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INTERACTION OF BENZIMIDAZOLE-2-THIONE WITH PROPARGYL BROMIDE AND 1,3-DIBROMOPROPYNE*

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Interaction of benzimidazole-2-thione with propargyl bromide under found conditions permitted the direct synthesis of 2-(2-propynylsulfanyl)-3H-1,3-benzimidazolium bromide, the base 2-(2-propynylsulfanyl)-1H-1,3-benzimidazole, stable crystalline 2-(1,2-propadienylsulfanyl)-1H-1,3-benzimidazole, and 3-methyl[1,3]thiazolo[3,2-a][1,3]benzimidazole. The reaction of benzimidazole-2-thione with 1,3-dibromopropyne in chloroform or absolute methanol gave 2-(3-bromo-2-propynylsulfanyl)-3H-1,3-benzimidazolium bromide, and in absolute methanole in the presence of a twofold excess of sodium methoxide the reaction proceeded stereo- and regioselectively to give 3-[(Z)-bromomethylidene][1,3]thiazolo[3,2-a][1,3]benzimidazole.

Keywords: benzimidazole-2-thione, 2-(3-bromo-2-propynylsulfanyl)-3H-1,3-benzimidazolium bromide, 3-[(*Z*)-bromomethylidene][1,3]thiazolo[3,2-*a*][1,3]benzimidazole, 1,3-dibromopropyne, 3-methyl-[1,3]thiazolo[3,2-*a*][1,3]benzimidazole, 2-(1,2-propadienylsulfanyl)-1H-1,3-benzimidazole, propargyl bromide, 2-(2-propynylsulfanyl)-1H-1,3-benzimidazole, 2-(2-propynylsulfanyl)-3H-1,3-benzimidazolium bromide, intramolecular cyclization.

Thiones of nitrogen-containing heterocycles have excited the attention of researchers because of their synthetic possibilities and useful properties. The reactions of these compounds with derivatives of acetylene have been relatively little studied until now. It is known that 4-thiouracil- and 3-sulfanyl-1,2,4-triazine-5-one react with propargyl bromide and 1-bromo-2-butyne in the presence of catalysts (NaOMe, $PdCl_2(PhCN)_2$) to form substituted thiazolo[2,3-*c*]pyrimidin-5-ones and thiazolo[2,3-*c*]-1,2,4-triazin-4-ones [1]. Analogous products were obtained from the reaction of these compounds with 1-acyl-2-bromoacetylenes in DMF in the presence of triethylamine [2, 3]. It was reported that the products of the reactions of benzimidazole-2-thione with acetylenic ketones and dibenzoylacetylene in MeOH, MeCN were 2-(acylvinylsulfanyl)benzimidazoles [4]. Reactions of benzimidazole-2-thione with esters of phenylpropiolic, acrylic, and acetylenedicarboxylic acids were studied [5-8]. The reaction of benzimdazole-2-thione with 2-cyano-1-phenylacetylene in dioxane in the presence of KOH gave 2-imino-4-phenyl-benzimidazo[2,3-*b*]-1,3-thiazine [9].

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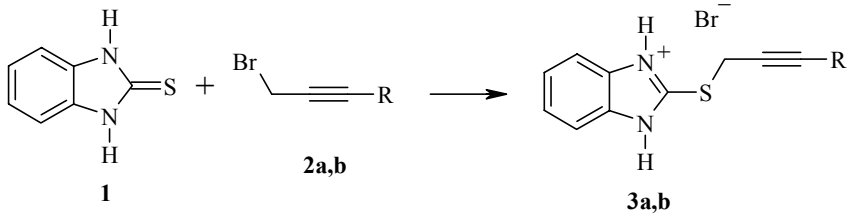
In the present work we have established that benzimidazole-2-thione (**1**) readily underwent nucleophilic substitution with propargyl bromide **2a** or 1,3-dibromopropyne **2b** in dry chloroform or absolute methanol to give 2-(2-propynylsulfanyl)-3H-1,3-benzimidazolium bromide (**3a**) or 2-(3-bromo-2-propynylsulfanyl)-3H-1,3-benzimidazolium bromide (**3b**) in yields of 78 and 87% respectively.

