CONCISE SYNTHESIS OF NITIDINE BY PALLADIUM-ASSISTED BIARYL COUPLING REACTION¶

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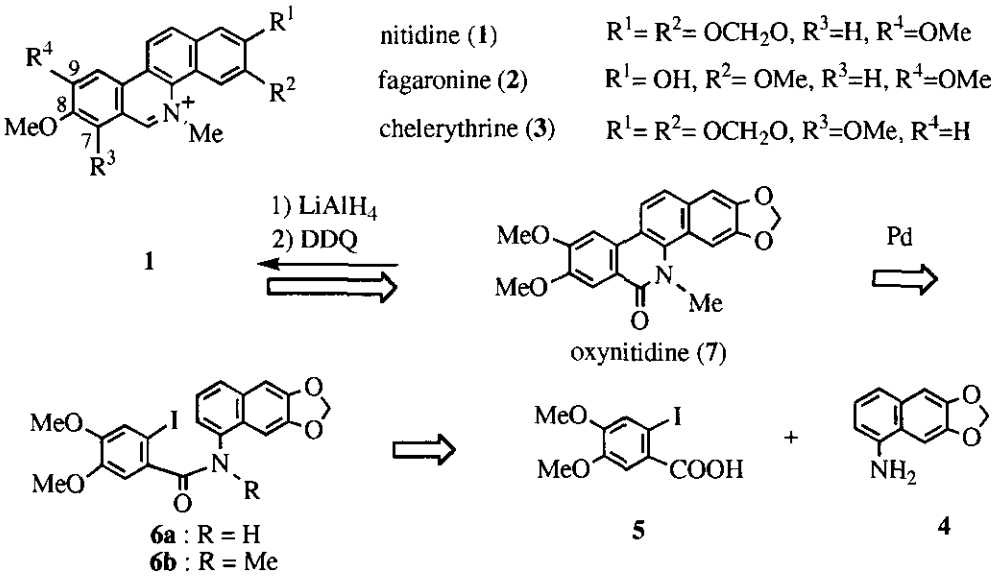
Abstract---Formal total synthesis of nitidine (**1**) was accomplished *via* oxynitidine (**7**) by the internal aryl-aryl coupling reaction of iodo-amide (**6**) using palladium-assisted cyclization reaction.

Fully aromatized benzo[*c*]phenanthridine alkaloids have been reported to be a continuing challenge for organic synthesis due to their potent pharmcological activity, in particular the strong antileukemic activity of 8,9-dioxygenated alkaloids such as nitidine (**1**) and fagaronine (**2**).[1] Extensive efforts have been directed toward the development of convenient method of synthesizing the nitidine type of alkaloids.[1a,2] However, the reported methods involve several disadvantages such as numerous steps, low total yield and/or absence of generality.



Scheme 1

¶ This paper is dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.

Recently, we reported a convenient method for synthesizing chelerythrine (**3**) using an internal aryl-aryl coupling reaction induced by palladium.[3] To develop a general method for synthesizing benzo[*c*]-phenanthridine alkaloids such as **1** and **3**, we designed a plan to synthesize **1** utilizing this methodology, as shown in Scheme 1. Since the coupling product (**7**), oxynitidine, had already been converted to nitidine (**1**) by reduction with $LiAlH_4$ and oxidation with DDQ,[2c] the synthesis of **7** indicates formal synthesis of **1**.

Results and discussion

A starting material (**6b**) for the cyclization reaction was prepared from naphthylamine (**4**) and benzoic acid (**5**) as follows. The amine (**4**)[2k] was synthesized by methylenation of 2,3-dihydroxy-5-nitronaphthalene[4] with CH_2Br_2 in the presence of CsF, followed by a catalytic hydrogenation with 20% Pd-C under hydrogen atmosphere in a 68% yield. The acid (**5**) was synthesized by oxidation of 2-iodo-4,5-dimethoxybenz-aldehyde[5] with sodium chlorite and 35% hydrogen peroxide in a 98% yield. Then, successive treatment of **5** with oxalyl chloride and **4** in the presence of NEt_3 afforded an amide (**6a**) in an 82% yield. Finally, methylation of **6a** with methyl iodide in the presence of sodium hydride in DMF gave *N*-methyl amide (**6b**) in a 96% yield.

