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An organocatalytic multi-molecular cascade reaction for the synthesis of acetate functionalized 1,4-dihydropyridines

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ABSTRACT

An organocatalytic cascade reaction involving the incorporation of alkyl propiolates and primary amines has been realized for the facile synthesis of 1,4-dihydropyridines (1,4-DHPs) bearing a C4 acetate fragment. This method allows rapid and atom economical generation of *N*-aryl, *N*-alkyl, and *NH* 1,4-DHPs with moderate to excellent yields.

1. Introduction

Heterocycles are central backbones of numerous natural products, pharmaceutically active molecules and biologically relevant compounds. As one of the most well-known privileged heterocyclic structures, the 1,4-DHP has showed up ubiquitously in clinic drugs and biologically active lead compounds.[1] In addition, new biological functions on 1,4-DHPs scaffolds have continuously been discovered in recent years along with the daily increasing availability of new synthetic strategies.[2] More over, 1,4-DHPs are also known as useful reactants in the synthesis of complex organic molecules by acting as the cyclic backbone donors.[3] The versatile known utilities as well as the high application of 1,4-DHPs in different research areas have accordingly stimulated the everlasting research interest in the synthesis of 1,4-DHPs, especially in the manner of diversity-oriented synthesis.[4]

As the first authentic diversity-oriented method toward 1,4-DHPs synthesis, the Hantzsch multicomponent reaction has tremendously contributed to the chemistry of 1,4-DHPs,[5] which also inspired the splendid research advances in 1,4-DHPs synthesis with new approaches. During the past decades, a large number of outstanding works have been reported allowing the synthesis of 1,4-DHPs in great span of structural diversity, especially in the fashion of multicomponent reactions.[6] A common feature of most known multicomponent methods, however, is that an aldehyde must be used to donate the formyl group. Such kind of synthetic methods result in the consequence of limited product diversity since most known multicomponent 1,4-DHPs syntheses provide 4-aryl or 4-alkyl 1,4-DHPs by relying on the aldehyde as the donor of C4 fragment of the ring. In this regard, discovering new electrophilic component to alternate aldehyde constitutes a main current challenge in the synthesis of diverse 1,4-DHPs libraries.

One interesting example using unconventional electrophile to enable the multi-molecular synthesis of 1,4-DHPs is the reactions of alkyl propiolates and amines. Ajavakom et al. have[7] developed the stepwise method for the synthesis of 4-acetate functionalized 1,4-DHPs by using the prior prepared enamino ester as the key building block in the presence of $TiCl_4$ (Eq 1 in Scheme 1). The employment of metal catalyst, however, is usually not favored, especially in the efforts of preparing biologically relevant products. To avoid the reliance on metal catalyst, finding alternative metal-free approach for the synthesis of these products is therefore of high significance.

We have recently developed an efficient secondary amine-based organocatalytic strategy to activate propiolates by forming reactive *N*,*N*-disubstituted enamino ester intermediate and have successfully established a series of novel cascade reactions for diversity-oriented synthesis by making use of this key activation protocol.[8] As our ongoing efforts in disclosing the application of this catalytic method, we wish to report herein the organocatalytic synthesis of 4-acetate 1,4-DHPs via the multi-molecular reactions of propiolates and primary amines in aqueous media (Eq 2 in Scheme 1).

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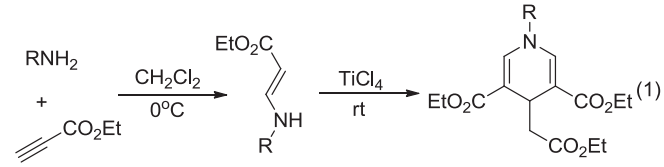
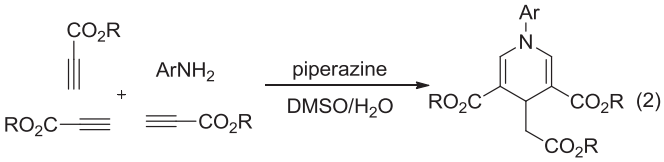
Previous work: metal-catalyzed multi-molecular synthesis of 1,4-DHPs



This work: Organocatalytic multi-molecular synthesis of 1,4-DHPs



Scheme 1. Metal-catalyzed and organocatalytic multi-molecular synthesis of 1,4-DHPs.

