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L-Proline-catalyzed five-component domino reaction leading to multifunctionalized 1,2,3,4-tetrahydropyridines

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ABSTRACT

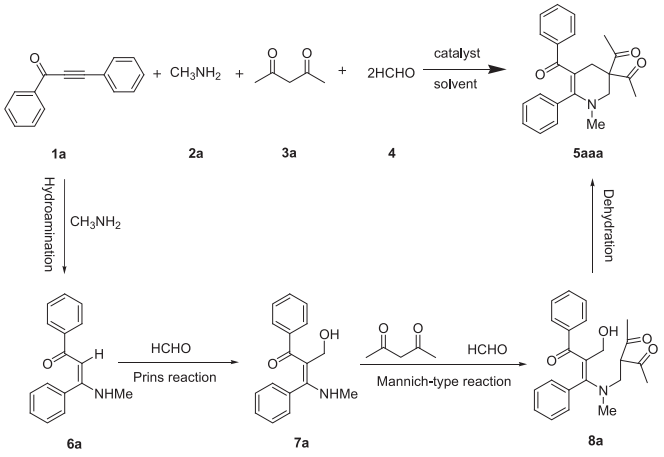
Multifunctionalized 1,2,3,4-tetrahydropyridines are concisely synthesized in good yields via L-proline-catalyzed or L-proline/$FeCl_3$-cocatalyzed one-pot multicomponent reactions (MCRs). The MCRs involve a domino hydroamination/prins reaction/Mannich-type reaction/intramolecular dehydration–cyclization process. The molecular structure of **5baa**, one of multifunctionalized 1,2,3,4-tetrahydropyridines, was confirmed by single-crystal X-ray diffraction.

1. Introduction

Multicomponent reactions (MCRs) have emerged as a powerful tool in synthetic organic chemistry. Compared with conventional methods, MCRs exhibit high levels of efficiency and diversity, as they offer rapid and convergent construction of complex molecular skeletons from common starting materials in one-pot, and these reactions are environmentally friendly and proceed with excellent chemoselectivities.[1,2] Therefore, designing novel MCRs for constructing valuable compounds remains the interest of synthetic chemists.

Tetrahydropyridines are one of the fundamental heterocycles, which have been the subject of intense research for their outstanding biological properties and wide range of applications to pharmaceutical compounds and synthetic intermediates.[3] Although there are some reports for the synthesis of tetrahydropyridines, these methods are not always satisfactory with respect to ease of operation, yield, applicability and the regioselectivity of the products.[4] Besides, very few efficient methods of formation 1,2,3,4-tetrahydropyridines are described in the literatures.[4d,5]

Over the past few years, we have developed a series of heterocyclic compounds, such as tetrahydropyrimidines,[6] 3,6-dihydro-2*H*-1,3-oxazines,[7] 1,3-oxazine-6-ones,[8] 1,4-dihydropyridines,[9] 1,2,3,4-tetrahydropyridines[5g] through the MCR methods. During our ongoing research on the synthesis of other nitrogen-containing heterocycles, we found a novel multicomponent coupling strategy to synthesize multisubstituted 1,2,3,4-tetrahydropyridine derivatives. Our approach could briefly comprise four sequential processes (Scheme 1): (1) two-component hydroamination;[10] (2) two-component prins reaction;[11] (3) three-component Mannich-type reaction; (4) intramolecular dehydration-cyclization.



Scheme 1. The domino processes leading to multisubstituted 1,2,3,4-tetrahydropyridine.

2. Results and discussion

On the basis of our previous work on the L-proline-catalyzed synthesis of highly functionalized multisubstituted 1,4-dihydropyridines,[9,12] we initially examined the reaction in ethanol solvent at room temperature, the reaction did not give target product (Table 1, entry 1). To our delight, the reaction gave satisfying results in DMF at 100 °C (Table 1, entry 2). Without any catalysts, the reaction was carried out inefficiently, and the desired product was obtained in a poor yield of 33% (Table 1, entry 3). Next,

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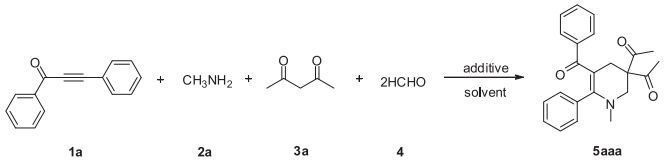
Table 1
Optimization of reaction conditions[a]



Entry	Additive	Solvent	Yield[b] (%)
1[c]	L-Proline	EtOH	n.p.
2	L-Proline	DMF	87 (83)
3	None	DMF	33
4	L-Proline	EtOH	Trace
5	L-Proline	Toluene	65
6	L-Proline	CH_3CN	64
7	L-Proline	THF	56
8	L-Proline	DMSO	77
9	Pyridine	DMF	75
10	DABCO	DMF	77
11	Et_3N	DMF	46
12	NaOH	DMF	35
13	Na_2CO_3	DMF	36
14	CH_3COONa	DMF	39
15[d]	L-Proline	DMF	68
16[e]	L-Proline	DMF	75

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3a** (1.5 mmol), **4** (2 mmol), and additive (0.1 mmol, 10 mol %) in solvent (3.0 mL) at 100 °C for 12 h.
[b] Determined by GC. Number in parenthesis is isolated yield.
[c] Room temperature.
[d] 60 °C.
[e] 6 h.

