Novel Synthesis of Some 2-Aminochromene Derivatives using Nano-sized Zirconium Oxide as Catalyst

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Novel Synthesis of Some 2-Aminochromene Derivatives using Nano-sized Zirconium Oxide as Catalyst

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Chromenes (benzopyrans) which are components of many biologically active compounds1,2 are of increasing significance. They are used as anti-hypertensive,3 hypoglycemic,4 cardio-protective5, anti-tumor6 and anti-HIV7 agents. They also have shown anti-cancer8–10, analgesic11, anti-inflammatory12,13, anti-bacterial14,15, anti-viral and anti-oxidant16 activities. Some chromenes are utilized in the preparation of macrocyclic ligands17,18 and others display photochromic properties.19,20 On the basis of previously reported preparation of indenes (1) from the three-component condensation of some acetophenones, dimethyl acetylenedicarboxylate and cyclohexylisocyanide (via the thermal isomerization of initially generated iminolactones),21 we decided to carry out the reaction with hydroxyacetophenones 4a-c. However, the expected indenes (1) were formed in less than 5% yields, the major products being compounds of type 2 (better than 90% yields, Figure 1). Such compounds had been reported earlier22 as by-products of the synthesis of chromene and indene derivatives.

Since compounds 2 are essentially unreactive and since the presence of the hydroxy group on the ring makes it impossible to generate indenes in useful yields, zirconium oxide (ZrO2) and anhydrous zinc chloride (ZnCl2), previously employed successfully as catalysts for the preparation of N-substituted 4-arylquinolines,23 were tried in this reaction. To our pleasant surprise, the use of either one of these catalysts led to chromenes 5a (about 50% yield) instead of indenes (1) or compounds of type 2. As a continuation of our interest in the synthesis of chromene derivatives,24–26 we now report a novel and
simple procedure for the preparation of some new 2-amino-4H-chromenes (5) using nano-sized zirconium oxide (Scheme 1).

Although zirconium oxide gave better results than zinc chloride, nano-scale ZrO₂ was an even more effective catalyst. Of the various solvents studied in the preparation of 5a and 5d, methylene chloride proved to be the best choice (Table 1).

Compounds 5a-5h were obtained in excellent yields using nano-sized ZrO₂ in methylene chloride at room temperature. None of regioisomer 6 could be detected with 3-hydroxyacetophenone (4b) as a substrate, most likely because of steric factors.

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>Catalyst</th>
<th>CH₂Cl₂</th>
<th>p-Xylene</th>
<th>Toluene</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>ZnCl₂</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>ZrO₂</td>
<td>50</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Nano-ZrO₂</td>
<td>87</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>5d</td>
<td>ZnCl₂</td>
<td>10</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>ZrO₂</td>
<td>55</td>
<td>45</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Nano-ZrO₂</td>
<td>93</td>
<td>55</td>
<td>50</td>
</tr>
</tbody>
</table>
Although no mechanistic study has not yet been carried out, one might speculate that addition of the isocyanide to dimethyl acetylenedicarboxylate could lead to the adduct 7 while complexation with nano-sized ZrO$_2$ would deactivate the hydroxy group. Attack by intermediate 7 on the complexed acetophenones might then give ketenimines 8 and thence finally to the 2-amino-4H-chromenes 5 after aqueous work-up (Scheme 2). We had previously described the synthesis of 2-amino-4H-pyran via ketenimines as intermediates.$^{27,28}$ Support for the participation of ketenimine 8 was provided by the presence of an absorption band at around 2065 cm$^{-1}$ in the IR spectra of reaction mixtures. In the early stages of the reaction, this peak increased to reach to its maximum intensity after 120–140 minutes; several attempts to isolate the putative ketenimines 8 were unsuccessful. The reaction was deemed complete when the absorption band at 2065 cm$^{-1}$ disappeared after reflux of the mixture at about 45°C. The final products 5a-h were obtained by addition of water and stirring for 2 hours. They were easily isolated, purified by extraction into n-hexane and washing the organic phase with water, followed by recrystallization. Other substituted phenols, such as methoxyphenols, chlorophenols and nitrophenols were used but the yields of the chromenes were generally less than 50%. Further investigations of this route and its mechanism are currently in progress.

X-ray crystal structure determination of single crystals of compound 5a obtained by slow crystallization from EtOH confirmed unambiguously its proposed structure (Fig. 2).
It can be seen that the ring containing the oxygen atom of the pyran ring has a boat conformation and the CO$_2$CH$_3$ group on the chiral carbon (C$_9$) is away from the CO$_2$CH$_3$ group on the unsaturated carbon (C$_{10}$).

