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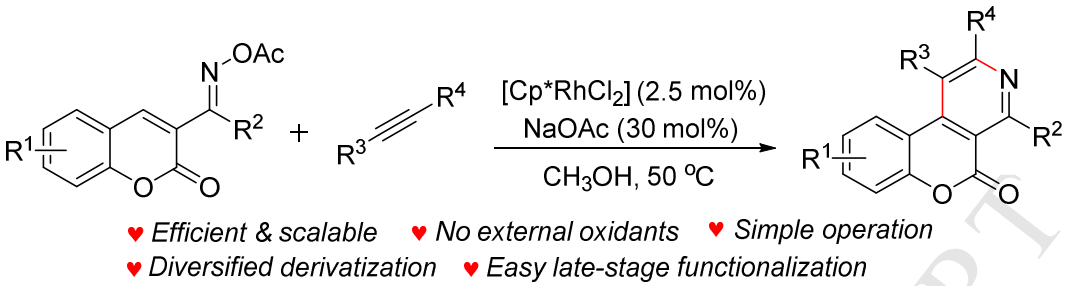
Graphic Abstract



Title

Synthesis of Chromeno[3,4-*c*]pyridines by Rhodium(III)-Catalyzed Annulation of Coumarinyl Ketoxime Esters and Alkynes

Authors

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Abstract

An efficient, scalable synthetic method of chromeno[3,4-*c*]pyridine scaffolds through redox-neutral [4+2] annulation between coumarinyl ketoxime esters and internal alkynes has been developed using the rhodium(III) catalytic system. The present transformation proceeds under mild conditions, features good functional group compatibility and obivates the use of external oxidants. Ready access to pyridine derivatives bearing three carbon substituents is exemplified.

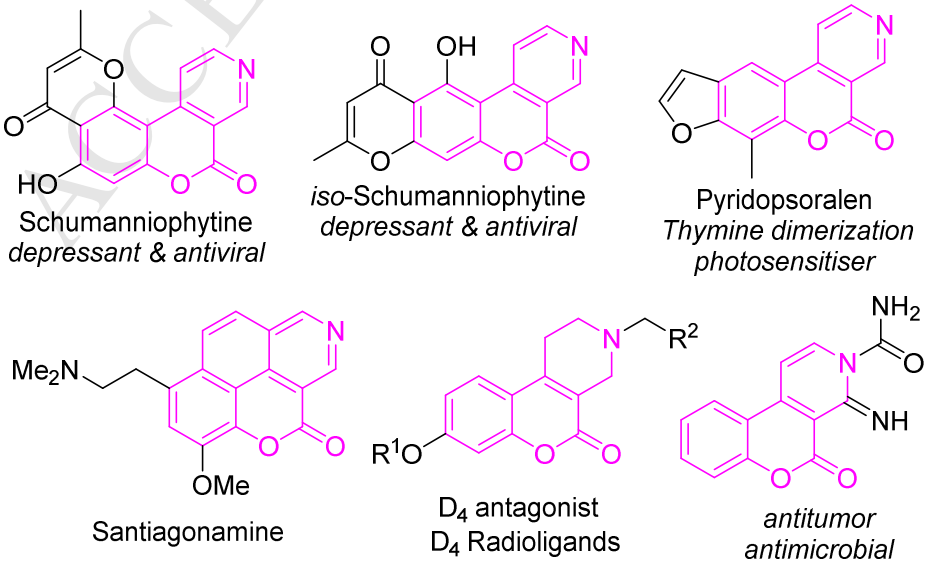
Keywords

Chromenopyridines; Coumarins; Oxime esters; Alkynes; Rhodium; C-H activation

1. Introduction

The coumarin (2*H*-chromen-2-one) and pyridine cores constitute two families of fundamental privileged heterocyclic scaffolds in a variety of naturally-occurring products and bioactive compounds.[1-4] As the fused derivatives from these two fragments, chromeno[3,4-*c*]pyridin-5-ones have proven to be an emerging group of tricyclic molecular hybrids found in the parent framework of several natural and artificial bioactive molecules (Figure 1).[5-14] These chromenopyridine derivatives have exhibited a diverse array of biological activities (depressant, antiviral, antipsychotic, antitumor and antimicrobial *et al*),[5-9] photophysical properties,[10,11] and the potential of dopamine D4 receptor labeling agents.[12,13] As such, elegant synthetic methods for the preparation of this scaffold have been established, to date, to build up libraries of chromenopyridines for the promising applicability in medicinal and material realms. One traditional strategy lies upon the lactonization of 4-arylnicotinic acid derivatives in the presence of polyphosphoric acid (PPA) or boron

Figure 1 Natural products and bioactive molecules incorporating chromeno[3,4-*c*]pyridine nucleus



tribromide.[15-19] Another traditional one involves the multi-component condensation of salicylaldehydes, cyanoacetates (or malononitrile), and ketones using ammonium acetate as catalyst and nitrogen source, generally providing 4-amino chromeno[3,4-*c*] pyridin-5-ones.[20,21] Noteworthy, its variant can generate a chromenopyridinone scaffold bearing three carbon-centered groups at the C1,2,4 positions of the pyridine unit when salicylaldehydes and methyl 3-aminocrotonate were used instead.[22] In recent decade, the inverse electron demand Diels-Alder reaction has turned out to be a powerful tool for the construction of the dihydro-derivatives, which readily undergo further dehydrogenative aromatization to produce their saturated heterocycles.[23-25] In 2014, Xiao's group developed a tandem protocol for access to C4-functionalized *N*-aryl chromeno[3,4-*c*]pyridine-5-ones using 4-alkynyl-3-formylcoumarins as a novel building block.[26] In 2016, Villemin and his co-workers disclosed an efficient and practical procedure for the synthesis of 4-alkamino chromeno[3,4-*c*]pyridine-5 -ones through the reaction of 4-(2-dimethylamino)vinyl-3-cyanocoumarin with primary alkylamines.[27] In 2018, Chen et al. reported $CuCl_2$-catalyzed tandem reaction of the Blaise reaction intermediates and 3-cyanocoumarins to efficiently afford 4-amino-1,2-disubstituted chromeno[3,4-*c*]pyridine derivatives (Scheme 1, a).[28] Later on, Li et al. presented a redox-neutral rhodium(II)-catalyzed C-H carboxylation for oxochromenopyridine derivatives from 2-pyridylphenols with CO_2 in the presence of phosphine ligand (Scheme 1, b).[29] Despite the impressive achievements made to date, the development of versatile and efficient methods for the assembly of the chromeno[3,4-c]pyridine derivatives, especially bearing the carbon-centered

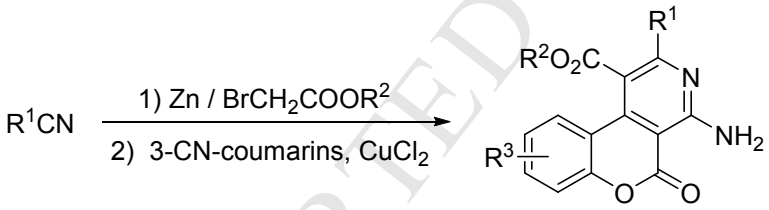
functionalities at all three C-positions of a pyridine moiety, remains highly challenging but desirable.

