Fluoroalkyl-containing lithium β-diketonates in the synthesis of 1,2,4-triazolo[1,5-*a*]pyrimidines

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Cyclocondensation of fluorine-containing lithium β-diketonates with 3-amino-1,2,4-triazoles afforded 7-fluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidines.

Key words: fluorine-containing lithium β-diketonates, 3-amino-1,2,4-triazoles, 7-fluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidines.

Earlier, we showed[1,2] that fluorine-containing lithium β-diketonates **1** are more accessible and convenient "building blocks" than the corresponding β-diketones for construction of various heterocycles. For instance, efficient methods for the synthesis of fused heterocycles with nitrogen as a bridgehead atom, *viz.*, 1,2,4-triazolo[3,4-*b*]pyridazines and pyrazolo[1,5-*a*]pyrimidines, were proposed.[1,2]

In the present study, salts **1** were used to obtain another type of fluoroalkylazoloazines, *viz.*, 7-fluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidines. Reactions of salts **1** with 3-amino-1,2,4-triazoles **2** were carried out under the same conditions as for their reactions with 4-amino-1,2,4-triazole and 3-aminopyrazoles.[1,2]

At the first reaction step, the formation of two isomeric β-aminovinyl ketones (AVK) **3** and **4** is possible; the cyclization of either can also occur at two nucleophilic centers (N(2) and N(4)). Thus, the reaction can yield four isomeric triazolopyrimidines **5**—**8** (Scheme 1). However, only one isomer was actually obtained in all of the reactions studied, which is indicated by a single set of resonance signals in the ^{1}H, ^{19}F, and ^{13}C NMR spectra of the triazolopyrimidines synthesized. The formation of isomers **5** seems to be most probable from the following reasons. The reactions of salts **1** with aliphatic and aromatic amines predominantly yield AVK,[1] which are similar to intermediates **3**. Cyclization of the latter at the nucleophilic N(2) center is more probable; this atom is included in the hydrazine fragment of the triazole ring and thus is more nucleophilic than the N(4) atom (see Scheme 1). Moreover, triazolo[1,5-*a*]pyrimidines **5** are thermodynamically more stable than triazolo[4,3-*a*]pyrimidines **6**.[3] The Dimroth rearrangement[4] into triazolo[1,5-*a*]pyrimidines **5** is also possible under these reaction conditions.

To verify this assumption, we synthesized model triazolopyrimidines **5i,j** by reactions of AVK **9** with aminotriazoles **2a,b** (Scheme 2).

In this case, the first reaction step exclusively affords AVK **3a,b** (it is well known that AVK containing a β-amino group to a substituent R^F undergo transamination in reactions with amines but do not isomerize[5,6]). Based on comparison of the ^{1}H and ^{19}F NMR data for compounds **5i,j** and 2-benzylthio-5-methyl-7-trifluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidine, which was structurally characterized by X-ray diffraction analysis,[7] we assigned a structure of 5-methyl-7-trifluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidines **5i,j** to the cyclization products of AVK **3a,b**.

The chemical shifts of the reference signals in the ^{1}H, ^{19}F, and ^{13}C NMR spectra of compounds **5i,j** and products of the reactions of lithium β-diketonates **1** with 3-amino-1,2,4-triazoles **2** are very close together (Tables 1, 2). The characteristics of the ^{1}H, ^{19}F, and ^{13}C NMR spectra of compounds **5a**—**j** and pyrazolo[1,5-*a*]pyrimidines, the structures of which were determined earlier (with the use of X-ray diffraction analysis as well),[2] are also close. Comparison of the chemical shifts of the C atoms of the CF_3 and HCF_2 groups, the C(7) and C(6) atoms, and the *ipso*-C atoms of the Ph substituent in triazolo- and pyrazolopyrimidines provides especially indicative results.

The aforesaid data suggest that 7-fluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidines **5** is a preferable structure for the products of the reactions of lithium β-diketonates **1** with 3-amino-1,2,4-triazoles **2**.

