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Synthesis of 2,6-disubstituted pyrido[2,3-*b*][1,4]oxazines

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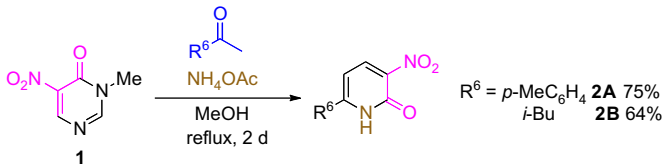
ABSTRACT

A new preparative method for pyrido[2,3-*b*][1,4]oxazines from 6-substituted 3-nitro-2-pyridones is demonstrated. This method consists of two steps: O-alkylation and reductive cyclization. In the former step, the bulkiness of both starting nitropyridones and C2 reagents is found to be essential for avoiding N-alkylation, which undergoes O-alkylation efficiently. The subsequent reductive cyclization affords pyridoxazines with carbon substituents at both the 2- and the 6-positions that have not been available.

1. Introduction

Ring transformation that uses electron-deficient heterocyclic compounds is one of the powerful methods for synthesizing polyfunctionalized compounds that are not easily prepared by an alternative procedure.[1–3] 3-Methyl-5-nitropyrimidin-4(3*H*)-one (**1**) serves as an excellent substrate for this reaction, which proceeds three components ring transformation with ketones in the presence of ammonium acetate to afford 6-substituted 3-nitropyridin-2(1*H*)-ones **2** (Scheme 1).[4–6] The vicinal functionalities of **2** are considered to be useful for approaching for [*b*]-fused bicyclic pyridines; thus, we focused on the construction of an 1,4-oxazine ring whose oxygen atom is derived from a 2-oxo group and nitrogen atom is derived from a 3-nitro group. Namely, the introduction of a C2 unit on the oxo group and the subsequent reductive cyclization are studied for synthesizing pyrido[2,3-*b*][1,4]oxazines (PyOAs).



Scheme 1. Ring transformation affording nitropyridones **2**.

Fused 1,4-oxazines are often seen as a partial structure in natural products and pharmaceuticals; however, most of the synthetic studies are focused on benzo[1,4]oxazines,[7–10] pyrido[3,2-*b*]oxazines,[11,12] and pyrimido[2,3-*b*][1,4]oxazines.[13] On the contrary, only several synthetic studies have been reported with regard to PyOAs. One preparative method for PyOAs uses 3-amino-2-chloropyridines[14,15] or 3-nitro-2-chloropyridines[16,17] as precursors by modifying a nitrogen substituent at the 3-position and by substituting a 2-chloro group with nucleophilic alkoxide. 2-Bromo-3-hydroxypyridines can be used as precursors although an oxygen atom is substituted at the 3-position, in which Smile rearrangement proceeds after condensation of a 3-hydroxy group with α-chloroacetamide.[18] On the other hand, several other preparative methods employing 2-pyridones as starting materials are also reported. When 3-bis(2-chloroethyl)amino-2-pyridone is used, the oxo group undergoes nucleophilic substitution at one of the chloro atoms to yield PyOA having a 2-chloroethyl group at the 1-position.[19] In the case of 3,5-dinitropyridone, O-alkylation with 1,2-dichloroethane followed by reductive cyclization leads to PyOA.[20] These preparative methods are surely easy; however, the scarce availability of multiple substituted pyridines significantly limits substituents that can be introduced in the PyOA framework. Namely, only oxy and oxo groups are seen at the 2-position of PyOAs.[14–20] With regard to the 6-position, carbon substituents cannot be introduced except at a few instances.[21–25]

From this viewpoint, nitropyridones **2** in Scheme 1 are suitable precursors for PyOAs having an aryl and an alkyl group at the 6-position since the substituent at this position is modified easily by changing ketone that is used for the ring transformation. In the

