One-Pot 'On-solvent' Multicomponent Protocol for the Synthesis of Medicinally Relevant 4*H*-Pyrano[3,2-*c*]quinoline Scaffold

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'One-pot' AcONa-catalyzed transformation of salicylaldehydes, malononitrile and 4-hydroxy-1-methylquinolin-2(1*H*)-one in the presence of a minimal quantity of EtOH results in fast (3 min) and efficient formation of unknown 2-amino-4-(2-hydroxyaryl)-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitriles in 85–98% yields, which are potential pharmaceutical agents for treating disorders responsive to the induction of apoptosis, antiproliferation, or vascular disruption. This efficient 'on-solvent' approach to the 4*H*-pyrano[3,2-*c*]quinoline scaffold represents a novel synthetic concept for multicomponent reaction (MCR) strategy and allows to combine the synthetic virtues of conventional MCR with ecological benefits and convenience of facile 'on-solvent' procedure.

Introduction. – The discovery of novel synthetic methodologies to facilitate the preparation of compound libraries is a pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry [1]. One approach to address this challenge involves the development of multicomponent reactions (MCR), in which three or more reactants are combined in a single reaction flask (one-pot process) to generate a product incorporating most of the atoms contained in the starting materials [2]. The multicomponent reaction (MCR) strategy has sufficient advantages over conventional linear-type synthesis due to its flexible, convergent, and atom efficient nature [2]. The rapid assembly of molecular diversity utilizing MCRs has received a great deal of attention in the search for novel lead structures, especially for the design and construction of elaborate small-molecule heterocyclic frameworks possessing enhanced 'drug-like' properties [3]. These reactions can be performed under mild conditions, provide good yields, have superior atom economies, entail low costs, have wide scopes, and provide high bond-forming efficiencies [4]. In addition, some of such reactions are popular, because they can be carried out in environmentally benign solvents, such as H_2O [5].

Recently the term 'on-water' reactions was specially introduced [6]. 'On-water' reactions are a group of organic reactions that take place as an emulsion in H_2O and that exhibit an unusual reaction rate acceleration compared to the same reaction in an organic solvent or compared to the corresponding solvent-free reaction. This effect has been known for many years, but in 2005, researchers in the group of *Sharpless* presented a systematic study of this phenomenon [6a].

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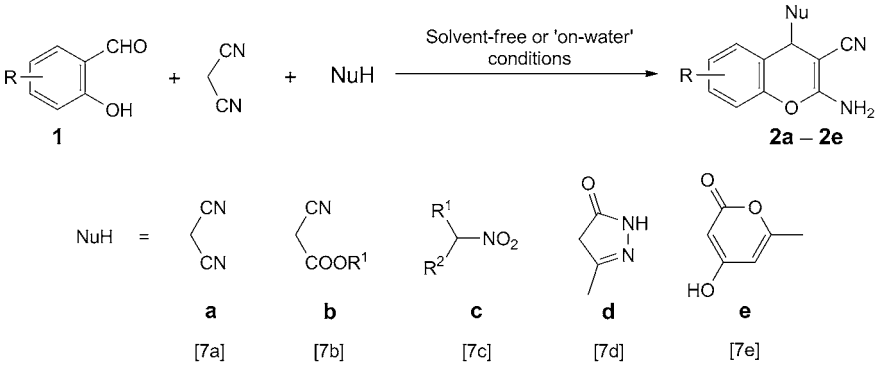
Scheme 1. *Multicomponent Solvent-Free or 'On-water' Transformations of Salicylaldehydes* **1***, Malononitrile, and Nucleophiles into 2-Amino-3-cyano-4*H*-chromene Scaffold* **2**



In our previous articles, we have accomplished several one-pot multicomponent solvent-free or 'on-water' processes between salicylaldehydes **1**, malononitrile, and nucleophiles resulting in 2-amino-4*H*-chromene scaffold **2** formation according to *Scheme 1* [7].

The effect of H_2O or alcohol additivities on the yield of 2-amino-4*H*-chromene was studied for the multicomponent transformation of salicylaldehyde, malononitrile, and alkylcyanoacetate into alkyl (2-amino-3-cyano-4*H*-chromene-4-yl)cyanoacetates **2b** [7b]. The best yields of **2b** were achieved, when the reaction was carried out as emulsion in a MeOH/H_2O mixture in the presence of AcONa at ambient temperature. It was the first example of an 'on-solvent' process in our studies.

Among different types of chromene systems, 2-amino-4*H*-chromenes are of particular utility, since they belong to privileged medicinal scaffolds, and are used for the treatment of viral hepatitis [8a], *Alzheimer*'s disease [8b], cardiovascular disorders, epilepsy, inflammatory bowel syndrome [8c], hypertension, and atherosclerosis [8d].

Increasing interest to 2-amino-4*H*-chromene derivatives bearing a nitrile group is connected with their application in the treatment of human inflammatory diseases such as carcinoma [9a], arthritis [9b], leukemia [9c], and in cancer therapy [10].

Results and Discussion. – In the present study, we report our results on the multicomponent 'on-solvent' transformation of salicylaldehydes **1**, malononitrile, and 4-hydroxy-1-methylquinolin-2(1*H*)-one as nucleophile.

