Palladium(0)-catalyzed Ring Expansion Reactions of Hydroxy Methoxyallenylisoindolinones via Inter- and Intramolecular Carbopalladation Using Aryl and Vinyl Halides

Yoshimitsu Nagao,*[a] Satoru Tanaka,[a] Akiharu Ueki,[a] Ill-Yun Jeong,[a] Shigeki Sano,[a] Motoo Shiro[b]

[a] Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi Tokushima 770-8505, Japan
Fax +81(88)6339503; E-mail: ynagao@ph2.tokushima-u.ac.jp

[b] Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196-8666, Japan

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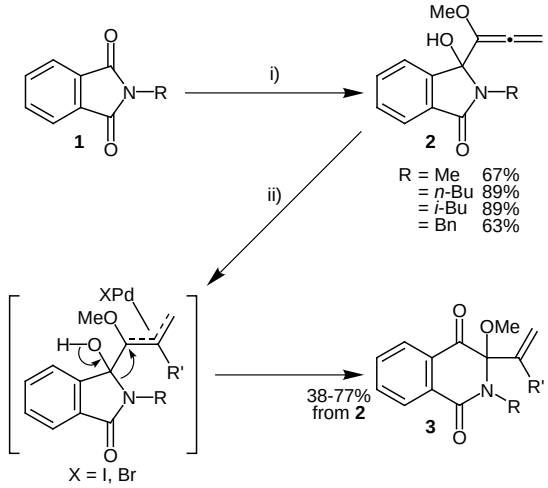
Abstract: Palladium(0)-catalyzed one-atom ring expansion of various hydroxy methoxyallenylisoindolinones **2** proceeded in the presence of aryl and vinyl halides to give the corresponding isoquinolinediones **3** in various yields. Tandem intramolecular carbopalladation-heterocyclic ring expansion reaction of compound **5** was also achieved to give a tetracyclic compound **6**.

Key words: allene, heterocycle, palladium, ring expansion, tandem reaction

As the ring expansion reactions have proved to be efficient tactics for the syntheses of various biologically active products and drugs,[1] recent efforts in our laboratory have focused on the base-mediated or palladium(0)-mediated ring expansion reactions using various hydroxy allenyl cyclic compounds.[2] In the previous ring expansion reactions, we achieved a palladium(0)-catalyzed tandem carbopalladation-heterocyclic one-atom ring expansion of hydroxy methylallenylisoindolinones based on the Heck-type reaction conditions giving the corresponding methyl vinyl isoquinolinediones.[2a,b,d] However, the methyl group of isoquinolinediones may restrict the flexibility of further synthetic application of the product. Therefore, we attempted the palladium(0)-catalyzed ring expansion reactions of more useful hydroxy methoxyallenylisoindolinones using aryl and vinyl halides, the results of which are herein described.

The starting hydroxy methoxyallenylisoindolinones **2** (63–89% yields) were prepared by treatment of the corresponding *N*-alkylphthalimides **1** with 1.0 mol equivalent of lithio methoxyallene[3] in THF at –78 °C for 1 hour.[4] The structures of **2** were confirmed by their characteristic spectroscopic data [^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99–3.50 (s, 3 H, OMe), 3.09–3.35 (s, 1 H, OH), 5.68–5.79 (d, 1 H, *J* = 8.5–8.6 Hz, allene H), and 5.74–5.84 (d, 1 H, *J* = 8.5–8.6 Hz, allene H); IR (KBr or neat): 3213–3296 (OH), 1955–1966 (allenyl) cm^{-1}; high resolution MS (M^+)] and elemental analyses. The ring expansion reactions were performed as follows. Namely, the compounds **2** were refluxed with 10 mol% of $Pd(PPh_3)_4$, 3 mol equivalents of K_2CO_3, and 4 mol equivalents of aryl iodides or an excess amount of vinyl bromide in THF for the indicated reaction times to give the corresponding *N*-alkylisoquinoline-1,4-diones **3** in 38–77% yields, respectively.[5] All experimental results are summarized in Scheme 1 and the Table. The structures of **3** were determined by their spectroscopic data [^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.78–3.27 (s, 3 H, OMe), 5.43–5.60 (s, 1 H, olefin H), and 5.57–6.02 (s, 1 H, olefin H); IR (neat): 1698–1715 (ketone), 1654–1660 (amide) cm^{-1}; high resolution MS (M^+)] and elemental analyses. The new *N*-alkylisoquinoline-1,4-diones, bearing a butadien-2-yl group, seem to be useful for the Diels–Alder reactions toward the syntheses of azasteroidal compounds.



Scheme 1 *Reagents and conditions*: i) methoxyallene (1.2 mol equiv), *n*-BuLi (1.0 mol equiv), THF, –78 °C. ii) $Pd(PPh_3)_4$ (10 mol%), R'-X (4 mol equiv), K_2CO_3 (3 mol equiv), THF, reflux.