To date, aryl ketoxime derivatives serve as key precursors to enable versatile and flexible access to isoquinoline/pyridine scaffolds through the directed aryl/vinyl sp^2 C-H activation.[30-38] As our continuing efforts to develop new methodologies to readily access potentially bioactive heterocyclic compounds,[39-45] herein, we present an efficient synthetic method of highly substituted chromeno[3,4-*c*]pyridin-5-ones from coumarinyl ketone *O*-acetyl oximes and internal alkynes utilizing the redox-neutral rhodium(III) catalytic system without any external oxidants, wherein the oxime N-O

Scheme 1 Recent work and our contribution regarding the synthesis of the chromeno[3,4-*c*]pyridin-5-one scaffold

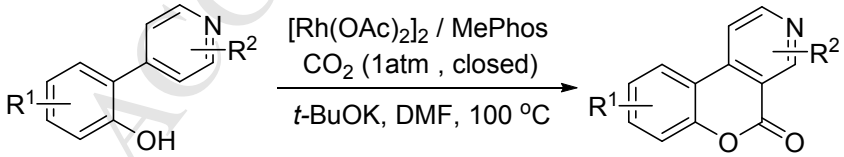
Recent work

(a) Cu(II)-catalyzed tandem reaction of zinc reagent (*Chen, 2018*)



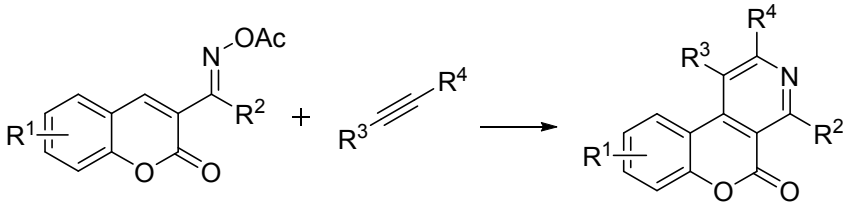
- *Excess zinc reagents in situ generated, and two steps required*

(b) Rh(II)-catalyzed aryl C-H carboxylation with CO_2 (*Li, 2018*)



- *Phosphine ligand and excess base required*

This work

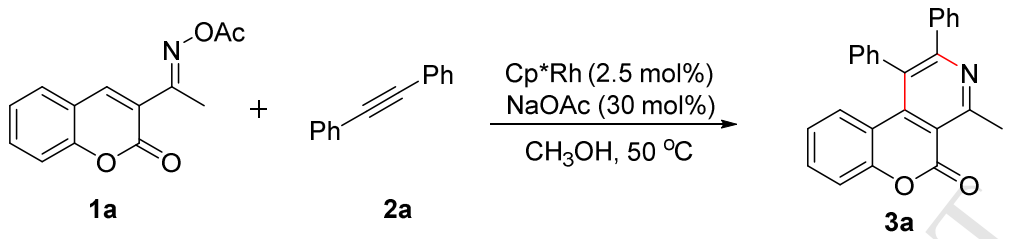


section functions both as a directing group and as an internal oxidant to sustain the catalytic rhodacycle (Scheme 1).

2. Results and discussion

Initially, we screened 3-acylcoumarinyl oxime, its methyl ether and acetyl ester as the potential directing group using the combination of $[Cp^*RhCl_2]_2$-NaOAc as the catalytic system without any external oxidants. Pleasingly, it was found that its acetyl ester **1a** worked well with 1,2-diphenylethyne (**2a**) in methanol at 60 ^oC to deliver the tricyclic chromeno[3,4-*c*]pyridine **3a** in 80% yield (Table S-1, entry 1, in the Supporting Information). Then we chose the reaction of **1a** with **2a** as a model reaction to identify the cyclization conditions. The replacement of $[Cp^*RhCl_2]_2$ with $[Ru(p\text{-cymene})Cl_2]_2$ or $Cp^*Co(CO)I_2$ failed to generate the tricyclic product **3a**, with all the starting materials recovered (Table 1, entry 2). The other acetates such as KOAc and CsOAc gave as comparable efficiency as NaOAc, while the carbonate and phosphate tested could hardly work (Table 1, entry 3 vs 4). The solvent effects were investigated and the reaction efficacy was found to show a considerable dependence on the medium environment. The use of EtOH as a solvent delivered a good yield of 70%, whereas the utilization of HFIP, with a smaller pK_a value, lowered the yield to 30% (Table 1, entry 5). The polar aprotic DMF and DMSO were ineffective solvents for such a transformation (Table 1, entry 6). Besides, the silver additives, reaction temperatures and time were identified to impose limited impact on the reaction yields (Table 1, entries 7-9). Notably, the reaction at the lower temperature of 50 ^oC resulted in the formation of **3a** in a comparable yield of 81% (Table 1, entry 1).

Table 1 Parameters Optimization for the annulation[a]



1a **2a** **3a**

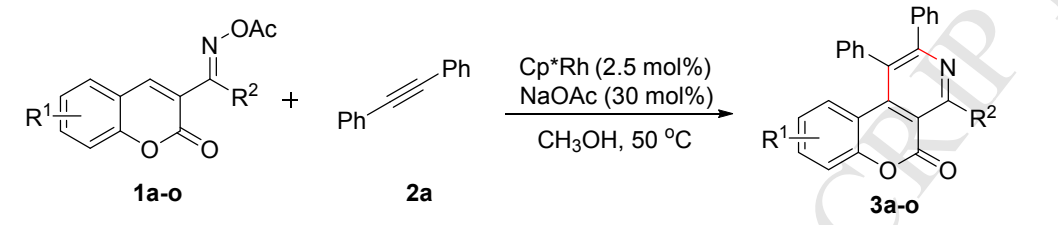
Entry	Deviation from standard conditions	Yield [%][b]
1	none	81
2[c]	[Ru(*p*-cymene)Cl_2]$_2$ or Cp*Co(CO)I_2 instead	N.R.
3[c]	KOAc or CsOAc instead	78, 76
4[c]	Cs_2CO_3 or K_3PO_4 instead	trace
5[c]	EtOH, DCE or HFIP instead	20-70
6[c]	DMF or DMSO instead	N.R.
7[c]	silver salts (20 mol%) added	75-80
8	30 °C, 60 °C, or 80 °C	65-80
9	4 h, 6 h, or 12 h	70-77

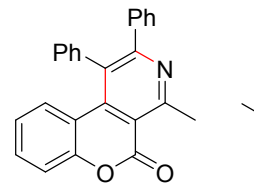
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), [Cp*$RhCl_2$]$_2$ (2.5 mol%), NaOAc (30 mol%), MeOH (1.5 mL), sealed with stirring at 50 °C for 8 hours under Ar. [b] The yields are for the isolated products. [c]The reactions were performed at 60 °C. N.R. means no reaction.

Having established the optimal conditions, we turned to the investigation of the generality and substrate scopes of oxime ester-directed annulation of coumarins **1** with alkynes **2** catalyzed by the Cp*Rh (III) system. Firstly, in the case of 1,2-diphenylethyne (**2a**), an array of 3-acylcoumarinyl oxime esters **1a-o** were subjected to this rhodium(III)-catalyzed C-H functionalization of coumarins. As is depicted in Table 2, the present protocol proved applicable to various coumarins with Me, OMe, and Br on the benzene moiety of the coumarin scaffold. Noteworthily, the C-Br bond could survive this catalytic condition, thus offering a potential opportunity for late-stage functionalization.[46,47] The electron donating groups are preferable to the electron withdrawing ones in the reaction yields (**3b** vs **3e**). Furthermore, it was found that the OMe group in the 7-position (**3d**) was unfavorable to the catalytic annulation.

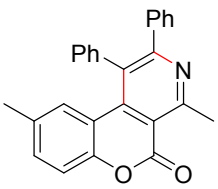
The R^2 tethered to the C=N portion of the oxime esters **1** varied from methyl to a bulkier fragment including Et, *n*-Pr, and Ph, leading to the decrease in the reaction efficiency (**3a**, **3f-h**). Prolonging the reaction time up to 16-20 h could help improve

Table 2 Scope with respect to the coumarinyl oxime esters[a]

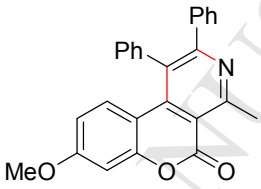




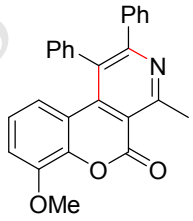
3a, 81% (79%)[b]



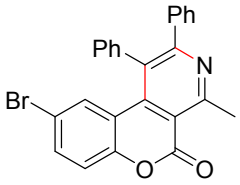
3b, 92%



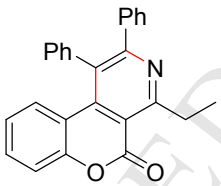
3c, 73%



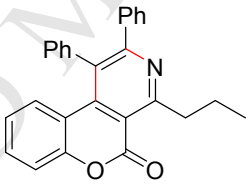
3d, 61%



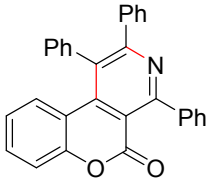
3e, 70%



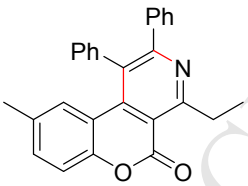
3f, 63%



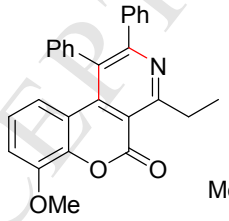
3g, 69% (20 h)



