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Fluoro-containing Heterocycles. IV.* Synthesis of Benzimidazole Derivatives**

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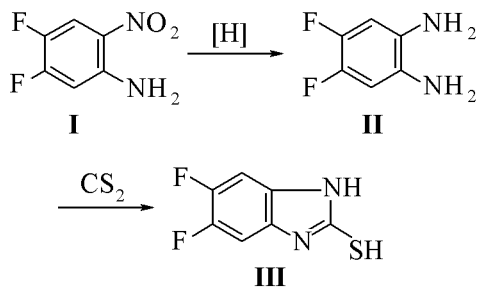
Abstract—2-Mercapto-5,6-difluorobenzimidazole reacts with aliphatic and alicyclic ketones in acetic acid in the presence of catalytic amount of sulfuric acid to afford fluorinated derivatives of 2,3-disubstituted benz[4,5]imidazo[2,1-b][1,3]thiazoles. Reaction with aromatic α-haloketones occurs in another way: to furnish 2-phenylacylthio-5,6-difluorobenzimidazoles that in the system acetic anhydride—pyridine undergo cyclization into the corresponding fluorinated derivatives of benz[4,5]imidazo[2,1-b][1,3]thiazoles.

Compounds of the benzimidazole series play significant role among farmaceuticals: spasmolytic drug dibazole, neuroleptics pimozide, droperidole, antihistaminic preparation astemizole etc. [2]. Benzimidazo[2,1-b]thiazoles are commonly prepared from 2-mercaptobenzimidazole by reaction with α-haloketones [3–7]. Recently an original preparation method was developed for the benzimidazo[2,1-b]-thiazoles proceeding from reaction of the mercapto-benzimidazole with ketones in acetic acid medium [8].

Aryl(heteroaryl)thioacetophenones are known to form in reactions of the corresponding thiols with the derivatives of phenacyl halides [9–11], with ketones and aldehydes in the presence of iodine [12], and also with aromatic ketones in acetic acid in the presence of sulfuric acid as a catalyst [8]. The behavior in these reactions of fluoro-containing benzimidazoles was not studied before. The interest to these compounds is due to the high biological activity of a number among these substances, and therewith the biological activity thereof is significantly stronger than that of the nonfluorinated analogs [13]. We report here on the first synthesis of fluorinated derivatives of benzimidazo[2,1-b]thiazoles that contains a large promise for the search of biologically active substances.

The synthesis of initial 2-mercapto-5,6-difluoro-benzimidazole (**III**) was carried out along Scheme 1. By the reduction of 2-nitro-4,5-difluoroaniline (**I**) [14] with hydrogen on Ni-Ra catalyst was obtained diamine **II**, and its condensation with carbon disulfide in ethanol in the presence of triethylamine afforded azole **III**.

Scheme 1.



By the reaction of 2-mercapto-5,6-difluorobenz-imidazole (**III**) with aliphatic ketones, e.g. acetone, methyl ethyl ketone, acetylacetone, benzoylacetone, ethyl acetoacetate, in acetic acid in the presence of catalytic amounts of sulfuric acid we obtained the corresponding 2-R-3-methyl-6,7-difluorobenzimid-azo[2,1-b]thiazoles **IVa–e** in 30–40% yield. Alicyclic ketones, as cyclopentanone, cyclohexanone, cyclo-heptanone, in reaction with thiol **III** under similar conditions ($AcOH–H_2SO_4$) afforded tetracyclic compounds **Va–c** in 45–60% yield (Scheme 2).

The mechanism of benzimidazo[2,1-b]thiazoles formation we did not study. It is presumable ana-logous to published data [8] that the reaction involves an intermediate disulfide formation which further undergoes cyclization with enols. The structure of compounds **IVa–e** and **Va–c** obtained and also the

* Communication III see [1].

