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Solvent-free cascade assembling of salicylic aldehydes and malononitrile: rapid and efficient approach to 2-amino-4*H*-chromene scaffold

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Solvent-free NaOAc- or KF-catalyzed assembling of salicylic aldehydes with two molecules of malononitrile affords (2-amino-3-cyano-4*H*-chromen-4-yl)malononitriles in 94–99% yields within 10 min.

The concept of 'privileged medicinal structures or scaffolds', originally introduced by Merck researchers, has recently emerged as one of the guiding principles of modern drug discovery.[1,2] Privileged scaffolds commonly consist of rigid ring, including hetero ring, systems that present appended residues in well-defined orientations required for target recognition.[2]

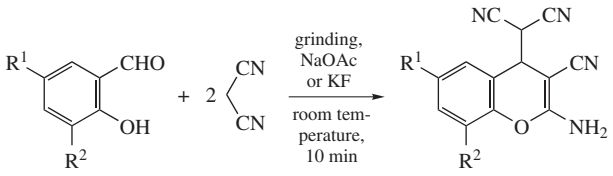
Functionalized chromenes have played in ever increasing role in the synthetic approaches to promising compounds in medicinal chemistry.[3–5] Among them, 2-amino-4*H*-chromenes are of particular utility as they belong to privileged medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced spasmolytic, diuretic, anticoagulant, and antianaphylactic activities.[6–8] The current interest in 2-amino-4*H*-chromene derivatives bearing nitrile functionality arises from their potential application in the treatment of human inflammatory TNFα-mediated diseases, such as rheumatoid and psoriatic arthritis, and in cancer therapy.[9–12]

The progress in the field of solvent-free reactions have provided organic chemists with a new simple efficient synthetic principle,[13] which meets, moreover, with the most important goal of 'green chemistry'. On the other hand, cascade reactions represent powerful means to construct complex molecules from readily available starting materials by combining two or more reactions into a single transformation.[14] The implication of the solvent-free process in base-activated cascade reactions is highly promising as it allows one to combine the synthetic virtues of the conventional cascade strategy with the ecological benefits and convenience of the solvent-free procedure.

Recently, we have found electrocatalytic cascade process for transformation of salicylic aldehydes and malononitrile into substituted 2-amino-4*H*-chromenes[15] and solvent-free Knoevenagel reaction of isatins with malononitriles carried out in mortar by grinding.[16] However, cascade solvent-free process for synthesis of medicinally priviledged 2-amino-4*H*-chromene scaffold from salicylic aldehydes and malononitrile is not yet known. Thus, we were prompted to use a convenient and facile solvent-free cascade procedure for the synthesis of 2-amino-4*H*-chromenes from these reactants.

Here we report our results on cascade reaction of salicylic aldehydes **1a–g** and malononitrile in mortar under solvent-free conditions (Scheme 1, Table 1).†

No reaction occurred without catalyst in mortar on grinding (Table 1, entry 1). In the presence of only 1 mol% of NaOAc, the product **2a** was obtained in 82% yield in 10 min (entry 2). Using



1a–g **2a–g**

a $R^1 = R^2 = H$
b $R^1 = Me$, $R^2 = H$
c $R^1 = Cl$, $R^2 = H$
d $R^1 = Br$, $R^2 = H$
e $R^1 = NO_2$, $R^2 = H$
f $R^1 = H$, $R^2 = OMe$
g $R^1 = H$, $R^2 = OEt$

Scheme 1

Table 1 Solvent-free transformation of salicylic aldehydes **1a–g** (2 mmol) and malononitrile (4 mmol) into 2-amino-4*H*-chromenes **2a–g** (20 °C, grinding).

Salicylic aldehyde	Base (1 mol%)	Time/ min	2-Amino-4*H*-chromene	Isolated yield (%)
1a	—	10	**2a**	0
1a	NaOAc	10	**2a**	82
1a	KF	10	**2a**	97
1a	KF	5	**2a**	91
1b	KF	10	**2b**	98
1c	KF	10	**2c**	95
1d	KF	10	**2d**	96
1e	KF	10	**2e**	95
1f	KF	10	**2f**	97
1g	KF	10	**2g**	99

1 mol% of KF within 10 min enhanced this yield to 97%, while within 5 min the yield was 91%.

