Acylimines of hexafluoroacetone and methyl trifluoropyruvate in cyclocondensation with 2-aminopyridines

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Cyclocondensation of acylimines of hexafluoroacetone and methyl trifluoropyruvate with 2-aminopyridines afforded earlier unknown fluoro-containing 2*H*-pyrido[1,2-*a*][1,3,5]triazines.

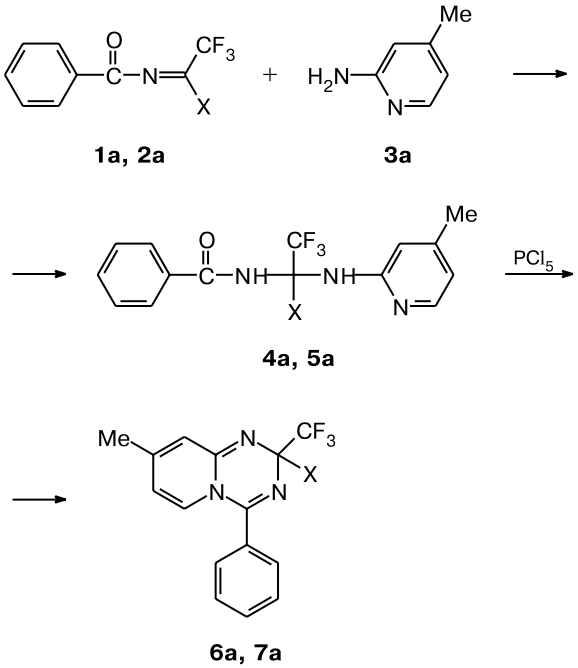
Key words: acylimines, hexafluoroacetone, methyl trifluoropyruvate, 2-aminopyridines, 2*H*-pyrido[1,2-*a*][1,3,5]triazines, heterocyclization, organofluorine compounds.

It is known that acylimines of hexafluoroacetone (HFA) and methyl trifluoropyruvate (MTFP) in cyclocondensation with bisnucleophiles act as 1,3- and 1,2-bis-electrophilic reagents[1,2] and serve as promising starting material for the synthesis of various fluoro-containing heterocycles. For instance, dehydration of adducts of HFA perfluoroacylimines and perfluorocarboxamides with oleum gives 1,3,5-oxadiazines;[3] reactions of HFA and MTFP benzoylimines with 6-aminouracil give[4] pyrimido- and pyrrolopyrimidines, respectively; dehydration of the adduct of HFA ethoxycarbonylimine and 2-aminopyrimidine with PCl_5 gives pyridotriazine.[5] In the present work, we studied the cyclocondensation of HFA and MTFP acylimines with 2-aminopyridines, which yields earlier unknown fluoro-containing 2*H*-pyrido[1,2-*a*][1,3,5]triazines. The compounds obtained can be regarded as potential biologically active substances. Pyridotriazines are known to exhibit high fungicidal,[6] antimitotic,[7] and cytostatic activities.[8,9]

The transformations studied follow a two-step scheme: (1) addition of 2-aminopyridine to the C=N bond of imines **1** and **2** to give adducts **4** and **5** and (2) dehydration of adducts **4** and **5** with PCl_5 to 2*H*-pyrido[1,2-*a*][1,3,5]triazines **6** and **7**. In the case of 2-amino-4-methylpyridine (**3a**), intermediate adducts **4a** and **5a** (Scheme 1) were isolated in the individual state and characterized.

The cyclocondensation of 2-aminopyridines **3b—f** with acylimines of HFA (**1b—f**) and MTFP (**2b—e**) (equimolar amounts of the reagents were mixed in benzene at 20 °C; after the exothermic reaction was completed, PCl_5 was added and the reaction mixture was refluxed until the precipitate dissolved; intermediate adducts were not isolated) afforded 2,2-bis(trifluoromethyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazines **6b—h** and methyl 2-trifluoromethyl-2*H*-pyrido[1,2-*a*][1,3,5]triazine-2-carboxylates **7b—f** in 55 to 74% yields (Scheme 2).