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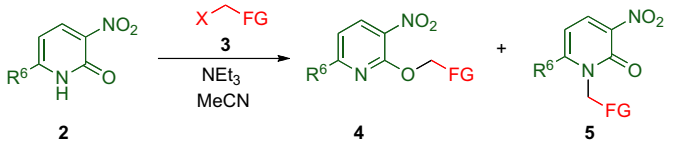
present study, we employ pyridones **2A** and **2B** derived from *p*-methylacetophenone and 4-methyl-2-pentanone, respectively,[4–6] and unsubstituted pyridone **2C**.[26] Furthermore, we also attempt to modify the 2-position of PyOA by using C2 reagents such as phenacyl bromide **3a**, chloroacetone **3b**, bromoacetonitrile **3c**, and ethyl chloroacetate **3d**. As a result, various PyOAs having substituents at the 2- and the 6-positions will be conveniently synthesized by changing a combination of pyridones **2** and C2 reagents **3**.

2. Results and discussion

When pyridone **2A** was allowed to react with phenacyl bromide **3a** in the presence of triethylamine in acetonitrile, O-phenacylation proceeded efficiently so as to afford **4Aa** in 94% yield (Table 1, run 1). Although N-phenacylation leading to **5Aa** is also possible, the observation of only single absorption of a carbonyl group at 1697 cm^{-1} in the IR spectrum indicated that the product was **4Aa**. Similarly isobutylpyridone **2B** underwent the reaction to yield *O*-phenacylated product **4Ba** (run 2). Contrary to these results, unsubstituted pyridone **2C** (R^6=H) afforded *N*-phenacylated product **5Ca** whose IR spectrum exhibited two absorptions for carbonyl groups at 1692 and 1671 cm^{-1} (run 3). In addition, the structure of **5Ca** was supported by the observation of a correlation between a methylene group and a proton at the 6-position in the ^1H–^1H NOESY 2D spectrum. Other C2 reagents **3b–d** also reacted with pyridones **2A** and **2B** to afford corresponding *O*-alkylated products **4Ab–d** and **4Bb–d**, respectively, despite the necessity of reflux conditions (runs 4–9). In a combination of **2B** and small C2 reagent **3c**, two kinds of cyanomethylated products were formed. The major product was **4Bc** and the minor one was tentatively assigned to *N*-alkylated product **5Bc** by ^1H NMR of a mixture with **4Bc** because of difficult isolation (run 7). In the present reaction, O-alkylation precedes while alkylation of 2-pyridones[27–31] or 2-quinolones[32–34] tends to afford more stable *N*-alkylated products.[35,36] The formation of **5Ca** indicates congestion around a ring nitrogen and is necessary for causing O-alkylation predominantly, which consequently enables the subsequent construction of a [*b*]-fused oxazine ring.

Table 1
O-Alkylation of nitropyridones **2**



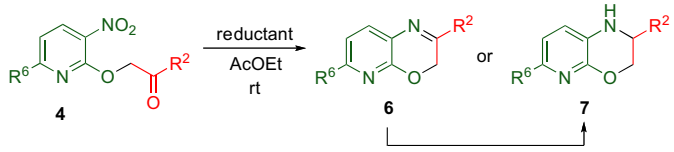
2 **4** **5**

Run	Nitropyridine		C2 Reagent			Conditions			Yield/%	
	R^6		FG	X		Temp/°C	Time/h		**4**	**5**
1	*p*-Tol	**2A**	PhCO	Br	**3a**	rt	24	**Aa**	94	0
2	*i*-Bu	**2B**	PhCO	Br	**3a**	rt	24	**Ba**	70	0
3	H	**2C**	PhCO	Br	**3a**	rt	24	**Ca**	0	90
4	*p*-Tol	**2A**	MeCO	Cl	**3b**	80	10	**Ab**	88	0
5	*i*-Bu	**2B**	MeCO	Cl	**3b**	80	10	**Bb**	64	0
6	*p*-Tol	**2A**	CN	Br	**3c**	80	10	**Ac**	62	0
7	*i*-Bu	**2B**	CN	Br	**3c**	80	10	**Bc**	46[a]	28[a]
8	*p*-Tol	**2A**	COOEt	Cl	**3d**	80	10	**Ad**	94	0
9	*i*-Bu	**2B**	COOEt	Cl	**3d**	80	10	**Bd**	69	0

[a] Determined by ^1H NMR.

