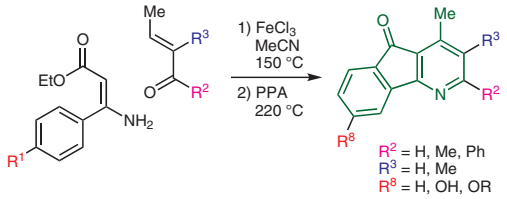
Synthesis M. Arita et al. Paper

Facile Synthesis of Onychines

Mao Arita[a]
Soichi Yokoyama[a,b]
Haruyasu Asahara*[a,b,c]
Nagatoshi Nishiwaki*[a,b]

[a] School of Environmental Science and Engineering, Kochi University of Technology, Kami, Kochi 782-8502, Japan
nishiwaki.nagatoshi@kochi-tach.ac.jp
[b] Research Center for Material Science and Engineering, Kochi University of Technology, Kami, Kochi 782-8502, Japan
[c] Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan



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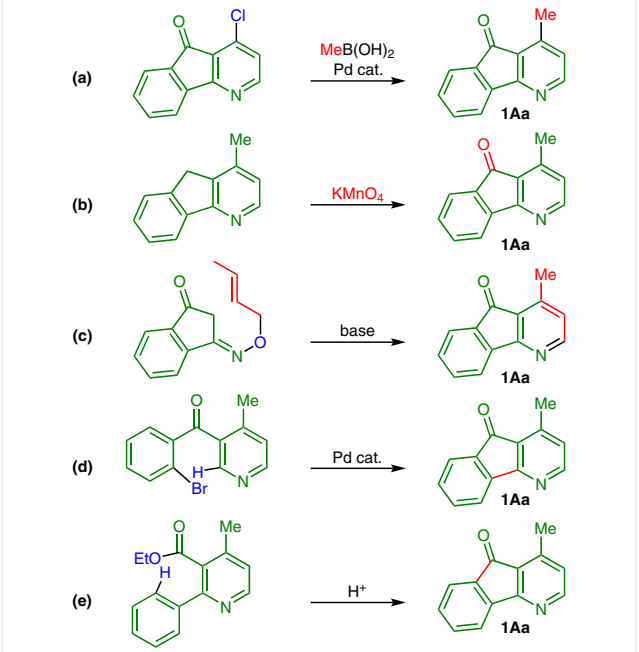
Abstract The $FeCl_3$-mediated condensation of an α-phenylenamino ester and an enone proceeds efficiently to afford a 2-phenylnicotinate. The subsequent intramolecular Friedel–Crafts reaction yielded an onychine framework. Modifications at the 2-, 3-, and 8-positions of the onychine framework were easily achieved by altering the enamino esters and enones, which facilitated the discovery of potentially bioactive compounds.

Key words onychine, polysubstituted nicotinates, iron(III) chloride, intramolecular Friedel–Crafts reaction, enone

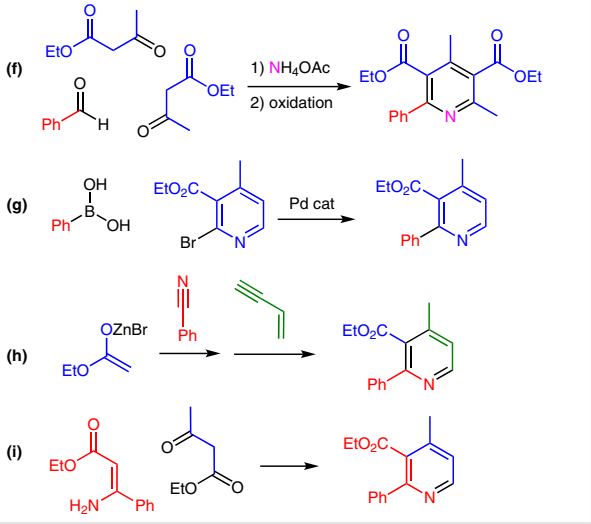
Onychine is an alkaloid isolated from the root bark of trees belonging to the Annonaceae family, such as *Onychopetalum amazonicum*,[1] *Guatteria dielsina Rodrigues, W. A.*,[2] and *Cleistopholis patens*,[3] which are large trees found throughout West Africa. The structure of onychine was determined as 4-aza-1-methylfluorenone later by Koyama et al.[4] Onychine also serves as a precursor of eupolauridine, isolated from members of the Annonaceae family such as *Eupomatia laurina R. Br.*[5] and *Cananga odorata Hook. F. et Thomas*.[6] Recently, onychine derivatives have attracted much attention because of their high bioactivity, including antifungal activity and cytotoxicity.[7] From the standpoint of finding new biologically active compounds, the development of a facile synthetic method for versatile substituted onychines is urgently required.

Several synthetic methods for onychine (**1Aa**) are shown in Scheme 1. In Methods **a**[8] and **b**,[9] **1Aa** is obtained by modification of 4-azafluorenone derivatives; however, it is not easy to construct the fundamental framework beforehand. Other approaches, including the construction of a 4-azafluorenone framework, are also reported (Methods **c**–**e**). When *O*-crotyloxime derived from 1, 3-indanedione was treated under basic conditions, **1Aa** is synthesized in a single step, which involves the rearrangement of the crotyl group followed by intramolecular condensation forming a pyridine ring (Method **c**).[10] Onychine (**1Aa**) is also obtained by forming a C–C bond between the pyridine ring and the substituent; palladium-catalyzed intramolecular cross-coupling of 3-(2-bromobenzoyl)-4-methylpyridine (Method **d**)[11] and intramolecular Friedel–Crafts acylation of ethyl 4-methyl-2-phenylnicotinate (Method **e**)[12] have been reported. Thus, while several routes to obtain onychine have been established, the difficulty in obtaining the starting materials limits the synthesis of versatile substituted onychines.



