Unusual scission of 3,7-dichlorobisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine by nucleophiles

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The reaction of 3,7-dichlorobisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine with MeONa in MeOH afforded 3-chloro-5,6-dimethoxyisothiazolo[4,5-*b*]pyrazine. The reactions of the former with benzylamine, morpholine, and aniline gave rise to the corresponding *N*,*N*′-bis(5-amino-3-chloroisothiazol-4-yl)diazenes. In the case of benzylamine, 3,7-bis(benzylamino)bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine was isolated as a by-product. The crystal structure of *N*,*N*′-bis(5-benzylamino-3-chloroisothiazol-4-yl)diazene was established by X-ray diffraction analysis.

Key words: 3,7-disubstituted bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines, *N*,*N*′-bis(5-amino-3-chloroisothiazol-4-yl)diazenes, 3-chloro-5,6-dimethoxythiazolo[4,5-*b*]pyrazine, nucleophilic substitution.

Previously,[1—3] we have synthesized 3,7-disubstituted bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines, which are representatives of a new heterocyclic system, by reductive condensation of 4-dibromoamino-3-R-5-haloisothiazoles in the presence of the Cu^0—collidine system or under the action of light.

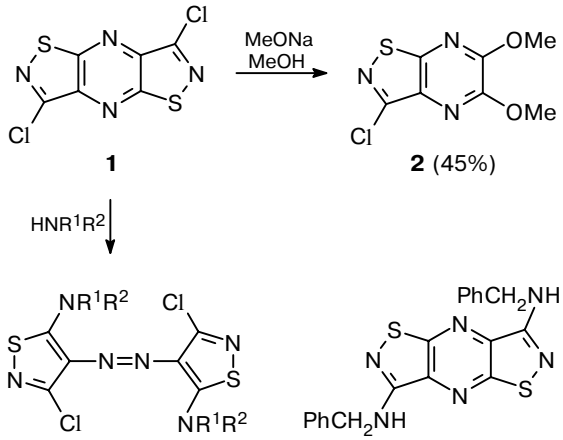
With the aim of preparing 3,7-dialkyloxy- and 3,7-diaminobisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines, we studied the reactions of the 3,7-dichloro derivative (**1**) with the methoxide anion and amines.

Results and Discussion

It is known[4] that the chlorine atom in 3-chloro-1,2-benzoisothiazoles can be replaced by the amino or alkoxy groups under the action of amines or alkoxide anions, respectively. However, the reactions of 3,7-dichlorobisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (**1**) with the above-mentioned nucleophiles were found to afford products of isothiazole or pyrazine ring-opening (**2**—**5**) rather than products of replacement of the halogen atom. The direction of the reaction is governed by the nature of the nucleophile.

Thus the reaction of compound **1** with MeONa in MeOH resulted in the opening of one isothiazole ring to form 3-chloro-5,6-dimethoxyisothiazolo[4,5-*b*]pyrazine (**2**) in 45% yield. The reactions of heterocycle **1** with benzylamine, morpholine, and aniline gave rise to the corresponding *N*,*N*′-bis(5-amino-3-chloroisothiazol-4-yl)diazenes **3**—**5**, which did not contain the pyrazine ring (the yields were 25—28%). The reaction of compound **1** with benzylamine afforded diazene **3** along with 3,7-bis(benzylamino)bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (**6**) in low yield (5%) (Scheme 1).

Scheme 1



3: R^1 = H, R^2 = CH_2Ph (28%)
4: R^1 = H, R^2 = Ph (26%)
5: R^1R^2 = —$(CH_2)_2O(CH_2)_2$— (28%)
6 (5%)

Apparently, the reactions of compound **1** with nucleophiles begin with the attack of the nucleophile at the C atom of the heterocycle bound to the S atom. The direction of the electron density shift in the molecule