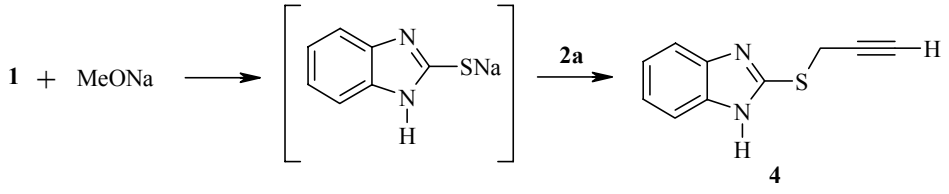


1 **2a,b** **3a,b**

2, **3 a** R = H, **b** R = Br

Absorption bands of the triple bond are present in the IR spectra of bromides **3a,b** at 2110 and 2220 cm^{-1}. A signal of the C≡CH proton appeared at 3.42 ppm in the ^1H NMR spectrum of the bromide **3a**. Signals of the carbon atoms of the ≡CH and ≡CBr groups appeared at 76.20 and 46.87 ppm respectively in the ^{13}C NMR spectra of compounds **3a,b.**

The order of mixing of the reagents played an important role in the direction of the reaction. For example, when the thione **1** was added to sodium methoxide solution (in 1:1 ratio) with subsequent addition of propargyl bromide **2a** and heating to 60°C for 3h, 2-(2-propynylsulfanyl)-1H-1,3-benzimidazole (**4**) in 66% yield. The absorption band of the triple bond at 3293 cm^{-1} was present in the IR spectrum of compound **4.** The signal of the terminal ≡CH group was observed at 3.18 ppm in the ^1H NMR spectrum and signals of the carbon atoms of acetylenic bond at 74.03 and 80.03 ppm in the ^{13}C NMR spectrum.



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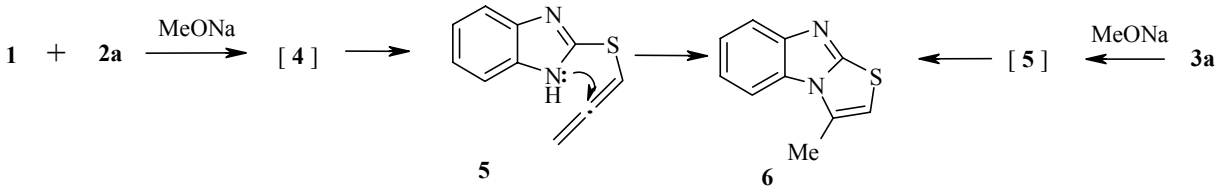
When the reaction of thione **1** with propargyl bromide **2a** was carried out in absolute MeOH with subsequent generation of an equimolar quantity of sodium methoxide *in situ* at 60°C for 3 h, the air-stable crystalline product with an allenic structure – 2-(1,2-propadienylsulfanyl)-1H-1,3-benzimidazole (**5**) – was produced in 81% yield.



5 **6**

There is an intense absorption band of the allene group –HC=C=CH_2 at 1945 cm^{-1} in the IR spectrum of compound **5**. In the ^1H NMR spectrum, signals of the =CH proton as a triplet at 6.62 ppm and of the =CH_2 group as a doublet at 5.29 ppm are present. Signals of the =CH_2 and =CH groups at 80.65 and 82.23 ppm and of the allenic carbon (=C=) at 207.94 ppm were observed in the ^{13}C NMR spectrum.

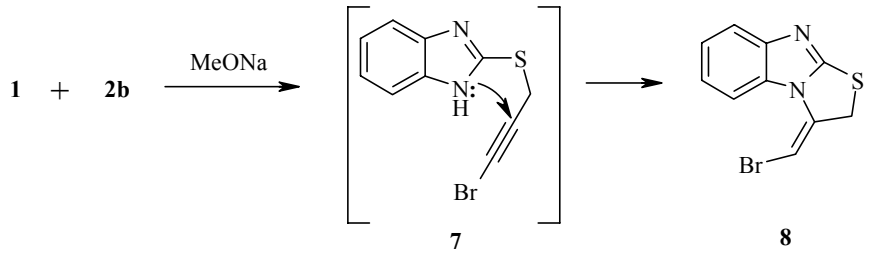
The base catalyzed acetylene-allene isomerization has been studied in detail in a number of papers [10-14] and we have described it earlier [15, 16].

