Solvent-free One-pot Approach for Synthesis of Substituted 2-Aminochromenes

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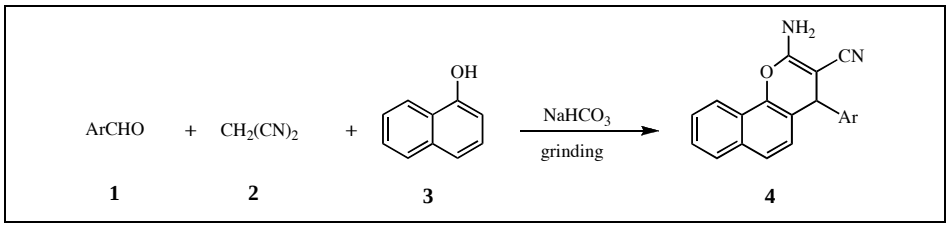

A solvent-free one-pot approach for the preparation of 2-aminochromenes in the presence of $NaHCO_3$ by grinding was described. Its advantages are easy work-up, mild reaction condition, high yield and environmental compatibility.

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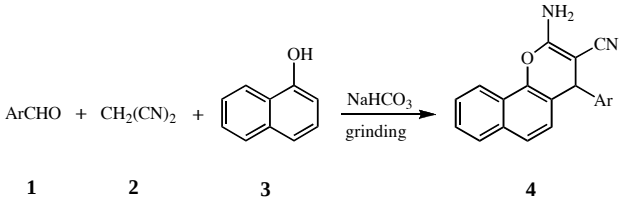
In 21st century, with increasing environmental concerns, the chemists are devoted to research for new processes that are less harmful to human health and environment. Several years ago, the solvent-free reaction under grinding condition, developed by Toda, F.; Tanaka, K. and coworkers, has caused much attention in organic synthesis. The numerous successful reactions widely used in a variety of organic syntheses have been reported such as Aldol condensation [1], Dieckmann condensation [2], Biginelli reaction [3], Grignard reaction [4], Knoevenagel condensation [5], Reformatsky reaction [6], cyclopropanation reaction [7], oxidation [8], reduction [9], and rearrangement reaction [10]. The advantages of this methodology are higher efficiency, milder condition, operational simplicity, low cost and environmental acceptability. The potential of this methodology has started to emerge, but there is still great need for exploring it.

Chromenes have attracted much interest due to their useful biological and pharmacological properties, such as antiinflammator [11], antitubercular agent [12], antitumor agent [13], inhibitor [14], potassium channel activator [15]. In addition, some chromenes derivatives possess valuable optical properties [16]. As part of our ongoing program on developing green methods for preparation of biologically active compounds, we report a solvent-free one-pot approach for the preparation of 2-aminochromenes in the presence of $NaHCO_3$ by grinding. (Scheme 1).

Scheme 1



The base plays a crucial role in this reaction, which involves Knoevenagel condensation and Michael addition reaction. First we tested the K_2CO_3 used as base. In the initial experiment, the mixture of aromatic aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), 1-naphthol **3** (2 mmol), and K_2CO_3 (2 mmol) was ground at room temperature. After the starting materials were consumed, the expected 2-aminochromene (entry 1-3) were obtained in 67-74% yield, but some deep color by-products were produced. They reduce the yield and increase the difficulty of the separation and purification. We thought that these by-

Table 1

The results of the optimization of bases

Entry	Ar	Naphthol	Base	Reaction Time (h)	Yield (%)
1	$4\text{-}ClC_6H_4$	1-Naphthol	K_2CO_3	1.5	74
2	$4\text{-}NO_2C_6H_4$	1-Naphthol	K_2CO_3	1.5	71
3	$4\text{-}CH_3OC_6H_4$	1-Naphthol	K_2CO_3	1.5	67
4	$4\text{-}ClC_6H_4$	1-Naphthol	$NaHCO_3$	1.5	93
5	$4\text{-}NO_2C_6H_4$	1-Naphthol	$NaHCO_3$	1.5	82
6	$4\text{-}CH_3OC_6H_4$	1-Naphthol	$NaHCO_3$	1.5	79

products resulted from K_2CO_3. When the reaction was carried out with $NaHCO_3$ as base instead of K_2CO_3 under the same conditions, the yields of corresponding 2-aminochromenes were 79-93 % (entry 3-5) and no the deep color by-products were found. The results of the experiments are shown in Table 1.

To investigate the scope and limitation of this process, various aromatic aldehydes were tested under the same condition. The results are shown in Table 2. The aromatic aldehydes, bearing either electron-donating or electron-withdrawing substituents all worked well, giving high yields.

