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$AlCl_3$-PROMOTED CYCLIZATION OF β-KETO DERIVATIVES WITH *IN SITU* GENERATED ENAMINES UNDER SOLVENT-FREE HIGH SPEED BALL MILLING: AN EFFICIENT ONE-POT ACCESS TO POLYSUBSTITUTED 1,4-DIHYDROPYRIDINES

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Abstract – Under high speed ball milling (HSBM), a simple method for efficient synthesis of structurally diverse polysubstituted 1,4-dihydropyridines is developed via $AlCl_3$-promoted Robinson-like cyclization of β-keto derivatives with *in situ* generated enamines. This one-pot protocol exhibits the advantages of high chemoselectivity, short reaction time, good functional group tolerance, mild reaction condition and easy work-up.

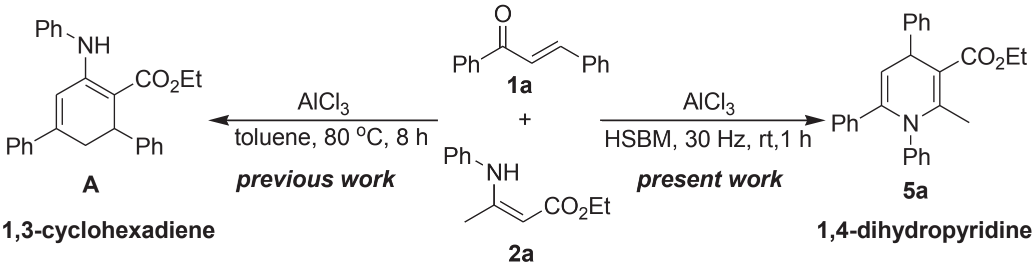
INTRODUCTION

1,4-Dihydropyridines (DHPs) represent one of the most important N-heterocycles in biologically active and naturally occurring molecules, and have been widely applied in medicinal chemistry or pharmacology.[1,2] DHPs can also be employed as key intermediates for synthesis of nitrogen-containing alkaloids,[3] as model compounds for coenzyme nicotinamide adenine dinucleotide (NADH),[4] and as a H_2 surrogate for certain hydrogenation.[5] Therefore, a great deal of efforts have been devoted for synthesis of elaborated and diverse 1,4-DHPs, and various synthetic methods have been established.[2,6] Among them, the Hantzsch reaction is a concise and conventional access to symmetrical 1,4-DHPs. In contrast, unsymmetrical 1,4-DHPs provide much larger structural diversity with more synthetic and biological interests. Although unsymmetrical 1,4-DHPs have also been achieved through modified Hantzsch-like reactions by using two different 1,3-dicarbonyl compounds, they often suffer from side reactions forming symmetrical 1,4-DHPs or limited substrate scope.[7] Thus the development of more efficient methods for unsymmetrical 1,4-DHPs is highly desired. Some strategies have been explored to achieve this point by multicomponent cyclization reactions from 1,3-dicarbonyl compounds, α,β-unsaturated aldehydes/ketones and amines.[8] Frankly, many available approaches to unsymmetrical polysubstituted 1,4-DHPs are powerful enough, but most methods involve special or expensive catalysts, and the reactions were often performed in organic solvents at relatively high temperature for long reaction time. In many cases, preliminary preparation of precursors is involved. To overcome these problems for more environmental and economical construction of such N-heterocycles, herein we wish to present an $AlCl_3$-promoted cyclization of β-keto derivatives with *in situ* generated enamines by high speed ball milling under solvent-free conditions. Using this mechanochemical technique,[9,10] a simple protocol is successfully developed for efficient synthesis of various polysubstituted 1,4-dihydropyridines in a greener way.

RESULTS AND DISCUSSION

Initially, we selected $AlCl_3$-promoted reaction of chalcone (**1a**) with β-enamino ester (**2a**) as the model reaction for tentative investigation (Table 1).