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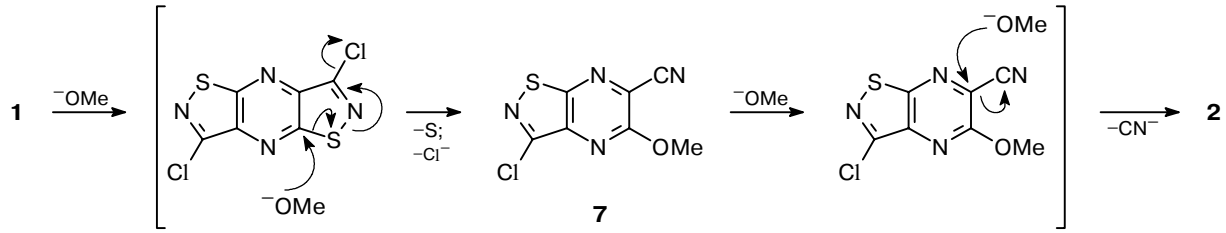
Scheme 2



depends on the type of the nucleophile. The reaction with MeO^- results apparently in the cleavage of the C—S and S—N bonds in the isothiazole ring and elimination of Cl^-. The nucleophilic replacement of the cyano group in intermediate 3-chloro-6-cyano-5-methoxyisothiazolo[4,5-*b*]pyrazine (**7**) under the action of the second molecule of the nucleophile gives rise to the final product (**2**) (Scheme 2).

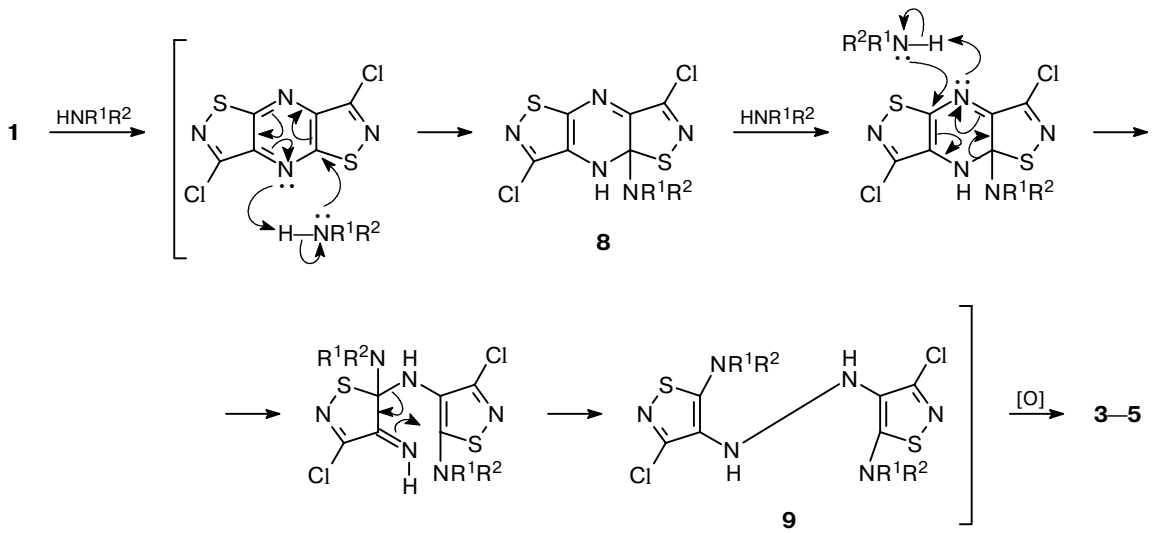
Apparently, the first stage of the reactions with amines formally involves the addition of amine at the C=N bond of the pyrazine ring to give the dihydropyrazine derivative (**8**). Subsequent addition of the second amine molecule, rearrangement, and oxidation of the hydrazo group in intermediate **9** (for example, by atmospheric oxygen) afford diazenes (**3**—**5**) as the final reaction products (Scheme 3).

We believe that the difference in the behavior of compound **1** in the reactions with the alkoxide anion and the amines is attributable, on the one hand, to the difference in their basicities and, on the other hand, to the presence of the labile H atom in the amines due to which the latter can add at the multiple bonds of the pyrazine ring.