In addition to the X-ray analysis of 5a, the structure of compounds 5a-h were confirmed on the basis of their elemental analyses, IR, $^1$H, $^{13}$C NMR and mass spectral data (Table 3). The mass spectra of these compounds displayed molecular ion peaks at the expected m/z values. Although the compounds 5a-c and 5d-h have the same molecular weight and their fragmentation patterns involve loss of similar fragments, their signals were not of same intensities. Their $^1$H and $^{13}$C NMR spectra confirmed the proposed structures. (Table 3) The IR spectra of 5a-h showed a broad absorption for N-H (3215–3432 cm$^{-1}$) which did not change upon dilution with CCl$_4$ thus suggesting the presence of an intramolecular hydrogen bond in agreement with the X-ray analysis data. The X-ray

### Table 2

Yields, mps and Elemental Analysis of 5a-h

<table>
<thead>
<tr>
<th>Cmpd.</th>
<th>Yields (%)</th>
<th>mp (°C)</th>
<th>Color</th>
<th>Elemental Analysis (calculated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>5a$^1$</td>
<td>87</td>
<td>109–110</td>
<td>Light yellow</td>
<td>65.09(65.10)</td>
</tr>
<tr>
<td>5b$^1$</td>
<td>89</td>
<td>107–108</td>
<td>Light yellow</td>
<td>65.14(65.10)</td>
</tr>
<tr>
<td>5c$^1$</td>
<td>86</td>
<td>106–107</td>
<td>Light yellow</td>
<td>65.15(65.10)</td>
</tr>
<tr>
<td>5d$^2$</td>
<td>85</td>
<td>109–110</td>
<td>Pale green</td>
<td>66.79(66.83)</td>
</tr>
<tr>
<td>5e$^2$</td>
<td>90</td>
<td>112–113</td>
<td>Light yellow</td>
<td>66.78(66.83)</td>
</tr>
<tr>
<td>5f$^2$</td>
<td>91</td>
<td>110–111</td>
<td>Pale green</td>
<td>66.80(66.83)</td>
</tr>
<tr>
<td>5g$^3$</td>
<td>84</td>
<td>118–120</td>
<td>Light yellow</td>
<td>65.54(65.82)</td>
</tr>
<tr>
<td>5h$^4$</td>
<td>80</td>
<td>131–133</td>
<td>Yellow</td>
<td>69.38(69.47)</td>
</tr>
</tbody>
</table>

$^1$Formula: C$_{21}$H$_{25}$NO$_6$; M.W. (387.43), $^2$Formula: C$_{22}$H$_{21}$NO$_6$; M.W. (395.40), $^3$Formula: C$_{22}$H$_{27}$NO$_6$; M.W. (401.45), $^4$Formula: C$_{26}$H$_{27}$NO$_6$; M.W. (449.50)
Table 3
Spectroscopic Data of 5a-h

