Chapter 7

Synthesis of 2-methyl-4-substituted tetrahydroquinoline derivatives via Imino Diels-Alder reaction using Copper dipyridine dichloride as a catalyst.
7.1 Introduction

One of the most challenging tasks in modern organic chemistry is the synthesis of natural products containing heterocyclic ring. Among numerous families of natural products, the chemistry of tetrahydroquinoline derivatives has long been an area of intense interest for organic chemists due to the presence of these scaffolds within the framework of numerous biologically active natural products and pharmaceutical agents.\(^1\) Tetrahydroquinolines with N-heterocycle moiety exhibit interesting properties\(^2,3\) that make them attractive for synthetic and pharmacological use, while the synthesis of 4-N-heterocycle-substituted 1,2,3,4-tetrahydroquinolines has been scarcely explored.\(^3\) The imino Diels-Alder reaction is a well-established route for the synthesis of 1,2,3,4-tetrahydroquinolines. Therefore their synthesis via newer and atom economical\(^4\) approaches have been the subject of current research.\(^5,6\) Since the pioneering work of Povarov,\(^7\) this reaction has been extensively studied with use of different Lewis acids, such as BF\(_3\)OEt\(_2\),\(^8\) GbCl\(_3\),\(^9\) InCl\(_3\),\(^10\) LiClO\(_4\),\(^11,12\) ZrCl\(_4\),\(^13\) BiCl\(_3\),\(^14\) SbCl\(_3\)\(^15\) and protic acids such as TFA,\(^16\) TsOH,\(^17\) (COOH)\(_2\).\(^18\) Although the imino Diels-Alder reaction promoted by Lewis acid is known, however, many of these methods suffer from some limitations such as more than stoichiometric amounts of the Lewis acid are required due to co-ordination of the Lewis acid to the imine nitrogen. Further most of these acids are moisture sensitive and get easily decomposed or deactivated in the presence of water and are thus difficult to handle. Moreover, these reactions having some drawbacks like drastic reaction conditions, prolonged reaction time, tedious workup procedures and co-occurrence of side reactions, low yields, and expensive reagents/catalysts. Some of the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Further disposal of these acids leads to environmental pollution. Therefore, the search continues for a better catalyst for the synthesis of tetrahydroquinolines in terms of operational simplicity, reusability of catalyst, low cost and greater selectivity.
7.2 Methods for the synthesis of tetrahydroquinoline derivatives

We present herein few reports of tetrahydroquinoline derivatives and of biological interest.

K. Ding et al. reported copper-catalyzed coupling reaction of amino acid and aryl halide, followed by intramolecular cyclization of $N$-aryl-1-hydroxyl-3-propylamines under the Swern’s condition as the key steps, (S)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoline was synthesized as an example of optically pure 2-functionalized 1,2,3,4-tetrahydroquinolines.

InCl$_3$ is found to be an efficient catalyst for the Intramolecular Imino Diels–Alder (IMIDA) reaction of aldimines derived from aromatic amines and $O$-allyl derivatives of salicylaldehydes to afford the corresponding tetrahydrochromano[4,3-b]quinolines in excellent yields under mild conditions in a short reaction times.

V. Getautis et al. reported a hole transporting materials containing the 1-phenyl-1,2,3,4-tetrahydroquinoline hydrazone moiety and investigated as potential new materials for electrophotography. These TMs exhibit high hole drift mobilities and good compatibility with PC, and they possess the chemically active epoxy group, which enables them to be used as potential starting materials in the synthesis of various TM materials for optoelectronic devices.
A one-pot reaction for the formation of tetrahydroquinolines based on the reaction of $N$-methyl-$N$-alkylanilines and vinyl ethers in the presence of t-butylhydroperoxide using CuCl$_2$ as the catalyst was developed by X. Yang.$^{22}$

W. Chen et al.,$^{23}$ reported simple and convenient procedure for the synthesis of 3-aryl-1,2,3,4-tetrahydroquinolines by reductive ring closure of 2-phenyl-3-(2-nitrophenyl)-propionitrile derivatives in high yields.

