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Studies on chemoselective synthesis of 1,4- and 1,2-dihydropyridine derivatives by a Hantzsch-like reaction: a combined experimental and DFT study†

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In the experimental process of preparing diethyl 3,5-dicarboxylate-1,4-dihydropyridine (1,4-DHP) by a Hantzsch-like reaction, it was found that a by-product named diethyl 3,5-dicarboxylate-1,2-dihydropyridine (1,2-DHP) was produced in the reaction. To discuss this phenomenon, the effects of the reaction conditions on the yield ratio of 1,4-DHP and 1,2-DHP were studied by using aromatic amines, aromatic aldehydes and ethyl propiolate as raw materials. The mechanisms for the formation of 1,4-DHP and 1,2-DHP were proposed based on the isolated intermediate named diethyl 4-((phenylamino)methylene)pent-2-enedioate generated by the Michael addition of aniline and ethyl propiolate. The transition state structures were optimized and the reaction energy barriers of intermediates in the speculated mechanisms were calculated by DFT calculations at the M062X/def2TZVP//B3LYP-D3/def-SVP level. It was found that the reaction energy barriers and dominant configurations of intermediates **IM2** and **IM3'** are the determinants for the chemoselectivity. Together, these results demonstrate a high chemoselectivity in the synthesis of 1,4-DHPs and 1,2-DHPs by a Hantzsch-like reaction and that 1,4-DHPs and 1,2-DHPs can be easily obtained under different conditions.

Introduction

There are five possible isomers in dihydropyridines (DHPs) due to the position difference of double bonds; among them, 1,4-dihydropyridines (1,4-DHPs) and 1,2-dihydropyridines (1,2-DHPs) are the two most common isomers.[1,2] 1,4-DHPs have widely been used as a critical scaffold for the synthesis of calcium channel inhibitors. Clinically, 1,4-DHPs represented by nifedipine have developed into an important class of drugs for treating cardiovascular and cerebrovascular diseases.[3,4] 1,4-DHPs also have important applications in the fields of antitumor drugs and antibacterial drugs.[3,5–7] Unlike 1,4-DHPs, 1,2-DHPs cannot directly show biological pharmacological activities, but they have served as important raw materials for the synthesis of many natural alkaloids and drugs with biological activities.[1,8] For example, 1,2-DHPs were used as the lead compounds for the synthesis of 2-azabicyclo[2.2.2]octane, which is an important skeleton for the synthesis of iberg base, potato base and oseltamivir.[9]

The synthesis of 1,4-DHPs was first reported by Hantzsch in the 1880s, which was performed by one-pot condensation of aldehydes with ethyl acetoacetate and ammonia either in acetic acid or by refluxing in alcohols.[10] Since then, there has been continuous research on the improvement of the Hantzsch reaction. The application of simple multifunctional synthetic building blocks based on α,β-unsaturated ketenes, aldehydes and amines has greatly promoted the development of new methods for the synthesis of 1,4-DHPs. To date, multicomponent synthesis based on the Hantzsch reaction, also called a Hantzsch-like reaction, has become the main way to synthesize 1,4-DHPs.[11–15] The synthesis of 1,2-DHPs was first reported by Fowler, which was performed by sodium borohydride reduction of *N*-acylpyridinium salts.[16] Since then, the reduction method of pyridinium salts has been widely used in the synthesis of 1,2-DHPs.[17–21] In addition, the annulation reaction between unsaturated imines and alkynes has also been used for the formation of 1,2-DHPs.[22–27]

When diethyl 3,5-dicarboxylate-1,4-dihydropyridine (1,4-DHP) was synthesized by a Hantzsch-like reaction with ethyl propiolate as the synthetic block, it was found that a by-product named diethyl 3,5-dicarboxylate-1,2-dihydropyridine (1,2-DHP) appeared in the reaction (Scheme 1). The similarity of polarity between the two DHPs increased the difficulty of separation and purification. By exploring the reaction conditions, and according to the guidance of the possible mecha-

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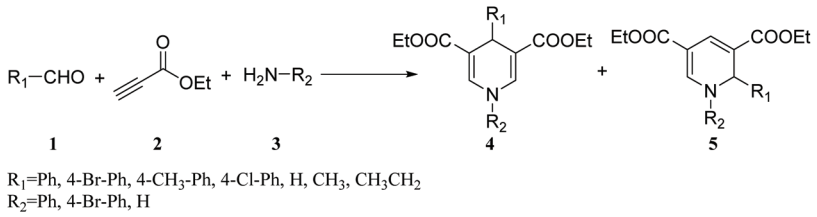


Scheme 1 Synthesis of 1,4-DHPs **4** and 1,2-DHPs **5** by a Hantzsch-like reaction.

nism, 1,4-DHP and 1,2-DHP derivatives were produced with high chemoselectivity under different conditions, which is of great significance in terms of chemical reaction efficiency and atom economy. To the best of our knowledge, a theoretical mechanistic study of the chemoselectivity of 1,4-DHPs and 1,2-DHPs in a Hantzsch-like reaction has never been reported. These study results will provide us with an in-depth understanding of the essential reasons for the simultaneous production of 1,4-DHP and 1,2-DHP in a Hantzsch-like reaction and provide experimental and theoretical foundations for the following studies of chemical synthesis and drug development based on these two types of DHP skeletons.

Results and discussion

Synthesis of 1,4-DHPs 4

At the beginning, our original intention was to synthesize 1,4-DHPs. However, when 1,4-DHPs were synthesized by the multi-component synthesis method with ethyl propiolate as the synthetic block, it was found that a small amount of 1,2-DHPs was produced in the reaction. In order to discuss this phenomenon, taking the synthesis of diethyl 1,4-diphenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**) as an example, the effects of the reaction conditions on the yields and yield ratios of **4** and **5** were studied. The effects of the solvent, temperature and catalyst on the yields and yield ratios of **4a** and **5a** were investigated and are shown in Tables 1 and 2.

Table 1 Effect of the solvent and temperature on the yield and yield ratio of **4a** and **5a**[a]

Entry	Solvent	T (°C)	Time[b] (h)	Yield[c] (%) **4a**	Yield[c] (%) **5a**	Yield ratio (**4a** : **5a**)
1	EtOH	78	12	56	12	4.7 : 1
2	DMSO	189	10	37	18	2.1 : 1
3	1,4-Dioxane	101	12	52	11	4.7 : 1
4	CH_3CN	82	12	50	8	6.3 : 1
5	DCE	84	12	50	14	3.6 : 1
6	DCM	40	24	Trace	Trace	—
7	THF	66	17	48	14	3.4 : 1
8	Toluene	110	12	51	10	5.1 : 1

[a] All reactions were carried out with 1 equivalent of both aldehyde and amine and 2 equivalents of ethyl propiolate, with 10% equivalent of glacial acetic acid as the catalyst. [b] The reaction time was determined by complete conversion of aniline monitored by TLC. [c] Isolated yields after column chromatography.

Table 2 Effect of the catalyst on the yield and yield ratio of **4a** and **5a**[a]

Entry	Catalyst	Time[b] (h)	Yield[c] (%) **4a**	Yield[c] (%) **5a**	Yield ratio (**4a** : **5a**)
1	AcOH	12	56	12	4.7 : 1
2	TFA	12	59	15	3.9 : 1
3	*p*-TsOH	8	63	15	4.2 : 1
4	$AlCl_3$	12	53	13	4.1 : 1
5	$TiCl_4$	12	51	8	6.4 : 1
6	—	48	Trace	Trace	—

[a] All reactions were carried out with 1 equivalent of both aldehyde and amine and 2 equivalents of ethyl propiolate, with ethanol as the solvent and heated to reflux until the reaction was complete. [b] The reaction time was determined by complete conversion of aniline monitored by TLC. [c] Isolated yields after column chromatography.

