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Organocatalysed three-component domino synthesis of 1,4-dihydropyridines under solvent free conditions

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Abstract

An organocatalysed protocol for one-pot synthesis of 1,4-dihydropyridines via three-component coupling of cinnamaldehyde, aniline and β-keto esters under solvent free conditions at ambient temperature is reported. The reaction is generally very fast and the products are obtained in high yield. The catalytic activity of small organic molecules like amino acids (acidic, basic and neutral), ephedrine and cinchona alkaloids was studied.

Keywords: Organocatalyst; Multi-component; 1,4-Dihydropyridines; Domino synthesis; Solvent free

1. Introduction

The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and one of key paradigms of modern drug discovery. One approach to address this challenge involves the use of multi-component reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting material. Due to intrinsic atom economy, selectivity underlying such reaction, simpler procedure, equipment, time and energy saving as well as environmental friendliness MCRs are gaining much importance in both academia and industry.[1–4]

1,4-Dihydropyridines (1,4-DHPs) and their derivatives are important class of bioactive molecules in the field of drug and pharmaceuticals. These compounds are well known as calcium channel modulators and have emerged as one of the most important classes of drugs for the treatment of hypertension.[5] Various clinically used cardiovascular agents[6,7] such as nifedipine, nicardipine, amlodipine and other related derivatives are dihydropyridyl compounds effective in the treatment of hypertension. 1,4-Dihydropyridine derivatives possess a variety of biological activities such as HIV protease inhibition,[8,9] MDR reversal,[10–12] radioprotection,[13] vasodilator,[14] antitumour, bronchodilator and hepatoprotective activity.[15] These examples clearly indicate the remarkable potential of novel dihydropyridine derivatives as a source of valuable drug candidate.

Due to the potential importance of 1,4-dihydropyridyl compounds from a pharmaceutical, industrial and synthetic point of view, various methods for their preparation has been reported.[16–26] Hantzsch reaction is very useful in dihydropyridine synthesis but *N*-substituted, 5-unsubstituted or 5,6-unsubstituted dihydropyridines cannot be synthesised by Hantzsch reaction protocol. Ishar et al. have synthesised some *N*-aryl-5,6-unsubstituted-1,4-dihydropyridines via a regioselective [4+2] cycloaddition of 1-aryl-4-phenyl-1-azadienes with allenic esters.[27] Recently, Menéndez et al. synthesised 5,6-unsubstituted dihydropyridines[28] but even using inert/anhydrous conditions the products were isolated in moderate yields (61–74%). Similar multi-component reactions for the synthesis of substituted piperidines, dihydropyridones and tetrahydropyrans were also recently reported.[29,30]

Nowadays there is an increasing awareness of urgent necessity to limit, as far as possible, any source of pollution. Facing

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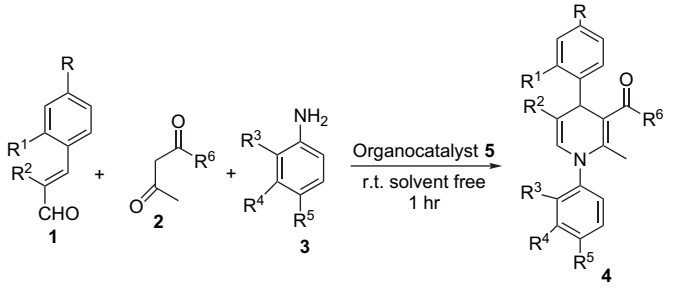
up to these facts, chemists have to dedicate numerous efforts to the development of clean technologies. This new challenge has led to a growing interest in the displacement of organic reaction in aqueous media[31–33] and solvent free conditions.[34–40]

The catalytic property of small organic molecules like cinchona alkaloids and amino acids is well known (aldol,[41,42] Mannich,[43,44] Michael,[45,46] Diels–Alder,[47,48] α-amination reactions and Knoevenagel type reactions[49,50]). Small organic molecules have been shown as quite promising and highly efficient organocatalysts for multi-component reactions.[51–54] Recently, we reported an organocatalysed multi-component reaction of an aldehyde, acetoacetate ester, cyclic 1,3-diketone and ammonium acetate to form polyhydroquinoline derivatives.[55] Thus, we decided to use the organocatalysts for the multi-component reaction of acetoacetate ester, cinnamaldehyde and anilines to yield *N*-aryl 5-unsubstituted or 5,6-unsubstituted 1,4-dihydropyridines (Scheme 1).



