Palladium-Catalyzed Intramolecular Cyclization of *o*-Ethynylbenzoic Acids and *o*-Ethynylbenzamides: Preparation of Isocoumarins and Isoquinolin-1-ones

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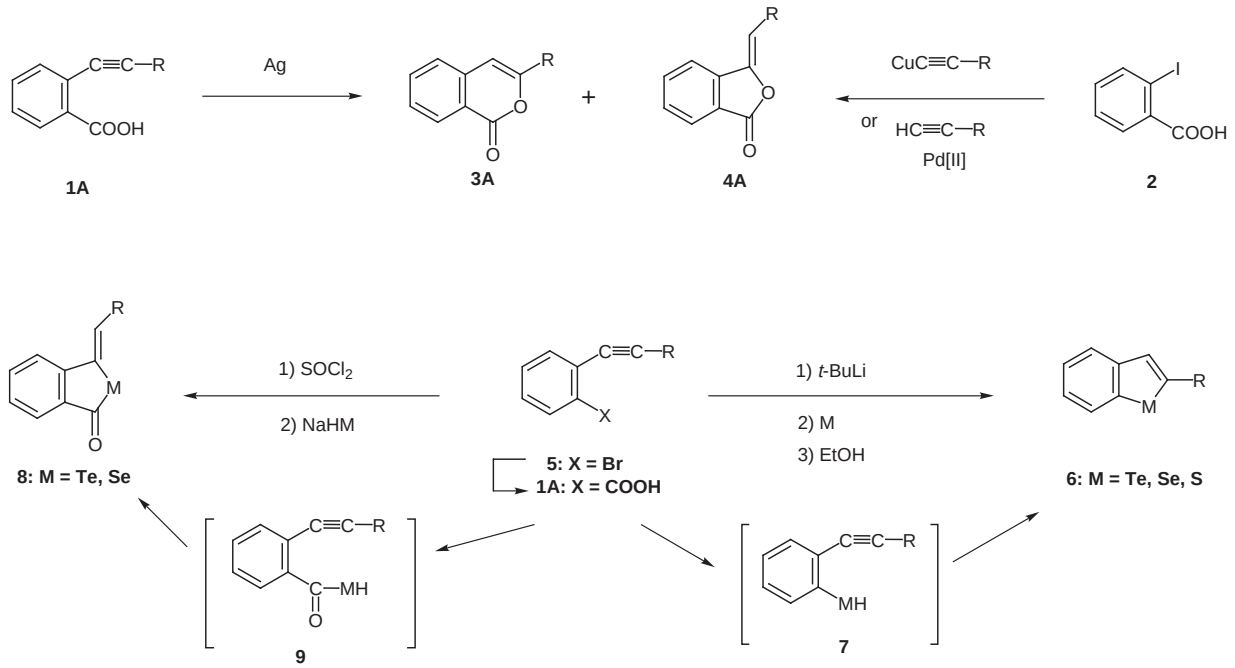
Abstract: Treatment of the *o*-ethynylbenzoic acids **1A** with a catalytic amount of Pd(II) and triethylamine resulted in the *6-endo-dig* cyclization to give the 3-substituted isocoumarins **3** as major products in moderate to good yields. Similarly, the palladium-catalyzed cyclization of *o*-ethynylbenzamides **1B** also proceeded but afforded only the isoquinolin-1-ones **3B**.

Key words: *o*-ethynylbenzoic acid, *o*-ethynylbenzamide, *6-endo-dig* cyclization, isocoumarin, isoquinolin-1-one

Heterocyclic ring formation by the intramolecular annulations of carboxylic acids,[1] alcohols,[2,3] amines[4,5] and amides[6] to a carbon–carbon triple bond is a well-documented procedure. Mercuric salts,[7] ruthenium[3] and palladium(II)[1,2,4,6] have been used as effective catalysts for the above ring-closure reactions. Various synthetic methods for the preparation of the isocoumarin skeleton have been investigated. In particular, the 3-substituted derivatives[8] are attractive synthetic targets because of their biological and pharmacological activities. Recently, the palladium-catalyzed cyclization of *o*-alkenylbenzoic acids[9] for the synthesis of isocoumarins was described. It has also been reported that silver salts[10] were effective for the *5-exo-dig* cyclization of the *o*-alkynylbenzoic acids **1A** affording the phthalides as major products. Castro and co-workers[11] described that the reaction of *o*-halobenzoic acid **2** with cuprous acetylides resulted in a direct ring closure to give the 3-methylidenephthalides **4A**. Moreover, the palladium–copper-catalyzed heteroannulation of *o*-iodobenzoic acid **2** with alk-1-ynes affording the 3-alkylidenephthalides (major products) and the isocoumarins (minor products) was reported by Kundu and co-workers.[12] Among them, cyclization of the *o*-alkynylbenzoic acids **1A** catalyzed by palladium has not yet been reported.