Scheme 1 Commonly routes for the synthesis of onychine (**1Aa**)

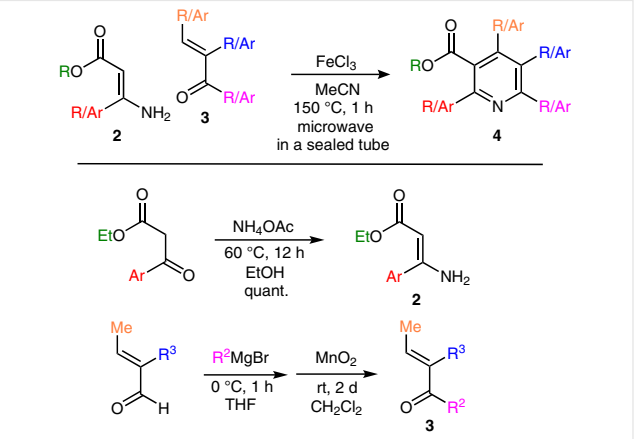
Among these routes, Method **e** is rather considered to have potential from the viewpoint of modification of the onychine framework. In Scheme 2, commonly used synthetic methods for the precursor, 4-methyl-2-phenylnicotinates, are shown. Although Hantzsch reaction (Method **f**) is the most commonly used method for synthesizing nicotinates, the products always have two ester functions, and the control of regioselectivity is necessary.[13] The Suzuki–Miyaura cross-coupling reaction (Method **g**),[14] three component condensation of zinc enolate (Method **h**),[15] and condensation of enamino ester with β-keto ester (Method **i**)[16] are also acceptable; however, modification of the starting 2-bromonicotinate, enyne, and keto ester is not easily achieved (Scheme 2). This prevents the introduction of desired substituents at the preferred position of the onychine framework via Method **e**.



Scheme 2 Common routes for the synthesis of 4-methyl-2-phenylnicotinates

Meanwhile, we recently demonstrated an efficient synthetic method for polysubstituted nicotinates through iron(III) chloride mediated condensation of an enamino ester **2** with an α,β-unsaturated carbonyl compound **3**, both of which are easily available commercially or by simple reactions. This protocol facilitates the modification of the pyridine ring by altering substrates **2** and **3** (Scheme 3).[17] Indeed, the desired alkyl/aryl groups could be introduced into the chosen positions of the nicotinate framework **4**. This feature prompted us to study the synthesis of 2-arylated nicotinates **4** and the subsequent conversion into onychines **1**, which could overcome the disadvantages of the conventional methods.

When the α-phenyl enamino ester **2A** was reacted with crotonaldehyde (**3a**) in the presence of iron(III) chloride at 150 °C, ethyl 4-methyl-2-phenylnicotinate (**4Aa**) was

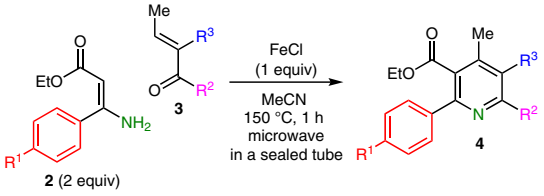


Scheme 3 Synthesis of nicotinates **4** possessing different substituents

obtained in 74% yield (Table 1, entry 1). Similarly, α-methylated aldehyde **3b** underwent the reaction to afford tetrasubstituted pyridine **4Ab** in comparable yield (entry 2). Unsaturated ketones **3c** and **3d** could also be used as substrate to give the corresponding nicotinates **4Ac** and **4Ad**, respectively (entries 3 and 4). In the case of **3c**, the low reaction efficiency could be due to the instability of the enone **3c**, causing it to decompose in air (entry 3). On the other hand, the phenyl ketone **3d** was sufficiently stable and showed similar reactivity to the unsaturated aldehyde **3a** (entry 4). Next, modification of the aryl group was studied. When the electron-rich enamino ester **2B** was used, the condensation proceeded similarly to afford the corresponding nicotinates **4Ba–4Bd** (entries 5–8). Ester **2B** is more reactive than **2A**, and reacted with **3c** before its decomposition, which resulted in the formation of **4Bc** in higher yield (entry 7). Electron-poor enamino ester **2C** also afforded nicotinate **4Ca** without significant decrease of the yield (entry 9).

