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‘On-solvent’ new domino reaction of salicylaldehyde, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-one: fast and efficient approach to medicinally relevant 4-pyridinyl-2-amino-4*H*-chromene scaffold

Michail N. Elinson,* Fedor V. Ryzhkov, Anatoly N. Vereshchagin, Alexander D. Korshunov, Roman A. Novikov and Mikhail P. Egorov

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: + 7 499 135 5328; e-mail elinson@ioc.ac.ru

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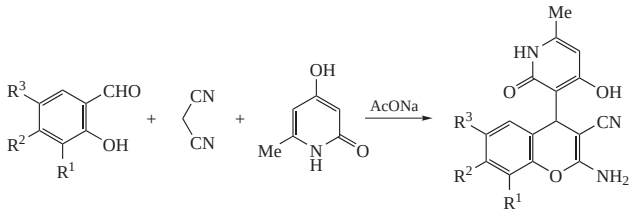
Sodium acetate catalyzed assembling of salicylaldehydes, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-one in small amount of ethanol gives rapidly (5 min) substituted 4-pyridinyl-2-amino-4*H*-chromenes in 82–99% yields. This novel domino reaction opens the fast, facile, and flexible way to the new type of functionalized 2-amino-4*H*-chromene scaffold containing uracil-like moiety, which are relevant compounds for diverse biomedical applications.

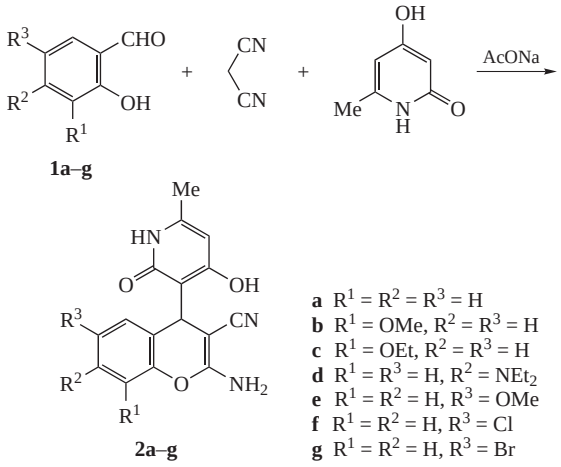


Domino reaction[1] is an actual modern way to reach ‘ideal’ synthesis[2] through atom and step economy in the one-pot PASE process.[3,4] It allows the organic synthesis of complex multinuclear molecules to be accomplished, in which many bonds are consequently constructed from simple acyclic precursors.

The next step to ‘ideal’ synthesis is domino reaction under solvent-free conditions in accordance with the modern demands of green chemistry.[5,6] However, solvent-assisted, ‘on solvent’[7,8] and ‘on water’[9–11] reactions have much more application areas, as compared with solvent-free mechano-chemical processes, due to their flexibility, high rate and selectivity, as well as reduced reaction time. Thus, solvent-assisted domino reactions, which combine efficiency of domino processes with the most part of ‘green chemistry’ merits, have attracted a great interest of researchers in last decade.

The design of functional organic and hybrid molecular systems has shown outstanding recent growth and is a high priority in the development of new technologies and novel functional materials.[12,13] In this connection, the concept of ‘privileged medicinal structures or scaffolds’ has emerged as one of the guiding principles of drug discovery design. These privileged scaffolds commonly consist of rigid hetero ring system that assigns well-defined orientation of appended functionalities for target recognition.[14]

The chromene moiety is known as important structural element in both synthetic and natural pharmacologically active compounds.[15,16] Among different types of chromene systems, 2-amino-4*H*-chromenes are of particular utility as they belong to privileged medicinal scaffolds used for treatment of viral hepatitis,[17] Alzheimer’s disease,[18] cardiovascular disorders[19] as well as hypertension and artherosclerosis.[20] Increasing interest to 2-amino-4*H*-chromene derivatives bearing nitrile group is due to their application in the treatment of human inflammatory diseases[21,22] and in cancer therapy.[23–26] The 4-hydroxy-6-methylpyridin-2(1*H*)-one scaffold has also attracted attention. This moiety is a part of natural pyrimidine nucleoside that is involved in RNA and bio-membrane synthesis,[27] galactose metabolism,[28] modulation of reproduction,[29] regulation of body temperature,[30] and peripheral and central nervous systems activities.[31,32] The value of biological activity of uracil-like moiety is not overestimated. Thus, combinations of pharmacologically active 2-amino-4*H*-chromene systems with a bioactive 4-hydroxy-6-methylpyridin-2(1*H*)-one fragment should force evolve and multiplicate properties of both scaffolds.



