Chemistry of Heterocyclic Compounds, Vol. 45, No. 12, 2009

SYNTHESIS OF POLYHETEROCYCLIC COMPOUNDS DERIVED FROM 6-AMINO-4-ARYL-2-R-4H-FURO[2,3-*b*]PYRAN-5-CARBONITRILES

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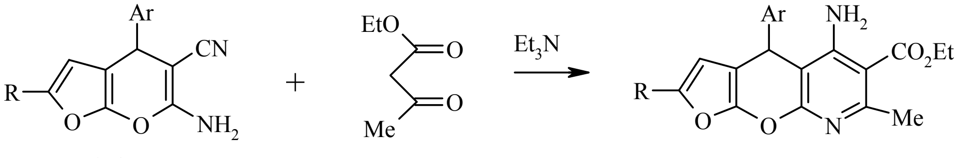
Syntheses were developed for 4-aryl-6-ethoxy-2-R-furo[2,3-b]pyridine-5-carbonitriles and ethyl esters of 5-amino-4-aryl-7-methyl-2-R-1,9-dioxa-8-azacyclopenta[b]naphthalene-6-carboxylic acids based on the reaction of 6-amino-4-aryl-2-R-4H-furo[2,3-b]pyran-5-carbonitriles with ethyl acetoacetate and nucleophilic recyclization. The mechanisms of these reactions are considered.

Keywords: 6-amino-4-aryl-2-R-4H-furo[2,3-*b*]pyran-5-carbonitriles, 4-aryl-6-ethoxy-2-R-furo-[2,3-*b*]pyridine-5-carbonitriles, ethyl acetoacetate, ethyl esters of 5-amino-4-aryl-7-methyl-2-R-4H-1,9-dioxa-8-aza-cyclopenta[*b*]naphthalene-6-carboxylic acids, recyclization.

6-Amino-4-aryl-2-R-4H-furo[2,3-*b*]pyran-5-carbonitriles **1-3** are an important class of heterocyclic compounds, which hold considerable interest in light of their various chemical transformations and practical applications [1]. These bifunctional compounds, containing vicinal nitrile and amino groups, are promising starting materials for obtaining previously not readily available fused heterocyclic systems. The synthesis of carbonitriles **1-3** employs the base-catalyzed Michael condensation of 5-aryl-3-arylmethylene-3H-furan-2-ones with malononitrile [2].

The reaction of carbonitriles **1-3** with a C-nucleophile, namely, ethyl acetoacetate, upon heating in ethanol at reflux in the presence of catalytic amounts of triethylamine gives ethyl esters of 5-amino-4-aryl-7-methyl-2-R-4H-1,9-dioxa-8-azacyclopenta[*b*]naphthalene-6-carboxylic acids **4-6**.



1–3 **4–6**

1, **4** R = Ph; **2**, **5** R = 4-MeC_6H_4, **3**, **6** R = 4-$MeOC_6H_4$; **1–6** Ar = 2-ClC_6H_4

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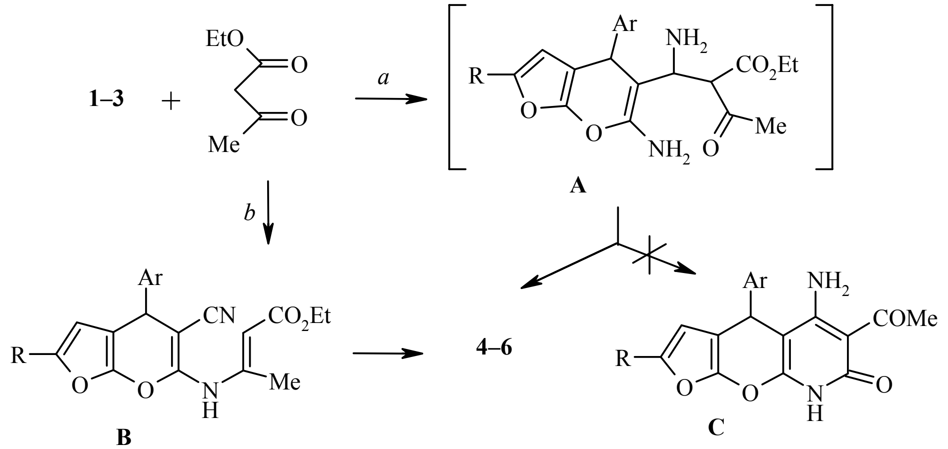
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1812-1816, December, 2009. Original article submitted March 22, 2009.

