Synthesis of (7-polyfluoroalkyl)pyrazolo[1,5-*a*]pyrimidines based on lithium fluorine-containing β-diketonates

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The reactions of Li enolates of fluorine-containing β-diketones with 3-aminopyrazoles afforded (7-polyfluoroalkyl)pyrazolo[1,5-*a*]pyrimidines. The structure of 3-bromo-2-methyl-5-phenyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine was established by X-ray diffraction analysis.

Key words: Li enolates of fluorine-containing β-diketones, 3-aminopyrazoles, (7-fluoroalkyl)pyrazolo[1,5-*a*]pyrimidines.

In recent years, the use of fluoroalkyl-containing synthons for insertion of fluorine-containing fragments into organic, including heterocyclic, compounds has attracted growing interest.

Recently,[1] we have proposed new fluorine-containing synthons, *viz.*, Li enolates of fluorinated β-diketones **1**. These compounds, which can readily be prepared according to the version of the Claisen condensation developed by us, serve as intermediates in the synthesis of the corresponding β-diketones and β-hydroxy ketones.[2—4] Enolates **1** can be used as synthetic equivalents of fluorine-containing β-diketones for the preparation of fluoroalkyl-substituted pyrazoles, 5-hydroxy-4,5-dihydroisoxazoles, 2-aminopyrimidines, 1,5-benzodiazepines, 1,5-naphthodiazepines, pyrimidinethiols, and triazolopyridazines.[1]

In the present study, we demonstrated that enolates **1** are convenient synthons for the preparation of fluoroalkyl-containing fused azaheterocycles with the bridgehead N atom, in particular, for the synthesis of pyrazolo[1,5-*a*]pyrimidines.*

* Nonfluorinated 3-substituted 5,7-dialkylpyrazolo[1,5-*a*]pyrimidines are selective inhibitors *in vitro* of cyclic adenosine monophosphate phosphodiesterase.[5] In the cited study, fluorine-containing compounds of this series, *viz.*, 5,7-bis(trifluoromethyl)- and 3-fluoro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidines, were synthesized and their antidepressant properties were examined; however, their spectroscopic characteristics were lacking.

Results and Discussion

Enolates **1a—c** readily react with equimolar amounts of 3-aminopyrazoles **2a—d** in AcOH at ~40 °C or with boiling (Scheme 1). The synthetic procedure is simple and the target products **3a—f** can be obtained in 52—87% yields depending on the purity of the starting enolate. This approach can be applied to the synthesis of pyrazolo[1,5-*a*]pyrimidines whose pyrazole ring contains functional groups capable of undergoing further transformations.

In all cases, only one of the possible regioisomers was obtained as evidenced by the presence of the only set of resonance signals in the ^{1}H, ^{19}F, and ^{13}C NMR spectra of the resulting pyrazolo[1,5-*a*]pyrimidines.

The reactions of enolates of unsymmetrical β-dicarbonyl compounds **1** with aminopyrazoles can afford two different intermediates (**A** or **B**) followed by their condensation to form pyrazolopyrimidines **3** or **4**. It is more likely that the formation of isomer **3** proceeds *via* β-aminovinyl ketones **A** as evidenced by the results of our previous studies[1,6] on the structures of the products obtained in reactions of unsymmetrical polyfluorinated β-diketones and their Li enolates with amines.

This suggestion was confirmed by the results of X-ray diffraction analysis of pyrazolopyrimidine **3c** (Fig. 1). The bond lengths and bond angles in compound **3c** are given in Tables 1 and 2, respectively.