3-Methyl[1,3]thiazolo[3,2-*a*][1,3]benzimidazole (**6**) was formed in 75% yield on the reaction of an equimolar amount of sodium methoxide with the allenyl sulfide **5** in methanol solution. It was also observed that the allenyl sulfide **5** underwent intramolecular cyclization on standing in DMSO solution at 20-25°C. It was shown by ^{1}H NMR spectroscopy that the ratio of the compounds was **5:6** = 1:1 after 24 h, and on standing for 1 month the basic product was compound **6** (ratio of compounds **5:6** = 1:6).

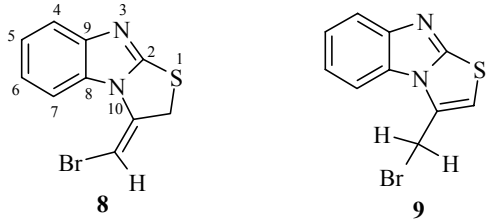
Compound **6** was obtained in 68% yield by the interaction of bromide **3a** with a twofold excess of sodium methoxide in absolute methanol at 60°C. Evidently the allene intermediate **5** was formed during the reaction and then cyclized to the tricyclic product **6**. Compound **6** was also produced in 79% yield by the interaction of the thione starting material **1** with propargyl bromide **2a** in absolute methanol in the presence of a twofold excess of sodium methoxide.

The ^{1}H NMR spectrum of compound **6** includes signals of the CH_3 protons as a doublet at 2.73 ppm and of the =CH proton at 6.85 ppm. The ^{13} NMR spectrum includes signals of the carbon atoms of the =CH and CH_3 groups at 105.30 and 13.39 ppm.

Reaction of equimolar amounts of thione **1** with 1,3-dibromopropyne **2b** in absolute methanol with subsequent addition of a twofold excess of sodium methoxide led to the formation in 63% yield of 3-[(*Z*)-bromomethylidene][1,3]thiazolo[3,2-*a*][1,3]benzimidazole (**8**). Evidently the reaction includes the intermediate formation of 2-(3-bromo-2-propynylsulfanyl)-3H-1,3-benzimidazole (**7**) which cyclizes to the *Z*-isomer under the reaction conditions. Its formation may be explained by the stereoselective *anti* addition of the nitrogen atom to the triple bond activated by the bromine atom.



The formation of the isomeric compound **9** with an endocyclic double bond might be predicted. However the ^{1}H and ^{13}C NMR spectra confirm structure **8** unambiguously. In the undecoupled ^{13}C NMR spectrum of the heterocycle **8** the signal of atom C-2 is observed as a triplet (159.05 ppm) by coupling to the protons of the methylene group (4.64 pm, ^3J = 2.6 Hz). Moreover in the two-dimensional HMBC ^{1}H-^{13}C NMR spectrum the protons of the CH_2 group have cross peaks with C-2 and with the carbon atoms of the C=CHBr (136.02 ppm) and =CHBr (85.51 ppm) groups. The 2D NOESY ^{1}H-^{1}H NMR spectrum indicates the presence of a cross-peak between the CH_2 protons and the =CHBr proton. On this basis it can be confirmed that the compound obtained is the *Z*-isomer **8**.



EXPEIMENTAL

IR spectra of KBr tablets were recorded with a Specord IR-75 instrument. ^{1}H, ^{13}C, and ^{15}N NMR spectra of DMSO-d_6 solutions at 27°C were record with Bruker DPX-400 and Bruker AV-400 spectrometers (400, 100, and 40.56 MHz respectively). Values of the ^{1}H and ^{13}C chemical shifts were measured relative to TMS; the precision of measurements were 0.01 and 0.02 respectively. J_{CH} coupling constants were determined with a precision of 0.1 Hz. For assigning the signals and determining molecular structures heteronuclear two-dimensional ^{1}H-^{13}C NMR spectroscopy – HSQC (Heteronuclear Single Quantum Correlation) and HMBC (Heteronuclear Multiple Bond Correlation) and NOESY ^{1}H-^{1}H methods were used. The ^{15}N chemical shifts were determined with a precision of 0.1 Hz relative to CH_3NO_2 as external reference, using the 2D HMBC-gp ^{1}H-^{15}N method.

