Russian Chemical Bulletin, International Edition, Vol. 49, No. 7, July, 2000

Synthesis and X-ray diffraction studies of 3-cyano-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidine derivatives

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Reactions of 2-chloro-1-cyano-2-trifluoromethylethylenes with 2-aminopyridines were studied. According to the data of NMR spectroscopy and X-ray diffraction analysis, the first stage of the reaction involves alkenylation of the exocyclic nitrogen atom of 2-aminopyridines followed by formation of pyrido[1,2-*a*]pyrimidines.

Key words: 2-chloro-1-cyano-2-trifluoromethylethylenes, 2-aminopyridines, pyrido[1,2-*a*]pyrimidines, intramolecular cyclization, X-ray diffraction analysis, molecular and crystal structures.

The intense progress in the chemistry and pharmacology of pyrido[1,2-*a*]pyrimidines revealed a broad spectrum of biological activities of this class of compounds.[1] Generally, the pyridopyrimidine ring is constructed by condensation based on the amidine fragment of 2-aminopyridine or its derivatives with various acylating and alkylating agents. In this connection, it was of interest to study the behavior of 2-chloro-1-cyano-2-trifluoromethylethylenes **1** and **2** in these reactions. The reactions of these compounds with amidines afforded pyrimidine derivatives.[2]

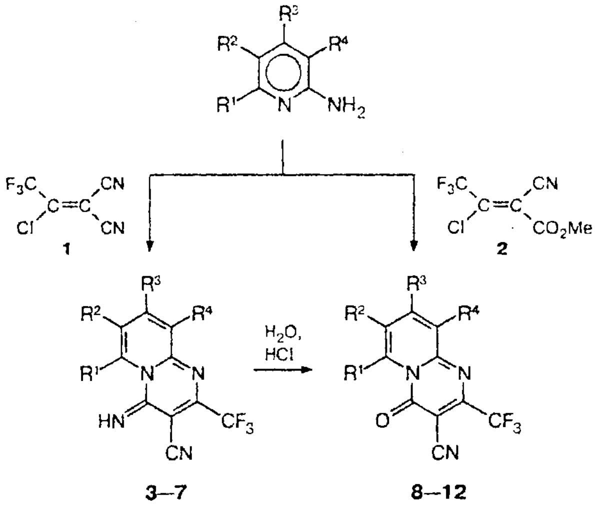
We demonstrated that the reactions of 2-chloro-1,1-dicyano-2-trifluoromethylethylene (**1**) with 2-aminopyridine and 2-aminopicolines in chloroform at room temperature afforded 3-cyano-4-imino-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidines **3—7** in 51—84% yields. An excess of 2-aminopyridine (procedure **A**) or triethylamine (procedure **B**) can be used to trap hydrogen chloride that formed in the course of the reaction (see the Experimental section).

Under analogous conditions, the reactions of 2-aminopyridine and 2-aminopicolines with 2-chloro-1-cyano-1-methoxycarbonyl-2-trifluoromethylethylene (**2**) afforded 3-cyano-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **8—12** in 23—53% yields.

Apparently, the reactions proceeded through alkenylation of the amino group of aminopyridine with 2-chloroethylene followed by intramolecular cyclization. In the case of alkene **2**, cyclization proceeded with the participation of the methoxycarbonyl fragment rather than of the nitrile group, which was confirmed by acid hydrolysis of the imino groups of compounds **3—7** to form pyridopyrimidines **8—12** (Scheme 1).

The structures of the resulting compounds were confirmed by the data of ^{1}H and ^{19}F NMR and IR spectroscopy and elemental analysis.

Scheme 1



$R^1 = R^2 = R^3 = R^4 = H$ (**3**, **8**)
$R^1 = R^2 = R^4 = H$, $R^3 = Me$ (**4**, **9**)
$R^1 = Me$, $R^2 = R^3 = R^4 = H$ (**5**, **10**)
$R^1 = R^3 = R^4 = H$, $R^2 = Me$ (**6**, **11**)
$R^1 = R^2 = R^3 = H$, $R^4 = Me$ (**7**, **12**)

The structure of compound **6** was unambiguously established by X-ray diffraction study (the overall view of the molecule is shown in Fig. 1). There are four symmetrically independent molecules per asymmetric unit cell. The geometric parameters of the independent molecules have very close values (Table 1). All molecules are planar: the deviations of the atoms from the mean planes of the molecules are in the range of 0.019—0.032 Å (the average value is 0.025 Å). The

Published in *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 7, pp. 1261—1264, July, 2000.