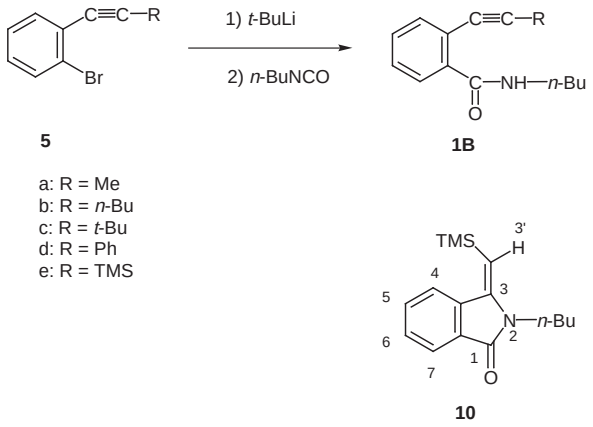
On the other hand, we have previously reported the synthesis of the five-membered heterocycles **6**, **8** containing a chalcogen element (Te, Se or S) as shown in Scheme 1.[13,14] The tellurophenes, selenophenes and thiophenes **6**[13] are easily obtained from the *o*-bromoethynylbenzenes **5** via the intermediates **7** in one pot. Compounds **9**,[14] which are the chalcogeno analogs of the parent benzoic acids **1A**, were regio- and stereospecifically cyclized to give the tel-



Scheme 1

luro- or seleno-phthalides **8** without any catalysts. Furthermore, we have recently demonstrated the synthesis of the tellurium- or selenium-containing heterocycles using an intramolecular ring closure involving a carbon–carbon triple bond.[15] In connection with our studies, we became interested in the palladium-catalyzed cyclization of the *o*-ethynylbenzoic acids **1A**. In this paper, we describe simple methods for the palladium-catalyzed regioselective ring closure of the *o*-ethynylbenzoic acids **1A** and the *o*-ethynylbenzamides **1B**, which led to the isocoumarins **3A** and the isoquinolinones **3B** as major products, respectively.

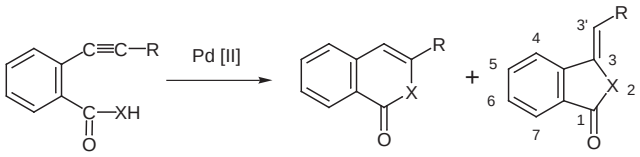
The key starting materials, the *o*-ethynylbenzoic acids **1A**, were already prepared in our previous work,[14] and the *o*-ethynylbenzamides **1B** were also easily obtained from the *o*-bromoethynylbenzenes **5**[13a] as shown in Scheme 2. Compounds **5** were lithiated with *tert*-BuLi in anhydrous THF at –80 °C and then treated with butyl isocyanate (BuNCO) to afford the benzamides **1B** in one pot in good yields (66–90%) except for the TMS derivatives **5e**, which gave the amide **1Be** in 27% yield together with the direct cyclized product **10** (59% yield) under these conditions.



Scheme 2

Cyclization of the *o*-ethynylbenzoic acids **1A** was first examined. Thermal (e.g., refluxing in xylene), acid (e.g., TsOH) or silver salt (e.g., $AgNO_3$) promoted and anionic (e.g., BuLi) cyclization could not proceed, while $PdCl_2(Ph_3P)_2$, $PdPhCH_2Cl(Ph_3P)_2$, $PdCl_2$ and $Pd(OAc)_2$ were less effective for this reaction. $PdCl_2(MeCN)_2$ and $PdCl_2(PhCN)_2$ usually gave good results for the cyclization of **1A**. Acetonitrile is the most suitable solvent, and the addition of a base (e.g. triethylamine) was essential for the reaction. In certain cases (**1Aa–d**), the isocoumarins **3A**, which were produced by the 6-*endo*-*dig* cyclization of **1A**, were found to be the predominant products. It is noted that the phthalides **4A**, the 5-*exo*-*dig* reaction products, were also obtained when the substituent was *t*-Bu, Ph or TMS. This ring-closure result clearly indicates that these benzoic acids **1Ac–e** having a bulky group at the end of the triple bond have more difficulty during the 6-*endo*-*dig* ring closure due to their steric hindrance. Thus, the 5-*exo*-*dig* reaction also proceeded. All the isocoumarins **3A** and the phthalides **4A** were well characterized by satisfactory spectroscopic (MS, IR and ^1H NMR) and analytical data, and the isocoumarins **3Aa–d** were identical with the authentic samples.[16] The stereochemistry of the alkene moiety of **4A** and **10** was determined by the nuclear Overhauser enhancement (NOE) measurement. In the case of the former, the NOE was observed between the 3'-H and the aromatic 4-H in the 400 MHz ^1H NMR spectra of **4Ac**. Thus, the alkene moiety was determined to have (*Z*)-stereochemistry. The latter has the NOE between the alkenic 3'-H and the methylene protons of the butyl group at the C-2 position. Thus, the stereochemistry of the alkene moiety of **10** was determined to be the (*E*)-form.