Scheme 1. Organocatalysed synthesis of 1,4-dihydropyridines.

2. Results and discussion

Initially, we tried this reaction with simple secondary amines as catalyst but the reaction gave a complex mixture and the desired product was isolated in low yield. Then we screened a number of organocatalysts **5a–5h** for efficient coupling of anilines, β-keto esters and cinnamaldehydes. Amino acids have the advantage of having both the amine (which could catalyse the reaction via nucleophilic enamine formation) and carboxylic acid (which could catalyse the reaction via protonation of substrate) functional groups. So we screened acidic, basic and neutral amino acids to optimise the reaction conditions. We also studied the catalytic activity of ephedrine and cinchona alkaloids over the reaction. The reaction of aniline, cinnamaldehyde and ethyl acetoacetate was taken as model to optimise the reaction conditions and catalyst.

In our initial experiments, aniline (1 mmol), cinnamaldehyde (1 mmol), and L-proline (10 mol %) were stirred for 20 min at room temperature under solvent free conditions. Then ethyl acetoacetate (1 mmol) was added to it and further stirred for 1 h. In the other experiment aniline, cinnamaldehyde, ethyl acetoacetate and L-proline were all added together and the mixture was stirred for 1 h. In both cases **4a** was isolated in same yield (90%). Thus it was concluded that simultaneous addition of three components was equally well as stepwise addition. We further tested the catalytic activity of other amino acids and alkaloids.

Table 1
Screening of organocatalysts for coupling of aniline, cinnamaldehyde and ethyl acetoacetate[a]

Entry	Organocatalyst		Catalyst (mol %)	Reaction time (h)	Yield[b] (%)
1	(−)-Cinchonidine	**5a**	10	2	45
2	(−)-Ephedrine	**5b**	10	2	48
3	L-Lysine	**5c**	10	2	50
4	L-Histidine	**5d**	10	2	55
5	L-Glutamic acid	**5e**	10	2	68
6	L-Asparatic acid	**5f**	10	2	71
7	L-Proline	**5g**	10	1	90
8	L-Pipecolic acid	**5h**	10	1	85
9	L-Proline	**5g**	20	1	90
10	L-Proline	**5g**	5	1	70

[a] Reaction conditions: aniline (1 mmol), cinnamaldehyde (1 mmol), ethyl acetoacetate (1 mmol), catalyst **5** (10 mol %), solvent free.
[b] Isolated yield.

Alkaloids like cinchonidine and ephedrine were found not very good as the product **4a** and were isolated in low yields (45 and 48%). Basic amino acids like L-lysine and L-histidine also resulted in poor conversion of **4a**. Acidic amino acids were found somewhat better but best results were obtained with neutral amino acids like L-proline (90%) and L-pipecolic acid (85%). Catalyst of 10 mol % was sufficient to push the reaction forward and increasing the amount of catalyst did not result to any significant improvement in the yield (entry 9, Table 1). Reducing the amount of catalyst below 10 mol % resulted in a lower yield (entry 10, Table 1). Thus, reactions were carried out with 10 mol % of the catalyst. The results of this study are shown in Table 1.

In order to study the solvent effect over the reaction and comparison of efficiency of catalysts, we carried out the reactions in different solvents. With **5g** and **5h** in less polar solvents like CH_2Cl_2 and THF, poor yields were obtained. In more polar solvents like methanol and ethanol better yields were obtained. However, the best results were obtained with **5g** under solvent free conditions. The results of this study are shown in Table 2.

