

Efficient and facile 'on-solvent' multicomponent synthesis of medicinally privileged pyrano[3,2-c] pyridine scaffold

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Abstract The new type of 'on-solvent' multicomponent reaction was found: transformation of benzaldehydes, malononitrile and 4-hydroxy-6-methylpyridin-2(1H)-one in the presence of sodium acetate as catalyst in a small amount of ethanol results in formation of substituted 2-amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitriles in excellent 92–99% yields. This novel 'one-pot' process opens an efficient and convenient way to functionalize pyrano[3,2-c]pyridine systems, which are promising compounds for different biomedical applications.

Keywords Aldehydes · Malononitrile · 4–Hydroxy-6-methylpyridin-2(1H)-one · Pyrano[3,2-c]pyridines · Multicomponent reactions · Sodium acetate catalyst

Introduction

Using multicomponent reactions (MCRs), as a part of domino reactions [1], is the most common modern way for ideal compound synthesis. The MCR method combines in a 'one-pot' reaction at least three reactants through 'one-pot' transformation to obtain new, pure and useful complex molecules [2]. In many cases, the multicomponent processes are a significant part of the pot, atom and step economy (PASE) strategy [3], which claims pot and step economy and introduces also atom economy, which means the number of atoms of all starting reagents should constitute the final compound.

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The development of eco-friendly green approaches to chemical synthesis and the elimination of volatile organic solvents in organic synthesis is one of the most demanding goals in organic chemistry. In recent decades, it was found that many reactions could proceed under solvent-free conditions. Such reactions in many cases occurred more selectively than those carried out in solvents. Solvent-free reactions have emerged as a powerful tool for creating new complex organic compounds by much greener methods, as compared with classical organic synthesis [4].

However, solvent-assisted ('on-solvent') methods in comparison with solventless mechano-chemical processes have much more application areas due to more flexibility, high rates and selectivity, as well as reduced reaction time [5]. Thus, the 'onsolvent' method combining these merits is a new and useful tool for modern organic chemistry.

In recent years, design of new functional organic systems and heterocyclic systems has gained much more attention and has become a high priority. The added interest has generated the notion of "privileged medicinal structures or scaffolds" and takes it as guiding principle of drug discovery [6]. These privileged scaffolds are commonly composed of a rigid cyclic hetero compound system that assigns well-defined orientation of appended functionalities for target recognition [7].

As a 'privileged medicinal structure,' pyrano[3,2-c] pyridine scaffold has received substantial attention because it is associated with significant pharmacological activity, such as antimicrobial [8], antiviral [9] and anti-angiogenic activities [10]. Besides, the fact that YCM1008A is known as a Ca²⁺ inhibitor [11], there was a report about pyrano[3,2-c] pyridine anti-cancer activity [12]. Pyrano[3,2-c] pyridine is also part of zanthosimuline—an alkaloid with application in treatment of different drug-resistant cancer types [13] (Fig. 1).

A two-step, non-multicomponent method for synthesis of pyrano[3,2-c]pyridines has been suggested, but the desired compounds were not obtained with sufficient overall yields [14, 15].

The first multicomponent approach to pyrano[3,2-c]pyridines was based on a reaction of aldehydes, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-one in refluxing ethanol (50 min) in the presence of Et₃N as catalyst [12], but in many cases the yields were in the range 75–80%; and in some cases, additional crystallisation from dimethylformamide (DMF) was needed.

As for other known multicomponent processes, pyrano[3,2-c]pyridines were prepared using heating at 80 °C for 2–3 h in [bmim][BF₄] as a solvent [16]. In addition



Fig. 1 Drugs containing a pyrano[3,2-c]pyridine moiety

to a sufficiently complex method and special procedure for isolation pyrano[3,2-*c*] pyridines, it should be mentioned that [bmim][BF₄] is an extremely expensive and acutely toxic ionic liquid, hazardous to the aquatic environment. Recently Cu₂O nanoparticles supported on natural nanozeolite clinoptilolite were reported as catalyst for synthesis of pyrano[3,2-*c*]pyridines [17], but this method deals with synthesis of only three samples of substituted pyrano[3,2-*c*]pyridines and, moreover, Cu₂O nano-catalyst for this method was obtained through a sufficiently complex 6-day, two-step procedure. (Hexadecyltrimethylazanium)₃[SiW₁₂]-Li⁺-natural montmorillonite nanocatalyst was also suggested for synthesis of pyrano[3,2-*c*]pyridines [18], and, again, a difficult 8-day, three-step procedure was needed to prepare the catalyst.

