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FEATURES OF (BENZO)IMIDAZO[2,1-*B*][1,3]THIAZINE MEZYLATES REACTION WITH NUCLEOPHILIC REAGENTS

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Abstract. Peculiarities of the course of the methanesulfoderivatives of (benzo)imidazo[2,1-*b*][1,3]thiazines reactions with a number of nucleophilic reagents were studied. It was determined that they react nonselectively with potassium thiocyanate to form a mixture of thio- and isothiocyanate derivatives. When interacting with sodium azide, nucleophilic substitution competes with an elimination reaction. The latter is dominant in the reaction with sodium cyanide. The spatial structure of one of the isomer elimination products, 4*H*-benzo[4,5]imidazo[2,1-*b*][1,3] thiazine, was established by X-ray structural analysis.

Keywords: (benzo)imidazo[2,1-*b*][1,3]thiazines, nucleophilic substitution reaction, elimination reaction, thio (isothio)cyanato and azido derivatives.

1. Introduction

Recently, the attention of specialists in the field of medical and pharmaceutical chemistry is increasingly focused on the design and synthesis of functional condensed heterocyclic systems, among which azole-azine structures occupy a prominent place.[1-6] Among the latter, it is worth highlighting various derivatives of imidazo[2,1-b][1,3]thiazines, which are characterized by a wide spectrum of biological activity. In particular, compounds with antioxidant,[7] antibacterial,[8] antiviral,[9] antituberculosis,[10] and antitrypanocidal[11] effects and cytotoxic effects on non-cancerous F2408 and cancerous 5RP7 cells[12] were found among them. The imidazothiazine ring is an important pharmacophore fragment of inhibitors of the cannabinoid-activated protein GPR18,[13] reversible inhibitors of TbAdoMetDC of African trypanosomiasis,[14] and also a potential agent in the therapy of Chagas disease.[11]

Nucleophilic substitution reaction in basic scaffolds is one of the powerful tools for structural modification of biologically attractive heterocyclic compounds.[15-17] This, in turn, prompted researchers both to search for new variants of such reactions based on available substrates and to involve new nucleophilic reagents. Generally, the use of nucleophilic substitution reactions in heterocyclic cores yielded a number of compounds interesting in terms of structure and properties, which can directly be used as objects of bioscreening studies, and act as synthetic blocks for the construction of more complex molecular structures. However, the information is quite scarce regarding the modification of the (benzo)[4,5]imidazo[2,1-*b*][1,3] thiazine core by nucleophilic transformations. That is why it seemed advisable to study the possibility of hydroxyl group participation in available hydroxy(benzo) imidazo[2,1-*b*][1,3]thiazines in substitution reactions with various types of nucleophilic reagents.

2. Experimental

2.1. Materials and Methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 126 MHz, respectively) in pulsed Fourier mode in DMSO-d_6 and in $CDCl_3$, with TMS as the internal standard. Mass spectra were recorded on an Agilent LC/MSD SL instrument, Zorbax SB-C18 column, 4.6×15 mm, 1.8 μm (PN 82(c)75-932), DMSO-d_6 as the solvent, electrospray ionization at atmospheric pressure. Elemental analysis was performed on a PerkinElmer CHN Analyzer 2400 series in the analytical laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Melting points were determined according to a Kofler table and are uncorrected. Reagents and solvents were purchased from UKRORGSYNTEZ LTD. Merck 60 (40–63 μ) silica gel was used for column chromatography.

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2.2. Synthesis of Benzo[4,5]imidazo[2,1-*b*][1,3]thiazinyl Methanesulfonates 2a-c

0.12 mL (6.7 mmol) of methanesulfochloride was added to the solution of 6.4 mmol of (benzo)[4,5]imidazo[2,1-*b*][1,3]thiazine **1a-c** in 20 mL of dry pyridine. The reaction mixture was stirred at room temperature for 48 h, the resulting suspension was poured onto ice, the formed precipitate was filtered and dried in a drying cabinet.