Y. Yamamoto,$^{24}$ developed a method for the synthesis of 2-substituted tetrahydroquinolines via the Pd(0)-catalyzed intramolecular hydroamination of anilino-alkynes. The application of this methodology was implemented for the synthesis of alkaloids such as ((±)-angustureine and ((±)-galipinine. The method reported herein will be applicable for the synthesis of natural products containing tetrahydroquinoline moiety.
V. Getautis,\textsuperscript{25} reported the synthesis of 1,1\textsuperscript{1}-diphenyl-1,2,3,4,1\textsuperscript{1},2\textsuperscript{1},3\textsuperscript{1},4\textsuperscript{1}-octahydro-6,6\textsuperscript{1}-biquinolinyl-3,3\textsuperscript{1}-diol was performed both by cyclization of \(N,N\textsuperscript{d}-d\text{(3-chloro-2-hydroxypropyl)}-N,N\textsuperscript{d}-diphenylbenzidine and oxidative dimerization of 3-hydroxy-1-phenyl-1,2,3,4-tetrahydroquinoline.

Jian-Mei Lu and Min Shi\textsuperscript{26} have developed an effective lewis acid catalyzed synthesis of pyrrolidine and 1,2,3,4-tetrahydro-quinoline derivatives by the reactions of arylvinylidene-cyclopropanes with ethyl (arylimino)acetates under mild conditions. The reaction is believed to proceed \textit{via} [3 + 2] cycloaddition or intramolecular Friedel-Crafts reaction pathways, depending on the electronic nature both of 2 and the \(R_1\) or \(R_2\) aromatic groups of arylvinylidenecyclopropanes.
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H. Yanai et al., reported a convenient synthetic method for 2-polyfluoroalkylated quinoline systems through the efficient generation of perfluoroalkylated imine from α-vinylanilines and perfluorinated hemiacetals or aldehyde hydrates was developed.

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{CF}_3 & \quad \text{CF}_3
\end{align*}
\]

G. Broginni et al., reported enantiopure 4-amino-3-hydroxymethyl-1,2,3,4-tetrahydroquinolines by using an intramolecular cycloaddition of chiral nitrones prepared from aldehydes and (R)-a-(hydroxymethyl)benzylhydroxyl amine. Reaction times of the nitrone cycloaddition were optimized by activation under MW-assisted conditions.

\[
\begin{align*}
\text{R} & \quad \text{R''} \\
\text{CHO} & \quad \text{CHO} \\
\text{CO}_2\text{Et} & \quad \text{Ph} \\
\text{MeSO}_4 & \quad \text{MeSO}_4
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{H, CH}_3, \text{OCH}_3 \\
\text{R''} & = \text{H, OCH}_3
\end{align*}
\]
N. Shindoh et al.,\textsuperscript{29} have found the Tf$_2$NH acts as an autotandem catalyst, which activates an inverse electron demand hetero-Diels–Alder reaction and successive oxidative aromatization, to give substituted quinolines from aldimines with allylsilanes. Notably, a multicomponent strategy is also available. In the course of this study, they made two new catalytic aspects of Tf$_2$NH. To the best of our knowledge, Tf$_2$NH is the first example of a catalyst for inverse electron demand hetero-Diels–Alder reactions of aryl aldimines with allylsilanes. Second, tetrahydroquinoline can be oxidized into quinoline by the assistance of imine as an oxidant in the presence of catalytic amounts of Tf$_2$NH.

Jie Zhou and Bai Ling Xu\textsuperscript{30} reported synthesis of 1,2,3,4-tetrahydroquinoline derivatives by one-pot aza Diels-Alder reaction of substituted aromatic amines, ethyl glyoxylate and benzyl vinylcarbamate or N-benzyloxycarbonyl 2-pyrroline in hexafluoroisopropanols.

Z. Xue et al.,\textsuperscript{31} found an viologen $N,N^\prime$-dicyanomethyl-4,4$^1$-bipyridinium.2PF$_6$, which induce an aza Diels–Alder reaction of $N$-arylimines with $N$-vinylpyrrolidinone or $N$-vinylcarbazole, producing tetrahydroquinoline derivatives with cis/trans selectivities in high yields.
W. Zhang et al.,\textsuperscript{32} reported TPT catalyzed convenient photochemical approach for 4-(carbazol-9-yl)-2-aryl-tetrahydroquinolines in high yields.

\[ \begin{align*}
X = H, Cl, CH_3, OCH_3 \\
y = H, Cl, NO_2, OCH_3
\end{align*} \]

V. P. Zaitsev et al.,\textsuperscript{33} reported synthesis of 2-Furyl-4-substituted and furo[2,3-c]-condensed 1,2,3,4-tetrahydro-1,10-phenanthrolines from 8-aminoquinolines using the Povarov reaction.

