Acylimines of hexafluoroacetone in cyclocondensation with C,N-binucleophiles

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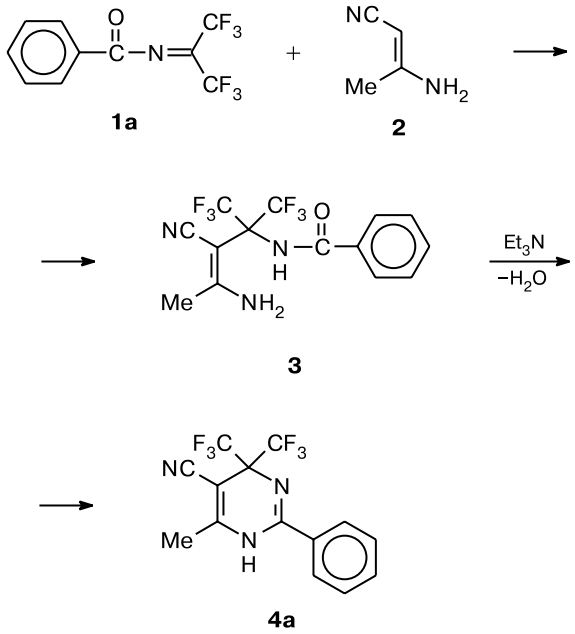
The reactions of acylimines of hexafluoroacetone with 1,3-C,N-binucleophiles giving rise to fluorine-containing 1,4-dihydropyrimidines, including fused compounds, were studied.

Key words: acylimines, hexafluoroacetone, 2-aminocrotononitrile, *N*-substituted 3-aminocyclohexenones, 6-aminouracils, 6-aminothiouracils, 1,4-dihydropyrimidines, 4,6,7,8-tetrahydroquinazolin-5-ones, cyclocondensation, cyclization, bromination.

Acylimines of hexafluoroacetone serve as synthons for the synthesis of various heterocyclic compounds containing geminal trifluoromethyl groups and are used as heterodienes and dienophiles in cycloaddition with nitriles,[1,2] derivatives of trivalent phosphorus acids,[3] and cyclopentadiene[4] as well as 1,3-bielectrophilic reagents in cyclocondensation with 1,3-binucleophiles[5,6] to give oxadiazines, oxazaphospholenes, azanorbornenes, and dihydrotriazines, respectively. In the present study, we examined the synthetic possibilities of acylimines of hexafluoroacetone **1** as 1,3-bielectrophilic reagents for the preparation of 1,4-dihydropyrimidines by cyclocondensation with 1,3-C,N-binucleophiles. It should be noted that 1,4-dihydropyrimidines, including fluorine-containing derivatives, belong to a promising class of biologically active compounds. Some representatives of this class are α_1-adrenoreceptor antagonists,[7] cytostatics, and compounds having the anti-HIV activity.[8]

The reactions of acylimines with 1,3-C,N-binucleophiles, *viz.*, 2-aminocrotononitrile, 6-aminouracils, 6-aminothiouracils, and *N*-substituted 3-aminocyclohexenones, involve the following two steps (Scheme 1): the addition of a binucleophile at the C=N bond of imine **1** followed by cyclization with water elimination. In the case of 2-aminocrotononitrile **2**, we isolated and identified the addition product, *viz.*, the corresponding benzamide **3**. Heating of the latter in DMF in the presence of catalytic amounts of Et_3N afforded 1,4-dihydropyrimidine **4a**.

Scheme 1



Cyclocondensation of imines **1a—k** with 2-aminocrotononitrile **2**, 6-aminouracils **5a—d**, 6-aminothiouracils **6a,b**, and *N*-substituted 3-aminocyclohexenones **7a—c** (equimolar amounts of the reagents were mixed in DMF at 20 °C and, after completion of the exothermic reaction, the mixture was heated in the presence of catalytic amounts of Et_3N at 90—100 °C for 5 h without isolation of intermediate addition products) afforded 1,4-dihydropyrimidines **4a—f**, dihydropyrimido[4,5-*d*]pyrimidine-2,4-diones **8a—g**, 2-thioxotetrahydropyrimido[4,5-*d*]pyrimidin-4-ones **9a,b**, and tetrahydro-1*H*-quinazolin-5-ones **10a—d** (Scheme 2).