6,7-Dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazin-6-yl methanesulfonate 2a. Yield: 51 %, mp 409-411 K. Crystallize from propanol-2. ^{1}H NMR spectrum, DMSO-d_6, δ, ppm (*J*, Hz): 3.35 s (3H, CH_3), 3.44-3.49 m (1H, SCH_2), 3.62-3.66 m (1H, SCH_2), 4.30-4.40 m (2H, NCH_2), 5.50-5.54 m (1H, CH), 7.03 s (1H, $CH_{imidazole}$), 7.30 c (1H, $CH_{imidazole}$). ^{13}C NMR spectrum, DMSO-d_6, δ, ppm: 29.9 (C^7), 38.4 (CH_3), 49.3 (C^5), 70.2 (C^6), 122.8 (C^3), 126.8 (C^2), 136.1 (C^{8a}). Mass spectrum, *m/z*: 235 $[M+H]^+$. Found, %: C 35.80; H 4.29; N 11.94. $C_7H_{10}N_2O_3S_2$. Calculated, %: C 35.88; H 4.30; N 11.96.

2,3-Diphenyl-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazin-6-yl methanesulfonate 2b. Yield: 86 %, mp 438-440 K. Crystallize from propanol-2. ^{1}H NMR spectrum, DMSO-d_6, δ, ppm (*J*, Hz): 3.30 s (3H, CH_3), 3.46-3.51 m (1H, SCH_2), 3.61-3.64 m (1H, SCH_2), 3.85-3.89 m (1H, NCH_2), 4.11-4.15 m (1H, NCH_2), 5.47-5.50 m (1H, CH), 7.11-7.15 m (1H, Ar), 7.18-7.21 m (2H, Ar), 7.33-7.39 m (4H, Ar), 7.47-7.54 m (3H, Ar). ^{13}C NMR spectrum, DMSO-d_6, δ, ppm: 29.4 (C^7), 38.3 (CH_3), 48.1 (C^5), 70.4 (C^6), 126.5, 126.9, 128.6, 129.4, 129.7 (C, Ar), 129.8 (C^2), 130.0, 131.1, 134.4 (C, Ar), 136.6 (C^3), 136.8 (C^{8a}). Mass spectrum, *m/z*: 387 $[M+H]^+$. Found, %: C 59.03; H 4.66; N 7.23. $C_{19}H_{18}N_2O_3S_2$. Calculated, %: C 59.05; H 4.69; N 7.25.

3,4-Dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazin-3-yl methanesulfonate 2c. Yield: 84 %, mp 438-440 K. Crystallize from propanol-2. ^{1}H NMR spectrum, DMSO-d_6, δ, ppm (*J*, Hz): 3.36 s (3H, CH_3), 3.54-3.58 m (1H, SCH_2), 3.73-3.77 m (1H, SCH_2), 4.42-4.46 m (1H, NCH_2), 4.54-4.58 m (1H, NCH_2), 5.65-5.69 m (1H, CH), 7.18-7.20 m (2H, Ar), 7.47-7.50 m (2H, Ar). ^{13}C NMR spectrum, DMSO-d_6, δ, ppm: 29.7 (C^2), 38.4 (CH_3), 47.2 (C^4), 69.9 (C^3), 109.4 (C^9), 117.6 (C^6), 121.8 (C^7), 122.7 (C^8), 136.0 (C^{5a}), 142.6 (C^{9a}), 145.9 (C^{10a}). Mass spectrum, *m/z*: 285 $[M+H]^+$. Found, %: C 46.37; H 4.24; N 9.83. $C_{11}H_{12}N_2O_3S_2$. Calculated, %: C 46.46; H 4.25; N 9.85.

2.3. Synthesis of Thio- 3a-c and Isothiocyanato(benzo)imidazo[2,1-*b*][1,3]thiazines 4a,b

0.33 g (3.4 mmol) of KSCN was added to solution of 1.7 mmol of mesylate **2a-c** in 10 mL of dry DMFA. The reaction mixture was heated at 373 K for 10 h, the solvent was evaporated under reduced pressure, the resulting residue was treated with water and extracted with $CHCl_3$. The organic layer was dried with Na_2SO_4 and evaporated, the residue was separated by a column chromatography (eluent $CHCl_3$-MeOH, 150:1).