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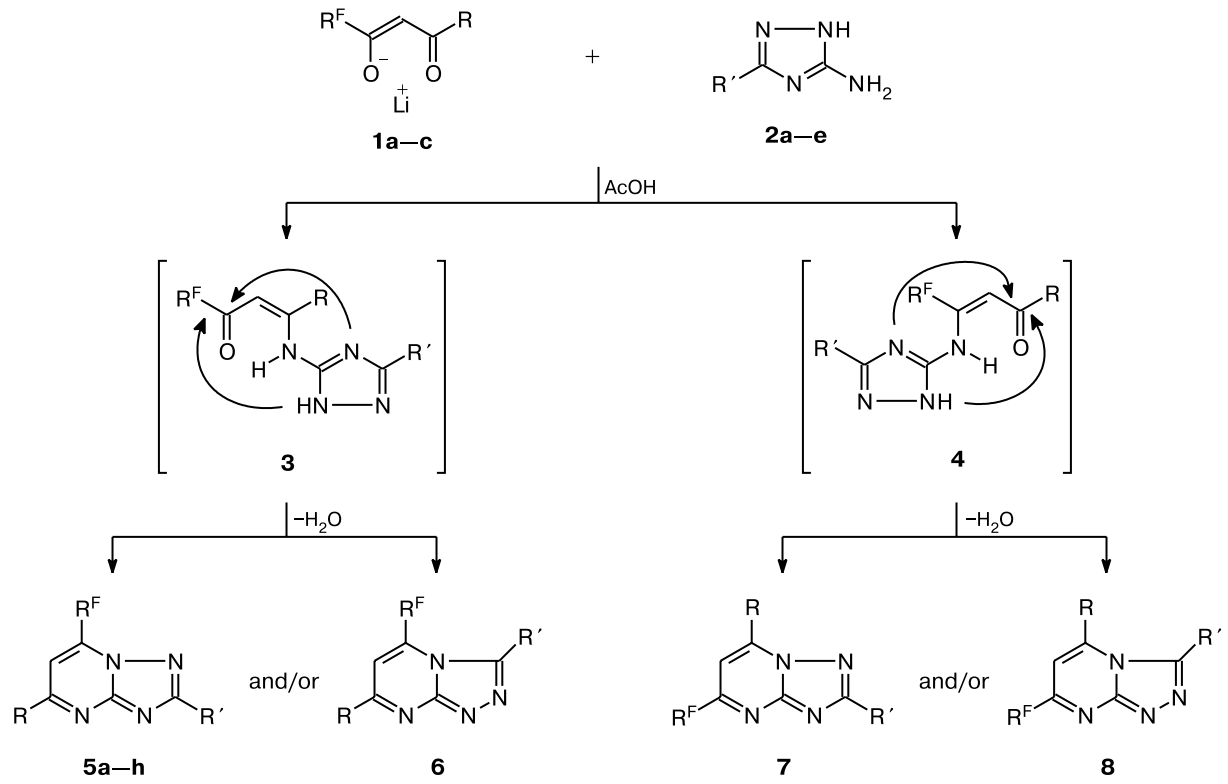
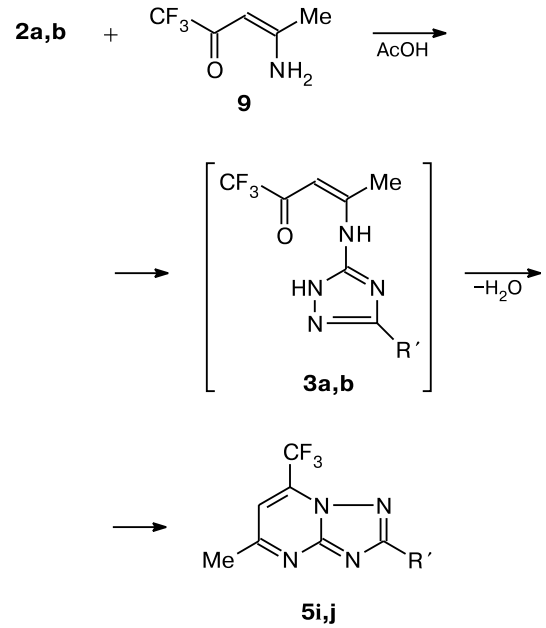
Scheme 1