Surprisingly, the solvent-free AcONa catalyzed reaction of salicylaldehyde **1a**, malononitrile, and 4-hydroxy-1-methylquinolin-2(1*H*)-one at ambient conditions in mortar with grinding resulted in formation of 2-amino-5,6-dihydro-4-(2-hydroxyphenyl)-6-methyl-5-oxo-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile **3a** in 19% yield instead of the expected chromene compound **2f** (*Scheme 2*; *Table 1*, *Entry 1*).

In this case, a new type of the multicomponent process (nonchromene-type) was realized, where the salicylaldehyde reacts as an aromatic aldehyde, and is not involved in the formation of a chromene system. Recently, we have accomplished a one-pot electrocatalytic multicomponent approach to functionalized pyrano[3,2-*c*]quinoline

Scheme 2. *Multicomponent Transformation of Salicylaldehyde* **1a**, *Malononitrile, and 4-Hydroxy-1-methylquinolin-2(1*H*)-one on Solvent-Free and Electrocatalytical Conditions*

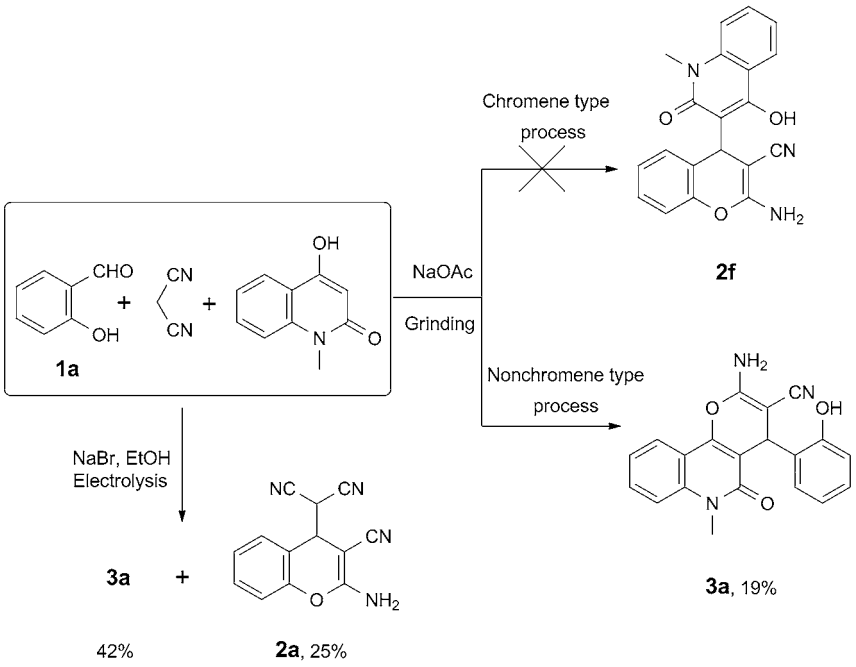


Table 1. *Multicomponent Transformation of Salicylaldehyde* **1a**, *Malononitrile, and 4-Hydroxy-1-methylquinolin-2(1*H*)-one*[a])

Entry	Base [mol-%]	Additive [ml]	Conditions	Time [min]	Yield of **3a** [%]
1	AcONa, 10	–	grinding, r.t.	10	19[b])
2	AcONa, 10	H_2O, 2	grinding, r.t.	10	35[b])
3	KF, 10	H_2O, 2	grinding, r.t.	10	29[b])
4	AcONa, 10	EtOH, 2	grinding, r.t.	10	45[b])
5	AcONa, 10	EtOH, 2	stirring, 78°	10	93[c])
6	AcONa, 10	EtOH, 2	stirring, 78°	3	95[c])
7	AcONa, 10	EtOH + H_2O, 1 + 1	stirring, 78°	3	63[c])
8	AcONa, 10	MeOH, 2	stirring, 64°	10	87[c])
9	AcONa, 10	PrOH, 2	stirring, 80°	10	79[c])

[a]) Emulsion of salicylaldehyde (**1a**, 5 mmol, 0.61 g), malononitrile (5 mmol, 0.33 g), 4-hydroxy-1-methylquinolin-2(1*H*)-one (5 mmol, 0.875 g), and AcONa (0.5 mmol, 40 mg). [b]) NMR data (^{t}BuOH as standard). [c]) Yield of isolated product.

scaffold from benzaldehydes, malononitrile, and 4-hydroxy-1-methylquinolin-2(1*H*)-one [11]. But when we used this electrocatalytic procedure (*Scheme 2*), pyrano[3,2-*c*]quinoline **3a** was obtained in only 42% yield (NMR data), together with a side product **2a** in 25% (NMR data).

The 4*H*-pyrano[3,2-*c*]quinoline scaffold is of particular interest due to the fact that this scaffold was found in many natural alkaloids [12] with anti-inflammatory [13] and cancer cell growth-inhibitory activity [14]. Recently, the 4*H*-pyrano[3,2-*c*]quinoline scaffold was found to display low nanomolar antiproliferative activity to induce apoptosis in human cancer cell lines and to be microtubule-targeting agent [15], and a new method for the synthesis of 4*H*-pyrano[3,2-*c*]pyridine scaffold from benzaldehydes (but not from salicylaldehydes), malononitrile, and 4-hydroxy-1-methylquinolin-2(1*H*)-one in the presence of nanozeolite clinoptilolite in H_2O under reflux was suggested [16].