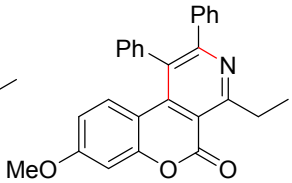
3h, 49%



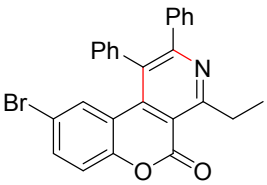
3i, 68%



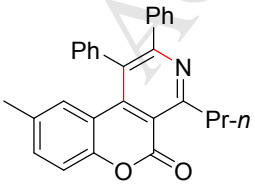
3j, 53%



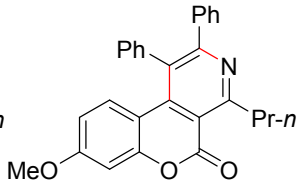
3k, 70% (16 h)



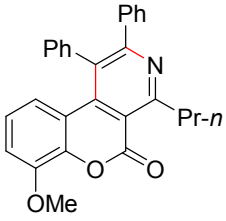
3l, 64%



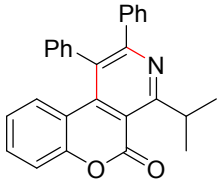
3m, 85% (20 h)



3n, 67% (20 h)



3o, 59% (18 h)



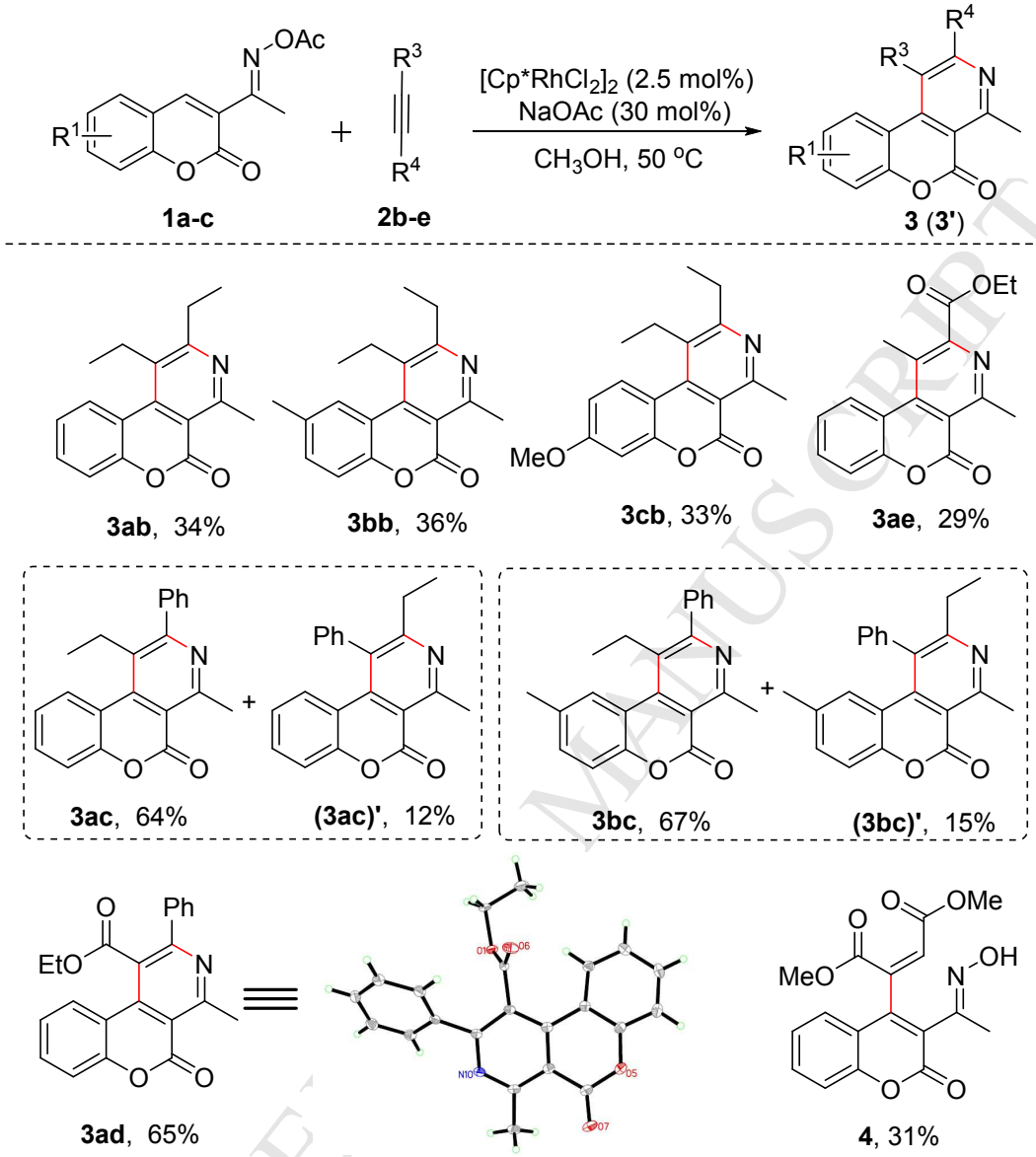
3p, 0%[c]

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), NaOAc (30 mol%), MeOH (1.5 mL), sealed with stirring at 50 °C for 8 hours unless otherwise stated under Ar. The yield are for the isolated products. [b]In 5-mmol scale. [c]Use of *Z*-**1p** as substrate.

the yields of the cyclized products **3g**, **3k**, **3m-o**. To our surprise, chromenopyridine **3h** was obtained in 49% yield from an *E*/*Z*-isomeric mixture of **1h** (*E*/*Z* = 1:4.9), and the potential 3-(isoquinolin-1-yl)coumarin product resulted from oxime ester-directed activation of the phenyl C-H bond was not observed , suggesting that in the case of **1h** the *Z*-conformer may isomerize to the *E*-conformer under the reaction conditions. When R^2 was an *iso*-propyl, the predominant *Z*-conformer of **1p** was isolated, and found to be an inert substrate for such a transformation.

Next, we set out to examine the alkynes **2**. Generally, the use of internal alkynes successfully enabled the C-H functionalization of coumarins **1** (Table 3). The presence of an aryl group in alkynes **1** exerted constructive influence on the reaction efficiency. Just like diphenylethyne (**2a)**, other phenylacetyne **2c-d** performed well to form chromeno[3,4-*c*]pyridines **3** in good (total) yields (65%-82%), whereas the alkynes bearing no aryl groups **2b** and **2e** gave their annulated products in low yields (29%-36%), and even dimethyl but-2-ynedioate was reacted to access no cyclized product, solely providing an alkenylated coumarinyl ketoxime **4** in 31% yield. Increasing the loading of **2b** to 3 equiv could enhance the yield of **3ab** to 42%. It is worth noting that the unsymmetrical alkynes led to the formation of chromenopridines **3** in a regioisomeric ratio of more than 4 (**3ac** + (**3ac)′**, **3bc** + (**3bc)′**), and in the case of the substrates **2d-e**, only the major isomers were isolated by means of the preparative thin-layer chromatography, **3ad** of which were identified by X-ray diffraction[48] (Section 6, in the Supporting Information). This may be ascribed to the substituent steric effects of internal alkynes.

Table 3 Scope with respect to the alkynes[a]

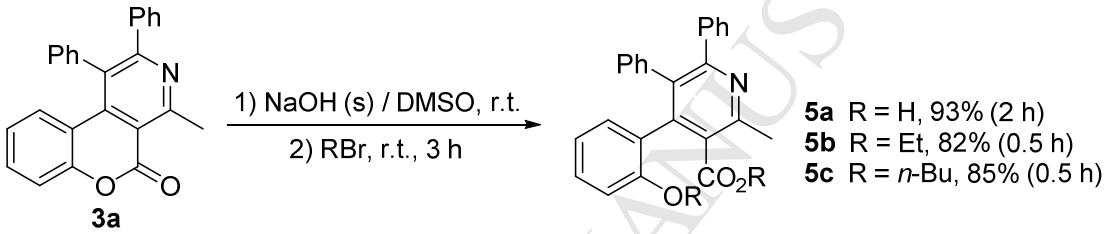


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), NaOAc (30 mol%), MeOH (1.5 mL), sealed with stirring at 50 °C for 8 hours under Ar. The yield are for the isolated products.

