A CONVENIENT SYNTHESIS OF BENZO[*C*]PHENANTHRIDINE ALKALOID, CHELERYTHRINE, BY THE PALLADIUM-ASSISTED INTERNAL BIARYL COUPLING REACTION

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Total synthesis of chelerythrine, a benzo[*c*]phenanthridine alkaloid, was accomplished *via* the internal aryl-aryl coupling reaction of halo-amide (**4**) by the palladium-assisted cyclization reaction.

KEY WORDS internal biaryl coupling; Heck type reaction; halo-amide; benz[*c*]phenanthridine alkaloid; chelerythrine

Benzo[*c*]phenanthridine alkaloids have attracted much attention because of their potent pharmacological activities.[1] Recently, it was reported that chelerythrine (**1**)[2] and isofagaridine (**2**)[3] inhibited protein kinase C and DNA topoisomerase I, respectively. Although several reports on the total synthesis of chelerythrine have been published,[4] the methods had some disadvantages such as many steps, low yield, and/or no generality. Therefore, we planned to develop a convenient synthetic method for **1**.

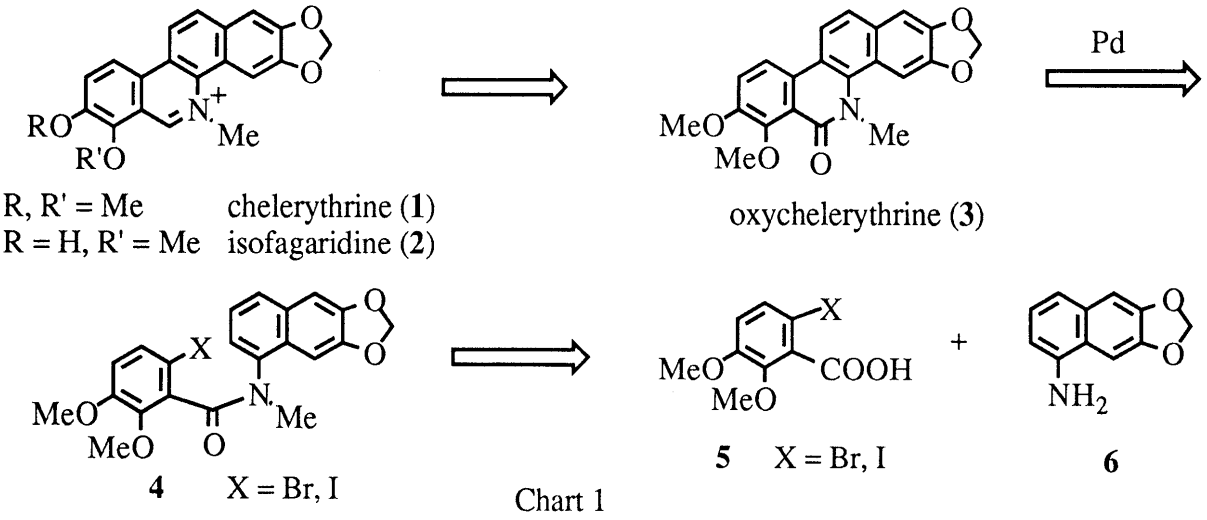

Chart 1

The cross-coupling reaction with palladium catalyst has been an extremely useful tool in organic synthesis.[5] We designed the synthetic plan for **1** involving an internal biaryl cyclization by palladium as a key reaction,[6] as shown in Chart 1. Since the coupling product (**3**), oxycheleryth-rine, had already been converted into chelerythrine (**1**),[4e] the synthesis of **3** indicates a formal synthesis of **1**. It was reported that an internal coupling reaction of bromo-amide (**7b**) with a Pd reagent proceeded in 50% yield.[6a] In order to improve the yield, the reaction was re-examined using purified $Pd(OAc)_2$,[7] phosphine ligand and base. The results are summarized in Table 1. On

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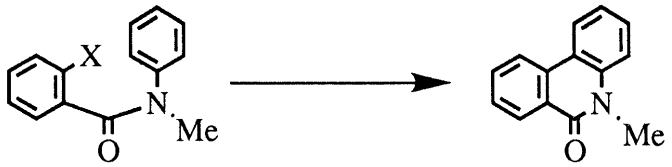


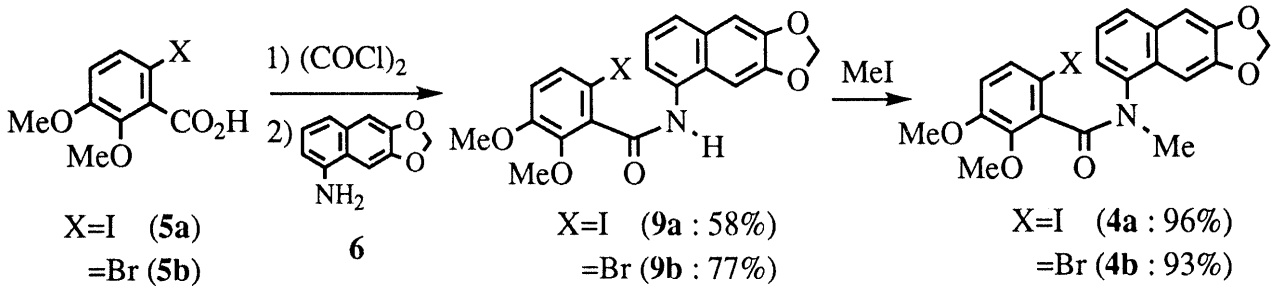
7a X=I
7b X=Br

8

Table 1. Results of Cyclization Reaction of 2-Halo-*N*-methyl-*N*-phenylbenzamide (**7**)[a)]

X	Run	$Pd(OAc)_2$ (eq.)	Ligand	Base	Solvent	Temp.	Time	Yield (%) **8**	Yield (%) S.M.
I	1	0.05	PPh_3	Ag_2CO_3	DMF	Refl.	40 min	79	—
	2	0.2	PPh_3	Ag_2CO_3	DMF	Refl.	15 min	93	—
	3	0.2	POT	Ag_2CO_3	DMF	Refl.	15 min	93	—
	4	0.2	PPh_3	Ag_2CO_3	DMF	30-35°C	35 h	85	—
	5	0.2	PPh_3	Ag_2CO_3	Xylene	30-35°C	23 h	93	—
	6	0.2	PPh_3	Ag_2CO_3	Benzene	Refl.	10 min	98	—
	7	0.2	PPh_3	Ag_2CO_3	CH_3CN	Refl.	15 min	95	—
	8	0.2	PPh_3	$^iPr_2NEt$	DMF	Refl.	4.5 h	21	7
	9	0.2	PPh_3	$^iPr_2NEt$	Benzene	Refl.	6 h	45	14
Br	10	1.0	PPh_3	Ag_2CO_3	DMF	Refl.	60 h	75	7
	11	0.2	POT	Ag_2CO_3	DMF	Refl.	1.5 h	99	—

a) All reactions were carried out using $Pd(OAc)_2$ and ligand in a ratio of 1 : 2 and 2 mol equivalent of base.



X=I (**5a**)
=Br (**5b**)

6

X=I (**9a** : 58%)
=Br (**9b** : 77%)

X=I (**4a** : 96%)
=Br (**4b** : 93%)

Chart 2

Table 2. Results of Cyclization Reaction of 6-Halo-2,3-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (**4**) to Oxychelerythrine (**3**)[a)]

X	Run	$Pd(OAc)_2$ (eq.)	Ligand	Base	Solvent	Temp.	Time	Yield (%) **3**
I	1	0.2	PPh_3	Ag_2CO_3	DMF	Refl.	20 min	85
	2	0.2	POT	Ag_2CO_3	DMF	Refl.	20 min	94
Br	3	0.2	PPh_3	Ag_2CO_3	DMF	Refl.	2 h	79
	4	0.2	POT	Ag_2CO_3	DMF	Refl.	3 h	96

a) All reactions were carried out in the presence of ligand (0.4 eq) and base (2 eq).

using 0.2 eq of $Pd(OAc)_2$, PPh_3, and Ag_2CO_3, the solvent had no crucial effect on the internal coupling rection of iodo-amide (**7a**), although Ag_2CO_3 was superior to Hünig base. On the other hand, the coupling reaction of bromo-amide (**7b**) proceeded slowly even when using a stoichiometric amount of $Pd(OAc)_2$ in the presence of PPh_3 as a ligand in DMF (see run10 in Table 1). However, on using tris(2-methylphenyl)phosphine (POT) as ligand, the reaction proceeded smoothly using 0.2 eq of $Pd(OAc)_2$ and gave phenanthridone (**8**) in an excellent yield (see run 11 in Table 1).

Next, we applied these methods to the synthesis of oxychelerythrine (**3**) from halo-amides (**4**), which were prepared from iodo-acid (**5a**)[8] or bromo-acid (**5b**)[9] and naphthylamine (**6**),[10] as shown in Chart 2. The results are summarized in Table 2. The coupling reaction of both halo-amides (**4**) with $Pd(OAc)_2$, PPh_3 or POT and Ag_2CO_3 in DMF under reflux afforded oxychelerythrine (**3**) in an excellent yield, although iodo-amide (**4a**) was more reactive than bromo-amide (**4b**).

In conclusion, the present method using the Pd reagent is very convenient and effective for preparing benzo[*c*]phenanthridine alkaloids. We are now investigating the generality of this method.

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