Scheme 1

Recently we have accomplished different types of ‘on-water’[33–36] and ‘on-solvent’[37–39] transformations. Here, we report our results on the novel efficient multicomponent assembling of salicylaldehydes **1a–g**, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-one into new 2-amino-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4*H*-chromene-3-carbonitriles **2a–g** (Scheme 1, Tables 1 and 2).

At the first stage, previously unknown chromene **2a** was obtained under mild solvent-free conditions upon 15–30 min

Table 1 Multicomponent transformation of salicylaldehyde **1a**, malononitrile and 6-hydroxy-4-methylpyridin-2(1*H*)-one into substituted 2-amino-4*H*-chromene **2a**.

Entry	Catalyst (10 mol%)	Additive (volume/ml)	*t*/min	*T*/ °C	Yield of **2a** (%)
1	KF	Solvent-free[a]	15	25	50[c]
2	AcONa	Solvent-free[a]	15	25	53[c]
3	AcONa	Solvent-free[a]	30	25	67[c]
4	KF	H_2O (2)[a]	15	25	23[c]
5	AcONa	H_2O (2)[a]	15	25	27[c]
6	AcONa	H_2O (5)[b]	15	80	43[c]
7	–	EtOH (5)[b]	15	78	67[c]
8	AcONa	EtOH (5)[b]	15	78	99[d]
9	AcONa	EtOH (5)[b]	5	78	98[d]
10	AcONa	EtOH (5)[b]	3	78	95[d]
11	AcONa	EtOH (5)[b]	1	78	93[d]
12	AcONa	EtOH (3)[b]	5	78	99[d]

[a] Salicylaldehyde **1a** (3 mmol), 6-hydroxy-4-methylpyridin-2(1*H*)-one (3 mmol) and malononitrile (3 mmol) were grinded with a pestle in mortar. [b] The same reactants were mixed in a flask with magnetic stirrer. [c] NMR data. [d] Isolated yield.

grinding in a mortar.† Performing the reaction in the presence of 10 mol% of KF as a catalyst afforded product **2a** in 50% yield in 15 min (Table 1, entry 1). With 10 mol% of AcONa as a catalyst, 53% yield of **2a** was achieved (entry 2). There was no sufficient growth in the yield of **2a** on prolongation of the reaction to 30 min (entry 3).

'On-water' reaction of salicylaldehyde **1a**, malononitrile and 6-hydroxy-4-methylpyridin-2(1*H*)-one with 10 mol% of KF or AcONa and addition of H_2O (2 ml) at ambient temperature within 15 min (Table 1, entries 4 and 5) gave chromene **2a** in only 23 and 27% yields, respectively. Raising the temperature to 80 °C allows one to achieve 43% yield of **2a** (entry 6). Analogous conditions with reflux in EtOH without any catalyst provided 67% yield of **2a** (entry 7). In the presence of 10 mol% of AcONa as a catalyst, the same conditions provided 99% yield (entry 8). The similar result (98%) was obtained with reducing the reaction time to 5 min (entry 9). On further reducing the reaction time, the yields were somewhat lower (entries 10, 11). Ultimately, the optimal 'on-solvent' conditions for carrying out the reaction comprised utilizing 3 ml of EtOH in the presence of 10 mol% AcONa at 78 °C (5 min) with 99% yield of **2a** (entry 12).

Under these optimal 'on-solvent' conditions,‡ new substituted 2-amino-4*H*-chromenes **2a**–**g** were obtained in good to excellent 82–99% yields (Table 2).

As practically pure products **2a**–**g** were formed in the end of the reaction, the reaction mixture was only filtered and dried to afford pure **2a**–**g**. Only in some cases additional recrystallization from ethanol was needed. Thus, 'on-solvent' procedure for synthesis of the new substituted 2-amino-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4*H*-chromene-3-carbonitriles **2a**–**g** found by us is one step closer to the 'ideal synthesis'.[40]

