

Fluorinated triazinones from hexafluoroacetone ethoxycarbonylimine

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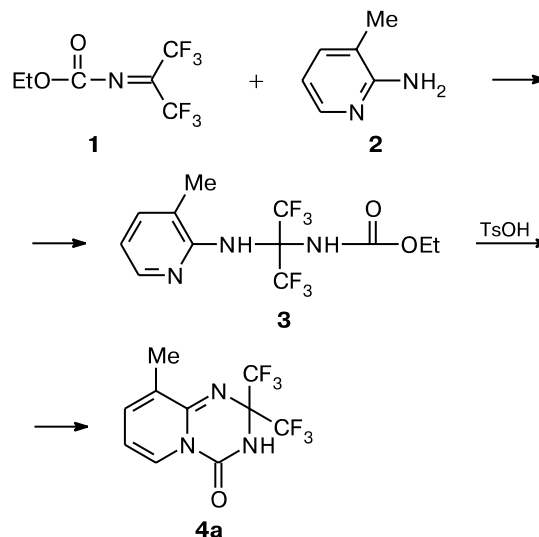
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The behavior of hexafluoroacetone ethoxycarbonylimine in cyclocondensation with different binucleophiles of the amidine type, viz., amino derivatives of N- and N,S-heterocycles, was studied. A preparative method for the synthesis of previously unknown annelated 2,2-bis(trifluoromethyl)-1,3,5-triazinones was developed.

Key words: ethoxycarbonylimine of hexafluoroacetone, 2-aminopyridines, 2-aminothiazolines, 2-aminothiazoles, 2-aminothiadiazoles, 2-aminobenzothiazoles, substituted annelated 2,2-bis(trifluoromethyl)-1,3,5-triazin-4(3*H*)-ones, cyclocondensation.

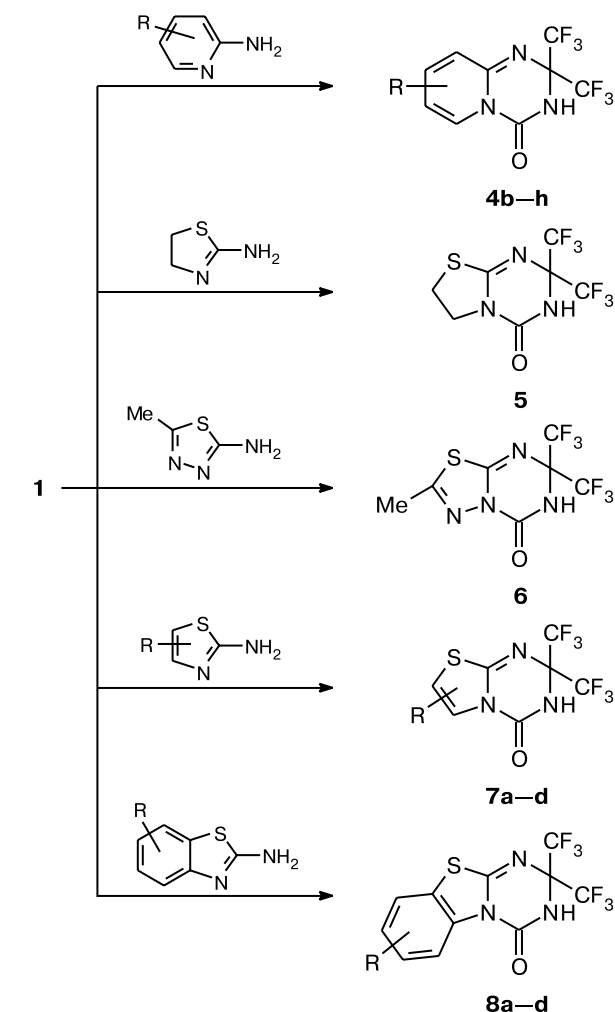
The synthesis of heterocyclic compounds containing substituents with the fluorine atom is a promising direction of the organofluorine chemistry, because the replacement of the hydrogen atom in the heterocyclic system by polyfluoroalkyl groups is known to exert a substantial effect on the physicochemical and biological properties of the compounds.¹ In this connection, we developed a method for the syntheses of various fluorinated triazinones from accessible hexafluoroacetone ethoxycarbonylimine (**1**) and binucleophiles of the amidine type. The study was prerequisites by the known published data on the cyclocondensation of binucleophiles of the amidine type (2-aminopyridines and 2-aminothiadiazoles) with phenoxycarbonyl isocyanate,² chloroformyl isocyanate,^{3,4} and ethoxycarbonyl isothiocyanate⁵ affording triazinones and thioxotriazinones and by the previously studied reaction of imine **1** with 2-aminobenzothiazole (xylene, 140 °C, TsOH, 6 h) to form fluorine-containing fluorenone, whose structure was proved by X-ray diffraction analysis.⁶ Continuing this investigation, we studied the transformation of imine **1** in cyclocondensation with different heterocycles of the amidine type: substituted 2-aminopyridines, 2-aminothiazoline, 2-aminothiadiazole, substituted 2-aminothiazoles, and 2-aminobenzothiazoles. This allowed us to develop a convenient approach to the syntheses of previously unknown annelated 2,2-bis(trifluoromethyl)-1,3,5-triazin-4(*H*)-ones.

