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Visible light photocatalytic cascade cyclization reaction between glycine derivatives and *β*-ketoesters using $Ir(ppy)_3$

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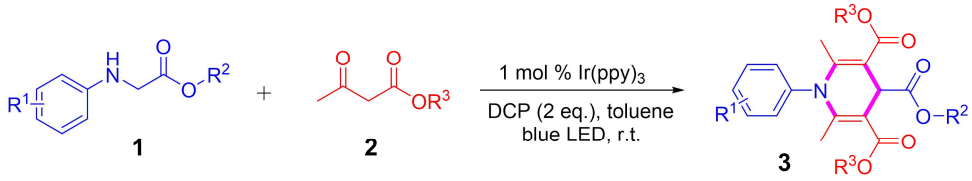

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ABSTRACT

Visible light photocatalytic cascade cyclization reaction between glycine derivatives and *β*-ketoesters using $Ir(ppy)_3$ as a catalyst and dicumyl peroxide (DCP) as an oxidant was described. A series of *N*-aryl glycine esters proceeded the cyclization smoothly with β-ketoesters at room temperature, affording the desired 1,4-dihydropyridines (1,4-DHPs) in satisfactory yields. A possible mechanism for the cascade cyclization reaction by visible light photoredox catalysis was also proposed. This protocol not only provides an efficient and convenient approach to synthetize various 1,4-dihydropyridines, but also has potential utilities for the construction of bioactive molecules.

1. Introduction

Oxidative C-H functionalization has emerged in recent years as a powerful technique to construct complex molecules from simple starting materials in organic synthesis [1]. Among them, much attention has been attracted to the visible light photoredox-mediated C-H functionalization from the chemists due to its inherent characteristics of environmental benignity, sustainability and ease to handle [2]. Glycine is the simplest and readily available natural amino acids. Direct oxidative α-C-H functionalization of glycine via visible light photoredox catalysis provides a reliable and attractive strategy to afford structurally diverse α-amino acid derivatives [3]. In 2015, Wu et al revealed a cross-coupling hydrogen evolution reaction of glycine derivatives with *β*-keto esters by the synergistic catalysis of $Ru(bpy)_3(PF_6)_2$ and $Co(dmgH)_2pyCl$ under visible light irradiation [3a]. In 2016, Xiao's group reported a visible-light-initiated photocatalytic crossing-coupling reaction of glycine derivatives with aryl ketones and aldehyde to 1,2-amino alcohols [3b]. Although much progress has been achieved, the development of simple and efficient methods for the preparation of potentially useful organic molecules through C-H functionalization under mild conditions is still highly desired.

As an important class of nitrogen-containing heterocycles, 1,4-dihydropyridines (1,4-DHPs) are widely prevalent in a great number of natural products, biologically active molecules and pharmaceuticals [4-5]. In particularly, 1,4-DHPs possess a broad range of biological properties such as anticonvulsant activity [6], antitumor [7], antitubercular [8], anti-inflammatory [9], *etc*. Several commercially available drugs like amlodipine, nicardipine, felodipine, nifedipine and nimodipine contain 1,4-DHP moiety in their core structure. Owing to these intriguing characteristics and utilization, considerable research efforts have been devoted to access various 1,4-dihydropyridine derivatives by synthetic and medicinal chemists over the years [5]. Cascade reaction, which can generate more chemical bonds in a one set of fixed conditions and one-pot process during the reaction, has been extensively applied to the construction of various bioactive molecules, natural products and functional materials [10]. In 2014, Jia *et al* disclosed a radical cation salt-prompted C-H oxidation/C-N bond cleavage to access a variety of 1,4-

