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

Sh. Javanshir*, M. Safari and M.G. Dekamin

Department of Chemistry, Iran University of Science and Technology, Tehran, P. O. Box 16844-13114, Iran.

Received 15 February 2013; received in revised form 10 June 2013; accepted 20 August 2013

KEYWORDS
Multicomponent reactions (MCRs); Green chemistry; 4H-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-4H-chromene by the domino Knoevenagel-Michael-cyclization reactions of aromatic aldehydes, resorcinol and malononitrile in the presence of a catalytic amount of Na2CO3 under grinding conditions.

© 2014 Sharif University of Technology. All rights reserved.

1. Introduction

4H-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]. 4H-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-4H-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 4H-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-4H 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/Al2O3 [26] could be mentioned for this three-component reaction. Furthermore, Makarem 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
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-4H-chromene derivatives (4a-j) using resorcinol (2), different aromatic aldehydes (1a-j) and malononitrile (3) at 25-50°C in the presence of Na₂CO₃ 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 4H-chromene core. Typical examples include cyclic or acyclic 1,3-dicarbonyls [30,31], naphthal 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 NH₄OAc was used as the fourth component of the reaction. This implies that ring closure of the chromene core takes place prior to imine bond formation required for Hantzsch 1,4-dihydroquinoline product (Table 1, entry 2) [29]. Furthermore, Na₂CO₃ 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 Na₂CO₃ 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% Na₂CO₃, 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 enamionitrile, 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-dimethylamino benzaldehyde (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 4H-chromene derivatives (4a-j)

---

**Scheme 1.** Synthesis of 2-amino-3-cyano-7-hydroxy-4H-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-1H-chromene (4a)\(^a\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Mol %</th>
<th>Time (min)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^c)</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>NH(_4)OAc</td>
<td>10</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>Na(_2)CO(_3)</td>
<td>10</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>NaOH</td>
<td>10</td>
<td>30</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>KOH</td>
<td>10</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>Et(_3)N</td>
<td>10</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>Na(_2)CO(_3)</td>
<td>20</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>Na(_2)CO(_3)</td>
<td>15</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>Na(_2)CO(_3)</td>
<td>5</td>
<td>30</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>Na(_2)CO(_3)</td>
<td>1</td>
<td>30</td>
<td>55</td>
</tr>
</tbody>
</table>

\(^a\): 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\(^a\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Product</th>
<th>T (°C)</th>
<th>Time (min)</th>
<th>Yield(^b) (%)</th>
<th>M(_p) (°C)</th>
<th>Lit. M(_p) (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C(_6)H(_5)</td>
<td>4a</td>
<td>50</td>
<td>30</td>
<td>92</td>
<td>234-236</td>
<td>235-236 [27]</td>
</tr>
<tr>
<td>2</td>
<td>3-O(_2)N-C(_6)H(_4)</td>
<td>4b</td>
<td>r.t</td>
<td>20</td>
<td>89</td>
<td>180-191</td>
<td>169-170 [15]</td>
</tr>
<tr>
<td>3</td>
<td>4-O(_2)N-C(_6)H(_4)</td>
<td>4c</td>
<td>r.t</td>
<td>20</td>
<td>86</td>
<td>211-213</td>
<td>This work</td>
</tr>
<tr>
<td>4</td>
<td>4-NC-C(_6)H(_4)</td>
<td>4d</td>
<td>50</td>
<td>30</td>
<td>85</td>
<td>198-200</td>
<td>This work</td>
</tr>
<tr>
<td>5</td>
<td>4-F-C(_6)H(_4)</td>
<td>4e</td>
<td>50</td>
<td>50</td>
<td>87</td>
<td>190-192</td>
<td>187-189 [27]</td>
</tr>
<tr>
<td>6</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>4f</td>
<td>50</td>
<td>30</td>
<td>88</td>
<td>162-164</td>
<td>163-164 [27]</td>
</tr>
<tr>
<td>7</td>
<td>2-Cl-C(_6)H(_4)</td>
<td>4g</td>
<td>50</td>
<td>40</td>
<td>80</td>
<td>184-186</td>
<td>185-187 [19]</td>
</tr>
<tr>
<td>8</td>
<td>4-Br-C(_6)H(_4)</td>
<td>4h</td>
<td>50</td>
<td>50</td>
<td>79</td>
<td>227-229</td>
<td>224-226 [15]</td>
</tr>
<tr>
<td>9</td>
<td>4-MeO-C(_6)H(_4)</td>
<td>4i</td>
<td>50</td>
<td>30</td>
<td>84</td>
<td>112-114</td>
<td>111-112 [27]</td>
</tr>
<tr>
<td>10</td>
<td>4-(CH(_3))(_2)-N-C(_6)H(_4)</td>
<td>4j</td>
<td>r.t</td>
<td>30</td>
<td>87</td>
<td>182-183</td>
<td>193-195 [13]</td>
</tr>
</tbody>
</table>

