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Graphical Abstract

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Iodine-Catalyzed Aerobic Oxidative Formal [4+2] Annulation for the Construction of Polyfunctionalized Pyridines

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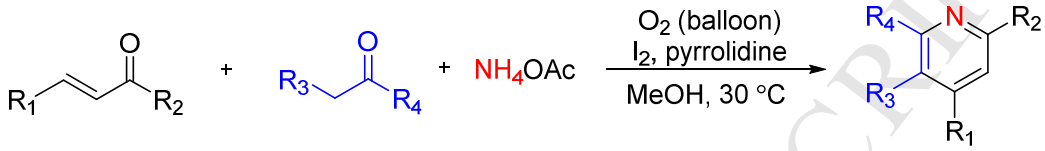

39 examples, up to 92% yield

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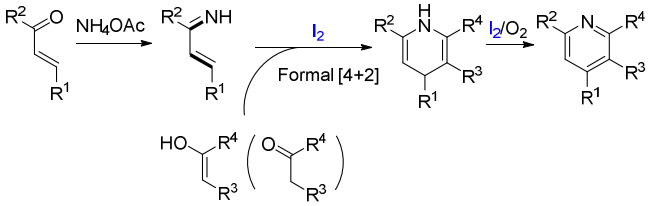
ABSTRACT

An iodine-catalyzed aerobic oxidative formal [4+2] annulation for the construction of polyfunctionalized pyridines in one step has been developed through the green reaction system of catalytic amounts of molecular iodine and amine in combination with oxygen. Various ketones and aldehydes were able to react with different chalcones and β, γ-unsaturated α-ketoesters through this reaction strategy. Synthetically, this iodine catalytic system could be scaled up with good efficiency.

1. Introduction

The direct construction of substituted pyridines has continued to capture the attention of the synthetic community due to their major applications in coordination chemistry[1], material sciences[2], super-molecular chemistry[3], catalysis[4], organo-catalysis[5], medicinal chemistry[6] and natural product synthesis[7]. Of all the investigations into the synthesis of pyridines[8], most of the efforts have been devoted to multicomponent reactions (MCRs) which usually involves the condensation of carbonyl compounds with ammonia under harsh conditions like high temperature and microwave irradiation[9]. Given the increasing demand for more environmentally acceptable processes, synthetic methods for polysubstituted pyridines employing mild and cheap conditions are still desirable.

Recently iodine-mediated organic transformations have undergone rapid advances[10], because iodine is inexpensive, low toxicity, and readily available. Moreover, iodine catalysis has evident advantages over acid catalysis and transition-metal catalysis, such as less health and safety problems; greater atom economy; and greener, milder reaction conditions. While understanding of the exact role of iodine species in those types of transformations has not been fully established, iodine can serve as both an alternative catalyst for Lewis acid, and a mediator for oxidation simultaneously, thus making it possible to promote an oxidative coupling/annulation. For example, Wang group has developed an iodine-catalyzed oxidative amination of N-alkylamides, ethers, and alcohols with orthocarbonyl-substituted anilines for the synthesis of quinazolines.[11] Wang and Ji *et al.* described an efficient I_2/TBPB mediated oxidative formal [4+1] cycloaddition of N-tosylhydrazones with anilines for the construction of 1,2,3-triazoles under metal-free and azide-free conditions.[12] Lei group reported an iodine-catalyzed oxidative annulation of β-keto esters or 2-pyridinyl-β-esters with alkenes providing a simple and selective way for the synthesis of dihydrofurans and indolizines in one step.[13] These emblematic examples have proved iodine-catalyzed oxidative annulation to be an effective approach for the synthesis of heterocycles, but the same strategy has rarely been applied in the synthesis of pyridines from simple starting materials.



Scheme 1. Proposed aerobic oxidative formal [4+2] annulation

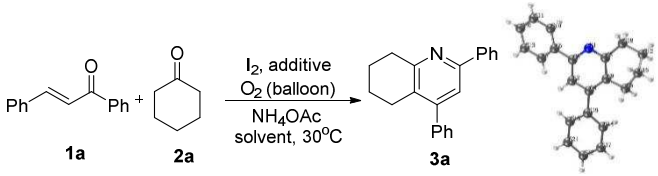
With continuous interest in the mild synthesis of heterocycles[14], we proposed an iodine -catalyzed aerobic oxidative formal [4+2] annulation of NH_4OAc, α, β-unsaturated carbonyls, and ketones/aldehydes to form polyfunctionalized pyridines. Iodine was expected to catalyze the formal [4+2] annulation of in situ generated 1-azadiene with a ketone/aldehyde, as well as the aromatization of dihydropyridines through aerobic oxidation to furnish the polyfunctionalized pyridines. (Scheme 1).

2. Results and discussion.

To test the idea, we commenced our study by the reaction of chalcone **1a**, cyclohexanone and ammonium acetate with 20

mol% I_2 under oxygen atmosphere (balloon). The reaction resulted in desired pyridine **3a** with 14% yield after stirring for 12 hours at 30 °C, and the pyridine structure was confirmed by single-crystal X-ray diffraction analysis (entry 1, table 1). We envisaged that the inferior yield could be caused by the poor activity of enol serving as the dienophile in the [4+2] annulation. Given that enamine was proven to be better dienophile in similar transformation[15], various amines were tested to enhance the enamine formation. As a result, significant improvement in yields were observed for most of the reactions with 20 mol% amines added (entries 2-6, table 1), and pyrrolidine was found to be the best among all amines examined (entry 6, table 1). Subsequently, the evaluation of solvents reveals that alcoholic solvents were superior to DCM, THF and MeCN, while DMSO and DMF were found to be ineffective.

Table 1. Optimization of Reaction Conditions[a]

