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An efficient method for construction of tetrahydroisoquinoline skeleton via double cyclization process using *ortho*-vinylbenzaldehydes and amino alcohols: application to the synthesis of (*S*)-cryptostyline II

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Abstract

Thermal double cyclization reaction using *ortho*-vinylbenzaldehyde and 3-aminopropanols proceeded smoothly to give isoquinoline derivatives via 6π-azaelectrocyclization pathway. The method was applied to the efficient synthesis of (*S*)-cryptostyline II.

Keywords: 6π-Azaelectrocyclization; Tetrahydroisoquinoline; Double cyclization process; (*S*)-Cryptostyline II

Stereoselective thermal pericyclic ring-closure process of 1-azatrienes has been known as a useful synthetic tool of nitrogen heterocycles.[1,2] Hsung reported a stereoselective 6π-electron electrocyclic ring closure of chiral 1-azatrienes, derived from vinylogous amides with α,β-unsaturated iminium salts.[3] Katsumura developed the asymmetric electrocyclic ring closure system using *cis*-1-amino-2-indanols as chiral auxiliaries.[4] In the course of our ongoing program concerning the synthesis of nitrogen-heterocyclic compounds, we have recently reported a facile synthesis of 1,2-dihydroisoquinoline frameworks via a three component reaction using *ortho*-alkynylaryl aldehydes, primary amines, and pronucleophiles under metal-catalyzed[5] and metal-free conditions,[6] respectively. As an extension, we were interested in the use of *ortho*-vinylbenzaldehydes for synthesis of chiral isoquinoline derivatives[7] through 6π-azaelectrocyclization reaction.[8] In this paper, we report a double cyclization process using *ortho*-vinylbenzaldehyde and 3-aminopropanols, which produces tetrahydroisoquinoline derivatives in good to high yields. Furthermore, the protocol was applied to a synthesis of (*S*)-cryptostyline II by using (*R*)-phenylglycinol as a chiral auxiliary.

The reactions of *ortho*-vinylbenzaldehyde **1** with 3-aminopropanols **2** were examined and the results are summarized in Table 1. When the reaction of **1** with **2a** (R = H) was carried out in $(CH_2Cl)_2$ under reflux condition, the corresponding hexahydrooxazinoisoquinoline **3a** was obtained in 34% yield (entry 1). Optimization experiments revealed that 1,4-dioxane was a suitable solvent and the chemical yield was dramatically increased to 80% yield (entry 3). Besides 1,4-dioxane, toluene, and DMSO were also effective (entries 4 and 5). Previously, Beke et al. have reported that the reaction of **1** with amines in alkaline alcoholic solution gave the corresponding 1-alkoxy-substituted tetrahydroisoquinoline products.[9] On the other hand, the present reaction proceeds with stoichiometric amount of aminoalcohols without any additional bases. We anticipated that the use of **2b**, having *gem*-dimethyl groups in the carbon tether, might accelerate the reaction rate due to the Thorpe–Ingold effect.[10] However, no acceleration was observed (entries 5 and 6). These results suggest that the *N*,*O*-acetal ring closure process would not be the rate-determining step. We also conducted the reaction of **1** with simple amine, such as 1-phenylethylamine, instead

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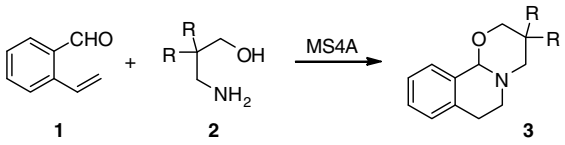
Table 1
Domino reaction of *ortho*-vinylbenzaldehyde **1** with 3-aminopropanols **2**[a]



1 **2** **3**

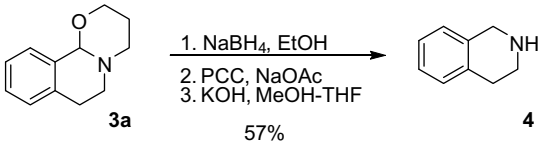
Entry	2	R	Solvent	Conditions	Compound 3	Yield[b] (%)
1	**2a**	H	$(CH_2Cl)_2$	Reflux, 22 h	**3a**	34
2	**2a**	H	CH_3CN	Reflux, 24 h	**3a**	56
3	**2a**	H	1,4-Dioxane	100 °C, 22 h	**3a**	80
4	**2a**	H	Toluene	100 °C, 22 h	**3a**	70
5	**2a**	H	DMSO	100 °C, 15 h	**3a**	76
6	**2b**	Me	DMSO	100 °C, 16 h	**3b**	73

[a] All reactions were carried out using **1** and 3-aminopropanol **2** in the presence of MS4A.
[b] Isolated yields.

of aminoalcohol **2**. Although the corresponding imine was formed quantitatively, the cyclized product was not obtained at all. This result clearly indicated that the participation of the hydroxyl group in aminoalcohols was important for the construction of isoquinoline frameworks. The product **3a** can be converted to tetrahydroisoquinoline **4** easily. Reduction with $NaBH_4$, followed by PCC oxidation gave β-amino aldehyde, which was treated under basic conditions to produce **4** in 57% overall yield (Scheme 1).[11]

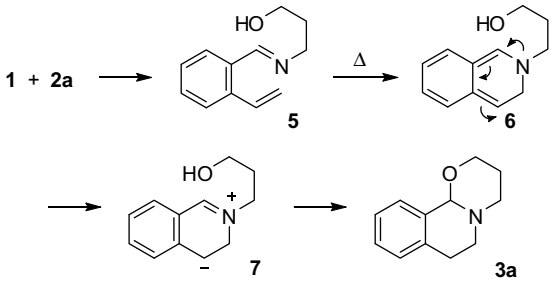
A plausible reaction mechanism was shown in Scheme 2. The reaction of aldehyde **1** and amino alcohol **2a** gives aldimine **5**, which undergoes the thermal 6π-azaelectrocyclization to afford 2,3-dihydroisoquinoline **6**. Then, intramolecular nucleophilic attack of hydroxyl group of **6** to C-1 position occurs to afford **3a** through the formation of **7**.[4d]

Since the reaction of **1** with **2** proceeded unexpectedly easily, we next applied this method for synthesis of chiral isoquinolines by use of chiral amino alcohols. Yamato has reported the diastereoselective synthesis of **9** using *ortho*-(2-bromoethyl)benzaldehyde with (*R*)-phenylglycinol **8** under basic conditions, which was found to be a versatile synthetic precursor of several tetrahydroisoquinoline alkaloids.[12] We examined the reaction of **1** with **8** in 1,4-dioxane at 100 °C for 1 d. As we expected, the reaction

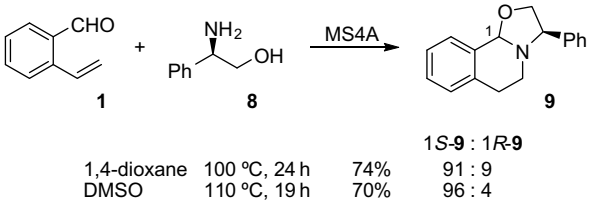


3a **4**

Scheme 1.



Scheme 2.



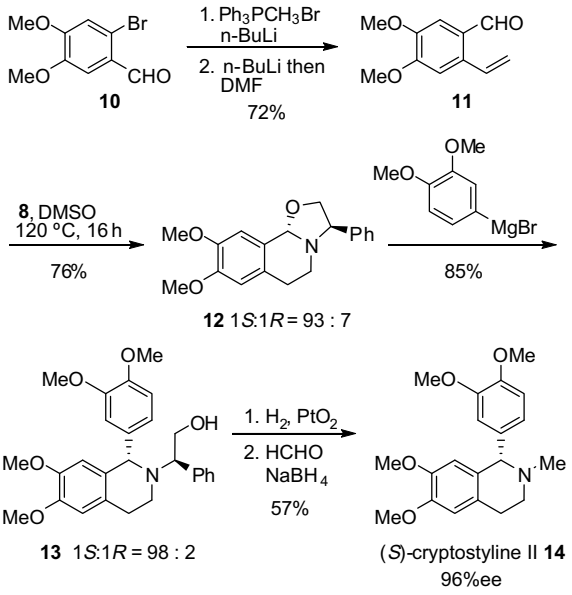
Scheme 3.

proceeded smoothly and 1*S*-isomer of **9** was obtained stereoselectively (Scheme 3). The selectivity was increased up to 96:4 by conducting the reaction in DMSO as solvent.

The preparation of **9** is representative. To a mixture of *ortho*-vinylbenzaldehyde **1** (0.5 mmol) and MS4A in DMSO (2 mL) was added (*R*)-phenylglycinol **8** (0.5 mmol) and the resulting mixture was stirred at 110 °C for 19 h. After the mixture was cooled to rt, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography (basic silica gel, hexane/AcOEt as eluent) to give **9** (0.35 mmol) in 70% yield (1*S*:1*R* = 96:4).

On the basis of these results, we applied the present reaction for the synthesis of (*S*)-cryptostyline II **14**,[13] which was isolated from the plant *Cryptostylis fulva* (Scheme 4).[14] Some analog of the cryptostylines have been studied as bladder-selective muscarinic M_3 receptor antagonists and are therefore of considerable biological significance.[15] The requisite starting material, 4,5-dimethoxy-2-vinylbenzaldehyde **11**, was prepared easily from commercially available 6-bromoveratraldehyde **10** in two steps in 72% overall yield.[16] The reaction of **11** with (*R*)-phenylglycinol **8** proceeded smoothly under thermal condition to give 1*S*-**12** stereoselectively over 1*R*-isomer and the ratio was 93:7.[17] The conversion of **12** to (*S*)-cryptostyline II was carried out according to the literature.[12b,18] Treatment of **12** with Grignard reagent, derived from 4-bromo-1,2-dimethoxybenzene, gave **13** in 85% yield with 96% dr.[19] Removal of the auxiliary by hydrogenation, followed by N-methylation gave (*S*)-cryptostyline II **14** with 96% ee in 57% overall yield.[20]

In conclusion, an efficient synthetic method of isoquinoline derivatives was developed through the double



Scheme 4.

cyclization protocol using *ortho*-vinylbenzaldehyde and 3-aminopropanols. The present method was applied to the synthesis of chiral (*S*)-cryptostyline II by using (*R*)-phenylglycinol as a chiral auxiliary. It is believed that the reaction proceeds through the thermal 6π-azaelectrocyclization and cyclic *N*,*O*-acetal formation. The obtained products are known as versatile intermediates for various kinds of bioactive tetrahydroisoquinoline alkaloids. Further studies to extend the scope of synthetic utility are in progress in our laboratory.

Acknowledgment

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16. *Procedure for 4,5-dimethoxy-2-vinyl-benzaldehyde* **11**: To a solution of methyltriphenylphosphonium bromide (8.0 g, 22.4 mmol) in THF (50 mL) was added a 1.6 M solution of *n*-BuLi (14 mL, 22.4 mmol) at 0 °C and the mixture was stirred for 1 h. To the mixture was added a solution of 6-bromoveratraldehyde (4.9 g, 20 mmol) in THF (50 mL). After the mixture was stirred for 4 h at rt, a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O twice. The combined extracts were dried over $MgSO_4$ and evaporated to leave the crude product, which was purified by column chromatography (silica gel, hexane/AcOEt = 9/1 as eluent) to give 1-bromo-4,5-dimethoxy-2-vinylbenzene (3.8 g, 15.6 mmol) in 76% yield as a colorless oil. To a solution of 1-bromo-4,5-dimethoxy-2-vinylbenzene (3.56 g, 14.6 mmol) in THF (30 mL) was added a 1.6 M solution of *n*-BuLi (9.5 mL, 15.2 mmol) at −78 °C and the mixture was stirred for 40 min. To the mixture was added DMF (1.16 mL, 15.0 mmol) and the mixture was stirred for overnight at rt. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O twice. The combined extracts were dried over

$MgSO_4$ and evaporated to leave the crude product, which was purified by column chromatography (silica gel, hexane/AcOEt = 3/1 as eluent) to give **11** (2.65 g, 13.8 mmol) in 95% yield as a colorless solid.

17. *Procedure for (3R,10bS)-8,9-dimethoxy-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinoline* **12**: To a mixture of **11** (384 mg, 2.0 mmol) and MS4A in DMSO (2 mL) was added (*R*)-phenylglycinol **8** (288 mg, 2.1 mmol) and the resulting mixture was stirred at 120 °C for 16 h. After the mixture was cooled to rt, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography (basic silica gel, hexane/AcOEt = 3/1 as eluent) to give **12** (475 mg, 1.53 mmol) in 76% yield (1*S*:1*R* = 93:7) as a colorless solid. Mp = 114–115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46–7.43 (m, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.30–7.27 (m, 2H), 6.90 (s, 1H), 6.66 (s, 1H), 5.40 (s, 1H), 4.47 (dd, J = 7.8, 6.8 Hz, 1H), 4.31 (dd, J = 6.8, 6.3 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.80 (dd, J = 7.8, 6.3 Hz, 1H), 3.08–2.91 (m, 3H), 2.77–2.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.8, 147.6, 141.6, 128.5, 127.8, 127.1, 126.5, 124.6, 110.6, 110.4, 90.0, 71.1, 68.4, 55.9, 55.8, 46.8, 28.6; IR (neat); 2944, 2813, 1608, 1515, 1380, 1260, 1228, 1123, 1028, 1012, 922, 858, 781, 710 cm^{-1}; Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.10; H, 6.76; N, 4.59.
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19. *Procedure for R-2-((S)-1-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethanol* **13**: To a suspension of magnesium turnings (0.3 g, 12.5 mmol) in THF (3 mL) was added 4-bromoveratrole (0.25 mL, 1.73 mmol) and the mixture was stirred for 1 h at rt. The resulting Grignard reagent was added to a solution of **12** (156 mg, 0.5 mmol) in THF (4 mL) at −78 °C and the mixture was allowed to warm to rt. After the mixture was stirred for 2 h at rt, a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with AcOEt three times. The combined extracts were dried over Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography (basic silica gel, hexane/AcOEt = 1/2 as eluent) to give **13** (191 mg, 0.43 mmol) in 85% yield (1*S*:1*R* = 98:2) as a yellow solid. Mp = 58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.36 (m, 2H), 7.36–7.28 (m, 3H), 6.72 (dd, J = 5.1, 3.2 Hz, 2H), 6.63 (s, 1H), 6.59 (dd, J = 8.3, 1.7 Hz, 1H), 6.20 (s, 1H), 4.71 (s, 1H), 4.02 (dd, J = 11.0, 6.3 Hz, 1H), 3.96 (dd, J = 11.0, 4.6 Hz, 1H), 3.91–3.86 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 3.17 (ddd, J = 13.4, 9.5, 5.1 Hz, 1H), 3.06 (dt, J = 13.4, 4.6 Hz, 1H), 2.93 (ddd, J = 16.6, 9.5, 5.1 Hz, 1H), 3.06 (dt, J = 16.6, 4.6 Hz, 1H); ^{13}C NMR (CDCl3, 100 MHz) δ 148.5, 147.9, 147.4, 147.0, 140.6, 137.0, 128.5, 128.4, 128.0, 127.6, 126.7, 121.3, 112.1, 111.6, 110.9, 110.2, 64.7, 63.0, 62.7, 55.9, 55.8, 55.8, 55.7, 41.2, 25.3; IR (neat); 2935, 2905, 2833, 2253, 1607, 1509, 1462, 1224, 1025, 910, 726, 700 cm^{-1}; Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.12. Found: C, 72.01; H, 7.10; N, 2.95.
20. *Procedure for (S)-crystostyline II* **14**: To a suspension of PtO_2 (50 mg, 0.22 mmol) in MeOH (4 mL) were added **13** (173 mg, 0.39 mmol) and AcOH (0.1 mL) successively and the mixture was stirred under H_2 atmosphere for 12 h at rt. After removal of the catalyst by filtration, a saturated aqueous solution of $NaHCO_3$ was added to the filtrate and the mixture was extracted with AcOEt three times. The combined extracts were dried over Na_2SO_4 and evaporated to leave the crude product, which was dissolved in MeOH (2 mL). To the mixture was added a 30% formaldehyde solution (0.7 mL, 7 mmol) and it was stirred for 2 h at rt. After addition of $NaBH_4$ (19 mg, 0.5 mmol), the mixture was stirred for 10 h at rt. A saturated aqueous solution of NH_4Cl and a saturated aqueous solution of $NaHCO_3$ were added successively and the mixture was extracted with AcOEt three times. The combined extracts were dried over Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography (basic silica gel, hexane/AcOEt = 1/4 as eluent) to give **14** (77 mg, 0.22 mmol) as a colorless solid in 57% overall yield for two steps. The α_D value of synthetic (*S*)-cryptostyline II {$[\alpha]_D^{25}$ +55.4 (*c* 0.327, $CHCl_3$)} was identical to that of natural (*S*)-cryptostyline II {$[\alpha]_D^{25}$ +58 (*c* 0.28, $CHCl_3$)}.[14]