Next, reductive cyclization was studied. When *O*-phenacylated pyridine **4Aa** was treated with tin(II) chloride in ethyl acetate, the reaction mixture was complicated; however, it was successful to isolate the desired 2,6-disubstituted PyOA **6Aa** in 27% yield from the reaction mixture (Table 2, run 1). Further, PyOA **6Ba** was isolated in 12% yield from **4Ba** in a similar manner (run 2). The complication of the reaction mixture could be avoided by using Raney nickel under hydrogen atmosphere, and PyOAs **6Aa** and **6Ba** were afforded in considerably improved 78% and 61% yields, respectively (runs 3 and 4). In cases of *O*-acetylmethyl derivatives **4Ab** and **4Bb**, PyOAs **7Ab** and **7Bb** were obtained instead of **6Ab** and **6Bb** as a result of further hydrogenation because the C=N bond is not conjugated with a substituent at the 2-position (runs 5 and 6). On the other hand, the reductive cyclizations of *O*-cyanomethylpyridines **4Ac** and **4Bc** failed yielding complex mixtures without any detectable bicyclic products formed via amidine intermediate[37,38] under the employed conditions. Since *O*-(ethoxycarbonyl)methylpyridines **4Ad** and **4Bd** were less reactive than *O*-acylmethyl derivatives, only the reduction of a nitro group occurred without cyclization leading to 3-aminopyridines **8Ad** and **8Bd**, respectively. The cyclizations of **8Ad** and **8Bd** were successfully performed upon treatment with *p*-toluenesulfonic acid to afford lactam-type PyOAs **9Ad** and **9Bd** in high yields (Scheme 2).

Table 2
Reductive cyclization leading to PyOAs **6** and **7**



4 **6** **7**

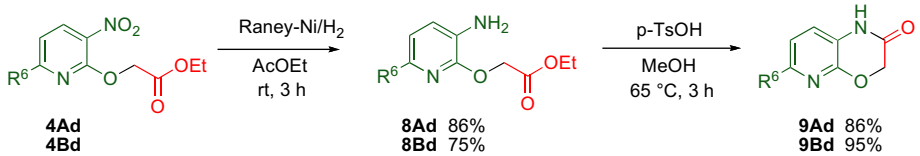
Run	Nitropyridine	Reductant	Time/h	Product			Yield/%
				R^6	R^2		
1	**4Aa**	$SnCl_2$	24	*p*-Tol	Ph	**6Aa**	27
2	**4Ba**	$SnCl_2$	24	*i*-Bu	Ph	**6Ba**	12
3	**4Aa**	Raney-Ni/H_2	3	*p*-Tol	Ph	**6Aa**	78
4	**4Ba**	Raney-Ni/H_2	3	*i*-Bu	Ph	**6Ba**	61
5	**4Ab**	Raney-Ni/H_2	3	*p*-Tol	Me	**7Ab**	58
6	**4Bb**	Raney-Ni/H_2	3	*i*-Bu	Me	**7Bb**	79

In summary, we have presented a novel preparative method for PyOAs having substituents at the 2- and the 6-positions. The 2-position of PyOA can be modified by changing C2 reagents and the 6-position can be modified by changing ketone in a step of the ring transformation. Since all experiments require only simple manipulations, this method is applicable for the preparation of versatile 2,6-disubstituted PyOAs that are useful in the research of new biologically active compounds.

