Modification of biologically active amides and amines with fluoro-containing heterocycles

5*. Fluoro-containing heterocyclic derivatives of 2-amino-1,3,4-thiadiazoles

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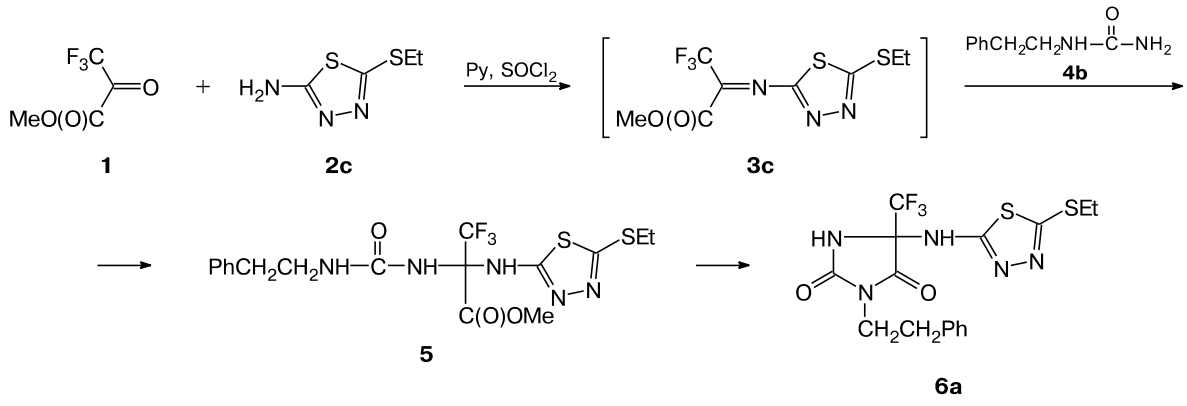
An approach to modification of biologically active 2-amino-1,3,4-thiadiazoles with fluoro-containing five-membered heterocycles was proposed. The approach involves reactions of imines (generated *in situ* from 2-amino-1,3,4-thiadiazoles and methyl trifluoropyruvate) with 1,3-binucleophiles such as 6-aminouracils, 6-aminothiouracils, N-substituted 3-aminocyclohexenones, N-substituted ureas, N-substituted benzamidines, and 3-aminocrotononitrile.

Key words: 2-amino-1,3,4-thiadiazoles, methyl trifluoropyruvate, 1,3,4-thiadiazol-2-ylimines, 6-aminouracils, 6-aminothiouracils, N-substituted 3-aminocyclohexenones, N-substituted ureas, N-substituted benzamidines, 3-aminocrotononitrile, fluoro-containing dihydro-1*H*-pyrroles, hexahydro-1*H*-indoles, hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidines, imidazolidine-2,4-diones, cyclocondensation.

1,3,4-Thiadiazole derivatives are successfully used as herbicides[2] and fungicides[3] in agricultural chemistry and as bactericides in medical practice.[4] The 2-amino-1,3,4-thiadiazole fragment is also employed for molecular design of biologically active compounds (*e.g.*, sulfaethidole, a streptocide derivative).[5] The goal of the present study was to modify 2-amino-1,3,4-thiadiazoles with trifluoromethyl-containing five-membered heterocycles using reactions of methyl trifluoropyruvate **1** and 1,3-N,N- and 1,3-C,N-binucleophiles with 2-amino-1,3,4-thiadiazoles **2a**—**c**. The prerequisite for this work was the data from systematic investigations of the behavior of acylimines of methyl trifluoropyruvate in cyclocondensation reactions with 1,3-*N*,*N*- and 1,3-*C*,*N*-binucleophiles, which yield trifluoromethyl-containing five-membered heterocycles,[6—10] as well as modification of streptocide[11] and piracetam.[12]

Following known literature routes to N-substituted imines of methyl trifluoropyruvate, we failed to obtain the starting biselectrophilic synthons (1,3,4-thiadiazol-2-ylimines of methyl trifluoropyruvate (**3a**—**c**)) in the individual state.[13] For this reason, imines **3a**—**c** were generat-

Scheme 1



* For Part 4, see Ref. 1.