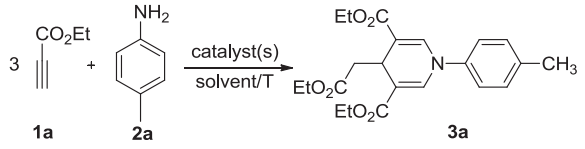
2. Results and discussion

To start the investigation, the model reaction of ethyl propiolate **1a** and *p*-methylaniline **2a** was tentatively run under either the presence of only TMSCl or piperazine, which were found both unable to produce target product **3a** (entries 1–2, Table 1). On the other hand, the simultaneous employment of TMSCl and piperazine in the reaction allowed smooth production of **3a** (entry 3, Table 1). Systematic optimization on the reaction medium suggested that the aqueous DMSO could provide much higher yield of **3a** than all other examined solvents (entries 4–10, Table 1). In addition, the variation in the acidic catalyst or the secondary amine species didn't lead to the occurrence of improved result (entries 11–15, Table 1). Subsequent optimization on reaction temperature proved that 120 °C was more proper (entries 16–17, Table 1) than other screened temperatures. Finally, the examination on the loading of piperazine was able to further increase the yield of **3a** when 20 mol % piperazine was subjected (entries 18–19, Table 1).

Based on the results from optimization experiment, the scope of this organocatalytic synthesis toward 1,4-DHPs was examined. As shown by the results in Table 2, the present synthetic method displayed excellent tolerance to the synthesis of 4-acetate 1,4-DHPs by employing different propiolates and primary amines. The products were generally obtained with moderate to excellent yield. Notably, not only the aryl amines containing different substituents such as alkyl, alkoxyl etc. were generally applicable for the synthesis, the alkyl primary amines, including those conventional ones and the one containing sensitive substituent such as 2-hydroxyl ethylamine (**3p**) could also be smoothly transformed to corresponding products. A tendency suggested by the results was that electron deficient amines such as those anilines containing electron withdrawing group provided corresponding 1,4-DHPs with evidently lower yield (**3c**, **3d**, **3f**, **3r**), and the *ortho*-substitution on the aniline also hindered the formation of corresponding products to some extent (**3g**, **3h**, **3i**, **3j**, **3t**, **3u**). Interestingly, the alkyl amines, both linear ones with and without branched structure participated the reaction to afford *N*-alkyl 1,4-DHPs with high yield probably because of their higher nucleophilicity (**3l**–**3o**). No expect product was observed when 4-nitroaniline was employed, and the result could be attributed to the much weaker nucleophilicity of the amino group resulted by the strong electron withdrawing effect of the nitro substituent.

In order to probe more comprehensively the application of the present method in 1,4-DHPs synthesis, the reaction between ethyl propiolate **1a** and ammonium acetate **4** was executed under the standard reaction. To our delight, the reaction was found to provide

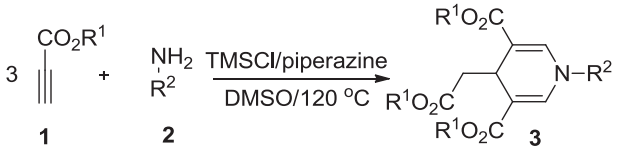
Table 1
Optimization on reaction conditions[a]



Entry	Solvent(v/v)	Catalyst	Amine	Yield(%)[b]
1	DMSO	TMSCl	No	Trace
2	DMSO	No	Piperazine	Trace
3	DMSO	TMSCl	Piperazine	20
4	DMF	TMSCl	Piperazine	15
5	*i*-PrOH	TMSCl	Piperazine	27
6	H_2O	TMSCl	Piperazine	Trace
7	Toluene	TMSCl	Piperazine	37
8	DMSO/H_2O(1.5/0.5)	TMSCl	Piperazine	40
9	DMSO/H_2O(0.5/1.5)	TMSCl	Piperazine	45
10	DMSO/H_2O(1/1)	TMSCl	Piperazine	65
11	DMSO/H_2O(1/1)	*P*-TSA	Piperazine	Trace
12	DMSO/H_2O(1/1)	AcOH	Piperazine	Trace
13	DMSO/H_2O(1/1)	$FeCl_3$	Piperazine	Trace
14	DMSO/H_2O(1/1)	TMSCl	Morpholine	26
15	DMSO/H_2O(1/1)	TMSCl	Dimethylamine	38
16[c]	DMSO/H_2O(1/1)	TMSCl	Piperazine	57
17[d]	DMSO/H_2O(1/1)	TMSCl	Piperazine	50
18[e]	DMSO/H_2O(1/1)	TMSCl	Piperazine	83
19[f]	DMSO/H_2O(1/1)	TMSCl	Piperazine	42

[a] General conditions: ethyl propiolate (0.9 mmol), 4-methylaniline (0.3 mmol), catalyst (0.06 mmol), secondary amine (0.12 mmol) were stirred for 12 h by heating at 120 °C in 2.0 mL solvent(s).
[b] Yield of isolated products base on 0.3 mmol.
[c] The temperature was 110 °C.
[d] The temperature was 130 °C.
[e] The piperazine was 0.06 mmol.
[f] The piperazine was 0.03 mmol.