Then, the ring closure of the synthesized nicotinate **4Aa**[16] was attempted under acidic conditions (Table 2). Ester **4Aa** was consumed upon heating at 180 °C in polyphosphoric acid (PPA), and **1Aa** was obtained in a yield of 20% (Table 2, entry 1). The yield of **1A** increased to 45% as the reaction temperature was increased to 220 °C (entry 2). However, the yield of **1Aa** decreased at a still higher temperature (entry 3), and the optimal temperature for the ring closure was determined to be 220 °C. Reaction time was also studied. When the reaction was stopped at 15 minutes, nicotinate **4Aa** was almost consumed, but onychine (**1Aa**) was obtained in just 6% yield. In this reaction, nicotinic acid **5** was obtained in 46% yield, suggesting that the ring closure proceeds in two steps via the nicotinic acid intermediate **5** (entry 4). Indeed, the isolated **5** was converted into onychine (**1Aa**) in 40% yield upon heating at 220 °C for 1 hour in PPA. The yield of onychine (**1Aa**) increased with the

Table 1 Synthesis of 2-Arylated Nicotinates **4**



Entry	Enamino ester **2**		Enone **3**			Product	Yield (%)
	R^1		R^2	R^3			
1	H	**2A**	H	H	**3a**	**4Aa**	74
2	H	**2A**	H	Me	**3b**	**4Ab**	60
3	H	**2A**	Me	Me	**3c**	**4Ac**	35
4	H	**2A**	Ph	H	**3d**	**4Ad**	54
5	OMe	**2B**	H	H	**3a**	**4Ba**	74
6	OMe	**2B**	H	Me	**3b**	**4Bb**	56
7	OMe	**2B**	Me	Me	**3c**	**4Bc**	50
8	OMe	**2B**	Ph	H	**3d**	**4Bd**	65
9	NO_2	**2C**	H	H	**3a**	**4Ca**	71

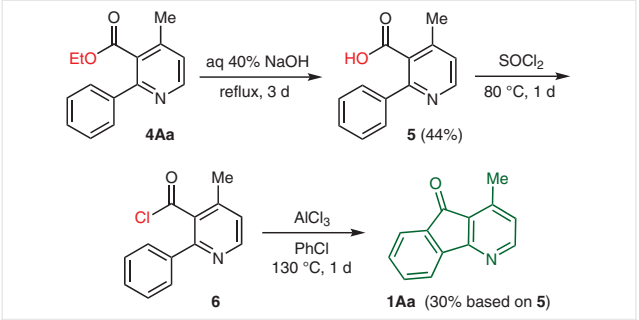
reaction time (entries 4–6), and the yield reached 56% upon heating for 1 hour (entry 6). However, no positive effect was observed for even longer reaction times (entry 7).

Table 2 Study of Reaction Conditions for the Cyclization of **4**

Entry	Temp (°C)	Time (h)	Yield of **1Aa** (%)	Recovery of **4Aa** (%)
1	180	4	20	5
2	220	4	45	0
3	240	4	33	0
4[a]	220	0.25	6	7
5	220	0.5	20	3
6	220	1	56	0
7	220	2	49	0

[a] An amount of 46% of nicotinic acid **5** was formed.

Since the cyclization was found to occur via nicotinic acid **5** in PPA, another synthetic method was studied, that involved three steps: hydrolysis of ester **4Aa**, conversion into acyl chloride **6**, and intramolecular Friedel–Crafts reaction (Scheme 4). However, the onychine (**1Aa**) was obtained in 13% overall yield, which was lower than that of the one-step ring closure of **4Aa** conducted in PPA.

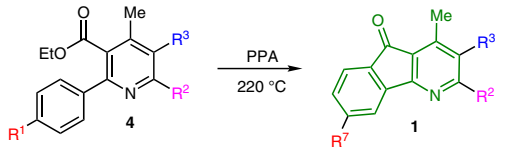


Scheme 4 Synthesis of **1Aa** from **4Aa** via nicotinic acid **5**

This protocol was applied to the substituted nicotinates **4Ab–4Ad** under the obtained optimum conditions (Table 3, entries 1–3). When nicotinates **4Ab** and **4Ac** were employed, yields of products **1Ab** and **1Ac** were somewhat lower than that of **1Aa**, which is presumably due to the steric repulsion from the adjacent methyl group or due to its electron-donating effect (entries 1 and 2). On the contrary, the nicotinate **4Ad**[15] revealed similar reactivity to **4Aa** despite the presence of a bulky phenyl group (entry 3). When 2-(4-methoxyphenyl)nicotinate **4Ba**[7a,16] was subjected to this ring closure, only a trace amount of **1Ba**[18] was detected because the methoxy group serves as an electron-withdrawing group at the *meta*-position (entry 4). Furthermore, hydrolysis of the methoxy group also occurred. This problem was addressed by carrying out the reaction for a longer duration to increase the yield of **1Ba** to 31% (entry 5). Other 2-(4-methoxyphenyl)nicotinates **4Bb–4Bd** exhibited similar reactivity to **4Ba** leading to **1Bb–1Bd**, respectively (entries 6–8). However, nicotinate **4Ca** possessing a

stronger electron-withdrawing group afforded only a complex reaction mixture under the same reaction conditions (entry 9).

Table 3 Synthesis of Other Onychine Derivatives **1**

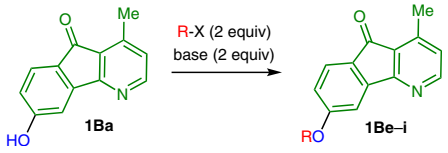


Entry	Nicotinate				Time (h)	Product		Yield (%)
	R^1	R^2	R^3			R^7		
1	H	H	Me	**4Ab**	1	H	**1Ab**	44
2	H	Me	Me	**4Ac**	1	H	**1Ac**	39
3	H	Ph	H	**4Ad**	1	H	**1Ad**	54
4	OMe	H	H	**4Ba**	1	OH	**1Ba**	3
5	OMe	H	H	**4Ba**	4	OH	**1Ba**	31
6	OMe	H	Me	**4Bb**	4	OH	**1Bb**	20
7	OMe	Me	Me	**4Bc**	4	OH	**1Bc**	13
8	OMe	Ph	H	**4Bd**	4	OH	**1Bd**	31
9	NO_2	H	H	**4Ca**	4	NO_2	**1Ca**	0

