Synthesis of fluoro-containing pyrimidinones from hexafluoroacetone(ethoxycarbonylimine)

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Cyclocondensation of hexafluoroacetone(ethoxycarbonylimine) with various 1,3-C,N-bisnucleophiles afforded novel bis(trifluoromethyl)pyrimidinones, including fused ones, in preparative yields.

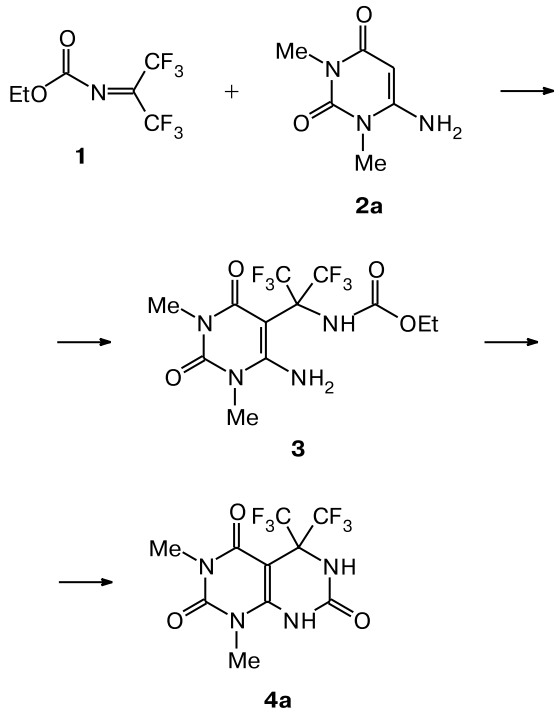
Key words: hexafluoroacetone(ethoxycarbonylimine), 1,3-C,N-bisnucleophiles, pyrimidine-2,4-diones, pyrimido[4,5-*d*]pyrimidine-2,4,7-triones, 4,6,7,8-tetrahydropyrimidine-2,6-diones, pyrimido[4,5-*d*]pyrimidine-2,5-diones, heterocyclization, organofluorine compounds.

Alkoxycarbonylimines of hexafluoroacetone, as well as its acylimines, are starting materials for the synthesis of various heterocyclic compounds containing geminal trifluoromethyl groups. These are used as heterodienes and dienophiles in cycloaddition reactions with *N*-cyano amines,[1] nitriles,[2] phosphorus(III) acid derivatives,[3,4] and cyclopentadiene[2] and as 1,3-biselectrophilic reagents in cyclocondensation reactions with 1,3-bisnucleophiles.[5,6] In the present work, we obtained a number of novel 2,2-bis(trifluoromethyl)pyrimidinones by cyclocondensation of 1,3-C,N-bisnucleophiles with readily available hexafluoroacetone(ethoxycarbonylimine). Some substituted pyrimidinones were reported to exhibit various types of biological (*e.g.*, antimicrobial[7] and antiviral[8]) activity and to be inhibitors of serine proteases.[9] All this makes it topical to search for routes to compounds of this class.

In this reaction, we used 6-aminouracil, 6-aminothiouracil, *N*-substituted 3-aminocyclohexenones, 3-aminocrotononitrile, and 6-aminopyrimidinones as bisnucleophilic reagents.

It was found that hexafluoroacetone(ethoxycarbonylimine) (**1**), like its benzoylimine,[5] exothermically reacts at 20 °C with *N*,*N*-dimethyl-6-aminouracil (**2a**) to give C(5)-alkyl derivative **3**. This product was converted into dihydropyrimidopyrimidinetrione **4a** by heating in DMF (1 h, 90 °C) in the presence of catalytic amounts of Et_3N (Scheme 1).

Scheme 1



The cyclocondensation of imine **1** with 6-aminouracils **2b—e**, 6-aminothiouracils **5a—d**, 3-aminocyclohexenones **6a—g**, 3-aminocrotononitrile (**7**), and 6-aminopyrimidinones **8a,b** (equimolar amounts of the reagents were mixed in DMF at 20 °C; after the exothermic reaction was completed, the mixture was heated at 90—100 °C for 5 h in the presence of catalytic amounts of Et_3N; no intermediate adducts were isolated) yielded pyrimidinones **4b—e**, **9a—d**, **10a—g**, **11**, and **12a,b**, respectively (Scheme 2).

