**PEG-400 as an efficient and recyclable reaction medium for the synthesis of polyhydroquinolines via Hantzsch reaction**

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**ABSTRACT:** Polyhydroquinoline derivatives have been prepared efficiently in a one-pot synthesis via Hantzsch condensation using PEG-400 as reaction medium. The present method does not involve any hazardous organic solvents or toxic catalysts. The present methodology offers several advantages such as simple procedure, excellent yields with shorter reaction times and purification of products by non-chromatographic methods.

**Keywords:** polyhydroquinoline derivatives; Hantzsch condensation; green chemistry; PEG-400

**Introduction**

Polyhydroquinoline nucleus is a fertile source of biologically important molecules possessing various important pharmacological properties such as vasodilator, anti-hypertensive, bronchodilator, anti-therosclerotic, hepto-protective, anti-tumor, anti-mutagenic, geroprotective and anti-diabetic agents [1]. Polyhydroquinolines have found commercial utility as calcium channel blockers as exemplified by therapeutic agents such as Nifedine, Nitrendipine and Nimodipine [2]. These examples clearly demonstrate the remarkable potential of polyhydroquinoline derivatives as a source of valuable drugs. Owing to the wide range of pharmacological and biological activities, the synthesis of imidazoles has become an important target in current years. There are several methods reported in literature for the synthesis of polyhydroquinoline derivatives in the synthesis.

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of various drug sources, reported in many classical methods such as conventional heating [3, 4], the progress in this field is remarkable for microwave irradiation and ultrasound [5, 6], various catalysts such as trimethylsilyl chloride (TMSCl) [7], molecular iodine [8], L-proline [9], Yb(OTf)$_3$ [10], ceric ammonium nitrate [11], iron (III) trifluoroacetate [12], heteropoly acid [13], Sc(OTf)$_3$ [14], microwave irradiation [15], Bakers’ yeast [16] p-TSA [17], grinding [18], by refluxing in water[19] and nanosized nickel [20]. However, most of the reported methodologies still have certain limitations such as expensive catalysts, toxicity of solvents, restrictions for large scale applications, critical product isolation procedures, difficulty in recovery of high boiling solvents, excessive amounts of catalysts and generation of large amounts of toxic wastes in scaling up for industrial applications leading to environmental issues. Thus, the development of a simple and efficient method under catalyst free conditions for constructing these polyhydroquinolines has been advocated.

In the recent years, PEG emerged as a powerful phase transfer catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable in various organic transformations [21], such as for example, Heck reaction [22], catalytic hydrogenations [23], asymmetric dihydroxylation reaction [24], Baylis-Hillman reaction [25], Biginelli reaction [26], Suzuki-Miyaura reaction, Stille cross-coupling reaction [27], Wacker reaction [28] and asymmetric aldol reaction [29]. This inspired us to focus on the aspect of synthesis of biologically active polyhydroquinolines derivatives under catalyst free conditions by using PEG-400 as an eco-friendly and recyclable media.

**Material and Methods**

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a Perkin Elmer spectrometer. $^1$H-NMR spectra were recorded on a Gemini 300-MHz instrument in CDCl$_3$ as solvent and TMS as an internal standard. The purity of products was checked by thin-layer chromatography (TLC) on silica-gel.

**Typical procedure for the synthesis of 2-amino-4H-chromenes 4(a-l)**

A mixture of aldehyde 1 (1 mmol), dimedone 2 (1 mmol), ethyl acetoacetate 3 (1 mmol) and ammonium acetate (1 mmol) in PEG-400 (5ml) was stirred at 80 °C in 25 mL round bottom flask for the appropriate time mentioned in Table 2. The progress of reaction was monitored by TLC. After completion of reaction, the separated solid was filtered and recrystallized from ethyl alcohol. The progress of reaction was monitored by thin layer chromatography ($n$-hexane:EtOAc, 8:2). After completion of reaction the reaction mass was cooled to room temperature and then poured on cold water. The
obtained solid was filtered, washed with water and crude solid was crystallized from ethanol. The aqueous filtrate was distilled at 100 °C to remove water and thus separated PEG-400 was reused.

**Spectroscopic data of synthesized some principal compounds**

**Compound (4a):** IR (KBr, cm⁻¹): 3305, 3052, 2967, 1679, 1633, 1351, 762; ¹H-NMR (CDCl₃ δ, ppm): 1.12 (6H, s, 2CH₃), 1.23 (3H, t, J=7.1 Hz, CH₃), 1.71 (3H, s, CH₃), 2.31-2.35 (4H, m, 2CH₂), 4.11 (2H, q, J = 7.1 Hz, CH₂), 5.05 (1H, s, ArCH), 6.41 (1H, br., s, NH), 6.75 (2H, d, J = 8.1 Hz, Ar-H), 7.22 (2H, d, J = 8.1 Hz, Ar-H).