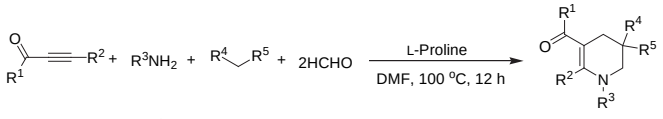
the solvents were evaluated. Except ethanol, other solvents such as toluene, CH_3CN, THF, and DMSO proved to be appropriate (Table 1, entries 4–8). The reaction also showed a significant dependence on bases, and L-proline proved to be superior to other bases (Table 1, entries 2 and 9–14). The lower temperature and the shortened reaction time can reduce the product yield (Table 1, entries 15 and 16).

On the basis of these results, the optimal conditions involved the following parameters: L-proline as catalyst, and DMF as solvent, with reaction temperature at 100 °C for 12 h. Under these optimized conditions, a study on the substrate scope was carried out, and the results are summarized in Table 2.

In order to determine the structures of this series of compound definitively, a single crystal of **5baa** was obtained by slow crystallization from ethyl acetate and its structure was established by single-crystal X-ray analysis (Fig. 1).

Under the above optimized conditions, the scope of this new MCR process was next examined using various readily available starting materials (Table 2). It was pleasing to find that all the reactions afforded the corresponding products in good yields. The alkynones with different substituted groups on the benzene ring had no obvious impact to the reaction. The heterocyclic alkynone (Table 2, entry 9) and the cyclohexyl alkynone (Table 2, entry 10) afforded the corresponding products in high yields. Unfortunately, only the simple primary amines, such as methylamine and ethylamine, were suitable for the reaction. Moreover, a series of active methylene compounds were compatible for the reaction.[13] When the reaction substrates were switched from β-diketones to malononitrile, the reactions could be carried out smoothly to give the corresponding products with higher yields (Table 2, entries 1–11).

Table 2
L-Proline-catalyzed synthesis of polysubstituted 1,2,3,4-tetrahydropyridines via the MCRs[a]



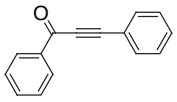
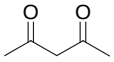
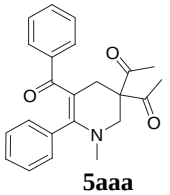
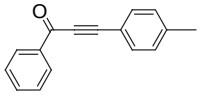
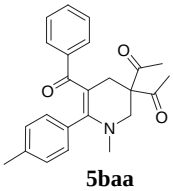
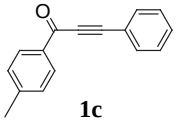
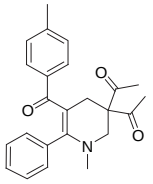
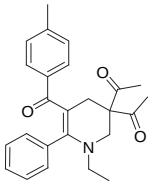
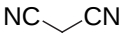
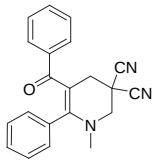
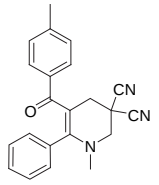
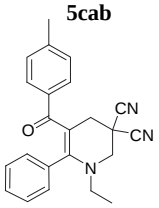
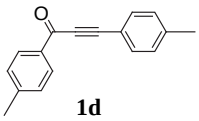
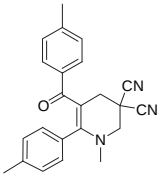
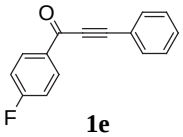
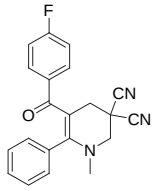
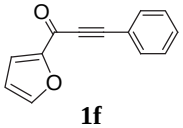
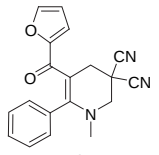
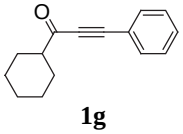
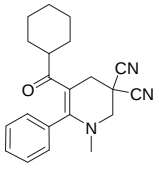
Entry	Alkynone	Amine	Active methylene compound	Product	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	 **5aaa**	83
2	 **1b**	**2a**	**3a**	 **5baa**	84
3	 **1c**	**2a**	**3a**	 **5caa**	81

Table 2 (*continued*)