It can be seen from Table 1 that the reaction solvent and temperature have no obvious influence on the yields of **4a** and **5a**; the yields of **4a** and **5a** were about 50% and 10% respectively except in DCM. The yields of **4a** and **5a** were 56% and 12% respectively in ethanol at a temperature of 78 °C, and they were 37% and 18% in DMSO at a high temperature of 189 °C in a relatively short reaction time. The reaction solvent and temperature have no obvious influence on the yield ratio of **4a** and **5a**; the ratio is about 5 : 1 except in DCM and DMSO. This shows that too high or too low reaction temperature is not conducive to the reaction.

As can be seen from Table 2, different catalysts have medium impacts on the yield and production efficiency of **4a** and **5a**. Generally speaking, the catalytic effect of a protonic acid is the best, and the yield of **4a** increases with the enhancement of protonic acid acidity. When *p*-TsOH is used as the catalyst, the reaction effect is the best, and the reaction time is 8 h. The catalysts had no obvious influence on the yield ratios of **4a** and **5a**; the ratio was about 5 : 1.

Referring to the above experimental results, ethanol was used as the solvent and *p*-TsOH as the catalyst, and ten different substituted 1,4-DHPs (**4**) were synthesized at the reflux temperature; the yields and yield ratios of **4** and **5** are shown in Table 3.

It can be seen from Table 3 that the substituents of aldehydes and amines have a certain influence on the yield of **4**. When the substituents of amines are the same, the yields of **4** with aromatic aldehydes were higher than those with aliphatic aldehydes, which can been seen from the yields of **4a** (63%, R_1 = Ph, R_2 = Ph), **4j** (55%, R_1 = H, R_2 = Ph), **4f** (59%, R_1 = 4-Cl-

Table 3 Yields and yield ratios of 4 and 5[a]

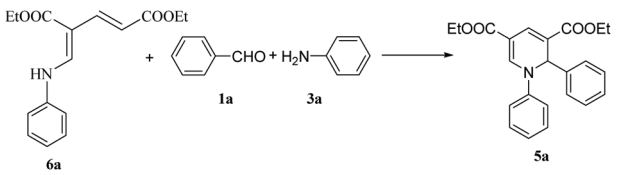
Entry	R_1	R_2	Yield[b] (%) 4	5	Yield ratio (4 : 5)
1	Ph	Ph	**4a**, 63	**5a**, 15	4.2 : 1
2	4-Br-Ph	Ph	**4b**, 65	**5b**, 10	6.5 : 1
3	Ph	4-Br-Ph	**4c**, 61	**5c**, 12	5.1 : 1
4	Ph	H	**4d**, 56	**5d**, 11	5.1 : 1
5	4-CH_3-Ph	H	**4e**, 50	**5e**, 13	3.8 : 1
6	4-Cl-Ph	H	**4f**, 59	**5f**, 9	6.6 : 1
7	H	H	**4g**, 55	**5g**, 8	6.9 : 1
8	CH_3	H	**4h**, 53	**5h**, 10	5.3 : 1
9	CH_3CH_2	H	**4i**, 54	**5i**, 13	4.2 : 1
10	H	Ph	**4j**, 55	**5j**, 15	3.7 : 1

[a] All reactions were carried out with 1 equivalent of both aldehyde and amine and 2 equivalents of ethyl propiolate, with ethanol as the solvent and 10% equivalent of *p*-TsOH as the catalyst and heated to reflux until the reaction was complete. [b] Isolated yields after column chromatography.

Ph, R_2 = H) and **4h** (53%, R_1 = CH_3, R_2 = H). The yield of **4** is improved when the substituent on aromatic aldehyde is an electron-withdrawing group, for example, the yield of **4f** (R_1 = 4-Cl-Ph, R_2 = H) was 59% and those of **4d** (R_1 = Ph, R_2 = H) and **4e** (R_1 = 4-CH_3-Ph, R_2 = H) were 56% and 50%, respectively. When using the same aldehyde, the yields of **4** with aromatic amines were higher than that of ammonium acetate, which can be seen from the yields of **4a** (63%, R_1 = Ph, R_2 = Ph), **4d** (56%, R_1 = Ph, R_2 = H), **4g** (55%, R_1 = H, R_2 = H) and **4j** (55%, R_1 = H, R_2 = Ph). The different substituted aldehydes and amines have no obvious influence on the yield of **5**; the yield of **5** was about 10%, and the yield ratio of **4** and **5** was about 5 : 1.

Theoretical calculation analysis

It's worth mentioning that the major byproduct **6a** was isolated in about 8% yield during the synthesis of 1,4-DHP **4a**, which can continue reacting with an equivalent amount of benzaldehyde and aniline, and finally a certain amount of **5a** was obtained (Scheme 2). The products **6a** were isolated as *s-trans*-(2*E*,4*Z*)-diethyl-4-((phenylamino)methylene)pent-2-enedioate and *s-cis*-(2*E*,4*Z*)-diethyl-4-((phenylamino)methylene) pent-2-enedioate (Fig. 1). The 2*E* stereochemistry was established on the basis of the large $J_{H,H}$ value of 15.7 Hz between the C2 hydrogen atom and the C3 hydrogen atom, while the 4*Z* stereochemistry was inferred on the basis of the fact that the diagonal signals were observed, correlation at (7.76, 6.19 ppm) and (7.76, 7.48 ppm), assigned to the proton of C4′



Scheme 2 Synthesis of 1,2-DHPs **5a** from byproduct **6a**.

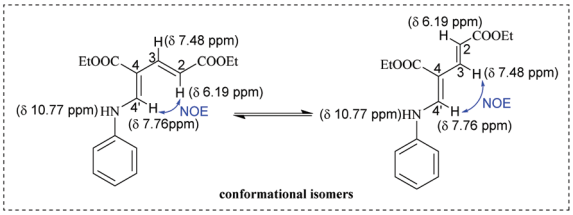


Fig. 1 Stereochemistry determination of intermediate **6a**.

