Green approach to the design of functionalized medicinally privileged 4-aryl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile scaffold

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Key words: multicomponent reaction, aromatic aldehyde, malononitrile, pyrazolones, Knoevenagel reaction, Michael reaction, pyranopyrazoles.

Multicomponent condensation of aromatic aldehydes, malononitrile and 3-methyl-2-pyrazoline-5-one in the presence of water leads to 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in 89-92% yields.

Functionalized pyrano[2,3-*c*]pyrazoles have a broad spectrum of biological activities [1-7]. These compounds are known as different biologically active substances, including antibiotics [1, 2, 3], enzyme inhibitors [4, 5, 6], antifungal [7] and anticancer [2] drugs. In this regard, the development of simple and effective methods of obtaining functionally substituted pyrano[2,3-*c*]pyrazoles is an important task.

Though methods of pyrano[2,3-*c*]pyrazoles synthesis have long been documented, so far, all of them 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 the most known example of this type [8,10]). This way of synthesis includes Knoevenagel condensation of aromatic aldehyde and malononitrile, Michael reaction of formed product with 3-methyl-2-pyrazolin-5-one and final cyclization of Knoevenagel-Michael adduct to appropriate pyrano[2,3-*c*]pyrazole (Scheme 1) [8].

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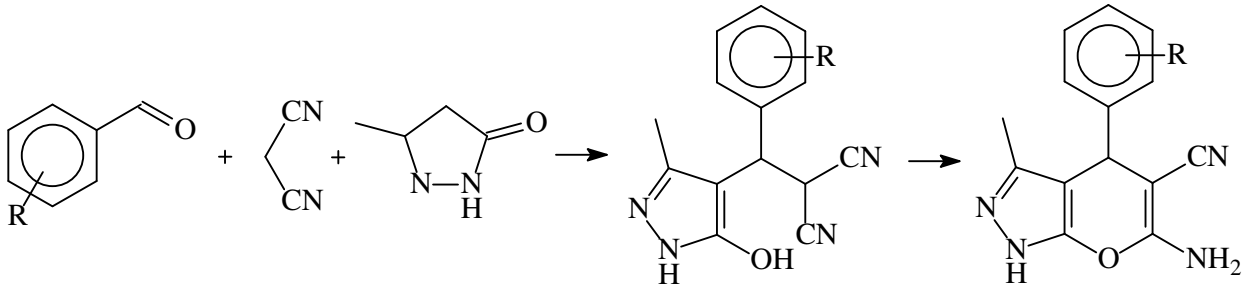
Scheme 1.

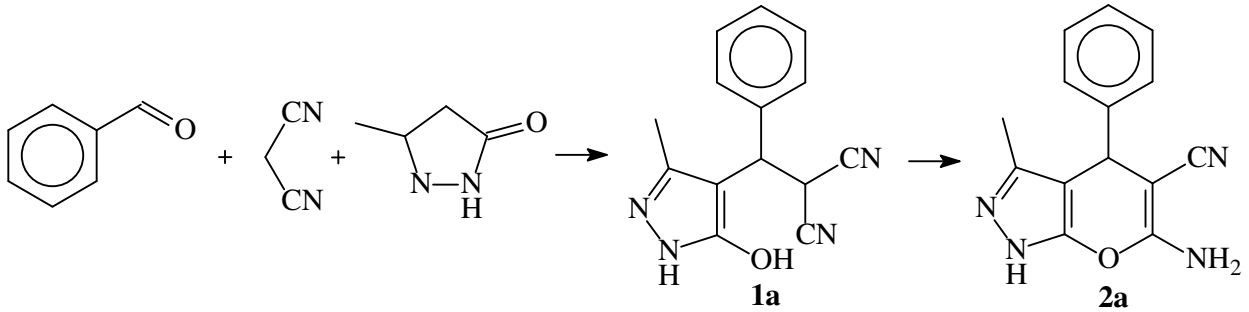


The main disadvantages of known processes are: large volumes of toxic solvents (methanol, 1,4-dioxane), inconvenient catalysts (organic amines, magnesium oxide and sodium methanolate) and long reaction time (more than 6 hours) [8, 10].