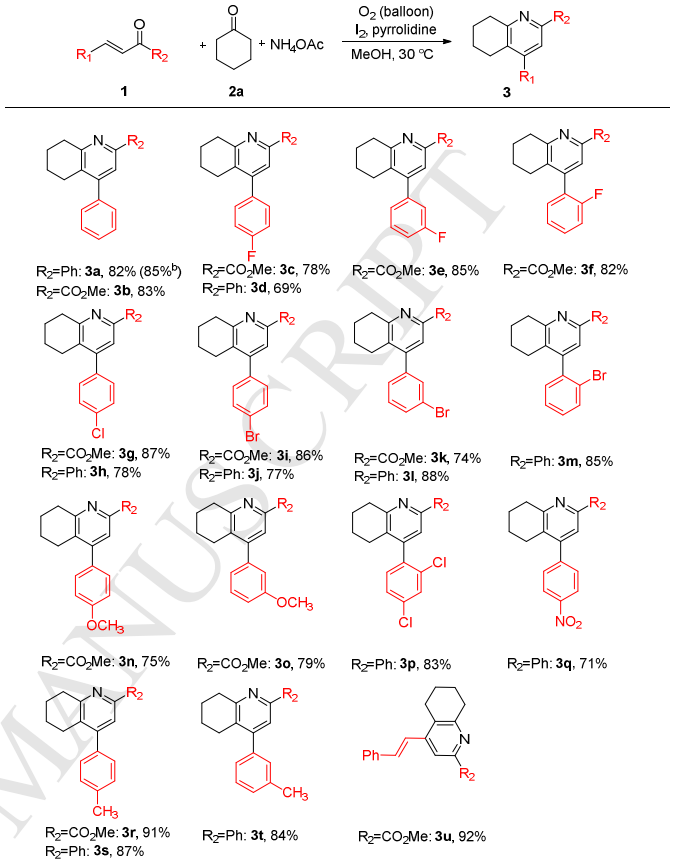


entry	solvent	additive	time (h)	yield[b] (%)
1	MeCN	none	12	14
2	MeCN	Me2NH•HCl	12	45
3	MeCN	L-proline	12	51
4	MeCN	piperidine	12	32
5	MeCN	morpholine	12	15
6	MeCN	pyrrolidine	12	59
7	DCM	pyrrolidine	12	22
8	THF	pyrrolidine	12	35
9	DMSO	pyrrolidine	12	trace
10	DMF	pyrrolidine	12	trace
11	EtOH	pyrrolidine	8	78
12	MeOH	pyrrolidine	8	82

[a]0.5 mmol of **1a**, 0.6 mmol of **2**, 0.6 mmol of NH_4OAc, 0.1 mmol of I_2, 0.1 mmol of additive, 1.5 mL of MeOH, 30 °C, O_2 ballon. [b]isolated yield.

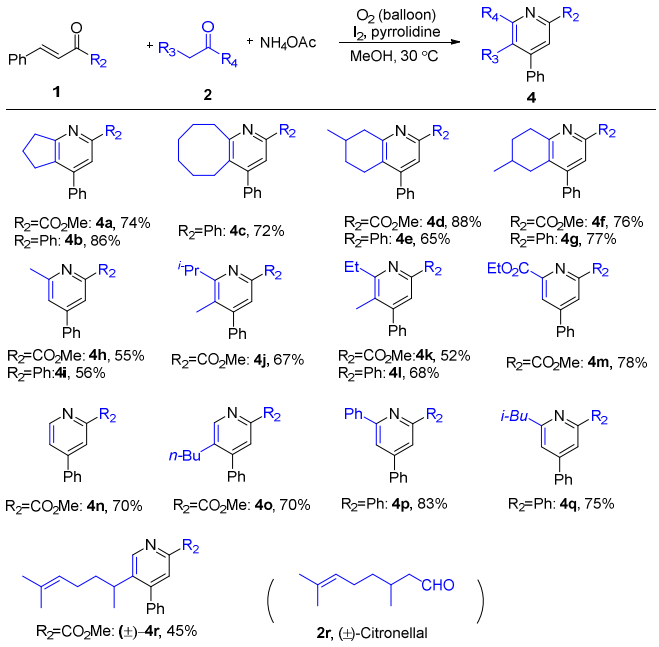
With the identification of optimized conditions for aerobic oxidative formal [4+2] annulation, the scope of α, β-unsaturated carbonyls was evaluated (Scheme 2). It was determined that most of the tested chalcones provided good to excellent yields. To our delight, diverse β, γ-unsaturated α-ketoesters were also found to be suitable for the transformation. The generality was investigated using 21 different enones to reflect differing electronic and steric factors. Substrates with both electron-donating and -withdrawing groups on the para-position of the benzene ring reacted smoothly in good to excellent yields, and strong electron-withdrawing group $–NO_2$ can be tolerated (**3q**). The substrates with a meta-substituent (**3e**, **3k**, **3l**, **3o** and **3t**) also worked very well leading to desired products in yield comparable to that of para-substitution. Notably, the reaction was found to be tolerant with steric hindrance, since ortho-substituted and 2,4-disubstituted substrates (**3f**, **3m**, **3p**) can be transformed to desired products in up to 85% yield. Moreover, substrates with ortho-, meta- and para-fluorine group on the aromatic ring could afford fluorine-contained pyridine derivatives in good yield, which should be of interest to medical chemistry (**3c**-**3f**). For other substituent, substrate **1u** containing a cinnamyl-group on the aromatic ring could also undergo the reaction and the corresponding product **3u** was furnished in a 92% yield. Notably the scalability and preparative utility of the developed methodology was exemplified by the fact that the desired product **3a** was obtained with even a slightly better yield when the reaction was scaled up to 20 mmol.

Scheme 2. Substrate scope of enones[a]



[a]0.5 mmol of **1**, 0.6 mmol of **2a**, 0.6 mmol of NH_4OAc, 0.1 mmol of I_2, 0.1 mmol of pyrrolidine, 1.5 mL of MeOH, 30 °C, O_2 ballon. [b]20 mmol of **1**.

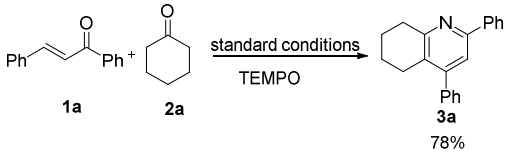
Scheme 3. Substrate scope of aldehydes/ketones[a]



[a]0.5 mmol of **1**, 0.6 mmol of **2**, 0.6 mmol of NH_4OAc, 0.1 mmol of I_2, 0.1 mmol of pyrrolidine, 1.5 mL of MeOH, 30 °C, O_2 ballon.

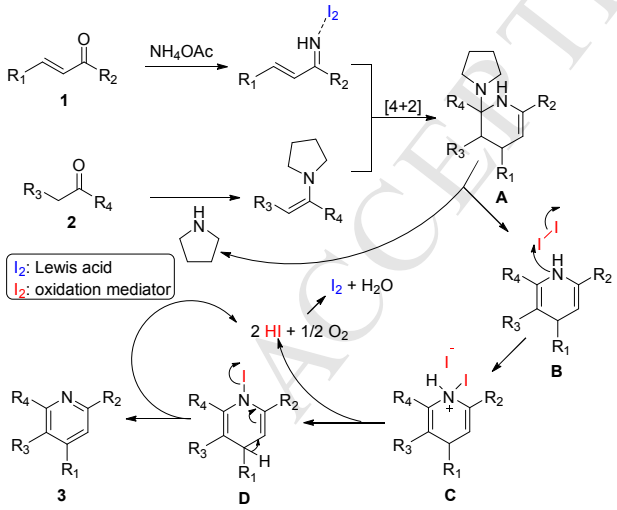
The scope of carbonyl compounds was explored for this reaction and a wide range of ketones were chosen to react with chalcones or β, γ-unsaturated α-ketoesters (Scheme 3). As a result, cyclic ketones of different ring-size (**4a**-**4c**), and various substituted cyclohexanones (**4d**-**4g**) were transformed into the corresponding pyridines in good yield (65–86%), while acyclic ketones can give 52-85% yield (**4h**-**4m**, **4p**, and **4q**). Notably, for the unsymmetrical ketones，reactions occurred exclusively to the α-carbons of less steric hindrance leading to exclusive regioselectivitiy (**4d, 4e, 4j** and **4q**). Moreover, the methodology was also applicable to aldehydes, including various simple aldehydes (**4n**-**4o**) and citronellal (**4r**), a naturally occurred aldehyde, which could also be converted to corresponding pyridine in moderate yield.