H and the hydrogen of C2H/C3H; meanwhile, weak NOE cross-peaks between NH and CH_3 (1.40, 10.72 ppm) were observed (Fig. 2). Moreover, if the *s-cis* conformation exists singly, the NOE cross-peaks between C4′H and C2H (7.76, 6.19 ppm) will be more intensive than those between C4′H and C3H (7.76, 7.48 ppm) or the NOE cross-peaks between C4′H and C3H will not be observed; if the *s-trans* conformation exists singly, only the NOE cross-peaks between C4′H and C3H (7.76, 7.48 ppm) can be observed. But in fact, two NOE cross-peaks were observed and the NOE cross-peaks between C4′H and C3H (7.76, 7.48 ppm) are more intensive, indicating the presence of *s-trans*/*s-cis* equilibrium and the dominant conformation is the *s-trans* conformation. The results of stereochemistry are consistent with the previous literature which reported the construction of a functionalized conjugated diene motif using a silica gel-promoted method.[28]

The discovery of **6a** has great significance to explore the synthetic conditions and speculate the reaction mechanism. It can be seen from Tables 1–3 that a small amount of 1,2-DHPs (**5**) is always produced in the reactions. This fact makes us wonder why a small amount of 1,2-DHPs exists when 1,4-DHPs are produced in this reaction. To clarify this phenomenon, a mechanistic study of these reaction pathways was performed by DFT calculations. Given the little effects of substituents on the chemoselectivity of 1,4-DHPs and 1,2-DHPs, the synthesis reaction of **4a** and **5a** was used as a model for theoretical calculations. Referring to the literature on the synthesis of DHPs and the separation of intermediate **6a**, mechanisms were proposed for the formation of 1,4-DHP and 1,2-DHP (Scheme 3).[1,29,30] There are two paths for this process: path a is the formation of 1,4-DHP **4a** and path b is the formation of 1,2-DHP **5a**. In path a, *trans* intermediate **IM2** is first generated. Then, intermediate **IM3** is produced through a nucleophilic substitution reaction between **IM2** and benzaldehyde. Later, after intramolecular H migration and a rearrangement reaction and loss of a molecule of water, intermediate **IM4** is obtained. After that, an intermolecular [4 + 2] cyclization reaction between intermediate **IM4** and ethyl propiolate occurs and finally **4a** is obtained. Different from path a, in path b, *cis* **IM3′** is first generated by the Michael addition reaction of ethyl propiolate and aniline. Subsequently, zwitterionic intermediate **IM4′** is formed by the Michael addition of **IM3′** onto ethyl propiolate. This zwitterionic intermediate is reactive and can be stabilized by proton transfer to give intermediate **6a**. Then, **6a** and a Schiff base intermediate produced by the nucleophilic addition reaction of benzaldehyde and aniline

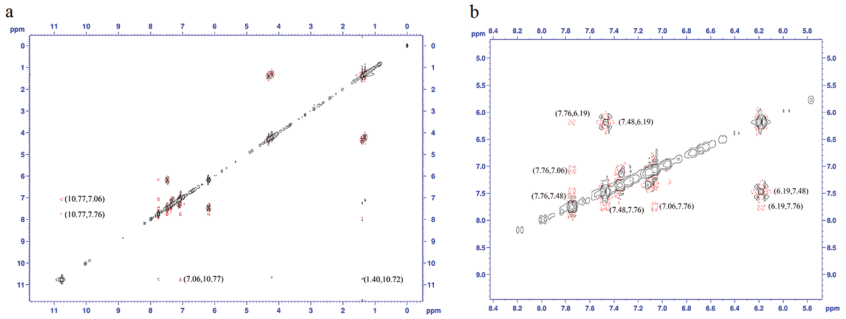
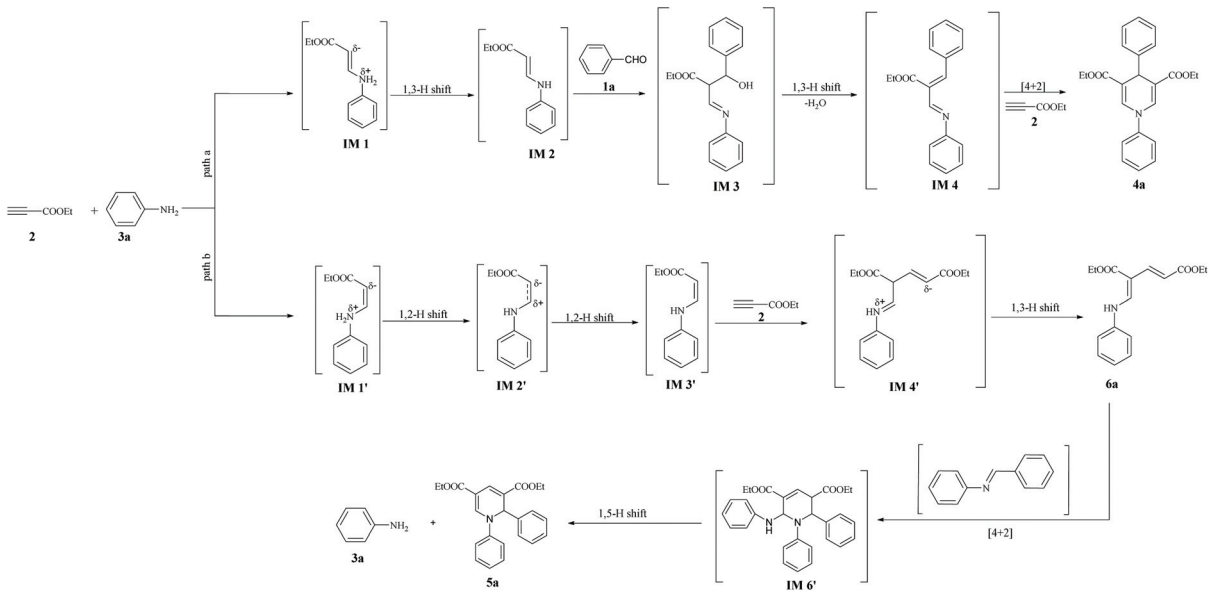


Fig. 2 (a) NOESY spectrum of **6a** and (b) local amplified NOESY spectrum of **6a**.



Scheme 3 Possible mechanism of 1,4-DHPs **4** and 1,2-DHPs **5**.

undergo an intermolecular [4 + 2] cyclization reaction to obtain intermediate **IM6′**. Ultimately, 1,2-DHP **5a** is generated through proton transfer and elimination of aniline as well as a rearrangement reaction.

In order to investigate the favorable paths shown in Scheme 3, DFT calculations were carried out at the M062X/def2TZVP//B3LYP-D3/def-SVP level, and the calculations included the solvent effect. For the sake of simplicity, the catalytic effect is not considered. The calculated free energies of path a and path b are shown in Fig. 3. The optimized structures of the pivotal intermediate (**IM**) and transition states (**TS**) are presented in the ESI.†

In the following discussion, the Gibbs free energies of ethyl propiolate and aniline were set as the energy reference point. All structures were optimized using one low energy conformation throughout. For the sake of simplicity, a full conformational search of those structures was not performed and there may be other conformations with lower energy, but the energy differences between different conformations are likely very small and therefore unlikely to affect our conclusions. To verify this, the energies of the key intermediates and transition states of other conformations (denoted "New") were calculated and the data are presented in the ESI.† In summary, for

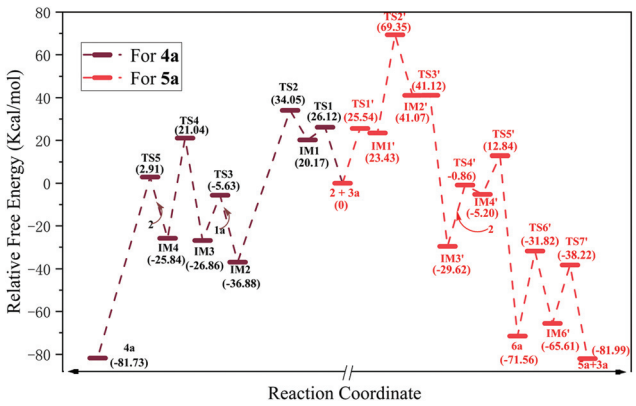


Fig. 3 Energy profile of path a for **4a** and path b for **5a** without considering the catalytic effect.

