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ORIGINAL PAPER

Solvent-free and 'on-water' multicomponent assembling of aldehydes, 3-methyl-2-pyrazoline-5-one, and malononitrile: fast and efficient approach to medicinally relevant pyrano[2,3-*c*]pyrazole scaffold

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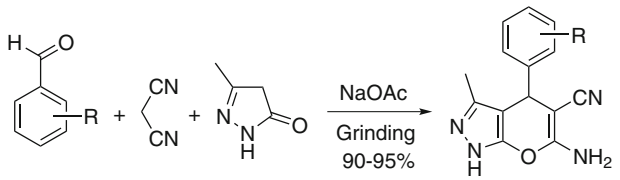
Abstract Sodium acetate-catalyzed multicomponent reaction of aldehydes, 3-methyl-2-pyrazoline-5-one, and malononitrile initiated by grinding in mortar in the presence of small quantities of water results in the fast (15 min) and efficient formation of substituted pyrano[2,3-*c*]pyrazoles in 90–95 % yields. The developed fast multicomponent approach to the substituted pyrano[2,3-*c*]pyrazoles—the known pharmacologically active substances such as antibiotics, enzyme inhibitors, and anticancer drugs—is beneficial from the viewpoint of diversity-oriented large-scale processes and represents fast efficient and environmentally benign synthetic concept for multicomponent reactions strategy.

Graphical abstract



Keywords Solvent-free · Catalysis · Carbanions · Cyclizations · Heterocycles · Green chemistry

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Introduction

In recent years, the demand for clean and efficient chemical synthesis has become of serious importance and the elimination of volatile organic solvents in organic synthesis is now one of the most important goals in 'green chemistry' [1]. Among the proposed solutions, solvent-free conditions are most popular and it is often claimed that the best solvent is no solvent [2]. The implication of the solvent-free process in base-activated multicomponent reactions is highly promising as it allows for the combination of the synthetic virtues of the conventional multicomponent strategy with the ecological benefits and convenience of the solvent-free procedure.

The concept of "privileged medicinal scaffolds" has become one of the guiding principles in drug discovery [3, 4]. Privileged scaffolds commonly consist of rigid ring, including hetero ring, systems that present appended residues in well-defined orientations required for target recognition [4, 5].

Pyrano[2,3-*c*]pyrazole scaffold has a broad spectrum of biological activities [6–11]. Substituted pyrano[2,3-*c*]pyrazoles are known as different pharmacologically active substances, including antibiotics [6–8], enzyme inhibitors [9–11], and anticancer drugs [7, 8]. The methods of pyrano[2,3-*c*]pyrazoles synthesis have been long documented and consist of two main groups: (1) two-step synthesis [12–14] and (2) 'one-pot' multicomponent process. The multicomponent process usually includes Knoevenagel condensation of 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 [15–21]. The main disadvantages of the known processes are large volumes of toxic solvents [15–18], 10–20 mol % of expensive or

complex catalysts (indium(III) chloride [19], $H_{14}[NaP_5W_{30}O_{110}]$ [20], ethylenediammonium diformate in PEG_{600} [21]) and specific reaction conditions (sonication [19] and microwave irradiation [20]). The four component methods starting from ethyl acetoacetate, hydrazine hydrate, malononitrile, and aldehydes having the same types of disadvantages are also known [22–25]. Besides, the known multicomponent methods are usually characterized by long and complex isolation stage.

Thus, the all known procedures for the synthesis of pyrano[2,3-*c*]pyrazoles have their merits, but the essence of fast facile and convenient multicomponent solventless methodology is yet not known and should to be developed.

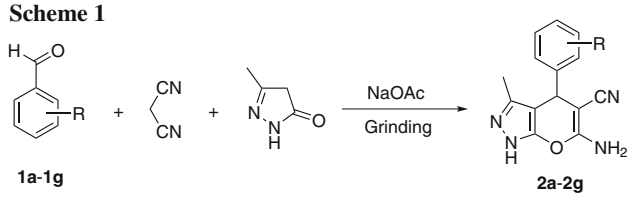
Recently, we have accomplished solvent-free cascade and multicomponent assembling of 2-amino-4*H*-chromene scaffold from salicylaldehydes and malononitrile [26], salicylaldehydes and cyanoacetates [27], and both from salicylaldehyde, malononitrile or cyanoacetate, and nitroalkanes [28].