Although hydrolysis of a methoxy group occurred during the cyclization of **1Ba**, the formed phenolic hydroxy group can be modified upon treatment with electrophiles in the presence of a base (Table 4). When **1Ba** was treated with alkyl bromides in DMF, the O-alkylated products **1Be** and **1Bf** were obtained (Table 4, entries 1 and 2). Allylation was possible by treatment with allyl chloride in acetone under mild conditions to afford **1Bg** in high yield (entry 3). O-Acetylation was also achieved in a similar manner to give an ester **1Bh** (entry 4). Trifluoromethanesulfonic anhydride could also be used as an electrophile, and the corresponding triflate **1Bi** could be prepared (entry 5).

In summary, a facile method for synthesizing onychines was developed by the condensation of an enamino ester with an α,β-unsaturated carbonyl compound in the presence of $FeCl_3$, followed by intramolecular Friedel–Crafts reaction. This method facilitates the modification of the onychine framework by altering only the starting enamino esters and enones, although the electron-withdrawing group on the 2-phenyl group prevented the second cyclization step. Furthermore, hydrolysis of a methoxy group was found to occur during the cyclization when 2-(4-methoxyphenyl)nicotinate was heated in PPA. The hydroxy group was easily modified upon treatment with electrophiles such as alkyl halides, acetyl chloride, and triflic anhydride, which consequently afforded diverse onychine derivatives. The present method will be useful for research of biological activity of onychine and its derivatives.

Table 4 Modification of the Phenolic Hydroxy Group



Entry	RX	Base	Solvent	Temp (°C)	Time (h)	Product	Yield (%)
1	PrBr	K_2CO_3	DMF	80	14	**1Be**	93
2	$PhCH_2Br$	K_2CO_3	DMF	80	14	**1Bf**	67
3	AllylCl	K_2CO_3	acetone	25	5	**1Bg**	83
4	AcCl	K_2CO_3	DMF	25	14	**1Bh**	53
5	CF_3SO_2OTf	NEt_3	MeCN	25	14	**1Bi**	55

^1H and ^{13}C NMR spectra were recorded on Bruker DPX-400 spectrometer (400 MHz and 100 MHz, respectively) in $CDCl_3$ using TMS as an internal standard. The assignments of the ^{13}C NMR were performed by DEPT experiments. A Shimadzu IR spectrophotometer equipped with an ATR detector were used to record IR spectra. High-resolution mass spectra were obtained on an AB SCEIX Triplet TOF 4600 mass spectrometer. Melting points were recorded on a SRS-Optimelt automated melting point system and are uncorrected. Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification.

Ethyl 4-Methyl-2-phenylpyridine-3-carboxylate (4Aa);[16] Typical Procedure

To a solution of ethyl 3-amino-4-phenyl-2-butenoate (**2A**; 2.28 g, 12 mmol) in MeCN (15 mL) were added 2-butenal (**3a**; 0.5 mL, 6.0 mmol) and $FeCl_3$ (1.0 g, 6.0 mmol), and the resultant solution was heated at 150 °C for 1 h under microwave irradiation. After evaporation of the solvent under reduced pressure, the residue was washed with H_2O (3 × 30 mL), and then extracted with chloroform (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc 8:2) to afford **4Aa** as a yellow oil; yield: 1.04 g (74%, 4.4 mmol).

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.50 (1 H, d, *J* = 4.8 Hz), 7.52–7.49 (2 H, m), 7.36–7.32 (3 H, m), 7.06 (1 H, d, *J* = 4.8 Hz), 4.18 (2 H, q, *J* = 7.2 Hz), 2.36 (3 H, s), 0.94 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.6 (C), 149.5 (CH), 145.5 (C), 140.0 (C), 129.2 (C), 128.6 (CH), 128.3 (CH), 123.6 (CH), 61.3 (CH_2), 19.3 (CH_3), 13.6 (CH_3).

Ethyl 4,5-Dimethyl-2-phenylpyridine-3-carboxylate (4Ab)

Yield: 0.92 g (60%, 3.6 mmol): colorless plates; mp 59.1–59.9 °C.

IR (ATR): 1722, 1244, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.45 (1 H, s), 7.57–7.55 (2 H, m), 7.42–7.36 (3 H, m), 4.13 (2 H, q, *J* = 7.1 Hz), 2.32 (3 H, s), 2.31 (3 H, s), 1.02 (3 H, t, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.61 (C), 154.4 (C), 150.2 (CH), 143.5 (C), 140.1 (C), 130.7 (C), 129.3 (C), 128.3 (CH), 128.24 (CH), 128.23 (CH), 61.4 (CH_2), 16.6 (CH_3), 16.2 (CH_3), 13.6 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}NO_2$: 256.1132; found: 256.1139.

Ethyl 4,5,6-Trimethyl-2-phenylpyridine-3-carboxylate (4Ac)

Yield: 0.56 g (35%, 2.1 mmol); colorless solid; mp 96.4–96.9 °C.