Table 1. $AlCl_3$-Promoted reaction of chalcone (**1a**) and β-enamino ester (**2a**): stirring in dry toluene vs solvent-free HSBM[a]



Entry	Cat. Amount (equiv.)	Condition	Product (Yield)[b]
1	1.00	HSBM, rt, 1 h	**5a** (87%)
2	0.75	HSBM, rt, 1 h	**5a** (87%)
3	0.50	HSBM, rt, 1 h	**5a** (54%)
4	1.00	toluene, rt, 8 h	**5a** (51%)
5	1.00	toluene, 80 °C, 8 h	**A** (88%)
6	0.75	toluene, 80 °C, 8 h	**A** (57%)
7	0.50	toluene, 80 °C, 8 h	**A** (32%)

[a] Reactions were carried out with **1a** (0.5 mmol), **2a** (0.5 mmol) and $AlCl_3$ (designated) under HSBM at room temperature with a vibration frequency of 30 Hz (entries 1–3) or stirring in 5 mL toluene (entries 4–7).
[b] Isolated yield combined from two parallel runs.

The reaction was firstly carried out under solvent-free HSBM at room temperature for one hour, and it afforded the desired product 1,4-dihydropyridine **5a** in very high chemoselectivity with yields varying from the usage of $AlCl_3$ (Table 1, entries 1–3). The results demonstrated that 0.75 equivalent of $AlCl_3$ is necessary and enough to provide a practically satisfactory 87% isolated yield. Traditionally, $AlCl_3$ involved reactions in organic solvent often need relatively large usage of the catalyst because it is very sensitive to moisture, and the employed solvent should be strictly dried before use. Furthermore, large presence of $AlCl_3$ would lead to colloid emulsion during extraction, thus make the afterward treatment somewhat tedious. In contrast, herein applied sealing and solvent-free condition helps to reduce the dosage of $AlCl_3$. It is more worthy to point out that product **5a** can be obtained by direct loading of the resulted reaction mixture on silica gel chromatography column for purification. Therefore, the work-up of this protocol is simple and convenient. When this reaction was performed by stirring in toluene at room temperature, 1,4-dihydropyridine **5a** was also formed with only 51% yield even after 8 hours, and the starting materials remained a lot (Table 1, entry 4). When heated at 80 ºC as reported,[11] the reaction afforded 1,3-cyclohexadiene **A** as the main product, accompanying with trace of desired product **5a** (Table 1, entries 5–7). This distinctly different chemoselectivity can be easily understood from the mature reaction mechanism, which involves Michael addition of enamine **2a** to C=C in chalcone **1a** and cascade attack to C=O in **1a** from N or Me (Figure 1). Low temperature prefers to attacking C=O from N for generation of 1,4-dihydropyridine **5a**, while high temperature favours attacking C=O from Me to form 1,3-cyclohexadiene **A**. In other words, **A** is thermodynamic controlling product and **5a** is kinetic controlling product. The high efficiency for generation of **5a** under solvent-free HSBM at room temperature may be ascribed to high local concentration of the reactants, which may result in an enhanced second-order reaction rate and thus prefer to selective formation of kinetic controlling product.[12]

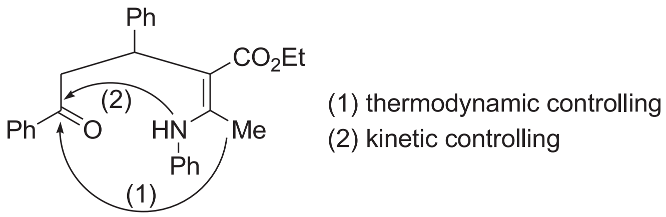
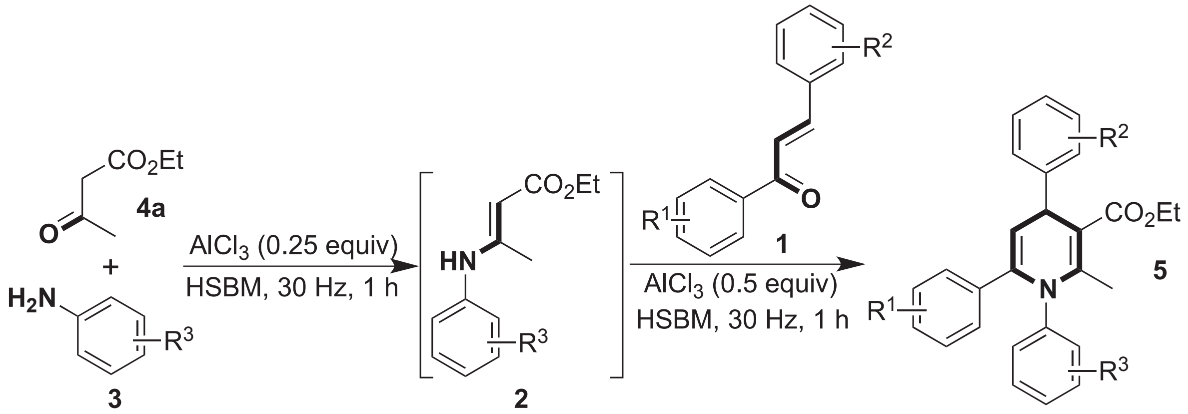