3. Experimental

3.1. General

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. All the reagents and solvents were commercially available and used as received. The ^1H



4Ad **4Bd** **8Ad** 86% **8Bd** 75% **9Ad** 86% **9Bd** 95%

Scheme 2. Synthesis of 6-subsitituted 2-oxo-PyOAs **9Ad** and **9Bd**.

NMR spectra were measured on a Bruker DPX-400 with TMS as an internal standard, and the ^{13}C NMR spectra were measured on a Bruker DPX-400 or JEOL AL-400 spectrometer at 100 MHz. Assignments of ^{13}C NMR spectra were performed by DEPT experiments. The IR spectra were recorded on a JASCO FT/IR-4200 Spectrophotometer. The mass spectra were recorded on a JEOL JMS-AX505HA. The elemental microanalyses were performed using a Yanaco MT-6 CHN corder.

3.2. O-Phenacylation of nitropyridone 2A

To a solution of pyridone **2A** (114 mg, 0.5 mmol) in acetonitrile (10 mL), phenacyl bromide (398 mg, 2 mmol), and triethylamine (0.35 mL, 2.5 mmol) were added, and the resultant mixture was stirred at room temperature for 1 day. After removal of the solvent under reduced pressure, the residue was treated with column chromatography on silica gel to afford *O*-phenacylated product **4Aa** (eluted with chloroform, 164 mg, 0.47 mmol, 94% yield). Reactions of other pyridones and C2 reagents were performed in a similar way.

3.3. 2-Benzoylmethoxy-6-(4-methylphenyl)-3-nitropyridine 4Aa

Pale yellow solid. Mp 148–149 °C (dec). ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 5.81 (s, 2H), 7.13 (d, J=8.2 Hz, 2H), 7.44 (d, J=8.2 Hz, 1H), 7.52 (dd, J=8.2, 7.8 Hz, 2H), 7.66 (t, J=7.8 Hz, 1H), 7.69 (d, J=8.2 Hz, 2H), 8.03 (d, J=8.2 Hz, 2H), 8.43 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3), 68.7 (CH_2), 113.1 (CH), 125.9 (CH), 127.4 (CH), 128.0 (CH), 128.9 (CH), 129.6 (CH), 133.6 (C), 133.8 (C), 134.8 (C), 136.8 (CH), 141.3 (C), 154.9 (C), 160.3 (C), 193.3 (C); IR (KBr) 1697, 1579, 1373 cm^{-1}; MS (FAB) 349 (M^++1, 100). Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.97; H, 4.60; N, 8.05. Found: C, 68.80; H, 4.69; N, 8.01.

3.4. 2-Benzoylmethoxy-6-isobutyl-3-nitropyridine 4Ba

Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J=6.6 Hz, 6H), 1.8–2.0 (m, 1H), 2.47 (d, J=7.1 Hz, 2H), 5.75 (s, 2H), 6.83 (d, J=8.1 Hz, 1H), 7.51 (dd, J=7.3, 7.1 Hz, 2H), 7.62 (tt, J=7.3, 1.4 Hz, 1H), 7.97 (dd, J=7.1, 1.4 Hz, 2H), 8.27 (d, J=8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2 (CH_3), 28.5 (CH), 46.8 (CH_2), 68.3 (CH_2), 117.1 (CH), 127.8 (CH), 128.8 (CH), 131.3 (C), 133.7 (CH), 134.6 (C), 135.8 (CH), 154.6 (C), 165.7 (C), 193.1 (C); IR (neat) 1705, 1519, 1344 cm^{-1}; MS (FAB) 315 (M^++1, 100). Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.97; H, 5.73; N, 8.92. Found: C, 65.64; H, 5.73; N, 8.29.