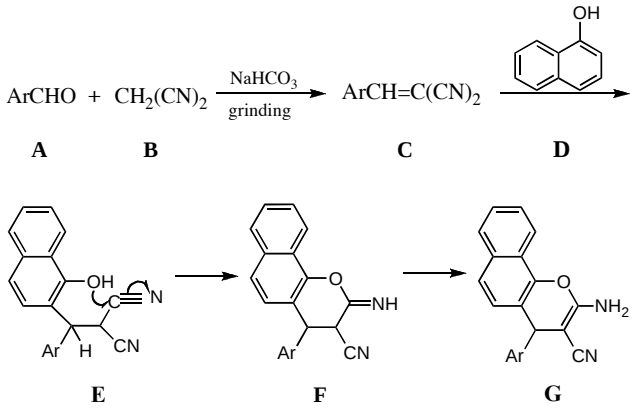
Table 2

Synthesis of 2-aminochromenes in the presence of $NaHCO_3$ with grinding

Entry	Product	Ar	Naphthol	Reaction Time (h)	Yield %
1	**4a**	C_6H_5	1-Naphthol	1.5	77
2	**4b**	4-ClC_6H_4	1-Naphthol	1.5	93
3	**4c**	2-ClC_6H_4	1-Naphthol	1.5	87
4	**4d**	2,4-$Cl_2C_6H_3$	1-Naphthol	1.5	89
5	**4e**	4-$NO_2C_6H_4$	1-Naphthol	1.5	82
6	**4f**	4-$CH_3OC_6H_4$	1-Naphthol	1.5	79
7	**4g**	4-ClC_6H_4	2-Naphthol	1.5	86
8	**4h**	4-$NO_2C_6H_4$	2-Naphthol	1.5	79

A plausible mechanism for this process may probably involve following key steps. (Scheme 2)
(1) The arylidenemalononitriles **C** is formed *via* Knoevenagel condensation reaction of aromatic aldehyde and malononitrile with $NaHCO_3$ used as base. (2) The compound **E** is given through Michael addition in which naphthol employed as nucleophile attacks on arylidene-malononitriles **C**. (3) The intramolecular nucleophilic addition reaction, involving the hydroxyl group and the cyano group in compound **E**, takes place and the imine **F** is generated. (4) The 2-aminochromene **G** is afforded through tautomerization of imine **F**

Scheme 2



In summary, a solvent-free one-pot process for the preparation of 2-aminochromenes in the presence of $NaHCO_3$ by grinding was achieved. Its advantages are easy work-up, mild reaction condition, high yield and environmental compatibility.

EXPERIMENTAL

General Experimental Conditions. All reagents were obtained from a commercial source and used without purification in the preparation of 2-aminochromenes. Melting points are uncorrected. Melting points were determined on WRS-1 digital melting point apparatus made by Shanghai physical instrument factory (SPOIF), China. IR spectra were measured in KBr on a PE-580B spectrometer. ^{1}H NMR spectra were recorded at a Bruker AM-300, using $CDCl_3$ as solvent and TMS as internal reference.

General procedure for preparing 2-aminochromenes (4a-h). A mixture of an aromatic aldehyde (2 mmol), malononitrile (132 mg, 2 mmol), naphthol (288 mg, 2 mmol) and $NaHCO_3$ (84 mg, 2 mmol) is ground at room temperature with the glass mortar and pestle. The reaction is monitored by TLC. The precipitate is collected by suction filtration and washed with water. The product is recrystallized by EtOH.

2-Amino-4-phenyl-4*H*-benzo[*h*]chromene-3-carbonitrile 4a. mp 210-211 ℃ (Lit [17] 206-207 ℃). ^{1}H nmr (300 Hz, deuteriochloroform): δ (ppm) 4.75 (s, 2H, NH_2), 4.87 (s, 1H), 7.02 (d, 1H), 7.22-7.33 (m, 5H, ArH), 7.50-7.59 (m, 3H), 7.79 (d, 1H), 8.18 (d, 1H). ir (potassium bromide): 3447(NH_2), 2204 (CN), 1655, 1605 cm^{-1}. *Anal.* calcd. for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.39; H, 4.75; N, 9.38.

2-Amino-4-(4-chlorophenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile 4b. mp 235–236 ℃ (Lit [17] 231-232 ℃). ^{1}H nmr (300 Hz, deuteriochloroform): δ (ppm) 4.76 (s, 2H, NH_2), 4.87 (s, 1H), 6.98 (d, 1H), 7.17 (d, J= 8.5 Hz, 2H, ArH), 7.29 (d, J=8.5 Hz, 2H, ArH), 7.51-7.60 (m, 3H), 7.80 (d, 1H), 8.19 (d, 1H). ir (potassium bromide): 3452 (NH_2), 2203 (CN), 1667, 1601 cm^{-1}. *Anal.* calcd. For $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.94; N, 8.42. Found: C, 72.10; H, 3.89; N, 8.33.

