Indium(III) Chloride/Silica Gel-Promoted Facile and Rapid Cyclization of 2-Aminochalcones to 2-Aryl-2,3-dihydroquinolin-4(1H)-ones under Solvent-Free Conditions

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Received 3 September 2003; revised 6 October 2003

Abstract: A convenient environmentally friendly method for the cyclization of 2-aminochalcones to 2-aryl-2,3-dihydroquinolin-4(1H)-ones on the surface of silica gel impregnated with indium(III) chloride under microwave irradiation without any solvent has been reported.

Key words: indium(III) chloride/silica gel, 2-aminochalcones, microwave, solvent-free conditions

Substituted 2,3-dihydroquinolin-4(1H)-ones display various pharmacological activities. They also serve as valuable precursors to medicinally important but not readily accessible 2-aryl-2,3-dihydroquinolin-4(1H)-ones. Many of these procedures involve the use of corrosive reagents such as orthophosphoric acid, acetic acid or strong alkali. Furthermore many of them are of limited synthetic scope due to low yields, long reaction time, large amount of catalyst or solvent used. However, there is no report on the synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones from 2-aminochalcones using indium halides. Therefore the development of new methods that lead to convenient procedures and better yields are of interest. In recent years, there has been increasing interest on solid supported reagents coupled with microwave irradiation, due to the benefits of enhanced reaction rates, improved yields, cleaner reaction profiles, greater selectivity and operational simplicity.

In continuation of our interest on indium(III) chloride-catalyzed reactions and surface solid state reactions coupled with microwave irradiation, we report an efficient and rapid method for the synthesis of 2,3-dihydroquinolin-4(1H)-ones through the cyclization of 2-aminochalcones using InCl₃ supported on silica gel under solvent-free conditions (Scheme 1).

The experimental procedure is simple. 2-Aminoachalcone was added to silica gel impregnated with indium(III) chloride (20 mol%) and the whole mass was stirred for 5 minutes for uniform mixing. Then the mixture was irradiated by microwave in a domestic microwave oven for 2 minutes as required to complete the reaction. The reaction mixture was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate–hexane (1:9) to afford the product in 88% yield (Scheme 1).

A screening of the efficiency of other Lewis acids revealed that Fe(III), Cu(I), and urea nitrate salts were ineffective as catalysts. Zn(II), Bi(III) salts can lead to the formation of the product in low yields (Scheme 2). The reaction did not occur in the presence of silica gel alone confirming the efficiency of the indium(III) chloride as catalyst on the cyclization of 2-aminochalcones. The results are summarized in Table 1.

Table 1 The Effect of the Catalysts on the Cyclization of 2-Aminoachalcone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>ZnCl₂</td>
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<tr>
<td>2</td>
<td>FeCl₃·6H₂O</td>
<td>10</td>
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<tr>
<td>3</td>
<td>BiCl₃</td>
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<tr>
<td>4</td>
<td>CuCl</td>
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</tr>
<tr>
<td>5</td>
<td>NH₂CONH₂·HNO₃</td>
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</tr>
<tr>
<td>6</td>
<td>InCl₃</td>
<td>88</td>
</tr>
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</table>

a 20 Mol% of the catalyst was impregnated with silica gel (2 g) and irradiated in microwave oven for 2 min at 650 W.
b Isolated yield.

SYNTHESIS 2004, No. 1, pp 0063–0068
Advanced online publication: 09.12.2003
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A wide range of substituted and structurally diverse 2-aminochalcones were subjected to this procedure to synthesize the corresponding products in high yields and the results are summarized in Table 2. The cyclization of 2-aminochalcones bearing nitro group (entry 9 Table 2), in the presence of acetic acid and orthophosphoric acid, or silica gel doped with \( p \)-tolouenesulfonic acid gave a complex mixture of products in very low yields compared to the reaction carried out in the presence of indium(III) chloride/silica gel under microwave irradiation which resulted in 75% yield. The reaction rates and yields were dramatically enhanced by microwave irradiation. This is due to a greater absorption of microwave energy by the polar solid support as well as polar reactants, which generates heat energy as required to promote the cyclization reaction.

The present study has unequivocally confirmed that conventional heating in acetonitrile/indium(III) chloride and longer reaction times (2–3 h) required for cyclization of 2-aminochalcones are improved using microwave irradiation, which is becoming an alternate and substitute heating source. For example, the treatment of 2-aminochalcone (entry 10, Table 2) in the presence of indium(III) chloride/silica gel under microwave irradiation at 650 W for 1.5 minutes gave the corresponding quinolinone in 90% yield after filtration through a small silica gel column, whereas under conventional heating conditions, the quinolinone was obtained in 75% yield after 2 hours of refluxing in acetonitrile. Invariably, the products obtained by microwave irradiation were purified with more ease.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Aminoalcholone</th>
<th>Product</th>
<th>Microwave Heating Time (Min)</th>
<th>Yield (%)</th>
<th>Conventional Heating Time (h)</th>
<th>Yield (%)</th>
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<td>75</td>
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Table 2  InCl₃/Silica Gel-Catalyzed Cyclization of 2-Aminoalcholones
Presumably, the mechanism of this process involves intramolecular Michael addition of amino group to the $\alpha,\beta$-unsaturated ketone followed by subsequent cyclization under the catalysis of InCl$_3$/silica gel as delineated in Scheme 3.

In general, the reactions are fast, clean and high yielding except the reaction (entry 11, Table 2) where dihydrobenzofuropyridinone was obtained in 55% yield (Scheme 4). When the corresponding 2-aminochalcone was subjected to microwave irradiation under the catalysis of InCl$_3$/silica gel 30% of the starting material was recovered. The same reaction under conventional method gave 10% of the product and 75% of the starting material was recovered.

In conclusion, the present procedure catalyzed by indium(III) chloride on a silica gel surface provides an efficient and rapid synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones from 2-aminochalcones under solvent free conditions. The notable advantages of this procedure are: (a) operational simplicity; (b) fast and clean reaction; (c) high yield; and (d) general applicability accommodating a variety of substitutions on both rings. We believe that this procedure will provide a better scope and more practical alternative to the existing procedures for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones.

![Scheme 3](image)

![Scheme 4](image)

**Table 2**  
InCl$_3$/Silica Gel-Catalyzed Cyclization of 2-Aminochalcones (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Aminochalcone</th>
<th>Product$^a$</th>
<th>Microwave Heating Time (Min)</th>
<th>Yield ($^b$)</th>
<th>Conventional Heating Time (h)</th>
<th>Yield ($^c$)</th>
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<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
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<td>90</td>
<td>2</td>
<td>75</td>
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<td>11</td>
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<td><img src="image" alt="Image" /></td>
<td>5</td>
<td>55</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

$^a$ All products were characterized by IR, $^1$H NMR, and mass spectra.  
$^b$ Microwave irradiation was carried out at 650 W (BPL, India).  
$^c$ Conventional heating in acetonitrile.
2-Aminochalcones were prepared using appropriate aldehyde and 2-aminoacetophenone by an earlier reported procedure.\textsuperscript{1} ZnCl\textsubscript{2}, BiCl\textsubscript{3}, and CuCl\textsubscript{2} were obtained from E-Merck India Ltd, InCl\textsubscript{3} and 2-aminoacetophenone (Aldrich) were used as purchased. Reagent grade MeCN was used. THF was distilled over sodium-benzophenone before use. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany). IR spectra were taken as neat for liquid compounds and as KBr pellets for solids on a Perkin-Elmer Spectrum RXI FT-IR spectrometer. \textsuperscript{1}H NMR (500 MHz) and \textsuperscript{13}C NMR (125 MHz) spectra were recorded in CDCl\textsubscript{3} solutions with TMS as an internal standard. Mole fraction chromatography was performed on silica gel (60–120 mesh, SRL, India).

2-Aminochalcone (0.1 g, 0.42 mmol) was added to silica gel impregnated with InCl\textsubscript{3} (19 mg, 20 mol%), prepared by adding a solution of InCl\textsubscript{3} in a minimum amount of THF to silica gel (2 g, 100–200 mesh activated by heating for 4 h at 150 °C before use), followed by complete evaporation of solvent under vacuum.

A mixture of the corresponding 2-aminochalcone (1.2 g, 5 mmol) was added to silica gel impregnated with InCl\textsubscript{3} (0.23 g, 20 mol%), prepared by adding a solution of InCl\textsubscript{3} in THF (5 mL) to silica gel (3 g, 100–200 mesh activated by heating for 4 h at 150 °C before use), followed by complete evaporation of solvent under vacuum. The whole mixture was stirred for 5 min for uniform mixing and was then transferred to a glass tube and then inserted in an alumina bath (100 g, 60 GF254, Fisher scientific bath 6.8 cm diameter) inside the microwave oven. The compound was irradiated by microwave in a domestic microwave oven (BPL, India) at 650 W for 2 min. On completion, the reaction mixture was directly charged onto a small silica gel column and eluted with a mixture of EtOAc–hexane (1:9) to afford the pure product in 86% yield (1.03 g).

2-Phenyl-2,3-dihydroquinolin-4(1H)-one (Entry 1, Table 2)

Pale yellow solid; mp 149–149 °C (Lit.\textsuperscript{10} mp 148–150 °C).

IR (KBr): 3303 (NH), 1638 cm$^{-1}$ (C=O).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): $\delta$ = 7.84 (dd, 1 H, H-5), 7.48–6.69 (m, 7 H), 4.70 (dd, 1 H, H-2, $J$ = 3.8, 11.9 Hz), 4.67 (br s, 1 H, NH), 2.84 (m, 2 H), 2.36 (s, 3 H, CH\textsubscript{3}).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): $\delta$ = 193.6, 151.7, 138.3, 138.1, 135.4, 129.7, 127.6, 126.6, 119.0, 118.4, 116.0, 58.2, 46.5, 21.4.

MS: $m/z$ = 237 (M$^+$).

Anal. Calcd for C\textsubscript{16}H\textsubscript{14}NO: C, 80.69; H, 5.87; N, 6.12. Found: C, 80.60; H, 5.73; N, 6.12.

2-(4-Methylphenyl)-2,3-dihydroquinolin-4(1H)-one (Entry 2, Table 2)

Pale yellow solid; mp 148–149 °C (Lit.\textsuperscript{8} mp 149 °C).

IR (KBr): 3313 (NH), 1648 cm$^{-1}$ (C=O).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): $\delta$ = 7.86 (dd, 1 H, H-5), 7.50–6.70 (m, 8 H), 4.74 (dd, 1 H, H-2, $J$ = 3.4, 13.2 Hz), 4.60 (br s, 1 H, NH), 2.85 (m, 2 H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): $\delta$ = 193.4, 151.7, 141.1, 135.5, 129.0, 128.5, 127.6, 126.7, 119.0, 118.5, 116.0, 58.5, 46.5.

MS: $m/z$ = 223 (M$^+$).

Anal. Calcd for C\textsubscript{17}H\textsubscript{15}NO: C, 80.98; H, 5.87; N, 5.86. Found: C, 80.12; H, 6.10; N, 5.16.

2-(2-Chlorophenyl)-2,3-dihydroquinolin-4(1H)-one (Entry 3, Table 2)

Yellow solid; mp 146–147 °C.

IR (KBr): 3303 (NH), 1638 cm$^{-1}$ (C=O).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): $\delta$ = 7.85 (dd, 1 H, H-5), 7.68–6.69 (m, 7 H), 5.24 (dd, 1 H, H-2, $J$ = 4.0, 12.6 Hz), 4.64 (br s, 1 H, NH), 2.89 (m, 2 H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): $\delta$ = 193.0, 151.7, 138.4, 135.5, 133.8, 130.0, 129.4, 127.64, 127.5, 119.0, 118.6, 116.2, 54.2, 44.1.