Scheme 4. Control experiment



To understand the role of iodine in this aerobic oxidative formal [4+2] annulation, we reacted chalcone **1a**, cyclohexanone and ammonium acetate under our standard reaction protocol with additional TEMPO (2.0 equiv.) as a radical scavenger. In this experiment, we observed the formation of **3a** in 78% yield and no TEMPO-bound intermediate was detected (scheme 4). Therefore, we think that a radical-based reaction mechanism can be excluded. A plausible mechanism was proposed in scheme 5. Initially, the reaction of ketone with amine gives an enamine which can undergo [4+2] annulation with chalcone in the presence of I_2. The resulting intermediate **A** generates intermediate **B** by removing one molecular amine. Subsequently intermediate **B** reacts with I_2 to form **C** which can give **D** by elimination of one molecular HI. Finally **3** is obtained through elimination of another molecular HI. Notably, two molecular HI generated in situ are oxidized by oxygen to regenerate iodine to complete the I_2/I^- catalytic cycle.

Scheme 5. A plausible mechanism



3. Conclusion.

We have developed an iodine-catalyzed aerobic oxidative formal [4+2] annulation for the construction of polyfunctionalized pyridines in one step. Catalytic amounts of molecular iodine and amine in combination with oxygen was proven to be an effective alternative reaction system for traditional harsh conditions in these transformations. Various ketones and aldehydes were able to react with different chalcones and β, γ-unsaturated α-ketoesters through this reaction strategy. Synthetically, this iodine catalytic system could be scaled up to 20 mmol with good efficiency.

4. Experimental section

4.1. General

Unless otherwise indicated, all commercial reagents and solvents were used without additional purification. Chemical shifts (in parts per million) of ^{1}H NMR spectra were referenced to tetramethylsilane (δ 0) in $CDCl_3$ as an internal standard. ^{13}C NMR spectra were calibrated with $CDCl_3$ (δ 77.00).

4.2 General procedures for pyridines

To a solution of α，β-unsaturated carbonyl (0.5 mmol) in 1.5 mL methanol was added ketone or aldehyde (0.6 mmol), iodine (0.1 mmol), pyrrolidine (0.1 mmol) and ammonium acetate (0.6 mmol). The reaction mixture was stirred at 30 ℃ under oxygen atmosphere (balloon). The reaction was monitored by thin layer chromatography (TLC). When the reaction was completed, it was diluted with water and extracted with ethyl acetate 3 times. Removal of solvent followed by column chromatography afforded desired products.

*4.2.1. 2,4-diphenyl-5,6,7,8-tetrahydroquinoline (**3a**).* 82% yield (215 mg), white solid, M.p. 107-108 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.96 (s, 1H), 7.33-7.47 (m, 9H), 3.09 (t, J = 6.4 Hz, 2H), 2.65 (t, J = 6.4 Hz, 2H), 1.91-1.97 (m, 2H), 1.72-1.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$)δ 157.5, 154.2, 150.1, 139.6, 128.5, 128.4, 128.3, 128.2, 127.6, 126.7, 118.9, 33.3, 27.2, 23.0, 22.9. MS (ESI, m/z) 286.3 (M + H^+), 308.3 (M + Na^+). IR (film) ν/cm^{-1} 3066(m), 2950(s), 1593(vs), 1387(vs), 1221(m), 773(vs). Anal. calcd for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.29; H, 6.60; N, 5.11.

*4.2.2. Methyl 4-phenyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3b**).* 76% yield (215 mg), white solid, M.p. 119-120 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.77 (s, 1H), 7.35-7.41 (m, 3H), 7.23-7.26 (m, 2H), 3.93 (s, 3H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 6.4 Hz, 2H), 1.84-1.90 (m, 2H), 1.64-1.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.3, 150.2, 144.6, 138.3, 134.1, 128.3, 127.9, 123.4, 52.6, 33.1, 27.6, 22.5, 22.4. MS (ESI, *m/z*) 268.3 (M + H^+), 290.3 (M + Na^+). IR (film) *ν*/cm^{-1} 2947(s), 1711(vs), 1583(m), 1454(m), 1248(vs), 1130(s), 702(s). Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.31; H, 6.34; N, 5.32.

*4.2.3. Methyl 4-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3c**).* 75% yield (270 mg),white solid, M.p. 103-104 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.75 (s, 1H), 7.22-7.24 (m, 2H), 7.08 (t, *J* = 8.0 Hz, 2H), 3.93 (s, 3H), 3.05 (t, *J* = 8.0 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 1.84-1.90 (m, 2H), 1.67-1.73 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 162.5 (d, *J* = 247.3 Hz), 158.6, 149.4, 144.8, 134.3(4) (d, *J* = 2.4 Hz), 134.2(8), 130.2 (d, *J* = 7.9 Hz), 123.5, 115.5 (d, *J* = 21.2 Hz), 52.8, 33.2, 27.8, 22.6, 22.5. MS (ESI, *m/z*) 286.3 (M + H^+), 308.3 (M + Na^+). IR (film) *ν*/cm^{-1} 2948(s), 1731(vs), 1609(m), 1508(s), 1254(vs), 1130(m), 846(s). Anal. calcd for $C_{17}H_{16}FNO_2$: C, 71.56; H, 5.65; N, 4.91. Found: C, 71.64; H, 5.43; N, 4.99.