**Compound (4b):** IR (KBr, cm⁻¹): 3310, 3042, 2967, 1679, 1630, 1498, 1351, 1200, 752; ¹H-NMR (CDCl₃ δ, ppm): 1.11 (6H, s, 2CH₃), 1.20 (3H, t, J=7.1 Hz, CH₃), 1.73 (3H, s, CH₃), 2.31-2.35 (4H, m, 2CH₂), 3.62 (3H, s, OCH₃), 4.11 (2H, q, J = 7.1 Hz, CH₂), 5.05 (1H, s, ArCH), 6.41 (1H, br., s, NH), 6.82 (2H, d, J = 8.1 Hz, Ar-H), 7.22 (2H, d, J = 8.1 Hz, Ar-H).

**Compound (4c):** IR (KBr, cm⁻¹): 3302, 3274, 3043, 2940, 1656, 1587, 1478, 1344, 1223, 767; ¹H-NMR (CDCl₃ δ, ppm): 1.18 (6H, s, 2CH₃), 1.19 (3H, t, J = 7.1 Hz, CH₃), 1.83 (3H, s, CH₃), 2.40-2.50 (4H, m, 2CH₂), 4.16 (2H, q, J = 7.1 Hz, CH₂), 5.35 (1H, s, ArCH), 5.95 (1H, br., s, NH), 7.66 (2H, d, J = 8.7 Hz, Ar-H), 8.20 (2H, d, J = 8.2 Hz Ar-H).

**Compound (4d):** IR (KBr, cm⁻¹): 3305, 3280, 3052, 2967, 1679, 1637, 1460, 1351, 1218, 769; ¹H-NMR (CDCl₃ δ, ppm): 1.11 (6H, s, 2CH₃), 1.21 (3H, t, J = 7.1 Hz, CH₃), 1.74 (3H, s, CH₃), 2.32-2.37 (4H, m, 2CH₂), 4.62 (1H, s, OH), 4.11 (2H, q, J = 7.1 Hz, CH₂), 5.05 (1H, s, ArCH), 5.95 (1H, br., s, NH), 6.97 (2H, d, J = 8.1 Hz, Ar-H), 7.22 (2H, d, J = 8.1 Hz, Ar-H).

**Compound (4e):** IR (KBr, cm⁻¹): 3305, 3052, 2967, 1679, 1637, 1540, 1460, 1351, 1218, 769; ¹H-NMR (CDCl₃ δ, ppm): 1.13 (6H, s, 2CH₃), 1.23 (3H, t, J = 7.1 Hz, CH₃), 1.71 (3H, s, CH₃), 2.30-2.34 (4H, m, 2CH₂), 4.12 (2H, q, J = 7.1 Hz, CH₂), 5.02 (1H, s, ArCH), 6.42 (1H, br., s, NH), 7.97 (2H, d, J = 8.1 Hz, Ar-H), 7.20 (2H, d, J = 8.1 Hz, Ar-H).

**Compound (4f):** IR (KBr, cm⁻¹): 3303, 3054, 2960, 1653, 1632, 1524, 1460, 1351, 1212, 760; ¹H-NMR (CDCl₃ δ, ppm): 1.10 (6H, s, 2CH₃), 1.23 (3H, t, J = 7.1 Hz, CH₃), 1.71 (3H, s, CH₃), 2.30-2.34 (4H, m, 2CH₂), 4.12 (2H, q, J = 7.1 Hz, CH₂), 5.02 (1H, s, ArCH), 6.42 (1H, br., s, NH), 8.17 (2H, d, J = 8.1 Hz, Ar-H), 7.30 (2H, d, J = 8.1 Hz, Ar-H).

**Compound (4g):** IR (KBr, cm⁻¹): 3305, 3052, 2967, 1679, 1637, 1548, 1460, 1351, 1218, 710, 776; ¹H-NMR (CDCl₃ δ, ppm): 1.13 (6H, s, 2CH₃), 1.22 (3H, t, J = 7.1 Hz, CH₃), 1.73 (3H, s, CH₃), 2.31-2.34 (4H, m, 2CH₂), 4.10 (2H, q, J = 7.1 Hz, CH₂), 5.14
(1H, s, ArCH), 6.40 (1H, br., s, NH), 7.31 (1H, d, Ar-H), 7.82 (1H, d, Ar-H), 7.72 (1H, s, Ar-H), 7.52 (1H, t, Ar-H).