Table 1. Principal bond lengths (*d*) in independent molecules I—IV of compound **6**

Bond	*d*/Å			
	I	II	III	IV
N(1)—C(2)	1.332(8)	1.331(8)	1.329(8)	1.319(8)
N(1)—C(10)	1.355(8)	1.361(8)	1.353(8)	1.359(8)
N(5)—C(10)	1.369(7)	1.366(8)	1.370(8)	1.367(8)
N(5)—C(6)	1.380(8)	1.369(7)	1.386(8)	1.378(8)
N(5)—C(4)	1.444(8)	1.453(8)	1.442(8)	1.450(8)
N(13)—C(12)	1.149(8)	1.157(8)	1.153(8)	1.154(8)
N(14)—C(4)	1.253(8)	1.267(8)	1.268(8)	1.270(8)
C(2)—C(3)	1.373(9)	1.366(8)	1.380(8)	1.374(8)
C(2)—C(11)	1.493(10)	1.502(9)	1.495(9)	1.522(9)
C(3)—C(12)	1.428(11)	1.430(10)	1.422(10)	1.418(10)
C(3)—C(4)	1.450(9)	1.449(9)	1.441(9)	1.458(9)
C(6)—C(7)	1.348(9)	1.348(9)	1.356(9)	1.344(9)
C(7)—C(8)	1.426(9)	1.407(9)	1.425(9)	1.404(9)
C(7)—C(15)	1.505(10)	1.509(10)	1.496(10)	1.502(10)
C(8)—C(9)	1.341(9)	1.344(10)	1.359(10)	1.350(10)
C(9)—C(10)	1.406(9)	1.396(9)	1.407(9)	1.405(9)

folding angles along the N(5)—C(10) bond line are no more than 2.0°—3.6° (the average value is 2.8°). The bond lengths and bond angles have standard values[3] (see Table 1). The differences in the corresponding bond lengths and bond angles in the independent molecules are no greater than the experimental error and are apparently attributable to the different environment in the crystal. This is particularly true of the C—F bonds, whose lengths are in the range of 1.245(8)—1.360(8) Å. The N(1)—C(2) and N(1)—C(10) bond lengths are equalized. Their average values are 1.328(8) and 1.357(8) Å, respectively, which is, apparently, indicative of the electron density delocalization. The C(3)—C(12)—N(13) angle at the carbon atom of the nitrile group varies from 176.6(7)° to 177.7(7)° (the average value is 176.9(7)°).

The distinguishing feature of the crystal packing of compound **6** is the large number of crystallographically independent molecules ($Z = 4$). The arrangement of the independent molecules in the unit cell is shown in Fig. 2 (the projection onto the *XY0* plane). The calculations and analysis of the positions of the molecules demonstrated that the crystallographically independent molecules in pairs are related to each other by a set of pseudosymmetry operations (Table 2) involving a system of pseudocenters of symmetry and two translations *t*, which form an angle of 120.6°. All pseudocenters lie in the plane described by the equation $-0.536x + 0.737y + 21.928z = 2.774$, which is accurate to 0.005 Å. This plane forms an angle of 3.8° with the *XY0* plane and intersects the *0Z* axis at the point 2.774 Å. The molecules are linked in stable local fragments (layers) through the weak N(14)—H(14)...N(13) intermolecular hydrogen bonds formed by pairs of molecules I and IV and molecules II and III with the following parameters: N(14)...N(13C), 3.085(8) Å; N(14)—H(14), 0.84(5) Å; H(14)...N(13C), 2.31(5) Å; N(14)—H(14)...N(13C), 156(3)°; and N(14B)...N(13A), 3.067(8) Å;

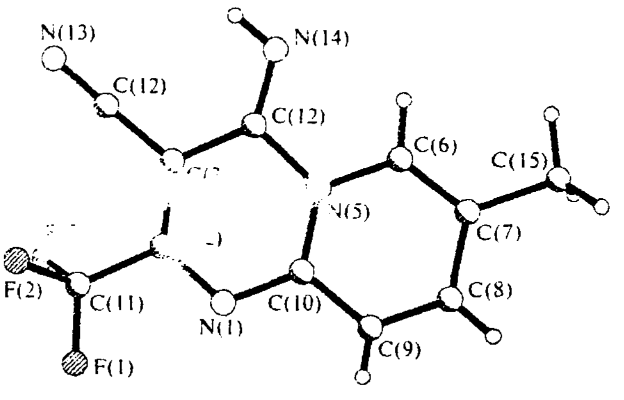


Fig. 1. Overall view of molecule **6**.

