Chemistry of Heterocyclic Compounds, Vol. 45, No. 6, 2009

SYNTHESIS OF 6-AMINO-4-ARYL-2R-4H-FURO[2,3-*b*]PYRAN-5-CARBONITRILES BASED ON THE CONDENSATION OF 3-ARYLMETHYLENE-3H-FURAN-2-ONES WITH MALONONITRILE

T. V. Aniskova[1]* and A. Yu. Yegorova[1]

Methods were developed for the synthesis of 6-amino-4-aryl-2R-4H-furo[2,3-b]pyran-5-carbonitriles based on the reaction of 3-arylmethylene-3H-furan-2-ones with malononitrile and also using a multicomponent reaction. The reaction schemes are discussed.

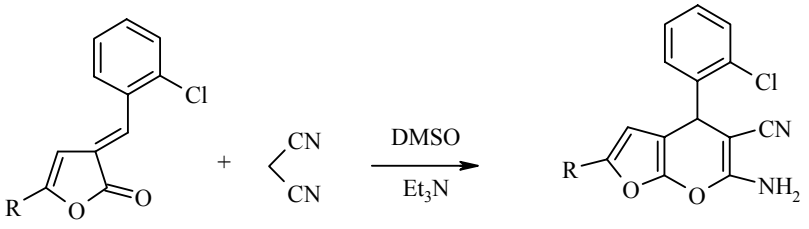
Keywords: 3-arylmethylene-3H-furan-2-ones, substituted furo[2,3-*b*]pyran-5-carbonitriles, malononitrile, Michael condensation.

The ability of 3-arylmethylene-3H-furan-2-ones to take part in Michael condensation as acceptors was used earlier in the reaction with cyclohexanone [1], acetylacetone [2], and acetoacetic ester [3].

In a continuation of investigations into the reactivity of 3-arylmethylene-3H-furan-2-ones with methylene-active compounds their behavior in reaction with malononitrile was studied.

The presence of the highly reactive methylene and cyano groups in malononitrile makes it possible to use this compound as a reagent for cyclizations leading to the formation of carbo- and heterocyclic compounds.

The reaction of 5-aryl-3-arylmethylene-3H-furan-2-ones **1**-**4** with malononitrile was realized by heating the reagents in solution in DMSO in a molar ratio of 1:1 in the presence of catalytic amounts of triethylamine.



1–4 **5–8**

1, **5** R = C_5H_{11}; **2**, **6** R = Ph; **3**, **7** R = *p*-Tol; **4**, **8** R = 3-$MeOC_6H_4$

* To whom correspondence should be addressed, e-mail: aniskovatv@mail.ru.

[1] N. G. Chernyshevskii Saratov State University, Saratov 410012, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 836-840, June, 2009. Original article submitted October 13, 2008.

TABLE 1. The Physicochemical Characteristics of the Michael Condensation Products **5-8**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
5	$C_{19}H_{19}ClN_2O_2$	66.45 / 66.57	5.50 / 5.59	8.35 / 8.17	105-107	70
6	$C_{20}H_{13}ClN_2O_2$	68.48 / 68.87	3.39 / 3.76	8.51 / 8.03	122-124	63 (A) 73 (B) 58 (C)
7	$C_{21}H_{15}ClN_2O_2$	69.46 / 69.52	4.43 / 4.17	7.26 / 7.72	145-147	65 (A) 80 (B) 63 (C)
8	$C_{21}H_{15}ClN_2O_3$	66.23 / 66.58	4.32 / 3.99	7.54 / 7.40	153-155	68

6-Amino-4-aryl-2R-4H-furo[2,3-*b*]pyran-5-carbonitriles **5-8** were isolated with yields of up to 70% (Table 1). The IR spectra of compounds **5-8** contain stretching vibrations in the region of 2240-2220 (CN), 3450-3400 (NH_2), and 3160-3155 cm^{-1} (vibrations of the furan ring). The ^1H NMR spectra contain the following characteristic signals: A singlet at 6.41-6.45 for the proton of the furan ring; a signal in the downfield region at 6.97-7.20 (2H, br. s) for the protons of the amino group; a singlet at 4.97-4.80 ppm for the proton at the tertiary carbon atom H-4. The protons of the aromatic substituents appear as a series of signals at 7.26-7.75 ppm (Table 2).

