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Novel synthetic route to 1,4-dihydropyridines from β-amino acrylates by using titanium(IV) chloride under facile conditions

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ABSTRACT

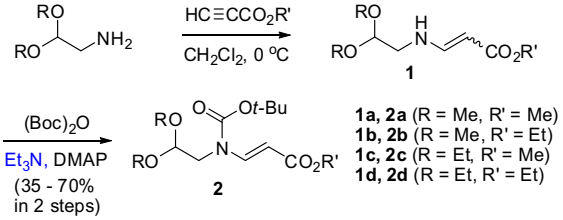
The reactions of Boc-β-amido- and β-amino acrylates, in which the C=C possesses both nucleophilic and electrophilic sites, were investigated under acidic conditions. The trifluoroacetic-acid induced cyclization of the β-amido acrylates to the corresponding oxazolidin-2-ones involves a rarely seen nucleophilic attack of the carbamate carbonyl group. The cyclotrimerization of β-amino acrylates to *N*-substituted 1,4-dihydropyridines was observed in the presence of a Lewis acid. High yields of 1,4-dihydropyridines (70–83%) were readily obtained by using substoichiometric amount $TiCl_4$ under mild condition. The cyclotrimerization is presumably occurring via a Hantzsch related mechanism involving three addition/elimination reactions of the amphiphilically reactive C=C.

1. Introduction

Enamines are often used as important intermediates for C–C bond formation in total synthesis of many natural products and drug candidates.[1–6] Due to their high reactivity, they are rarely isolated and often generated in situ. One of the most classic examples of enamine reaction is the Mannich reaction in which the enamines are generated from carbonyl compounds and amines.[7] Enamines can be used for the cyclization to allow an efficient synthesis of various vital building blocks in natural products, such as pyrrole.[8] In most cases, enamines are utilized as nucleophiles due to the electron donating nature of the nitrogen lone pair electrons. Incorporation of an electron-withdrawing group on the other terminus can lead to interesting amphiphilic reactivity of the enamine. In order to gain a better understanding for designing the amphiphilic synthons, the preparation of isolable enamines is essential that should lead to greater application of this class of compounds. In this work, we synthesized and isolated β-amino acrylates, which are the enamines bearing an electron-withdrawing group that possess both nucleophilic and electrophilic sites. Our study of these enamines lead to novel synthetic methods for oxazolidinones and 1,4-dihydropyridines.

2. Results and discussion

In order to synthesize β-amino acrylates **1** and β-amido acrylates **2**, the experiments were easily undertaken following Macdonald's method (Scheme 1).[9] β-Amino acrylates **1** were synthesized by addition reaction of a primary amine to alkyl propiolate in CH_2Cl_2 at 0 °C. The products were simply obtained by solvent evaporation in excellent yields and purities as witnessed by ^1H NMR spectroscopy. However, the products existed as a mixture of cis and trans isomers. We initially protected the amino group with *tert*-butoxycarbonyl (Boc) group to obtain the more stable β-amido acrylates **2** in fair to good yields. It should be noted that the *cis* enamine was observed by ^1H NMR as the major adduct from the first step, probably due to the preferred intramolecular hydrogen bonding between the carbonyl oxygen and the amino proton.[10] However, only the trans isomer of the Boc-protected product was



Scheme 1. Synthesis of substrates **1** and **2**.

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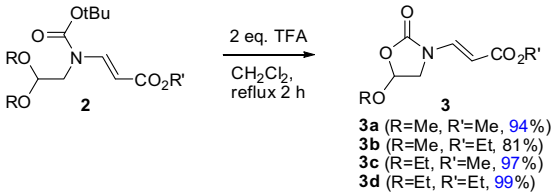
isolated from the second step, indicating the geometrical isomerization to the less sterically strained form under the reaction condition.

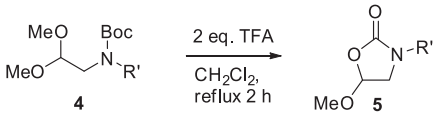
Treatment of **2** with trifluoroacetic acid (TFA) in CH_2Cl_2 gave rise to oxazolidin-2-one **3** in high yields (Scheme 2) without the simple Boc protecting group. Apparently, Boc-enamide **2** underwent a 5-*exo*-*trig* cyclization, presumably via the attack of the carbamate carbonyl oxygen to the oxonium carbon to form an oxazolidinone ring. A similar cyclization involving Au-catalyzed nucleophilic attack onto an activated alkyne has recently been reported.[11]



Scheme 2. TFA-induced intramolecular cyclization of **2**.

To demonstrate the generality of the cyclization, the reaction was further investigated using related Boc-protected secondary amines. The treatment of **4** with TFA cleanly produced oxazolidin-2-ones **5** in high yields (Table 1) comparable to other methods starting from amino alcohols[12], aziridines[13] or epoxides[14] precursors.

Table 1
Cyclization yields of **4** to oxazolidin-2-one **5**

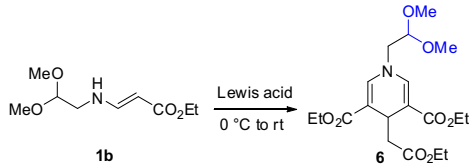


Entry	Substrate	R′	Product	Yield (%)
1	**2b**	CH=CHCO$_2$Et	**3b**	81 (95)[a]
2	**4a**	Bn	**5a**	84
3	**4b**	4-Nitrobenzyl	**5b**	92
4	**4c**	Naphthalenyl methyl	**5c**	84

[a] Yield obtained from GC.

In the formation of oxazolidinone ring, the C=C in enamides **2** did not participate in the cyclization neither did it decompose under the strongly acidic TFA treatment. The relatively unreactive C=C is attributed to the presence of the electron-withdrawing Boc group. We thus turned our attention back to the unprotected β-amino acrylates **1**, which contain both nucleophilic and electrophilic sites on their double bond. As the utilization of enamine intermediates are usually performed under basic conditions due to their unstability,[15] it would be of general interest to examine if the C=C in β-amino acrylates can take part in any cyclization under acidic conditions. Unfortunately, the initial attempt to isolate β-amino acrylate **1** was not successful due to its decomposition on a silica gel column. However, with preelution of the silica gel with 1% triethylamine (Et_3N) in hexane, β-amino acrylate **1** could be isolated and found to be reasonably stable at room temperature for a week. By treating **1b** with TFA in CH_2Cl_2 at 0 °C or at reflux failed to give any characterizable products. When Lewis acids, such as $BF_3{\cdot}OEt_2$, $AlCl_3$, and $TiCl_4$ were used in place of TFA, 1,4-dihydropyridine **6** was obtained in low yields while the use of $AlMe_2Cl$ gave no reaction (Table 2). Although the formation of 1,4-dihydropyridine observed here is closely related to Hantzsch reaction,[16] the reaction was noted to proceed at a significantly lower temperature. However, the product yields obtained from these initial results are not satisfactory, which is likely due to the decomposition of the acetal group in β-amino acrylate **1b** under the acidic conditions.

