Chapter 2

Cellulose/Proline Promoted Highly Efficient Synthesis of Polyhydroquinoline Scaffolds
2.1.1. Introduction:

Multi-component reactions are the processes in which three or more substrates can react to produce complex heterocyclic scaffold, with advantages of practical and time-saving reactions conditions. Thus, MCRs have attracted considerable interest in combinatorial chemistry to generate libraries of compounds promote drug discovery and automated synthesis.\(^1\)

Dihydropyridines (DHP) are privileged scaffold in the medicinal chemistry for drug discovery. DHP motif exhibits a wide range of important pharmacological activities such as calcium channel antagonist for the treatment of cardiovascular diseases, hypertension and multidrug resistance (MDR) proteins. Besides these, DHP also shows other important activities like anti-inflammatory,\(^2\) anti-cancer,\(^3\) anti-hypertensive,\(^4\) anti-viral,\(^5\) anti-oxidant,\(^6\) non-competitive topoisomerase inhibitors,\(^7\) and HIV protease inhibitors etc.\(^8\)

DHP backbone Scaffolds are very useful for the treatment of various diseases, Some of the representative DHP motif containing well-known medicine drugs are felodipine,\(^9\) isradipine,\(^10\) amlodipine,\(^11\) and nemadipine B,\(^12\) as shown in Figure 1.

![Representative bioactive dihydropyridines Compounds](image)

**Figure 1:** Representative bioactive dihydropyridines Compounds.

Henceforth mentioned bio-significance of DHP, organic chemists have dedicated extensive efforts for the development of new and scalable synthetic methods. Various reports have been published for the preparation of DHP derivatives, including transition metal complexes\(^13-16\) and organo-catalysts.\(^17,18\)
However, the homogeneous catalysts are expensive and difficult to recycle, making the reported protocol less adaptable. To overcome these limitations, polymer-supported catalysts were studied as an alternative for the organic transformations. Cellulose is one abundant natural polymer which could be the most suitable material as solid support for catalyst in organic transformation and as well co-catalyst. Thus, natural cellulosics are highly attractive and optimistic candidates for investigating activity as solid support for the catalysts. Recently, various organic transformations were successfully reported using cellulose such as conversion to cyclic carbonate from an epoxide,\textsuperscript{19} Heck reactions, Sonogashira coupling,\textsuperscript{20} and Tsuji-Trost N-allylations.\textsuperscript{21} These developed protocol using cellulose, found an active, green, economical and environmentally friendly processes. Mechanistically, the hydrogen bonding interaction of cellulose in combination with water is more effective than other organic solvents.\textsuperscript{22} Considering the advantages of cellulose we have developed a cellulose supported proline-catalyzed Multi-component approach for the synthesis of series of DHP derivatives in a green solvent (water) under mild reaction conditions.
2.1.2. Review of literature:

1. D. Elhamifar approach:

D. Elhamifar and co-workers have developed iron porphyrin complex supported (ILOS@Fe/TSPP) over organosilica based alkyl-imidazolium ionic liquid. It was successfully used for the Hantzsch reaction to prepare a variety of polyhydroquinolines derivatives with considerable yields.\(^{23}\)

![Scheme 1](image1)

2. S. Yu approach:

S. Yu et al. have effectively employed quaternary ammonium salt, Choline chloride as a catalyst for the Hantzsch type reaction in ethanol at an elevated temperature for the synthesis of polyhydroquinoline derivatives.\(^{24}\)

![Scheme 2](image2)

3. L. Shiri approach:

They have developed the protocol for the synthesis of DHP using catalyst Sulfamic acid immobilized on amino-functionalized magnetic nanoparticles (MNPs/DETASA), which could be recycled employing magnetic field.\(^{25}\)

![Scheme 3](image3)
4. L. Shiri approach:
L. Shiri has developed the protocol for the synthesis of DHP derivatives by using silica supported Nickel nitrate/Ferric oxide complex as magnetically separable nickel catalyst. Catalysis could be applicable with water, and as well as solvent-free conditions; the developed synthetic protocol could be served as environmentally friendly, ideal and fascinating.  

![Scheme 4](image)

5. M. Kazemi approach:
Another heterogeneous magnetically separable nano solid catalyst has been developed by K. Kazemi and co-worker, using Cu(II) complex immobilized over Fe$_3$O$_4$ nanoparticles functionalized with diethylenetriamine (Fe$_3$O$_4$–DETA–Cu(II)). The developed protocol was successfully employed with the solvent-free condition for the synthesis of polyhydroquinoline derivatives.

![Scheme 5](image)

6. F. Shirini approach:
F. Shirini and co-worker, have developed the quaternary ammonium salt of DABCO (NS-C$_4$(DABCO-SO$_3$H)$_2$)·4Cl). It was efficiently used for the advancement of the one-pot synthesis of hexahydroquinolines via one-pot MCRs of aryl aldehydes, 1,3-cyclohexanedione derivatives, β-ketoesters and NH$_2$OAc under solvent-free conditions.
7. **S. Otokesh approach:**

S. Otokesh *et al.* has prepared nanoparticle Nano-gama-Fe$_2$O$_3$-SO$_3$H, and used as a catalyst in Hantzsch type reaction in a solvent-free condition at 60 °C for the synthesis of polyhydroquinoline derivatives.$^{29}$

8. **A. Yaghoubi approach:**

Yaghoubi and co-worker have prepared periodic mesoporous organosilica supported Propylsulfonic acid (PMO-ICSPrSO$_3$H), was successively used to catalyze the multicomponent synthesis of polyhydroquinoline derivatives from dimedone, different aldehydes, ethyl acetoacetate and ammonium acetate under mild reaction conditions in short times and good yields in EtOH.$^{30}$
9. B. Maleki approach:
Maleki et al. has used silica supported SbCl$_3$ as the heterogeneous catalyst for the multicomponent synthesis of DHP derivatives under the solvent-free condition at 120 °C.$^{31}$

![Scheme 9](image)

10. A. V. Dhanunjaya approach:
Dhanunjaya and co-worker have employed polymer supported sulfonic acid as an efficient and green approach has been developed for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation reaction directly from corresponding substituted aromatic and aliphatic aldehydes, β-keto compounds, active methylene compounds, and ammonium chloride.$^{32}$

![Scheme 10](image)
2.1.3. Present Work:

We have described an efficient system for the synthesis of 1,4-dihydropyridine scaffolds (Hantzsch reaction) by using cellulose/proline-catalyzed system in an aqueous medium. As the catalyst is heterogeneous, from the reaction medium it could be easily recovered and reused several times without significant loss in the catalytic activity. The desired product 1,4-dihydropyridine derivative was obtained in good to excellent yields. The process is environmentally friendly. Mechanistically, the presence of numerous free hydroxyl groups on cellulose surface could form a hydrogen bond with carbonyl substrates to accelerate the reactions in a short time.
2.1.4. General procedure:

General Synthetic procedure of DHP derivatives:

To the suspension of Dimedone (1 mmol) and ethyl acetoacetate (1 mmol) along with cellulose/proline catalyst (0.1gm/10 mol %) in 10mL of water were added at RT. The resulting reaction mass was stirred for 10 min, followed by addition of benzaldehyde (1 mmol) and ammonium acetate (1 mmol) and stirred further 1-2 h. The progress of the reaction was monitored by TLC. After completion, 10 mL ethyl acetate was added and filtrated through Whatman paper. The filtrate was extracted with ethyl acetate (10 ml X 2). Collective organic phase was dried over the anhy. Na$_2$SO$_4$. The solvent was removed under the reduced pressure. The crude product was purified using column chromatography, to obtained corresponding DHP derivatives. The products were confirmed by $^1$H NMR, $^{13}$C NMR, mass spectra.

2.1.5. Results and Discussion:

Initially, the carbonyls substrates benzaldehyde, dimedone, ethyl acetoacetate, and NH$_4$OAc mixture was reacted in the presence of 0.1g of cellulose in H$_2$O at rt. As our optimized reaction conditions was depicted in Table 1.

Figure 2 Proline analogs P1-P4 were used as co-catalyst with Cellulose

The reactions without any catalyst, on prolongation up to 12h and the desired product, was not obtained (entry 1). The same reaction performed with 0.1g cellulose, without any co-catalyst desired product DHP-5 in only 23% yield (entry 2). As literature precedence the desired product could be obtained at a higher temperature, so further when the reaction performed at elevated temperature (110 °C) the desired compound 5 was obtained in 52% yield (entry 3).
Further to optimize the yields and reaction conditions, these results encourage us to switch over the combination for cellulose/proline catalyst.\textsuperscript{17} Thus reaction was performed using 10 mol\% of proline based co-catalyst (P2) and interestingly afforded desire compound 1,4-DHP in excellent yield (92\%) but enatio-enrichment observed was very low optical rotation ([\alpha]_D^{20} -0.41). It was noteworthy that the improvement in the yield of 1,4-DHP in the presence of cellulose/proline combination system was may due to the hydroxyl groups of cellulose playing the main role in promoting the binding of hydroxy sites to various carbonyl functionality of substrates and facilitating proline to form enamine intermediates.

Table 1: Synthesis of Polyhydroquinoline (DHP) in the presence of Cellulose/proline System.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cellulose (g)</th>
<th>Co-catalyst (10 mol%)</th>
<th>Time (h)</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>ND\textsuperscript{c}</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>-</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>3\textsuperscript{d}</td>
<td>0.1</td>
<td>-</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>P1</td>
<td>1</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>P2</td>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>P3</td>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>P4</td>
<td>1</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>P2</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>0.3</td>
<td>P2</td>
<td>1.5</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>0.01</td>
<td>P2</td>
<td>4</td>
<td>72</td>
</tr>
<tr>
<td>11\textsuperscript{e}</td>
<td>0.1</td>
<td>P2</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>12\textsuperscript{f}</td>
<td>0.1</td>
<td>P2</td>
<td>1.5</td>
<td>77</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions were carried out in water (10 ml) at 1.0 mmol of dimedone, 1 equiv. of Arylaldehyde, 1 equiv. of ethyl acetoacetate, 1 equiv. of NH\textsubscript{4}OAc, cellulose, and co-catalyst. \textsuperscript{b}isolated yield. \textsuperscript{c}ND- not detected. \textsuperscript{d}the reaction was carried out at 110 °C. \textsuperscript{e}bacterial produced cellulose used. \textsuperscript{f}the reaction performed in absence of H\textsubscript{2}O.
Additionally, when we screened various other proline analogs such as \textbf{P1, P2, P3,} and \textbf{P4} (figure 2). Unfortunately, the obtained product was racemic, but the yield of the desired product was good to excellent, out of screened co-catalyst the \textbf{P2} was found to be the best among them, and with the combination of cellulose at \textit{rt} for 1h, afforded \textbf{DHP 5} in 62-92% yield (entry 4-7). Further, the catalyst (cellulose) loading was optimized by varying amount of cellulose (0.01 to 0.3 g), the best outcome, concerning yield and the time was when 0.1g cellulose was used with co-catalyst \textbf{P2}. (Entry 9-10, Table 1). The reaction was also carried out with bacteria produced cellulose, gave 63% yield after 1h at room temperature. In the absence of cellulose (entry 8) and neat (entry 12) conditions affect the formation of the desired product \textbf{5}, and also the reaction was significantly sluggish.

\begin{center}
\textbf{Table 2:} Synthesis of Polyhydroquinoline using Cellulose/proline catalyst in H$_2$O.$^a$
\end{center}
Unless otherwise indicated all reactions were carried under the same condition as entry 5 in Table 1.