\[ \begin{align*}
X = N, CH \\
R = H, Cl, Br
\end{align*} \]

7.3 Present work

Prompted by these observations, in the present chapter Copper dipyridine dichloride\textsuperscript{34} (CuPy$_2$Cl$_2$) were used as an efficient lewis acid catalyst. It is water tolerant and reusable & can effectively promote some of the organic reactions.\textsuperscript{35-37} CuPy$_2$Cl$_2$ is easier to handle than metal halides such as ZrCl$_4$, BiCl$_3$, SbCl$_3$, and protic acids such as TFA or TsOH. In the quest for developing a less toxic, potential green catalyst, we thought of using CuPy$_2$Cl$_2$ as a catalyst to synthesize the 2-methyl-4-substituted tetrahydroquinoline derivatives.
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The schematic representation of tetrahydroquinoline derivatives were shown in Scheme-1, 2 & 3. The targeted compounds are synthesized by the reaction of \( p \)-substituted anilines with \( N \)-vinyl pyrrolidinone, \( N \)-vinyl carbazole and \( N \)-vinyl caprolactam in presence of CuPy\(_2\)Cl\(_2\) as a catalyst stirring in acetonitrile solvent at 40-50 \(^\circ\)C, for the appropriate time (Table 1). After completion of reaction as indicated by TLC, the reaction mixture was quenched with saturated aqueous NaHCO\(_3\) solution and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure.

Scheme -1:

Scheme -2:

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Where \( R \) =
(a) H  
(b) Cl  
(c) F  
(d) CH\(_3\)  
(e) OCH\(_3\)
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7.4 Materials and methods

The melting points of the products were determined by open capillaries on a Buchi apparatus and are uncorrected. The IR spectra were recorded on a Nicolet Impact-5700 FT-IR Spectrophotometer using KBr pellets. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance-300F 300 MHz spectrometer in CDCl$_3$ using TMS as an internal standard with $^{1}$H resonant frequency of 300 MHz and $^{13}$C resonant frequency of 75 MHz. D$_2$O exchange was applied to confirm the assignment of the signals of NH protons. The Mass spectra were recorded on a Shimadzu GC-2010. The elemental analysis was carried out by using HERAUS CHN rapid analyzer. The homogeneity of the compounds was described by TLC detected by UV light and iodine vapors. All chemical reagents were obtained from Fluka, sd fine and Merck chemical companies and were used without purification.

7.5 Experimental procedure

Synthesis of 2-methyl-4-substituted tetrahydroquinoline derivatives

A mixture of the $p$- substituted anilines (1) (5 mmol), N-vinylcarbazole (4) (12 mmol), N-vinylcaprolactam (6) (12 mmol) and CuPy$_2$Cl$_2$ (0.01 mmol) in acetonitrile (5mL) was stirred at 45-50 °C temperature for the appropriate time (Table 2). After completion of reaction as indicated by TLC, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ solution (20 mL) and extracted with ethyl acetate (2X15 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. After extraction, the water layer containing the catalyst could be evaporated under reduced pressure to give a catalyst back with blue colored solid. The recovered catalyst was washed with ether, dried at 85 °C for 2 h under high-pressure prior to use in the further reaction. The residue, thus obtained was purified by column chromatography using silica gel (60–120 mesh) and eluted with petroleum ether: ethyl acetate (8:2) to afford tetrahydroquinoline derivatives THQ(19-28).
7.6 Results and discussion

In view of the current trust in catalytic process, there is merit in developing a new catalytic method for the formation of 2-methyl-4-substituted tetrahydroquinolines. Now, we have found that an imino Diels-Alder reaction can be conveniently performed under neutral and mild conditions in the presence of catalytic amount of CuPy₂Cl₂. Because of the presence of two pyridine rings, the electron deficiency increases on the nitrogen so it efficiently acts as a Lewis acid.

Preliminary studies were carried out to study the effect of solvents and temperature on the model reaction of p-chloro-aniline (5 mmol) and N-vinylcarbazole (12 mmol) in the presence of 0.01 mmol of CuPy₂Cl₂, and the results are summarized (Table 2). Though the reaction proceeds at room temperature, the isolated yields are low and the reaction was sluggish. At 50 °C, the reaction proceeds smoothly and gave desired products in excellent yields by using acetonitrile as solvent.