The transformations under study occur *via* the two-step scheme: addition of the binucleophile to the C=N bond of imine **1** followed by ring closure with elimination of EtOH. In the case of 2-amino-3-methylpyridine (**2**), we isolated and identified the addition product, viz., corresponding aminal **3**, which is transformed into triazinone **4a** upon boiling in DMF under the acid catalysis conditions (TsOH).



The cyclocondensation of imine **1** with 2-aminopyridines, 2-aminothiazoline, 2-aminothiadiazole, 2-aminothiazole, and 2-aminobenzothiazoles (equimolar amounts of the reactants were mixed in DMF at 20 °C and, after completion of the exothermic reaction, the mixture was refluxed for 1 h in the presence of catalytic amounts of TsOH without isolation of intermediate addition products) afforded pyridotriazinones **4b–h**, tetrahydrothiazolotriazinone **5**, thiadiazolotriazinone **6**, thiazolotriazinones **7a–d**, and benzothiazolotriazinones **8a–d**.

Triazinones **4–8** are solid crystalline substances obtained in 60–80% yields, whose compositions and structures were confirmed by elemental analysis and NMR spectroscopic data. The signals of the NH proton at 10–11 ppm and signals of the geminal trifluoromethyl groups at –1–3 ppm are characteristic in the ¹H and ¹⁹F NMR spectra.

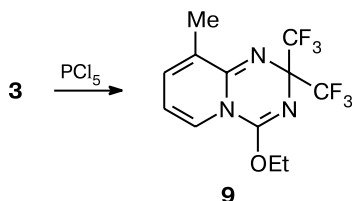


4: R = H (**b**), 7-Me (**c**), 8-Me (**d**), 7-Br (**e**), 7-Cl (**f**), 9-Cl-7-CF₃ (**g**), 7,8-Cl₂ (**h**)

7: R = H (**a**), 7-Me (**b**), (CH₂)₄ (**c**), 7-SO₂-C₆H₄-NO₂ (**d**)

8: R = 7-Cl (**a**), 7-C₂H₅O (**b**), 7-NO₂ (**c**), 7-MeSO₂ (**d**)

It should be noted that the cyclocondensation step in the transformations under study occurs through EtOH elimination and, moreover, can be accompanied by dehydration under certain conditions. For example, boiling of amination **3** in benzene with an equimolar amount of PCl₅ gives pyridotriazine **9** in 84% yield.



Thus, the transformations of hexafluoroacetone ethoxycarbonylimine in cyclocondensation with binucleophiles of the amidine type provide various fluorinated

triazinones, whose accessibility is determined by the accessibility of the binucleophile, taking into account the previously developed preparative method for the synthesis of hexafluoroacetone ethoxycarbonylimine.⁷

Experimental

¹H and ¹⁹F NMR spectra were recorded on a Bruker DXP 200 spectrometer. Melting points were determined in a glass capillary. Hexafluoroacetone ethoxycarbonylimine was synthesized according to a known procedure.⁷ The starting binucleophiles of the amidine type, viz., 2-aminopyridine, 2-amino-3-methylpyridine, 2-amino-5-methylpyridine, 2-amino-6-methylpyridine, 2-amino-5-bromopyridine, 2-amino-5-chloropyridine, 2-amino-3-chloro-5-trifluoromethylpyridine, 2-amino-4,5-dichloropyridine, 2-aminothiazoline, 2-amino-5-methylthiadiazole, 2-aminothiazole, 2-amino-5-methylthiazole, 2-amino-4,5,6,7-tetrahydrobenzothiazole, 2-amino-5-(4-nitrophenylsulfonylthiazole), 2-amino-6-chlorobenzothiazole, 2-amino-6-ethoxybenzothiazole, 2-amino-6-nitrobenzothiazole, and 2-amino-6-methylsulfonylbenzothiazole (Aldrich), were used without purification.