Scheme 1



X = CF_3 (**1a**, **4a**, **6a**); C(O)OMe (**2a**, **5a**, **7a**)

Pyridotriazines **6a—h** and **7a—f** are crystalline solids; their compositions and structures were proved by elemental analysis, NMR spectroscopy, and chemical transformations. Their ^{19}F NMR spectra show characteristic signals at δ −1.0 to 1.0 for geminal trifluoromethyl groups (**6a—h**) and a trifluoromethyl group (**7a—f**).

The reaction of ester **7a** with hydrazine hydrate in MeOH gave 2*H*-pyrido[1,2-*a*][1,3,5]triazine-2-carbohydrazide **8** (Scheme 3).

Thus, the annelation of substituted 2-aminopyridines with HFA and MTFP acylimines proceeds *via* the

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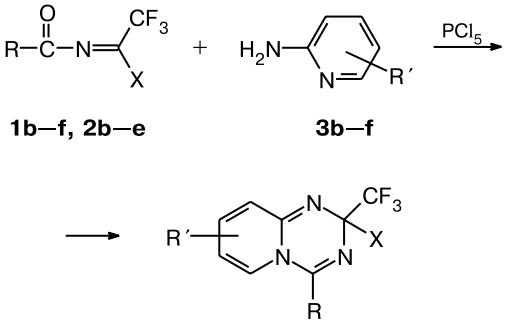
Scheme 2



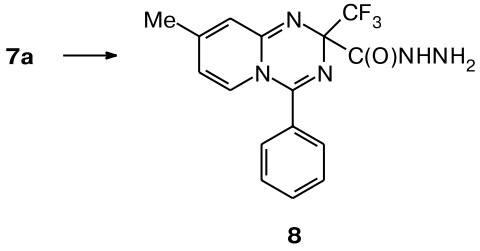
1b—f, 2b—e **3b—f**

6b—h, 7b—f

X = CF_3 (**1b—f**, **6b—h**); C(O)OMe (**2b—e**, **7b—f**)

1: R = Me (**b**), 3-MeC_6H_4 (**c**), 4-FC_6H_4 (**d**), 2-FC_6H_4 (**e**), 4-ClC_6H_4 (**f**)
2: R = 4-MeC_6H_4 (**b**), 4-FC_6H_4 (**c**), 3-FC_6H_4 (**d**), 2-furyl (**e**)
3: R′ = H (**b**), 3-Me (**c**), 5-Me (**d**), 5-Cl (**e**), 3,5-Cl_2 (**f**)
6: R = Me, R′ = 7,8-Cl_2 (**b**), R = 2-MeC_6H_4, R′ = H (**c**); R = 2-MeC_6H_4, R′ = 7-Cl (**d**); R = 4-FC_6H_4, R′ = 9-Me (**e**); R = 2-FC_6H_4, R′ = 7-Me (**f**); R = 4-ClC_6H_4, R′ = 7,9-Cl_2 (**g**); R = 4-$MeOC_6H_4$, R′ = 7-Me (**h**)
7: R = 4-MeC_6H_4, R′ = 8-Me (**b**); R = 4-FC_6H_4, R′ = 9-Me (**c**); R = 4-FC_6H_4, R′ = 8-Me (**d**); R = 3-FC_6H_4, R′ = 9-Me (**e**); R = 2-furyl, R′ = H (**f**)

Scheme 3



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cyclocondensation mechanism to yield 2*H*-pyrido[1,2-*a*][1,3,5]triazine derivatives. The compounds obtained are promising from the viewpoint of medicinal and combinatorial chemistry.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer. Melting points were determined in a glass capillary. Acylimines of HFA **1a—f** and MTFP **2a—e** were prepared according to known procedures.[10,11] The starting substituted 2-aminopyridines **3a—f** (Aldrich Co.) were used as purchased.