Considering our results on the solvent-free transformation of C–H acids and salicylaldehydes as well as the certain biomedical application of pyrano[2,3-*c*]pyrazoles mentioned above, we were prompted to design a convenient fast and facile solvent-free methodology for the efficient synthesis of substituted pyrano[2,3-*c*]pyrazoles based on multicomponent reaction of aldehydes, 3-methyl-2-pyrazoline-5-one, and malononitrile in connection with demands of 'green chemistry'.

Results and discussion

As it follows from introduction we were prompted to design a fast convenient and facile solvent-free methodology for the efficient synthesis of functionalized pyrano[2,3-*c*]pyrazole system based on multicomponent reaction of aldehydes **1a–1g**, 3-methyl-2-pyrazolin-5-one, and malononitrile. Thus, in the present study we report our results on multicomponent transformation of aldehydes **1a–1g**, 3-methyl-2-pyrazolin-5-one, and malononitrile into substituted pyrano[2,3-*c*]pyrazoles **2a–2g** under solvent-free conditions by grinding in mortar (Scheme 1; Tables 1, 2).

Scheme 1



1a-1g 2a-2g

a: R = H, **b**: R = 4-Me, **c**: R = 4-*t*-Bu, **d**: R = 4-OMe, **e**: R = 4-Cl, **f**: R = 3-Br, **g**: R = 4-F

Table 1 Solvent-free multicomponent transformation of aldehyde **1a**, 3-methyl-2-pyrazoline-5-one, and malononitrile by grinding in mortar

Entry	Additive of water/cm^3	Base	Quantity of base/mol%	Time/min	Product	Yield/%[a]
1	–	–	–	5	**3**	45[b]
2	–	–	–	10	**3**	63[b]
3	–	–	–	15	**3**	71
4	0.5	–	–	15	**3**	80
5	1.0	–	–	15	**3**	88
6	2.0	–	–	15	**3**	90
7	–	NaOH	10	15	**2a**	65
8	–	NaOAc	10	15	**2a**	70
9	1.0	NaOH	10	15	**2a**	81
10	1.0	NaOH	10	15	**2a**	85
11	1.0	NaOAc	20	15	**2a**	95

2 mmol of aldehyde **1a**, 2 mmol of 3-methyl-2-pyrazoline-5-one, 2 mmol of malononitrile, grinding at 20 °C

[a] Isolated yield

[b] NMR data

Table 2 Solvent-free cascade transformation of aldehyde **1a–1g**, 3-methyl-2-pyrazoline-5-one, and malononitrile into substituted pyrano[2,3-*c*]pyrazoles **2a–2g** by grinding in mortar

Entry	Aldehyde	*R*	Product	Yield/%[a]
1	**1a**	H	**2a**	95
2	**1b**	4-Me	**2b**	91
3	**1c**	4-*t*-Bu	**2c**	93
4	**1d**	4-MeO	**2d**	90
5	**1e**	4-Cl	**2e**	92
6	**1f**	3-Br	**2f**	91
7	**1g**	4-F	**2g**	93

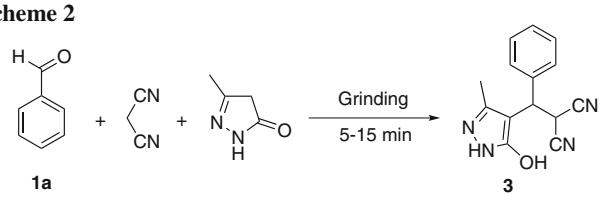
2 mmol of aldehyde **1**, 2 mmol of 3-methyl-2-pyrazoline-5-one, 2 mmol of malononitrile, 1 cm^3 of H_2O, and 0.4 mmol NaOAc, 15 min grinding at 20 °C

