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SYNTHESIS OF PYRIDO[3,4-*d*]PYRIMIDINES BY CONDENSATION OF ETHYL 1-BENZYL-3-OXOPIPERIDINE-4-CARBOXYLATE WITH MORPHOLINE-4-CARBOXAMIDINE

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A method has been developed for the synthesis of 4-amino-substituted 7-benzyl-2-morpholin-4-yl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidines by condensation of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate with morpholine-4-carboxamidine and subsequent reaction of the 7-benzyl-2-morpholin-4-yl-5,6,7,8-tetrahydro-3H-pyrido[3,4-d]pyrimidin-4-one with trifluoromethanesulfonic anhydride and secondary amines.

Keywords: Ethyl 1-benzyl-3-oxopiperidine-4-carboxylate, morpholine-4-carboxamidine, pyrido[3,4-*d*]-pyrimidines, condensation.

Pyrido[3,4-*d*]pyrimidines show high biological activity, particularly in their selective inhibition of tyrosine kinase fully suppressing the growth of many forms of malignant tumors [1-3]. Individual members of this class of compounds are α_1-adrenoceptor antagonists and are used in medicine for nervous dysfunction [4]. They also efficiently inhibit the action of dehydrofolate reductase causing the death of many pathogenic microorganisms [5]. The direction and efficiency of the biological activity of the pyrido[3,4-*d*]pyrimidines in general depend on the substituents in the pyridopyrimidine ring. The most common methods of synthesizing pyrido[3,4-*d*]pyrimidines are the cyclization reactions of 3-acylaminoisonicotinic acid derivatives with acetic anhydride and then ammonia [6-8] or *via* the condensation of 3-aminoisonicotinic acid or its esters, amides, and nitriles with formic acid, formamide, cyanamides, amidines, or *ortho* esters [3, 7-9]. More rarely, pyrido-[3,4-*d*]pyrimidines are prepared by the condensation of 1-benzyl-3-oxopiperidine-4-carboxylic acid esters with amidines [4, 10], the synthetic potential of which remains largely unexplored.

With the aim of developing novel synthetic methods for pyrido[3,4-*d*]pyrimidines we have now studied the condensation of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate (**1**) with morpholine-4-carboxamidine (**2**) and the subsequent reactions of the 7-benzyl-2-morpholin-4-yl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-one (**3**) obtained with trifluoromethanesulfonic anhydride and secondary amines.

Condensation of the keto ester **1** with an equimolar amount of the carboxamidine **2** was carried out in ethanol with boiling using 3 equivalents of sodium ethylate as catalyst. The reaction was monitored by TLC which showed that it was completed after 3 h and gave a new compound. According to elemental analytical, IR, ^{1}H NMR, and mass spectroscopic analysis (Table 3) the reaction product is compound **3** (yield 87%).