Next, we examined the ring closure reaction of *N*-butyl-*o*-ethynylbenzamides **1B**. $PdPhCH_2Cl(Ph_3P)_2$ was found to be a more effective catalyst than $PdCl_2(MeCN)_2$ in this reaction. The reaction of **1B** with this palladium catalyst and Et_3N in refluxing THF afforded the 3-substituted isoquinolin-1-ones **3Ba**, **b**, **d**, which were the sole isolated characterized products. In this case, the 5-*exo*-*dig* cyclization products **4B** were not obtained in spite of the careful experiment. The ring closure of the amides **1Bc** and **1Be**, which have a bulky group, also did not occur because of their definite steric hindrance at the adjacent position. The starting materials were decomposed without giving any products under these conditions. These results are summarized in Scheme 3.



1A: X = O
B: X = N*n*-Bu

		3	4
Aa	R = Me	81%	—
b	Bu	73%	—
c	*t*-Bu	48%	38%
d	Ph	56%	23%
e	TMS	31%	41%
Ba	R = Me	75%	—
b	Bu	77%	—
d	Ph	64%	—

Scheme 3

Mps were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were determined with a Hitachi 270–30 spectrometer. Mass spectra (MS) and HRMS were recorded on a JEOL JMS-DX300 instrument. NMR spectra were determined with a PMX-60SI (60 MHz), JEOL EX-90A (90 MHz) or JEOL JNM-GSX 400 (400 MHz) spectrometer in $CDCl_3$ using

TMS as internal standard. Microanalyses were performed in the Microanalytical Laboratory of this Faculty.

***N*-Butyl-*o*-ethynylbenzamide 1B; Typical Procedure**

To a stirring solution of *o*-bromoethynylbenzene **5** (10 mmol) in anhyd THF (50 mL) at –80 °C under Ar was slowly added *t*-BuLi (1.6 mol/l in pentane solution, 9.38 ml, 15 mmol). The mixture was stirred under these conditions for 1 h. A solution of BuNCO (1.49 g, 15 mmol) in THF (5 mL) was added to the mixture, and then the cooling bath was removed. The mixture allowed to warm to r.t., and stirred for an additional 12h. The mixture was quenched by pouring into ice-water, and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was washed with brine (2 x 100 mL), dried ($MgSO_4$), and evaporated in vacuo. The resulting residue was chromatographed on silica gel using CH_2Cl_2–acetone (30:1) as eluent to give pure **1B**. The crystalline product was recrystallized from EtOAc–hexane. In the case of TMS derivative **5e**, the isoindolone **10** was also obtained in these conditions.

1Ba (R = Me): colorless prisms, mp 79–80 °C; yield: 1.53 g (71%).

MS: *m/z* = 215 (M^+).

IR: ν = 3272 (NH), 2214 (CC), 1640 cm^{-1} (C=0).

^{1}H NMR (60 MHz): δ = 0.97, 1.2–1.8 and 3.45 (3H, t, *J* = 6 Hz, 4H, m and 2H, br t, *J* = 6 Hz, *N*-Bu), 2.06 (3H, s, Me), 7.2–7.5 and 7.9–8.1 (3H, m and 1H, m, PhH), 7.7 (1H, br, NH).

Anal. Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.92; H, 7.87; N, 6.62.

1Bb (R = Bu): colorless prisms, mp 57–60 °C; yield: 2.05 g (80%).

MS: *m/z* = 257 (M^+).

IR: ν = 3284 (NH), 2232 (CC), 1644 cm^{-1} (C=O).

^{1}H NMR (60 MHz): δ = 1.0, 1.1–1.9, 2.47 and 3.46 (6H, m, 8H, m, 2H, t, *J* = 6 Hz and 2H, br t, *J* = 6 Hz, *N*-Bu and Bu), 7.3–7.5 and 8.0–8.1 (3H, m and 1H, m, PhH), 7.6 (1H, br NH).

