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ONE-POT SYNTHESIS OF 2-(2-ALKOXY-5-AMINO-4-CYANO-2-METHYLFURAN-3(2H)-YLIDENE)MALONONITRILES

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A new preparative method was developed for the synthesis of 2-(2-alkoxy-5-amino-4-cyano-2-methyl-3(2H)-ylidene)malononitriles in a single stage from readily obtainable reagents.

Keywords: dihydrofurans, enamino nitriles, tetracyanocyclopropanes, multicomponent reaction, *one-pot* synthesis.

At present multicomponent systems have begun to be used ever more widely for the synthesis of various heterocyclic systems [1, 2]. Their advantages are a decrease in the amount of solvents used and an increase in the yields of the targeted compounds on account of the reduction in the number of stages in the synthesis. Moreover, the development of convenient methods of production has stimulated research into the reactivity of previously not readily obtainable compounds. We have developed a single-stage method for the synthesis of 2-(2-alkoxy-5-amino-4-cyanofuran-3(2H)-ylidene)malononitriles [3]. On account of the laborious nature of their production and the high cost of the reagents in the previously developed method of synthesis [3] their chemical properties have remained practically uninvestigated. The presence of the enamino nitrile and ylidene-malononitrile fragments in their structure makes it possible to use them as starting compounds in the synthesis of complex heterocyclic structures. In addition, the appearance of biological activity is possible in these compounds since representatives exhibiting anti-inflammatory and antimicrobial activity are known among compounds of the dihydrofuran series [4-8].

The main point of the method that we developed is the reaction of methylglyoxal **1**, malononitrile, monobromomalononitrile, and an aliphatic alcohol **2**, which also acts as solvent. In the course of the reaction 2-(2-alkoxy-5-amino-4-cyano-2-methylfuran-3-(2H)-ylidene)malononitriles **4a-h** are formed in one technological stage with yields of 53-69% (Table 1).

We established that the transformations take place through the formation of 3-acetylcyclopropane-1,1,2,2-tetracarbonitrile (**3**) [9], which was isolated from the reaction mixture with small yields and identified on the basis of data from IR spectroscopy and mass spectrometry.

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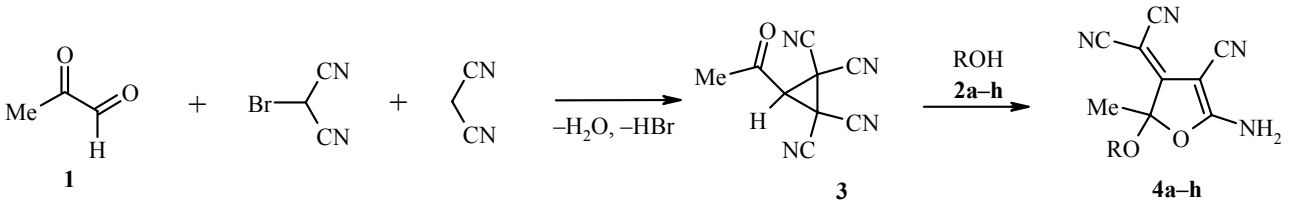
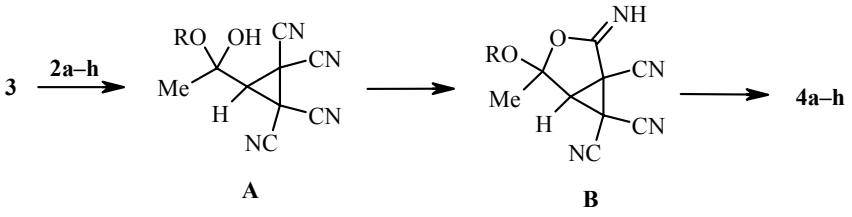


2,4 **a** R = Pr, **b** R = *i*-Pr, **c** R = Bn, **d** R = Et, **e** R = *i*-Bu, **f** R = *s*-Bu, **g** R = *n*-Bu, **h** R = Me

The formation of compound **3** at the intermediate stage is probably similar to the formation of 3-aroylcyclopropane-1,1,2,2-tetracarbonitrile, a method for the synthesis of which we developed earlier [10]. The reaction of the cyclopropane **3** isolated from the reaction mixture with the alcohols **2a-h** also leads to the formation of the dihydrofurans **4a-h** with yields of 58-72% (Table 1).