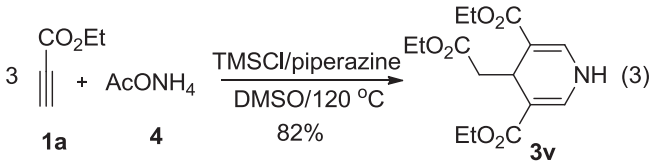
Table 2
Scope of the organocatalytic multi-molecular 1,4-DHPs synthesis[a]



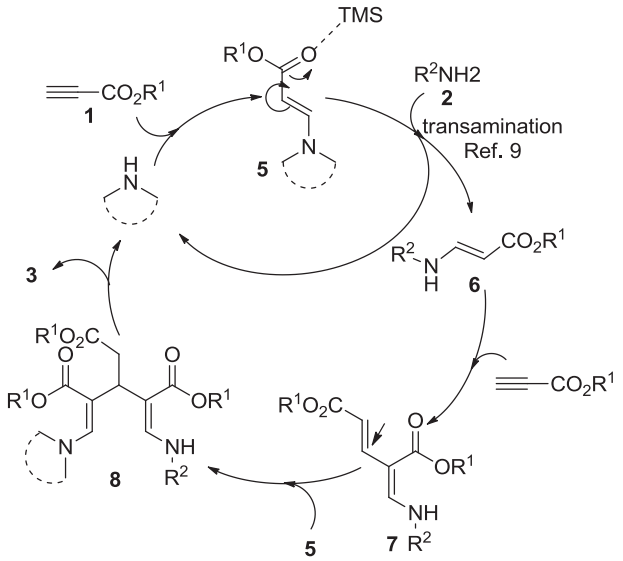
R^1	R^2	Product	Yield[b] (%)[b]
Et	4-MeC_6H_4	**3a**	83
Et	4-MeOC_6H_4	**3b**	77
Et	4-BrC_6H_4	**3c**	61
Et	4-ClC_6H_4	**3d**	69
Et	3-OHC_6H_4	**3e**	45
Et	3-ClC_6H_4	**3f**	60
Et	2-MeC_6H_4	**3g**	53
Et	2-ClC_6H_4	**3h**	63
Et	2-MeOC_6H_4	**3i**	49
Et	2,4-$Me_2C_6H_4$	**3j**	51
Et	C_6H_5	**3k**	75
Et	*i*-Propyl	**3l**	81
Et	*n*-Butyl	**3m**	78
Et	*i*-Butyl	**3n**	77
Et	Benzyl	**3o**	84
Et	CH_2CH_2OH	**3p**	83
Me	4-MeC_6H_4	**3q**	62
Me	4-BrC_6H_4	**3r**	54
Me	4-MeOC_6H_4	**3s**	61
Me	2-ClC_6H_4	**3t**	53
Me	2,4-$Me_2C_6H_4$	**3u**	52
Et	4-$NO_2C_6H_4$	—	nr

[a] General conditions: **1** (0.9 mmol), **2** (0.3 mmol), TMSCl (0.06 mmol), piperazine (0.06 mmol) were stirred for 12 h by heating at 120 °C in mixed DMSO/water (1 mL/1 mL).
[b] Yield of isolated product.

NH-containing 1,4-DHP **3v** with excellent yield (Eq 3), demonstrating the highly broad application scope of this organocatalytic procedure.



According to the results from the present work and our previous investigation on secondary amine-catalyzed multi-molecular synthesis involving propiolates, the mechanism of the present reaction has been proposed and outlined in Scheme 2. The reaction has firstly been initiated via the rapid formation of enamino ester intermediate **5** via the addition of secondary amine to propiolate **1**. The easy transamination[9] of **5** with primary amine leads to the occurrence of NH-containing enamino ester **6** in the presence of acidic catalyst. The Michael addition of the nucleophilic α-carbon to another propiolate molecule provides intermediate **7**, which undergoes a further Michael addition by intermediate **5** to afford bis-enaminoesters **8**. The intramolecular transamination on **8** yields the target 1,4-DHPs **3**.



Scheme 2. The proposed reaction mechanism.

In conclusion, by employing a secondary amine-based organocatalytic strategy, we have successfully developed a multi-molecular protocol for the synthesis of 1,4-DHPs bearing 4-acetate substructure. This method doesn't require any metal catalyst and has exhibited excellent tolerance to the synthesis of *N*-aryl, *N*-alkyl, and NH 1,4-DHPs, which will reasonably be a useful route to complement those known methods on 1,4-DHPs synthesis.