14-DHP, Original_IM2: −36.88 kcal mol^{-1} *vs.* New_IM2: −37.40 kcal mol^{-1}, Original_TS3: −5.63 kcal mol^{-1} *vs.* New_TS3: −6.35 kcal mol^{-1}, Original_IM3: −26.87 kcal mol^{-1} *vs.* New_IM3: −26.90 kcal mol^{-1}, Original_TS4: 21.04 kcal mol^{-1} *vs.* New_TS4: 21.73 kcal mol^{-1}. For 12-DHP, Original_6a: −71.56 kcal mol^{-1} *vs.* New_6a: −71.27 kcal mol^{-1}, Original_TS6′: −31.82 kcal mol^{-1} *vs.* New_TS6′: −33.38 kcal mol^{-1}.

As shown in Fig. 3, in the process of forming 1,4-DHP **4a**, the rate-determining states are **IM2** and **TS4**,[31] which thus has a barrier of 57.92 kcal mol^{-1}. In the process of forming 1,2-DHP **5a**, the rate-determining states are **2** + **3a** and **TS2′**, which thus has a barrier of 69.35 kcal mol^{-1}. The calculated barrier is too high, so it is necessary to consider the influence of the catalyst on the reaction path. Specifically, in the process of the hydrogen transfer reaction, it is necessary to consider the influence of some traces of water or solvent since those proton transfer processes might be facilitated by a proton-transfer shuttle.[32] In the nucleophilic addition reaction, the effect of traces of acid on the reaction should be considered.

As shown in Fig. 4, there are three steps in the process of 1,3-H migration to generate *trans* intermediate **IM2**; the barrier can be lowered by using a water H-transfer shuttle. Compared with direct 1,3-H migration, the barrier is reduced by 9.64 and 13.14 kcal mol^{-1} respectively by using one water molecule and two water molecules as the H-transfer shuttle. In the process of the transformation from **IM2** to **IM4**, when the catalysis of acetic acid and water is considered, the barrier is also reduced.

As shown in Fig. 5, a direct transformation from **IM1′** to **IM3′** was found with the help of a water proton-transfer shuttle. The transition state energy can be further lowered to 49.42 (**TS3′_W**) and 37.28 kcal mol^{-1} (**TS3′_2W**), respectively. During the conversion of **IM4′** to **6a**, the energy barrier was reduced by 8.86 kcal mol^{-1} using a water proton-transfer shuttle.

The specific mechanism for theoretical calculations was speculated with the synthesis of **4a** and **5a** as a model (Scheme 4). The calculated free energies of path a and path b are shown in Fig. 6.

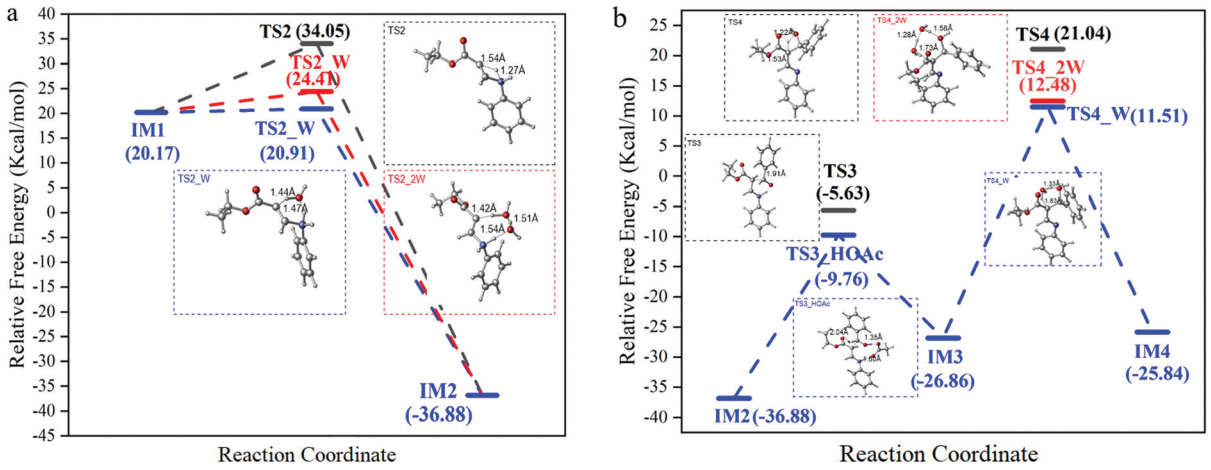


Fig. 4 Energy profile from **IM1** to **IM2** (a) and **IM2** to **IM4** (b) facilitated by the proton-transfer shuttles.

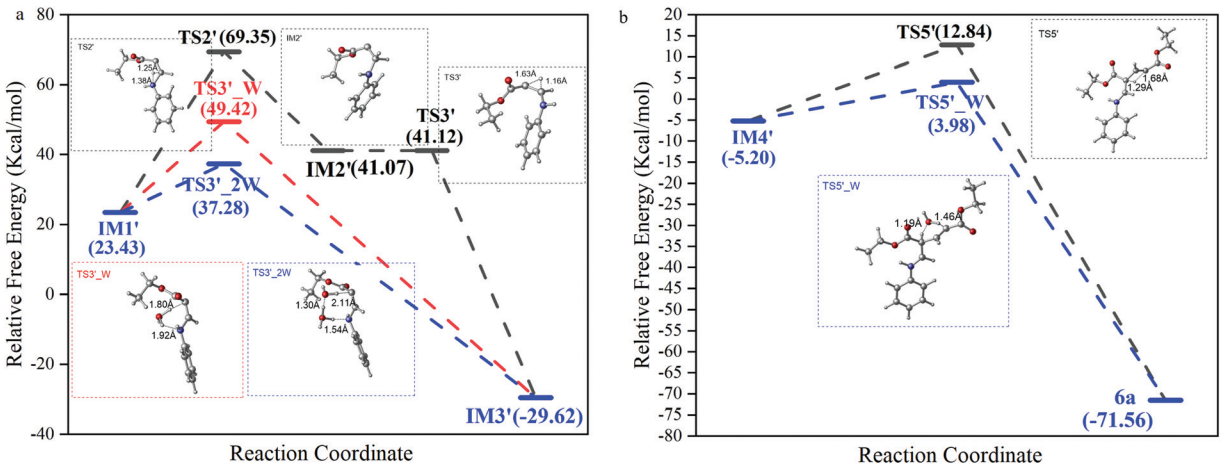
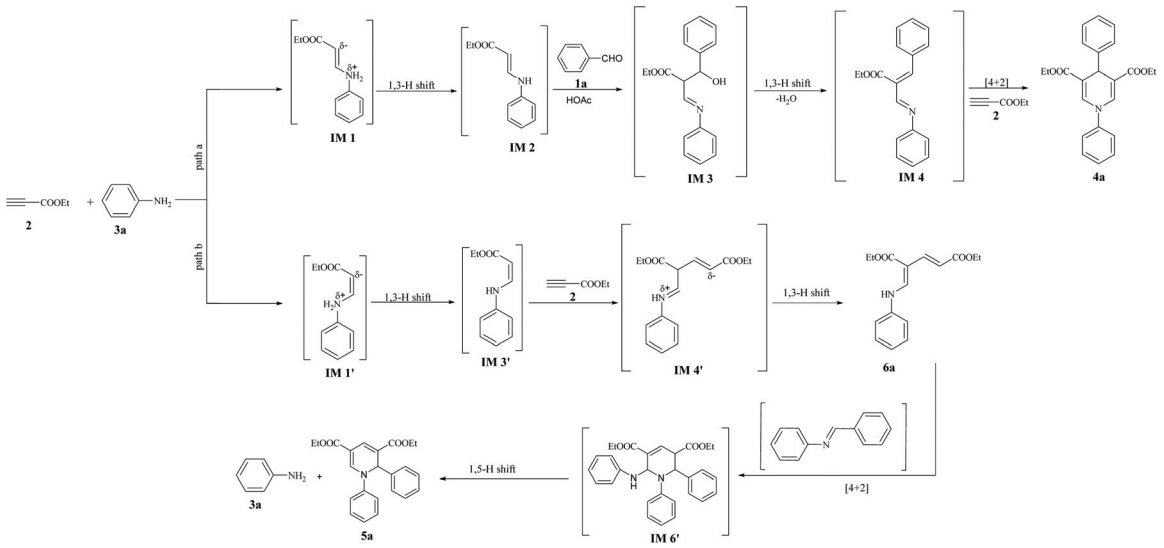