Table 1. Yields, melting points, and elemental analysis data for compounds **6b—h** and **7a—f**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
6b	75	92—94	34.27	1.34	10.78	$C_{10}H_5Cl_2F_6N_3$
			34.12	1.43	11.94	
6c	72	144—146	53.31	3.27	11.61	$C_{16}H_{11}F_6N_3$
			53.49	3.09	11.70	
6d	65	126—128	48.63	2.39	10.83	$C_{16}H_{10}ClF_6N_3$
			48.81	2.56	10.67	
6e	72	138—140	51.12	2.49	11.02	$C_{16}H_{10}F_7N_3$
			50.94	2.67	11.14	
6f	68	140—142	50.78	2.49	11.32	$C_{16}H_{10}F_7N_3$
			50.94	2.67	11.14	
6g	64	141—142	40.34	1.51	9.19	$C_{15}H_6Cl_3F_6N_3$
			40.16	1.35	9.37	
6h	60	115—117	52.29	3.49	10.61	$C_{17}H_{13}F_6N_3O$
			52.45	3.37	10.79	
7a	58	137—139	58.31	4.22	12.21	$C_{17}H_{14}F_3N_3O_2$
			58.45	4.04	12.03	
7b	64	147—149	59.33	4.28	11.75	$C_{18}H_{16}F_3N_3O_2$
			59.50	4.44	11.57	
7c	55	143—145	55.41	3.42	11.26	$C_{17}H_{13}F_4N_3O_2$
			55.59	3.57	11.44	
7d	73	102—104	55.40	3.38	11.62	$C_{17}H_{13}F_4N_3O_2$
			55.59	3.57	11.44	
7e	69	133—135	55.44	3.39	11.29	$C_{17}H_{13}F_4N_3O_2$
			55.59	3.57	11.44	
7f	62	151—152	51.57	3.25	12.77	$C_{14}H_{10}F_3N_3O_3$
			51.70	3.10	12.92	

***N*-[1,1,1,3,3,3-Hexafluoro-2-(4-methylpyridin-2-ylamino)propan-2-yl]benzamide (4a).** 2-Amino-4-methylpyridine (**3a**) (1.08 g, 0.01 mol) was added to a solution of imine **1a** (2.69 g, 0.01 mol) in benzene (20 mL). After the exothermic reaction was completed, the solvent was removed and the residue was recrystallized from benzene—hexane (1 : 1) to give benzamide **4a** (3.25 g, 86%), m.p. 118—120 °C. Found (%): C, 50.77; H, 3.29; N, 11.32. $C_{16}H_{13}F_6N_3O$. Calculated (%): C, 50.94; H, 3.47; N, 11.14. ^{1}H NMR (DMSO-d_6), δ: 2.27 (s, 3 H, Me); 6.61 (d, 1 H, H arom., J = 8.0 Hz); 7.02 (s, 1 H, H arom.); 7.19 (s, 1 H, NH); 7.49, 7.92 (both m, 3 H each, H arom.); 12.68 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 4.68 (s).

Methyl 2-benzoylamino-3,3,3-trifluoro-2-(4-methylpyridin-2-ylamino)propionate (5a) was obtained analogously from imine **2a** (0.01 mol) and 2-amino-4-methylpyridine (**3a**) (0.01 mol). The yield of compound **5a** was 3.15 g (86%), m.p. 156—158 °C. Found (%): C, 55.41; H, 4.22; N, 11.31. $C_{17}H_{16}F_3N_3O_3$. Calculated (%): C, 55.59; H, 4.39; N, 11.44. ^{1}H NMR (DMSO-d_6), δ: 2.17 (s, 3 H, Me); 3.79 (s, 3 H, MeO); 6.42 (d, 1 H, H arom., J = 7.8 Hz); 6.67 (s, 1 H, H arom.); 7.19 (s, 1 H, NH); 7.42 (m, 3 H, H arom.); 7.64 (s, 1 H, NH); 7.83 (m, 3 H, H arom.); 9.14 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 2.62 (s).

8-Methyl-4-phenyl-2,2-bis(trifluoromethyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (6a). ***A.*** A mixture of benzamide **4a** (3.77 g, 0.01 mol) and PCl_5 (2.09 g, 0.01 mol) in benzene (50 mL) was refluxed to homogenization. The solvent and $POCl_3$ were removed and the residue was recrystallized from hexane to give triazine **6a** (2.55 g, 71%), m.p. 121—123 °C. Found (%): C, 55.31; H, 3.22; N, 11.51. $C_{16}H_{11}F_6N_3$. Calculated (%): C, 53.49; H, 3.09; N, 11.70. ^{1}H NMR (DMSO-d_6), δ: 2.13 (s, 3 H, Me); 5.85 (d, 1 H, H arom., J = 7.9 Hz); 6.56 (s, 1 H, H arom.); 6.96 (d, 1 H, H arom., J = 8.0 Hz); 7.55 (m, 5 H, H arom.). ^{19}F NMR (DMSO-d_6), δ: −1.04 (s).