Figure 1. Illustration of attacking pathway for formation of **A** and **5a**

During the optimization study, we found that enamines **2** can also be directly obtained from the corresponding anilines **3** and ethyl acetoacetate **4a** with almost quantitative yield in presence of catalytic amount of $AlCl_3$ by solvent-free HSBM. Therefore, we next aimed to one-pot synthesis of polysubstituted 1,4-dihydropyridines **5** from various chalcones **1** and *in situ* generated enamines **2** by stepwise work under the standard HSBM condition. As expected, all reactions in these cases still proceeded smoothly and the corresponding polysubstituted 1,4-DHPs **5** were obtained in good to excellent yields (Table 2). It should be pointed out that direct milling of **1**, **3**, **4a** and $AlCl_3$ without stepwise operation led to very complicated results.

Table 2. $AlCl_3$-Promoted one-pot synthesis of polysubstituted 1,4-DHPs **5** from chalcones **1**, anilines **3** and ethyl acetoacetate **4a** under solvent-free HSBM[a,b]



5a (R^1 = H, R^2 = H, R^3 = H): 82%
5b (R^1 = H, R^2 = H, R^3 = 4-Me): 83%
5c (R^1 = H, R^2 = H, R^3 = 4-MeO): 86%
5d (R^1 = H, R^2 = 4-Me, R^3 = H): 77%
5e (R^1 = 4-Br, R^2 = H, R^3 = H): 79%
5f (R^1 = H, R^2 = 4-Br, R^3 = H): 82%

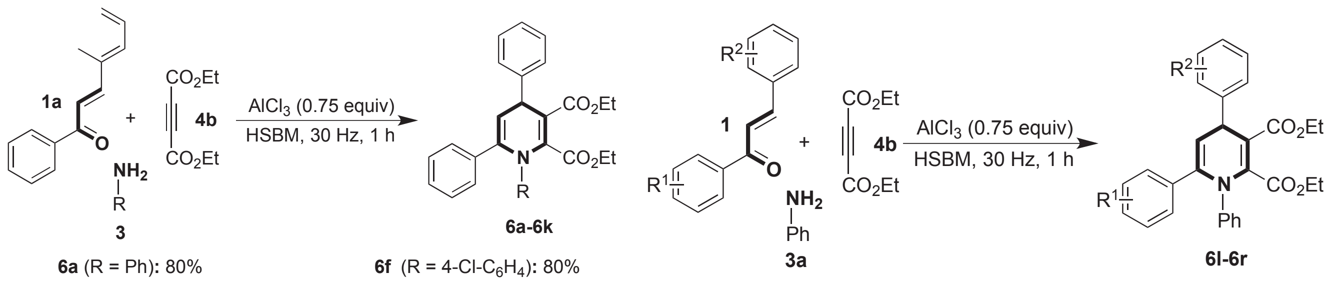
[a] Reactions were carried out with anilines **3** (0.55 mmol), **4a** (0.55 mmol), $AlCl_3$ (0.125 mmol), afterward added chalcones **1** (0.5 mmol) and $AlCl_3$ (0.25 mmol) under HSBM (30 Hz, rt).
[b] Isolated yield combined from two parallel runs.