Pyrimidinones **4** and **9—12** were obtained in 69—88% yields as crystalline solids. Their compositions and structures were confirmed by elemental analysis and NMR spectroscopy. The ^1H and ^{19}F NMR spectra contain char-

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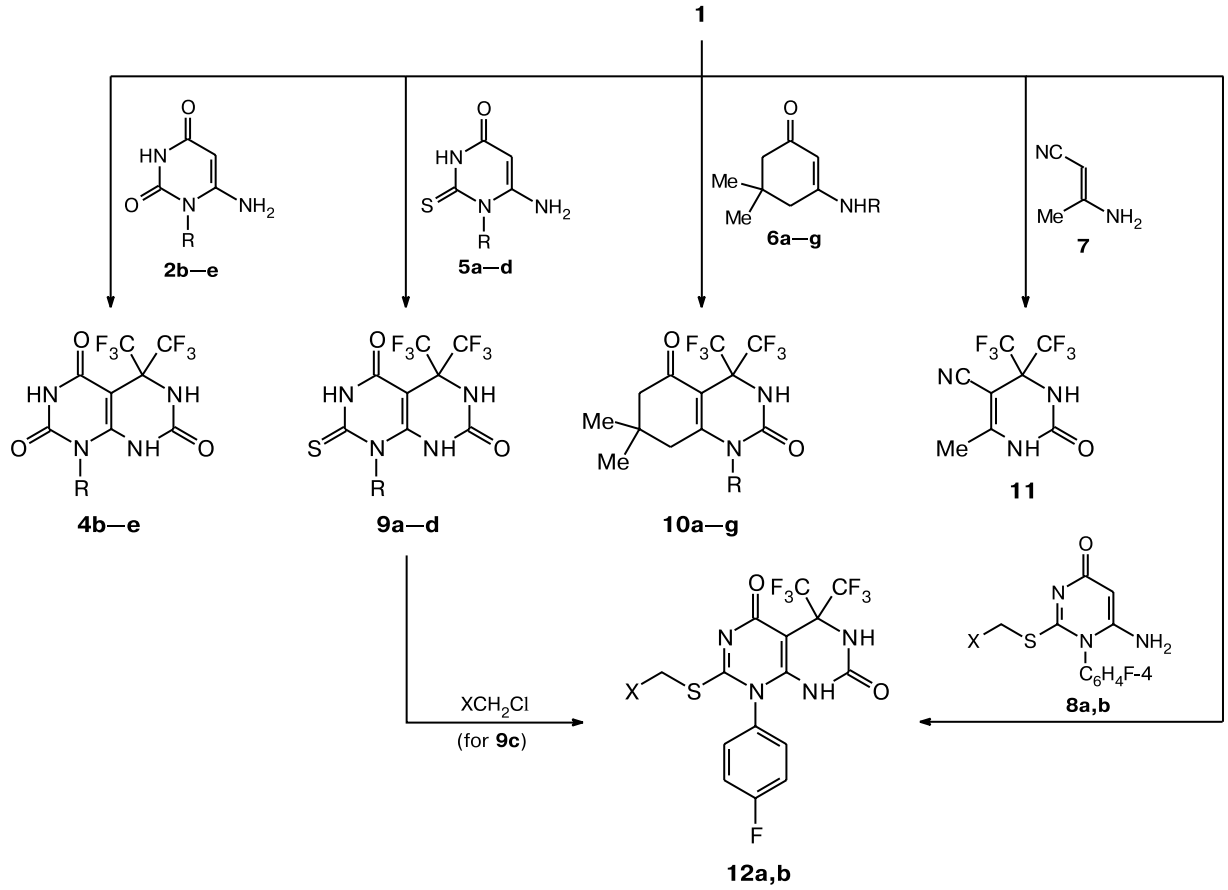
Scheme 2

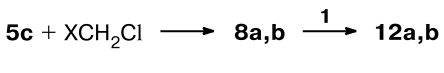


2,4: R = Me (**b**), Ph (**c**), 4-MeC_6H_4 (**d**), CH_2Ph (**e**); **5, 9:** R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-FC_6H_4 (**c**), CH_2CH_2Ph (**d**);
6, 10: R = Bu (**a**), 4-FC_6H_4 (**b**), 3-ClC_6H_4 (**c**), CH_2Ph (**d**), CH_2CH_2Ph (**e**), 2-$ClC_6H_4CH_2$ (**f**), (furan-2-yl)methyl (**g**);
8, 12: X = Ph (**a**), CO_2Et (**b**)

acteristic signals at δ 9.0—12.0 for NH protons and at δ 2.8—6.4 for geminal CF_3 groups.