3. Experimental section

3.1. General experimental information

All experiments were carried out at open atmosphere. All chemicals and solvents used in the experiments were obtained from commercial sources and used directly without further treatment. ^{1}H and ^{13}C NMR were recorded in 400 MHz apparatus in $CDCl_3$. The frequencies for ^{1}H NMR and ^{13}C NMR test are 400 MHz and 100 MHz, respectively. The chemical shifts were reported in ppm with TMS as internal standard. Melting points were tested in X-4A instrument without correcting temperature, and the HRMS were obtained under ESI model.

3.2. General procedure for the synthesis of 1,4-DHPs 3

To a 25 mL round-bottom flask was added alkyl propiolate **1** (0.9 mmol), primary amine **2** (0.3 mmol), piperazine (0.06 mmol), TMSCl (0.06 mmol) and DMSO/water (1 mL/1 mL). The resulting mixture was heated to 120 °C, and reacted at the same temperature for 12 h. After completion of the reaction, the resulting solution was mixed with water (10 mL), and then extracted with ethyl acetate (3×10 mL). The combined organic phase was dried over anhydrous Na_2SO_4. The solid was filtered away and the solvent was removed at reduced pressure. Target products were acquired by the purification of the residue via silica gel flash column chromatography (V_{EtOAc}:V_{PET}=1:10).

*3.2.1. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-p-tolyl-1,4-dihydropyridine-3,5-dicarboxylate (**3a**).* Brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 2H), 7.22 (d, 2H, *J*=7.2 Hz), 7.12 (d, 2H, *J*=7.6 Hz), 4.28–4.21 (m, 5H), 4.07–4.01 (m, 2H), 2.59 (d, 2H, *J*=4.8 Hz), 2.37 (s, 3H), 1.31 (t, 6H, *J*=6.4 Hz), 1.18 (t, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 166.8, 140.7, 137.9, 136.3, 130.3, 120.9, 107.8, 60.3, 60.1, 40.6, 29.6, 20.8, 14.4, 14.2; ESI-HRMS: Calcd for $C_{22}H_{27}NO_6Na$ $[M+Na]^+$: 424.1731; Found: 424,1777.

*3.2.2. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylat (**3b**).*[7] Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 2H), 7.16 (d, 2H, *J*=7.6 Hz), 6.93 (d, 2H, *J*=8.0 Hz), 4.26–4.20 (m, 5H), 4.07–4.02 (m, 2H), 3.83 (s, 3H), 2.58 (d, 2H, *J*=7.6 Hz), 1.30 (t, 6H, *J*=6.4 Hz), 1.19 (t, 3H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 166.8, 158.2, 138.4, 136.6, 123.0, 114.9, 107.5, 60.3, 60.0, 55.6, 40.6, 29.5, 14.4, 14.2.

*3.2.3. Diethyl-1-(4-bromophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3c**).* Green liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, 2H, *J*=7.2 Hz), 7.12 (d, 2H, *J*=8.4 Hz), 4.26–4.22 (m, 5H), 4.05–4.00 (m, 2H), 2.60 (d, 2H, *J*=4.4 Hz), 1.31 (t, 6H, *J*=7.2 Hz), 1.18 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 166.9, 142.4, 137.5, 133.3, 122.7, 119.9, 109.2, 60.9, 60.5, 40.7, 29.9, 14.8, 14.6; ESI-HRMS: Calcd for $C_{21}H_{24}NO_6BrNa$ $[M+Na]^+$: 488.0679; Found: 488.0704.

*3.2.4. Diethyl-1-(4-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3d**).* Brown solid; mp 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 2H), 7.39 (d, 2H, *J*=8.8 Hz), 7.17 (d, 2H, *J*=8.4 Hz), 4.26–4.22 (m, 5H), 4.06–4.00 (m, 2H), 2.60 (d, 2H, *J*=4.8 Hz), 1.31 (t, 6H, *J*=6.8 Hz), 1.18 (t, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 166.6, 141.6, 137.2, 131.9, 129.9, 122.0, 108.7, 60.4, 60.1, 40.3, 29.5, 14.4, 14.2; ESI-HRMS: Calcd for $C_{21}H_{24}NO_6ClNa$ $[M+Na]^+$: 444.1184; Found: 444.1208.

*3.2.5. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(3-hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3e**).* Brown solid; mp 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 2H), 7.20 (t, 1H, *J*=8.0 Hz), 6.76–6.69 (m, 3H), 4.28–4.22 (m, 5H), 4.09–4.03 (m, 2H), 2.60 (d, 2H, *J*=4.4 Hz), 1.31 (t, 6H, *J*=6.8 Hz), 1.19 (t, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 167.1, 157.5, 144.1, 137.8, 130.6, 113.5, 112.0, 108.1, 108.0, 60.6, 60.4, 40.7, 29.7, 14.4, 14.1; ESI-HRMS: Calcd for $C_{21}H_{25}NO_7Na$ $[M+Na]^+$: 426.1523; Found: 426.1518.

