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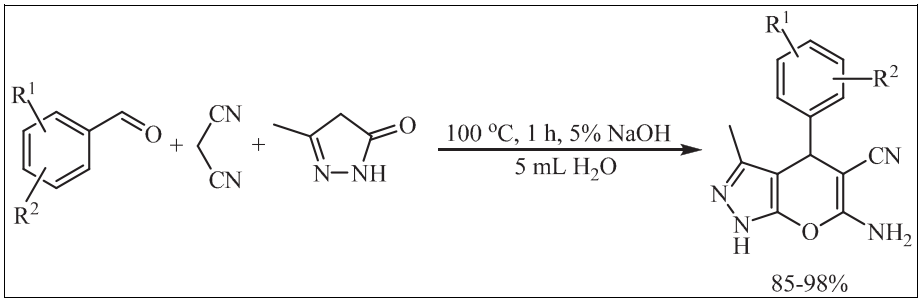

"On water" multicomponent condensation of aromatic aldehydes, malononitrile, and 3-methyl-2-pyrazoline-5-one in the presence of sodium hydroxide as catalyst leads to 6-amino-3-methyl-4-aryl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitriles in 85–98% yields.

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INTRODUCTION

Functionalized pyrano[2,3-*c*]pyrazoles have a broad spectrum of biological activities [1–5]. These compounds are known as different pharmacologically active substances, including antibiotics [1,2], enzyme inhibitors [3–5], and anticancer drugs [2]. The methods of pyrano[2,3-*c*]pyrazoles synthesis have long been documented and consist of two main groups: (1) two-step synthesis and (2) "one-pot" multicomponent condensation. The reaction of aromatic aldehydes, malononitrile, and 3-methyl-2-pyrazoline-5-one is well known and most efficient way to pyrano[2,3-*c*] pyrazoles [6–12]. This multicomponent process includes Knoevenagel condensation of aromatic aldehyde and malononitrile, Michael reaction of formed Knoevenagel adduct with 3-methyl-2-pyrazolin-5-one, and final cyclization step to appropriate pyrano[2,3-*c*]pyrazole. The main disadvantages of the known processes are large volumes of toxic solvents [6–8,11,12], 10–20 mol% of expensive or complex catalysts (indium(III) chloride [9], $H_{14}[NaP_5W_{30}O_{110}]$ [10]), and specific reaction conditions: sonication [11] and microwave irradiation [9,12]). Also, the most part of known methods are characterized by long and complex isolation stage. Thus, we were prompted to design ecologically convenient simple and efficient method for synthesis of substituted pyrano[2,3-*c*]pyrazoles in connection with demands of "green chemistry".

RESULTS AND DISCUSSION

In the present study, we report our results on the direct "one-pot" transformation of aromatic aldehydes **1a–g**, malononitrile, and 3-methyl-2-pyrazolin-5-one to pyrano [2,3-*c*]pyrazoles **2a–g** under solvent-free conditions or in the presence of small amounts of such ecologically pure solvent as water, according with the requirements of "green chemistry" (Scheme 1).

First, to evaluate the synthetic potential of the solvent-free procedure and to optimize the general conditions, the multicomponent condensation of benzaldehyde **1a**, malononitrile, and 3-methyl-2-pyrazolin-5-one under solvent-free conditions was studied (Table 1, Scheme 2).

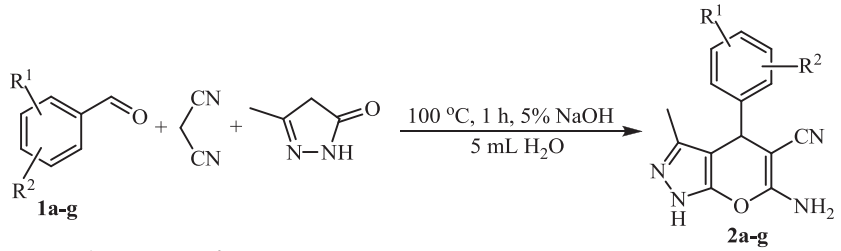
It was found that under solvent-free conditions, formation of both open **3a** and cyclic **2a** forms was observed (Table 1). Moreover, some other by-products [benzalmalononitrile and 4,4′-(phenylmethanediyl)bis(3-methyl-1*H*-pyrazol-5-ol)] were found in the reaction mixture in 5–12% yields.

Then, the water, as the most ecologically pure solvent, was chosen as a solvent for the carrying out of the multicomponent reaction of benzaldehyde, malononitrile, and 3-methyl-2-pyrazoline-5-one. Sodium hydroxide was chosen as a base catalyst because it is not toxic, cheap and is the strongest base in water conditions.