IR (ATR): 1724, 1259, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.56–7.54 (2 H, m), 7.40–7.35 (3 H, m), 4.10 (2 H, q, *J* = 7.2 Hz), 2.60 (3 H, s), 2.31 (3 H, s), 2.27 (3 H, s), 0.99 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.6 (C), 157.1 (C), 152.9 (C), 142.9 (C), 140.5 (C), 128.7 (C), 128.3 (CH), 128.21 (CH), 128.17 (CH), 127.6 (C), 61.3 (CH_2), 23.6 (CH_3), 16.8 (CH_3), 14.9 (CH_3), 13.6 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}NO_2$: 270.1489; found: 270.1483.

Ethyl 4-Methyl-2,6-diphenylpyridine-3-carboxylate (4Ad)[15]

Yield: 1.03 g (54%, 3.3 mmol); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.10–8.07 (2 H, m), 7.97–7.93 (1 H, m), 7.70–7.68 (2 H, m), 7.17 (1 H, s), 7.48–7.40 (5 H, m), 4.14 (2 H, q, *J* = 7.1 Hz), 2.49 (3 H, s), 1.03 (3 H, t, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.0 (C), 157.1 (C), 156.6 (C), 146.3 (C), 140.4 (C), 138.6 (C), 129.3 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.4 (C), 127.2 (CH), 120.1 (CH), 61.3 (CH_2), 19.7 (CH_3), 13.7 (CH_3).

Ethyl 2-(4-Methoxyphenyl)-4-methylpyridine-3-carboxylate (4Ba)[16]

Yield: 1.20 g (74%, 4.4 mmol); yellow solid; mp 57.7–58.3 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.53 (1 H, d, *J* = 5.0 Hz), 7.54 (2 H, d, *J* = 8.9 Hz), 7.09 (1 H, d, *J* = 5.0 Hz), 6.94 (2 H, d, *J* = 8.9 Hz), 4.17 (2 H, q, *J* = 7.1 Hz), 3.84 (3 H, s), 2.40 (3 H, s), 1.01 (3 H, t, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.9 (C), 160.1 (C), 156.1 (C), 149.5 (CH), 145.3 (C), 132.6 (C), 129.6 (CH), 123.1 (CH), 113.7 (CH), 61.4 (CH_2), 55.3 (CH_3), 19.3 (CH_3), 13.8 (CH_3).

Ethyl 2-(4-methoxyphenyl)-4,5-dimethylpyridine-3-carboxylate (4Bb)

Yield: 0.96 g (56%, 3.4 mmol); yellow solid; mp 75.6–76.3 °C.

IR (ATR): 1719, 1248, 1176 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.42 (1 H, s) 7.52 (2 H, d, *J* = 8.8 Hz), 6.93 (2 H, d, *J* = 8.8 Hz), 4.17 (2 H, q, *J* = 7.2 Hz), 3.83 (3 H, s), 2.30 (3 H, s), 2.29 (3 H, s), 1.09 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.4 (C), 159.9 (C), 153.9 (C), 150.2 (CH), 143.3 (C), 132.7 (C), 130.2 (C), 129.6 (CH), 129.5 (CH), 129.0 (C), 113.9 (CH), 113.7 (CH), 61.4 (CH_2), 55.3 (CH_3), 16.6 (CH_3), 16.2 (CH_3), 13.8 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}NO_3$: 286.1438; found: 286.1424.

Ethyl2-(4-Methoxyphenyl)-4,5,6-trimethylpyridine-3-carboxylate (4Bc)

Yield: 0.90 g (50%, 3.0 mmol); yellow solid; mp 85.9–86.8 °C.

IR (ATR): 1718, 1515, 1248, 1173 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51 (2 H, d, *J* = 8.8 Hz), 6.92 (2 H, d, *J* = 8.8 Hz), 4.14 (2 H, q, *J* = 7.1 Hz), 3.82 (3 H, s), 2.58 (3 H, s), 2.29 (3 H, s), 2.25 (3 H, s), 1.07 (3 H, t, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.8 (C), 159.8 (C), 156.9 (C), 152.3 (C), 142.7 (C), 133.0 (C), 130.9 (CH), 130.6 (CH), 129.6 (CH), 128.2 (C), 127.4 (C), 113.7 (CH), 61.2 (CH_2), 55.3 (CH_3), 23.6 (CH_3), 16.8 (CH_3), 14.9 (CH_3), 13.8 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}NO_3$: 300.1594; found: 300.1580.

Ethyl 2-(4-Methoxyphenyl)-4-methyl-6-phenylpyridine-3-carboxylate (4Bd)

Yield: 1.35 g (65%, 3.9 mmol); yellow oil.

IR (ATR): 1718, 1514, 1268, 1250, 1177, 1093, 694 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.09 (2 H, d, *J* = 6.8 Hz), 7.67 (2 H, d, *J* = 8.8 Hz), 7.53 (1 H, br q, *J* = 0.4 Hz), 7.48–7.41 (3 H, m), 6.96 (2 H, d, *J* = 8.8 Hz), 4.20 (2 H, q, *J* = 7.1 Hz), 3.85 (3 H, s), 2.47 (3 H, br d, *J* = 0.4 Hz), 1.11 (3 H, t, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.4 (C), 157.0 (C), 160.2 (C), 156.0 (C), 146.2 (C), 138.8 (C), 133.0 (C), 129.9 (CH), 129.3 (CH), 128.7 (CH), 127.2 (CH), 127.1 (C), 119.6 (CH), 113.7 (CH), 61.4 (CH_2), 55.4 (CH_3), 19.7 (CH_3), 13.9 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}NO_3$: 348.1594; found: 348.1596.