*3.2.6. Diethyl-1-(3-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3f**).* Brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 2H), 7.36 (t, 1H, *J*=8.0 Hz), 7.24 (s, 2H), 7.13 (d, 1H, *J*=7.6 Hz), 4.27–4.25 (m, 5H), 4.07–4.01 (m, 2H), 2.61 (d, 2H, *J*=3.2 Hz), 1.32 (t, 6H, *J*=6.0 Hz), 1.18 (t, 3H, *J*=6.8 Hz); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 171.6, 166.5, 144.0, 137.0, 135.5, 130.9, 126.4, 120.9, 118.7, 109.1, 60.5, 60.1, 40.3, 29.6, 14.4, 14.2; ESI-HRMS: Calcd for $C_{21}H_{25}NO_6Cl$ $[M+H]^+$: 422.1365; Found: 422.1373.

*3.2.7. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-o-tolyl-1,4-dihydropyridine-3,5-dicarboxylate (**3g**).* Yellow solid; mp 80–81 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, 3H, *J*=5.2 Hz), 7.26 (s, 2H), 7.18 (d, 1H, *J*=6.4 Hz), 4.31 (t, 1H, *J*=4.4 Hz), 4.24–4.19 (m, 4H), 4.11–4.06 (m, 2H), 2.63 (d, 2H, *J*=4.4 Hz), 2.32 (s, 3H), 1.28 (t, 6H, *J*=6.4 Hz), 1.22 (t, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 167.2, 142.8, 139.8, 134.6, 132.1, 128.7, 127.7, 126.5, 106.9, 60.6, 60.4, 40.8, 29.9, 18.1, 14.8, 14.6; ESI-HRMS: Calcd for $C_{22}H_{27}NO_6Na$ $[M+Na]^+$: 424.1731; Found: 424.1759.

*3.2.8. Diethyl-1-(2-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3h**).* Yellow solid; mp 94–95 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 2H, *J*=7.2 Hz), 7.35 (s, 2H), 7.30 (s, 2H), 7.29 (s, 1H), 4.29 (t, 1H, *J*=4.8 Hz), 4.25–4.20 (m, 4H), 4.11–4.06 (m, 2H), 2.62 (d, 2H, *J*=4.8 Hz), 1.29 (t, 6H, *J*=7.2 Hz), 1.22 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 166.6, 140.5, 138.9, 131.0, 130.5, 129.3, 128.2, 127.6, 107.4, 60.3, 60.1, 40.5, 29.4, 14.4, 14.2; ESI-HRMS: Calcd for $C_{21}H_{24}NO_6ClNa$ $[M+Na]^+$: 444.1184; Found: 444.1185.

*3.2.9. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(2-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3i**).* Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 2H), 7.32 (d, 1H, *J*=7.2 Hz), 7.21 (d, 1H, *J*=7.2 Hz), 7.02 (d, 2H, *J*=5.2 Hz), 4.30 (t, 1H, *J*=4.8 Hz), 4.25–4.20 (m, 4H), 4.12–4.06 (m, 2H), 3.88 (s, 3H), 2.61 (d, 2H, *J*=4.8 Hz), 1.30 (t, 6H, *J*=7.2 Hz), 1.23 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 166.8, 153.5, 139.8, 131.8, 128.9, 126.1, 121.0, 112.2, 106.6, 60.0, 59.9, 55.8, 40.7, 29.4, 14.3, 14.1; ESI-HRMS: Calcd for $C_{22}H_{27}NO_7Na$ $[M+Na]^+$: 440.1680; Found: 440.1706.

*3.2.10. Diethyl-1-(2,4-dimethylphenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3j**).* Yellow solid; mp 76–77 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 2H), 7.10 (s, 1H), 7.06 (s, 2H), 4.30 (t, 1H, *J*=4.8 Hz), 4.24–4.18 (m, 4H), 4.11–4.05 (m, 2H), 2.61 (d, 2H, *J*=4.8 Hz), 2.35 (s, 3H), 2.27 (s, 3H), 1.28 (t, 6H, *J*=7.6 Hz), 1.22 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 165.3, 138.5, 138.1, 136.8, 132.4, 130.7, 126.3, 124.4, 104.8, 58.6, 58.5, 39.0, 28.0, 19.5, 16.0, 12.8, 12.7; ESI-HRMS: Calcd for $C_{23}H_{29}NO_6Na$ $[M+Na]^+$: 438.1887; Found: 438.1891.

