Guanidine in the synthesis of perfluoroalkylpyrimidines and perfluoroalkyl-*s*-triazines

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Perfluoro-2-methylpent-2-ene and perfluoro-5-azanon-4-ene react with guanidine hydrochloride in the presence of triethylamine to give 2-amino-6-fluoro-4-pentafluoroethyl-5-trifluoromethylpyrimidine and 2-amino-4,6-bis(heptafluoropropyl)-1,3,5-triazine, respectively. The structure of the former product was confirmed by X-ray diffraction analysis.

Key words: perfluoro-2-methylpent-2-ene, perfluoro-5-azanon-4-ene, guanidine hydrochloride, perfluoroalkylpyrimidines, perfluoroalkyl-*s*-triazines.

Interest in perfluoroalkylated heterocyclic compounds is largely due to the fact that they sometimes have enhanced biological activity, which can be used to create a new generation of agricultural and medicinal preparations.[1—3] Perfluoroalkylated N-containing heterocycles can be obtained by various methods, including such important ones as the reactions of perfluoroolefins with binucleophiles having, *e.g.*, 1,3-nucleophilic centers on the nitrogen atoms.[4] Of special interest are nucleophilic reagents with several nucleophilic centers such as guanidine, as their reactions with perfluoroolefins can yield heterocyclic compounds containing an amino group. For example, the reaction of guanidine hydrochloride (**1**) with a trimer of tetrafluoroethylene affords 2-amino-4,5,6-tris(trifluoromethyl)pyrimidine.[5] Perfluoroolefins can be modified to synthesize heterocyclic compounds with different perfluoroalkyl groups.

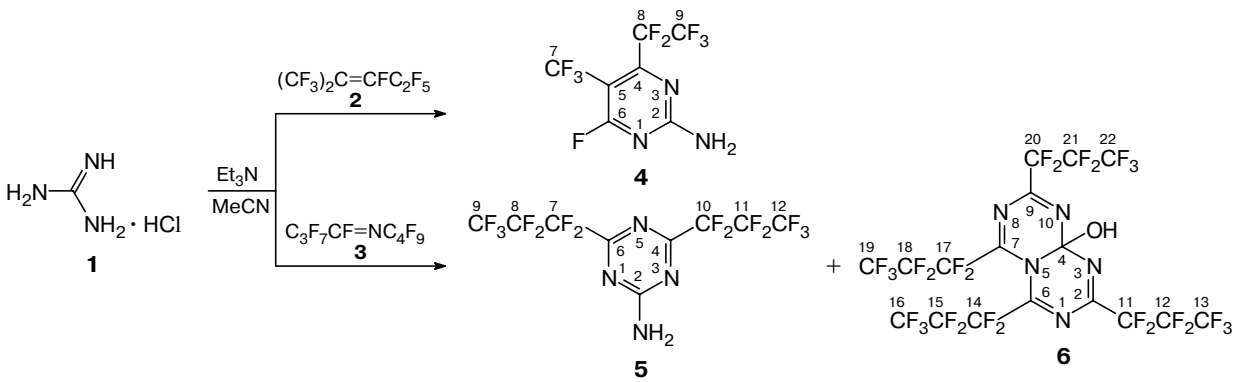
In the present work, the reactions of guanidine hydrochloride (**1**) with perfluoro-2-methylpent-2-ene (**2**) and perfluoro-5-azanon-4-ene (**3**) in the presence of triethylamine were studied.[4]

One could expect that either compounds **4** and **5** or bicyclic products would be formed. Previously, we showed[6] that 2-aminopyridine reacts with compounds **2** and **3** to give bicyclic heterocycles.

It was found that the reaction of compound **1** with **2** in the presence of Et_3N affords 2-amino-4-pentafluoroethyl-5-trifluoromethyl-6-fluoropyrimidine (**4**) (Scheme 1). Under these conditions, product **4** does not react with perfluoroalkene **2**.