The structure of pyrimidopyrimidinedione **9c** was additionally confirmed by chemical transformations. For instance, keeping of equimolar amounts of compound **9c**, triethylamine, and benzyl chloride or ethyl chloroacetate in DMF at 20 °C for 12 h gave pyrimidopyrimidinediones **12a,b** (see Scheme 2). Compounds **12a,b** were also obtained independently *via S*-alkylation of aminothiouracil **5c** with activated chlorides XCH_2Cl (X = Ph and CO_2Et) followed by cyclocondensation of the resulting aminopyrimidinones **8a,b** with imine **1** into compounds **12a,b** (Scheme 3).

Scheme 3



X = Ph, CO_2Et

Thus, the cyclocondensation reactions of hexafluoroacetone(ethoxycarbonylimine) with enamines allowed the preparation of various novel (including fused) 2,2-bis(trifluoromethyl)pyrimidinones.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer. Melting points were determined in glass capillaries. Hexafluoroacetone(ethoxycarbonylimine) (**1**) was prepared according to a known procedure.[10] The starting 6-aminouracils **2**,[11] 6-aminothiouracils **5**,[11] and 3-aminocyclohexenones **6** [12] were prepared according to available procedures. 3-Aminocrotononitrile (Aldrich) was used as purchased.

6-Amino-5-(2-ethoxycarbonylamino-1,1,1,3,3,3-hexafluoropropan-2-yl)-1,3-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (3). A mixture of imine **1** (2.37 g, 0.01 mol) and aminouracil **2a** (1.55 g, 0.01 mol) in DMF (10 mL) was stirred at 20 °C for 1 h and poured into water (50 mL). The precipitate that formed was filtered off and recrystallized from benzene to give compound **3** (3.15 g, 80%), m.p. 199—201 °C. Found (%): C, 36.58;

H, 3.47; N, 14.11. $C_{12}H_{14}F_6N_4O_4$. Calculated (%): C, 36.74; H, 3.60; N, 14.28. ^{1}H NMR (DMSO-d_6), δ: 1.22 (t, 3 H, CMe, J = 7.1 Hz); 3.16, 3.32 (both s, 3 H each, NMe); 4.08 (q, 2 H, CH_2O, J = 7.1 Hz); 6.66 (s, 2 H, NH_2); 8.04 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 5.29, 17.76 (both s, 1 : 1).

1,3-Dimethyl-5,5-bis(trifluoromethyl)-5,8-dihydro-1*H*,6*H*-pyrimido[4,5-*d*]pyrimidine-2,4,7-trione (4a). ***A.*** Triethylamine (0.2 mL) was added to a solution of compound **3** (3.92 g, 0.01 mol) in DMF (10 mL). The reaction mixture was heated at 90—100 °C for 5 h, cooled, and poured into water (50 mL). The precipitate that formed was filtered off and recrystallized from 50% EtOH to give compound **4a** (3.22 g, 86%), m.p. 291—293 °C. Found (%): C, 34.51; H, 2.15; N, 16.11. $C_{10}H_8F_6N_4O_3$. Calculated (%): C, 34.69; H, 2.33; N, 16.18. ^{1}H NMR (DMSO-d_6), δ: 3.21, 3.42 (both s, 3 H each, NMe); 8.95, 10.62 (both s, 1 H each, NH). ^{19}F NMR (DMSO-d_6), δ: 5.41 (s).

B. A mixture of imine **1** (2.37 g, 0.01 mol) and aminouracil **2a** (1.55 g, 0.01 mol) in DMF (10 mL) was stirred at 20 °C for 1 h and Et_3N (0.2 mL) was added. The reaction mixture was heated at 90—100 °C for 5 h, cooled, and poured into water (50 mL). The precipitate that formed was filtered off and recrystallized from 50% EtOH to give compound **4a** (3.11 g, 83%).

