An efficient synthesis of polyhydroquinolines using basic ionic liquid

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[Bmim]OH has been found to be an effective catalyst cum solvent for one pot multicomponent synthesis of polyhydroquinoline derivatives using four component Hantzsch condensation.

Keywords: Multicomponent reaction, green approach, polyhydroquinoline, basic ionic liquid, Hantzsch reaction

Diversity-oriented synthesis (DOS) continues to be an area of importance at the interface of organic synthesis and chemical biology/material science. At the heart of DOS are the methods needed for an efficient generation of functionally diverse small molecules, especially those possessing skeletons found in natural products, drug-like molecules and materials. A powerful method for generating such molecules is by sequential multicomponent reactions (MCRs) with further increase in molecular complexity and diversity. The use of a benign and recyclable catalyst/solvent with high activity and selectivity is an interesting and rapidly growing area of synthetic chemistry. In this context, ionic liquids (ILs) have attracted considerable interest as environmentally benign reaction media, catalysts and reagents.

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are analogs of NADH coenzymes and an important class of drugs. These compounds exhibit various medicinal functions such as neuroprotectant, platelet anti-aggregatory, cerebral antischismic activity in the treatment of Alzheimer’s disease and chemosensitizing activity in tumor therapy. Current literature reveals that they can cure the disordered heart ratio as the chain-cutting agent of factor IV channel and also have calcium channel agonist–antagonist modulation activities. The remarkable potential of dihydropyridine derivatives is well documented as a source of valuable ‘drug candidates’ viz., amlodipine A, nifedipine B, and nifludipine C (Ref 18).

Due to the vast medicinal utility of 1,4-DHPs, various methods for their synthesis have been recently reported employing conventional heating, solar thermal energy, ionic liquid, metal triflates, solvent free, HY-Zeolite, montmorillonite K-10 (Ref 25), cerium(IV) ammonium nitrate, iron(III) trifluoroacetate, HClO4-SiO2 (Ref 28), heteropoly acid, molecular iodine, PTSA, L-proline and derivatives, nickel, polymers, and baker’s yeast. Although these methods have their own merits, many of them are plagued by the limitations of longer reaction time, lower product yield, harsh conditions, and use of hazardous catalysts. It is important to note that most of the methods described above invariably make use of Lewis acids as catalyst, and to the best of the knowledge, there exists only one report using triphenylphosphine as a base in the aforementioned Hantzsch reaction. Consequently, there exists enough scope and motivation to undertake an eco-safe and base-catalyzed method to construct such medicinally significant scaffolds.

Results and Discussion

Considering the preceding discussion and as a part of the interest in developing green protocols, herein is described an efficient, one-pot, solvent-free four-
component synthesis of polyhydroquinolines 5 in excellent yields using aromatic aldehydes 1, dimedone 2, ethyl acetoacetate 3 and ammonium acetate 4 in the presence of [Bmim]OH at 80°C (Scheme I).

With an objective to nurture a green approach and to refrain from the use of acid catalysts, it was thought worthwhile to exploit the synthetic potential of [Bmim]OH for the synthesis of polyhydroquinolines. To optimize the reaction conditions, the catalytic activity of [Bmim]OH in ethanol was studied in a typical multicomponent reaction of benzaldehyde 1a, dimedone, ethyl acetoacetate and ammonium acetate under conventional conditions. The outcome is shown in Table I. The use of 10, 15 and 20 mol % of [Bmim]OH (Table I, entries 1-3) in ethanol promoted the reaction with successive increase in the product yield. However, when the model reaction was carried out using [Bmim]OH as the sole solvent, 94% yield of 5a was obtained at 80°C (entry 6). A further increase in the temperature did not improve the product yield any more (entry 7).

