Synthesis of *N*-haloacyl and *N*-hetarylthioacyl derivatives of 2-amino-5-aryl-6*H*-1,3,4-thiadiazine*

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Conditions for *N*-acylation of 2-amino-5-aryl-6*H*-1,3,4-thiadiazines with trifluoroacetic anhydride and halogen-substituted carboxylic acid halides with retention of the initial heterocyclic system were found. 5-Aryl-2-haloacylamino-6*H*-1,3,4-thiadiazines were obtained in preparative yields. Their reactions with hetarenethiols afforded *N*-hetarylthioacyl derivatives.

Key words: *N*-haloacyl and *N*-hetarylthioacyl derivatives of 2-amino-5-aryl-6*H*-1,3,4-thiadiazines, hetarenethiols, acylation, alkylation.

Interest in the synthesis of 6*H*-1,3,4-thiadiazine derivatives, which belong to the six-membered nonaromatic heterocyclic system, has substantially grown in the last few decades.[1—3] This is largely due to a broad spectrum of biological (*e.g.*, fungicidal,[4] antiviral,[5] antiinflammatory,[6] vasodilator,[7] *etc.*) activity of such derivatives. In addition, 6*H*-1,3,4-thiadiazines show unusual reactivities. An important feature that largely determines their specific chemical properties is easy elimination of the S atom from the six-membered ring leading to pyrazole derivatives. Such transformations can be initiated thermally (by heating neat reagents or their solutions in nonpolar organic solvents[8]), in reactions with nucleophiles[9] and acylating reagents,[10] under the action of UV irradiation, and other factors. In addition, known intramolecular rearrangements of 6*H*-1,3,4-thiadiazines result in ring contraction leading to thiazole,[11] 1,2,3-thiadiazole,[12] and 1,3,4-thiadiazole derivatives.[13] Because of this, the thiadiazine ring is often unstable in most chemical reactions. Such features of its reactivity make it difficult to obtain novel functional derivatives of this heterocycle and limit the range of its accessible derivatives.[2]

Treatment of 6*H*-1,3,4-thiadiazine derivatives with acylating reagents mostly results in ring contraction leading to five-membered heterocycles. For instance, the use of acetic anhydride gives acylated pyrazole derivatives.[10,14] Known examples of acylation of 2-amino-6*H*-1,3,4-thiadiazines with retention of the initial heterocyclic system are few. Acylation of 5,6-dialkyl(diaryl)-2-amino-6*H*-1,3,4-thiadiazines with diketene yields 2-acylamino derivatives.[15] Benzoylation of 5-substituted 2-aminothiadiazines in the presence of pyridine can give, depending on the solvent and the ratio of the starting reagents, benzoylation products at both the amino group of the side chain and at the ring N atoms.[16,17]

The goal of the present work was to study the possibility of acylating 2-amino-5-aryl-6*H*-1,3,4-thiadiazines at the exocyclic N atom without involving the heterocyclic ring. We were going to use functionalized acylating reagents to obtain acylation products and study some of their chemical transformations, also occurring with retention of the 6*H*-1,3,4-thiadiazine fragment.

The starting 2-amino-5-phenyl- (**1a**), 2-amino-5-(4-methylphenyl)- (**1b**), and 2-amino-5-(4-bromophenyl)-6*H*-1,3,4-thiadiazines (**1c**) were prepared from appropriate α-haloacetophenones and thiosemicarbazide.[18] Compounds **1a—c** were acylated with trifluoroacetic anhydride, chloroacetyl chloride, bromoacetyl bromide, 2-bromobutyryl bromide, and 4-fluorobenzoyl chloride. As a result, we found the conditions for high-yielding acylation of amines **1a—c** at the exocyclic amino group with retention of the initial cyclic structure.

For instance, treatment of amines **1a—c** with an excess of trifluoroacetic anhydride in benzene at room temperature gave the corresponding trifluoroacetamides **2a—c** (Scheme 1).

Treatment of amines **1a,b** with chloroacetyl chloride in acetonitrile in the presence of pyridine at room temperature afforded chloroacetamides **3a,b**. Acylation of amine **1c** under these conditions did not yield the corresponding chloroacetamide (TLC data), the starting amine being mainly recovered unchanged. At the same time, the action of bromoacetyl bromide on amine **1c** under analogous conditions gave acylation product **3c** in a virtually quantitative yield. Products **4a—c** were obtained with

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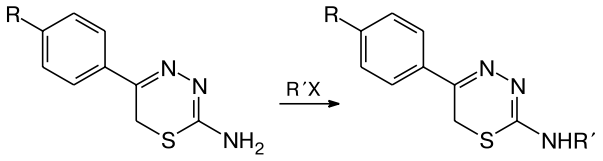
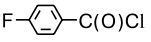
Scheme 1



1a—c **2a—c**, **3a—c**, **4a—c**, **5**

R = H (**1a—4a**), Me (**1b—4b**, **5**), Br (**1c—4c**)

Reagent R′X	Product
$(CF_3CO)_2O$	**2a—c***
$ClCH_2C(O)Cl$	**3a,b**
$BrCH_2C(O)Br$	**3c**
Et(Br)CHC(O)Br	**4a—c**
	**5**

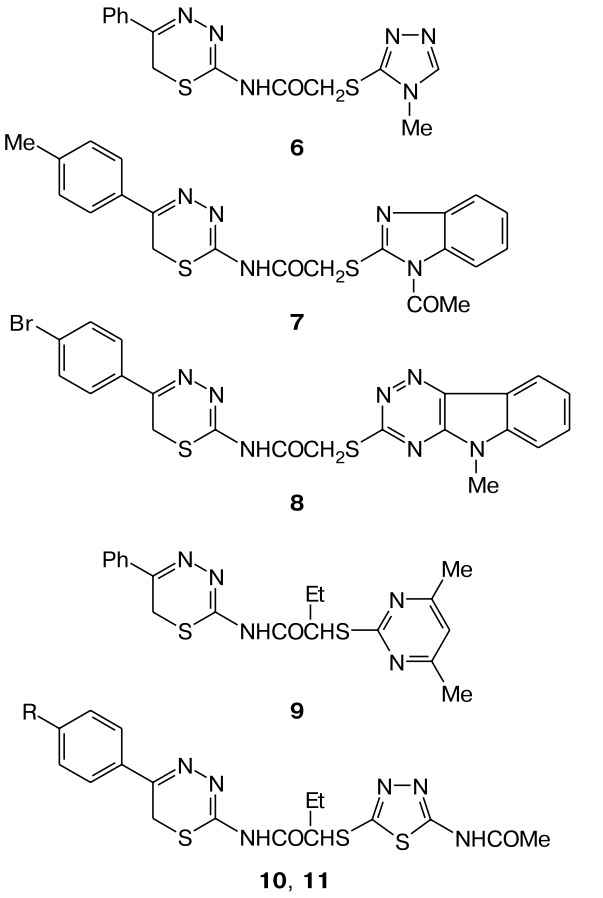
* R′ = CF_3CO

2-bromobutyryl bromide as an acylating reagent (see Scheme 1).

The acylation conditions for the synthesis of compounds **3a—c** can be used to obtain other 2-acylamino-5-aryl-6*H*-1,3,4-thiadiazines. For instance, amine **1b** was easily acylated with 4-fluorobenzoyl chloride under these conditions to give derivative **5**. It should be noted that for all products **3a—c** and **4a—c** containing a mobile halogen atom in the acyl substituent, the ^{1}H NMR spectra were unsatisfactory. Apparently, the heterocycle in these compounds can break down or undergo 6*H* → 4*H* tautomerization[19] under conditions of spectra recording. The compounds obtained were identified from mass spectra and elemental analysis data. When exposed to electron impact, most of these compounds produce molecular ions.

The ^{1}H NMR spectra of compounds **2a—c** and **5** unambiguously indicate that their thiadiazine rings exist only in the 6*H*-form. The signals for two protons at the C(6) atom of the heterocycle appear as a singlet at δ 3.9—4.0, which agrees with the literature data.[13—16] A signal for the proton at the N(4) atom of the heterocycle, which is usually shifted downfield (δ 5.6), is absent.[18—21]

To examine the possibility of using 2-acylamino-5-aryl-6*H*-1,3,4-thiadiazines **3a—c** and **4a—c** in the synthesis of novel derivatives of this heterocyclic system (tendency toward reactions occurring with retention of the initial heterocycle) and prove their structures more rigorously, we studied their reactions with heterocyclic thiols. Alkylation of thiols was chosen because this reaction can be effected under sufficiently mild conditions[22] (room temperature during the synthesis and isolation of products and the absence of strong bases in the reaction medium). This would prevent any transformation of the thiadiazine ring. In addition, according to literature data, most of the thiols employed exhibit biological (*e.g.*, antihypoxic[23] and bactericidal[24]) activities and alkylation products can be of interest for a study of their biological activity. We found that 2-haloacylamino-5-aryl-6*H*-1,3,4-thiadiazines **3a—c** and **4a—c** can alkylate heterocyclic thiols under mild conditions to give the corresponding 5-aryl-2-hetarylthioacetyl(butyryl)amino-6*H*-1,3,4-thiadiazines **6—11**.



R = Me (**10**), Br (**11**)

It should be noted that in contrast to acyl derivatives **3a—c** and **4a—c**, the mass spectra of sulfides **6—11** contain no molecular ion peaks. The most intense peaks are due to the fragments formed upon cleavage of the S—acyl bond and to aromatic nitriles.

To sum up, we found mild conditions for acylation of 2-amino-5-aryl-6*H*-1,3,4-thiadiazines with retention of the initial heterocyclic structure. Alkylation of hetarenethiols with haloacylaminothiadiazines showed that halogen derivatives can serve as convenient starting materials for the synthesis of other 2-amino-5-aryl-6*H*-1,3,4-thiadiazine derivatives containing pharmacophore groups.

The yields and selected physicochemical characteristics of the products obtained are given in Table 1. Their spectroscopic characteristics are summarized in Tables 2 and 3.

Table 1. Yields and selected physicochemical characteristics of 2-amino-5-aryl-6*H*-1,3,4-thiadiazines **2—11**

Compound	Yield (%)	M.p. /°C	R_f (eluent)*	Found / Calculated (%)				Molecular formula
				C	H	N	Hal	
2a	79	166—167	0.74 (A)	45.65 45.99	2.76 2.81	14.33 14.63	— —	$C_{11}H_8F_3N_3OS$
2b	82	197—198	0.88 (B)	48.15 47.84	3.52 3.35	14.02 13.95	— —	$C_{12}H_{10}F_3N_3OS$
2c	76	182—183	0.67 (A)	36.28 36.08	2.05 1.93	11.24 11.48	— —	$C_{11}H_7BrF_3N_3OS$
3a	84	173—175	0.63 (B)	49.02 49.35	3.98 3.76	15.31 15.69	13.04 13.24	$C_{11}H_{10}ClN_3OS$
3b	81	191—193	0.61 (B)	51.71 51.15	4.47 4.29	15.01 14.91	12.77 12.58	$C_{12}H_{12}ClN_3OS$
3c	90	173—175	0.69 (A)	33.12 33.78	2.27 2.32	10.44 10.74	39.78 40.86	$C_{11}H_9Br_2N_3OS$
4a	69	133—135	0.78 (B)	46.12 45.89	4.00 4.15	12.16 12.35	23.33 23.48	$C_{13}H_{14}BrN_3OS$
4b	88	128—130	0.74 (B)	47.66 47.47	4.62 4.55	11.54 11.86	22.19 22.55	$C_{14}H_{16}BrN_3OS$
4c	98	154—157	0.73 (B)	37.17 37.25	3.09 3.13	10.20 10.03	38.72 38.13	$C_{13}H_{13}Br_2N_3OS$
5	82	206—207	0.64 (B)	61.58 62.37	4.04 4.31	12.46 12.84	— —	$C_{17}H_{14}FN_3OS$
6	74	161—163	0.35 (B)	48.14 48.54	4.02 4.07	24.64 24.26	— —	$C_{14}H_{14}N_6OS_2$
7	85	175—177	0.55 (B)	57.98 57,65	4.74 4.38	15.70 16.01	— —	$C_{21}H_{19}N_5O_2S_2$
8	77	182—184	0.25 (B)	47.67 47.91	3.18 3.06	15.02 15.18	18.06 18.62	$C_{21}H_{16}BrN_7OS_2$
9	82	167—169	0.64 (B)	56.66 57.12	5.12 5.30	18.00 17.53	— —	$C_{19}H_{21}N_5OS_2$
10	79	197—198	0.11 (B)	46.01 46.20	4.22 4.49	18.88 18.73	— —	$C_{18}H_{20}N_6O_2S_3$
11	72	184—186	0.44 (B)	39.18 39.77	3.80 3.34	15.85 16.37	15.22 15.56	$C_{17}H_{17}BrN_6O_2S_3$

* The eluent was benzene—ethyl acetate (5 : 1) (A) and (3 : 1) (B).

Table 2. ^{1}H NMR, IR, and mass spectra of 2-amino-5-aryl-6*H*-1,3,4-thiadiazines **2a—c** and **5—11**

Compound	IR, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$) δ, J/Hz	MS, m/z (I_{rel} (%))
2a	3214, 1646, 1612, 1560, 1488, 1446, 1368, 1346, 1292, 1214, 1150, 1086, 1010, 922, 880, 810, 792, 766, 722	4.00 (s, 2 H, C(6)H$_2$); 7.65 (m, 5 H, Ph); 13.45 (s, 1 H, NH)	287 $[M]^+$ (36), 218 $[M - CF_3]^+$ (100), 191 $[M - COCF_3]^+$ (26), 69 $[CF_3]^+$ (68)
2b	3220, 1648, 1604, 1568, 1484, 1436, 1372, 1344, 1288, 1212, 1152, 1092, 1008, 928, 872, 812, 784, 736	2.32 (s, Me); 4.05 (s, 2 H, C(6)H$_2$); 7.36, 7.86 (AA´BB´, 4 H, Ar, ^3J = 7.5); 13.55 (s, 1 H, NH)	301 $[M]^+$ (54), 232 $[M - CF_3]^+$ (100), 205 $[M - COCF_3]^+$ (11), 91 $[CH_2Ph]^+$ (32), 69 $[CF_3]^+$ (89)

(*to be continued*)

Table 2 (*continued*)

Compound	IR, ν/cm^{-1}	^1H NMR (DMSO-d_6) δ, J/Hz	MS, m/z (I_{rel} (%))
2c	3210, 1642, 1614, 1554, 1480, 1446, 1368, 1346, 1210, 1146, 1082, 1022, 926, 874, 802, 786, 762, 720	4.05 (s, 2 H, C(6)H_2); 7.76, 7.90 (AA´BB´, 4 H, Ar, ^3J = 7.4); 13.70 (s, 1 H, NH)	367 [M (^{81}Br)]$^+$ (11), 365 [M (^{79}Br)]$^+$ (13), 298 [M (^{81}Br) – CF_3]$^+$ (92), 296 [M (^{79}Br) – CF_3]$^+$ (100), 270 [M (^{81}Br) – $COCF_3$]$^+$ (24), 268 [M (^{79}Br) – $COCF_3$]$^+$ (28), 157 [$^{81}BrC_6H_4$]$^+$ (30), 155 [$^{79}BrC_6H_4$]$^+$ (34), 69 [CF_3]$^+$ (68)
5	3280, 2932, 1698, 1640, 1568, 1502, 1454, 1402, 1346, 1280, 1202, 1164, 1122, 1088, 1060, 1014, 990, 934, 886, 824, 748	2.40 (s, 3 H, Me); 3.88 (s, 2 H, C(6)H_2); 7.36 (m, 4 H, Ar); 7.82, 7.20 (both m, 2 H each, Ar); 12.65 (s, 1 H, NH)	327 [M]$^+$ (11), 205 [starting amine]$^+$ (42), 123 [4-COC_6H_4F] (72), 95 [C_6H_4F] (34), 117 [4-MeC_6H_4CN]$^+$ (27), 91 [CH_2Ph]$^+$ (100)
6	3180, 3128, 2854, 1700, 1648, 1620, 1572, 1544, 1516, 1468, 1448, 1408, 1368, 1324, 1272, 1196, 1180, 1164, 1112, 1012, 1004, 952, 912, 884, 852, 828, 800, 772, 740, 708	3.62 (s, 3 H, Me); 3.74 (s, 2 H, CH_2CO); 4.15 (s, 2 H, C(6)H_2); 7.50 (m, 3 H, Ph); 7.95 (m, 2 H, Ph); 8.55 (s, 1 H, CH triaz. ring); 12.30 (s, 1 H, NH)	231 [M – starting thiol]$^+$ (28), 191 [starting amine]$^+$ (15), 115 [starting thiol]$^+$ (100), 103 [PhCN]$^+$ (88), 77 [Ph]$^+$ (68)
7	3208, 2972, 2912, 1708, 1700, 1608, 1496, 1480, 1456, 1432, 1376, 1320, 1300, 1260, 1188, 1148, 1104, 1044, 1012, 984, 944, 916, 856, 820, 780, 760, 752, 740, 712	2.30 (s, 3 H, CH_3Ar); 2.82 (s, 3 H, MeCO); 3.72 (s, 2 H, C(6)H_2); 4.28 (s, 2 H, CH_2CO); 7.35 (m, 4 H, Ar); 7.60 (d, 1 H, C(4)H benzimidazole, ^3J = 6.6); 7.84 (m, 3 H, Ar); 12.20 (s, 1 H, NH)	245 [M – starting thiol]$^+$ (18), 205 [starting amine]$^+$ (38), 162 [starting amine – COMe]$^+$ (24), 117 [4-MeC_6H_4CN]$^+$ (100), 91 [4-MeC_6H_4]$^+$ (56)
8	3380, 3060, 2932, 1676, 1616, 1580, 1492, 1476, 1412, 1384, 1356, 1320, 1272, 1196, 1176, 1164, 1108, 1100, 1072, 1004, 992, 940, 872, 812, 748, 724	3.70 (s, 2 H, C(6)H_2); 3.84 (s, NMe); 4.36 (s, 2 H, CH_2CO); 7.44—8.35 (m, 8 H, 4 H Ar, 4 H Het); 12.30 (s, 1 H, NH)	311 [M (^{81}Br) – starting thiol]$^+$ (5), 309 [M (^{79}Br) – starting thiol]$^+$ (5), 257 [starting thiol + CH_2CO]$^+$ (42), 216 [starting thiol]$^+$ (100), 201 [starting thiol – Me]$^+$ (7), 184 [4-$^{81}BrC_6H_4CN$+1]$^+$ (12), 182 [4-$^{79}BrC_6H_4CN$+1]$^+$ (12)
9	3162, 3112, 2894, 1680, 1642, 1572, 1536, 1512, 1450, 1412, 1352, 1326, 1272, 1206, 1164, 1006, 990, 962, 922, 874, 838, 794, 770, 730, 714	1.05 (t, 3 H, MeCH_2, ^3J = 10.2); 2.00 (m, 2 H, MeCH_2 ^3J = 10.2); 2.34 (s, 6 H, 2 CH_3 Het); 4.05 (s, 2 H, C(6)H_2); 4.62 (t, 1 H, CHCH_2, ^3J = 8.2); 7.00 (s, 1 H, C(4)H pyrimidine); 7.52 (m, 3 H, Ph); 7.96 (m, 2 H, Ph); 12.10 (s, 1 H, NH)	399 [M]$^+$ (4), 259 [M – starting thiol]$^+$ (42), 191 [starting amine]$^+$ (40), 140 [starting thiol]$^+$ (78), 103 [PhCN]$^+$ (100), 77 [Ph]$^+$ (46)
10	3156, 3032, 2872, 1688, 1560, 1412, 1344, 1312, 1276, 12561164, 1088, 1052, 1000, 960, 912, 884, 808, 724, 704	1.10 (t, 3 H, MeCH_2, ^3J = 10.4); 1.96 (q, 2 H, MeCH_2, ^3J = 10.4); 2.22 (s, 3 H, CH_3Ar); 2.88 (s, 3 H, MeCO); 3.78 (s, 2 H, 3 C(6)H_2); 4.26 (t, 1 H, CHCH_2 ^3J = 8.2); 7.32, 7.82 (AA´BB´, 4 H, Ar, ^3J = 8.4); 12.35, 12.55 (both s, 1 H each, NH)	273 [M – starting thiol]$^+$ (4), 205 [starting amine]$^+$ (36), 162 [starting amine – COMe]$^+$ (5), 117 [4-MeC_6H_4CN]$^+$ (100), 91 [4-MeC_6H_4]$^+$ (33)
11	3186, 3134, 2872, 1688, 1640, 1612, 1534, 1512, 1474, 1438, 1420, 1366, 1334, 1254, 1176, 1164, 1012, 1000, 966, 914, 888, 828, 810, 776, 732	1.00 (t, 3 H, MeCH_2, ^3J = 9.8); 1.98 (q, 2 H, MeCH_2, ^3J = 9.8); 2.70 (s, 3 H, MeCO); 3.82 (s, 2 H, C(6)H_2); 4.40 (t, 1 H, CHCH_2, ^3J = 7.6); 7.66, 7.94 (AA´BB´, 4 H, Ar, ^3J = 8.2); 12.45, 12.65 (both s, 1 H each, NH)	339 [M (^{81}Br) – starting thiol]$^+$ (7), 337 [M (^{79}Br) – starting thiol]$^+$ (8), 244 [starting thiol + CH(Et)CO]$^+$ (62), 201 [starting thiol + CH(Et)CO – – MeCO]$^+$ (36), 175 [starting thiol]$^+$ (100), 184 [4-$^{81}BrC_6H_4CN$+1]$^+$ (16), 182 [4-$^{79}BrC_6H_4CN$+1]$^+$ (18), 133 [5-amino-1,3,4-thiadiazole-2-thiol]$^+$ (74)

Table 3. IR and mass spectra of 2-amino-5-aryl-6*H*-1,3,4-thiadiazines **3a—c** and **4a—c**

Compound	IR, ν/cm^{-1}	MS, m/z (I_{rel} (%))
3a	2884, 1696, 1636, 1612, 1580, 1544, 1420, 1332, 1208, 1112, 1096, 1012, 952, 916, 864, 800, 780, 760, 744, 708	269 [M (^{37}Cl)]$^+$ (4), 267 [M (^{35}Cl)]$^+$ (10), 231 [M − HCl]$^+$ (32), 218 [M − CH_2Cl]$^+$ (76), 103 [C_6H_5CN]$^+$ (80), 91 [CH_2Ph]$^+$ (26), 79 [$CH_2CO(^{37}Cl)$]$^+$ (30), 77 [$CH_2CO(^{35}Cl)$]$^+$ (100)
3b	2882, 1692, 1640, 1576, 1544, 1416, 1336, 1208, 1104, 1012, 956, 916, 868, 836, 812, 788, 748, 720	283 [M (^{37}Cl)]$^+$ (8), 281 [M (^{35}Cl)]$^+$ (23), 245 [M − HCl]$^+$ (7), 232 [M − CH_2Cl]$^+$ (100), 117 [4-MeC_6H_4CN]$^+$ (42), 91 [CH_2Ph]$^+$ (26), 79 [$CH_2CO(^{37}Cl)$]$^+$ (4), 77 [$CH_2CO(^{35}Cl)$]$^+$ (15)
3c	2960, 2892, 1728, 1636, 1616, 1572, 1454, 1420, 1412, 1328, 1196, 1108, 1076, 1004, 952, 840, 756, 712	393 [M (^{81}Br + ^{81}Br)]$^+$ (8), 391 [M (^{79}Br + ^{81}Br)]$^+$ (15), 389 [M (^{79}Br + ^{79}Br)]$^+$ (8), 311 [393 − H^{81}Br, 391 − H^{79}Br]$^+$ (36), 309 [391 − H^{81}Br, 389 − H^{79}Br]$^+$ (32), 298 [311 − CH_2]$^+$ (100), 296 [309 − CH_2]$^+$ (92), 271 [starting amine (^{81}Br)]$^+$ (34), 269 [starting amine (^{79}Br)]$^+$ (36), 183 [4-$^{81}BrC_6H_4CN$]$^+$ (76), 181 [4-$^{79}BrC_6H_4CN$]$^+$ (60), 102 [C_6H_4CN]$^+$ (68)
4a	3112, 2970, 2870, 1674, 1612, 1562, 1492, 1460, 1376, 1328, 1276, 1180, 1074, 1016, 816, 770, 712	341 [M (^{81}Br)]$^+$ (6), 339 [M (^{79}Br)]$^+$ (6), 309 [M (^{81}Br) − S]$^+$ (14), 308 [M (^{81}Br) − SH]$^+$ (22), 307 [M (^{81}Br) − H_2S, M (^{79}Br) − S]$^+$ (100), 218 [M − EtCHBr]$^+$ (15), 134 [4-PhC(Me)=NNH_2] (24), 103 [PhCN]$^+$ (55)
4b	3104, 2968, 2876, 1672, 1604, 1564, 1492, 1456, 1380, 1324, 1276, 1248, 1184, 1116, 1072, 1052, 1020, 820, 764, 712	323 [M (^{81}Br) − S]$^+$ (8), 322 [M (^{81}Br) − SH]$^+$ (22), 321 [M (^{81}Br) − H_2S, M (^{79}Br) − S]$^+$ (100), 232 [M − EtCHBr]$^+$ (26), 148 [4-MeC_6H_4C(Me)=NNH_2] (9), 117 [4-MeC_6H_4CN]$^+$ (22), 91 [CH_2Ph]$^+$ (53)
4c	3152, 2968, 2904, 1704, 1688, 1632, 1588, 1560, 1492, 1392, 1324, 1272, 1208, 1160, 1076, 960, 924, 900, 820, 804, 752, 704, 660	340 [M (^{81}Br + ^{81}Br) − ^{81}Br]$^+$ (7), 339 [M (^{81}Br + ^{81}Br) − H^{81}Br]$^+$ (9), 338 [M (^{81}Br + ^{79}Br) − ^{81}Br, M (^{81}Br + ^{79}Br) − ^{79}Br]$^+$ (7), 337 [M (^{81}Br + ^{79}Br) − H^{81}Br, M (^{81}Br + ^{79}Br) − H^{79}Br]$^+$ (6), 298 [M (^{81}Br + ^{81}Br) − $EtCH_2{}^{81}$Br, M (^{81}Br + ^{79}Br) − $EtCH_2{}^{79}$Br]$^+$ (96), 296 [M (^{81}Br + ^{79}Br) − $EtCH_2{}^{81}$Br, M (^{79}Br + ^{79}Br) − $EtCH_2{}^{79}$Br]$^+$ (90), 271 [starting amine (^{81}Br)]$^+$ (17), 269 [starting amine (^{79}Br)]$^+$ (19), 183 [4-$^{81}BrC_6H_4CN$]$^+$ (48), 181 [4-$^{79}BrC_6H_4CN$]$^+$ (49), 102 [C_6H_4CN]$^+$ (100)

Experimental

IR spectra were recorded on a UR-20 spectrometer (KBr pellets). ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz). Mass spectra were recorded on a Finnigan MAT INCOS-50 spectrometer (EI, 70 eV). Melting points were determined on a Boetius PHMK 05 instrument. Thin-layer chromatography was carried out on Silufol UV-254 plates (spot visualization under UV light).

***N*-(5-Aryl-6*H*-1,3,4-thiadiazin-2-yl)trifluoroacetamides 2a—c (general procedure).** Trifluoroacetic anhydride (5.25 g, 25 mmol) was added dropwise at 0—5 °C (cooling with ice) to a suspension of the starting amine **1a—c** (10 mmol) in dry benzene (30 mL). The reaction mixture was kept at room temperature for 4—5 h and concentrated under reduced pressure. The residue was treated with ether, filtered off, and recrystallized from ethanol.

***N*-(5-Aryl-6*H*-1,3,4-thiadiazin-2-yl)haloacetamides 3a—c (general procedure).** Dry pyridine (0.95 g, 12 mmol) was added at 0—5 °C (cooling with ice) to a suspension of the starting amine **1a—c** (10 mmol) in dry acetonitrile (50 mL). Then chloroacetyl chloride (1.36 g, 12 mmol) (for amine **1c**, bromoacetyl bromide (2.42 g, 12 mmol)) was added dropwise. The reaction mixture was stirred at room temperature for 20 h and poured into water (150 mL). The precipitate that formed was filtered off, washed with water, and dried in air. The dry product was washed with acetone and ether.

***N*-(5-Aryl-6*H*-1,3,4-thiadiazin-2-yl)-2-bromobutyramides 4a—c (general procedure).** Dry pyridine (0.95 g, 12 mmol) was added at 0—5 °C (cooling with ice) to a suspension of the starting amine **1a—c** (10 mmol) in dry acetonitrile (50 mL). Then 2-bromobutyryl bromide (2.76 g, 12 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 4—5 h and poured into water (150 mL). The precipitate that formed was filtered off, washed with water, and dried in air. The dry product was washed with ether.

***N*-[5-(4-Tolyl)-6*H*-1,3,4-thiadiazin-2-yl]-4-fluorobenzamide (5).** Dry pyridine (0.95 g, 12 mmol) was added at 0—5 °C (cooling with ice) to a suspension of 2-amino-5-(4-tolyl)-6*H*-1,3,4-thiadiazine (**1b**) (2.05 g, 10 mmol) in dry acetonitrile (50 mL). Then 4-fluorobenzoyl chloride (1.90 g, 12 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 4—5 h and poured into water (150 mL). The precipitate that formed was filtered off, washed with water, and dried in air. The dry product was washed with ether and recrystallized from aqueous DMF.

***N*-(5-Aryl-6*H*-1,3,4-thiadiazin-2-yl)-2-hetarylthioacetamides 6—8 and *N*-(5-aryl-6*H*-1,3,4-thiadiazin-2-yl)-2-hetarylthiobutyramides 9—11 (general procedure).** A suspension of a thiol (10.5 mmol) and Na_2CO_3 (1.27 g, 12 mmol) in DMF (40 mL) was stirred for 10—15 min and then compound **3a—c** or **4a—c** (10 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and poured into water (200 mL). The precipitate that formed was filtered off, washed with water, and

dried in air. The dry product was suspended in acetone, stirred for 10—15 min, filtered off, and washed with acetone and ether. *N*-(5-Phenyl-6*H*-1,3,4-thiadiazin-2-yl)-2-(4,6-dimethylpyrimidin-2-ylthio)butyramide (**9**) was washed with ether and crystallized from ethanol.

References

1. H. Beyer, *Z. Chem*., 1969, **9**, 361.
2. C. V. Usol´tseva, G. P. Andronnikova, and V. S. Mokrushin, *Khim. Geterotsikl. Soedin.*, 1991, 435 [*Chem. Heterocycl. Compd*., 1991, **37**, 4 (Engl. Transl.)].
3. A. P. Novikova, N. M. Petrova, and O. N. Chupakhin, *Khim. Geterotsikl. Soedin.*, 1991, 1443 [*Chem. Heterocycl. Compd*., 1991, **37**, 11 (Engl. Transl.)].
4. Z. El-Gendy, R. M. Abdel-Rahmab, and M. S. Abdel-Malik, *Indian J. Chem*., 1989, **288**, 479.
5. S. K. Kotovskaya, L. A. Tyurina, E. Yu. Chernova, G. A. Mokrushina, O. N. Chupakhin, A. P. Novikova, and V. I. Il´enko, *Khim.-Farm. Zh.*, 1989, **23**, 310 [*Pharm. Chem. J*., 1989, **23** (Engl. Transl.)].
6. A. B. Tomchin, I. A. Zhmykhova, M. M. Ponomareva, L. V. Pastushenkov, and E. G. Gromova, *Khim.-Farm. Zh.*, 1986, **20**, 1051 [*Pharm. Chem. J*., 1986, **20** (Engl. Transl.)].
7. W. J. Coates, H. D. Prain, M. L. Reeves, and B. H. Warrington, *J. Med. Chem*., 1990, **33**, 1735.
8. E. Bulka and W. D. Pfeiffer, *J. Prakt. Chem*., 1976, **318**, 971.
9. W. D. Pfeiffer, K. Geisler, H. Rossenberg, and E. Bulka, *Z. Chem*., 1982, **22**, 137.
10. W. D. Pfeiffer and E. Bulka, *Z. Chem*., 1976, **16**, 80.
11. R. E. Busby and T. W. Dominey, *J. Chem. Soc., Perkin Trans. 2*, 1980, 890.
12. G. Ege, Ph. Arnold, G. Jooss, and R. Noronha, *Liebigs Ann. Chem.*, 1977, 791.
13. A. E. Baydar, G. Boyd, and P. F. Lindley, *Chem. Commun*., 1981, 1003.
14. H. Beyer, H. Honeck, and Z. Reichelt, *Liebigs Ann. Chem.*, 1970, **741**, 45.
15. N. Yoshida, K. Wachi, and K. Tanaka, Jpn Pat. 74-110697; *Chem. Abstrs*, 1975, **82**, 171095.
16. E. E. Campaigne and T. Selby, US Pat. 4 254 259; *Chem. Abstrs*, 1981, **95**, 25150.
17. T. D. Thibault, US Pat. 4 436 549; *Chem. Abstrs*, 1984, **101**, 23510.
18. A. P. Novikova, N. M. Petrova, L. G. Egorova, and I. E. Bragina, *Khim. Geterotsikl. Soedin.*, 1991, 843 [*Chem. Heterocycl. Compd*., 1991, **37**, 6 (Engl. Transl.)].
19. K. Hirai and T. Ishiba, *Chem. Pharm. Bull*., 1978, **26**, 3017.
20. H. Johne, K. Seifert, S. Johne, and E. Bulka, *Pharmazie*, 1978, **33**, 259.
21. I. Ya. Poplavskii, A. P. Novikova, L. A. Chechulina, and L. P. Sidorova, *Khim. Geterotsikl. Soedin.*, 1976, 1051 [*Chem. Heterocycl. Compd*., 1976, **22**, 8 (Engl. Transl.)].
22. A. S. Kulikov and N. N. Makhova, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 137 [*Russ. Chem. Bull*., 1998, **47**, 139 (Engl. Transl.)].
23. A. A. Hassan, N. K. Mohamed, B. A. Ali, and A.-F. E. Murad, *Tetrahedron*, 1994, **50**, 9997.
24. V. Klimesova, L. Zahajska, K. Waisser, J. Kaustova, and U. Moellmann, *Farmaco*, 2004, **59**, 279.

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