We were also interested to study the enantioselectivity of the reaction. Unfortunately, in L-proline catalysed reactions, poor enantioselectivity (<20%) was observed under solvent free conditions, however, when the reaction was carried out

Table 2
Comparative study of solvent effect over organocatalysed reaction[a]

Entry	Solvent	Yield of **4a**[b] (%)	
		L-Proline **5g**	L-Pipecolic acid **5h**
1	CH_2Cl_2	38	32
2	THF	46	40
3	CH_3CN	60	58
4	MeOH	75	74
5	EtOH	78	75
6	None	90	85

[a] Reaction conditions: aniline (1 mmol), cinnamaldehyde (1 mmol), ethyl acetoacetate (1 mmol), catalyst **5g/5h** (10 mol %), rt.
[b] Isolated yield.

Table 3
Organocatalysed domino synthesis of 1,4-dihydropyridines[a]

Entry	R	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield[b] (%)
1	H	H	H	H	H	H	OC_2H_5	**4a**	90
2	H	H	H	H	H	CH_3	OC_2H_5	**4b**	88
3	H	H	H	H	H	F	OC_2H_5	**4c**	89
4	H	H	H	H	H	Cl	OC_2H_5	**4d**	85
5	H	H	H	H	H	Br	OC_2H_5	**4e**	88
6	H	NO_2	H	H	H	H	OC_2H_5	**4f**	90
7	H	H	H	H	H	H	OCH_3	**4g**	89
8	H	H	H	H	H	OCH_3	OCH_3	**4h**	88
9	H	H	CH_3	H	H	H	OCH_3	**4i**	92
10	OCH_3	H	H	H	H	H	OCH_3	**4j**	87
11	H	H	CH_3	H	Cl	H	OCH_3	**4k**	91
12	H	H	CH_3	CH_3	H	H	OCH_3	**4l**	90
13	H	H	H	H	H	H	O^{t}Bu	**4m**	81
14	H	H	H	H	H	Cl	O^{t}Bu	**4n**	80

[a] Reaction conditions: aniline (1 mmol), cinnamaldehyde (1 mmol), acetoacetate ester (1 mmol), L-proline (10 mol %), solvent free, rt.
[b] Isolated yield.

in polar solvents like MeOH or EtOH, improved enantioselectivities (40%) were observed.

In order to study the generality of this procedure a number of 1,4-dihydropyridines using **5g** as catalyst under solvent free conditions were synthesised. The reaction generally gave high yields of products. The electron donating as well as electron withdrawing groups in aniline are well tolerated.

We also attempted to carry out the reaction with aliphatic primary amines. But the reaction was unsuccessful and gave a complex mixture. Ethyl and methyl acetoacetate gave high yields but in case *tert*-butyl acetoacetate yields were somewhat lower. 4-Methoxy-cinnamaldehyde and 2-nitro-cinnamaldehyde both gave reasonably high yields of products. α-Methyl cinnamaldehyde yielded better yields in comparison to cinnamaldehyde. The results of this study are shown in Table 3.

In order to study the mechanism of the reaction, we carried out the following two experiments. In the first experiment, Schiff base **6a** was prepared by stirring aniline, cinnamaldehyde and L-proline for 20 min. Then it was treated with ethyl acetoacetate in the presence of L-proline. In another experiment aniline and ethyl acetoacetate were heated at 100 °C to form an enamine **7a**, which was then treated with cinnamaldehyde in the presence of L-proline (10 mol %) at rt. In the first experiment **4a** was isolated in 88% and in second experiment in 69% yield. Thus, It appears that the reaction follows any or both of the following possible pathways: (a) initial formation of an α,β-unsaturated imine, which then undergoes proline catalysed 1,4-conjugate addition with acetoacetate ester followed by cyclisation–dehydration to give **4a**; (b) initial formation of enamine with acetoacetate ester and aniline, which then undergoes a 1,4-conjugate addition with cinnamaldehyde followed by cyclisation–dehydration to give **4a** (Scheme 2).