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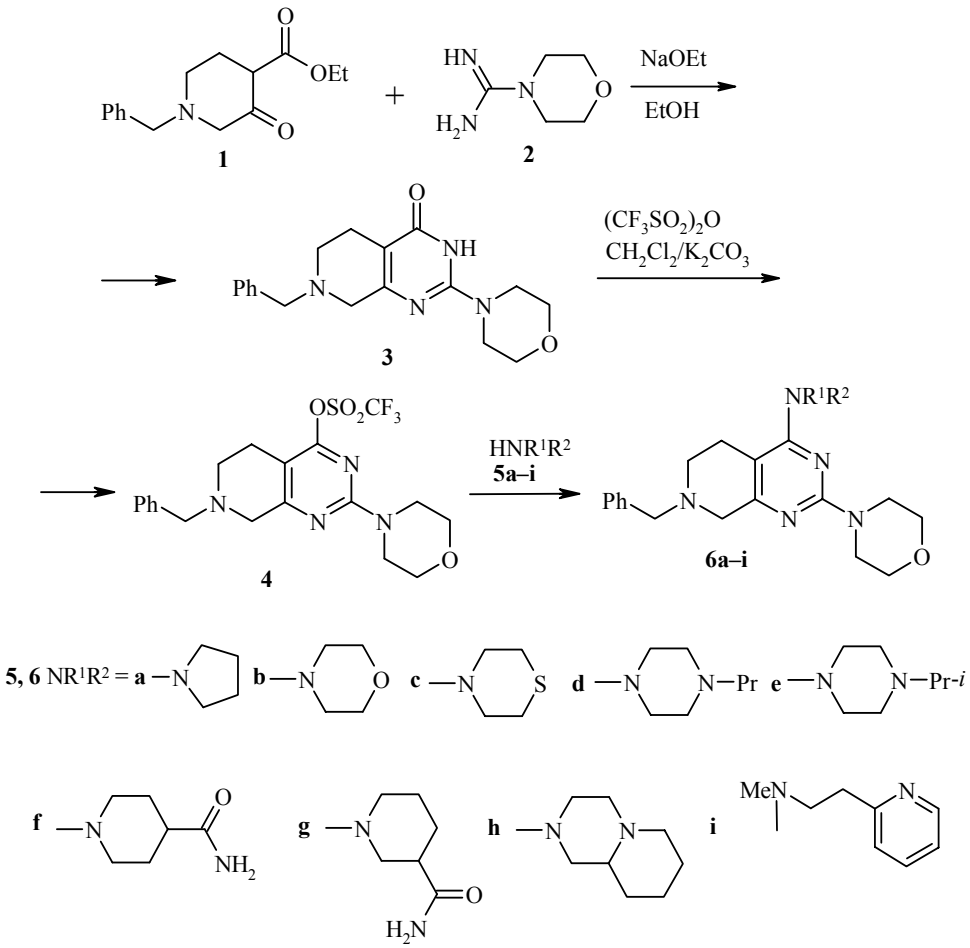
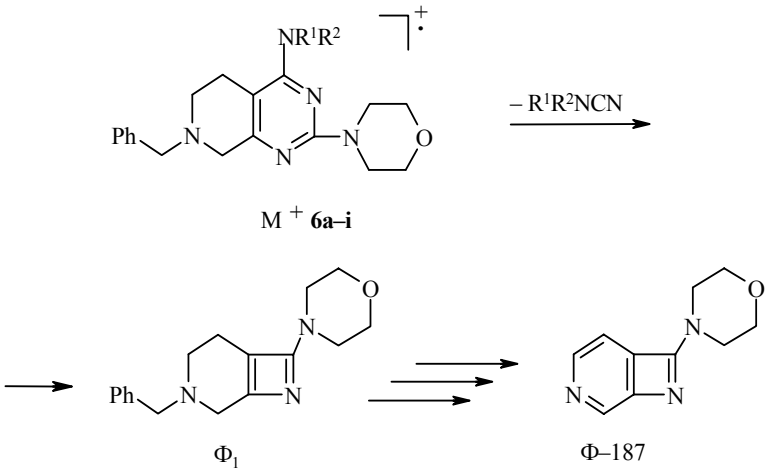


TABLE 1. Characteristics of Compounds **3** and **6a-i**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3	$C_{18}H_{22}N_4O_2$	66.46 / 66.24	6.96 / 6.80	16.96 / 17.17	247-248	87
6a	$C_{22}H_{29}N_5O$	69.87 / 69.63	7.96 / 7.70	18.28 / 18.45	125-126	76
6b	$C_{22}H_{29}N_5O_2$	66.93 / 66.81	7.57 / 7.39	17.54 / 17.71	147-148	72
6c	$C_{22}H_{29}N_5OS$	64.41 / 64.20	7.29 / 7.10	16.82 / 17.02	137-138	70
6d	$C_{25}H_{36}N_6O$	69.02 / 68.78	8.48 / 8.31	18.98 / 19.25	107-108	69
6e	$C_{25}H_{36}N_6O$	68.94 / 68.78	8.54 / 8.31	19.02 / 19.25	128-129	71
6f	$C_{24}H_{32}N_6O_2$	66.26 / 66.03	7.51 / 7.39	19.06 / 19.25	190-191	74
6g	$C_{24}H_{32}N_6O_2$	66.28 / 66.03	7.57 / 7.39	18.96 / 19.25	177-178	73
6h	$C_{26}H_{36}N_6O$	69.82 / 69.61	8.31 / 8.09	18.46 / 18.73	101-102	70
6i	$C_{26}H_{32}N_6O$	70.52 / 70.24	7.43 / 7.25	18.78 / 18.90	103-104	67