1-Methyl-5,5-bis(trifluoromethyl)-5,8-dihydro-1*H*,6*H*-pyrimido[4,5-*d*]pyrimidine-2,4,7-trione (4b), 1-phenyl-5,5-bis(trifluoromethyl)-5,8-dihydro-1*H*,6*H*-pyrimido[4,5-*d*]pyrimidine-2,4,7-trione (4c), 1-(4-methylphenyl)-5,5-bis(trifluoromethyl)-5,8-dihydro-1*H*,6*H*-pyrimido[4,5-*d*]pyrimidine-2,4,7-trione (4d), 1-benzyl-5,5-bis(trifluoromethyl)-5,8-dihydro-1*H*,6*H*-pyrimido[4,5-*d*]pyrimidine-2,4,7-trione (4e), 8-phenyl-7-thioxo-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-pyrimido[4,5-*d*]pyrimidine-2,5-dione (9a), 8-(4-methylphenyl)-7-thioxo-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-pyrimido[4,5-*d*]pyrimidine-2,5-dione (9b), 8-(4-fluorophenyl)-7-thioxo-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-pyrimido[4,5-*d*]pyrimidine-2,5-dione (9c), 8-phenethyl-7-thioxo-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-pyrimido[4,5-*d*]pyrimidine-2,5-dione (9d), 1-butyl-7,7-dimethyl-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-

Table 1. Yields, melting points, and elemental analysis data for compounds **4b**—**e**, **9a**—**d**, **10a**—**g**, and **11**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
4b	72	315—317	32.38	1.67	16.69	$C_9H_6F_6N_4O_3$
			32.54	1.82	16.87	
4c	82	260—262	42.48	2.18	14.39	$C_{14}H_8F_6N_4O_3$
			42.65	2.05	14.21	
4d	78	316—318	44.01	2.63	13.89	$C_{15}H_{10}F_6N_4O_3$
			44.16	2.47	13.72	
4e	76	324—326	44.31	2.31	13.86	$C_{15}H_{10}F_6N_4O_3$
			44.13	2.47	13.72	
9a	75	312—314	40.82	1.84	13.81	$C_{14}H_8F_6N_4O_2S$
			40.98	1.97	13.66	
9b	71	246—248	42.28	2.21	13.38	$C_{15}H_{10}F_6N_4O_2S$
			42.46	2.38	13.20	
9c	69	287—289	39.41	1.48	12.91	$C_{14}H_7F_7N_4O_2S$
			39.26	1.65	13.08	
9d	82	256—258	43.66	2.59	12.93	$C_{16}H_{12}F_6N_4O_2S$
			43.84	2.76	12.78	
10a	75	218—220	49.61	5.07	7.17	$C_{16}H_{20}F_6N_2O_2$
			49.74	5.22	7.25	
10b	71	279—291	50.77	3.39	6.72	$C_{18}H_{15}F_7N_2O_2$
			50.95	3.56	6.60	
10c	69	215—217	49.21	3.27	6.21	$C_{18}H_{15}ClF_6N_2O_2$
			49.05	3.43	6.36	
10d	82	225—227	54.11	4.45	6.81	$C_{19}H_{18}F_6N_2O_2$
			54.29	4.32	6.66	
10e	77	218—220	55.12	4.47	6.27	$C_{20}H_{20}F_6N_2O_2$
			55.30	4.64	6.45	
10f	70	241—242	50.01	3.59	6.33	$C_{18}H_{15}ClF_6N_2O_2$
			50.18	3.77	6.16	
10g	79	283—285	49.72	3.79	6.67	$C_{17}H_{16}F_6N_2O_3$
			49.76	3.93	6.83	
11	88	301—303	35.33	1.69	15.22	$C_8H_5F_6N_3O$
			35.18	1.85	15.38	

dione (10a), 1-(4-fluorophenyl)-7,7-dimethyl-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione (10b), 1-(3-chlorophenyl)-7,7-dimethyl-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione (10c), 1-benzyl-7,7-dimethyl-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione (10d), 7,7-dimethyl-1-phenethyl-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione (10e), 1-(2-chlorobenzyl)-7,7-dimethyl-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione (10f), 1-furfuryl-7,7-dimethyl-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione (10g), and 6-methyl-2-oxo-4,4-bis(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (11) were obtained from imine **1** (0.01 mol) and the corresponding enamines (0.01 mol) as described for pyrimidinone **4a**. The yields, melting points, and spectroscopic characteristics of compounds **4b**—**e**, **9a**—**d**, **10a**—**g**, and **11** are given in Tables 1 and 2.

