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# TRIFLUOROMETHYL-SUBSTITUTED DI- AND TETRAHYDROAZOLOPYRIMIDINES

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*The condensation of 4,4,4-trifluoro-1-phenylbut-1-en-3-one with 2-aminobenzimidazole, 3-amino-1,2,4-triazole, and 5-aminotetrazole gives hydroxy-substituted tetrahydro derivatives of pyrimido[1,2-a]-benzimidazole, and of 1,2,4-triazolo-, and tetrazolo[1,5-a]pyrimidine. Dehydration of them to the corresponding dihydroazolopyrimidines has been carried out. An X-ray structural investigation was carried out and the molecular structure of 5-hydroxy-7-phenyl-5-trifluoromethyl-4,5,5,7-tetrahydrotetrazolo[1,5-a]pyrimidine is discussed.*

**Keywords:** azolopyrimidines, trifluoromethyl-substituted unsaturated ketones, heterocyclization, stereochemistry.

The synthetic availability of trifluoromethyl-substituted unsaturated carbonyl compounds, which has been increasing for some time past, has attracted attention to heterocyclization reactions based on them [1]. In the present work the interaction has been studied of 4,4,4-trifluoro-1-phenylbut-1-en-3-one **2** with 3-amino-1,2,4-triazole **1a**, 5-aminotetrazole **1b**, and 2-aminobenzimidazole **1c**. It is known [2] that the interaction of aromatic unsaturated ketones with aminoazoles leads to the formation of dihydro derivatives of azolopyrimidine systems. However the literature data on the heterocyclization reaction of ketone **2** shows the possibility of isolating hydroxy-substituted tetrahydroheterocycles, the hemiaminal structure of which is stabilized by the strong electron-withdrawing influence of the $CF_3$ group. In fact maintaining solutions of amines **1a-c** and ketone **2** in methanol for 2 days led to the formation of hydroxy-substituted tetrahydroazolopyrimidines **3a-c**. On carrying out the cyclocondensation in boiling methanol exclusively dihydro derivatives **4a-c** were isolated from the reaction mixture. The desired dehydration of compounds **3a-c** into dihydroazolopyrimidines **4a-c** was effected by the action of *p*-toluenesulfonic acid (Scheme 1).

The IR spectra of compounds **3** and **4** in KBr disks contain broad absorption bands at 3235-3410 $cm^{-1}$ ($\nu_{OH}$, $\nu_{NH}$). An intense band was also present at 1615-1630 $cm^{-1}$ ($\nu_{C=C}$) in the spectra of compounds **4**.

The $^1H$ NMR spectra of the tetrahydro derivatives **3** are characterized by the presence of signals for the aromatic protons, the protons of the NH and OH groups, and also for an ABX system of protons for the $CHCH_2$ fragment of the tetrahydropyrimidine nucleus. In the spectra of compounds **4** the singlet of the hydroxyl proton is lost, the signal of the NH proton is regularly displaced towards lower field, and the signals of the CH protons are displayed as two doublets, one of which (=CH) is broadened due to long range coupling with the imino group proton (Table 2).

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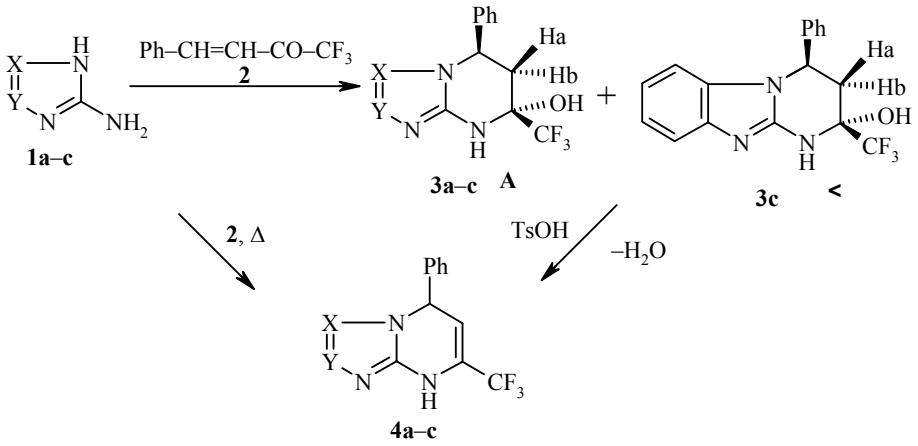
Scheme 1