When the reaction was performed in different solvents such as dichloromethane, methanol, ethanol, THF and toluene, the observed yield was low (Table 2). However, the acetonitrile was found to be the best for the catalytic reaction in terms of yield and reaction time. In a control experiment, it was observed that in the absence of the catalyst, the reaction did not proceed in room temperature and also at higher temperatures.

Thus, in presence of 0.01 mmol of CuPy₂Cl₂, p-chloro-aniline (1) was treated with N-vinylcarbazole in acetonitrile at 50 °C. After 2 h the 9-(6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-9H-carbazole was obtained in good yield (Scheme 1). These compounds were established by IR, ¹H NMR, ¹³C NMR and mass spectral analysis.

Similarly, p-substituted anilines reacted smoothly with N-vinylcarbazole and N-vinylcaprolactam (Scheme 1 & 2) to give corresponding tetrahydroquinolines THQ(19-28) in 80-95% yields (Table 1) in the presence of 0.01 mmol of CuPy₂Cl₂ in acetonitrile at 45-50 °C. In IR, the NH in all derivatives are observed around 3320-3360 cm⁻¹ and C=O at the region 1670.0 to 1678.3 cm⁻¹. In ¹H NMR
the NH peak was observed around 3-5 ppm and disappeared on D$_2$O addition and remaining all protons was observed in the expected regions.

Based on previous reports$^{38-40}$ and on the NMR data, all the substituted tetrahydroquinoline exist as the cis-diastereomers. Their structural elucidation was based on $^1$H NMR. The $J$ values of H$_2$ and H$_4$ was found to be 7.88 Hz and 6.80 Hz, respectively. The X-ray analysis of the compound(s) is under progress.

In conclusion, we are reporting the CuPy$_2$Cl$_2$ is an efficient and reusable catalyst for the synthesis of 2-methyl-4-substituted tetrahydroquinoline derivatives. The present protocol provides easy work-up procedure, non-toxic, cost efficiency providing reusability of the catalyst with excellent yields make this method a valid contribution to the exiting methodologies of tetrahydroquinolines.

All the newly synthesized compounds described in this chapter were screened for their in vitro anti-microbial, DNA Cleavage and in vivo pharmacological activities. Results are included in Chapter 9.

**Proposed Reaction Pathway**

From these results, we propose the following possible mechanism$^{41,42}$ to account for the reaction. In a first step, the reaction must proceed by $N$-vinyl tautomerization to the iminium species and nucleophilic substitution at vinyl carbon and favoring the intermolecular proton transformation leading to N-C bond formation. In second step, reaction of second equivalent of the vinyl substrate leading to the formation of Ar-C-C bond formation (Scheme -3).
Scheme -3:
9-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-9H-carbazole (THQ19)

Colorless crystalline solid: mp. 124-126°C (90%); (Recrystallization solvent = Chloroform); IR (KBr): ν (cm⁻¹): 3417(NH), 2923(CH of aromatic ring); ¹H NMR (300 MHz, CDCl₃, δ ppm): 1.30 (d, 3H, J = 6.2 Hz), 2.195 (dd, 2H, J = 11.7, 6.1, 2.0 Hz), 2.49 (m, 1H), 3.848(dd, 1H, J = 11.8, 6.2), 5.95(d, 1H, J = 8.5), 6.49(d, 1H, J = 8.4), 6.90(d, 1H, J = 8.6), 7.05-8.11(m, 8H); ¹³C NMR (100 MHz, CDCl₃, δ ppm): 22.05, 34.20, 47.62, 51.39, 107.95, 110.56, 112.33, 115.76, 119.10, 119.43, 120.47, 121.21, 123.36, 125.40, 125.82, 127.24, 128.43, 139.49; GC-MS: m/z = 313; Anal. Calcd for C₂₂H₂₀N₂: C, 84.58; H, 6.45; N, 8.97 %. Found: C, 84.10; H, 6.40; N, 8.93 %.