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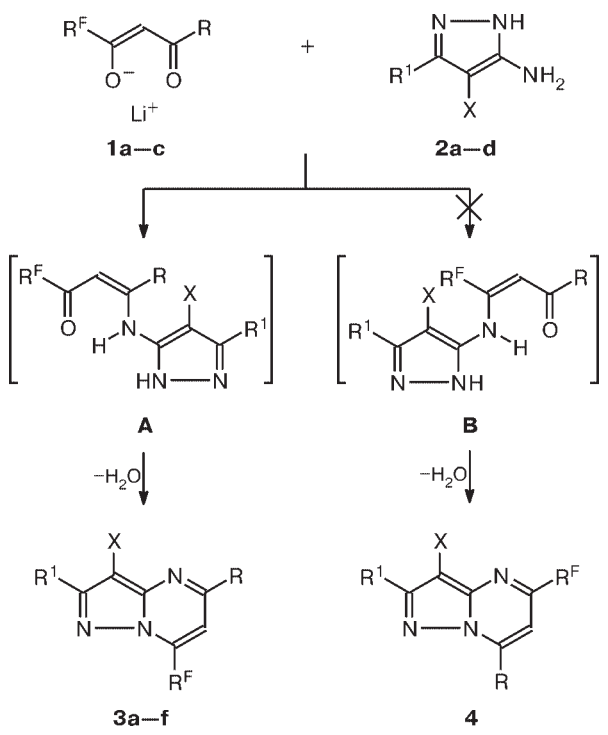
Scheme 1



1: R^F = CF_3 (**a**), HCF_2 (**b**), C_4F_9 (**c**); R = Ph (**a,b**), Me (**c**)
2: R^1 = H (**a,d**), Me (**b,c**); X = H (**a,b**), Br (**c**), COOEt (**d**)
3: R^F = CF_3 (**a—d**), HCF_2 (**e**), C_4F_9 (**f**); R = Ph (**a—e**), Me (**f**); R^1 = H (**a,d,e**), Me (**b,c,f**); X = H (**a,b,f**), Br (**c**), COOEt (**d,e**)

The bicyclic fragment is virtually planar (to within ±0.079(4) Å), which is favorable for the formation of the common π-conjugated system of the pyrazole and pyrimidine rings. This conjugated system is characteristic of all the compounds of this type reported in the literature.[7—10] (Four structures containing the same bicyclic pyrazolopyrimidine framework[7—10] were found in the Cambridge Structural Database[11]). Comparison of the bond lengths with the statistical mean values for pyrazoles and pyrimidines[12] confirms the electron density redistribution within the bicyclic fragment. Thus the C(6)—C(7) and C(5)—N(4) bond lengths in the pyrimidine ring (1.341(5) and 1.317(4) Å, respectively) are smaller than the statistical mean lengths (1.387(18) and 1.339(15) Å, respectively) of the corresponding bonds in pyrimidines.[12] However, it should be noted that the C(6)—C(7) bond length is also smaller than the known bond lengths for pyrazolopyrimidines, which range from 1.355[10] to 1.394 Å.[7] The C(6)—C(5) and C(7)—N(7a) bond lengths in the pyrimidine ring (1.437(7) and 1.368(4) Å, respectively) are, on the contrary, larger than the statistical mean values (1.387(18) and 1.339(15) Å, respectively). In the pyrazole ring, the N(1)—C(2) and C(3a)—C(3) bond

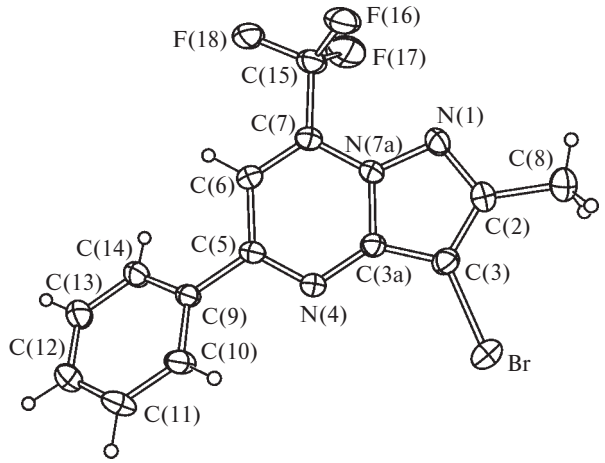


Fig. 1. Molecular structure of 3-bromo-2-methyl-5-phenyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**3c**).