To demonstrate the applicability of this protocol in organic synthesis, we carried out the rhodium(III)-catalyzed [4+2] annulation of coumarinyl ketoxime **1a** with alkyne **2a** in a 5 mmol scale, successfully affording the chromenopyridine **3a** in 79% yield (Table 2). Furthermore, the resulting products can be utilized for late-stage functionalization via the conventional hydrolysis of the coumarin moiety, the

reduction of the carbonyl group, and the directed C-H activation of the 2-phenylpyridine skeleton. Herein, fully substituted pyridines were derived simply from chromenopyridine **3a** in excellent yields through the hydrolysis under the solid NaOH/DMSO system, followed by acidification or alkylation with alkyl bromide (**5a**-**c**). Thus, this chemistry will provide a great potential for the synthesis of highly substituted pyridine derivatives widely used in the pharmaceutical and material fields.

Scheme 2 Facile access to all-carbon substituted pyridines from chromenopyridines

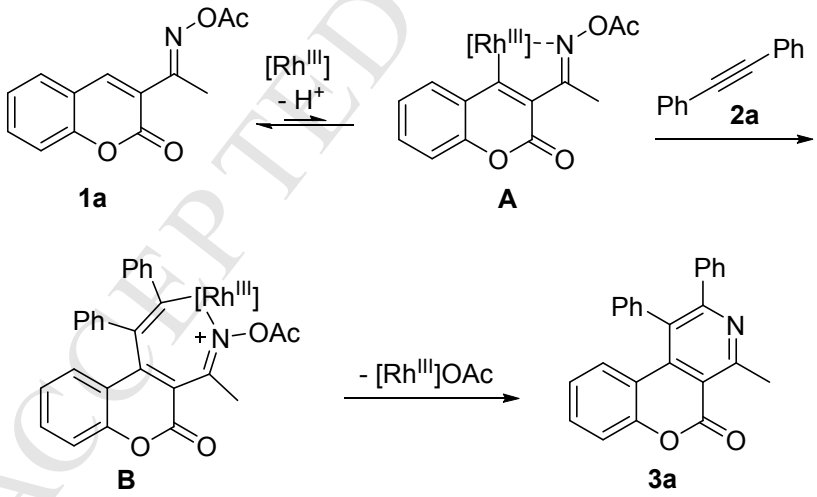


To probe the mechanistic principles of this present transformation catalyzed by the rhodium(III) catalytic system, a series of reactions were carried out including the intermolecular competitive experiment and deuteration reactions (Section 4, in the Supporting Information). When the oxime esters **1c** (with a Me group) and **1d** (with a Br group) competed in the same reaction, the electron-rich substrate **1c** was preferred to the electron-deficient one **1d**, affording their corresponding products **3c**-**d** in the yields of 54% and 6%, respectively. This difference can be rationalized by a concerted base-assisted internal electrophilic substitution (IES)-type C-H activation mechanism.[49] When substrate **1a** was reacted with or without alkyne in MeOD, deuteration was observed at the C4 position of the deacetylated oxime **6a** (18% D) and the methyl group of the product **3a** (n = 2.64, -CH_nD_{3-n}). These results could imply that the *ortho*-C-H rhodation may occur in the initial reaction step, and an

intermediate with a more acidic methyl group might exist in the catalytic annulation process.

Based on our experimental observations and previous rhodium(III) catalytic chemistry,[50-54] a tentative mechanism was proposed for this 3,4-fused coumarin formation (Scheme 3). First, *ortho*-C-H rhodation of coumarinyl oxime ester **1a** takes place with the chelating assistance of oxime ester sp^2 nitrogen to generate (2-oxo-2*H*-chromen-4-yl)rhodium intermediate **A**. Insertion of **A** to alkyne **2a** delivers rhodacyclic iminium cation species **B**, which then undergoes a concerted redox process to generate chromenopyridine **3a**, along with the regeneration of rhodium(III) species.

Scheme 3 A proposed catalytic mechanism



3. Conclusion

In summary, we have developed an efficient redox-neutral protocol for the construction of chromeno[3,4-*c*]pyridine scaffolds through the [4+2] annulation of coumarinyl ketoxime ester with internal alkynes catalyzed by the well-known Cp*Rh

system. The present annulation proceeds under mild reaction conditions, featuring good functional tolerance and easy scale-up. The late-stage functionalization of the resulting chromeno[3,4-*c*]pyridines enables ready access to highly substituted pyridine derivatives. This protocol will find its potential application in the synthesis of fused azaheterocycles and polycarbon substutited pyridines with excellent biological and physical properties.

4. Experimental section

4.1. General Information

All solvents and reagents were purchased from the suppliers and used without further purification unless otherwise noted. The melting points (uncorrected) were taken on an X4 Electrothermal Micromelting point meter. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in solvents $CDCl_3$ or DMSO-d_6 at room temperature on Bruker Avance III 400 spectrometer. The chemical-shift scale is based on internal TMS. High-solution mass spectra were acquired on Waters UPLC/Xevo G2 quadrupole time-of-flight tandem mass spectrometry (Xevo G2 Q-TOF).

4.2. Typical procedure for the synthesis of the oxime esters 1

Cyclization: A 50-mL round-bottom flask was charged with substituted salicylaldehyde (5 mmol), 2-acyl acetate (7.5 mmol), piperidine (5 mol%) and ethanol (20 mL), and then refluxed in an oil-bath for 5 hours (TLC monitoring). The reaction mixture was poured into iced water, and filtered to afford 3-acyl coumarin as light yellow solid.

Oximination: 3-Acyl coumarin (2 mmol), hydroxylamine hydrochloride (3 mmol),

distilled water (0.26 mL), and ethanol (3.2 mL) were charged in a 25-mL round-bottom flask, and stirred for 12 hours (TLC monitoring). After completion, the resulting mixture was filtered and then washed with water to give its corresponding oxime as white solid.

O-Acylation: Oxime (1.5 mmol) and acetic anhydride (1.65 mmol) were treated in dichloromethane (5 mL) at room temperature for 12 hours (TLC monitoring). The mixture was neutralized with aqueous saturated sodium carbonate till pH = 7, and subjected to extraction, dryness, and concentration. Precursors **1** were obtained through recrystallization of light yellow residues in a mixture of dichloromethane and petroleum ether or flash chromatography.

4.2.1. *(E)-3-(1-(acetoxyimino)ethyl)-2H-chromen-2-one (**1a**)*

White solid, 298 mg, 81% yield, m.p. 132 – 133 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.61 – 7.56 (m, 2H), 7.37 – 7.30 (m, 2H), 2.41 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 161.8, 159.2, 154.3, 143.2, 132.0, 129.0, 124.9, 123.6, 118.5, 116.7, 19.6, 15.8. HRMS (ESI): Calcd for $C_{13}H_{12}NO_4$ $[M+H]^+$: 246.0766; Found: 246.0760.

4.2.2. *(E)-3-(1-(acetoxyimino)ethyl)-6-methyl-2H-chromen-2-one (**1b**)*

White solid, 354 mg, 91% yield, m.p. 160 – 163 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.35 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 2.43 (s, 3H), 2.42 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 162.0, 159.4, 152.5, 143.2, 134.7, 134.0, 128.6, 123.4, 118.2, 116.4, 20.8, 19.6, 15.8. HRMS (ESI): Calcd for $C_{14}H_{14}NO_4$ $[M+H]^+$: 260.0923; Found: 260.0922.

4.2.3. *(E)-3-(1-(acetoxyimino)ethyl)-7-methoxy-2H-chromen-2-one (**1c**)*

White solid, 359 mg, yield 87%, m.p. 149 – 152 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.83 (s, 1H), 3.90 (s, 3H), 2.40 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 163.9, 162.1, 159.5, 156.4, 143.4, 130.1, 119.7, 113.4, 112.2, 100.5, 55.9, 19.6, 15.8. HRMS (ESI): Calcd for $C_{14}H_{14}NO_5$ $[M+H]^+$: 276.0872; Found: 276.0880.

4.2.4. *(E)-3-(1-(acetoxyimino)ethyl)-8-methoxy-2H-chromen-2-one (**1d**)*

White solid, 293 mg, 71% yield, m.p. 199 – 202 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 3.98 (s, 3H), 2.41 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 161.9, 158.7, 147.1, 144.0, 143.4, 124.8, 123.8, 120.3, 119.1, 114.6, 56.3, 19.6, 15.8. HRMS (ESI): Calcd for $C_{14}H_{14}NO_5$ $[M+H]^+$: 276.0872; Found: 276.0880.