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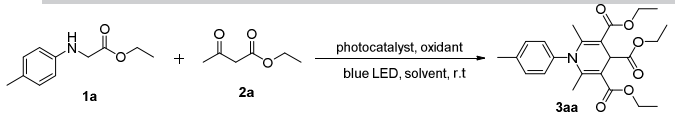
Table 1 Optimization of the reaction conditions[a]



entry	photocatalyst	oxidant	solvent	yield(%)[b]
1	Acr^+-Mes-ClO_4^-	air	toluene	40
2	Methylene blue	air	toluene	51
3	$Ir(ppy)_3$	air	toluene	60
4	$Ru(bpy_3)Cl_2•6H_2O$	air	toluene	N.P.[c]
5	Eosin Y	air	toluene	N.P.[c]
6	Rose Bengal	air	toluene	trace
7	$Ir(ppy)_3$	$K_2S_2O_8$	toluene	27
8	$Ir(ppy)_3$	O_2	toluene	47
9	$Ir(ppy)_3$	TBHP	toluene	trace
10	$Ir(ppy)_3$	TBPB	toluene	57
11	$Ir(ppy)_3$	DTBP	toluene	65
12	$Ir(ppy)_3$	DCP	toluene	68
13	$Ir(ppy)_3$	DCP	DCM	31
14	$Ir(ppy)_3$	DCP	DCE	32
15	$Ir(ppy)_3$	DCP	THF	34
16	$Ir(ppy)_3$	DCP	DMSO	30
17	$Ir(ppy)_3$	DCP	PhCl	47
18	$Ir(ppy)_3$	DCP	xylene	67
19[d]	--	DCP	toluene	trace
20[e]	$Ir(ppy)_3$	DCP	toluene	N.P.[c]

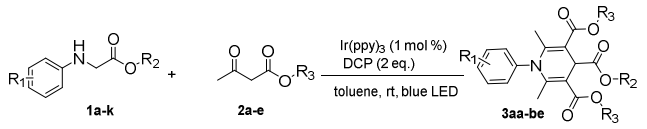
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.44 mmol), catalyst (1 mol %), oxidant (2 equiv.), solvent (2 mL) at room temperature under irradiation of 18 W blue LED light for 12 hrs.
[b] Isolated yield based on **1a**.
[c] N.P. = No product.
[d] In the absence of a catalyst.
[e] The reaction was carried out in dark.

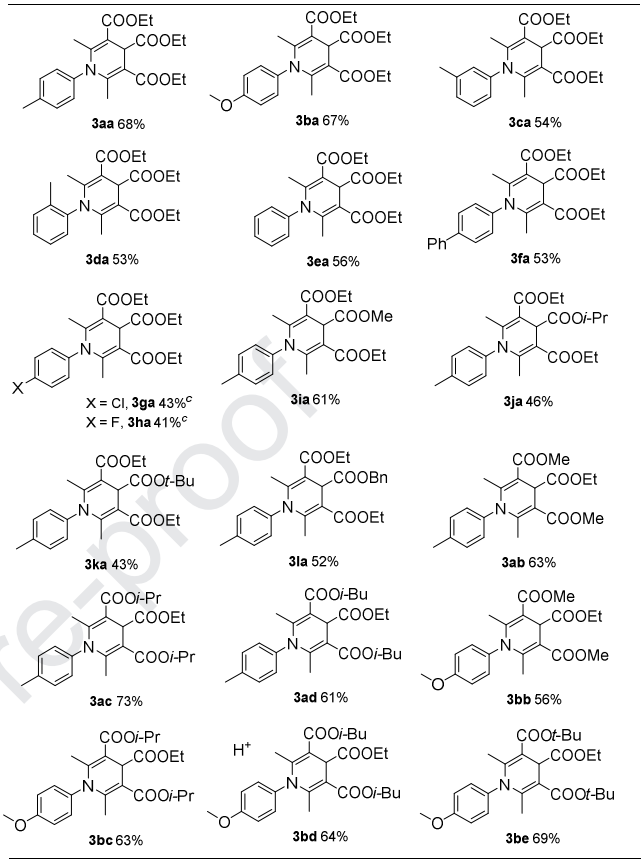
dihydropyridines with TMSCl as an additive [11a]. In 2016, our group developed an aerobic oxidative coupling/ cyclization of glycine derivatives with 1,3-dicarbonyl compounds to afford various 1,4-dihydropyridines by copper catalysis [11b]. In view of the biological importance of 1,4-dihydropyridines, and as our ongoing efforts on C-H functionalization reactions [12], we herein present a simple and efficient cascade cyclization reaction of glycine esters with *β*-ketoesters to synthetize polysubstituted 1,4-dihydropyridines using visible light photoredox catalysis at room temperature.

