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## Solvent-Free Synthesis of 2-Amino-4H-Chromenes Catalyzed by Sodium Carbonate

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### Abstract

Solvent-free synthesis of substituted 2-amino-4H-chromenes is described using sodium carbonate as a green and reusable catalyst. The procedure is very simple, efficient and environmentally friendly as it does not use any toxic auxiliary or solvent.

### Introduction

2-Amino-4H-chromenes represent an important class of compounds being the main components of many naturally occurring products. The basic structural framework of chromenes for example is a common feature of many tannins and polyphenols<sup>1</sup> found in tea, fruits, vegetables and red wine and these compounds have become more important as a result of their health-promoting effects. Fused chromenes are biologically active compounds with a wide spectrum of activities such as antimicrobial,<sup>2</sup> mutagenic,<sup>4</sup> antiviral,<sup>5,6</sup> antiproliferative,<sup>7</sup> antitumoral<sup>8</sup> and central nervous system activities.<sup>9</sup> Solvent-free and one-pot multicomponent condensations represent very powerful green chemical technology procedures from both the economical and synthetic point of view and represent a possible instrument to perform a near ideal synthesis because they enhance the rate of many organic reactions and afford quantitative yields.

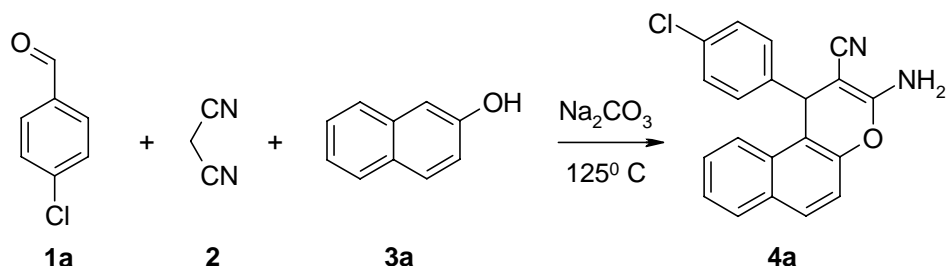
2-Amino-4H-chromenes are generally prepared by refluxing malononitrile, an aldehyde and an activated phenol in the presence of hazardous organic bases like piperidine in organic solvents such as ethanol and acetonitrile for several hours.<sup>10</sup> Recently, relatively benign catalysts such as cetyltrimethylammonium chloride (CTACl),<sup>11</sup> montmorillonite KSF clay, KF/Al<sub>2</sub>O<sub>3</sub>,<sup>12</sup> TiC,<sup>13</sup> triethylamine,<sup>14</sup> basic alumina,<sup>15</sup> MgO,<sup>16</sup> Heteropolyacid<sup>17</sup>, basic ionic liquids,<sup>18</sup> and iodine/K<sub>2</sub>CO<sub>3</sub><sup>19</sup> have been used in this reaction. However, the application of some of these methods is limited due to their moderate yields of the products, longer reaction times and laborious workup procedures. Furthermore, some of these catalysts such as MgO and basic alumina can only catalyze the condensation reaction of aromatic aldehydes and malononitrile with active  $\alpha$ -naphthol, and are not suitable for less active  $\beta$ -naphthols, whereas other catalysts require longer reaction times, laborious workup procedures and afford only moderate yields. For these reasons the development of an environmentally benign and simple procedure for synthesis of 2-

amino-4H-chromenes has thus become particularly fascinating and remains a great challenge.

Herein we wish to report three-component condensation of aldehydes and malononitrile with  $\alpha$ - and  $\beta$ -naphthols with excellent yields.

## Results and Discussions

In a representative experiment, 1.0 mmol of *p*-chlorobenzaldehyde **1a**, 1.0 mmol of malononitrile **2** and 1.0 mmol of  $\beta$ -naphthol **3a** were mixed with 0.1 mmol sodium carbonate and heated for 30 min at 125°C to afford **4a** in 99% yield (Scheme 1).