4.2.5. *(E)-3-(1-(acetoxyimino)ethyl)-6-bromo-2H-chromen-2-one (**1e**)*

White solid, 447 mg, 92% yield, m.p. 218 – 220 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.70 – 7.68 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 1H), 2.41 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 161.4, 158.5, 153.1, 141.7, 135.7, 131.1, 124.7, 120.0, 118.4, 117.5, 19.6, 15.7. HRMS (ESI): Calcd for $C_{13}H_{11}BrNO_4$ $[M+H]^+$: 323.9871; Found: 323.9875.

4.2.6. *(E)-3-(1-(acetoxyimino)propyl)-2H-chromen-2-one (**1f**)*

White solid, 331 mg, 85% yield, m.p. 130 – 131 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.61 – 7.55 (m, 2H), 7.37 – 7.30 (m, 2H), 2.93 (q, *J* = 7.6 Hz, 2H), 2.26 (s, 3H), 1.17 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 166.8, 159.2,

154.3, 144.0, 132.9, 128.9, 124.9, 122.8, 118.5, 116.7, 22.4, 19.6, 10.5. HRMS (ESI): Calcd for $C_{14}H_{14}NO_4$ $[M+H]^+$: 260.0923; Found: 260.0922.

4.2.7. *(E)-3-(1-(acetoxyimino)butyl)-2H-chromen-2-one (**1g**)*

White solid, 365 mg, 89% yield, m.p. 99 – 101 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.64 – 7.58 (m, 2H), 7.40 (m, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.28 (s, 3H), 1.61 (sext, *J* = 7.6 Hz, 2H), 1.00 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 165.8, 159.2, 154.3, 143.9, 132.9, 128.9, 124.9, 123.0, 118.5, 116.7, 30.5, 19.7, 19.6, 14.1. HRMS (ESI): Calcd for $C_{15}H_{16}NO_4$ $[M+H]^+$: 274.1079; Found: 274.1073.

4.2.8. *3-((Acetoxyimino)(phenyl)methyl)-2H-chromen-2-one (**1h**)*

E-/Z-isomeric mixture = 1: 4.9 (based on the 4-C-H). White solid, 396 mg, 86% yield, m.p. 138 – 140 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 0.16H), 7.75 – 7.34 (m, 9.83H), 2.18 and 2.16 (2s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 168.3, 161.0, 158.2, 157.4, 154.6, 154.2, 144.7, 143.3, 133.1, 132.7, 131.5, 130.9, 130.6, 129.0, 128.8, 128.7, 128.6, 128.4, 128.1, 125.0, 124.9, 123.5, 121.7, 118.5, 118.0, 117.0, 116.8, 19.7, 19.6. HRMS (ESI): Calcd for $C_{18}H_{14}NO_4$ $[M+H]^+$: 308.0923; Found: 308.0920.

4.2.9. *(E)-3-(1-(acetoxyimino)propyl)-6-methyl-2H-chromen-2-one (**1i**)*

White solid, 365 mg, 89% yield, m.p. 100 – 102 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.32 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 2.91 (q, *J* = 7.6 Hz, 2H), 2.40 (s, 3H), 2.25 (s, 3H), 1.16 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 166.9, 159.4, 152.5, 144.0, 134.7, 134.0, 128.5, 122.6, 118.2, 116.3, 22.4, 20.7, 19.6, 10.5. HRMS (ESI): Calcd for $C_{15}H_{16}NO_4$ $[M+H]^+$: 274.1079;

Found: 274.1073.

4.2.10. *(E)-3-(1-(acetoxyimino)propyl)-8-methoxy-2H-chromen-2-one (**1j**)*

White solid, 390 mg, 90% yield, m.p. 126 – 128 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 3.99 (s, 3H), 2.94 (q, *J* = 7.5 Hz, 2H), 2.26 (s, 3H), 1.17 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 166.8, 158.6, 147.1, 144.1, 144.0, 124.8, 123.0, 120.1, 119.2, 114.6, 56.3, 22.3, 19.6, 10.5. HRMS (ESI): Calcd for $C_{15}H_{16}NO_5$ $[M+H]^+$: 290.1028; Found: 290.1024.

4.2.11. *(E)-3-(1-(acetoxyimino)propyl)-7-methoxy-2H-chromen-2-one (**1k**)*

White solid, 360 mg, 83% yield, m.p. 118 – 120 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.83 (s, 1H), 3.90 (s, 3H), 2.92 (q, *J* = 7.5 Hz, 2H), 2.25 (s, 3H), 1.16 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.1, 163.8, 159.5, 156.4, 144.1, 129.9, 119.0, 113.3, 112.2, 100.5, 55.9, 22.4, 19.6, 10.6. HRMS (ESI): Calcd for $C_{15}H_{16}NO_5$ $[M+H]^+$: 290.1028; Found: 290.1024.

4.2.12. *(E)-3-(1-(acetoxyimino)propyl)-6-bromo-2H-chromen-2-one (**1l**)*

White solid, 416 mg, 82% yield, m.p. 158 – 160 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.68 – 7.66 (m, 2H), 7.25 (d, *J* = 8.6 Hz, 1H), 2.91 (q, *J* = 7.5 Hz, 2H), 2.26 (s, 3H), 1.16 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.3, 158.5, 153.1, 142.5, 135.6, 131.0, 124.0, 120.0, 118.4, 117.5, 22.4, 19.6, 10.5. HRMS (ESI): Calcd for $C_{14}H_{13}BrNO_4$ $[M+H]^+$: 338.0028; Found: 338.0034.

4.2.13. *(E)-3-(1-(acetoxyimino)butyl)-6-methyl-2H-chromen-2-one (**1m**)*

White solid, 401 mg, 93% yield, m.p. 92 – 94 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.97 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.33 (s, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 2.26 (s, 3H), 1.58 (sext, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 165.8, 159.3, 152.4, 143.8, 134.7, 134.0, 128.5, 122.8, 118.2, 116.3, 30.5, 20.7, 19.6, 19.5, 14.0. HRMS (ESI): Calcd for $C_{16}H_{18}NO_4$ $[M+H]^+$: 288.1236; Found: 288.1230.

4.2.14. *(E)-3-(1-(acetoxyimino)butyl)-7-methoxy-2H-chromen-2-one (**1n**)*

White solid, 368 mg, 81% yield, m.p. 83 – 85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.83 (s, 1H), 3.90 (s, 3H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.25 (s, 3H), 1.59 (sext, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 166.0, 163.8, 159.5, 156.4, 144.0, 129.9, 119.1, 113.3, 112.2, 100.5, 55.9, 30.5, 19.7, 19.6, 14.1. HRMS (ESI): Calcd for $C_{16}H_{18}NO_5$ $[M+H]^+$: 304.1185; Found: 304.1191.

4.2.15. *(E)-3-(1-(acetoxyimino)butyl)-8-methoxy-2H-chromen-2-one (**1o**)*

White solid, 382 mg, 84% yield, m.p. 116 – 118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.29 – 7.23 (m, 1H), 7.15 – 7.12 (m, 2H), 3.98 (s, 3H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.25 (s, 3H), 1.57 (sext, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 165.8, 158.6, 147.1, 144.04, 143.98, 124.8, 123.2, 120.1, 119.1, 114.6, 56.3, 30.4, 19.6, 19.5, 14.0. HRMS (ESI): Calcd for $C_{16}H_{18}NO_5$ $[M+H]^+$: 304.1185; Found: 304.1191.

4.3. Typical Procedure for the Synthesis of the Cyclization Products

To a 10-mL reaction tube was sequentially added **1a** (0.3 mmol, 74 mg), **2a** (0.36 mmol, 64 mg), $[Cp^*RhCl_2]_2$ (2.5 mol%), NaOAc (30 mol%), and MeOH (1.5 mL).

Then the tube was sealed and stirred at 50 ^{o}C for 8 hours unless stated otherwise. After the reaction completion, the reaction mixture was filtered over a short column of silica, and purified by preparative thin-layer chromatography (petroleum ether/ethyl acetate, 20/1, v/v) to give the tricyclic product **3a**.