B. 2-Amino-4-methylpyridine (**3a**) (1.08 g, 0.01 mol) was added to a solution of imine **1a** (2.69 g, 0.01 mol) in benzene (50 mL). After the exothermic reaction was completed, PCl_5 (2.09 g, 0.01 mol) was added and the reaction mixture was refluxed to homogenization. The solvent and $POCl_3$ were removed and the residue was recrystallized from hexane to give triazine **6a** (2.12 g, 56%), m.p. 121—123 °C.

7,8-Dichloro-4-methyl-2,2-bis(trifluoromethyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (6b), 4-(2-methylphenyl)-2,2-bis(trifluoromethyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (6c), 7-chloro-4-(2-methylphenyl)-2,2-bis(trifluoromethyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (6d), 4-(4-fluorophenyl)-9-methyl-2,2-bis(trifluoromethyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (6e), 4-(2-fluorophenyl)-7-methyl-2,2-bis(trifluoromethyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (6f), 7,9-dichloro-4-(4-chlorophenyl)-2,2-bis(trifluoromethyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (6g), 4-(4-methoxyphenyl)-7-methyl-2,2-bis(trifluoromethyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (6h), methyl 8-methyl-4-phenyl-2-trifluoromethyl-2*H*-pyrido[1,2-*a*][1,3,5]triazine-2-carboxylate (7a), methyl 8-methyl-4-(4-methylphenyl)-2-trifluoromethyl-2*H*-pyrido[1,2-*a*][1,3,5]triazine-2-carboxylate (7b), methyl 4-(4-fluorophenyl)-9-methyl-2-trifluoromethyl-2*H*-pyrido[1,2-*a*][1,3,5]triazine-2-carboxylate (7c), methyl 4-(4-fluoro-

Table 2. ^{1}H and ^{19}F NMR spectra of compounds **6b—h** and **7a—f** (in DMSO-d_6)