The structure of compound **4** was confirmed by IR and ^{13}C and ^{19}F NMR data and unambiguously determined by X-ray diffraction analysis (Fig. 1). The C_2F_5 group is oriented so that the torsion C(5)—C(6)—C(8)—C(9) angle equals 99.5(4)°. A similar orientation of this group was found earlier in the CF_3—C=C—C_2F_5 fragment.[7,8] However, a torsion angle in such structures is often ~160°.[9,10] The bond lengths in

Scheme 1



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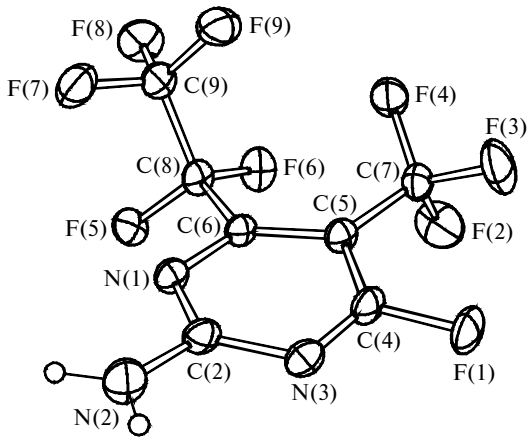


Fig. 1. Molecular structure of compound **4**.

molecule **4** are mostly standard. Note that the N(3)—C(4) (1.297(6) Å) and C(2)—N(2) bonds (1.319(6) Å) are shorter than the mean values (1.334(11) and 1.345(32) Å, respectively) calculated from the data of the Cambridge Crystallographic Database[11] for the 2-aminopyrimidine fragment (averaging over 39 fragments). A small boatlike distortion is observed in the heterocycle, the C(2) and C(5) atoms deviating from the plane of the N(1), N(3), C(4), and C(6) atoms by 0.078(3) and 0.075(3) Å, respectively. In crystal, the molecules of **4** are joined together by hydrogen bonds *via* both the fluorine atoms and the nitrogen atoms of the pyrimidine framework: N(2)—H(2A)...N(1) (0.90(6), 2.44(6) Å, 174(5)°), N(2)—H(2B)...N(3) (0.65(4), 2.77(4) Å, 152(5)°), and N(2)—H(2A)...F(6) (0.90(6), 2.52(5) Å, 117(4)°) to form infinite chains along the *a* axis (Fig. 2).

Compound **1** reacts with imine **3** to yield a mixture of products **5** and **6** (see Scheme 1). Compound **6** results from the reaction of perfluoroimine **3** with triazine **5**, suggesting that imine **3** is more reactive than perfluoroalkene **2**.

One can assume that compound **5** is formed according to Scheme 2.

