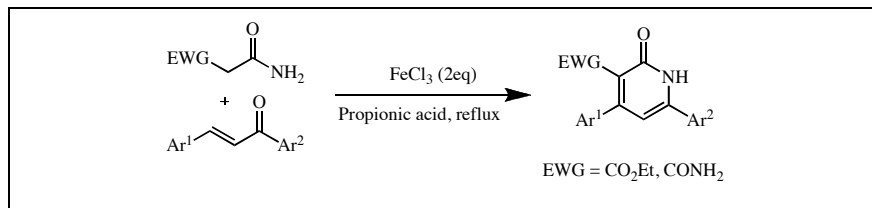


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A facile approach was developed on assembly of the 2-pyridone nucleus by ferric chloride promoted [3+3] cycloaddition in propionic acid. The tandem process involves cyclization of Michael adduct followed by aromatization. Thus, different substituted 1,2-dihydro-2-oxo-3-pyridinecarboxylate and 1,2-dihydro-2-oxo-3-pyridinecarboxamide derivatives were prepared in good yields from various enones with malonamic ester and malonamide, respectively

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INTRODUCTION

Considerable attention was given to the assembly of 2-pyridone rings due to a number of natural and synthetic compounds containing the 2-pyridone moiety which possess potent pharmacological and agrochemical activities [1]. Generally, two main synthetic approaches to elaborate 2-pyridone rings, one is by conversion from other heterocycles, the other is by condensation from acyclic compounds. Among them, [3+3] annulation is one of the most efficient strategies to rapidly construct 2-pyridone scaffolds and the key of [3+3] annulation is the aromatization of the possible intermediate dihydropyridone. Recently, Ciufolini developed a one-step procedure to prepare substituted 3-cyano-2-pyridones from various enones and cyanoacetamide in DMSO using *t*-BuOK as a base under an oxygen atmosphere. The proposed mechanism involves a single electron transfer (SET) process, which enables the aromatization of the ring [2-4]. Later, Katritzky reported a benzotriazole-assisted preparation of 3-unsubstituted 2-pyridones which concerns cyclization of Michael adduct and subsequent aromatization by dehydration and loss of benzotriazole [5-6]. Although these base-promoted [3+3] annulation approaches have been applied successfully in total synthesis and solid-phase synthesis, limitations still exist. As mentioned by Ciufolini, upon base-promoted reaction with enones, malonamide produced only Michael adducts without any 2-pyridones, while malonamic ester afforded hydrolyzed product 2-oxo-3-pyridinecarboxylic acids. In order to overcome the limitations and enlarge the scope of [3+3] annulation to attain 2-pyridones, we herein provided an efficient approach promoted by FeCl₃ to carry

out the preparation of 1,2-dihydro-2-oxo-3-pyridinecarboxylate and 1,2-dihydro-2-oxo-3-pyridinecarboxamide derivatives from enones with malonamic ester and malonamide, respectively.

RESULTS AND DISCUSSION

Scheme 1

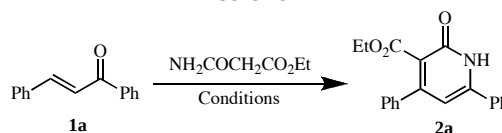


Table 1

Preparation of **2a** under conditions.^a

Entry	Catalyst	Ratio ^b	Yield (%) ^c
1	1eq FeCl ₃	1:1	30
2	2eq FeCl ₃	1:1	60
3	2eq FeCl ₃ ·6H ₂ O	1:1	48
4	2eq Fe ₂ (SO ₄) ₃ ·9H ₂ O	1:1	35
5	2eq Fe(NO ₃) ₃ ·9H ₂ O	1:1	20
6	2eq FeCl ₃	1:1.2	65

^aThe reaction time is 1h. ^bRatio is **1a**: ethyl 3-amino-3-oxopropionate.

^cYield of purified product after flash chromatography.