Thus, all the above-mentioned methods for preparing pyrano[3,2-c]pyridines are important, but the efficient and facile multicomponent 'on-solvent' methodology is still unknown and should be created.

Recently we have realized 'on-water' efficient multicomponent transformations of carbonyl compounds and C–H acids [19–21] as well as 'on-solvent' multicomponent procedures for 4H-pyrano[3,2-c]quinoline synthesis [22] and 'on-solvent' multicomponent assembly of salicylaldehydes, malononitrile and 4-hydroxy-6-methyl-2H-pyran-2-one [23].

Taking into consideration our results in this area and the biomedical value of pyrano[3,2-*c*]pyridines derivatives, we would like to develop an 'on-solvent' methodology for the efficient and facile multicomponent transformations of aldehydes **1a–i**, malononitrile and and 4–hydroxy-6-methylpyridin-2(1*H*)-on into functionalized pyrano[3,2-*c*]pyridines **2a–i** (Scheme 1).

Experimental

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded in DMSO- d_6 with a Bruker Avance II 300 spectrometer at ambient temperature. Chemical shift values are relative to Me₄Si. 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.

General procedure for preparation of functionalized pyrano[3,2-c]pyridines

Aldehyde 1 (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methylpyridin-2(1H)one (3 mmol) and AcONa (0.3 mmol) were refluxed in 5 mL of ethanol for 1 h. After the reaction was finished, the solid was filtered, washed with cold ethanol and dried to isolate pure substituted 2-amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitriles **2a–i**.

2-Amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (2a) White solid; yield 0.82 g, (98%); m.p.: 280–282 °C [lit. m.p.: 279– 282 °C (Baghbanian et al. 2014)]; ¹H NMR (300 MHz, DMSO-d₆): δ 2.16 (s, 3H, CH₃), 4.31 (s, 1H, CH), 5.89 (s, 1H, CH), 7.00 (s, 2H, NH₂), 7.14–7.22 (m, 3H, Ar), 7.27–7.31 (m, 2H, Ar), 11.52 (s, 1H, NH).

2-*Amino*-7-*methyl*-5-*oxo*-4-(4-*methylphenyl*)-5,6-*dihydro*-4*H*-*pyrano*[3,2-*c*]*pyridine*-3-*carbonitrile* (**2b**) White solid; yield 0.83 g, (94%); m.p.: 264–266 °C, dec.; ¹H NMR (300 MHz, DMSO-d₆): δ 2.15 (s, 3H, CH₃), 2.26 (s, 3H, CH₃), 4.27 (s, 1H, CH), 5.88 (s, 1H, CH), 6.97 (s, 2H, NH₂), 7.02–7.10 (m, 4H, Ar), 11.52 (s, 1H, NH); ¹³C NMR (75 MHz, DMSO-d₆): δ 18.4, 20.6, 35.8, 57.9, 95.8, 106.4, 120.1, 127.2 (2C), 128.8 (2C), 135.5, 141.9, 145.5, 156.5, 159.1, 161.7; IR (KBr): ν = 3457, 3326, 2198, 1669, 1638, 1599, 1385, 1265, 1141, 591 cm⁻¹; MS (m/z, relative intensity %): 293 [M⁺] (76), 212 (25), 202 (100), 168 (24), 84 (24), 66 (32), 42 (48), 39 (35), 27 (30), 15 (29). Found (%): C, 69.56; H, 5.21; N, 14.28. Calcd. for C₁₇H₁₅N₃O₂ (293.12; %): C, 69.61; H, 5.15; N, 14.33.