Table 1. Bond lengths (*d*) in the structure of **3c**

Bond	*d*/Å	Bond	*d*/Å
Br—C(3)	1.864(3)	C(7)—N(7a)	1.361(4)
N(1)—C(2)	1.343(5)	C(7)—C(15)	1.496(5)
N(1)—N(7a)	1.352(4)	C(9)—C(14)	1.376(5)
C(2)—C(3)	1.389(5)	C(9)—C(10)	1.386(5)
C(2)—C(8)	1.479(6)	C(10)—C(11)	1.370(5)
C(3)—C(3a)	1.376(5)	C(11)—C(12)	1.368(6)
C(3a)—N(4)	1.347(4)	C(12)—C(13)	1.372(6)
C(3a)—N(7a)	1.389(4)	C(13)—C(14)	1.383(5)
N(4)—C(5)	1.317(4)	C(15)—F(17)	1.314(5)
C(5)—C(6)	1.437(4)	C(15)—F(18)	1.323(4)
C(5)—C(9)	1.475(4)	C(15)—F(16)	1.328(5)
C(6)—C(7)	1.341(5)		

Table 2. Selected bond angles (ω) in the structure of **3c**

Angle	ω/deg
C(2)—N(1)—N(7a)	104.4(3)
N(1)—C(2)—C(3)	111.1(3)
C(3)—C(2)—C(8)	128.6(4)
C(3a)—C(3)—C(2)	107.4(3)
C(2)—C(3)—Br	126.4(3)
N(4)—C(3a)—N(7a)	122.2(3)
C(3)—C(3a)—N(7a)	104.1(3)
C(5)—N(4)—C(3a)	118.1(3)
N(4)—C(5)—C(6)	121.3(3)
C(6)—C(5)—C(9)	120.8(3)
C(7)—C(6)—C(5)	119.8(3)
C(6)—C(7)—N(7a)	118.6(3)
C(6)—C(7)—C(15)	124.3(3)
N(1)—N(7a)—C(3a)	113.0(3)
C(7)—N(7a)—C(3a)	120.0(3)

lengths (1.343(5) and 1.376(5) Å, respectively) are larger (1.329(14) and 1.341(12) Å for pyrazoles[12]), whereas the N(7a)—N(1) and C(2)—C(3) bond lengths (1.352(4) and 1.389(5) Å, respectively) are smaller than the statistical mean values for pyrazoles (1.366(19) and 1.410(16) Å, respectively).[12] The N(7a)—C(3a) bond (1.389(4) Å) is elongated as compared to the analogous bonds in pyrazoles and pyrimidines (1.357(12) and 1.333(13) Å, respectively),[12] but this bond length is consistent with the data for pyrazolopyrimidines (from 1.390[7] to 1.397 Å)[10].

The angle between the planes of the bicyclic fragment and the phenyl ring is 29.3(2)°. The intermolecular Br...Br distance (3.659(1) Å) is smaller than the sum of the van der Waals radii (3.9 Å for Br[13]).

The spectroscopic characteristics of compound **3c** correspond to those for CF_3-containing pyrazolo[1,5-*a*]pyrimidines.* For the latter compounds, a procedure has been recently proposed[14,15] for the identification of the 5-R- and 7-R-regioisomers based on the chemical shifts of the protons of the Me groups in ^{1}H NMR spectra and of the C atoms of the alkyl groups, the C(5) and C(7) atoms of the pyrimidine ring, and the *ipso*-C atoms of the Ph group in ^{13}C NMR spectra.

The ^{1}H and ^{13}C NMR spectra of compounds **3a,b,d—f** were interpreted by comparing them with the spectra of compound **3c** and the published data.[14,15] The assignment of the protonated C atoms in compound **3e** was made using the 2D HETCOR experiment based on correlations through the spin-spin coupling constants $^1J_{C,H}$.

The signals for the C(7) atoms in compounds **3a,c,d** occur as characteristic quartets at δ 134—135 with the spin-spin coupling constants $^2J_{C,F} \approx 37$—38 Hz. The signal for the C(7) atom in compound **3e** occurs as a triplet at δ 139.7 with the spin-spin coupling constant $^2J_{C,F} \approx 28$ Hz.

The ^{13}C NMR spectra of compounds **3a,c,d,e** also have signals for the C(5) (δ 155—159) and C_{ipso}(Ph) (δ 135—136) atoms.

The mass spectra of compounds **3a,c** have molecular ion peaks and fragmentation peaks $[M - F]^+$, $[M - CF_3]^+$, $[Ph]^+$ (*m/z* 77), and $[CF_3]^+$ (*m/z* 69). The mass spectra of the compounds under consideration have no peaks responsible for specific fragmentation of the fused azaheterocycle.

