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Convenient synthesis of 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[4,5-*b*]- and [2,3-*b*]-1,5-oxazocine-6-ones

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Abstract—A convenient and diversity-oriented method for synthesis of the novel 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[4,5-*b*]-1,5-oxazocine-6-one skeleton **1** and the very rarely described 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocine-6-one skeleton **2**, featuring cyclization using nucleophilic aromatic substitution (S_NAr) and Suzuki coupling, is described.

In the course of our drug discovery programs targeting potent and selective NK_1 antagonists, potentially useful for the clinical treatment of a wide range of conditions such as pain, migraine, nausea, and urinary incontinence,[1] we required a convenient method for general synthesis of 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[4,5-*b*]-1,5-oxazocine-6-one and 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocine-6-one skeletons (**1** and **2** in Fig. 1).

Interestingly, the 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido-[4,5-*b*]-1,5-oxazocine-6-one skeleton **1** constitutes a novel class of compound whose synthesis has not been reported previously. On the other hand, there has been only one precedent for synthesis of the 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocine-6-one skeleton **2** reported by the Takeda group.[2] Their method, however, involves a seven-step process from acetophenone, which is not only inefficient for the synthesis of many compounds with structural diversity for compound **2**, but is also unavailable for the synthesis of the desired compound **1**. We therefore developed a convenient method for the synthesis of **1** and **2**. Herein, we describe a novel diversity-oriented approach for synthesis of the 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[4,5-*b*]-1,5-oxazocine-6-one and 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocine-6-one skeletons.

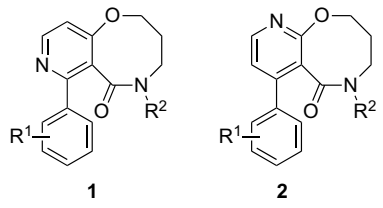

Figure 1.

The retrosynthetic scheme for the pyridooxazocines is shown in Scheme 1. The desired compounds **1** and **2** might be constructed from the chloride **3** or iodide **4** by the Suzuki coupling reaction. The bicyclic compounds **3** and **4** could be constructed from the carboxylic acid **7** by condensation with aminopropanol **8** and a subsequent nucleophilic intramolecular cyclization reaction using nucleophilic aromatic substitution (S_NAr). The regioselectivity of the cyclization could be controlled because the different leaving groups at the C-2 and C-4 positions in the pyridine ring (chloride and iodide, respectively) might create a difference of reactivity in the S_NAr reaction.

2-Chloro-4-iodopyridine-3-carboxylic acid **7** was prepared from 2-chloro-3-iodopyridine **9**[3] by the known method[4] with slight modification. Treatment of 2-chloro-3-iodopyridine **9** with LDA at −78 °C, followed by quenching with carbon dioxide, and then hydrolyzation with hydrochloric acid gave the 2-chloro-4-iodopyridine-3-carboxylic acid **7** in good yield. Subsequent