Fig. 5 Energy profile from **IM1′** to **IM3′** (a) and **IM4′** to **6a** (b) facilitated by the proton-transfer shuttles.



Scheme 4 Specific mechanism of 1,4-DHPs **4** and 1,2-DHPs **5**.

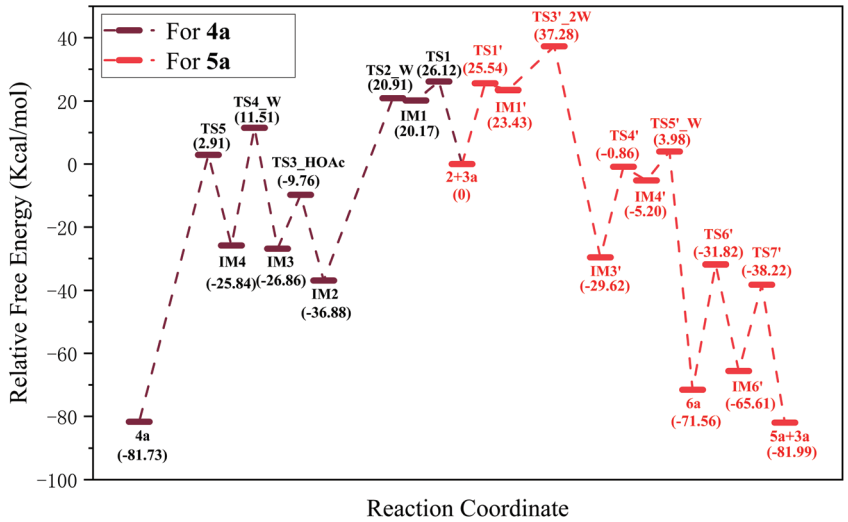


Fig. 6 Energy profile of path a for **4a** and path b for **5a** catalyzed by water and HOAc.

As shown in Fig. 6, there are two steps in the process of Michael addition of aniline onto ethyl propiolate to generate *trans* intermediate **IM2**. First, the nitrogen atom of aniline attacked the terminal carbon atom of ethyl propiolate to form intermediate **IM1** through transition state **TS1**. Then **IM1** underwent 1,3-H migration to form **IM2**; the barrier of these two steps is 26.12 kcal mol^{-1}. **IM2** passed through 3 transition states (**TS3_HOAc**, **TS4_W**, **TS5**) and 2 intermediates (**IM3**, **IM4**) to finally generate **4a**. The rate-determining states of the reaction are **IM2** and **TS4_W**, which thus has a barrier of 48.39 kcal mol^{-1}.

Similarly, the production of *cis* intermediate **IM3′** also needs two steps. Intermediate **IM1′** was formed firstly through transition state **TS1′**. Then it underwent 1,3-H migration with the help of a water proton-transfer shuttle to form **IM3′**; the barrier of these two steps is 37.28 kcal mol^{-1}. **IM3′** passed through 4 transition states (**TS4′**, **TS5′_W**, **TS6′**, **TS7′**) and 3 intermediates (**IM4′**, **6a**, **IM6′**) to finally generate **5a**. The rate-determining states of the reaction are **6a** and **TS6′**, which thus has a barrier of 39.74 kcal mol^{-1}.

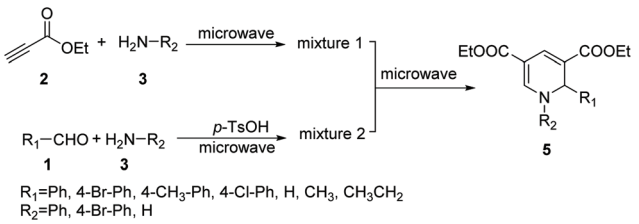
The formation energy barrier of **IM3′** is higher than that of **IM2** (37.28 kcal mol^{-1} *vs.* 26.12 kcal mol^{-1}), and the same tendency can also be noticed when comparing their free energies (**IM2**: −36.88 kcal mol^{-1}; **IM3′**: −29.62 kcal mol^{-1}), suggesting that the generation of **IM2** is more favorable than that of **IM3′** both kinetically and thermodynamically. Starting from **IM2**, **4a** is finally obtained, and starting from **IM3′**, **5a** is obtained, so the yield of **4a** is greater than that of **5a** in this reaction.

Synthesis of 1,2-DHPs 5

The reason why a small amount of **5a** is always produced in the synthesis reaction of **4a** was found through a mechanistic study of the reaction pathways by DFT calculations. Under the guidance of this result, the synthesis process of 1,2-DHPs **5** was explored. It was found that the essential step in the synthesis process of **5a** is the intermolecular [4 + 2] cyclization reaction between **6a** and a Schiff base intermediate which was produced by the nucleophilic addition reaction of benzaldehyde and aniline. In order to overcome the reaction energy barriers, a microwave reaction experiment was conducted. We noticed that **4a** is the dominant product in the one-pot experiment. In order to obtain the inferior product **5a** instead of **4a**, it seems feasible to design a stepwise one-pot reaction, and the reaction design route is shown in Scheme 5.

Firstly, using ethanol as a solvent to carry out the reaction at the reflux temperature, the influence of the microwave power on the yield of **5a** was studied. The results are presented in Table 4.

It can be seen that the microwave power has significant influence on the yield and production efficiency of **5a**. When the microwave power is 80 W, the yield of **5a** is only 12% and the reaction time is 4 h. When the microwave power is 120 W, the reaction time decreases to 3 h and the yield of **5a** increases to 22%. Compared with 120 W, when the microwave power is increased to 150 W, the yield shows only a slight increase, but it can be clearly observed from TLC that the reaction system becomes miscellaneous, which increases the difficulty of separation. This shows that too high or too low power is not conducive to the reaction.



Scheme 5 A stepwise one-pot synthesis of 1,2-DHPs **5** under microwave irradiation.

Table 4 Effect of the microwave power on the yield of **5a**

Entry	Microwave power (W)	Time[a] (h)	Yield, **5a**[b] (%)	Yield, **4a**[b] (%)
1	80	4	12	Trace
2	100	4	15	Trace
3	120	3	22	Trace
4	150	3	23	Trace

[a] Total time for 3 steps. [b] Total yield of the three-step reaction, isolated yields after column chromatography.