Entry	Alkynone	Amine	Active methylene compound	Product	Yield[b] (%)
4	**1c**	 **2b**	**3a**	 **5cba**	77
5	**1a**	**2a**	 **3b**	 **5aab**	86
6	**1c**	**2a**	**3b**	 **5cab**	82
7	**1c**	**2b**	**3b**	 **5cbb**	82
8	 **1d**	**2a**	**3b**	 **5dab**	89
9	 **1e**	**2a**	**3b**	 **5eab**	78
10	 **1f**	**2a**	**3b**	 **5fab**	83
11	 **1g**	**2a**	**3b**	 **5gab**	84

(*continued on next page*)

Table 2 (*continued*)

Entry	Alkynone	Amine	Active methylene compound	Product	Yield[b] (%)
12	**1a**	**2a**	EtOOC COOEt **3c**	**5aac**	68
13	**1f**	**2a**	**3c**	**5fac**	64
14	**1a**	**2a**	O CO_2Et **3d**	**5aad**	78
15	**1c**	**2a**	**3d**	**5cad**	83
16	**1a**	**2a**	O Ph CO_2Et **3e**	**5aae**	74

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), **3** (1.5 mmol), **4** (2 mmol), and L-proline (10 mol %) in DMF (3.0 mL) at 100 °C for 12 h.
[b] Isolated yield.

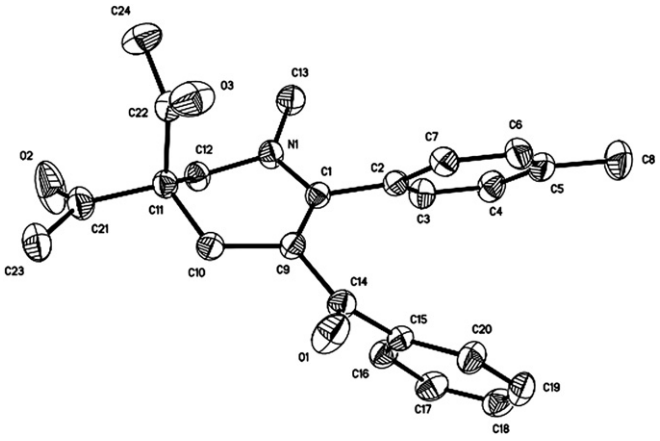


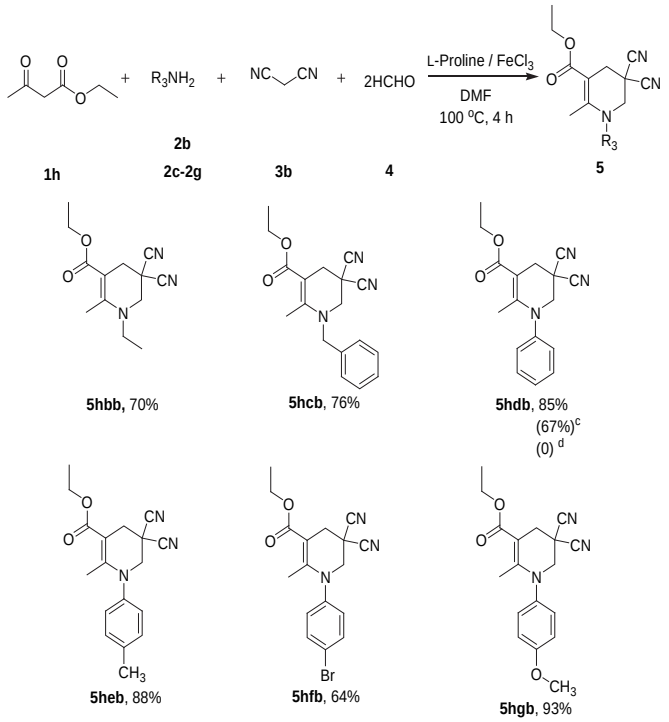
Fig. 1. X-ray structure of **5baa**.

When β-diketones were replaced with diethyl malonate, the reaction gave the products with lower yields (Table 2, entries 12–13). This meant that steric effect had much influence on the reaction.

For further exploration the scope of the MCRs, L-proline/$FeCl_3$-cocatalyzed system was developed. Table 2 has showed an elegant method for the synthesis of multifunctionalized 1,2,3,4-tetrahydropyridines, but the substrates were limited to the aromatic alkynones and aliphatic amines. Herein we got a series of 1,2,3,4-tetrahydropyridines from ethyl acetoacetate, amines, malononitrile, and formaldehyde via L-proline/$FeCl_3$-cocatalyzed five-component domino reactions (Scheme 2).[2b,14] The reaction did not proceed without $FeCl_3$, and gave a reduced yield without L-proline. Aromatic amines with electron-donating attached to the benzene rings gave higher yields than the electron-withdrawing groups (Scheme 2, **5heb**, **5hfb**, and **5hgb**).