Then, cyclization reaction of **6b** using Pd reagent to oxynitidine (**7**) was examined and the results are summarized in the Table. Using 0.2 eq. of $Pd(OAc)_2$, PPh_3 or POT, and Ag_2CO_3 in DMF, which created successful reaction conditions for synthesis of chelerythrine (**3**),[3] coupling reaction of **6b** did not proceed in a satisfactory yield (see runs 1-4), even using POT as a ligand (see run 4) in contrast to synthesizing chelerythrine (**3**).[3] Using one equivalent amount of $Pd(OAc)_2$, cyclization reaction

Table. Results of Cyclization Reaction of 2-Iodo-4,5-dimethoxy-*N*-methyl-*N*-(6,7- methylenedioxy-1-naphthyl)benzamide (**6b**) to Oxynitidine (**7**)[a]

run	$Pd(OAc)_2$ (eq)	ligand	(L/Pd)[b]	base	time	yield(%)	
						7	S.M.
1	0.2	PPh_3	(2)	Ag_2CO_3	5 h	30	54
2	0.2	PPh_3	(2)	Ag_2CO_3	43 h	32	16
3	0.2	PPh_3	(2)	Ag_2CO_3	7 day	33	7
4	0.2	POT[c]	(2)	Ag_2CO_3	5 h	64	16
5	1.0	PPh_3	(2)	Ag_2CO_3	5 h	60	21
6	1.0	PPh_3	(2)	Ag_2CO_3	43 h	88	10
7	1.0	POT	(2)	Ag_2CO_3	2 h	89	–
8	0.2	DPPP[d]	(1)	Ag_2CO_3	2 h	56	8
9	1.0	DPPP	(1)	Ag_2CO_3	1 h	55	–

a) All reactions were carried out under an argon atmosphere using $Pd(OAc)_2$ and ligand in the ratio indicated in the Table and 2 mol equivalents of base in DMF under reflux. b) Molar ratio between ligand and Pd. c) POT : tris(2-methylphenyl)phosphine. d) DPPP : 1,3-bis(diphenylphosphino)propane.

proceeded in a high yield (see runs 6 and 7). However, bidentate ligand (DPPP) was not effective for cyclization reaction (see runs 8 and 9).

In conclusion, the present method using the palladium-assisted cyclization reaction is effective for synthesis of not only the chelerythrine type but also the nitidine type of alkaloids. Synthetic studies on benzo[*c*]phenanthridine alkaloids using Pd reagent are currently underway.

EXPERIMENTAL

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol on a JASCO A-102 or JASCO FT/IR 350 spectrophotometer and ^{1}H- and ^{13}C-NMR spectra in deuteriochloroform on a Hitachi R-1500 (60 MHz) or Varian VXR-200 (200 MHz) spectrometer unless otherwise stated. NMR data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants are given in hertz. Fast atom bombardment-mass spectra (FAB-MS) were obtained on a VG-70SE spectrometer. Column chromatography was carried out on silica gel (Wako gel C-200 or Merck, silica gel 60, No. 9385). All experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous $MgSO_4$, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

6,7-Methylenedioxy-1-naphthylamine (4)

To a stirred suspension of 2,3-dihydroxy-5-nitronaphthalene[4] (7.4 g, 36.1 mmol) and dry CsF (40.2 g, 264 mmol) in dry DMF (120 mL) was added CH_2Br_2 (3.8 mL, 54.1 mmol), and then the mixture was heated at 110°C while stirring for 2 h. The reaction mixture was diluted with AcOEt and filtered through a bed of celite. The filtrate was then washed with 5% aqueous NaOH and brine. The residue in AcOEt was subjected to column chromatography on silica gel. Elution with hexane : AcOEt (5 : 1) gave 2,3-methylenedioxy-5-nitronaphthalene (6.16 g, 79%) as yellow needles (from AcOEt-hexane), mp 163–166°C. IR (KBr) cm^{-1}: 1525, 1320. ^{1}H-NMR (60 MHz) δ : 6.11 (2H, s, OCH_2O), 7.16 (1H, s, 1-H), 7.33(1H, dd, *J*=7.7, 7.7 Hz, 7-H), 7.94 (1H, s, 4-H), 8.09 (2H, dd, *J*=7.7, 1.4 Hz, 6- and 8-H). *Anal.* Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.24; N, 6.45. Found : C, 60.96; H, 3.17; N, 6.15.

A mixture of 2,3-methylenedioxy-5-nitronaphthalene (6.16 g, 28.4 mmol) and 20% Pd-C (1.34 g) in EtOH (180 mL) was hydrogenated at rt and atmospheric pressure until absorption of hydrogen ceased. The catalyst was removed by filtering and the fitrate was evaporated. The residue was recrystallized from aqueous EtOH to provide **4** (4.74 g, 89%) as yellow plates, mp 155–157°C (lit.,[2k] 152–154°C). FAB-MS (positive ion mode) m/z: 188 [M$^+$+1]. *Anal.* Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found : C, 70.58; H, 4.90; N, 7.39.