4.3.1. *4-Methyl-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one (**3a**)*

White solid, 88 mg, 81% yield, m.p. 243 – 246 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 7.19 (s, 5H), 7.12 (d, *J* = 6.4 Hz, 2H), 6.82 (d, *J* = 8 Hz, 1H), 6.75 (t, *J* = 7.4 Hz, 1H), 3.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 162.3, 160.1, 152.6, 141.8, 139.9, 138.3, 131.5, 130.8 (2C), 129.6 (2C), 129.4, 129.2 (2C), 128.8, 128.1, 127.9, 127.7 (2C), 123.3, 117.5, 117.3, 114.6, 27.5. HRMS (ESI): Calcd for $C_{25}H_{18}NO_2$ $[M+H]^+$: 364.1338; Found: 364.1340.

4.3.2. *4,9-Dimethyl-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one (**3b**)*

White solid, 104 mg, yield 92%, m.p. 233 – 236 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 3H), 7.21 – 7.17 (m, 7H), 7.12 (d, *J* = 7.2 Hz, 2H), 6.48 (s, 1H), 3.17 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 162.0, 160.3, 150.7, 141.9, 139.9, 138.5, 132.5, 132.3, 130.8 (2C), 129.7 (2C), 129.4, 129.2, 129.1 (2C), 127.9, 127.9, 127.7 (2C), 117.0, 116.8, 114.7, 27.5, 20.9; HRMS (ESI): Calcd for $C_{26}H_{20}NO_2$ $[M+H]^+$: 378.1494; Found: 378.1492.

4.3.3. *8-Methoxy-4-methyl-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one(**3c**)*

White solid, 86 mg, 73% yield, m.p. 222 – 224 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.31 (m, 3H), 7.18 (s, 5H), 7.12 (d, *J* = 4.8 Hz, 2H), 6.79 (s, 1H), 6.68 (d, *J* = 9.2 Hz, 1H), 6.33 (d, *J* = 9.2 Hz, 1H), 3.80 (s, 3H), 3.15 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 162.8, 162.0, 160.3, 154.4, 142.1, 140.0, 138.5, 130.8 (2C), 129.9, 129.5 (2C), 129.2 (2C), 128.6, 128.0, 127. 8, 127.6 (2C), 113.5, 111.1, 110.2, 101.2, 55.6, 27.5. HRMS (ESI): Calcd for $C_{26}H_{20}NO_3$ $[M+H]^+$: 394.1443; Found: 394.1446.

4.3.4. *7-Methoxy-4-methyl-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one(**3d**)*

White solid, 72 mg, 61% yield, m.p. 252 – 254 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 3H), 7.19 (s, 5H), 7.11 (d, *J* = 6.8 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.69 (t, *J* = 8.2 Hz, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 3.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 162.3, 159.5, 147.6, 142.7, 142.0, 139.9, 138.4, 130.9 (2C), 129.6, 129.57 (2C), 129.1 (2C), 128.0, 127.8, 127.6 (2C), 122.6, 120.2, 118.1, 114.6, 113.1, 56.3, 27.5. HRMS (ESI): Calcd for $C_{26}H_{20}NO_3$ $[M+H]^+$: 394.1443; Found: 394.1446.

4.3.5. *9-Bromo-4-methyl-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one (**3e**)*

White solid, 93 mg, 70% yield, m.p. 239 – 241 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 1H), 7.42 – 7.36 (m, 3H), 7.22 – 7.11 (m, 8H), 6.81 (s, 1H), 3.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.4, 159.5, 151.5, 140.6, 139.5, 137.6, 134.2, 131.8, 130.5 (2C), 129.6 (2C), 129.5 (2C), 128.5, 128.1, 127.7 (2C), 119.0, 119.0, 116.1, 114.4, 114.0, 27.5. HRMS (ESI): Calcd for $C_{25}H_{17}BrNO_2$ $[M+H]^+$: 422.0443; Found: 442.0448.

4.3.6. *4-Ethyl-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one (**3f**)*

White solid, 71 mg, 63% yield, m.p. 236 – 238 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 5H), 7.20 (s, 5H), 7.13 (d, *J* = 7.2 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.75 (t, *J* = 7.6 Hz, 1H), 3.59 (q, *J* = 7.3 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 167.4, 162.2, 159.7, 152.6, 142.0, 140.0, 138.5, 131.4, 130.8 (2C), 129.7 (2C), 129.2 (2C), 129.16 (2C), 128.8, 128.1, 127.9, 127.8, 127.6 (2C), 123.2, 117.4, 114.0, 32.3, 13.5. HRMS (ESI): Calcd for $C_{26}H_{20}NO_2$ $[M+H]^+$: 378.1494; Found: 378.1496.

4.3.7. *1,2-Diphenyl-4-propyl-5H-chromeno[3,4-c]pyridin-5-one (**3g**)*

White solid, 81 mg, 69% yield, m.p. 168 – 170 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 5H), 7.19 (s, 5H), 7.12 (d, *J* = 6.4 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 3.54 (t, *J* = 7.6 Hz, 2H), 1.90 (sext, *J* = 7.4 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 162.1, 159.7, 152. 6, 141.9, 140.0, 138.5, 131.4, 130.8 (2C), 129.7 (2C), 129.2 (2C), 129.2, 128.8, 128.1, 127.9, 127.6 (2C), 123.2, 117.4, 117.4, 114.1, 40.8, 22.8, 14.5. HRMS (ESI): Calcd for $C_{27}H_{22}NO_2[M+H]^+$: 392.1651; Found: 392.1656.

4.3.8. *1,2,4-Triphenyl-5H-chromeno[3,4-c]pyridin-5-one (**3h**)*[55]

White solid, 63 mg, 49% yield, m.p. 292 – 294 °C (lit.[20]: 280 – 282 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (app s, 2H), 7.47 (app s, 3H), 7.40 – 7.31 (m, 5H), 7.27 (d, *J* = 6.8 Hz, 2H), 7.21 – 7.16 (m, 5H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 162.0, 159.3, 152.7, 142.5, 141.1, 139.6, 138.2, 131.6, 130.9 (2C), 130.0 (2C), 129.7, 129.4 (2C), 129.2 (2C), 128.9, 128.8, 128.3, 128.1, 128.0 (2C), 127.6 (2C), 123.3, 117.6, 117.4, 113.4. HRMS (ESI): Calcd for $C_{30}H_{20}NO_2$ $[M+H]^+$: 426.1494; Found: 426.1494.

4.3.9. *4-Ethyl-9-methyl-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one (**3i**)*

White solid, 80 mg, 68% yield, m.p. 218 – 220 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 3H), 7.26 – 7.12 (m, 9H), 6.48 (s, 1H), 3.58 (q, *J* = 7.3 Hz, 2H), 1.89 (s, 3H), 1.44 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 161.9, 159.8, 150.6, 142.1, 140.0, 138.7, 132.4, 132.2, 130.8 (2C), 129.8 (2C), 129.3, 129.1 (2C), 127.9, 127.8, 127.6 (2C), 116.9, 116.8, 114.1, 32.3, 20.9, 13.5. HRMS (ESI): Calcd for $C_{27}H_{22}NO_2$ $[M+H]^+$: 392.1651; Found: 392.1651.

4.3.10. *4-Ethyl-7-methoxy-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one (**3j**)*

White solid, 65 mg, 53% yield, m.p. 263 – 265 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 3H), 7.19 (s, 5H), 7.11 (d, *J* = 7.2 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.68 (t, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 3.94 (s, 3H), 3.59 (q, *J* = 7.3 Hz, 2H), 1.44 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 162.2, 159.1, 147.6, 142.6, 142.2, 140.0, 138.5, 130.9 (2C), 129.7 (2C), 129.4, 129.1 (2C), 128.0, 127.8, 127.6 (2C), 122.5, 120.2, 118.1, 114.0, 113.0, 56.3, 32.2, 13.5. HRMS (ESI): Calcd for $C_{27}H_{22}NO_3$ $[M+H]^+$: 408.1600; Found: 408.1604.

4.3.11. *4-Ethyl-8-methoxy-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one (**3k**)*

White solid, 86 mg, 70% yield, m.p. 246 – 249 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.31 (m, 3H), 7.19 (s, 5H), 7.12 (d, *J* = 6.8 Hz, 2H), 6.77 (s, 1H), 6.67 (d, *J* = 9.6 Hz, 1H), 6.31 (d, *J* = 9.2 Hz, 1H), 3.79 (s, 3H), 3.56 (q, *J* = 7.3 Hz, 2H), 1.43 (t, *J* = 9.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 161.9, 161.9, 159.9, 154.3, 142.3, 140.2, 138.7, 130.9 (2C), 129.89, 129.7 (2C), 129.2 (2C), 128.4, 128.0, 127.8, 127.6 (2C), 112.9, 111.0, 110.3, 101.1, 55.6, 32.3, 13.6. HRMS (ESI): Calcd for $C_{27}H_{22}NO_3$ $[M+H]^+$: 408.1600; Found:408.1604.