3. Conclusions

In conclusion, we have developed a new strategy that provides an efficient synthesis of multisubstituted 1,2,3,4-tetrahydropyridines and is therefore complementary to the construction of small heterocyclic molecules in our laboratory. Our method involves mild reaction conditions, uses very simple and accessible starting materials and solvents, as well as an inexpensive and non-toxic catalyst. It also has the additional advantage of proceeding with high



Scheme 2. L-Proline/$FeCl_3$-cocatalyzed synthesis of polysubstituted 1,2,3,4-tetrahydropyridines via the MCRs[a, b]; [a] Reaction conditions: ethyl acetoacetate (1 mmol), amines (1 mmol), malononitrile (1.5 mmol), formaldehyde (2 mmol), L-proline (10 mol %) and $FeCl_3$ (10 mol %) in DMF (3.0 mL) at 100 °C for 4 h [b] Isolated yield. [c] Without L-proline. [d] Without $FeCl_3$.

atom economy and having water as the only side product. Further synthetic applications and studies of the mechanism of the MCRs are underway.

4. Experimental

4.1. General

All the reactions were carried out under air atmosphere in a round bottom flask equipped with magnetic stir bar. Melting points were measured with a BÜCHI B-545 melting point instrument and were uncorrected. GC–MS was obtained using electron ionization (EI). IR spectra were obtained as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Brucher Vector 22 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance 400 or 600 MHz NMR spectrometer and, respectively, referenced to 7.27 and 77.0 ppm for chloroform-*d* with TMS as internal standard. TLC was performed using commercially prepared 100–400 mesh silica gel plates (GF_{254}), and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.

4.2. General procedure for the synthesis of multifunctionalized 1,2,3,4-tetrahydropyridines (5aaa–5aae)

To a mixture of alkynone **1** (1 mmol) and amine **2** (1 mmol), 3 mL DMF was added successively. The mixture was stirred at room temperature for 30 min. Subsequently, active methylene compound **3** (1.5 mmol), 38% formaldehyde **4** (160 mg, 2 mmol), and L-proline (11.5 mg, 0.1 mmol) were added, and the stirring was continued in a round bottom flask at 100 °C for another 12 h. The progress of the reaction was followed by TLC. After cooling, the reaction was diluted with water and extracted with diethyl ether (15 mL×3). The ether layer was then washed with saturated salt water and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the crude product was purified by preparative TLC (GF_{254}) with petroleum ether/ethyl acetate (10:1 to 4:1) as eluent to afford the desired products **5aaa**–**5aae**.

*4.2.1. 1,1′-(5-Benzoyl-1-methyl-6-phenyl-1,2,3,4-tetrahydropyridine-3,3-diyl)diethanone (**5aaa**).* Yellow viscous oil. IR (KBr): 2926, 1741, 1688, 1545, 1366, 1244, 1049, 761 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.10–7.08 (m, 2H), 7.02–6.89 (m, 8H), 3.72 (s, 2H), 3.26 (s, 2H), 2.68 (s, 3H), 2.27 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.3, 196.5, 158.3, 142.2, 134.8, 130.1, 129.1, 128.5, 128.2, 127.8, 127.1, 105.9, 65.5, 53.8, 41.0, 29.9, 26.7. MS (EI) *m*/*z*: 361, 319, 118, 105, 77, 43, 28. Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.61; H, 6.33; N, 3.84.

*4.2.2. 1,1′-(5-Benzoyl-1-methyl-6-p-tolyl-1,2,3,4-tetrahydropyridine-3,3-diyl)diethanone (**5baa**).* Yellow crystal, mp: 177–178 °C. IR (KBr): 2921, 1743, 1693, 1547, 1367, 1243, 1048, 755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.05–6.90 (m, 5H), 6.74 (s, 4H), 3.69 (s, 2H), 3.23 (s, 2H), 2.69 (s, 3H), 2.25 (s, 6H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.4, 196.6, 158.7, 142.4, 138.7, 131.9, 130.1, 128.7, 128.4, 128.1, 127.0, 105.7, 65.5, 53.7, 41.0, 29.8, 26.7, 21.0. MS (EI) *m*/*z*: 375, 333, 332, 105, 77, 32, 28. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.91; H, 6.64; N, 3.77.

*4.2.3. 1,1′-(1-Methyl-5-(4-methylbenzoyl)-6-phenyl-1,2,3,4-tetrahydropyridine-3,3-diyl)diethanone (**5caa**).* Yellow viscous oil. IR (KBr): 2929, 1742, 1688, 1534, 1357, 1242, 1048, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.03–6.95 (m, 5H), 6.88 (d, 2H, *J*=8.0 Hz), 6.74 (d, 2H, *J*=8.0 Hz), 3.68 (s, 2H), 3.20 (s, 2H), 2.65 (s, 3H), 2.24 (s, 6H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.4, 196.5, 157.4, 142.4, 139.4, 135.1, 130.1, 129.1, 128.4, 127.8, 127.7, 105.9, 65.5, 53.7, 41.0, 29.8, 26.7, 21.2. MS (EI) *m*/*z*: 375, 333, 332, 119, 118, 91, 28. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.92; H, 6.63; N, 3.80.