Anal. Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01; N, 5.44. Found: C, 78.66; H, 9.16; N, 5.49.

1Bc (R = *t*-Bu): colorless oil; yield: 2.30 g (90%).

MS: *m/z* = 257 (M^+).

IR: ν = 3324 (NH), 2236 (CC), 1654 cm^{-1} (C=O).

^{1}H NMR (60 MHz): δ = 0.95, 1.2–1.7 and 3.44 (3H, t, *J* = 6 Hz, 4H, m and 2H, br t, *J* = 6 Hz, *N*-Bu), 1.34 (9H, s, *t*-Bu), 7.2–7.5 and 7.9–8.1 (3H, m and 1H m, PhH), 7.9 (1H, br, NH).

HRMS *m/z*: M^+ Calcd for $C_{17}H_{23}ON$: 257.1780. Found 257.1774.

1Bd (R = Ph): colorless prisms, mp 123–125 °C; yield: 1.83 g (66%).

MS: *m/z* = 277 (M^+).

IR: ν = 3276 (NH), 2224 (CC), 1642 cm^{-1} (C=O).

^{1}H NMR (60 MHz): δ = 0.84, 1.2–1.8 and 3.50 (3H, t, *J* = 6 Hz, 4H, m and 2H, br t, *J* = 6 Hz, *N*-Bu), 7.1–7.7 and 7.9–8.1 (9H, m and 1H m, PhH and NH).

Anal. Calcd. for $C_{19}H_{19}ON$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.10; H, 7.15; N, 5.12.

1Be (R = TMS): yellow oil; yield: 0.74 g (27%).

MS: *m/z* = 273 (M^+).

IR: ν = 3120 (NH), 2160 (CC), 1664 cm^{-1} (C=O).

^{1}H NMR (60 MHz): δ = 0.25 (9H, s, TMS), 0.93, 1.2–1.7 and 3.44 (3H, t, *J* = 6.0 Hz, 4H, m and 2H, br t, *J* = 7 Hz, *N*-Bu), 7.2–7.5 and 7.8–8.0 (3H, m and 1H, m, PhH), 7.7 (1H, br, NH).

HRMS *m/z*: M^+ Calcd for $C_{16}H_{23}ONSi$: 273.1549. Found: 273.1551.

(*E*)-*N*-Butyl-3-(2'-trimethylsilyl)methylideneisoindolone 10

Yellow oil; 1.60 g (59%).

MS: *m/z* = 273 (M^+).

IR: ν = 1712 cm^{-1} (C=O).

^{1}H NMR (400 MHz): δ = 0.29 (9H, s, TMS), 0.83–0.92, 1.29–1.36, 1.53–1.62 and 3.69–3.73 (3H, m, 2H, m, 2H, m and 2H, m, *N*-Bu), 5.23 (1H, s, 3'-H), 7.42–7.78 (4H, m, PhH).

HRMS *m/z*: M^+ Calcd for $C_{16}H_{23}ONSi$: 273.1549. Found: 273.1549.

Cyclization *o*-Ethynylbenzoic Acid 1A: Fomation of Isocoumarin 3A and (*Z*)-3-Methylidenephthalide 4A; Typical Procedure

To a mixture of **1A** (1mmol) and Et_3N (0.5 ml) in anhyd THF (20 mL) was added $PdCl_2(MeCN)_2$ (25 mg, 0.1 mmol). The mixture was stirred at r.t. until disappearance of the starting material (about 6–12 h). Water was added to the mixture, and the resulting aqueous mixture was extracted with Et_2O (3 x 50 mL). The combined organic extract was washed with brine (2 x 100 mL) dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel using hexane–CH_2Cl_2 (1:2) as eluent to give **3A** and **4A**. The crystalline product was recrystallized from hexane.

3Aa (R = Me): colorless prisms, mp 69–73 °C (lit.[16] mp 71 °C); 130 mg (81%).

3Ab (R = Bu): colorless prisms, mp 45–46 °C (lit.[16] mp 44 °C); 147 mg (73%).

3Ac (R = *t*-Bu): colorless prisms, mp 62–65 °C (lit.[16] mp 61 °C); 97 mg (48%).

4Ac (R = *t*-Bu): colorless prisms, mp 90–91 °C; yield: 77 mg (38%).

MS: *m/z* = 202 (M^+).

IR: ν = 1788 cm^{-1} (C=O).

^{1}H NMR (90 MHz): δ = 1.32 (9H, s, *t*-Bu), 5.60 (1H, s, 3'-H), 7.48–7.68 and 7.88 (3H, m and 1H, d, *J* = 7.7 Hz, PhH).

Anal Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C,76.64; H, 7.05.

