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STEREOSELECTIVE SYNTHESIS OF 1-INDANYLIDENE SUBSTITUTED HETEROAROMATIC DERIVATIVES VIA Pd-CATALYZED TANDEM INSERTION AND CROSS COUPLING REACTIONS

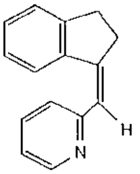
Fen-Tair Luo* and Ren-Tzong Wang
Institute of Chemistry, Academia Sinica,
Nankang, Taipei, Taiwan, R.O.C.

Abstract - Treatment of 4-(*o*-iodophenyl)-1-butyne with a variety of heteroarylzinc chlorides in the presence of a catalytic amount of $Pd(PPh_3)_4$ gave (*Z*)-1-indanylidene substituted heteroaromatics in moderate to good yields with high *Z*-selectivities.

The palladium-catalyzed reactions of either alkynes and alkenes with organic halides or organozinc chlorides with organic halides have been extensively studied to provide a good approach to form carbon-carbon bond.[1-4] Although particular attention has been paid to the former type reaction, also known as "Heck reaction", the number of papers reporting the potential utility of the Pd(II)-intermediate, obtained from the insertion of alkyne group,are still very small.[5-12]

Recently we have found that the Pd(II)-intermediate obtained in situ from intramolecular arylation of alkynes can be further cross coupled with phenylzinc chloride and gave stereo-defined exocyclic indan and tetralin derivatives.[13] The undesired coupling products were obtained only in 2-25% yields.

We now report that a variety of heteroarylzinc chlorides can indeed be readily cross coupled with the Pd(II)-intermediate, obtained rapidly from 4-(*o*-iodophenyl)-1-butyne(**1**)and a catalytic amount of $Pd(PPh_3)_4$, to give (*Z*)-1-indanylidene substituted heteroaromatics in moderate to good yields. As representative heteroaromatics 2- and 3-pyridyl, 2-furyl, 2-thienyl, 2-N-methylpyrrolyl, and 2-benzothiazolyl were chosen. As indicated by the structures of the products(**2**) to **7** as well as by the results summarized in the Table I, syntheses of the stereo-defined 1-indanylidene substituted systems can now be readily achieved by the Pd-catalyzed intramolecular insertion and cross coupling processes. Their stereochemistry was again determined by their ^{1}H-nmr as well as 2D NOESY



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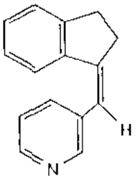

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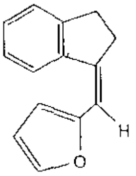

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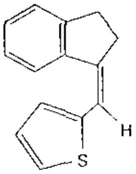

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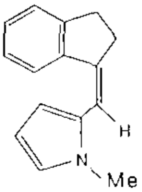

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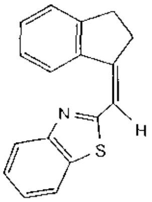

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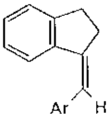
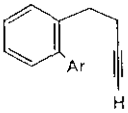
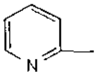
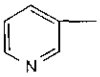
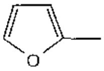
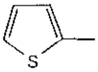
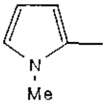
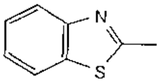
Table 1. The Reaction of **1** with Heteroarylzinc Chlorides in the Presence of Pd(0) Catalyst.

Entry	Heteroarylzinc Chloride [a] ArZnCl Ar =	Product 	Yield [b] (%)	Byproduct (%)[b] 
1		**2**	66	trace
2		**3**	53	trace
3		**4**	58	**8** (28)
4		**5**	74	**9** (6)
5		**6**	52	**10** (33)
6		**7**	70	**11** (21)

[a] Heteroarylzinc chlorides were prepared by treating the corresponding organolithium[15] with one equivalent of dry $ZnCl_2$ in THF.