2-*Amino*-4-(4-ethylphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbo-nitrile (2c) White solid; yield 0.90 g, (98%); m.p.: 255–257 °C, dec.; ¹H NMR (300 MHz, DMSO-d₆): δ 1.17 (t, *J* = 7.5 Hz, 3H, CH₃), 2.16 (s, 3H, CH₃), 2.56 (q, *J* = 7.5 Hz, 2H, CH₂) 4.28 (s, 1H, CH), 5.89 (s, 1H, CH), 6.98 (s, 2H, NH₂), 7.05–7.14 (m, 4H, Ar), 11.52 (s, 1H, NH); ¹³C NMR (75 MHz, DMSO-d₆): δ 15.6, 18.5, 27.8, 35.8, 57.9, 95.7, 106.4, 120.1, 127.2 (2C), 127.6 (2C), 141.9, 142.2, 145.4, 156.4, 159.1, 161.7 ppm; IR (KBr): ν = 3453, 3295, 3178, 2197, 1674, 1640, 1603, 1384, 1142, 593 cm⁻¹; MS (m/z, relative intensity %): 307 [M⁺] (12), 212 (10), 203 (11), 202 (100), 84 (9), 77 (10), 66 (10), 42 (23), 29 (11), 27 (13). Found (%): C, 70.31; H, 5.67; N, 13.62. Calcd. for C₁₈H₁₇N₃O₂ (307.13; %): C, 70.34; H, 5.58; N, 13.67.

2-*Amino-4-(3-methoxyphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-car-bonitrile* (2d) White solid; yield 0.88 g, (95%); m.p.: 264-266 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 2.14 (s, 3H, CH₃), 3.71 (s, 3H, CH₃), 4.28 (s, 1H, CH), 5.87 (s, 1H, CH), 6.67 (s, 1H, Ar), 6.70–6.80 (m, 2H, Ar), 6.97 (s, 2H, NH₂), 7.19 (t, J = 8.2 Hz 1H, Ar), 11.50 (s, 1H, NH); ¹³C NMR (75 MHz, DMSO-d₆): δ 18.4, 36.1, 54.9, 57.6, 95.8, 106.1, 111.3, 113.6, 119.4, 120.0, 129.4, 145.6, 146.4, 156.6, 159.1, 159.2, 161.7; IR (KBr): $\nu = 3293$, 2197, 1666, 1601, 1487, 1385, 1263, 1139, 1050, 782 cm⁻¹; MS (m/z, relative intensity %): 309 ([M⁺], 35), 265 (5), 242 (3), 202 (100), 184 (5), 149 (2), 127 (2), 92 (6), 77 (13), 42 (33). Found (%): C, 65.95; H, 4.93; N, 13.47. Calcd. for C₁₇H₁₅N₃O₃ (309.32; %): C, 66.01; H, 4.89; N, 13.58.

2-Amino-4-(3-fluorophenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbo-nitrile (2e) White solid; yield 0.91 g, (97%); m.p.: 292–294 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 2.17 (s, 3H, CH₃), 4.37 (s, 1H, CH), 5.90 (s, 1H, CH), 6.92–7.05 (m, 3H, Ar), 7.08 (s, 2H, NH₂), 7.30–7.38 (m, 1H, Ar), 11.56 (s, 1H, NH); ¹³C NMR (75 MHz, DMSO-d₆): δ 18.3, 36.0, 57.1, 95.8, 105.5, 113.3 (d, J = 21.0 Hz), 114.0 (d, J = 21.0 Hz), 119.8, 123.3 (d, J = 2.2 Hz), 130.1 (d, J = 7.5 Hz), 145.9, 147.7 (d, J = 7.5 Hz), 156.6, 159.2, 161.6, 162.0 (d, $J = 243.3 \text{ Hz}; \text{ IR (KBr): } \nu = 3334, 2193, 1674, 1605, 1484, 1388, 1250, 1143, 783, 584 \text{ cm}^{-1}; \text{ MS (m/z, relative intensity %): } 297 ([M⁺], 36), 253 (5), 223 (2), 202 (100), 184 (5), 158 (4), 133 (2), 95 (21), 75 (19), 42 (19). Found (%): C, 64.59; H, 4.03; F, 6.33; N, 14.08; Calcd. for C₁₆H₁₂FN₃O₂ (297.28; %): C, 64.64; H, 4.07; F, 6.39; N, 14.13.$