1: $R^F = CF_3$, R = Ph (**a**); $R^F = HCF_2$, R = Ph (**b**); $R^F = R = CF_3$ (**c**)
2: R′ = H (**a**), SMe (**b**), CF_3 (**c**), COOH (**d**), Me (**e**)

5: $R^F = CF_3$ (**a—e**), HCF_2 (**f—h**); R = Ph (**a—d, f—h**), CF_3 (**e**); R′ = H (**a, f**), Me (**c**), SMe (**d, e, g**), CF_3 (**b, h**)

Scheme 2

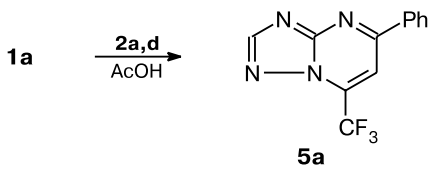


R′ = H (**3a**, **5j**), SMe (**3b**, **5i**)

The reactions of salts **1a,b** with 3-amino-5-trifluoromethyl-1,2,4-triazole (**2c**) open the possibility of synthesizing 1,2,4-triazolo[1,5-*a*]pyrimidines containing fluoroalkyl substituents in both rings (compounds **5b,h**).

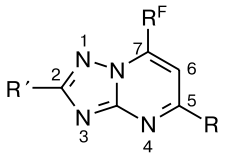
The reaction of salt **1a** with 5-amino-1,2,4-triazole-3-carboxylic acid (**2d**) is accompanied by decarboxylation to give triazolopyrimidine **5a**, which is identical with a product obtained in the reaction of salt **1a** with aminotriazole **2a** (Scheme 3).

Scheme 3



The mass spectra of compounds **5d,h** contain no peaks due to specific fragmentation of azolopyrimidine, as in the case of 7-fluoroalkylpyrazolo[1,5-*a*]pyrimidines.[2] Their spectra show molecular ion peaks and peaks of the $[M - F]^+$, $[M - R^F]^+$, $[R^F]^+$, $[R]^+$, and $[R']^+$ fragments.

Table 1. ^{1}H and ^{19}F NMR spectra of compounds **5a—j**



Compound	R^F	R	R´	NMR, δ (*J*/Hz)				
				^{19}F	^{1}H			
					R^F (t, 1 H)	R	R´	H(6) (s, 1 H)
5a	CF_3	Ph	H	93.38 (s, 3 F, CF_3)	—	7.55—7.60 (m, 3 H); 8.22—8.24 (m, 2 H)	8.62 (s, 1 H)	7.89
5b	CF_3	Ph	CF_3	93.72, 96.12 (both s, 3 F each, 2 CF_3)	—	7.57—7.65 (m, 3 H); 8.19—8.24 (m, 2 H)	—	8.01
5c	CF_3	Ph	Me	—	—	7.55 (m, 3 H); 8.19 (m, 2 H)	2.70 (s, 3 H)	7.79
5d	CF_3	Ph	SMe	93.28 (s, 3 F, CF_3)	—	7.55—7.58 (m, 3 H); 8.19—8.24 (m, 2 H)	2.76 (s, 3 H)	7.76
5e	CF_3	CF_3	SMe	93.13, 93.49 (both s, 3 F each, 2 CF_3)	—	—	2.78 (s, 3 H)	7.68
5f	HCF_2	Ph	H	37.97 (dd, 2 F, HCF_2, $^{2}J_{F,H}$ = 52.9, $^{4}J_{F,H}$ = 1.0)	7.34 ($^{2}J_{H,F}$ = 52.9)	7.31—7.60 (m, 3 H); 8.18—8.30 (m, 2 H)	8.56 (s, 1 H)	7.85
5g*	HCF_2	Ph	SMe	38.13 (d, 2 F, HCF_2, $^{2}J_{F,H}$ = 53.1)	7.48 ($^{2}J_{H,F}$ = 53.1)	7.54—7.57 (m, 3 H); 8.25—8.29 (m, 2 H)	2.71 (s, 3 H)	8.01
5h	HCF_2	Ph	CF_3	38.17 (d, 2 F, HCF_2, $^{2}J_{F,H}$ = 52.2); 96.08 (s, 3 F, CF_3)	7.35 ($^{2}J_{H,F}$ = 52.2)	7.56—7.63 (m, 3 H); 8.23—8.27 (m, 2 H)	—	7.98
5i	CF_3	Me	SMe	93.13 (s, 3 F, CF_3)	—	2.73 (s, 3 H)	3.05 (s, 3 H)	7.18
5j	CF_3	Me	H	93.26 (s, 3 F, CF_3)	—	2.84 (s, 3 H)	8.58 (s, 1 H)	7.34