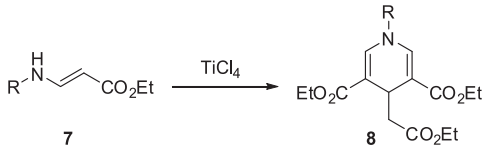
Table 2
Optimization for 1,4-dihydropyridine **6** formation



Entry	Acid	Amount (equiv)	Solvent	Time	**1b** (%)	**6** (%)
1	BF_3OEt_2	0.3	THF	10 h	—	17
2	$AlCl_3$	0.3	THF	3 h	—	<10
3	Me_2AlCl	0.5	THF	10 h	98	—
4	$TiCl_4$	0.2	DCM	10 h	—	33

A number of related β-amino acrylates (**7**) without acetal moiety were prepared and used as the cyclization substrates. According to the yields presented in Table 2, $TiCl_4$ was selected for reaction optimization on these β-amino acrylate substrates. Treatment of β-amino acrylates **7** with a substoichiometric amount of $TiCl_4$ resulted in the formation of dyhydropyridine **8** containing various *N*-substituents in excellent yield (Table 3). In the case of *N*-aromatic β-amino acrylates (entries 5–11), the higher amount of $TiCl_4$ is required for the high percent yield (compare entries 7 to 6 and 9 to 8). Although the synthesis of 1,4-dihydropyridines can be previously achieved by several methods such as Michael condensation,[17] reduction of pyridines[18] and others,[19] harsh conditions are generally required and low yields are often obtained due to the competitive formation of 1,2-regioisomer. The high yields and mild condition of this Lewis acid-induced cyclization of enamines can thus be an attractive alternative method for 1,4-dihydropyridine synthesis.

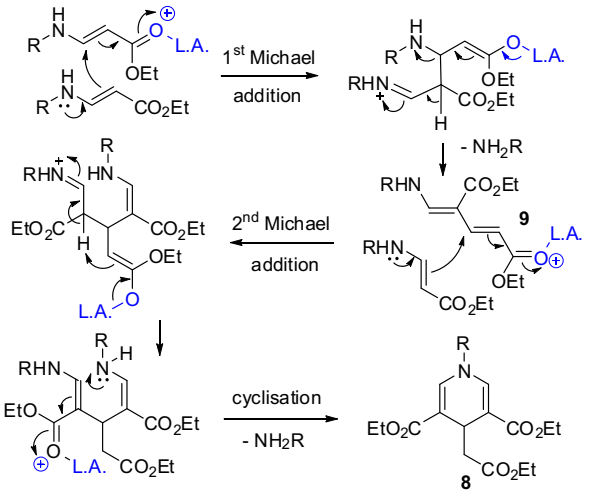
Table 3
Syntheses of a series of 1,4-dihydropyridine derivatives **8** at 0 °C to room temperature for overnight



Entry	Substrate	R	Amount (equiv)	Product	Yield (%)
1	**7a**	*n*-Bu	0.2	**8a**	81
2	**7b**	*n*-$C_{18}H_{37}$	0.2	**8b**	83
3	**7c**	Bn	0.2	**8c**	79
4	**7d**	$HOCH_2CH_2$	0.2	**8d**	81
5	**7e**	Ph	0.5	**8e**	82
6	**7f**	*p*-MeO–Ph	0.2	**8f**	52
7			0.5	**8f**	76
8	**7g**	*p*-I–Ph	0.2	**8g**	58
9			0.5	**8g**	79
10	**7h**	*p*-F–Ph	0.5	**8h**	70
11	**7i**	*m*-Cl–Ph	0.5	**8i**	76

A few modified Hantzsch reactions using Lewis acid have recently been reported. Vohra et al. reported the Lewis acid-catalyzed synthesis of dihydropyridines from the condensation of enamines and α,β-unsaturated aldehydes.[20] Kikuchi et al. have noted a formation of 1,4-dihydropyridine derivatives from the reaction between aniline and ethyl propiolate in the presence of $Sc(OTf)_3$.[21] We believe that this reaction should also proceed through the enamine intermediate similar to our observation.

We also isolated dimer **9** (R=Ph) as a minor product during condition optimization suggesting that the cyclotrimerization occurs via the formation of a dimeric intermediate according to the proposed mechanism shown in Scheme 3.



Scheme 3. Purposed mechanism of 1,4-dihydropyridine **8** formation.

The reaction presumably started with Lewis acid-catalyzed Michael addition followed by amine elimination to give the dimer. Owing to the amphiphilic reactivities of the C=C in the β-amino acrylate, one C=C can play a role of nucleophile while another plays an electrophilic role in the addition step. The dimer undergoes the second addition/elimination series to form the trimer. The final intramolecular addition/elimination results in the dihydropyridine **8**. In total, the dihydropyridine ring is derived from three addition/elimination steps involving three molecules of β-amino acrylate.

3. Conclusion

In conclusion, β-amino acrylates containing both nucleophilic and electrophilic sites were synthesized and their reactions under acidic conditions were investigated. With Boc protecting group, the C=C in the β-amido acrylates is unreactive and the cyclization using TFA involves the attack of the carbamate carbonyl group to an electrophilic site to give oxazolidin-2-one in high yield. Without the protecting group, the C=C in β-amino acrylates functions as both nucleophile and electrophile in series of addition/elimination leading to the efficient formation of 1,4-dihydropyridine ring when treated with $TiCl_4$ at 0 °C to room temperature.

4. Experimental

4.1. General

The NMR spectra were recorded with a Varian Mercury YH400 NMR spectrometer at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR using solutions in $CDCl_3$. Chemical shifts (δ) are shown in part per million relative to the residual proton resonance of $CHCl_3$ at 7.26 ppm and solvent carbon resonance of $CDCl_3$ 77.0 ppm for ^{1}H and ^{13}C, respectively. Coupling constants values (J) are shown in hertz (Hz). The IR spectra were collected with the Nicolet 6700 FT-IR spectrometer equipped with a global source and DTGS detector in region 4000–400 cm^{-1}. The HRMS spectra were measured on an electrospray ionization mass spectrometer (micrOTOF, Bruker Daltomics). Elemental (C, H, N) analysis was performed on PE 2400 Series II elemental analyzer (Perkin-Elmer, USA). Gas chromatographic analyzes were conducted on a Shimadzu GC-14A chromatograph. Reagents were purchased from commercial suppliers and used freshly. Dichloromethane (CH_2Cl_2) was dried over CaH_2 and distilled prior to use. Tetrahydrofuran (THF) was dried over sodium/benzophenone and distilled just before use. Other solvents were dried and distilled according to standard procedures. Reactions progress and purity of compounds were monitored by thin layer chromatography using silica plates (Merck F_{245}). Silica gel 60 (SiO_2, Merck 70–230 mesh ASTM, no. 7734) was used for flash column chromatography.