*4.2.4. 1,1′-(1-Ethyl-5-(4-methylbenzoyl)-6-phenyl-1,2,3,4-tetrahydropyridine-3,3-diyl)diethanone (**5cba**).* Yellow viscous oil. IR (KBr): 2928, 1743, 1699, 1545, 1359, 1224, 1075, 755, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.01 (d, 2H, *J*=8.0 Hz), 6.99–6.88 (m, 5H), 6.74 (d, 2H, *J*=8.0 Hz), 3.68 (s, 2H), 3.18 (s, 2H), 2.92–2.86 (m, 2H), 2.25 (s, 6H), 2.14 (s, 3H), 1.01 (t, 3H, *J*=6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.7, 196.9, 157.0, 142.7, 139.4, 135.3, 129.8, 128.6, 128.3, 127.8, 127.7, 105.9, 64.9, 50.7, 47.0, 30.3, 26.8, 21.2, 14.0. MS (EI) *m*/*z*: 389, 347, 346, 119, 91, 43. Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.26; H, 6.93; N, 3.67.

*4.2.5. 5-Benzoyl-1-methyl-6-phenyl-1,2-dihydropyrid- ine-3,3(4H)-dicarbonitrile (**5aab**).* White crystal, mp: 225–226 °C. IR (KBr): 2926, 2351, 1672, 1607, 1559, 1382, 1267, 738, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.25–7.23 (m, 2H), 7.11–7.00 (m, 8H), 3.93 (s, 2H), 3.43 (s, 2H), 2.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=195.9, 155.7, 140.3, 133.8, 129.9, 129.8, 129.2, 127.9, 127.8, 126.9, 113.6, 106.6, 56.3, 41.3, 35.0, 28.3. MS (EI) *m*/*z*: 327, 223, 222, 207, 105, 77, 44. Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.28; H, 5.17; N, 12.79.

*4.2.6. 1-Methyl-5-(4-methylbenzoyl)-6-phenyl-1,2-di- hydropyridine-3,3(4H)-dicarbonitrile (**5cab**).* White crystal, mp: 186–187 °C. IR (KBr): 2926, 2370, 1687, 1609, 1570, 1385, 1271, 827, 746, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.16 (d, 2H, *J*=8.0 Hz), 7.06–7.03 (m, 5H), 6.80 (d, 2H, *J*=8.0 Hz), 3.90 (s, 2H), 3.38 (s, 2H), 2.83 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.3, 155.6, 140.9, 137.6, 134.3, 130.3, 129.5, 128.6, 128.1, 128.0, 114.1, 107.1, 56.6, 41.8, 35.4, 28.5, 21.3. MS (EI)

m/*z*: 341, 222, 207, 119, 91, 32, 28. Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 77.18; H, 5.69; N, 12.26.

*4.2.7. 1-Ethyl-5-(4-methylbenzoyl)-6-phenyl-1,2-dihy- dropyridine-3,3(4H)-dicarbonitrile (**5cbb**).* White crystal, mp: 192–193 °C. IR (KBr): 2927, 2362, 1688, 1604, 1554, 1361, 1272, 751, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.14 (d, 2H, *J*=8.0 Hz), 7.08–7.03 (m, 5H), 6.81 (d, 2H, *J*=8.0 Hz), 3.87 (s, 2H), 3.38 (s, 2H), 3.08–3.03 (m, 2H), 2.17 (s, 3H), 1.09 (t, 3H, *J*=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.5, 155.3, 140.7, 138.0, 134.6, 130.1, 129.4, 128.5, 128.1, 128.1, 114.2, 106.2, 53.3, 47.6, 35.6, 28.6, 21.3, 14.5. MS (EI) *m*/*z*: 355, 354, 237, 236, 119, 104, 91, 65, 28. Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.98, H, 5.88; N, 11.78.

*4.2.8. 1-Methyl-5-(4-methylbenzoyl)-6-p-tolyl-1,2-dihydropyridine-3,3(4H)-dicarbonitrile (**5dab**).* White crystal, mp: 208–209 °C. IR (KBr): 2921, 2312, 1689, 1605, 1541, 1357, 1274, 819 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.15 (d, 2H, *J*=8.0 Hz), 6.93 (d, 2H, *J*=8.0 Hz), 6.84–6.80 (m, 4H), 3.89 (s, 2H), 3.36 (s, 2H), 2.84 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.4, 155.9, 140.7, 139.7, 137.7, 131.4, 130.2, 128.8, 128.6, 128.0, 114.2, 106.9, 56.6, 41.8, 35.5, 28.6, 21.3. MS (EI) *m*/*z*: 355, 236, 119, 91, 28. Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.99; H, 5.88; N, 11.86.

