$FeCl_3$-Promoted [3+3] Cycloaddition: Efficient Preparation of 1,2-Dihydro-2-oxo-3-pyridinecarboxylate and 1,2-Dihydro-2-oxo-3-pyridinecarboxamide Derivatives

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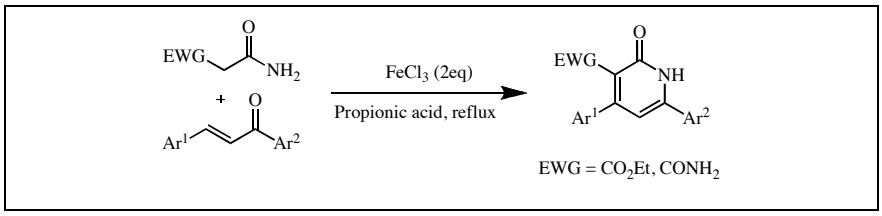

A facile approach was developed on assembly of the 2-pyridone nucleus by ferric chloride promoted [3+3] cycloaddition in propionic acid. The tandem process involves cyclization of Michael adduct followed by aromatization. Thus, different substituted 1,2-dihydro-2-oxo-3-pyridinecarboxylate and 1,2-dihydro-2-oxo-3-pyridinecarboxamide 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 $FeCl_3$ 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

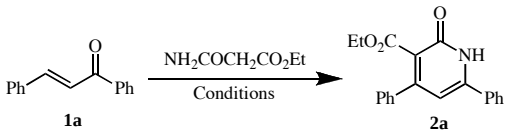


Table 1

Preparation of **2a** under conditions.[a]

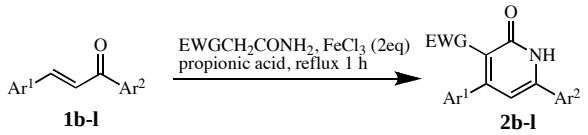
Entry	Catalyst	Ratio[b]	Yield (%)[c]
1	1eq $FeCl_3$	1:1	30
2	2eq $FeCl_3$	1:1	60
3	2eq $FeCl_3 \cdot 6H_2O$	1:1	48
4	2eq $Fe_2(SO_4)_3 \cdot 9H_2O$	1:1	35
5	2eq $Fe(NO_3)_3 \cdot 9H_2O$	1:1	20
6	2eq $FeCl_3$	1:1.2	65

[a]The reaction time is 1h. [b]Ratio is **1a**: ethyl 3-amino-3-oxo-propionate. [c]Yield 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-oxo-propionate as a model system (Scheme 1, Table 1). When **1a** and ethyl 3-amino-3-oxo-propionate were treated with 1.0 eq $FeCl_3$ 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 $FeCl_3$ 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 $FeCl_3 \cdot 6H_2O$, $Fe_2(SO_4)_3 \cdot 9H_2O$ and $Fe(NO_3)_3 \cdot 9H_2O$ 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



1b-l **2b-l**

Table 2

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

Entry	Ar^1	Ar^2	EWG	Yield(%)[a]
2b	4-$CH_3OC_6H_4$	C_6H_5	CO_2Et	71
2c	4-ClC_6H_4	C_6H_5	CO_2Et	75
2d	3-ClC_6H_4	C_6H_5	CO_2Et	65
2e	2-ClC_6H_4	C_6H_5	CO_2Et	60
2f	C_6H_5	2,5-$Cl_2C_6H_3$	CO_2Et	70
2g	C_6H_5	C_6H_5	$CONH_2$	70
2h	C_6H_5	4-PhC_6H_4	$CONH_2$	65
2i	C_6H_5	4-ClC_6H_4	$CONH_2$	60
2j	4-$CH_3C_6H_4$	C_6H_5	$CONH_2$	68
2k	4-ClC_6H_4	C_6H_5	$CONH_2$	75
2l	3,4-$Cl_2C_6H_3$	4-$CH_3C_6H_4$	$CONH_2$	70

[a]Yield 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] cyclo-addition 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.

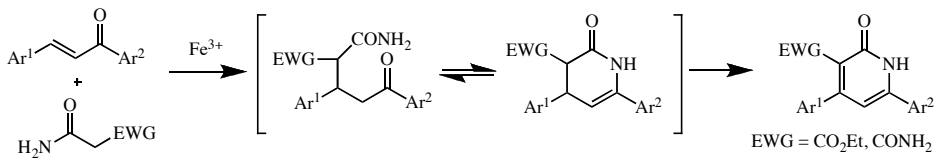
In summary, a novel approach was developed for the preparation of 1,2-dihydro-2-oxo-3-pyridinecarboxylates and 1,2-dihydro-2-oxo-3-pyridinecarboxamides, which can be further modified as lead compounds such as cytokine inhibitors [7] and anaplastic lymphoma kinase inhibitors [8]. The [3+3] cycloaddition 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 Shimider IDP440 spectrometer as KBr pellets. ^{1}H 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 ($MgSO_4$) 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 ($CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{20}H_{17}NO_3$: 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 ($CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{21}H_{19}NO_4$: 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 ($CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{20}H_{16}ClNO_3$: 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 ($CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{20}H_{16}ClNO_3$: 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 ($CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{20}H_{16}ClNO_3$: 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 ($CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{20}H_{15}Cl_2NO_3$: 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-d_6) 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 $C_{18}H_{14}N_2O_2$: 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-d_6) 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 $C_{24}H_{18}N_2O_2$: 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-d_6) 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 $C_{18}H_{13}ClN_2O_2$: 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-d_6) 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 $C_{19}H_{16}N_2O_2$: 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-d_6) 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 $C_{18}H_{13}ClN_2O_2$: 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-d_6) 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 $C_{19}H_{14}Cl_2N_2O_2$: C, 61.14; H, 3.78; N, 7.51. Found: C, 61.11; H, 3.74; N, 7.41.

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