**Compound(4h):** IR (KBr, cm⁻¹): 3309, 3056, 2952, 1645, 1621, 1468, 1361, 1232, 761; ¹H-NMR (CDCl₃ δ ppm): 1.12 (6H, s, 2CH₃), 1.22 (3H, t, J=7.1Hz, CH₃), 1.79 (3H, s, CH₃), 2.32-2.35 (4H, m, 2CH₂), 4.15 (2H, q, J = 7.1 Hz, CH₂), 5.10 (1H, s, ArCH), 6.51 (1H, br., s, NH), 6.95 (2H, d, J = 8.1 Hz, Ar-H), 7.22 (2H, d, J = 8.1 Hz, Ar-H).

**Compound(4i):** IR (KBr, cm⁻¹): 3305, 3056, 2945, 1645, 1621, 1468, 1361, 1242, 742; ¹H-NMR (CDCl₃ δ ppm): 1.12 (6H, s, 2CH₃), 1.22 (3H, t, J=7.1Hz, CH₃), 1.79 (3H, s, CH₃), 2.32-2.35 (4H, m, 2CH₂), 4.15 (2H, q, J = 7.1 Hz, CH₂), 5.10 (1H, s, ArCH), 6.51 (1H, br., s, NH), 7.30-7.26 (m, 1H), 7.22-7.19 (m, 1H), 7.13-7.10 (m, 1H),

**Compound(4j):** IR (KBr, cm⁻¹): 3267, 3020, 2977, 1632, 1515, 1375, 1217, 754; ¹H-NMR (CDCl₃, δ ppm): 1.09 (6H, s, 2CH₃), 1.22 (3H, t, J=7.1Hz, CH₃), 1.79 (3H, s, CH₃), 2.22-2.52 (4H, m, 2CH₂),4.11 (2H, q, J = 7.1 Hz, CH₂), 5.09 (1H, s, ArCH), 5.98 (1H, br.,s, NH), 7.11 (2H, d, J = 8.2 Hz, ArH), 7.12 (2H, d, J = 8.3 Hz,ArH), 2.85 (6H, s, N[CH₃]₂)

**Compound(4k):** IR (KBr, cm⁻¹): 3312, 3285, 3046, 2910, 1612, 1601, 1458, 1351, 1212, 761; ¹H-NMR (CDCl₃, δ ppm): 1.02 (6H, s, 2CH₃), 1.11 (3H, t, J=7.1Hz, CH₃), 1.75 (3H, s, CH₃), 5.12 (1H, s, OH) 2.41-2.45 (4H, m, 2CH₂). 4.22 (2H, q, J = 7.1 Hz, CH₂), 5.15 (1H, s, ArCH), 6.22 (1H, br., s, NH), 6.95 (1H, d, Ar-H), 7.12 (1H, d, Ar-H), 6.72 (1H, s, Ar-H), 7.52 (1H, t, Ar-H).

**Results and Discussion**

In continuation of our research work on the development of novel synthetic methodologies [30], herein, we have reported a highly efficient route for the synthesis of polyhydroquinolines from one-pot four component coupling of an aromatic aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in PEG-400 (Scheme 1).

![Scheme 1. Synthesis of polyhydroquinoline derivatives under PEG-400 mediated conditions.](image-url)
In the initial studies, the reaction of a benzaldehyde (1a) as a representative aldehyde, dimedone (2), ethyl acetoacetate (3) and ammonium acetate was performed in different solvents (5 mL) and at different temperature without any added catalyst to obtain the products. The compound 4a has been considered as a standard model reaction product for the optimization of reaction condition. It was observed that among the tested solvents (Table 1, entries 4–9). The reaction in PEG-400 was more facile and proceeded to give best yield (93%) when the reaction mixture was stirred at 80 °C for 45 min. Moreover, there are many potential advantages of replacing these volatile or toxic organic solvents with PEG-400. So PEG-400 is the optimal reaction media for the reaction at 80 °C.