2. Results and discussion

Our investigation began with the model reaction of *N*-4-methylphenylglycine ethyl ester **1a** and ethyl acetoacetate **2a** in the presence of 1 mol % Acr^+-Mes-ClO_4^- (9-Mesityl-10-methylacridinium Perchlorate) in toluene under irradiation of 18 W blue LED light at room temperature. To our delight, the desired cyclization product **3aa** was isolated with a yield of 40% (entry 1, Table 1). Encouraged by this result, a variety of common photocatalysts such as $Ir(ppy)_3$, methylene blue, $Ru(bpy_3)Cl_2•6H_2O$, eosin Y and rose bengal were explored to improve the reaction efficiency (entries 2-6, Table 1). Screening results revealed that $Ir(ppy)_3$ showed the best catalytic efficiency, resulting the desired product **3aa** with a yield of 60%. Next, a series of oxidants including $K_2S_2O_8$, O_2, *tert*-butyl hydroperoxide (TBHP), *tert*-butyl peroxybenzoate (TBPB), di-*tert*-butyl peroxide (DTBP) and dicumyl peroxyide (DCP) were tested, and DCP was the best choice, leading to the product **3aa** in 68% yield (compare entries 3, 7-11 with 12, Table 1). Among various solvents screened, toluene was the most effective reaction medium than others such as DCE, THF, PhCl and DMSO (compare entries 13-18 with 12, Table 1). A similar yield of **3aa** was obtained in xylene (entry 18, Table 1). In the absence of a photocatalyst, only a trace amount of product **3aa** was detected (entry 19, Table 1). When the reaction was performed in dark, no desired product **3aa** was observed (entry 20, Table 1). The result suggested that both visible light and photocatalyst were crucial to this transformation. After exploring different parameters, we defined the cascade cyclization reaction of *N*-4-methylphenylglycine ethyl ester **1a** and ethyl acetoacetate **2a** in the presence of 1 mol % of $Ir(ppy)_3$, DCP (2 equiv.) in toluene (2 mL) at room temperature under irradiation of 18 W blue LED light as the standard conditions.

Table 2 Cascade cyclization of glycine esters **1a-l** with *β*-ketoesters **2a-e** by visible light photoredox catalysis[a,b]

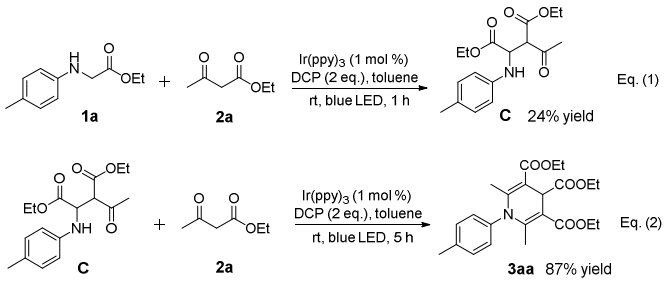




[a] Reaction conditions: **1** (0.2 mmol), **2** (0.44 mmol), $Ir(ppy)_3$ (1 mol %), DCP (2 equiv.), toluene (2 mL) at room temperature under irradiation of 18 W blue LED light for 12 hrs.
[b] Isolated yield based on **1**.
[c] For 36 hrs.