After the best-optimized condition in hand, to analyze the generality of developed protocol, cellulose/proline catalyst system was screened with a variety of aryl aldehydes and 1,3-dicarbonyl compounds under one-pot conditions, the obtained results were summarized in table 2. It can be seen that both the aromatic aldehydes, containing electron-donating groups such as -OR, -OH and electron-withdrawing groups, such as Cl, Br, F, and NO$_2$ are reacted successfully, the corresponding polyhydroquinoline 5a-5q are obtained in good to excellent yields. When the reaction was performed using recycled cellulose/proline system for three times, afforded desire 5j in 82-92% yield without loss of catalytic activity (entry 10). The cellulose/proline P2 catalyst system could be used three times with the slight loss of catalytic activity after three cycles due to the leaching of co-catalyst P2 during the isolation of the product.

The advantage of the combination of cellulose/proline showed higher efficiency and recyclable system several times. Reaction with 1, 3-cyclohexanedione in the presence of cellulose promoted/proline catalyst afforded the corresponding products 5l-5q in high yield (entries 12-17).
2.1.6. Plausible Mechanism:

Figure 3: Possible mechanism of cellulose/proline-catalyzed DHP synthesis
2.1.7. Spectral Data:

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

![](image1)

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.42 (s, 1 H), 7.31 (d, $J = 7.6$ Hz, 2 H), 7.19 (t, $J = 7.4$ Hz, 2 H), 7.12 - 7.06 (m, 1 H), 5.05 (s, 1 H), 4.10 - 4.03 (m, 2 H), 2.30 (s, 3 H), 2.25 - 2.20 (m, 2 H), 2.19 - 2.08 (m, 2 H), 1.21 (t, $J = 7.1$ Hz, 3 H), 1.04 (s, 3 H), 0.92 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 196.2, 167.8, 149.9, 147.4, 144.3, 128.2, 128.0, 126.2, 111.8, 106.0, 59.9, 51.0, 40.8, 36.8, 32.8, 29.7, 27.2, 19.2, 14.4. HRMS-ESI (m/z): calcd for C$_{21}$H$_{25}$NO$_3$ [M + H]$^+$ 340.4330, found 340.4334.

**Ethyl-4-(3,4-dihydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(5a):**

![](image2)

$^1$H NMR (CD$_3$OD, 400 MHz): δ 6.68 (1H, s), 6.54 (2H, s), 4.84 (2H, s), 4.81 (1H, s), 4.06-4.00 (2H, m), 3.28 (1H, s), 2.42-2.24 (2H, dd), 2.31 (3H, s), 2.19-2.06 (2H, dd), 1.20-1.17 (3H, t), 1.04 (3H, s), 0.91 (3H, s); $^{13}$C NMR (CD$_3$OD, 100 MHz): δ 197.11, 168.20, 150.85, 144.09, 142.91, 139.29, 118.91, 114.87, 111.05, 105.53, 59.40, 50.00, 39.65, 35.49, 32.03, 28.17, 25.73, 17.12, 13.14. HRMS-ESI (m/z): calcd for C$_{21}$H$_{25}$NO$_5$ [M + H]$^+$ 371.4330, found 371.4331.
Ethyl-4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5b):  

\[
\text{Ethyl-4-(2-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5e):}
\]

1H NMR (CDCl₃, 400 MHz): δ 7.30-7.33 (2H, d), 7.18-7.16 (2H, d), 6.29 (1H, s), 5.00 (1H, s), 4.08-4.03 (2H, m), 2.37 (3H, s), 2.35-2.23 (2H, dd), 2.21-2.12 (2H, dd), 1.20-1.18 (3H, t), 1.07 (3H, s), 0.92 (3H, s); 13C NMR (CDCl₃, 100 MHz): δ 195.61, 167.44, 149.44, 143.73, 133.09, 129.68, 127.13, 126.34, 110.83, 110.27, 105.21, 59.29, 50.55, 40.89, 35.84, 32.48, 29.10, 27.10, 18.98, 14.17. HRMS-ESI (m/z): calcd for C₂₁H₂₄BrNO₃ [M + H]^+ 418.3310, found 418.3309.