Keywords: S_NAr; Nucleophilic aromatic substitution; Suzuki coupling; Pyrido[4,5-*b*]-1,5-oxazocine-6-one; Pyrido[2,3-*b*]-1,5-oxazocine-6-one.
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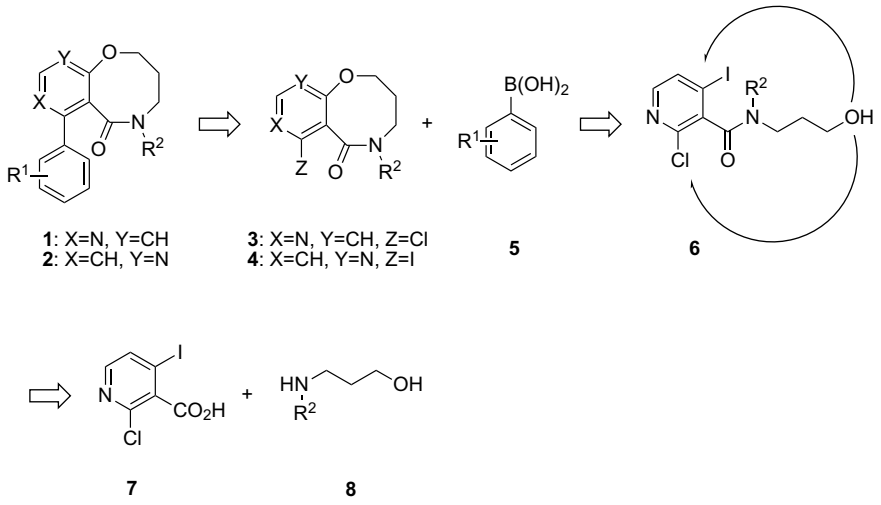
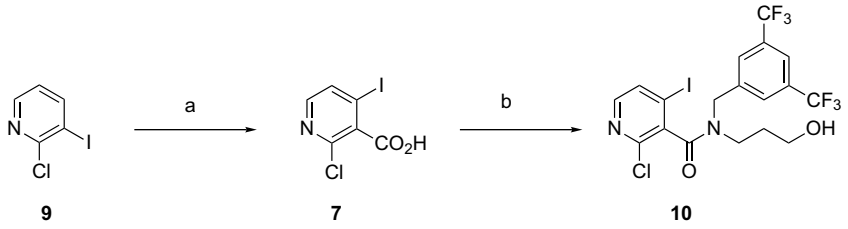


Scheme 1.



Scheme 2. Reagents and conditions: (a) 1. LDA, THF, −78 °C, 5 h, 2. CO_2, 1 h, 3. HCl, rt, 1 h, 81%; (b) 1. $SOCl_2$, DMF, reflux, 3h, 2. 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-propanol, THF, 0 °C, 1 h then rt, 2 h, 92%.

treatment with thionyl chloride under reflux, followed by condensation with 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-propanol, afforded the alcohol **10** (Scheme 2).

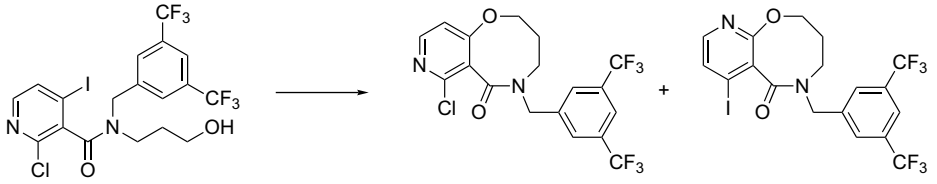
Conversion of the alcohol **10** to bicyclic compounds **11** and **12** was carried out under several conditions and the results are summarized in Table 1. Less-polar-aprotic conditions in the presence of a strong base (entries 1 and 2) afforded only **12** as a single regio-isomer, that is, only the C-2 position on the pyridine ring underwent a nucleophilic reaction. Interestingly, polar-protic conditions with various bases (entries 4–9) gave a mixture of **11** and **12**, in different respective ratios. In particular, use of K_2CO_3 as the base (entry 7) gave a good yield of **11**. Next, the effect of solvent was studied (entries 10–12). In particular, H_2O–EtOH was found to be a suitable solvent for obtaining **11**. The exact mechanism responsible for the regioselectivity of this cyclization is unclear. The formation of **12**, where chloride was replaced prior to iodide, seems to fit reasonably well with the results of common S_NAr;[5] however, the formation of **11** cannot be interpreted. Compounds **11** and **12** were easily separable by column chromatography and isolated in reasonable yields.[6] These compounds were identified by MS and ^1H NMR, respectively,[7,8] and it was possible to differentiate between them by MS (chloride or iodide) and ^1H NMR (aromatic protons at C-10 for **11** and C-8 for **12**; δ 6.80 and 7.69, respectively).