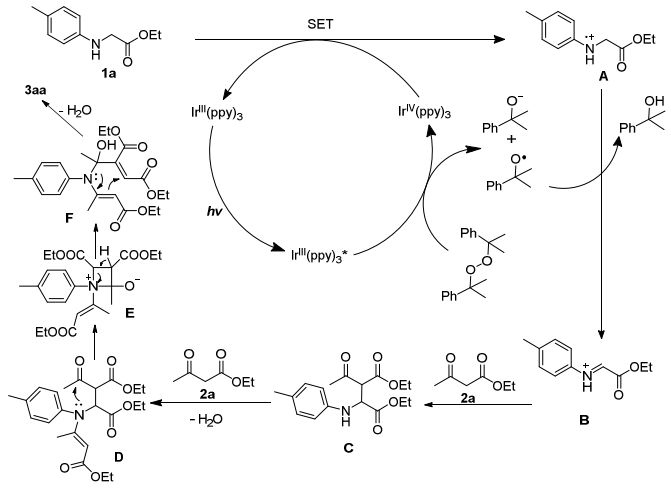
With the preliminary optimized reaction conditions in hand, a range of *N*-aryl glycine esters **1** and *β*-ketoesters **2a** were examined. As shown in Table 2, a large array of *N*-aryl glycine esters **1a-k** underwent the cascade cyclization readily with ethyl acetoacetate **2a**, affording the corresponding products **3aa-la** in satisfactory yields. For example, *N*-arylglycine ethyl ester **1a-g** bearing either electron-donating or electron-withdrawing groups on the *N*-benzene rings performed the reaction well with ethyl acetoacetate **2a**, producing the corresponding products **3aa-ha** in 41-68% yields. It was observed that the reactivity of the electron-donating substituents was superior to that of the electron-withdrawing substituents on the the *para-position* of the benzene rings of *N*-arylglycine esters. Notably, the synthetically valuable

halogen groups, like fluoro and chloro were well tolerated with the current conditions. Besides, *N*-arylglycine esters **1i-l** possessing a number of different ester groups, such as methyl, isopropyl, *tert*-butyl and benzyl esters, were also compatible with the standard conditions, providing the desired products **3ia-3la** in moderate to good yields. On the other hand, a diverse range of *β*-ketoesters were investigated with *N*-arylglycine ester **1a** or **1b** under the standard conditions. The experimental results revealed that *β*-ketoesters **2b-e** including methyl, isopropyl and isobutyl acetoacetate proceeded the cascade cyclization reaction readily with *N*-arylglycine ester **1a** or **1b**, affording the corresponding products **3ab**-**3ad**, **3bb-be** in good yields. Unfortunately, when acetylacetone was used instead of **2a** with **1a** under the standard reaction conditions, only a trace amount of the desired product was observed.



Scheme 1 Control experiments

To elucidate the underlying reaction mechanism, we examined the conversion of the oxidative coupling of **1a** with ethyl acetoacetate **2a** under the standard conditions after 1 h. As expected, coupling intermediate **C** was detected by the ESI mass spectrometry analysis, albeit with a low isolated yield. Moreover, when the reaction of intermediate **C** and **2a** was dealt under standard condition at room temperature, the desired product **3aa** was obtained in 87% yield (Scheme 1). On the basis of the experimental results and reported literatures [11,13], a tentative mechanism for the cascade cyclization reaction is proposed, as depicted in Scheme 2. Firstly, upon irradiation with visible-light, photocatalyst $Ir^{III}(ppy)_3$ can readily accept a photon to generate the photoexcited state $*Ir^{III}(ppy)_3$, which acts as a strong reductant to reduce DCP via single electron transfer (SET) to form $Ir^{IV}(ppy)_3$ [3b,13]. At the same time, DCP undergoes a cleavage to afford an alkoxy radical and an alkoxy anion. Subsequently, glycine ester **1a** gives a single electron to $Ir^{IV}(ppy)_3$ to produce the radical cation **A**, and regenerates the ground-state photocatalyst. Next, alkoxy radical abstracts a hydrogen atom from **A**, giving rise to the iminium ion **B**. Then,



Scheme 2 Possible mechanism

nucleophilic attack on the iminium ion **B** by an ethyl acetoacetate **2a** affords intermediate **C**, which further reacts with another ethyl acetoacetate **2a**, and followed by dehydration to provide intermediate **D**. Immediately, intermediate **D** via the rearrangement, elimination to afford intermediate **F** [14b]. Ultimately, the following intramolecular Micheal addition and loss of water in **F** generates the desired product **3aa**.

