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Research Note

A facile and green three-component synthesis of 2-amino-3-cyano-7-hydroxy-4*H*-chromenes on grinding

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Multicomponent reactions (MCRs); Green chemistry; 4*H*-chromene derivatives; Resorcinol; Malononitrile.

Abstract. A simple, efficient and one-pot method has been developed for the synthesis of densely functionalized aryl derivatives of 2-amino-3-cyano-7-hydroxy-4*H*-chromene by the domino Knoevenagel-Michael-cyclization reactions of aromatic aldehydes, resorcinol and malononitrile in the presence of a catalytic amount of Na_2CO_3 under grinding conditions.

1. Introduction

4*H*-chromene and its derivatives constitute a major class of naturally occurring compounds [1,2]. They occur considerably in plants, including edible vegetables and fruits [3]. This moiety is widely found in natural alkaloids, flavonoids, tocopherols and anthocyanins [4]. 4*H*-chromene derivatives demonstrate a wide range of biological activity and have received great interest as therapeutic agents, due to their low toxicity and use rates [5,6]. Some representative pharmaceutical applications include anticancer [7,8], antioxidant [9], antiproliferative [10], antibacterial, antiviral [11], and central nervous system active drugs [12]. The current interest in 2-amino-4*H*-chromene derivatives arises from their potential applications in the treatment of human inflammatory TNFα-mediated diseases, such as rheumatoid and psoriatic arthritis, and in cancer therapy [13]. Widespread interest in the 4*H*-chromene-containing structures has led to extensive study of their synthesis [14]. Along this line, several procedures have been reported for the synthesis of 2-amino-4*H* chromene derivatives using diverse enol components, malononitrile and the corresponding aldehydes in the presence of different catalysts. Amongst recent catalytic systems, DBU [15], DABCO [16], piperidine [17], morpholine [18], triethyl amine [19], hexamethylenetetramine [20], ionic liquid [21], cetyltrimethylammonium chloride (CTAC) [22], triethylbenzylammonium chloride (TEBC) [23], PEG-400 [24], $Ca(OH)_2$ [25], and KF/Al_2O_3 [26] could be mentioned for this three-component reaction. Furthermore, Makerem et al. have reported an electro-chemically induced multicomponent condensation of resorcinol, malononitrile and aromatic aldehydes, in the presence of NaBr, as an electrolyte in propanol [27].

However, almost all these methods suffer from long reaction time, high temperature, use of solvents or expensive and hazardous catalysts, and problems associated with the reusability of the catalysts. Therefore, the introduction of milder, faster and more environmentally benign methods resulting in higher yields is still in great demand. Furthermore, a solvent-free technique represents a cost effective, clean, rapid and safe procedure. Grinding is a useful tool to bring together different solid compounds as the reaction components. Formation of an eutectic melt with uniform

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distribution of the reacting components in a controlled way has been assumed prior to the reaction [28,29].

Herein, we wish to report a facile, three-component procedure for the selective synthesis of 2-amino-3-cyano-7-hydroxy-4*H*-chromene derivatives (**4a-j**) using resorcinol (**2**), different aromatic aldehydes (**1a-j**) and malononitrile (**3**) at 25-50°C in the presence of Na_2CO_3 under grinding conditions (Scheme 1).

2. Results and discussion

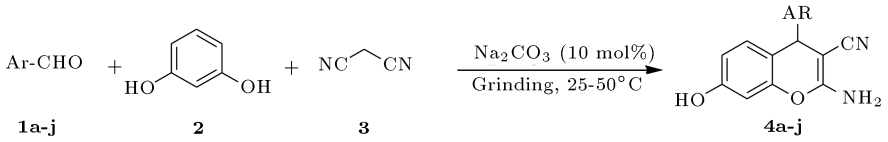
A survey of recent literature reveals that different compounds have been used to serve as the enol component in the reaction sequence to construct the 4*H*-chromene core. Typical examples include cyclic or acyclic 1,3-dicarbonyls [30,31], naphthol isomers or 2-hydroxynaphthalene-1,4-dione [19,26], 4-hydroxycoumarin [18,20] and resorcinol. Interestingly, resorcinol demonstrates different regioselectivity compared to the other enol components, i.e. it reacts at C-4 rather than C-2 (Scheme 2) [15,16,19,27].