*3.2.11. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**3k**).*[7] Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 2H), 7.43 (t, 1H, *J*=7.6 Hz), 7.27 (s, 1H), 7.23 (d, 2H, *J*=7.2 Hz), 4.28–4.22 (m, 5H), 4.05–4.01 (m, 2H), 2.60 (d, 2H, *J*=4.8 Hz), 1.31 (t, 6H, *J*=6.8 Hz), 1.18 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 166.8, 143.1, 137.7, 129.8, 126.4, 120.8, 108.3, 60.4, 60.1, 40.5, 29.6, 14.4, 14.2.

*3.2.12. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-isopropyl-1,4-dihydropyridine-3,5-dicarboxylate (**3l**).* Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 2H), 4.22–4.18 (m, 5H), 4.06–4.00 (m, 2H), 3.66–3.62 (m, 1H), 2.45 (d, 2H, *J*=4.8 Hz), 1.30 (t, 12H, *J*=6.4 Hz), 1.21 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 166.9, 137.2, 105.8, 59.9, 59.8, 55.4, 40.8, 30.0, 21.9, 14.3, 14.1; ESI-HRMS: Calcd for $C_{18}H_{27}NO_6Na$ $[M+Na]^+$: 376.1731; Found: 376.1727.

*3.2.13. Diethyl-1-butyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3m**).*[7] Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 (s, 2H), 4.21–4.19 (m, 5H), 4.06–4.01 (m, 2H), 3.31 (t, 2H, *J*=6.4 Hz), 2.46 (d, 2H, *J*=2.8 Hz), 1.61 (t, 2H, *J*=6.8 Hz), 1.37 (t, 2H, *J*=6.8 Hz), 1.29 (t, 6H, *J*=6.4 Hz), 1.21 (t, 3H, *J*=6.4 Hz), 0.95 (t, 3H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 166.8, 139.3, 105.7, 60.0, 59.8, 54.6, 40.9, 32.2, 29.5, 19.4, 14.3, 14.1, 13.6.

*3.2.14. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-isobutyl-1,4-dihydropyridine-3,5-dicarboxylate (**3n**).* Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.11 (s, 2H), 4.21–4.19 (m, 5H), 4.06–4.01 (m, 2H), 3.12 (d, 2H, *J*=6.8 Hz), 2.46 (d, 2H, *J*=3.2 Hz), 1.93–1.90 (m, 1H), 1.30 (t, 6H, *J*=6.4 Hz), 1.21 (t, 3H, *J*=7.2 Hz), 0.95 (d, 6H, *J*=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 166.9, 139.6, 105.5, 62.5, 60.0, 59.8, 41.0, 29.5, 29.4, 19.5, 14.3, 14.1; ESI-HRMS: Calcd for $C_{20}H_{23}NO_6Na$ $[M+Na]^+$: 390.1887; Found: 390.1885.

*3.2.15. Diethyl-1-benzyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3o**).*[7] Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.30 (m, 3H), 7.24 (d, 2H, *J*=7.6 Hz), 7.20 (s, 2H), 4.50 (s, 2H), 4.24 (t, 1H, *J*=4.4 Hz), 4.21–4.16 (m, 4H), 4.02–3.97 (m, 2H), 2.51 (d, 2H, *J*=4.4 Hz), 1.27 (t, 6H, *J*=7.2 Hz), 1.16 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 166.7, 139.5, 136.0, 129.0, 128.2, 127.1, 106.4, 60.1, 59.9, 58.0, 40.8, 29.6, 14.3, 14.1.

*3.2.16. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3p**).*[7] Yellow solid; mp 72–74 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 2H), 4.22–4.18 (m, 4H), 4.09 (s, 1H), 4.06–4.01 (m, 2H), 3.88 (s, 1H), 3.76 (s, 2H), 3.45 (s, 2H), 2.62 (s, 2H), 1.29 (t, 6H, *J*=6.8 Hz), 1.20 (t, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 166.8, 140.2, 105.3, 61.6, 60.2, 60.0, 57.5, 39.3, 28.7, 14.3, 14.0.

*3.2.17. Dimethyl-4-(2-methoxy-2-oxoethyl)-1-p-tolyl-1,4-dihydropyridine-3,5-dicarboxylate (**3q**).* Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 2H), 7.21 (d, 2H, *J*=3.2 Hz), 7.11 (d, 2H,*J*=8.0 Hz), 4.26 (t, 3H, *J*=4.8 Hz), 3.76 (s, 6H), 3.59 (s, 3H), 2.59 (d, 2H, *J*=4.4 Hz), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 167.2, 140.6, 138.1, 136.5, 130.3, 120.8, 107.5, 51.6, 51.4, 40.6, 29.5, 20.9; ESI-HRMS: Calcd for $C_{19}H_{21}NO_6Na$ $[M+Na]^+$: 382.1261; Found: 382.1262.