3.5. 1-Benzoylmethyl-3-nitro-2-pyridone 5Ca

Yellowish brown needles. Mp 143–144 °C (dec). ^1H NMR (400 MHz, DMSO-d_6) δ 5.70 (s, 2H), 6.55 (dd J=7.7, 6.6 Hz, 1H), 7.62 (dd, J=7.6, 7.3 Hz, 2H), 7.75 (t, J=7.6 Hz, 1H), 8.08 (d, J=7.3 Hz, 1H), 8.18 (dd, J=6.6, 2.0 Hz, 1H), 8.51 (dd, J=7.7, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 58.9 (CH_2), 106.5 (CH), 131.0 (CH), 132.0 (CH), 132.2 (C), 137.2 (CH), 141.0 (CH), 142.5 (C), 150.1 (CH), 156.6 (C), 195.0 (C); IR (KBr) 1692, 1671, 1536, 1349 cm^{-1}; MS (FAB) 259 (M^++1, 100). Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.88; N, 10.85. Found: C, 60.41; H, 3.91; N, 10.92.

3.6. 2-Acetylmethoxy-6-(4-methylphenyl)-3-nitropyridine 4Ab

Yellow solid. Mp 166–167 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.42 (s, 3H), 5.11 (s, 2H), 7.29 (d, J=8.2 Hz, 2H), 7.49 (d, J=8.4 Hz, 1H), 7.84 (d, J=8.2 Hz, 2H), 8.44 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3), 26.5 (CH_3), 71.1 (CH_2), 113.2 (CH), 127.4 (CH), 129.8 (CH), 131.4 (C), 133.5 (C), 133.8 (C), 136.8 (CH), 141.6 (C), 154.7 (C), 159.5 (C), 203.6 (C); IR (KBr) 1722, 1582, 1334 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.94; H, 4.90; N, 9.79. Found: C, 62.88; H, 5.03; N, 9.86.

3.7. 2-Acetylmethoxy-6-isobutyl-3-nitropyridine 4Bb

Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J=6.7 Hz, 6H), 2.0–2.1 (m, 1H), 2.26 (s, 3H), 2.59 (d, J=7.2 Hz, 2H), 5.02 (s, 2H), 6.88 (d, J=8.1 Hz, 1H), 8.28 (d, J=8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (CH_3), 26.4 (CH), 28.7 (CH_3), 47.0 (CH_2), 70.7 (CH_2), 117.2 (CH), 131.3 (C), 135.9 (CH), 154.5 (C), 165.9 (C), 203.2 (C); IR (neat) 1738, 1519, 1345 cm^{-1}; MS (FAB) 253 (M^++1, 100). Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.20; H, 6.32; N, 11.02.

3.8. 2-Cyanomethoxy-6-(4-methylphenyl)-3-nitropyridine 4Ac

Yellow solid. Mp 185–186 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 5.52 (s, 2H), 7.38 (d, J=8.1 Hz, 2H), 7.93 (d, J=8.4 Hz, 1H), 8.17 (d, J=8.1 Hz, 2H), 8.60 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.6 (CH_3), 53.4 (CH_2), 116.1 (CH), 118.0 (C), 129.2 (CH), 131.3 (CH), 133.1 (C), 134.5 (C), 139.2 (CH), 143.0 (C), 154.5 (C), 159.8 (C); IR (KBr) 1585, 1335 cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.09; N, 15.61. Found: C, 62.63; H, 4.24; N, 15.47.

3.9. 2-Cyanomethoxy-6-isobutyl-3-nitropyridine 4Bc

Yellow solid. Mp 187–188 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J=6.7 Hz, 6H), 2.1–2.4 (m, 1H), 2.71 (d, J=7.2 Hz, 2H), 5.16 (s, 2H), 7.01 (d, J=8.1 Hz, 1H), 8.33 (d, J=8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4 (CH_3), 28.7 (CH), 47.0 (CH_2), 50.9 (CH_2), 114.8 (C), 118.5 (CH), 125.9 (C), 136.2 (CH), 152.9 (C), 166.2 (C); IR (KBr) 1597, 1347 cm^{-1}. Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.17; H, 5.53; N, 17.87. Found: C, 55.92; H, 5.96; N, 17.67.