In order to evaluate the synthetic potential of the proposed procedure and to optimize the general conditions, the condensation reaction of benzaldehyde (**1a**), resorcinol (**2**) and malononitrile (**3**) was studied using different bases under grinding conditions as the model reaction.

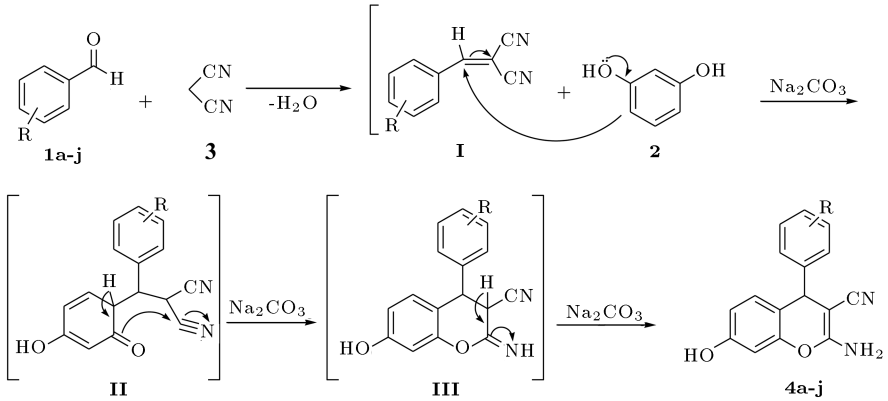
The results have been summarized in Table 1. It was observed that the reaction did not proceed completely in the absence of a basic catalyst at room temperature (Table 1, entry 1). Indeed, the Knoevenagel product (Scheme 2, intermediate I) was obtained after 30 min grinding of the reaction mixture and resorcinol was not involved in the next reaction [32,33]. However, the desired product **4a** was formed in good yields after addition of 10 mol% of a different basic catalyst and by heating the reaction mixture at 50°C. On the other hand, the corresponding hydroquinoline was not detected when NH_4OAc was used as the fourth component of the reaction. This implies that ring closure of the chromenecore takes place prior to imine bond formation required for Hanztsch 1,4-dihydroquinoline product (Table 1, entry 2) [29]. Furthermore, Na_2CO_3 afforded higher yield (92%) compared to other basic catalysts (Table 1, entry 3). After completion of the reaction, a simple work up afforded the desired product. We then turned our attention to optimize the amount of catalyst. It was discovered that 10 mol% of Na_2CO_3 was the optimum amount for this transformation at 50°C (Table 1, entries 7-10).

Encouraged by these results, aromatic aldehydes bearing both electron-withdrawing and electron-donating groups were subjected to three component condensation reactions under optimized reaction conditions (10 mol% Na_2CO_3, 50°C, grinding). The results have been summarized in Table 2. High to excellent yields of the desired products **4a-i** were obtained, selectively, in a simple procedure. By-products, such as enaminonitrile, malononitrile self-condensation adducts, and reduced products, were not detected in the reaction mixture [15,32].

Interestingly, the condensations of 3-nitrobenzaldehyde (**4b**), 4-nitrobenzaldehyde (**4c**) and 4-dimethylaminobenzaldehyde (**4j**) were completed at room temperature in relatively short reaction time (entries 2, 3 and 9). This would be promising for large scale preparation of 4*H*-chromene derivatives (**4a-j**)

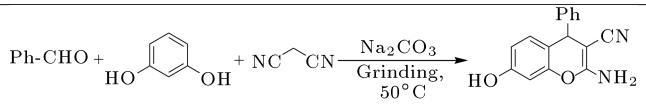


Scheme 1. Synthesis of 2-amino-3-cyano-7-hydroxy-4*H*-chromenes by grinding.



Scheme 2. Proposed mechanism for the synthesis of **4a-j**.

Table 1. Optimization of the reaction conditions for the three-component synthesis of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*-chromene (**4a**)[a].



1a **2** **3** **4a**

Entry	Base	Mol %	Time (min)	Yield[b] (%)
1[c]	-	-	30	-
2	NH_4OAc	10	30	84
3	Na_2CO_3	10	30	92
4	NaOH	10	30	86
5	KOH	10	30	85
6	Et_3N	10	30	85
7	Na_2CO_3	20	30	90
8	Na_2CO_3	15	30	92
9	Na_2CO_3	5	30	76
10	Na_2CO_3	1	30	55

[a]: Reaction conditions: benzaldehyde (2.0 mmol), resorcinol (2.0 mmol), malononitrile (2.0 mmol) and required amount of catalyst, 50°C, grinding;
[b]: Isolated yield (average of at least 2 runs);
[c]: Reaction was performed at room temperature.

