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SYNTHESIS OF 2-PYRIDYL-SUBSTITUTED DERIVATIVES OF 7-BENZYL-5,6,7,8-TETRA-HYDROPYRIDO[3,4-*d*]PYRIMIDINE

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A method has been developed for the synthesis of 2-pyridyl-substituted derivatives of 7-benzyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine based on the condensation of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate with pyridyl-2-, pyridyl-3-, and pyridyl-4-carboxamidines and subsequent reactions of 7-benzyl-2-pyridyl-5,6,7,8-tetrahydro-3H-pyrido[3,4-d]pyrimidin-4-ones with trifluoromethanesulfonic anhydride and secondary amines.

Keywords: ethyl 1-benzyl-3-oxopiperidine-4-carboxylate, pyridinecarboxyamidines, pyrido[3,4-*d*]pyrimidines, condensation.

Pyrido[3,4-*d*]pyrimidines have high biological activity, in particular they selectively inhibit tyrosine kinase, completely inhibit the growth of many forms of malignant tumors [1-3]. Separate examples of this class of compounds are antagonistic to α_1-adrenoreceptors and are used in medicine for the treatment of nervous disorders [4] and also effectively inhibit the activity of dehydrofolate reductase, and cause the death of many pathogenic microorganisms [5]. The direction and effectiveness of the biological effects of pyrido[3,4-*d*]-pyrimidines frequently depends on the substituents in the pyridopyrimidine nucleus. In previous papers we have shown that suitable method for the synthesis of pyrido[3,4-*d*]pyrimidines is the condensation of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate (**1**) with morpholine- and pyrrolidine-substituted carboxamidines, which permit the preparation in high yields of derivatives of 7-benzyl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-ones [6, 7]. In this work we have studied the condensation of the keto ester **1** with pyridinecarboxamidines **2a-c** and the reactions of the intermediate 7-benzyl-2-pyridyl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-ones **3a-c** with trifluoromethanesulfonyl anhydride and amines.

Boiling an ethanolic solution of the keto ester **1** with an equimolar amount of amidines **2a-c** in the presence of 3 equivalents of EtONa for 3 h led to the formation of new compounds. According to their elemental analyses, IR, ^{1}H NMR spectroscopy and mass spectrometry (Tables 1-3), the compounds formed are derivatives of 7-benzyl-2-pyridyl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-ones **3a-c**, in yields of 71-76%.

The pyridopyrimidines **3a-c** have promise as starting materials for the synthesis of derivatives of 7-benzyl-2-pyridyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine. Thus by use of the reaction of compounds **3a-c** with trifluoromethanesulfonic anhydride with amines, we obtained 4-amino-7-benzyl-2-pyridyl-5,6,7,8-tetra-hydropyrido[3,4-*d*]pyrimidines **5a-f** in high yields.

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Table 1. Characteristics of Compounds **3a-c** and **5a-f**

Compound	Empirical formula	Found, % / Calculated, %			mp,°C	Yield, %
		C	H	N		
3a	$C_{19}H_{18}N_4O$	71.51 71.68	5.84 5.70	17.38 17.60	149-150	71
3b	$C_{19}H_{18}N_4O$	71.48 71.68	5.93 5.70	17.44 17.60	232-234	76
3c	$C_{19}H_{18}N_4O$	71.46 71.68	5.87 5.70	17.46 17.60	210-211	72
5a	$C_{23}H_{25}N_5$	74.12 74.36	6.99 6.78	18.89 18.85	197-199	75
5b	$C_{23}H_{25}N_5O$	71.04 71.29	6.73 6.50	18.14 18.07	163-164	74
5c	$C_{25}H_{30}N_6$	72.31 72.43	7.44 7.29	20.25 20.27	139-140	71
5d	$C_{27}H_{27}N_5O$	73.93 74.12	6.47 6.22	16.13 16.01	146-148	69
5e	$C_{27}H_{28}N_6$	74.01 74.29	6.70 6.46	19.29 19.25	128-129	70
5f	$C_{23}H_{27}N_5$	73.71 73.96	7.34 7.28	18.95 18.75	91-92	68