2-*Amino-4-(3-chlorophenyl)*-7-*methyl*-5-*oxo*-5,6-*dihydro-4H-pyrano[3,2-c]pyridine-3-carbo-nitrile (2<i>f*) White solid; yield 0.89 g, (95%); m.p.: 290-292 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 2.16 (s, 3H, CH₃), 4.35 (s, 1H, CH), 5.90 (s, 1H, CH), 7.08 (s, 2H, NH₂), 7.13 (d, J = 8.0 Hz, 1H, Ar), 7.18 (s, 1H, Ar), 7.23–7.37 (m, 2H, Ar), 11.56 (s, 1H, NH); ¹³C NMR (75 MHz, DMSO-d6): δ 18.4, 36.0, 57.0, 95.8, 105.4, 119.8, 126.1, 126.5, 127.1, 130.2, 132.8, 146.0, 147.3, 156.6, 159.2, 161.6; IR (KBr): ν = 3173, 2200, 1666, 1397, 1253, 1141, 1053, 886, 777, 691 cm⁻¹; MS (m/z, relative intensity %): 315 ([M⁺], ³⁷Cl, 9), 313 ([M⁺], ³⁵Cl, 27), 297 (4), 269 (3), 246 (2), 202 (100), 184 (5), 157 (2), 111 (16), 75 (20), 42 (26). Found (%): C, 61.37; H, 3.82; Cl, 11.17; N, 13.32. Calcd. for C₁₆H₁₂ClN₃O₂ (313,74; %): C, 61.25; H, 3.86; Cl, 11.30; N, 13.39.

2-amino-4-(3-bromophenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbo-nitrile (**2g**) White solid; yield 1.06 g, (99%); m.p.: 282–284 °C, dec.; ¹H NMR (300 MHz, DMSO-d₆): δ 2.17 (s, 3H, CH₃), 4.35 (s, 1H, CH), 5.91 (s, 1H, CH), 7.10 (s, 2H, NH₂), 7.17 (d, J = 7.7 Hz, 1H, Ar), 7.25–7.32 (m, 2H, Ar), 7.41 (d, J = 7.7 Hz, 1H, Ar), 11.58 (s, 1H, NH); ¹³C NMR (75 MHz, DMSO-d6): δ 18.3, 35.8, 57.8, 95.8, 106.4, 120.1, 127.2 (2c), 128.7 (2C), 135.5, 141.9, 145.5, 159.1, 161.7 ppm; IR (KBr): $\nu = 3363$, 3313, 3175, 2200, 1665, 1631, 1396, 1253, 1140, 603 cm⁻¹; MS (m/z, relative intensity %): 359 [M⁺] (7), 357 (7), 212 (2), 203 (13), 202 (100), 184 (3), 157 (3), 76 (3), 42 (4), 14 (3). Found (%): C, 53.61; H, 3.43; Br, 22.31; N, 11.71. Calcd. for C₁₆H₁₂BrN₃O₂ (358.19; %): C, 53.65; H, 3.38; Br, 22.31; N, 11.73.