\(^a\): Reaction conditions: aromatic aldehyde (2.0 mmol), resorcinol (2.0 mmol), malononitrile (2.0 mmol), Na\(_2\)CO\(_3\) (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-4H-chromenes derivatives (4a-j) catalyzed by Na\(_2\)CO\(_3\) 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\(_2\)CO\(_3\) 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-4H-chromene derivatives has been established through domino Knoevenagel-Michael-cyclization reactions by avoiding the use of a solvent or microwave irradiation.
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-d6 at 500 and 125 MHz, respectively, on a Bruker DRX-500 AVANCE spectrometer. The chemical shifts are given in ppm ($\delta$), with respect to TMS. Elemental (CHN) analysis was performed on a Perkin Elmer 2400 II CHN/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$_2$CO$_3$ (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-4H-chromene 4a. Brown solid; m.p. 211-213°C; IR (KBr): ν 3466, 3340, 2192, 1645, 1580 cm$^{-1}$; $^1$H NMR (DMSO-d6, 500 MHz): $\delta$ 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): $\delta$ 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. Caled for C$_{10}$H$_7$N$_2$O$_2$: C 72.57, H 4.58, N 10.69; Found C 72.72, H 4.46, N 10.39.

Table 3. Comparison of different methods in three-component synthesis of 2-amino-3-cyano-7-hydroxy-1-phenyl-4H-chromene 4a-a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>T (°C)/MW power</th>
<th>Time (min)</th>
<th>Yield$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Propanol</td>
<td>NaBr$^b$</td>
<td>r.t</td>
<td>90</td>
<td>83 [27]</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>TEA</td>
<td>300 W</td>
<td>3</td>
<td>82 [19]</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol</td>
<td>DABCO</td>
<td>r.t</td>
<td>120-240</td>
<td>75 [16]</td>
</tr>
<tr>
<td>4</td>
<td>Ethanol</td>
<td>DBU</td>
<td>300 W</td>
<td>3</td>
<td>94 [15]</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>Na$_2$CO$_3$</td>
<td>50</td>
<td>40</td>
<td>92 (Present work)</td>
</tr>
</tbody>
</table>

$^a$: All yields are based on benzaldehyde; $^b$: NaBr was used as electrolyte.

Acknowledgment

We are grateful for the financial support from the Research Council of Iran University of Science and Technology (IUST), Iran.

References


**Biographies**

**Shahrzad Javanshir** was born in Tehran, Iran in 1960. She received her BS and MS degrees in Chemistry and Organic Chemistry in 1983 and 1985, respectively, from the University of Claude Bernard Lyon I, France, and her PhD degree in Organic Chemistry, in 2007, from Alzahra University, Tehran, Iran. She is currently Assistant Professor of Organic Chemistry at Iran University of Science and Technology, Tehran, Iran. Her research interests include organic synthesis (heterocyclic and medicinal chemistry), green chemistry and catalysis.

**Mostafa Safari** was born in Shahrekord, Iran, in 1985. He obtained his BS degree in Chemistry from Isfahan University of Technology, Iran, in 2006 and his MS degree in Organic Chemistry from Iran University of Science and Technology, Tehran, Iran, in 2011. He is currently a PhD degree student at Isfahan University of Technology, Iran.

**Mohammad G. Delamin** was born in Nahavand, Iran, in 1972. He received a BS degree in Chemistry from Shahid Chamran University, Ahwaz, Iran, in 1995, a MS degree in Organic Chemistry from Shahid Beheshti University, Tehran, Iran, in 1997, and a PhD degree in the same subject from Sharif University of Technology (SUT), Tehran, Iran, in 2002. He is currently Associate Professor of Organic Chemistry at Iran University of Science and Technology, Tehran, Iran. His research interests involve green and environmentally-benign chemistry, heterogeneous catalysis and organocatalysis, nanotechnology and pharmaceuticals.