Light-induced synthesis of 3,7-disubstituted bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines from 3-substituted 4-dibromoamino-5-haloisothiazoles

S. G. Zlotin, A. V. Bobrov, and K. S. Chunikhin*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: L121@cacr.ioc.ac.ru

A new procedure was developed for the synthesis of 3,7-disubstituted bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines from 3-substituted 4-dibromoamino-5-haloisothiazoles under UV irradiation. *N,N′*-Bis(5-haloisothiazol-4-yl)diazenes were obtained as by-products.

Key words: bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines, dibromoamines, dibromoisocyanuric acid, 4-amino-5-haloisothiazoles, UV irradiation.

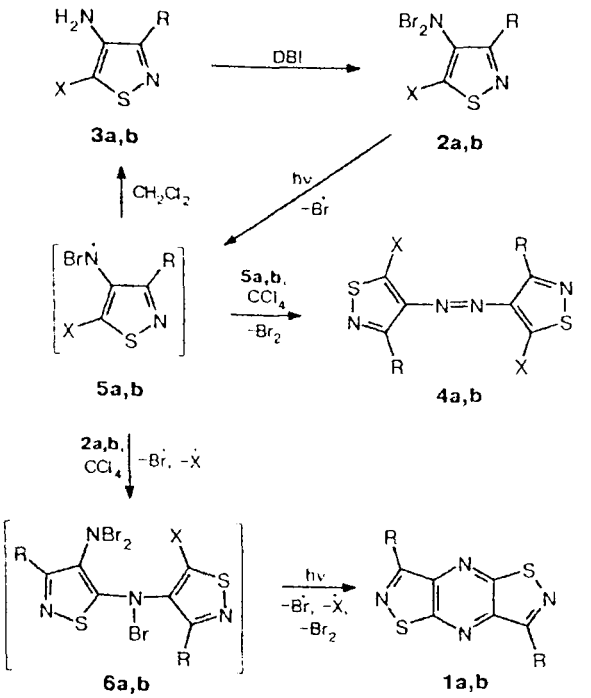
Previously,[1] we have reported the unexpected formation of 3,7-dichlorobisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (**1a**), which is the first representative of a new heterocyclic system, in the reaction of 3,5-dichloro-4-(dibromoamino)isothiazole (**2a**) with a copper–collidine system. Taking into account the ability of Cu atoms to initiate the homolytic cleavage of N—Hal bonds,[2] it can be suggested that the process is radical in character and, consequently, can proceed under the action of other initiators of radical reactions, in particular, under irradiation with UV light.

We used 3,5-dichloro-4-(dibromoamino)isothiazole (**2a**) and 5-bromo-4-dibromoamino-3-methylisothiazole (**2b**) in our experiments. Compound **2b** was prepared analogously to **2a**[1] by the reaction of 4-amino-5-bromo-3-methylisothioazole (**3b**)[3] with dibromoisocyanuric acid (DBI).[4] A solution of dibromoamine **2b** in CCl_4 remained unchanged in the dark at +5 °C for one day. However, compound **2b** gradually decomposed at room temperature. The structure of **2b** was confirmed by ^1H and ^{13}C NMR spectroscopy.

It was found that when irradiated with the use of a Hg lamp, compound **2** entered into the reaction, which was accompanied by the cleavage of the N—Br bond. The final result of this reaction was governed by the nature of the solvent used. Thus, when exposed in CH_2Cl_2 for 10 min, *N,N*-dibromoamine **2a** was virtually completely converted into 4-amino-3,5-dichloroisothiazole (**3a**). At the same time, irradiation of solutions of **2a,b** in CCl_4 afforded 3,7-disubstituted bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines **1a** and **1b**, respectively, as the major products. Under the above-mentioned conditions, the yields of **1a** and **1b** were 76% and 58%, respectively (Scheme 1).

N,N′-Bis(isothiazol-4-yl)diazenes **4a** and **4b** were isolated as by-products of the photochemical reactions

Scheme 1



a: R = X = Cl;
b: R = Me, X = Br

of **2a,b** in CCl_4 in 13% and 37% yields, respectively. Taking into account that compounds **1a,b** and **4a,b** are very poorly soluble in organic solvents, which made the application of TLC difficult, individual products **1a** and **4a** were isolated by fractional crystallization (from DMF)

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and compounds **1b** and **4b** were isolated by sublimation. It should be emphasized that the yield of 3,7-dichlorobisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (**1a**) achieved (76%) was higher than the yield of the above-mentioned compound in the reaction with the participation of the Cu^0—collidine system[1] (67%). Because of this as well as owing to the fact that quartz vessels are not necessary here (the reactions proceeded readily in glass flasks), this procedure proves to be preparatively valuable.

Apparently, the reactions of compounds **2a,b** under study proceeded through the formation of radicals **5a,b** initiated with light, subsequent conversions being governed by the nature of the solvent used. In CH_2Cl_2, radical **5a** was apparently stabilized through a sequence of reactions of detachment of hydrogen atoms from the solvent and dehalogenation to form 4-amino-3,5-dichloroisothiazole (**3a**). In CCl_4, an alternative scheme of reactions was apparently realized, which involved the replacement of the halogen atom at the C(5) atom in dibromoamine **2** by radical **5**, dehalogenation of adduct **6** formed, and its cyclization to 3,7-disubstituted bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine **1**. In this case, the nature of the halogen atom at position 5 of the isothiazole ring has, evidently, no noticeable effect on the course of the reaction. Within the framework of the proposed scheme, the formation of diazenes **4a,b** is explained by recombination of radicals **5a,b** and dehalogenation of the *N,N′*-dibromohydrazine formed. The formation of nitrenes in the course of the reaction, for example, as a result of the detachment of the Br radical from intermediates **5a,b**, seems to be highly improbable because products of insertion of nitrenes into C—H and (or) C—Cl bonds of the solvent were absent among the compounds isolated.