Initial studies were carried out using 1,3-diphenyl-2-propen-1-one (**1a**) and ethyl 3-amino-3-oxopropionate as a model system (Scheme 1, Table 1). When **1a** and ethyl 3-amino-3-oxopropionate were treated with 1.0 eq FeCl₃ in propionic acid at reflux temperature, after an hour the anticipated ethyl 1,2-dihydro-2-oxo-3-pyridinecarboxylate was obtained in 30% yield (entry 1). However, when 2eq of FeCl₃ was employed, the yield increased to 60% (entry

2). Control experiment without any FeCl_3 showed no product detected as well as intermediate dihydropyridone. In addition, other iron salts such as $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{Fe}_2(\text{SO}_4)_3 \cdot 9\text{H}_2\text{O}$ and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ were tested but gave inferior results (entry 3-5). The presence of crystallization water may inhibit keto-amide cyclization process and different counter-anions of iron salts also affect the reaction. Optimization of the ratio of **1a** and ethyl 3-amino-3-oxo-propionate resulted in slight improvement of the yield (entry 6).

Scheme 2

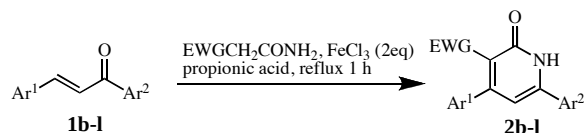


Table 2

FeCl_3 -promoted Preparation of **2b-l**.

Entry	Ar ¹	Ar ²	EWG	Yield(%) ^a
2b	4-CH ₃ OC ₆ H ₄	C ₆ H ₅	CO ₂ Et	71
2c	4-ClC ₆ H ₄	C ₆ H ₅	CO ₂ Et	75
2d	3-ClC ₆ H ₄	C ₆ H ₅	CO ₂ Et	65
2e	2-ClC ₆ H ₄	C ₆ H ₅	CO ₂ Et	60
2f	C ₆ H ₅	2,5-Cl ₂ C ₆ H ₃	CO ₂ Et	70
2g	C ₆ H ₅	C ₆ H ₅	CONH ₂	70
2h	C ₆ H ₅	4-PhC ₆ H ₄	CONH ₂	65
2i	C ₆ H ₅	4-ClC ₆ H ₄	CONH ₂	60
2j	4-CH ₃ C ₆ H ₄	C ₆ H ₅	CONH ₂	68
2k	4-ClC ₆ H ₄	C ₆ H ₅	CONH ₂	75
2l	3,4-Cl ₂ C ₆ H ₃	4-CH ₃ C ₆ H ₄	CONH ₂	70

^aYield of isolated products after flash chromatography.

According to the optimized condition, various substrates were tested to screen the scope of this reaction. As shown in Table 2, enones with electron-withdrawing and electron-donating substituents underwent [3+3] cycloaddition smoothly and converted into the corresponding ethyl 1,2-dihydro-2-oxo-3-pyridine-carboxylates (**2b-f**) in the yield ranging from 65% to 75%. Among them, enone containing *o*-chloro substituent displays lower reactivity than corresponding *p*-substituted enone. On the other hand, different substituted 1,2-dihydro-2-oxo-3-pyridinecarboxamides (**2g-l**) were obtained conveniently in 60-70% yield from various enones and malonamide according to the procedure similar to ethyl 1,2-dihydro-2-

oxo-3-pyridinecarboxylates. In addition, attempt to prepare 1,2-dihydro-2-oxo-3-pyridinecarbonitrile from 1,3-diphenyl-2-propen-1-one and cyanoacetamide proved to be unsuccessful, which led to the formation of 1,2-dihydro-2-oxo-3-pyridinecarboxamide.

A proposed mechanism for the formation of ethyl 1,2-dihydro-2-oxo-3-pyridinecarboxylates and 1,2-dihydro-2-oxo-3-pyridinecarboxamides by FeCl_3 -promoted [3+3] cycloaddition between enones with malonamic ester and malonamide consists of Michael addition and cyclization of amide-ketone followed by aromatization of 3,4-dihydro-2-pyridone (Scheme 3). This cycloaddition with excellent regioselectivity and functional group tolerance is different from those base-promoted [3+3] annulation and the proposed intermediate 3,4-dihydro-2-pyridone was aromatized without employing extra oxidants or leaving groups.