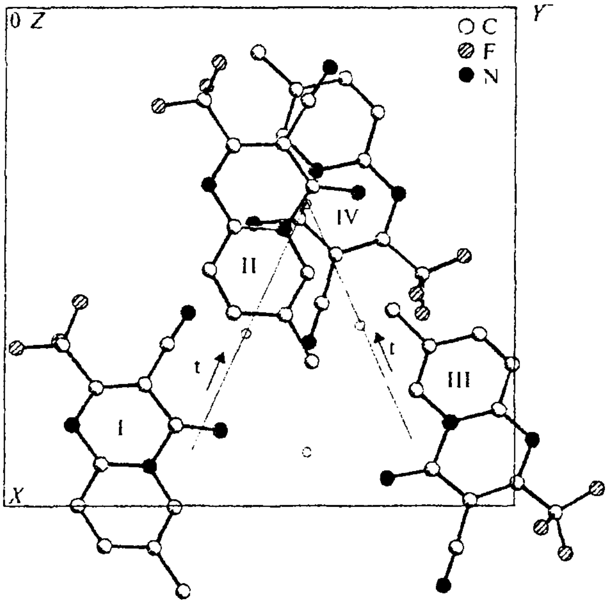


Fig. 2. Arrangement of the independent molecules in the unit cell (a projection onto the *XY0* plane).

Table 2. Pseudosymmetry operations relating the crystallographically independent molecules I—IV in compound **6**

Molecules	Pseudoelement	Position of the pseudoelement		
		x/*a*	*y*/*b*	*z*/*c*
I—II	1 [a]	0.379	0.583	0.116
I—IV	1 [a]	0.62	0.449	0.126
II—III	1 [a]	0.628	0.716	0.117
III—IV	1 [a]	0.868	0.582	0.128
I—III	8.02 [b]			
II—IV	7.69 [b]			

[a] Inversion center. [b] *t*/Å is the translation.

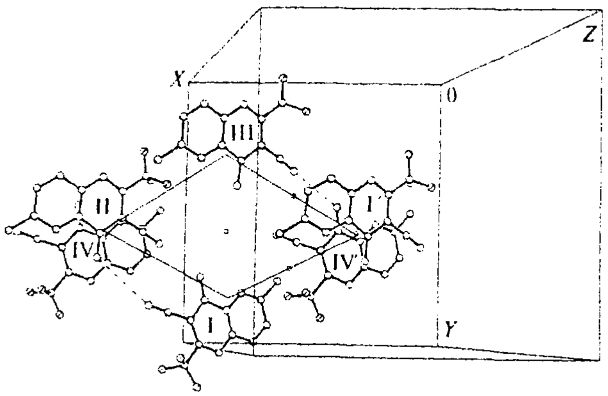


Fig. 3. Pseudohexagonal unit cell in the crystal.

N(14B)—H(14B), 0.93(5) Å; H(14B)...N(13A), 2.19(5) Å; N(14B)—H(14B)...N(13A), 154(3)°. A two-dimensional pseudohexagonal unit cell can be distinguished in these layers (Fig. 3). In the real crystal, the crystal structure is constructed as a superposition of these layers. However, this superposition occurs with a shift preventing the formation of the crystallographic hexagonal symmetry.

Experimental

The ^{1}H and ^{19}F NMR spectra were recorded on Bruker AMX-400 and Bruker WP-200 SY spectrometers operating at 400.13 and 188.31 MHz, respectively.

The ^{1}H chemical shifts were measured relative to the residual signal of the deuterated solvent and were referenced to Me_4Si. The ^{19}F chemical shifts were measured relative to CF_3COOH (the external standard). The R_f values of the resulting compounds are given for Silufol UV 254 plates (Kavalier) in the 1 : 1 and 3 : 1 CCl_4—acetone systems. The compounds were detected from UV absorption. The IR spectra $(\nu/\text{cm}^{-})^{1}$ were measured on a UR-20 spectrometer. Crystals of compound **6** ($C_{11}H_7F_3N_4$) are monoclinic, at −120 °C, a = 13.954(5), b = 14.050(4), c = 22.332(7) Å, β = 102.70(3)°, V = 4271(3) Å^3, d_{calc} = 1.569 g cm^{-3}, Z' = 4, space group $P2_1/c$. The unit cell parameters and intensities of 5301 independent reflections were measured on an automated four-circle Siemens P3/PC diffractometer (λ-Mo-Kα radiation, graphite monochromator, θ/2θ scanning technique, $\theta_{\max}$ = 26°). The structure was solved by the direct method, which revealed all nonhydrogen atoms, and refined by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms. All hydrogen atoms (except for the hydrogen atom at the N(1) atom) were located from difference Fourier syntheses and refined isotropically. The final values of the R factors were as follows: R = 0.075 based on 3201 reflections with $I > 2\sigma(I)$ and R_w = 0.215 based on 5251 reflections. All calculations were carried out using the SHELXTL PLUS program package (PC version). The atomic coordinates and isotropic equivalent (isotropic for the H atoms) thermal parameters were deposited with the Cambridge Structural Database.