MS: $m/z$ = 257 (M$^+$).

Anal. Calcd for C\textsubscript{16}H\textsubscript{13}ClNO: C, 69.91; H, 4.69; N, 5.43. Found: C, 70.10; H, 4.75; N, 5.3.

2-(3-Chlorophenyl)-2,3-dihydroquinolin-4(1H)-one (Entry 4, Table 2)

Yellow solid; mp 162–163 °C.

IR (KBr): 3313 (NH), 1648 cm$^{-1}$ (C=O).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): $\delta$ = 7.86 (dd, 1 H, H-5), 7.59–6.62 (m, 7 H), 5.02 (dd, 1 H, H-2, $J$ = 3.9, 12.2 Hz), 4.54 (br s, 1 H, NH), 2.90 (m, 2 H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): $\delta$ = 192.9, 152.7, 139.4, 135.2, 132.9, 129.9, 129.4, 128.64, 127.5, 119.7, 118.6, 116.2, 53.8, 45.1.

MS: $m/z$ = 257 (M$^+$).

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2-(4-Chlorophenyl)-2,3-dihydroquinolin-4(1H)-one (Entry 7, Table 2)
Colorless solid; mp 208–210 °C. IR (neat): 3292 (NH), 1624 cm⁻¹ (C=O).  
1H NMR (500 MHz, CDCl₃): δ = 7.86 (dd, 1 H, H-5), 7.58–6.70 (m, 7 H), 4.87 (dd, 1 H, H-2, J = 4.0, 13.2 Hz), 4.48 (br s, 1 H, NH), 3.86 (s, 6 H, OCH₃), 2.85 (m, 2 H).  
13C NMR (125 MHz, CDCl₃): ę = 193.7, 159.7, 151.7, 135.4, 133.1, 127.9, 127.6, 119.0, 118.4, 116.0, 114.3, 58.0, 55.4, 46.4.  
MS: m/z = 253 (M⁺). 
Anal. Calcd for C₁₇H₁₅NO₂: C, 75.87; H, 5.9; N, 5.53; Found: C, 75.94; H, 5.81; N, 5.41. 
"2-(4-Methoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (Entry 10, Table 2) 
Pale yellow solid; mp 188–189 °C. IR (KBr): 3332 (NH), 1624 cm⁻¹ (C=O).  
1H NMR (500 MHz, CDCl₃): δ = 7.86 (dd, 1 H, H-5), 7.58–6.70 (m, 7 H), 4.90 (dd, 1 H, H-2, J = 3.4, 14.3 Hz), 4.66 (br s, 1 H, NH), 4.39 (q, 2 H, J = 7.4, 6.85 Hz), 2.85 (m, 2 H), 1.45 (t, 3 H, J = 6.85 Hz).  
13C NMR (125 MHz, CDCl₃): ę = 193.0, 159.9, 140.4, 139.9, 135.4, 131.5, 127.7, 126.1, 124.3, 123.2, 120.6, 119.2, 119.0, 118.7, 118.3, 116.0, 108.8, 108.7, 59.0, 47.2, 37.7, 13.9.  
MS: m/z = 340 (M⁺). 
Anal. Calcd for C₁₆H₁₄NO₂: C, 81.15; H, 5.92; N, 8.23; Found C, 80.98; H, 6.1; N, 8.01.
2-(3-Nitrophenyl)-2,3-dihydroquinolin-4(1H)-one (Entry 11, Table 2) 
Pale yellow solid; mp 178.3, 156.1, 146.5, 138.2, 137.7, 132.3, 131.0, 129.5, 127.5, 123.2, 123.1, 119.9, 113.0, 59.4, 40.2, 21.2.  
MS: m/z = 277.4 (M⁺). 
Anal. Calcd for C₁₈H₁₁N₂O: C, 77.96; H, 5.45; N, 5.05; Found C, 78.0; H, 5.3; N, 5.1.

Acknowledgment
One of the authors, H. K., expresses his gratitude to CSIR, New Delhi for a research fellowship.

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