Compound	δ (J/Hz)	
	^{1}H	^{19}F
6b	2.48 (s, 3 H, Me); 7.32, 7.84 (both s, 1 H each, H arom.)	0.82 (s)
6c	2.28 (s, 3 H, Me); 5.93 (t, 1 H, H arom., J = 7.5); 6.66 (m, 2 H, H arom.); 7.06 (m, 1 H, H arom.); 7.28—7.41 (m, 4 H, H arom.)	0.86 (s)
6d	2.29 (s, 3 H, Me); 6.74 (m, 2 H, H arom.); 7.07 (d, 1 H, H arom., J = 8.1); 7.30—7.52 (m, 4 H, H arom.)	0.70 (s)
6e	2.16 (s, 3 H, Me); 5.95 (t, 1 H, H arom., J = 7.6); 6.97 (m, 2 H, H arom.); 7.27 (t, 2 H, H arom., J = 7.9); 7.59 (m, 2 H, H arom.)	−0.67 (s, 3 F); 28.82 (m, 1 F)
6f	1.98 (s, 3 H, Me); 6.62 (d, 2 H, H arom., J = 7.9); 6.96 (d, 1 H, H arom., J = 7.8); 7.37 (m, 2 H, H arom.); 7.51, 7.78 (both m, 1 H each, H arom.)	−0.81 (s, 3 F); −34.55 (m, 1 F)
6g	7.23, 7.38 (both s, 1 H each, H arom.); 7.53, 7.66 (both d, 2 H each, H arom., J = 7.8)	0.55 (s)
6h	1.96 (s, 3 H, Me); 3.88 (s, 3 H, MeO); 6.64 (d, 1 H, H arom., J = 7.7); 6.90 (s, 1 H, H arom.); 6.93—7.07 (m, 3 H, H arom.); 7.49 (d, 2 H, H arom., J = 7.8)	0.52 (s)
7a	2.13 (s, 3 H, Me); 3.80 (s, 3 H, MeO); 5.78 (d, 1 H, H arom., J = 8.1); 6.42 (s, 1 H, H arom.); 6.91 (d, 1 H, H arom., J = 8.0); 7.53 (m, 5 H, H arom.)	−0.26 (s)
7b	2.17, 2.48 (both s, 3 H each, Me); 3.84 (s, 3 H, MeO); 5.88 (d, 1 H, H arom., J = 7.7); 6.45 (s, 1 H, H arom.); 6.96 (d, 1 H, H arom., J = 7.7); 7.33, 7.47 (both d, 2 H each, H arom., J = 8.0)	−0.12 (s)
7c	2.11 (s, 3 H, Me); 3.82 (s, 3 H, MeO); 5.84 (t, 1 H, H arom., J = 7.8); 6.86 (m, 2 H, H arom.); 7.25 (t, 2 H, H arom., J = 7.5); 7.57 (m, 2 H, H arom.)	0.35 (s, 3 F); −29.36 (m, 1 F)
7d	2.09 (s, 3 H, Me); 3.81 (s, 3 H, MeO); 5.74 (d, 1 H, H arom., J = 7.7); 6.49 (s, 1 H, H arom.); 6.82 (d, 1 H, H arom., J = 7.9); 7.18 (t, 2 H, H arom., J = 7.7); 7.57 (m, 2 H, H arom.)	−0.55 (s, 3 F); 29.02 (m, 1 F)
7e	2.11 (s, 3 H, Me); 3.83 (s, 3 H, MeO); 5.91 (t, 1 H, H arom., J = 7.9); 6.84 (d, 2 H, H arom., J = 7.9); 7.27—7.36 (m, 3 H, H arom.); 7.52 (m, 3 H, H arom.)	−0.16 (s, 3 F); −33.44 (m, 1 F)
7f	3.78 (s, 3 H, MeO); 6.05 (t, 1 H, H arom., J = 7.7); 6.61—6.67 (m, 2 H, H arom.); 6.98—7.09 (m, 1 H, H arom.); 7.16, 7.44 (both d, 1 H each, H arom., J = 8.1); 7.83 (m, 1 H, H arom.)	0.07 (s)

phenyl)-8-methyl-2-trifluoromethyl-2*H*-pyrido[1,2-*a*][1,3,5]triazine-2-carboxylate (7d), methyl 4-(3-fluorophenyl)-9-methyl-2-trifluoromethyl-2*H*-pyrido[1,2-*a*][1,3,5]triazine-2-carboxylate (7e), and methyl 4-(2-furyl)-2-trifluoromethyl-2*H*-pyrido[1,2-*a*][1,3,5]triazine-2-carboxylate (7f) were obtained from imine **1** or **2** (0.01 mol), 2-aminopyridines **3** (0.01 mol), and PCl_5 (0.01 mol) as described for triazine **6a**. The yields, melting points, and spectroscopic characteristics of compounds **6b—h** and **7a—f** are given in Tables 1 and 2.

8-Methyl-4-phenyl-2-trifluoromethyl-2*H*-pyrido[1,2-*a*][1,3,5]triazine-2-carbohydrazide (8). Hydrazine hydrate (1.01 g, 0.02 mol) was added to a solution of triazine **7a** (3.49 g, 0.01 mol) in MeOH (20 mL). The reaction mixture was kept at 20 °C for 24 h and the precipitate that formed was filtered off and recrystallized from 50% EtOH. The yield of hydrazide **8** was 2.75 g (79%), m.p. 168—170 °C. Found (%): C, 55.19; H, 4.21; N, 19.88. $C_{16}H_{14}F_3N_5O$. Calculated (%): C, 55.02; H, 4.04; N, 20.05. ^{1}H NMR (DMSO-d_6), δ: 2.14 (s, 3 H, Me); 4.16 (s, 2 H, NH_2); 5.76 (d, 1 H, H arom., J = 7.6 Hz); 6.46 (s, 1 H, H arom.); 6.92 (d, 1 H, H arom., J = 7.6 Hz); 7.54 (m, 5 H, H arom.); 8.74 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: −0.94.

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