4.3.12. *9-Bromo-4-ethyl-1,2-diphenyl-5H-chromeno[3,4-c]pyridin-5-one (**3l**)*

White solid, 101 mg, 74% yield, m.p. 248 – 250 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 4H), 7.26 – 7.16 (m, 6H), 7.12 (d, *J* = 7.2 Hz, 2H), 6.80 (s, 1H), 3.58 (q, *J* = 7.5 Hz, 2H), 1.44 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 162.3, 159.1, 151.4, 140.7, 139.7, 137.8, 134.1, 131.8, 130.5 (2C), 129.8 (2C), 129.5 (2C), 129.2, 128.5, 128.1, 127.7 (2C), 118.9, 118.9, 115.9, 113.8, 32.2, 13.4. HRMS (ESI): Calcd for $C_{26}H_{19}BrNO_2$ $[M+H]^+$: 456.0599; Found: 456.0601.

4.3.13. *9-Methyl-1,2-diphenyl-4-propyl-5H-chromeno[3,4-c]pyridin-5-one (**3m**)*

White solid, 103 mg, 85% yield, m.p. 189 – 192 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 3H), 7.24 – 7.20 (m, 5H), 7.15 – 7.11 (m, 4H), 6.47 (s, 1H), 3.53 (t, *J* = 7.8 Hz, 2H), 1.96 – 1.86 (m, 5H), 1.10 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 161.8, 159.9, 150. 6, 142.1, 140.0, 138.7, 132.4, 132.2, 130.8 (2C), 129.8 (2C), 129.3, 129.2 (2C), 127.9, 127.9, 127.6 (2C), 116.9, 116.8, 114.2, 40.9, 22.8, 21.0, 14.5. HRMS (ESI): Calcd for $C_{28}H_{24}NO_2$ $[M+H]^+$: 406.1807; Found: 406.1810.

4.3.14. *8-Methoxy-1,2-diphenyl-4-propyl-5H-chromeno[3,4-c]pyridin-5-one (**3n**)*

White solid, 85 mg, 67% yield, m.p. 196 – 198 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.30 (m, 3H), 7.18 (s, 5H), 7.11 (d, *J* = 6.8 Hz, 2H), 6.76 (s, 1H), 6.67 (d, *J* = 9.2 Hz, 1H), 6.31 (d, *J* = 9.2 Hz, 1H), 3.78 (s, 3H), 3.51 (t, *J* = 7.6 Hz, 2H), 1.99 (sext, *J* = 7.3 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 161.9, 161.8, 159.9, 154.3, 142.3, 140.1, 138.6, 130.9 (2C), 129.9, 129.7 (2C), 129.2 (2C),

128.4, 128.0, 127.8, 127.6 (2C), 113.0, 111.0, 110.3, 101.1, 55.6, 40.8, 22.9, 14.5. HRMS (ESI): Calcd for $C_{27}H_{22}NO_2$ $[M+H]^+$: 392.1656; Found: 392.1651.

4.3.15. *7-Methoxy-1,2-diphenyl-4-propyl-5H-chromeno[3,4-c]pyridin-5-one (**3o**)*

White solid, 76 mg, 60% yield, m.p. 208 – 210 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.29 (m, 3H), 7.19 (s, 5H), 7.11 (d, *J* = 6.8 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.68 (t, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 3.55 (t, *J* = 7.4, 2H), 1.95 – 1.86 (m, 2H), 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 162.1, 159.1, 147.6, 142.6, 142.2, 140.1, 138.5, 130.9 (2C), 129.7 (2C), 129.3, 129.1 (2C), 128.0, 127.8, 127.6 (2C), 122.5, 120.2, 118.2, 114.1, 113.0, 56.3, 40.7, 22.8, 14.4. HRMS (ESI): Calcd for $C_{28}H_{24}NO_3$ $[M+H]^+$: 422.1756; Found: 422.1753.

4.3.16. *1,2-Diethyl-4-methyl-5H-chromeno[3,4-c]pyridin-5-one (**3ab**)*

White solid, 27 mg, 34% yield, m.p. 138 – 140 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.23 (m, 2H), 3.07 (q, *J* = 7.3 Hz, 2H), 2.98 – 2.92 (m, 5H), 1.43 (t, *J* = 7.4 Hz, 3H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 160.9, 160.4, 152.2, 141.7, 131.3, 129.1, 127.8, 123.9, 117.9, 114.3, 28.9, 27.2, 23.1, 14.4, 14.1. HRMS (ESI): Calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1338; Found: 268.1335.

4.3.17. *1,2-Diethyl-4,9-dimethyl-5H-chromeno[3,4-c]pyridin-5-one (**3bb**)*

White solid, 30 mg, 36% yield, m.p. 104 – 107 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 3.14 (q, *J* = 7.2 Hz, 2H), 3.04 – 2.99 (m, 5H), 2.46 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 160.9, 160. 6, 150.2, 141.8, 133.2, 132.1,

129.0, 127.9, 117.5, 114.3, 28.9, 27.2, 23.1, 21.5, 14.4, 14.1. HRMS (ESI): Calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$: 282.1494; Found: 282.1496.

4.3.18. *1,2-Diethyl-8-methoxy-4-methyl-5H-chromeno[3,4-c]pyridin-5-one (**3cb**)*

White solid, 29 mg, 33% yield, m.p. 155 – 157 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.2 Hz, 1H), 6.91 – 6.88 (m, 1H), 6.85 (t, *J* = 2.6 Hz, 1H), 3.92 (d, *J* = 1.6 Hz, 3H), 3.13 (q, *J* = 7.5 Hz, 2H), 3.04 – 2.99 (m, 5H), 1.49 (t, *J* = 7.4 Hz, 3H), 1.38 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 161.7, 160.9, 160.5, 153.9, 142.0, 128.9, 128.2, 113.2, 111.7, 110.7, 101.5, 55.7, 28.9, 27.2, 23.0, 14.3, 14.1. HRMS (ESI): Calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1443; Found: 298.1445.

4.3.19. *1-Ethyl-4-methyl-2-phenyl-5H-chromeno[3,4-c]pyridin-5-one (**3ac**)*

White solid, 61 mg, 64% yield, m.p. 182 – 184 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.54 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.27 – 7.26 (m, 3H), 6.78 – 6.73 (m, 2H), 3.12 (s, 3H), 2.62 (q, *J* = 7.5 Hz, 2H), 1.16 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 163.0, 160.2, 152.6, 140.8, 138.9, 131.3, 129.8 (2C), 129.5 (2C), 129.2, 128.6, 128.4, 123.3, 117.5, 117.3, 113.6, 29.9, 27.5, 13.8. HRMS (ESI): Calcd for $C_{21}H_{18}NO_2$ $[M+H]^+$: 316.1338; Found: 316.1342.

4.3.20. *2-Ethyl-4-methyl-1-phenyl-5H-chromeno[3,4-c]pyridin-5-one ((**3ac**)′)*

White solid, 11 mg, 12% yield, m.p. 167 – 169 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.49 (m, 6H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 3.20 (q, *J* = 7.2 Hz, 2H), 3.08 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 160.7, 160.2, 152.3, 142.5, 140.9, 131.6, 130.1, 128.53

(2C), 128.47 (2C), 128.4, 127.9, 124.1, 117.9, 117.8, 115.3, 27.3, 24.5, 14.1. HRMS (ESI): Calcd for $C_{21}H_{18}NO_2$ $[M+H]^+$: 316.1338; Found: 316.1342.

4.3.21. *1-Ethyl-4,9-dimethyl-2-phenyl-5H-chromeno[3,4-c]pyridin-5-one (**3bc**)*

White solid, 66 mg, 67% yield, m.p. 138 – 140 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 3H), 7.26 (s, 2H), 7.14 (s, 2H), 6.43 (s, 1H), 3.12 (s, 3H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.91 (s, 3H), 1.17 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.0, 160.4, 150.6, 140.9, 139.0, 132.5, 132.1, 129.7 (2C), 129. 6 (2C), 129.2, 129.1, 128.3, 117.0, 116.8, 113.7, 29.9, 27.6, 21.0, 13.8. HRMS (ESI): Calcd for $C_{22}H_{20}NO_2$ $[M+H]^+$: 330.1494; Found: 330.1494.