2-Amino-4-(2-chlorophenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile 4c. mp 241.2–242 ℃ (Lit [17] 236-237 ℃). ^{1}H nmr (300 Hz, deuteriochloroform): δ (ppm) 4.79 (s, 2H, NH_2), 5.56 (s, 1H), 7.06 (d, 1H), 7.16-7.19 (m, 2H, ArH), 7.38-7.41 (m, 2H, ArH), 7.49-7.60 (m, 3H), 7.78 (d, 1H), 8.17 (d, 1H). ir (potassium bromide): 3477 (NH_2), 2191 (CN), 1662, 1602 cm^{-1}. *Anal.* calcd. For $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.94; N, 8.42. Found: C, 71.83; H, 3.84; N, 8.30.

2-Amino-4-(2,4-dichlorophenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile 4d. mp 219–220 ℃ (Lit [17] 213-215 ℃). ^{1}H nmr (300

Hz, deuteriochloroform): δ (ppm) 4.85 (s, 2H, NH_2), 5.50 (s, 1H), 7.00 (d, 1H), 7.08-7.18 (m, 3H, ArH), 7.41-7.61(m, 3H), 7.79 (d, 1H), 8.16 (d, 1H). ir (potassium bromide): 3455 (NH_2), 2198 (CN), 1666, 1601 cm^{-1}. *Anal.* calcd. for *Anal.* calcd. For $C_{20}H_{12}Cl_2N_2O$: C, 65.41 H, 3.29; N, 7.63. Found: C, 65.24; H, 3.39; N, 7.33.

2-Amino-4-(4-nitrophenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile 4e. mp 242–243 ℃ (Lit [17] 239-241 ℃). ^{1}H nmr (300 Hz,deuteriochloroform): δ (ppm) 4.85 (s, 2H, NH_2), 5.52 (s, 1H), 7.01 (d, 1H), 7.09-7.19 (m, 2H, ArH), 7.42-7.52 (m, 2H, ArH), 7.54-7.78 (m, 3H), 7.79 (d, 1H), 8.17 (d, 1H). ir (potassium bromide): 3454 (NH_2), 2191 (CN), 1665, 1600 cm^{-1}. *Anal.* calcd. for $C_{20}H_{13}N_3O_3$: C, 69.96; H, 3.82; N, 12.24. Found: C, 69.90; H, 3.77; N, 12.61.

2-Amino-4-(4-methoxyphenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile 4f. mp 188-189 ℃ (Lit [17] 182-183 ℃). ^{1}H nmr (300 Hz,deuteriochloroform): δ (ppm) 3.76 (s, 3H, CH_3O) 4.86 (s, 2H, NH_2), 5.02 (s, 1H), 6.81 (d, 1H), 7.32 (d, *J*=8.7 Hz, 2H, ArH), 7.41 (d, *J*=8.7 Hz, 2H, ArH), 7.50-7.59 (m, 3H), 7.79 (d, 1H), 8.18 (d, 1H). ir (potassium bromide): 3478 (NH_2), 2191 (CN), 1656, 1595 cm^{-1}. *Anal.* calcd. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.78; H, 4.92; N, 8.69.

2-Amino-4-(4-chlorophenyl)-4*H*-benzo[*f*]chromene-3-carbonitrile 4g. mp 199-200 ℃ (Lit [17] 206-208 ℃). ^{1}H nmr (300 Hz,deuteriochloroform): δ (ppm). 5.03 (s, 1H), 7.14 (s, 2H, NH_2), 7.30-7.33 (m, 1H), 7.40-7.46 (m, 1H), 7.50 (d, 2H), 7.66-7.77 (m, 4H), 7.83 (d, 2H). ir (potassium bromide): 3379 (NH_2), 2190 (CN), 1631, 1584 cm^{-1}. *Anal.* calcd. For $C_{20}H_{13}ClN_2O$: C, 72,18; H, 3.94; N, 8.42. Found: C, 72.20; H, 3.77; N, 8.47.

2-Amino-4-(4-nitrophenyl)-4*H*-benzo[*f*]chromene-3-carbonitrile 4h. mp 182-183 ℃ (Lit [17] 185-186 ℃). ^{1}H nmr (300 Hz, deuteriochloroform): δ (ppm) 5.51 (s, 1H), 7.26 (s, 2H, NH_2), 7.50-7.54 (m, 3H), 7.74 (s, 2H), 7.84-7.87 (m, 5H), ir (potassium bromide): 3450 (NH_2), 2226 (CN), 1640, 1584 cm^{-1}. $C_{20}H_{13}N_3O_3$: C, 69.96; H, 3.82; N, 12.24. Found: C, 69.77; H, 3.83; N, 12.33.

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