*4.2.4. 4-(4-fluorophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (**3d**).* 69% yield (105 mg), yellow solid, M.p. 131-132 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.96-7.98 (m, 2H), 7.30-7.46 (m, 6H), 7.12-7.16 (m, 2H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 1.91-1.97 (m, 2H), 1.74-1.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 161.1, 156.0 (d, *J* = 340 Hz), 149.2, 139.6, 135.6 (d, *J* = 2.6 Hz), 130.2 (d, *J* = 8.1 Hz), 128.6, 128.5, 128.4, 126.8,

119.0, 115.3 (d, *J* = 21.5 Hz), 33.3, 27.2, 23.0(4), 22.9(9). MS (ESI, *m/z*) 304.3 (M + H^+), 326.3 (M + Na^+). IR (film) *v*/cm^{-1} 3040(m), 2965(s), 1605(s), 1515(vs), 1221(vs), 849(vs). Anal. calcd for $C_{21}H_{18}FN$: C, 83.14; H, 5.98; N, 4.62. Found: C, 83.05; H, 5.94; N, 4.69.

*4.2.5. Methyl 4-(3-fluorophenyl)-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3e**)*. 68% yield (164 mg), white solid, M.p. 76-77 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.83 (s, 1H), 7.42-7.47 (m,1H), 7.02-7.16（m，3H）, 4.01 (s, 3H), 3.13 (t, *J* = 6.4 Hz, 2H), 2.71 (t, *J* = 6.4 Hz, 2H), 1.94-1.97 (m, 2H), 1.77-1.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 162.5 (d, *J* = 245.2 Hz), 158.7, 149.1 (d, *J* = 2.6 Hz), 144.8, 140.5 (d, *J* = 6.8 Hz), 134.1, 130.1 (d, *J* = 8.1 Hz), 124.2 (d, *J* = 2.8 Hz), 123.3, 115.6 (d, *J* = 21.8 Hz), 115.1 (d, *J* = 20.7 Hz), 52.8, 33.2, 27.7, 22.6, 22.5. MS (ESI, *m/z*) 286.2 (M + H^+), 308.2 (M + Na^+). IR (film) *v*/cm^{-1} 2961(vs), 1723(vs), 1445(s), 1264(s), 1117(m), 788(s). Anal. calcd for $C_{17}H_{16}FNO_2$: C, 71.56; H, 5.65; N, 4.91. Found: C, 71.43; H, 5.57; N, 5.11.

*4.2.6. Methyl 4-(2-fluorophenyl)-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3f**)*. 66% yield (144 mg), white solid, M.p. 75-76 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.85 (s, 1H), 7.41-7.46 (m,1H), 7.16-7.26（m，3H）, 4.00 (s, 3H), 3.13 (t, *J* = 6.4 Hz, 2H), 2.56-2.70 (m, 2H) 1.92-1.96 (m, 2H), 1.70-1.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 158.9 (d, *J* = 246.0 Hz), 158.3, 144.7 (d, *J* = 14.5 Hz), 135.4, 130.5 (d, *J* = 2.8 Hz), 130.3 (d, *J* = 7.9 Hz), 125.8 (d, *J* = 15.8 Hz), 124.3 (d, *J* = 3.0 Hz), 123.9, 115.7 (d, *J* = 22.2 Hz), 52.7, 33.1, 26.8 (d, *J* = 2.9 Hz), 22.6, 22.2. MS (ESI, *m/z*) 286.2 (M + H^+), 308.2 (M + Na^+). IR (film) *v*/cm^{-1} 2934(vs), 1706(vs), 1584(m), 1264(s), 762(s), 615(w). Anal. calcd for $C_{17}H_{16}FNO_2$: C, 71.56; H, 5.65; N, 4.91. Found: C, 71.48; H, 5.33; N, 4.76.

*4.2.7. Methyl 4-(4-chlorophenyl)-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3g**)*. 85% yield (235 mg), white solid, M.p. 128-129 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.74 (s, 1H), 7.36-7.38 (m, 2H), 7.17-7.20 (m, 2H), 3.93 (s, 3H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 1.85-1.88 (m, 2H), 1.68-1.71 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.6, 149.1, 144.8, 136.8, 134.3, 134.1, 129.8, 128.7, 123.3, 52.8, 33.2, 27.7, 22.6, 22.5. MS (ESI, *m/z*) 302.2 (M + H^+), 324.2 (M + Na^+). IR (film) *v*/cm^{-1} 2931(s), 1716(vs), 1609(m), 1500(s), 1446(s), 1354(s), 1246(vs), 1124(s), 839(s). Anal. calcd for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64. Found: C, 67.87; H, 5.44; N, 4.85.

*4.2.8. 4-(4-chlorophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (**3h**)*. 78% yield (210 mg), yellow solid, M.p. 136-137 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.95-7.97 (m, 2H), 7.26-7.46 (m, 8H), 3.08 (t, *J* = 6.4 Hz, 2H), 2.62 (t, *J* = 6.4 Hz, 2H), 1.91-1.95 (m, 2H), 1.74-1.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.4, 149.0, 139.6, 138.1, 133.8, 129.9, 128.7, 128.6, 128.5, 128.3, 126.8, 118.9, 33.3, 27.2, 23.1, 23.0. MS (ESI, *m/z*) 320.3 (M + H^+), 342.3 (M + Na^+) . IR (film) *v*/cm^{-1} 2939(vs), 2835(m), 1581(s), 1363(m), 1105(vs), 823(s). Anal. calcd for $C_{21}H_{18}ClN$: C, 78.86; H, 5.67; N, 4.38. Found: C, 78.92; H, 5.63; N, 4.41.

*4.2.9. Methyl 4-(4-bromophenyl)-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3i**)*. Petroleum ether/ethyl acetate = 2:1, 69% yield (168 mg), white solid, M.p. 163-164 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.74 (s, 1H), 7.51-7.55 (m,2H), 7.11-7.14 (m,2H), 3.93 (s, 3H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 1.85-1.89 (m, 2H), 1.68-1.71 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.7, 149.2, 144.9, 137.3, 134.1, 131.7, 130.1, 123.3, 122.5, 52.8, 33.2, 27.7, 22.6, 22.5. MS (ESI, *m/z*) 346.2 (M + H^+), 368.2 (M + Na^+). IR (film) *v*/cm^{-1} 2955(m), 1709(vs), 1585(m), 1455(m), 1239(vs), 1130(s), 823(s). Anal. calcd for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05. Found: C, 59.12; H, 4.54; N, 4.23.

*4.2.10. 4-(4-bromophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (**3j**)*. 77% yield (198 mg), yellow solid, M.p. 138-139 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.96-7.98 (m, 2H), 7.21-7.61 (m, 8H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 1.91-1.97 (m, 2H), 1.75-1.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.4, 148.9, 139.5, 138.5, 131.5, 130.2, 128.6, 128.5, 128.2, 126.8, 122.0, 118.7, 33.3, 27.2, 23.0, 22.9. MS (ESI, *m/z*) 364.2 (M + H^+), 386.2 (M + Na^+). IR (film) *v*/cm^{-1} 2939(vs), 1605(vs), 1439(vs), 1081(s), 1017(s), 773(s). Anal. calcd for $C_{21}H_{18}BrN$: C, 69.24; H, 4.98; N, 3.85. Found: C, 69.26; H, 4.97; N, 3.88.