4.2. Preparation of 5-alkoxy-2-oxazolidinones (3)

To the solution of enamide **2** (1 equiv) in CH_2Cl_2 (14 mM), TFA (2 equiv) was slowly added and the reaction mixture was refluxed for 5 h. The mixture was quenched by 0.2 M $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The collected organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude oil was purified by flash chromatography, eluting with EtOAc/petroleum ether (1:7 to 1:3 v/v), to provide the corresponding oxaolidin-2-one **3**.

*4.2.1. (E)-Methyl-3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate (**3a**).* Synthesized according to above procedure 4.2 from enamide **2a** (300 mg, 0.31 mmol) as a yellow oil (293 mg, 94%); R_f (25% EtOAc/hexane) 0.05; δ_H (400 MHz, $CDCl_3$): 7.93 (1H, d, J 14.2 Hz, NC*H*=CH), 5.55 (1H, dd, J 2.4, 6.4 Hz, C*H*OMe), 5.14 (1H, d, J 14.1 Hz, NCH=C*H*), 3.84 (1H, dd, J 6.4, 10.7 Hz, NCH_AH_BCH), 3.74 (3H, s, CO_2Me), 3.57 (3H, s, O*Me*), 3.52 (1H, dd, J 2.4, 10.7 Hz, NCH_AH_BCH); δ_H (100 MHz, $CDCl_3$): 166.8, 153.1, 137.8, 100.3, 98.9, 56.9, 51.5, 48.8; HRMS (ESI): MH^+, found 224.0529. $C_8H_{11}NNaO_5^+$ requires 224.0529.

*4.2.2. (E)-Ethyl-3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate (**3b**).* Synthesized according to above procedure 4.2 from enamide **2b** (98 mg, 0.32 mmol) as a yellow oil (58 mg, 81%); R_f (25% EtOAc/hexane) 0.08; δ_H (400 MHz, $CDCl_3$): 7.93 (1H, d, J 14.2 Hz, NC*H*=CH), 5.55 (1H, dd, J 2.5, 6.4 Hz, C*H*OMe), 5.13 (1H, d, J 14.1 Hz, NCH=C*H*), 4.20 (2H, q, CO_2CH_2), 3.84 (1H, dd, J 6.4, 10.6 Hz, NCH_AH_BCH), 3.57 (3H, s, O*Me*), 3.53 (1H, dd, J 2.5, 10.6 Hz, NCH_AH_BCH), 1.26 (3H, t, J 7.1 Hz CH_2CH_3); δ_C (100 MHz, $CDCl_3$): 166.9, 153.2, 137.9, 100.2, 97.8, 65.7, 51.2, 48.9, 14.8; Elem. Anal. Found C, 50.44%; H, 6.12%; N, 6.51% (calcd for $C_9H_{13}NO_5$; C, 50.23%; H, 6.09%; N, 6.51%).

*4.2.3. (E)-Methyl-3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate (**3c**).* Synthesized according to above procedure 4.2 from enamide **2c** (98 mg, 0.31 mmol) as a pale yellow oil (65 mg, 97%); R_f (25% EtOAc/hexane) 0.11; δ_H (400 MHz, $CDCl_3$): 7.93 (1H, d, J 14.2, NC*H*=CH), 5.65 (1H, dd, J 2.5, 6.4 Hz, C*H*OEt), 5.13 (1H, d, J 14.2 Hz, NCH=C*H*), 3.99–3.91 (1H, m, OC$H_AH_BCH_3$), 3.84 (1H, dd, J 6.4, 10.6 Hz, NCH_AH_BCH), 3.73 (3H, s, CO_2CH_3), 3.72–3.64 (1H, m, OC$H_AH_BCH_3$), 3.53 (1H, dd, J 2.5, 10.6 Hz, NCH_AH_BCH), 1.26 (3H, t, J 7.1 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$): 166.9, 153.2, 137.9, 100.2, 97.8, 65.7, 51.2, 48.9,14.8; Elem. Anal. Found C, 50.44%; H, 6.12%; N, 6.51% (calcd for $C_9H_{13}NO_5$; C, 50.23%; H, 6.09%; N, 6.51%).

*4.2.4. (E)-Ethyl-3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate (**3d**).* Synthesized according to above procedure 4.2 from enamide **2d** (107 mg, 0.32 mmol) as a pale yellow oil (74 mg, 99%); R_f (25% EtOAc/hexane) 0.14; δ_H (400 MHz, $CDCl_3$): 7.93 (1H, d, J 14.1 Hz, NC*H*=CH), 5.65 (1H, dd, J 2.3, 6.4 Hz, OC*H*CH_2), 5.12 (1H, d, J 14.1 Hz, NCH=C*H*), 4.19 (2H, q, J 7.2 Hz, $CO_2CH_2CH_3$), 3.99–3.91 (1H, m, OC$H_AH_BCH_3$), 3.84 (1H, dd, J 6.4, 10.6 Hz, NCH_AH_BCH), 3.72–3.64 (1H, m, OC$H_AH_BCH_3$), 3.52 (1H, dd, J 2.3, 10.6 Hz, NCH_AH_BCH), 1.28 (3H, t, J 7.2 Hz, $CO_2CH_2CH_3$), 1.26 (3H, t, J 7.2 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$): 166.4, 153.2, 137.6, 100.6, 97.8, 65.6, 60.2, 48.9, 14.7, 14.2; Elem. Anal. Found C, 52.31%; H, 6.68%; N, 6.16% (calcd for $C_{10}H_{15}NO_5$; C, 52.40%; H, 6.60%; N, 6.11%).

*4.2.5. 3-Benzyl-5-methoxyoxazolidin-2-one (**5a**).* Synthesized according to above procedure 4.2 from enamide **4a** (500 mg, 1.69 mmol) as a pale yellow oil (295 mg, 84%); δ_H (400 MHz, $CDCl_3$):

7.37–7.25 (5H, m, C_6H_5), 5.34 (1H, dd, *J* 6.4, 2.3 Hz, C*H*OMe), 4.48 (1H, d, *J* 15.0 Hz ArCH_AH_B) 4.42 (1H, d, *J* 15.0 Hz, ArCH_AH_B), 3.90–3.45 (4H, m, *Me*, and NCH_aH_b), 3.21 (1H, dd, *J* 10.0, 2.3 Hz, NCH_aH_b); δ_C (100 MHz, $CDCl_3$): 156.3, 135.1, 128.4, 127.6, 127.5 97.8, 55.8, 49.8, 47.3; HRMS (ESI): MH^+, found 208.0973. $C_{11}H_{14}NO_3^+$ requires 208.0968.

*4.2.6. 5-Methoxy-3-(4-nitrobenzyl)oxazolidin-2-one (**5b**).* Synthesized according to above procedure 4.2 from enamide **4b** (66 mg, 0.19 mmol) as a colorless oil (45 mg, 92%); R_f (50% EtOAc/hexane) 0.13; ν_{max}(neat) 3099, 3073, 2916, 2845, 1746, 1525, 1345 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 8.21 (2H, d, *J* 8.6 Hz, 3-Ar*H*), 7.44 (2H, d, *J* 8.4 Hz, 2-Ar*H*), 5.39 (1H, dd, *J* 6.3, 2.1 Hz, C*H*OMe), 4.61 (1H, d, *J* 15.9 Hz, Ar–CH_AH_B), 4.48 (1H, d, *J* 15.9 Hz, Ar–CH_AH_B), 3.60 (1H, dd, *J* 9.9, 6.3 Hz, NCH_aH_b), 3.52 (3H, s, *Me*), 3.25 (1H, dd, *J* 9.9, 2.1 Hz, NCH_aH_b); δ_C (100 MHz, $CDCl_3$): 156.6, 147.6, 142.9, 128.4 (2C), 124.0 (2C), 98.1, 56.3, 50.4, 47.0; HRMS (ESI): MNa^+, found 275.0664. $C_{11}H_{12}N_2NaO_5^+$ requires 275.0638.

*4.2.7. 5-Methoxy-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (**5c**).* Synthesized according to above procedure 4.2 from enamide **4c** (45 mg, 0.13 mmol) as a colorless oil (28 mg, 84%); R_f (50% EtOAc/hexane) 0.50; ν_{max} (neat) 3049, 3001, 2933, 2837, 1745, 1481, 1217 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 8.12 (1H, d, *J* 8.3 Hz, Ar*H*), 7.86 (2H, dd, *J* 16.2, 7.8 Hz, Ar*H*), 7.62–7.49 (2H, m, Ar*H*), 7.48–7.35 (2H, m, Ar*H*), 5.32–5.24 (1H, m, C*H*OMe), 5.00 (1H, d, *J* 14.8 Hz, Ar–CH_AH_B), 4.80 (1H, d, *J* 14.8 Hz, Ar–CH_AH_B), 3.47 (3H, s, *Me*), 3.39 (1H, dd, *J* 10.1, 6.5 Hz, NCH_AH_B), 3.15 (1H, dd, *J* 10.1, 2.4 Hz, NCH_AH_B); δ_C (100 MHz, $CDCl_3$): 156.2, 133.8, 131.4, 130.9, 129.1, 128.7, 127.2, 126.9, 126.2, 125.1, 123.4, 98.0, 56.1, 50.2, 46.1; HRMS (ESI): MNa^+, found 280.0970. $C_{15}H_{15}NNaO_3^+$ requires 280.0944.

4.3. Preparation of aliphatic enamine substrates (1b, 7a–d)

To the solution of aliphatic amine (1 equiv) in CH_2Cl_2 (0.2 M), ethyl propiolate (1.2 equiv) was slowly added and the reaction mixture was stirred overnight at room temperature under nitrogen atmosphere. The mixture was evaporated in vacuo and condensed residue was purified by column chromatography (EtOAc/hexane=1:10) to provide the corresponding ethyl β-amino acrylate (**7a**–**d**).

*4.3.1. Ethyl-3-(2,2-dimethoxyethylamino)acrylate (**1b**).* Synthesized according to above procedure 4.3 from aminoacetaldehyde dimethylacetal (500 mg, 4.76 mmol) as a pale yellow oil (880 mg, 91%) as a cis-isomer; R_f (25% EtOAc/hexane) 0.25; ν_{max} (neat) 3350, 2986, 2937, 2837, 1663, 1618, 1476, 1372, 1194, 1125, 1070 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.79 (1H, s (br), N*H*), 6.57 (1H, ddd, *J* 13.0, 8.1, 1.4 Hz, =C*H*N), 4.46 (1H, dd, *J* 8.1, 1.7 Hz, C*H*=CHN), 4.30 (1H, dt, *J* 5.3, 1.6 Hz, C*H*$(OMe)_2$), 4.08 (2H, dq, *J* 7.1, 1.7 Hz, OCH_2CH_3), 3.38 (6H, 2s, OMe), 3.21 (2H, t, *J* 5.8 Hz, NCH_2), 1.23 (3H, dt, *J* 7.1, 1.7 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$): 170.6, 152.3, 103.9, 82.8, 58.6, 54.6 (2C), 50.3, 14.5; HRMS (ESI): MNa^+, found 226.1042. $C_9H_{17}NNaO_4^+$ requires 226.1050.

*4.3.2. Ethyl-3-(butylamino)acrylate (**7a**).* Synthesized according to above general procedure 4.3 from *n*-butylamine (450 mg, 6.15 mmol) as a pale yellow oil (917 mg, 87%) as a 1:3 mixture of trans- and cis-isomers; R_f (25% EtOAc/hexane) 0.45; ν_{max} (neat) 3332, 2960, 2929, 2873, 1667, 1625, 1479, 1198, 1149, 1052 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.94–7.64 (0.75H, br, N*H* (*cis*)), 7.46 (0.25H, dd, *J* 13.1, 8.1 Hz, =C*H*N (*trans*)), 6.58 (0.75H, dd, *J* 13.2, 8.0 Hz, =C*H*N (*cis*)), 4.67 (0.50H, d (br), *J* 13.2 Hz, N*H* (*trans*) and C*H*=CHN (*trans*)), 4.39 (0.75H, d, *J* 8.0 Hz, C*H*=CHN (*cis*)), 4.11–4.00 (2H, m, CH_2–N), 3.11 (1.50H, dd, *J* 13.2, 6.6 Hz, OCH_2CH_3 (*cis*)), 2.99 (0.50H, dd, *J* 12.6, 6.7 Hz, OCH_2CH_3 (*trans*)), 1.59–1.39 (2H, m, NCH_2CH_2), 1.32 (2H, dq, *J* 14.6, 7.2 Hz, N$(CH_2)_2CH_2$), 1.21 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 0.88 (3H, t, *J* 7.3 Hz, N$(CH_2)_3CH_3$); δ_C (100 MHz, $CDCl_3$): 170.8 (*cis*), 169.6 (*trans*), 152.3, 85.1 (*trans*), 81.2 (*cis*), 58.8 (*trans*), 58.4 (*cis*), 48.2, 33.2, 19.6, 14.5, 13.6; HRMS (ESI): MNa^+, found 194.1159. $C_9H_{17}NNaO_2^+$ requires 194.1151.

*4.3.3. Ethyl-3-(octadecylamino)acrylate (**7b**).* Synthesized according to above general procedure 4.3 from octadecylamine (200 mg, 0.74 mmol) as a yellow solid (254 mg, 93%) as a cis-isomer; mp 59–63 °C; R_f (25% EtOAc/hexane) 0.75; ν_{max} (neat) 3332, 2920, 2851, 1665, 1614, 1466, 1194, 1149, 1039 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.90–7.75 (1H, m, N*H*), 6.61 (1H, dd, *J* 13.2, 8.0 Hz, =C*H*N), 4.43 (1H, d, *J* 8.0 Hz, C*H*=CHN), 4.10 (2H, td, *J* 14.2, 5.0 Hz, CH_2N), 3.13 (2H, q, *J* 6.7 Hz, OCH_2CH_3), 1.51 (2H, td, *J* 14.1, 7.0 Hz, NCH_2CH_2), 1.35–1.13 (33H, m, OCH_2CH_3 and N$(CH_2)_2(CH_2)_{15}$), 0.87 (3H, t, *J* 6.8 Hz, N$(CH_2)_{17}CH_3$); δ_C (100 MHz, $CDCl_3$): 152.4, 81.2, 58.6, 48.7, 31.9, 31.3, 29.7–29.6 (10C, br), 29.5, 29.4, 29.3, 26.5, 22.7, 14.6, 14.1; HRMS (ESI): MH^+, found 368.3523. $C_{23}H_{46}NO_2^+$ requires 368.3523.

*4.3.4. Ethyl-3-(benzylamino)acrylate (**7c**).* Synthesized according to above general procedure 4.3 from benzyl amine (500 mg, 4.67 mmol) as a pale yellow oil (862 mg, 90%) as a 1:2 mixture of trans- and cis-isomers; R_f (25% EtOAc/hexane) 0.35; ν_{max} (neat) 3333, 3056, 3023, 2977, 2937, 2900, 1668, 1612, 1483, 1452, 1191, 1142, 1055 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 8.20–8.00 (0.67H, br, N*H* (*cis*)), 7.58 (0.33H, dd, *J* 13.2, 8.0 Hz, =C*H*N (*trans*)), 7.40–7.19 (5H, m, *Ph*), 6.69 (0.67H, dd, *J* 13.0, 8.1 Hz, =C*H*N (*cis*)), 4.90–4.70 (0.66H, d (br), *J* 13.3 Hz, N*H* (*trans*) and C*H*=CHN (*trans*)), 4.54 (0.67H, d, *J* 8.1 Hz, C*H*=CHN (*cis*)), 4.34 (0.67H, d, *J* 6.0 Hz, NCH_2 (*cis*)), 4.21 (0.33H, d, *J* 5.3 Hz, NCH_2 (*trans*)), 4.12 (2H, q, *J* 7.1 Hz, OCH_2), 1.25 (3H, dt, *J* 7.1, 3.3 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$): 170.8 (*cis*), 169.5 (*trans*), 152.0, 138.5, 128.8 (*trans*), 128.7 (*cis*), 127.8 (*trans*), 127.5 (*cis*), 127.1, 86.8 (*trans*), 82.8 (*cis*), 59.0 (*trans*), 58.7 (*cis*), 52.1, 14.5; HRMS (ESI): MNa^+, found 228.0993. $C_{12}H_{15}NNaO_2^+$ requires 228.0995.

*4.3.5. Ethyl-3-(2-hydroxyethylamino)acrylate (**7d**).* Synthesized according to above general procedure 4.3 from 2-hydroxyethylamine (200 mg, 3.27 mmol) as a pale yellow solid (494 mg, 95%) as a 1:1 mixture of trans- and cis-isomers; mp 36–38 °C; R_f (50% EtOAc/hexane) 0.20; ν_{max} (neat) 3346, 2976, 2930, 1666, 1606, 1162, 1050 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 8.00–7.80 (0.5H, br, N*H* (*cis*)), 7.53 (0.5H, dd, *J* 13.3, 8.3 Hz, =C*H*N (*trans*)), 6.66 (0.5H, dd, *J* 13.1, 8.0 Hz, =C*H*N (*cis*)), 5.10–5.00 (0.5H, br, N*H* (*trans*)), 4.74 (0.5H, d, *J* 13.3 Hz, C*H*=CHN (*trans*)), 4.50 (0.5H, d, *J* 8.0 Hz, C*H*=CHN (*cis*)), 4.11 (2H, 2q, *J* 7.1 Hz, OCH_2), 3.77 (1H, t, *J* 5.0 Hz, NCH_2 (*cis*)), 3.69 (1H, t, *J* 4.7 Hz, NCH_2 (*trans*)), 3.30 (1H, dd, *J* 11.2, 5.5 Hz, HOCH_2 (*cis*)), 3.20 (1H, dd, *J* 10.5, 5.3 Hz, HOCH_2 (*trans*)), 2.43–2.32 (0.5H, br, OH (*cis*)), 2.32–2.20 (0.5H, br, OH (*trans*)), 1.25 (3H, dt, *J* 7.1, 2.5 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$): 171.0 (*cis*), 169.9 (*trans*), 152.6, 86.1 (*trans*), 82.6 (*cis*), 62.6, 59.1 (*cis*), 58.8 (*trans*), 50.7, 14.5; HRMS (ESI): MNa^+, found 182.0798. $C_7H_{13}NNaO_3^+$ requires 182.0788.

4.4. Preparation of aromatic enamine substrates (7e–i)

To the solution of ethyl propiolate (1.2 equiv) in $ClCH_2CH_2Cl$ (20 mM), copper(I) iodide (0.5 equiv) and aromatic amine (1 equiv) were dispersed and the reaction mixture was stirred for 10 min. The reaction mixture was then heated at 60 °C overnight. The reaction products were filtered, evaporated, and condensed residue was purified by column chromatography (EtOAc/hexane=1:10 v/v) to provide the corresponding aromatic enamine (**7e**–**i**).

*4.4.1. Ethyl-3-(phenylamino)acrylate (**7e**).* Synthesized according to above procedure 4.4 from aniline (500 mg, 5.37 mmol) as

a colorless oil (564 mg, 55%) as a cis-isomer; R_f (10% EtOAc/hexane) 0.50; ν_{max} (neat) 3307, 3054, 3031, 2982, 1667, 1628, 1598, 1488, 1453, 1242, 1190 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 9.92 (1H, d (br), *J* 11.7 Hz, N*H*), 7.36–7.18 (3H, m, =C*H*N and *ortho*-C_6H_5), 7.05–6.88 (3H, m, *meta*-C_6H_5 and *para*-C_6H_5), 4.85 (1H, d, *J* 8.3 Hz, C*H*=CHN), 4.19 (2H, q, *J* 7.1 Hz, OCH_2), 1.31 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$): 170.3, 142.9, 140.6, 129.6 (2C), 122.4, 115.2 (2C), 87.3, 59.2, 14.4; HRMS (ESI): MNa^+, found 214.0715. $C_{11}H_{13}NNaO_2^+$ requires 214.0838.

*4.4.2. Ethyl-3-(4-methoxyphenylamino)acrylate (**7f**).* Synthesized according to above procedure 4.4 from 4-methoxyaniline (500 mg, 4.05 mmol) as a yellow oil (296 mg, 33%) as a *cis*-isomer; R_f (17% EtOAc/hexane) 0.38; ν_{max} (neat) 3274, 3073, 3037, 2976, 2950, 1615, 1589, 1508, 1482, 1277, 1164 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 9.81 (1H, d (br), *J* 12.6 Hz, N*H*), 7.15 (1H, dd, *J* 12.8, 8.3 Hz, =C*H*N), 6.91 (2H, d, *J* 9.0 Hz, *meta*-C_6H_4), 6.85 (2H, d, *J* 9.0 Hz, *ortho*-C_6H_4), 4.77 (1H, d, *J* 8.2 Hz, C*H*=CHN), 4.17 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.78 (3H, s, O*Me*), 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$): 170.5, 155.4, 144.1, 134.4, 116.9 (2C), 114.9 (2C), 86.0, 59.1, 55.5, 14.5; HRMS (ESI): MNa^+, found 244.0828. $C_{12}H_{15}NNaO_3^+$ requires 244.0944.