The Suzuki coupling reaction of **11** and **12** with arylboronic acids (1.5 equiv) yielded the desired 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]- and [4,5-*b*]-1,5-oxazocine-6-ones (**1a–d**, **2a–e**) in good yield, using 10 mol% $Pd(PPh_3)_4$ and 2 M Na_2CO_3 (5 equiv) in a 2:1 toluene/1,4-dioxane mixture for 5–7 h.[9] The coupling reaction proceeded equally well using chloride **11** or iodide **12**.

In the ^1H NMR spectra of **2d**, the aryl protons and oxazocine ring protons appeared as broad signals, but the benzylic methylene proton signals did not change. These data indicate that the rotation about the biaryl bond could be restricted for **2d** on a NMR timescale at room temperature.[2] Thus, although the separation of the isomers of **2d** using high-performance liquid chromatography has not been a success, **2d** presumably exists as a mixture of diastereomers,[2,10] which result from the two axial chiralities (aryl and amide). The compounds other than **2d** did not exhibit these effects (Table 2).

In summary, we have developed a convenient method for synthesis of the very rarely described 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[4,5-*b*]-1,5-oxazocine-6-one and 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazo-

Table 1. Studies of cyclization of alcohol **10**

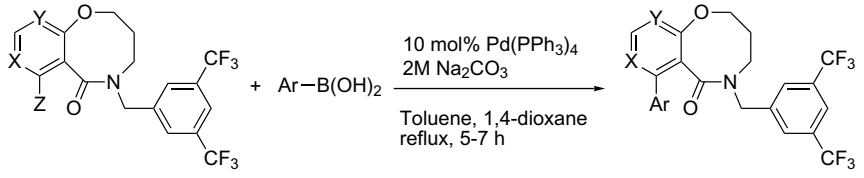


10 **11** **12**

Entry	Base	Solvent	Condition	Total yield (%)	Ratio (**11**:**12**)
1	NaH	THF	rt, 1 h	42	Only **12**
2	NaH	Toluene	50 °C, 8 h	53	Only **12**
3	NaH	DMF	0 °C, 1 h	—[a]	—
4	*t*-BuOK	EtOH	rt, 10 h	70	79:21
5	KOH	EtOH	rt, 1 h	59	68:32
6	Cs_2CO_3	EtOH	50 °C, 8 h	59	66:34
7	K_2CO_3	EtOH	50 °C, 8 h	80	84:16
8	Na_2CO_3	EtOH	80 °C, 16 h	14	71:29
9	$KHCO_3$	EtOH	80 °C, 16 h	70	80:20
10	K_2CO_3	DMF	100 °C, 1 h	28	71:29
11	K_2CO_3	*i*-PrOH	80 °C, 12 h	54	41:59
12	K_2CO_3	H_2O–EtOH (1:1 v/v)	100 °C, 12 h	87	83:17

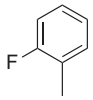
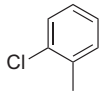
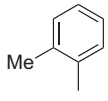
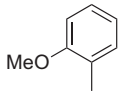
[a] Decomposition.

Table 2. The Suzuki coupling reaction **11** and **12** with substituted boronic acid



11, X=N, Y=CH, Z=Cl
12, X=CH, Y=N, Z=I

1a-d, **2a-e**

Entry	**12** or **13**	Ar	Products	Yield (%)
1	**11**		**1a**[11]	60
2	**12**		**2a**[12]	80
3	**11**		**1b**	87
4	**12**		**2b**	77
5	**11**		**1c**	83
6	**12**		**2c**	87
7	**11**		**1d**	98
8	**12**		**2d**	99
9	**12**		**2e**	86

cine-6-one skeletons starting from 2-chloro-3-iodopyridine, making good use of intramolecular cyclization using S_NAr for formation of the oxazocine ring and Suzuki coupling for formation of the biaryl bond. Details of the NK_1 antagonist activity of these compounds will be published separately.