Ethyl 1,1,1,3,3,3-hexafluoro-2-(3-methylpyridin-1-yl)amino-prop-2-yl carbamate (3). 2-Amino-3-methylpyridine (**2**) (0.01 mol) was added with stirring to a solution of imine **1** (0.01 mol) in benzene (20 mL). After completion of the exothermic reaction, benzene was evaporated, and the residue was recrystallized from 50% EtOH. Amination **3** (2.9 g) was obtained in 84% yield, m.p. 47–48 °C. Found (%): C, 41.62; H, 3.71; N, 11.98. C₁₂H₁₃F₆N₃O₂. Calculated (%): C, 41.75; H, 3.80; N, 12.17. ¹H NMR (CDCl₃), δ: 1.15 (t, 3 H, CH₃CH₂, J = 7 Hz); 2.23 (s, H, Me); 4.00 (q, 2 H, CH₂, J = 7 Hz); 5.88 (s, 1 H, NH); 6.81 (t, 1 H, J = 8 Hz); 7.45 (d, 1 H, J = 8 Hz); 7.98 (d, 1 H, J = 8 Hz); 9.3 (s, NH). ¹⁹F NMR (CDCl₃), δ: 2.99 s.

9-Methyl-2,2-bis(trifluoromethyl)-2,3-dihydropyrido[1,2-a][1,3,5]triazin-4(3H)-one (4a). A mixture of amination **3** (0.01 mol) and TsOH (0.05 g) in DMF (5 mL) was refluxed for 1 h, and H₂O (50 mL) was added to the mixture. A precipitate formed was recrystallized from 50% EtOH, and compound **4a** (2.4 g) was obtained in 80.3% yield, m.p. 208–210 °C.

B. Imine **1** (0.01 mol) was added to a solution of 2-amino-3-methylpyridine (**2**) (0.01 mol) in DMF (5 mL). After completion of the exothermic reaction, TsOH (0.05 g) was added, the reaction mixture was refluxed for 1 h, and H₂O (50 mL) was added. A precipitate formed was recrystallized from 50% EtOH. Compound **4a** was obtained in 73.5% yield (2.2 g), m.p. 208–210 °C.

4-Ethoxy-9-methyl-2,2-bis(trifluoromethyl)-2H-pyrido[1,2-a][1,3,5]triazine (9). A mixture of amination **3** (0.01 mol) and PCl₅ (0.01 mol) in benzene (50 mL) was refluxed until a precipitate dissolved. Benzene and POCl₃ were evaporated, and the residue was recrystallized from hexane. Compound **9** was obtained in 84% yield (2.9 g), m.p. 102–104 °C. Found (%): C, 43.91; H, 3.21; N, 12.68. C₁₂H₁₃F₆N₃O₂. Calculated (%): C, 44.05; H, 3.39; N, 12.84. ¹H NMR (CDCl₃), δ: 1.40 (t, 3 H, CH₃CH₂, J = 7 Hz); 2.00 (s, H, Me); 4.45 (q, 2 H, CH₂, J = 7 Hz); 6.10 (t, 1 H, J = 8 Hz); 7.45 (d, 1 H, J = 8 Hz); 7.05 (d, 1 H, J = 8 Hz). ¹⁹F NMR (CDCl₃), δ: –2.52 s.

2,2-Bis(trifluoromethyl)-2,3-dihydropyrido[1,2-a][1,3,5]triazin-4(3H)-one (4b), 7-methyl-2,2-bis(trifluoromethyl)-2,3-

Table 1. Characteristics of compounds **4a–h**, **5**, **6**, **7a–d**, and **8a–d**

Com- pound	Yield (%)	M.p. /°C	Found (%)			Molecular formula	Com- pound	Yield (%)	M.p. /°C	Found (%)			Molecular formula
			Calculated	C	H	N				Calculated	C	H	N
4a	73.5	208–210	40.33	2.51	14.24	C ₁₀ H ₇ F ₆ N ₃ O	6	77	186–188	27.39	1.47	18.48	C ₇ H ₄ F ₆ N ₄ OS
			40.15	2.36	14.05					27.46	1.32	18.30	
4b	69	151–153	38.09	1.95	14.56	C ₉ H ₅ F ₆ N ₃ O	7a	61	144–145	29.04	1.22	14.54	C ₇ H ₃ F ₆ N ₃ OS
			37.91	1.77	14.74					28.87	1.04	14.43	
4c	71	189–190	39.98	2.53	14.22	C ₁₀ H ₇ F ₆ N ₃ O	7b	70	150–151	31.60	1.53	13.58	C ₈ H ₅ F ₆ N ₃ OS
			40.15	2.36	14.05					31.48	1.65	13.77	
4d	76	208–209	40.32	2.18	13.87	C ₁₀ H ₇ F ₆ N ₃ O	7c	66	151–153	38.44	2.81	12.31	C ₈ H ₁₂ F ₃ NO ₃
			40.15	2.36	14.05					38.27	2.63	12.17	
4e	68	183–185	29.50	1.28	11.37	C ₉ H ₄ BrF ₆ N ₃ O	7d	64	285–287	32.89	1.09	11.59	C ₇ H ₉ ClF ₃ NO ₃
			29.69	1.11	11.54					32.78	1.27	11.76	
4f	81	196–198	33.64	1.09	12.96	C ₉ H ₄ ClF ₆ N ₃ O	8a	78	232–234	35.33	1.21	11.34	C ₁₂ H ₁₂ F ₃ NO ₃
			33.82	1.26	13.15					35.17	1.07	11.19	
4g	63	187–188	30.89	0.90	10.59	C ₇ H ₉ ClF ₉ NO ₃	8b	71	221–223	40.39	2.52	11.10	C ₇ H ₁₁ F ₃ N ₂ O ₃
			30.99	0.78	10.84					40.53	2.35	10.91	
4h	78	1889–191	30.72	1.03	11.59	C ₉ H ₃ Cl ₂ F ₆ N ₃ O	8c	69	277–279	34.39	0.91	14.68	C ₈ H ₁₁ F ₃ N ₂ O ₄
			30.53	0.85	11.87					34.21	1.04	14.51	
5	71.4	181–182	28.49	1.53	14.15	C ₇ H ₅ F ₆ N ₃ OS	8d	79	281–283	34.21	1.49	9.85	C ₈ H ₁₁ F ₃ N ₂ O ₄
			28.68	1.72	14.33					34.37	1.68	10.02	

dihydropyrido[1,2-*a*][1,3,5]triazin-4(3*H*)-one (**4c**), 8-methyl-2,2-bis(trifluoromethyl)-2,3-dihydropyrido[1,2-*a*][1,3,5]triazin-4(3*H*)-one (**4d**), 7-bromo-2,2-bis(trifluoromethyl)-2,3-dihydropyrido[1,2-*a*][1,3,5]triazin-4(3*H*)-one (**4e**), 7-chloro-2,2-bis(trifluoromethyl)-2,3-dihydropyrido[1,2-*a*][1,3,5]triazin-4(3*H*)-one (**4f**), 9-chloro-2,2,7-tris(trifluoromethyl)-2,3-dihydropyrido[1,2-*a*][1,3,5]triazin-4(3*H*)-one (**4g**), 7,8-dichloro-2,2-bis(trifluoromethyl)-2,3-dihydropyrido[1,2-*a*][1,3,5]triazin-

4(3*H*)-one (**4h**), 2,2-bis(trifluoromethyl)-2,3,6,7-tetrahydrothiazolo[3,2-*a*][1,3,5]triazin-4(3*H*)-one (**5**), 2-methyl-7,7-bis(trifluoromethyl)-6,7-dihydro[1,3,4]thiadiazolo[3,2-*a*][1,3,5]triazin-5(6*H*)-one (**6**), 2,2-bis(trifluoromethyl)-2,3-dihydrothiazolo[3,2-*a*][1,3,5]triazin-4(3*H*)-one (**7a**), 7-methyl-2,2-bis(trifluoromethyl)-2,3-dihydrothiazolo[3,2-*a*][1,3,5]triazin-4(3*H*)-one (**7b**), 2,2-bis(trifluoromethyl)-2,3,5,6,7,8,9-hexahydrobenzo[*f*]thiazolo[3,2-*a*][1,3,5]triazin-

Table 2. Spectroscopic characteristics of compounds **4a–h**, **5**, **6**, **7a–d**, and **8a–d** (DMSO-*d*₆)