*4.4.3. (Z)-Ethyl-3-(4-iodophenylamino)acrylate (**7g**).* In this case, synthesized according to above procedure 4.4 from 4-iodoaniline (1.01 g, 4.61 mmol) in CH_2Cl_2 solution at room temperature as a white solid (1.21 g, 83%) as a *cis*-isomer; mp 90–95 °C; R_f (20% EtOAc/hexane) 0.50; ν_{max} (neat) 3294, 3084, 2971, 1666, 1625, 1584, 1470, 1196 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 9.89 (1H, d (br), *J* 11.6 Hz, N*H*), 7.57 (2H, d, *J* 8.7 Hz, *meta*-C_6H_4), 7.17 (1H, dd, *J* 12.5, 8.4 Hz, =C*H*N), 6.73 (2H, d, *J* 8.7 Hz, *ortho*-C_6H_4), 4.87 (1H, d, *J* 8.4 Hz, C*H*=CHN), 4.17 (2H, q, *J* 7.1 Hz, OCH_2), 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$): 170.2, 142.2, 140.4, 138.4(2C), 117.2(2C), 88.4, 84.6, 59.4, 14.4; HRMS (ESI): MH^+, found 317.9985. $C_{12}H_{15}NNaO_3^+$ requires 317.9986.

*4.4.4. Ethyl-3-(4-fluorophenylamino)acrylate (**7h**).* Synthesized according to above procedure 4.4 from 4-fluoroaniline (500 mg, 4.50 mmol) as a yellow solid (556 mg, 59%) as a *cis*-isomer; mp 35–38 °C; R_f (10% EtOAc/hexane) 0.50; ν_{max} (neat) 3305, 3275, 3071, 3948, 2980, 1665, 1624, 1600, 1509, 1478, 1197 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 9.87 (1H, d (br), *J* 11.5 Hz, N*H*), 7.15 (1H, dd, *J* 12.6, 8.3 Hz, =C*H*N), 7.06–6.95 (2H, m, *meta*-C_6H_4), 6.95–6.85 (2H, m, *ortho*-C_6H_4), 4.82 (1H, d, *J* 8.3 Hz, C*H*=CHN), 4.17 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 1.34–1.27 (3H, m, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$): 170.4, 158.5 (d, *J* 241.3 Hz, *C*F), 143.4, 137.0, 116.7 (2C, d, *J* 7.9 Hz, CFCH*C*H), 116.3 (2C, d, *J* 23.0 Hz, CF*C*H), 87.3, 59.3, 14.4; HRMS (ESI): MNa^+, found 232.0663. $C_{11}H_{12}FNNaO_2^+$ requires 232.0744.

*4.4.5. Ethyl-3-(3-chlorophenylamino)acrylate (**7i**).* Synthesized according to above procedure 4.4 from 3-chloroaniline (411 mg, 3.22 mmol) as a yellow solid (392 mg, 54%) as a *cis*-isomer; mp 51–52 °C; R_f (10% EtOAc/hexane) 0.48; ν_{max} (neat) 3067, 2982, 2927, 2898, 1670, 1635, 1599, 1469, 1203 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 9.91 (1H, d (br), *J* 11.8 Hz, N*H*), 7.19 (2H, td, *J* 12.5, 7.2 Hz, =C*H*N and 2-Ar*H*), 6.95 (2H, d, *J* 6.7 Hz, 4-Ar*H* and 6-Ar*H*), 6.81 (1H, d, *J* 7.8 Hz, 5-Ar*H*), 4.88 (1H, d, *J* 8.4 Hz, C*H*=CHN), 4.18 (2H, q, *J* 7.1 Hz, OCH_2), 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$): 170.2, 142.2, 141.9, 135.4, 130.6, 122.3, 115.1, 113.6, 88.7, 59.5, 14.4; HRMS (ESI): MNa^+, found 248.0346. $C_{11}H_{12}{}^{35}ClNNaO_2^+$ requires 248.0449.

4.5. Preparation of 1,4-dihydropyridines (6, 8a–i)

To a solution of *N*-substituted β-amino acrylates **7** (1 equiv) in dried CH_2Cl_2 (0.1 M) in an ice bath, $TiCl_4$ (0.2 equiv in the case of *N*-aliphatic β-amino acrylates **1b** and **7a–d** or 0.5 equiv in the case of *N*-aromatic β-amino acrylates **7e–i**) was added rapidly and the reaction mixture was stirred overnight at room temperature under nitrogen atmosphere. After the solution was quenched with ice, distilled deionized water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (25 mL). The organic potions were combined and neutralized by addition of 0.1 M aq $NaHCO_3$ solution. The organic phase was washed three times with deionized water (3×25 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane=1:50 to 1:3) to provide the corresponding dihydropyridines **6**, **8a–d**.

*4.5.1. Diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**6**).* Synthesized according to above general procedure 4.5 from ethyl-3-(2,2-dimethoxyethylamino)acrylate **1b** (577 mg, 2.84 mmol) as a pale yellow oil (33 mg, 81%); R_f (25% EtOAc/hexane) 0.38; ν_{max} (neat) 2981, 2934, 1731, 1705, 1583, 1415, 1250, 1184, 1079 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.15 (2H, s, C*H*=C), 4.39 (1H, t, *J* 5.1 Hz, C*H*$(OMe)_2$), 4.23–4.16 (5H, m, DHP–$CO_2CH_2CH_3$ and C*H*CH_2CO_2Et), 4.03 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 3.43 (6H, s, OMe), 3.37 (2H, d, *J* 5.1 Hz, NCH_2), 2.47 (2H, d, *J* 5.0 Hz, CH_2CO_2Et), 1.29 (6H, t, *J* 7.1 Hz, DHP–$CO_2CH_2CH_3$), 1.21 (3H, t, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 171.7, 166.9 (2C), 139.8 (2C), 106.1 (2C), 103.4, 60.1 (2C), 59.9, 56.4, 55.1 (2C), 40.7, 29.2, 14.4 (2C), 14.1; HRMS (ESI): MH^+, found 400.1971. $C_{19}H_{30}NO_8^+$ requires 400.1967.