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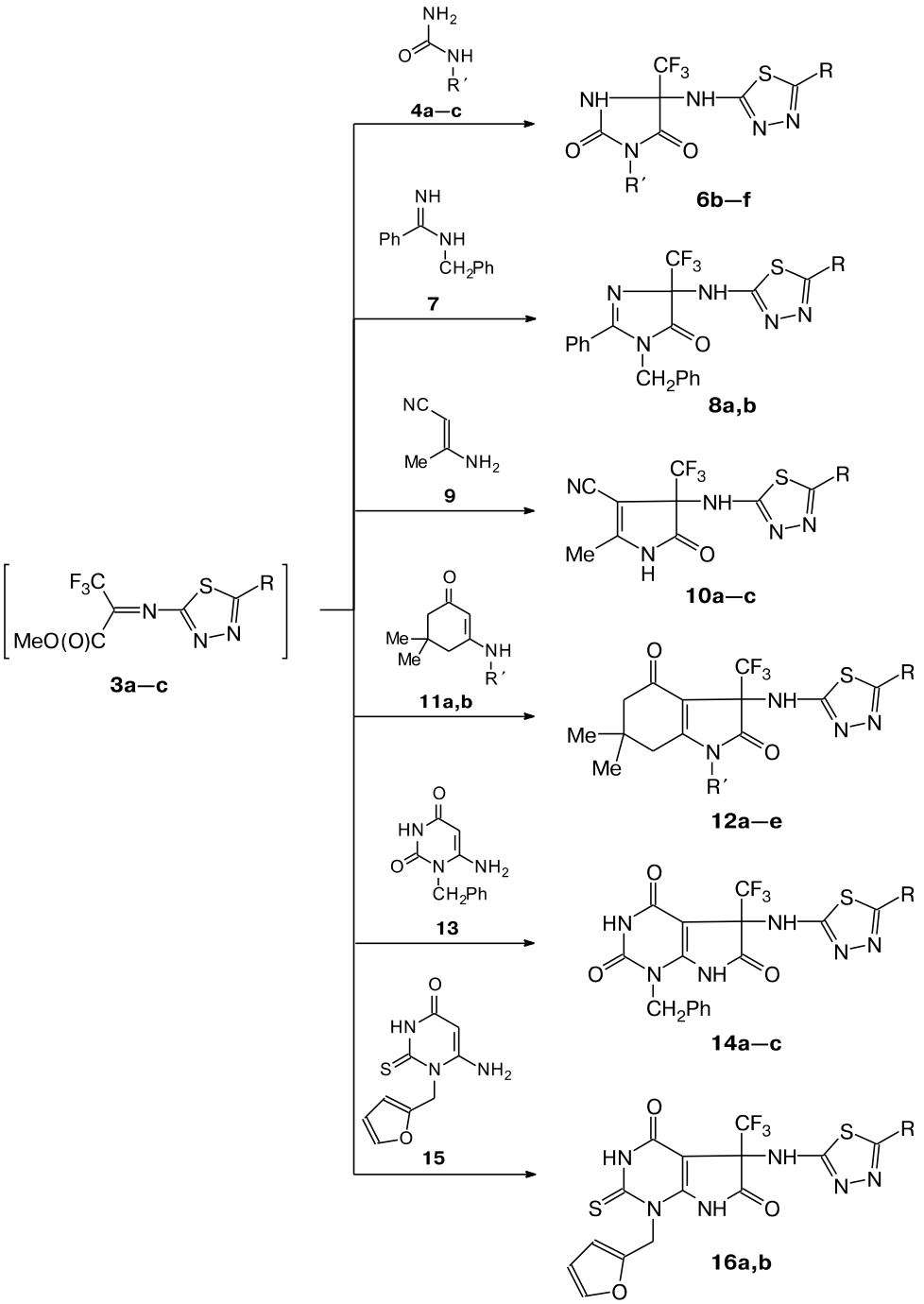
Scheme 2



Compound	R
3a	Me
3b	Et
3c	EtS
8a	Me
8b	EtS
10a	Me
10b	Et
10c	EtS

Compound	R
14a	Me
14b	Et
14c	EtS
16a	Et
16b	EtS

Compound	R′
4a	CH_2Ph
4b	CH_2CH_2Ph
4c	$CH_2C_6H_4$-OMe-4
11a	CH_2Ph
11b	CH_2CH_2Ph