Reactions of 2-chloro-1-cyano-2-trifluoromethylethylenes with 2-aminopyridines. ***A.*** A solution of 2-chloro-1-cyano-2-trifluoromethylethylene (**1** or **2**: 0.01 mol) in chloroform (10 mL) was added dropwise with stirring to a solution of the corresponding 2-aminopyridine (0.02 mol) in chloroform (50 mL) at 0—20 °C. The reaction mixture was stirred at 20 °C for 2 h. The solvent was removed *in vacuo* and the residue was washed with water, dried over P_2O_5 *in vacuo*, and recrystallized from ethanol.

B. A solution of 2-chloro-1-cyano-2-trifluoromethylethylene (**1** or **2**; 0.01 mol) in chloroform (10 mL) was added dropwise with stirring to a solution of the corresponding 2-aminopyridine (0.01 mol) and triethylamine (0.01 mol) in chloroform (50 mL) at 0—20 °C. The reaction mixture was stirred at 20 °C for 2 h. The solvent was removed *in vacuo* and the residue was washed with water, dried over P_2O_5 *in vacuo*, and recrystallized from ethanol.

Hydrolysis of iminopyridopyrimidines 3—7. Water (5 mL) and concentrated hydrochloric acid (1 mL) were added to a solution of the corresponding iminopyridopyrimidine **3—7** (1 mmol) in ethanol (15 mL). The reaction mixture was heated to boiling and refluxed for 3—5 h. The course of the reaction was monitored by TLC. The solvent was removed *in vacuo* and the residue was recrystallized from ethanol. The identity of the resulting products **8—12** was confirmed by IR and ^{1}H and ^{19}F NMR spectroscopy.

3-Cyano-4-imino-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]-pyrimidine (3). The yield was 84% (procedure *A*), m.p. 244—245 °C, R_f 0.60 (1 : 1). Found (%): C, 50.30; H, 2.13; F, 23.90; N, 23.63. $C_{10}H_5F_3N_4$. Calculated (%): C, 50.42; H, 2.10; F,

Table 3. ^{1}H and ^{19}F NMR spectra (δ) of compounds **3—12**

Compound	^{1}H NMR							^{19}F NMR
	δH(6)	δH(7)	δH(8)	δH(9)	δMe	δNH	J_{HH}/Hz	δCF_3
3	9.50 d^a	7.65 m	8.32 m	7.78 d	—	8.22 br.s	$J_{6,7}$ = 7.2; $J_{8,9}$ = 9.6	9.78 s^a
4	9.37 d^a	7.51 dd	—	7.60 br.s	2.65 s	8.08 br.s	$J_{6,7}$ = 7.2; $J_{7,9}$ = 2.0	9.75 s^a
5	—	7.06 d^b	8.00 t	7.14 d	2.50 s	—	$J_{7,8}$ = $J_{8,9}$ = 9.0	8.40 s^c
6	9.27 s^d	—	7.90 d	7.63 d	2.51 s	7.95 br.s	$J_{8,9}$ = 9.5	8.50 s^c
7	9.36 d^d	7.27 t	7.88 d	—	2.59 s	8.00 br.s	$J_{6,7}$ = $J_{7,8}$ = 9.0	8.41 s^c
8	9.32 d^a	7.89 t	8.53 dd	8.11 d	—	—	$J_{6,7}$ = $J_{7,8}$ = 9.0; $J_{8,9}$ = 9.5	10.13 s^a
9	9.19 d^a	7.74 dd	—	7.93 br.s	2.72 s	—	$J_{6,7}$ = 7.3; $J_{7,9}$ = 2.0	10.00 s^a
10	—	7.15 d^d	7.93 t	7.70 d	3.15 s	—	$J_{7,8}$ = $J_{8,9}$ = 9.3	8.48 s^c
11	9.04 s^d	—	8.08 d	7.91 d	2.56 s	—	$J_{8,9}$ = 9.7	9.00 s^c
12	9.18 d^d	7.51 t	8.07 d	—	2.71 s	—	$J_{6,7}$ = $J_{7,8}$ = 9.0	8.85 s^c

[a] Acetone-d_6. [b] DMSO-d_6. [c] Chloroform (stabilization relative to external D_2O). [d] Dichloromethane-d_2.