The reaction mechanism may include attack by the alcohols on the carbonyl group of cyclopropane with the formation of the hemiketal **A**. This is then followed by intramolecular heterocyclization with participation of the sterically close hydroxyl and cyano groups and the formation of the furan ring of the intermediate **B**. The final compound **4** is formed as a result of subsequent opening of the three-membered ring.

In the IR spectra of compounds **4** there are strong bands of stretching vibrations characteristic of the conjugated cyano groups in the region of 2216-2218, for the C=C bond of the dicyanomethylene fragment in the region of 1688-1695, and two broad bands in the regions of 3108-3150 and 3257-3288 cm^{-1} characteristic of the amino group. The structures of the synthesized compounds were supported by data from the IR, ^1H NMR (Table 2), and mass spectra.

TABLE 1. Data from Elemental Analysis, Melting Points, and Yields of Compounds **4a-h**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	
		C	H	N		A	B
4a	$C_{12}H_{12}N_4O_2$	59.12 / 59.01	4.87 / 4.95	22.79 / 22.94	184	67	72
4b	$C_{12}H_{12}N_4O_2$	59.16 / 59.01	4.88 / 4.95	22.88 / 22.94	188	62	66
4c	$C_{16}H_{12}N_4O_2$	65.63 / 65.75	4.09 / 4.14	19.05 / 19.17	237	53	58
C4d	$C_{11}H_{10}N_4O_2$	57.32 / 57.39	4.28 / 4.38	24.27 / 24.34	182	66	78
4e	$C_{13}H_{14}N_4O_2$	60.40 / 60.45	5.39 / 5.46	21.56 / 21.69	185	62	67
4f	$C_{13}H_{14}N_4O_2$	60.41 / 60.45	5.42 / 5.46	21.62 / 21.69	190	69	65
4g	$C_{13}H_{14}N_4O_2$	60.52 / 60.45	5.47 / 5.46	21.62 / 21.69	188	67	64
4h	$C_{10}H_8N_4O_2$	55.51 / 55.55	3.68 / 3.73	25.95 / 25.91	240	69	83

TABLE 2. Spectral Characteristics of Compounds **4a-h**

Compound	IR spectrum, ν, cm^{-1} (N–H, C≡N, C=C)	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	Mass spectrum, *m/z* $[M]^+$
4a	3272, 3136, 2216, 1690	10.18 (1H, s, NH_2); 10.12 (1H, s, NH_2); 3.37 (2H, m, $OC\underline{H}_2CH_2CH_3$); 1.78 (3H, s, CH_3); 1.56 (2H, m, $OCH_2C\underline{H}_2CH_3$); 0.9 (3H, t, *J* = 7.3, $OCH_2CH_2C\underline{H}_3$)	244
4b	3274, 3137, 2216, 1688	10.20 (1H, s, NH_2); 10.13 (1H, s, NH_2); 3.85 (1H, m, $OC\underline{H}(CH_3)_2$); 1.78 (3H, s, CH_3); 1.20 (3H, d, *J* = 6.1, CH_3), 1.14 (3H, d, *J* = 6.1, CH_3)	244
4c	3276, 3131, 2215, 1693	10.27 (1H, s, NH_2); 10.23 (1H, s, NH_2); 7.37 (5H, m, C_6H_5); 4.50 (2H, m, $OC\underline{H}_2C_6H_5$); 1.84 (3H, s, CH_3)	292
4d	3258, 3112, 2217, 1693	10.20 (1H, s, NH_2); 10.15 (1H, s, NH_2); 3.46 (2H, m, $OC\underline{H}_2CH_3$); 1.77 (3H, s, CH_3); 1.17 (3H, t, *J* = 6.7, $OCH_2C\underline{H}_3$)	230
4e	3283, 3143, 2216, 1688	10.18 (1H, s, NH_2); 10.12 (1H, s, NH_2); 3.18 (2H, m, $OC\underline{H}_2CH(CH_3)_2$); 1.80 (3H, s, CH_3); 1.80 (1H, m, $OCH_2C\underline{H}(CH_3)_2$); 0.9 (3H, d, *J* = 6.7, CH_3); 0.89 (3H, d, *J* = 6.7, CH_3)	258
4f	3283, 3153, 2216, 1689	10.19 (1H, s, NH_2); 10.12 (1H, s, NH_2); 3.7 (1H, m, $OC\underline{H}(CH_3)CH_2CH_3$); 1.80 (3H, s, CH_3); 1.51 (2H, m, $C\underline{H}_2CH_3$); 1.12 (3H, d, *J* = 6.1, CH_3); 0.85 (3H, t, *J* = 6.4, $CH_2C\underline{H}_3$)	258
4g	3282, 3136, 2216, 1689	10.18 (1H, s, NH_2); 10.12 (1H, s, NH_2); 3.40 (2H, m, $OC\underline{H}_2CH_2CH_2CH_3$); 1.77 (3H, s, CH_3); 1.52 (2H, m, $OCH_2C\underline{H}_2CH_2CH_3$); 1.36 (2H, m, $OCH_2CH_2C\underline{H}_2CH_3$); 0.88 (3H, t, *J* = 7.4, $OCH_2CH_2CH_2C\underline{H}_3$)	258
4h	3263, 3109, 2221, 1695	10.19 (2H, s, NH_2); 3.32 (3H, s, OCH_3); 1.77 (3H, s, CH_3)	216