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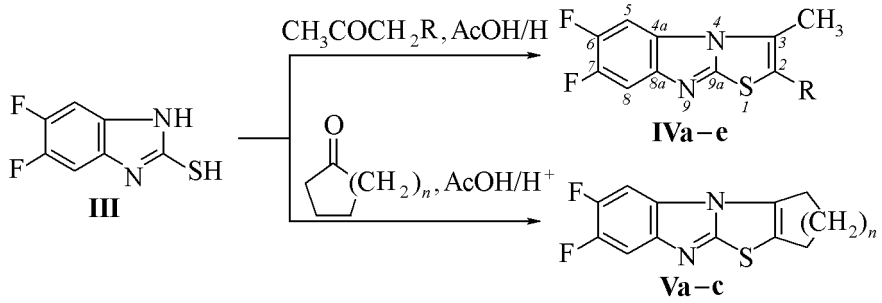
Scheme 2.



IV), R = H (**a**), CH_3 (**b**), $COCH_3$ (**c**), COC_6H_5 (**d**), $COOC_2H_5$ (**e**); **V**, *n* = 1 (**a**), 2 (**b**), 3 (**c**).

regio orientation of the fused fragment in benzimidazo[2,1-b]thiazoles **IVa–e** was unambiguously proved by ^1H and ^{13}C NMR spectra and by experiments with the nuclear Overhauser effect registration. For instance, the irradiation on the frequency corresponding to the methyl protons resonance in compound **IVe** (δ 3.08) resulted in increase of the intensity of the signal belonging to the proton H^5 at δ 8.18 ppm by 18%; this fact unambiguously proved the position of the substituents in the thiazole ring.

The 2-mercaptobenzimidazole is known to react with aromatic ketones containing electron-donor substituents in *para*-position affording cleanly the corresponding 2-phenacylthiobenzimidazoles [8]. In reaction with aromatic ketones of 2-mercapto-5,6-difluorobenzimidazole (**III**) the effect of two fluorine atoms although remote from the reaction site nonetheless was decisive, and we failed to obtain by this method fluorinated derivatives of 2-phenacylthiobenzimidazoles. Therefore we prepared aryl and heteryl derivatives of fluorinated benzimidazo[2,1-b]thiazoles via two-step synthesis through α-haloacetophenones.

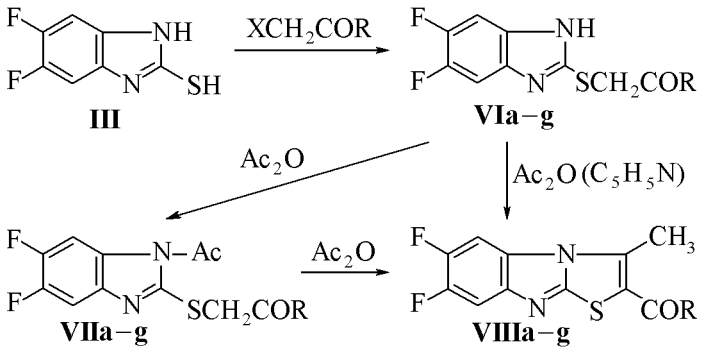
We obtained substituted 2-phenacylthio-5,6-difluorobenzimidazoles **VIa–g** by reaction of thiol