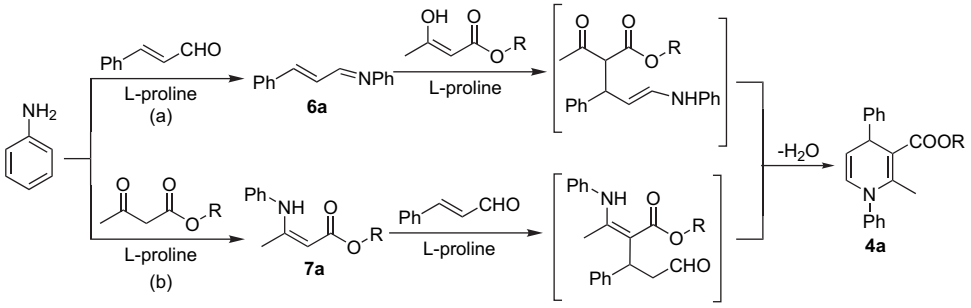
3. Conclusion

In conclusion, we have developed a high yielding reaction protocol for the synthesis of a variety of 1,4-dihydropyridines via organocatalysed three-component coupling of cinnamaldehyde, anilines and alkyl acetoacetates under solvent free conditions. The reaction does not require the use of any volatile organic solvents as well as harmful metal catalysts. Thus this is an ecofriendly and environmentally friendly procedure for the synthesis of *N*-substituted and 5-unsubstituted or 5,6-unsubstituted 1,4-dihydropyridines.

4. Experimental

4.1. Materials and general

All the reactions were carried out at room temperature, that is, 28–32 °C. All the reagents were purchased from Sigma-Aldrich Chemical Company and Lancaster. NMR spectra were obtained using the Brucker DRX 200 and 300 MHz



Scheme 2. Proposed mechanism for organocatalysed coupling of aniline, cinnamaldehyde and ethyl acetoacetate.

spectrometer. Chemical shifts (δ) are given in parts per million relative to TMS, coupling constants (J) in hertz. Mass spectra were obtained using JEOL SX-102 (ESI) instrument. IR spectra were taken on VARIAN FT-IR spectrometer. Elemental analysis was preformed using a Perkin Elmer Autosystem XL Analyzer. All compounds isolated (**4a**–**4n**) were oily. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualised with UV light.

4.2. Typical experimental procedure for the synthesis of 1,4-dihydropyridines (*4*)

Cinnamaldehyde (1 mmol), aniline (1 mmol), acetoacetate ester (1 mmol) and L-proline (10 mol %) were taken in 25 ml RB flask and stirred for 1 h. After completion the reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated to give a crude product, which after purification from silica gel column chromatography yielded **4a** (90%).

4.3. Analytical and spectral data

4.3.1. 2-Methyl-1,4-diphenyl-1,4-dihydro-pyridine-3-carboxylic acid ethyl ester (*4a*)[27]

MS (ESI) m/z=320 (M+H). IR (neat, cm^{-1}): 1691, 1568, 1221. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.19 (t, 3H, J=7.1 Hz, CH_3), 2.21 (s, 3H, CH_3), 4.08 (q, 2H, J=7.1 Hz, OCH_2), 4.75 (d, 1H, J=5.5 Hz, CH), 5.07 (dd, 1H, J=5.5 and 7.6 Hz, CH), 6.23 (d, 1H, J=7.6 Hz, CH), 7.24–7.47 (m, 10H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.7, 19.2, 40.6, 59.9, 102.1, 107.9, 126.6, 127.8, 127.9, 128.0, 128.8, 129.9, 130.0, 144.1, 148.4, 148.9, 169.2. Analysis calculated for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.82; H, 6.50; N, 4.27.

4.3.2. 2-Methyl-4-phenyl-1-(4-methylphenyl)-1,4-dihydro-pyridine-3-carboxylic acid ethyl ester (*4b*)[27]

MS (ESI) m/z=334 (M+H). IR (neat, cm^{-1}): 1691, 1568, 1222. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.19 (t, 3H, J=7.1 Hz, CH_3), 2.21 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.08 (q, 2H, J=7.1 Hz, OCH_2), 4.75 (d, 1H, J=5.4 Hz, CH), 5.05 (dd, 1H, J=5.4 and 7.6 Hz, CH), 6.19 (d, 1H, J=7.6 Hz, CH), 7.14 (d, 2H, J=8.2 Hz, ArH), 7.25–7.44 (m, 7H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.6, 19.1, 23.1, 40.7, 59.8, 101.7, 107.7, 126.6, 127.8, 128.0, 128.7, 130.0, 130.6, 137.7, 141.5, 148.7, 149.1, 169.3. Analysis calculated for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.12; H, 6.80; N, 4.27.