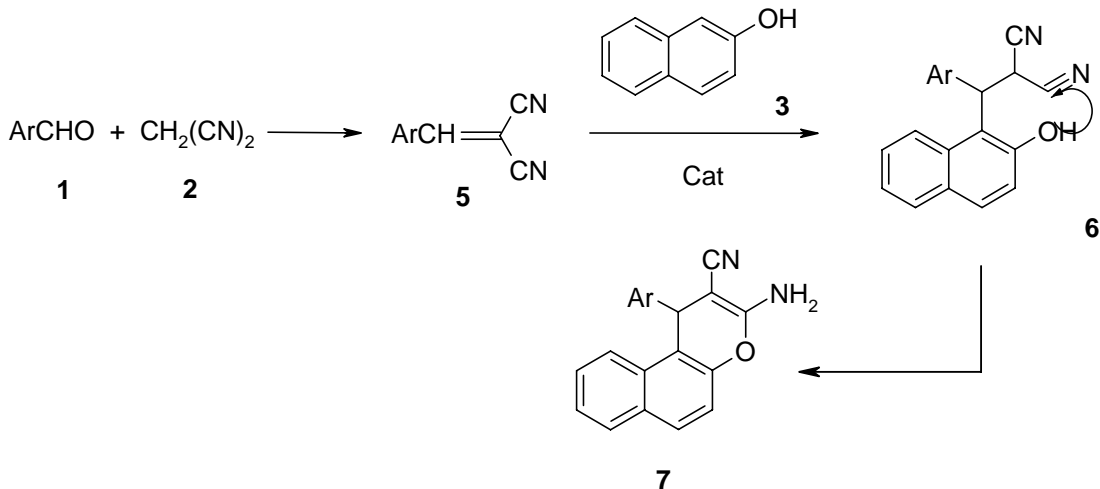
Scheme 1

Various basic or acidic catalysts (10% mol eq. each) have been examined in order to find the best catalyst (Table 1). As reported in Table 1, sodium carbonate was found to be the best catalyst for synthesis of 2-amino-4H-chromenes.

Table 1. Effect of various catalysts on preparation of **4a**

Catalyst	Time(h)	Yield (%)
$\text{Na}_2\text{CO}_3$	1	>99
$\text{NaHCO}_3$	1	89
$\text{SiO}_2$	4	60
$\text{Al}_2\text{O}_3$	3.5	55
$\text{Na}_2\text{SO}_4$	3.5	67

Possible following mechanism is suggested for the reaction. At first, *Knoevenagel* condensation of aldehyde **1** with malononitrile **2** affords quantitatively **5** containing the electron-poor C=C double bond. As we previously reported,<sup>12</sup> the reaction easily occurs under solvent-free condition and without adding any catalyst. Then it follows the C-alkylation of the phenolic ring at the *ortho* position giving the intermediate **6**. We examined this step without using a catalyst for 4 hours at 125°C and found that no remarkable reaction occurred. The nucleophilic attack of the phenolic OH to the CN moiety was the final step to afford **7** (Scheme 2).<sup>20</sup>



**Scheme 2.** Possible mechanism for the preparation of **7**

Different 2-Amino-4H-Chromenes have been prepared by the similar method. The results are summarized in the Table 2.

**Table 2.** Synthesis of 2-Amino-4H-Chromenes. under solvent-free conditions catalyzed by sodium carbonate

Entry	Ar	Phenol	Product	Time (min)	Yield (%)	Mp (°C) (lit.)
1	<i>p</i> -Cl	$\alpha$ -naphthol	<b>7a</b>	30	99	228-230 (230-232)
2	<i>p</i> -Cl	$\beta$ -naphthol	<b>7b</b>	60	100	203-205 (206-208)
3	<i>p</i> -NO <sub>2</sub>	$\alpha$ -naphthol	<b>7c</b>	60	91	210-212 (190)
4	<i>p</i> -NO <sub>2</sub>	$\beta$ -naphthol	<b>7d</b>	120	90	185-186 (187-188)
5	<i>p</i> -OMe	$\alpha$ -naphthol	<b>7e</b>	40	91	179-181 (176-179)
6	<i>p</i> -OMe	$\beta$ -naphthol	<b>7f</b>	120	88	188-189 (182-183)
7	<i>o</i> -Cl	$\alpha$ -naphthol	<b>7g</b>	30	96	231-232 (236)
8	<i>o</i> -Cl	$\beta$ -naphthol	<b>7h</b>	40	94	254-256 (259-261)

## Conclusion

In conclusion, 2-amino-4H-chromenes were prepared in a simple and solvent-free method. The procedure is very simple, efficient and environmentally friendly as it does not use any auxiliary or solvent and toxic catalyst.

## Acknowledgment

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## Experimental Section

Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Shimadzu 8400s FT-IR spectrometer using potassium bromide pellets. 500MHz <sup>1</sup>H NMR spectra were recorded on a DRX-500 Avance Bruker spectrometer. The chemical shifts are reported in ppm ( $\delta$ -scale) relative to internal TMS and coupling constants are reported in DMSO ( $d_6$ ). Reagents are obtained from commercial resource. Commercially available reagents were used without further purification. Products are all known compounds and were identified by comparing of their physical and spectra data with those reported in the literature.

### General procedure for 2-Amino-4H-Chromenes.

In a typical experiment, a stoichiometric mixture of an aldehyde (**1**), malononitrile (**2**), and  $\beta$ -naphthol (**3a**) (1.0 mmol each) and sodium carbonate (0.1 mmol) were ball-milled for 10 min. The result mixture was heated in a 50 mL round bottom flask in a drying oven at 125°C. After cooling, the mixture was washed with hot water and purified by recrystallization from hot ethanol, if necessary. The results are summarized in Table 2.