To summarize, Li enolates of fluorinated β-diketones **1**, like the corresponding β-diketones,[14,15] react with 3-aminopyrazoles to form only one of the possible regioisomers of pyrazolo[1,5-*a*]pyrimidines containing the fluoroalkyl substituent at position 7. However, enolates **1** are reagents of choice because they allow one to substantially simplify the synthetic procedure due to elimination of the necessity for purification and, in some cases, isolation of β-diketones.

* The compounds were prepared by cyclocondensation of substituted aminopyrazoles with 1,1,1-trifluoromethyl-containing β-diketones in AcOH or by fusion of the reagents.[14,15] However, the experimental details and the yields of the target products were not reported in the cited studies.

Experimental

The synthesis of enolates **1a—c** has been reported previously.[1] 3-Aminopyrazoles **2a—d** were prepared according to known procedures.[16—18] The course of the reactions was monitored by TLC on Silufol UV-254 plates ($CHCl_3$ and CCl_4 were used as eluents). The purities of the reaction products were checked by two-dimensional TLC. The compounds were visualized using aqueous solutions of $Cu(OAc)_2$ and $KMnO_4$.

The IR spectra were recorded on a Specord IR-75 spectrometer in thin layers (20 μm) for liquid samples and in Nujol mulls for solids.

The ^{1}H and ^{13}C NMR spectra were measured on a Bruker DRX-400 spectrometer (400 and 100 MHz) in $CDCl_3$ with Me_4Si as the internal standard. The ^{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.

The mass spectra (EI) were obtained on a MAT INCOS 50 spectrometer (the energy of ionizing electrons was 70 eV, direct inlet of the sample into the ion source).

5-Phenyl-7-trifluoromethylpyrazolo[1.5-*a*]pyrimidine (3a). A solution of enolate **1a** (1 g, 4.5 mmol) and 3-aminopyrazole (**2a**) (0.58 g, 4.5 mmol) in glacial AcOH (5 mL) was refluxed for 10 h and then the reaction mixture was poured onto ice. The precipitate that formed was filtered off, dried, and recrystallized from hexane. Compound **3a** was obtained in a yield of 0.96 g (85%), m.p. 105—106 °C. Found (%): C, 59.57; H, 3.11; F, 21.65; N, 15.93. $C_{13}H_8F_3N_3$. Calculated (%): C, 59.31; H, 3.04; F, 21.67; N, 15.97. IR, ν/cm^{-1}: 1550 (C=C); 1620 (C=N). ^{1}H NMR, δ: 6.87 (s, 1 H, H(3)); 7.62 (s, 1 H, H(6)); 7.52 and 8.09 (both m, 3 H + 2 H, Ph); 8.25 (s, 1 H, H(2)). ^{13}C NMR, δ: 98.35 (s, C(3)); 103.68 (q, C(6), $^3J_{C,F}$ = 4.4 Hz); 119.64 (q, CF_3, $^1J_{C,F}$ = 274.9 Hz); 127.20 (s, *o*-C); 129.07 (s, *m*-C); 131.01 (s, *p*-C); 134.36 (q, C(7), $^2J_{C,F}$ = 37.1 Hz); 133.44 (s, C_{ipso}); 146.27 (s, C(2)); 155.30 (s, C(5)); 149.69 (s, C(3a)). ^{19}F NMR, δ: 92.82 (CF_3). MS, *m/z*: 263 $[M]^+$.

2-Methyl-5-phenyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (3b). A solution of enolate **1a** (1 g, 4.5 mmol) and 3-amino-5-methylpyrazole (**2b**) (0.22 g, 4.5 mmol) in AcOH (5 mL) was kept at 40 °C for one day and then the reaction mixture was poured onto ice. The precipitate that formed was filtered off, dried, and recrystallized from hexane. Compound **3b** was obtained in a yield of 0.9 g (72%), m.p. 123—124 °C. Found (%): C, 60.63; H, 3.69; N, 15.45. $C_{14}H_{10}F_3N_3$. Calculated (%): C, 60.65; H, 3.61; N, 15.16. IR, ν/cm^{-1}: 1610 (C=N); 1545 (C=C). ^{1}H NMR, δ: 2.70 (s, 3 H, Me); 6.64 (s, 1 H, H(3)); 7.58 and 8.21 (both m, 3 H + 2 H, Ph); 7.79 (s, 1 H, H(6)).