4.3.22. *2-Ethyl-4,9-dimethyl-1-phenyl-5H-chromeno[3,4-c]pyridin-5-one ((**3bc**)')*

White solid, 15 mg, 15% yield, m.p. 164 – 167 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.55 – 7.52 (m, 5H), 7.40 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 3.25 (q, *J* = 7.3 Hz, 2H), 3.11 (s, 3H), 2.50 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 160. 7, 160.4, 150.3, 142.7, 141.0, 133.4, 132.5, 130.0, 128.6, 128.5, 128.4, 128.0, 117.6, 117.4, 115.4, 27.3, 24.5, 21.4, 14.1. HRMS (ESI): Calcd for $C_{22}H_{20}NO_2$ $[M+H]^+$: 330.1494; Found: 330.1494.

4.3.23. *Ethyl 4-methyl-5-oxo-2-phenyl-5H-chromeno[3,4-c]pyridine-1-carboxylate (**3ad**)*

White solid, 70 mg, 65% yield, m.p. 120 – 122 ^oC. ^1H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.54 (s, 5H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.00 (s, 3H), 1.03 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.7, 163.7, 159.4, 158.9, 152.5, 140.0,

138.8, 133.7, 129.8, 128.8 (2C), 128.76 (2C), 125.9, 125.1, 121.8, 118.2, 115.3, 114.5, 62.8, 27.6, 13.6. HRMS (ESI): Calcd for $C_{22}H_{18}NO_4$ $[M+H]^+$: 360.1236; Found: 360.1235.

4.3.24. *Ethyl 1,4-dimethyl-5-oxo-5H-chromeno[3,4-c]pyridine-2-carboxylate (**3ae**)*

White solid, 26 mg, 29% yield, m.p. 128 – 131 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 5.6 Hz, 1H), 4.52 (q, *J* = 6.9 Hz, 2H), 3.07 (s, 3H), 2.67 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 164.6, 159.4, 159.2, 152.5, 139.8, 132.7, 125.7, 124.3, 121.9, 118.0, 115.5, 113.2, 62.6, 27.3, 23.3, 13.9. HRMS (ESI): Calcd for $C_{17}H_{16}NO_4$ $[M+H]^+$: 298.1079; Found: 298.1084.

4.3.25. *Dimethyl 2-(3-((E)-1-(hydroxyimino)ethyl)-2-oxo-2H-chromen-4-yl)maleate (**4**)*

The same procedure for compounds **3** was used. White solid, 32 mg, yield 31%. ^1H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 6.11 (s, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.4, 162.7, 159.8, 158.9, 154.1, 153.2, 143.3, 133.6, 129.9, 125.4, 123.0, 118.7, 116.6, 107.2, 53.5, 52.2, 40.6, 40.4, 40.2, 40.0, 39.8, 39. 6, 39.4, 15.4. HRMS (ESI): Calcd for $C1_7H_{16}NO_7$ $[M+H]^+$: 346.0927; Found: 346.0930.

4.4. Synthesis of Fully Substituted Pyridines 5 through Hydrolysis and Subsequent Alkylation

4.4.1. *4-(2-Hydroxyphenyl)-2-methyl-5,6-diphenylnicotinic acid (**5a**)*

To a 10-mL vial was added **3a** (0.1 mmol, 36 mg), solid sodium hydroxide (0.2 mmol, 8 mg) and DMSO (0.3 mL). The reaction system was stirred at room temperature for 2 hours. And then hydrochloric acid (1 M) was added dropwise until no more precipitate formed. The precipitate was collected and the filtrate was extracted with ethyl acetate (20 mL × 3) followed by washing with saturated brine. The combined crude product was subjected to purification to furnish **5a**. White solid, 35 mg, 93% yield, m.p. 209 – 211 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 – 7.19 (m, 5H), 7.00 – 6.96 (m, 5H), 6.89 (d, J = 7.2 Hz, 2H), 6.61 (t, J = 7.2 Hz, 2H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6, 156.7, 154.7, 152.0, 145.4, 140.8, 138.0, 133.7, 130.9, 130.6, 130.1 (2C), 129.4, 127.9 (2C), 127.8, 126.9, 124.5, 118.3, 115.2, 23.0. HRMS (ESI): Calcd for $C_{25}H_{20}NO_3$ $[M+H]^+$: 382.1443; Found: 382.1444.

4.4.2. *Ethyl 4-(2-ethoxyphenyl)-2-methyl-5,6-diphenylnicotinate (**5b**)*

To a 10-mL vial was added **3a** (0.1 mmol, 36 mg), solid sodium hydroxide (0.24 mmol, 10 mg) and DMSO (0.3 mL). The reaction system was stirred at room temperature for 0.5 hour. And then to the reaction system was added bromoethane (0.24 mmol, 26 mg), and stirred for additional 3 hours. Standard work-up furnished **5b**. White solid, 36 mg, 82% yield, m.p. 154 – 156 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.27 (m, 2H), 7.17 – 7.10 (m, 4H), 7.00 – 6.76 (m, 7H), 6.61 (d, J = 8.4 Hz, 1H), 4.00 (q, J = 6.9 Hz, 2H), 3.83 (quint, J = 7.5 Hz, 1H), 3.61 (quint, J = 7.5 Hz, 1H), 2.72 (s, 3H), 1.20 (t, J = 6.8 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 157.6, 155.5, 153.6, 145.9, 140.5, 137.6, 133.3, 130.7, 130.0 (2C), 129.2, 128.7, 127.6 (2C), 127.5, 127.0 (2C overlapped), 126.5, 126.4, 119.5,

110.9, 63.3, 61.0, 23.2, 14.6, 13.6. HRMS (ESI): Calcd for $C_{29}H_{28}NO_3$ $[M+H]^+$: 438.2069; Found: 438.2065.

4.4.3. *n-Butyl 4-(2-butoxyphenyl)-2-methyl-5,6-diphenylnicotinate (**5c**)*

The procedure for **5b** was applied except with 1-bromo-*n*-butane (0.24 mmol, 0.033 g) instead. White solid, 42 mg, 85% yield, m.p. 101 – 103 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 2H), 7.16 – 7.09 (m, 4H), 7.00 – 6.74 (m, 7H), 6.61 (d, *J* = 8.4 Hz, 1H), 3.94 (t, *J* = 6.2 Hz, 2H), 3.73 (q, *J* = 7.6 Hz, 1H), 3.56 (q, *J* = 7.5 Hz, 1H), 2.71 (s, 3H), 1.62 – 1.55 (m, 2H), 1.30 – 1.26 (m, 4H), 1.20 – 1.11 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 157.5, 155.7, 153.5, 145.8, 140.5, 137.6, 133.3, 130.8 (2C overlapped), 130.5, 129.9 (2C), 129.2, 128.9, 127.6 (2C), 127.5, 127.0 (2C overlapped), 126.5, 126.4, 119.5, 111.0, 67.6, 64.9, 31.1, 30.3, 23.2, 19.2, 19.0, 13.8, 13.7. HRMS (ESI): Calcd for $C_{33}H_{36}NO_3$ $[M+H]^+$: 494.2695; Found: 494.2691.

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Supplemental data

Crystalographic data for **3ad** (1902110) has been deposited at the Cambridge Crystallographic Database Centre and can be found at http://www.ccdc.ac.uk.

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48. Crystal Data for $C_{22}H_{17}NO_4$ (M = 359.36 g/mol): monoclinic, space group $P2_1$, a = 10.6868(7) Å, b = 7.2723(5) Å, c = 11.2116(8) Å, β = 101.187(6)°, V = 854.78(10) $Å^3$, Z = 2, T = 173.00(10) K, $\mu(MoK_\alpha)$ = 0.097 mm^{-1}, D_{calc} = 1.396 g/cm^3, 3268 reflections measured (6.716° ≤ 2Θ ≤ 52.036°), 2315 unique (R_{int} = 0.0189, R_{sigma} = 0.0376) which were used in all calculations. The final R_1 was 0.0397 (>2 sigma(I)) and wR_2 was 0.0980 (all data).

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