Compounds **4** and **8—10** were prepared in the crystalline state in 67—85% yields. Their compositions and structures were confirmed by elemental analysis and NMR spectroscopy. The ^{19}F NMR spectra show characteristic signals of the geminal trifluoromethyl groups at δ 2—6.

Like *N*-allylthioureas,[9] pyrimido[4,5-*d*]pyrimidine-4-diones **9a,b** containing the *N*-allylthioamide fragment are

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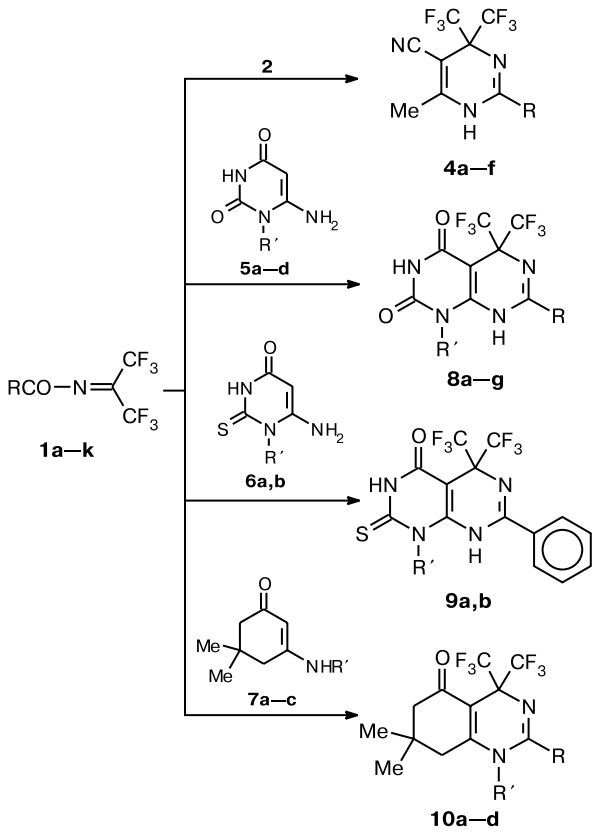
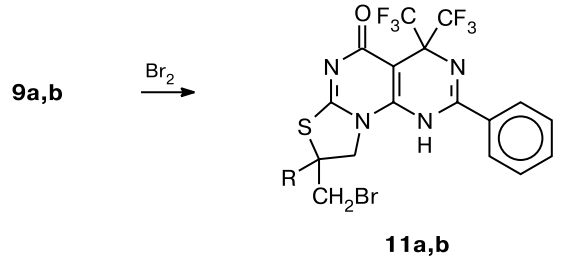
Scheme 2



1: R = Ph (**a**), Me (**b**), Et (**c**), 3-MeC_6H_4 (**d**), 4-$MeOC_6H_4$ (**e**), 3-ClC_6H_4 (**f**), 4-ClC_6H_4 (**g**), 2-FC_6H_4 (**h**), 3-FC_6H_4 (**i**), 4-FC_6H_4 (**j**), 3-pyridyl (**k**);
4: R = Ph (**a**), Me (**b**), 3-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 3-ClC_6H_4 (**e**), 2-FC_6H_4 (**f**);
5: R′ = Ph (**a**), 4-ClC_6H_4 (**b**), 2-FC_6H_4 (**c**), 4-FC_6H_4 (**d**);
6, 9: R′ = All (**a**), methallyl (**b**);
7: R′ = $PhCH_2$ (**a**), 2-$C_5H_4NCH_2$ (**b**), 3-$C_5H_4NCH_2$ (**c**);
8: R = Me, R′ = 4-FC_6H_4 (**a**); R = 2-FC_6H_4, R′ = 4-ClC_6H_4 (**b**); R = 3-FC_6H_4, R′ = 4-FC_6H_4 (**c**); R = 4-FC_6H_4, R′ = 2-FC_6H_4 (**d**); R = 4-FC_6H_4, R′ = 4-ClC_6H_4 (**e**); R = 4-ClC_6H_4, R′ = Ph (**f**); R = 4-ClC_6H_4, R′ = 2-FC_6H_4 (**g**);
10: R = Me, R′ = 2-$C_5H_4NCH_2$ (**a**); R = Me, R′ = 3-$C_5H_4NCH_2$ (**b**); R = Et, R′ = $PhCH_2$ (**c**); R = 3-$C_5H_4NCH_2$, R′ = $PhCH_2$ (**d**)

Scheme 3



11: R = H (**a**), Me (**b**)

brominated to form thiatetraazacyclopenta[*a*]naphthalenones **11a,b** (Scheme 3).