3.10. 1-Cyanomethyl-6-isobutyl-3-nitro -2-pyridone 5Bc

Brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J=6.6 Hz, 6H), 2.0–2.1 (m, 1H), 2.70 (d, J=7.3 Hz, 2H), 5.05 (s, 2H), 6.26 (d, J=8.0 Hz, 1H), 8.37 (d, J=8.0 Hz, 1H); IR (neat) 1682, 1551, 1335 cm^{-1}. Since separation with **4Bc** could not be performed enough, sufficient analytical data were not obtained.

3.11. 2-(Ethoxycarbonyl)methoxy-6-(4-methylphenyl)-3-nitropyridine 4Ad

Pale yellow solid. Mp 134–135 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 3H), 2.43 (s, 3H), 4.24 (q, J=7.1 Hz, 2H), 5.11 (s, 2H), 7.29 (d, J=8.1 Hz, 2H), 7.50 (d, J=8.4 Hz, 1H), 7.90 (d, J=8.1 Hz, 2H), 8.43 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 21.4 (CH_3), 61.3 (CH_2), 63.7 (CH_2), 113.0 (CH), 127.4 (CH), 129.7 (CH), 132.5 (C), 133.4 (C), 136.8 (CH), 141.6 (C), 154.8 (C), 159.1 (C), 168.2 (C); IR (KBr) 1754, 1583, 1339 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.76; H, 5.06; N, 8.86. Found: C, 60.66; H, 5.18; N, 8.89.

3.12. 2-(Ethoxycarbonyl)methoxy-6-isobutyl-3-nitropyridine 4Bd

Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J=6.7 Hz, 6H), 1.26 (t, J=7.2 Hz, 3H), 2.0–2.2 (m, 1H), 2.59 (d, J=7.2 Hz, 2H), 4.21 (q, J=7.2 Hz, 2H), 5.03 (s, 2H), 6.88 (d, J=8.1 Hz, 1H), 8.28 (d, J=8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.3 (CH_3), 28.6 (CH), 46.9 (CH_2), 61.2 (CH_2), 63.3 (CH_2), 117.3 (CH), 131.3 (C), 135.9 (CH), 154.5 (C), 165.7 (C), 168.2 (C); IR (neat) 1759, 1596, 1348 cm^{-1}; MS (FAB) 283 (M^++1, 100). Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found C, 54.93; H, 6.46; N, 9.72.

3.13. Reductive cyclization of 4Aa leading to PyOA 6Aa

To a solution of *O*-phenacylpyridine **4Aa** (296 mg, 0.85 mmol) in ethyl acetate (50 mL), Raney-Ni was added, which was prepared from 50 wt% Ni–Al (1.46 g, 12.4 mmol) and 20% NaOH aq. A hydrogen balloon was equipped and the mixture was stirred at room temperature for 2 h. After filtration of Raney-Ni, the filtrate was concentrated. Recrystallization of the residue from ethyl acetate afforded PyOA **6Aa** (200 mg, 0.66 mmol, 78%) as yellow needles. Other reductive cyclizations were performed in a similar way.

3.14. 6-(4-Methylphenyl)-2-phenylpyrido[2,3-*b*]-[1,4]oxazine 6Aa

Yellow needles (from EtOAc). Mp 158–162 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 5.43 (s, 2H), 7.25 (d, J=8.0 Hz, 2H), 7.45–7.5 (m, 4H), 7.74 (d, J=7.8 Hz, 1H), 7.9–7.5 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4 (CH_3), 64.3 (CH_2), 114.4 (CH), 125.6 (CH), 125.8 (CH), 127.9 (CH), 128.5 (CH), 130.7 (CH), 133.7 (C), 134.3 (C), 135.3 (CH), 138.3 (C), 152.3 (C), 153.7 (C), 156.5 (C), 157.7 (C); MS (FAB) 301 (M^++1, 100). Anal. Calcd for $C_{20}H_{16}N_2O$: C, 80.00; H, 5.33; N, 9.33. Found: C, 80.00; H, 5.27; N, 9.28.