As above mentioned, this reaction can be essentially considered as Robinson-like cyclization of α,β-unsaturated ketones with enamines. Therefore, we envision that reactions of other β-keto derivatives with *in situ* generated enamines from amines and acetylenedicarboxylate can also afford the corresponding 1,4-dihydropyridines in diversity. Therefore, we next performed one-pot reaction of a large variety of substituted chalcones **1** and amines **2** with acetylenedicarboxylate **4b** for diverse synthesis of polysubstituted 1,4-dihydropyridines **6** without stepwise operation. The results are outlined in Table 3.

As shown in Table 3, the multiple-component reactions were carried out without stepwise operation for generation of enamine in these cases, and good to excellent yields were still achieved. The reactions exhibited broad scope of substrates with good functional group tolerance. Either electron-withdrawing or electron-donating groups in para-, meta- or ortho-position worked well. In general, substituents in chalcones display no obvious electronic or steric effect, while aliphatic amines and aromatic amines bearing electron-donating groups showed higher efficiency.

It is noted that 1,4-dihydropyridines **6d** and **6v** are obtained as a mixture of *syn* and *anti* conformers approximately in a 1:2 proportion (Figure 2), which is determined with respect to the Me in the N-aromatic ring and the CH in the 4-position of the DHP ring (see ^{1}H NMR spectra in Supporting Information). Just as previously reported, the plane of 1,4-DHP and the plane of N-aromatic ring are forced to be orthogonal to each other due to the steric hindrance exerted by the *ortho*-methyl group, and the energy barrier involved in the interconversion of these two isomers is sufficiently high to allow the observation of separate NMR signals at ambient temperature. The DHP ring resembles a pseudoboat conformation, in which the *anti* conformer would be slightly more stable than the *syn* conformer.[13]

Table 3. $AlCl_3$-Promoted one-pot synthesis of polysubstituted 1,4-DHPs **6** from chalcones **1**, amines **3** and acetylenedicarboxylate **4b** under solvent-free HSBM[a,b]

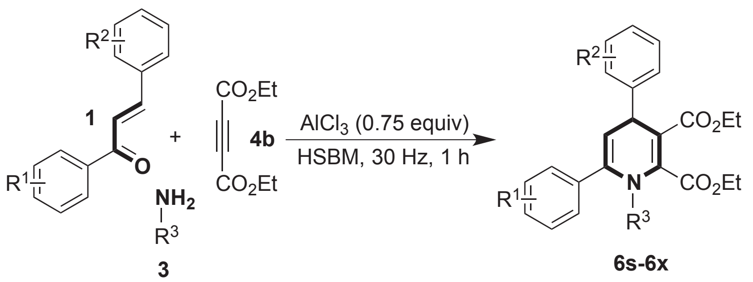


6a (R = Ph): 80%
6b (R = 4-Me-C_6H_4): 93%
6c (R = 3-Me-C_6H_4): 94%
6d (R = 2-Me-C_6H_4): 94%
conformers ***syn*** : ***anti*** = 1 : 2
6e (R = 4-MeO-C_6H_4): 90%

6f (R = 4-Cl-C_6H_4): 80%
6g (R = 3-Cl-C_6H_4): 87%
6h (R = 4-Br-C_6H_4): 80%
6i (R = $PhCH_2$): 97%
6j (R = 4-Cl-$C_6H_4CH_2$): 95%
6k (R = $Me(CH_2)_5$): 92%

6l (R^1 = H, R^2 = 4-Me): 65%
6m (R^1 = H, R^2 = 4-Br): 80%
6n (R^1 = H, R^2 = 3-Br): 78%
6o (R^1 = H, R^2 = 3,4-Cl): 75%

6p (R^1 = 4-MeO, R^2 = H): 75%
6q (R^1 = 4-Br, R^2 = H): 65%
6r (R^1 = 3,4-Cl, R^2 = H): 57%