On the next stage, to optimize the general procedure, 'on-water' and 'on-solvent' conditions, AcONa-initiated multicomponent transformation of salicylaldehyde **1a**, malononitrile, and 4-hydroxy-1-methylquinolin-2(1*H*)-one into 4*H*-pyrano[3,2-*c*]quinoline **3a** was studied (*Table 1*, *Scheme 3*).

'On-water' reaction of salicylaldehyde **1a**, malononitrile, and 4-hydroxy-1-methylquinolin-2(1*H*)-one in the presence of AcONa or KF affords **3a** in 35% and 29%, respectively (*Table 1*, *Entries 2* and *3*). 'On-ethanol' (*Entry 4*) the yield increased up to 45%. Increasing the temperature up to 78° (*Entry 5*) further increases the yield up to 93%. The best yield (95%) of **3a** was achieved when the reaction was carried out as emulsion in EtOH in the presence of AcONa as catalyst at 78° for 3 min (*Entry 6*), which is comparable with the timing of the processes under microwave irradiation.

Under the optimum conditions thus found (10 mol-% of AcONa, 78°, reaction time 3 min, small additives of EtOH (2 ml, 1.6 g, total weight of organic compounds is more than 1.8 g), needed to emulsify the mixture, 2-amino-5,6-dihydro-4-(2-hydroxyphenyl)-6-methyl-5-oxo-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitriles **3a – 3g** were obtained in excellent 88 – 98% yields (*Table 2*).

Thus, to confirm the structure **3** for our compounds, X-ray powder diffraction (XRD) has been accomplished for compounds **3c** and **3e**. Results are presented in *Fig. 1* and in the *Exper. Part*.

Scheme 3. *Multicomponent Transformation of Salicylaldehydes* **1a – 1g**, *Malononitrile, and 4-Hydroxy-1-methylquinolin-2(1*H*)-one into Pyrano[3,2-*c*]quinolines* **3a – 3g**

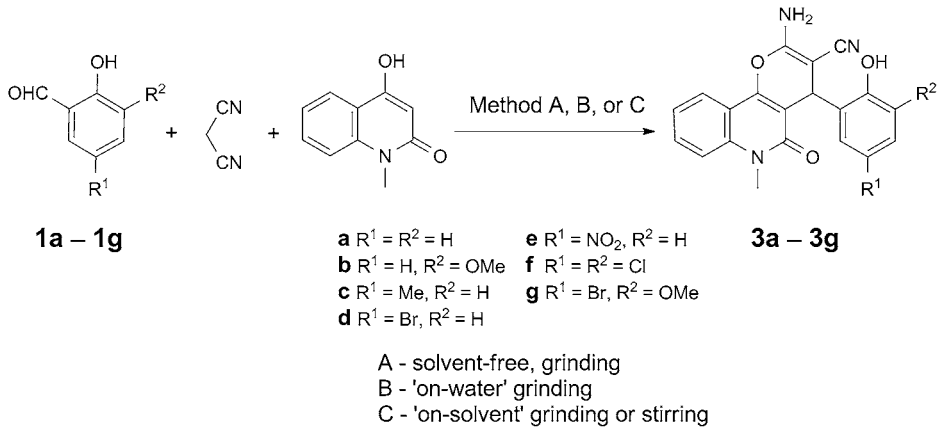
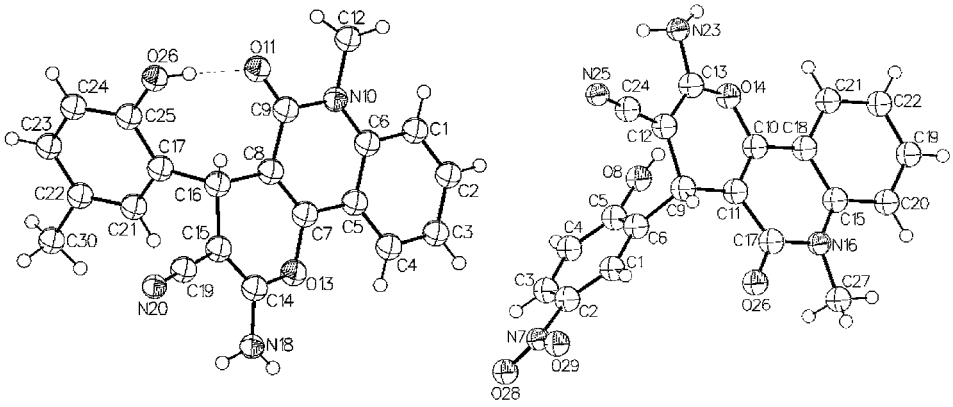


Table 2. *Multicomponent Transformation of Salicylaldehydes* **1a – 1g**, *Malononitrile and 4-Hydroxy-1-methylquinolin-2(1*H*)-one 'On-ethanol' into Pyrano[3,2-*c*]quinolines* **3a – 3g**[a])