In the present study we report our results on the direct 'one-pot' transformation of aromatic aldehydes, malononitrile and 3-metil-2-pyrazolin-5-one to pyrano[2,3-*c*]pyrazoles under solvent-free conditions and in presence of small amounts of water, according with the requirements of "green chemistry".

First, to evaluate the synthetic potential of the proposed procedure and to optimize the general conditions, the multicomponent condensation of benzaldehyde, malononitrile and 3-methyl-2-pyrazolin-5-one into 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile **2a** was studied (Tables 1, 2, Scheme 2).

Scheme 2.



1a **2a**

Table 1. Multicomponent condensation of benzaldehyde, malononitrile and 3-methyl-2-pyrazoline-5-one without solvent.[a]

№	Base	Amount of base (% mol.)	Time (min.)	temperature	Yield 1a (%)[b]	Yield 2a (%)[b]
1	KF	10	15	60	61	22
2	KF	10	60	60	46	35
3	NaOAc	10	15	60	76	12
4	NaOH	2	15	60	67	0

[a] Benzaldehyde (5 mmoles, 0.53 g), malononitrile (5 mmoles, 0.33 g), 3-methyl-2-pyrazolin-5-one (5 mmoles, 0,49 g).

[b] ^{1}H NMR data.

Reactions without solvent were not successful. As a result, there were a lot of co-products (benzalmalononitrile and 4,4'-(phenylmethanediyl)bis(3-methyl-1H-pyrazol-5-ol). Reactions in water were much more successful.

Table 2. Multicomponent condensation of benzaldehyde, malononitrile and 3-methyl-2-pyrazoline-5-one in presence of water.[a]

№	Excess of $CH_2(CN)_2$	Base	Amount of base (% mol.)	Time (min.)	Temperature	Yield 1a (%)[b]	Yield 2a (%)[b]
1	0%	-	-	15	60	100	0
2	0%	NaOH	2	15	60	94	0
3	0%	NaOH	5	15	60	85	7
4	0%	NaOH	5	60	60	77	10
5	0%	NaOH	5	60	100	0	95
7	10%	NaOH	5	60	100	0	100

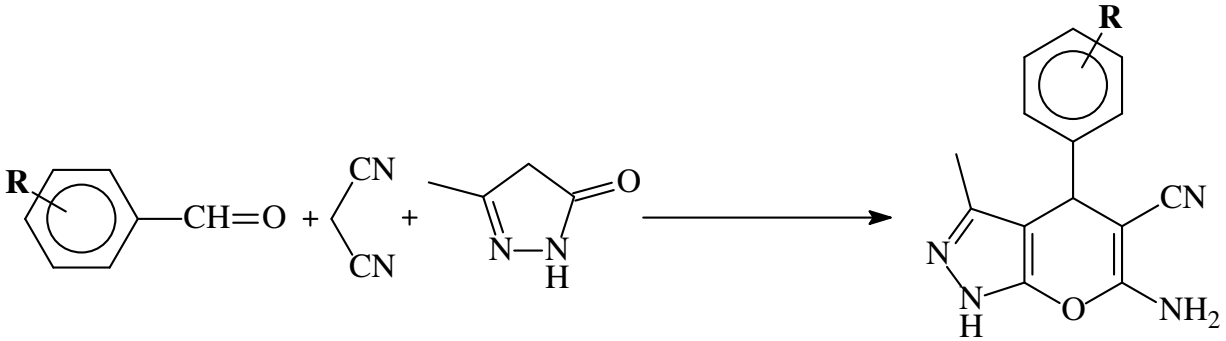
[a] Benzaldehyde (5 mmoles, 0.53 g), malononitrile (5 or 5.5 mmoles, 0.33 or 0,36 g), 3-methyl-2-pyrazolin-5-one (5 mmoles, 0,49 g), 5 ml of H_2O.

[b] ^{1}H NMR data.