2-*amino*-4-(2-*hydroxy*-3,5-*diiodophenyl*)-7-*methyl*-5-*oxo*-5,6-*dihydro*-4H-*pyrano*[3,2-*c*]*pyri-dine*-3-*carbonitrile* (2*h*) White solid; yield 1.51 g, (92%); m.p.: 264–266 °C, dec.; ¹H NMR (300 MHz, DMSO-d₆): δ 2.09 (s, 3H, CH₃), 4.72 (s, 1H, CH), 6.14 (s, 1H, CH), 7.21 (s, 1H, Ar), 7.10 (s, 2H, NH₂), 7.88 (s, 1H, Ar), 11.87 (s, 1H, NH), 12.32 (s, 1H, OH); ¹³C NMR (75 MHz, DMSO-d6): δ 18.4, 30.9, 55.3, 83.7, 91.3, 98.6, 105.9, 119.5, 134.4, 136.8, 144.3, 146.3, 154.5, 157.6, 160.4, 163.9 ppm; IR (KBr): ν = 3442, 3303, 2927, 2197, 1667, 1634, 1397, 1261, 1147, 601 cm⁻¹; MS (m/z, relative intensity %): 547 [M⁺] (3), 441 (1), 422 (100), 346 (34), 296 (22), 254 (17), 202 (13), 127 (37), 84 (18), 62 (9). Found (%): C, 35.10; H, 2.10; I, 46.35; N, 7.61. Calcd. for C₁₆H₁₁I₂N₃O₃ (547.09; %): C, 35.13; H, 2.03; I, 46.39; N, 7.68.

2-amino-4-(5-bromo-2-hydroxy-3-methoxyphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano-[3,2-c]pyridine-3-carbonitrile (2i) White solid; yield 1.13 g, (93%); m.p.: 262–264 °C, dec.; ¹H NMR (300 MHz, DMSO-d₆): δ 2.13 (s, 3H, CH₃), 3.73 (s, 3H, OCH₃), 4.59 (s, 1H, CH), 5.91 (s, 1H, CH), 6.58 (s, 1H, Ar), 6.91 (s, 1H, Ar), 7.00 (s, 2H, NH₂), 9.60 (s, 1H, OH), 11.76 (s, 1H, NH); ¹³C NMR (75 MHz, DMSO-d6): δ 18.3, 30.6, 56.0 (2C), 96.9, 105.6, 110.1, 113.3, 119.9, 122.6, 133.3, 143.7, 145.6, 149.6, 157.3, 159.9, 162.6 ppm; IR (KBr): ν = 3433, 3324, 2192, 1663, 1603, 1402, 1300, 1247, 1066, 587 cm⁻¹; MS (m/z, relative intensity %): 405 [M⁺] (4), 403 [M⁺] (4), 278 (100), 280 (99), 237 (12), 235 (12), 202 (20), 125 (25), 84 (12), 15 (7). Found (%): C, 50.48; H, 3.60; Br, 19.70; N, 10.30. Calcd. for C₁₇H₁₄BrN₃O₄ (404.21; %): C, 50.51; H, 3.49; Br, 19.77; N, 10.40.

X-ray powder diffraction (XRD)

The powder pattern of **2i** was measured on a Bruker D8 Advance Vario diffractometer with a LynxEye detector and Ge (111) monochromator, λ (CuK α_1) = 1.54060 Å, $\theta/2\theta$ scan from 6.0° to 90°, step size 0.009169°, in transmission mode, with the sample deposited between Mylar films.

The pattern was indexed using the SVD Index [24] as implemented in TOPAS 5.0 software [25]. The model for the solution and refinement was prepared basing on a PBE/L2 [26] calculation of SK90 using PRIRODA software [27]. The solution were obtained using the parallel tempering method as implemented in FOX [28] and Rietveld-refined in TOPAS 5.0. The structure was refined using soft (parabolic) restraints; distribution of the deviations of the bond lengths from restrained values (Δd) contained no outliers, indicating a consistent structural model according to approach outlined in [29]. By variation of individual bond restraints until they produced outliers, we estimated the average half uncertainty window (HUW) for the refinement as HUW = 0.20(10) Å [30].

Crystal Data for (2*i*): $C_{17}H_{14}BrN_3O_4$ (M = 404.21 g/mol): triclinic, space group P-1 (no. 2), a = 9.0010(3) Å, b = 9.6599(3) Å, c = 12.5185(3) Å, $a = 115.2308(18)^\circ$, $\beta = 103.311(2)^\circ$, $\gamma = 60.3510(16)^\circ$, V = 855.45(5) Å³, Z = 2, T = 298 K, $\mu(CuK\alpha_1) = 3.524$ mm⁻¹, Dcalc = 1.569 g/cm₃. At an average Δd of 0.01 Å ($K_1 = 68$), the refinement converged to $R_{WP}/R_{WP}/R_{P}/R_{P}/R_{Bragg}$ values of 4.24/9.24/3.07/8.76/1.62%, with goodness of the fit (GOF) = 8.06 (Fig. 2).