**1**, **3**, **4** **a** X= N, Y = CH; **b** X = N, Y = N; **c** X+Y = *o*-$C_6H_4$

The presence in the molecules of **3** of two chiral centers raises the problems of the stereoselectivity of the reactions forming them and of the steric configuration of the substances obtained. It was shown previously in [1] that the condensation of ketone **2** with binucleophiles as a rule proceeds stereoselectively and leads to a heterocycle with a *cis*-configuration of the phenyl and trifluoromethyl substituents. In fact, in the $^1$H NMR spectra of compounds **3a,b** (including the unpurified reaction products) there were no signs of doubling of individual groups of signals, which indicates the formation of only one of the possible diastereomers. The spectrum of compound **3c** corresponds to a mixture of steric isomers **A** and **B** of this substance in a ratio of ~3:1 (according to the integrated intensities of the corresponding signals). The value of the coupling constant $J_{AX}$ = 11.8-13.9 Hz both for compounds **3a,b** and for both diastereoisomers of compound **3c**, typical for constants of a $J_{aa}$ type, also indicates the equatorial orientation of the phenyl substituent in the molecules of these substances (including both diastereomeric forms of **3c**). The chemical shifts of all the protons of the tetrahydropyridine ring of compounds **3a,b** and of diastereoisomer **A** of compound **3c** were close in value (see Table 2). The signal of the $H_B$ proton of diastereomer **B** of compound **3c** was markedly displaced (by ~0.3 ppm) towards low field compared with the signal of this proton in the spectrum of isomer **A** and in the spectra of compounds **3a,b**. This phenomenon must be linked in isomer **B** with a change of the spatial orientation of the hydroxyl and trifluoromethyl groups relative to the equatorial proton $H_B$, which enables assignment of the molecules of compound **3a,b** and of the predominant diastereomer **A** of compound **3c** to one isomeric series. The formation of compound **4c** on dehydration of **3c** serves as additional confirmation for this.

TABLE 1. Characteristics of Compounds **3a-c**, **4a-c**

| Com-pound | Empirical formula | Found, % / Calculated, % | mp, °C | Yield, % |
|---|---|---|---|---|
| **3a** | $C_{12}H_{11}N_4OF_3$ | 19.68 / 19.71 | 176-177 | 55 |
| **3b** | $C_{11}H_{10}N_5OF_3$ | 24.55 / 24.55 | 163-164 | 72 |
| **3c** | $C_{17}H_{14}N_3OF_3$ | 12.63 / 12.61 | 264 | 80 |
| **4a** | $C_{12}H_9N_4F_3$ | 21.03 / 21.04 | 119-121 | 61 |
| **4b** | $C_{11}H_8N_5F_3$ | 26.18 / 26.21 | 219-220 | 86 |
| **4c** | $C_{17}H_{12}N_3F_3$ | 13.34 / 13.33 | 231-233 | 93 |