* The ^{1}H NMR spectrum was recorded in DMSO-d_6.

Table 2. ^{13}C NMR spectra of compounds **5a,e—j**

Compound	δ (*J*/Hz)							
	R^F	C(7)	R	C(5)	C(2)	C(6)	C(3a)	R´
5a [a]	118.84 (q, $^{1}J_{C,F}$ = 274.9)	135.66 (q, $^{2}J_{C,F}$ = 39.7)	135.07 (C_{ipso})	161.87	157.29	105.54 (q, $^{3}J_{C,F}$ = 3.8)	156.29	—
5e [a]	118.20 (q, $^{1}J_{C,F}$ = 275.8)	135.50 (q, $^{2}J_{C,F}$ = 39.9)	119.66 (q, $^{1}J_{C,F}$ = 276.0)	150.90 (q, $^{2}J_{C,F}$ = 38.5)	174.37	103.22 (q, $^{3}J_{C,F}$ = 2.3)	155.57	13.92
5f [a]	107.78 (t, $^{1}J_{C,F}$ = 242.5)	140.07 (t, $^{2}J_{C,F}$ = 28.4)	135.53 (C_{ipso})	162.19	156.99	104.24 (t, $^{3}J_{C,F}$ = 4.7)	155.82	—
5g [a]	107.63 (t, $^{1}J_{C,F}$ = 242.3)	138.78 (t, $^{2}J_{C,F}$ = 28.6)	135.46 (C_{ipso})	170.85	161.20	102.83 (t, $^{3}J_{C,F}$ = 4.5)	156.20	13.94
5h [a]	107.38 (t, $^{1}J_{C,F}$ = 243.3)	140.69 (t, $^{2}J_{C,F}$ = 28.8)	134.69 (C_{ipso})	163.77	158.2 (q, $^{2}J_{C,F}$ = 40.3)	105.95 (t, $^{3}J_{C,F}$ = 4.6)	155.75	118.82 (q, $^{1}J_{C,F}$ = 271.5)
5i [b]	118.30 (q, $^{1}J_{C,F}$ = 280.2)	133.69 (q, $^{2}J_{C,F}$ = 38.9)	25.36	164.84	156.49	107.62 (q, $^{3}J_{C,F}$ = 3.7)	148.04	13.97
5j [b]	118.75 (q, $^{1}J_{C,F}$ = 274.8)	134.96 (q, $^{2}J_{C,F}$ = 38.8)	25.56	165.73	156.76	109.16 (q, $^{3}J_{C,F}$ = 3.7)	155.92	—

[a] Obtained from lithium β-diketonate.
[b] Obtained from β-aminovinyl ketone.

Experimental

Salts **1a—c** and AVK **9** were prepared as described earlier.[1] 3-Aminotriazoles **2a—e** were synthesized according to the known procedures.[8—10] IR spectra were recorded on a Specord IR-75 spectrometer in a 20-μm layer (for liquid samples) and Vaseline oil (for solid samples). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 instrument (400 and 100 MHz) in $CDCl_3$ with Me_4Si as the standard; ^{19}F NMR spectra were recorded on a Tesla BS-587A spectrometer (75.3 MHz) in $CDCl_3$ with C_6F_6 as the internal standard. Mass spectra were obtained with a MAT INCOS50 spectrometer (ionizing voltage 70 eV, direct inlet probe). TLC was performed on Silufol UV-254 plates in $CHCl_3$ and CCl_4 as eluents; spots were visualized with aqueous solutions of $Cu(OAc)_2$ and $KMnO_4$.