*4.5.2. Diethyl-1-butyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8a**).* Synthesized according to above general procedure 4.5 from ethyl-3-(butylamino)acrylate **7a** (450 mg, 2.63 mmol) as a pale yellow oil (262 mg, 81%); R_f (25% EtOAc/hexane) 0.28; ν_{max} (neat) 2975, 2957, 2932, 1731, 1699, 1580, 1196, 1081 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.12 (2H, s, C*H*=C), 4.23–4.15 (5H, m, DHP–$CO_2CH_2CH_3$ and C*H*CH_2CO_2Et), 4.03 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 3.30 (2H, t, *J* 7.2 Hz, NCH_2), 2.45 (2H, d, *J* 5.0 Hz, CH_2CO_2Et), 1.66–1.53 (2H, m, NCH_2CH_2), 1.41–1.31 (2H, m, N$CH_2CH_2CH_2$), 1.29 (6H, t, *J* 7.1 Hz, DHP–$CO_2CH_2CH_3$), 1.20 (3H, t, *J* 7.2 Hz, $CH_2CO_2CH_2CH_3$), 0.95 (3H, t, *J* 7.3 Hz, N$(CH_2)_3CH_3$); δ_C (100 MHz, $CDCl_3$): 171.7, 166.9 (2C), 139.3 (2C), 105.7 (2C), 60.0 (2C), 59.9, 54.7, 40.9, 32.3, 29.5, 19.5, 14.4 (2C), 14.1, 13.6; HRMS (ESI): MNa^+, found 390.1887. $C_{19}H_{29}NNaO_6^+$ requires 390.1887.

*4.5.3. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-octadecyl-1,4-dihydropyridine-3,5dicarboxylate (**8b**).* Synthesized according to above general procedure 4.5 from ethyl-3-(octadecylamino)acrylate **7b** (318 mg, 0.87 mmol) as a pale yellow oil (134 mg, 83%); R_f (25% EtOAc/hexane) 0.20; ν_{max} (neat) 2929, 2850, 1736, 1697, 1211, 1175, 1072 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.12 (2H, s, C*H*=C), 4.23–4.15 (5H, *m*, DHP–$CO_2CH_2CH_3$, and C*H*CH_2CO_2Et), 4.02 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 3.28 (2H, t, *J* 7.3 Hz, NCH_2), 2.45 (2H, d, *J* 5.0 Hz, CH_2CO_2Et), 1.65–1.55 (2H, m, NCH_2CH_2), 1.43–1.11 (39H, m, DHP–$CO_2CH_2CH_3$, and $CH_2CO_2CH_2CH_3$ and *N*-$(CH_2)_2(CH_2)_{15}CH_3$), 0.87 (3H, t, *J* 6.8 Hz, N$(CH_2)_{17}CH_3$); δ_C (100 MHz, $CDCl_3$): 171.7, 166.9 (2C), 139.3 (2C), 105.7 (2C), 60.0 (2C), 59.9, 54.9, 40.9, 31.9, 30.3, 29.8–29.6 (11C, br), 29.5, 29.3, 26.2, 22.7, 14.4 (2C), 14.2, 14.1; HRMS (ESI): MH^+, found 564.4259. $C_{33}H_{58}NO_6^+$ requires 564.4259.

*4.5.4. Diethyl-1-benzyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8c**).* Synthesized according to above general procedure 4.5 from ethyl-3-(benzylamino)acrylate **7c** (401 mg, 1.95 mmol) as a pale yellow oil (207 mg, 79%); R_f (25% EtOAc/hexane) 0.25; ν_{max} (neat) 3060, 3029, 2979, 2928, 1731, 1698, 1582, 1241, 1186, 1077 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.47–7.21 (5H, m, *Ph*), 7.19 (2H, s, C*H*=C), 4.50 (2H, s, NCH_2), 4.23–4.13 (5H, m, DHP–$CO_2CH_2CH_3$, and C*H*CH_2CO_2Et), 3.99 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 2.50 (2H, d, *J* 5.0 Hz, CH_2CO_2Et), 1.27 (6H, t, *J* 7.1 Hz, DHP–$CO_2CH_2CH_3$), 1.16 (3H, t, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 171.7, 166.7 (2C), 139.4 (2C), 129.0 (2C), 128.2 (2C), 127.1, 109.9, 106.4 (2C), 60.1 (2C), 59.9,

58.0, 40.8, 29.5, 14.3 (2C), 14.1; HRMS (ESI): MH^+, found 402.1916. $C_{22}H_{28}NO_6^+$ requires 402.1911.

*4.5.5. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8d**).* Synthesized according to above general procedure 4.5 from ethyl-3-(2-hydroxyethylamino) acrylate **7d** (500 mg, 31.4 mmol) as a pale yellow solid (303 mg, 81%); mp 73–75 °C; R_f (50% EtOAc/hexane) 0.20; ν_{max} (neat) 3625–3200 (br), 2981, 2940, 1724, 1699, 1579, 1229, 1185, 1069 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.17 (2H, s, C*H*=C), 4.27–4.10 (4H, m, DHP–$CO_2CH_2CH_3$), 4.07 (1H, t, *J* 3.7 Hz, *CH*CH_2CO_2Et), 4.02 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 3.88–3.81 (1H, m, OH), 3.78–3.70 (2H, m, $HOCH_2$), 3.49–3.37 (2H, m, CH_2–N), 2.64 (2H, d, *J* 3.7 Hz, CH_2CO_2Et), 1.28 (6H, t, *J* 7.1 Hz, DHP–$CO_2CH_2CH_3$), 1.18 (3H, t, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 173.9, 166.8 (2C), 140.3 (2C), 105.3 (2C), 61.7, 60.3 (2C), 60.1, 57.6, 39.1, 28.6, 14.4 (2C), 14.0; HRMS (ESI): MH^+, found 356.1704. $C_{17}H_{26}NO_7^+$ requires 356.1704.

*4.5.6. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**8e**).* Synthesized according to above general procedure 4.5 from ethyl-3-(phenylamino)acrylate **7e** (480 mg, 2.51 mmol) as a pale yellow oil (265 mg, 82%); R_f (17% EtOAc/hexane) 0.25; ν_{max} (neat) 3063, 2975, 2935, 1734, 1704, 1596, 1586, 1495, 1235, 1204, 1072 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.58 (2H, s, C*H*=C), 7.42 (2H, t, *J* 7.9 Hz, *meta*-C_6H_5), 7.30–7.19 (3H, m, *ortho*-C_6H_5, and *para*-C_6H_5), 4.30–4.17 (5H, m, DHP–$CO_2CH_2CH_3$, and *CH*CH_2CO_2Et), 4.03 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 2.59 (2H, d, *J* 4.8 Hz, CH_2CO_2Et), 1.30 (6H, t, *J* 7.1 Hz, DHP–$CO_2CH_2CH_3$), 1.17 (3H, t, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 171.7, 166.7 (2C), 143.0, 137.6 (2C), 129.8 (2C), 126.4, 120.8 (2C), 108.2 (2C), 60.3 (2C), 60.1, 40.5, 29.6, 14.4 (2C), 14.2; All data are identical to that of the literature compound.[21]

*4.5.7. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8f**).* Synthesized according to above general procedure 4.5 from ethyl-3-(4-methoxyphenylamino) acrylate **7f** (356 mg, 1.61 mmol) as a pale yellow oil (170 mg, 76%), R_f (25% EtOAc/hexane) 0.30; ν_{max} (neat) 3079, 3039, 2977, 2934, 1738, 1702, 1599, 1582, 1518, 1229, 1205, 1079 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.46 (2H, s, C*H*=C), 7.15 (2H, d, *J* 9.0 Hz, *meta*-C_6H_4), 6.92 (2H, d, *J* 9.0 Hz, *ortho*-C_6H_4), 4.28–4.17 (5H, m, DHP–$CO_2CH_2CH_3$ and *CH*CH_2CO_2Et), 4.04 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 3.82 (3H, s, O*Me*), 2.57 (2H, d, *J* 4.8 Hz, CH_2CO_2Et), 1.29 (6H, t, *J* 7.1 Hz, DHP–$CO_2CH_2CH_3$), 1.18 (3H, t, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 171.7, 166.8 (2C), 158.2, 138.3 (2C), 136.6, 122.9 (2C), 114.8 (2C), 107.5 (2C), 60.3 (2C), 60.0, 55.6, 40.6, 29.5, 14.4 (2C), 14.2; HRMS (ESI): MH^+, found 418.1860. $C_{22}H_{28}NO_7^+$, requires 418.1860.