Compound	R	R′
6b	Me	CH_2CH_2Ph
6c	Me	$CH_2C_6H_4$-OMe-4
6d	Et	CH_2Ph
6e	Et	CH_2CH_2Ph
6f	EtS	CH_2Ph
12a	Me	CH_2Ph
12b	Me	CH_2CH_2Ph
12c	Et	CH_2CH_2Ph
12d	EtS	CH_2Ph
12e	EtS	CH_2CH_2Ph

ed *in situ* by successively adding pyridine, methyl trifluoropyruvate **2**, and thionyl chloride to a solution of 2-amino-1,3,4-thiadiazoles **2a—c** in DMF. The generated imines **3a—c** underwent cyclocondensation with 1,3-C,N- and 1,3-N,N-binucleophiles. The reactions of imines **3a—c** with 1,3-binucleophiles follow the cyclocondensation mechanism involving (1) addition of the binucleophile to the C=N bond and (2) heterocyclization with elimination of methanol. In the case of 2-amino-5-ethylsulfanyl[1,3,4]-thiadiazole **2c** and phenethylurea **4b**, adduct **5** was isolated in the individual state and characterized. When heated in DMF at 90—100 °C for 2 h in the presence of catalytic amounts of Et_3N, adduct **5** underwent intramolecular cyclization into imidazolidine-2,4-dione **6a** (Scheme 1).

Reactions of *in situ* generated imines **3a—c** with 1,3-binucleophiles such as N-substituted ureas **4a—c**, *N*-benzylbenzamidine **7**, 3-aminocrotononitrile **9**, N-substituted 3-aminocyclohexenones **11a,b**, 6-aminouracil **13**, and 6-aminothiouracil **15** were carried out in DMF at 90—100 °C for 2 h in the presence of catalytic amounts of Et_3N without isolating intermediate adducts (Scheme 2). Cyclocondensation of imines **3a—c** with binucleophiles **4a—c**, **7**, **9**, **11a,b**, **13**, and **15** gave the corresponding heterocyclic compounds **6a—f**, **8a**,**b**, **10a—c**, **12a**,**b**, **14a—c**, and **16a**,**b**.

Fluoro-containing heterocyclic products **6**, **8**, **10**, **12**, **14**, and **16** are crystalline solids; their compositions and structures were determined from elemental analysis data and ^1H and ^{19}F NMR spectra. The ^{19}F NMR spectra show characteristic signals at δ –0.7—0.9 for compound **6**, at δ 0.3—0.4 for compound **8**, at δ 2.0—2.3 for compound **10**, and at δ 3.6—3.9 for compounds **12**, **14**, and **16**.

To sum up, the reactions of 2-amino-1,3,4-thiadiazoles with methyl trifluoropyruvate and 1,3-C,N- and N,N-binucleophiles in the presence of the dehydrating system $Py/SOCl_2$ seem to be a promising synthetic way of modifying the amine function of biologically active heterylamines with various trifluoromethyl-containing five-membered heterocycles.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer (200.13 (^1H) and 188.29 MHz (^{19}F)) with $SiMe_4$ as the internal standard and CF_3COOH as the external standard, respectively. Melting points were determined in glass capillaries. The starting reagents N-substituted 3-aminocyclohexenones **11a,b** were prepared according to a known procedure.[14] 6-Aminouracil **13** and 6-aminothiouracil **15**,[15] N-substituted ureas **4a—c**, 3-aminocrotononitrile **9**, methyl trifluoropyruvate **1**, and 2-amino-1,3,4-thiadiazoles **2a—c** (Aldrich) were used as purchased.

Methyl 2-(5-ethylsulfanyl[1,3,4]thiadiazol-2-ylamino)-3,3,3-trifluoro-2-(3-phenethylureido)propionate (5). Pyridine (1.56 g, 0.02 mol) and methyl trifluoropyruvate **1** (1.56 g, 0.01 mol) were successively added to a stirred solution of 1.62 g (0.01 mol) 2-amino-5-ethylsulfanyl[1,3,4]thiadiazole **2c** in DMF (20 mL). The reaction mixture was stirred for 30 min and, after addition of $SOCl_2$ (1.19 g, 0.01 mol), for 1 h. Then phenethylurea (1.64 g, 0.01 mol) was added. The reaction mixture was stirred at 20 °C for 1 h and poured into water (50 mL). The precipitate that formed was filtered off and recrystallized from 50% EtOH. The yield, melting point, elemental analysis data, and spectroscopic characteristics of compound **5** are given in Tables 1 and 2.