*4.2.11. Methyl 4-(3-bromophenyl)-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3k**)*. 72% yield (150 mg),white solid, M.p. 1086-107 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.73 (s, 1H), 7.47-7.50 (m,1H), 7.40 (t, *J* = 1.6 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.16-7.18 (m,1H), 3.93 (s, 3H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.62 (t, *J* = 6.4 Hz, 2H), 1.85-1.88 (m, 2H), 1.68-1.71 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 158.5, 148.6, 144.7, 140.3, 133.9, 131.2, 131.0, 129.9, 126.9, 123.1, 122.3, 52.7, 33.0, 27.5, 22.5, 22.3. MS (ESI, *m/z*) 346.1 (M + H^+), 368.1 (M + Na^+). IR (film) *v*/cm^{-1} 3055(m), 2948(s), 1731(vs), 1577(s), 1423(vs), 1355(s), 1231(vs), 1130(s), 1008(m), 793(s). Anal. calcd for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05. Found: C, 58.88; H, 4.73; N, 3.92.

*4.2.12. 4-(3-bromophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (**3l**)*. 88% yield (277 mg), yellow solid, M.p. 139-140 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.98-8.00 (m, 2H), 7.29-7.58 (m, 8H), 3.11 (t, *J* = 6.4 Hz, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 1.94-2.00 (m, 2H), 1.77-1.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.4, 148.6, 141.7, 139.4, 131.4, 130.7, 129.8, 128.6, 128.5, 128.1, 127.2, 126.8, 122.4, 118.7, 33.3, 27.1, 23.0, 22.9. MS (ESI, *m/z*) 346.2 (M + H^+), 368.2 (M + Na^+). IR (film) *v*/cm^{-1} 3066(w), 2951(s), 2834(w), 1593(s), 1451(vs), 1067(w). Anal. calcd for $C_{21}H_{18}BrN$: C, 69.24; H, 4.98; N, 3.85. Found: C, 69.27; H, 4.97; N, 3.89.

*4.2.13. 4-(2-bromophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (**3m**)*. 85% yield (257 mg), yellow solid, M.p. 87-88 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.97-7.99 (m, 2H), 7.66-7.68 (m, 1H), 7.19-7.45 (m, 7H), 3.06-3.11 (m, 2H), 2.36-2.56 (m, 2H), 1.90-1.98 (m, 2H), 1.74-1.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 154.1, 149.3, 140.4, 139.5, 132.7, 129.9, 129.3, 128.8, 128.5, 128.4, 127.3, 126.8, 122.4, 118.5, 33.3, 26.4, 23.0, 22.7. MS (ESI, *m/z*) 346.2 (M + H^+), 368.2 (M + Na^+). IR (film) *v*/cm^{-1} 3052(w), 2939(s), 2848(w), 1567(s), 1439(vs), 1017(s). Anal. calcd for $C_{21}H_{18}BrN$: C, 69.24; H, 4.98; N, 3.85. Found: C, 69.28; H, 4.99; N, 3.84.

*4.2.14. Methyl 4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3n**)*. 66% yield (336 mg),white solid, M.p. 99-100 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.76 (s, 1H), 7.17(5)-7.18(0) (m, 2H), 6.90-6.92 (m, 2H), 3.92 (s, 3H), 3.80 (s, 3H), 3.04 (t, *J* = 6.4 Hz, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 1.84-1.87 (m, 2H), 1.66-1.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 159.4, 158.3, 150.0, 144.6, 134.4, 130.6, 129.7, 123.7, 113.8, 55.2, 52.7, 33.2, 27.9, 22.7, 22.6. MS (ESI, *m/z*) 298.2 (M + H^+), 320.2 (M + Na^+). IR (film) *v*/cm^{-1} 2940(s), 1716(vs), 1615(s), 1508(vs), 1239(vs), 1130(s), 1031(s), 831(m). Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.68; H, 6.58; N, 4.67.

*4.2.15. Methyl 4-(3-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3o**)*. 75% yield (188 mg),white solid, M.p. 58-59 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.84 (s, 1H), 7.37 (t, *J* = 8.0 Hz, 1H),6.94-6.97 (m,1H), 6.86-6.89 (m,1H),6.82-6.83 (m,1H),3.99 (s, 3H), 3.85 (s, 3H), 3.11 (t, *J* = 6.4 Hz, 2H), 2.71 (t, *J* = 6.4 Hz, 2H), 1.92-1.94 (m, 2H), 1.74-1.77 (m, 2H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 166.2, 159.5, 158.5, 150.3, 144.7, 139.9, 134.3, 129.6, 123.5, 120.8, 114.2, 113.5, 55.3, 52.8, 33.3, 27.8, 22.7, 22.6. MS (ESI, *m/z*) 298.2 (M + H^+), 320.2 (M + Na^+). IR (film) *v*/cm^{-1} 3055(w), 2944(s), 1731(vs), 1584(s), 1255(s), 1038(s), 788(m). Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.92; H, 6.36; N, 4.87.

*4.2.16. 4-(2,4-dichlorophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (**3p**).* 83% yield (208 mg), yellow solid, M.p. 140-141 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.96-7.98 (m, 2H), 7.30-7.52 (m, 6H), 7.15-7.17 (m, 1H), 3.06-3.11 (m, 2H), 2.37-2.55 (m, 2H), 1.91-1.96 (m, 2H), 1.75-1.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.3, 146.7, 139.4, 137.0, 134.4, 133.4, 131.0, 129.5, 129.0, 128.6(1), 128.5(6), 127.2, 126.8, 118.6, 33.3, 26.4, 23.0, 22.7. MS (ESI, *m/z*) 354.2 (M + H^+), 376.2 (M + Na^+). IR (film) *v*/cm^{-1} 2939(s), 1605(s), 1541(m), 1491(vs), 1094(m), 837(vs). Anal. calcd for $C_{21}H_{17}Cl_2N$: C, 71.20; H, 4.84; N, 3.95. Found: C, 71.22; H, 4.86; N, 3.94.

*4.2.17. 4-(4-nitrophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (**3q**).* 71% yield (190 mg), yellow solid, M.p. 188-189 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.31-8.34 (m, 2H), 7.96-7.98 (m, 2H), 7.37-7.54 (m, 6H), 3.11 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 1.94-1.97 (m, 2H), 1.77-1.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 154.6, 147.9, 147.4, 146.4, 139.2, 129.6, 128.8, 128.7, 127.8, 126.8, 123.6, 118.3, 33.3, 27.2, 22.9(1), 22.8(5). MS (ESI, *m/z*) 331.2 (M + H^+), 353.2 (M + Na^+). IR (film) *v*/cm^{-1} 3066(s), 2950(s), 2835(s), 1529(vs), 1337(vs), 823(vs). Anal. calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.36; H, 5.48; N, 8.49.