2-Iodo-4,5-dimethoxybenzoic Acid (5)

To a stirred mixture of 2-iodo-4,5-dimethoxybenzaldehyde[5] (10.0 g, 34.2 mmol), sodium phosphate monobasic dihydrate (1.21 g, 7.74 mmol), and 35% hydrogen peroxide (5.0 mL, 51.4 mmol) in CH_3CN (300 mL) and water (15 mL) was added a solution of sodium chlorite (80%; 5.61 g, 49.6 mmol) in water (15 mL) and then the whole was stirred at 10°C for 5 h. After the decomposition of excess hydrogen peroxide with 10% aqueous sodium hydrogen sulfite solution, the mixture was poured into water and extracted with AcOEt. The crystalline residue was recrystallized from $CHCl_3$-hexane to provide **5** (10.3 g, 98%) as colorless needles, mp 204.5–205.5°C (lit.,[5] 159–160°C). FAB-MS (positive ion mode) m/z: 309 [M^++1]. *Anal.* Calcd for $C_9H_9O_4I$: C, 35.09; H, 2.94. Found : C, 34.80; H, 2.90.

2-Iodo-4,5-dimethoxy-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (6a)

A few drops of dry DMF and oxalyl chloride (1.43 g, 11.3 mmol) were added to a solution of **5** (1.74 g, 5.63 mmol) in dry CH_2Cl_2 (80 mL) and the stirred mixture was refluxed for 90 min. Then the mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of **4** (0.98 g, 5.35 mmol) in dry CH_2Cl_2 (40 mL) and dry NEt_3 (0.68 g, 6.67 mmol) and the whole was stirred for 1 h at rt. The reaction mixture was concentrated to dryness and diluted with CH_2Cl_2, then washed with 10% HCl and brine. The residue was recrystallized from $CHCl_3$-hexane to provide **6a** (2.08 g, 82%) as colorless plates, mp 233–236°C. IR (KBr) cm^{-1}: 3340, 1670. ^{1}H-NMR (200 MHz) δ : 3.83 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.15 (2H, s, OCH_2O), 7.25-7.68 (7H, m, aromatic protons), 10.18 (1H, br s, NH). FAB-MS (positive ion mode) m/z: 478 [M^++1]. *Anal.* Calcd for $C_{20}H_{16}NO_5I$: C, 50.33; H, 3.38; N, 2.93. Found : C, 50.04; H, 3.51; N, 2.84.

2-Iodo-4,5-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (6b)

To a suspension of **6a** (3.20g, 6.71 mmol) and NaH (62.5%, 773 mg, 20.1 mmol) in dry DMF (150 mL) was added methyl iodide (0.46 mL, 7.38 mmol). After stirring for 30 min at rt, the reaction mixture was diluted with ether and washed with 10% HCl and brine. The residue in AcOEt-hexane was subjected to column chromatography on silica gel. Elution with hexane : AcOEt (2 : 1) gave **6b** (3.18 g, 96.4%) as pale yellow prisms (from AcOEt), mp 196.5–197.5°C. IR (KBr) cm^{-1}: 1650, 1380. ^{1}H-NMR (200 MHz) δ : 3.25 (3H, s, NCH_3), 3.53 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 6.07 (2H, s, OCH_2O), 6.41-7.51 (7H, m, aromatic protons). FAB-MS (positive ion mode) m/z: 492 [M^++1]. *Anal.* Calcd for $C_{21}H_{18}NO_5I$: C, 51.34; H, 3.69; N, 2.85. Found : C, 51.32; H, 3.72; N, 2.67.

General Procedure for Cyclization Reaction of Amide (6b) by Palladium Reagent.

Reaction of **6b** (30.8 mg, 62.7 μmol) with $Pd(OAc)_2$, phosphine ligand, and silver carbonate (36.4 mg, 125 μmol) in dry DMF (3 mL) was carried out under the reaction conditions indicated in the Table. The reaction mixture was diluted with ether and the precipitates were removed by filtering. The filtrate was washed with 1*N* HCl, sat. aqueous $NaHCO_3$ solution and brine. The residue in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with $CHCl_3$ gave **6b**. Successive elution with the same solvent gave oxynitidine (**7**) as colorless needles (from MeCN), mp 291–292°C (lit.,[6] 290–291°C). This compound was identical with an authentic sample of oxynitidine (**7**).[6]

ACKNOWLEDGEMENT

This research was supported by a Grant-in-Aid for Scientific Research (No. 09672144) from the Ministry of Education, Science, Sports, and Culture. The authors are indebted to Professor T. Ishikawa, Faculty of Pharmaceutical Sciences, Chiba University, for providing us with an authentic sample of oxynitidine and to the SC-NMR Laboratory of Okayama University for the ^{1}H-NMR experiments.

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Received, 16th March, 1998