Under optimum conditions thus found (1 mol% of KF as catalyst, reaction time 10 min) 2-amino-4*H*-chromenes **2a–g** were obtained in excellent 95–99% yields. The workup was very simple: the reaction mixture was only washed with water (2×5 ml) and dried under reduced pressure to isolate pure 2-amino-4*H*-chromenes **2**. Therefore, in our procedure organic solvents

† *General (typical) procedure*. A mixture of salicylic aldehyde **1** (2 mmol), malononitrile (4 mmol) and KF (0.02 mmol) was mixed thoroughly in a mortar with pestle followed by grinding for 10 min. The resultant mixture was washed with water (2×5 ml) and dried under reduced pressure.

For characteristics of (2-amino-3-cyano-4*H*-chromen-4-yl)malononitriles **2a–g**, see Online Supplementary Materials.

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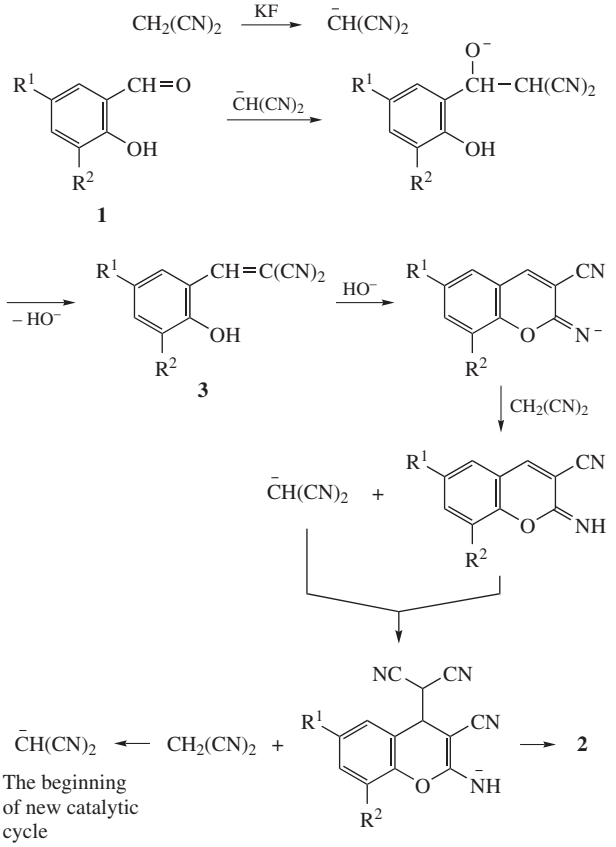
were not also used on the isolation step, which can be regarded as the 'ideal synthesis'.[17]

Taking into consideration the above results and the data on non catalytic 'on water' Knoevenagel condensation of isatins with malononitrile[16] the following mechanism for the transformation studied was proposed (Scheme 2). At the first step of the catalytic cycle, KF-initiated deprotonation of malononitrile leads to the formation of malononitrile anion. Next, the Knoevenagel condensation of malononitrile anion and salicylic aldehyde **1** takes place with elimination of hydroxide anion and formation of corresponding benzylidenemalononitrile **3**.[18] The subsequent intramolecular cyclization of the Knoevenagel adduct **3** followed by the addition of the second malononitrile anion gives (4*H*-chromen-4-yl)malononitrile **2** with regeneration of malononitrile anion at the last stage, which continues the catalytic chain process by the interaction with the next molecule of salicylic aldehyde.

Thus, the simple solvent-free catalytic system comprising only 1 mol% KF can produce, under mild conditions, a fast (10 min) and selective multicomponent cascade transformation of salicylic aldehydes **1a–g** and malononitrile into medicinally relevant 2-amino-4*H*-chromenes **2a–g** in 95–99% yields. The procedure requires simple equipment; it is easily carried out, organic solvents are not used on the isolation step. Thus, this efficient and fast catalytic approach to 2-amino-4*H*-chromenes allows the synthetic virtues of conventional cascade process to be combined with ecological benefits and convenience of facile solvent-free procedure.



Scheme 2

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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.2013.03.014.

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