Table 1. ^1H and ^{13}C NMR spectra of benzimidazothiazoles **IVe** and **Va**

Atom no.	Characteristics	Atom		Number no.	Characteristics	Compd. no.	
		IVe	**Va**			**IVe**	**Va**
C^2	δ	111.60	123.42	C^8	δ	105.94[a]	105.42a
C^3	δ	139.29	133.16		$^1J(C^8, H^8)$	168.0	166.0
C^{4a}	δ	125.02	123.79		$^2J(C^8, F^7)$	20.4	20.2
	$^3J(C^{4a}, F^6)$	11.3	11.4	C^{8a}	δ	143.56	141.62
	$^4J(C^{4a}, F^7)$	1.1	–		$^3J(C^{8a}, F^7)$	11.1	11.1
H^5	δ	8.18	7.85		$^4J(C^{8a}, F^6)$	1.4	1.3
	$^3J(H^5, F^6)$	10.5	10.0	C^{9a}	δ	154.88	161.74
	$^4J(H^5, F^7)$	7.5	7.0		$^5J(C^{9a}, F^7)$	2.4	–
C^5	δ	101.29[a]	98.71[a]		$^5J(C^{9a}, F^6)$	0.9	–
	$^1J(C^5, H^5)$	170.0	168.0	Other			
	$^2J(C^5, F^6)$	24.1	23.5	signals			
C^6	δ	145.57[b]	145.26[b]	$3\text{-}CH_3$	δ	12.72[c]	–
	$^1J(C^6, F^6)$	269.9	239.6	$2\text{-}CH_3$	δ	13.78[c]	–
	$^2J(C^6, F^7)$	15.3	15.6	$2\text{-}CH_2$	δ	61.45	–
C^7	δ	147.47[b]	146.84[b]	C=O	δ	161.12	–
	$^1J(C^7, F^7)$	271.6	239.2	$(CH_2)_3$	δ		24.85,
	$^2J(C^7, F^6)$	14.8	15.0				25.52,
H^8	δ	7.77	7.65				27.40
	$^3J(H^8, F^7)$	11.0	11.5				
	$^4J(H^8, F^6)$	7.5	7.5				

[a, b] The assignment of signals may be reversed. [c] The signals are assigned from ^{13}C spectra.

Scheme 3.



R = Ph (**a**), 2-$CH_3C_6H_4$ (**b**), 4-BrC_6H_4 (**c**), 4-ClC_6H_4 (**d**), 2,4-$Cl_2C_6H_3$ (**e**), 2,4-$(CH_3O)_2C_6H_3$ (**f**), 2-tienyl (**g**); X = Cl, Br.

III with α-haloketones at room temperature in ethanol in the presence of triethylamine (Scheme 3). It should be noted that in contrast to the procedure with the use of 2-mercaptobenzimidazole potassium salt described in the literature in our case it is necessary to use the organic bases to exclude the alkaline hydrolysis of fluorine in initial compound **III** and also to significantly simplify the isolation of the target product. Compounds **VIa–g** react with acetic anhydride at room temperature to furnish the corresponding N-acetyl derivatives **VIIa–g**. The heating of compounds **VIa–g** in a mixture acetic anhydride–pyridine gives rise to their acylation and cyclodehydration to yield 2-aroyl-3-methyl-6,7-difluorobenzimidazo[2,1-b]thiazoles (**VIIIa–g**). Compound **VIIIa** was also obtained at heating of N-acetyl derivative **VIIa** in acetic anhydride.

Thus fluorinated derivatives of benzimidazo[2,1-b]thiazoles can be prepared either in one stage by reaction of 2-mercapto-5,6-difluorobenzimidazole with aliphatic ketones in $AcOH–H_2SO_4$ or in two stages: First in reaction with the aromatic α-haloketones form 2-phenacylthio-5,6-difluorobenzimidazoles that in the Ac_2O–pyridine medium undergo acylation and cyclodehydration into the corresponding benz[4,5]imidazo[2,1-b][1,3]thiazoles.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on spectrometers Bruker WH-250 and DRX-500, internal reference TMS. Yields, melting points, elemental analyses, and ^1H NMR spectra of compounds synthesized are presented in Table 2.

1,2-diamino-4,5-difluorobenzene (II). Into a high-pressure reactor was charged 174.1 g (1 mol) of 2-nitro-3,4-difluoroaniline (**I**), 200 ml of anhydrous ethanol, and 14 g of Ni-Ra catalyst, and then hydrogen to 3.2 atmosphere pressure. The stirring and heating were switched on, and the reduction continued at 60–70°C for 7 h. On cooling the reaction mixture the catalyst was filtered off. The most part of the solvent was distilled off in a vacuum, and on cooling the residue precipitated dark-gray crystals of diamine **II**. Yield 199 g (82%).

