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Formal Synthesis of Nitidine through Palladium-Catalyzed Isocoumarin Synthesis

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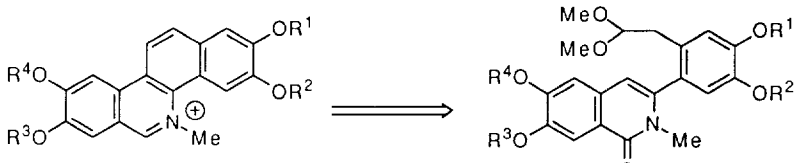
Abstract: The isoquinolone intermediate **9** for the synthesis of nitidine was synthesized through palladium-catalyzed formation of isocoumarin **7** from *o*-styrylbenzoic acid derivative **5**, which was prepared from palladium-catalyzed coupling reactions of aryl iodide **1** and **2** with vinylsilane.

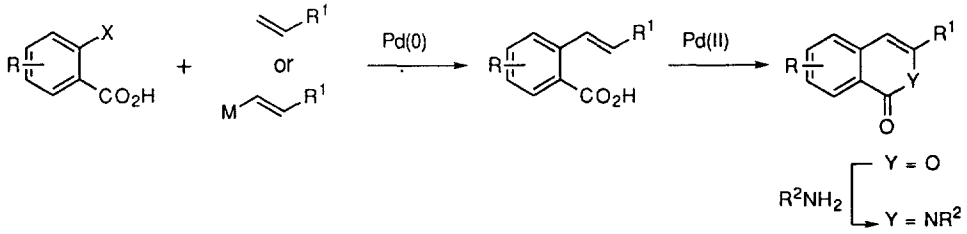
The fully aromatized benzo[*c*]phenanthridine alkaloids have attracted much attention because of their potential pharmacological activity, in particular their strong antileukemic activity[1]. Extensive efforts have been directed toward the development of convenient syntheses of nitidine and fagaronine[2]. We already reported that fully aromatized benzo[*c*]phenanthridine alkaloids were efficiently synthesized from the isoquinolone intermediates derived from protoberberines by a biogenetic process[3] (**Scheme 1**). Our attention is now focused on synthesis of the isoquinolone intermediate[4] from the corresponding isocoumarin, which was formed by the palladium-catalyzed cyclization of *o*-styrylbenzoic acid derivative.



Nitidine	$R^1 + R^2 = CH_2$, $R^3 = R^4 = Me$
Avicine	$R^1 + R^2 = R^3 + R^4 = CH_2$
Fagaronine	$R^1 = H$, $R^2 = R^3 = R^4 = Me$

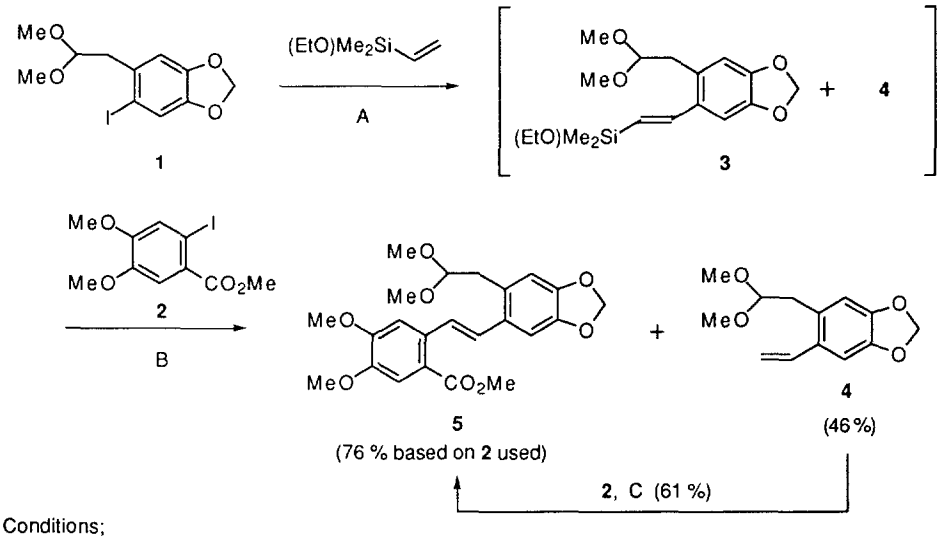
Scheme 1

Recently we reported that cyclization of *o*-alkenylbenzoic acids, which were easily prepared by the Heck-type reaction or cross-coupling reaction of halobenzoate, in the presence of catalytic amount of $PdCl_2(CH_3CN)_2$ and benzoquinone led to 3-substituted isocoumarins in high yield[5] (**Scheme 2**). The 3-substituted isocoumarins thus obtained were converted to isoquinolone derivatives by treatment with primary amine or ammonia.



Scheme 2

Methyl *o*-styrylbenzoate derivative **5** was prepared by the incorporation of two aryl groups to the ethylene part (**Scheme 3**). Aryl iodide **1**[6] and **2** were chosen as the starting materials. Tetrabutylammonium hydrogen sulfate-promoted Heck-type reaction[7] of aryl iodide **2** with styrene derivative **4** , which was prepared by the cross-coupling reaction of **1** and a vinylmetal compound[8], gave the desired *o*-styrylbenzoate derivative **5**[9] in 61 % yield (condition C). To increase the yield of **5**, we applied a sequential procedure namely: the Heck reaction of **1** with ethoxydimethylvinylsilane in triethylamine[10] followed by the cross-coupling reaction of the product, styrylsilane **3**[11], with **2**. The Heck reaction of **1** proceeded smoothly to give the styrylsilane derivative **3** accompanied by the vinylated product **4** (condition A)[12]. After removal of ammonium salt and all volatiles, the residue was reacted with **2** in the presence of a Pd catalyst and fluoride anion (condition B). The conversion yield of **5** by this sequential procedure[13] reached 76 % based on **2** used.



Conditions;

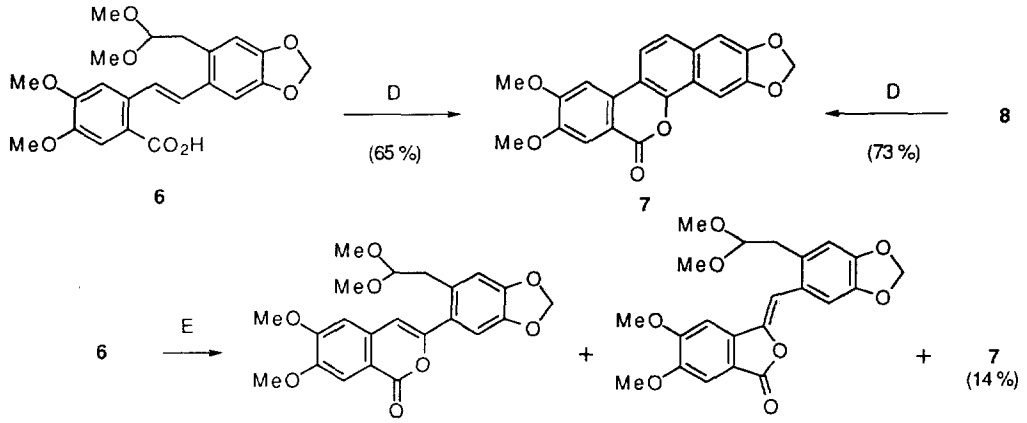
A : $PdCl_2(PPh_3)_2$ (2 mol%), Et_3N, 90°C / 12 h

B : $[(allyl)PdCl]_2$ (5mol%), $(EtO)_3P$ (10mol%), Bu_4NF (1.2 eq), THF, 60°C / 2 h

C : $Pd(OAc)_2$ (10mol%), PPh_3 (20mol%), $Bu_4N{\cdot}HSO_4$ (1.0 eq), $NaHCO_3$ (4 eq), MS-3A, DMF, 80°C / 32 h

Scheme 3

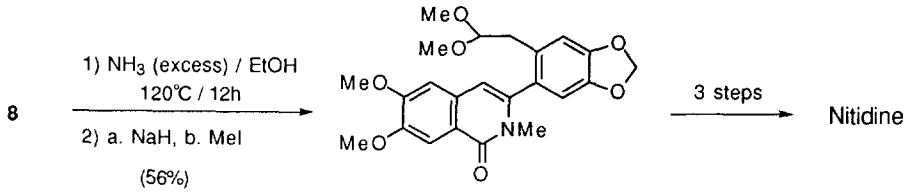
The cyclization of *o*-styrylbenzoic acid derivative **6**, which was prepared by hydrolysis of **5**, was carried out by the use of a catalytic amount of $PdCl_2(CH_3CN)_2$ and benzoquinone (**Scheme 4**). Unfortunately, the prolonged reaction time yielded benzo[*d*]naphtho[*1,2-b*]pyran-6-one derivative **7**[9]. Monitoring the reaction carefully, we found that the cyclization proceeded rapidly to form the isocoumarin derivative **8**[9] and the benzylidenephthalide derivative **9**[9]. The optimum condition gave **8** in 48 % yield accompanied by **9** (4 %) and **7** (14 %). Isocoumarin **8** was found to be converted to **7** under the same conditions through the cationic cyclization by the action of a palladium reagent as a Lewis acid[14].



Conditions;
D : $PdCl_2(CH_3CN)_2$ (10mol%), 1,4-benzoquinone (2.0 eq), THF r.t. / 18 h
E : $PdCl_2(CH_3CN)_2$ (20 mol%), 1,4-benzoquinone (2.0 eq), THF, 30°C / 1 h

Scheme 4

Finally, treatment of **8** with ammonia followed by N-methylation gave the desired isoquinolone **10**[15] in 56% yield, which had already been converted to nitidine[3b] (**Scheme 5**). In conclusion, the strategy presented here provides a new methodology for the construction of benzo[*c*]phenanthridine alkaloids.



Scheme 5

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8. The reaction of ethoxydimethylvinylsilane as mentioned in reference 11 gave **4** in 78 % yield using 10 mol% of Pd catalyst. In the case of vinyltributyltin, 87 % yield was achieved under the condition of the following reference: McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, 52, 422-424.
9. All new compounds gave satisfactory spectroscopic and analytical data. Representative data for selected compounds; **5**: mp 147-148°C. IR ($CHCl_3$): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.99 (d, 2H, J = 5 Hz), 3.33 (s, 6H), 3.91 (s, 3H), 3,99 (s, 3H), 4.04 (s, 3H), 4.50 (t, 1H, J = 5 Hz), 5.95 (s, 2H), 6.73 (s, 1H), 7.13 (s, 1H), 7.16 (d, 1H, J = 16 Hz), 7.18 (s, 1H), 7.48 (s, 1H), 7.79 (d, 1H, J = 16 Hz). Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.18; H, 6.09. Found: C, 64.29; H, 6.09. **7**: mp 192-193°C. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 4.04 (s, 3H), 4.12 (s, 3H), 6.11 (s, 2H), 7.15 (s, 1H), 7.49 (s, 1H), 7.58 (d, 1H, J = 9 Hz), 7.81 (s, 1H), 7.84 (d, 1H, J = 9 Hz), 7.88 (s, 1H). Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.57; H, 4.03. Found: C, 68.64; H, 3.80. **8**: mp 142-143°C. IR ($CHCl_3$): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.89 (d, 2H, J = 5 Hz), 3.34 (s, 6H), 4.00 (s, 3H), 4.02 (s, 3H), 4.61 (t, 1H, J = 5 Hz), 6.01 (s, 2H), 6.54 (s, 1H), 6.83 (s, 1H), 6.89 (s, 1H), 6.93 (s, 1H), 7.68 (s, 1H). Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.78; H, 5.43. **9**: mp 205-206°C. IR ($CHCl_3$): 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 3.02 (d, 2H, J = 5 Hz), 3.36 (s, 6H), 3.97 (s, 3H), 4.06 (s, 3H), 4.49 (t, 1H, J = 5 Hz), 5.98 (s, 2H), 6.55 (s, 1H), 6.77 (s, 1H), 7.09 (s, 1H), 7.29 (s, 1H), 7.70 (s, 1H). Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.68; H, 5.49.
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12. Isolation of vinylsiline **3** was difficult, so the yield of **3** (ca. 50 %) was determined by ^{1}H-NMR.
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15. Treatment of **8** with methylamine did not give **10**. The spectroscopic and analytical data of **10** were identified with those of the previously synthesized product[3b].

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