2-(2-Propynylsulfanyl)-3H-1,3-benzimidazolium Bromide (3a). A solution of propargyl bromide **2a** (0.6 g, 5 mmol) in dry chloroform (15 ml) was added with stirring to a solution of thione **1** (0.75 g, 5 mmol) in dry chloroform (20 ml), stirring was continued for 3 h at 60°C. The reaction mixture was cooled to 0°C, the precipitate was filtered off, washed on the filter with a small amount of ether, and dried in vacuumo. Yield 1.05 g (78%); mp 194-196°C (ethanol). IR spectrum, ν, cm^{-1}: 590 (C–S); 1455 (CH_2, def); 1520, 1615 (C=N, C=C); 2110 (C≡C); 2940 (CH_2, stretch); 3220 (NH in ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.42 (1H, t, *J* = 2.4, =CH); 4.42 (2H, d, *J* = 2.4, CH_2); 7.48-7.73 (4H, m, C_6H_4); 11.52 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 21.87 (CH_2); 76.20 (≡CH); 78.37 (CH_2–C ≡); 113.53, 125.43, 132.98 (C arom); 148.54 (HN–C–S). ^{15}N NMR spectrum, δ, ppm: -209.3 (NH). Found, %: C 44.61; H 3.38; Br 30.17; N 9.98; S 11.74. $C_{10}H_9BrN_2S$. Calculated, %: C 44.61; H 3.35; Br 29.74; N 10.41; S 11.90.

Compound **3a** was obtained in 38% yield when the reaction was carried out in absolute methanol.

2-(3-Bromo-2-propynylsulfanyl)-3H-1,3-benzimidazolium Bromide (3b). A solution of 1,3-dibromopropyne **2b** (0.99 g, 5 mmol) in absolute methanol (15 ml) was added to a solution of thione **1** (0.75 g, 5 mmol) in absolute methanol (20 ml) and the mixture was stirred at 20°C for 2 h. Yield 1,52 g (87%), colorless crystals; mp 135-137°C (ethanol). IR spectrum, ν, cm^{-1}: 615 (C–S); 1415 (CH_2, def); 1520, 1625 (C=N, C=C); 2220 (C≡C); 2940 (CH_2, stretch); 3465 (NH). ^{1}H NMR spectrum, δ, ppm: 4.35 (2H, s, CH_2); 7.40-7.66 (4H, m, C_6H_4); 11.55 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 22.54 (CH_2); 46.87 (≡CBr); 74.83 (CH_2–C≡); 113.72, 124.79, 134.36 (C arom); 148.3 (HN–C–S). ^{15}N NMR spectrum, δ ppm: -209.5 (NH). Found, %: C 34.25; H 2.38, Br 45.65; N 8.25; S 9.16. $C_{10}H_8Br_2N_2S$. Calculated, %: C 34.48; H 2.30; Br 45.98; N 8.06, S 9.20.

2-(2-Propynylsulfanyl)-1H-1,3-benzimidazole (4). To a solution of sodium methoxide, prepared from sodium (0.12 g, 5 mmol) in absolute methanol (20 ml), thione **1** (0.75 g, 5 mmol) was slowly added, the mixture was stirred for 20 min at room temperature, then propargyl bromide **2a** (0.6 g, 5 mmol) in absolute methanol (10 ml) was added dropwise. The reaction mixture was heated to 60°C for 3 h with stirring. It was then cooled to 0°C, the precipitate which formed was filtered off, washed on the filter with water, and dried in vacuum. Yield 0.56 g (66%); mp 164-165°C (ether). IR spectrum, ν, cm^{-1}: 637 (C–S); 1443 (CH_2, def); 1506, 1516 (C=C, C=N); 3293 (C≡C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.18 (1H, t, ^{4}J = 2.5, ≡CH); 4.14 (2H, d, ^{4}J = 2.5, CH_2); 7.15-7.47 (4H, m, C_6H_4); 12.20 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 19.74 (CH_2); 74.03 (=CH); 80.03 (CH_2–C); 114.30-140.20 (C arom); 148.24 (C-2). Found, %: C 63.55; H 3.96; N 14.65; S 16.85. $C_{10}H_8N_2S$. Calculated, %: 62.83; H 4.26; N 14.89; S 17.02.

