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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

Fen-Tair Luo* and Ren-Tzong Wang
Institute of Chemistry, Academia Sinica, Nankang, Taipei, Taiwan, Republic of China

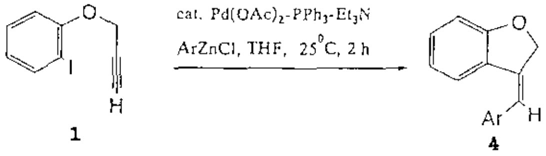
Abstract- The title compound was prepared in fair to good yields from 1-iodo-2-(2-propynyloxy)benzene and arylzinc chloride via tandem insertion and cross coupling reaction catalyzed by pertinent palladium catalyst, such as palladium acetate and triphenylphosphine.

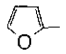
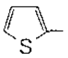
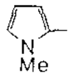
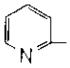
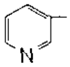
Recently, work by Grigg[1] and ourselves[2,3] has demonstrated that the Pd(II)-intermediate obtained in situ from intramolecular insertion of alkynes can be further cross coupled with aryl– or heteroarylzinc chloride to give stereo-defined *exocyclic* indan, tetralin, and indole derivatives in fair to 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 $Pd(PPh_3)_4$ 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 $Pd(PPh_3)_4$ 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 system[5] including palladium acetate

Table I.

The Reaction of 1 with Arylzinc Chloride in the Presence of Palladium Catalyst[a]



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 ^{1}H-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 ≥95% by hplc, glc, ^{1}H-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-iodophenol[7] (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°C/3 mm. ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.54 (t, J = 2.3 Hz, 1 H), 4.77 (d, J = 2.3 Hz, 2 H), 6.77 (dt, J = 1.0, 7.7 Hz, 1 H), 7.00 (dd, J = 1.0, 7.7 Hz, 1 H), 7.33 (dt, J = 1.4, 7.7 Hz, 1 H), 7.79 (dd, J = 1.4, 7.7 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) υ 3290, 2120, 1470, 1020, 750 cm^{-1}. Ms m/z 258 (M^+), 219, 191, 131. Hrms Calcd for C_9H_7OI 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}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}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 $C_{15}H_{12}O$ 208.0888, found 208.0889. Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.75; H, 5.99.

(Z)-2,3-Dihydro-3-(2-furanylmethylene)benzofuran (5): ^{1}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}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 $C_{13}H_{10}O_2$ 198.0681, found 198.0681. Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.08. Found: C, 78.96; H, 5.21.

(Z)-2,3-Dihydro-3-(2-thiofenylmethylene)benzofuran (6): ^{1}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}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) υ 1460, 1210, 990, 840, 750, 700 cm^{-1}. Ms m/z 214 (M^+), 213, 184, 171, 152. Hrms Calcd for $C_{13}H_{10}OS$ 214.0452, found 214.0446. Anal. Calcd for $C_{13}H_{10}OS$: C, 72.87; H, 4.70. Found: C, 72.66; H, 4.81.

(Z)-2,3-Dihydro-3-(2-N-methylpyrrolylmethylene)benzofuran (7): ^{1}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}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) υ 1465, 1300, 1210, 990, 750, 710 cm^{-1}. Ms m/z 211 (M^+), 196, 182, 167, 152, 141. Hrms Calcd for $C_{14}H_{13}NO$ 211.0997, found 211.1004. Anal. Calcd for $C_{14}H_{13}NO$: 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}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}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) υ 1636, 1584, 1466, 1210, 1150, 1095, 1025, 750 cm^{-1}. Ms m/z 209 (M^+), 180, 152, 131. Hrms Calcd for $C_{14}H_{11}NO$ 209.0841, found 209.0850. Anal. Calcd for $C_{14}H_{11}NO$: 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}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}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) υ 1643, 1586, 1452, 1140, 1095, 1020, 749 cm^{-1}. Ms m/z

209 (M^+), 208, 180, 152, 131. Hrms Calcd for $C_{14}H_{11}NO$ 209.0841, found 209.0851. Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.62; H, 5.36; N, 6.86.

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