Subsequently, an intramolecular carbopalladation-heterocyclic ring expansion of hydroxy methoxyallenylisoindolinone **5** was attempted. Compound **5**, obtained by treatment of *N*-*o*-iodobenzylphthalimide **4** with 1.2 mol equivalents of lithio methoxyallene in THF at –78 °C for 1 hour, was allowed to react with 10 mol% of $Pd(PPh_3)_4$ and 3 mol equivalents of K_2CO_3 in THF under reflux for 19 hours to afford the desired tetracyclic crystalline product **6** [mp 134–135 °C (from *n*-hexane–Et_2O–CH_2Cl_2)] in 37% yield (Scheme 2). The structure of **6** was explicitly

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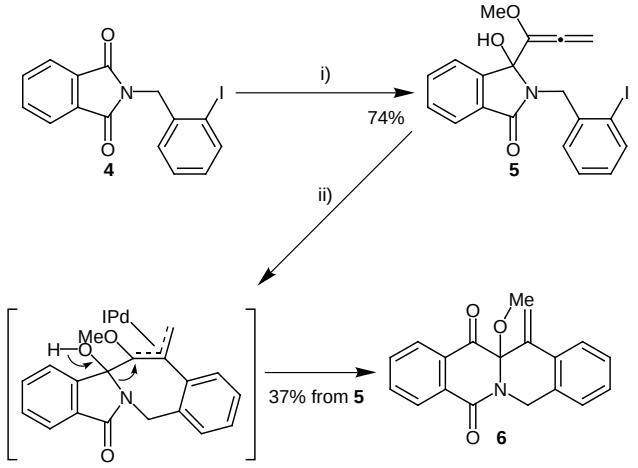
Table Conversion of Hydroxy Methoxyallenylisoindolinones **2** to *N*-Alkylisoquinoline-1,4-diones **3**[a]

R	R′	X	Time (h)	Yield (%)[b]	R	R′	X	Time (h)	Yield (%)[b]
Me	Ph	I	45	61	*i*-Bu	Ph	I	60	73
Me	*p*-MePh	I	48	77	*i*-Bu	*p*-MePh	I	44	62
Me	*p*-MeOPh	I	20	75	*i*-Bu	*p*-MeOPh	I	24	38
Me	vinyl	Br	21	67	*i*-Bu	vinyl	Br	22	73
n-Bu	Ph	I	96	62	Bn	Ph	I	60	74
n-Bu	*p*-MePh	I	48	46	Bn	*p*-MePh	I	60	69
n-Bu	*p*-MeOPh	I	33	44	Bn	*p*-MeOPh	I	21	51
n-Bu	vinyl	Br	41	67	Bn	vinyl	Br	20	65

[a] 4 Mol eq. of aryl iodide (R′-X) or an excess amount of vinyl bromide was employed.
[b] Isolated yields after purification by silica gel column chromatography.



Scheme 2 *Reagents and conditions*: i) methoxyallene (1.2 mol equiv), *n*-BuLi (1.2 mol equiv), THF, –78 °C, 1 h. ii) $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3 mol equiv), THF, reflux, 19 h.

determined by X-ray crystallographic analysis, as shown in the Figure.[6]

A possible reaction mechanism for the palladium(0)-catalyzed inter- and intramolecular carbopalladation-heterocyclic ring expansion reactions of hydroxy methoxyallenylisoindolinones can be rationalized in a manner similar to those for the previously reported ring expansion reactions.[2a]

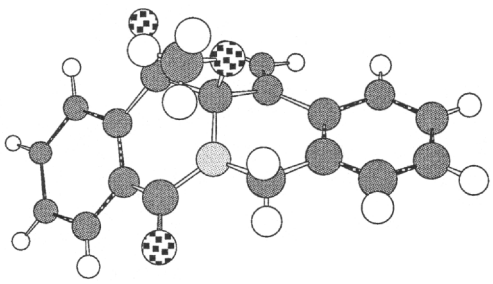


Figure Computer-generated drawing from the X-ray coordinates of **6**

In conclusion, we have demonstrated palladium(0)-catalyzed syntheses of various new *N*-alkylisoquinoline-1,4-diones bearing 3-methoxy and 3-vinyl [or 3-butadien-2-yl] groups. Intramolecular tandem carbopalladation-heterocyclic ring expansion reaction proved to be convenient for the expeditious synthesis of a tetracyclic quinolitidine derivative.

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(4) **Typical Experimental Procedure for Synthesis of a Hydroxy Methoxyallenylisoindolinone 2 (R = Me)**: A solution of methoxyallene (1.14 g, 16.27 mmol) in anhyd THF (17 mL) was treated with 1.61 M *n*-butyllithium in *n*-hexane (8.44 mL, 13.59 mmol) under N_2 atmosphere at –30 °C and stirred for 10 min. Then the solution was added to a THF (20 mL) solution of *N*-methylphthalimide **1** (R = Me) (2.19 g, 13.59 mmol) at –78 °C. After being stirred at –78 °C for 10 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to afford the crude product, which was purified by column chromatography on silica gel to give compound **2** (R = Me) (2.09 g, 67%) as yellow powder.

(5) **Typical Experimental Procedure for the intermolecular Ring Expansion Reaction**: A mixture of *N*-methyl-3-hydroxy-3-(1-methoxypropadienyl)isoindolin-1-one(**2**) (R = Me) (0.10 g, 0.43 mmol), $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol), K_2CO_3 (0.18 g, 1.30 mmol), and 4-iodotoluene (0.38 g, 1.74 mmol) in anhyd THF (8.6 mL) was refluxed under N_2 atmosphere for 48 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to afford the crude product, which was purified by column chromatography on silica gel with hexane–EtOAc (8:1) to give *N*-methyl-3-methoxy-3-[1-(*p*-methylphenyl)ether-2,3-dihydroisoquinoline]-1,4-dione **3** (R = Me, R′ = *p*-MePh) (0.104 g, 77%) as a pale yellow oil.

(6) X-ray data for **4**: $C_{19}H_{15}NO_3$, MW = 305.33, yellow prismatic crystal, monoclinic, space group $P2_1/c$ (#14), a = 7.836(1) Å, b = 26.084(5) Å, c = 7.770(1) Å, V = 1477.7(4) $Å^3$, β = 111.50(1)°, Z = 4, R = 0.067, Rw = 0.130.