Therefore, acylimines of hexafluoroacetone can be successfully used as 1,3-bielectrophiles in the synthesis of various previously unknown 4,4-bis(trifluoromethyl)-1,4-dihydropyrimidines, including fused derivatives. The ease of the preparation of the latter is determined primarily by the ease of the preparation of 1,3-C,N-binucleophiles, the available procedures for the synthesis of acylimines of hexafluoroacetone,[1,10] and the experimental simplicity of the developed method.

Table 1. Yields, melting points, and elemental analysis data for compounds **4a—f**, **8a—g**, **9a,b**, and **10a—d**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula
4a	72	197—199	50.61 / 50.46	2.87 / 2.72	12.75 / 12.61	$C_{14}H_9F_6N_3$
4b	76	176—178	39.69 / 39.86	2.44 / 2.60	15.66 / 15.50	$C_9H_7F_6N$
4c	81	192—194	51.73 / 51.88	3.05 / 3.19	12.27 / 12.10	$C_{15}H_{11}F_6N_3$
4d	79	152—154	49.73 / 49.60	3.19 / 3.05	11.42 / 11.57	$C_{15}H_{11}F_6N_3O$
4e	85	187—189	45.58 / 45.73	2.04 / 2.19	11.28 / 11.43	$C_{14}H_8ClF_6N_3$
4f	69	131—133	48.74 / 47.88	2.46 / 2.30	11.81 / 11.96	$C_{14}H_8F_7N_3$
8a	75	296—298	43.76 / 43.92	2.07 / 2.21	13.51 / 13.66	$C_{15}H_9F_7N_4O_2$
8b	77	259—261	47.54 / 47.40	2.11 / 1.99	11.22 / 11.06	$C_{20}H_{10}ClF_7N_4O_2$
8c	76	311—313	50.15 / 48.99	2.21 / 2.06	11.28 / 11.43	$C_{20}H_{10}F_8N_4O_2$
8d	68	308—310	48.84 / 48.99	1.91 / 2.06	11.28 / 11.43	$C_{20}H_{10}F_8N_4O_2$
8e	83	311—313	47.24 / 47.40	2.13 / 1.99	11.22 / 11.06	$C_{20}H_{10}ClF_7N_4O_2$
8f	78	281—283	49.01 / 49.15	2.43 / 2.27	11.31 / 11.46	$C_{20}H_{11}ClF_6N_4O_2$
8g	77	292—294	47.53 / 47.40	2.14 / 1.99	11.19 / 11.06	$C_{20}H_{10}ClF_7N_4O_2$
9a	76	211—213	47.15 / 47.01	2.63 / 2.78	12.77 / 12.90	$C_{17}H_{12}F_6N_4OS$
9b	79	196—197	48.09 / 48.22	2.31 / 3.15	12.34 / 12.50	$C_{18}H_{14}F_6N_4OS$
10a	82	134—136	54.27 / 54.42	4.41 / 4.57	10.19 / 10.02	$C_{19}H_{19}F_6N_3O$
10b	78	157—159	54.26 / 54.42	4.71 / 4.57	10.13 / 10.02	$C_{19}H_{19}F_6N_3O$
10c	74	182—183	58.16 / 58.33	5.29 / 5.13	6.32 / 6.48	$C_{21}H_{22}F_6N_2O$
10d	79	201—203	59.71 / 59.88	4.56 / 4.40	8.84 / 8.73	$C_{24}H_{21}F_6N_3O$

Experimental

The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer in DMSO-d_6. The melting points were determined in a glass capillary. Acylimines of hexafluoroacetone **1a—k**,[10] the starting 6-aminouracils, 6-aminothiouracils,[11] and 3-aminocyclohexenones[12] were synthesized according to procedures described earlier. Methyl ether and 2-aminocrotononitrile (Aldrich) were used without preliminary purification.