<table>
<thead>
<tr>
<th>Cmpd.</th>
<th>$^1$H NMR (δ)</th>
<th>$^{13}$C NMR (δ)</th>
<th>MS (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>1.34-1.42, 1.71-1.77 (10 H, 5m CH$_2$ of cyclohexyl); 2.02 (3H, s, CH$_3$ of COMe); 3.46, 3.69 (6H, 2s, CH$_3$ of CO$_2$Me); 3.83 (1H, m, CH of cyclohexyl); 4.70 (1H, s, CH); 7.12-7.26, 7.53-7.56 (3H, 3m, Ar protons); 8.75 (1H, brs, NH)</td>
<td>24.93, 25.84, 33.99, 34.33, 387 (M$^+$, 20)</td>
<td>40.48, 50.52 (cyclohexyl carbons); 31.05 (CH$_3$ of COMe); 41.48 (13CH-CO$_2$Me); 51.38, 52.92 (2CH$_3$ of CO$_2$Me); 121.38, 124.58, 128.55, (Ar carbons); 156.71, 160.18 (olefinic carbons); 387 (M$^+$, 20)</td>
</tr>
<tr>
<td>5b</td>
<td>1.34-1.43, 1.71-1.77 (10 H, 5m CH$_2$ of cyclohexyl); 2.01 (3H, s, CH$_3$ of COMe); 3.46, 3.68 (6H, 2s, CH$_3$ of CO$_2$Me); 3.80 (1H, m, CH of cyclohexyl); 4.73 (1H, s, CH); 7.11-7.25, 7.52-7.54 (3H, 3m, Ar protons); 8.73 (1H, brs, NH)</td>
<td>24.92, 25.81, 34.00, 34.35, 387 (M$^+$, 43)</td>
<td>40.50, 50.54 (cyclohexyl carbons); 31.09 (CH$_3$ of COMe); 41.51 (13CH-CO$_2$Me); 51.40, 52.94 (2CH$_3$ of CO$_2$Me); 121.41, 124.58, 128.58, 129.66, 133.19, 147.78, (Ar carbons); 156.73, 160.20 (olefinic carbons); 387 (M$^+$, 20)</td>
</tr>
<tr>
<td>5c</td>
<td>1.35-1.43, 1.72-1.78 (10 H, 5m CH$_2$ of cyclohexyl); 2.03 (3H, s, CH$_3$ of COMe); 3.47, 3.69 (6H, 2s, CH$_3$ of CO$_2$Me); 3.81 (1H, m, CH of cyclohexyl);</td>
<td>24.93, 25.82, 33.98, 34.31, 387 (M$^+$, 26)</td>
<td>40.51, 50.56 (cyclohexyl carbons); 31.10 (CH$_3$ of COMe); 41.52 (13CH-CO$_2$Me); 60, 55, 43</td>
</tr>
</tbody>
</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Cmpd.</th>
<th>$^1$H NMR (δ)</th>
<th>$^{13}$C NMR (δ)</th>
<th>MS (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.75 (1H, s, CH); 7.12-7.26, 7.53-7.55 (3H, 3m, Ar protons); 8.76 (1H, brs, NH)</td>
<td>51.40, 52.94 (2CH$_3$ of CO$_2$Me); 121.42, 124.56, 128.53, 129.69, 133.20, 147.77 (Ar carbons); 156.75, 160.24 (olefinic carbons); 172.19, 174.22 (2C=O of CO$_2$Me); 198.70 (C = O)</td>
<td>213 (M$^+$-CH$_3$CO, C$_6$H$_3$NH, CH$_3$OH, 35)</td>
<td>118 (C$_6$H$_3$CH$_3$CO$^+$, 42), 43</td>
</tr>
<tr>
<td>5d</td>
<td>2.19 (3H, s, CH$_3$ of COMe); 3.58, 3.73 (6H, 2s, CH$_3$ of CO$_2$Me); 3.98 (2H, s, CH$_2$ of benzyl); 4.69 (1H, s, CH); 6.95-7.09, 7.35-7.52, 7.83-7.85 (8H, 7m, Ph and Ar protons); 8.53 (1H, brs, NH)</td>
<td>32.35 (CH$_3$ of COMe); 112.92, 114.22, 122.85, 129.35, 130.52 (Ar carbons); 34.65 (CH$_2$ of benzyl); 43.59 ($^{13}$CH-CO$_2$Me); 52.43, 52.54 (2CH$_3$ of CO$_2$Me); 112.90, 114.25, 122.93, 129.40, 130.89 (Ar carbons); 130.98, 133.56, 134.43, 135.45 (Ph and Ar carbons); 156.81, 162.22 (olefinic carbons);</td>
<td>395 (M$^+$, 13)</td>
</tr>
<tr>
<td>5e</td>
<td>2.29 (3H, s, CH$_3$ of COMe); 3.56, 3.71 (6H, 2s, CH$_3$ of CO$_2$Me); 3.95 (2H, s, CH$_2$ of benzyl); 4.71 (1H, s, CH); 6.94-7.10, 7.35-7.52, 7.84-7.86 (8H, 7m, Ph and Ar protons); 8.59 (1H, brs, NH)</td>
<td>32.31 (CH$_3$ of COMe); 34.62 (CH$_2$ of benzyl); 43.99 ($^{13}$CH-CO$_2$Me); 52.43, 52.58 (2CH$_3$ of CO$_2$Me); 112.90, 114.25, 122.93, 129.40, 130.89 (Ar carbons); 130.98, 133.56, 134.43, 135.45 (Ph and Ar carbons); 156.81, 162.22 (olefinic carbons); 172.43, 174.51 (2C=O of CO$_2$Me); 198.16 (C = O)</td>
<td>395 (M$^+$, 32) 352 (M$^+$-CH$_3$CO, CH$_3$CO, 23) 335 (M$^+$-CH$_3$COOH, 79) 320 (M$^+$-CH$_3$CO, C$_6$H$_3$CH$_2$-NH, 100) 184 (M$^+$-C$_6$H$_5$CH$_2$, 2 CH$_3$COOH, 85) 91, 77, 43</td>
</tr>
</tbody>
</table>

(Continued on next page)
### Table 3

Spectroscopic Data of 5a-h (Continued)

