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Mendeleev Commun., 2019, **29**, 581–583

Mendeleev Communications

Multicomponent assembling of salicylaldehydes, kojic acid and malonic acid derivatives

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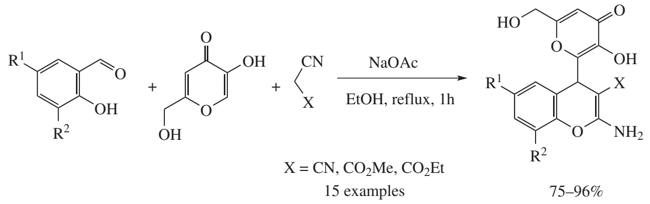
DOI: 10.1016/j.mencom.2019.09.035

A multicomponent one-pot environmentally benign transformation of salicylaldehydes, kojic acid and malononitrile or its derivativies, catalyzed by sodium acetate, in a small amount of ethanol results in efficient formation of new substituted 2-amino-4-[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]-4*H*-chromene-3-carbonitriles or -3-carboxylates in 75–96% yields.



In the last decade, multicomponent reactions (MCRs) have become a widely accepted approach to heterocyclic systems with diverse pharmaceutical applications. This one-pot method allows one to increase the overall yield of products due to combining several reactions in one step without isolation and purification[1] as well as lowering the use of environmentally dangerous reagents according to principles of green chemistry. These benefits of MCRs correspond to the concept of ideal synthesis[2] and engage researchers to investigate novel multicomponent reactions for the synthesis and the following pharmaceutical screening of the product libraries.

Kojic acid, or 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one, is a polyfunctional heterocycle with weakly acidic vinylic hydroxy group,[3] extracted originally from *Aspergillus oryzae*[4] and used mainly in food production and cosmetics.[5] It is also known as an inhibitor of tyrosinase.[6] Kojic acid derivatives were found to demonstrate antimicrobial,[7] anti-inflammatory,[8] antiviral[9] and anti-HIV[10] effects.

The chromene scaffold is another widely used oxygen-containing structure,[11] examples are warfarin as anticoagulant[12] and 2-amino-3-cyano-4*H*-chromenes as potential anticancer agents.[13] Considering our interest to multicomponent one-pot transformations of carbonyl compounds and CH-acids,[14] we planned to combine the scaffolds of kojic acid and chromene, similarly to the known reaction of salicylaldehyde, kojic acid and 2-phenylindole with the formation of 3-hydroxy-6-(hydroxymethyl)-2-[(2-hydroxyphenyl)(2-phenyl-1*H*-indol-3-yl)methyl]-4*H*-pyran-4-one under solvent-free conditions,[7] as well as the transformation of 3-methoxysalicylaldehyde **1c** or 5-bromosalicylaldehyde **1f**, kojic acid and malononitrile **2a** to 2-amino-6-(hydroxymethyl)-4-(2-hydroxyphenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles **3a**,**b** (Scheme 1)[15,16] and also multicomponent transformation of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-phenylisoxazol-5(4*H*)-one[17] or 3-methyl-2-pyrazolin-5-one.[18]