The process was carried out as "one-pot" reaction by stirring of suspension of benzaldehyde **1a**, malononitrile, and 3-methyl-2-pyrazolin-5-one in water, in the presence of sodium hydroxide. When stirring of the reaction mixture for 15 min at 60°C without base (Table 2, entry 1), the open form **3a** was obtained in 100% yield. Addition of NaOH (Table 2, entries 2–4) resulted in partial cyclization of **3a** into **2a**, but the yield of **2a** was still low.

Increasing the temperature of the reaction to 100°C (Table 2, entry 5) provides full cyclization of **3a** to pyrano[2,3-*c*]pyrazole **2a**, but 4,4′-(phenylmethanediyl)bis (3-methyl-1*H*-pyrazol-5-ol) was also found in the reaction

Scheme 1



1a-g **2a-g**

a R^1 = H R^2 = H
b R^1 = 4-Me R^2 = H
c R^1 = 4-F R^2 = H
d R^1 = 4-Cl R^2 = H
e R^1 = 4-OMe R^2 = H
f R^1 = 3-OMe R^2 = 4-OMe
g R^1 = 4-NO2 R^2 = H

Table 1

Multicomponent condensation of benzaldehyde **1a**, malononitrile, and 3-methyl-2-pyrazoline-5-one under solvent-free conditions.[a]

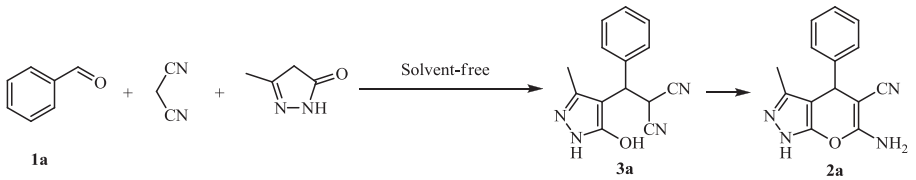
Entry	Catalyst	Time (min)	Temperature (°C)	Yield **3a** (%)[b]	Yield **2a**(%)[b]
1	—	15	60	74	17
2	KF	15	60	61	22
3	KF	60	60	46	38
4	NaOAc	15	60	78	14
5	NaOAc	60	60	72	23

[a]Benzaldehyde **1a** (5 mmol), malononitrile (5 mmol), 3-methyl-2-pyrazolin-5-one (5 mmol), catalyst (0.5 mmol).
[b]^{1}H NMR data.

mixture in small amount (5%) because of partial polymerization of malononitrile in alkaline medium [13]. To compensate the loss of malononitrile, 10% excess of malononitrile was used in further experiments (Table 2, entries 6 and 7). Thus, under optimal conditions (10% excess of malononitrile, 100°C, 5 mol% NaOH, 1 h), pyrano[2,3-*c*]pyrazole **2a** was isolated in 98% yield.

Under these optimal conditions thus found, that is, 10% excess of malononitrile, 100°C, 1 h, 5 mol% NaOH in water, the benzaldehydes **1a–g**, malononitrile, and 3-methyl-2-pyrazolin-5-one were transformed into corresponding substituted pyrano[2,3-*c*]pyrazoles **2a–g** in 85–98% yields (Scheme 1, Table 3).

Scheme 2



1a **3a** **2a**

Table 2

Multicomponent condensation of benzaldehyde **1a**, malononitrile, and 3-methyl-2-pyrazoline-5-one in the presence of water and sodium hydroxide.[a]

Entry	Excess of $CH_2(CN)_2$	Catalyst	Amount of base (%mol)	Time (min)	Temperature (°C)	Yield **3a** (%)[b]	Yield **2a** (%)[b]
1	—	—	—	15	60	100	0
2	—	NaOH	2	15	60	88	7
3	—	NaOH	5	15	60	81	15
4	—	NaOH	5	60	60	65	33
5	—	NaOH	5	60	100	0	95
6	10%	NaOH	5	30	100	5	93
7	10%	NaOH	5	60	100	0	100

[a]Benzaldehyde **1a** (5 mmol), malononitrile (5–5.5 mmol), 3-methyl-2-pyrazolin-5-one (5 mmol), 5 mL of H_2O.
[b]^{1}H NMR data.

Table 3

Multicomponent condensation of aromatic aldehydes **1a–g**, malononitrile, and 3-methyl-2-pyrazoline-5-one into pyrano[2,3-*c*]pyrazoles **3a–g**.[a]

Aldehyde	R^1	R^2	Pyrano[2,3-*c*] pyrazoles	Yield (%)[b]
1a	H	H	**3a**	98
1b	4-Me	H	**3b**	93
1c	4-F	H	**3c**	90
1d	4-Cl	H	**3d**	85
1e	4-OMe	H	**3e**	89
1f	3-OMe	4-OMe	**3f**	94
1g	4-NO_2	H	**3g**	86

[a]Aromatic aldehyde (5 mmol), malononitrile (5.5 mmol, 0.36 g), 3-methyl-2-pyrazolin-5-one (5 mmol, 0.49 g), sodium hydroxide (0.25 mmol, 0.01 g), water (5 mL), 100°C, 60 min.
[b]Isolated yields.