***N*-[3-Amino-2-cyano-1,1-bis(trifluoromethyl)but-2-enyl]benzamide (3).** 2-Aminocrotononitrile **2** (0.82 g, 0.01 mol) was added to a solution of imine **1a** (2.69 g, 0.01 mol) in benzene (20 mL). After completion of the exothermic reaction, the benzene was evaporated and the residue was recrystallized from a 1 : 1 benzene—hexane mixture. Benzamide **3** was obtained in a yield of 3.2 g (91.1%), m.p. 161—162 °C. Found (%): C, 47.71; H, 3.03; N, 1.79. $C_{14}H_{11}F_6N_3O$. Calculated (%): C, 47.87; H, 3.16; N, 11.96. ^{1}H NMR, δ: 2.17 (s, 3 H, Me); 6.59 (br.s, 2 H, NH_2); 7.51 (m, 3 H, CH_{Ar}); 7.89 (d, 2 H, CH_{Ar}, J = 6.7 Hz); 8.62 (s, 1 H, NH). ^{19}F NMR, δ: 9.17 (s).

6-Methyl-2-phenyl-4,4-bis(trifluoromethyl)-1,4-dihydropyrimidine-5-carbonitrile (4a). ***A.*** A solution of benzamide **3** (1.75 g, 0.005 mol) and Et_3N (0.2 mL) in DMF (10 mL) was heated at 90—100 °C for 5 h. Then the reaction mixture was cooled and poured into water (50 mL). The precipitate that formed was recrystallized from 50% EtOH and compound **4a** was obtained in a yield of 1.2 g (72%), m.p. 197—199 °C.

B. A solution of benzoylimine **1** (2.69 g, 0.01 mol) and 2-aminocrotononitrile **2** (0.82 g, 0.01 mol) in DMF (10 mL) was stirred at 20 °C for 1 h. Then 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. Compound **4a** was obtained in a yield of 2.7 g (81%), m.p. 197—199 °C.

Table 2. ^{1}H and ^{19}F NMR spectra of compounds **4a—f**, **8a—g**, **9a,b**, and **10a—d** in DMSO-d_6