Ethyl 4-Methyl-2-(4-nitrophenyl)pyridine-3-carboxylate (4Ca)

Yield: 1.22 g (71%, 4.3 mmol); yellow oil.

IR (ATR): 1725, 1523, 1349 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.60 (1 H, d, *J* = 5.4 Hz), 8.28 (2 H, d, *J* = 8.8 Hz), 7.76 (2 H, d, *J* = 8.8 Hz), 7.24 (1 H, d, *J* = 5.4 Hz), 4.16 (2 H, q, *J* = 7.1 Hz), 2.46 (3 H, s), 1.08 (3 H, t, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_3), 19.5 (CH_3), 61.8 (CH_2), 123.5 (CH), 123.8 (C), 124.8 (CH), 129.4 (CH), 146.2 (C), 146.3 (C), 147.9 (C), 149.9 (CH), 154.3 (C), 167.8 (C).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_2O_4$: 287.1026; found: 287.1025.

4-Methyl-2-phenylpyridine-3-carboxylic Acid (5)

To a solution of NaOH (3.2 g, 80 mmol) in H_2O (8 mL) was added ethyl 4-methyl-2-phenylpyridine-3-carboxylate (**4Aa**; 484 mg, 2.0 mmol), and the resultant solution was heated at 100 °C for 3 d. After washing with CH_2Cl_2 (3 × 30 mL), the pH value of the aqueous layer was adjusted to 4, and concentrated under reduced pressure. The residue was extracted with hot MeOH (3 × 10 mL), and the MeOH was evaporated. The residue was subjected to flash column chromatography on silica gel (MeOH/CH_2Cl_2 1:3) to afford **5** as a white powder; yield: 188 mg (44%, 0.88 mmol); mp 100.5–101.2 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.50 (2 H, d, *J* = 4.9 Hz), 7.70–7.68 (2 H, m), 7.43–7.41 (3 H, m), 7.26 (1 H, d, *J* = 4.9 Hz), 3.17 (1 H, s), 2.34 (3 H, s).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.3 (C), 153.5 (C), 148.3 (CH), 143.6 (C), 140.0 (C), 128.3 (CH), 128.2 (CH), 127.9 (CH), 123.6 (CH), 18.9 (CH_3).

4-Methyl-5*H*-indeno[1, 2-*b*] pyridin-5-one (Onychine, 1Aa);[8–12] **Typical Procedure**

A solution of ethyl 4-methyl-2-phenylpyridine-3-carboxylate (**4Aa**; 33.2 mg, 0.14 mmol) in polyphosphoric acid (1 mL) was heated at 220 °C for 1 h. After the pH value of the mixture was adjusted to 8, the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic

layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford onychine (**1Aa**) as yellow needles; yield: 15.3 mg (56%, 0.078 mmol); mp 137.2–137.4 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (1 H, d, *J* = 5.3 Hz), 7.79 (1 H, dd, *J* = 7.4, 1.1 Hz), 7.62 (1 H, dd, *J* = 7.4, 1.1 Hz), 7.51 (1 H, ddd, *J* = 7.4, 7.4, 1.1 Hz), 7.35 (1 H, ddd, *J* = 7.4, 7.4, 1.1 Hz), 6.91 (1 H, d, *J* = 5.3 Hz), 2.63 (3 H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 192.8 (C), 164.7 (C), 151.9 (CH), 148.2 (C), 142.4 (C), 135.1 (CH), 134.8 (C), 131.1 (CH), 126.1 (C), 126.0 (CH), 123.8 (CH), 121.3 (CH), 17.4 (CH_3).

3,4-Dimethyl-5*H*-indeno[1, 2-*b*] pyridin-5-one (1Ab)

Yield: 12.9 mg (44%, 0.062 mmol); yellow needles; mp 144.6–145.3 °C.

IR (ATR): 1711, 746 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.28 (s, 1 H), 7.78 (1 H, dd, *J* = 7.6, 1.2 Hz), 7.66 (1 H, dd, *J* = 7.6, 1.2 Hz), 7.55 (1 H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.38 (1 H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 2.58 (3 H, s), 2.27 (3 H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.7 (C), 163.4 (C), 153.0 (CH), 146.7 (C), 143.1 (C), 135.1 (C), 134.9 (CH), 133.3 (C), 130.4 (CH), 125.6 (C), 123.7 (CH), 120.4 (CH), 16.1 (CH_3), 13.4 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}NO$: 210.0913; found: 210.0912.

2,3,4-Trimethyl-5*H*-indeno[1, 2-*b*] pyridin-5-one (1Ac)

Yield: 12.2 mg (39%, 0.055 mmol); yellow needles; mp 154.5–155.4 °C.

IR (ATR): 1706, 886, 745 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.70 (1 H, d, *J* =7.4 Hz), 7.56 (1 H, d, *J* = 7.4 Hz), 7.44 (1 H, ddd, *J* = 7.4, 7.4, 1.2 Hz), 7.28 (1 H, ddd, *J* = 7.4, 7.4, 1.2 Hz), 2.51 (3 H, s), 2.50 (3 H, s), 2.13 (3 H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 192.8 (C), 161.3 (C), 160.1 (C), 145.1 (C), 142.1 (C), 134.2 (C), 133.6 (CH), 129.9 (C), 129.1 (CH), 123.0 (C), 122.4 (CH), 119.2 (CH), 23.0 (CH_3), 13.3 (CH_3), 12.6 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}NO$: 224.1069; found: 224.1070.