Taking into consideration our and literature [6,7] data, the following reaction scheme was proposed for the direct multicomponent transformation of aromatic aldehydes, malononitrile, and 3-methyl-2-pyrazolin-5-one into substituted pyrano[2,3-*c*]pyrazoles.

First, by the action of base, the anions of malononitrile arise in the solution, and then, by the usual way, Knoevenagel condensation of carbonyl compound with anion of malononitrile takes place with the formation of arylidenemalononitrile. Addition of 3-methyl-2-pyrazolyn-5-one to arylidenemalononitrile leads to anion **A**, which cyclized into anion **B**. Subsequent protonation of anion **B** leads to the corresponding pyrano[2,3-*c*]pyrazoles **3a–g** (Scheme 3).

CONCLUSION

In conclusion, "one-pot" multicomponent reaction of aromatic aldehydes, malononitrile, and 3-methyl-2-pyrazoline-5-one in a small amount of water ("on water reaction" [15]) in the presence of 5 mol% of sodium hydroxide leads to pyrano[2,3-*c*]pyrazoles selectively in excellent yields. This novel multicomponent process offers an efficient and convenient way to create pyrano[2,3-*c*]pyrazoles, the prominent compounds with approved different biomedical applications [1–5]. The procedure utilizes inexpensive reagents, it is easily carried out, and the work up is not complicated. Pyrano[2,3-*c*]pyrazoles are crystallized directly from the reaction mixture; consequently, the isolation includes only filtration and washing with cold water. Thus, the proposed process is more efficient and environmentally friendly compared with those known today.

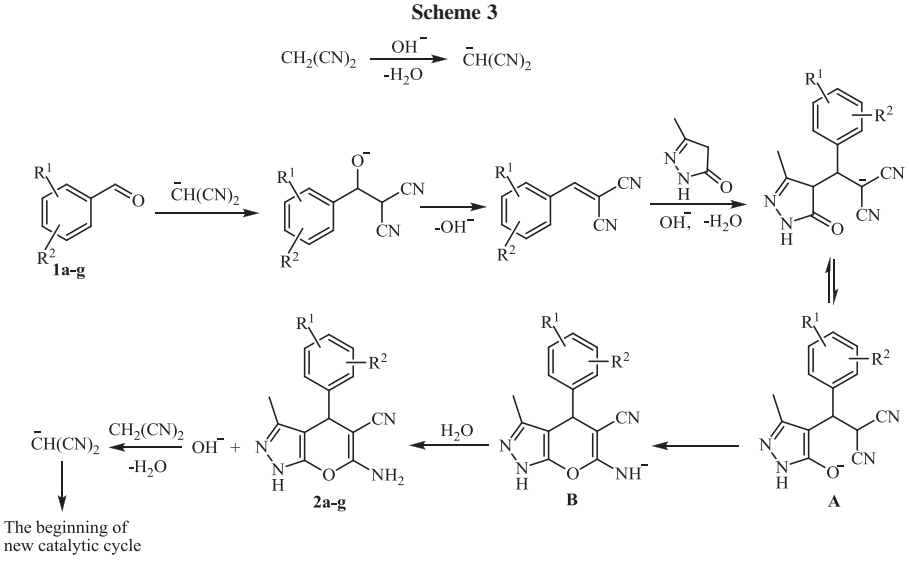
EXPERIMENTAL

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance II 300 (300 MHz) spectrometer in DMSO-d_6 solutions at ambient temperature. Chemical shifts are given in δ scale relative to Me_4Si. IR spectra were registered with a SPECORD M82 spectrometer in KBr pellets. Mass spectra (EI, 70 eV) were obtained directly with a Finningan MAT INCOS 50 spectrometer. All materials were purchased from Aldrich (Sigma-Aldrich Company Ltd., The Old Brickyard, New Road, Gillingham, Dorset, SP8 4XT, UK) and Acros (ACRUS, Leninsky Prospekt 47, 117913 Moscow, Russian Federation).

General solvent-free procedure. A mixture of benzaldehyde (5 mmol, 0.53 g), malononitrile (5 mmol, 0.33 g), 3-methyl-2-pyrazolin-5-one (5 mmol, 0.49 g), and base (0.5 mmol if used) was stirred at 60°C. Then, the reaction mixture was cooled and suspended in cold water (5 mL). The suspension was filtered, washed with cold water (2 × 10 mL), and dried at 20 mmHg.