6s (R^1 = H, R^2 = 4-Br, R^3 = 4-MeO-C_6H_4): 68%; **6t** (R^1 = H, R^2 = 3-Br, R^3 = 4-MeO-C_6H_4): 69%
6u (R^1 = H, R^2 = 4-Br, R^3 = 3-Me-C_6H_4): 81%; **6v** (R^1 = H, R^2 = 4-Br, R^3 = 2-Me-C_6H_4): 72%
conformers ***syn*** : ***anti*** = 1 : 2
6w (R^1 = H, R^2 = 4-Br, R^3 = 4-Cl-C_6H_4): 50%; **6x** (R^1 = H, R^2 = 4-Br, R^3 = $PhCH_2$): 92%

[a] Reactions were carried out with chalcones **1** (0.5 mmol), amines **3** (0.55 mmol), **4b** (0.55 mmol) and $AlCl_3$ (0.375 mmol) under HSBM (30 Hz, rt).
[b] Isolated yield combined from two parallel runs.

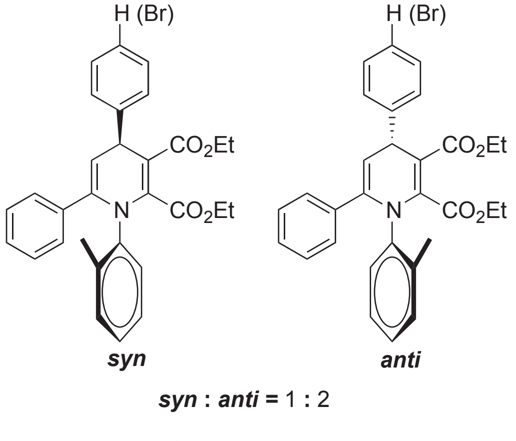
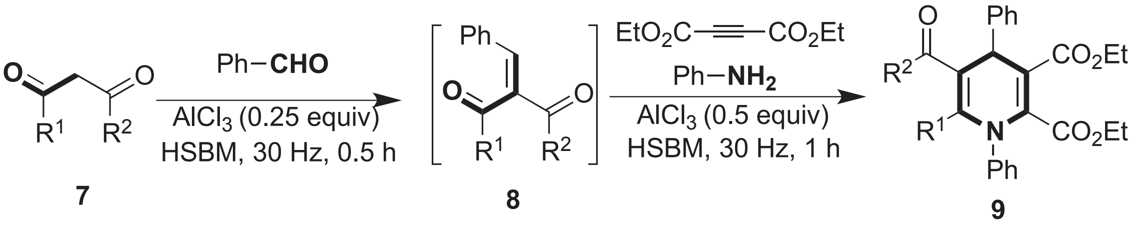
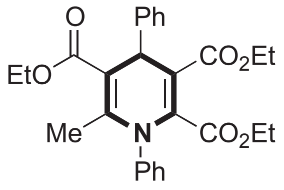


Figure 2. *Syn* and *anti* conformers of **6d** and **6v**

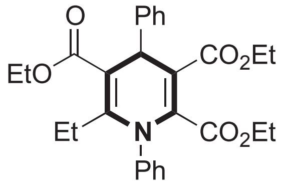
Still under this solvent-free HSBM condition, we further investigated the cascade cyclization reaction of aniline, acetylenedicarboxylate with α,β-unsaturated ketones **8**, which was *in situ* generated through Knoevenagel condensation of benzaldehyde with β-ketoester **7** with stepwise operation. Gratifyingly, the corresponding fully substituted 1,4-DHPs **9** was obtained in excellent yields (Table 4).

Table 4. $AlCl_3$-Promoted one-pot synthesis of fully substituted 1,4-DHPs **9** under solvent-free HSBM[a,b]