3-Bromo-2-methyl-5-phenyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (3c). A solution of enolate **1a** (1 g, 4.5 mmol)

and 3-amino-4-bromo-5-methylpyrazole (**2c**) (0.80 g, 4.5 mmol) in AcOH (5 mL) was kept at 40 °C for one week. Then the solution was neutralized with $NaHCO_3$ and the product was extracted with $CHCl_3$. The extract was dried with $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from hexane. Compound **3c** was obtained in a yield of 1.3 g (87%), m.p. 178—180 °C. Found (%): C, 46.35; H, 2.53; F, 15.33; N, 11.30. $C_{14}H_9BrF_3N_3$. Calculated (%): C, 47.19; H, 2.53; F, 16.01; N, 11.80. IR, ν/cm^{-1}: 1545 (C=C); 1610 (C=N). ^{1}H NMR, δ: 2.57 (s, 3 H, Me); 7.53 and 8.14 (both m, 3 H + 2 H, Ph); 7.57 (s, 1 H, H(6)). ^{13}C NMR, δ: 13.52 (s, CH_3); 87.33 (s, C(3)); 103.57 (q, C(6), $^3J_{C,F}$ = 4.1 Hz); 119.41 (q, CF_3, $^1J_{C,F}$ = 274.7 Hz); 127.42 (s, *o*-C); 129.18 (s, *m*-C); 131.36 (s, *p*-C); 134.29 (q, C(7), $^2J_{C,F}$ = 37.2 Hz); 135.90 (s, C_{ipso}); 146.66 (s, C(2)); 155.88 (s, C(5)); 155.35 (s, C(3a)). MS, *m/z*: 356 $[M]^+$.

Ethyl 5-phenyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (3d). A solution of enolate **1a** (1 g, 4.5 mmol) and ethyl 3-aminopyrazole-4-carboxylate (**2d**) (0.7 g, 4.5 mmol) in AcOH (5 mL) was refluxed for 10 h and then the reaction mixture was poured onto ice. The precipitate that formed was filtered off and reprecipitated with hexane from $CHCl_3$. Compound **3d** was obtained in a yield of 0.78 g (52%), m.p. 129 °C. Found (%): C, 56.51; H, 3.87; N, 12.94. $C_{16}H_{12}F_3N_3O_2$. Calculated (%): C, 57.31; H, 3.58; N, 12.53. IR, ν/cm^{-1}: 1573 (C=C); 1635 (C=N); 1700 (C=O). ^{1}H NMR, δ: 1.47 (t, 3 H, Me, *J* = 7.2 Hz); 4.42 (q, 2 H, CH_2, *J* = 7.2 Hz); 7.26 and 7.56 (both m, 3 H + 2 H, Ph); 7.48 (s, 1 H, H(6)); 7.78 (s, 1 H, H(2)). ^{13}C NMR, δ: 14.37 (s, $OCH_2\underline{C}H_3$); 60.48 (s, $O\underline{C}H_2CH_3$); 104.38 (s, C(3)); 104.69 (q, C(6), $^3J_{C,F}$ = 4.1 Hz); 119.20 (q, CF_3, $^1J_{C,F}$ = 275.0 Hz); 127.67 (s, *o*-C); 129.16 (s, *m*-C); 131.93 (s, *p*-C); 135.10 (q, C(7), $^2J_{C,F}$ = 37.8 Hz); 135.33 (s, C_{ipso}); 148.52 (s, C(2)); 158.51 (s, C(5)); 148.50 (s, C(3a)); 161.98 (s, $\underline{C}O_2Et$). ^{19}F NMR, δ: 93.39 (CF_3).