The crystallographic data for **2i** was deposited in CCDC with reference code 1474235.

Results and discussion

In the present study we wish to report the first multicomponent solvent-assisted synthesis of substituted pyrano[3,2-c]pyridines from benzaldehydes, malononitrile and 4–hydroxy-6-methylpyridin-2(1*H*)-one (Scheme 1, Tables 1, 2).

In the beginning of this research, the multicomponent reaction of benzaldehyde **1a**, malononintrile and 4-hydroxy-6-methylpyridin-2(1H)-one with formation of 2-amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*]-pyridine-3-carbonitrile (**2a**) was studied (Table 1).



Fig. 2 The experimental (*blue line*) and calculated (*red line*) powder patterns for SK90 at K1 = 68 and their difference (*grey curve*). (Color figure online)



Scheme 1 Multicomponent transformation of aldehydes 1a-i, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-one into pyrano[3,2-*c*]pyridines 2a-i

Solvent-free reaction of benzaldehyde **1a**, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-one with potassium fluoride as a catalyst (entry 1, Table 1) resulted in the formation of **2a** with 59% yield in 30 min. In the presence of 10 mol% of AcONa as catalyst, pyrano[3,2-*c*]pyridine **2a** was obtained at a higher 67% yield (entry 2), thereby determining the more optimal catalyst. When benzaldehyde **1a**, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-one in the presence of 10 mol% of AcONa were refluxed with 1 ml of ethanol 60 min, the yield of **2a** increased up to 82% (entry 3). Using 3 and 5 ml of ethanol resulted in in increasing yield of **2a** (entries 4 and 5) up to 92 and 98%, respectively. The best result was obtained using 5 ml of ethanol as a solvent (entry 5) with 98% yield in 60 min (optimal condition).

 K_2CO_3 was less effective as catalyst and led to only 43% yield of pyrano[3,2-*c*] pyridine **2a** (entry 6).

Further increasing the quantity of ethanol or reducing the reaction time to 45 min resulted in decreasing the yield of **2a** to 91 and 89% (entries 7 and 8).

Entry	Solvent, mL	Base, mol%	Tempera- ture, °C	Time, min	Yield of $2a (\%)^c$	
1	Solvent-free ^a	lvent-free ^a KF, 10%		30	59^d	
2	Solvent-free ^a	AcONa, 10%	25	30	67^d	
3	EtOH, 1^b	AcONa, 10%	78	60	85	
4	EtOH, 3^b	AcONa, 10%	78	60	92	
5	EtOH, 5^b	AcONa, 10%	78	60	98	
6	EtOH, 5^b	K ₂ CO ₃ , 10%	78	60	43^{d}	
7	EtOH, 8^b	AcONa, 10%	78	60	91	
8	EtOH, 5^b	AcONa, 10%	78	45	89	
9	EtOH, 5^b	_	78	60	15^{d}	
10	H ₂ O, 5 ^b	AcONa, 10%	80	60	8^d	
11	$\mathrm{THF}^{e}, 5^{b}$	AcONa, 10%	66	60	3^d	
12	MeCN	AcONa, 10%		60	41^{d}	

Table 1 Multicomponent transformation of aldehyde 1a, malononitrile and 4-hydroxy-6-methylpyridin-2(1H)-one into pyrano[3,2-c]pyridine 2a

^{*a*}Benzaldehyde **1a** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methylpyridin-2(1H)-one (3 mmol) and catalyst were grinded with a pestle and mortar 30 min

^bBenzaldehyde **1a** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methylpyridin-2(1H)-one (3 mmol), catalyst and solvent were refluxed with magnetic stirrer