9-(6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-9H-carbazole (THQ20)

Colorless crystalline solid: mp: 128-130°C (91%); (Recrystallization solvent = Chloroform); IR (KBr): ν (cm⁻¹): 3417(NH), 2921(CH of aromatic ring); ¹H NMR (300 MHz, CDCl₃, δ ppm): 1.58 (d, 3H, J = 6.1 Hz), 1.95 (dd, 2H, J = 11.4, 6.0, 2.6 Hz), 3.45 (m, 1H), 5.5 (dd, 1H, J = 11.6, 6.0), 4.1 (s,1H, NH), 6.75 (s, 1H), 6.49 (d, 1H, J = 8.5), 6.97(d, 1H, J=8.6), 7.19-8.11(m, 8H) ppm. ¹³C NMR (75 MHz, CDCl₃, δ ppm): = 21.39, 37.0, 51.0, 55.1, 108.45, 110.90, 111.0, 112.1, 112.95, 115.1, 119.6, 119.83, 120.78, 121.7, 123.2, 126.05, 128.78, 129.55, 133.4, 141.75, 143.3, 145.66; GC-MS: m/z=346. Anal. Calcd for C₂₂H₁₉ClN₂ : C, 76.18; H, 5.52; N , 8.08 %; Found: C, 76.15; H, 5.48; N, 8.05 %.

9-(6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-9H-carbazole (THQ21)

Colorless crystalline solid: mp: 131-133°C (91%); (Recrystallization solvent = Chloroform); IR (KBr): ν (cm⁻¹): 3420(NH), 2921(CH of aromatic ring), 807(CF); ¹H NMR (300 MHz, CDCl₃, δ ppm): 1.49 (d, 3H, J = 6.5 Hz), 1.84 (dd, 2H, J = 11.2, 6.3, 2.8 Hz), 3.43 (m, 1H), 5.3 (dd, 1H, J = 11.4, 6.5), 4.5 (s,1H, NH), 6.71 (s, 1H), 6.46 (d, 1H, J = 8.9), 6.93(d, 1H, J=8.9), 7.14-8.16
(m, 8H); $^{13}$C NMR (75 MHz, CDCl$_3$, $\delta$ ppm): 22.61, 35.22, 48.12, 52.26, 108.64, 111.02, 112.76, 114.76, 118.61, 119.29, 119.68, 121.74, 123.29, 124.74, 125.89, 126.41, 127.18, 128.09, 128.76, 139.86, 141.72, 145.69; GC-MS: m/z=330. Anal. Calcd for C$_{22}$H$_{19}$FN$_2$: C, 79.97; H, 5.80; N, 8.48 %; Found: C, 79.94; H, 5.75; N, 8.45 %.

9-(2,6-dimethyl-1,2,3,4-tetrahydroquinolin-4-yl)-9H-carbazole (THQ22)

Colorless crystalline solid: mp: 124-126°C (92%); (Recrystallization solvent = Chloroform); IR (KBr): ν (cm$^{-1}$): 3426(NH), 2919(CH of aromatic ring); $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 1.42 (d, 3H, $J = 6.2$ Hz), 1.89 (dd, 2H, $J = 11.6$, 6.4, 2.6 Hz), 2.35(s, 3H), 3.21 (m, 1H), 4.95 (dd, 1H, $J = 11.1$, 6.0), 4.5 (s,1H, NH), 6.70 (s, 1H), 6.26 (d, 1H, $J = 8.5$), 6.66(d, 1H, $J=8.8$), 7.14-8.16 (m, 8H); $^{13}$C NMR (75 MHz, CDCl$_3$, $\delta$ ppm): 21.1, 21.3, 47.02, 51.0, 55.22, 108.64, 111.0, 111.02, 112.28, 112.76, 114.76, 115.1, 118.61, 119.6, 120.5, 121.74, 123.29, 125.89, 127.18, 128.09, 133.1, 140.3, 141.69; GC-MS: m/z=326; Anal. Calcd for C$_{23}$H$_{22}$N$_2$: C, 84.63; H, 6.79; N, 8.58 %; Found: C, 84.58; H, 6.75; N, 8.55 %.

9-(6-methoxy-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-9H-carbazole (THQ23)

Colorless crystalline solid: mp: 114-116°C (91%); (Recrystallization solvent = Chloroform). IR (KBr): ν (cm$^{-1}$): 3418(NH), 2922(CH of aromatic ring); $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 1.34 (d, 3H, $J = 6.3$ Hz), 1.89 (dd, 2H, $J = 11.5$, 6.6, 2.6 Hz), 3.65(s, 3H), 2.38 (m, 1H), 2.79(m, 1H), 4.95 (d, 1H, $J = 11.2$), 6.43 (s, 1H), 6.27 (d, 1H, $J = 8.6$), 6.42(d, 1H, $J=8.8$), 7.14-7.58 (m, 8H); $^{13}$C NMR (75 MHz, CDCl$_3$, $\delta$ ppm): 21.0, 47.0, 51.0, 55.9, 59.4, 111.6, 112.28, 113.1, 114.7, 118.9, 119.6, 120.5, 122.2, 124.4, 130.7, 137.9, 145.9; GC-MS: m/z=342; Anal. Calcd for C$_{23}$H$_{22}$N$_2$O : C, 80.67; H, 6.48; N, 8.18 %; Found: C, 80.65; H, 6.44; N, 8.12 %.
l-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one (THQ24)