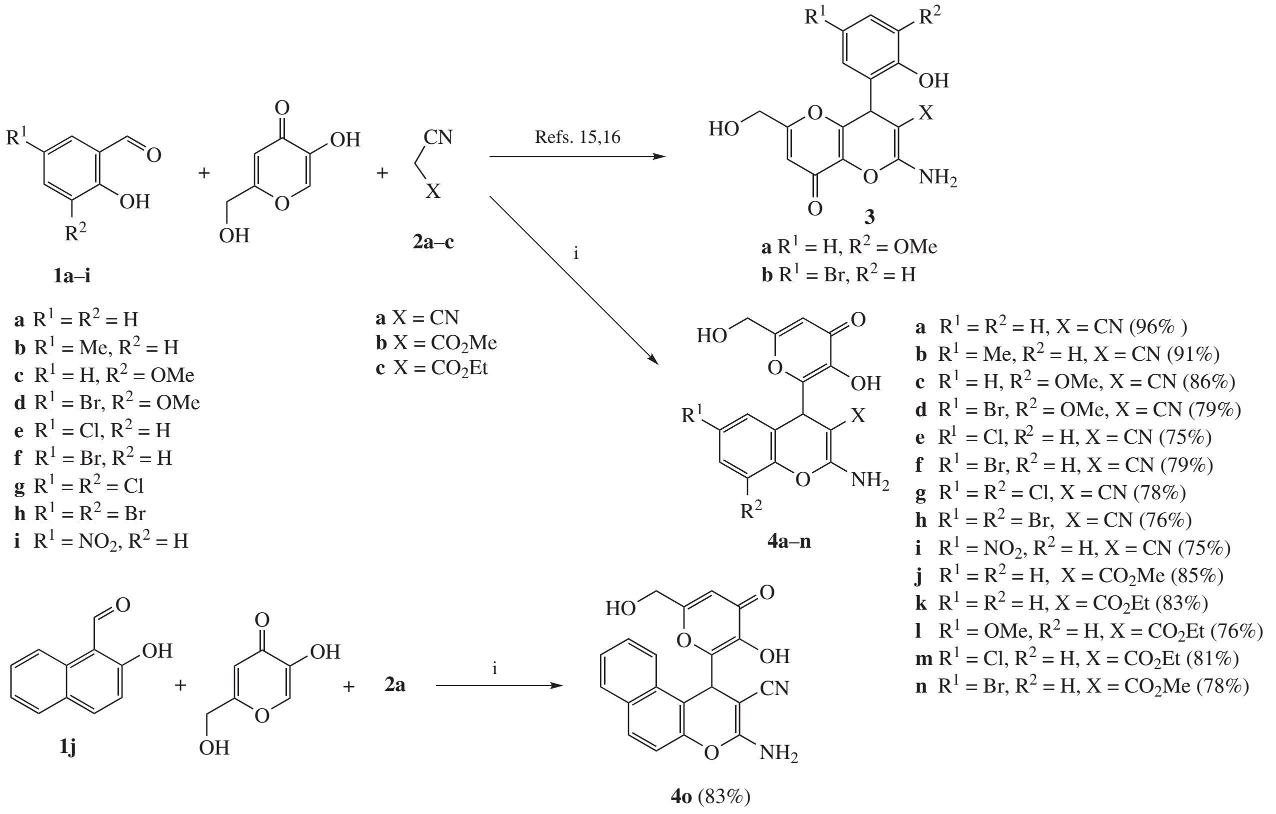
In this work, we report our results on the new one-pot transformation of salicylaldehydes **1a**–**j**, kojic acid and malononitrile **2a**, methyl or ethyl cyanoacetates **2b**,**c** into 2-amino-4-[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]-4*H*-chromenes **4a**–**o** (Scheme 1, Table 1).

We started with the synthesis of 2-amino-4-[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]-4*H*-chromene-3-carbonitrile **4a** from salicylaldehyde **1a**, kojic acid and malononitrile **2a** under so-called solvent-free and on-water

Table 1 Synthesis of 2-amino-4*H*-chromene-3-carbonitrile **4a** from salicylaldehyde **1a**, kojic acid and malononitrile **2a**.

Entry	Solvent	Catalyst	Time/h	Temperature/°C	Yield of **4a** (%)
1	Solvent-free[a]	-	0.3	25	16[c]
2	Solvent-free[a]	KF	0.3	25	41[c]
3	Solvent-free[a]	AcONa	0.3	25	43[c]
4	H_2O[b]	-	1	80	25[c]
5	H_2O[b]	AcONa	1	80	37[c]
6	H_2O[b]	NaOH	1	80	42[c]
7	EtOH[b]	-	1	78	55[c]
8	EtOH[b]	KF	1	78	73[d]
9	EtOH[b]	NaOH	1	78	78[d]
10	EtOH[b]	Et_3N	1	78	84[d]
11	EtOH[b]	AcONa	1	78	96[d]
12	EtOH[b]	AcONa	0.5	78	75[d]
13	MeOH[b]	AcONa	1	65	88[d]
14	*n*-PrOH[b]	AcONa	1	98	92[d]

