L-proline: An efficient catalyst for the synthesis of quinoline derivatives in aqueous media

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ABSTRACT

An efficient and direct procedure for the synthesis of benzo[h]-indeno[1,2-b]-quinoline derivatives has been described. The procedure employs a three-component condensation reaction in one-pot using 2H-indene-1, 3-dione, naphthalen-1-amine and aldehydes in the presence of catalytic amount of L-proline in aqueous media.

Keywords: Quinoline derivatives, Aqueous media, Multicomponent reactions, L-proline.

1. Introduction

Multicomponent reactions (MCRs) are special types of synthetically useful organic reactions in which three or more different starting materials react to a final product in a one-pot procedure [1]. The prospect of implementing MCRs without using toxic catalysts in solvent-free conditions as well as in water solutions is another existing strategy of laboratories since will complement the significant characters of MCRs to ideally satisfy the green chemistry’s principles [2]. Water is a desirable solvent for chemical reactions because it is safe, non-toxic, environmentally friendly, readily available and cheap in compared to organic solvents [3].

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications as biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important [4-6]. Among them, quinoline derivatives are very interesting compound which accure in various natural products, especially in alkaloids [7]. It is known that many quinoline containing compounds are integral to a large number of synthetic drug substances with activities including antimalarial, anti-inflammatory, antiasthmatic and antihypersensitive activities [8].

Recently, the commercially available and inexpensive amino acid L-proline has been elegantly used to catalyze many reaction such as the Mannich reaction and the direct asymmetric Aldol reaction [9]. Very recently, L-proline has also been effectively used as a versatile organocatalyst in various organic transformations [10]. L-proline exploited as an efficient organocatalyst in the organic synthetic routes for carbon-carbon and carbon heteroatom bonds formation [11]. In the present study, we extend the scope of the L-proline-catalyzed synthesis of benzo[h]-indeno[1,2-b]-quinoline derivatives.

One of the way for the synthesis of quinoline compounds is, condensation of aldehydes, aromatic amine and CH acids [11,12]. In this study, we investigated a three component condensation of aldehydes with naphthalen-1-amine and 1,3-indandione in aqueous media. Previous studies showed that the synthesis of these compounds with similar structure can be conducted by multi-step reactions or complicated starting materials, and they also achieved 1,4-dihydropiridinones or were forced to convert these compounds to pyridine in harsh conditions [13,14].

2. Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature.
IR spectra were recorded on a Shimadzu IR-470 spectrometer with KBr plates. 1HNMR and 13CNMR spectra were recorded on a Bruker Avance-400 MHz spectrometer.

2.1. General procedure
To a stirred mixture of 2H-indene-1,3-diones, 1 0.146 g (1 mmol), an aldehyde derivatives 3α-g (1 mmol) in 6 mL solution of water and ethanol, 5:1 (v/v), was added a catalytic amount of L-proline (30 mol%). The mixture was stirred at 80 °C (oil bath) for about 10 min, until to yield intermediates 7α-g (monitored by TLC on silica gel using a 3:1 mixture of ethyl acetate/n-hexane). Subsequently, 0.143 g (1 mmol) of naphthalen-1-amine 2 was added to this mixture. The reaction was then stirred at same conditions about 20 min. The reaction mixture was filtered and the obtained precipitate washed with hot ethanol (95.5%).

Selected spectral data

**Benzo[h]-10-(3-methoxy phenyl)-1H-indeno [1,2-b] quinoline -11-one (4a):**

Yellow crystals (0.31 g) 81%, m.p.: 254-256 °C. IR (KBr): ν = 3070 (C-H str.), 1700 (C=O str.), 1600, 1570, 1480, 1400, 1345, 1324, 1291, 1285, 1256, 1252, 1243, 1242, 1245, 1218, 1140, 1130, 1125, 1080, 1010, 985, 870, 805, 790, 750, 730 cm-1. 1HNMR (400 MHz, DMSO-d6): δ = 9.56 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 7.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.66-7.52 (m, 5H), 7.47 (d, J = 7.9 Hz, 1H), 7.40-7.31 (m, 3H), 7.21-7.19 (m, 2H) ppm. 13CNMR (100 MHz, DMSO-d6): δ = 190.3 (C=O), 148.7, 146.0, 143.2, 136.9, 136.4, 134.5, 134.1, 132.6, 132.4, 132.1, 131.8, 131.6, 131.2, 130.2, 128.7, 128.5, 128.2, 125.6, 124.8, 124.2, 123.9, 123.5, 122.9, 121.8 (25 C aromatic) ppm. Anal. Calcd. for C57H33NO2; C 83.70, H 4.42, N 3.71; Found C 83.62, H 4.69, N 3.71.

**Benzo[h]-10-(2-chloro phenyl)-1H-indeno [1,2-b] quinoline -11-one (4b):**

Yellow crystals (0.30 g) 78%, m.p.: 47-249 °C. IR (KBr): ν = 3070 (C-H str.), 2920, 2820, 1700 (C=O str.), 1600, 1580, 1575, 1485, 1455, 1259, 840, 810, 755 cm-1. 1HNMR (400 MHz, DMSO-d6): δ = 9.53 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 7.4 Hz, 1H), 8.21 (d, J = 7.4 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.40-7.31 (m, 3H), 7.21-7.19 (m, 2H) ppm. 13CNMR (100 MHz, DMSO-d6): δ = 191.2 (C=O), 162.2, 157.5, 149.7, 144.7, 144.4, 137.6, 135.4, 135.0, 132.2, 131.5, 131.1, 130.9, 129.5, 128.1, 127.9, 127.5, 126.2, 126.0, 124.8, 124.6, 124.1, 123.0, 121.8, 120.9, 111.6 (25C aromatic), 56.0 (O-CH3) ppm. Anal. Calcd. for C57H33NO2; C 83.70, H 4.42, N 3.62; Found C 83.40, H 4.68, N 3.71.

**Benzo[h]-10-(4-bromo phenyl)-1H-indeno [1,2-b] quinoline -11-one (4d):**

Yellow crystals (0.35 g) 76%, m.p.: 283-285 °C. IR (KBr): ν = 3070 (C-H str.), 1700 (C=O str.), 1605, 1580, 1570, 1470, 1455, 1040 (C-Cl str.), 830, 805, 790, 750, 730 cm-1. 1HNMR (400 MHz, DMSO-d6): δ = 9.22 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 7.0 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.62-7.44 (m, 5H), 7.41 (d, J =
8.0Hz, 1H), 7.38-7.30 (m, 3H), 7.20-7.17 (m, 2H) ppm.  

\[^{13}\text{C}]\text{NMR}\ (100\ \text{MHz, DMSO}): \delta = 190.1\ (C=O), 160.0, 159.0, 143.9, 143.4, 140.5, 136.7, 136.6, 134.7, 132.6, 132.1, 131.5, 131.3, 131.2, 130.3, 129.9, 129.0, 128.6, 128.3, 127.8, 125.5, 124.9, 124.3, 123.6, 122.0 (25 C aromatic) ppm. Anal. Calcd. for C\text{26}H\text{14}Cl\text{NO}; C 76.96, H 3.60, N 3.57; Found C 76.89, H 3.52, N 3.64.

**Benzo[h]-10-(2,4-dichloro phenyl)-1H-indeno [1,2-b] quinoline -11-one (4g):**

Yellow crystals (0.34 g) 80%, m.p.: 243-245 °C. IR (KBr): $\tilde{\nu} = 3080\ \text{(C-H str.)}, 1710\ \text{(C=O str.)}, 1605, 1570, 1470, 1100, 1060\ \text{(C-Cl str.)}, 850, 838, 810, 790, 770, 750\ \text{cm}^{-1}$. \[^{1}\text{H}]\text{NMR}\ (400\ \text{MHz, DMSO-d}_6): \delta = 9.54\ (d, \ J = 8.1\ Hz, 1H), 8.24\ (d, \ J = 7.4\ Hz, 1H), 7.93\ (d, \ J = 7.8\ Hz, 1H), 7.83-7.69\ (m, 5H), 7.38\ (d, \ J = 8.6\ Hz, 1H), 7.34\ (d, \ J = 8.6\ Hz, 1H) ppm. \[^{13}\text{C}]\text{NMR}\ (100\ \text{MHz, DMSO-d}_6): \delta = 190.1\ (C=O), 161.6, 148.9, 143.4, 142.7, 136.7, 136.1, 135.0, 134.7, 133.6, 132.9, 132.7, 131.8, 131.2, 130.3, 129.5, 129.2, 128.7, 128.3, 128.1, 125.5, 124.7, 124.4, 124.1, 123.5, 122.0 (25 C aromatic) ppm. Anal. Calcd. for C\text{26}H\text{13}Cl\text{2}NO; C 73.25, H 3.07, N 3.29; Found C 73.89, H 3.13, N 3.37.

### 3. Results and Discussion

To optimize the reaction conditions the reaction between 2\text{H}-indene-1,3-dione 1, naphthalen-1-amine 2, and 4-methoxy benzaldehyde 3, was selected as a model reaction. As Table 1 shows, in the presence of L-proline (30 mol %), the 5:1 ratio (v/v) of water and ethanol is the solvent of choice for driving the reaction efficiently. In the same conditions but without L-proline the yield of product was low even after 5h. The best yield was obtained in the water:ethanol as a mixed solvent. Also, the product was obtained in very low yield under solvent-free conditions after 6 h at 80 °C. Similar reactivity with other aldehydes, both kinds of bearing substituents at 2-position or electron-withdrawing groups, well defines the scope of this inherently convergent synthetic method. The results are summarized in Table 2.

**Table 1. Optimization of reaction conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Catalyst (mol %)</th>
<th>Reaction time</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH (reflux)</td>
<td>p-TSA (30)</td>
<td>4 h</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>MeOH (reflux)</td>
<td>p-TSA (30)</td>
<td>4 h</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>CH\text{3}CN (reflux)</td>
<td>p-TSA (30)</td>
<td>7 h</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>Water (reflux)</td>
<td>p-TSA (30)</td>
<td>8 h\text{a}</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>Water: EtOH (5:1, 80 °C)</td>
<td>p-TSA</td>
<td>2 h</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>EtOH (reflux)</td>
<td>L-proline (30)</td>
<td>40 min</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>Water: EtOH (5:1, 80 °C)</td>
<td>L-proline (30)</td>
<td>40 min</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>Water: EtOH (5:1, 80 °C)</td>
<td>L-proline (20)</td>
<td>40 min</td>
<td>69</td>
</tr>
<tr>
<td>9</td>
<td>EtOH (reflux)</td>
<td>TiO\text{2} (30)</td>
<td>40 min</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>Water: EtOH (5:1, 80 °C)</td>
<td>-</td>
<td>5 h</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>Solvent-free</td>
<td>L-proline (30)</td>
<td>24 h (r.t.) or 6 h (80 °C)</td>
<td>Trace \text{c}</td>
</tr>
</tbody>
</table>

\text{aThe reaction was carried out with 4-methoxy benzaldehyde (1 mmol), 2\text{H}-indene-1,3-dione (1 mmol), naphthalen-1-amine (1 mmol) and L-proline (30 mol %) and was run under oil bath 80 °C.}

\text{bIsolated yields.}

\text{cThis reaction was examined in two conditions, at room temperature for 24 h and at 80 °C for 6 h.}
Table 2. Synthesis of quinoline derivatives 4a-g.

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Product</th>
<th>Reaction time (min)</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3a) (X = 4-OMe)</td>
<td>4a</td>
<td>40</td>
<td>81</td>
</tr>
<tr>
<td>(3b) (X = 2-OMe)</td>
<td>4b</td>
<td>45</td>
<td>78</td>
</tr>
<tr>
<td>(3c) (X = 3-OMe)</td>
<td>4c</td>
<td>30</td>
<td>76</td>
</tr>
<tr>
<td>(3d) (X = 4-Br)</td>
<td>4d</td>
<td>30</td>
<td>81</td>
</tr>
<tr>
<td>(3e) (X = 4-Cl)</td>
<td>4e</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>(3f) (X = 2-Cl)</td>
<td>4f</td>
<td>30</td>
<td>76</td>
</tr>
<tr>
<td>(3g) (X = 2,4-Cl)</td>
<td>4h</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The reaction was carried out with benzaldehyde derivatives (1 mmol), 2H-indene-1,3-dione (1 mmol), naphthalen-1-amine (1 mmol) and L-proline (30 mol %) and was run under oil bath 80 °C.

\textsuperscript{b}Isolated yields.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and yield. A reasonable mechanism for the formation of benzo[h]-indeno [1,2-b]-quinoline 4a-g from this three-component reaction is depicted in Scheme 2. L-proline catalyzed the formation of iminium ion 5a-g in a reversible reaction with aldehydes. The higher reactivity of the iminium ion compared to carbonyl species could facilitate kneovenagel condensation between aldehydes and 2H-indene-1,3-dione 1, via intermediate 6a-g and after the elimination of L-proline, 7a-g might be produced as an intermediate, which upon Michael addition of naphthalen-1-amine 2 followed by cyclocondensation and elimination of H₂O gave the 1,4-dihydropyridines 8a-g, and finally 4a-g are produced in the presence of air oxygen (pathway A), (Scheme 2).

Alternatively, the key intermediates 8a-g may be produced by condensation of 2H-indene-1,3-dione 1 with the preformed imine derived from the reaction between aldehydes and naphthalen-1-amine 2 (pathway B). The fact that the yield of products of pathway B is low (<10% for 4a at the same conditions) may lend to support the proposal that the pathway A, is more likely. Encouraged by these fascinating results, we attempted to expand the scope of method by using aniline derivatives in place of naphthalen-1-amine partner. However, our efforts to take aniline derivatives into a similar reaction remained entirely unsuccessful. This observation may be attributed to the more aromatic character of anilines, respect to naphthalenamines which are prone to act as enamine reagents. Attempts to bring aliphatic aldehydes and heterocycle aldehyde, such as indoline-3-carbaldehyde, with 2H-indene-1,3-dione and naphthalen-1-amine were unsatisfactory as they gained multiple of products polluted with unreacted substrates or otherwise completely remained unreactive. All the products were simply separated and purified by recrystallization. It is important to point out that no co-product, specially, 1,4-dihydropyridines derivatives was observed in the reaction medium. All the products were characterized by their IR, \(^1\)H NMR, and \(^{13}\)C NMR spectral data as well as elemental analysis. The IR spectrum of 4a, for example, reveals well defined molecular vibrations including the characteristic band relating to C=O stretching at 1720 cm\(^{-1}\). The \(^1\)H NMR spectrum of 4a exhibited a single sharp resonance due to the methoxy (δ=3.98) protons along with resonances (δ=7.15–9.53 ppm) for the aromatic protons. We not observed signals for N-H and methine, that proved our heterocyclic is pyridine not 1,4-dihydropyridine. Furthermore the \(^{13}\)C NMR spectrum of 4a showed the expected signals in agreement with structure of product.

Finally, the recycling of L-proline has also been investigated by using the preparation of 4a as a model. Since the poor solubility of products in the reaction media, they were easily separated by simple filtration and the filtrate was subjected to subsequent run of the reaction by charging with the same substrates. Catalyst recycling showed that yield of reaction had not decreased after five runs (Yield decreased from 81 to 78%).
4. Conclusions
In conclusion, a mild, green and efficient route for the synthesis of benzo[\(h\)]-indeno[1,2-b]-quinolines utilizing L-proline as a catalyst effectiveness and excellent solubility in aqueous media, was introduced here. The L-proline plays as a catalyst and can be reused for several times. Other advantages of the present method are: requiring no metal catalysts, high yields, cheap and easy work-up, and short reaction times and also, quinoline derivatives were achieved without using any oxidants.

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References