Table I — Optimization of reaction conditions for the multicomponent synthesis of 5a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Bmim]OH (10)</td>
<td>EtOH</td>
<td>80</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>[Bmim]OH (15)</td>
<td>EtOH</td>
<td>80</td>
<td>30</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>[Bmim]OH (20)</td>
<td>EtOH</td>
<td>80</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>[Bmim]OH</td>
<td>RT</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>[Bmim]OH</td>
<td>60</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>[Bmim]OH</td>
<td>80</td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>[Bmim]OH</td>
<td>100</td>
<td>10</td>
<td>94</td>
</tr>
</tbody>
</table>

aIsolated yield

Adopting the investigated optimum conditions (entry 6), a number of aromatic aldehydes 1a-o were allowed to undergo multicomponent reaction with 2, 3 and 4 in a molar ratio of 1:1:1:1.2 in the ionic liquid [Bmim]OH (0.2 mL) affording the corresponding polyhydroquinolines 5a-o in excellent yields in 10 min (Table II). The physical and spectral data of all the products are in full agreement with their assigned structures. It is worthwhile to mention that the ionic liquid [Bmim]OH was recovered and recycled upto five times with no loss or diminution in its amount and efficacy (cf. Table II, entry 8). After each and every recycle, the purity of the ionic liquid was reaffirmed from spectroscopic data.

In conclusion, the present report demonstrates an efficient use of a basic ionic liquid [Bmim]OH for multicomponent synthesis of polyhydroquinolines by the condensation of aromatic aldehydes, dimedone, ethyl acetoacetate and ammonium acetate. These heterocycles are manifested in a broad range of biologically and pharmacologically active molecules. The advantages include excellent yields, easier work-up, lesser reaction time and green credentials.

Experimental Section

All the chemicals were procured from Aldrich, USA, and E. Merck, Germany and were used as
Table II — [Bmim]OH-mediated Hantzsch condensation to polyhydroquinoline derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (Ar)</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield(^a) (%)</th>
<th>m.p. [Lit.] (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C(_2)H(_5)</td>
<td>5(a)</td>
<td>10</td>
<td>94</td>
<td>203-204 [202-205 (Ref 32c)]</td>
</tr>
<tr>
<td>2</td>
<td>4-CH(_3)C(_2)H(_4)</td>
<td>5(b)</td>
<td>10</td>
<td>96</td>
<td>259-61 [260-61 (Ref 32c)]</td>
</tr>
<tr>
<td>3</td>
<td>4-CH(_2)OC(_6)H(_4)</td>
<td>5(c)</td>
<td>10</td>
<td>97</td>
<td>256-57 [257-59 (Ref 32c)]</td>
</tr>
<tr>
<td>4</td>
<td>4-CIC(_2)H(_4)</td>
<td>5(d)</td>
<td>10</td>
<td>96</td>
<td>231-33 [232-34 (Ref 32c)]</td>
</tr>
<tr>
<td>5</td>
<td>4-BrC(_2)H(_4)</td>
<td>5(e)</td>
<td>10</td>
<td>94</td>
<td>252-54 [251-53 (Ref 32c)]</td>
</tr>
<tr>
<td>6</td>
<td>3-BrC(_2)H(_4)</td>
<td>5(f)</td>
<td>10</td>
<td>93</td>
<td>235-36 [234-36 (Ref 15)]</td>
</tr>
<tr>
<td>7</td>
<td>4-FC(_2)H(_4)</td>
<td>5(g)</td>
<td>10</td>
<td>95</td>
<td>183-85 [184-86 (Ref 22a)]</td>
</tr>
<tr>
<td>8</td>
<td>4-NO(_2)C(_2)H(_4)</td>
<td>5(h)</td>
<td>10</td>
<td>93(^b)</td>
<td>243-45 [241-43 (Ref 32c)]</td>
</tr>
<tr>
<td>9</td>
<td>3-NO(_2)C(_2)H(_4)</td>
<td>5(i)</td>
<td>10</td>
<td>91</td>
<td>176-77 [176-79 (Ref 32c)]</td>
</tr>
<tr>
<td>10</td>
<td>2-NO(_2)C(_2)H(_4)</td>
<td>5(j)</td>
<td>10</td>
<td>92</td>
<td>209-10 [208-11 (Ref 32c)]</td>
</tr>
<tr>
<td>11</td>
<td>2,4-Cl(_2)-C(_6)H(_4)</td>
<td>5(k)</td>
<td>10</td>
<td>90</td>
<td>239-41 [240-42 (Ref 22a)]</td>
</tr>
<tr>
<td>12</td>
<td>4-(CH(_3)(_2))NC(_6)H(_4)</td>
<td>5(l)</td>
<td>10</td>
<td>95</td>
<td>232-33 [229-31 (Ref 22a)]</td>
</tr>
<tr>
<td>13</td>
<td>4-HOC(_6)H(_4)</td>
<td>5(m)</td>
<td>10</td>
<td>94</td>
<td>233-35 [232-34 (Ref 22a)]</td>
</tr>
<tr>
<td>14</td>
<td>2-Furyl</td>
<td>5(n)</td>
<td>10</td>
<td>92</td>
<td>246-47 [246-48 (Ref 22a)]</td>
</tr>
<tr>
<td>15</td>
<td>2-Thienyl</td>
<td>5(o)</td>
<td>10</td>
<td>93</td>
<td>240-42 [238-40 (Ref 22a)]</td>
</tr>
</tbody>
</table>