TABLE 2. $^1$H NMR Spectra of Compounds **3a-c**, **4a-c** in DMSO-$d_6$

| Compound | Chemical shifts, δ, ppm (coupling constant *J*, Hz) | | | | | |
|---|---|---|---|---|---|---|
| | 6-H | | 7-H (1H) | Aromatic protons (m) | OH (1H, br. s) | NH (1H, br. s) |
| | $H_A$ (1H) | $H_B$ (1H) | | | | |
| **3a** | 2.22 (dd, *J* = -13.3, *J* = 12.5) | 2.42 (dd, *J* = 4.7) | 5.27 (dd) | 7.29-7.44 | 11.9 | 8.7 |
| **3b** | 2.35 (dd, *J* = 13.2, *J* = 12.1) | 2.44 (dd, *J* = 4.6) | 5.54 | 7.39-7.48 | 9.3 | 7.6 |
| **3c** | 2.28 (dd, *J* = -13.1, *J* = 11.8); 2.43* (dd, *J* = -14.3, *J* = 13.9) | 2.47 (dd, *J* = 4.4); 2.74* (dd, *J* = 6.0) | 5.42; 5.52* | 5.84-7.50 | 8.9 | *[2] |
| **4a** | 5.60 (1H, d) | | 6.27 (br. d, *J* = 3.8) | 7.05-7.55 | — | 10.8 |
| **4b** | 5.62 (1H, d) | | 6.57 (br. d, *J* = 2.6) | 7.20-7.44 | — | 11.37 |
| **4c** | 5.52 (1H, d) | | 6.37 (br. d, *J* = 3.9) | 6.75-7.43 | — | 11.5 |

* Diastereomer **B**. Ratio **A** : **B**, 3:1.
*[2] Overlapped by aromatic proton signals.

The structure of compound **3b** (including its relative configuration) was established unequivocally by an X-ray structural investigation (Fig. 1, Table 3). The results showed the diequatorial disposition of the phenyl and trifluoromethyl substituents in the **3b** molecule. In view of the features of the $^1$H NMR spectra of

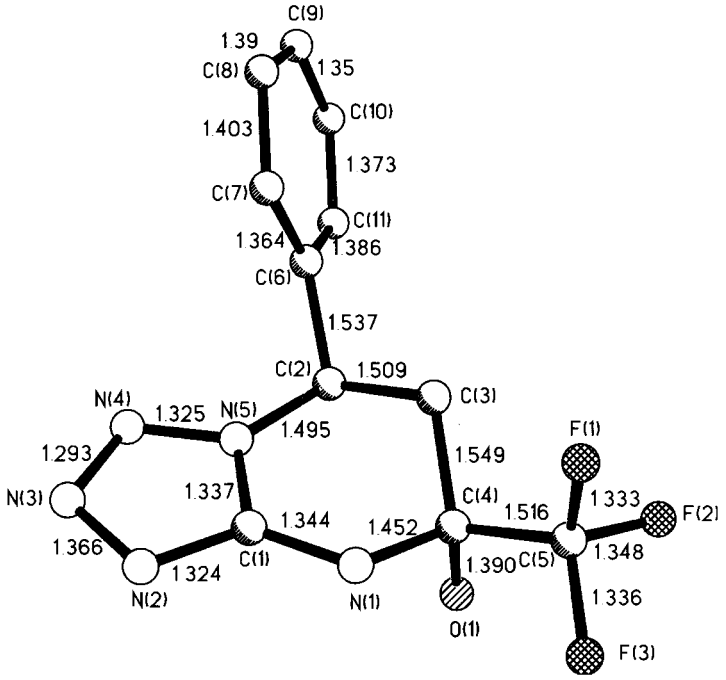



Fig. 1. Structure of the **3b** molecule (without hydrogen atoms) with bond lengths (Å).

TABLE 3. Bond Lengths (*l*) in the Molecule of Compound **3b**

| Bond | *l*, Å | Bond | *l*, Å |
|---|---|---|---|
| F(1)–C(5) | 1.333(8) | F(2)–C(5) | 1.348(7) |
| F(3)–C(5) | 1.336(6) | O(1)–C(4) | 1.390(6) |
| N(1)–C(1) | 1.344(6) | N(1)–C(4) | 1.452(6) |
| N(2)–C(1) | 1.324(7) | N(2)–N(3) | 1.366(7) |
| N(3)–N(4) | 1.293(6) | N(4)–N(5) | 1.325(6) |
| N(5)–C(1) | 1.337(6) | N(5)–C(2) | 1.495(6) |
| C(2)–C(3) | 1.509(7) | C(2)–C(6) | 1.537(7) |
| C(3)–C(4) | 1.549(7) | C(4)–C(5) | 1.516(8) |
| C(6)–C(7) | 1.364(8) | C(6)–C(11) | 1.386(7) |
| C(7)–C(8) | 1.403(8) | C(8)–C(9) | 1.39(1) |
| C(9)–C(10) | 1.35(1) | C(10)–C(11) | 1.373(8) |