*4.2.9. 5-(4-Fluorobenzoyl)-1-methyl-6-phenyl-1,2-dihydropyridine-3,3(4H)-dicarbonitrile (**5eab**).* White crystal, mp: 190–191 °C. IR (KBr): 2926, 2365, 1687, 1608, 1375, 1271, 745, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.27–7.23 (m, 2H), 7.14–7.05 (m, 5H), 6.70–6.66 (m, 2H), 3.93 (s, 2H), 3.42 (s, 2H), 2.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=195.0, 156.5, 136.9, 134.1, 130.8, 130.7, 130.4, 130.0, 128.4, 114.3, 106.8, 56.6, 42.0, 35.3, 28.8. MS (EI) *m*/*z*: 345, 223, 222, 122, 118, 94. Anal. Calcd for $C_{21}H_{16}FN_3O$: C, 73.03; H, 4.67; N, 12.17. Found: C, 73.21; H, 4.60; N, 12.21.

*4.2.10. 5-(Furan-2-carbonyl)-1-methyl-6-phenyl-1,2-dihydropyr-idine-3,3(4H)-dicarbonitrile (**5fab**).* White crystal, mp: 229–230 °C. IR (KBr): 2376, 1688, 1592, 1545, 1383, 1272, 758, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.22–7.19 (m, 5H), 7.09 (s, 1H), 6.57 (d, 1H, *J*=3.2 Hz), 6.10–6.09 (m, 1H), 3.90 (s, 2H), 3.38 (s, 2H), 2.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=182.3, 155.1, 152.7, 144.0, 134.0, 129.4, 129.2, 127.8, 115.9, 113.6, 111.0, 106.1, 56.3, 41.5, 34.6, 28.2. MS (EI) *m*/*z*: 317, 222, 207, 206, 32, 28. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 72.14; H, 4.66; N, 13.29.

*4.2.11. 5-(Cyclohexanecarbonyl)-1-methyl-6-phenyl-1,2-dihydropyr-idine-3,3(4H)-dicarbonitrile (**5gab**).* White crystal, mp: 163–164 °C. IR (KBr): 2926, 2361, 1698, 1616, 1547, 1378, 1260, 769, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.49–7.42 (m, 3H), 7.30–7.28 (m, 2H), 3.78 (s, 2H), 3.19 (s, 2H), 2.80 (s, 3H), 1.50–0.95 (m, 9H), 0.57–0.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.0, 155.0, 135.4, 130.1, 129.3, 129.0, 114.1, 107.6, 56.2, 47.9, 41.7, 34.8, 29.7, 29.1, 25.7, 25.6. MS (EI) *m*/*z*: 333, 251, 250, 118, 55, 28. Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.48; H, 7.12; N, 12.64.

*4.2.12. 5-Benzoyl-1-methyl-6-phenyl-1,2-dihydropyr-idine-3,3(4H)-dicarboxylate (**5aac**).* Yellow viscous oil. IR (KBr): 2928, 1613, 1553, 1382, 1256, 767, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.17–7.15 (m, 2H), 7.03–6.94 (m, 8H), 4.24–4.19 (m, 4H), 3.75 (s, 2H), 3.17 (s, 2H), 2.66 (s, 3H), 1.25 (t, 6H, *J*=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.6, 169.8, 157.5, 142.4, 135.5, 130.2, 129.1, 128.6, 128.3, 127.8, 127.1, 107.3, 61.8, 54.5, 53.1, 40.9, 31.2, 14.0. MS (EI) *m*/*z*: 421, 349, 348, 249, 170, 118, 105, 77, 28. Anal. Calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.36, H, 6.38; N, 3.27.

*4.2.13. Diethyl 5-(furan-2-carbonyl)-1-methyl-6-phenyl-1,2-dihy-dropyridine-3,3(4H)-dicarboxylate (**5fac**).* Yellow viscous oil. IR (KBr): 2981, 1732, 1599, 1547, 1360, 1263, 754, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.14–7.09 (m, 5H), 7.07 (s, 1H), 6.44 (d, 1H, *J*=3.2 Hz), 6.04–6.03 (m, 1H), 4.21–4.16 (m, 4H), 3.73 (s, 2H), 3.17 (s, 2H), 2.70 (s, 3H), 1.22 (t, 6H, *J*=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=182.9, 169.6, 156.9, 153.9, 143.5, 135.7, 129.6, 128.6, 127.8, 115.0, 110.9, 106.6, 61.7, 54.5, 53.1, 40.9, 30.9, 14.0. MS (EI) *m*/*z*: 411, 339, 338, 214, 118, 95, 28. Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.35; H, 5.99; N, 3.45.