Table 2. Condensation of aromatic aldehydes **1a-j**, resorcinol **2** and malononitrile **3** under the optimized conditions[a].

Entry	Ar	Product	*T* (°C)	Time (min)	Yield[b] (%)	M.p (°C)	Lit. M.p (°C)
1	C_6H_5	**4a**	50	30	92	234-236	235-236 [27]
2	3-O_2N-C_6H_4	**4b**	r.t	20	89	189-191	169-170 [15]
3	4-O_2N-C_6H_4	**4c**	r.t	20	86	211-213	This work
4	4-NC-C_6H_4	**4d**	50	30	85	198-200	This work
5	4-F-C_6H_4	**4e**	50	50	87	190-192	187-189 [27]
6	4-Cl-C_6H_4	**4f**	50	30	88	162-164	163-164 [27]
7	2-Cl-C_6H_4	**4g**	50	40	80	184-186	185-187 [19]
8	4-Br-C_6H_4	**4h**	50	50	79	227-229	224-226 [15]
9	4-MeO-C_6H_4	**4i**	50	30	84	112-114	111-112 [27]
10	4-$(CH3)_2N$-C_6H_4	**4j**	r.t	30	87	182-183	193-195 [15]

[a]: Reaction conditions: aromatic aldehyde (2.0 mmol), resorcinol (2.0 mmol), malononitrile (2.0 mmol), Na_2CO_3 (0.2 mmol, 0.021 g), 50°C (unless otherwise noted), grinding;
[b]: Isolated yields (average of at least 2 runs).

using industrial techniques, such as ball-milling [34,35]. Aliphatic aldehydes, such as isobutyraldehyde, dihydrocinnamaldehyde and cinnamaldehyde, produced mixtures of products in low yields under the above optimized conditions. This may be attributed to the undesired aldol condensation or Michael addition as the side reactions [30].

In order to show the advantages of the present method, we have compared the present protocol with some of those reported in the literature (Table 3). The following mechanism can be proposed for condensation of different aldehydes (1), resorcinol (2) and malononitrile 3 to afford 2-amino-4*H*-chromenes derivatives (**4a-j**) catalyzed by Na_2CO_3 on grinding (Scheme 2).

According to the results obtained, formation of the Knoevenagel product (intermediate I) is the first step of this condensation. This step proceeds even in the absence of any catalyst [15]. Subsequent Michael addition of **2** was facilitated by Na_2CO_3 to give intermediate II, which produced the desired products (**4a-j**) through intermediate III.

3. Conclusions

In summary, a green, efficient, rapid and simple procedure for the preparation of densely functionalized 2-amino-3-cyano-7-hydroxy-4*H*-chromene derivatives has been established through domino Knoevenagel-Michael-cyclization reactions by avoiding the use of a solvent or microwave irradiation.

Table 3. Comparison of different methods in three-component synthesis of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*-chromene **4a**[a].

Entry	Solvent	Catalyst	T (°C)/MW power	Time (min)	Yield[a] (%)
1	Propanol	NaBr[b]	r.t	90	83 [27]
2	-	TEA	300 W	3	82 [19]
3	Ethanol	DABCO	r.t	120-240	75 [16]
4	Ethanol	DBU	100 W	3	94 [15]
5	-	Na_2CO_3	50	40	92 (Present work)

[a]: All yields are based on benzaldehyde;

[b]: NaBr was used as electrolyte.

4. Experimental

4.1. General

Melting points were determined on an Electrothermal 9100 apparatus. FT IR spectra were recorded on a Shimadzu FT IR-8400S spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-*d*6 at 500 and 125 MHz, respectively, on a Bruker DRX-500 AVANCE spectrometer. The chemical shifts are given in ppm (δ), with respect to TMS. Elemental (C H N S) analysis was performed on a Perkin Elmer 2400 II CHNS/O elemental analyzer. All commercially available chemicals were purchased from Aldrich and Merck and used without further purification, except for benzaldehyde, which was freshly distilled before use.