2-Mercapto-5,6-difluorobenzimidazole (III). A mixture of 20 g (0.14 mol) of diamine **II** in 240 ml of ethanol, 25.3 ml (31.9 g, 0.42 mol) of carbon disulfide, and 31.9 ml (28.3 g, 0.28 mol) of triethylamine was heated under reflux on a water bath for 4 h. Then the solvent was distilled off, and the residue was poured into 240 ml of water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 21 g (81%), mp 220°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.05 m (2H, $H^{4,7}$), 12.48 br.s (1H, NH).

2,3-Substituted 6,7-difluorobenz[4,5]imidazo-[2,1-*b*][1,3]thiazoles IVa–e, Va–c. A mixture of 10 mmol ot thiol **III** and 15 mmol of an appropriate ketone was boiled for 4 h in 40 ml of acetic acid containing 5–10 drops of H_2SO_4. The reaction mixture was cooled, diluted with 80 ml of water, and neutralized with aqueous NH_4OH till pH 7. The precipitate was filtered off, dried, and recrystallized.

2-Phenacylthio-5,6-difluorobenzimidazoles VIa–g. In 20 ml of ethanol was dissolved 10 mmol of thiol **III**, was added dropwise at stirring 10 mmol of triethylamine and then by portions 10 mmol of aromatic α-haloketone. The precipitate started to form nearly immediately. The reaction mixture was maintained for 2–12 h at 18–20°C. The precipitate was filtered off, dried, and recrystallized.

3-Acetyl-2-phenacylthio-5,6-difluorobenzimidazoles VIIa–g. A mixture of 10 mmol of compound **VIa–g** and 10 ml of acetic anhydride was stirred at

Table 2. Characteristics of synthesized compounds

Compd. no.	Yield, %	mp, °C (solvent for crystallization)	^{1}H NMR spectrum, ppm	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IVa[a]	38	175–177 (EtOH–H2O)	2.69 s (3H, CH_3), 6.38 s (1H, H2[2]), 7.56 m (2H, H[5'*])	53.31	2.54	12.34	$C_{10}H_2F_2N_2S$	53.58	2.70	12.49
IVb[a]	40	265–267 (EtOH)	2.36 s (3H, CH_3), 2.58 s (3H, CH_3), 7.51 m (2H, H[5'*])	55.69	3.54	11.82	$C_{11}H_8F_2N_2S$	55.47	3.39	11.76