6-Amino-2-benzylsulfanyl-1-(4-fluorophenyl)-1,4-dihydropyrimidin-4-one (8a). A mixture of 6-aminothiouracil **5c** (2.37 g, 0.01 mol), benzyl chloride (1.27 g, 0.01 mol), and Et_3N (1.01 g, 0.01 mol) in DMF (20 mL) was kept at 20 °C for 12 h and poured into water (50 mL). The precipitate that formed was filtered off and recrystallized from 50% EtOH to give compound **8a** (2.6 g, 80%), m.p. 187—189 °C. Found (%): C, 62.21; H, 4.17; N, 12.97. $C_{17}H_{14}FN_3OS$. Calculated (%): C, 62.37; H, 4.31; N, 12.84. ^{1}H NMR (DMSO-d_6), δ: 4.25 (s, 2 H, CH_2); 5.07 (s, 1 H, CH); 5.95 (s, 2 H, NH_2); 7.31 (m, 7 H, H arom.); 7.45 (m, 2 H, H arom.). ^{19}F NMR (DMSO-d_6), δ: −30.92 (m).

Ethyl {[6-amino-1-(4-fluorophenyl)-4-oxo-1,4-dihydropyrimidin-2-yl]sulfanyl}acetate (8b) was obtained analogously from aminothiouracil **5c** (0.01 mol) and ethyl chloroacetate (0.01 mol). The yield of compound **8b** was 2.4 g (74%), m.p. 208—210 °C. Found (%): C, 52.13; H, 4.18; N, 12.85. $C_{14}H_{14}FN_3O_3S$. Calculated (%): C, 52.00; H, 4.36; N, 13.00. ^{1}H NMR (DMSO-d_6), δ: 1.25 (t, 3 H, Me, J = 7.2 Hz); 3.82 (s, 2 H, CH_2); 4.14 (q, 2 H, CH_2, J = 7.2 Hz); 5.07 (s, 1 H, CH); 6.05 (s, 2 H, NH_2); 7.36, 7.52 (both m, 2 H each, H arom.). ^{19}F NMR (DMSO-d_6), δ: −31.62 (m).

7-Benzylsulfanyl-8-(4-fluorophenyl)-4,4-bis(trifluoromethyl)-1,2,3,4,5,8-hexahydropyrimido[4,5-*d*]pyrimidine-2,5-dione (12a). ***A.*** A mixture of imine **1** (2.37 g, 0.01 mol), pyrimidinone **8a** (3.27 g, 0.01 mol), and Et_3N (0.2 mL) in DMF (10 mL) was heated at 90—100 °C for 5 h, cooled, and poured into water (50 mL). The precipitate that formed was filtered off and recrystallized from 50% EtOH to give compound **12a** (4.2 g, 81%), m.p. 220—222 °C. Found (%): C, 48.49; H, 2,68; N, 10.65. $C_{21}H_{13}F_7N_4O_2S$. Calculated (%): C, 48.65; H, 2.53; N, 10.81. ^{1}H NMR (DMSO-d_6), δ: 4.28 (s, 2 H, CH_2); 7.37 (m, 8 H, 7 H arom. + NH); 7.68 (m, 2 H, H arom.); 8.73 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 5.75 (s, 6 F); −30.09 (m, 1 F).

Table 2. ^{1}H and ^{19}F NMR spectra of compounds **4b**—**e**, **9a**—**d**, **10a**—**g**, and **11** (in DMSO-d_6)