3. Conclusions

In summary, we have achieved a simple and convenient visible-light-induced photocatalytic cascade cyclization reaction of glycine derivatives with *β*-ketoesters using dicumyl peroxide (DCP) as an oxidant. A wide range of *N*-aryl glycine esters proceed the cascade cyclization readily with various *β*-ketoesters to provide the corresponding polysubstituted 1,4-dihydropyridines in satisfactory yields. A possible mechanism for the cascade cyclization by visible light photoredox catalysis is also proposed. The synthetic protocol features good functional group tolerance, mild conditions and simple operation, and has potential to be used to synthetize natural products as well as biologically active molecules.

4. Experimental section

4.1. General information

Unless otherwise indicated, all reagents were purchased from commercial distributors and used without further purification. ^{1}H NMR and ^{13}C NMR were recorded at 400 MHz and 100 MHz, respectively, using tetramethylsilane as an internal reference. High-resolution mass spectra (HRMS) were measured on a quadrupole time-of-flight (Q-TOF) mass spectrometer instrument with an electrospray ionization (ESI) source. Melting points were uncorrected. Flash column chromatography was performed over silica gel 200-300 mesh. Thin-layer chromatography (TLC) was carried out with silica gel GF254 plates. *N*-Aryl glycine esters **1** were prepared according to the previous reported protocols [11].

4.2. General procedure for the cascade cyclization of glycine derivatives with β-ketoesters

To a solution of glycine derivatives **1** (0.2 mmol), β-keto esters **2** (0.44 mmol) in toluene (2 mL) was added $Ir(ppy)_3$ (0.002 mmol, 1.31 mg) and DCP (0.4 mmol, 108.15 mg). Then, the reaction mixture was stirred at room temperature under irradiation of 18 W blue LED light. After the reaction was completed, the resulting mixture was concentrated under vacuum and the residue was subjected to column chromatography (silica gel, petroleum ether/ethyl acetate as an eluent) to afford the corresponding coupling products **3aa**.

*4.2.1. Triethyl 1,4-dihydro-2,6-dimethyl-1-p-tolyl-pyridine-3,4,5-tricarboxylate (**3aa**) [11b]*

Yellow oil (56.5 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 4.85 (s, 1H), 4.23-4.14 (m, 6H), 2.38 (s, 3H), 2.03 (s, 6H), 1.28 (t, *J* = 7.2 Hz, 6H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 167.6, 149.0, 138.7, 137.5, 130.1, 130.0, 101.0, 60.6, 60.1, 40.1, 21.1, 18.2, 14.3, 14.2.

*4.2.2. Triethyl 1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethyl-pyridine-3,4,5-tricarboxylate (**3ba**) [14a]*

Yellow solid (57.8 mg, 67%); mp 107.3-108.2 °C (lit. 108.2-109.5°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.84 (s, 1H), 4.23-4.09 (m, 6H), 3.81 (s, 3H), 2.04 (s, 6H), 1.29 (t, *J* = 7.2 Hz, 6H), 1.24 (t, *J* = 7.2

Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 167.5, 159.4, 149.3, 132.7, 131.3, 114.4, 101.1, 60.6, 60.1, 55.5, 40.1, 18.2, 14.3, 14.2.

*4.2.3. Triethyl 1,4-dihydro-2,6-dimethyl-1-m-tolylpyridine-3,4,5-tricarboxylate (**3ca**) [11b]*

Yellow oil (44.8 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.27 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 6.0 Hz, 2H), 4.85 (s, 1H), 4.25-4.10 (m, 6H), 2.35 (s, 3H), 2.03 (s, 6H), 1.28 (t, *J* = 7.0 Hz, 6H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 167.6, 148.9, 140.1, 139.6, 130.9, 129.4, 129.0, 127.5, 101.0, 60.6, 60.1, 40.1, 21.2, 18.2, 14.3, 14.2.