[a] Isolated yield

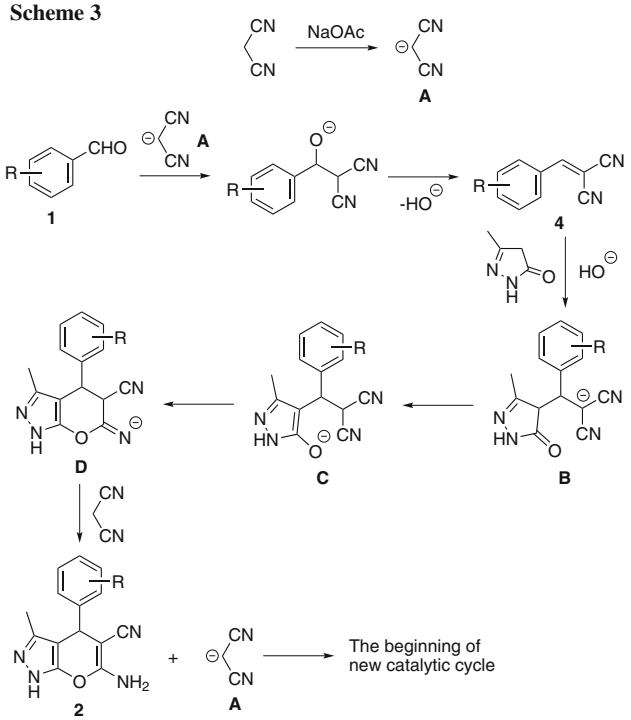
First, to evaluate the synthetic potential of the procedure proposed and to optimize the general conditions, the solvent-free transformation of aldehyde **1a**, 3-methyl-2-pyrazolin-5-one, and malononitrile was studied under usual stirring conditions in mortar (Table 1). Solvent-free reaction of benzaldehyde (**1a**), 3-methyl-2-pyrazolin-5-one, and malononitrile in mortar with grinding without catalysts resulted in formation of [(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)(phenyl)methyl]malononitrile (**3**) in 45–71 % yield (Scheme 2; Table 1, entries 1–3).

Recently, we have found that Knoevenagel condensation of isatins with malononitrile which was performed by grinding at room temperature in the absence of any catalysts but in the presence of 1–5 equivalents of water

Scheme 2



Scheme 3



resulted in formation of substituted (2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)malononitriles in 89–99 % yields as result of the 'on water' reaction [29]. Thus, the next experiments were carried out in the presence of 0.5–2.0 cm^3 of water (Table 1, entries 4–6). Addition of small quantity of water led to increasing yield of [(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)(phenyl)methyl]malononitrile (**3**) up to 80–90 % (Table 1, entries 4–6). However, under solvent-free conditions in the presence of catalytic quantities of NaOH or NaOAc, pyrano[2,3-*c*]pyrazole **2a** was obtained in 65 and 70 % yields, respectively (Table 1, entries 7, 8). The best 95 % yield of pyrano[2,3-*c*]pyrazole **2a** was achieved when the reaction was carried in the presence of 20 mol% of NaOAc and with addition of small quantity of water, reaction time 15 min (Table 1, entry 11). Under the optimal conditions thus found, aldehydes **1a**–**1g**, 3-methyl-2-pyrazolin-5-one, and malononitrile were transformed into corresponding substituted pyrano[2,3-*c*]pyrazoles **2a**–**2g** in 90–95 % yields (Table 2).

With the above results taken into consideration and the mechanistic data on solvent-free cascade process for the transformation of salicylaldehydes and malononitrile into substituted 2-amino-4*H*-chromenes [26], the following mechanism for the solvent-free cascade transformation of aldehydes **1a**–**1g**, malononitrile, and 3-methyl-2-pyrazolin-5-one into substituted pyrano[2,3-*c*]pyrazoles **2a**–**2g** is proposed. The initiation step of the catalytic cycle begins with the deprotonation of a molecule of malononitrile by the action of sodium acetate, which leads to the formation of malononitrile anion **A** (Scheme 3). The following process represents a typical multicomponent reaction. Knoevenagel condensation of the anion **A** with aldehyde **1** takes place with the elimination of a hydroxide anion and formation of Knoevenagel adduct **4** [30]. The subsequent hydroxide-promoted Michael addition of 3-methyl-2-pyrazolin-5-one to electron-deficient arylidenemalononitrile **4** results in formation of anions **B** and **C**. Cyclization of anion **C** with subsequent protonation of anion **D** leads to the formation of corresponding pyrano[2,3-*c*]pyrazoles **2** with the regeneration of malononitrile anion **A** at the last step of the catalytic cycle (Scheme 3).