2-(1,2-Propadienylsulfanyl)-1H-1,3-benzimidazole (5). A solution of propargyl bromide **2a** (0.6 g, 5 mmol) in absolute methanol (15 ml) was added with stirring to a solution of thione **1** (0.75 g, 5 mmol) in absolute methanol (20 ml), followed by finely divided metallic sodium (0.12 g). The reaction mixture was stirred for 3 h at 60°C, cooled to 0°C, and the precipitate which formed was filtered off, washed on the filter with water until neutral, and dried in vacuum. Yield 0.76 g (81%), colorless crystals; mp 198-200°C. IR

spectrum, ν, cm^{-1}: 545 (C–S); 1510 (C=N); 1945 (C=C=C); 1440 (CH_2, def); 3005 (CH_2, stretch); 3450 (NH in ring). ^1H NMR spectrum, δ, ppm *(J*, Hz): 5.29 (2H, d, *J* = 6.2, $=CH_2$); 6.62 (1H, t, *J* = 6.2, CH=); 7.14-7.47 (4H, m, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 80.65 ($=CH_2$); 82.23 (CH=); 121.50, 121.55, 175.50 (C arom); 140.00 1132 N=C–S); 207.84 (=C=). Found, %: C 63.77; H 4.56; N 14.60; S 16.89. $C_{10}H_8N_2S$. Calculated, %: C 63.83, H 4.26, N 14.89, S 17.02.

3-Methyl[1,3]thiazolo[3,2-*a*][1,3]benzimidazole (6). A. Propargyl bromide **2a** (0.6 g 5 mmol) was added to a solution of thione **1** (0.75 g, 5 mmol) in absolute methanol (20 ml); followed by a solution of sodium methoxide (0.23 g sodium in 15 ml absolute methanol). The mixture was stirred for 24 h. Yield 0.74 g (79%), colorless crystals; mp 159-161°C. IR spectrum, ν, cm^{-1}: 560 (C–S); 1520, 1675 (C=N, C=C); 2970 (CH_3). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.73 (3H, d, *J* = 1.3, CH_3); 6.85 (1H, q, *J* = 1.3, =CH); 7.24-7.95 (4H, m, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 105.30 (=CH); 13.39 (CH_3); 111.38, 118.38, 120.42, 122.95, 130.08, 147.99 (C arom); 130.29 (S–CH=); 156.61 (N=C–S). ^{15}N NMR spectrum: δ, ppm: -162.4 (N=C-S); -190.1 (N–C=CH). Found, %: C 63.60; H 4.05; N 14.44; S 16.88. $C_{10}H_8N_2S$. Calculated, %: C 63.83; H 4.26; N 14.89; S 17.02.

B. A solution of sodium methoxide (0.09 g sodium in 20 ml absolute methanol) was added to a solution of bromide **3a** (0.54 g, 2 mmol) in absolute methanol (10 ml) at 60°C over 3 h. Yield of compound **6** 0.26 g (68%); mp 159-161°C.

C. A solution of sodium methoxide (0.05 g sodium in 5 ml methanol) was added to a solution of allenyl sulfide **5** (0.38g, 2 mmol) in absolute methanol (15 ml) at 60°C over 3 h. Yield of compound **6** 0.28 g (75%); mp 162-163°C.

3-[(*Z*)-Bromomethylidene[1,3]thiazolo[3,2-*a*][1,3]benzimidazole (8). A solution of 1,3-dibromo-propyne **2b** in absolute methanol (15 ml) was added to a solution of thione **1** (0.75 g, 5 mmol) in absolute methanol (20 ml) and then, with stirring, a solution of sodium methoxide (0.24 g sodium in 15 ml absolute methanol) was added. The reaction mixture was heated to 60°C, stirred for 3h, cooled to 0°C, and the precipitate formed was filtered off, washed on the filter with water until neutral, and dried in vacuum. Yield 0.92 g (69%), colorless crystals; mp 103-105°C. IR spectrum, ν, cm^{-1}: 630 (C–S); 1450 (CH_2, def); 1530, 1615 (C=N, C=C); 2930 (CH_3, stretch). ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.64 (2H, d, *J* = 1.3, CH_2); 6.43 (1H, t, *J* = 1.3, =CHBr); 7.23-8.02 (4H, m, C_6H_4); 11.54 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 41.60 (CH_2); 85.51 (=CHBr); 114.66, 118.42, 122.07, 123,12, 131.65, 148.46 (C arom); 136.02 (C=CHBr); 159.05 (N–C–S). ^{15}N NMR spectrum, δ, pm: -148.1 (N=C–S); -209.7 (N–C=CHBr). Found, %: C 45.12; H 2.64; Br 30.05; N 10.22, S 12.18. $C_{10}H_7BrN_2S$. Calculated, %: C 44.94; H 2.62; Br 29.96; N 10.49; S 11.99.

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