Table 5 Effect of the material ratio on the yield of **5a**

Entry	Material ratio (**1a : 2 : 3a**)	Time[a] (h)	Yield, **5a**[b] (%)	Yield, **4a**[b] (%)
1	1 : 2 : 2	3	22	Trace
2	1 : 2 : 1.5	3	14	Trace
3	1 : 2 : 3	3	20	Trace
4	2 : 2 : 2	3	20	Trace
5	1 : 4 : 2	3	28	Trace
6	1 : 6 : 2	3	46	Trace
7	1 : 8 : 2	3	46	Trace

[a] Total time for 3 steps. [b] Total yield of the three-step reaction, isolated yields after column chromatography.

Then, under the conditions of ethanol as a solvent, a microwave power of 120 W and a temperature of 78 °C, the influence of the material ratio on the yield of **5a** was investigated. The results are presented in Table 5.

It can be seen from Table 5 that the yield of **5a** was basically unchanged upon increasing the amount of benzaldehyde (**1a**) with the same amount of ethyl propiolate (**2**) and aniline (**3a**). When the amounts of **2** and **1a** were unchanged, the yield of **5a** increased with increasing amount of **3a**. The yield of **5a** increased with increasing amount of **2** when the amounts of **3a** and **1a** were unchanged. When **1a : 2 : 3a** = 1 : 6 : 2, the yield of **5a** reached the maximum, and **4a** was not produced in all reactions, thus realizing the selective synthesis of **5a**.

Ten different substituted 1,2-DHPs (**5**) were synthesized at the reflux temperature and under microwave irradiation using ethanol as the solvent. The yields are shown in Table 6.

It can be seen from Table 6 that the substituents of aldehydes and amines have a certain influence on the yield of **5**. When the substituents of amines are the same, the yields of **5**

Table 6 The yields of 1,2-dihydropyridine-3,5-dicarboxylates **5**[a]

Entry	R_1	R_2	**5**, yield[b] (%)
1	Ph	Ph	**5a**, 46
2	4-Br-Ph	Ph	**5b**, 49
3	Ph	4-Br-Ph	**5c**, 39
4	Ph	H	**5d**, 41
5	4-CH_3-Ph	H	**5e**, 38
6	4-Cl-Ph	H	**5f**, 44
7	H	H	**5g**, 27
8	CH_3	H	**5h**, 37
9	CH_3CH_2	H	**5i**, 35
10	H	Ph	**5j**, 31

[a] All reactions were carried out by a stepwise one-pot method. 3 equivalents of ethyl propiolate and 1 equivalent of aniline were heated with ethanol as the solvent under microwave irradiation with a power of 120 W; after 1 hour, mixture 1 was obtained. Meanwhile, 1 equivalent of benzaldehyde and 1 equivalent of aniline were added into a round bottom flask with ethanol as the solvent and 10% equivalent of *p*-TsOH as the catalyst and heated to reflux under microwave irradiation with a power of 120 W to obtain mixture 2. Then, mixture 2 was added to mixture 1 and heated for 1 hour at 120 W microwave power. [b] Total yield of the three-step reaction, isolated yields after column chromatography.

with aromatic aldehydes were higher than those with aliphatic aldehydes, which can be seen from the yields of **5a** (46%, R_1 = Ph, R_2 = Ph) and **5j** (41%, R_1 = H, R_2 = Ph). The yields of **5** (R_1 = aryl) were improved by an electron-withdrawing group, for example, the yield of **5f** (R_1 = 4-C1-Ph, R_2 = H) was 44% and that of **5d** (R_1 = Ph, R_2 = H) was 41%. When using the same aldehyde, the yields of **5** with aromatic amines were higher than that of ammonium acetate, which can be seen from the yields of **5a** (46%, R_1 = Ph, R_2 = Ph) and **5d** (41%, R_1 = Ph, R_2 = H). When the substituent on the aromatic amine is an electron-withdrawing group, the nucleophilic activity of the aromatic amine is reduced, such as **5a** (46%, R_1 = Ph, R_2 = Ph) and **5c** (39%, R_1 = Ph, R_2 = 4-Br-Ph). It was also worth mentioning that 1,4-DHP derivatives **4** were not found in all reactions; the chemoselectivity is excellent in the case of the stepwise one-pot reaction.

Conclusion

A series of diethyl 3,5-dicarboxylate-1,4-dihydropyridines (1,4-DHPs) were synthesized with moderate yields by a Hantzsch-like reaction using aromatic amines, aromatic aldehydes and ethyl propiolate as raw materials. Unexpectedly, it was found that a by-product named diethyl 3,5-dicarboxylate-1,2-dihydropyridine (1,2-DHP) was produced in the reaction. Based on the results of the effects of the reaction conditions on the yield and yield ratio of 1,4-DHPs and 1,2-DHPs, especially on the separation of the intermediate named diethyl-4-((phenylamino)methylene)pent-2-enedioate, the possible mechanisms for the formation of 1,4-DHPs and 1,2-DHPs were speculated. DFT calculations were used to optimize the transition state structures and calculate the energy barriers of the intermediates at the M062X/def2TZVP//B3LYP-D3/def-SVP level. In the paths of the synthesis of 1,4-DHPs and 1,2-DHPs, the reaction energy barriers and dominant configurations of intermediates **IM2** and **IM3′** are the determinants for the chemoselectivity. The *trans* intermediate **IM2** was formed with an energy barrier of 26.12 kcal mol^{-1} and the *cis* intermediate **IM3′** was formed with an energy barrier of 37.28 kcal mol^{-1}. The free energies of **IM2** and **IM3′** (−36.88 kcal mol^{-1} and −29.62 kcal mol^{-1}) also suggest that the formation of 1,4-DHPs is more favorable than that of 1,2-DHPs thermodynamically. Under the guidance of the theoretical calculation results, the synthesis process of 1,2-DHPs was explored through a stepwise one-pot reaction. In order to overcome the reaction energy barriers and decrease the reaction time, a microwave irradiation experiment was conducted. Finally, 1,4-DHPs and 1,2-DHPs were obtained with high chemoselectivity by a Hantzsch-like reaction under different conditions.

Experiments and methods

Physical measurements

All chemicals were purchased from commercial sources and used without further purification. Thin-layer chromatography (TLC) was conducted on silica gel 60 F254 plates (Merck KGaA). The NMR experiments were performed on a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H NMR spectra and 100 MHz for ^{13}C NMR spectra at ambient temperature (25 °C) using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. Electrospray ionization mass spectra (ESI-MS) were measured on a ZAB-HS & ESQUIRE6000 mass spectrometer.

Computational details

The geometrical structures of all the stationary points along the reaction paths were optimized at the B3LYP-D3/def-SVP theoretical level.[33–37] Frequency analysis calculations were carried out at the same level to classify the located stationary points as minima (no imaginary frequency) and transition states (only one imaginary frequency). The thermodynamic correction data used in this paper were obtained at 298.15 K and 1 atm. Intrinsic reaction coordinate (IRC) pathways have also been calculated for all the transition states to determine whether these transition states could connect the reactants, intermediates or products.[38] The single point energies of all the optimized structures were calculated at the M062X/def2-TZVP level.[39,40] The polarized continuum model (PCM) was used in a Self-Consistent Reaction Field (SCRF) for modelling ethanol solvent.[41,42] All of the quantum chemical calculations were performed using the Gaussian 09 program package.[43] The diagrams of molecular structures were plotted using the CYLview program and the electrostatic potential (ESP) on the molecular vdW surface was rendered using the VMD 1.9.2 software.[44,45] All other wavefunction analyses were performed using Multiwfn 3.8.[46]

General synthetic procedures

General procedure for the synthesis of 1,4-hydropyridines (4). 2 mmol ethyl propiolate, 1 mmol aniline and 1 mmol benzaldehyde were added into a round bottom flask with ethanol as the solvent and 0.1 mmol *p*-TsOH as the catalyst. Under nitrogen protection, the reaction mixture was heated to reflux until the completion of the reaction (TLC detection). After cooling to room temperature, the solvent was removed by reduced pressure distillation, 10 mL of water was added, and the mixture was extracted with ethyl acetate (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20 : 1 to 8 : 1) to obtain a light yellow solid of 1,4-dihydropyridines **4**.