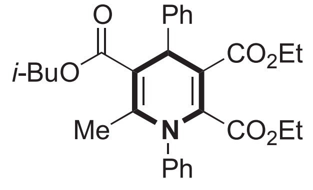




9a, 92%



9b, 85%



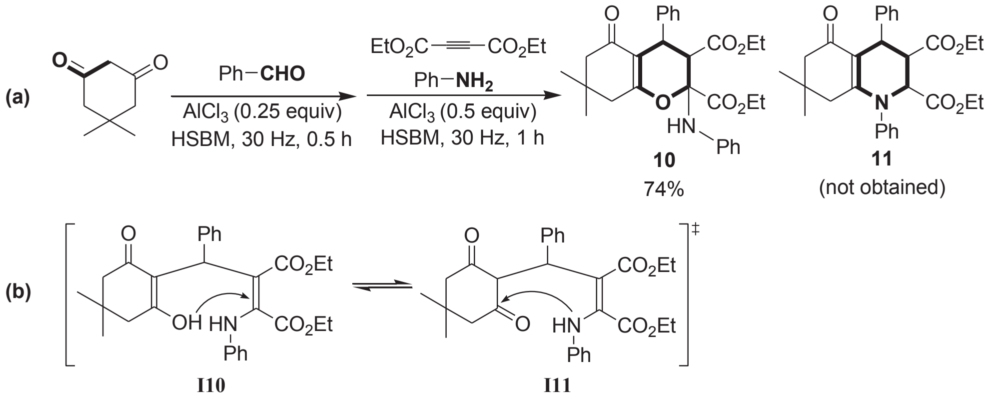
9c, 91%

[a] Reactions were carried out with **7** (0.5 mmol), PhCHO (0.55 mmol), $AlCl_3$ (0.125 mmol), afterward added $PhNH_2$ (0.55 mmol), acetylenedicarboxylate (0.55 mmol) and $AlCl_3$ (0.25 mmol) under HSBM (30 Hz, rt).

[b] Isolated yield combined from two parallel runs.

When 5,5-dimethyl-1,3-cyclohexanedione was employed to perform this reaction, it exclusively afforded 3,4-dihydro-*2H*-pyran **10**, and not any 1,4-dihydropyridine **11** was obtained (Scheme 1a). This chemoselectivity is consistent with the result from reaction performed in EtOH at room temperature, in which **10** was obtained in 70% yield after stirring for 24 hours.[14] While heating in AcOH at 80-90 °C for 12 hours, the reaction gave **11** in 60% yield.[15] Similarly as above discussed for the formation of **A** and **5a** from chalcone **1a** and β-enamino ester **2a**, this obvious difference of chemoselectivity may also be resulted from thermodynamic controlling vs kinetic controlling. Specifically, low temperature and high concentration of substrates prefers to intramolecular addition of enol **I10** to form dihydropyran **10**, while high temperature favors intramolecular condensation and successive dehydration of adduct **I11** to form dihydropyridine **11**, which has higher thermodynamic stability (Scheme 1b).

To ensure if this solvent-free HSBM protocol can be developed into a more practical method for synthesis of 1,4-DHPs, we selected **5a** and **6a** as the model products for larger scale synthesis. When the reactions for synthesis of **5a** and **6a** were carried out in a scale of 5 mmol, comparable yields were still achieved with relatively longer reaction time (Scheme 2, for experimental details, see Supporting Information).



Scheme 1. Formation of 3,4-dihydro-2*H*-pyran **10** *vs* 1,4-DHP **11**

$$\begin{array}{c}\mathbf{3a}\ (5.5\ \text{mmol})\\ +\\ \mathbf{4a}\ (5.5\ \text{mmol})\end{array} \xrightarrow[\text{HSBM, 30 Hz, 1.5 h}]{\text{AlCl}_3\ (0.25\ \text{equiv})} [\ \mathbf{2a}\ ] \xrightarrow[\text{HSBM, 30 Hz, 2 h}]{\begin{array}{c}\mathbf{1a}\ (5.0\ \text{mmol})\\ \text{AlCl}_3\ (0.5\ \text{equiv})\end{array}} \mathbf{5a}\ \ (1.58\ \text{g, 80\%})$$

$$\begin{array}{c}\mathbf{1a}\ (5.0\ \text{mmol})\\ +\\ \mathbf{3a}\ (5.5\ \text{mmol})\\ +\\ \mathbf{4b}\ (5.5\ \text{mmol})\end{array} \xrightarrow[\text{HSBM, 30 Hz, 2 h}]{\text{AlCl}_3\ (0.75\ \text{equiv})} \mathbf{6a}\ \ (1.83\ \text{g, 81\%})$$