4.3.3. 1-(4-Fluorophenyl)-2-methyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylic acid ethyl ester (*4c*)[27]

MS (ESI) m/z=338 (M+H). IR (neat, cm^{-1}): 1693, 1569, 1216. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.19 (t, 3H, J=7.1 Hz, CH_3), 2.20 (s, 3H, CH_3), 4.09 (q, 2H, J=7.1 Hz, OCH_2), 4.75 (d, 1H, J=5.4 Hz, CH), 5.06 (dd, 1H, J=5.4, 7.6 Hz, CH), 6.14 (d, 1H, J=7.6 Hz, CH), 7.11–7.20 (m, 5H, ArH), 7.24–7.33 (m, 4H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.7, 19.0, 40.6, 59.9, 102.3, 108.0, 116.9 (d, J=22.6 Hz), 126.6, 128.0, 128.8, 129.8 (d, J=8.2 Hz), 129.9, 140.1 (d, J=3.8 Hz), 148.2, 148.8, 161.9 (d, J=247.2 Hz), 169.1. Analysis calculated for $C_{21}H_{20}FNO_2$: C, 74.76; H, 5.97; N, 4.15. Found: C, 74.61; H, 5.82; N, 4.07.

4.3.4. 1-(4-Chlorophenyl)-2-methyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylic acid ethyl ester (*4d*)[27]

MS (ESI) m/z=355 (M+H). IR (neat, cm^{-1}): 1693, 1568, 1222. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.18 (t, 3H, J=7.1 Hz, CH_3), 2.19 (s, 3H, CH_3), 4.07 (q, 2H, J=7.1 Hz, OCH_2), 4.73 (d, 1H, J=5.4 Hz, CH), 5.07 (dd, 1H, J=5.4 and 7.6 Hz, CH); 6.16 (d, 1H, J=7.6 Hz, CH), 7.16–7.44 (m, 9H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.6, 19.1, 40.6, 59.9, 102.9, 108.2, 126.7, 127.9, 128.8, 129.2, 129.5, 130.2, 133.4, 142.6, 147.7, 148.6, 169.1. Analysis calculated for $C_{21}H_{20}ClNO_2$: C, 71.28; H, 5.70; N, 3.96. Found: C, 71.11; H, 5.85; N, 3.87.

4.3.5. 1-(4-Bromophenyl)-2-methyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylic acid ethyl ester (*4e*)[28]

MS (ESI) m/z=399 (M+H). IR (neat, cm^{-1}): 1691, 1565, 1221. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.18 (t, 3H, J=7.1 Hz, CH_3), 2.20 (s, 3H, CH_3), 4.08 (q, 2H, J=7.1 Hz, OCH_2), 4.74 (d, 1H, J=5.5 Hz, CH), 5.07 (dd, 1H, J=5.5 and 7.6 Hz, CH); 6.17(d, 1H, J=7.6 Hz, CH), 7.12 (d, 2H, J=8.1 Hz, ArH), 7.23–7.38 (m, 5H, ArH), 7.58 (d, 2H, J=8.1 Hz, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 4.7, 19.2, 40.6, 60.1, 103.0, 108.3, 121.3, 126.7, 128.0, 128.8, 29.5, 129.6, 135.2, 143.1, 147.6, 148.6, 169.0. Analysis calculated for $C_{21}H_{20}BrNO_2$: C, 63.33; H, 5.06; N, 3.52. Found: C, 63.22; H, 5.05; N, 3.37.