Entry	Salicylaldehyde	R^1	R^2	Product	Yield [%][b])
1	**1a**	H	H	**3a**	95
2	**1b**	H	MeO	**3b**	95
3	**1c**	Me	H	**3c**	88
4	**1d**	Br	H	**3d**	88
5	**1e**	NO_2	H	**3e**	98
6	**1f**	Cl	Cl	**3f**	95
7	**1g**	Br	MeO	**3g**	92

[a]) Emulsion of salicylaldehyde (**1**, 5 mmol), malononitrile (5 mmol, 0.33 g), 4-hydroxy-1-methylquinolin-2(1*H*)-one (5 mmol, 0.875 g), and AcONa (0.5 mmol, 40 mg) in 2 ml of EtOH was vigorously stirring in 5 ml flask for 3 min. [b]) Yield of isolated product.

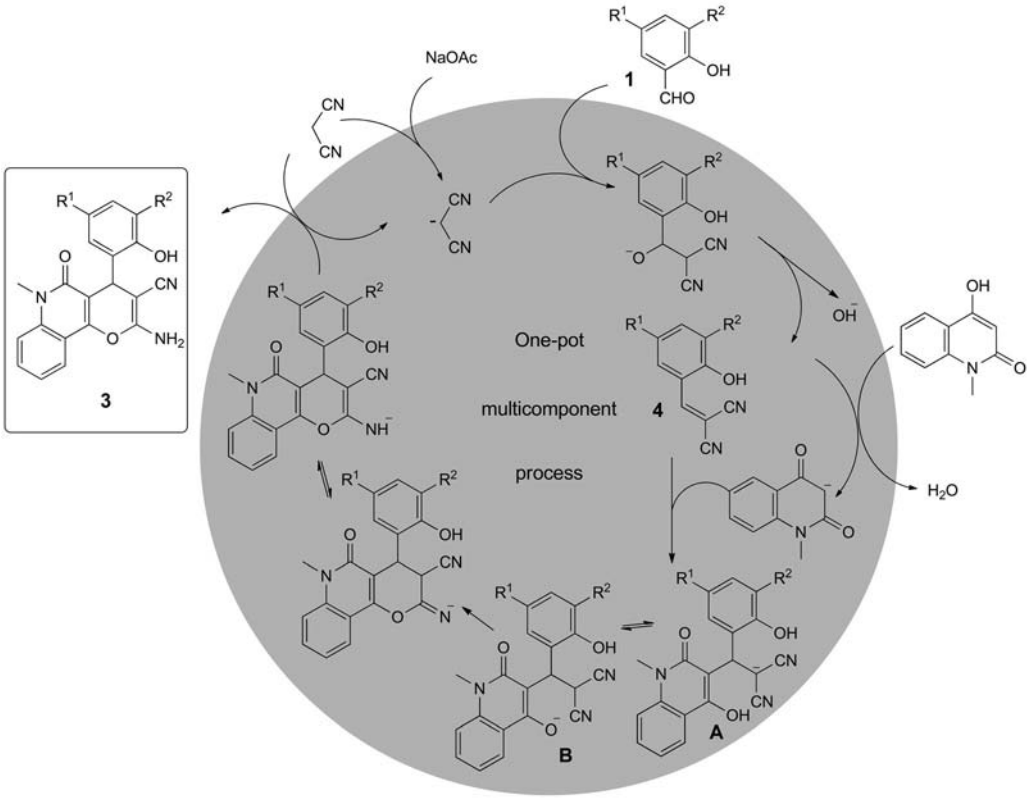


3c **3e**

Figure. *Molecular structures of* **3c** *and* **3e** *in crystal.* Atoms are represented by spheres indicating their isotropic thermal displacements (rj50%).

The mechanism of the multicomponent assembling of benzaldehydes, malononitrile, and 4-hydroxy-1-methylquinolin-2(1*H*)-one into pyrano[3,2-*c*]quinolines **3** is known [11]. The initiation step of the catalytic cycle begins with the deprotonation of malononitrile by the action of AcONa, which leads to the anion of malononitrile (*Scheme 4*). Then, *Knoevenagel* condensation of salicylaldehyde **1** with the malononitrile anion takes place in the solution, with the elimination of OH^- and formation of the corresponding (2-hydroxybenzylidene)malononitrile **4** [16]. The subsequent OH^- promoted *Michael* addition of 4-hydroxy-1-methylquinolin-2(1*H*)-one to the *Knoevenagel* adduct **4** leads to the anion **A**, as a key intermediate. Its tautomerization to the anion **B** followed by intramolecular cyclization leads to the corresponding 4*H*-pyrano[3,2-*c*]quinoline **3** with regeneration of the anion of malononitrile at the last step, which continues the catalytic chain process by the interaction with the next molecule of salicylaldehyde **1**.