[b] Isolated yields of pure products.

spectral analyses. While the yield of uncyclized products obtained from either 2-pyridyl- or 3-pyridylzinc chloride is only trace amount, the isolated yields of uncyclized products (**8**-**11**) are between 6-33%.

On the basis of the current study, it is clear that this methodology could be extended to the preparation of other valuable derivatives of stereo-defined and carbo-substituted heteroaromatics. In fact, until the present time, the preparation of (*Z*)-1-indanylidene substituted heteroaromatics has rarely been reported.[14]

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). 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 all title compounds was judged to be ≥95% by gc, ^{1}H-nmr, as well as ^{13}C-nmr spectra analysis. Zinc chloride was dried before use at 100°C at 1 mmHg for 3 h. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use.

(*Z*)-2-(1-Indanylidenemethyl)pyridine **2**. A Representative Procedure for Pd-Catalyzed Stereoselective Synthesis of 1-Indanylidene Substituted Heteroaromatics via Insertion and Cross Coupling Reactions. To a mixture of 4-(*o*-iodophenyl)-1-butyne (0.77 g, 3 mmol) in 5 ml of THF were sequentially added $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol) in 2 ml of THF and 2-pyridylzinc chloride solution, prepared by mixing 2-pyridyllithium[15] (9 ml of 1 N in THF) and zinc chloride solution (9 ml of 1 N in THF) at 0°C, over a period of 2 h. The reaction mixture was then stirred at room temperature for another 8 h. The reaction mixture was quenched by adding water (10 ml) at 0°C and the organic layer was extracted with diethyl ether (20 ml x 3). The combined organic layer was washed with water (10 ml) and brine (10 ml), dried over magnesium sulfate, filtered, concentrated, and purified by column chromatography (hexane/ether = 10/1) to give **2** (0.41 g, 1.98 mmol) as a colorless liquid in 66% yield and trace (<2%) amount of the uncyclized product 2-[2-(3-butynyl)phenyl]pyridine. **2**: ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.9-3.1 (m, 4 H), 6.63 (s, 1 H), 7.03 (dt, J = 0.7, 7.8 Hz, 1 H), 7.1-7.3 (m, 3 H), 7.39 (d, J = 7.8 Hz, 1 H), 7.64 (dt, J = 1.8, 7.8 Hz, 1 H), 7.77 (d, J = 7.8 Hz, 1 H), 8.64 (d, J = 4.8 Hz, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 29.96, 35.01, 120.86, 121.15, 123.64, 125.07, 125.34, 125.68, 128.72, 135.89, 138.83, 146.87, 149.17, 149.33, 156.75 ppm. Ir (neat) ν 1580, 1425, 755 cm^{-1}. Ms m/z 207 (M^+). Hrms calcd for $C_{15}H_{13}N$ 207.1048, found 207.1048. Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.68; H, 6.09; N, 6.98.

(*Z*)-3-(1-Indanylidenemethyl)pyridine **3**: 53% Yield. Colorless oil. ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.9-3.1 (m, 4 H), 6.52 (s, 1 H), 6.95 (t, 7.2 Hz, 1 H), 7.1-7.3 (m, 4 H), 7.69 (d, J = 7.5 Hz, 1 H), 8.51 (dd, J = 1.7, 4.8 Hz, 1 H), 8.6-8.7

(m, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 30.02, 34.18, 117.13, 123.11, 123.91, 125.44, 125.88, 128.55, 134.03, 135.74, 138.97, 145.79, 147.68, 148.94, 149.70 ppm. Ir (neat) ν 765, 710 cm^{-1}. Ms m/z 207 (M$^+$). Hrms calcd for $C_{15}H_{13}N$ 207.1048, found 207.1038. Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.65; H, 6.01; N, 6.82.