Scheme 2. Solvent-free HSBM synthesis of **5a** and **6a** in gram scale

In summary, an $AlCl_3$-promoted Robinson-like cyclization from β-keto derivatives with *in situ* generated enamines has been investigated under solvent-free high speed ball milling. These one-pot reactions furnished highly efficient synthesis of structurally diverse polysubstituted 1,4-DHPs with high yields even in gram scale. Comparing with traditional methods, this protocol exhibits the advantages of higher chemoselectivity, significantly shorter reaction time, milder reaction condition and easier work-up. These merits make the present method a practical alternative to unsymmetrical polysubstituted 1,4-dihydropyridines.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AV300 or AV400 NMR instrument. All melting points were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. High-resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF-QII mass instrument (ESI). The mixer mill MM 400 (Retsch GmbH, Germany) was used for all ball-milling reactions, and the reaction vessels are titanium-alloyed jars lined with PTFE (neat volume: 4 mL) or stainless jars (neat volume: 25 mL). The milling balls are titanium-alloyed of 6.0 mm in diameter or stainless of 8.0 mm in diameter. TLC was performed on precoated glass-back plates and visualized with UV light at 254 nm. Flash column chromatography was performed on silica gel with petroleum ether-ethyl acetate as the eluent.

Starting Materials.

Chalcones **1**[16] and enamine **2a**[17] were prepared according to previously reported procedures. All other chemicals used in this study were commercially available.

Typical Procedure for Ball-Milling Synthesis of Products 5.

Ethyl 2-methyl-1,4,6-triphenyl-1,4-dihydropyridine-3-carboxylate (5a): Aniline (0.051 g, 0.55 mmol), ethyl acetoacetate (0.072 g, 0.55 mmol), $AlCl_3$ (0.017 g, 0.125 mmol), together with two titanium-alloyed balls of 6.0 mm in diameter, were introduced into a titanium-alloyed jar lined with PTFE (4 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were sealed with screw caps, fixed on the vibration arms of a ball-milling apparatus (mixer mill MM400, Retsch GmbH, Haan, Germany) and were vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for 30 min. After the vessels were opened, chalcone (0.104 g, 0.5 mmol) and $AlCl_3$ (0.033 g, 0.25 mmol) were added into the two parallel jars, respectively. The vessels were sealed again and continued to vibrate for 60 min (30 Hz). The resulted mixtures were combined and directly loaded on silica gel chromatography column for purification with EtOAc/petroleum ether as the eluent, affording the desired product **5a** as white solid. mp 85–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49–7.47 (m, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.23 (tt, J = 7.2, 1.4 Hz, 1H), 7.20–7.16 (m, 2H), 7.12–7.06 (m, 8H), 5.14 (d, J = 6.0 Hz, 1H), 4.79 (d, J = 6.0 Hz, 1H), 4.07 (qd, J = 7.2, 2.4 Hz, 2H), 2.22 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.0, 149.7, 148.5, 142.0, 140.1, 137.4, 130.7, 129.3, 128.7, 128.5, 127.7, 127.5, 127.3 (2C), 126.2, 110.3, 102.9, 59.7, 40.7, 19.2, 14.3; HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{26}NO_2$ $[M+H]^+$: 396.1964; found: 396.1958.

Typical Procedure for Ball-Milling Synthesis of Products 6.