Compound	δ (J/Hz)	
	^{1}H	^{19}F
4a	2.38 (s, 3 H, Me); 7.53 (m, 3 H, CH_{Ar}); 7.93 (d, 2 H, CH_{Ar}, J = 7.1); 10.86 (s, 1 H, NH)	2.68 (s)
4b	2.04, 2.17 (both s, 3 H each, Me); 9.81 (br.s, 1 H, NH)	2.52 (s)
4c	2.32, 2.45 (both s, 3 H each, Me); 7.33, 7.68 (both m, 2 H each, CH_{Ar}); 10.81 (s, 1 H, NH)	2.73 (s)
4d	2.11 (s, 3 H, Me); 3.87 (s, 3 H, MeO); 6.89, 7.84 (both d, 2 H each, CH_{Ar}, J = 8.0); 8.40 (s, 1 H, NH)	3.59 (s)
4e	2.34 (s, 3 H, Me); 7.47, 7.89 (both m, 2 H each, CH_{Ar}); 10.91 (s, 1 H, NH)	3.12 (s)
4f	2.29 (s, 3 H, Me); 7.24, 7.55 (both m, 2 H each, CH_{Ar}); 10.98 (s, 1 H, NH)	3.10 (s, 6 F); −34.86 (m, 1 F)
8a	2.02 (s, 3 H, Me); 7.08 (m, 4 H, CH_{Ar}); 9.73, 11.27 (both s, 1 H each, NH)	4.82 (s, 6 F); −29.05 (m, 1 F)
8b	7.12—7.23 (m, 5 H, CH_{Ar}); 7.43 (d, 2 H, CH_{Ar}, J = 8.8); 7.53 (m, 1 H, CH_{Ar}); 9.81, 11.46 (both s, 1 H each, NH)	5.06 (s, 6 F); −34.56 (m, 1 F)
8c	7.19 (m, 5 H, CH_{Ar}); 7.42 (m, 2 H, CH_{Ar}); 7.39 (m, 1 H, CH_{Ar}); 9.55, 11.39 (both s, 1 H each, NH)	5.48 (s, 6 F); −34.64, −35.45 (both m, 1 F each)
8d	7.09 (m, 2 H, CH_{Ar}); 7.29 (m, 3 H, CH_{Ar}); 7.48 (m, 2 H, CH_{Ar}); 7.71 (m, 1 H, CH_{Ar}); 9.60, 11.48 (both s, 1 H each, NH)	5.16 (s, 6 F); −28.14, −42.79 (both m, 1 F each)
8e	7.04 (m, 2 H, CH_{Ar}); 7.23, 7.42 (both d, 2 H each, CH_{Ar}, J = 7.7); 7.63 (m, 2 H, CH_{Ar}); 9.55, 11.34 (both s, 1 H each, NH)	5.46 (s, 6 F); −28.43 (m, 1 F)
8f	7.21 (m, 2 H, CH_{Ar}); 7.36 (d, 2 H, CH_{Ar}, J = 7.7); 7.47 (m, 3 H, CH_{Ar}); 7.63 (d, 2 H, CH_{Ar}, J = 7.7); 9.58, 11.38 (both s, 1 H each, NH)	5.44 (s)
8g	7.24 (m, 4 H, CH_{Ar}); 7.46, 7.73 (both m, 2 H each, CH_{Ar}); 9.71, 11.48 (both s, 1 H each, NH)	5.30 (s, 6 F); −43.04 (m, 1 F)
9a	5.21 (m, 2 H, CH_2N); 5.36 (m, 2 H, CH_2=); 5.96 (m, 1 H, CH=); 7.55 (m, 3 H, CH_{Ar}); 7.94 (d, 2 H, CH_{Ar}, J = 7.9); 9.99, 12.44 (both s, 1 H each, NH)	5.43 (s)
9b	1.93 (s, 3 H, Me); 4.51, 4.81 (both s, 1 H each, CH_2N); 5.24 (s, 2 H, CH_2=); 7.47—7.64 (m, 3 H, CH_{Ar}); 7.87 (d, 2 H, CH_{Ar}, J = 6.8); 10.02, 12.60 (both s, 1 H each, NH)	5.44 (s)
10a	1.01 (s, 6 H, Me); 2.22 (s, 2 H, CH_2); 2.26 (s, 3 H, Me); 2.56, 5.09 (both s, 2 H each, CH_2); 7.28 (m, 2 H, CH_{Ar}); 7.78 (t, 1 H, CH_{Ar}, J = 7.6); 8.54 (d, 1 H, CH_{Ar}, J = 7.6)	6.39 (s)
10b	1.02 (s, 6 H, Me), 2.25 (s, 2 H, CH_2), 2.28 (s, 3 H, Me), 2.56, 5.11 (both s, 2 H each, CH_2); 7.35, 7.48 (both m, 1 H each, CH_{Ar}), 8.44 (s, 1 H, CH_{Ar}), 8.55 (d, 1 H, CH_{Ar}, J = 7.5)	6.10 (s)
10c	0.94 (s, 6 H, Me); 1.12 (t, 3 H, Me, J = 7.5); 2.18 (s, 2 H, CH_2); 2.52—2.61 (m, 4 H, CH_2 + CH_2); 4.97 (s, 2 H, CH_2); 7.23 (d, 2 H, CH_{Ar}, J = 8); 7.27—7.32 (m, 3 H, CH_{Ar})	5.97 (s)
10d	0.97, 1.03 (both s, 3 H each, Me); 2.17 (AB system, 2 H, CH_2, J = 11.4); 2.48 (m, 2 H, CH_2); 4.87 (s, 2 H, CH_2); 7.23—7.41 (m, 6 H, CH_{Ar}); 8.22 (d, 1 H, CH_{Ar}, J = 7.8); 6.67 (m, 2 H, CH_{Ar})	5.03 (s)