*3.2.18. Dimethyl-1-(4-bromophenyl)-4-(2-methoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3r**).* Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 4H, *J*=2.4 Hz), 7.13 (s, 2H), 4.23 (t, 1H, *J*=4.4 Hz), 3.78 (s, 6H), 3.59 (s, 3H), 2.61 (d, 2H, *J*=4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 166.9, 141.9, 137.4, 132.9, 122.3, 119.7, 108.5, 51.7, 51.4, 40.3, 29.4; ESI-HRMS: Calcd for $C_{18}H_{18}NO_6BrNa$ $[M+Na]^+$: 446.0210; Found: 446.0235.

*3.2.19. Dimethyl-4-(2-methoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3s**).* Yellow solid; mp 95–96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 2H), 7.16 (d, 2H, *J*=9.2 Hz), 6.93 (d, 2H, *J*=8.8 Hz), 4.25 (t, 1H, *J*=4.8 Hz), 3.82 (s, 3H), 3.76 (s, 6H), 3.60 (s, 3H), 2.59 (d, 2H, *J*=4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 167.2, 158.2, 138.6, 136.5, 122.9, 114.9, 107.1, 55.6, 51.5, 51.4, 40.6, 29.4; ESI-HRMS: Calcd for $C_{19}H_{21}NO_7Na$ $[M+Na]^+$: 398.1210; Found: 398.1209.

*3.2.20. Dimethyl-1-(2-chlorophenyl)-4-(2-methoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3t**).* Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 1H, *J*=7.6 Hz), 7.34 (d, 3H, *J*=2.0 Hz), 7.32 (s, 2H), 4.28 (t, 1H, *J*=4.8 Hz), 3.75 (s, 6H), 3.64 (s, 3H), 2.63 (d, 2H, *J*=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 167.0, 140.4, 139.1, 131.0, 130.5, 129.4, 128.2, 127.4, 107.1, 51.6, 51.4, 40.5, 29.3; ESI-HRMS: Calcd for $C_{18}H_{18}NO_6ClNa$ $[M+Na]^+$: 402.0715; Found: 402.0725.

*3.2.21. Dimethyl-1-(2,4-dimethylphenyl)-4-(2-methoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3u**).* Yellow liquid; ^1H NMR

(400 MHz, $CDCl_3$): δ 7.26 (s, 2H), 7.10 (s, 2H), 7.06 (s, 2H), 4.30 (t, 1H, J=4.8 Hz), 3.74 (s, 3H), 3.64 (s, 3H), 2.62 (d, 2H, J=4.8 Hz), 2.35 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 167.2, 139.9, 139.8, 138.4, 133.7, 132.2, 127.9, 125.8, 106.0, 51.4, 52.3, 40.5, 29.4, 20.9, 17.5; ESI-HRMS: Calcd for $C_{20}H_{23}NO_6Na$ $[M+Na]^+$: 396.1418; Found: 396.1415.

*3.2.22. Diethyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3v**).* Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.32 (d, 2H, J=5.2 Hz), 4.22–4.19 (m, 5H), 4.08–4.03 (m, 2H), 2.49 (d, 2H, J=3.2 Hz), 1.30 (t, 6H, J=6.8 Hz), 1.24 (t, 3H, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 167.2, 136.1, 105.3, 60.2, 60.1, 41.0, 29.7, 14.3, 14.0; ESI-HRMS: Calcd for $C_{15}H_{21}NO_6Na$ $[M+Na]^+$: 334.1261; Found: 334.1264.

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra of all products) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.06.101.