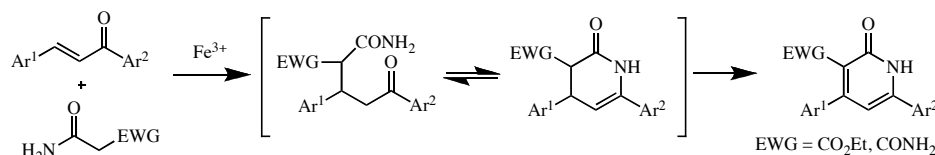
In summary, a novel approach was developed for the preparation of 1,2-dihydro-2-oxo-3-pyridinecarboxylates and 1,2-dihydro-2-oxo-3-pyridinecarboxamides, which can be further modified as lead compounds such as cytokine inhibitors [7] and anaplastic lymphoma kinase inhibitors [8]. The [3+3] cycloaddition promoted by FeCl_3 in acid media involves cyclization of Michael adduct amide-ketone and subsequent aromatization, which is supplementary to the existing approaches for the assembly of 2-pyridone derivatives. Besides, the novel [3+3] cycloaddition also shows another application of FeCl_3 in organic synthesis [9-11]. Further explorations of this procedure are in progress.

EXPERIMENTAL

All melting points were determined on a Yanaco apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IDP440 spectrometer as KBr pellets. ¹H NMR spectra were recorded on a Bruker DPX-300 spectrometer. MS spectra were taken on a VG-ZAB-HS mass spectrometer at 70 eV. Elemental analyses were performed on a Perkin-Elmer 240C instrument.

General procedure for the preparation of ethyl 1,2-dihydro-2-oxo-3-pyridinecarboxylates 2a-f and 1,2-dihydro-2-oxo-3-pyridinecarboxamides 2g-l. Enones **2a-l** (2.5 mmol), ethyl 3-amino-3-oxo-propionate (3.0 mmol) or malonamide (3.0 mmol) and FeCl_3 (5.0 mmol) were dissolved in propionic acid (5.0 mL) and the formed solution was refluxed for 1 h. After cooling, the mixture was poured into 1.0 N HCl (30 mL), then extracted by CHCl_3 (3 × 30 mL). The combined organic layer was washed successively with aq NaHCO_3 (30 mL) and H_2O (30

Scheme 3



mL). The organic layer was dried (MgSO₄) and the solvent was removed by distillation. The crude products obtained were purified by flash column chromatography to give 1,2-dihydro-2-oxo-3-pyridinecarboxylates **2a-f** and 1,2-dihydro-2-oxo-3-pyridinecarboxamides **2g-l**.

Ethyl 1,2-dihydro-4,6-diphenyl-2-oxo-3-pyridine-carboxylate (2a). This compound was obtained as white solids (HOAc-EtOH), mp 202-204°; ir: 1724, 1629 cm⁻¹; ¹H nmr (CDCl₃): δ 1.06 (t, 3H, J = 7.1 Hz), 4.17 (q, 2H, J = 7.1 Hz), 6.65 (s, 1H), 7.44-7.52 (m, 8H), 7.87-7.91 (m, 2H), 13.13 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 14.2, 61.6, 107.2, 121.6, 127.5, 127.9, 128.9, 129.5, 130.9, 133.2, 138.6, 148.4, 153.6, 163.1, 166.9; ms: m/z 320 (M+1, 20), 319 (M⁺, 88), 245 (100). *Anal.* Calcd. for C₂₀H₁₇NO₃: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.42; H, 5.27; N, 4.34.

Ethyl 1,2-dihydro-4-(4-methoxyphenyl)-2-oxo-6-phenyl-3-pyridinecarboxylate (2b). This compound was obtained as white solids (HOAc-EtOH), mp 218-220°; ir: 1724, 1618 cm⁻¹; ¹H nmr (CDCl₃): δ 1.13 (t, 3H, J = 7.1 Hz), 3.87 (s, 3H), 4.21 (q, 2H, J = 7.1 Hz), 6.62 (s, 1H), 6.94-6.99 (m, 2H), 7.43-7.52 (m, 5H), 7.84-7.87 (m, 2H), 12.75 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 13.8, 55.2, 61.1, 106.8, 113.9, 120.8, 127.0, 128.9, 130.3, 132.9, 147.5, 152.5, 160.3, 162.6, 166.6; ms: m/z 351 (M+2, 4), 349 (M⁺, 100), 275 (75). *Anal.* Calcd. for C₂₁H₁₉NO₄: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.13; H, 5.65; N, 4.00.