*Diethyl 1,4-diphenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**).*[25] Yield 63%; ^{1}H NMR (400 MHz, chloroform-*d*) *δ*: 7.67 (s, 2H), 7.47 (dd, *J* = 8.7, 7.2 Hz, 2H), 7.39–7.34 (m, 2H), 7.34–7.27 (m, 4H), 7.24 (s, 1H), 7.20–7.14 (m, 1H), 4.96 (s, 1H), 4.19–4.03 (m, 4H), 1.20 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) *δ*: 166.80, 146.10, 143.21, 135.55, 129.93, 128.40, 128.04, 126.58, 126.33, 120.75, 111.06, 60.27, 37.74, 14.24.

*Diethyl 4-(4-bromophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4b**).*[25] Yield 65%; ^{1}H NMR (400 MHz, chloro-

form-*d*) δ: 7.66 (s, 2H), 7.50–7.44 (m, 2H), 7.41–7.36 (m, 2H), 7.34–7.28 (m, 3H), 7.25 (d, J = 8.2 Hz, 2H), 4.94 (s, 1H), 4.11 (m, 4H), 1.20 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 166.59, 145.19, 143.07, 135.74, 131.13, 130.18, 129.98, 126.51, 120.79, 120.48, 110.55, 60.38, 37.38, 14.26.

*Diethyl 1-(4-bromophenyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4c**).*[15] Yield 61%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.61 (s, 2H), 7.62–7.53 (m, 2H), 7.38–7.32 (m, 2H), 7.29–7.23 (m, 2H), 7.21–7.14 (m, 3H), 4.95 (s, 1H), 4.18–4.03 (m, 4H), 1.20 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 166.62, 145.77, 142.18, 134.94, 132.99, 128.39, 128.09, 126.68, 122.20, 119.44, 111.63, 60.40, 37.70, 14.22.

*Diethyl 4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4d**).*[47] Yield 56%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.38–7.31 (m, 2H), 7.31–7.21 (m, 4H), 7.19–7.11 (m, 1H), 6.81 (brs, 1H), 4.89 (s, 1H), 4.16–3.98 (m, 4H), 1.19 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 167.26, 146.97, 133.87, 128.29, 127.96, 126.41, 108.32, 60.04, 37.65, 14.19.

*Diethyl 3,5-dicarboxylate-4-(p-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate (**4e**).*[48] Yield 50%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.29 (d, J = 5.3 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 7.7 Hz, 2H), 6.55–6.52 (m, 1H), 4.85 (s, 1H), 4.16–3.99 (m, 4H), 2.28 (s, 3H), 1.20 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 167.22, 144.12, 135.90, 133.61, 128.71, 128.16, 108.55, 60.05, 37.12, 21.12, 14.25.

*Diethyl 4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**4f**).*[49] Yield 59%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.33 (m, 2H), 7.30–7.26 (m, 2H), 7.23–7.18 (m, 2H), 6.41 (d, J = 13.0 Hz, 1H), 4.88 (s, 1H), 4.17–4.00 (m, 4H), 1.19 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 166.95, 145.44, 133.73, 132.10, 129.72, 128.10, 108.23, 60.18, 37.21, 14.23.

*Diethyl 1,4-dihydropyridine-3,5-dicarboxylate (**4g**).*[47] Yield 55%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.10 (d, J = 5.0 Hz, 2H), 6.60 (brs, 1H), 4.24–4.13 (m, 4H), 3.25 (s, 2H), 1.28 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 167.73, 135.08, 104.15, 60.01, 21.71, 14.37.

*Diethyl 4-methyl-1,4-dihydropyridine-3,5-dicarboxylate (**4h**).*[50] Yield 53%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.20 (d, J = 5.2 Hz, 2H), 6.63 (brs, 1H), 4.26–4.12 (m, 4H), 3.79 (q, J = 6.4 Hz, 1H), 1.32–1.26 (m, 6H), 1.11 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 167.54, 134.33, 108.98, 59.97, 26.30, 23.31, 14.39.

*Diethyl 4-ethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4i**).* Yield 54%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.30 (d, J = 5.3 Hz, 2H), 6.35 (brs, 1H), 4.26–4.12 (m, 4H), 3.92 (t, J = 4.6 Hz, 1H), 1.49 (qd, J = 7.5, 4.4 Hz, 2H), 1.29 (t, J = 7.1 Hz, 6H), 0.79 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, chloroform-*d*) δ: 167.61, 135.23, 106.68, 59.97, 31.78, 28.19, 14.40, 8.63. HRMS (ESI), m/z calcd 254.1387 for $C_{23}H_{24}NO_4$ $[M + H]^+$, found 254.1385.

*Diethyl 1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4j**).*[47] Yield 55%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.47–7.37 (m, 4H), 7.26–7.16 (m, 3H), 4.23 (q, J = 7.1 Hz, 4H), 3.34 (s, 2H), 1.30 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 167.31, 143.20, 136.95, 129.78, 125.91, 120.29, 107.08, 60.28, 21.98, 14.45.

*Diethyl 4-((phenylamino)methylene)pent-2-enedioate (**6a**).*[28] Yield 8%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 10.77 (d, J = 13.1 Hz, 1H), 7.76 (d, J = 13.1 Hz, 1H), 7.48 (d, J = 15.7 Hz, 1H), 7.36 (dd, J = 8.5, 7.3 Hz, 2H), 7.18–7.03 (m, 3H), 6.19 (d, J = 15.7 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 168.97, 168.42, 147.73, 142.29, 139.38, 129.88, 124.38, 116.60, 111.05, 98.59, 60.44, 59.91, 14.48, 14.42.

General procedure for the synthesis of 1,2-hydropyridines (5). 3 mmol ethyl propiolate and 1 mmol aniline were heated under microwave irradiation with a power of 120 W and at a temperature of 78 °C; after 1 hour, mixture 1 was obtained. Meanwhile, 1 mmol benzaldehyde and 1 mmol aniline were added into a round bottom flask with ethanol as the solvent and 0.1 mmol *p*-TsOH as the catalyst and heated to reflux under microwave irradiation with a power of 120 W until the completion of the reaction (TLC detection) to obtain mixture 2. Then, mixture 2 was added to mixture 1 and heated for 1 hour at 120 W microwave power. After cooling to room temperature, the solvent was removed by reduced pressure distillation, 10 mL of water was added, and the mixture was extracted with ethyl acetate (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20 : 1 to 8 : 1) to obtain a light yellow oil of 1,2-dihydropyridines **5**.