4.3.6. 2-Methyl-4-(2-nitrophenyl)-1-phenyl-1,4-dihydro-pyridine-3-carboxylic acid ethyl ester (*4f*)[28]

MS (ESI) m/z=365 (M+H). IR (neat, cm^{-1}): 1694, 1568, 1524, 1355, 1222. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.95 (t, 3H, J=7.1 Hz, CH_3), 2.24 (s, 3H, CH_3), 3.90 (q, 2H, J=7.1 Hz, OCH_2), 5.21–5.25 (m, 2H, CH), 6.14–6.16 (m, 1H, CH), 7.22–7.50 (m, 6H, ArH), 7.62–7.65 (m, 1H, ArH), 7.75 (dd, 2H, J=8.1 and 1.5 Hz, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.3, 19.0, 36.6, 59.9, 100.6, 106.6, 123.6, 127.1, 128.0, 128.1, 130.1, 130.4, 131.6, 133.6, 143.7, 143.8, 148.2, 150.3, 168.3. Analysis calculated for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.17; H, 5.40; N, 7.54.

4.3.7. 2-Methyl-1,4-diphenyl-1,4-dihydro-pyridine-3-carboxylic acid methyl ester (*4g*)

MS (ESI) m/z=306 (M+H). IR (neat, cm^{-1}): 3062, 2943, 1688, 1570, 1225. ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.07 (s, 3H, CH_3), 3.50 (s, 3H, OCH_3), 4.58 (d, J=5.6 Hz, 1H, CH), 4.61 (dd, J=5.6 and 7.6 Hz, 1H, CH), 6.08 (d, J=7.8 Hz, 1H, CH), 7.07–7.37 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.1, 40.4, 51.1, 101.8, 107.8, 126.5, 126.9, 127.4, 127.7, 127.9, 128.1, 128.2, 128.9, 129.0, 129.5,

129.9, 144.0, 148.6, 148.7, 169.6. Analysis calculated for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.60; H, 6.22; N, 4.48.

4.3.8. 1-(4-Methoxy-phenyl)-2,5-dimethyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylic acid methyl ester (**4h**)

MS (ESI) *m*/*z*=350 (M+H). IR (neat, cm^{-1}): 2947, 1690, 1567, 1508, 1439. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.59 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.51 (s, 1H, CH), 6.00 (d, *J*=1.3 Hz, 1H, CH), 6.94–6.99 (m, 2H, ArH), 7.13–7.42 (m, 7H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 12.8, 12.9, 44.0, 48.8, 54.2, 98.6, 113.4, 114.1, 124.4, 124.5, 124.9, 126.4, 126.6, 126.7, 126.8, 127.5, 127.6, 127.7, 135.4, 145.6, 146.8, 157.3, 168.0. Analysis calculated for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 76.54; H, 6.57; N, 3.98.

4.3.9. 2,5-Dimethyl-1,4-diphenyl-1,4-dihydro-pyridine-3-carboxylic acid methyl ester (**4i**)

MS (ESI): *m*/*z*=320 (M+H). IR (neat, cm^{-1}): 2945, 1690, 1567, 1493, 1382, 1226. ^1H NMR ($CDCl_3$, 300 MHz) δ: ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.48 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.50 (s, 3H, OCH_3), 4.39 (s, 1H, CH), 5.96 (d, *J*=1.3 Hz, 1H, CH), 7.09–7.37 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 17.3, 17.4, 44.5, 50.5, 99.7, 114.7, 124.4, 125.1, 126.1, 126.5, 126.7, 127.1, 128.5, 142.7, 145.6, 146.5, 168.2. Analysis calculated for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.82; H, 6.58; N, 4.31.

4.3.10. 4-(4-Methoxy-phenyl)-2-methyl-1-phenyl-1,4-dihydro-pyridine-3-carboxylic acid methyl ester (**4j**)

MS (ESI) *m*/*z*=336 (M+H). IR (neat, cm^{-1}): 2946, 1692, 1595, 1236. ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.15 (s, 3H, CH_3), 3.45 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.96–5.05 (m, 2H, CH), 5.91 (d, *J*=7.4 Hz, 1H, CH), 6.77–6.86 (m, 2H, ArH), 7.07–7.31(m, 7H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.0, 33.9, 51.0, 55.7, 107.6, 110.7, 121.2, 121.4, 127.2, 127.5, 128.0, 128.3, 129.5, 129.8, 156.0, 168.0. Analysis calculated for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.02; H, 6.18; N, 4.11.