The role of water in our multicomponent process is to accelerate all singular organic reactions. This effect of using water was known earlier [31]. Recently it was shown that several uni- and bimolecular reactions are greatly accelerated when carried out in vigorously stirred aqueous suspensions [32]. The experiments were performed with one or two liquids, water-insoluble reaction partners or, occasionally, a mixture of one liquid and one solid. Although the absence of detailed-kinetic experiments, the yields of pure products after varying reaction times convincingly demonstrate that the rates are higher than those under solvent-free ("neat") or homogeneous conditions [32].

Thus, sodium acetate as catalyst can produce under grinding conditions in the presence of small quantities of water, a fast (15 min) and selective multicomponent transformation of aldehydes, 3-methyl-2-pyrazolin-5-one, and malononitrile into substituted pyrano[2,3-*c*]pyrazoles in 90–95 % yields. This new process opens an efficient and convenient multicomponent way to create substituted pyrano[2,3-*c*]pyrazoles, the promising compounds for different biomedical applications. This catalytic procedure utilizes simple equipment; it is easily carried out and is valuable from the viewpoint of environmentally benign diversity-oriented large-scale processes. This efficient and fast approach to substituted pyrano[2,3-*c*]pyrazoles represents a new synthetic concept for multicomponent reactions which integrate solvent-free and 'on water' reaction procedures, and allows for the combination of the synthetic virtues of solvent-free MCR

with ecological benefits of 'on water' reactions and convenience of sodium acetate-catalyzed procedure.

Experimental

All melting points were measured with a Gallenkamp melting-point apparatus. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with a Bruker Avance II 300 spectrometer at ambient temperature. Chemical shift values are relative to Me_4Si. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass spectra (EI, 70 eV) were obtained directly with a Kratos MS-30 spectrometer. All chemicals used in this study were commercially available.

General procedure

A mixture of benzaldehyde **1** (2 mmol), 0.13 g malononitrile (2 mmol), 0.20 g 3-methyl-2-pyrazolin-5-one (2 mmol), and 0.02 g sodium acetate (0.4 mmol) in the presence of 1 cm^3 of H_2O was grinded thoroughly in mortar for 15 min. The resulting mixture was air dried to cause crystallization of the product. Crude solid was then put on filter, rinsed with water (2 × 2 cm^3), and dried with water pump.

*6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (**2a**)*
Yield 95 %; m.p.: 244–245 °C (Ref. [15] m.p.: 244–245 °C and ^{1}H NMR data).

*6-Amino-3-methyl-4-(4-methylphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**2b**)*
Yield 91 %; m.p.: 197–198 °C (Ref. [15] m.p.:197–198 °C and ^{1}H NMR data).

6-Amino-4-(4-tert-butylphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**2c**, $C_{18}H_{20}N_4O$)
Yield 93 %; m.p.: 230–231 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.26$ (s, 9H, 3 CH_3), 1.80 (s, 3H, CH_3), 4.54 (s, 1H, CH), 6.83 (s, 2H, NH_2), 7.08 (d, $J = 8.1$ Hz, 2H, Ar), 7.33 (d, $J = 8.1$ Hz, 2H, Ar), 12.31 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 9.8$, 31.2 (3C), 34.1, 35.7, 57.3, 97.7, 120.9, 125.1 (2C), 127.0 (2C), 135.5, 141.5, 148.8, 154.7, 160.9 ppm; IR (KBr): $\bar{\nu} = 3{,}478$, 3,242, 3,130, 2,965, 2,195, 1,638, 1,594, 1,488, 1,400, 1,054 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 308 ($[M]^+$, 43), 293 (9), 251 (21), 242 (74), 227 (37), 185 (15), 176 (98), 175 (100), 141 (15), 115 (16).

*6-Amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**2d**)*
Yield 90 %; m.p.: 224–225 °C (Ref. [15] m.p.: 225–226 °C and ^{1}H NMR data).

*6-Amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**2e**)*
Yield 92 %; m.p.: 250–252 °C (Ref. [15] 252–253 °C and ^{1}H NMR data).

*6-Amino-4-(3-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**2f**)*
Yield 91 %; m.p.: 224–225 °C (Ref. [15] m.p.: 223–224 °C and ^{1}H NMR data).

*6-Amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**2g**)*
Yield 93 %; m.p.: 222–223 °C (Ref. [15] m.p.: 223–224 °C and ^{1}H NMR data).

*[(5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(phenyl)methyl]-malononitrile (**3**)*
Yield 90 %; m.p.: 256–258 °C (Ref. [15] m.p.: 258–259 °C and ^{1}H NMR data).

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