3Ad (R = Ph): yellow prisms, mp 87–88 °C (lit.[16] mp 87–88 °C); 124 mg (56%).

4Ad (R = Ph): colorless prisms, mp 86–88 °C; yield: 51 mg (23%).

MS: *m/z* = 222 (M^+).

IR: ν = 1766 cm^{-1} (C=O).

^{1}H NMR (90 MHz): δ = 6.46 (1H, s, 3'-H), 7.70–8.47 (9H, m, PhH).

HRMS *m/z*: M^+ Calcd for $C_{15}H_{10}O_2$: 222.0681. Found: 222.0685.

3Ae (R = TMS): colorless oil; yield: 68 mg (31%).

MS: *m/z* = 218 (M^+).

IR: ν = 1726 cm^{-1} (C=O).

^{1}H NMR (90 MHz): δ = 0.28 (9H, s, TMS), 6.70 (1H, s, 4-H), 7.35–7.89 and 8.23–8.43 (3H, m and 1H, m, PhH).

HRMS *m/z*: M^+ Calcd for $C_{12}H_{14}O_2Si$: 218.0763. Found: 218.0761.

4Ae (R = TMS): yellow oil; yield: 89 mg (41%).

MS: *m/z* = 218 (M^+).

IR: ν = 1788 cm^{-1} (C=O).

^{1}H NMR (90 MHz): δ = 0.28 (9H, s, TMS), 5.66 (1H, s, 3'-H), 7.50–8.01 (4H, m, PhH).

HRMS *m/z*: M^+ Calcd for $C_{12}H_{14}O_2Si$: 218.0763. Found: 218.0765.

Cyclization *N*-Butyl-*o*-ethynylbenzamide 1B: Fomation of Isoquinolin-1-one 3B; Typical Procedure

To a mixture of **1B** (1mmol) and Et_3N (0.5 mL) in anhyd THF (20 mL) was added $PdPhCH_2Cl(Ph_3P)_2$ (25 mg, 0.03 mmol). The mixture was refluxed with stirring until disappearance of the starting material (about 12–20 h). Water was added to the mixture, and the resulting aqueous mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extract was washed with brine (2 x 100 mL) dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel using CH_2Cl_2–acetone (30: 1) as eluent to give **3B**.

***N*-Butyl-3-methylisoquinolin-1-one 3Ba (R = Me)**

Yellow oil, yield: 161 mg (75%).

MS: *m/z* = 215 (M^+).

IR: ν = 1656 cm^{-1} (C=O).

^{1}H NMR (90 MHz): δ = 0.97, 1.17–1.91 and 3.47 (3H, t, *J* = 6.4 Hz, 4H, m and 2H, t, *J* = 6.5 Hz, *N*-Bu), 2.12 (3H, s, Me),5.86 (1H, s, 4-H), 7.01–7.55 and 8.18 (3H, m and 1H, d, *J* = 7.0 Hz, PhH).

HRMS *m/z*: M^+ Calcd for $C_{14}H_{17}ON$: 215.1310. Found 215.1310.

***N*-Butyl-3-butylisoquinolin-1-one 3Bb (R = Bu)**

Yellow oil; yield: 198 mg (77%).

MS: *m/z* = 257 (M^+).

IR: ν = 1654 cm^{-1} (C=O).

^{1}H NMR (90 MHz): δ = 0.72–1.93, 2.36 and 3.49 (14 H, m, 2H, t, *J* = 6.0 Hz and 2H, t, *J* = 7.0 Hz, Bu and *N*-Bu), 5.83 (1H, s, 4-H), 6.97–7.54 and 8.17 (3H, m and 1H, d, *J* = 7.4 Hz, PhH).

HRMS *m/z*: M^+ Calcd for $C_{17}H_{23}ON$: 257.1780. Found 257.1779.

***N*-Butyl-3-phenylisoquinolin-1-one 3Bd (R = Ph)**

Yellow oil; yield: 177 mg (64%).

MS: *m/z* = 277 (M^+).

IR: ν = 1642 cm^{-1} (C=O).

^{1}H NMR (90 MHz): δ = 0.98, 1.33–1.90 and 3.64 (3H, t, *J* = 6.6 Hz, 4H, m and 2H, t, *J* = 6.6 Hz, *N*-Bu), 6.56 (1H, s, 4-H), 7.27–7.47, 7.70–7.89 and 8.21 (5H, m, 3H, m and 1H, dd, *J* = 6.2, 2.2 Hz, PhH).

HRMS *m/z*: M^+ Calcd for $C_{19}H_{19}ON$: 277.1467. Found 277.1461.

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