4-Amino-substituted pyrido[3,4-*d*]pyrimidine derivatives are generally synthesized in two stages, initially by chlorination of 3H-pyrido[3,4-*d*]pyrimidin-4-ones using $SOCl_2$ or $POCl_3$ and then exchange of the chlorine atom in the intermediate 4-chloropyrido[3,4-*d*]pyrimidines for an amino group [3]. Another possible method for the synthesis of the 4-aminopyrido[3,4-*d*]pyrimidines might be the reaction of 3H-pyrido-[3,4-*d*]pyrimidin-4-ones with trifluoromethanesulfonic anhydride and then with amines [11]. Reaction of compound **3** with trifluoromethanesulfonic anhydride was carried out in methylene chloride at -40ºC and gave the triflate derivative **4** in 90% yield. This compound reacted with the amines **5a-i** upon refluxing in dioxane to give compounds **6a-i** in 67-76% yield.



The composition and structure of compounds **6a-i** were confirmed by elemental analysis, IR and ^{1}H NMR spectroscopy, and mass spectrometry (Tables 1-3). Interesting information about the properties of compounds **6a-i** can be deduced from the mass spectrometric data.

The presence in the mass spectra of strong peaks for the molecular ions (I_{rel} 100 %) together with the small number of lower intensity peaks (< 20%) for the fragment ions point to a marked stability of compounds **6a-i** towards electron impact (Table 2). One of the most intense peaks in the mass spectra of all of the

TABLE 2. IR and Mass Spectra of Compounds **3** and **6a-i**

Com-pound	IR spectrum (KBr), ν, cm^{-1}	Mass spectrum, *m/z* (I_{rel}, %)
3	3380 (NH), 1725 (C=O), 1610, 1585, 1574, 1545 (C=N, C=C)	326 [M]$^+$ (100), 236 (18), 187 (40), 163 (30)
6a	1590, 1575, 1535 (C=N, C=C)	379 [M]$^+$ (100), 282 (5), 236 (7), 213 (5), 187 (7)
6b	1590, 1575, 1535 (C=N, C=C)	395 [M]$^+$ (100), 277 (14), 187 (5)
6c	1588, 1573, 1540 (C=N, C=C)	411 [M]$^+$ (100), 187 (10)
6d	1585, 1570, 1535 (C=N, C=C)	436 [M]$^+$ (100), 187 (12), 163 (5)
6e	1585, 1572, 1535 (C=N, C=C)	436 [M]$^+$ (100), 187 (15), 163 (17)
6f	3350, 3180 (NH), 1725 (C=O), 1645, 1620 (NH), 1585, 1570, 1530 (C=N, C=C)	436 [M]$^+$ (100), 187 (5)
6g	3345, 3175 (NH), 1730 (C=O), 1640, 1615 (NH), 1585, 1570, 1530 (C=N, C=C)	436 [M]$^+$ (100), 187 (17), 163 (8)
6h	1585, 1570, 1535 (C=N, C=C)	448 [M]$^+$ (100), 256 (7), 187 (7), 163 (8)
6i	1590, 1585, 1570, 1540, 1530 (C=N, C=C)	444 [M]$^+$ (100), 187 (8), 176 (12), 106 (8)

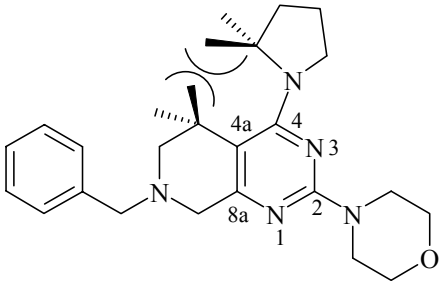
TABLE 3. ^{1}H NMR Spectra of Compounds **3** and **6a-i**