7-Difluoromethyl-5-phenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (5f). A solution of salt **1b** (1 g, 5 mmol) and 3-amino-1,2,4-triazole **2a** (0.7 g, 5 mmol) in AcOH was kept at 40 °C for seven days. Then the solution was poured into ice, the product was extracted with ether, and the extract was dried over $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography and recrystallized from hexane to give compound **5f** (0.25 g, 55%), m.p. 192—194 °C. Found (%): C, 58.56; H, 3.08; F, 15.30; N, 22.90. $C_{12}H_8F_2N_4$. Calculated (%): C, 58.53; H, 3.25; F, 15.44; N, 22.76. IR, ν/cm^{-1}: 1540 (C=C); 1620 (C=N).

Compounds **5a—e,g,h** were obtained analogously.

5-Phenyl-7-trifluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (5a). ***A.*** Compound **5a** was obtained from salt **1a** (1 g, 5 mmol) and 3-amino-1,2,4-triazole (**2a**) (0.5 g, 5 mmol). The yield of compound **5a** was 0.68 g (55%), m.p. 142—143 °C. Found (%): C, 54.06; H, 2.27; N, 20.28. $C_{12}H_7F_3N_4$. Calculated (%): C, 54.54; H, 2.65; N, 21.21. IR, ν/cm^{-1}: 1610 (C=N).

B. Refluxing of salt **1a** (1.0 g, 4.5 mmol) with 5-amino-1,2,4-triazole-3-carboxylic acid (**2d**) (0.6 g, 4.5 mmol) for 5 h gave compound **5a** (0.35 g, 29%), m.p. 142—143 °C. The elemental analysis data show a good agreement with the calculated values. The IR and ^{1}H NMR spectra are identical with those of compound **5a** obtained according to procedure ***A***.

5-Phenyl-2,7-di(trifluoromethyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (5b). Compound **5b** was obtained from salt **1a** (0.8 g, 3.6 mmol) and 3-amino-5-trifluoromethyl-1,2,4-triazole (**2c**) (0.5 g, 3.6 mmol). The yield of compound **5b** was 0.25 g (21%), m.p. 121—123 °C. Found (%): C, 47.04; H, 1.76; F, 33.82; N, 16.85. $C_{13}H_6F_6N_4$. Calculated (%): C, 46.98; H, 1.80; F, 34.33; N, 16.86. IR, ν/cm^{-1}: 1630 (C=N).

2-Methyl-5-phenyl-7-trifluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (5c). Compound **5c** was obtained from salt **1a** (1 g, 4.5 mmol) and 3-amino-5-methyl-1,2,4-triazole (**2e**) (0.44 g, 4.5 mmol). The yield of compound **5c** was 0.3 g (25%), subl. >180 °C. Found (%): C, 56.15; H, 3.38; F, 20.51; N, 19.93. $C_{13}H_9F_3N_4$. Calculated (%): C, 56.11; H, 3.24; F, 20.50; N, 20.14. IR, ν/cm^{-1}: 1545 (C=C); 1610 (C=N).

2-Methylthio-5-phenyl-7-trifluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (5d). Compound **5d** was obtained from salt **1a** (1 g, 4.5 mmol) and 3-amino-5-methylthio-1,2,4-triazole (**2b**) (0.58 g, 4.5 mmol). The yield of compound **5d** was 0.93 g (65%), m.p. 135—137 °C. Found (%): C, 50.20; H, 2.95; F, 17.87; N, 18.47. $C_{13}H_9F_3N_4S$. Calculated (%): C, 50.32; H, 2.90; F, 18.38; N, 18.06. IR, ν/cm^{-1}: 1610 (C=N); 1540 (C=C). MS, m/z (I_{rel} (%)): 310 $[M]^+$ (88), 309 $[M - H]^+$ (39), 291 $[M - F]^+$ (7), 263 $[M - SCH_3]^+$ (13), 77 $[Ph]^+$ (54), 69 $[CF_3]^+$ (11), 47 $[SCH_3]^+$ (46), 40 (100).