Compound	δ (*J*/Hz)	
	^{1}H	^{19}F
4b	3.38 (s, 3 H, Me); 8.98, 10.57, 11.28 (all s, 1 H each, NH)	5.49 (s)
4c	7.29 (m, 2 H, H arom.); 7.51 (m, 3 H, H arom.); 8.86, 9.37, 11.40 (all s, 1 H each, NH)	5.40 (s)
4d	2.42 (s, 3 H, Me); 7.18, 7.29 (both d, 2 H each, H arom., J = 8.1); 8.78, 9.05, 11.32 (all s, 1 H each, NH)	5.44 (s)
4e	5.33 (s, 2 H, CH_2); 7.17 (d, 2 H, H arom., J = 7.8); 7.25 (t, 1 H, H arom., J = 7.8); 7.33 (t, 2 H, H arom., J = 7.8); 8.78, 9.05, 11.32 (all s, 1 H each, NH)	5.31 (s)
9a	7.41—7.64 (m, 5 H, H arom.); 9.12, 9.67, 12.96 (all s, 1 H each, NH)	6.27 (s)
9b	2.46 (s, 3 H, Me); 7.18, 7.21 (both d, 2 H each, H arom., J = 8.0); 7.38 (s, 1 H, NH); 9.05, 12.75 (both br.s, 1 H each, NH)	6.44 (s)
9c	7.31 (m, 3 H, H arom. + NH); 7.38 (m, 2 H, H arom.); 8.97 (s, 1 H, NH); 12.76 (br.s, 1 H, NH)	5.50 (s, 6 F); −33.35 (m, 1 F)
9d	3.05, 4.97 (both m, 2 H each, CH_2); 7.14—7.44 (m, 5 H, H arom.); 9.11, 10.97, 12.67 (all s, 1 H each, NH)	6.25 (s)
10a	0.96 (t, 3 H, Me, J = 7.6); 1.06 (s, 6 H, 2 Me); 1.28—1.61 (m, 4 H, 2 CH_2); 2.21, 2.58 (both s, 2 H each, CH_2 ring); 3.73 (m, 2 H, NCH_2); 8.71 (s, 1 H, NH)	6.11 (s)
10b	0.98 (s, 6 H, 2 Me); 2.18, 2.23 (both s, 2 H each, CH_2); 7.14—7.32 (m, 4 H, H arom.); 9.04 (s, 1 H, NH)	5.78 (s, 6 F); −33.91 (m, 1 F)
10c	1.05 (s, 6 H, 2 Me); 2.14, 2.25 (both s, 2 H each, CH_2); 7.22 (m, 1 H, H arom.); 7.34 (s, 1 H, H arom.); 7.51—7.62 (m, 2 H, H arom.); 9.21 (s, 1 H, NH)	6.12 (s)
10d	0.94 (s, 6 H, 2 Me); 2.23, 2.55 (both m, 2 H each, CH_2); 5.11 (s, 2 H, NCH_2); 7.17 (d, 2 H, H arom., J = 8.1); 7.33 (m, 3 H, H arom.); 9.04 (s, 1 H, NH)	6.38 (s)
10e	0.93 (s, 6 H, 2 Me); 2.11, 2.22 (both s, 2 H each, CH_2); 2.83 (m, 2 H, $NC\underline{H}_2CH_2$); 3.94 (m, 2 H, NCH_2); 7.20—7.31 (m, 5 H, H arom.); 8.79 (s, 1 H, NH)	6.30 (s)
10f	0.92 (s, 6 H, 2 Me); 2.12, 2.41 (both s, 2 H each, CH_2); 5.03 (s, 2 H, NCH_2); 6.96 (t, 1 H, H arom., J = 7.8); 7.27, 7.42 (both m, 2 H each, H arom.); 9.15 (s, 1 H, NH)	6.22 (s)
10g	1.07 (s, 6 H, 2 Me); 2.27, 2.76 (both m, 2 H each, CH_2); 5.05 (s, 2 H, NCH_2); 6.24, 6.37, 7.44 (all s, 1 H each, H arom.); 8.89 (s, 1 H, NH)	6.18 (s)
11	2.18 (s, 3 H, Me); 9.12, 10.62 (both s, 1 H each, NH)	2.82 (s)

B. A mixture of pyrimidopyrimidinedione **9c** (4.28 g, 0.01 mol), benzyl chloride (1.27 g, 0.01 mol), and Et_3N (1.01 g, 0.01 mol) in DMF (20 mL) was kept at 20 °C for 12 h and poured into water (50 mL). The precipitate that formed was filtered off and recrystallized from 50% EtOH to give compound **12a** (3.9 g, 75%), m.p. 220—222 °C.

Ethyl {[1-(4-fluorophenyl)-4,7-dioxo-5,5-bis(trifluoromethyl)-1,4,5,6,7,8-hexahydropyrimido[4,5-*d*]pyrimidin-2-yl]sulfanyl}acetate (12b). ***A.*** Ester **12b** was obtained analogously from imine **1** (0.01 mol) and pyrimidinone **8b** (0.01 mol). The yield of compound **12b** was 4.0 g (78%), m.p. 254—256 °C. Found (%): C, 42.21; H, 2.38; N, 10.76. $C_{18}H_{13}F_7N_4O_4S$. Calculated (%): C, 42.03; H, 2.55; N, 10.89. ^{1}H NMR (DMSO-d_6), δ: 1.22 (t, 3 H, Me, J = 7.6 Hz); 3.92 (s, 2 H, CH_2); 4.16 (q, 2 H, CH_2O, J = 7.6 Hz); 7.49, 7.75 (both m, 2 H each, H arom.); 9.01 (s, 1 H, NH); 10.04 (br.s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 5.73 (s, 6 F); −30.08 (m, 1 F).

B. Ester **12b** was obtained from pyrimidopyrimidinedione **9c** (0.01 mol) and ethyl chloroacetate (0.01 mol) as described for compound **12a**. The yield of compound **12b** was 3.8 g (74%), m.p. 254—256 °C.

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