compounds **3a-c** the **3a** molecule and isomer **A** of compound **3c** must be assigned to the same isomeric series. Thus in the reactions of ketone **2** with amines **1a-c** the previously noted regularity [1] of the preferential formation of tetrahydrocyclic systems with a *cis*-configuration of the $CF_3$ and $C_6H_5$ groups in reactions of this ketone with binucleophiles is retained.

According to the X-ray structural data the tetrahydro ring of the **3b** molecule is in a distorted *half-chair* conformation. The $C_{(3)}$ and $C_{(4)}$ atoms deviate from the mean-square plane of the remaining ring atoms by -0.49 and 0.25 Å respectively.

The phenyl substituent at the $C_{(2)}$ atom is in the equatorial position (torsion angle $C_{(1)}$–$N_{(5)}$–$C_{(2)}$–$C_{(6)}$ is -143.3(5)°) and is folded relative to the $N_{(5)}$–$C_{(2)}$ bond by 43.9(7)° (torsion angle $N_{(5)}$–$C_{(2)}$–$C_{(6)}$–$C_{(7)}$). The hydroxyl group at the $C_{(4)}$ atom occupies an axial position, but the trifluoromethyl substituent is equatorial (torsion angles $C_{(1)}$–$N_{(1)}$–$C_{(4)}$–$O_{(1)}$ is -80.1 (5)°, $C_{(1)}$–$N_{(1)}$–$C_{(4)}$–$C_{(5)}$ 160.4(4)°).

The bond lengths in the tetrazole fragment were close to the bond lengths in related compounds [3-5]. The $N_{(5)}$–$C_{(2)}$ bond at 1.495(6) Å and $C_{(2)}$–$C_{(6)}$ at 1.537(7) Å are somewhat long compared with their mean values of 1.469 and 1.513 Å respectively [6], which may probably be explained by some steric strain in this fragment as indicated by the short 3a-H···$C_{(7)}$ contact at 2.82 Å at a total of van der Waals radii of 2.87 Å [7].

In the crystal too shortened intramolecular contacts were detected for 3a-H···$F_{(1)}$ at 2.50 Å, $H_{(1N)}$···$F_{(3)}$ at 2.45 Å (total of van der Waals radii 2.56 Å) and a shortened intermolecular contact for $H_{(2)}$···$N_{(3)}$ (*x*-1, *y*, *z*) at 2.56 Å (2.66 Å).

TABLE 4. Some Valence (ω) and Torsion (τ) Angles in the Molecule of Compound **3b**

| Angle | ω, deg. | Angle | τ, deg. |
|---|---|---|---|
| N(5)–C(2)–C(3) | 105.3(3) | C(2)–N(5)–C(1)–N(1) | 8.4(7) |
| N(5)–C(2)–C(6) | 110.4(4) | C(4)–N(1)–C(1)–N(5) | -17.7(7) |
| O(1)–C(4)–N(1) | 109.7(4) | C(1)–N(5)–C(2)–C(3) | -25.2(6) |
| O(1)–C(4)–C(3) | 112.3(4) | C(1)–N(5)–C(2)–C(6) | -143.3(5) |
| N(1)–C(4)–C(5) | 107.6(4) | N(5)–C(2)–C(3)–C(4) | 50.9(5) |
| C(5)–C(4)–C(3) | 109.4(4) | C(1)–N(1)–C(4)–O(1) | -80.1(5) |
| C(7)–C(6)–C(2) | 122.8(4) | C(1)–N(1)–C(4)–C(5) | 160.4(4) |
| C(11)–C(6)–C(2) | 117.9(5) | C(1)–N(1)–C(4)–C(3) | 42.5(6) |
| | | C(2)–C(3)–C(4)–N(1) | -62.0(5) |
| | | C(3)–C(4)–C(5)–F(1) | 51.6(6) |
| | | N(5)–C(2)–C(6)–C(7) | 43.9(7) |