Table 1. Yields, melting points, and elemental analysis data for compounds **5**, **6**, **8**, **10**, **12**, **14**, and **16**

Compound	Yield (%)	M.p./°C	Found / Calculated (%) C	H	N	Molecular formula
5	86	154—155	44.05 / 43.87	4.35 / 4.11	15.11 / 15.33	$C_{17}H_{20}F_3N_5O_3S_2$
6a	88 (*A*) 72 (*B*)	183—184	44.54 / 44.71	3.74 / 3.57	16.23 / 16.05	$C_{16}H_{16}F_3N_5O_2S_2$
6b	83	180—182	46.75 / 46.58	3.66 / 3.84	18.17 / 18.01	$C_{15}H_{14}F_3N_5O_2S$
6c	82	175—177	44.89 / 44.65	3.52 / 3.28	17.45 / 17.33	$C_{15}H_{14}F_3N_5O_3S$
6d	69	172—174	46.75 / 46.92	3.66 / 3.88	18.17 / 18.36	$C_{15}H_{14}F_3N_5O_2S$
6e	75	169—171	48.12 / 48.31	4.04 / 3.88	17.53 / 17.37	$C_{16}H_{16}F_3N_5O_2S$
6f	78	153—155	43.16 / 43.32	3.38 / 3.56	16.78 / 16.54	$C_{15}H_{14}F_3N_5O_2S_2$
8a	73	180—182	55.68 / 55.85	3.74 / 3.56	16.23 / 16.06	$C_{20}H_{16}F_3N_5OS$
8b	75	168—170	52.82 / 52.61	3.80 / 4.02	14.67 / 14.44	$C_{21}H_{18}F_3N_5OS_2$
10a	62	238—239	39.61 / 39.45	2.66 / 2.48	18.79 / 18.95	$C_{10}H_8F_3N_5OS$
10b	68	224—226	41.64 / 41.89	3.18 / 3.41	22.07 / 22.25	$C_{11}H_{10}F_3N_5OS$
10c	71	234—236	37.82 / 37.99	2.89 / 3.05	20.05 / 19.83	$C_{11}H_{10}F_3N_5OS_2$
12a	73	180—182	55.99 / 56.18	4.70 / 4.52	12.44 / 12.26	$C_{21}H_{21}F_3N_4O_2S$
12b	69	184—186	56.89 / 56.67	4.99 / 4.81	12.06 / 11.85	$C_{22}H_{23}F_3N_4O_2S$
12c	72	175—176	57.73 / 57.91	5.27 / 5.03	11.71 / 11.89	$C_{23}H_{25}F_3N_4O_2S$
12d	63	184—185	53.21 / 53.38	4.67 / 4.52	11.28 / 11.03	$C_{22}H_{23}F_3N_4O_2S_2$
12e	68	167—168	54.10 / 54.31	4.94 / 5.12	10.97 / 11.18	$C_{23}H_{25}F_3N_4O_2S_2$
14a	77	278—279	49.43 / 49.22	3.23 / 3.06	16.01 / 15.85	$C_{18}H_{14}F_3N_5O_3S$
14b	79	271—273	50.55 / 50.28	3.57 / 3.38	15.51 / 15.69	$C_{19}H_{16}F_3N_5O_3S$
14c	74	265—266	47.02 / 46.84	3.34 / 3.16	14.48 / 14.69	$C_{19}H_{16}F_3N_5O_3S_2$
16a	82	245—246	44.64 / 44.45	3.08 / 3.31	15.31 / 15.59	$C_{17}H_{14}F_3N_5O_3S_2$
16b	80	235—237	41.71 / 41.50	2.88 / 2.63	14.31 / 14.13	$C_{17}H_{14}F_3N_5O_3S_3$

Table 2. ^{1}H and ^{19}F NMR spectra of compounds **5**, **6**, **8**, **10**, **12**, **14**, and **16** in DMSO-d_6