(*Z*)-2-(1-Indanylidenemethyl)furan 4: 58% Yield. Colorless oil. ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.8-3.1 (m, 4 H), 6.3-6.4 (m, 2 H), 6.4-6.5 (m, 1 H), 7.1-7.3 (m, 3 H), 7.45 (t, J = 0.7 Hz, 1 H), 8.1-8.2 (m, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 29.95, 35.33, 108.89, 109.03, 111.18, 124.92, 126.08, 128.29, 139.06, 140.91, 142.44, 148.92, 152.35 ppm. Ir (neat) ν 765, 725 cm^{-1}. Ms m/z 196 (M$^+$). Hrms calcd for $C_{14}H_{12}O$ 196.0888, found 196.0884. Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.37; H, 6.28.

(*Z*)-2-(1-Indanylidenemethyl)thiophene 5: 74% Yield. Colorless oil. ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.9-3.0 (m, 4 H), 6.53 (br s, 1 H), 7.0-7.1 (m, 3 H), 7.17 (dt, J = 1.1, 7.5 Hz, 1 H), 7.2-7.3 (m, 2 H), 7.49 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 29.97, 34.13, 113.10, 124.33, 124.47, 125.19, 125.73, 125.83, 127.02, 128.40, 139.15, 140.32, 145.83, 148.79 ppm. Ir (neat) ν 850, 755, 695 cm^{-1}. Ms m/z 212 (M$^+$). Hrms calcd for $C_{14}H_{12}S$ 212.0660, found 212.0663. Anal. Calcd for $C_{14}H_{12}S$: C, 79.20; H, 5.70. Found: C, 79.03; H, 5.51.

(*Z*)-2-(1-Indanylidenemethyl)-N-methylpyrrole 6: 52% Yield. Colorless oil. ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.9-3.0 (m, 4 H), 3.49 (s, 3 H), 6.1-6.2 (m, 1 H), 6.2-6.3 (m, 1 H), 6.30 (s, 1 H), 6.6-6.7 (m, 1 H), 7.02 (t, J = 8.0 Hz, 1 H), 7.16 (dt, J = 1.0, 7.1 Hz, 1 H), 7.2-7.3 (m, 2 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 29.90, 33.29, 33.83, 107.31, 107.74, 110.84, 121.30, 123.72, 125.02, 126.11, 128.14, 129.95, 131.89, 145.71, 148.37 ppm. Ir (neat) ν 760, 710 cm^{-1}. Ms m/z 209 (M$^+$). Hrms calcd for $C_{15}H_{15}N$ 209.1204, found 209.1205. Anal. Calcd for $C_{15}H_{15}N$: C, 86.09; H, 7.22; N, 6.69. Found: C, 85.77; H, 7.08; N, 6.45.

(*Z*)-2-(1-Indanylidenemethyl)benzothiazole 7: 70% Yield. mp 89-89.5°C. ^{1}H-Nmr ($CDCl_3$, TMS) δ 3.0-3.1 (br s, 4 H), 6.70 (s, 1 H), 7.2-7.5 (m, 5 H), 7.86 (dt, J = 0.7, 7.8 Hz, 1 H), 8.07 (dt, J = 0.6, 8.1 Hz, 1 H), 8.88 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 29.79, 35.47, 112.51, 121.18, 122.81, 124.69, 124.94, 125.88, 126.23, 126.91, 130.09, 135.40, 138.21, 150.16, 152.07, 154.09, 164.77 ppm. Ms m/z 263 (M$^+$). Hrms calcd for $C_{17}H_{13}NS$ 263.0769, found 263.0749. Anal. Calcd for $C_{17}H_{13}NS$: C, 77.53; H, 4.97; N, 5.32. Found: C, 77.21; H, 4.86; N, 5.54.