2,6-Dimethyl-4,4-bis(trifluoromethyl)-1,4-dihydropyrimidine-5-carbonitrile (4b), 6-methyl-2-(3-tolyl)-4,4-bis(trifluoromethyl)-1,4-dihydropyrimidine-5-carbonitrile (4c), 2-(4-methoxyphenyl)-6-methyl-4,4-bis(trifluoromethyl)-1,4-dihydropyrimidine-5-carbonitrile (4d), 2-(3-chlorophenyl)-6-methyl-4,4-bis(trifluoromethyl)-1,4-dihydropyrimidine-5-carbonitrile (4e), 2-(2-fluorophenyl)-6-methyl-4,4-bis(trifluoromethyl)-1,4-dihydropyrimidine-5-carbonitrile (4f), 1-(4-fluorophenyl)-7-methyl-5,5-bis(trifluoromethyl)-5,8-dihydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8a), 1-(4-chlorophenyl)-7-(2-fluorophenyl)-5-bis(trifluoromethyl)-5,8-dihydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8b), 7-(3-fluorophenyl)-1-(4-fluorophenyl)-5,5-bis(trifluoromethyl)-5,8-dihydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8c), 1-(2-fluorophenyl)-7-(4-fluorophenyl)-5,5-bis(trifluoromethyl)-5,8-dihydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8d), 1-(4-chlorophenyl)-7-(4-fluorophenyl)-5,5-bis(trifluoromethyl)-5,8-dihydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8e), 7-(4-chlorophenyl)-1-phenyl-5,5-bis(trifluoromethyl)-5,8-dihydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8f), 7-(4-chlorophenyl)-1-(2-fluorophenyl)-5,5-bis(trifluoromethyl)-5,8-dihydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8g), 1-allyl-7-phenyl-2-thioxo-5,5-bis(trifluoromethyl)-2,3,5,8-tetrahydro-1*H*-pyrimido[4,5-*d*]pyrimidin-4-one (9a), 1-(2-methylallyl-2-thioxo)-5,5-bis(trifluoromethyl)-7-phenyl-2,3,5,8-tetrahydro-1*H*-pyrimido[4,5-*d*]pyrimidin-4-one (9b), 2,7,7-trimethyl-1-(pyridin-2-ylmethyl)-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*-quinazolin-5-one (10a), 2,7,7-trimethyl-1-(pyridin-3-ylmethyl)-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*-quinazolin-5-one (10b), 1-benzyl-2-ethyl-7,7-dimethyl-4,4-bis(trifluoromethyl)-4,6,7-tetrahydro-1*H*-quinazolin-5-one (10c), and 1-benzyl-7,7-dimethyl-2-(pyridin-3-yl)-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*-quinazolin-5-one (10d) were prepared analogously to pyrimidinone **4a** from acylimines **1a—k** (0.01 mol) and the corresponding binucleophiles **5a—d**, **6a,b**, and **7a,c** (0.01 mol). The yields, the melting points, and the spectroscopic characteristics of compounds **4a—f**, **8a—g**, **9a,b**, and **10a—d** are given in Tables 1 and 2.

2-Bromomethyl-8-phenyl-6,6-bis(trifluoromethyl)-1,2,6,9-tetrahydro-3-thia-4,7,9,9b-tetraazacyclopenta[*a*]naphthalen-5-one (11a). Bromine (0.8 g, 0.005 mol) was added to a suspension of pyrimidinone **9a** (2.17 g, 0.005 mol) in EtOH (20 mL) at 20 °C. The reaction mixture was stirred for 1 h, diluted with H_2O (50 mL), and neutralized with a 10% NaOH solution. The precipitate that formed was filtered off and recrystallized from 50% EtOH. Compound **11a** was obtained in a yield of 2.1 g (82%), m.p. 144—146 °C. Found (%): C, 38.62; H, 2.33; N, 10.77. $C_{17}H_{11}BrF_6N_4OS$. Calculated (%): C, 39.78; H, 2.16; N, 10.92. ^{1}H NMR, δ: 3.69 (m, 2 H, CH_2Br); 4.37 (m, 1 H, CHS); 4.49 and 4.71 (both m, 1 H each, CH_2N); 7.61 (m, 3 H, CH_{Ar}); 7.94 (m, 2 H, CH_{Ar}); 9.67 (s, 1 H, NH). ^{19}F NMR, δ: 5.95 (s).

2-Bromomethyl-2-methyl-8-phenyl-6,6-bis(trifluoromethyl)-1,2,6,9-tetrahydro-3-thia-4,7,9,9b-tetraazacyclopenta[*a*]naphthalen-5-one (11b) was prepared analogously to **11a** from compound **9b** (2.24 g) in a yield of 2.2 g (83%), m.p. 151—153 °C. Found (%): C, 41.17; H, 2.37; N, 10.47. $C_{18}H_{13}BrF_6N_4OS$. Calculated (%): C, 41.00; H, 2.49; N, 10.63. ^{1}H NMR, δ: 1.82 (s, 3 H, Me); 4.02 (AB system, 2 H, CH_2, J = 10.4 Hz); 4.24 and 4.80 (both d, 1 H each, CH_2Br, J = 12.5 Hz); 7.55 (m, 3 H, CH_{Ar}); 7.93 (d, 2 H, CH_{Ar}, J = 8.0 Hz); 9.72 (s, 1 H, NH). ^{19}F NMR, δ: 5.76 (s).

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