The process was carried out in one experimental stage by stirring of suspension of benzaldehyde, malononitrile and 3-methyl-2-pyrazolin-5-one in water, in the presence of sodium hydroxide. Optimal conditions for the process are: 10% excess of malononitrile, 100°C, 5 mol.% NaOH and 60 minutes. A decrease in the temperature to 60°C led to decrease in the yield of the target product, and **1a** was found in the reaction mixture. A decrease in the base amount to 2 mol.% led to decrease of cyclization rate, so there was only **1a** in the reaction mixture. A decrease in the time of reaction also led to decrease of yield of pyrano[2,3-*c*]pyrazole because cyclization did not have sufficient time to go completely. The necessity of using excess malononitrile can be explained by its partial polymerization in alkaline medium [9].

Under the optimal conditions thus found, i.e., 10% excess of malononitrile, 100°C, 5 mol.% NaOH, 60 min. in 5 ml of water, the substituted benzaldehydes **3a-d**, malononitrile and 3-methyl-2-pyrazolin-5-one were transformed into corresponding substituted pyrano[2,3-*c*]pyrazoles **2a–d** in 89–92% yields (Scheme 3, Table 3).

Scheme 3.



3b-d **2b-d**

Compounds **2,3**	R
b	4-Me
c	4-F
d	4-OMe

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

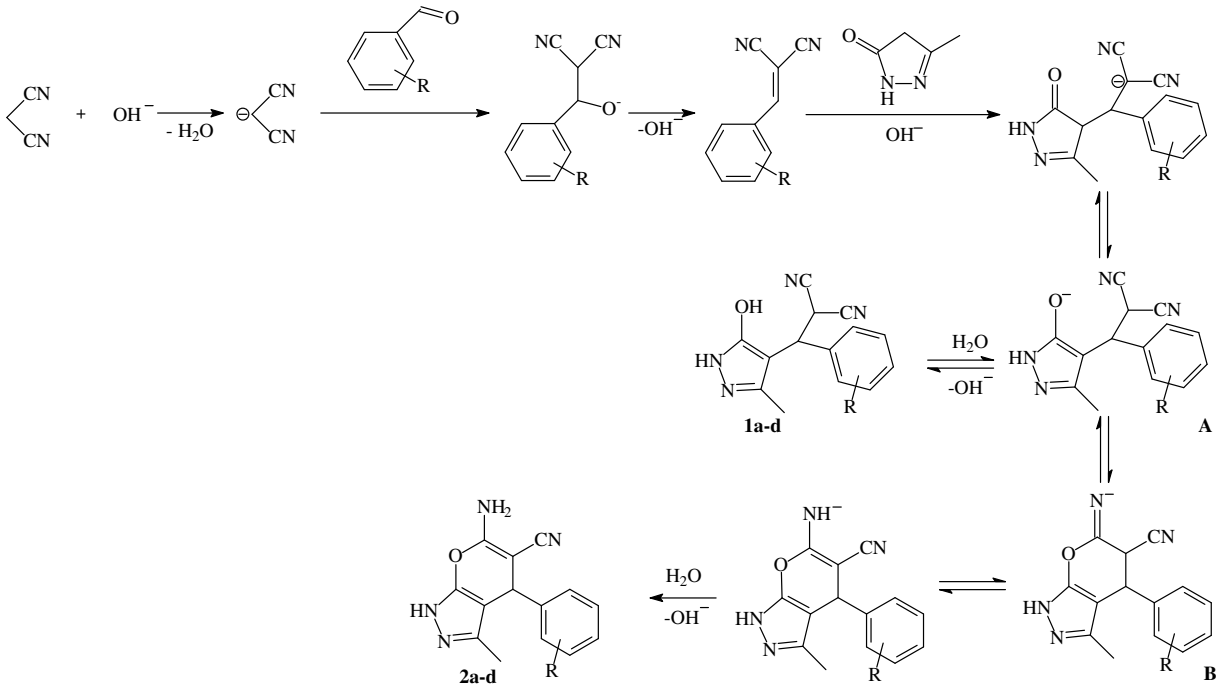
Aldehyde	R	Pyrano[2,3-*c*]pyrazoles	Yield (%)[b]
3a	H	**2a**	92
3b	4-Me	**2b**	90
3c	4-F	**2c**	90
3d	4-OMe	**2d**	89

[a] Aromatic aldehyde (5 mmoles), malononitrile (5,5 mmoles, 0.36 g), 3-methyl-2-pyrazolin-5-one (5 mmoles, 0,49 g), sodium hydroxide (0.25 mmoles, 0.01 g), 5 ml of water, 100 °C, 60 min.