Com-pound	^{1}H NMR spectrum, DMSO-d_6, δ, ppm. (*J*, HZ)					
	5-CH_2, br. s	6-CH_2, br. s	8-CH_2, s	$CH_2C_6H_5$	2-$N(CH_2)_4O$, m	NR^1R^2
3	2.50	2.68	3.7	3.15 (2H, s), 7.2-7.4 (5H, m)	3.5 (4H), 3.6 (4H)	11.1 (1H, br. s)
6a	2.58	2.68	3.7	3.30 (2H, s), 7.2-7.4 (5H, m)	3.6 (8H)	1.65 (4H, m, CH_2); 3.40 (4H, br. s, NCH_2)
6b	2.58	2.68	3.7	3.30 (2H, s), 7.2-7.4 (5H, m)	3.6 (8H)	3.20 (4H, m, NCH_2); 3.60 (4H, br. s, NCH_2)
6c	2.65	2.70	3.7	3.28 (2H, s), 7.2-7.4 (5H, m)	3.6 (8H)	2.60 (4H, br. s, SCH_2); 3.50 (4H, br. s, NCH_2)
6d	2.72	2.72	3.7	3.28 (2H, s), 7.2-7.4 (5H, m)	3.6 (8H)	0.9 (3H, t, *J* = 7.1, CH_3); 1.50 (2H, m, CH_2); 2.30 (2H, br. s, NCH_2); 2.48 (4H, m, NCH_2); 3.40 (4H, br. s, NCH_2)
6e	2.63	2.70	3.7	3.30 (2H, s), 7.2-7.4 (5H, m)	3.6 (8H)	0.95 (6H, d, *J* = 6.4, CH_3); 2.40 (4H, br. s, NCH_2); 2.60 (1H, m, NCH); 3.20 (4H, br. s, NCH_2)
6f	2.64	2.70	3.7	3.30 (2H, s), 7.2-7.4 (5H, m)	3.6 (8H)	1.54 (2H, m, N-CH_2); 1.70 (2H, m, N-CH_2); 2.40 (1H, m, γ-CH); 2.70 (4H, t, *J* = 6.2, NCH_2); 3.72 (4H, t, *J* = 6.3, NCH_2); 6.74 and 7.14 (2H, br. s, $CONH_2$)
6g	2.72	2.72	3.7	3.30 (2H, s), 7.2-7.4 (5H, m)	3.6 (8H)	1.50 (2H, m, N-CH_2); 1.65 (2H, m, γ-CH_2); 1.70 (2H, m, N-CH_2); 2.45 (1H, m, H-N); 2.98 (4H, t, *J* = 6.2, NCH_2); 3.72 (4H, t, *J* = 6.2, NCH_2); 5.15 and 5.92 (2H, br. s, $CONH_2$)
6h	2.64	2.70	3.7	3.35 (2H, s), 7.2-7.4 (5H, m)	3.6 (8H)	1.0-2.1 (9H, m, CH, CH_2); 2.15 (2H, m, NCH_2); 2.70 (2H, m, NCH_2); 2.90 and 3.45 (2H, d, *J* = 6.2,NCH_2)
6i	2.60	2.68	3.7	3.45 (2H, s), 7.2-7.4 (5H, m)	3.6 (8H)	2.38 (3H, s, NCH_3); 2.95 (2H, t, *J* = 6.5,CH_2); 3.58 (2H, m, NCH_2); 7.18 (2H, m, H-N pyridine); 7.65 (1H, m, H-γ pyridine); 8.00 (1H, d, *J* = 4.8, H-α pyridine)

compounds **6a-i** is the ion peak at mass 187 which suggests a unified decomposition scheme for the given compounds, the product being the ion not containing the NR^1R^2 fragment. Analysis of the mass spectra shows (Table 2) that the first stage of the fragmentation process of compounds **6a-i** involves elimination of the fragments $R^1R^2N–CN$ from the molecular ions with formation of the ions Φ_1 which then undergo elimination of the benzyl substituent and dehydrogenation to form the relatively stable Φ-187 ions.

The elimination of the $R^1R^2N–CN$ fragments from the molecular ions was confirmed by PM3 semiempirical calculations for the given compounds and also for their radical cations. Hence, for example, the calculations showed that the neutral molecule of compound **6a** has a marked lengthening of the $C_{(4)}–C_{(4a)}$ bond and an anomalously large $N–C_{(4)}–C_{(4a)}$ valence angle as a result of repulsion of the pyrrolidine substituent by the hydrogen atoms of the piperidine ring.

These effects are even more clearly seen in the radical cation RC-**6a** in which the $C_{(4)}–C_{(4a)}$ and $C_{(2)}–N_{(3)}$ bonds are lengthened by 0.0220 and 0.0011 Å respectively and the $N_{(1)}–C_{(8a)}$ bond shortened by 0.0341 Å when compared with the analogous bonds in the neutral molecule **6a** (Table 4). The distortion of the $N–C_{(4)}–C_{(4a)}$ valence angles and strong lengthening of the $C_{(4)}–C_{(4a\}}$ bond in the molecules **6a** and radical cation RC-**6a** points to a marked strain energy, lowering of which is achieved *via* the elimination of the $R^1R^2N–CN$ fragment. The lengthening of the $C_{(4)}–C_{(4a)}$ and $C_{(2)}–N_{(3)}$ bonds in the series of molecules **6a** and RC-**6a** governs only the initial stage of the process which is completed by full dissociation of the given bonds.



6a, RC-**6a**

The synthesized pyridopyrimidines **3** and **6a-i** are white, crystalline compounds which are poorly soluble in water and in nonpolar organic solvents. The higher melting point of compounds **6f,g** is due to the presence in the molecules of carboxamide groups capable of forming hydrogen bonds.

This study has shown that condensation of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate with morpholine-4-carboxamidine and subsequent reaction of the 7-benzyl-2-morpholin-4-yl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-one with trifluoromethanesulfonic anhydride and amines gives high yields of a range of 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine derivatives.

TABLE 4. Individual PM3 Calculated Valence Angles (ω) and Bond Lengths (*l*) in the Pyridopyrimidine Molecule **6a** and its Radical Cation RC-**6a**

Angle	ω, deg		Bond	*l*, Å	
	6a	RC-**6a**		**6a**	RC-**6a**
$C_{(4a)}–C_{(4)}–N$	127.7	127.9	$N_{(1)}–C_{(8a)}$	1.3651	1.3310
$N_{(3)}–C_{(4)}–N$	111.8	111.1	$C_{(2)}–N_{(3)}$	1.3677	1.3688
			$C_{(4)}–C_{(4a)}$	1.4223	1.4443

EXPERIMENTAL

IR spectra were taken on a Specord M-80 and ^{1}H NMR spectra on a Bruker AMX-400 instrument (400 MHz) using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT-90 instrument with an ionization energy of 70 eV. Column chromatography was carried out on L40/100 grade silica gel. Monitoring of the reactions was performed by TLC on Silufol UV-254 plates.

The geometry of the molecule of the pyridopyrimidine **6a** and its radical cation RC-**6a** were calculated out using the PM3 semiempirical method occurring in the HyperChem program package [12]. All of the calculations were performed with full optimization of the geometric parameters.

Keto ester **1** used in this work came from the company Acros. The method of preparing compound **2** has been reported in [13].

7-Benzyl-2-morpholin-4-yl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-one (3). Compound **2** hydrochloride (24.8 g, 0.15 mol) portionwise and then the keto ester **1** (35.5 g, 0.148 mol) dropwise were added to a stirred solution of NaOEt prepared from Na (3.5 g, 0.15 mol) and absolute ethanol (200 ml). The reaction mixture was refluxed for 3 h and ethanol (100 ml) was then distilled off *in vacuo*. Ammonium chloride was added to the remaining solution to saturation and the precipitate was filtered off, washed with water, dried in air, and recrystallized from ethyl acetate.

4-Amino-7-benzyl-2-morpholin-4-yl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidines (6a-i) (General Method). Trifluoromethanesulfonic anhydride (3.28 g, 12 mmol) was added dropwise to a stirred suspension of compound **3** (2.36 g, 10 mmol) and K_2CO_3 (4 g, 30 mmol) in dry methylene chloride (150 ml) cooled to -40ºC. The reaction mixture was slowly raised to room temperature, stirred at this temperature for 2 h, and poured into water (200 ml). The organic layer was separated, dried over Na_2SO_4, and chromatographed on a short silica gel column. Solvent was distilled off *in vacuo* and the residue was dissolved in dry dioxane (150 ml). K_2CO_3 (4 g, 30 mmol) and the corresponding amine (15 mmol) were added to the solution which was then refluxed for 2 h. The product was cooled, poured into water (300 ml), extracted with ethyl acetate, and the extract was dried over Na_2SO_4 and chromatographed on a short silica gel column. Solvent was removed *in vacuo* and the residue was dried and recrystallized from ethyl acetate.

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