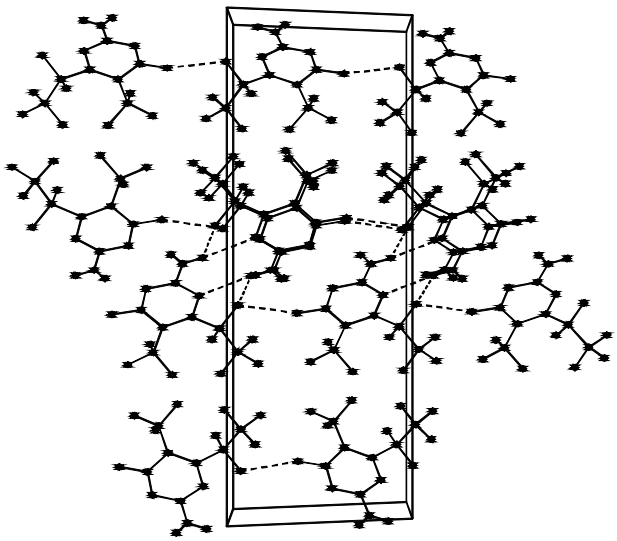


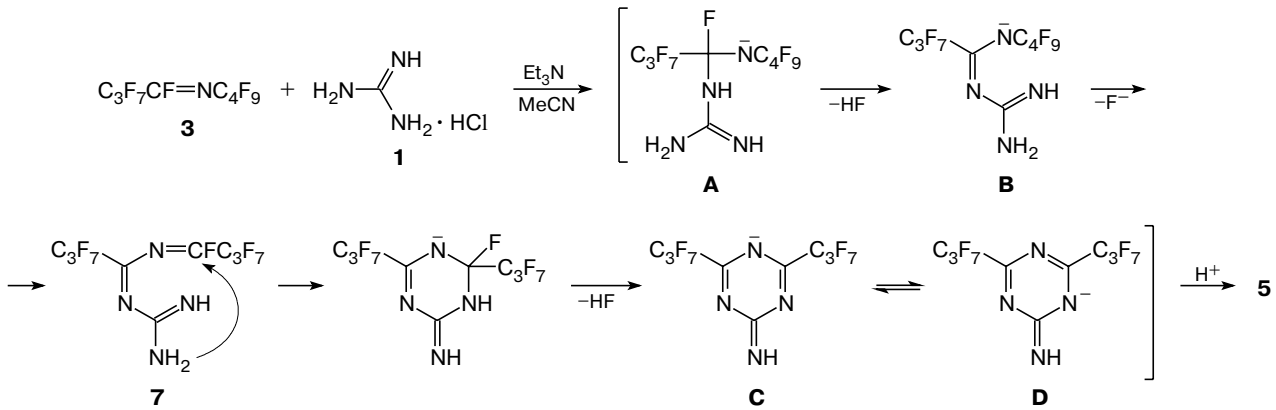
Fig. 2. Molecular packing in compound **4** (projection along the *c* axis is shown).

Apparently, the amino N atom of guanidine initially attacks the carbon atom of the C=N bond to generate N-anion **A**. Hydrogen fluoride may be eliminated therefrom to give N-anion **B**, which releases the fluoride ion from the CF_2 fragment to form compound **7**. Intramolecular nucleophilic cyclization affords *s*-triazine **5** through intermediate anions **C** and **D**. It is the formation of the second C=N bond that is the key stage of the reaction of compound **3** with guanidine. It was quite natural to expect that other systems containing the N=C—N fragment can also react with strong C-electrophiles.

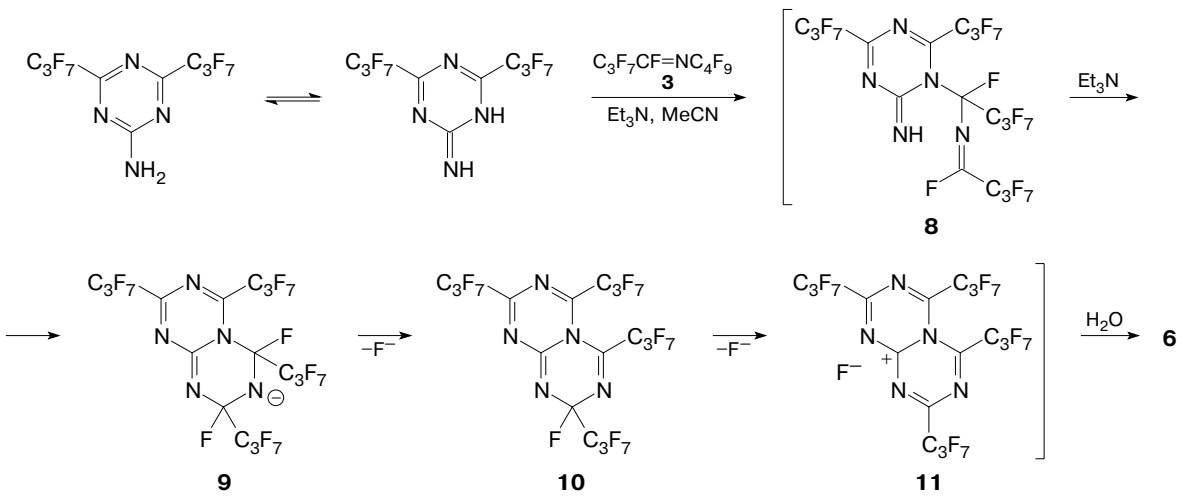
Indeed, the structural features of compound **5** allows it to react with imine **3**, yielding product **6** (Scheme 3).