23.95; N, 23.53. IR, ν/cm^{-1}: 3310 (NH); 2230 (CN); 1655, 1635, 1575, 1500.

3-Cyano-4-imino-8-methyl-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidine (4). The yield was 73% (procedure *A*), m.p. 187—188 °C, R_f 0.49 (3 : 1). Found (%): C, 52.32; H, 2.80; F, 22.64; N, 22.23. $C_{11}H_7F_3N_4$. Calculated (%): C, 52.38; H, 2.78; F, 22.62; N, 22.22. IR, ν/cm^{-1}: 3300 (NH); 2230 (CN); 1650, 1580, 1500.

3-Cyano-4-imino-6-methyl-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidine (5). The yield was 56% (procedure *B*), m.p. 157—158 °C, R_f 0.51 (3 : 1). Found (%): C, 52.30; H, 2.84; F, 22.68; N, 22.19. $C_{11}H_7F_3N_4$. Calculated (%): C, 52.38; H, 2.78; F, 22.62; N, 22.22.

3-Cyano-4-imino-7-methyl-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidine (6). The yield was 56% (procedure *B*), m.p. 167—168 °C, R_f 0.49 (3 : 1). Found (%): C, 52.29; H, 2.81; F, 22.66; N, 22.26. $C_{11}H_7F_3N_4$. Calculated (%): C, 52.38; H, 2.78; F, 22.62; N, 22.22.

3-Cyano-4-imino-9-methyl-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidine (7). The yield was 51% (procedure *B*), m.p. 187—188 °C, R_f 0.44 (3 : 1). Found (%): C, 52.33; H, 2.80; F, 22.60; N, 22.27. $C_{11}H_7F_3N_4$. Calculated (%): C, 52.38; H, 2.78; F, 22.62; N, 22.22.

3-Cyano-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (8). The yield was 53% (procedure *A*), m.p. 213—214 °C, R_f 0.55 (1 : 1). Found (%): C, 50.32; H, 1.70; F, 22.84; N, 17.60. $C_{10}H_4F_3N_3O$. Calculated (%): C, 50.21; H, 1.67; F, 22.85; N, 17.57.

3-Cyano-8-methyl-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (9). The yield was 65% (procedure *A*), m.p. 150—152 °C, R_f 0.33 (3 : 1). Found (%): C, 52.02; H, 2.40; F, 22.54; N, 16.66. $C_{11}H_6F_3N_3O$. Calculated (%): C, 52.17; H, 2.37; F, 22.53; N, 16.60. IR, ν/cm^{-1}: 2215 (CN); 2205, 1710 (C=O); 1660 (broad).

3-Cyano-6-methyl-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (10). The yield was 38% (procedure *B*), m.p. 173—174 °C, R_f 0.41 (3 : 1). Found (%): C, 52.09; H, 2.38; F, 22.57; N, 16.62. $C_{11}H_6F_3N_3O$. Calculated (%): C, 52.17; H, 2.37; F, 22.53; N, 16.60.

3-Cyano-7-methyl-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (11). The yield was 30% (procedure *B*), m.p. 220—221 °C, R_f 0.49 (3 : 1). Found (%): C, 52.12; H, 2.38; F, 22.52; N, 16.63. $C_{11}H_6F_3N_3O$. Calculated (%): C, 52.17; H, 2.37; F, 22.53; N, 16.60.

3-Cyano-9-methyl-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (12). The yield was 23% (procedure *B*), m.p. 177—178 °C, R_f 0.52 (3 : 1). Found (%): C, 52.10; H, 2.36; F, 22.57; N, 16.68. $C_{11}H_6F_3N_3O$. Calculated (%): C, 52.17; H, 2.37; F, 22.53; N, 16.60

The NMR spectra of compounds **3—12** are given in Table 3.

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Received December 27, 1999;
in revised form March 29, 2000