2-[2-(3-Butynyl)phenyl]furan **8**: 28% Yield. Colorless oil. ^{1}H-Nmr ($CDCl_3$, TMS) δ 1.98 (t, J = 2.6 Hz, 1 H), 2.47 (dt, J = 2.6, 7.5 Hz, 2 H), 3.07 (t, J = 7.5 Hz, 2 H), 6.4-6.5 (m, 2 H), 7.2-7.3 (m, 3 H), 7.5-7.6 (m, 2 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 19.72, 33.25, 68.68, 83.84, 108.04, 111.18, 126.52, 127.80, 128.23, 129.93, 130.25, 137.29, 141.95, 153.47 ppm. Ir (neat) ν 3300, 1010, 760, 740, 640 cm^{-1}. Ms m/z 196 (M$^+$). Hrms calcd for $C_{14}H_{12}O$ 196.0888, found 196.0878. Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.47; H, 6.29.

2-[2-(3-Butynyl)phenyl]thiophene **9**: 6% Yield. Colorless oil. ^{1}H-Nmr ($CDCl_3$, TMS) δ 1.95 (t, J = 2.6 Hz, 1 H), 2.39 (dt, J = 2.6, 7.2 Hz, 2 H), 2.98 (t, J = 7.2 Hz, 2 H), 7.0-7.1 (m, 2 H), 7.2-7.4 (m, 5 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 20.01, 32.39, 68.78, 83.66, 125.34, 126.34, 126.44, 127.01, 128.05, 129.59, 131.19, 133.94, 138.73, 142.21 ppm. Ir (neat) ν 3300, 760, 700, 640 cm^{-1}. Ms m/z 212 (M$^+$). Hrms calcd for $C_{14}H_{12}S$ 212.0660, found 212.0661. Anal. Calcd for $C_{14}H_{12}S$: C, 79.20; H, 5.70. Found: C, 79.01; H, 5.52.

2-[2-(3-Butynyl)phenyl]-N-methylpyrrole **10**: 33% Yield. Colorless oil. ^{1}H-Nmr ($CDCl_3$, TMS) δ 1.91 (t, J = 2.6 Hz, 1 H), 2.29 (dt, J = 2.6, 7.4 Hz, 2 H), 2.76 (t, J = 7.4 Hz, 2 H), 3.38 (s, 3 H), 6.07 (dd, J = 1.8, 3.5 Hz, 1 H), 6.20 (dd, J = 2.7, 3.5 Hz, 1 H), 6.70 (dd, J = 1.8, 2.7 Hz, 1 H), 7.2-7.4 (m, 4 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 19.53, 32.24, 34.05, 68.64, 83.82, 107.27, 108.68, 121.64, 126.02, 128.03, 129.19, 131.54, 132.08, 132.78, 140.51 ppm. Ir (neat) ν 3300, 1475, 1310, 760, 710, 640 cm^{-1}. Ms m/z 209 (M$^+$). Hrms calcd for $C_{15}H_{15}N$ 209.1204, found 209.1206. Anal. Calcd for $C_{15}H_{15}N$: C, 86.09; H, 7.22; N, 6.69. Found: C, 85.97; H, 7.20; N, 6.85.

2-[2-(3-Butynyl)phenyl]benzothiazole **11**: 21% Yield. Colorless oil. ^{1}H-Nmr ($CDCl_3$, TMS) δ 1.95 (t, J = 2.7 Hz, 1 H), 2.59 (dt, J = 2.7, 7.5 Hz, 2 H), 3.29 (t, J = 7.5 Hz, 2 H), 7.3-7.6 (m, 5 H), 7.71 (d, J = 7.2 Hz, 1 H), 7.94 (d, J = 7.8 Hz, 1 H), 8.10 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 20.21, 32.87, 68.74, 83.96, 121.26, 123.47, 125.12, 126.06, 126.74, 129.95, 130.87, 131.11, 132.68, 135.45, 139.60 153.89 ppm. Ir (neat) ν 3300, 1435, 960, 760, 730, 630 cm^{-1}. Ms m/z 263 (M$^+$). Hrms calcd for $C_{17}H_{13}NS$ 263.0769, found 263.0771. Anal. Calcd for $C_{17}H_{13}NS$: C, 77.53; H, 4.97; N, 5.32. Found: C, 77.40; H, 4.73; N, 5.50.

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