[a] **1a** (3 mmol), kojic acid (3 mmol) and **2a** (3 mmol) were ground in mortar with 10 mol% of catalyst or without catalyst. [b] **1a** (3 mmol), kojic acid (3 mmol) and **2a** (3 mmol) were heated in solvent (5 ml) with 10 mol% of catalyst or without catalyst. [c] NMR yield. [d] Isolated yield.



Scheme 1 *Reagents and conditions*: i, 10 mol% AcONa (cat.), EtOH, reflux, 1h.

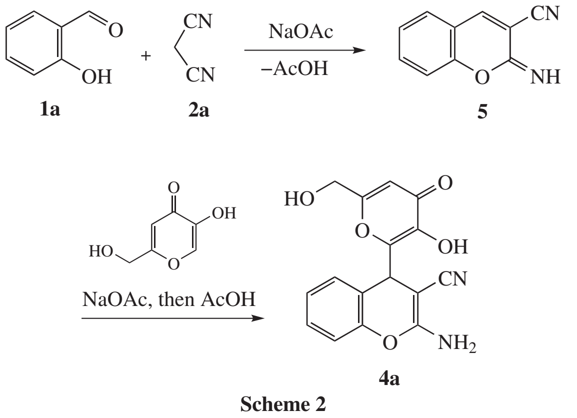
reaction conditions due to their known efficiency and selectivity[19,20] (Table 1, entries 1–6). It was found that the new compound **4a** was formed under these conditions in 16–43% yield.

The next series of experiments was carried out under so-called solvent assisted conditions,[21–23] assuming in general the absence of full solubility of components, in the minimal amount (5 ml) of alcohol as a solvent. Reaction in boiling ethanol afforded compound **4a** in 55% yield (Table 1, entry 7).

Among catalytic reactions in alcohols, the best yield (96%) was obtained with 10 mol% AcONa as a catalyst in boiling ethanol for 1 h (Table 1, entry 11). The decrease in reaction time or the use of methanol or propanol as a solvent led to lowering the product yields to 75, 88 and 92%, respectively (Table 1, entries 12–14).

Under the optimal conditions, namely 10 mol% AcONa as a catalyst and reflux for 1 h in ethanol, the new substituted 2-amino-4*H*-chromenes **4a–o** were obtained in 75–96% yields (see Scheme 1).

The structures of all the new compounds **4a–o** were confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy data as well as by mass spectrometry and elemental analysis results (see Online Supplementary Materials). The structure of compound **4a** was also confirmed by two-dimensional ^{1}H,^{13}C-HMBC spectrum.



Scheme 2

With these results and taking into consideration the mechanistic data on multicomponent formation of 2-amino-4*H*-chromene-3-carbonitrile scaffold from carbonyl compounds and CH-acids,[24,25] we propose the following mechanism for the multicomponent transformation (Scheme 2). At the first step, the formation of the Knoevenagel adduct from salicylaldehyde **1a** and malononitrile **2a** occurs, followed by the Pinner intramolecular cyclization leading to imine **5**. A nucleophilic attack of kojic acid with subsequent protonation results in the 2-amino-4*H*-chromene-3-carbonitrile **4a** formation.

In summary, the new efficient one-pot multicomponent reaction of salicylaldehydes, kojic acid and malononitrile or its derivatives catalyzed by sodium acetate in ethanol leads to the new substituted 2-amino-4-[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]-4*H*-chromene-3-carbonitriles or -3-carboxylates in high yields. The low cost environmental friendly catalyst, simple equipment and workup procedure are utilized in the elaborated protocol.

This work was supported by the RF President Council (project no. MD-545.2019.3).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.09.035.

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Received: 1st April 2019; Com. 19/5871