Thus, we have developed a new preparative method for the synthesis of 2-(2-alkoxy-5-amino-4-cyano-2-methylfuran-3(2H)-ylidene)malononitriles **4a-h** and have proposed a possible mechanism for the reaction.

EXPERIMENTAL

The reactions and the purity of the synthesized substances were monitored by TLC on Silufol UV-254 plates (development in UV light, with iodine vapor, and by thermal decomposition). The IR spectra were recorded in vaseline oil on an FSM-1202 Fourier spectrometer. The ^{1}H NMR spectra were obtained on a Bruker DRX-500 spectrometer (500 MHz) in DMSO-d_6 with TMS as internal standard. The mass spectra were obtained on a Shimadzu GCMS-QP 2010S DI instrument (EI 70 eV).

Monobromomalononitrile. To a solution of malononitrile (6.6 g. 0.1 mol) in a mixture of water (20 ml) and 2-propanol (20 ml) with vigorous stirring we added in small portions bromine (16 g, 0.1 mol). The temperature of the reaction mixture was kept in the range of 20-25°C, the mixture was stirred for a further 15 min, and it was then left at 0°C for 10 h. The precipitate that separated was filtered off and washed with cold water.

2-(2-Alkoxy-5-amino-4-cyano-2-methylfuran-3(2H)-ylidene)malononitrile 4a-h (General Method). A. To a solution of methylglyoxal **1** (0.72 g, 0.01 mol) in aliphatic alcohol (20 ml) with stirring we added in one portion malononitrile (0.66 g, 0.01 mol) and after it had completely dissolved monobromomalononitrile (1.45 g, 0.01 mol). After some time a precipitate separated, and it gradually dissolved. The mixture was left covered

until the cyclopropane had completely disappeared. It was then evaporated, and 10 ml of water was added. The precipitate was filtered off and washed with water. The product was purified by reprecipitation from the respective alcohol with water.

B. A mixture 3-acetylcyclopropane-1,1,2,2-tetracarbonitrile (1.88 g, 0.01 mol) and aliphatic alcohol **2a-h** (20 ml) was boiled for 3 h. It was then evaporated to dryness, water (10 ml) was added, and the precipitate was filtered off and washed with water.

3-Acetylcyclopropane-1,1,2,2-tetracarbonitrile (3). To a solution of methylglyoxal **1** (0.72 g, 0.01 mol) in aliphatic alcohol (20 ml) with stirring we added in one portion malononitrile (0.66 g, 0.01 mol) and after it had completely dissolved monobromomalononitrile (1.45 g, 0.01 mol). The precipitate that separated after a short time was filtered off and washed with alcohol and with water, and compound **3** was obtained; mp 184°C. IR spectrum, ν, cm^{-1}: 3059, 2265, 1730. Mass spectrum, *m*/*z*: 184 $[M]^+$.

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