Ethyl 4-(4-chlorophenyl)-1,2-dihydro-2-oxo-6-phenyl-3-pyridinecarboxylate (2c). This compound was obtained as white solids (HOAc-EtOH), mp 238-240°; ir: 1728, 1626 cm⁻¹; ¹H nmr (CDCl₃): δ 1.10 (t, 3H, J = 7.1 Hz), 4.19 (q, 2H, J = 7.1 Hz), 6.60 (s, 1H), 7.43 (s, 4H), 7.48-7.52 (m, 3H), 7.84-7.87 (m, 2H), 12.76 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 14.2, 61.8, 107.1, 121.3, 127.5, 129.2, 129.3, 129.5, 131.3, 133.1, 135.7, 136.9, 148.8, 152.4, 162.9, 166.6; ms: m/z 355 (M+2, 32), 353 (M⁺, 100), 279 (76). *Anal.* Calcd. for C₂₀H₁₆ClNO₃: C, 67.90; H, 4.56; N, 3.96. Found: C, 67.87; H, 4.53; N, 4.10.

Ethyl 4-(3-chlorophenyl)-1,2-dihydro-2-oxo-6-phenyl-3-pyridinecarboxylate (2d). This compound was obtained as white solids (HOAc-EtOH), mp 165-167°; ir: 1734, 1623 cm⁻¹; ¹H nmr (CDCl₃): δ 1.11 (t, 3H, J = 7.1 Hz), 4.20 (q, 2H, J = 7.1 Hz), 6.60 (s, 1H), 7.36-7.44 (m, 3H), 7.49-7.53 (m, 4H), 7.85-7.89 (m, 2H), 13.26 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 13.8, 61.3, 106.3, 121.1, 125.7, 127.1, 127.6, 129.0, 129.8, 130.6, 132.5, 134.4, 139.7, 148.4, 151.5, 162.6, 166.0; ms: m/z 355 (M+2, 33), 353 (M⁺, 100), 279 (75). *Anal.* Calcd. for C₂₀H₁₆ClNO₃: C, 67.90; H, 4.56; N, 3.96. Found: C, 67.73; H, 4.60; N, 4.28.

Ethyl 4-(2-chlorophenyl)-1,2-dihydro-2-oxo-6-phenyl-3-pyridinecarboxylate (2e). This compound was obtained as white solids (HOAc-EtOH), mp 198-200°; ir: 1728, 1627 cm⁻¹; ¹H nmr (CDCl₃): δ 0.94 (t, 3H, J = 7.1 Hz), 4.08 (q, 2H, J = 7.1 Hz), 6.67 (s, 1H), 7.31-7.39 (m, 3H), 7.46-7.53 (m, 4H), 7.92-7.94 (m, 2H), 12.76 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 13.5, 61.0, 108.6, 126.5, 127.2, 128.9, 129.3, 129.4, 129.6, 130.5, 131.8, 133.3, 137.6, 150.1, 151.9, 163.1, 166.0; ms: m/z 355 (M+2, 2), 353 (M⁺, 6), 290 (100). *Anal.* Calcd. for C₂₀H₁₆ClNO₃: C, 67.90; H, 4.56; N, 3.96. Found: C, 67.80; H, 4.62; N, 3.98.

Ethyl 6-(2,5-dichlorophenyl)-1,2-dihydro-2-oxo-4-phenyl-3-pyridinecarboxylate (2f). This compound was obtained as white solids (HOAc-EtOH), mp 218-220°; ir: 1730, 1624 cm⁻¹; ¹H nmr (CDCl₃): δ 1.05 (t, 3H, J = 7.1 Hz), 4.15 (q, 2H, J = 7.1 Hz), 6.55 (s, 1H), 7.36 (d, 1H, J = 8.7 Hz), 7.37-7.48 (m, 6H), 7.56 (d, 1H, J = 2.3 Hz), 12.67 (s, 1H); ¹³C NMR (75 MHz,

CDCl₃): δ 13.7, 61.3, 110.7, 122.0, 127.5, 128.5, 129.1, 130.8, 130.9, 131.4, 133.0, 133.8, 137.5, 144.3, 152.2, 162.3, 166.0; ms: m/z 391 (M+4, 9), 389 (M+2, 60), 387 (M⁺, 100), 315 (94). *Anal.* Calcd. for C₂₀H₁₅Cl₂NO₃: C, 61.87; H, 3.89; N, 3.61. Found: C, 61.88; H, 4.01; N, 3.78.

1,2-Dihydro-4,6-diphenyl-2-oxo-3-pyridinecarboxamide (2g). This compound was obtained as white solids (HOAc-EtOH), mp 228-230°; ir: 1662, 1629 cm⁻¹; ¹H nmr (DMSO-d₆): δ 6.63 (s, 1H), 7.29 (s, 1H), 7.42-7.50 (m, 6H), 7.57-7.60 (m, 2H), 7.73 (s, 1H), 7.83-7.86 (m, 2H), 12.04 (s, 1H); ms: m/z 290 (M⁺, 1), 289 (M-1, 8), 272 (100). *Anal.* Calcd. for C₁₈H₁₄N₂O₂: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.49; H, 4.83; N, 9.68.