*4.2.4. Triethyl 1,4-dihydro-2,6-dimethyl-1-o-tolylpyridine-3,4,5-tricarboxylate (**3da**)*

Yellow oil (44.0 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 6.2 Hz, 2H), 4.87 (s, 1H), 4.24-4.14 (m, 6H), 2.37 (s, 3H), 2.05 (s, 6H), 1.32-1.24 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 167.4, 148.9, 138.5, 137.3, 130.0, 129.8, 100.9, 60.5, 60.0, 40.0, 21.0, 18.1, 14.2, 14.1. HRMS (ESI) calcd for $C_{23}H_{30}NO_6$ $(M+H)^+$ 416.2068, found 416.2064.

*4.2.5. Triethyl 1,4-dihydro-2,6-dimethyl-1-phenylpyridine-3,4,5-tricarboxylate (**3ea**) [11b]*

Yellow oil (44.9 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.39 (m, 3H), 7.19 (dd, *J* = 7.8, 2 Hz, 2H), 4.87 (s, 1H), 4.28-4.11 (m, 6H), 2.04 (s, 6H), 1.32-1.23 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 167.5, 148.8, 140.2, 130.5, 129.4, 128.7, 101.2, 60.7, 60.2, 40.1, 18.2, 14.3, 14.2.

*4.2.6. Triethyl 1-([1,1'-biphenyl]-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3fa**) [11b]*

Yellow solid (50.6 mg, 53%); mp 108.7-109 °C (lit. 108-109°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 7.6 Hz, 2H), 7.11 (d, J = 7.6 Hz, 2H), 7.10 (t, J = 7.6 Hz, 2H), 6.91 (t, J = 7.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 2H), 4.55 (s, 1H), 3.95-3.81 (m, 6H), 1.76 (s, 6H), 0.98 (t, J = 7.2 Hz, 6H), 0.91 (t, J = 7.0 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 167.5, 148.8, 141.6, 139.7, 139.3, 130.8, 129.0, 128.0, 127.9, 127.2, 101.4, 60.7, 60.2, 40.2, 18.3, 14.3, 14.2.

*4.2.7. Triethyl 1-(4-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,4,5-tricarboxylate (**3ga**) [11b]*

Yellow oil (40.0 mg, 43%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J*=8.4 Hz, 2H), 4.83 (s, 1H), 4.25-4.09 (m, 6H), 2.05 (s, 6H), 1.32 (t, *J* = 7.0 Hz, 6H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 167.4, 148.4, 138.8, 134.8, 131.8, 129.7, 101.8, 60.7, 60.3, 40.1, 18.2, 14.3, 14.3.

*4.2.8. Triethyl 1-(4-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,4,5-tricarboxylate (**3ha**) [11b]*

Yellow solid (34.4 mg, 41%); mp 119.0-120.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.55 (s, 1H), 3.95-3.81 (m, 6H), 1.74 (s, 6H), 1.01 (t, *J* = 7.1 Hz, 6H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO): δ 173.8, 167.3, 162.3 (d, $J_{C\text{-}F}$ = 248.3 Hz), 148.6, 136.1, 132.2 (d, $J_{C\text{-}F}$ = 8.1 Hz), 116.3 (d, $J_{C\text{-}F}$ = 22.5 Hz), 101.7, 60.7, 60.2, 40.1, 18.1, 14.3, 14.2.

*4.2.9. 3,5-Diethyl 4-methyl 1,4-dihydro-2,6-dimethyl-1-p-tolylpyridine-3,4,5-tricarboxylate (**3ia**) [11b]*

Yellow oil (48.9 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 4.84 (s, 1H), 4.24-4.14 (m, 6H), 2.36 (s, 3H), 2.02 (s, 6H), 1.26 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 167.5, 149.1, 138.7, 137.4, 130.1, 130.0, 100.9, 60.1, 51.9, 39.9, 21.1, 18.2, 14.3.