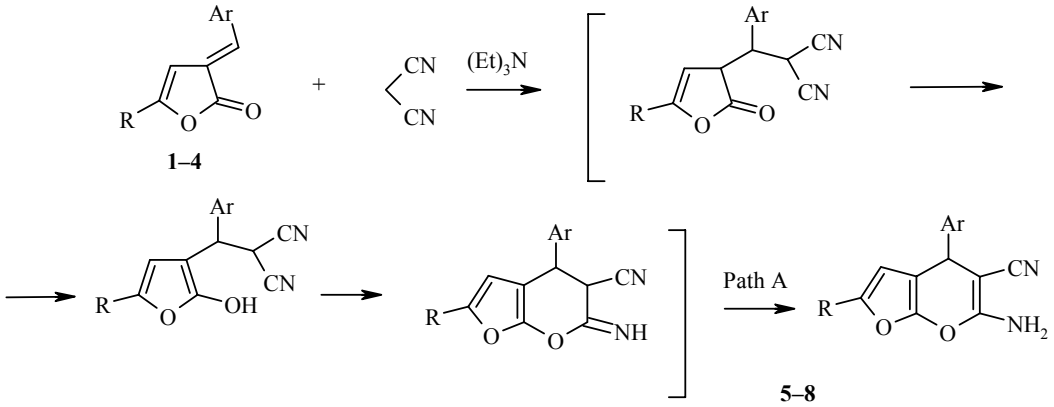
The reaction of 5-aryl-3-arylmethylene-3H-furan-2-ones **1-4** with malononitrile in the presence of an organic base (triethylamine) is of the cascade heterocyclization type (path A). The carbanion of malononitrile is generated under the conditions of base catalysis and then adds at the exocyclic C=C bond with the formation of Michael adducts. Subsequent nucleophilic addition of the hydroxy group of the furan ring to the cyano group of the side chain leads to the cyclization products 6-amino-4-aryl-2R-4H-furo[2,3-*b*]pyran-5-carbonitriles **5-8**.

The furo[2,3-*b*]pyran-5-carbonitriles in turn are polyfunctional compounds having high chemical activity and various biological effects, giving rise to the prospect of finding and developing effective methods for the synthesis of compounds of this series.

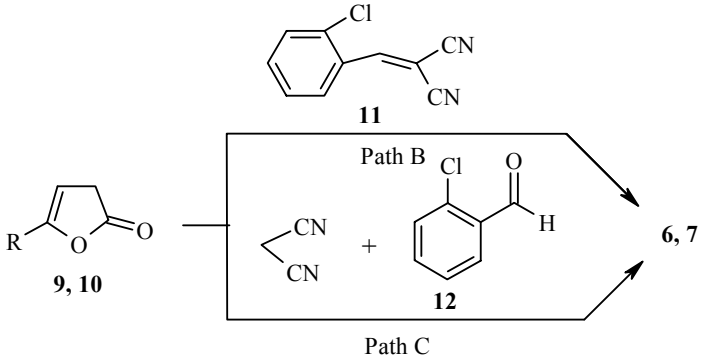
In this connection we developed alternative methods based on the use of 5-R-3H-furan-2-ones **9** and **10** as Michael condensation addends. They are polyfunctional compounds, making them promising for targeted organic synthesis in various types of reactions, including tandem reactions. Furan-2-ones behave as CH acids under the conditions of base catalysis and are capable of acting as addends in the Michael reaction with

TABLE 2. The ^1H NMR Spectra of Compounds **5-8**

Compound	Chemical shifts, δ, ppm					
	Furyl (1H, s)	CH-Ar (1H, s)	NH_2 (2H, s)	Ar (4H, m)	R	CH_3
5	6.00	4.74	6.98	7.05-7.15	1.31-2.35 (11H, m)	—
6	6.41	4.97	7.04	7.26-7.45	7.34-7.65 (5H, m)	—
7	6.45	4.80	7.20	7.30-7.50	7.39-7.53 (4H, m)	2.35
8	6.40	4.88	7.15	6.90-7.17	7.43-7.56 (4H, m)	3.73



α,β-unsaturated compounds like unsaturated nitriles. We studied the reaction of unsubstituted 5-R-3H-furan-2-ones **9** and **10** with the unsaturated nitrile **11**, which was produced by the reaction of an aromatic aldehyde in a 1:1 molar ratio with malononitrile in DMSO in the presence of triethylamine. The reaction begins with Michael addition of the furan-2-ones **9** and **10** at the activated double bond of the unsaturated nitrile **11**, followed by nucleophilic attack at the carbon atom of the cyano group, leading to the formation of a pyran ring and the formation of compounds **6** and **7** (path B).