6-[1,1'-Biphenyl]-4-yl-1,2-dihydro-2-oxo-4-phenyl-3-pyridinecarboxamide (2h). This compound was obtained as white solids (HOAc-EtOH), mp 266-270°; ir: 1669, 1624 cm⁻¹; ¹H nmr (DMSO-d₆): δ 6.72 (s, 1H), 7.32 (s, 1H), 7.38-7.52 (m, 7H), 7.59-7.63 (m, 2H), 7.73-7.81 (m, 4H), 7.96 (d, 2H, J = 8.4 Hz), 12.06 (s, 1H); ms: m/z 366 (M⁺, 6), 365 (M-1, 45), 348 (100). *Anal.* Calcd. for C₂₄H₁₈N₂O₂: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.61; H, 4.97; N, 7.61.

6-(4-Chlorophenyl)-1,2-dihydro-2-oxo-4-phenyl-3-pyridinecarboxamide (2i). This compound was obtained as white solids (HOAc-EtOH), mp 239-240°; ir: 1669, 1620 cm⁻¹; ¹H nmr (DMSO-d₆): δ 6.74 (s, 1H), 7.32 (s, 1H), 7.38-7.49 (m, 3H), 7.53-7.61 (m, 4H), 7.73 (s, 1H), 7.90 (d, 2H, J = 8.4 Hz), 11.99 (s, 1H); ms: m/z 326 (M+2, 0.3), 324 (M⁺, 1), 323 (M-1, 14), 308 (36), 306 (100). *Anal.* Calcd. for C₁₈H₁₃ClN₂O₂: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.51; H, 4.11; N, 8.67.

1,2-Dihydro-4-(4-methylphenyl)-2-oxo-6-phenyl-3-pyridinecarboxamide (2j). This compound was obtained as white solids (HOAc-EtOH), mp 246-248°; ir: 1648, 1627 cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.34 (s, 3H), 6.60 (s, 1H), 7.22-7.24 (m, 3H), 7.47-7.50 (m, 5H), 7.69 (s, 1H), 7.82-7.84 (m, 2H), 11.99 (s, 1H); ms: m/z 304 (M⁺, 2), 303 (M-1, 9), 286(100). *Anal.* Calcd. for C₁₉H₁₆N₂O₂: C, 74.99; H, 5.30; N, 9.20. Found: C, 74.98; H, 5.26; N, 9.12.

4-(4-Chlorophenyl)-1,2-dihydro-2-oxo-6-phenyl-3-pyridinecarboxamide (2k). This compound was obtained as white solids (HOAc-EtOH), mp 238-240°; ir: 1665, 1640 cm⁻¹; ¹H nmr (DMSO-d₆): δ 6.63 (s, 1H), 7.34 (s, 1H), 7.49-7.59 (m, 7H) 7.83-7.85 (m, 3H), 12.10 (s, 1H); ms: m/z 326 (M+2, 0.6), 324 (M⁺, 3), 323 (M-1, 13), 308 (22), 306 (100). *Anal.* Calcd. for C₁₈H₁₃ClN₂O₂: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.71; H, 4.02; N, 8.74.

4-(3,4-Dichlorophenyl)-1,2-dihydro-6-(4-methylphenyl)-2-oxo-3-pyridinecarboxamide (2l). This compound was obtained as white solids (HOAc-EtOH), mp 250-252°; ir: 1665, 1630 cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.35 (s, 3H) 6.63 (s, 1H), 7.30 (d, 2H, J = 8.4 Hz) 7.39 (s, 1H), 7.48-7.51 (m, 1H), 7.68-7.78 (m, 4H), 7.92 (s, 1H), 12.12 (s, 1H); ms: m/z 375 (M+3, 0.4), 374 (M+2, 0.9), 373 (M+1, 9), 372 (M⁺, 3), 371 (M-1, 26), 356 (26), 354 (100). *Anal.* Calcd. for C₁₉H₁₄Cl₂N₂O₂: C, 61.14; H, 3.78; N, 7.51. Found: C, 61.11; H, 3.74; N, 7.41.

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