Experimental

The ^1H and ^{13}C NMR spectra were obtained in DMSO-d_6 and in a mixture of CCl_4 and $CDCl_3$ on a Bruker AM-300 spectrometer operating at 300.13 (^1H) and 62.9 (^{13}C) MHz. The ^1H and ^{13}C chemical shifts were measured relative to DMSO-d_6 (δ 2.50 and 39.5) and $CDCl_3$ (δ 7.27 and 76.9). TLC was carried out on Silpearl UV-250 silica gel using benzene as the eluent. 4-Amino-5-bromo-3-methylisothiazole (**3b**) was prepared according to a procedure reported previously.[3] Dibromoisocyanuric acid was prepared according to a known procedure.[4] A mercury-quartz OKN-11 emitter equipped with a DRT-220 mercury lamp (850 W) without a filter was used as the radiation source.

5-Bromo-4-dibromoamino-3-methylisothiazole (2b). DBI (0.60 g, 2.09 mmol) was added to a solution of 4-amino-5-bromo-3-methylisothiazole (**3b**) (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 was filtered off and washed with CCl_4 (1 mL). The TLC analysis of the mother liquor showed the presence of only one product (**2b**), R_f 0.8. ^1H NMR (CCl_4—$CDCl_3$), δ: 2.19 (s, 3 H, CH_3). ^{13}C NMR (CCl_4—$CDCl_3$), δ: 30.6 (CH_3), 109.3 (C—Br), 139.4 (C—NBr_2), 156.7 (C—CH_3).

Reactions of 4-dibromoaminoisothiazoles 2a and 2b in CH_2Cl_2 and CCl_4 under irradiation with UV light. *A.* A solution of 3,5-dichloro-4-(dibromoamino)isothiazole (**2a**)[1] (0.20 g, 0.61 mmol) in anhydrous CH_2Cl_2 (5 mL) was placed into a glass flask and irradiated with UV light at 20 °C for 10 min. The solvent was removed and the residue was crystallized from hexane. 4-Amino-3,5-dichloroisothiazole (**3a**) was obtained in a yield of 0.09 g (87%), m.p. 78—79 °C (*cf.* Ref 5: m.p. 79 °C).

B. A solution of 4-dibromoaminoisothiazole (**2a** or **2b**) in CCl_4 (prepared from the corresponding 4-aminoisothiazole **3a** or **3b** (1.39 mmol) as described above) was irradiated with UV light at 30—35 °C for 5—6 h. Shortly after the beginning of irradiation, the solution turned brown. After completion of exposure, the reaction mixture contained products **1a,b** and **4a,b**, while the initial compounds **2a** and **2b** were virtually absent (according to the TLC data). The solvent and the halogens that liberated in the reaction were removed *in vacuo* and then hexane (5 mL) was added to the residue. The precipitate was filtered off, washed with hexane (1 mL), and dried under an air stream. The resulting mixture of **1a** and **4a** was dissolved in hot DMF (1 mL). The precipitate that formed upon cooling was filtered off and dried. *N,N′*-Bis(3,5-dichloroisothiazol-4-yl)diazene (**4a**) was obtained in a yield of 0.03 g (13%), m.p. 218—220 °C (*cf.* Ref. 1: m.p. 219—220 °C). The mother liquor was diluted with water (1 mL). The precipitate that formed was filtered off and dried. 3,7-Dichlorobisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (**1a**) was obtained in a yield of 0.14 g (76%), m.p. 208—209 °C (*cf.* Ref. 1: m.p. 207—208 °C). According to the TLC data, compounds **1a** and **4a** are identical to the products prepared according to a procedure reported previously.[1]

A mixture of products **1b** and **4b** was subjected to sublimation at 90 °C (2 Torr). 3,7-Dimethylbisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (**1b**) was obtained as yellow crystals in a yield of 0.09 g (58%), m.p. 179—181 °C, R_f 0.45. ^1H NMR (DMSO-d_6), δ: 2.88 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6), δ: 17.1 (CH_3), 141.6 (C(4)), 162.2 (C—CH_3), 163.0 (C—S). MS, *m/z* (*I* (%)): 222 $[M]^+$ (100), 181 $[M - CH_3CN]^+$ (16), 140 $[M - 2\,CH_3CN]^+$ (23), 73 $[CH_3C{=}N{=}S]^+$ (14). Found (%): C, 44.08; H, 2.75; N, 25.31; S, 28.95. $C_8H_6N_4S_2$. Calculated (%): C, 43.24; H, 2.70; N, 25.23; S, 28.83.

According to the data of TLC, the residue remaining after sublimation was virtually pure *N,N′*-bis(5-bromo-3-methylisothiazol-4-yl)diazene (**4b**) obtained as yellow-orange crystals in a yield of 0.10 g (37%), m.p. 187—189 °C (AcOH), R_f 0.60. ^1H NMR (DMSO-d_6), δ: 2.65 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6), δ: 20.3 (CH_3), 136.6 (C—Br), 146.6 (C—N=N), 161.9 (C-CH_3). Found (%): C, 26.08; H, 1.69; Br, 42.07; N, 15.01; S, 16.93. $C_8H_6Br_2N_4S_2$. Calculated (%): C, 25.13; H, 1.57; Br, 41.88; N, 14.66; S, 16.75.

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