Compound	^{1}H NMR (δ, *J*/Hz)	^{19}F NMR (δ (s))
5	1.36 (t, 3 H, Me, *J* = 7.5); 2.60 (t, 2 H, CH_2, *J* = 6.8); 3.03—3.20 (m, 4 H, CH_2 + CH_2); 3.80 (s, 3 H, MeO); 6.50 (t, 1 H, NH, *J* = 6.8); 7.00—7.26 (m, 5 H, CH_{Ar}); 7.58, 8.46 (both s, 1 H, NH)	2.82
6a	1.38 (t, 3 H, Me, *J* = 7.8); 2.92 (t, 2 H, CH_2, *J* = 7.5); 3.14 (q, 2 H, CH_2, *J* = 7.3); 3.68 (t, 2 H, CH_2, *J* = 7.5); 7.06—7.34 (m, 5 H, CH_{Ar}); 9.19, 9.23 (both s, 1 H, NH)	−0.75
6b	2.54 (s, 3 H, Me); 2.98 (t, 2 H, CH_2, *J* = 7.7); 3.72 (m, 2 H, CH_2); 7.09—7.37 (m, 5 H, CH_{Ar}); 9.13, 9.27 (both s, 1 H, NH)	−0.70
6c	2.55 (s, 3 H, Me); 3.79 (s, 3 H, MeO); 4.61 (m, 2 H, CH_2); 6.84, 7.29 (both d, 2 H, CH_{Ar}, *J* = 8.6); 9.15, 9.35 (both s, 1 H, NH)	−0.92
6d	1.30 (t, 3 H, Me, *J* = 7.6); 2.86 (q, 2 H, CH_2, *J* = 7.6); 4.65 (m, 2 H, CH_2); 7.11—7.42 (m, 5 H, CH_{Ar}); 9.16, 9.35 (both s, 1 H, NH)	−0.74
6e	1.31 (t, 3 H, Me, *J* = 7.5); 2.80—3.04 (m, 4 H, CH_2 + CH_2); 3.69 (m, 2 H, CH_2); 7.07—7.35 (m, 5 H, CH_{Ar}); 9.15, 9.24 (both s, 1 H, NH)	−0.58
6j	1.39 (t, 3 H, Me, *J* = 7.6); 3.12 (q, 2 H, CH_2, *J* = 7.6); 4.17 (m, 2 H, CH_2); 7.00 (m, 2 H, CH_{Ar}); 7.15 (m, 3 H, CH_{Ar}); 7.68, 8.59 (both s, 1 H, NH)	−0.71
8a	2.30 (s, 3 H, Me); 4.77 (s, 2 H, CH_2); 7.18—7.37 (m, 5 H, CH_{Ar}); 7.40—7.54 (m, 5 H, CH_{Ar}); 8.94 (s, 1 H, NH)	0.40
8b	1.40 (t, 3 H, Me, *J* = 7.3); 3.05 (q, 2 H, CH_2, *J* = 7.3); 4.79 (q, 2 H, CH_2, *J* = 10.3); 7.23, 7.24—7.54 (both m, 5 H, CH_{Ar}); 7.49 (m, 5 H, CH_{Ar}); 9.37 (s, 1 H, NH)	0.30
10a	2.28, 2.55 (both s, 3 H, Me); 9.02, 11.35 (both s, 1 H, NH)	2.27
10b	1.27 (t, 3 H, Me, *J* = 7.1); 2.22 (s, 3 H, Me); 2.84 (q, 2 H, CH_2, *J* = 7.1); 8.98, 11.28 (both s, 1 H, NH)	2.22
10c	1.37 (t, 3 H, Me, *J* = 7.3); 2.25 (s, 3 H, Me); 3.11 (q, 2 H, CH_2, *J* = 7.3); 9.14, 11.32 (both s, 1 H, NH)	2.03