IVb[b]	38	202–203 (EtOH)	2.56 s (3H, $COCH_3$), 3.08 s (3H, CH_3), 7.64 m (2H, H[5'*])	54.32	3.17	10.74	$C_{12}H_8F_2N_2OS$	54.15	3.04	10.52
IVd[a]	34	200–202 (EtOH)	2.86 s (3H, CH_3), 7.59 m (5H, COC6H5), 7.83 m (2H, H[5'*])	61.94	2.90	8.60	$C_{17}H_{10}F_2N_2OS$	62.20	3.07	8.53
IVe[a]	32	175–177 (EtOH–H2O)	1.41 t (3H, OCH_2CH_3), 3.08 s (3H, CH_3), 4.40 q (2H, OCH_2CH_3), 7.60 m (2H, H[5'*])	52.60	3.52	9.60	$C_{13}H_{10}F_2N_{202}S$	52.71	3.41	9.45
Va[a]	45	230–232 (EtOH)	2.37, 3.01, 3.12 m [6H, $(CH_2)3$], 7.44 m (2H, [5'*])	57.30	3.41	11.09	C12H8F2N2S	57.61	3.23	11.19
Vb[a]	57	203–20 (EtOH)	5 2.00, 2.72, 2.96 m [8H, $(CH_2)_4$], 7.47 m (2H, [5'*])	59.34	3.96	10.74	$C_{13}H_{10}F_2N_2S$	59.09	3.82	10.60
Vc[a]	59	173–175 (EtOH)	2.05, 2.76, 3.16 m [10H, $(CH_2)_5$], 7.52 m (2H, [5'*])	60.24	4.18	9.94	$C_{14}H_{12}F_2N_2S$	60.43	4.36	10.07
VIa[b]	64	170–172 (EtOH)	4.75 s (2H, CH_2), 7.47 m (5H, C_6H_5), 8.03 m (2H, B[4–7]), 10.00 br.s (1H, NH)	58.85	3.57	9.02	$C_{15}H_{10}F_2N_2OS$	59.20	3.31	9.21
VIIa[b]	91	158 (CH_3CN)	2.84 s (3H, $COCH_3$), 4.88 s (2H, CH_2), 7.62 m (5H, C6H5), 8.05 m (2H, B[4–7])	58.68	3.61	8.02	$C_{17}H_{12}F_2N_2OS$	58.95	3.61	8.02
VIIIa[b]	66	192–193 (EtOH)	2.74 s (3H, CH_3), 7.59 m (5H, C6H5), 7.81 m (2H, H)	62.00	2.97	8.40	$C_{17}H_{10}F_2N_2OS$	62.18	3.07	8.53
VIb[b]	83	176–177 (CH_3CN)	2.41 s, 3H, CH_3), 4.80 s (2H, CH_2), 7.29 m (4H, $C_6H_4CH_3$), 7.65 m (2H, B[4–7])	60.14	3.92	8.62	$C_{16}H_{12}F_2N_2OS$	60.36	3.80	8.80
VIIb[b]	56	115–116 (EtOH)	2.40 s (3H, CH_3), 2.83 s (3H, $COCH_3$), 4.68 s (2H, CH_2), 7.34 m (4H, $C_6H_4CH_3$), 7.88 m (2H, B.[4–7])	60.13	4.00	7.90	$C_{18}H_{14}F_2N_{202}S$	59.99	3.92	7.78
VIIIb[b]	86	223–225 (CH_2CN)	2.36 s (3H, CH_3), 2.57 s (3H, CH_3), 7.41 m (4H, $C_6H_4CH_3$), 7.82 m (2H, H[5'])	62.94	3.42	8.24	$C_{18}H_{12}F_2N_2OS$	63.14	3.53	8.18
VIc[b]	74	198–199 (EtOH)	4.92 s (2H, CH_2), 7.50 m (4H, C_6H_4Br), 7.98 m (2H, B[4–7]), 12.62 br.s (1H, NH)	46.94	2.49	7.37	$C_{15}H_9BrF_2N_2OS$	47.01	2.37	7.31