Ethyl 7-difluoromethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (3e). A solution of enolate **1b** (1 g, 4.9 mmol) and ethyl 3-aminopyrazole-4-carboxylate (**2d**) (0.76 g, 4.9 mmol) in AcOH (5 mL) was refluxed for 10 h and then the reaction mixture was poured onto ice. The precipitate that formed was dried and reprecipitated with hexane from $CHCl_3$. Compound **3e** was obtained in a yield of 0.99 g (64%), m.p. 137 °C. Found (%): C, 59.21; H, 4.44; N, 13.18. $C_{16}H_{13}F_2N_3O_2$. Calculated (%): C, 60.56; H, 4.10; N, 13.24. IR, ν/cm^{-1}: 1560 (C=C); 1624 (C=N); 1710 (C=O). ^{1}H NMR, δ: 1.46 (t, 3 H, Me, *J* = 7.2 Hz); 4.49 (q, 2 H, CH_2, *J* = 7.2 Hz); 7.38 (t, 1 H, HCF_2, *J* = 52.4 Hz); 7.54 and 8.24 (both m, 3 H + 2 H, Ph); 7.72 (s, 1 H, H(6)); 8.59 (s, 1 H, H(2)). ^{13}C NMR, δ: 14.41 (s, $OCH_2\underline{C}H_3$); 60.40 (s, $O\underline{C}H_2CH_3$); 103.18 (t, C(6), $^3J_{C,F}$ = 4.9 Hz); 104.04 (s, C(3)); 107.96 (t, HCF_2, $^1J_{C,F}$ = 241.6 Hz); 127.71 (s, *o*-C); 129.09 (s, *m*-C); 131.69 (s, *p*-C); 135.78 (s, C_{ipso}); 139.67 (t, C(7), $^2J_{C,F}$ = 28.1 Hz); 147.93 (s, C(3a)); 148.24 (s, C(2)); 159.07 (s, C(5)); 162.22 (s, $\underline{C}O_2Et$). ^{19}F NMR, δ: 37.36 (d, HCF_2, $^2J_{F,H}$ = 52.4 Hz).

2,5-Dimethyl-7-nonafluorobutylpyrazolo[1,5-*a*]pyrimidine (3f). A solution of enolate **1c** (1 g, 3.2 mmol) and 3-amino-5-methylpyrazole (**2b**) (0.31 g, 3.2 mmol) in AcOH (5 mL) was refluxed for 6 h, poured onto ice, and extracted with ether. The solvent was evaporated and the residue was chromatographed on a column with silica gel L 100/250 ($CHCl_3$ as the eluent). The solvent was evaporated and yellow compound **3f** was obtained in a yield of 0.9 g (78%), m.p. 101 °C. Found (%): C, 39.40; H, 2.11; N, 11.43. $C_{12}H_8F_9N_3$. Calculated (%): C, 39.45; H, 2.19; N, 11.50. IR, ν/cm^{-1}: 1620 (C=N); 1555 (C=C). ^{1}H NMR, δ: 2.51 and 2.64 (both s, 3 H each, Me); 6.48 (s, H(3)); 6.88 (s, H(6)). ^{19}F NMR, δ: 81.19 (tt, C(4′)F_3, *J* = 9.8 Hz, *J* = 2.4 Hz); 48.99 (t, C(1′)F_2, *J* = 12.7 Hz); 41.58 (m, C(2′)F_2); 36.17 (m, C(3′)F_2).

X-ray diffraction study of compound 3c. X-ray diffraction data were collected on a Bruker P4 diffractometer (graphite monochromator, Mo-Kα radiation, θ/2θ scanning technique, 2θ < 50°). The pale-yellow crystals are monoclinic, *a* = 9.958(2), *b* = 13.112(3), *c* = 10.370(2) Å, β = 90.13(1)°, *V* = 1354.0(5) Å^3, space group $P2_1/c$, $C_{14}H_9BrF_3N_3$, *Z* = 4, molecular weight 356.15, d_{calc} = 1.747 g cm^{-3}, μ = 3.066 mm^{-1}. The intensities of 2336 independent reflections were measured from a crystal with dimensions of 0.33×0.54×0.80 mm. The absorption corrections were applied taking into account the crystal habitus (transmission was 0.23—0.39). The structure was solved by direct methods using the SHELXS-86 program package and refined by the least-squares method in the anisotropic-isotropic approximation using the SHELXL-97 program package to wR_2 = 0.1043, *S* = 1.041 for all reflections (*R* = 0.0392 for 1622 $F > 4\sigma$). The positions of the H atoms were revealed from the difference electron density synthesis and refined isotropically. The molecular structure of 3-bromo-2-methyl-5-phenyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine **3c** is shown in Fig. 1. The complete tables of the atomic coordinates and thermal parameters were deposited with the Cambridge Structural Database.

The mass spectra were measured within the framework of the Free Spectra Program of the Oak Ridge National Laboratory (USA) (Grant IPP, Project ORS-T2-0175-RU) and the Chemical Block Int. Company.

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