12a	0.99, 1.06 (both s, 3 H, Me); 2.13 (AB system, 2 H, CH_2, *J* = 15.09); 2.45 (d, 2 H, CH_2, *J* = 4.2); 2.51 (s, 3 H, Me); 4.97 (AB system, 2 H, CH_2, *J* = 10.20); 7.24—7.51 (m, 5 H, CH_{Ar}); 9.00 (s, 1 H, NH)	3.81
12b	0.97 (s, 6 H, Me); 2.07 (m, 2 H, CH_2); 2.17 (m, 2 H, CH_2); 2.96 (m, 2 H, CH_2); 3.85 (m, 2 H, CH_2); 7.15—7.43 (m, 5 H, CH_{Ar}); 8.92 (s, 1 H, NH)	3.95
12c	0.94 (s, 6 H, Me); 1.30 (t, 3 H, Me, *J* = 7.7); 1.97—2.21 (m, 4 H, CH_2); 2.85 (q, 2 H, CH_2, *J* = 7.7); 2.95 (t, 2 H, CH_2, *J* = 6.8); 3.83 (t, 2 H, CH_2, *J* = 6.8); 7.10—7.40 (m, 5 H, CH_{Ar}); 8.93 (s, 1 H, NH)	3.98
12d	1.01, 1.07 (both s, 3 H, Me); 1.42 (t, 3 H, Me, *J* = 7.4); 2.16 (m, 2 H, CH_2); 2.50 (m, 2 H, CH_2); 3.14 (q, 2 H, CH_2, *J* = 7.4); 4.93 (m, 2 H, CH_2); 7.24—7.52 (m, 5 H, CH_{Ar}); 9.17 (s, 1 H, NH)	3.89
12e	0.91 (s, 6 H, Me); 1.35 (t, 3 H, Me, *J* = 7.5); 1.98—2.15 (m, 4 H, CH_2); 2.96 (t, 2 H, CH_2, *J* = 6.6); 3.11 (q, 2 H, CH_2, *J* = 7.5); 3.86 (t, 2 H, CH_2, *J* = 6.6); 7.14—7.42 (m, 5 H, CH_{Ar}); 9.09 (s, 1 H, NH)	3.93
14a	2.55 (s, 3 H, Me); 5.14 (m, 2 H, CH_2); 7.46 (m, 5 H, CH_{Ar}); 9.12 (s, 1 H, NH); 11.02 (s, 1 H, NH); 12.34 (s, 1 H, NH)	3.61
14b	1.35 (t, 2 H, Me, *J* = 7.5); 2.89 (q, 2 H, CH_2, *J* = 7.4); 5.01 (m, 2 H, CH_2); 7.38 (m, 5 H, CH_{Ar}); 9.13 (s, 1 H, NH); 11.0 (s, 1 H, NH); 12.32 (s, 1 H, NH)	3.65
14c	1.45 (t, 2 H, Me, *J* = 7.4); 3.21 (q, 2 H, CH_2, *J* = 7.4); 5.14 (m, 2 H, CH_2); 7.40 (m, 5 H, CH_{Ar}); 9.28 (s, 1 H, NH); 11.03 (s, 1 H, NH); 12.35 (s, 1 H, NH)	3.59
16a	1.31 (t, 3 H, Me, *J* = 7.7); 2.88 (q, 2 H, CH_2, *J* = 7.7); 6.39, 6.49 (both m, 1 H, CH_{Ar}); 7.52 (m, 1 H, CH_{Ar}); 9.16, 12.42 (both s, 1 H, NH)	3.74
16b	1.37 (t, 3 H, Me, *J* = 7.2); 3.05 (q, 2 H CH_2, *J* = 7.2); 6.34, 6.45 (both m, 1 H, CH_{Ar}); 7.49 (m, 1 H, CH_{Ar}); 9.28, 12.40 (both s, 1 H, NH)	3.71