*4.2.10. 3,5-Diethyl 4-isopropyl 1,4-dihydro-2,6-dimethyl-1-p-tolyl-pyridine-3,4,5-tricarboxylate (**3ja**) [11b]*

Yellow oil (39.5 mg, 46%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 5.00-4.93 (m, 1H), 4.80 (s, 1H), 4.26-4.12 (m, 4H), 2.38 (s, 3H), 2.03 (s, 6H), 1.32 (t, *J* = 7.0 Hz, 6H), 1.20 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 167.6, 148.9, 138.6, 137.6, 130.1, 130.0, 101.1, 67.8, 60.1, 40.3, 21.8, 21.1, 18.2, 14.4.

*4.2.11. 4-tert-Butyl 3,5-diethyl 1,4-dihydro-2,6-dimethyl-1-p-tolyl-pyridine-3,4,5-tricarbxylate (**3ka**) [11b]*

Yellow oil (38.1 mg, 43%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 4.76 (s, 1H), 4.23-4.15 (m, 4H), 2.37 (s, 3H), 2.02 (s, 6H), 1.42 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 167.7, 148.4, 138.6, 137.6, 130.1, 130.0, 101.5, 80.2, 60.0, 40.9, 28.0, 21.1, 18.1, 14.4.

*4.2.12. 4-Benzyl 3,5-diethyl 1,4-dihydro-2,6-dimethyl-1-p-tolyl-pyridine- 3,4,5-tricarboxylate (**3la**) [11b]*

Yellow solid (49.6 mg, 52%); mp 116-118 °C (lit. 116-118 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.30 (m, 5H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 7.7 Hz, 2H), 5.13 (s, 2H), 4.97 (s, 1H), 4.18-4.13 (m, 4H), 2.37 (s, 3H), 2.03 (s, 6H), 1.23 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 166.3, 158.5, 148.0, 132.0, 130.5, 113.5, 66.5, 59.7, 54.6, 39.3, 21.2, 21.0, 17.3, 13.4.

*4.2.13. Ethyl 3,5-diacetyl-1,4-dihydro-1-(4-methphenyl)-2,6-dimethylpyridine-4-carboxylate (**3ab**) [14b]*

Yellow oil (48.8 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 4.83 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.70 (d, *J* = 8.1 Hz, 6H), 2.35 (s, 3H), 2.02 (s, 6H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 167.9, 149.4, 138.8, 137.4, 130.0, 129.7, 100.6, 60.7, 51.4, 39.9, 29.7, 21.1, 18.17, 14.2.

*4.2.14. 4-Ethyl 3,5-diisopropyl 1,4-dihydro-1-(4-methphenyl)-2,6-dimethylpyridine-3,4,5-tricarboxylate (**3ac**)*

Yellow oil (64.7 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 7.6 Hz, 2H), 4.66 (dt, *J* = 12.4, 6.2 Hz, 2H), 4.45 (s, 1H), 3.75 (q, *J* = 7.1 Hz, 2H), 2.06 (s, 3H), 1.65 (s, 6H), 0.93 (m, 12H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2 166.3, 147.8, 137.8, 136.8, 129.4, 129.1, 112.4, 66.5, 59.7, 39.5, 21.1, 20.3, 17.3, 13.5; HRMS (ESI) calcd for $C_{25}H_{34}NO_6$ $(M+H)^+$ 444.2381, found 444.2377.

*4.2.15. 4-Ethyl 3,5-diisobutyl 1,4-dihydro-1-(4-methphenyl)-2,6-dimethylpyridine-3,4,5-tricarboxylate (**3ad**)*

Yellow oil (57.4 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 4.95 (s, 1H), 4.12 (dt, *J* = 7.1, 5.9 Hz, 2H), 3.92 (p, *J* = 4.3 Hz, 3H), 2.38 (s, 1H), 2.06 (s, 3H), 2.00 (s, 6H), 1.95 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 167.2, 149.2, 138.5, 137.2, 129.8, 70.5, 60.9, 39.6, 27.6, 20.9, 19.0, 17.9, 14.0; HRMS (ESI) calcd for $C_{27}H_{38}NO_6$ $(M+H)^+$ 472.2694, found 472.2696.

