 (C—S); 153.0 (C—Ph); 156.2 (C—N=N); 130.8 (*o*-C); 130.3 (*p*-C); 129.1 (*m*-C). MS, m/z (I_{rel} (%)): 506 [M^+] (100). Found (%): C, 43.63; H, 1.87; Br, 31.03; N, 11.09; S, 12.38. $C_{18}H_{10}Br_2N_4S_2$. Calculated (%): C, 42.71; H, 1.9; Br, 31.57; N, 11.07; S, 12.67.

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