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Sodium acetate catalyzed multicomponent approach to medicinally privileged 2-amino-4*H*-chromene scaffold from salicylaldehydes, malononitrile and cyanoacetates

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Sodium acetate-catalyzed multicomponent assembling of salicylaldehydes, malononitrile and cyanoacetates in water–alcohol mixture (1 : 1) at ambient temperature affords alkyl (2-amino-3-cyano-4*H*-chromen-4-yl)cyanoacetates in 88–95% yields.

Multicomponent reaction (MCR) is a one-pot assembling of three or more reactants to form a target compound without isolation of any intermediate.[1] MCR designed to produce biologically active compounds has become an important area of research in organic, combinatorial and medicinal chemistry.[2]

Sodium acetate is inexpensive, nontoxic and readily available catalyst for some organic reactions. It was used as weakly base catalyst for aldol condensation of aromatic aldehydes and acid anhydrides (Perkin reaction),[3] for Knoevenagel condensation of carbonyl compounds[4] and for condensation of hippuric acid with aromatic aldehydes (Erlenmeyer–Plöchl reaction).[5] We have earlier found sodium acetate to catalyze multicomponent cyclization of benzaldehydes, malononitrile and acetone into *cis*-4-dicyanomethylene-2,6-diarylcyclohexane-1,1-dicarbonitrile.[6] Recently sodium acetate was used as catalyst for multicomponent reaction of diethyl but-2-enedioate, malononitrile, formaldehyde and aromatic amine to form multisubstituted 1,2,3,4-tetrahydropyridines.[7]

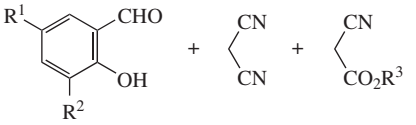
The concept of 'privileged medicinal structures or scaffolds' has emerged as one of the guiding principles of modern drug discovery.[8] Privileged scaffolds commonly consist of rigid hetero ring systems that present appended residues in well-defined orientations required for target recognition.[8]

Functionalized chromenes have played important role in the synthetic approaches to promising compounds in the field of medicinal chemistry.[9–11] 2-Amino-4*H*-chromenes belong to privileged medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced spasmolytic, diuretic, anticoagulant and antianaphylactic activities.[12–14] 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.[15–18]

Recently we have found electrocatalytic multicomponent transformation of salicylaldehydes, malononitrile and CH acids into substituted 2-amino-4*H*-chromenes[19,20] and have also accomplished solvent-free cascade reaction of salicylaldehydes and malononitrile.[21] These results present a challenge to design a simple and efficient multicomponent synthesis of 2-amino-4*H*-chromene scaffold from the above reactants under base catalysis.

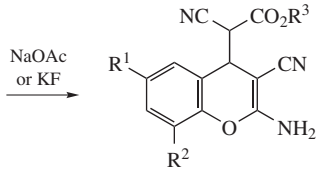
In the present study we report our results on MCR between salicylaldehydes **1a–f**, malononitrile and cyanoacetates **2a**,**b** under solvent-free conditions, in water, in alcohols and in small quantity of water–alcohol (1 : 1) mixtures as emulsion (Scheme 1, Tables 1 and 2).[†]

When co-grinding in a mortar salicylaldehyde **1a** (3 mmol), malononitrile (3 mmol) and methyl cyanoacetate **2a** (3 mmol) in the presence of 10 mol% KF (30 min), 2-amino-4*H*-chromene **3a** was obtained only in 53% yield (Table 1, entry 1). It should be mentioned that analogous cascade reaction of salicylaldehyde with two molecules of malononitrile under similar conditions proceeds faster (10 min) giving (2-amino-3-cyano-4*H*-chromen-4-yl)malononitriles in 94–99% yields even when using of only 1 mol% KF.[21]



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

2a $R^3 = Me$
2b $R^3 = Et$



3a $R^1 = R^2 = H$, $R^3 = Me$
3b $R^1 = R^2 = H$, $R^3 = Et$
3c $R^1 = R^3 = Me$, $R^2 = H$
3d $R^1 = Cl$, $R^2 = H$, $R^3 = Me$
3e $R^1 = Br$, $R^2 = H$, $R^3 = Me$
3f $R^1 = H$, $R^2 = OMe$, $R^3 = Me$
3g $R^1 = Br$, $R^2 = OMe$, $R^3 = Me$

Scheme 1

[†] *General procedure*. Emulsion of salicylaldehyde **1** (3 mmol), malononitrile (3 mmol), cyanoacetate **2** (3 mmol) and NaOAc (0.3 mmol) in 2 ml of water–alchohol (1 : 1) was mixed thoroughly for 1 h. The resultant mixture was filtered off, washed with 2 ml of water–alchohol (1 : 1) and dried under reduced pressure. For characteristics of alkyl (2-amino-3-cyano-4*H*-chromen-4-yl)cyanoacetates **3a–g**, see Online Supplementary Materials.