*4.2.14. Ethyl 3-acetyl-5-benzoyl-1-methyl-6-phenyl-1,2,3,4-tetrahy-dropyridine-3-carboxylate (**5aad**).* Reddish brown oil. IR (KBr): 2984, 1710, 1605, 1547, 1364, 1230, 730, 705 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ=7.12–7.10 (m, 2H), 7.03–6.91 (m, 8H), 4.26–4.25 (m, 2H), 3.82–3.67 (m, 2H), 3.27–3.20 (m, 2H), 2.69 (s, 3H), 2.33 (s, 3H), 1.29 (t, 3H, *J*=7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ=203.3, 196.3, 170.0, 158.3, 142.4, 135.2, 129.0, 128.7, 128.1, 127.1, 106.0, 61.9, 58.5, 53.8, 40.9, 30.9, 26.3, 14.0. MS (EI) *m*/*z*: 391, 349, 348, 118, 105, 77, 28. Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.81; H, 6.33; N, 3.44.

*4.2.15. Ethyl 3-acetyl-1-methyl-5-(4-methylbenzoyl)-6-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate (**5cad**).* Reddish brown oil. IR (KBr): 2982, 1711, 1605, 1544, 1363, 1234, 822, 749, 705 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ=7.04 (d, 2H, *J*=7.8 Hz), 7.00–6.91 (m, 5H), 6.75 (d, 2H, *J*=7.8 Hz), 4.25–4.21 (m, 2H), 3.78–3.64 (m, 2H), 3.23–3.15 (m, 2H), 2.66 (s, 3H), 2.29 (s, 3H), 2.14 (s, 3H), 1.27 (t, 3H, *J*=7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ=203.4, 196.4, 170.1, 157.7, 139.4, 135.4, 128.5, 128.4, 127.8, 127.7, 106.2, 61.9, 58.6, 53.8, 40.9, 31.1, 26.4, 21.2, 14.1. MS (EI) *m*/*z*: 405, 363, 362, 170, 119, 118, 118, 91. Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 73.88; H, 6.82; N, 3.47.

*4.2.16. Ethyl 3,5-dibenzoyl-1-methyl-6-phenyl-1,2,3,4-tetrahydropyr-idine-3-carboxylate (**5aae**).* Yellow crystal, mp: 142–143 °C. IR (KBr): 2926, 1730, 1680, 1546, 1360, 1261, 1236, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.96–7.94 (m, 2H), 7.57–7.42 (m, 3H), 7.11–6.92 (m, 10H), 4.20–4.17 (m, 2H), 3.95–3.86 (m, 2H), 3.63–3.03 (m, 2H), 2.69 (s, 3H), 1.27 (t, 3H, *J*=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.6, 195.5, 171.2, 158.3, 142.4, 135.6, 135.4, 133.1, 129.0, 128.7, 128.6, 128.3, 127.8, 127.0, 108.3, 61.8, 56.8, 55.9, 40.8, 32.3, 13.8. MS (ESI) *m*/*z*: 453. Anal. Calcd for $C_{29}H_{27}NO_4$: C, 76.80; H, 6.00; N, 3.09. Found: C, 76.96; H, 5.51; N, 3.06.

4.3. General procedure for the synthesis of multifunctionalized 1,2,3,4-tetrahydropyridines (5hbb–5hgb)

A mixture of ethyl acetoacetate **1h** (130 mg, 1 mmol), amines **2** (1 mmol), malononitrile **3b** (66 mg, 1 mmol), 38% formaldehyde **4** (160 mg, 2 mmol), $FeCl_3$ (16 mg, 0.1 mmol), and L-proline (11.5 mg, 0.1 mmol) was heated in DMF (3 ml) with stirring in a round bottom flask at 100 °C for 4 h. The progress of the reaction was followed by TLC. After cooling, the reaction was diluted with water and extracted with diethyl ether (15 mL×3). The ether layer was then washed with saturated salt water and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the crude product was purified by preparative TLC (GF_{254}) with petroleum ether/ethyl acetate (10:1 to 4:1) as eluent to afford the desired products **5hbb**–**5hgb**.

*4.3.1. Ethyl 5,5-dicyano-1-ethyl-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5hbb**).* Yellow viscous oil, IR_{max} (KBr): 2977, 2260, 1766, 1681, 1568, 1424, 1256, 1202, 1160, 1106 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=4.16–4.11 (m, 2H), 3.64 (s, 2H), 3.44–3.39 (m, 2H), 3.10 (s, 2H), 2.49 (s, 3H), 1.28 (t, 3H, *J*=7.2), 1.21 (t, 3H, *J*=7.2). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.1, 154.1, 114.3, 90.7, 59.7, 53.5, 46.3, 34.2, 29.3, 15.9, 14.5, 14.1. MS (EI) *m*/*z*: 247, 202, 174, 135,

42, 29, 28. Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.25; H, 6.85; N, 17.04.