^cIsolated yields

^dAccording to ¹H NMR data

^eTetrahydrofuran as solvent

Table 2Multicomponenttransformation of aldehydes1a-i, malononitrile and 4-hydroxy-6- methylpyridin-	Entry	Aldehyde	R ¹	R ²	R ³	R ⁴	Pyrano[3,2- c]- pyridine 2 , yield $(\%)^{b}$
2(1H)-one into pyrano[3,2-c]	1	1a	Н	Н	Н	Н	2a , 98
pyridiles 2 4–1	2	1b	Н	Н	Me	Н	2b , 94
	3	1c	Н	Н	Et	Н	2c , 98
	4	1d	Н	OMe	Н	Н	2d , 95
	5	1e	Н	F	Н	Н	2e , 97
	6	1f	Н	Cl		Н	2f , 95
	7	1g	Н	Br	Н	Н	2g , 99
	8	1h	OH	Ι	Н	Ι	2h , 92
	9	1i	OH	OMe	Н	Br	2i , 93

^aAldehyde **1a-i** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methylpyridin-2(1*H*)-one (3 mmol), AcONa (0.3 mmol) and ethanol (5 mL) were refluxed for 60 min

^bIsolated yields

Water, tetrahydrofuran and acetonitrile were less suitable as solvents and afforded formation of 2a in only the range 3–41% (entries 10–12).

It should be mentioned, that AcONa is a cheap and environmentally benign catalyst for different organic transformations. It is usually used as a weakly base catalyst



Fig. 3 Molecular structure of 2i in crystal form. Atoms are represented by spheres indicating their isotropic thermal displacements ($\rho = 50\%$)

for aldol condensation of aromatic aldehydes and acid anhydrides. It was found that sodium acetate catalyzes reaction of aryl aldehydes, malononitrile and acetone into cis-4-dicyanomethylene-2,6-diarylcyclohexane-1,1-dicarbonitriles [31]. Sodium acetate was also used as the catalyst for transformation of diethyl but-2-enedioate, malononitrile, formaldehyde and aromatic amine into 1,2,3,4-tetrahydropiridines [32].

Under optimum conditions (entry 5, Table 1), the multicomponent reactions of aldehydes **1a–i**, malononitrile and 4–hydroxy-6-methylpyridin-2(1H)-one in an emulsion of ethanol were carried out (Table 2).

Under optimal conditions (Table 2), pyrano[3,2-c]pyridines **2a–i** were obtained in 92–99% yields. The isolation procedure was very simple. After the reaction was finished, the solid was filtered, washed with cold ethanol and dried to isolate pure substituted 2-amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles **2a–i**.

The structure of pyrano[3,2-c] pyridine **2i** was additionally confirmed with using powder X-ray diffraction study (Fig. 3).

The mechanism of the pyrano[3,2-c] pyridine **2** formation is shown in Scheme 2. It is conceivable that after formation of malononitrile anion, the initial stage leads to the Knoevenagel product **A** from condensation of benzaldehyde **1** and malononitrile anion with the extraction of hydroxide anion [33]. Then, a nucleophilic attack of 4-hydroxy-6-methylpyridin-2(1*H*)-one results in anion **B** formation. An intramolecular cyclization of anion **B** affords the intermediate anion **C**. The second intramolecular nucleophilic attack with following protonation by another molecule of malononitrile and tautomerization produces pyrano[3,2-c] pyridine **2**.



Scheme 2 Mechanism of multicomponent transformation of aldehydes 1, malononitrile and 4–hydroxy-6-methylpyridin-2(1*H*)-one into pyrano[3,2-*c*]pyridines 2

Conclusions

The highly efficient multicomponent 'on-solvent' transformation of aldehydes, malononitrile and 4–hydroxy-6-methylpyridin-2(1H)-one catalyzed by NaOAc in an emulsion of ethanol results in the formation of substituted 2-amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles in excellent yields. This 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 technique for substituted 2-amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles **2** formation represents the novel synthetic concept, pot, atom and step economy (PASE) 'on-solvent' multicomponent strategy, which provides a new line of approach towards developing environmentally friendly synthetic technologies.

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