Acknowledgements

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6. *Cyclization procedure*: Compounds (**10**–**12**): compound **10** (6.86 g, 12.1 mmol) was dissolved in THF (60 mL) at 0 °C, and NaH (581 mg, 14.5 mmol) was added, and the mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1 h. The reaction mixture was cooled at 0 °C, and water was added. The resulting mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel chromatography (AcOEt–hexane = 2:1 v/v) to give compound **12** (7.69 g, 42%).
   Compounds (**10**–**11**): compound **10** (1.74 g, 3.07 mmol) was dissolved in EtOH (30 mL), and K_2CO_3 (2.12 g, 15.3 mmol) was added, and the mixture was stirred under reflux for 6 h. Following the work-up procedure as described above afforded compound **11** (950 mg, 71%).
7. 7-Chloro-3,4,5,6-tetrahydro-2*H*-pyrido[4,5-*b*]-1,5-oxazocine-6-one (**11**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97–2.18 (2H, m), 3.23–3.32 (1H, m), 3.63–3.74 (1H, m), 4.06 (1H, d, J = 15 Hz), 4.22–4.30 (1H, m), 4.44–4.53 (1H, m), 5.64 (1H, d, J = 15 Hz), 6.80 (1H, d, J = 5.5 Hz), 7.84 (1H, s), 7 88 (2H, s), 8.17 (1H, d, J = 5.5 Hz); HRMS (EI) calcd for $C_{18}H_{13}ClF_6N_2O_2$ (M^+) 438.0570, found 438.0571.
8. 7-Iodo-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocine-6-one (**12**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73–1.81 (1H, m), 2.21–2.34 (1H, m), 3.18–3.27 (1H, m), 3.40–3.50 (1H, m), 4.14 (1H, d, J = 16 Hz), 4.22–4.30 (1H, m), 4.46–4.68 (1H, m), 5.71 (1H, d, J = 16 Hz), 7.69 (1H, d, J = 5.3 Hz), 7.83 (1H, s), 7.94 (2H, s), 8.01 (1H, d, J = 5.3 Hz); HRMS (EI) calcd for $C_{18}H_{13}F_6IN_2O_2$ (M^+) 529.9926, found 529.9907.
9. Suzuki coupling (**12**–**2a**): compound **12** (1.00 g, 1.89 mmol) and phenyl boronic acid (417 mg, 3.42 mmol) were dissolved in toluene (10 mL) and 1,4-dioxane (5 mL), then 2 M Na_2CO_3 (10 mL) and $Pd(PPh_3)_4$ (132 mg, 0.114 mmol) was added, and the mixture was stirred under reflux for 7 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, then washed with 2 M Na_2CO_3 and brine, and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by recrystallization from isopropanol to give compound **2a** (729 mg, 80%).
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11. 7-Phenyl-3,4,5,6-tetrahydro-2*H*-pyrido[4,5-*b*]-1,5-oxazocine-6-one (**1a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97–2.18 (2H, m), 3.39–3.47 (1H, m), 3.38–3.98 (1H, m), 4.12 (1H, d, J = 15 Hz), 4.13–4.22 (1H, m), 4.43–4.50 (1H, m), 5.38 (1H, d, J = 15 Hz), 6.87 (1H, d, J = 5.5 Hz), 7.25–7.43 (5H, m), 7.76 (2H, s), 7.86 (1H, s), 8.49 (1H, d, J = 5.5 Hz); HRMS (EI) calcd for $C_{24}H_{18}F_6N_2O_2$ (M^+) 480.1272, found 480.1261.
12. 7-Phenyl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocine-6-one (**2a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73–1.82 (1H, m), 2.26–2.39 (1H, m), 3.32–3.40 (1H, m), 3.69–3.78 (1H, m), 4.17 (1H, d, J = 15 Hz), 4.27–4.37 (1H, m), 4.63–4.70 (1H, m), 5.51 (1H, d, J = 15 Hz), 7.16 (1H, d, J = 5.5 Hz), 7.25–7.70 (5H, m), 7.71 (2H, s), 7.83 (1H, s), 8.41 (1H, d, J = 5.5 Hz); HRMS (EI) calcd for $C_{24}H_{18}F_6N_2O_2$ (M^+) 480.1272, found 480.1286.