The IR spectra of esters **4-6** display bands for stretching vibrations of the ester groups at 1735-1715 cm^{-1} (broad), NH_2 group at 3450-3350 cm^{-1} (two narrow bands), and the pyridine ring at 3050-3030, 1200-1180, and 1590-1550 cm^{-1}.

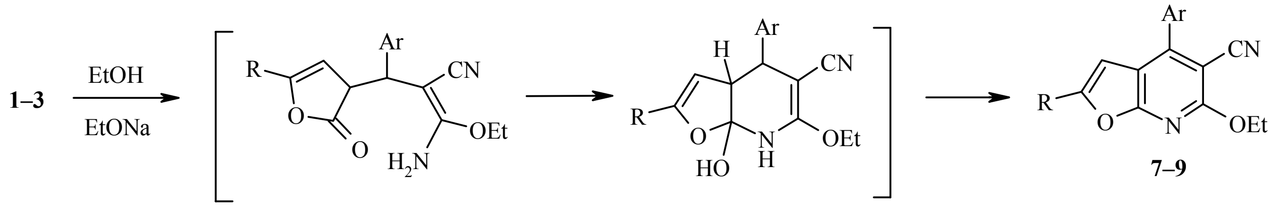
Characteristic signals in the ^1H NMR spectra of esters **4-6**, which confirm their structure, are the broad signal for the amino group at 9.30-9.35 ppm, triplet for the ester methyl group protons at 1.30-1.35 ppm, quartet for the ester methylene group protons at 4.06-4.12 ppm, and signal for the methyl group at C-7 at 2.25-2.32 ppm.



The existence of several reaction sites in the starting compounds would lead us to expect a complex reaction leading to several reaction products. Generation of the ethyl acetoacetate carbanion occurs under base catalysis conditions, followed by the addition of this carbanion at the nitrile group carbon atom to give β-aminoester **A**, which undergoes intramolecular heterocyclization due to attack of the carbonyl carbon atom of ethyl acetoacetate by the enamine amino group to give the pyridine ring in esters **4-6** (pathway *a*). An alternative pathway involving attack of the amino group at C-2 of the pyran ring to give pyridone structure **C** does not take place under the conditions studied. We cannot exclude initial attack of the amino group in carbonitriles **1-3** at the oxo group of ethyl acetoacetate to give aminoprotonate **B**, which subsequently undergoes cyclization involving the substrate cyano group (pathway *b*) to give esters **4-6**.

Upon the action of sodium alcoholate, furopyrans **1-3** recyclize upon heating in ethanol to give 4-aryl-6-ethoxy-2-R-furo[2,3-*b*]pyridine-5-carbonitriles **7-9**.

The IR spectra of pyridinecarbonitriles **7-9** have bands for the stretching vibrations of the cyano group at 2215-2210 cm^{-1} and –C–O–C– group at 1130-1120 cm^{-1} but lack bands for amino and cyano groups, which supports the formation of the indicated products.



1, 7 R = Ph; **2, 8** R = 4-MeC_6H_4; **3, 9** R = 4-$MeOC_6H_4$, **1**–**3**, **7**–**9** Ar = 2-ClC_6H_4

The ^1H NMR spectra of pyridinecarbonitriles **7-9**, in contrast to the spectra of the starting compounds, display a series of upfield signals at 1.42-1.47 and 4.20-4.30 ppm, while the amino group proton signal at ~9.3 ppm is lacking.

TABLE 1. Physicochemical Characteristics of the Ethyl Esters of 5-Amino-4-aryl-7-methyl-2-R-4H-1,9-dioxa-8-azacyclopenta[*b*]pyridine-5-carbonitriles **7-9**