*Diethyl 1,2-diphenyl-1,2-dihydropyridine-3,5-dicarboxylate (**5a**).*[27] Yield 46%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 8.11 (s, 1H), 7.72 (s, 1H), 7.45–7.37 (m, 2H), 7.37–7.27 (m, 5H), 7.25–7.11 (m, 3H), 6.16 (s, 1H), 4.33–4.15 (m, 4H), 1.34 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 165.84, 165.78, 144.87, 144.44, 141.47, 130.68, 129.52, 128.76, 128.15, 126.19, 125.94, 121.06, 114.48, 103.43, 61.22, 60.56, 60.08, 14.55, 14.36.

*Diethyl 2-(4-bromophenyl)-1-phenyl-1,2-dihydropyridine-3,5-dicarboxylate (**5b**).* Yield 49%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 8.08 (t, J = 1.2 Hz, 1H), 7.72 (d, J = 1.1 Hz, 1H), 7.43–7.39 (m, 2H), 7.38–7.31 (m, 2H), 7.31–7.20 (m, 3H), 7.16–7.11 (m, 2H), 6.12 (d, J = 1.3 Hz, 1H), 4.30–4.25 (m, 2H), 4.25–4.12 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 165.70, 165.65, 144.84, 144.21, 140.39, 131.91, 130.88, 129.65, 127.77, 126.43, 122.20, 121.07, 114.07, 103.41, 60.78, 60.69, 60.19, 14.55, 14.37. HRMS (ESI), m/z calcd 456.0805 for $C_{23}H_{23}BrNO_4$ $[M + H]^+$, found 456.0802.

*Diethyl 1-(4-bromophenyl)-2-phenyl-1,2-dihydropyridine-3,5-dicarboxylate (**5c**).* Yield 39%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 8.04 (t, J = 1.3 Hz, 1H), 7.70 (d, J = 1.0 Hz, 1H), 7.47–7.41 (m, 2H), 7.41–7.35 (m, 2H), 7.33–7.26 (m, 3H), 7.06–7.00 (m, 2H), 6.09 (d, J = 1.2 Hz, 1H), 4.32–4.06 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 165.72, 165.61, 144.11, 143.42, 141.06, 132.58, 130.39, 128.89, 128.35, 125.89, 122.40, 119.39, 115.12, 104.07, 61.12, 60.69, 60.24, 14.54, 14.36. HRMS (ESI), m/z calcd 456.0805 for $C_{23}H_{23}BrNO_4$ $[M + H]^+$, found 456.0806.

*Diethyl 2-phenyl-1,2-dihydropyridine-3,5-dicarboxylate (**5d**).* Yield 41%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.74 (s, 1H), 7.63 (d, J = 7.0 Hz, 1H), 7.40 (d, J = 7.3 Hz, 2H), 7.31 (m, 3H), 5.75 (s, 1H), 5.66 (s, 1H), 4.21 (q, J = 7.3 Hz, 2H), 4.10 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 166.06, 166.01, 146.57, 143.56, 132.83, 128.76, 128.30, 126.76, 112.90, 97.05, 60.23, 59.71, 55.45, 14.53, 14.23. HRMS (ESI), m/z calcd 302.1387 for $C_{17}H_{20}NO_4$ $[M + H]^+$, found 302.1391.

*Diethyl 2-(p-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (**5e**).* Yield 38%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.73 (s, 1H), 7.62 (d, J = 6.9 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 5.73–5.66 (m, 1H), 5.62 (d, J = 2.7 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.15–4.02 (m, 2H), 2.32 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 165.92, 165.89, 146.07, 140.83, 138.24, 132.44, 129.48, 126.71, 113.52, 97.39, 60.21, 59.71, 55.27, 21.18, 14.57, 14.27. HRMS (ESI), m/z calcd 316.1543 for $C_{18}H_{22}NO_4$ $[M + H]^+$, found 316.1541.

*Diethyl 2-(4-chlorophenyl)-1,2-dihydropyridine-3,5-dicarboxylate (**5f**).* Yield 44%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.72 (d, J = 1.5 Hz, 1H), 7.62 (dd, J = 6.9, 1.5 Hz, 1H), 7.34–7.26 (m, 4H), 6.07 (dd, J = 7.4, 3.0 Hz, 1H), 5.63 (d, J = 2.9 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.15–4.03 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 165.89, 165.81, 146.28, 142.01, 134.18, 132.80, 128.94, 128.19, 112.93, 97.42, 60.38, 59.85, 54.85, 14.54, 14.26. HRMS (ESI), m/z calcd 336.0997 for $C_{17}H_{19}ClNO_4$ $[M + H]^+$, found 336.1002.

*Diethyl 1,2-dihydropyridine-3,5-dicarboxylate (**5g**).* Yield 27%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.58 (dd, J = 7.2, 1.5 Hz, 1H), 7.49 (d, J = 1.4 Hz, 1H), 5.88 (s, 1H), 4.42–4.36 (m, 2H), 4.18 (p, J = 7.1 Hz, 4H), 1.29 (td, J = 7.1, 5.3 Hz, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 166.12, 165.88, 149.35, 134.10, 108.38, 97.42, 60.25, 59.58, 41.86, 14.54, 14.38. HRMS (ESI), m/z calcd 226.1074 for $C_{11}H_{16}NO_4$ $[M + H]^+$, found 226.1071.

*Diethyl 2-methyl-1,2-dihydropyridine-3,5-dicarboxylate (**5h**).* Yield 37%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.62–7.56 (m, 2H), 5.64 (s, 1H), 4.69 (qd, J = 6.3, 3.4 Hz, 1H), 4.20 (qd, J = 7.1, 3.8 Hz, 4H), 1.30 (td, J = 7.1, 3.6 Hz, 6H), 1.21 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 166.06, 165.97, 146.60, 132.44, 113.79, 98.03, 60.18, 59.65, 47.22, 22.59, 14.56, 14.39. HRMS (ESI), m/z calcd 240.1230 for $C_{12}H_{18}NO_4$ $[M + H]^+$, found 240.1235.

*Diethyl 2-ethyl-1,2-dihydropyridine-3,5-dicarboxylate (**5i**).* Yield 35%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.67–7.59 (m, 2H), 5.85 (s, 1H), 4.56 (dt, J = 7.6, 3.8 Hz, 1H), 4.27–4.14 (m, 4H), 1.52–1.39 (m, 2H), 1.30 (td, J = 7.1, 3.2 Hz, 6H), 0.91 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 166.22, 166.13, 147.21, 133.19, 112.35, 98.40, 60.16, 59.63, 52.72, 29.06, 14.55, 14.38, 8.41. HRMS (ESI), m/z calcd 254.1387 for $C_{23}H_{24}NO_4$ $[M + H]^+$, found 254.1392.

*Diethyl 1-phenyl-1,2-dihydropyridine-3,5-dicarboxylate (**5j**).* Yield 31%; ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.91 (s, 1H), 7.64 (s, 1H), 7.50–7.40 (m, 2H), 7.27–7.18 (m, 3H), 4.73 (s, 2H), 4.26 (m, 4H), 1.34 (m, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ: 165.69, 165.34, 145.57, 143.95, 132.45, 129.52, 125.51, 118.70, 110.81, 102.71, 60.43, 59.93, 47.42, 14.55, 14.41. HRMS (ESI), m/z calcd 302.1387 for $C_{17}H_{20}NO_4$ $[M + H]^+$, found 302.1391.

Conflicts of interest

There are no conflicts to declare.

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