Probably, the amino N atom of the *s*-triazine ring initially attacks the C atom at the double bond of a second molecule of imine **3** to give compound **8**, which undergoes intramolecular cyclization *via* the double C=N bond and the NH fragment into N-anion **9**. Elimination

Scheme 2



Scheme 3



of a F^- anion from the CFC_3F_7 fragment produces compound **10**, which is transformed into salt **11** by releasing another F^- anion. When treated with water, salt **11** yields product **6**.

Hence, the reactions of perfluoroazaalkenes containing the N—C—NH fragment with nucleophilic reagents can be used for constructing bicyclic nitrogen-containing heterocycles with perfluoroalkyl groups.

Experimental

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker SY spectrometer (200, 50, and 188 MHz, respectively) with Me_4Si and C_6F_6 as the internal standards. IR spectra were recorded on a Specord M-80 spectrometer (CCl_4). Mass spectra were obtained on a Finnigan MAT 8200 chromato-mass-spectrometer (EI, 70 eV). UV spectra were recorded in ethanolic solutions on a Karl Zeiss Jena Specord M-40 spectrometer. Melting points were determined on a Kofler hot stage. Anhydrous diethyl ether was prepared by drying it with anhydrous $CaCl_2$ and distilling over metallic sodium in an inert atmosphere.

2-Amino-6-fluoro-4-pentafluoroethyl-5-trifluoromethylpyrimidine (4). Compound **1** (4.47 g, 0.05 mol) was added in small portions over 0.5 h with stirring and cooling to 0 °C to a solution of perfluoroalkene **2** (15 g, 0.05 mol) and Et_3N (20.2 g, 0.2 mol) in 60 mL of dry ether. The reaction mixture was warmed to 20 °C, kept at this temperature for 24 h, and then poured into water. The product was extracted with CH_2Cl_2, and the extract was dried with $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography on silica gel in CH_2Cl_2—acetone (7 : 1). The yield of compound **4** was 12.5 g (83%), m.p. 98—99 °C. IR, ν/cm^{-1}: 1224—1145 (C—F); 1270, 1300, 1324, 1395 (C—N); 1517, 1544 (C=N); 1607, 1665 (C=C); 3350, 3454 (NH_2). UV (EtOH), λ_{max}/nm (ε): 260 (23000), 300 (3400). MS, *m/z* (I_{rel} (%)): 299 $[M]^+$ (100), 280 $[M - F]^+$ (33.17), 230 $[M - CF_3]^+$ (38.50), 210 $[M - CF_3 - HF]^+$ (7.18), 180 $[M - C_2F_5]^+$ (20.73), 160 $[M - C_2F_5 - HF]^+$ (11.79), 119 $[C_2F_5]^+$ (2.01), 100 $[CF_2{=}CF_2]^+$ (1.98), 69 $[CF_3]^+$ (9.86), 42 $[H_2NCN]^+$ (3.06). Found (%): C, 28.09; H, 0.67; F, 57.19; N. 14.05; $[M]^+$ 299.0105. $C_7H_2F_9N_3$. Calculated (%): C, 28.68; H, 0.90; F, 56.50; N. 13.72; M = 299.0108. ^{19}F NMR ($(CD_3)_2CO$), δ: 52.0 (q, 2 F, F(8), J = 19.5 Hz); 82.7 (s, 3 F, F(9)); 108.4 (q, 3 F, F(7), J = 19.5 Hz); 109.4 (q, F, F(6), J = 19.9 Hz). ^1H NMR ($(CD_3)_2CO$), δ: 7.71 (m, NH_2). ^{13}C NMR (CD_2Cl_2), δ: 51.2 (q, C(5), $^2J_{C,F}$ = 22.9 Hz); 110.3 (tq, C(8), $^1J_{C,F}$ = 259.3 Hz, $^2J_{C,F}$ = 36.7 Hz, $^4J_{C,F}$ = 5.6 Hz); 118.0 (qt, C(9), $^1J_{C,F}$ = 286.5 Hz, $^2J_{C,F}$ = 35.3 Hz); 121.3 (q, C(7), $^1J_{C,F}$ = 270.9 Hz, $^3J_{C-F}$ = 6.7 Hz); 157.6 (t, C(4), $^2J_{C,F}$ = 23.0 Hz); 162.8 (t, C(2), $^4J_{C,F}$ = 21.6 Hz); 166.8 (d, C(6), $^1J_{C,F}$ = 254.7 Hz).