Compound	Empirical formula	Found, % / Calculated, % C	Found, % / Calculated, % H	Found, % / Calculated, % N	mp, °C	Yield, %
4	$C_{26}H_{21}ClN_2O_4$	68.00 67.75	4.19 4.59	6.43 6.08	136-138	64
5	$C_{27}H_{23}ClN_2O_4$	67.90 68.28	5.38 4.88	6.30 5.90	153-155	71
6	$C_{27}H_{23}ClN_2O_5$	65.85 66.06	4.85 4.72	5.43 5.71	164-166	69
7	$C_{22}H_{15}ClN_2O_2$	70.24 70.50	4.33 4.03	7.53 7.47	161-162	75
8	$C_{23}H_{17}ClN_2O_2$	70.86 71.04	4.60 4.41	7.05 7.20	157-159	68
9	$C_{23}H_{17}ClN_2O_3$	68.52 68.23	4.64 4.23	7.23 6.92	168-170	82

TABLE 2. ^{1}H NMR Spectra of Esters **4-6** and Carbonitriles **7-9**

Compound	Chemical shifts, δ, ppm (*J*, Hz)								
	Fur (1H, s)	Ar (m)	CH_3	H-4 (1H, s)	$OC\underline{H_2}CH_3$ (2H, m)	$OCH_2C\underline{H_3}$ (3H, t)	NH_2 (2H, s)	OCH_3	CH_3 (3H, s)
4	6.50	7.05-7.36 (9H)	2.55 (3H, s)	5.40	4.40	1.30 (*J* = 7.0)	9.30	—	—
5	6.53	7.13-7.38 (8H)	2.58 (3H, s)	5.75	4.45	1.35 (*J* = 6.8)	9.35	—	2.15
6	6.60	7.00-7.30 (8H)	2.62 (3H, s)	5.63	4.47	1.33 (*J* = 6.8)	9.32	3.45 (3H, s)	—
7	6.50	7.25-7.68 (9H)	—		4.20	1.42 (*J* = 6.4)		—	
8	6.64	7.15-7.50 (8H)	2.35		4.30	1.47 (*J* = 6.5)		—	
9	6.57	7.19-7.67 (8H)	—		4.27	1.45 (*J* = 6.4)		3.83	

The formation of the pyran ring in furopyrans **1-3** due to intramolecular reaction of the hydroxyl and cyano groups is reversible [3]. Under certain conditions, the pyran ring is opened by the action of nucleophilic reagents with subsequent cyclization and aromatization to give the pyridine ring due to attack of the amino group nitrogen atom. Nucleophilic addition of the alcoholate anion at the α-carbon atom of the pyran ring probably occurs initially, followed by opening of the heterocycle. Subsequent attack of the nitrogen atom at the carbonyl carbon atom of the lactone group, cyclization, and aromatization lead to formation of the pyridine ring.

EXPERIMENTAL

The IR spectra were taken on an FSM-1201 Fourier spectrometer for KBr pellets at 400-4000 cm^{-1}. The ^{1}H NMR spectra were taken on a Bruker MSL-400 spectrometer at 400 MHz at 20-25°C in $CDCl_3$ with TMS as the internal standard. Thin-layer chromatography was carried out on Silufol UV-254 plates with 2:2:1 hexane–ethyl acetate–chloroform and development by iodine vapor.

6-Amino-4-aryl-2-R-4H-furo[2,3-*b*]pyran-5-carbonitriles 1-3 were obtained by a standard method [2].

Ethyl Esters of 5-Amino-4-aryl-7-methyl-2-R-4H-1,9-dioxa-8-azacyclopenta[*b*]naphthalene-6-carboxylic Acids 4-6. Triethylamine (10 mmol) in ethanol was added to a mixture of 6-amino-4-aryl-2-R-4H-furo[2,3-*b*]pyran-5-carbonitrile **1-3** (10 mmol) and ethyl acetoacetate (15 mmol). The reaction mixture was heated at reflux for 5-8 h, poured into cold water, and neutralized by adding dilute hydrochloric acid. The precipitated crystals were filtered off and recrystallized from hexane.

4-Aryl-6-ethoxy-2-R-[2,3-*b*]pyridine-5-carbonitriles 7-9. A mixture of 6-amino-4-aryl-2-R-4H-furo-[2,3-*b*]pyran-5-carbonitrile **1-3** (10 mmol) and sodium alcoholate (10 mmol) in ethanol was heated for 3-4 h at reflux, poured into cold water, and neutralized by adding dilute hydrochloric acid. The crystals precipitated was filtered off and recrystallized from 2:1 hexane–2-propanol.

This work was carried out with the financial support of a grant from the Russian Federation President's Fund for State Support of Young Russian Scientists MK-635.2009.3.

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