[b] Isolated yield.

Taking into consideration our and literature[8, 10] 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, then by the usual way Knoevenagel condensation of carbonyl compound with anion of malononitrile takes place with the formation of arylidenemalononitrile. Addition of the 3-methyl-2-pyrazolyn-5-one to arylidenemalononitrile leads to anion **A**, which exist in the equilibrium with anion **B**. Subsequent protonation of anion **B** leads to the corresponding pyrano[2,3-*c*]pyrazoles **2a-d** (Scheme 4).

Scheme 4.



In conclusion, it was found that in optimal conditions the reaction between malononitrile, 3-methyl-2-pyrazoline-5-one and aromatic aldehydes in small amount of water and 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[1-7]. 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. Using small amounts of water allows to use the working capacity of a chemical reactor more efficiently and to avoid significant losses at the isolation stage. Thus, the proposed process is more efficient and environmentally friendly compared to those known today.

Experimental section

Chemicals were purchased from Aldrich® and Acros®. ^{1}H 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 relative to Me_4Si.

[(5-Hydroxy-3-methyl-1*H*-pyrazol-4-yl)(phenyl)methyl]propanedinitrile (1a)

Suspension of benzaldehyde (5 mmoles, 0.53 g), malononitrile (5 mmoles, 0.33 g) and 3-methyl-2-pyrazolin-5-one (5 mmoles, 0.49 g) in 5 ml of water was stirred at 60 ^{o}C for 15 min. Then reaction mixture was evaporated to dryness at 20 mm Hg to obtain **1a** as white solid. Yield 1.26 g (100%). Mp 255 ^{o}C (lit. mp[8] 258 – 259 ^{o}C). ^{1}H NMR: 2.19 (s, 3 H, CH_3); 4.63 (d, 1 H, J = 11.4 Hz, CH); 5.51 (d, 1 H, J = 11.4 Hz, CH); 7.2 – 7.55 (m, 5 H, Ph), 10.5 – 11.5 (br s, 2 H, NH, OH).

Synthesis of pyrano[2,3-*c*]pyrazoles 2a-d. General procedure.

Suspension of arylaldehyde (5 mmoles), malononitrile (5,5 mmoles), 3-methyl-2-pyrazolin-5-one (5 mmoles) and sodium hydroxide (0.25 mmoles) in 5 ml of water 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 mm Hg.

6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2a)

Pale yellow solid. Yield 1.15 g (92%). Mp 258 °C (lit. mp[8] 244 - 245 °C). ^{1}H NMR: 1.77 (s, 3 H, CH_3); 4.59 (s, 1 H, CH); 6.83 (s, 2 H, NH_2); 7.10 – 7.35 (m, 5 H, Ph); 12.08 (s, 1 H, NH).

6-Amino-3-methyl-4-(4-methylphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2b).

Pale yellow solid. Yield 1.19 g (90%). Mp 215 °C (lit. mp[8] 197 - 198 °C). ^{1}H NMR: 1.77 (s, 3 H, CH_3); 2.23 (s, 3 H, CH_3); 4.52 (s, 1 H, CH); 6.79 (s, 2 H, NH_2); 6.75 – 7.16 (m, 4 H, Ph); 12.08 (s, 1 H, 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 234 °C (lit. mp[8] 247 - 248 °C). ^{1}H NMR: 1.77 (s, 3 H, CH_3); 4.62 (s, 1 H, CH); 6.87 (s, 2 H, NH_2); 7.08 – 7.25 (m, 4 H, Ph); 12.11 (s, 1 H, NH).

6-Amino-3-methyl-4-[4-(methoxy)phenyl]-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2d).

Pale yellow solid. Yield 1.25 g (89%). Mp 220 °C (lit. mp[8] 225 - 226 °C). ^{1}H NMR: 1.78 (s, 3 H, CH_3); 3.72 (s, 3 H, OCH_3); 4.52 (s, 1 H, CH); 6.83 (s, 2 H, NH_2); 6.8 – 7.15 (m, 4 H, Ph); 12.08 (s, 1 H, NH).

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