3.15. 6-Isobutyl-2-phenylpyrido[2,3-*b*][1,4]oxazine 6Ba

Colorless needles. Mp 96–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J=6.6 Hz, 6H), 2.0–2.2 (m, 1H), 2.63 (d, J=7.2 Hz, 2H), 5.51 (s, 2H), 6.99 (d, J=8.0 Hz, 1H), 7.45–7.55 (m, 3H), 8.24 (dd, J=7.9, 1.7 Hz, 1H), 8.41 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4 (CH_3), 29.0 (CH), 47.1 (CH_2), 65.1 (CH_2), 118.9 (CH), 125.2 (C), 126.4 (CH), 128.8 (CH), 131.5 (CH), 134.7 (C), 135.7 (CH), 153.0 (C), 158.2 (C), 159.7 (C); MS (FAB) 267 (M^++1, 100). Anal. Calcd for $C_{20}H_{16}N_2O$: C, 76.69; H, 6.77; N, 10.53. Found: C, 76.30; H, 6.28; N, 10.30.

3.16. 1,2-Dihydro-2-methyl-6-(4-methylphenyl)pyrido-[2,3-*b*][1,4]oxazine 7Ab

Colorless needles. Mp 148–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, J=6.4 Hz, 3H), 2.28 (s, 3H), 3.45–3.55 (m, 1H), 3.65–3.80 (br, 1H), 3.90 (dd, J=10.7, 8.2 Hz, 1H), 4.29 (dd, J=10.7, 2.7 Hz, 1H), 6.81 (d, J=7.9 Hz, 1H), 7.1–7.2 (m, 3H), 7.75 (d, J=8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5 (CH_3), 21.2 (CH_3), 44.8 (CH), 71.0 (CH_2), 114.2 (CH), 122.5 (CH), 125.9 (CH), 127.6 (C), 129.2 (CH), 136.0 (C), 137.3 (C), 144.9 (C), 150.4 (C); IR (KBr) 3279 cm^{-1}; MS (FAB) 241 (M^++1, 100), 240 (69). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 75.00; H, 6.67; N, 11.67. Found: C, 74.84; H, 6.86; N, 11.48.

3.17. 1,2-Dihydro-6-isobutyl-2-methylpyrido[2,3-*b*]-[1,4]oxazine 7Bb

Pale yellow solid. Mp 81–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H), 1.95–2.1 (m, 1H), 2.43 (d, J=7.0 Hz, 2H), 3.5–3.6 (m, 1H), 3.6–3.8 (br, 1H), 3.92 (dd, J=10.6, 8.4 Hz, 1H), 4.32 (dd, J=10.6, 2.7 Hz, 1H), 6.55 (d, J=7.7 Hz, 1H), 6.78 (d, J=7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5 (CH_3), 22.4 (CH_3), 28.9 (CH_3), 31.0 (CH), 44.8 (CH), 46.4 (CH_2), 71.1 (CH_2), 117.3 (CH), 122.5 (CH), 126.2 (C), 149.1 (C), 150.5 (C); IR (KBr) 3229 cm^{-1}. Anal. Calcd for $C_{12}H_{18}NO$: C, 69.90; H, 8.74; N, 13.59. Found: C, 69.85; H, 9.11; N, 13.45.