Com- pound	¹ H NMR δ	¹⁹ F NMR δ (s)
4a	2.40 (s, 3 H, Me); 7.15–7.25 (m, 2 H); 7.46 (d, 1 H, <i>J</i> = 8); 10.25 (s, 1 H, NH)	–1.27
4b	6.10 (m, 1 H); 6.52 (d, 1 H, <i>J</i> = 8); 7.10 (m, 1 H); 7.80 (d, 1 H, <i>J</i> = 8); 10.15 (s, 1 H, NH)	–2.37
4c	2.02 (s, 3 H, Me); 6.52, 7.10 (both d, 1 H each, <i>J</i> = 8); 7.63 (s, 1 H); 10.14 (s, 1 H, NH)	–2.41
4d	2.20 (s, 3 H, Me); 6.02 (d, 1 H, <i>J</i> = 8); 6.40, 7.82 (both d, 1 H each, <i>J</i> = 8); 10.10 (s, 1 H, NH)	–2.01
4e	6.22, 6.90 (both d, 1 H each, <i>J</i> = 8); 7.70 (s, 1 H); 10.25 (s, 1 H, NH)	–3.75
4f	6.66, 7.27 (both d, 1 H each, <i>J</i> = 8); 7.90 (s, 1 H); 10.48 (s, 1 H, NH)	–3.05
4g	7.90 (s, 1 H); 8.25 (s, 1 H); 10.90 (s, 1 H, NH)	13.89 (3 F); –1.90 (6 F)
4h	7.49, 7.92 (both s, 1 H each); 10.66 (s, 1 H, NH)	–1.66
5	3.37, 4.10 (both t, 2 H each, <i>J</i> = 7); 9.42 (s, 1 H, NH)	–1.74
6	2.45 (s, 3 H); 10.10 (s, 1 H, NH)	–1.82
7a	6.62, 7.25 (both d, 1 H each, <i>J</i> = 8); 10.20 (s, 1 H, NH)	–2.01
7b	2.20 (s, 3 H); 6.95 (s, 1 H); 9.92 (s, 1 H, NH)	–2.04
7c	1.81 (br.s, 4 H); 2.34, 2.80 (both m, 2 H each); 9.72 (s, 1 H, NH)	–1.55
7d	8.20, 8.35 (both d, 2 H each, <i>J</i> = 8); 8.45 (d, 2 H, <i>J</i> = 8); 10.70 (s, 1 H, NH)	–1.95
8a	7.35 (d, 1 H); 7.72 (s, 1 H); 8.15 (d, 1 H, <i>J</i> = 8); 10.38 (s, 1 H, NH)	–1.28
8b	1.40 (t, 3 H, Me, <i>J</i> = 7); 4.02 (q, 2 H, CH ₂ O, <i>J</i> = 7); 6.80, 7.14 (both d, 1 H each, <i>J</i> = 8); 8.06 (s, 1 H); 10.10 (s, 1 H, NH)	–1.38
8c	8.20, 8.40 (both d, 1 H each, <i>J</i> = 8); 8.68 (s, 1 H); 10.55 (s, 1 H, NH)	–1.12
8d	3.20 (s, 3 H, Me); 7.92, 8.32 (both d, 1 H each, <i>J</i> = 8); 8.40, 10.53 (both s, 1 H each, NH)	–1.56

4(3*H*)-one (7c), 7-(4-nitrophenylsulfonyl)-2,2-bis(trifluoromethyl)-2,3-dihydrothiazolo[3,2-*a*][1,3,5]triazin-4(3*H*)-one (7d), 8-chloro-2,2-bis(trifluoromethyl)-2,3-dihydrobenzo[*f*]thiazolo[3,2-*a*][1,3,5]triazin-4(3*H*)-one (8a), 8-ethoxy-2,2-bis(trifluoromethyl)-2,3-dihydrobenzo[*f*]thiazolo[3,2-*a*][1,3,5]triazin-4(3*H*)-one (8b), 2,2-bis(trifluoromethyl)-8-nitro-2,3-dihydrobenzo[*f*]thiazolo[3,2-*a*][1,3,5]triazin-4(3*H*)-one (8c), and 8-methylsulfonyl-2,2-bis(trifluoromethyl)-2,3-dihydrobenzo[*f*]thiazolo[3,2-*a*][1,3,5]triazin-4(3*H*)-one (8d) were synthesized similarly to triazinone 4a from imine 1 (0.1 mol) and the corresponding amidine (0.1 mol). The yields, melting points, and spectroscopic characteristics of compounds 4a—h, 5, 6, 7a—d, and 8a—d are presented in Tables 1 and 2.

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