References and notes

1. (a) Hilgeroth, A. *Mini-Rev. Med. Chem.* **2002**, *2*, 235; (b) Ioan, P.; Carosati, E.; Micucci, M.; Gruciani, G.; Broccatelli, F.; Zhorov, B. S.; Chiarini, A.; Budriesi, R. *Curr. Med. Chem.* **2011**, *18*, 4901; (c) Carosati, E.; Ioan, P.; Micucci, M.; Broccatelli, F.; Gruciani, G.; Zhorov, B. S.; Chiarini, A.; Budriesi, R. *Curr. Med. Chem.* **2012**, *19*, 4306.
2. (a) Singh, R. K.; Prasad, D. N.; Bhardwaj, T. R. *Med. Chem. Res.* **2015**, *24*, 1534; (b) Shekari, F.; Sadeghpour, H.; Javidnia, K.; Saso, L.; Nazari, F.; Firuzi, O.; Min, R. *Eur. J. Pharmacol.* **2015**, *746*, 233; (c) Hilgeroth, A.; Baumert, C.; Coburger, C.; Seifert, M.; Krawczyk, S.; Hempel, C.; Neubauer, F.; Krug, M.; Molnar, J.; Lage, H. *Med. Chem.* **2013**, *9*, 487; (d) Locatelli, A.; Cosconati, S.; Micucci, M.; Leoni, A.; Marinelli, L.; Bedini, A.; Ioan, P.; Spampinato, S. M.; Novellino, E.; Chiarini, A.; Budriesi, R. *J. Med. Chem.* **2013**, *56*, 3966; (e) Sirisha, K.; Bikshapathi, D.; Achaiah, G.; Reddy, V. M. *Eur. J. Med. Chem.* **2011**, *46*, 1564; (f) Reimão, J. Q.; Scotti, M. T.; Tempone, A. G. *Bioorg. Med. Chem.* **2010**, *18*, 8044.
3. (a) Rudler, H.; Parlier, A.; Hamon, L.; Herson, P.; Daran, J. C. *Chem. Commun.* **2008**, 4150; (b) Schmaunz, C. E.; Mayer, P.; Wanner, K. T. *Synthesis* **2014**, *46*, 1630.
4. For reviews on 1,4-DHPs synthesis, see: (a) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223; (b) Wan, J.-P.; Liu, Y. *RSC Adv.* **2012**, *2*, 9763.
5. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.
6. (a) Liu, L.; Sarkisian, R.; Deng, Y.; Wang, H. *J. Org. Chem.* **2013**, *78*, 5751; (b) Wen, L.-R.; Liu, C.; Li, M.; Wang, L.-J. *J. Org. Chem.* **2010**, *75*, 7605; (c) Wan, J.-P.; Zhou, R.; Liu, Y.; Cai, M. *RSC Adv.* **2013**, *3*, 2477; (d) Kumar, R.; Andhare, N. H.; Shard, A.; Richa; Sinha, A. K. *RSC Adv.* **2014**, *4*, 19111; (e) Safari, J.; Zarnegar, Z. *RSC Adv.* **2013**, *3*, 26094; (f) Gati, W.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Beilstein J. Org. Chem.* **2012**, *8*, 2214; (g) Liu, Y.-p.; Liu, J.-m.; Wang, X.; Cheng, T.-m.; Li, R.-t. *Tetrahedron* **2013**, *69*, 5242; (h) Sun, J.; Sun, Y.; Gao, H.; Yan, C.-G. *Eur. J. Org. Chem.* **2011**, 6952; (i) Yan, S.-H.; Zhao, F.-Y.; Liu, H.-Y.; Deng, J.; Zhang, Z.-H. *J. Heterocycl. Chem.* **2012**, *49*, 1126; (j) Yang, J.; Wang, C.; Xie, X.; Li, H.; Li, Y. *Eur. J. Org. Chem.* **2010**, 4189; (k) Jiang, H.; Mai, R.; Cao, H.; Zhu, Q.; Liu, X. *Org. Biomol. Chem.* **2009**, *7*, 4943.
7. Sirijindalert, T.; Hansuthirakul, K.; Rashatasakhon, P.; Sukwattanasinitt, M.; Ajavakom, A. *Tetrahedron* **2010**, *66*, 5161.
8. (a) Wan, J.-P.; Lin, Y.; Huang, Q.; Liu, Y. *J. Org. Chem.* **2014**, *79*, 7232; (b) Wan, J.-P.; Lin, Y.; Hu, K.; Liu, Y. *Beilstein J. Org. Chem.* **2014**, *10*, 287; (c) Wan, J.; Zhou, Y.; Liu, Y.; Fang, Z.; Wen, C. *Chin. J. Chem.* **2014**, *32*, 219; (d) Wan, J.-P.; Lin, Y.; Jing, Y.; Xu, M.; Liu, Y. *Tetrahedron* **2014**, *70*, 7874; (e) Wan, J.-P.; Zhou, Y.; Jiang, K.; Ye, H. *Synthesis* **2014**, *46*, 3256.
9. For reaction based-on this kind of transamination, see: (a) Wan, J.-P.; Zhou, Y.; Cao, S. *J. Org. Chem.* **2014**, *79*, 9872; (b) Cao, S.; Xin, L.; Liu, Y.; Wan, J.-P.; Wen, C. *RSC Adv.* **2015**, *5*, 27372; (c) Wan, J.-P.; Wang, C.; Pan, Y. *Tetrahedron* **2011**, *67*, 922; (d) Liu, Y.; Zhou, R.; Wan, J.-P. *Synth. Commun.* **2013**, *43*, 2475; (e) Muthusaravanan, S.; Sasikumar, C.; Bala, B. D.; Perumal, S. *Green. Chem.* **2014**, *16*, 1297; (f) Cao, S.; Jing, Y.; Liu, Y.; Wan, J.-P. *Chin. J. Org. Chem.* **2014**, *34*, 876.