*4.2.18. Methyl 4-(p-tolyl)-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3r**).* 66% yield (280 mg),white solid,M.p. 107-108 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.76 (s, 1H), 7.19-7.21 (m, 2H), 7.13-7.15 (m, 2H), 3.93 (s, 3H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.36 (s, 3H), 1.85-1.88 (m, 2H), 1.67-1.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 158.3, 150.4, 144.7, 137.9, 135.5, 134.3, 129.0, 128.3, 123.6, 52.7, 33.2, 27.8, 22.7, 22.6, 21.2. MS (ESI, *m/z*) 282.2 (M + H^+), 304.2 (M + Na^+). IR (film) *v*/cm^{-1} 2940(vs), 1709(vs), 1594(s), 1517(s), 1446(vs), 1246(vs), 1124(vs), 808(vs). Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.74; H, 6.76; N, 5.11.

*4.2.19. 2-phenyl-4-(p-tolyl)-5,6,7,8-tetrahydroquinoline (**3s**).* 87% yield (197 mg), yellow solid, M.p. 105-106 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.96-7.98 (m, 2H), 7.25-7.46 (m, 8H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 2.42 (s, 3H), 1.92-1.95 (m, 2H), 1.74-1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 154.2, 150.2, 139.8, 137.5, 136.7, 128.9, 128.6, 128.4(4), 128.4(1), 128.3, 126.8, 119.1, 33.3, 27.3, 23.1, 23.0, 21.2. MS (ESI, *m/z*) 300.2 (M + H^+), 322.2 (M + Na^+). IR (film) *v*/cm^{-1} 3052(w), 2965(s), 2860(m), 1581(vs), 1427(vs), 811(s). Anal. calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.28; H, 7.09; N, 4.65.

*4.2.20. 2-phenyl-4-(m-tolyl)-5,6,7,8-tetrahydroquinoline (**3t**).* 84% yield (154 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.96-7.98 (m, 2H), 7.32-7.46 (m, 5H), 7.13-7.22 (m, 3H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 2.42 (s, 3H), 1.91-1.95 (m, 2H), 1.74-1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 154.0, 150.2, 139.6, 139.5, 137.7, 129.0, 128.4, 128.2, 128.0, 126.6, 125.4, 118.8, 33.2, 27.1, 23.0, 22.9, 21.3. MS (ESI, *m/z*) 300.2 (M + H^+), 322.2 (M + Na^+). IR (film) *v*/cm^{-1} 3052(w), 1605(vs), 1375(s), 1055(w), 887(m), 747(vs). Anal. calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.27; H, 7.08; N, 4.66.

*4.2.21. (E)-Methyl 4-styryl-5,6,7,8-tetrahydroquinoline-2-carboxylate (**3u**).* 71% yield (217 mg), white solid, M.p. 123-124 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.11 (s, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.19-7.36 (m, 5H), 3.95 (s, 3H), 2.82-3.02 (m, 4H), 1.57-1.59 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 158.5, 144.7, 144.6, 136.3, 134.7, 133.3, 128.8, 128.7, 127.0, 122.7, 118.7, 52.8, 33.4, 26.2, 22.4(1), 22.3(6). MS (ESI, *m/z*) 294.3 (M + H^+), 316.3 (M + Na^+). IR (film) *v*/cm^{-1} 2940(s), 1709(vs), 1585(m), 1455(s), 1224(vs), 970(m), 761(m). Anal. calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.54; H, 6.45; N, 4.89.

4.2.22. Methyl 4-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine-2-carboxylate (***4a***). 86% yield (125 mg), white solid, M.p. 108-109 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.97 (s, 1H), 7.38-7.47 (m, 5H), 3.96 (s, 3H), 3.12 (t, *J* = 7.6 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.07-2.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.2, 146.4, 145.8, 138.8, 137.6, 128.6, 128.1, 122.8, 52.7, 34.5, 31.0, 23.5. MS (ESI, *m/z*) 254.2 (M + H^+), 276.2 (M + Na^+). IR (film) *v*/cm^{-1} 2948(s), 1731(vs), 1585(s), 1361(m), 1239(vs), 993(m), 769(s). Anal. calcd for $C_{16}H_{15}NO_2$: C, 75.87; H,5.97; N, 5.53. Found: C, 75.69; H, 6.11; N, 5.65.

*4.2.23. 2,4-diphenyl-6,7-dihydro-5H-cyclopenta[b]pyridine (**4b**).* 86% yield (313 mg), white solid， M.p. 145-146 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.98-8.00 (m, 2H), 7.39-7.55 (m, 9H), 3.17 (t, *J* = 7.6 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.12-2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 156.4, 145.8, 139.9, 139.0, 133.0, 128.5, 128.3, 128.1(3), 128.0(6), 126.9, 117.9, 34.7, 30.5, 23.4. MS (ESI, *m/z*) 272.2 (M + H^+), 294.2 (M + Na^+). IR (film) *v*/cm^{-1} 3052(w), 2938(vs), 1605(vs), 1375(vs), 1017(s), 695(vs). Anal. calcd for $C_{20}H_{17}N$: C, 88.52; H, 6.31; N, 5.16. Found: C, 88.55; H, 6.33; N, 5.15.

*4.2.24. 2,4-diphenyl-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine (**4c**).* 72% yield (167 mg), white solid, M.p. 141-142 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.99-8.01 (m, 2H), 7.30-7.46 (m, 9H), 3.13 (t, *J* = 6.0 Hz, 2H), 2.76 (t, *J* = 6.0 Hz, 2H), 1.88-1.91 (m, 2H), 1.46-1.51 (m, 4H), 1.36-1.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 153.9, 150.3, 140.6, 139.7, 131.7, 128.6, 128.5, 128.3, 128.1, 127.5, 126.8, 119.7, 35.6, 31.3, 30.9, 27.1, 26.6, 25.8. MS (ESI, *m/z*) 314.2 (M + H^+), 336.2 (M + Na^+). IR (film) *v*/cm^{-1} 3052(w), 2912(vs), 1605(s), 1427(s), 1169(m), 773(vs). Anal. calcd for $C_{23}H_{23}N$: C, 88.13; H, 7.40; N, 4.47. Found: C, 88.15; H, 7.44; N, 4.45.