Scheme 4. *Mechanism of Transformation of Salicylaldehydes* **1**, *Malononitrile, and 4-Hydroxy-1-methylquinolin-2(1*H*)-one into Substituted Pyrano[3,2-*c*]quinolines* **3**



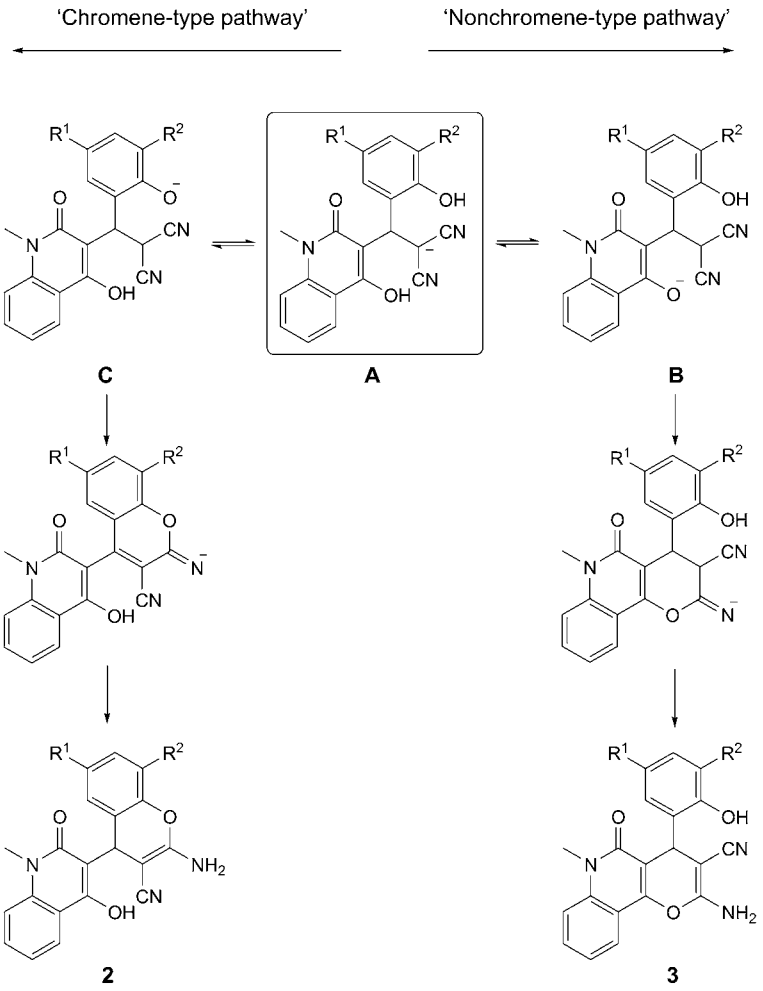
However, if the anion **A** is transformed into anion **C**, then the reaction would proceed *via* the 'chromene type pathway' (*Scheme 5*).

The pathway of the reaction strongly depends on the conditions of the process. There are processes known, where, depending on the conditions, is formed either chromene or the nonchromene product. Some examples of such reactions are given in *Table 3*.

As it shown from *Table 3*, the catalyst is crucial for the reaction pathway. So, $InCl_3$ promotes the formation of an anion like **C**, followed by intramolecular cyclization leads to chromene-type structure **2**. Other catalysts realize the nonchromene-type process *via* formation of anion like **B** leading to structure **3**.

Conclusions. – In conclusion, the simple technique can produce, under 'on-solvent' conditions, a very fast (3 min) and selective multicomponent transformation of salicylaldehydes, malononitrile, and 4-hydroxy-1-methylquinolin-2(1*H*)-one into substituted 4*H*-pyrano[3,2-*c*]quinolines – the promising compounds for different biomedical applications, in 88–98% yields. This process is realized *via* the 'nonchromene-type'

Scheme 5. *Chromene- and Nonchromene-Type Pathways*

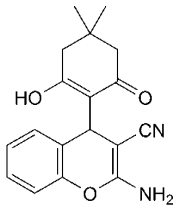
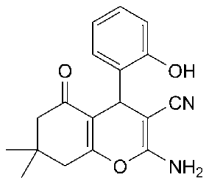
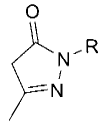
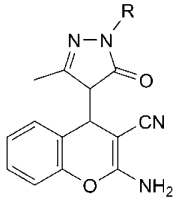
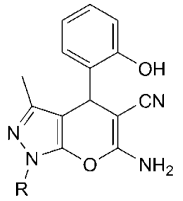
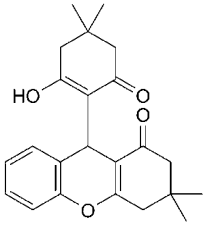
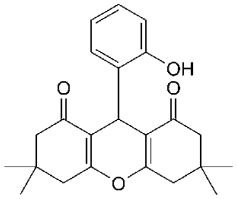


pathway. The developed multicomponent procedure requires simple and reasonable starting materials. It is easily carried out, and the reaction products are crystallized from the mixture. Earlier, the multicomponent transformation salicylaldehydes, malononitrile, and 4-hydroxy-1-methylquinolin-2(1*H*)-one into substituted pyrano [3,2-*c*]pyridones [16] was known.