General "on water" procedure. A suspension of benzaldehyde (5 mmol, 0.53 g), malononitrile (5 or 5.5 mmol, 0.33 or 0.36 g), 3-methyl-2-pyrazolin-5-one (5 mmol, 0.49 g), and sodium hydroxide (up to 0.25 mmol) was stirred in 5 mL of water. Then, the reaction

Scheme 3



mixture was cooled and diluted with 5 mL of water. The precipitate was filtered, washed with cold water (2 × 10 mL), and dried at 20 mmHg.

Synthesis of pyrano[2,3-c]pyrazoles 2a–g. General procedure. A suspension of arylaldehyde (5 mmol), malononitrile (5.5 mmol), 3-methyl-2-pyrazolin-5-one (5 mmol), and sodium hydroxide (0.25 mmol) in 5 mL of water was stirred at 100°C for 60 min. Then, the reaction mixture was cooled and diluted with 5 mL of water. The precipitate was filtered, washed with cold water (2 × 10 mL), and dried at 20 mmHg.

6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2a). Pale yellow solid. Yield 1.24 g (98%); mp 256–258°C (lit. mp [6] 244–245°C). ^{1}H NMR: 1.77 (s, 3H, CH_3), 4.59 (s, 1H, CH), 6.83 (s, 2H, NH_2), 7.10–7.35 (m, 5H, Ph), 12.08 (s, 1H, NH).

6-Amino-3-methyl-4-(4-methylphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2b). Pale yellow solid. Yield 1.23 g (93%); mp 213–215°C (lit. mp [6] 197–198°C). ^{1}H NMR: 1.77 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.52 (s, 1H, CH), 6.81 (s, 2H, NH_2), 7.04 (d, J = 7.3 Hz, 2H, Ar), 7.11 (d, J = 7.3 Hz, 2H, Ar), 12.08 (s, 1H, NH).

6-Amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2c). Pale yellow solid. Yield 1.20 g (90%); mp 244–245°C (lit. mp [14] 245°C). ^{1}H NMR: 1.77 (s, 3H, CH_3), 4.62 (s, 1H, CH), 6.87 (s, 2H, NH_2), 7.08–7.25 (m, 4H, Ar), 12.11 (s, 1H, NH).

6-Amino-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2d). Pale yellow solid. Yield 1.22 g (85%); mp 233–234°C (lit. mp [14] 233°C). ^{1}H NMR: 1.78 (s, 3H, CH_3), 4.63 (s, 1H, CH), 6.90 (s, 2H, NH_2), 7.19 (d, J = 8.4 Hz, 2H, Ar), 7.37 (d, J = 8.4 Hz, 2H, Ar), 12.12 (s, 1H, NH).

6-Amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2e). Pale yellow solid. Yield 1.25 g (89%); mp 224–225°C (lit. mp [6] 225–226°C). ^{1}H NMR: 1.78 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.52 (s, 1H, CH), 6.82 (s, 2H, NH_2), 6.87 (d, J = 8.4 Hz, 2H, Ar), 7.08 (d, J = 8.4 Hz, 2H, Ar), 12.08 (s, 1H, NH).

6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2f). White solid. Yield 1.46 g (94%); mp 201–203°C. ^{1}H NMR: 1.81 (s, 3H, CH_3), 3.70 (s, 6H, $2OCH_3$), 4.64 (s, 1H, CH), 6.83 (s, 2H, NH_2), 6.6–6.9 (m, 3H, Ar), 12.08 (s, 1H, NH). ^{13}C NMR: 9.8, 35.9, 55.4, 55.5, 57.5, 97.7, 111.3, 111.8, 119.5, 120.8, 133.6, 136.9, 147.6, 148.6, 154.7, 160.8 ppm. IR (KBr): ν_{max} 3458, 3254, 3123, 2191, 1638, 1599, 1515, 1491, 1398 cm^{-1}. MS, m/z (%) = 312 (M^+, 33), 281 (5), 246 (5), 175 (100), 138 (8), 79 (10), 42 (12). *Anal.* Calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.59; H, 5.14; N, 17.90.

6-Amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2g). Pale yellow solid. Yield 1.28 g (86%); mp 257–259°C (lit. mp [6] 251–252°C). ^{1}H NMR: 1.79 (s, 3H, CH_3), 4.81 (s, 1H, CH), 7.01 (s, 2H, NH_2), 7.46 (d, J = 8.8 Hz, 2H, Ar), 8.20 (d, J = 8.8 Hz, 2H, Ar), 12.18 (s, 1H, NH).

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