Table 1 Multicomponent assembling of salicylaldehyde **1a**, malononitrile and methyl cyanoacetate **2a** into 2-amino-4*H*-chromene **3a**.[a]

Entry	Base (mol%)	Conditions or solvent	Temperature/°C	Time/min	Yield of chromene **3a** (%)[b]
1	KF (10)	Solvent-free, grinding	20	30	53
2	KF (10)	Solvent-free	60	60	65
3	NaOAc (10)	Solvent-free	60	60	56
4	NaOAc (10)	H_2O	60	60	73
5	NaOH (10)	H_2O	60	60	70
6	NaOAc (10)	MeOH	20	60	75
7	NaOAc (10)	EtOH	20	60	78
8	NaOAc (10)	PrOH	20	60	66
9	NaOAc (10)	H_2O–MeOH (1:1)	20	60	95
10	NaOAc (5)	H_2O–MeOH (1:1)	20	60	93
11	NaOAc (10)	H_2O–MeOH (1:1)	20	30	79

[a] Salicylaldehyde **1a** (3 mmol), malononitrile (3 mmol), methyl cyanoacetate **2a** (3 mmol) without solvent or in 2 ml of water or alcohol; or in mixture 1 ml of water and 1 ml of methanol. [b] Isolated yields.

Table 2 Multicomponent transformation of salicylaldehydes **1a**–**f**, malononitrile and alkyl cyanoacetates **2a**,**b** into 2-amino-4*H*-chromenes **3a**–**g**.[a]

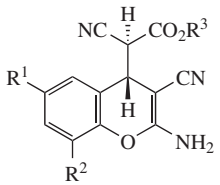
Salicylaldehyde	Cyanoacetate	2-Amino-4*H*-chromene	Yield (%)[b]	Diastereomeric ratio
1a	**2a**	**3a**	95	2:1
1a	**2b**	**3b**	89	4:3
1b	**2a**	**3c**	96	4:3
1c	**2a**	**3d**	93	3:1
1d	**2a**	**3e**	91	2:1
1e	**2a**	**3f**	88	2:1
1f	**2a**	**3g**	94	2:1

[a] Salicylaldehyde **1** (3 mmol), malononitrile (3 mmol), alkyl cyanoacetate **2** (3 mmol), NaOAc (0.3 mmol) in mixture 1 ml of water and 1 ml of methanol, 20 °C, 60 min. [b] Isolated yields.

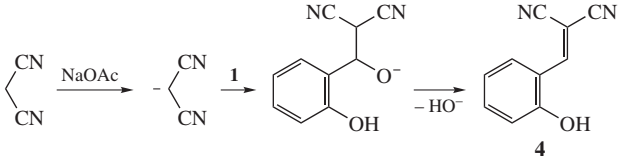
Solvent-free reaction of salicylaldehyde **1a**, malononitrile and methyl cyanoacetate **2a** in the presence of KF or NaOAc under heating (60 °C, 60 min) affords the product **3a** in 56–65% yield (Table 1, entries 2 and 3). In water under heating with NaOAc (entry 4) the yield rose to 73%. The similar results were obtained in alcohols with NaOAc, but without heating (entries 6–8). The best yields (93–95%) of 2-amino-4*H*-chromene **3a** were achieved when the reaction was carried out as emulsion in methanol–water mixture in the presence of NaOAc at ambient temperature (entries 9 and 10).

Under the optimum conditions thus found [10 mol% of NaOAc, ambient temperature, reaction time 60 min, small additives of water and alcohol (1:1) needed to emulsify the reaction mixture], 2-amino-4*H*-chromenes **3a**–**g** were obtained in excellent 88–95% yields (Table 2). As the reaction was clean, the final precipitate was filtered off, rinsed with minimum alcohol–water mixture and dried under reduced pressure to isolate pure 2-amino-4*H*-chromenes **3a**–**g**.

According to ^{1}H and ^{13}C NMR spectra, the obtained 2-amino-4*H*-chromenes **3a**–**g** were mixtures of two diastereoisomers (Table 2).