Experimental Part

General. All starting materials were obtained from commercial sources and used without further purification. M.p.: *Gallenkamp* melting point apparatus; uncorrected. IR Spectra: *Bruker ALPHA-T* FT-IR spectrometer, in KBr pellets. ^{1}H- and ^{13}C-NMR spectra: *Bruker AM-300* (300 and 75 MHz, resp.) instrument, at ambient temp. in (D_6)DMSO solns.; chemical shifts are given in δ relative to Me_4Si. HR-

Table 3. *Chromene- and Nonchromene-Type Three Component Reactions of Salicylaldehyde* **1a**

Entry			Chromene-type product	Condition (reference)	Nonchromene-type product	Condition (reference)
1	$CH_2(CN)_2$	Dimedone		$InCl_3$, EtOH, 20° ([17])		Catalyst[a]), H_2O, 100° ([18])
2	$CH_2(CN)_2$			$InCl_3$, EtOH, 20° ([17])		Catalyst[b]), solvent-free, r.t. ([19])
3	Dimedone	Dimedone		$InCl_3$, or P_2O_5, solvent-free, 100° ([20])		I_2, ^{i}PrOH, 100° ([21])

[a]) Poly 1-ethyl-3-vinylimidazolium hydroxide coated magnetic nanoparticle. [b]) Heptakis(6-deoxy-6-amino)β-cyclodextrin.

ESI-MS: *Bruker micrOTOF II* instrument; external or internal calibration was done with an *Electrospray Calibrant Solution* (*Fluka*).

The powder patterns of **3c** and **3e** were measured on *Bruker D8 Advance Vario* diffractometer with *LynxEye* detector and Ge(111) monochromator, $\lambda(CuK_{\alpha1}) = 1.54060$ Å, $\theta/2\theta$ scan from 5.4° to 90° for **3c** and from 6° to 90° for **3e**, stepsize 0.009169°. The measurement was performed in the transmission mode; the compounds were deposited between two *Mylar* films. The indexing was performed using TOPAS 4.2 software [22]. The model for the solution and refinement was prepared basing on a PBE/L2 [23] calculation of **3c** and **3e** using PRIRODA software [24]. The structure was solved with the FOX program [25] using the Parallel Tempering method and refined with TOPAS 4.2. *Rietveld* refinement and structure verification were performed using breakable restraints, a modification of 'Morse' restraint model [26].

General Procedure. A suspension of salicylaldehyde **1** (5 mmol), malononitrile (5 mmol, 0.33 g), 4-hydroxy-1-methylquinolin-2(1*H*)-one (5 mmol, 0.875 g), and AcONa (0.5 mmol, 0.04 g) in EtOH (2 ml) was heated in a 5 ml flask at 78° for 3 min. After the reaction was finished, the solid was filtered, washed with cold EtOH (2 ml) and dried to isolate pure product **3**.

*2-Amino-5,6-dihydro-4-(2-hydroxyphenyl)-6-methyl-5-oxo-4*H-*pyrano[3,2-*c*]quinoline-3-carbonitrile* (**3a**). Yield 1.64 g (95%). Yellowish solid. M.p. 227–228°. IR (KBr): 3453, 3295, 3182, 2195, 1675, 1610, 1581, 1384, 1265, 1155. ^{1}H-NMR: 3.54 (*s*, Me); 4.73 (*s*, CH); 6.67–6.72 (*m*, 2 arom. H); 6.97–7.03 (*m*, 2 arom. H); 7.10 (*s*, NH_2); 7.36–7.41 (*m*, 1 arom. H); 7.56 (*d*, *J* = 8.5, 1 arom. H); 7.67–7.72 (*m*, 1 arom. H); 8.02 (*d*, *J* = 7.9, 1 arom. H); 9.42 (*s*, OH). ^{13}C-NMR: 29.3; 32.8; 56.8; 108.5; 112.9; 114.9; 115.9; 118.9; 120.1; 122.0; 122.1; 127.7; 129.5; 129.9; 131.4; 138.4; 150.6; 155.1; 159.4; 160.2. MS: 345 (86, M^+), 301 (51), 262 (44), 252 (81), 175 (69), 170 (84), 143 (100), 115 (47), 104 (47), 77 (61). HR-ESI-MS: 368.1001 ($[M+Na]^+$, $C_{20}H_{15}N_3NaO_3^+$; calc. 368.1006).

*2-Amino-5,6-dihydro-4-(2-hydroxy-3-methoxyphenyl)-6-methyl-5-oxo-4*H-*pyrano[3,2-*c*]quinoline-3-carbonitrile* (**3b**). Yield 1.71 g (95%). Yellowish solid. M.p: 247–248°. IR (KBr): 3354, 3202, 2197, 1677, 1579, 1461, 1388, 1250, 1156, 1072. ^{1}H-NMR: 3.55 (*s*, Me); 3.75 (*s*, MeO); 4.81 (*s*, CH); 6.58–6.69 (*m*, 2 arom. H); 6.79 (*d*, *J* = 7.6, 1 arom. H); 7.09 (*s*, NH_2); 7.40–7.43 (*m*, 1 arom. H); 7.58 (*d*, *J* = 8.4, 1 arom. H); 7.68–7.73 (*m*, 1 arom. H); 8.04 (*d*, *J* = 7.9, 1 arom. H); 8.65 (*s*, OH). ^{13}C-NMR: 29.3; 32.3; 55.6; 56.9; 108.6; 110.1; 112.9; 114.9; 118.5; 120.0; 121.2; 122.1 (2C); 130.3; 131.4; 138.4; 144.2; 147.7; 150.6; 159.3; 160.2. MS: 375 (40, M^+), 331 (19), 292 (43), 252 (73), 200 (100), 175 (85), 146 (45), 132 (34), 104 (41), 77 (43). HR-ESI-MS: 398.1105 ($[M+Na]^+$, $C_{21}H_{17}N_3NaO_4^+$; calc. 398.1111).