Table 2. Spectra of Compounds **3a-c** and **5a-f**

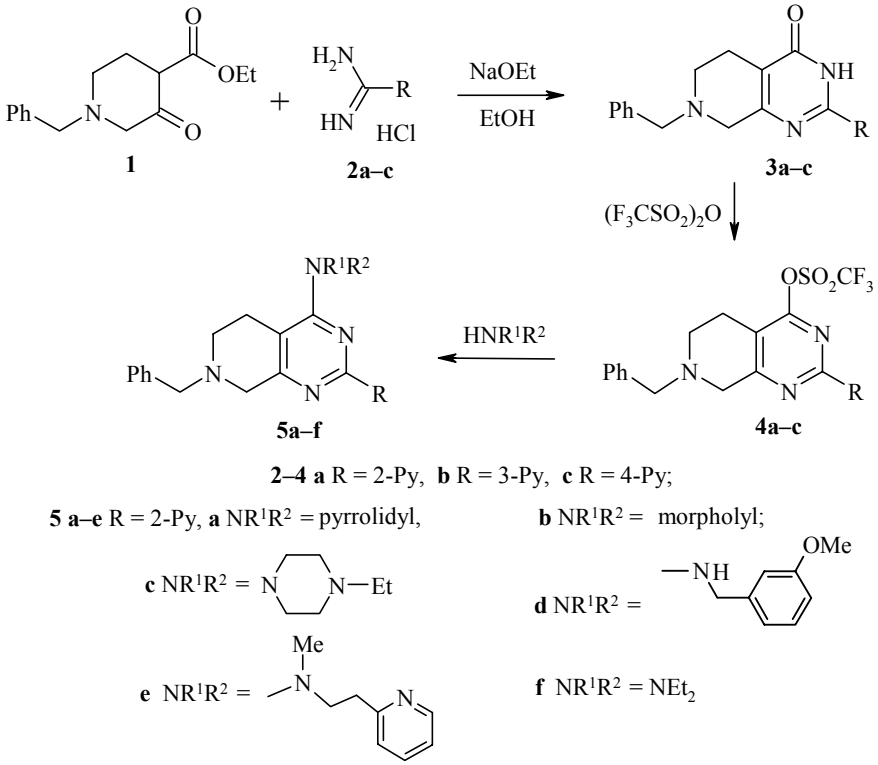
Compound	IR spectrum (KBr), ν, cm^{-1}	Mass spectrum, m/z (I_{rel} %)
3a	3320 (NH), 1730 (C=O), 1610, 1590, 1580, 1565, 1540 (C=N, C=C)	318 $[M]^+$ (100), 225 (55), 174 (5)
3b	3350 (NH), 1725 (C=O), 1610, 1595, 1585, 1570, 1545 (C=N, C=C)	318 $[M]^+$ (100), 225 (5)
3c	3350 (NH), 1725 (C=O), 1610, 1590, 1580, 1570, 1545 (C=N, C=C)	318 $[M]^+$ (100), 225 (5), 174 (5)
5a	1610, 1595, 1580, 1570, 1540 (C=N, C=C)	371 $[M]^+$ (100), 253 (10)
5b	1610, 1595, 1575, 1565, 1535 (C=N, C=C)	387 $[M]^+$ (100)
5c	1610, 1595, 1580, 1570, 1540 (C=N, C=C)	414 $[M]^+$ (100), 177 (8)
5d	3280 (NH), 1610, 1600, 1595, 1580, 1565, 1530 (C=N, C=C)	437 $[M]^+$ (100)
5e	1610, 1600, 1595, 1575, 1565, 1535 (C=N, C=C)	436 $[M]^+$ (100), 318 (5)
5f	1610, 1595, 1575, 1565, 1535 (C=N, C=C)	373 $[M]^+$ (100)

In the ^{1}H NMR spectra of all the compounds **5a-f** the signals of the methylene protons of the piperidine ring and the benzyl unit appear at 2.8 (t, J = 7.5 Hz, H-5), 2.9 (t, J = 7.5 Hz, H-6), 3.7 (s, H-8), 3.3-3.5 ppm (CH_2Ph) and five aromatic protons of the phenyl group at 7.2-7.4 ppm (Table 3), typical for all derivatives of 7-benzyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine [6]. In comparing the ^{1}H NMR spectra of compounds **3a-c** and **5a-f** it is interesting to note that the methylene protons in positions 5 and 6 of compounds **3a-c** are magnetically equivalent and appear as four-proton singlet at 2.75 ppm (Table 3).