The effect of temperature was also studied by carrying out the model reaction of product 4a in PEG-400 at different temperature. As shown in Table 1 (entries 1–5), the reaction did proceed but the yield is low in entry 5 (Table 1) as compared to entry 4 (Table 1) obtained even after longer reaction time, when the reaction temperature within 25 - 60°C. However, at elevated temperature at 80 °C using PEG-400 gave better results in terms of yield and reaction time. Hence, the conditions of entry 4, shown in Table 1, were the optimized reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent(5ml)</th>
<th>Temperature °C</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEG-400</td>
<td>25</td>
<td>110</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>PEG-400</td>
<td>40</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>PEG-400</td>
<td>60</td>
<td>55</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>PEG-400</td>
<td>80</td>
<td>45</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>PEG-400</td>
<td>100</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>Dichloromethane</td>
<td>40</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>Acetonitrile</td>
<td>78</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>Ethanol</td>
<td>75</td>
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<td>60</td>
</tr>
<tr>
<td>9</td>
<td>Methanol</td>
<td>63</td>
<td>60</td>
<td>55</td>
</tr>
</tbody>
</table>

In order to evaluate the generality of the process, we studied the reaction of various aldehydes 1, dimedone 2, ethyl acetoacetate 3, and ammonium acetate in PEG-400 at 80 °C. Aromatic aldehydes bearing electron withdrawing groups (such as nitro, chloro, bromo) or electron releasing groups (such as methyl, hydroxyl, methoxy, N,N-diamine), were smoothly converted to corresponding product (4) in excellent yields, except with 4-nitrobenzaldehyde requires longer reaction time. Results have shown that the substitution groups played a less significant role in governing the reactivity of the substrates. In the present procedure, PEG-400 not only acts as a phase transfer catalyst but also as a clean solvent by significantly enhancing the intramolecular cyclization.
Table 2. Synthesis of polyhydroquinoline (4a–4m) using PEG-400 as reaction medium at 80 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ar-</th>
<th>Time(min)</th>
<th>Yield (%)</th>
<th>Mp.(°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found</td>
</tr>
<tr>
<td>1</td>
<td>4a</td>
<td>C₆H₅</td>
<td>45</td>
<td>93</td>
<td>201-202</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>4-OCH₃C₆H₄</td>
<td>30</td>
<td>90</td>
<td>256-258</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>4-CH₃C₆H₄</td>
<td>35</td>
<td>89</td>
<td>259-261</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>4-OHC₆H₄</td>
<td>30</td>
<td>91</td>
<td>232-233</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>4-NO₂C₆H₄</td>
<td>110</td>
<td>92</td>
<td>242-243</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>4-ClC₆H₄</td>
<td>35</td>
<td>89</td>
<td>246-248</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>3-NO₂C₆H₄</td>
<td>90</td>
<td>94</td>
<td>175-177</td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>4-BrC₆H₄</td>
<td>40</td>
<td>91</td>
<td>253-254</td>
</tr>
<tr>
<td>9</td>
<td>4i</td>
<td>2-Furyl</td>
<td>25</td>
<td>89</td>
<td>247-249</td>
</tr>
<tr>
<td>10</td>
<td>4j</td>
<td>2-Thienyl</td>
<td>20</td>
<td>90</td>
<td>240-241</td>
</tr>
<tr>
<td>11</td>
<td>4k</td>
<td>4-N(CH₃)₂C₆H₄</td>
<td>25</td>
<td>85</td>
<td>231-233</td>
</tr>
<tr>
<td>12</td>
<td>4l</td>
<td>3-OHC₆H₄</td>
<td>55</td>
<td>93</td>
<td>219-220</td>
</tr>
</tbody>
</table>

To check the reusability of medium (PEG-400) we have performed the experiment using same reactants, benzaldehyde (1a), dimedone (2), ethyl acetoacetate (3) and ammonium acetate using PEG-400 and we found surprising results with this media.

After three successive runs we found the reaction proceed cleanly with good yields were summarized in Table 3, although a little weight loss of PEG-400 was observed from cycle to cycle due to mechanical loss. Further studies to develop the new clean environmentally benign PEG-400 towards the synthesis of biologically active compounds are progress.

Table 3. The recycling of polyethylene glycol for benzaldehyde derivative.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time(min.)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>45</td>
<td>93</td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>89</td>
</tr>
</tbody>
</table>

Conclusion

In conclusion, this paper describes a convenient and efficient process for the synthesis of polyhydroquinoline derivatives by use of PEG-400 at 80 °C as a recyclable medium without the addition of any additive or organic co-solvent. Present methodology offers very attractive features such as simple experimental procedure, reduced reaction times, higher yields and economic viability, when compared with conventional method.
as well as with other catalysts, and will have wide scope in organic synthesis.

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**References and Notes**


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