*4.5.8. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-iodophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8g**).* Synthesized according to above general procedure 4.5 from ethyl-3-(4-iodophenylamino)acrylate **7g** (928 mg, 2.93 mmol) as a pale yellow solid (396 mg, 79%); mp 61–66 °C; R_f (20% EtOAc/hexane) 0.20; ν_{max} (neat) 3083, 3063, 2974, 2931, 1731, 1704, 1625,1582, 1494, 1229 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.72 (2H, d, *J* 8.4 Hz, *meta*-C_6H_4), 7.51 (2H, s, C*H*=C), 6.98 (2H, d, *J* 8.4 Hz, *ortho*-C_6H_4), 4.30–4.14 (5H, m, DHP–$CO_2CH_2CH_3$, and *CH*CH_2CO_2Et), 4.01 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 2.59 (2H, d, *J* 4.7 Hz, CH_2CO_2Et), 1.30 (6H, t, *J* 7.1 Hz, DHP–$CO_2CH_2CH_3$), 1.16 (3H, t, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 171.5, 166.5 (2C), 142.7, 138.8 (2C), 136.9 (2C), 122.4 (2C), 108.9 (2C), 90.2, 60.4 (2C), 60.1, 40.3, 29.5, 14.3 (2C), 14.2; HRMS (ESI): MNa^+, found 536.0541. $C_{21}H_{24}INNaO_6^+$, requires 536.0540.

*4.5.9. Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8h**).* Synthesized according to above general procedure 4.5 from ethyl-3-(4-fluorophenylamino)acrylate **7h** (556 mg, 2.66 mmol) as a pale yellow solid (251 mg, 69%); mp 75–76 °C; R_f (25% EtOAc/hexane) 0.38; ν_{max} (neat) 3071, 2982, 2940, 1732, 1707, 1594, 1516, 1219, 1085 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.48 (2H, s, C*H*=C), 7.24–7.16 (2H, m, *meta*-C_6H_4), 7.11 (2H, t, *J* 8.5 Hz, *ortho*-C_6H_4), 4.28–4.18 (5H, m, DHP–$CO_2CH_2CH_3$ and *CH*CH_2CO_2Et), 4.03 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 2.59 (2H, d, *J* 4.8 Hz, CH_2CO_2Et), 1.30 (6H, t, *J* 7.1 Hz, DHP–$CO_2CH_2CH_3$), 1.18 (3H, t, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 171.7, 166.6 (2C), 160.9 (d, *J* 246.7 Hz, *C*F), 139.4, 137.8 (2C), 123.1 (2C, d, *J* 8.4 Hz, CFCHCH), 116.6 (2C, d, *J* 23.0 Hz, CFCH), 108.2 (2C), 60.4 (2C), 60.0, 40.4, 29.5, 14.4 (2C), 14.2; HRMS (ESI): MNa^+, found 428.1480. $C_{21}H_{24}FNNaO_6^+$, requires 428.1480.

*4.5.10. Diethyl-1-(3-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8i**).* Synthesized according to above general procedure 4.5 from ethyl-3-(3-chlorophenylamino) acrylate **7i** (346 mg, 1.53 mmol) as a pale yellow oil (164 mg, 76%); R_f (25% EtOAc/hexane) 0.30; ν_{max} (neat) 3072, 2976, 2935, 1729, 1707, 1594, 1483, 1207, 1081 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.54 (2H, s, C*H*=C), 7.40–7.10(4H, m,C_6H_4), 4.29–4.20 (5H, m, DHP–$CO_2CH_2CH_3$ and *CH*CH_2CO_2Et), 4.03 (2H, q, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$), 2.60 (2H, d, *J* 4.8 Hz, CH_2CO_2Et), 1.31 (6H, t, *J* 7.1 Hz, DHP–$CO_2CH_2CH_3$), 1.18 (3H, t, *J* 7.1 Hz, $CH_2CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 171.5, 166.4 (2C), 143.9, 136.9 (2C), 135.5, 130.8, 126.3, 120.8, 118.6, 109.0 (2C), 60.4 (2C), 60.0, 40.2, 29.5, 14.3 (2C), 14.1; HRMS (ESI): MNa^+, found 444.1184. $C_{21}H_{24}^{35}ClNNaO_6^+$, requires 444.1184.

*4.5.11. Synthesis of diethyl 4-((phenylamino)methylene)pent-2-enedioate (**9**).* To the solution of ethyl propiolate (651 mg, 6.64 mmol) in dried $ClCH_2CH_2Cl$ (20 mL) copper(I) iodide (409 mg, 2.15 mmol) and aniline (265 mg, 2.15 mmol) were dispersed and the reaction mixture was refluxed overnight. The reaction mixture was filtered and evaporated under reduced pressure. The condensed residue was purified by column chromatography (EtOAc/hexane=1:50 to 1:3) to provide the corresponding dihydropyridine **9**as a yellow oil (261 mg, 42%); R_f (25% EtOAc/hexane) 0.50; ν_{max} (neat) 3271, 3220, 3047, 2981, 1659, 1597, 1582, 1278, 1179, 1157,1029 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 10.78 (1H, d, *J* 13.2 Hz, N*H*), 7.76 (1H, d, *J* 13.2 Hz, C=C*H*), 7.48 (1H, d, *J* 15.7 Hz, CH=*CH*CO_2Et), 7.36 (2H, t, *J* 7.6 Hz, *meta*-C_6H_5), 7.19–7.00 (3H, m, *para*-C_6H_5 and *ortho*-C_6H_5), 6.18 (1H, d, *J* 15.7 Hz, C*H*=CHCO_2Et), 4.33 (1H, q, *J* 7.1 Hz, =$CCO_2CH_2CH_3$), 4.22 (1H, q, *J* 7.1 Hz, =$CHCO_2CH_2CH_3$), 1.40 (1H, t, *J* 7.1 Hz, =$CCO_2CH_2CH_3$), 1.31 (1H, t, *J* 7.1 Hz, =$CHCO_2CH_2CH_3$); HRMS (ESI): MNa^+, found 312.1205. $C_{16}H_{19}NNaO_4^+$, requires 312.1206. This data are fully identical to that of compound isolated in trace amount from the previous procedure 4.5.6.

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Supplementary data

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