Evidently amination of these compounds at position 4 is accompanied by considerable conformational changes in the annelated piperidine ring, as a result of which the methylene protons in positions 5 and 6 in compounds **5a-f** become magnetically nonequivalent.

TABLE 3. ^{1}H NMR Spectra of Compounds **3a-c** and **5a-f**

Com-pound	Chemical shifts, δ, ppm (DMSO-d_6); (*J*, Hz)						
	5-CH_2	6-CH_2	8-CH_2	$PhCH_2$	Py	NH	Signals ot the protons of the NR^1R^2 unit
3a	2.75 (s)	2.75 (s)	3.75 (s)	3.30 (s); 7.30 (m)	8.74 (1H, d, *J* = 5, H-6'); 8.30 (1H, d, *J* = 8, H-3'); 8.05 (1H, t, *J* = 8, H-4'); 7.65 (1H, dd, *J* = 5 and *J* = 8, H-5')	11.8	
3b	2.75 (s)	2.75 (s)	3.70 (s)	3.30 (s); 7.30 (m)	9.20 (1H, s, H-2'); 8.70 (1H, d, *J* = 5, H-6'); 8.36 (1H, d, *J* = 8, H-4'); 7.52 (1H, dd, *J* = 5 and *J* = 8, H-5')	12.7	
3c	2.78 (s)	2.78 (s)	3.70 (s)	3.30 (s); 7.30 (m)	8.78 (2H, d, *J* = 5, H-2',6'); 8.05 (2H, d, *J* = 5, H-3',5')	12.7	
5a	2.74 (t, *J* = 7.5)	2.84 (t, *J* = 7.5)	3.73 (s, *J* = 7.5)	3.32 (s); 7.30 (m)	8.68 (1H, d, *J* = 5, H-6'); 8.25 (1H, d, *J* = 8, H-3'); 7.86 (1H, t, *J* = 8, H-4'); 7.42 (1H, dd, *J* = 5 and *J* = 8, H-5')		1.87 (4H, m, CH_2); 3.62 (4H, m, NCH_2)
5b	2.82 (t, *J* = 7.5)	2.92 (t, *J* = 7.5)	3.73 (s)	3.50 (s); 7.30 (m)	8.70 (1H, d, *J* = 5, H-6'); 8.28 (1H, d, *J* = 8, H-3'); 7.90 (1H, t, *J* = 8, H-4'); 7.45 (1H, dd, *J* = 5 and *J* = 8, H-5')		3.40 (4H, m, NCH_2); 3.68 (4H, m, OCH_2)
5c	2.82 (t, *J* = 7.5)	2.92 (t, *J* = 7.5)	3.72 (s)	3.45 (s); 7.30 (m)	8.68 (1H, d, *J* = 5, 6'-H); 8.28 (1H, d, *J* = 8, H-3'); 7.90 (1H, t, *J* = 8, H-4'); 7.45 (1H, dd, *J* = 5 and *J* = 8, H-5')		1.04 (3H, t, *J* = 7.5, CH_3); 2.37 (2H, q, *J* = 7.5, CH_2); 3.40 (4H, m, NCH_2); 3.45 (4H, m, NCH_2)
5d	2.78 (t, *J* = 7.5)	2.88 (t, *J* = 7.5)	3.75 (s)	3.45 (s); 7.30 (m)	8.68 (1H, d, *J* = 5, H-6'); 8.22 (1H, d, *J* = 8, H-3'); 7.85 (1H, t, *J* = 8, H-4'); 7.35 (1H, dd, *J* = 5 and *J* = 8, H-5')		3.72 (3H, s, OCH_3); 4.68 (1H, d, *J* = 7.5, $NCH_2C_6H_5$); 6.77 (1H, d, *J* = 8.5, H-4'); 6.95 (1H, d, *J* = 8.5, H-6'); 7.02 (1H, s, H-2'); 7.25 (2H, m, NH and H-5')
5e	2.78 (t, *J* = 7.5)	2.88 (t, *J* = 7.5)	2.69 (s)	3.50 (s); 7.30 (m)	8.68 (1H, d, *J* = 5, H-6'); 8.28 (1H, d, *J* = 8, H-3'); 7.90 (1H, t, *J* = 8, H-4'); 7.45 (1H, dd, *J* = 5 and *J* = 8, H-5')		3.05 (2H, t, *J* = 7.5, $CH_2C_6H_5$); 3.20 (3H, s, NCH_3); 3.68 (3H, t, *J* = 7.5, NCH_2); 7.15 (1H, dd, *J* = 5 and *J* = 8, H-5'); 7.25 (1H, d, *J* = 8, H-3'); .64 (1H, t, *J* = 8, H-4'); 8.48 (1H, d, *J* = 5, H-6')
5f	2.80(t, *J* = 7.5)	2.90 (t, *J* = 7.5)	3.73 (s)	3.45 (s); 7.30 (m)	9.44 (1H, s, H-2'); 8.66 (1H, d, *J* = 5, H-6'); 8.54 (1H, d, *J* = 8, H-4'); 7.48 (1H, dd, *J* = 5 and *J* = 8, H-5')		1.10 (6H, t, *J* = 7.5, CH_3); 3.40 (4H, q, *J* = 7.5, NCH_2)