4.3.11. 1-(3-Chloro-phenyl)-2,5-dimethyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylic acid methyl ester (**4k**)

MS (ESI) *m*/*z*=354 (M+H). IR (neat, cm^{-1}): 2943, 1694, 1577, 1478, 1227. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.56 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 4.46 (s, 1H, CH), 6.03 (d, *J*=1.3 Hz, 1H, CH), 7.08–7.37 (m, 9H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 18.7, 18.9, 45.9, 51.1, 102.3, 116.6, 125.4, 126.1, 126.7, 127.8, 128.1, 128.6, 130.8, 135.4, 145.3, 146.7, 147.1, 169.4. Analysis calculated for $C_{21}H_{20}ClNO_2$: C, 71.28; H, 5.70; N, 3.96. Found: C, 71.12; H, 5.60; N, 3.87.

4.3.12. 1-(2,3-Dimethyl-phenyl)-2,5-dimethyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylic acid methyl ester (**4l**)

The compound was isolated as 1.13:1 rotamer mixture (**4la** major rotamer, **4lb** minor rotamer). MS (ESI) *m*/*z*=348 (M+H). IR (neat, cm^{-1}): 2938, 1690, 1566, 1385, 1231. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.58 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.19 and 2.25 (2s, **4la** and **4lb**, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.60 and 3.61 (2s, **4la** and **4lb**, 3H, OCH_3), 4.52 and 4.61 (2s, **4la** and **4lb**, 1H, CH), 5.78 and 5.87 (2d, *J*=1.0 Hz, **4la** and **4lb**, 1H, CH), 7.00–7.57 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 12.8, 12.9, 16.1, 16.3, 17.2, 17.3, 19.1, 19.2, 44.3, 44.5, 49.2, 97.3, 97.4, 98.7, 113.6, 114.2, 123.3, 123.9, 124.7, 124.8, 124.9, 125.1, 125.2, 125.3, 126.5, 126.7, 126.8, 127.4, 128.1, 128.2, 128.3, 133.8, 133.9, 134.0, 137.1, 137.5, 137.6, 141.1, 141.5, 145.6, 145.9, 146.9, 147.0, 148.5, 168.1, 168.2. Analysis calculated for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.42; H, 7.16; N, 3.97.

4.3.13. 2-Methyl-1,4-diphenyl-1,4-dihydro-pyridine-3-carboxylic acid tert-butyl ester (**4m**)[28]

MS (ESI) *m*/*z*=348 (M+H). IR (neat, cm^{-1}): 2956, 1690, 1571, 1235. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.34 (s, 9H, $3CH_3$), 2.16 (s, 3H, CH_3), 4.71 (d, 1H, *J*=5.1 Hz, CH), 5.00 (dd, 1H, *J*=5.1 and 7.7 Hz, CH), 6.16 (d, 1H, *J*=7.7 Hz, CH), 7.22–7.47 (m, 10H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.1, 28.6, 41.3, 79.6, 103.7, 107.6, 126.5, 127.6, 128.0, 128.7, 129.7, 129.9, 144.2, 147.2, 149.2, 168.0. Analysis calculated for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.40; H, 7.12; N, 3.90.

4.3.14. 1-(4-Chlorophenyl)-2-methyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylic acid tert-butyl ester (**4n**)[28]

MS (ESI) *m*/*z*=382 (M+H). IR (neat, cm^{-1}): 2966, 1691, 1570, 1236. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.33 (s, 9H, $3CH_3$), 2.14 (s, 3H, CH_3), 4.69 (d, 1H, *J*=5.1 Hz, CH), 4.99 (dd, 1H, *J*=5.1 and 7.7 Hz, CH), 6.10 (d, 1H, *J*=7.7 Hz, CH), 7.14–7.41 (m, 9H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.1, 28.6, 41.3, 79.7, 104.5, 108.0, 126.6, 127.9, 128.8, 129.2, 129.3, 130.1, 133.2, 142.8, 146.5, 148.9, 168.6. Analysis calculated for $C_{23}H_{24}ClNO_2$: C, 72.34; H, 6.33; N, 3.67. Found: C, 72.41; H, 6.23; N, 3.51.

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