4.1.1. General procedure for the synthesis of 2-amino-4H-chromenes 4a-i.

A mixture of aromatic aldehydes (**1a-j**) (2 mmol), resorcinol (2 mmol), malononitrile (2 mmol) and Na_2CO_3 (0.2 mmol) was ground using a mortar and pestle and kept at rt-50°C in a drying oven for 20-50 min. After completion of the reaction (monitored by TLC, 1:1 EtOAc/n-hexane), the mixtures were washed with hot water (5 mL) and filtered to remove the catalyst. The solid products (**4a-j**) were then purified by recrystallization from EtOH.

4.1.2. Spectral data for selected new products

2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*-chromene **4a**. m.p. 234-236°C; IR (KBr): ν 3427, 3335, 2189, 1649, 1581 cm^{-1}; ^{1}H NMR (DMSO-*d*6, 500 MHz): δ 4.62 (s, 1H, 4-H), 6.42 (d, J = 2.0 Hz, 1H, Ar-H), 6.49 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H, Ar-H), 6.81 (d, J = 8.0 Hz, 1H, Ar-H), 6.86 (s, 2H, NH_2), 7.17 (d, J = 7.0 Hz, 2H, Ar-H), 7.21 (d, J = 7.0 Hz, 1H, Ar-H), 7.31 (t, J = 7.0 Hz, 2H, Ar-H), 9.69 (s, 1H, OH); ^{13}C NMR (DMSO-d6): δ 57.2 (C-4), 103.0 (C-3), 113.2 (CN), 114.6, 121.5, 127.5, 128.2, 129.4, 130.8, 147.2, 149.7, 157.9, 161.1 (C-2); Anal. Calcd for $C_{16}H_{12}N_2O_2$: C 72.57, H 4.58, N 10.60; Found C 72.72, H 4.46, N 10.39.

2-Amino-3-cyano-7-hydroxy-4-(4-nitrophenyl)-4*H*-chromene **4c**. Brown solid; m.p. 211-213°C; IR (KBr): ν 3466, 3340, 2192, 1645, 1580 cm^{-1}; ^{1}H NMR (DMSO-d6, 500 MHz): δ 4.87 (s, 1H, 4-H), 6.46 (s, 1H, Ar-H), 6.51 (d, J = 8.0 Hz, 1H, Ar-H), 6.81 (d, J = 8.0 Hz, 1H, Ar-H), 7.03 (s, 2H, NH_2), 7.45 (d, J = 8.0 Hz, 2H, Ar-H), 8.19 (d, J = 8.0 Hz, 2H, Ar-H), 9.80 (s, 1H, OH); ^{13}C NMR (DMSO-d6): δ 56.0 (C-4), 103.3 (C-3), 113.2 (CN), 113.5, 121.2, 124.9, 129.6, 130.9, 147.2, 149.8, 154.7, 158.4, 161.3 (C-2); Anal. Calcd for $C_{16}H_{11}N_3O_4$: C 62.14, H 3.58, N 13.59; Found C 62.23, H 3.67, N 13.71.

2-Amino-3-cyano-7-hydroxy-4-(4-cyanophenyl)-4*H*-chromene **4d**. m.p. 198-200°C; IR (KBr): ν 3443, 3346, 2189, 1649, 1583 cm^{-1}; ^{1}H NMR (DMSO-d6, 500 MHz): δ 4.78 (s, 1H, 4-H), 6.43 (s, 1H, Ar-H), 6.50 (d, J = 8.0 Hz, 1H, Ar-H), 6.79 (d, J = 8.0 Hz, 1H, Ar-H), 6.99 (s, 2H, NH_2) 7.36 (d, J = 7.0 Hz, 2H, Ar-H), 7.78 (d, J = 7.0 Hz, 2H, Ar-H), 9.76 (s, 1H, OH); ^{13}C NMR (DMSO-d6): δ 56.1 (C-4), 103.2 (C-3), 110.4 (CN), 113.4 (CN-Ar), 113.5, 119.6, 121.2, 129.3, 130.8, 133.6, 149.8, 152.6, 158.3, 161.3 (C-2); Anal. Calcd for $C_{17}H_{11}N_3O_2$: C 70.58, H 3.83, N 14.53; Found C 70.64, H 3.81, N 14.70.

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