Reaction of perfluoro-5-azanon-4-ene (3) with guanidine hydrochloride (1). Compound **1** (8.68 g, 20 mmol) was added in small portions over 0.5 h with stirring and cooling to 0 °C (ice bath) to a solution of imine **3** (8.7 g, 20 mmol) and Et_3N (8.27 g, 80 mmol) in 70 mL of dry ether. The reaction mixture was kept at 0 °C for 3 h, then at 20 °C for 10 h, and poured into water. The solid product was filtered off. An additional portion of the product was extracted from the filtrate with CH_2Cl_2. The extract was dried with $MgSO_4$, and the solvent was removed. The residue was combined with the solid product and purified by column chromatography on silica gel in hexane—CH_2Cl_2 (4 : 1) to give two fractions.

Removal of the solvent from the first fraction gave **2-amino-4,6-bis(heptafluoropropyl)-1,3,5-triazine** (**5**) (5.2 g, 60%), b.p. 150—152 °C (0.8 Torr). IR, λ/cm^{-1}: 1200—1235 (C—F); 1338, 1404 (C—N); 1755 (C=N); 3418 and 3534 (NH_2). UV (EtOH), λ_{max}/nm (ε): 231 (7700), 295 (5600), 334 (5100). MS, *m/z* (I_{rel} (%)): 432 $[M]^+$ (51.04), 413 $[M - F]^+$ (29.10), 363 $[M - CF_3]^+$ (0.72), 313 $[M - C_2F_5]^+$ (56.31), 263 $[M - C_3F_7]^+$ (11.79), 169 $[C_3F_7]^+$ (30.51), 119 $[C_2F_5]^+$ (14.38), 100 $[CF_2{=}CF_2]^+$ (10.64), 69 $[CF_3]^+$ (57.15), 44 (100), 42 $[H_2NCN]^+$ (11.04). Found, *m/z*: 432.0054 $[M]^+$. $C_9H_2F_{14}N_4$. Calculated: 432.0056. ^{19}F NMR ($(CD_3)_2CO$), δ: 44.6 (s, 4 F, F(8), F(11)); 47.6 (q, 4 F, F(7), F(10), J = 9.5 Hz); 82.0 (t, 6 F, F(9), F(12), J = 9.5 Hz). ^1H NMR ($(CD_3)_2CO$), δ: 8.71 (d, NH_2). ^{13}C NMR (CD_2Cl_2), δ: 108.3 (th, C(8), C(11), $^1J_{C,F}$ = 266.3 Hz, $^2J_{C,F}$ = 37.7 Hz); 108.6 (tt, C(7), C(10), $^1J_{C,F}$ = 266.5 Hz, $^2J_{C,F}$ = 31.3 Hz); 120.3 (qt, C(9), C(12), $^1J_{C,F}$ = 287.5 Hz, $^2J_{C,F}$ = 33.7 Hz); 166.1 (t, C(4), C(6), $^2J_{C,F}$ = 26.6 Hz); 172.1 (C(2)).