6-Thiocyanato-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine 3a. Yield: 28 %, yellow oil. IR spectrum, ν, cm^{-1}: 2162 (SCN). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.25 dd (1H, ^2J = 12.0, ^3J = 8.0, SCH_2), 3.40 dd (1H, ^2J = 14.0, ^3J = 6.0, SCH_2), 4.21 dd (1H, ^2J = 12.0, ^3J = 4.0, NCH_2), 4.31 dd (1H, ^2J = 10.0, ^3J = 6.0, NCH_2), 4.48-4.54 m (1H, CH), 6.95 s (1H, $CH_{imidazole}$), 6.98 s (1H, $CH_{imidazole}$). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 37.8 (C^7), 48.8 (C^5), 51.0 (C^6), 110.4 (SCN), 116.8 (C^2), 134.0 (C^3), 146.8 (C^{8a}). Mass spectrum, *m/z*: 198 $[M+H]^+$. Found, %: C 42.87; H 3.52; N 21.43. $C_7H_7N_3S_2$. Calculated, %: C 42.62; H 3.58; N 21.30.

2,3-Diphenyl-6-thiocyanato-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine 3b. Yield: 45 %, mp 415-417 K. Crystallize from chloroform. IR spectrum, ν, cm^{-1}: 2155 (SCN). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.32 dd (1H, ^2J = 13.6, ^3J = 8.8, SCH_2), 3.46 dd (1H, ^2J = 13.8, ^3J = 6.2, SCH_2), 4.14 dd (1H, ^2J = 12.0, ^3J = 3.2, NCH_2), 4.31 dd (1H, ^2J = 11.6, ^3J = 6.8, NCH_2), 4.51-4.57 m (1H, CH), 7.34-7.36 m (3H, Ar), 7.41-7.45 m (5H, Ar), 7.49-7.50 m (2H, Ar). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 38.3 (C^7), 49.0 (C^5), 51.1 (C^6), 110.8 (SCN), 126.9, 127.0, 127.8, 128.3, 128.6, 129.1, 129.2, 130.1 (C, Ar), 134.2 (C^2), 142.9 (C^3), 146.5 (C^{8a}). Mass spectrum, *m/z*: 350 $[M+H]^+$. Found, %: C 65.17; H 4.32; N 12.00. $C_{19}H_{15}N_3S_2$. Calculated, %: C 65.30; H 4.33; N 12.02.

Mixture of 2,3-Diphenyl-6-thiocyanato-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine 3b and 2,3-Diphenyl-6-isothiocyanato-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine 4a. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.29-3.35 m (1H, SCH_2), 3.42-3.48 m (2H, SCH_2), 3.54-3.58 m (1H, SCH_2), 3.99-4.04 m (1H, NCH_2), 4.08-4.17 m (3H, NCH_2), 4.29-4.34 m (1H, CH), 4.51-4.57 m (1H, CH), 7.17-7.28 m (8H, Ar), 7.35-7.51 m (12H, Ar).

3-Thiocyanato-3,4-dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine 3c. Yield: 42 %, 417-418 K. Crystallize from chloroform. IR spectrum, ν, cm^{-1}: 2150 (SCN). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.55 dd (1H, ^2J = 12.0, ^3J = 8.0, SCH_2), 3.60-3.64 m (1H, SCH_2), 4.23-4.29 m (1H, CH), 4.42 dd (1H, ^2J = 12.0, ^3J = 8.0, NCH_2), 4.61 dd (1H, ^2J = 8.0, ^3J = 4.0, NCH_2), 7.26-7.32 m (3H, Ar), 7.65-7.67 m (1H, Ar). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 30.0 (C^2), 41.4 (C^4), 47.0 (C^3), 109.1 (C^6), 110.9 (SCN), 117.3 (C^9), 121.6 (C^7), 122.3 (C^8), 135.5 (C^{5a}), 142.8 (C^{9a}), 144.6 (C^{10a}). Mass spectrum, *m/z*: 248 $[M+H]^+$. Found, %: C 53.60; H

3.69; N 16.84. $C_{11}H_9N_3S_2$. Calculated, %: C 53.42; H 3.67; N 16.99.

3-Isothiocyanato-3,4-dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine 4b. Yield: 22 %, 404-406 K. Crystallize from chloroform. IR spectrum, ν, cm^{-1}: 1954 (NCS). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.32 dd (1H, ^2J = 12.0, ^3J = 8.0, SCH_2), 3.50 dd (1H, ^2J = 14.0, ^3J = 6.0, SCH_2), 4.40-4.48 m (2H, NCH_2), 4.64-4.70 m (1H, CH), 7.22-7.26 m (3H, Ar), 7.64-7.66 m (1H, Ar). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 38.4 (C^2), 47.6 (C^4), 52.8 (C^3), 110.4 (C^6), 113.1 (C^{5a}), 118.3 (C^9), 122.0 (C^7+C^8), 134.2 (C^{9a}), 149.0 (C^{10a}), 156.8 (NCS). Mass spectrum, *m/z*: 248 $[M+H]^+$. Found, %: C 53.65; H 3.62; N 17.13. $C_{11}H_9N_3S_2$. Calculated, %: C 53.42; H 3.67; N 16.99.

2.4. Synthesis of Azidoimidazo[2,1-*b*][1,3]thiazines 5a-c

0.28 g (4.25 mmol) of sodium azide was added to the solution of 1.7 mmol of mesylate **2a-c** in 10 mL of dry DMF and heated at 373 K for 10 h. The solvent was evaporated under reduced pressure, the resulting residue was treated with water and extracted with $CHCl_3$. The organic layer was dried with Na_2SO_4 and evaporated, the residue was separated by a column chromatography (eluent $CHCl_3$-MeOH, 50:1).

6-Azido-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine 5a. Yield: 32 %, brown oil. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.18-3.25 m (1H, SCH_2), 3.27-3.33 m (1H, SCH_2), 3.89-3.96 m (1H, NCH_2), 4.15-4.21 m (1H, NCH_2), 4.28-4.35 m (1H, CH), 6.85 s (1H, $CH_{imidazole}$), 6.98 s (1H, $CH_{imidazole}$). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 29.4 (C^7), 48.0 (C^5), 53.4 (C^6), 120.1 (C^2), 128.7 (C^3), 135.5 (C^{8a}). Mass spectrum, *m/z*: 182 $[M+H]^+$. Found, %: C 39.69; H 3.87; N 38.59. $C_6H_7N_5S$. Calculated, %: C 39.77; H 3.89; N 38.65.

6-Azido-2,3-diphenyl-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine 5b. Yield: 55 %, mp 413-414 K. Crystallize from chloroform. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.21 dd (1H, ^2J = 13.0, ^3J = 7.8, SCH_2), 3.29-3.33 m (1H, SCH_2), 3.67 dd (1H, ^2J = 13.4, ^3J = 7.0, NCH_2), 3.84 dd (1H, ^2J = 13.2, ^3J = 4.0, NCH_2), 4.24-4.29 m (1H, CH), 7.12-7.21 m (3H, Ar), 7.30-7.32 m (2H, Ar), 7.45-7.47 m (5H, Ar). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 29.3 (C^7), 47.8 (C^5), 53.9 (C^6), 126.6, 126.7, 128.1, 129.0, 129.2, 129.5, 129.7, 130.8 ($C_{arom.}$), 133.8 (C^2), 136.2 (C^3), 138.0 (C^{8a}). Mass spectrum, *m/z*: 334 $[M+H]^+$. Found, %: C 64.71; H 4.51; N 20.98. $C_{18}H_{15}N_5S$. Calculated, %: C 64.84; H 4.53; N 21.01.

3-Azido-3,4-dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine 5c. Yield: 46 %, mp 412-413 K. Crystallize from chloroform. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.21 dd (1H, ^2J = 12.8, ^3J = 8.0, SCH_2), 3.27-3.31 m (1H, SCH_2), 3.90 dd (1H, ^2J = 12.6, ^3J = 7.4, NCH_2), 4.14 dd (1H, ^2J = 12.4, ^3J = 4.4, NCH_2), 4.32-4.38 m (1H, CH), 7.08 d (1H, ^3J = 8.0, Ar), 7.16 t (1H, ^3J = 8.0 Ar), 7.22 t (1H, ^3J = 7.6, Ar), 7.59 d (1H, ^3J = 7.6, Ar). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 29.3 (C^2), 46.1 (C^4), 53.4 (C^3), 107.9 (C^6), 118.2 (C^9), 122.0 (C^7), 122.8 (C^8), 135.4 (C^{5a}), 143.0 (C^{9a}), 145.1 (C^{10a}). Mass spectrum, *m/z*: 232 $[M+H]^+$. Found, %: C 51.83; H 3.91; N 30.23. $C_{10}H_9N_5S$. Calculated, %: C 51.93; H 3.92; N 30.28.

2.5. Synthesis (benzo)imidazo[2,1-*b*][1,3]thiazine 6a,b, 7a,b

0.17 g (3.4 mmol) of sodium cyanide was added to the solution of 1.7 mmol of mesylate **2a-c** in 10 mL of dry DMFA and heated at 373 K for 10 h. The solvent was evaporated under reduced pressure, the resulting residue was treated with water and extracted with $CHCl_3$. The organic layer was dried with Na_2SO_4 and evaporated, the residue was separated by a column chromatography (eluent $CHCl_3$-MeOH, 150:1).

Mixture of 2,3-diphenyl-5*H*-imidazo[2,1-*b*][1,3]thiazine 6a and 2,3-diphenyl-7*H*-imidazo[2,1-*b*][1,3]thiazine 7a. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.57 d (2H, ^3J = 8.0, CH_2), 4.43-4.44 m (2H, CH_2), 5.45-5.50 m (1H, CH), 5.78-5.83 m (1H, CH), 6.34-6.37 m (1H, CH), 6.51-6.53 m (1H, CH), 7.12-7.24 m (6H, Ar), 7.33-7.35 m (4H, Ar), 7.44-7.53 m (10H, Ar).

4*H*-Benzo[4,5]imidazo[2,1-*b*][1,3]thiazine 6b. Yield: 34 %, 425-426 K. Crystallize from chloroform. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 4.93-4.94 m (2H, NCH_2), 6.08-6.12 m (1H, CH), 6.40-6.43 m (1H, CH), 7.30-7.34 m (3H, Ar), 7.71-7.73 m (1H, Ar). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 43.4 (C^4), 108.7 (C^6), 114.8 (C^3), 115.8 (C^2), 117.9 (C^9), 122.8 (C^7), 123.5 (C^8), 134.1 (C^{5a}), 142.9 (C^{9a}), 147.8 (C^{10a}). Mass spectrum, *m/z*: 350 $[M+H]^+$. Found, %: C 63.61; H 4.32; N 15.00. $C_{10}H_8N_2S$. Calculated, %: C 63.80; H 4.28; N 14.88.

Mixture of 4*H*-benzo[4,5]imidazo[2,1-*b*][1,3] thiazine 6b and 2*H*-benzo[4,5]imidazo[2,1-*b*][1,3] thiazine 7b. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 3.68-3.70 m (2H, SCH_2), 4.91-4.92 m (2H, NCH_2), 5.58-5.63 m (1H, CH), 6.06-6.09 m (1H, CH), 6.39-6.42 m (1H, CH),7.06-7.08 m (1H, CH), 7.24-7.31 m (6H, Ar), 7.64-7.71 m (2H, Ar).

2.6. X-Ray crystal structure determination

The yellow crystals of compound **6b** ($C_{10}H_8N_2S$) are monoclinic. At 293 K a = 6.0820(7), b = 12.1456(14), c = 12.3132(16) Å, β = 104.172(7)°, V = 881.89(19) Å^3, M_r = 188.24, Z = 4, space group $P2_1/c$, d_{calc} = 1.418 g/cm^3,

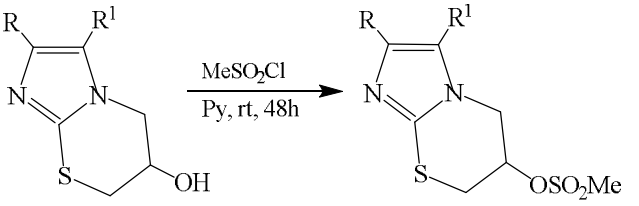
$\mu(MoK_\alpha) = 0.314$ mm^{-1}, $F(000) = 392$. Intensities of 12803 reflections (1550 independent, $R_{int} = 0.022$) were measured on the Bruker APEX II diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\Theta_{max} = 50°$). The structure was solved by a direct method using SHELXTL package.[18] Positions of the hydrogen atoms were located from electron density difference maps and refined using a "riding" model with $U_{iso} = 1.2U_{eq}$ of the carrier atom. Full-matrix least-squares refinement against F^2 in an anisotropic approximation for non-hydrogen atoms using 1550 reflections was converged to $wR_2 = 0.106$ ($R_1 = 0.039$ for 1263 reflections with $F>4\sigma(F)$, $S = 1.053$). The final atomic coordinates, and crystallographic data for molecule **6b** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on the request quoting the deposition numbers CCDC 2234051).

3. Results and Discussion

The reaction of nucleophilic substitution of nitrogen- and sulfur-containing fragments for a halogen atom or a hydroxyl group is known as a convenient and effective approach for directed functionalization of heterocyclic compounds. It is usually characterized by a significant degree of conversion and high yields of target products. However, imidazo[2,1-*b*][1,3]thiazine derivatives were not systematically studied in this kind of transformations, except for the report [19] that described the synthesis of 6-bromo-2,3-diphenylimidazo[2,1- *b*][1,3]thiazine and 3-chlorobenzo[4,5]imidazo[2,1-*b*][1,3]thiazine by halogenation of the corresponding 6(3)-hydroxy(benzo) imidazo[2,1-*b*] [1,3]thiazines. Therefore, we decided to investigate the possibility of using hydroxy-substituted (benzo)imidazo[2,1-*b*][1,3]thiazines[10, 20-22] as basic substrates in nucleophilic substitution reactions with sodium azide, potassium thiocyanate, and sodium cyanide.

Taking into account the fact that the hydroxyl group near the sp^3-hybridized third carbon atom does not play the role of a leaver in nucleophilic substitution reactions (unlike its protonated form), it was transformed in (benzo)imidazo[2,1-b][1,3]thiazines **1a-c** to a more nucleofugous mesylate group. For this purpose, the corresponding mesylates **2a-c** were obtained with yields of 51-86 % by treating heterocyclic alcohols **1a-c** with methanesulfonic acid chloroanhydride in a pyridine solution at room temperature (Scheme 1).

The structure of the synthesized compounds **2a-c** was reliably confirmed by a complex of physico-chemical researches, particularly by the results of ^{1}H and ^{13}C NMR measurements, in which the characteristic signal of the methyl group is recorded at 3.30-3.36 ppm and 38.23-38.4 ppm, respectively.



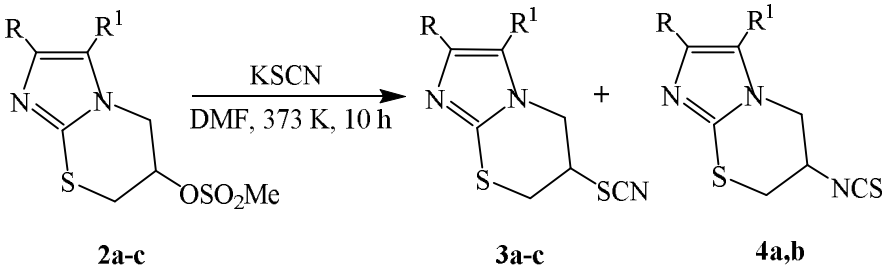
1a-c **2a-c**

1, 2 a R = R^1=H, **b** R = R^1=Ph, **c** RR^1 = (CH=CH)$_2$

Scheme 1. Synthesis of imidazo[2,1-*b*][1,3] thiazinyl methanesulfonates **2a-c**