*4.2.25. Methyl 7-methyl-4-phenyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (**4d**).* 72% yield (205 mg),yellow solid, M.p. 65-66 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.85 (s, 1H), 7.41-7.47 (m, 3H), 7.30-7.32 (m, 2H), 4.00 (s, 3H), 3.26 (q, *J* = 4.4 Hz, 1H), 2.65-2.76 (m, 2H), 1.86-2.05 (m, 2H), 1.27-1.33 (m, 2H), 1.12 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.2, 150.2, 144.8, 138.4, 133.6, 128.3, 128.2, 128.0, 123.5, 52.7, 41.7, 30.6, 28.9, 27.2, 21.5. MS (ESI, *m/z*) 282.2 (M + H^+), 304.2 (M + Na^+). IR (film) *v*/cm^{-1} 3446(m), 2944(vs), 2216(s), 1740(vs), 1445(m), 1134(m), 926(m). Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.01; H, 7.02; N, 4.87.

*4.2.26. 7-methyl-2,4-diphenyl-5,6,7,8-tetrahydroquinoline (**4e**).* 65% yield (198 mg), white solid， M.p. 102-103 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.97-7.99 (m, 2H), 7.33-7.48 (m, 9H), 3.19-3.24 (m, 1H), 2.66-2.71 (m, 2H), 1.85-2.05 (m, 2H), 1.26-1.39 (m, 2H), 1.13 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 154.3, 150.0, 139.8, 139.7, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 126.8, 119.0, 41.9, 31.2, 29.3, 26.9, 21.8. MS (ESI, *m/z*) 300.2 (M + H^+), 322.2 (M + Na^+). IR (film) *v*/cm^{-1} 3041(w), 2924(vs), 1567(vs), 1247(vs), 1067(vs), 823(vs). Anal. calcd for

$C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.28; H, 7.09; N, 4.66.

*4.2.27. Methyl 6-methyl-4-phenyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (**4f**)*. 74% yield (211 mg), yellow solid, M.p. 56-57 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.84 (s, 1H), 7.43-7.49 (m, 3H), 7.29-7.32 (m, 2H), 3.99 (s, 3H), 3.20-3.27 (m, 1H), 3.04-3.13 (m, 1H), 2.71-2.76 (m, 1H), 2.32-2.39 (m, 1H), 2.00-2.05 (m, 1H), 1.77-1.84 (m, 1H), 1.53-1.60(m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 158.2, 150.3, 144.7, 138.4, 133.8, 128.4(2), 128.4(0), 128.1, 123.6, 52.8, 36.1, 32.9, 30.9, 28.9, 21.5. MS (ESI, *m/z*) 282.2 (M + H^+), 304.2 (M + Na^+). IR (film) *v*/cm^{-1} 3420(w), 2961(s), 1723(vs), 1454(m), 1238(vs), 779(m), 692(m). Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.69; H, 7.08; N, 5.21.

*4.2.28. 6-methyl-2,4-diphenyl-5,6,7,8-tetrahydroquinoline (**4g**)*. 77% yield (213 mg), white solid, M.p. 109-110 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.96-7.99 (m, 2H), 7.33-7.49 (m, 9H), 3.04-3.22 (m, 2H), 2.66-2.71 (m, 1H), 2.28-2.35 (m, 1H), 1.79-2.03 (m, 2H), 1.51-1.61 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 154.1, 150.0, 139.5(3), 139.5(0), 128.4(1), 128.3(8), 128.3, 128.2, 127.7, 127.5, 126.7, 118.9, 35.5, 33.0, 31.2, 29.1, 21.6. MS (ESI, *m/z*) 300.2 (M + H^+), 322.2 (M + Na^+). IR (film) *v*/cm^{-1} 2938(vs), 1721(s), 1555(vs), 1427(vs), 1081(m), 773(vs). Anal. calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.27; H, 7.08; N, 4.66.

*4.2.29. Methyl 6-methyl-4-phenylpicolinate (**4h**)*. 84% yield (169 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.15 (d, *J* = 1.2 Hz, 1H), 7.61-7.63 (m, 2H), 7.50 (d, *J* = 1.2 Hz, 1H), 7.40-7.46 (m, 3H), 3.97 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 159.4, 149.7, 148.0, 137.3, 129.3, 129.1, 127.0, 124.4, 120.6, 52.9, 24.7. MS (ESI, *m/z*) 228.1 (M + H^+), 250.1 (M + Na^+). IR (film) *v*/cm^{-1} 2940(vs), 1724(vs), 1438(s), 1085(s), 1015(m), 769(vs), 692(s). calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.25; H, 5.47; N, 6.43.

*4.2.30. 2-methyl-4,6-diphenylpyridine (**4i**)*. 56% yield (112 mg), white solid, M.p. 72-73 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.02-8.04 (m, 2H), 7.67-7.69 (m, 3H), 7.41-7.52 (m, 6H), 7.32-7.33 (m, 1H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 157.6, 149.4, 139.8, 138.7, 128.9, 128.8, 128.7, 128.6, 127.1, 127.0(5), 126.9(9), 119.7, 116.0, 24.8. MS (ESI, *m/z*) 246.1 (M + H^+), 268.1 (M + Na^+). IR (film) *v*/cm^{-1} 3040(m), 1593(vs), 1387(s), 1209(w), 1041(m), 759(vs). Anal. calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71. Found: C, 88.15; H, 6.17; N, 5.68.

*4.2.31. Methyl 6-isopropyl-5-methyl-4-phenylpicolinate (**4j**)*. 85% yield (313 mg), yellow solid,M.p. 44-45 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.22 (d, *J* = 1.6 Hz, 1H), 7.69-7.71 (m, 2H), 7.47-7.54 (m, 3H), 4.03 (s, 3H), 2.17-2.25 (m, 1H), 1.58 (s, 3H), 0.97 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 162.7, 149.4, 148.3, 137.6, 129.3, 129.2, 127.1, 124.5, 120.8, 53.0, 47.5, 29.2, 22.4. MS (ESI, *m/z*) 270.2 (M + H^+). IR (film) *v*/cm^{-1} 2963(vs), 1716(vs), 1594(s), 1446(s), 1254(s), 769(m), 684(m). Anal. calcd for $C_{17}H_{19}NO_2$: C, 75.81; H,7.11; N, 5.20. Found: C, 75.77; H, 6.86; N, 5.33.

*4.2.32. Methyl 6-ethyl-5-methyl-4-phenylpicolinate (**4k**)*. 65% yield (305 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.88 (s, 1H), 7.43-7.49 (m, 3H), 7.31-7.33 (m, 2H), 4.00 (s, 3H), 3.02 (q, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 1.36 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.0, 150.7, 144.5, 139.1, 132.4, 128.6, 128.4, 128.0, 124.0, 52.7, 29.5, 16.0, 13.1. MS (ESI, *m/z*) 256.2 (M + H^+), 278.2 (M + Na^+). IR (film) *v*/cm^{-1} 2963(vs), 2239(w), 1747(vs), 1594(m), 1231(m), 778(s). Anal. calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.10; H, 6.63; N, 5.61.