Removal of the solvent from the second fraction (see the preceding experiment) and subsequent recrystallization from CH_2Cl_2 gave **2,4,6,8-tetrakis(heptafluoropropyl)-9a-hydroxy-[1,3,5]triazino[1,2-*a*][1,3,5]triazine** (**6**) (1.2 g, 15%), m.p. 104—105 °C. UV (EtOH), λ_{max}/nm (ε): 235 (1240), 290 (9500), 336 (5100). MS, m/z (I_{rel} (%)): 823 $[M]^+$ (33.16), 804 $[M - F]^+$ (54.79), 754 $[M - CF_3]^+$ (1.02), 704 $[M - C_2F_5]^+$ (1.81), 654 $[M - C_3F_7]^+$ (100), 626 (14.64) 169 $[C_3F_7]^+$ (99.39), 119 $[C_2F_5]^+$ (5.45), 100 $[CF_2{=}CF_2]^+$ (2.75), 69 $[CF_3]^+$ (45.47). Found (%): C, 24.79; H, 0.12; F, 64.64; N, 8.51. Calculated (%): C, 24.57; H, 0.09; F, 64.23; N, 8.26. $C_{17}HF_{28}N_5O$. ^{19}F NMR ($(CD_3)_2CO$), δ: 37.1 (s, 8 F, F(12), F(15), F(18), F(21)); 45.6 (qt, 8 F, F(11), F(14), F(17), F(20), J_{F-F} = 9.5 Hz); 82.6 (t, 12 F, F(13), F(16), F(19), F(22), J_{F-F} = 9.5 Hz). ^{13}C NMR (CD_2Cl_2), δ: 104.9 (tdt, C(12), C(15), C(18), C(21), $^1J_{C,F}$ = 266.2 Hz, $^2J_{C,F}$ = 32.2 Hz); 107.9 (tt, C(11), C(14), C(17), C(20), $^1J_{C,F}$ = 266.1 Hz, $^2J_{C,F}$ = 32.3 Hz); 114.1 (qt, C(13), C(16), C(19), C(22), $^1J_{C,F}$ = 287.2 Hz, $^2J_{C,F}$ = 33.6 Hz); 159.1 (t, C(2), C(6), C(7), C(9), $^2J_{C,F}$ = 26.3 Hz); 166.7 (C(4)).

X-ray diffraction analysis of compound 4 was performed on a Bruker P4 diffractometer with the use of single crystals grown by slowly evaporating methylene chloride from a solution of compound **4** at ~20 °C. The crystals of **4** are monoclinic: a = 8.470(2) Å, b = 22.536(5) Å, c = 5.319(1) Å, β = 105.64(2)°, V = 977.7(4) Å^3, space group $P2_1/c$, Z = 4, $C_7H_2F_9N_3$, μ = 0.247 mm^{-1}, d_{calc} = 2.032 g cm^{-3}, Mo-Kα, λ = 0.71073 Å. The crystal size is 0.2×0.43×0.8 mm. The intensities of 1685 independent reflections $2\theta < 50°$ were measured in the $\theta/2\theta$ scan mode. The structure was solved by the direct method with the use of the SHELXS-97 program. The parameters were refined by the least-squares method in the full-matrix anisotropic (isotropic for H atoms) approximation using the SHELXS-97 program. The final residuals are wR_2 = 0.1955, S = 1.042 (R_1 = 0.0638 for 1221 $F_0 > 4\sigma$).

The coordinates and equivalent isotropic parameters of the non-hydrogen atoms in structure **3** have been deposited with the Cambridge Crystallographic Database.

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