2–4 a R = 2-Py, **b** R = 3-Py, **c** R = 4-Py;

5 a–e R = 2-Py, **a** NR^1R^2 = pyrrolidyl, **b** NR^1R^2 = morpholyl;

c NR^1R^2 =

d NR^1R^2 =

e NR^1R^2 =

f $NR^1R^2 = NEt_2$

Analysis of the mass spectra (Table 2) shows that compounds **3a-c** and **5a-f** are uniformly stable to an electron impact, giving in most cases only molecular ion peaks on a background of a small number of peaks of fragmentation ions of low intensity (< 5%). The presence in the mass spectra of compounds **3a-c** of noticeable fragmentation ion peaks with a mass (*m/z*) of 225 (I_{rel} 5-55%) shows that one of the initial stages of the fragmentation of these compounds under an electron impact includes the cleavage of the benzyl unit and the formation of relatively stable ions of the protonated 2-pyridylpyrido[3,4-*d*]pyrimidin-4-ones.

The study carried out shows that the reaction of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate with pyridinecarboxamidines leads to production of 7-benzyl-2-pyridyl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]-pyrimidin-4-ones, which can be used further in the synthesis of various derivatives of 5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidines.

EXPERIMENTAL

IR spectra were recorded with a Specord M-80 spectrometer, ^{1}H NMR spectra on a Bruker AMX-400 (400 MHz) instrument with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT-90 instrument with an ionization energy of 70 eV. Silica gel (L 40/100) was used for column chromatography. The keto ester **1** used in this work was from Acros.

The method of preparing the amidines **2a-c** was described elsewhere [7].

7-Benzyl-2-pyridyl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-ones 3a-c. An amidine hydrochloride **2a-c** (23.6 g, 150 mmol) was added in small portions to a stirred solution of NaOEt, made from Na (7.0 g, 300 mmol) and absolute ethanol (300 ml), followed by the keto ester **1** (35.5 g, 148 mmol) added dropwise. The mixture was boiled for 3 h, the solvent was removed in vacuum, and a saturated solution of ammonium chloride was added to the residue. The material insoluble in water was filtered off, washed with water, methanol, and then ether, and dried in the air.

4-Amino-7-benzyl-2-pyridyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidines 5a-f. Triflurомethane-sulfonic anhydride (4.92 g, 12 mmol) was added dropwise with stirring to a suspension of compound **3a-c** (3.2 g, 10 mmol) in pyridine (50 ml) cooled to -20°C, after which the temperature was slowly increased to ~20°C, stirring was continued for 30 min, then the mixture was poured into water (500 ml). The precipitate was filtered off, washed with water and dried in the air. The dried precipitate was dissolved in dry dioxane (150 ml). K_2CO_3 (4 g, 30 mmol) and the corresponding amine (15 mmol) were added to this solution which was boiled for 3 h, cooled, and poured into water (300 ml), extracted with ethyl acetate. The extract was dried over Na_2SO_4 and chromatographed on a short column. The solvent was removed in vacuum, the residue was dried in the air and recrystallized from ethyl acetate.

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