<table>
<thead>
<tr>
<th>Cmpd.</th>
<th>1H NMR (δ)</th>
<th>13C NMR (δ)</th>
<th>MS (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5f</td>
<td>2.13 (3H, s, CH₃ of COMe); 3.59, 3.75 (6H, 2s, CH₃ of CO₂Me); 3.93 (2H, s, CH₂ of benzyl); 4.74 (1H, CH); 6.96–7.10, 7.35–7.53, 7.84–7.86 (8H, 7m, Ph and Ar protons); 8.58 (1H, brs, NH)</td>
<td>32.35 (CH₃ of COMe); 34.69 (CH₂ of benzyl); 44.00 (13CH-CO₂Me); 52.40, 52.62 (2CH₃ of CO₂Me); 112.94, 114.26, 122.95, 129.43, 130.92, 130.99, 133.59, 134.42, 135.53 (Ph and Ar carbons); 156.71, 162.22 (olefinic carbons); 172.43, 174.50 (2CDOO of CO₂Me); 198.11 (CDO)</td>
<td>395 (M⁺, 36) 352 (M⁺-CH₃CO, 20) 335 (M⁺-CH₃COOH, 90) 230 (M⁺-CH₃CO, C₆H₅CH₂, 2) 184 (M⁺-C₆H₅CH₂, 73) 91, 77, 43</td>
</tr>
<tr>
<td>5g</td>
<td>1.02 (3H, t, CH₃ of Et), 1.33–1.41, 1.72–1.79 (10 H, 5m, CH₂ of cyclohexyl); 2.55 (2H, q, CH₂ of COEt); 3.48, 3.69 (6H, 2s, CH₃ of CO₂Me); 3.82 (1H, m, CH of cyclohexyl); 4.74 (1H, s, CH); 7.12–7.26, 7.54–7.57 (3H, 3m, Ar protons); 8.78 (1H, brs, NH)</td>
<td>12.02 (CH₃ of Et) 24.94, 36; 25.85, 33.99, 34.34, 40.56, 50.59 (cyclohexyl carbons); 36.11 (CH₂ of COEt); 41.59 (13CH-CO₂Me); 51.45, 53.24 (2CH₃ of CO₂Me); 121.48, 124.63, 128.57, 129.66, 133.28, 147.70, 156.80, 160.44 (olefinic carbons); 172.23, 174.40 (2C = O of CO₂Me); 198.82 (CDO)</td>
<td>401 (M⁺, 20) 344 (M⁺-C₂H₅CO, 51) 341 (M⁺-CH₃COOH, 82) 246 (M⁺-C₂H₅CO, C₆H₁₁NH, 100) 199 (M⁺-C₂H₅CO, C₆H₁₁NH, CH₃OH, 29) 57</td>
</tr>
<tr>
<td>5h</td>
<td>1.38–1.49, 1.79–1.83 (10 H, 5m, CH₂ of cyclohexyl); 3.49, 3.72 (6H, 2s, CH₃ of CO₂Me); 3.84 (1H, m, CH of cyclohexyl); 4.77 (1H, s, CH); 7.13–7.28, 7.36–7.46, 7.55–7.78 (8H, 6m, Ar, Ph protons); 8.81 (1H, brs, NH)</td>
<td>24.94, 25.84, 34.02, 34.39, 40.58, 51.26 (cyclohexyl carbons); 41.62 (13CH-CO₂Me); 51.48, 53.44 (2CH₃ of CO₂Me); 121.53, 124.63, 128.63, 128.56, 129.78, 130.41, 132.52, 133.56, 137.56, 147.85 (Ar, Ph carbons); 156.86, 160.46 (olefinic carbons); 172.49, 174.392 (2C = O of CO₂Me); 198.93 (C = O)</td>
<td>449 (M⁺, 28) 389 (M⁺-CH₃COOH, 65) 344 (M⁺-PhCO, 45) 246 (M⁺-PhCO, C₆H₁₁NH, 100) 186 (M⁺-PhCO, C₆H₁₁NH, CH₃COOH, 56) 105, 77</td>
</tr>
</tbody>
</table>
analysis data showed details of the $N_1$-$H_1$---$O_6$ bond as follows:

\[
\begin{align*}
\text{d} (N_1-O_6) &= 2.69 \text{ Å} \\
\text{d} (N_1-H) &= 0.88 \text{ Å} \\
\text{d} (H_1-O_6) &= 1.97 \text{ Å} \\
\angle N_1-H_1---O_6 &= 138^\circ
\end{align*}
\]

The IR spectra of 5a-h displayed carbonyl absorptions for the acetyl groups at (1733–1752 cm$^{-1}$) and for the ester groups at 1691–1728 cm$^{-1}$ and at 1645–1683 cm$^{-1}$; the different position is probably a reflection of the intramolecular H-bonding. There were also four sharp C-O absorptions (1053–1091, 1120–1171, 1199–1225, 1270–1294 cm$^{-1}$) for 5a-h.