(*S**,*S**)-**3a**–**g**



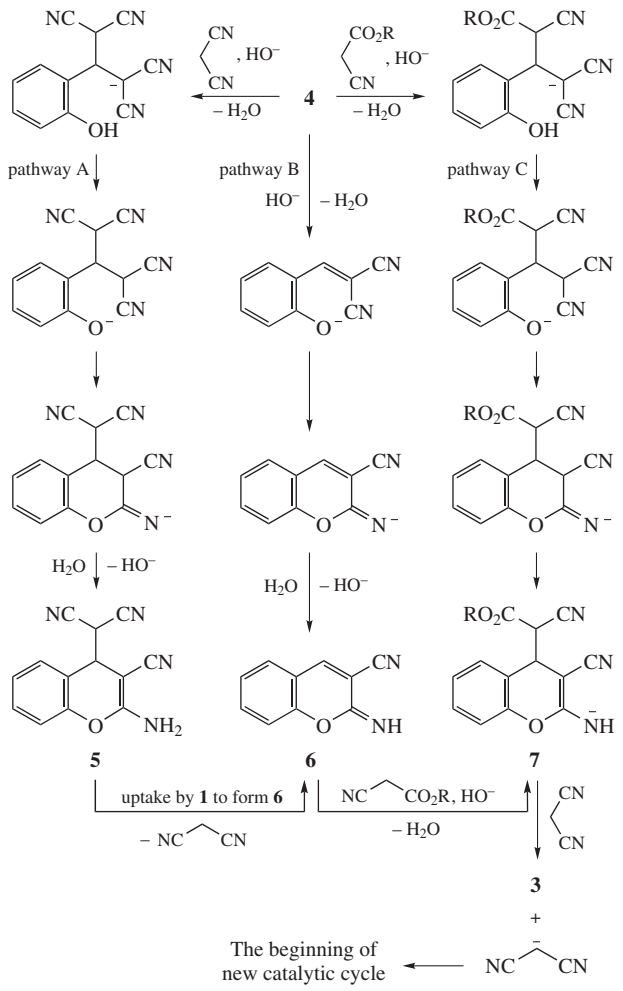
Scheme 2

From a thermodynamic point of view, the major diastereoisomer should possess (*S**,*S**)-configuration.

Taking into consideration the above results and the data on non-catalytic 'on water' Knoevenagel condensation of isatins with malononitrile,[22] and solvent-free reaction of salicylaldehyde with malononitrile and CH acids,[21] the mechanism for the herein studied transformation was proposed (Schemes 2, 3). At the first step of the catalytic cycle, NaOAc initiated deprotonation of malononitrile into its anion. Next, the Knoevenagel condensation of malononitrile anion and salicylaldehyde **1** with elimination of hydroxide anion leads to arylidenemalononitrile **4** (Scheme 2).[23] Further on, three reaction pathways are possible for the Knoevenagel adduct **4** (Scheme 3).

The Michael addition of malononitrile to the Knoevenagel adduct **4** followed by intramolecular cyclization leads to corresponding (2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile **5** (pathway A). Compound **5** was detected when the solvent-free reaction $CH_2(CN)_2$ + **1** + **2a** in the presence of NaOAc was interrupted in 15 min (15% yield) or 30 min (6% yield).

Previously, O'Callaghan *et al.*[24] noted that in alcoholic solution compound **5** could exist in equilibrium with the corresponding 2-imino-2*H*-chromene-3-carbonitrile **6** and malononitrile. If such



Scheme 3

an equilibrium exists in our case, the uptake of more acidic malononitrile from the equilibrium by salicylaldehyde **1** could facilitate the base-promoted addition of less acidic cyanoacetate **2** to 2-imino-2*H*-chromene **6**, which results in the full conversion of **5** into the desired 2-amino-4*H*-chromene **3**. This suggestion was especially confirmed by the reaction of salicylaldehyde **1** (3 mmol), cyanoacetate **2a** (6 mmol), and (2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile **5** (3 mmol) in the presence of NaOAc (0.3 mmol) in H_2O–MeOH (1 : 1, 2 ml) emulsion, leading in 1 h to 2-amino-4*H*-chromene **3a** in 89% isolated yield (see Scheme 3).

In conclusion, sodium acetate is a simple and efficient catalyst for the selective multicomponent assembling of salicylaldehydes **1a**–**f**, malononitrile and cyanoacetates **2a**,**b** into medicinally relevant 2-amino-4*H*-chromenes **3a**–**g** in excellent yields. The reaction is performed in water–alcohol emulsion under mild conditions. The procedure utilizes simple equipment, it is easily carried out and is valuable from the viewpoint of diversity-oriented large-scale processes. The results obtained represent a new synthetic concept for multicomponent reactions, and allow for the combination of the synthetic virtues of MCR processes in emulsion with ecological benefits.

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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.2014.04.016.

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