Light yellow crystalline solid: mp: 118-120°C (92%); (Recrystallization solvent = Chloroform): IR (KBr): ν (cm⁻¹): 3368(NH), 2923(CH of aromatic ring), 1658(CO); ¹H NMR (400 MHz, CDCl₃, δ ppm): 1.23 (d, 3H, J = 6.3 Hz), 2.09(dd, 2H, J = 11.2, 6.3, 2.4 Hz), 2.79(m, 1H), 4.87 (dd, 1H, J = 11.5, 6.3), 1.29(t, 2H), 1.55(m, 2H), 1.57(m, 2H), 2.18(t, 2H), 3.2(t, 2H), 4.5 (s,1H, NH), 6.49-6.91 (m, 4H); ¹³C NMR (75 MHz, CDCl₃, δ ppm): 21.3, 25.7, 31.8, 32.0, 32.2, 44.5, 46.6, 47.3, 50.7, 112.1, 116.7, 123.2, 126.5, 129.1, 143.3, 172.3; GC-MS: m/z=258; Anal. Calcd for C₁₆H₂₂N₂O : C, 74.38; H, 8.58; N, 10.84 %; Found: C, 74.35; H, 8.50; N, 10.85 %.

l-(6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one (THQ25)

Light yellow crystalline solid: mp: 122-124°C (93%); (Recrystallization solvent = Chloroform). IR (KBr): ν (cm⁻¹): 3362(NH), 2924(CH of aromatic ring), 1654(CO); ¹H NMR (400 MHz, CDCl₃, δ ppm): 1.26 (d, 3H, J = 6.1 Hz), 2.08(dd, 2H, J = 11.1, 6.4, 2.8 Hz), 2.79(m, 1H), 4.87 (dd, 1H, J = 11.5, 6.3), 1.29(t, 2H), 1.55(m, 2H), 1.57(m, 2H), 2.18(t, 2H), 3.2(t, 2H), 4.5 (s,1H, NH), 6.49-6.91 (m, 4H); ¹³C NMR (75 MHz, CDCl₃, δ ppm): 21.5, 25.7, 31.8, 32.0, 32.2, 44.0, 46.6, 47.3, 50.7, 113.5, 122.0, 126.9, 129.5, 129.6, 141.4, 172.0; GC-MS: m/z=292; Anal. Calcd for C₁₆H₂₁ClN₂O: C, 65.63; H, 7.23; N, 9.57 %; Found: C, 65.59; H, 7.18; N, 9.52 %.

l-(6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one (THQ26)

Light yellow crystalline solid: mp: 128-130°C (90%); (Recrystallization solvent = Chloroform): IR (KBr): ν (cm⁻¹): 3366(NH), 2919(CH of aromatic ring), 1657(CO); ¹H NMR (300 MHz, CDCl₃, δ ppm): 1.23 (d, 3H, J = 6.6 Hz), 2.03(dd, 2H, J = 11.0, 6.6, 2.4 Hz), 2.79(m, 1H), 4.85 (dd, 1H, J = 11.0, 6.6), 1.27(t, 2H), 1.53(m, 2H), 1.58(m, 2H), 2.20(t, 2H), 3.5(t, 2H), 4.2 (s,1H, NH), 6.61(s, 1H), 6.36(d, 1H, J = 8.6 Hz), 6.57(d, 1H, J = 6.8 Hz); ¹³C NMR (75 MHz, CDCl₃, δ
ppm): 22.1, 25.6, 31.8, 32.6, 44.5, 44.6, 46.6, 47.3, 50.7, 113.5, 113.7, 116.1, 124.8, 138.9, 150.3, 172.9; GC-MS: m/z=276; Anal. Calcd for C_{16}H_{21}FN_{2}O: C, 69.54; H, 7.66; N, 10.14 %. Found: C, 69.51; H, 7.62; N, 10.10 %.

