

STEREOSELECTIVE SYNTHESIS OF (Z)-2,3-DIHYDRO-3-(ARYLMETHYLENE)BENZOFURANS VIA THE PALLADIUM CATALYZED INSERTION AND CROSS COUPLING REACTION OF 1-iodo-2-(2-propynyloxy)benzene and arylzinc chloride

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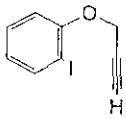
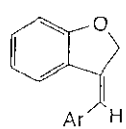
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Abstract- The title compound was prepared in fair to good yields from 1-iodo-2-(2-propynyloxy)benzene and arylzinc chloride via tandem insertion and cross coupling reaction catalyzed by pertinent palladium catalyst, such as palladium acetate and triphenylphosphine.

Recently, work by Grigg¹ and ourselves^{2,3} has demonstrated that the Pd(II)-intermediate obtained in situ from intramolecular insertion of alkynes can be further cross coupled with aryl- or heteroarylzinc chloride to give stereo-defined exocyclic indan, tetralin, and indole derivatives in fair to good yields. Herein we report that this procedure can provide a facile synthetic method for (Z)-3-coumaranylidene compound whose preparation has rarely been reported.⁴

We observed that Pd(PPh₃)₄ was a good catalyst for our previous studies^{2,3} but, to our chagrin, it works poorly in 1-iodo-2-(2-propynyloxy)benzene (1). For example, the reaction of 1 with phenylzinc chloride in the presence of a catalytic amount of Pd(PPh₃)₄ in THF gave 2-(2-propynyloxy)-biphenyl (2) and (Z)-2,3-dihydro-3-(phenylmethylene)benzofuran (3) in 45% and 18% yields, respectively. We then tried to use different palladium catalyst in order to optimize the yield of cyclized and coupled product (4). To our surprise, the catalytic system⁵ including palladium acetate

Table I.
The Reaction of **1** with Arylzinc Chloride in the Presence of Palladium Catalyst ^a

 1 $\xrightarrow[\text{ArZnCl, THF, } 25^{\circ}\text{C, 2 h}]{\text{cat. Pd(OAc)}_2\text{-PPh}_3\text{-Et}_3\text{N}}$  4		
Entry	ArZnCl Ar =	Product (Iso. Yield, %)
1	Ph-	3 (62) ^b
2		5 (44) ^b
3		6 (48) ^b
4		7 (54) ^c
5		8 (47) ^b
6		9 (64) ^b

^a See text. ^b Direct coupled product was undetectable by glc analysis.

^c Only trace amount (< 5%) of direct coupled product was obtained.

(0.1 equiv.), triphenylphosphine (0.25 equiv.), and triethylamine (3 equiv.) used in the reaction of **1** can provide not only fair to good yields of **4** but also very low yields of direct coupled products which are always undesired in our previous studies^{2,3} as shown in Table I. Thus, the reaction of **1** with phenylzinc chloride in this catalytic system gave **3** in 62% and undetectable (by glc analysis) amount of **2**. It should be pointed out that in the absence of the palladium catalyst or using 1 equiv. instead of 0.25 equiv. of triphenylphosphine, the desired product **3** was obtained in very low yields. The stereochemistry of **4** was determined by their ¹H-nmr as well as 2D NOESY spectra analyses.

EXPERIMENTAL SECTION

Melting points are uncorrected. Precoated silica gel 60F-254 on aluminum plates made by EM Chemical Company were used for thin layer chromatography. Purification by column chromatography was carried out with EM Reagents silica gel 60 (70-230 mesh ASTM). High pressure liquid chromatography (hplc) separation was performed at a flow rate of 3 ml/min by use of two Chemco Pak 10 x 250 columns packed with Chemcosorb 5-ODS-H. Glc analyses were performed on a 3.2 m x 3.1 mm column packed with SE-30 (5% on chromosorb W). The purity of each compound was judged to be $\geq 95\%$ by hplc, glc, ^1H -nmr, as well as ^{13}C -nmr spectra analyses. Zinc chloride was dried before use at 100°C at 1 mm for 3 h. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use.

1-Iodo-2-(2-propynyloxy)benzene (1)⁶: To a mixture of potassium carbonate (2.77 g, 20 mmol) and acetone (30 ml) was added 2-iodophenol⁷ (2.20 g, 10 mmol) under nitrogen atmosphere at room temperature. After stirring for 1 h at room temperature, to the mixture was added propargyl bromide (1.78 g, 15 mmol). The solution was then reflux for another 4 h. After removing large part of acetone by a rotatory evaporator, 20 ml of water was added to the mixture. The organic layer was extracted with diethyl ether (25 ml x 3). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and distilled to give 2.29 g (89% yield) of **1** as a colorless liquid. (**1**): bp $63-64^\circ\text{C}/3\text{ mm}$. ^1H -Nmr (CDCl_3 , TMS) δ 2.54 (t, $J = 2.3\text{ Hz}$, 1 H), 4.77 (d, $J = 2.3\text{ Hz}$, 2 H), 6.77 (dt, $J = 1.0, 7.7\text{ Hz}$, 1 H), 7.00 (dd, $J = 1.0, 7.7\text{ Hz}$, 1 H), 7.33 (dt, $J = 1.4, 7.7\text{ Hz}$, 1 H), 7.79 (dd, $J = 1.4, 7.7\text{ Hz}$, 1 H) ppm. ^{13}C -Nmr (CDCl_3 , TMS) δ 56.73, 75.99, 77.86, 86.42, 112.89, 123.27, 129.17, 139.49, 156.07 ppm. Ir (neat) ν 3290, 2120, 1470, 1020, 750 cm^{-1} . Ms m/z 258 (M^+), 219, 191, 131. Hrms Calcd for $\text{C}_9\text{H}_7\text{OI}$ 257.9542, found 257.9544.

(Z)-2,3-Dihydro-3-(phenylmethylene)benzofuran (3). A Representative Procedure for Pd-Catalyzed Stereoselective Synthesis of (Z)-2,3-Dihydro-3-(arylmethylene)benzofuran via Insertion and Cross Coupling Reactions. To a

mixture of 1-iodo-2-(2-propynyloxy)benzene (1) (1.29 g, 5 mmol) and triethylamine (2.1 ml, 15 mmol) in THF (25 ml) was added palladium acetate (0.11 g, 0.5 mmol) and triphenylphosphine (0.33 g, 1.25 mmol) in THF (10 ml) at 25°C. After stirring at 25°C for 10 min, phenylzinc chloride solution, prepared by mixing phenylmagnesium bromide (13.4 ml of 1.12 N in THF) and zinc chloride solution (15 ml of 1 N in THF) at 25°C, was added to the reaction mixture. The reaction mixture was then stirred for another 2 h and quenched by adding water (25 ml) at 0°C. The organic layer was extracted with diethyl ether (20 ml x 3). The combined organic layer was washed with water (15 ml) and brine (15 ml), dried over MgSO_4 , filtered, concentrated, and purified by column chromatography (silica gel, hexane/ether = 10/1) and hplc (methanol) to give (Z)-2,3-dihydro-3-(phenylmethylene)benzofuran (3) (0.65 g, 62% yield) as a colorless liquid. (3): $^1\text{H-Nmr}$ (CDCl_3 , TMS) δ 5.22 (d, J = 2.8 Hz, 2 H), 6.49 (t, J = 2.8 Hz, 1 H), 6.67 (t, J = 7.8 Hz, 1 H), 6.84 (d, J = 7.8 Hz, 1 H), 7.14 (t, J = 7.8 Hz, 1 H), 7.25-7.45 (m, 6 H) ppm. $^{13}\text{C-Nmr}$ (CDCl_3 , TMS) δ 75.97, 110.55, 117.94, 120.08, 123.68, 124.17, 127.07, 128.29, 130.51, 136.79 ppm. Ir (neat) ν 1470, 1200, 990, 750, 700 cm^{-1} . Ms m/z 208 (M^+), 207, 178, 131. Hrms Calcd for $\text{C}_{15}\text{H}_{12}\text{O}$ 208.0888, found 208.0889. Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{O}$: C, 86.51; H, 5.81. Found: C, 86.75; H, 5.99.

(Z)-2,3-Dihydro-3-(2-furanylmethylene)benzofuran (5): $^1\text{H-Nmr}$ (CDCl_3 , TMS) δ 5.21 (d, J = 2.6 Hz, 2 H), 6.16 (t, J = 2.6 Hz, 1 H), 6.35 (dt, J = 0.6, 3.3 Hz, 1 H), 6.47 (dd, J = 1.8, 3.3 Hz, 1 H), 6.84-6.97 (m, 2 H), 7.22 (dt, J = 1.4, 7.9 Hz, 1 H), 7.53-7.54 (m, 1 H), 8.34 (dd, J = 1.4, 7.8 Hz, 1 H) ppm. $^{13}\text{C-Nmr}$ (CDCl_3 , TMS) δ 76.53, 105.13, 109.97, 110.20, 111.51, 120.63, 124.05, 125.26, 130.70, 134.26, 141.69, 151.93, 165.54 ppm. Ir (neat) ν 1460, 1210, 1000, 750 cm^{-1} . Ms m/z 198 (M^+), 197, 169, 141, 115. Hrms Calcd for $\text{C}_{13}\text{H}_{10}\text{O}_2$ 198.0681, found 198.0681. Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{O}_2$: C, 78.77; H, 5.08. Found: C, 78.96; H, 5.21.

(Z)-2,3-Dihydro-3-(2-thiophenylmethylene)benzofuran (6): $^1\text{H-Nmr}$ (CDCl_3 , TMS) δ 5.20 (d, J = 2.7 Hz, 2 H), 6.44 (t, J = 2.7 Hz, 1 H), 6.74-6.88 (m, 2 H),

7.04-7.32 (m, 4 H), 7.65 (dd, $J = 1.2, 7.9$ Hz, 1 H) ppm. $^{13}\text{C-Nmr}$ (CDCl_3 , TMS) δ 76.08, 109.89, 110.60, 120.30, 123.90, 125.07, 126.54, 127.10, 130.87, 138.12, 138.93, 165.28 ppm. Ir (neat) ν 1460, 1210, 990, 840, 750, 700 cm^{-1} . Ms m/z 214 (M^+), 213, 184, 171, 152. Hrms Calcd for $\text{C}_{13}\text{H}_{10}\text{OS}$ 214.0452, found 214.0446. Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{OS}$: C, 72.87; H, 4.70. Found: C, 72.66; H, 4.81.

(Z)-2,3-Dihydro-3-(2-N-methylpyrrolylmethylene)benzofuran (7): $^1\text{H-Nmr}$ (CDCl_3 , TMS) δ 3.55 (s, 3 H), 5.23 (d, $J = 2.7$ Hz, 2 H), 6.17-6.22 (m, 2 H), 6.39-6.42 (m, 1 H), 6.66-6.87 (m, 3 H), 7.17 (dt, $J = 1.3, 7.6$ Hz, 1 H), 7.58 (dd, $J = 1.1, 7.7$ Hz, 1 H) ppm. $^{13}\text{C-Nmr}$ (CDCl_3 , TMS) δ 33.94, 75.95, 107.26, 107.52, 108.99, 110.31, 120.40, 122.14, 123.48, 124.53, 128.74, 130.49, 137.38, 164.96 ppm. Ir (neat) ν 1465, 1300, 1210, 990, 750, 710 cm^{-1} . Ms m/z 211 (M^+), 196, 182, 167, 152, 141. Hrms Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}$ 211.0997, found 211.1004. Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.75; H, 6.33; N, 6.83.

(Z)-2,3-Dihydro-3-(2-pyridinylmethylene)benzofuran (8): mp 44-45°C. $^1\text{H-Nmr}$ (CDCl_3 , TMS) δ 5.28 (d, $J = 2.7$ Hz, 2 H), 6.46 (t, $J = 2.7$ Hz, 1 H), 6.83-6.90 (m, 2 H), 7.13-7.34 (m, 3 H), 7.68 (dt, $J = 1.8, 7.7$ Hz, 1 H), 8.54 (d, $J = 7.1$ Hz, 1 H), 8.71 (d, $J = 4$ Hz, 1 H) ppm. $^{13}\text{C-Nmr}$ (CDCl_3 , TMS) δ 76.76, 110.38, 117.14, 120.38, 121.23, 123.95, 127.13, 131.64, 136.14, 140.78, 149.06, 155.51, 166.25 ppm. Ir (KBr) ν 1636, 1584, 1466, 1210, 1150, 1095, 1025, 750 cm^{-1} . Ms m/z 209 (M^+), 180, 152, 131. Hrms Calcd for $\text{C}_{14}\text{H}_{11}\text{NO}$ 209.0841, found 209.0850. Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{NO}$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.60; H, 5.38; N, 6.80.

(Z)-2,3-Dihydro-3-(3-pyridinylmethylene)benzofuran (9): mp 75-76°C. $^1\text{H-Nmr}$ (CDCl_3 , TMS) δ 5.24 (d, $J = 2.8$ Hz, 2 H), 6.40 (t, $J = 2.8$ Hz, 1 H), 6.70 (t, $J = 7.8$ Hz, 1 H), 6.87 (d, $J = 7.8$ Hz, 1 H), 7.15-7.36 (m, 3 H), 7.73 (d, $J = 7.8$ Hz, 1 H), 8.54 (dd, $J = 1.7, 4.9$ Hz, 1 H), 8.69 (d, $J = 2.1$ Hz, 1 H) ppm. $^{13}\text{C-Nmr}$ (CDCl_3 , TMS) δ 75.92, 110.93, 113.62, 120.38, 123.21, 123.46, 123.68, 131.21, 131.88, 132.72, 135.63, 139.42, 148.14, 149.49, 165.43 ppm. Ir (KBr) ν 1643, 1586, 1452, 1140, 1095, 1020, 749 cm^{-1} . Ms m/z

209 (M⁺), 208, 180, 152, 131. Hrms Calcd for C₁₄H₁₁NO 209.0841, found 209.0851. Anal. Calcd for C₁₄H₁₁NO: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.62; H, 5.36; N, 6.86.

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