*2-Amino-5,6-dihydro-4-(2-hydroxy-5-methylphenyl)-6-methyl-5-oxo-4*H-*pyrano[3,2-*c*]quinoline-3-carbonitrile* (**3c**). Yield 1.58 g (88%). White solid. M.p.: 236–237°. IR (KBr): 3323, 3187, 2200, 1677, 1619, 1583, 1493, 1416, 1386, 1154. ^{1}H-NMR: 2.13 (*s*, Me); 3.55 (*s*, Me); 4.70 (*s*, CH); 6.60 (*d*, *J* = 7.7, 1 arom. H); 6.79–6.82 (*m*, 2 arom. H); 7.09 (*s*, NH_2); 7.36–7.41 (*m*, 1 arom. H); 7.56 (*d*, *J* = 8.5, 1 arom. H); 7.67–7.72 (*m*, 1 arom. H); 8.03 (*d*, *J* = 7.8, 1 arom. H); 9.17 (*s*, OH). ^{13}C-NMR: 20.2; 29.3; 32.3; 56.9; 108.5; 112.9; 114.9; 115.9; 120.1; 122.1; 122.2; 127.2; 128.2; 129.6; 129.8; 131.4; 138.4; 150.6; 152.9; 159.4; 160.3. MS: 359 (85, M^+), 344 (25), 327 (18), 315 (44), 276 (66), 252 (100), 184 (73), 157 (39), 104 (35), 77 (58). HR-ESI-MS: 382.1158 ($[M+Na]^+$, $C_{21}H_{17}N_3NaO_3^+$ calc. 382.1162).

Crystal data for **3c**. $C_{21}H_{17}N_3O_3$ (M = 359.38): triclinic, space group *P*-1 (no. 2), $a = 7.54595(10)$ Å, $b = 9.56242(17)$ Å, $c = 13.8764(4)$ Å, $\alpha = 93.0131(16)°$, $\beta = 91.5017(19)°$, $\gamma = 116.9651(11)°$, $V = 889.79(3)$ Å^3, $Z = 2$, $T = 298$ K, $\mu(CuK_{\alpha1}) = 0.748$ mm^{-1}, $D_{calc} = 1.341$ g/mm^3, the refinement converged to $R_P/R_P'/R_{WP}/R_{WP}'/R_{Bragg}$ values of 2.920/9.013/4.175/9.342/0.965 with R_{exp}/R_{exp}' values of 0.872/1.951, $\chi^2 = 4.789$.

Crystallographic data reported for **3c** have been deposited with *Cambridge Crystallographic Data Centre* as supplementary publication. Copies of the data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html with the reference number CCDC-1028971.

*2-Amino-4-(5-bromo-2-hydroxyphenyl)-5,6-dihydro-6-methyl-5-oxo-4*H-*pyrano[3,2-*c*]quinoline-3-carbonitrile* (**3d**). Yield 1.87 g (88%). White solid. M.p.: 240–241°. IR (KBr): 3322, 3188, 2207, 1674, 1616, 1582, 1474, 1415, 1385, 1155. ^{1}H-NMR: 3.54 (*s*, Me); 4.68 (*s*, CH); 6.67 (*d*, *J* = 8.4, 1 arom. H); 7.12–7.18 (*m*, 2 arom. H + NH_2); 7.36–7.41 (*m*, 1 arom. H); 7.56 (*d*, *J* = 8.4, 1 arom. H); 7.67–7.72 (*m*, 1 arom. H); 8.01 (*d*, *J* = 7.8, 1 arom. H); 9.74 (*s*, OH). ^{13}C-NMR: 29.2; 33.3; 56.0; 107.5; 109.8; 112.7; 114.9; 118.0; 119.9; 122.1 (2C); 130.3; 131.5; 131.9; 132.3; 138.5; 150.7; 154.7; 159.5; 160.0. MS: 425 (47, M^+), 423 (53,

M^+), 379 (17), 344 (39), 327 (20), 252 (100), 221 (30), 175 (58), 114 (37), 77 (40). HR-ESI-MS: 448.0078 ($[M+Na]^+$, $C_{20}H_{14}BrN_3NaO_3^+$; calc. 448.0091).