Ethyl-4-(2-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5e):  

1H NMR (CDCl₃, 400 MHz): δ 7.30-7.33 (2H, d), 7.18-7.16 (2H, d), 6.29 (1H, s), 5.00 (1H, s), 4.08-4.03 (2H, m), 2.37 (3H, s), 2.35-2.23 (2H, dd), 2.21-2.12 (2H, dd), 1.20-1.18 (3H, t), 1.07 (3H, s), 0.92 (3H, s); 13C NMR (CDCl₃, 100 MHz): δ 195.61, 167.44, 149.44, 143.73, 133.09, 129.68, 127.13, 126.34, 110.83, 110.27, 105.21, 59.29, 50.55, 40.89, 35.84, 32.48, 29.10, 27.10, 18.98, 14.17. HRMS-ESI (m/z): calcd for C₂₁H₂₄ClNO₃ [M + H]^+ 373.8770, found 373.8767.
Ethyl 4-(3,5-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5g): \(^{17}\)

\[
\begin{align*}
\text{H NMR (CDCl}_3, 400 MHz): & \delta 6.55 (1H, s), 6.47 (2H, s), 6.23-6.22 (1H, t), 5.01 (1H, s), 4.10-4.05 (2H, m), 3.72 (6H, s), 2.34 (3H, s), 2.31-2.25 (2H, dd), 2.22-2.15 (2H, dd), 1.24-1.20 (3H, t), 1.05 (3H, s), 0.96 (3H, s); \\
\text{C NMR (CDCl}_3, 100 MHz): & \delta 195.54, 167.36, 160.26, 149.35, 143.35, 111.63, 106.36, 105.83, 97.78, 59.78, 55.11, 50.61, 40.92, 36.57, 32.62, 29.32, 27.18, 19.27, 14.28. \\
\text{HRMS-ESI (m/z): calcd for C}_{23}\text{H}_{29}\text{NO}_5 [ M + H]^+ 399.4870, found 399.4873.}
\end{align*}
\]

Ethyl-4-(2,4-dichlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8 hexahydroquinoline-3-carboxylate (5h): \(^{17}\)

\[
\begin{align*}
\text{H NMR (CDCl}_3, 400 MHz): & \delta 7.33-7.31 (1H, d), 7.24 (1H, s), 7.11-7.08 (1H, d), 6.53 (1H, s), 5.33 (1H, s), 4.07-3.99 (2H, m), 2.30 (3H, s), 2.29-2.21 (2H, dd), 2.18-2.09 (2H, dd), 1.19-1.16 (3H, t), 1.06 (3H, s), 0.94 (3H, s); \\
\text{C NMR (CDCl}_3, 100 MHz): & \delta 195.38, 167.18, 149.44, 142.38, 133.63, 132.83, 131.94, 129.13, 126.89, 111.07, 104.65, 60.09, 50.54, 40.90, 32.78, 29.10, 27.41, 19.23, 14.42. \\
\text{HRMS-ESI (m/z): calcd for C}_{21}\text{H}_{23}\text{Cl}_2\text{NO}_3 [ M + H]^+ 408.3190, found 408.3188.}
\end{align*}
\]
Ethyl-4-(2,5-difluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5i):  

![Chemical structure of 5i](image)

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.02 (1H, m), 6.84-6.74 (2H, m), 6.33 (1H, s), 5.19 (1H, s), 4.07-4.02 (2H, m), 2.38-2.26 (2H, dd), 2.34 (3H, s), 2.21-2.13 (2H, dd), 1.21-1.17 (3H, t), 1.08 (3H, s), 0.95 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 194.40, 166.90, 157.22, 157.07, 154.80, 150.45, 146.22, 136.80, 116.91-116.73, 114.64-114.31, 108.90, 102.43, 59.49, 50.51, 32.53-32.16, 29.45, 26.69, 18.66, 14.34.

HRMS-ESI (m/z): calcd for C$_{21}$H$_{23}$F$_2$NO$_3$[M + H]$^+$ 375.4158, found 375.4161.

Ethyl-4-(2-bromo-5-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5j):

![Chemical structure of 5j](image)

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.45 (s, 1 H), 7.38 (dd, $J = 5.5, 8.6$ Hz, 1 H), 7.07 (dd, $J = 2.7, 9.9$ Hz, 1 H), 6.73 - 6.64 (m, 1 H), 5.32 (s, 1 H), 4.07 (tdd, $J = 3.3, 6.9, 10.4$ Hz, 2 H), 2.31 - 2.26 (m, 1 H), 2.22 (s, 3 H), 2.19 (s, 1 H), 2.15 - 1.97 (m, 2 H), 1.17 (t, $J = 7.1$ Hz, 3 H), 1.03 (s, 3 H), 0.92 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 195.8, 167.4, 159.7, 149.7, 148.5, 144.3, 133.8, 118.5, 118.1, 117.5, 114.7, 105.3, 59.9, 50.8, 40.8, 38.2, 32.5, 27.3, 19.2, 14.4; HRMS-ESI (m/z): calcd for C$_{21}$H$_{23}$BrFNO$_3$[M + H]$^+$ 435.0845, found 435.0847.
Ethyl-4-(3-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5m): \(^{17}\)

\[
\text{1H NMR (CDCl}_3, \text{ 400 MHz)}: \delta 7.17-7.09 (2H, m), 6.99-6.95 (1H, d), 6.80-6.76 (2H, t), 6.28 (1H, s), 5.06 (1H, s), 4.09-4.04 (2H, m), 2.38 (3H, s), 2.33-2.26 (2H, d), 2.22-2.14 (2H, dd), 1.21-1.17 (3H, t), 1.07 (3H, s), 0.93 (3H, s); \text{13C NMR (CDCl}_3, \text{ 100 MHz)}: \delta 195.37, 167.19, 164.05, 161.57, 149.13, 143.51, 129.15, 114.77, 114.62, 112.92, 112.64, 111.64, 105.89, 59.94, 50.38, 40.87, 36.49, 32.89, 29.37, 26.86, 19.42, 14.26. \text{HRMS-ESI (m/z): calcd for C}_{21}\text{H}_{24}\text{FNO}_3 [\text{ M + H}]^+ 357.4254, \text{ found 357.4252.}
\]
2.1.8. Experimental spectra:

Ethyl-2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(5):

\[ \text{Ethyl} \ 2,7,7\text{-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(5):} \]

\[ ^1\text{H NMR, 400MHz, CDCl}_3 \]

Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(5):

\[ ^{13}\text{C NMR, 100MHz, CDCl}_3 \]
Ethyl 4-(2-bromo-5-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(5j):

\[ \text{Ethyl 4-(2-bromo-5-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(5j):} \]

\[ \text{\textsuperscript{1}H NMR, 400MHz, CDCl}_3 \]

\[ \text{Ethyl 4-(2-bromo-5-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(5j):} \]

\[ \text{\textsuperscript{12}C NMR, 100MHz, CDCl}_3 \]
2.1.9. Conclusion:

In conclusion, Hantzsch reaction for the synthesis of polyhydroquinoline derivatives was promoted by cellulose in aqueous conditions has been developed. The DHP yield was improved using Proline as co-catalyst in combination with cellulose for developing a simple, quick, efficient, and green method. Cellulose/Proline system was easily recovered and reused several times without significant loss of catalytic activity in an environmentally friendly process providing target compounds in good to excellent yields.
2.1.10. Bibliography:


