NATURAL ACID CATALYZED SYNTHESIS OF OCTAHYDROQUINAZOLINONE DERIVATIVES: A GREEN APPROACH

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ABSTRACT
The Biginelli reaction is a multiple component reaction that gives 3,4-dihydropyrimidine-2(1H)-one which is widely used in pharmaceutical industries as calcium channel blockers\(^1\), antihypertensive agent, and alpha-1-a-antagonists. The reaction of aromatic aldehydes, dimedone and urea/thiourea using lemon juice as a natural catalyst under solvent-free conditions and microwave-irradiation gives excellent yield. This eco-friendly reaction has many advantages like economical, environmental, mild reaction conditions and simple work-up with high product yield. The research work concluded that the lemon juice is a naturally available, inexpensive and efficient catalyst for the synthesis of octahydroquinazolinone derivatives. The advantages offered by this method are solvent-free reaction conditions, short reaction times, ease of product isolation, and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of octahydroquinazolinone derivatives.

KEYWORDS: Biginelli reaction, Lemon juice, Microwave-irradiation, Natural acid and Octahydroquinazolinones derivatives.

INTRODUCTION
The Biginelli reaction is a multiple component reaction that gives 3,4-dihydropyrimidine-2(1H)-one which is widely used in pharmaceutical industries as calcium channel blockers\(^1\), antihypertensive agent and alpha-1-a-antagonists.
In recent years, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones, which used cyclic β-diketones instead of open-chain dicarbonyl compounds. These octahydroquinazolinone derivatives have attracted considerable attention since they exhibit potent antibacterial activity against staphylococcus aureus, escherichia coli, pseudomonas aeruginosa\(^2\) and have calcium antagonist activity.\(^3,4\)

Several methods have been developed for the preparation of quinazolinone derivatives. These routes usually involved reaction of aldehydes with SOCl\(_2\) and pyridine, then with 2-aminobenzylamine in a refluxing solvent such as benzene or xylene with azeotropic water removal,\(^5\) refluxing in ethanol/acetic acid mixture\(^6\) and by reaction in alkali media.\(^7\)

There are very few reports for the synthesis of octahydroquinazolinone derivatives using catalysts such as TMSCl,\(^7\) Nafion-H,\(^8\) Conc. H\(_2\)SO\(_4\),\(^9\) and ionic liquid,\(^10\) \(p\)-TsOH,\(^11\) conc. HCl in ethanol,\(^12\) solid support of alumina\(^13\) Octahydroquinazolinone derivatives are also synthesized in absolute ethanol but with low yields of products (19-69%).\(^3\) However, many of these procedures suffer from one or more disadvantages such as harsh reaction conditions, prolonged time period, poor yields, use of hazardous and expensive catalysts. So the development of a clean, high-yielding and environmentally friendly approach is still desirable.

Among the challenges for chemists including discovery and development of inexpensive, non-hazardous and simple environmentally safe chemical processes for selective synthesis by identifying alternative reaction conditions and solvents that much improved selectivity, energy conservation and even less hazardous waste generation are not desirable and inherently safer chemical products. Therefore, to address depletion of natural resources and preservation of ecosystem is just urgent to develop so called “greener technologies” to make chemical agents for well being of human health. Due to acidic nature (pH = 3.0), aqueous Citrus lemon juice as a natural catalyst has been found to be a suitable replacement for various homogeneous acid catalysts.

Citrus aurantium, Citrus indica, Citrus limonium are some important species of citrus family commonly known as lemon. The lemon is indigenous to the north-west regions of India. It is now widely grown in all tropical and subtropical countries. In India it is also cultivated in home gardens. The main ingredients of lemon juice are moisture (85%), carbohydrates (11.2%), citric acid (5-7%), protein (1%), vitamin-C (0.5 %), fat (0.9 %), minerals (0.3 %),
fibers (1.6 %) and some other organic acids. As lemon juice is acidic in nature (pH ≈ 2-3) and percentage of citric acid (5-7%) is more than other acids, it worked as acid catalyst for various reactions such as synthesis of Schiff Base,[14] synthesis of Bis-, Tris-, Tetraindoles,[15] synthesis of 3,4-dihydropyrimidine-2(1H)-one,[16] Synthesis of Bis(indolyl)methanes[17] etc. For the present work, we have used extract of Citrus limonium species of lemon as natural catalyst for synthesis of octahydroquinazolinone derivatives.

During the last few years, ‘non-classical’ methods have been developed in organic synthesis in order to improve both yields, selectivity and experimental conditions.[18] Especially the use of microwave technology in conjunction with the use of solvent-free conditions allows expeditious and efficient procedures in organic synthesis.[19-22] However, great interest has been focused recently on “dry media” synthesis using inorganic solid supports under microwave-irradiation. The coupling of a microwave heating mode with the use of solid acid has allowed the synthesis of several organic compounds, with higher purity of products and very simplified ease of manipulation and work-up. They clearly constitute an eco-friendly ‘green’ approach.[23]

MATERIAL AND METHODS

Experimental General Procedure

A mixture of aromatic aldehydes 1(a-j) (1mmol), dimesdone 2 (1mmol) urea/thiourea 3 (1.5 mmol) and lemon juice (1 ml) was mixed properly with the help of glass rod and irradiated in a microwave oven at 360 W, as time indicated in Table 4. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 7:3). After completion of the reaction, the reaction mixture was cooled and dichloromethane (25 ml) was added. Organic solvent was evaporated under reduced pressure and solid compound was crystallized from absolute ethanol to afford the pure corresponding octahydroquinazolinone derivatives 4(a-j) in excellent yields. All the products were characterized from their spectral data.

Present Work

In present work we described the one-pot three component synthesis of octahydroquinazolinone derivatives from aromatic aldehydes, dimesdone and urea/thiourea using lemon juice as a catalyst under microwave-irradiation gives excellent yield 4(a-j).
RESULTS AND DISCUSSION

In continuation of our research work of developing methods in various organic transformations, we have developed a methodology for the synthesis of octahydroquinazolinone derivatives using lemon juice, which makes use of mild catalyst under microwave-irradiation and solvent-free conditions (Scheme 1).

The reaction of benzaldehyde (1a), dimedone (2) and urea (3) catalyzed by lemon juice under solvent-free conditions and microwave-irradiation, has been considered as a standard model reaction.

We also screened a number of different catalysts on the model reaction. When the reaction was carried out in the presence of KH$_2$PO$_4$, alum, acidic alumina, amberlite-IR 120, sulphamic acid, cellulose sulfuric acid under microwave-irradiation it gave lower yield of product even after prolonged reaction time. However, when the same reaction was conducted under microwave irradiation using lemon juice as a catalyst it gave excellent yields of product in short reaction time (Table 1, entry 6).

We have studied the catalyst concentration on model reaction. We have varied the concentration of catalyst to 1, 2 and 3ml. The results revealed that, when the reaction was carried out in the presence of 1ml of catalyst it better yield of product. At the same time when the quantity of catalyst was increased, the yields of the products were found to be constant. So, the use of 1 ml of catalyst appears to be optimal. The results obtained are summarized in (Table 2).
Moreover, we investigated the effect of different microwave power settings such as 180, 360, 540 and 720W. It was observed that, the irradiation at 360W gives better result (Table 3, entry 2).

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aldehydes, dimesdone and urea/thiourea using lemon juice as a catalyst under microwave-irradiation, the results are shown in Table 4. We have carried out the similar reaction with various aromatic aldehydes containing electron donating or electron withdrawing functional groups at different positions but it did not show any remarkable differences in the yields of product and reaction time. It was observed that the reaction of aromatic aldehydes with urea is very fast as compared to thiourea. The results obtained in the current method are illustrated in Table 4.

Table 1. Screening of Catalysts on the Model Reaction\textsuperscript{a}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts</th>
<th>Time (min)</th>
<th>Yield\textsuperscript{b} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KH\textsubscript{2}PO\textsubscript{4}</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>Alum</td>
<td>15</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Acidic alumina</td>
<td>15</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>Amberlite IR-120</td>
<td>15</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>Sulphamic acid</td>
<td>15</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>Cellulose sulfuric acid</td>
<td>15</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>Lemon juice</td>
<td>12</td>
<td>95</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction of benzaldehyde, dimesdone and urea in presence of lemon juice under microwave-irradiation and solvent-free condition. \textsuperscript{b}Isolated yield.

Table 2. Effect of Catalyst Concentration on Model Reaction\textsuperscript{a}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (ml)</th>
<th>Yield\textsuperscript{a} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>95</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction of benzaldehyde, dimesdone and urea in presence of lemon juice under microwave-irradiation and solvent-free condition. \textsuperscript{b}Isolated yield.
Table 3. Effect of Microwave Irradiation Powers for Synthesis of Octahydroquinazolinone derivatives 4a^a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Power (W)</th>
<th>Time (min.)</th>
<th>Yield (^b)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>180</td>
<td>12</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>360</td>
<td>12</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>540</td>
<td>12</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>720</td>
<td>12</td>
<td>82</td>
</tr>
</tbody>
</table>

^a(1 mmol) was treated with dimedone (1 mmol) and urea (1.5 mmol) in presence of lemon juice (1 ml) under microwave irradiation. ^bIsolated yield.

Table 4. Synthesis of Octahydroquinazolinone Derivatives Catalyzed by lemon juice Under Microwave-Irradiation^a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-CHO</th>
<th>X</th>
<th>Time (min.)</th>
<th>Yield^b (%)</th>
<th>M.p (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>H</td>
<td>O</td>
<td>12</td>
<td>95</td>
<td>290-293</td>
</tr>
<tr>
<td>4b</td>
<td>4-Cl</td>
<td>O</td>
<td>12</td>
<td>94</td>
<td>&gt;300</td>
</tr>
<tr>
<td>4c</td>
<td>3-OMe, 4-OH</td>
<td>O</td>
<td>15</td>
<td>90</td>
<td>193-195</td>
</tr>
<tr>
<td>4d</td>
<td>3-NO₂</td>
<td>O</td>
<td>15</td>
<td>92</td>
<td>298-299</td>
</tr>
<tr>
<td>4e</td>
<td>3-OMe</td>
<td>O</td>
<td>15</td>
<td>86</td>
<td>248-249</td>
</tr>
<tr>
<td>4f</td>
<td>3-Cl</td>
<td>O</td>
<td>15</td>
<td>85</td>
<td>282-284</td>
</tr>
<tr>
<td>4g</td>
<td>4-NO₂</td>
<td>O</td>
<td>16</td>
<td>93</td>
<td>302-304</td>
</tr>
<tr>
<td>4h</td>
<td>4-F</td>
<td>O</td>
<td>17</td>
<td>90</td>
<td>134-136</td>
</tr>
<tr>
<td>4i</td>
<td>H</td>
<td>S</td>
<td>17</td>
<td>87</td>
<td>283-285</td>
</tr>
<tr>
<td>4j</td>
<td>4-OMe</td>
<td>S</td>
<td>16</td>
<td>83</td>
<td>275-276</td>
</tr>
</tbody>
</table>

^aReaction Condition: 1 (a-j) (1 mmol), 2 (1 mmol), 3 (1.5 mmol) lemon juice (1 ml), under microwave-irradiation. ^bIsolated yield. All the products obtained were fully characterized by spectroscopic methods such as, ^1H NMR and mass spectroscopy and also comprised with the reference compounds.

CONCLUSIONS

The research work concluded that the lemon juice is a naturally available, inexpensive and efficient catalyst for the synthesis of octahydroquinazolinone derivatives. The advantages offered by this method are solvent-free reaction conditions, short reaction times, ease of product isolation, and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of octahydroquinazolinone derivatives.

REFERENCES