*2-Amino-5,6-dihydro-4-(2-hydroxy-5-nitrophenyl)-6-methyl-5-oxo-4*H-*pyrano[3,2-*c*]quinoline-3-carbonitrile* (**3e**). Yield 1.92 g (98%). Yellowish solid. M.p.: 212–214°. IR (KBr): 3475, 3334, 2192, 1677, 1569, 1382, 1336, 1291, 1263, 1160. ^{1}H-NMR: 3.54 (*s*, Me); 4.84 (*s*, CH); 6.89 (*d*, $J=8.8$, 1 arom. H); 7.24 (*s*, NH_2); 7.39–7.44 (*m*, 1 arom. H); 7.59 (*d*, $J=8.0$, 1 arom. H); 7.70–7.75 (*m*, 1 arom. H); 7.93–8.05 (*m*, 3 arom. H); 11.20 (br. *s*, OH). ^{13}C-NMR: 29.2; 33.4; 55.5; 107.1; 112.6; 115.0; 116.1; 119.8; 122.1; 122.2; 124.4; 125.5; 130.7; 131.6; 138.6; 139.3; 150.9; 159.5; 159.9; 162.0. MS: 390 (4, M^+), 373 (16), 307 (5), 252 (14), 215 (99), 175 (100), 146 (71), 132 (50), 114 (74), 77 (46). HR-ESI-MS: 413.0848 ($[M+Na]^+$, $C_{20}H_{14}N_4NaO_5^+$; calc. 413.0856).

Crystal data for **3e**. $C_{20}H_{14}N_4O_5$ ($M=390.35$): triclinic, space group *P*-1 (no. 2), $a=12.0576(2)$ Å, $b=11.6734(3)$ Å, $c=13.7110(3)$ Å, $\alpha=100.9920(15)°$, $\beta=96.3944(13)°$, $\gamma=104.6145(14)°$, $V=1807.15(7)$ Å^3, $Z=4$ ($Z'=2$), $T=298$ K, $\mu(CuK_{\alpha1})=0.890$ mm^{-1}, $D_{calc}=1.435$ g/mm^3, the refinement converged to $R_P/R_P'/R_{WP}/R_{WP}'/R_{Bragg}$ values of 2.092/11.414/3.017/11.634/1.420 with R_{exp}/R_{exp}' values of 0.520/2.004, $\chi^2=5.804$.

Crystallographic data reported for **3e** have been deposited with *Cambridge Crystallographic Data Centre* as supplementary publication. Copies of the data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html with the reference number CCDC-1028972.

*2-Amino-4-(3,5-dichloro-2-hydroxyphenyl)-5,6-dihydro-6-methyl-5-oxo-4*H-*pyrano[3,2-*c*]quinoline-3-carbonitrile* (**3f**). Yield 1.97 g (95%). White solid. M.p.: 254–256°. IR (KBr): 3355, 3203, 2212, 1679, 1578, 1459, 1386, 1320, 1232, 1153. ^{1}H-NMR: 3.57 (*s*, Me); 4.85 (*s*, CH); 7.05 (*s*, 1 arom. H); 7.33 (*s*, NH_2); 7.35–7.44 (*m*, 2 arom. H); 7.60 (*d*, $J=8.4$, 1 arom. H); 7.69–7.75 (*m*, 1 arom. H); 8.03 (*d*, $J=7.8$, 1 arom. H); 9.95 (br. *s*, OH). ^{13}C-NMR: 29.5; 33.3; 55.7; 107.4; 112.8; 115.1; 119.6; 122.2; 122.3; 122.4; 123.1; 127.5; 128.0; 131.8; 134.5; 138.4; 150.0; 150.9; 159.5; 160.4. MS: 415 (19, M^+), 413 (30, M^+), 378 (13), 330 (16), 252 (100), 238 (54), 211 (46), 175 (61), 146 (27), 104 (21). HR-ESI-MS: 436.0211 ($[M+Na]^+$, $C_{20}H_{13}Cl_2N_3NaO_3^+$; calc. 436.0226).

*2-Amino-4-(5-bromo-2-hydroxy-3-methoxyphenyl)-5,6-dihydro-6-methyl-5-oxo-4*H-*pyrano[3,2-*c*]quinoline-3-carbonitrile* (**3g**). Yield 2.09 g (92%). White solid. M.p.: 263–264°. IR (KBr): 3328, 3197, 2203, 1676, 1617, 1586, 1384, 1306, 1248, 1155. ^{1}H-NMR: 3.54 (*s*, Me); 3.75 (*s*, MeO); 4.75 (*s*, CH); 6.72 (*s*, 1 arom. H); 6.95 (*s*, 1 arom. H); 7.16 (*s*, NH_2); 7.36–7.41 (*m*, 1 arom. H); 7.57 (*d*, $J=8.4$, 1 arom. H); 7.68–7.73 (*m*, 1 arom. H); 8.02 (*d*, $J=7.9$, 1 arom. H); 8.95 (*s*, OH). ^{13}C-NMR: 29.3; 32.8; 56.1; 107.8; 109.5; 112.8; 113.2; 115.0; 119.9; 121.2; 122.2 (2C); 123.6; 131.5; 132.0; 138.5; 143.9; 148.8; 150.7; 159.3; 160.1. MS: 455 (13, M^+), 453 (12, M^+), 372 (16), 278 (91), 252 (97), 175 (100), 146 (45), 132 (34), 104 (33), 77 (28). HR-ESI-MS: 478.0188 ($[M+Na]^+$, $C_{21}H_{16}BrN_3NaO_4^+$; calc. 478.0197).

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