*4.2.33. 2-ethyl-3-methyl-4,6-diphenylpyridine (**4l**)*. 68% yield (145 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.02-8.04 (m, 2H), 7.31-7.45 (m, 9H), 2.95 (q, *J* = 7.6 Hz, 2H), 2.22 (s, 3H), 1.41 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 153.4, 150.3, 140.4, 139.7, 128.7, 128.5, 128.4, 128.3, 128.2, 127.9, 127.5, 126.6, 126.5, 118.9, 29.2, 15.3, 12.8.MS (ESI, *m/z*) 274.2 (M + H^+), 296.2 (M + Na^+). IR (film) *v*/cm^{-1} 2976(vs), 1939(m), 1683(vs), 1427(vs), 1209(s), 875(s). Anal. calcd for $C_{20}H_{19}N$: C, 87.87; H, 7.01; N, 5.12. Found: C, 87.82; H, 6.96; N, 5.14.

*4.2.34. 2-ethyl 6-methyl 4-phenylpyridine-2,6-dicarboxylate (**4m**)*. 74% yield (184 mg), white solid, M.p. 42-43 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.48-8.50 (m, 2H), 7.70-7.73 (m, 2H), 7.46-7.50 (m, 3H), 4.48 (q, *J* = 6.8 Hz, 2H), 4.01 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 164.8, 151.1, 149.2, 148.9, 136.2, 130.1, 129.4, 127.2, 125.6(4), 125.5(7), 62.5, 53.2, 14.3. MS (ESI, *m/z*) 286.1 (M + H^+). IR (film) *v*/cm^{-1} 2987(s), 2239 (m), 1716(vs), 1438(s), 1245(s), 1032(s), 908(s). Anal. calcd for $C_{16}H_{15}NO_4$: C, 67.36; H,5.30; N, 4.91. Found: C, 67.49; H, 5.54; N, 5.12.

*4.2.35. Methyl 4-phenylpicolinate (**4n**)*. 62% yield (347 mg), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.80-8.81 (m, 1H), 8.41 (d, *J* = 1.6 Hz, 1H) 7.50-7.73 (m, 6H), 4.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 150.1, 149.5, 148.3, 136.9, 129.5, 129.1, 126.9, 124.5, 122.9, 52.8. MS (ESI, *m/z*) 214.1 (M + H^+), 236.1 (M + Na^+). IR (film) *v*/cm^{-1} 3064(w), 3032(w), 2948(m), 2239(w), 1739(vs), 1608(s), 1438(s), 1316(s), 961(m), 754(s). Anal. calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.10; H, 5.45; N, 6.30.

*4.2.36. Methyl 5-butyl-4-phenylpicolinate (**4o**)*. 81% yield (317 mg), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.65 (s, 1H), 8.01 (s, 1H), 7.45-7.50 (m, 3H), 7.30-7.34 (m, 2H),4.02 (s, 3H), 2.71 (t, *J* = 8.0 Hz, 2H), 1.43-1.49 (m, 2H), 1.22-1.29 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 150.7, 149.8, 145.0, 139.3, 137.9, 128.2, 128.1, 127.9, 125.6, 52.3, 32.6, 29.7, 21.9, 13.3. MS (ESI, *m/z*) 270.2 (M + H^+), 292.2 (M + Na^+). IR (film) *v*/cm^{-1} 2961(vs), 1731(vs), 1454(m), 1108(m), 969(w), 701(w). Anal. calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.70; H, 6.86; N, 5.44.

*4.2.37. 2,4,6-triphenylpyridine (**4p**)*. 83% yield (171 mg), yellow solid, M.p. 138-139 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.20-8.22 (m, 4H), 7.90 (s, 2H), 7.75-7.77 (m, 2H), 7.43-7.56 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.2, 139.6, 139.1, 129.1, 129.0(1), 128.9(5), 128.7, 127.2, 127.1, 117.1. MS (ESI, *m/z*) 308.2 (M + H^+), 330.2 (M + Na^+). IR (film) *v*/cm^{-1} 3052(m), 1605(vs), 1401(s), 1055(m), 849(m), 683(vs). Anal. calcd for $C_{23}H_{17}N$: C, 89.87; H, 5.57; N, 4.56. Found: C, 89.89; H, 5.58; N, 4.55.

*4.2.38. 2-isobutyl-4,6-diphenylpyridine (**4q**)*. 77% yield (155 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.04-8.06 (m, 2H), 7.68-7.74 (m, 3H), 7.40-7.51 (m, 6H), 7.24-7.27 (m, 1H), 2.80 (d, *J* = 7.2 Hz, 2H), 2.24-2.33(m, 1H), 1.01 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 157.5, 149.2, 140.0, 139.0, 129.0, 128.8, 128.6(9), 128.6(5), 127.1, 120.0, 116.1, 47.8, 29.1, 22.6.MS (ESI, *m/z*) 288.3 (M + H^+), 310.3 (M + Na^+). IR (film) *v*/cm^{-1} 3028(vs), 1965(m), 1709(m), 1541(vs), 1093(vs), 875(vs). Anal. calcd for $C_{21}H_{21}N$: C, 87.76; H, 7.36; N, 4.87. Found: C, 87.79; H, 7.38; N, 4.86.

*4.2.39. Methyl 5-(6-methylhept-5-en-2-yl)-4-phenylpicolinate (**4r**)*. 92% yield (453 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.74 (s, 1H), 7.99 (s, 1H), 7.45-7.51 (m, 3H), 7.28-7.30 (m, 2H), 4.88 (t, *J* = 6.8 Hz, 1H), 4.03 (s, 3H), 3.02 (q, *J* = 7.2 Hz, 1H), 1.77-1.83 (m, 2H), 1.63-1.74 (m, 2H), 1.60 (s, 3H), 1.46

(s, 3H), 1.27 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 149.8, 148.6, 144.6, 144.1, 137.9, 131.7, 128.3, 128.2, 127.9, 125.7, 123.3, 52.4, 37.5, 32.5, 25.6, 25.3, 21.7, 17.3. MS (ESI, *m/*z) 324.3 (M + H^+), 346.3 (M + Na^+). IR (film) v/cm^{-1} 2935(vs), 2233(m), 1740(vs), 1573(m), 1428(s), 1307(w), 1247(w), 1125(m), 909(w), 709(m). Anal. calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.16; H, 7.87; N, 4.19.

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Supplementary data

Copies of ^{1}H and/or ^{13}C spectra for isolated products. Supplementary data associated with this article can be found online.

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