The structures of compounds **2**—**6** were confirmed by the data from ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The crystal structure of *N*,*N*′-bis(5-benzylamino-3-chloroisothiazol-4-yl)diazene (**3**) was established by X-ray diffraction analysis.

Centrosymmetrical molecule **3** (Fig. 1), except for the phenyl substituents, is virtually planar (the average deviation of the atoms from the plane is 0.04 Å). The dihedral angles between the plane of the central fragment and the planes of the phenyl rings are 75.86(7)°. The N(3) atom adopts the planar configuration (the sum of the bond angles is 359.7(2)°). The geometric parameters of the heterocycle have standard values. Noteworthy is only a slight shortening of the endocyclic C(1)—N(1) bond (1.300(3) Å) compared to the average value (1.32 Å) for 28 analogous fragments available in the Cambridge Structural Database[5] (a search was limited by organic structures characterized by $R < 10\%$ and the average error in coordinates of no higher than 0.01 Å). Both exocyclic C(2)—N(2) (1.383(3) Å) and C(3)—N(3) (1.333(3) Å) bond lengths are smaller than the average values[6] for the C_{ar}—N=N (1.431 Å) and C_{ar}—N(sp^2)H (1.353 Å) bond lengths, respectively. At the same time, the N(2)=N(2A) bond length (1.287(3) Å) is somewhat larger than the average value (1.255 Å)[6] for the C_{ar}—N=N—C_{ar} fragment. This is indicative of the

Scheme 3



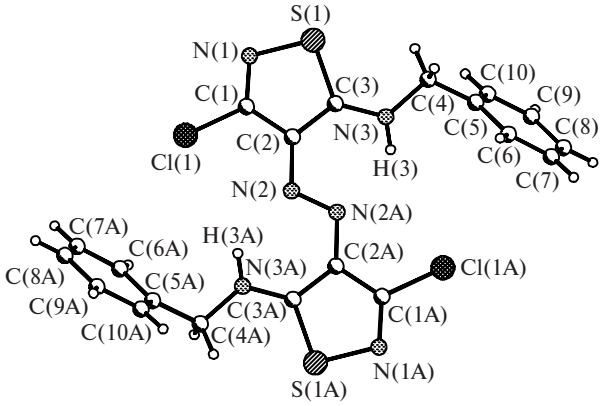


Fig. 1. Overall view of molecule **3**.

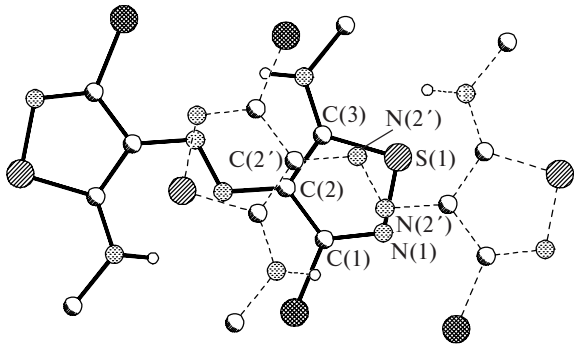


Fig. 3. Scheme of overlapping of the molecules from the adjacent layers in the structure of **3**.

presence of conjugation between the lone electron pair of the N(3) atom, the C(2)=C(3) bond of the heterocycle, and the diazo fragment.

In the molecule, a planar six-membered H ring is formed through the intramolecular N(3)—H(3)...N(2A) hydrogen bond (N(3)...N(2A), 2.745(3) Å; H(3)...N(2A), 2.11(2) Å; N(3)H(3)N(2A), 131(2)°).

In the crystal, the molecules are linked in parallel planar layers (Fig. 2). The shortest intermolecular contacts between the molecules in the layer (S(1)...S(1′), 3.353(2) Å) are shorter than the distance corresponding to the specific interaction (3.53 Å).[7] In spite of the rather large distance between the layers (3.41 Å), the fact that the diazo fragment of the molecule in one layer overlaps with the heterocycle of the molecule in the adjacent layer (Fig. 3) is indicative of possible interactions between the π systems of the overlapping fragments. The adjacent layers are linked through shortened contacts of the second type (S(1)...S(1″), 3.460(2) Å) perpendicular to the plane of the layer (the angle between the S(1)...S(1′) and S(1)...S(1″) contact lines is 92.67(4)°).

Experimental

The ^{1}H and ^{13}C NMR spectra (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) were recorded on a Bruker AM-300 spectrometer in DMSO-d_6. The ^{1}H and ^{13}C chemical shifts were measured relative to DMSO-d_6 (δ 2.50 and 39.5 relative to Me_4Si). TLC was carried out on silica gel Silpearl UV-250 in toluene. The solvents were dried according to standard procedures.[8]

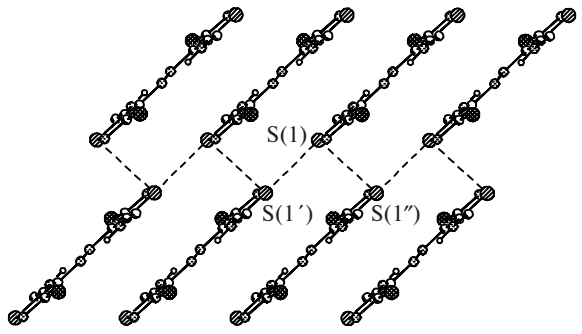


Fig. 2. Crystal packing of molecules **3**. The phenyl fragments are omitted.

Crystals of **3** are monoclinic, at 298 K, a = 4.929(1) Å, b = 27.494(9) Å, c = 8.051(2) Å, β = 100.28(2)°, V = 1073.5(5) Å^3, Z = 2, d_{calc} = 1.471 g cm^{-3}, space group $P2_1/n$, $C_{20}H_{16}Cl_2N_6S_2$, M = 475.41. The unit cell parameters and the intensities of 2454 reflections were measured on an automated Siemens P3/PC diffractometer (Mo-Kα radiation, θ/2θ scanning technique, $2\theta_{max}$ = 52°). The X-ray diffraction data were processed using the PROFIT program for the profile analysis.[9] The structure was solved by the direct method and refined anisotropically by the full-matrix least-squares method. The positions of the H atoms were located from the difference Fourier synthesis and refined isotropically. The final reliability factors were as follows: R_1 = 0.0393 based on $F(hkl)$ for 1372 reflections with $I > 2\sigma(I)$ and wR_2 = 0.1058 based on $F^2(hkl)$ for all 2108 independent reflections. A total of 168 parameters were refined.

All crystal-structural calculations were performed using the SHELXS-97 program package.[10] The atomic coordinates and the complete crystal-structural information on the structure of **3** were deposited with the Cambridge Structural Database.

3-Chloro-5,6-dimethoxyisothiazolo[4,5-*b*]pyrazine (2). Pyrazine **1** (0.10 g, 0.38 mmol) was added to a solution of MeONa prepared from Na (0.02 g, 0.95 mg-at.) in anhydrous MeOH (2 mL). The reaction mixture was stirred at 15 °C for 40 min, the solvent was removed *in vacuo*, and the residue was washed with hexane. Compound **2** was isolated by preparative TLC in benzene in a yield of 0.04 g (45%), m.p. 107—110 °C, R_f = 0.45. Found (%): C, 36.01; H, 2.72; Cl, 15.49; N, 17.95; S, 13.62. $C_7H_6ClN_3O_2S_2$. Calculated (%): C, 36.29; H, 2.61; Cl, 15.30; N, 18.14; S, 13.84. ^{1}H NMR, δ: 4.25 and 4.26 (both s, CH_3). MS, m/z: 231 [M$^+$].

***N,N′*-Bis(5-benzylamino-3-chloroisothiazol-4-yl)diazene (3) and 3,7-bis(benzylamino)bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (6).** Benzylamine (0.16 mL, 0.16 g, 1.52 mmol) was added to a suspension of pyrazine **1** (0.10 g, 0.38 mmol) in dry MeCN (2 mL). The reaction mixture was stirred at 15 °C for 5 h, the solvent was removed *in vacuo*, and the residue was chromatographed on a column with silica gel (toluene as the eluent). Compounds **3** (R_f = 0.43) and **6** (R_f = 0.32) were isolated in yields of 50 mg (28%) and 8 mg (5%), respectively. Compound **3**: m.p. 198—200 °C. Found (%): C, 50.85; H, 3.59; Cl, 14.63; N, 17.41; S, 13.18. $C_{20}H_{16}Cl_2N_6S_2$. Calculated (%): C, 50.53; H, 3.39; Cl, 14.91; N, 17.68; S, 13.49. ^{1}H NMR, δ: 4.52 (d, 2 H, CH_2, J = 7.5 Hz); 7.30—7.50 (m, 5 H, Ph); 9.30 (t, 1 H,

NH, J = 7.5 Hz). ^{13}C NMR, δ: 51.0 (CH_2); 128.1 (*p*-C, Ph); 128.2 (*m*-C, Ph); 128.8 (*o*-C, Ph); 135.7 (C—N=N); 147.6 (C—NH); 163.4 (C—Cl). MS, *m/z*: 474 [M^+]. Compound **6**: m.p. 208—210 °C. Found (%): C, 59.49; H, 3.86; N, 20.69; S, 15.93. $C_{20}H_{16}N_6S_2$. Calculated (%): C, 59.38; H, 3.99; N, 20.78; S, 15.85. ^{1}H NMR, δ: 4.80 (d, 2 H, CH_2, J = 7.5 Hz); 7.40—7.50 (m, 5 H, Ph); 8.60 (t, 1 H, NH, J = 7.5 Hz). ^{13}C NMR, δ: 44.8 (CH_2); 126.8 (*p*-C, Ph); 127.4 (*m*-C, Ph); 128.3 (*o*-C, Ph); 139.5 (C(4)); 155.9 (C—NH); 160.6 (C—S). MS, *m/z*: 404 [M^+].

***N,N′*-Bis(5-anilino-3-chloroisothiazol-4-yl)diazene (4).** The reaction of pyrazine **1** (0.10 g, 0.38 mmol) with aniline (0.14 g, 1.52 mmol) was carried out at 15 °C for 30 min. The precipitate that formed was filtered off and recrystallized from DMF. Compound **4** was obtained in a yield of 0.04 g (26%), m.p. 307—310 °C, R_f = 0.57. Found (%): C, 48.08; H, 2.61; Cl, 15.54; N, 18.58; S, 14.52. $C_{18}H_{12}Cl_2N_6S_2$. Calculated (%): C, 48.33; H, 2.70; Cl, 15.85; N, 18.79; S, 14.34. ^{1}H NMR, δ: 7.10—7.40 (m, 5 H, Ph); 9.10 (br.s, 1 H, NH). MS, *m/z*: 446 [M^+].

***N,N′*-Bis(3-chloro-5-morpholinoisothiazol-4-yl)diazene (5).** The reaction of pyrazine **1** (0.10 g, 0.38 mmol) with morpholine (0.13 g, 1.52 mmol) was carried out at 15 °C for 24 h. The precipitate that formed was filtered off and washed with acetonitrile (1.0 mL). Compound **5** was obtained in a yield of 0.03 g (25%), m.p. 235—240 °C, R_f = 0.45. Found (%): C, 38.80; H, 3.59; Cl, 16.01; N, 19.07; S, 14.54. $C_{14}H_{16}Cl_2N_6O_2S_2$. Calculated (%): C, 38.52; H, 3.70; Cl, 16.29; N, 19.30; S, 14.73. ^{1}H NMR, δ: 3.60 and 3.80 (both m, CH_2). ^{13}C NMR, δ: 50.39 (C—N); 64.9 (C—O); 141.4 (C—N=N); 170.1 (C—N); 185.1 (C—Cl). MS, *m/z*: 435 [M^+].

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