### Selected characterization data

**7a**: IR (KBr),  $\nu$  ( $\text{cm}^{-1}$ ): 3408, 3326, 2190, 1649, 1590; <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz),  $\delta$  (ppm): 5.36 (s, 1H, CH), 7.04 (s, 2H, NH<sub>2</sub>), 7.20-7.22 (d, 2H, J=8.2, ArH), 7.33-7.38 (m, 3H, ArH), 7.41-7.47 (m, 2H, ArH), 7.81-7.82 (d, 1H, J=8.02, ArH), 7.91-7.96 (m, 2H, ArH).

**7b**: IR (KBr),  $\nu$  ( $\text{cm}^{-1}$ ): 3452, 3334, 2190, 1666, 1590, 1409; <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz),  $\delta$  (ppm): 4.95 (s, 1H, CH), 7.09-7.11 (s, 2H, NH<sub>2</sub>), 7.19 (s, 2H, ArH), 7.27-7.29 (d, 2H, J=8.37, ArH), 7.39-7.36 (d, 2H, J=8.35, ArH), 7.57-7.66 (m, 3H, ArH), 7.89-7.91 (d, 1H, J=8.02, ArH), 8.24-8.26 (d, 1H, J=8.31, ArH),

## Conclusion

In conclusion, 2-amino-4H-chromenes were prepared in a simple and solvent-free method. The procedure is very simple, efficient and environmentally friendly as it does not use any auxiliary or solvent and reasonable catalyst.

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## Reference

1. (a) Jankun, J.; Selman, S. H.; Swiercz, R.; Skrzypczak-Jankun, E. *Nature* **1997**, 387, 56; (b) Covington, A. D. *Chem. Soc. Rev.* **1997**, 111; (c) van Rensburg, H.; van Heerden, P. S.; Bezuidenhout, B. C. B.; Ferreira, D. *Tetrahedron Lett.* **1997**, 38, 3089.

2. Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715.
3. Hiramoto, K.; Nasuhara, A.; Michiloshi, K.; Kato, T.; Kikugawa, K. *Mutat. Res.* **1997**, *47*, 395.
4. Smith, W. P.; Sollis, L. S.; Howes, D. P.; Cherry, C. P.; Starkey, D. I.; Cobley, N. K. *J. Med. Chem.* **1998**, *41*, 787.
5. Martinez, A. G.; Marco, L. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3165.
6. Dell, C. P.; Smith, C. W. European Patent Appl. EP537949, *Chem. Abstr.* **1993**, *119*, 139102d.
7. Bianchi, G.; Tava, A. *Agric. Biol. Chem.* **1987**, *51*, 2001.
8. Mohr, S. J.; Chirigos, M. A.; Fuhrman, F. S.; Pryor, J. W. *Cancer Res.* **1975**, *35*, 3750.
9. Eiden, F.; Denk, F. *Arch. Pharm. Weinheim Ger. (Arch. Pharm.)* **1991**, *324*, 353.
10. Elagamay, A. G. A.; El-Taweel, F. M. A. A. *Indian J. Chem. B* **1990**, *29*, 885.
11. Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacanni, A.; Righi, P.; Sartori, G. *Tetrahedron* **2001**, *57*, 1395.
12. Ballini, R.; Bigi, F.; Conforti, M. L.; *Catal. Today* **2000**, *60*, 305.
13. Wang, X.; Shi, D.; Tu, S. *Synth. Commun.* **2004**, *34*, 509.
14. Kumar, B. S.; Srinivasulu, N.; Udipi, R. H. *Russ. J. Org. Chem.* **2006**, *42*, 1813; Shestopalov, A. M.; Emelianova, Y. M.; Nesterov, V. N. *Russ. Chem. Bull. Int. Ed.* **2002**, *51*, 2239.
15. Maggi, R.; Ballini, R.; Sartori, G. *Tetrahedron Lett.* **2004**, *45*, 2297.
16. Kumar, D.; Reddy, V. B.; Mishra, B. G. *Tetrahedron* **2007**, *63*, 3093.
17. ; Heravi, M. M. ; Bakhtiari, Kh.; Zadsirjan, V.; Bamoharramb F. F.; Heravi O. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4262.
18. Gong, K.; Wang, H-L.; Fang, D.; Liu, Z.-L. *Catalysis Communications* **2008**, *9*, 650.
19. Ren, Y-M.; Cai, Ch. *Catalysis Communications* **2008**, *9*, 1017.
20. Abdel-Latif, F. F. *Indian J. Chem.* **1990**, *29B*, 664.