4-Methyl-2-phenyl-5*H*-indeno[1, 2-*b*] pyridin-5-one (1Ad)[19]

Yield: 20.6 mg (54%, 0.076 mmol); yellow solid; mp 121.3–121.6 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11 (2 H, d, *J* = 6.6 Hz), 7.93 (1 H, d, *J* = 7.4 Hz), 7.69 (1 H, d, *J* = 7.4 Hz), 7.57 (1 H, t, *J* = 7.4 Hz), 7.52–7.38 (5 H, m), 2.67 (3 H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.1 (C), 165.7 (C), 160.8 (C), 147.8 (C), 143.2 (C), 138.5 (C), 135.6 (C), 134.7 (CH), 130.7 (CH), 129.8 (CH), 128.8 (CH), 127.3 (CH), 124.5 (C), 123.5 (CH), 122.2 (CH), 120.9 (CH), 17.6 (CH_3).

8-Hydroxy-4-methyl-5*H*-indeno[1, 2-*b*] pyridin-5-one (1Ba)

Yield: 9.2 mg (31%, 0.043 mmol); yellow solid; mp 225.2–225.7 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.40 (1 H, d, *J* = 5.3 Hz), 7.64 (1 H, d, *J* = 7.4 Hz), 7.08–7.04 (3 H, m), 2.67 (3 H, s).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 192.6 (C), 165.1 (C), 160.4 (C), 152.8 (CH), 146.6 (C), 136.4 (C), 133.2 (C), 124.9 (C), 124.7 (CH), 122.1 (CH), 121.1 (CH), 110.4 (CH), 16.6 (CH_3).

8-Hydroxy-3,4-dimethyl-5*H*-indeno[1, 2-*b*] pyridin-5-one (1Bb)

Yield: 6.3 mg (20%, 0.028 mmol); yellow needles; mp 144.0–144.9 °C.

IR (ATR): 1719, 1515, 1295, 1250, 1176 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.2–10.3 (1 H, br), 8.29 (1 H, s), 7.59 (1 H, d, *J* = 7.8 Hz), 7.05–7.02 (2 H, m), 2.53 (3 H, s), 2.25 (3 H, s).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 193.0 (C), 163.3 (C), 160.0 (C), 152.6 (CH), 145.9 (C), 136.5 (C), 133.3 (C), 131.9 (C), 124.5 (C), 121.7 (CH), 121.2 (CH), 110.4 (CH), 15.3 (CH_3), 12.9 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}NO_2$: 226.0862; found: 226.0872.

8-Hydroxy-2,3,4-trimethyl-5*H*-indeno[1,2-*b*]pyridin-5-one (1Bc)

Yield: 4.4. mg (13%, 0.02 mmol); yellow solid; mp 143.0–143.4 °C.

IR (ATR): 1720, 1271 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.7–9.8 (1 H, br), 7.54 (1 H, d, *J* = 8.7 Hz), 7.01–6.99 (2 H, m), 2.52 (3 H, s), 2.52 (3 H, s), 2.17 (3 H, s).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 193.0 (C), 162.2 (C), 160.7 (C), 159.9 (C), 145.4 (C), 136.7 (C), 133.2 (C), 129.3 (C), 122.9 (C), 121.5 (CH), 120.8 (CH), 110.4 (CH), 23.7 (CH_3), 13.7 (CH_3), 13.1 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}NO_2$: 240.1019; found: 240.1029.

8-Hydroxy-2-phenyl-4-methyl-5*H*-indeno[1,2-*b*]pyridin-5-one (1Bd)

Yield: 12.5 mg (31%, 0.043 mmol); yellow solid; mp 191.2–191.7 °C.

IR (ATR): 1709, 1570, 1290, 1250, 803 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.9–9.8 (1 H, br), 8.14–8.12 (2 H, m), 7.73 (1 H, d, *J* = 8.0 Hz), 7.67 (1 H, s), 7.59–7.55 (3 H, m), 7.08–7.06 (2 H, m), 2.62 (3 H, s).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 192.2 (C), 165.5 (C), 160.5 (C), 159.2 (C), 147.4 (C), 137.7 (C), 137.2 (C), 133.1 (C), 129.9 (CH), 128.8 (CH), 127.1 (CH), 123.8 (C), 122.2 (CH), 121.0 (CH), 120.7 (CH), 110.4 (CH), 17.0 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}NO_2$: 288.1019; found: 288.1018.

4-Methyl-8-propoxy-5*H*-indeno[1,2-*b*]pyridin-5-one (1Be); Typical Procedure

To a solution of 7-hydroxy-4-methyl-5*H*-indeno[1, 2-*b*] pyridin-5-one (**1Ba**; 1.0 mg, 4.7 µmol) in DMF (1 mL), 1-bromopropane (0.71 µL, 9.5 µmol) was added, and the resultant solution was heated at 80 °C for 14 h. After evaporation, the residue was washed with H_2O (10 mL), and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **1Be** as a yellow solid; yield: 1.1 mg (93%, 4.3 µmol); mp 79.7–80.5 °C.