*4.3.2. Ethyl 1-benzyl-5,5-dicyano-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5hcb**).* Yellow viscous oil. IR (KBr): 2981, 2260, 1689, 1576, 1359, 1246, 1130, 734, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.41–7.20 (m, 5H), 4.60 (s, 2H), 4.19–4.14 (m, 2H), 3.59 (s, 2H), 3.15 (s, 2H), 2.56 (s, 3H), 1.30 (t, 3H, J=7.2). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.0, 154.3, 135.9, 129.2, 128.2, 126.7, 114.2, 91.8, 59.9, 54.8, 53.6, 34.2, 29.2, 16.6, 14.5. MS (EI) m/z: 309, 264, 236, 230, 158, 132, 91, 28. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.71; H, 6.27; N, 13.52.

*4.3.3. Ethyl 5,5-dicyano-2-methyl-1-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5hdb**).* Reddish brown oil. IR (KBr): 2981, 2260, 1684, 1575, 1355, 1246, 1138, 734, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.41–7.15 (m, 5H), 4.19–4.14 (m, 2H), 3.98 (s, 2H), 3.20 (s, 2H), 2.19 (s, 3H), 1.29 (t, 3H, J=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.7, 153.1, 143.8, 129.9, 127.8, 127.4, 114.1, 93.9, 59.9, 55.8, 34.2, 29.2, 19.2, 14.4. MS (EI) m/z: 295, 266, 250, 223, 222, 144, 118, 77. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.30; H, 5.72; N, 14.18.

*4.3.4. Ethyl 5,5-dicyano-2-methyl-1-p-tolyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5heb**).* Reddish brown oil. IR (KBr): 2982, 2260, 1691, 1579, 1514, 1452, 1383, 1246, 1140, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.18 (d, 2H, J=8.0 Hz), 7.03 (d, 2H, J=8.0 Hz), 4.18–4.12 (m, 2H), 3.95 (s, 2H), 3.19 (s, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 1.28 (t, 3H, J=7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ=166.8, 153.4, 141.3, 137.9, 130.5, 127.3, 114.2, 93.4, 59.9, 55.9, 34.3, 29.2, 21.0, 19.1, 14.4. MS (EI) m/z: 309, 264, 236, 230, 158, 132, 91, 28. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.62; H, 6.25; N, 13.62.

*4.3.5. Ethyl 1-(4-bromophenyl)-5,5-dicyano-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5hfb**).* Reddish brown oil. IR (KBr): 2981, 2260, 1694, 1577, 1513, 1487, 1383, 1244, 1145, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.54 (d, 2H, J=8.4 Hz), 7.06 (d, 2H, J=8.4 Hz), 4.22–4.16 (m, 2H), 3.98 (s, 2H), 3.21 (s, 2H), 2.21 (s, 3H), 1.31 (t, 3H, J=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.6, 152.3, 142.9, 133.1, 129.0, 121.4, 114.0, 95.4, 60.1, 55.7, 34.2, 29.2, 19.3, 14.4. MS (EI) m/z: 373, 328, 300, 296, 222, 220, 196, 155, 143, 75. Anal. Calcd for $C_{17}H_{16}BrN_3O_2$: C, 54.56; H, 4.31; Br, 21.35; N, 11.23. Found: C, 54.71; H, 4.26; Br, 21.38; N, 11.20.

*4.3.6. Ethyl 5,5-dicyano-1-(4-methoxyphenyl)-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5hgb**).* Reddish brown oil. IR (KBr): 2980, 2850, 2261, 1691, 1579, 1511, 1457, 1383, 1245, 1139, 831 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.08 (d, 2H, J=8.8 Hz), 6.89 (d, 2H, J=8.8 Hz), 4.17–4.12 (m, 2H), 3.93 (s, 2H), 3.80 (s, 3H), 3.19 (s, 2H), 2.16 (s, 3H), 1.28 (t, 3H, J=7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ=166.8, 159.0, 153.7, 136.6, 128.8, 115.0, 114.2, 92.9, 59.8, 56.1, 55.5, 34.2, 29.2, 19.0, 14.4. MS (EI) m/z: 325, 280, 252, 247, 232, 174, 148, 28. Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.61; H, 5.81; N, 12.85.

4.4. X-ray data

Crystal data for **5baa**. $C_{24}H_{25}NO_3$, M=375.45, monoclinic, a=6.1835 (12), b=26.950 (5) A, c=12.243 (2) Å, U=1983.6 (7) $Å^3$, T=293 (2) K, space group $P21/n$, 15,703 reflections measured, 3577 independent reflections (R_{int}=0.0506). The final wR (F^2) was 0.1799 (all data) and R_1 was 0.0541 for $I>2s$ (I). CCDC No. 779617.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.10.041.

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