5-(5-Ethylsulfanyl[1,3,4]thiadiazol-2-ylamino)-3-phenethyl-5-trifluoromethylimidazolidine-2,4-dione (6a). ***Method A.*** A solution of urea **5** (0.46 g, 0.001 mol) in Et_3N (0.05 g) was heated at 90—100 °C for 2 h. The reaction mixture was cooled and poured into water (50 mL). The precipitate that formed was filtered off and recrystallized from 50% EtOH.

Method B. Pyridine (1.56 g, 0.02 mol) and methyl trifluoropyruvate **1** (1.56 g, 0.01 mol) were successively added to a stirred solution of compound **2c** (1.62 g, 0.01 mol) in DMF (20 mL). The reaction mixture was stirred for 30 min and, after addition of $SOCl_2$ (1.19 g, 0.01 mol), for 1 h. Then phenethylurea **4b** (1.64 g, 0.01 mol) and Et_3N (0.1 g) were added. The reaction

mixture was stirred at 20 °C for 1 h, heated at 90—100 °C for 2 h, cooled, and poured into water (50 mL). The precipitate that formed was filtered off and recrystallized from 50% EtOH. The yield, melting point, elemental analysis data, and spectroscopic characteristics of compound **6a** are given in Tables 1 and 2.

5-(5-Methyl[1,3,4]thiadiazol-2-ylamino)-3-phenethyl-5-trifluoromethylimidazolidine-2,4-dione (6b), **3-(4-methoxybenzyl)-5-(5-methyl[1,3,4]thiadiazol-2-ylamino)-5-trifluoromethylimidazolidine-2,4-dione (6c)**, **3-benzyl-5-(5-ethyl[1,3,4]thiadiazol-2-ylamino)-5-trifluoromethylimidazolidine-2,4-dione (6d)**, **5-(5-ethyl[1,3,4]thiadiazol-2-ylamino)-3-phenethyl-5-trifluoromethylimidazolidine-2,4-dione (6e)**, **3-benzyl-5-(5-ethylsulfanyl-[1,3,4]thiadiazol-2-ylamino)-5-trifluoromethylimidazolidine-2,4-dione (6f)**, **3-benzyl-5-(5-methyl[1,3,4]thiadiazol-2-ylamino)-2-phenyl-5-trifluoromethyl-4,5-dihydroimidazol-4-one (8a)**, **3-benzyl-5-(5-ethylsulfanyl[1,3,4]thiadiazol-2-ylamino)-2-phenyl-5-trifluoromethyl-4,5-dihydroimidazol-4-one (8b)**, **2-methyl-4-(5-methyl[1,3,4]thiadiazol-2-ylamino)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (10a)**, **4-(5-ethyl-[1,3,4]thiadiazol-2-ylamino)-2-methyl-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (10b)**, **4-(5-ethylsulfanyl-[1,3,4]thiadiazol-2-ylamino)-2-methyl-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (10c)**, **1-benzyl-6,6-dimethyl-3-(5-methyl[1,3,4]thiadiazol-2-ylamino)-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (12a)**, **6,6-dimethyl-3-(5-methyl[1,3,4]thiadiazol-2-ylamino)-1-phenethyl-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (12b)**, **3-(5-ethyl[1,3,4]thiadiazol-2-ylamino)-6,6-dimethyl-1-phenethyl-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (12c)**, **1-benzyl-3-(5-ethylsulfanyl[1,3,4]thiadiazol-2-ylamino)-6,6-dimethyl-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (12d)**, **3-(5-ethylsulfanyl[1,3,4]thiadiazol-2-ylamino)-6,6-dimethyl-1-phenethyl-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (12e)**, **7-benzyl-3-(5-methyl[1,3,4]thiadiazol-2-ylamino)-3-trifluoromethyl-3,7-dihydro-1*H*-pyrrolo-[2,3-*b*]pyrimidine-2,4,6-trione (14a)**, **7-benzyl-3-(5-ethyl[1,3,4]-thiadiazol-2-ylamino)-3-trifluoromethyl-3,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyrimidine-2,4,6-trione (14b)**, **7-benzyl-3-(5-ethylsulfanyl[1,3,4]thiadiazol-2-ylamino)-3-trifluoromethyl-3,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyrimidine-2,4,6-trione (14c)**, **3-(5-ethyl[1,3,4]thiadiazol-2-ylamino)-7-furfuryl-6-thioxo-3-trifluoromethyl-3,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyrimidine-2,4-dione (16a)**, and **3-(5-ethylsulfanyl[1,3,4]thiadiazol-2-ylamino)-7-furfuryl-6-thioxo-3-trifluoromethyl-3,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyrimidine-2,4-dione (16b)** were obtained as described above for compound **6a** (method ***B***). The yields, melting points, elemental analysis data, and spectroscopic characteristics of compounds **6**, **8**, **10**, **12**, **14**, and **16** are given in Tables 1 and 2.

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