IR (ATR): 1716, 1567 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (1 H, d, *J* = 5.2 Hz), 7.71 (1 H, d, *J* = 8.4 Hz), 7.20 (1 H, d, *J* = 2.4 Hz), 7.06 (1 H, dd, *J* = 2.4, 8.4 Hz), 6.87 (1 H, d, *J* = 5.2 Hz), 3.99 (2 H, t, *J* = 6.4 Hz), 2.60 (3 H, s), 1.84 (2 H, tq, *J* = 6.4, 7.2 Hz), 1.06 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.2 (C), 165.8 (C), 161.9 (C), 152.7 (CH), 147.3 (C), 136.9 (C), 135.3 (C), 126.1 (C), 124.8 (CH), 122.1 (CH), 120.9 (CH), 109.5 (CH), 70.2 (CH_2), 22.5 (CH_2), 17.3 (CH_3), 10.4 (CH_3).

HRMS (ESI/TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}NO_2$: 254.1175; found: 254.1183.

8-Benzyloxy-4-methyl-5*H*-indeno[1, 2-*b*] pyridin-5-one (1Bf)

Yield: 0.95 mg (67%, 3.2 μmol); yellow needles; mp 140.3–141.1 °C.

IR (ATR): 1708, 1566, 1292, 999, 740 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (1 H, d, *J* = 5.2 Hz), 7.73 (1 H, d, *J* = 8.0 Hz), 7.45–7.36 (5 H, m), 7.29 (1 H, d, *J* = 2.4 Hz), 7.14 (1 H, dd, *J* = 2.4, 8.0 Hz), 6.87 (1 H, d, *J* = 5.2 Hz), 5.14 (2 H, s), 2.59 (3 H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.0 (C), 165.7 (C), 161.4 (C), 152.8 (CH), 147.4 (C), 136.9 (C), 136.2 (C), 135.8 (C), 128.7 (CH), 128.3 (CH), 127.5 (CH), 126.1 (C), 124.9 (CH), 122.1 (CH), 121.3 (CH), 109.9 (CH), 70.6 (CH_2), 17.3 (CH_3).

HRMS (ESI/TOF): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{16}NO_2$: 302.1175; found: 302.1175.

4-Methyl-8-(3-propenyloxy)-*5H*-indeno[1,2-*b*]pyridin-5-one (1Bg)

Yield: 0.98 mg (83%, 3.9 μmol); yellow needles; mp 80.9–81.9 °C.

IR (ATR): 1710, 1599, 1567 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (1 H, d, *J* = 5.6 Hz), 7.72 (1 H, d, *J* = 8.4 Hz), 7.22 (1 H, d, *J* = 2.4 Hz), 7.08 (1 H, dd, *J* = 8.4, 2.4 Hz), 6.88 (1 H, d, *J* = 5.6 Hz), 6.05 (1 H, ddt, *J* = 17.6, 10.4, 5.2 Hz), 5.42 (1 H, ddt, *J* = 17.6, 1.6, 1.6 Hz), 5.34 (1 H, ddt, *J* = 10.4, 1.6, 1.6 Hz), 4.62 (2 H, ddd, *J* = 5.2, 1.6, 1.6 Hz), 2.60 (3 H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.1 (C), 165.7 (C), 161.3 (C), 152.8 (CH), 147.4 (C), 136.9 (C), 135.7 (C), 132.5 (CH), 126.1 (C), 124.9 (CH), 122.1 (CH), 121.2 (CH), 118.2 (CH_2), 109.7 (CH), 69.27 (CH_2), 17.3 (CH_3).

HRMS (ESI/TOF): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{15}NO_2$: 252.1019; found: 252.1031.

8-Acetoxy-4-methyl-5*H*-indeno[1,2-*b*]pyridin-5-one (1Bh)

Yield: 0.63 mg (53%, 2.5 μmol); yellow oil.

IR (ATR): 1766, 1716, 1600, 1570, 1195, 740 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.41 (1 H, d, *J* = 5.2 Hz), 7.84 (1 H, d, *J* = 8.0 Hz), 7.43 (1 H, d, *J* = 2.4 Hz), 7.28 (1 H, dd, *J* = 8.0, 2.4 Hz), 6.96 (1 H, d, *J* = 5.2 Hz), 2.62 (3 H, s), 2.33 (3 H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.9 (C), 167.9 (C), 163.7 (C), 152.0 (CH), 151.9 (C), 146.8 (C), 138.3 (C), 135.4 (C), 126.8 (CH), 125.3 (C), 124.7 (CH), 120.8 (CH), 116.5 (CH), 20.0 (CH_3), 16.3 (CH_3).

HRMS (ESI/TOF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}NO_3$: 254.0811; found: 254.0821.

4-Methyl-8-(trifluoromethanesulfonyloxy)-5*H*-indeno[1, 2-*b*] pyridin-5-one (1Bi)

Yield: 0.89 mg (55%, 2.6 μmol); yellow needles; mp 95.3–96.0 °C.

IR (ATR): 1716, 1573, 1213, 1139, 732 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.47 (1 H, d, *J* = 5.2 Hz), 7.94 (1 H, d, *J* = 8.0 Hz), 7.59 (1 H, d, *J* = 8.0 Hz), 7.49 (1 H, d, *J* = 8.0, 2.4 Hz), 7.04 (1 H, d, *J* = 5.2 Hz), 2.65 (3 H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.7 (C), 163.8 (C), 153.5 (CH), 151.2 (C), 148.2 (C), 142.8 (C), 136.9 (C), 127.5 (CH), 126.4 (CH), 122.5 (CH), 117.1 (CH), 17.5 (CH_3).

HRMS (ESI/TOF): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_9F_3NO_4S$: 344.0198; found: 344.0208.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612058.

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