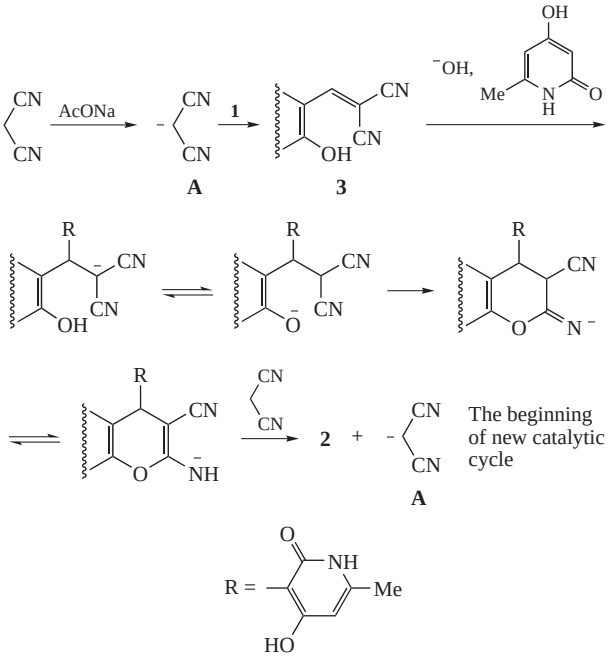
Table 2 Multicomponent transformation of salicylaldehydes **1a**–**g**, malononitrile and 6-hydroxy-4-methylpyridin-2(1*H*)-one into substituted 2-amino-4*H*-chromenes **2a**–**g**.[a]

Entry	Salicyl-aldehyde	R^1	R^2	R^3	Product	Isolated yield (%)
1	**1a**	H	H	H	**2a**	99
2	**1b**	OMe	H	H	**2b**	90
3	**1c**	OEt	H	H	**2c**	91
4	**1d**	H	NEt_2	H	**2d**	82
5	**1e**	H	H	OMe	**2e**	98
6	**1f**	H	H	Cl	**2f**	89
7	**1g**	H	H	Br	**2g**	99

[a] Salicylaldehyde **1** (3 mmol), malononitrile (3 mmol), 6-hydroxy-4-methylpyridin-2(1*H*)-one (3 mmol) and AcONa (0.3 mmol) were refluxed in 3 ml of ethanol for 5 min.

The structure of compound **2b** was confirmed by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy using 2D COSY, NOESY, HSQC, HMBC, long-range HMBC, and ^{15}N-HMBC spectra (for details, see Online Supplementary Materials).

With the above results taken into consideration and the mechanistic data on solvent-free cascade formation of 2-amino-4*H*-chromene scaffold from salicylaldehydes and malononitrile,[41] as well as from salicylaldehydes and cyanoacetates,[42] the following mechanism for the current transformation is proposed (Scheme 2). The initiation step of the catalytic cycle begins with deprotonation of malononitrile by the action of sodium acetate, which leads to malononitrile anion **A**.



Scheme 2

Attack of anion **A** on salicylaldehyde **1** occurs with elimination of hydroxide anion and formation of the Knoevenagel adduct **3**.[43] The subsequent hydroxide-promoted Michael addition of 6-hydroxy-4-methylpyridin-2(1*H*)-one to electron-deficient adduct **3** results in corresponding substituted 2-amino-4*H*-chromene **2** with the regeneration of the malononitrile anion **A** at the last step (see Scheme 2).

In conclusion, highly efficient fast (5 min) domino 'on-solvent' reaction between salicylaldehydes, malononitrile, and 6-hydroxy-

† *Solvent-free grinding procedure*. A mixture of salicylaldehyde **1** (3 mmol), malononitrile (3 mmol, 0.198 g), 4-hydroxy-6-methylpyridin-2(1*H*)-one (3 mmol, 0.375 g) and sodium acetate (0.3 mmol, 0.025 g) was mixed thoroughly with a pestle in a mortar followed by grinding for 15 min. The resulting mixture was air dried to cause crystallization of the product. The crude solid was then filtered, rinsed with water (2×2 ml) and air dried to analyze by ^{1}H NMR spectroscopy.

‡ *'On-solvent' procedure*. The same mixture of reactants as for solvent-free procedure in ethanol (3 ml) was refluxed for 5 min. The reaction mixture was cooled to –10 °C for 1 h, the solid phase was filtered off, rinsed with water (2×2 ml) and air dried to isolate pure 2-amino-4*H*-chromenes **2**. In some cases additional recrystallization from ethanol was needed.

For characteristics of products **2a**–**g**, see Online Supplementary Materials.

4-methylpyridin-2(1*H*)-one catalyzed by sodium acetate in small amount of ethanol leads to earlier unknown substituted 2-amino-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4*H*-chromene-3-carbonitriles. This new process opens an effective and facile one-pot way to create a novel type of uracil-like substituted 2-amino-4*H*-chromenes – the promising compounds for the treatment of human inflammatory TNFα-mediated diseases, cancer therapy, and different biomedical applications. The method meets modern requirements of organic synthesis, such as 'green chemistry' principles and high atom economy, and combines them with ecological and economic benefits of multicomponent and 'on-solvent' reactions. These advantages are valuable from the viewpoint of environmentally benign and diversity-oriented large-scale processes.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.11.006.

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