Diethyl 1,4,6-triphenyl-1,4-dihydropyridine-2,3-dicarboxylate (6a): Chalcone (0.104 g, 0.5 mmol), aniline (0.051 g, 0.55 mmol), diethyl acetylenedicarboxylate (0.094 g, 0.55 mmol) and $AlCl_3$ (0.050 g, 0.375 mmol), together with two titanium-alloyed balls of 6.0 mm in diameter, were introduced into a titanium-alloyed jar lined with PTFE (4 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were sealed with screw caps, fixed on the vibration arms of a ball-milling apparatus (mixer mill MM400, Retsch GmbH, Haan, Germany) and were vibrated vigorously at a rate of 1800 rounds per min (30 Hz) at room temperature for 60 min. The resulted mixtures were combined and directly loaded on silica gel chromatography column for purification with EtOAc/petroleum ether as the eluent, affording the desired product **6a** as white solid. mp 85–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.15–7.14 (m, 4H), 7.12–7.03 (m, 6H), 5.14 (d, J = 5.6 Hz, 1H), 4.75 (d, J = 5.2 Hz, 1H), 4.03 (qd, J = 7.2, 1.2 Hz, 2H), 4.01–3.89 (m, 2H), 1.09 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.7, 164.9, 147.3, 145.5, 140.5, 139.2, 136.1 (2C overlapped), 130.1, 129.1, 128.6 (2C), 128.0, 127.8, 127.7, 126.6, 110.8, 102.3, 61.6, 60.3, 39.9, 14.1, 13.6; HRMS (ESI-TOF): *m/z* calcd for $C_{29}H_{28}NO_4$ $[M+H]^+$: 454.2018; found: 454.2019.

Ball-Milling Synthesis of Products 9 and 10.

Triethyl 6-methyl-1,4-diphenyl-1,4-dihydropyridine-2,3,5-tricarboxylate (9a): Ethyl acetoacetate (0.065 g, 0.5 mmol), benzaldehyde (0.058 g, 0.55 mmol) and $AlCl_3$ (0.125 mmol), together with two titanium-alloyed balls of 6.0 mm in diameter, were introduced into a titanium-alloyed jar lined with PTFE (4 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were sealed with screw caps, fixed on the vibration arms of a ball-milling apparatus (mixer mill MM400, Retsch GmbH, Haan, Germany) and were vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for 30 min. After the vessels were opened, aniline (0.051 g, 0.55 mmol), diethyl acetylenedicarboxylate (0.094 g, 0.55 mmol) and $AlCl_3$ (0.033 g, 0.25 mmol) were added into the two parallel jars, respectively. The vessels were sealed again and continued to vibrate for 60 min (30 Hz). The resulted mixtures were combined and directly loaded on silica gel chromatography column for purification with EtOAc/petroleum ether as the eluent, affording the desired product **9a** as white solid. mp 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.41 (m, 5H), 7.34–7.26 (m, 4H), 7.22–7.19 (m, 1H), 5.12 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.10–4.06 (m, 2H), 3.94–3.79 (m, 2H), 2.07 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.7, 165.9, 164.1, 146.4, 146.1, 142.7, 138.7, 130.8, 129.4, 129.2, 128.3, 128.1, 126.7, 106.5, 105.4, 61.7, 60.7, 60.3, 38.5, 18.0, 14.3, 14.1, 13.6; HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{30}NO_6$ $[M+H]^+$: 464.2073; found: 464.2065.

Diethyl 7,7-dimethyl-5-oxo-4-phenyl-2-(phenylamino)-3,4,6,8-hexahydro-*2H*-chromene-2,3-dicarboxylate (10): White solid; mp 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27–7.23 (m, 2H), 7.20–7.13 (m, 5H), 6.87–6.83 (m, 3H), 5.67 (s, 1H), 4.19 (d, *J* = 11.6 Hz, 1H), 4.12–4.04 (m, 2H), 3.98–3.94 (m, 1H), 3.92–3.85 (m, 1H), 3.14 (d, *J* = 10.4 Hz, 1H), 2.62 (d, *J* = 18.0 Hz, 1H), 2.36 (dd, *J* = 17.6, 2.4 Hz, 1H), 2.17 (s, 2H), 1.16 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H), 1.02 (s, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.0, 171.2, 168.1, 166.5, 143.7, 141.2, 129.2, 128.6, 127.3, 126.9, 120.5, 115.7, 113.4, 87.8, 62.5, 61.8, 54.1, 50.8, 42.1, 39.2, 31.8, 29.4, 27.6, 14.0, 13.7; HRMS (ESI-TOF): *m/z* calcd for $C_{29}H_{34}NO_6$ $[M+H]^+$: 492.2386; found: 492.2388.

Characterization data on all other products accompanying with copies of NMR spectra for all products are available in the supporting information.

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