*4.2.16. 4-Ethyl 3,5-dimethyl 1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-3,4,5-tricarboxylate (**3bb**) [11b]*

Yellow solid (45.2 mg, 56%); mp 101-103.2 °C (lit.101-102 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 4.83 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.81 (s,3H), 3.72 (s, 3H), 3.75 (s, 3 H), 2.04 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 169.6, 161.3, 151.4, 132.9, 116.1, 102.4, 62.4, 57.2, 53.1, 41.6, 19.8, 15.9.

*4.2.17. 4-Ethyl 3,5-diisopropyl 1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-3,4,5-tricarboxylate (**3bc**) [11b]*

Yellow oil (57.9 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.09-5.02 (m, 2H), 4.82 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.02 (s, 6H), 1.27-1.23 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 166.3, 158.5, 148.0 , 132.0, 130.5, 113.5, 66.5, 59.7, 54.6, 39.3, 21.1 (d, *J* = 13.8 Hz), 17.3, 13.4.

*4.2.18. 3,5-Diisobutyl 4-ethyl 1,4-dihydro-1-(4-meth-oxyphenyl)-2,6-dimethylpyridine-3,4,5-tricarboxylate (**3bd**)*

Yellow oil (62.4 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.94 (s, 1H), 4.23-4.11 (m, 2H), 4.26-3.81 (m, 4H), 3.72 (s, 3H), 2.06 (s, 6H), 1.98-1.95 (m, 2H), 1.27-1.23 (m, 3H), 1.23 (d, *J* = 6.7 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 166.5, 158.5, 148.8, 131.8, 130.4, 113.5, 100.0, 69.5, 59.7, 54.5, 38.9, 26.9, 18.3, 17.0, 13.3; HRMS (ESI) calcd for $C_{27}H_{38}NO_7$ $(M+H)^+$ 488.2643, found 488.2644.

*4.2.19. 3,5-Di-tert-butyl 4-ethyl 1,4-dihydro-1-(4-meth-oxyphenyl)-2,6-dimethylpyridine-3,4,5-tricarboxylate (**3be**) [11b]*

Yellow oil (67.2 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 4.78 (s, 1H), 4.16-4.11 (m, 2H), 3.87 (s, 3H), 2.0 (s, 6H), 1.50 (t, *J* = 7.1 Hz, 18H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 164.5, 156.9, 145.9, 130.6, 129.0, 111.9, 100.0, 77.5, 58.1, 53.0, 38.4, 25.8, 15.6, 12.0.

*4.2.20. Diethyl 2-acetyl-3-(p-tolylamino)succinate (**C**) [14a]*

Yellow oil (15.4 mg, 24%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.2 Hz, 2H), 6.63 (dd, *J* = 8.4, 3.6 Hz, 2H), 4.70-4.68 (m, 1H), 4.39 (brs, 1H), 4.52-4.09 (m, 5H), 2.32 (s, 1.5H), 2.27 (s, 1.5H), 2.23 (s, 3H), 1.32-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 171.5, 171.4, 167.9, 167.8, 144.2, 143.9, 129.8, 129.7, 128.4, 114.4, 114.3, 61.8, 61.7, 61.6, 61.1, 60.8, 57.3, 56.7, 30.0, 29.8, 20.4, 14.0, 13.9; MS (ESI) *m/z*: $[M+H]^+$ 322, $[M+Na]^+$ 344.

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Highlights

• Visible light photocatalytic cascade cyclization reaction at room temperature.

• A wide range of *N*-aryl glycine esters proceed the cascade cyclization well with various *β*-ketoesters to afford diverse polysubstituted 1,4-dihydropyridines.

• A possible mechanism for the cascade cyclization reaction by visible light photoredox catalysis was also proposed on the basis of control experiments.

• The synthetic protocol features good functional group tolerance, mild conditions and simple operation.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: