Synthesis of 2-(imidazolylamino)benzothiazoles

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Treatment of derivatives of 5-phenylthioureido-3*H*-imidazole-4-carboxylic acid with bromine afforded 2-(imidazolylamino)benzothiazoles.

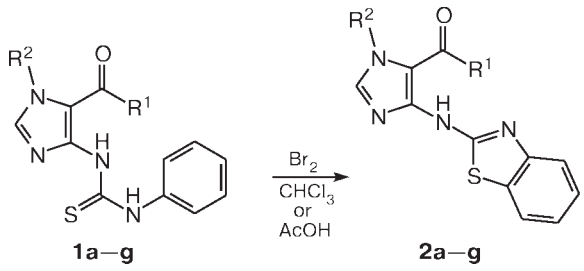
Key words: 2-aminobenzothiazole, oxidative cyclization, imidazolylphenylthiourea, imidazolylaminobenzothiazole.

Certain of 2-aminobenzothiazole derivatives have an action on the central nervous system,[1,2] possess antimicrobial and antibacterial properties,[3,4] serve as neuroleptic agents,[5—7] or act as plant growth regulators.[8,9] In this connection, the synthesis of new 2-aminobenzothiazole derivatives is of interest.

One of convenient procedures for the construction of the benzothiazole system involves oxidative cyclization of phenylthioureas with bromine (Hugerschoff's synthesis).[10] In the present study, we applied this procedure to the synthesis of new heteroaromatic derivatives of 2-aminobenzothiazole containing the imidazole ring bound to the amino group. 5-Imidazolylphenylthioureas **1a—g** were used as the starting compounds. The reactions of bromine with polyfunctional imidazolylthioureido derivatives **1a—g** can follow several pathways. Thus the imidazole and aromatic rings can undergo bromination,[11] fused imidazothiadiazoles can be produced,[12] or cyclization can occur to generate imidazole derivatives of 2-aminobenzothiazole. The latter process is analogous to the transformations of arylthioureas under the action of bromine.[13,14] Such oxidative transformations of *N*-(imidazol-5-yl)-*N´*-phenylthioureas have previously been unknown.

However, it appeared that the reactions of thioureas **1a—f** (R^1 = OEt, NH_2, or NHMe) with bromine afforded imidazolylaminobenzothiazoles **2a—f** as the only products in 50—77% yields (Scheme 1). The structures of the resulting compounds were confirmed by the ^{1}H NMR spectroscopic data. Thus the signal for the proton of the NH group of the thioureido fragment is absent and the resonance signals for only four aromatic protons are observed at δ 7.8—7.1. In addition, the character of splitting of these signals is typical of *o*-substituted aromatic systems (Table 1). Under analogous conditions, bromination of compound **1g** (R^1 = NHC_6H_4-Me-*p*) proceeded ambiguously to give a mixture of several products with similar chromatographic mobilities. We failed to isolate

Scheme 1



R^1 = OEt, R^2 = H (**a**); Et (**b**); Pr (**c**); CH_2COMe (**d**);
R^1 = NH_2, R^2 = H (**e**); R^1 = NHMe, R^2 = H (**f**);
R^1 = NHC_6H_4-Me-*p*, R^2 = H (**g**)

individual products from this mixture. Imidazolylaminobenzothiazole **2g** containing the arylamide functional group was prepared by the reaction performed in acetic acid at 70 °C. The molecular ions in the mass spectra of the resulting compounds correspond to the calculated *m/z* values (Table 2). Note that the type of fragmentation of the molecular ions is identical in all the mass spectra. Thus four most intense fragmentation ions are observed in all mass spectra at *m/z* 242 (Φ_1), 161 (Φ_2), 134 (Φ_3), and 108 (Φ_4) (Scheme 2).

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument (250.13 MHz) in a solution in DMSO-d_6 with $SiMe_4$ as the internal standard. The course of the reactions and the purities of the compounds were monitored by TLC on Sorbfil UV-254 plates using the 1 : 10 ethanol—chloroform system. The mass spectra were measured on a Varian MAT 311A instrument; the accelerating voltage was 3 kV; the energy of ionizing electrons was 70 eV. The melting points were not corrected. Compounds **1a—g** were prepared according to procedures described previously.[12,15]

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Table 1. ^{1}H NMR spectra of the compounds synthesized

Compound	δ (*J*/Hz)
2a	12.94, 9.11 (both br.s, 1 H each, 2 NH); 7.76 (d, 1 H, Ar, *J* = 7.9); 7.68 (s, 1 H, CH, Im); 7.55 (d, 1 H, Ar, *J* = 7.9); 7.33—7.11 (m, 2 H, Ar); 4.38 (q, 2 H, $O\underline{CH_2}CH_3$, *J* = 6.7); 1.40 (t, 3 H, $OCH_2\underline{CH_3}$, *J* = 6.7)
2b	8.04 (s, 1 H, CH, Im); 7.85 (d, 1 H, Ar, *J* = 7.9); 7.63 (d, 1 H, Ar, *J* = 8.2); 7.41—7.20 (m, 2 H, Ar); 5.00 (br.s, 1 H, NH); 4.46 (m, 4 H, $O\underline{CH_2}CH_3$, $N\underline{CH_2}CH_3$); 1.38 (m, 6 H, $OCH_2\underline{CH_3}$, $NCH_2\underline{CH_3}$)
2c	9.37 (br.s, 1 H, NH); 7.82 (s, 1 H, CH, Im); 7.76 (d, 1 H, Ar, *J* = 7.9); 7.56 (d, 1 H, Ar, *J* = 7.9); 7.34—7.11 (m, 2 H, Ar); 4.40 (q, 2 H, $O\underline{CH_2}CH_3$, *J* = 7.3); 4.21 (t, 2 H, $N\underline{CH_2}CH_2CH_3$); 1.79 (m, 2 H, $NCH_2\underline{CH_2}CH_3$); 1.42 (t, 3 H, $OCH_2\underline{CH_3}$, *J* = 7.3); 0.91 (t, 3 H, $NCH_2CH_2\underline{CH_3}$, *J* = 7.3)
2d	9.45 (br.s, 1 H, NH); 7.79 (s, 1 H, CH, Im); 7.76 (d, 1 H, Ar, *J* = 7.9); 7.56 (d, 1 H, Ar, *J* = 7.9); 7.34—7.12 (m, 2 H, Ar); 5.16 (s, 2 H, $N\underline{CH_2}COCH_3$); 4.33 (q, 2 H, $O\underline{CH_2}CH_3$, *J* = 7.3); 2.20 (s, 3 H, $NCH_2CO\underline{CH_3}$); 1.36 (t, 3 H, OCH_2CH_3, *J* = 7.3)
2e	12.39 (br.s, 1 H, NH, Im); 11.60, 10.21 (both br.s, 1 H each, $CONH_2$); 7.55—7.43 (m, 2 H, Ar, CH, Im); 7.24—7.06 (m, 4 H, Ar, NH)
2f	12.40 (br.s, 1 H, NH, Im); 8.33 (s, 1 H, CH, Im); 8.06 (br.s, 1 H, $\underline{NH}CH_3$); 7.76 (d, 1 H, Ar, *J* = 7.9); 7.52 (d, 1 H, Ar, *J* = 7.9); 7.40—7.17 (m, 2 H, Ar); 6.50 (br.s, 1 H, NH); 2.88 (d, 3 H, $NH\underline{CH_3}$, *J* = 4.8)
2g	10.10, 8.32 (both br.s, 1 H each, 2 NH); 7.91 (s, 1 H, CH, Im); 7.78 (d, 1 H, Ar, *J* = 6.7); 7.69—7.11 (AA´BB´, 4 H, Ar, *J* = 7.6); 7.56 (d, 1 H, Ar, *J* = 6.7); 7.38, 7.21 (both m, 1 H each, Ar); 2.31 (s, 3 H, CH_3)

The yields, the melting points, and the data from elemental analysis of compounds **2a—g** are given in Table 3. The spectroscopic characteristics of these compounds are listed in Tables 1 and 2.

Ethyl 5-(benzothiazol-2-ylamino)-3*H*-imidazole-4-carboxylate (2a), ethyl 5-(benzothiazol-2-ylamino)-3-ethyl-3*H*-imidazole-4-carboxylate (2b), ethyl 5-(benzothiazol-2-ylamino)-3-propyl-3*H*-imidazole-4-carboxylate (2c), and ethyl 5-(benzothiazol-2-ylamino)-3-(2-oxopropyl)-3*H*-imidazole-4-carboxylate (2d) (general procedure). A solution of Br_2 (0.72 mmol) in chloroform (2 mL) was added dropwise to a solution of 5-imidazolylphenylthiourea **1a—d** (0.72 mmol) in chloroform (10—20 mL). The reaction mixture was stirred at ~20 °C for 0.5 h and then filtered with charcoal. The solvent was evaporated and the residue was recrystallized from ethanol, filtered off, and dried.

Table 2. Mass spectra of the compounds synthesized

Compound	*m*/*z* (*I*$_{rel}$ (%))				
	$M^{\bullet+}$	Φ_1	Φ_2	Φ_3	Φ_4
2a	288 (35.42)	242 (100)	161 (14.54)	134 (32.22)	108 (8.51)
2b	316 (100)	(32.30)	(21.29)	(15.95)	(9.51)
2c	330 (100)	(72.32)	(19.32)	(16.75)	(7.58)
2d	344 (100)	(28.49)	(16.99)	(11.63)	(8.28)
2e	259 (53.07)	(100)	(17.08)	(50.72)	(14.55)
2f	273 (72.67)	(100)	(19.80)	(43.66)	(12.54)
2g	349 (32.93)	(39.48)	(18.67)	(15.84)	(100)

Scheme 2

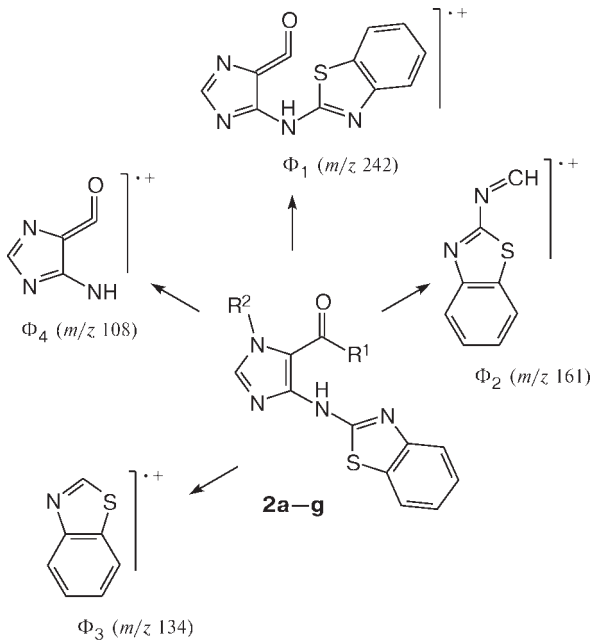

Table 3. Yields, melting points, and data from elemental analysis of the compounds synthesized

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula
			C	H	N	S	
2a	50	183—184	54.28 54.15	4.02 4.20	19.55 19.43	10.95 11.12	$C_{13}H_{12}N_4O_2S$
2b	62	217—218	56.79 56.95	5.19 5.10	17.90 17.71	9.96 10.13	$C_{15}H_{16}N_4O_2S$
2c	72	132—133	58.05 58.16	5.34 5.49	17.13 16.96	9.56 9.70	$C_{16}H_{18}N_4O_2S$
2d	74	212—213	55.97 55.80	4.79 4.68	16.10 16.27	9.49 9.31	$C_{16}H_{16}N_4O_3S$
2e	77	268—269	51.11 50.96	3.68 3.50	27.19 27.01	12.19 12.36	$C_{11}H_9N_5OS$
2f	62	233—234	52.91 52.73	3.91 4.06	25.80 25.62	11.55 11.73	$C_{12}H_{11}N_5OS$
2g	55	186—187	61.71 61.87	4.50 4.33	20.19 20.05	9.19 9.17	$C_{18}H_{15}N_5OS$

5-(Benzothiazol-2-ylamino)-3*H*-imidazole-4-carboxamide (2e). 5-Imidazolylphenylthiourea **1e** (0.72 mmol) was suspended in chloroform (50 mL), a solution of Br_2 (0.72 mmol) in chloroform (2 mL) was added dropwise, and the reaction mixture was stirred at ~20 °C for 1.5 h. The precipitate that formed was filtered off, washed with ethanol, reprecipitated with water from DMF, filtered off, and dried.

Methylamide of 5-(benzothiazol-2-ylamino)-3*H*-imidazole-4-carboxylic acid (2f). 5-Imidazolylphenylthiourea **1f** (0.72 mmol) was suspended in chloroform (50 mL), a solution of Br_2 (0.72 mmol) in chloroform (2 mL) was added, and the reaction mixture was stirred at ~20 °C for 2 h. The resulting solution was filtered with charcoal. Then the solvent was evaporated and the residue was crystallized from aqueous ethanol.

***p*-Tolylamide of 5-(benzothiazol-2-ylamino)-3*H*-imidazole-4-carboxylic acid (2g).** 5-Imidazolylphenylthiourea **1g** (0.72 mmol) was dissolved in AcOH (50 mL) at 70 °C. Then Br_2 (0.72 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 2 h, filtered with charcoal, and cooled. The precipitate that formed was filtered off and crystallized from ethanol.

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