2-Methylthio-5,7-di(trifluoromethyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (5e). Compound **5e** was obtained from salt **1c** (1.0 g, 4.6 mmol) and 3-amino-5-methylthio-1,2,4-triazole (**2b**) (0.6 g, 4.6 mmol). The yield of compound **5e** as an oil was 0.43 g (30%). Found (%): C, 31.94; H, 1.56; F, 37.80; N, 18.50. $C_8H_4F_6N_4S$. Calculated (%): C, 31.71; H, 1.33; F, 37.62; N, 18.48. IR, ν/cm^{-1}: 1550 (C=C); 1630 (C=N).

7-Difluoromethyl-2-methylthio-5-phenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (5g). Compound **5g** was obtained from salt **1b** (2.0 g, 10 mmol) and 3-amino-5-methylthio-1,2,4-triazole (**2b**) (1.3 g, 10 mmol). The yield of compound **5g** was 2.0 g (70%), m.p. 136—138 °C. Found (%): C, 53.54; H, 3.31; N, 19.28. $C_{13}H_{10}F_2N_4S$. Calculated (%): C, 53.42; H, 3.42; N, 19.18. IR, ν/cm^{-1}: 1550 (C=C); 1630 (C=N).

7-Difluoromethyl-5-phenyl-2-trifluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (5h). Compound **5h** was obtained from salt **1b** (1 g, 5 mmol) and 3-amino-5-trifluoromethyl-1,2,4-triazole (**2c**) (0.7 g, 5 mmol). The yield of compound **5h** was 0.5 g (32%), m.p. 102—105 °C. Found (%): C, 49.90; H, 1.92; F, 30.24; N, 18.06. $C_{13}H_7F_5N_4$. Calculated (%): C, 49.68; H, 2.23; F, 30.25; N, 17.83. IR, ν/cm^{-1}: 1540 (C=C); 1620 (C=N). MS, m/z (I_{rel} (%)): 314 $[M]^+$ (100), 295 $[M - F]^+$ (5), 263 $[M - HCF_2]^+$ (5), 117 $[M - CF_3 - HCF_2 - Ph]^+$ (5), 77 $[Ph]^+$ (12), 69 $[CF_3]^+$ (11), 51 $[HCF_2]^+$ (19).

5-Methyl-2-methylthio-7-trifluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (5i). 3-Amino-1,2,4-triazole **2b** (0.85 g, 6.5 mmol) was added to a solution of AVK **9** (1 g, 6.5 mmol) in AcOH. The reaction mixture was refluxed for 15 h and then poured into water. The precipitate that formed was filtered off and successively recrystallized from perfluorodimethylcyclohexane (carbohal) and *n*-hexane to give compound **5i** (0.96 g, 60%), m.p. 97—99 °C. Found (%): C, 39.36; H, 2.52; N, 22.19. $C_8H_7F_3N_4S$. Calculated (%): C, 38.74; H, 2.84; N, 22.58. IR, ν/cm^{-1}: 3050 (C_{Ar}—H); 1615 (C=N).

5-Methyl-7-trifluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (5j). By analogy, compound **5j** was obtained from AVK **9** (1 g, 6.5 mmol) and 3-amino-1,2,4-triazole **2a** (0.55 g, 6.5 mmol). The yield of compound **5j** was 0.90 g (65%), m.p. 100—102 °C. Found (%): C, 41.52; H, 2.52; F, 28.19; N, 27.49. $C_7H_5F_3N_4$. Calculated (%): C, 41.58; H, 2.48; F, 28.22; N, 27.72. IR, ν/cm^{-1} : 3080 (C_{Ar}—H); 1620 (C=N).

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