\[ \text{l-(2,6-dimethyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one (THQ27)} \]

\[ \text{Light yellow crystalline solid: mp: 125-127}^\circ \text{C (91%);} \]

(Recrystallization solvent = Chloroform). IR (KBr): υ (cm\(^{-1}\)): 3368(NH), 2920(CH of aromatic ring), 1651(CO); \(^1\text{H NMR (300 MHz, CDCl}_3, \delta \text{ ppm):} 1.28 \] (d, 3H, J = 6.0 Hz), 2.35(s, 2H, J = 11.1, 6.4, 2.8 Hz), 2.79(m, 1H), 4.87 (dd, 1H, J = 11.5, 6.3), 1.29(t, 2H), 1.55(m, 2H), 1.57(m, 2H), 2.18(t, 2H), 3.2(t, 2H), 4.5 (s,1H, NH), 6.49-6.91 (m, 4H); \(^13\text{C NMR (75 MHz, CDCl}_3, \delta \text{ ppm):} 21.5, 25.7, 31.8, 32.0, 32.2, 44.0, 46.6, 47.3, 50.7, 113.5, 122.0, 126.9, 129.5, 129.6, 141.4, 172.0; GC-MS: m/z=272; Anal. Calcd for C_{17}H_{24}N_{2}O: C, 74.96; H, 8.88; N, 10.28 %; Found: C, 74.90; H, 8.85; N, 10.23 %.

\[ \text{l-(6-methoxy-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one (THQ28)} \]

\[ \text{Light yellow crystalline solid: mp: 121-123}^\circ \text{C (93%);} \]

(Recrystallization solvent = Chloroform). IR (KBr): υ (cm\(^{-1}\)): 3365(NH), 2922(CH of aromatic ring), 1668(CO); \(^1\text{H NMR (300 MHz, CDCl}_3, \delta \text{ ppm):} 1.23 \] (d, 3H, J = 6.0 Hz), 2.36(s, 2H, J = 11.2, 6.6, 2.8 Hz), 2.79(m, 1H), 3.73(s, 3H), 4.84 (dd, 1H, J = 11.6, 6.3), 1.29(t, 2H), 1.55(m, 2H), 1.57(m, 2H), 2.18(t, 2H), 3.2(t, 2H), 4.5 (s,1H, NH), 6.31-6.75 (m, 4H); \(^13\text{C NMR (75 MHz, CDCl}_3, \delta \text{ ppm):} 20.9, 26.3, 31.2, 32.0, 34.9, 36.0, 45.3, 47.3, 50.7, 55.0, 112.3, 113.2, 114.3, 122.8, 137.9, 148.9, 175.4; GC-MS: m/z=288; Anal. Calcd for C_{17}H_{24}N_{2}O_{2}: C, 70.80; H, 8.39; N, 9.71 %. Found: C, 70.76; H, 8.36; N, 9.68 %.
### Table 1 CuPy$_2$Cl$_2$ catalyzed synthesis of 2-methyl-4-substituted tetrahydroquinoline

<table>
<thead>
<tr>
<th>Code</th>
<th>Substrate</th>
<th>N-Vinyl Compound</th>
<th>Product</th>
<th>Time (h)</th>
<th>m.p (°C)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THQ19</td>
<td></td>
<td></td>
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<td>2.0</td>
<td>124-126</td>
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<tr>
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<td>2.5</td>
<td>131-133</td>
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<tr>
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<tr>
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<tr>
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<td>118-120</td>
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<td>122-124</td>
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## Table 2: Effect of solvents in the synthesis of 2-methyl-4-substituted tetrahydroquinoline derivatives

<table>
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<th>p-chloro aniline (mmol)</th>
<th>N-vinyl carbazole (mmol)</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (b)</th>
</tr>
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<tbody>
<tr>
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<td>12</td>
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<td>CuPy₂Cl₂</td>
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<td>15</td>
<td>55</td>
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<tr>
<td>5</td>
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<td>CH₃CN</td>
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<td>10</td>
<td>60</td>
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<tr>
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<td>12</td>
<td>60</td>
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- 0.01 mmol CuPy₂Cl₂ catalyst loaded
- Isolated yields
Spectrum 1: IR Spectrum of compound THQ19
Spectrum 2: 1H NMR Spectrum of compound THQ19 in CDCl3
Spectrum 3: $^{13}C$ NMR Spectrum of compound THQ19 in CDCl$_3$
Spectrum 4: GC-MS Spectrum of compound THQ19
References