9 R = Ph; **10** R = *p*-Tol

Multicomponent cascade reactions are of particular interest as methods for the synthesis of polyfunctional carbo- and heterocyclic compounds. The substrates used in the three-component condensation contain several reaction centers, making various combinations of paired reactions of all the components possible (path C).

A Knoevenagel reaction of the aromatic aldehyde **12** with the dinitrile of malonic acid probably takes place initially, and this is followed by reaction of the furan-2-ones **9** and **10** with the unsaturated nitrile. Further cyclization leads to 6-amino-4-aryl-2R-4H-furo[2,3-*b*]pyran-5-carbonitriles **6** and **7**.

There is also another reaction path in which the aldehyde **12** reacts with the furan-2-ones **9** and **10** at the first stage, malononitrile adds to the reaction product, and heterocyclization occurs. We were, however, unable to isolate the intermediate, and this hinders the choice of initial reaction path.

The physicochemical characteristics of compounds **6** and **7** produced from the (arylmethylene)furan-2-ones and by the multicomponent reactions fully coincide.

Thus, the reaction of 5-R-3-arylmethylene-3H-furan-2-ones with malononitrile was studied. As a result products containing nitrile and amino groups are formed, and they open up paths for further functionalization of the obtained compounds and are, moreover, valuable biologically active substances in their own right.

EXPERIMENTAL

The IR spectra were recorded on an FSM-1201 Fourier spectrometer in tablets with KBr in the region of 400-4000 cm^{-1}. The ^1H NMR spectra were obtained in $CDCl_3$ on a Bruker MSL-400 spectrometer (400 MHz) at 20-25°C with TMS as internal standard. Thin-layer chromatography was performed on Silufol UV-254 plates in the 2:2:1 hexane–ethyl acetate–chloroform system with iodine vapor as developer.

The arylmethylene-substituted 3H-furan-2-ones **1**-**4** and 5-R-3H-furan-2-ones **9** and **10** were obtained by the known method [4].

6-Amino-4-aryl-2R-4H-furo[2,3-*b*]pyran-5-carbonitriles 5-8. A. To a mixture of the arylmethylene-substituted 3H-furan-2-one **1**-**4** (0.01 mol) and malononitrile (0.01 mol) we added a few drops of triethylamine in DMSO solution. The reaction mixture was heated for 4-5 h, poured into cold water, and neutralized with dilute HCl. The crystals that separated were filtered off and recrystallized from hexane (Tables 1 and 2).

B. To a mixture of 5-R-3H-furan-2-one **9** or **10** (0.01 mol) and the unsaturated nitrile **11** (0.01 mol), obtained by the method in [5], we added a few drops of triethylamine in DMSO solution. The mixture was treated similarly to method A.

C. To a mixture of 5-R-3H-furan-2-one **9** or **10** (0.01 mol), the aromatic aldehyde (0.01 mol), and malononitrile (0.01 mol) we added a few drops of triethylamine in DMSO solution. The mixture was treated similarly to method A.

REFERENCES

1. Z. Yu. Timofeeva and A. Yu. Yegorova, *Khim. Geterotsikl. Soedin.,* 823 (2007). [*Chem. Heterocycl. Comp.*, **43**, 690 (2007)].
2. A. Yu. Yegorova and V. V. Chadina, *Khim. Geterotsikl. Soedin.,* 1457 (2007). [*Chem. Heterocycl. Comp*., **43**, 1233 (2007)].
3. T. V. Aniskova, A. Yu. Yegorova, and V. V. Chadina, *Mendeleev Commun.*, **18**, 167 (2008).
4. V. A. Sedavkina, N. A. Morozova, A. Yu. Yegorova, and I. G. Ostroumov, *Khim. Geterotsikl. Soedin.,* 451 (1987). [*Chem. Heterocycl. Comp*., **23**, 377 (1987)].
5. A. M. Shestopalov, V. P. Litvinov, L. A. Rodinovskaya, and Yu. A. Sharanin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 146 (1991).