3.18. 3-Amino-2-(ethoxycarbonyl)methoxy-6-(4-methylphenyl)pyridine 8Ad

Pale yellow plates. Mp 104–107 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J=7.1 Hz, 3H), 2.36 (s, 3H), 3.75–4.0 (br, 2H), 4.26 (q, J=7.1 Hz, 2H), 4.98 (s, 2H), 6.96 (d, J=7.7 Hz, 1H), 7.19 (d, J=8.2 Hz, 2H), 7.23 (d, J=7.7 Hz, 1H), 7.78 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 21.2 (CH_3), 61.0 (CH_2), 62.7 (CH_2), 113.9 (CH), 121.8 (CH), 125.4 (CH), 129.2 (CH), 129.4 (C), 136.1 (C), 137.1 (C), 142.9 (C), 150.3 (C), 169.7 (C); IR (KBr) 3435, 3342, 1742, 1199 cm^{-1}; MS (FAB) 287 (M^++1, 56), 286 (100). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.13; H, 6.29; N, 9.79. Found: C, 67.28; H, 6.38; N, 9.68.

3.19. 3-Amino-2-(ethoxycarbonyl)methoxy-6-isobutylpyridine 8Bd

Pale yellow solid. Mp 39–40 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J=6.6 Hz, 6H), 1.27 (t, J=7.1 Hz, 3H), 1.9–2.1 (m, 1H), 2.38 (d, J=7.1 Hz, 2H), 3.4–3.7 (br, 2H), 4.21 (q, J=7.1 Hz, 2H), 4.88 (s, 2H), 6.53 (d, J=7.6 Hz, 1H), 6.84 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.4 (CH_3), 28.7 (CH), 46.0 (CH_2), 60.9 (CH_2), 62.5 (CH_2), 117.1 (CH), 121.8 (CH), 127.8 (C), 147.2 (C), 150.4 (C), 169.8 (C); IR (neat) 3462, 3366, 1752, 1193 cm^{-1}. Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.90; H, 7.94; N, 11.11. Found: C, 61.95; H, 8.17; N, 11.29.

3.20. Cyclization of 8Ad leading to PyOA 9Ad

To a solution of aminopyridine **8Ad** (86 mg, 0.3 mmol) in methanol (5 mL), *p*-toluenesulfonic acid (26 mg, 0.15 mmol) was added. After heating the solution under reflux for 3 h, 0.1 M Na_2CO_3aq (15 mL, 1.5 mmol) was added, and then the solution was extracted with ethyl acetate (20 mL×3). The organic layer was dried over $MgSO_4$ and concentrated to afford PyOA **9Ad** (62 mg, 0.26 mmol, 86%) as a pale yellow solid.

3.21. 1,2-Dihydro-6-(4-methylphenyl)-2-oxopyrido[2,3-*b*]-[1,4]oxazine 9Ad

Pale yellow solid. Mp 282–283 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H), 4.82 (s, 2H), 7.18 (d, J=8.1 Hz, 2H), 7.26 (d, J=8.0 Hz, 1H), 7.57 (d, J=8.0 Hz, 1H), 7.85 (d, J=8.1 Hz, 2H), 10.91 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7 (CH_3), 66.8 (CH_2), 114.4 (CH), 120.7 (C), 124.1 (CH), 125.7 (CH), 129.2 (CH), 134.9 (C), 137.8 (C), 147.7 (C), 150.0 (C), 163.9 (C); IR (KBr) 3179, 1690 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.67. Found: C, 70.00; H, 5.09; N, 11.57.

3.22. 1,2-Dihydro-6-isobutyl-2-oxopyrido[2,3-*b*]-[1,4]oxazine 9Bd

Yellow solid. Mp 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J=6.6 Hz, 6H), 2.0–2.1 (m, 1H), 2.53 (d, J=7.2 Hz, 2H), 4.83 (s, 2H), 6.77 (d, J=7.7 Hz, 1H), 7.09 (d, J=7.7 Hz, 1H), 9.3–9.6 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (CH_3), 29.0 (CH), 46.5 (CH_2), 67.2 (CH_2), 118.1 (C), 118.4 (CH), 124.2 (CH), 150.1 (C), 155.2 (C), 165.6 (C); IR (neat) 3195, 1716 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.80; N, 13.59. Found: C, 64.15; H, 7.00; N, 13.38.

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