Table 2. (Contd.)

Compd. no.	Yield, %	mp, °C (solvent for crystallization)	^{1}H NMR spectrum, ppm	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
VIIb[b]	84	169–170 (EtOH)	2.83 s (3H, $COCH_3$), 4.83 s (2H, CH_2), 7.62 m (4H, C_6H_4Br), 7.98 m (2H, $H^{4',7}$)	47.76	2.79	6.87	$Cl_7H_{11}BrF_2N_2O_2S$	48.01	2.61	6.59
VIIIc[b]	66	230–232 (CH_2CN)	2.76 s (3H, CH_3), 7.76 m (4H, C_6H_4Br), 7.88 m (2H, $H^{5',8}$)	50.36	2.23	7.00	$Cl_7H_9BrF_2N_2OS$	50.14	2.33	6.88
VId[b]	77	214–215 (EtOH–DMF)	4.93 s (2H, CH_2), 7.46 m (4H, C_6H_4Cl), 8.05 m (2H, $H^{4',7}$), 12.62 br.s (1H, NH)	53.14	2.82	8.34	$Cl_5H_9ClF_2N_2OS$	53.18	2.68	8.27
VIId[b]	78	177–178 (EtOH)	2.83 s (3H, $COCH_3$), 4.83 s (2H, CH_2), 7.62 m (4H, C_6H_4Cl), 8.06 m (2H, $H^{4',7}$)	53.47	2.80	7.40	$Cl_7H_{11}ClF_2N_2O_2S$	53.62	2.91	7.36
VIId[b]	69	221–222 (CH_2CN)	2.76 s (3H, CH_3), 7.85 m (4H, C_6H_4Cl), 7.84 m (2H, $H^{5'}$)	56.05	2.47	7.85	$Cl_7H_9ClF_2N_2OS$	56.27	2.50	7.72
VIa[b]	64	153–154 (EtOH)	4.72 s (2H, CH_2), 7.38 m (3H, $C_6H_3Cl_2$), 7.70 m (2H, $H^{4',7}$), 12.50 br.s (1H, NH)	48.50	2.34	7.68	$Cl_5H_8Cl_2F_2N_2OS$	48.27	2.16	7.51
VIIc[b]	69	158–159 (CH_2CN)	2.81 s (3H, $COCH_3$), 4.59 s (2H, CH_2), 7.46 m (3H, $C_6H_3Cl_2$), 7.83 m (2H, $H^{4',7}$)	48.98	2.36	6.75	$Cl_7H_{10}Cl_2F_2N_{202}S$	49.17	2.43	6.75
VIIIc[b]	81	264–266 (EtOH–DMF)	2.67 s (3H, CH_3), 7.65 m (3H, $C_6H_3Cl_2$), 7.89 m (2H, $H^{5'*}$)	51.12	1.93	7.22	$Cl_7H_8Cl_2F_2N_2OS$	51.40	2.03	7.05
VIe[b]	63	154–155 (EtOH)	3.87 s (3H, OCH_3), 3.98 s (3H, OCH_3), 4.76 s (2H, CH_2), 6.60 m (2H), 7.72 m (1H) [$C_6H_3(OCH_3)_2$] 7.32 m (2H, $H^{4',7}$)	55.94	3.99	7.65	$Cl_7H_{14}F_2N_{203}S$	56.03	3.87	7.69
VIIf[b]	79	178–179 (EtOH)	2.81 s (3H, $COCH_3$), 3.87 s (3H, OCH_3), 3.99 s (3H, OCH_3), 6.59 m (2H), 7.69 m (1H) [C6H3(OCH_3)2], 7.61 m (2H, $H^{4',7}$)	56.35	4.07	6.62	$Cl_9H_{16}F_2N_{204}S$	56.15	3.97	6.89
VIIIf[b]	84	190–191 (EtOH)	2.68 s (3H, CH_3), 3.87 s (3H, OCH_3), 3.88 s (3H, OCH_3), 6.63 m (2H), 7.35 m (1H) [C6H3(OCH_3)2] , 7.82 m (2H, $H^{5'*}$)	58.57	3.47	7.28	$Cl_9H_{14}F_2N_{203}S$	58.75	3.63	7.28
VIg[b]	64	170–171 (EtOH)	4.86 s (2H, CH_2), 7.26 m (3H, Tienyl), 8.00 m (2H, $H^{4',7}$), 12.64 br.s (1H, NH)	50.17	2.37	8.76	$Cl_3H_8F_2N_2OS_2$	50.31	2.60	9.03
VIIg[b]	48	147–148 (EtOH)	2.83 s (3H, $COCH_3$), 4.80 s (2H, CH_2), 7.55 m (3H, Tienyl), 8.02 m (2H, $H^{4',7}$)	51.50	2.64	7.97	$C_{15}H_9F_2N_2OS_2$	51.27	2.58	7.97
VIIIg[b]	55	201–203 (EtOH)	2.98 s (3H, CH_3), 7.56 m (3H, Tienyl), 8.03 m (2H, $H^{5'*}$)	54.01	2.37	8.38	$Cl_5H_8F_2N_2OS_2$	53.88	2.41	8.38

Solvents for recording NMR spectra: [a] $CDCl_3$, [b] DMSO-*d*41)$_6$.

18–20°C for 2–20 h, the precipitate was filtered off, dried, and recrystallized.

2-Aroyl-3-methyl-6,7-difluorobenz[4,5]imidazo-[2,1-*b*][1,3]thiazoles (VIIIa–g). In 15–30 ml of a mixture Ac_2O–pyridine 10 mmol of compound **VIa–g** was stirred for 3 h at 100–120°C. On cooling the reaction mixture was poured into 90 ml of ice water. Gradually precipitated crystals that were filtered off, dried, and recrystallized.

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