\(a\) Isolated yield.

\(^\text{b}\) Average yield of 5 recycles.

Received. IR spectra were recorded on a Jasco FT/IR-5300 spectrophotometer. NMR spectra were run on a Jeol AL300 FT-NMR spectrometer. Chemical shifts are given in \(\delta\) (ppm), relative to TMS as internal standard. Elemental microanalysis was performed on Exeter Analytical Inc. Model CE-440 CHN analyzer. Melting points were determined in open capillaries and are uncorrected.

**General procedure for the synthesis of polyhydroquinolines 5**

A mixture of aldehyde 1 (1 mmol), dimedone 2 (1 mmol), ethyl acetoacetate 3 (1 mmol), ammonium acetate 4 (1.2 mmol) and [Bmim]OH (0.2 mL) was placed in a preheated oil bath at 80°C for 10 min. Upon completion of the reaction (as indicated on TLC), the reaction mixture was cooled to RT and to it was added 10 mL water. The resulting solid was filtered, washed with water and purified from ethanol to afford the pure product 5. After isolation of the product, the remaining aqueous layer containing the ionic liquid was washed with ether (10 mL) to remove the organic impurities if any, and then dried under vacuum at 90-95°C for 2 h to provide purified [Bmim]OH, which was used in the subsequent runs without any further purification.

**Ethyl 4-(4-methylphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5b**

IR (KBr): 3276, 3078, 2960, 1702, 1646 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.16 (d, \(J = 8.4\) Hz, 2H), 7.03 (d, \(J = 8.4\) Hz, 2H), 5.69 (s, 1H), 5.07 (s, 1H), 4.09 (q, \(J = 7.2\) Hz, 2H), 2.37 (s, 3H), 2.29-2.16 (m, 4H), 1.23 (t, \(J = 7.2\) Hz, 3H), 1.06 (s, 3H), 0.95 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 195.68, 167.39, 148.74, 146.95, 143.71, 127.97, 127.83, 126.07, 112.01, 105.98, 59.73, 50.87, 44.02, 36.59, 32.73, 29.45, 29.06, 19.81, 19.23, 14.16. Anal. Calcd for C\(_{21}\)H\(_{25}\)NO\(_2\): C, 74.31; H, 7.42; N, 4.13. Found: C, 74.23; H, 7.48; N, 4.19%.

**Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5a**

IR (KBr): 3289, 3080, 2961, 1699, 1612 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.25-7.31 (m, 2H), 7.16-7.21 (m, 2H), 7.08-7.11 (m, 1H), 5.70 (s, 1H), 5.05 (s, 1H), 4.06 (q, \(J = 7.2\) Hz, 2H), 2.38 (s, 3H), 2.17-2.33 (m, 4H), 1.19 (t, \(J = 7.2\) Hz, 3H), 1.08 (s, 3H), 0.93 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 195.70, 167.47, 148.72, 147.05, 143.67, 127.96, 127.83, 125.98, 111.92, 105.93, 59.78, 50.72, 40.85, 36.55, 32.64, 29.41, 27.08, 19.24, 14.17. Anal. Calcd for C\(_{22}\)H\(_{36}\)NO\(_2\): C, 74.85; H, 7.66; N, 3.90%.
Ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5d. IR (KBr): 3276, 3199, 3077, 2964, 1707, 1648, 1604 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.27-7.24 (m, 2H), 7.19-7.15 (m, 2H), 6.46 (s, 1H), 5.04 (s, 1H), 4.04 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 2.34-2.12 (m, 4H), 1.18 (t, J = 7.1 Hz, 3H), 1.08 (s, 3H), 0.94 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 194.32, 165.98, 147.26, 144.34, 142.49, 130.32, 128.14, 126.40, 110.46, 104.42, 58.62, 49.42, 39.69, 34.97, 31.39, 28.13, 25.80, 18.05, 12.92. Anal. Calcd for C$_{28}$H$_{32}$NO: C, 71.61; H, 7.40; N, 3.70%.

Ethyl 4-(4-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5h. IR (KBr): 3285, 3203, 3078, 2964, 1676, 1605, 1515 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 8.07 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 5.75 (s, 1H), 5.15 (s, 1H), 4.04 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 2.11-2.35 (m, 4H), 1.17 (t, J = 7.2 Hz, 3H), 1.09 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 195.38, 166.82, 154.50, 148.88, 146.16, 144.48, 128.92, 123.28, 110.99, 104.83, 60.04, 50.57, 40.93, 37.18, 32.67, 29.32, 27.01, 19.37, 14.15. Anal. Calcd for C$_{32}$H$_{24}$N$_2$O: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.56; H, 6.33; N, 7.37%.

Ethyl 4-(3-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5i. IR (KBr): 3283, 3210, 3079, 2958, 1705, 1608, 1532 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 8.10 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 5.88 (s, 1H), 5.15 (s, 1H), 4.06 (q, J = 6.9 Hz, 2H), 2.41 (s, 3H), 2.36-2.12 (m, 4H), 1.19 (t, J = 6.9 Hz, 3H), 1.10 (s, 3H), 0.94 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 195.52, 166.90, 149.15, 148.20, 144.52, 134.73, 128.54, 122.81, 121.23, 111.09, 104.99, 60.02, 50.54, 40.84, 36.95, 32.70, 29.32, 27.02, 19.33, 14.13. Anal. Calcd for C$_{32}$H$_{24}$N$_2$O: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.70; H, 6.34; N, 7.20%.

Ethyl 2,7,7-trimethyl-4-(2-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5j. IR (KBr): 3292, 3084, 2964, 1697, 1616, 1528, 1487, 1381, 1341, 1283, 755 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.72-7.27 (m, 4H), 6.02 (s, 1H), 5.10 (s, 1H), 4.08 (q, J = 6.9 Hz, 2H), 2.45 (s, 3H), 2.39-2.15 (m, 4H), 1.15 (t, J = 6.9 Hz, 3H), 1.11 (s, 3H), 0.93 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 194.48, 167.02, 150.25, 148.17, 146.33, 142.49, 133.36, 131.12, 127.35, 124.05, 119.37, 103.54, 75.39, 50.54, 32.56, 32.37, 29.35, 26.86, 18.84, 14.35; Anal. Calcd for C$_{32}$H$_{24}$N$_2$O: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.50; H, 6.25; N, 7.21%.

Ethyl 4-(2,4-dichlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5k. IR (KBr): 3281, 3078, 2955, 1700, 1640 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.33 (d, J = 7.5 Hz, 1H), 7.24 (s, 1H), 7.11 (d, 1H, J = 7.5 Hz), 6.53 (s, 1H), 0.94 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 195.65, 167.55, 153.72, 149.27, 144.60, 138.63, 129.51, 112.17, 106.25, 59.84, 50.78, 40.97, 35.62, 29.41, 27.15, 19.31, 14.22. Anal. Calcd for C$_{32}$H$_{24}$FNO: C, 70.57; H, 6.77; N, 3.92. Found: C, 70.46; H, 6.74; N, 3.88%.
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References