In summary, our novel procedure constitutes a concise and efficient route for the synthesis of some new functionalized chromenes.

**Experimental section**

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland), Nano-sized ZrO$_2$ (CAS number 1314-23-4) was purchased (as a powder) from Sigma-Aldrich Co. and was used without further purification. Column chromatography was performed on silica gel (mesh size 0.015–0.04 mm) and TLC on pre-coated plastic sheets (25 DC$_{UV-254}$) respectively. Melting points were measured on Branstead Electrothermal melting point apparatus and are not corrected. Elemental analysis for C, H and N were performed using a Thermo Finnigan Flash EA1112 instrument. IR spectra were measured on a Shimadzu FT-IR-4300 spectrophotometer as KBr discs. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker 500 MHz spectrometer in CDCl$_3$ and DMSO-d$_6$ and chemical shifts were recorded in $\delta$ units using TMS as an internal standard. Mass spectra were acquired on a Finnigan-MAT 8430 spectrometer at an ionization potential of 70 ev.

### 8-Acetyl-2-cyclohexylamino-4H-chromene-3,4-dicarboxylic Acid Dimethyl Ester (5a).

#### Typical Procedure

To a stirred (stir bar, magnetic stirrer) mixture of 2-hydroxyacetophenone 4a (0.272 g, 2.0 mmol) and nano-sized ZrO$_2$ (0.025 g, 10 mol%) in dry CH$_2$Cl$_2$ (10 mL) in a three-neck flask at $-10^\circ$C were added dropwise under nitrogen gas over 2 hours, a solution of dimethyl acetylenedicarboxylate (0.28 g, 2.0 mmol) in dry CH$_2$Cl$_2$ (10 mL) and a solution of cyclohexyl isocyanide (0.22 g, 2 mmol) in dry CH$_2$Cl$_2$ (10 mL) simultaneously by two addition funnels. The mixture was stirred at room temperature for 2 h then refluxed at about 45$^\circ$C for 5 h. The progress of the reaction was monitored by IR; after the absorption band at 2065 cm$^{-1}$ had disappeared, water (20 mL) was added to the cooled reaction mixture which was stirred for 2 h. The organic phase was then separated and the solvent (CH$_2$Cl$_2$) was removed under reduced pressure. The residue was re-dissolved in diethyl ether or $n$-hexane ($n$-hexane was preferable if recrystallization was to be performed) and washed with water and recrystallized from ethyl acetate. Compound 5a was obtained as light yellow crystals (0.67 g, 87% yield), mp. 109–110$^\circ$C.

**IR (KBr):** 3412 (OH), 1649, 1623 (C = O), 1271, 1211, 1145 (C-O) cm$^{-1}$. **$^1$H NMR:** $\delta$ 1.34–1.42, 1.71–1.77 (10H, 5 m, CH$_2$ of cyclohexyl), 2.02 (3H, s, CH$_3$ of COMe), 3.64, 3.69 (6H, 2 s, CH$_3$ of CO$_2$Me), 3.83 (1H, m, CH of cyclohexyl), 4.70 (1H, s, CH), 7.12–7.26, 7.53–7.56 (3H, 3 m Ar hydrogens), 8.75 (1H, brs, NH). **$^{13}$C NMR:** $\delta$ 24.93, 30.84, 33.99, 34.33, 40.48, 50.52 (cyclohexyl carbons), 31.05 (CH$_3$ of COMe), 41.48 (13CH-
CO₂Me), 51.38, 52.92 (2CH₃ of CO₂Me), 121.38, 124.58, 128.55, 129.67, 133.19, 147.78, (Ar carbons), 156.71, 160.18 (olefinic carbons), 172.14, 174.01 (2C D₂Oo f CO₂Me), 198.60 (C D₂O), MS: m/z, 387 (M⁺ C, 20), 328 (M⁺CH₃CO, 48), 327 (M⁺-CH₃COOH, 100), 245 (M⁺-CH₃CO, C₆H₁₂N, 85), 213 (M⁺-CH₃CO, C₆H₁₂N, CH₃OH, 27) 60, 55. Anal. Calcd for C₂₁H₂₅NO₆: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.09; H, 6.54; N, 3.66.

The same procedure was used to obtain 5b-h in yields of 80–91%.

Acknowledgements

We thank the Research Council of the University of Tehran and PCRC for the financial support.

References

29. Crystallographic data for compound 5a have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 1062691. The data may be obtained free of charge via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).