## EXPERIMENTAL

**X-Ray Structural Investigation.** The crystals of 5-hydroxy-7-phenyl-5-trifluoromethyl-4,5,6,7-tetrahydrotetrazolo[1,5-*a*]pyrimidine **3b** were monoclinic, $C_{11}H_{10}F_3N_5O$, at 20°C $a$ = 6.429(2), $b$ = 7.334(2), $c$ = 26.94(1) Å, β = 95.07(3)°, $V$ = 1265.2(7) Å$^3$, M = 285.24, $Z$ = 4, space group $P2(1)/c$, $d_{calc}$ = 1.498 g/cm$^3$, μ(Mo$K\alpha$) = 0.132 mm$^{-1}$, $F$(000) = 584. The parameters of the unit cell and the intensities of 2194 reflections (2011 independent, $R_{int}$ = 0.154) were measured on a Siemens P3/PC automatic four-circle diffractometer (Mo$K\alpha$, graphite monochromator, 2θ/θ scanning, $2\theta_{max}$ = 50°).

The structure was solved by the direct method with the set of programs SHELX97 [8]. The positions of the hydrogen atoms were calculated geometrically and were refined with a riding model with $U_{iso} = nU_{eq}$ ($n$ = 1.5 for the hydroxyl group and $n$ = 1.2 for the remaining hydrogen atoms). The structure was refined on $F^2$ by the full-matrix least-squares method in an anisotropic approach for the nonhydrogen atoms to w$R_2$ = 0.23 for 2011 reflections ($R_1$ = 0.075 for 808 reflections with $F > 4\sigma(F)$, S = 0.882). Final bond lengths and angles are given in Tables 3 and 4.

The $^1$H NMR spectra were measured on a Varian Mercury-200 instrument (200 MHz) in DMSO-d$_6$ (internal standard was TMS). The IR spectra were obtained in KBr disks on a Specord IR-75 spectrometer. The homogeneity of compounds was checked by TLC on Silufol UV-254 plates, eluent was methanol.

**5-Hydroxy-7-phenyl-5-trifluoromethyl-4,5,6,7-tetrahydrotetrazolo[1,5-*a*]pyrimidine (3b).** A mixture of 5-aminotetrazole **1b** (0.85 g, 10 mmol) and 4,4,4-trifluoro-1-phenylbut-1-en-3-one **2** (2.0 g, 10 mmol) in methanol (25 ml) was stirred for 2 days at 25°C. The solution was evaporated to a volume of 10 ml and after cooling, compound **3b** (2.05 g, 72%) was filtered off; mp 163-164°C (methanol).

Compounds **3a** and **3c** were obtained analogously.

**5-Trifluoromethyl-7-phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine (4b).** A. A solution of **3b** (1.45 g, 5 mmol) and *p*-toluenesulfonic acid (0.1 g) in methanol (20 ml) was boiled for 2 h. The solution was evaporated to a volume of 10 ml, and compound **4b** (1.25 g, 86%) was filtered off; mp 219-220°C (methanol).

B. A mixture of 5-aminotetrazole **1b** (0.85 g, 10 mmol) and 4,4,4-trifluoro-1-phenylbut-1-en-3-one **2** (2.0 g, 10 mmol) in methanol (25 ml) was boiled for 10 h. The solution was evaporated to a volume of 10 ml, and compound **4b** (2.5 g, 90%) was filtered off.

Compounds **4a** and **4c** were obtained analogously.

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