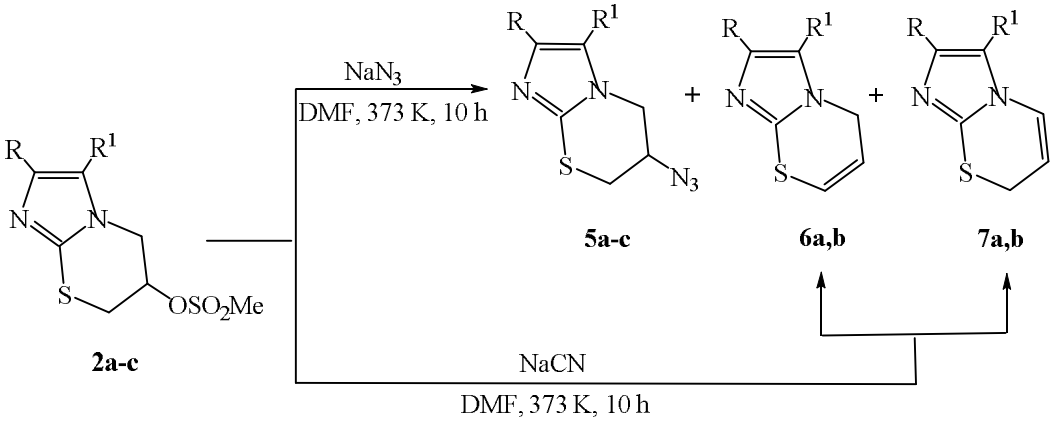
The optimal course of the reaction of mesylates **2a-c** with such an ambident nucleophile as potassium thiocyanate turned out to be heating the reagents in DMFA solution at 373 K for 10 hours. It was also established that in the case of methanesulfonate **2a** unsubstituted in the imidazole ring, the reaction proceeds selectively with the formation of 6-thiocyanatoimidazo[2,1-*b*][1,3]thiazine **3a** (Scheme 2). On the other hand, in the case of diphenyl-substituted **2b** and benzoannelated **2c** derivatives, it was revealed by the ^{1}H NMR spectroscopy method that a non-selective process is observed, leading to two types of isomeric substitution products, thiocyanatoimidazo[2,1-*b*]thiazines **3b,c** and isothiocyanatoimidazo[2,1-*b*]thiazines **4a,b** in the ratio **3b:4a** = 3.2:1; **3c:4b** = 2.5:1 (Scheme 2). The resulting mixture of products was separated by the column chromatography on silica gel using a mixture of $CHCl_3$:MeOH, 150:1 as an eluent. The preferred thiocyanates **3b,c** were isolated, and their structure was confirmed by IR spectra with narrow absorption bands of SCN groups at 2155-2162 cm^{-1} and ^{13}C NMR spectra with signals of carbon atoms of the thiocyanate group at 110.7-110.8 ppm. However, among the minor products only 3-isothiocyanato-3,4-dihydro-2*H*-benzo[4,5] imidazo[2,1-*b*][1,3]thiazine **4b** could be isolated. Its IR spectrum is characterized by a wide absorption band of the NCS group at 1954 cm^{-1}, and the ^{13}C NMR spectrum has the signal of the carbon atom of this group at 156.8 ppm.

The reaction of nucleophilic substitution of the mesylate group of compounds **2a-c** with sodium azide under similar reaction conditions is also non-selective. It was found in the case of mesylate **2a** that unidentified products of the destruction of the imidazothiazine core were formed along with the target azide **5a** (32 % yield). At the same time, diphenyl-substituted **2b** and benzoannelated **2c** mesylates react with the formation of a mixture of azides **5b,c** and structurally isomeric products of the elimination of methanesulfonic acid **6a,b** and **7a,b** (Scheme 3). The ratio of the latter determined by comparing the integral intensities of alkenyl protons in the reaction mixture was **6a:7a** = 1.6:1; **6b:7b** = 2:1. Purification and isolation of target azides **5a-c** were performed by the column chromatography on silica gel (eluent $CHCl_3$-MeOH, 50:1).



2, 3 a R = R^1=H, **b** R = R^1=Ph, **c** RR^1 = (CH=CH)$_2$;
4 a R = R^1=Ph, **b** RR^1 = (CH=CH)$_2$

Scheme 2. Synthesis of thio- and isothiocyanato(benzo)imidazo[2,1-*b*][1,3]thiazines **3a-c** and **4a,b**



2, 5 a R = R^1=H, **b** R = R^1=Ph, **c** RR^1 = (CH=CH)$_2$;
6, 7 a R = R^1=Ph, **b** RR^1 = (CH=CH)$_2$

Scheme 3. Synthesis of azidoimidazo[2,1-*b*][1,3]thiazines **5a-c** and products of elimination **6a,b, 7a,b**

Their own specifics were revealed in the reaction of compounds **2a-c** with sodium cyanide, a stronger reagent in terms of nucleophilicity and basicity compared to sodium azide[23] under the above reaction conditions. Thus, its interaction with mesylate **2a** is accompanied by the destruction of the imidazothiazine cycle, whereas in the case of diphenyl-substituted **2b** and benzoannelated **2c** derivatives, an isomer mixture of the elimination products is formed with the ratio **6a:7a** = 1.1:1; **6b:7b** = 2.5:1 (Scheme 3). Isomer **6b** was isolated by the column chromatography, while isomers **6a, 7a** could not be separated.

The results of measurements of ^{1}H, ^{13}C NMR and LC-MS spectra (see Sec. 2 Experimental) do not contradict the proposed structure of elimination products **6b** and **7b**. In addition, the physico-chemical characteristics of compound **6b** coincide with those of the compound obtained by the counter way of synthesis, cyclocondensation of N-(prop-2-ynyl)-o-phenyldiamine hydrochloride with carbon disulfide.[24] However, in order to clarify the stereochemical features of its structure, X-ray structural study was considered advisable.

The X-ray diffraction study has shown that the tricyclic fragment of compound **6b** has a linear structure (**Fig.**). All the non-hydrogen cyclic atoms lie within the plane with the accuracy of 0.02 Å despite of the Csp^3 hybridization of the C7 atom. Planar structure of the thiazine ring causes the shortening of the C7–C8 bond up to 1.468(3) Å as compared to its mean value of 1.506 Å.[25]

In the crystal phase, molecules **6b** form stacking dimers of the "head-to-tail" type due to both stacking interaction (the distance between π-systems is 3.46 Å, the shift of the π-systems to each other is 1.923 Å) and C–H…π hydrogen bonds (C7–H7b…C2' symmetry operation is 1-x,1-y,1-z, the H…C distance is 2.79 Å, the C–H…C bond angle is 154° and C7–H7b…C3' symmetry operation is 1-x,1-y,1-z, the H…C distance is 2.89 Å, the C–H…C bond angle is 126°).

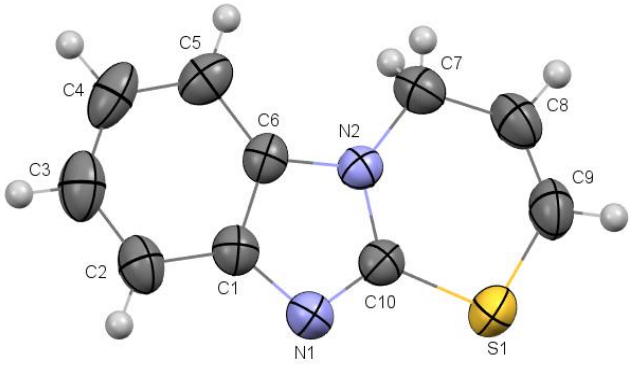


Figure. Molecular structure of compound **6b** according to X-ray diffraction data. For clarity, only one conformer is presented. Thermal ellipsoids are shown at **5**0% probability level

4. Conclusions

We investigated the particularities of the course of the reaction of (benzo)imidazo[2,1-*b*][1,3]thiazine mesylates with a number of typical nucleophilic reagents: potassium thiocyanate, sodium azide, and sodium cyanide. It was established that depending on their nucleophilicity, the formation of elimination products takes place along with substitution products. The spatial structure of the elimination product, 4*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine **6b**, was established by X-ray structural analysis.

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ОСОБЛИВОСТІ ВЗАЄМОДІЇ (БЕНЗО)ІМІДАЗО[2,1-B][1,3]ТІАЗИНМЕЗИЛАТІВ З НУКЛЕОФІЛЬНИМИ РЕАГЕНТАМИ

Анотація. *Вивчено особливості перебігу реакцій метансульфопохідних (бенз)імідазо[2,1-b][1,3]тіазинів з рядом нуклеофільних реагентів. Встановлено, що вони неселективно реагують із калію тіоціанатом, утворюючи суміш тіо- та ізотіоціанатопохідних. У свою чергу, у результаті взаємодії з натрію азидом поряд із нуклеофільним заміщенням має місце конкуруюча реакція елімінування. Остання реалізується як домінуюча в реакції з натрію ціанідом. Методом рентгеноструктурного аналізу встановлено просторову будову одного з ізомерних продуктів елімінування – 4H-бензо[4,5]імідазо[2,1-b][1,3]тіазину.*

Ключові слова: *(бензо)імідазо[2,1-b][1,3]тіазини, реакції нуклеофільного заміщення, реакції елімінування, тіо(ізотіо) ціанато- та азидопохідні.*