

Communication

A Facile, Mild And Efficient One-Pot Synthesis of 2-Substituted Indole Derivatives Catalyzed By Pd(PPh₃)₂Cl₂

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Abstract: 2-Phenylindoles were prepared by heteroannulation of 2-haloaniline derivatives and phenylacetylene under mild conditions in a one-pot reaction catalyzed by Pd(PPh₃)₂Cl₂.

Key words: One-pot synthesis, 2-phenylindole, palladium catalyst, heteroannulation.

Introduction

The indole ring system is found in many natural products, pharmaceutical agents and polymer materials [1]. The interesting chemical properties of indole have inspired chemists to design and synthesize a variety of indole derivatives [2]. The 2-aryl indole moiety is present in diverse biologically active molecules [3] displaying antiestrogen [3b,d] 5-H-T_{2A} antagonist [3f], anti-inflammatory [3a,c] and cytotoxic properties [3e]. Introduction of an aryl group into the 2- or 3-position of an indole ring is usually achieved either by *de novo* indole ring construction [2], as in the Fischer indole synthesis [3a], or via cross-coupling reactions of 2- or 3-indolylmetal species with an aryl halide [4] and related syntheses. These are the most commonly used routes and have been extensively reviewed [5]. Although many synthetic methods have been developed for indoles, palladium-mediated indole synthesis is one of the most active research fields [6]. Specifically, the palladium-catalyzed annulation of *o*-haloanilines with alkynes has received much attention, as it is a very convenient way

to synthesize 2- or 2,3-substituted indoles [7,8]. The Sonogashira cross-coupling reaction of haloanilines with terminal alkynes in the presence of Pd(0)-Cu(I) gives 2-alkynylanilines and the resulting coupled products have been cyclized to give 2-substituted indoles using various metal alkoxides [8f,9] and Lewis acids [10]. The annulation method is an effective way to prepare a variety of heterocycles [11]. We have recently reported the synthesis of various heterocyclic compounds [12] using Pd catalyzed reactions and in this communication we wish to now report the extension of our strategy to the synthesis of 2-phenylindoles.

Results and Discussion

In this reaction, we used a mixture of the aryl halide (0.075 mmol), phenylacetylene (1.5 mmol), Pd(PPh₃)₂Cl₂ (0.025 mmol), CuI (0.055 mmol) and triethylamine (2 mmol) in DMF (5 mL) at ambient temperature. The reaction provided 2-phenylindole as the major product. Next, we investigated the reaction of *N*-acetyl-2-iodoaniline with phenylacetylene as a model to study the intermolecular heteroannulation with the Pd(PPh₃)₂Cl₂ catalyst. This reaction also gave 2-phenylindole as the major product, instead of the expected *N*-acetyl-2-phenylindole. The deprotection of the acetyl group in the indole likely occurred as a result of the basic conditions of the reaction. *N*-methyl, *N*-benzyl and *N*-tosyl 2-haloanilines effectively reacted with phenylacetylene and the corresponding 2-phenylindole derivatives were obtained in good yields (Scheme 1, Table 1).

Scheme 1.

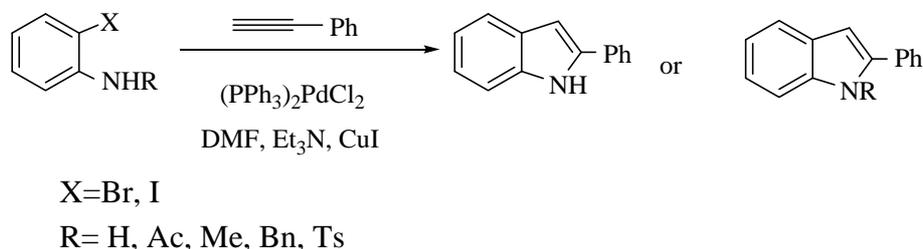
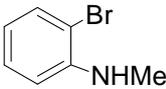
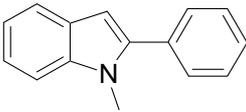
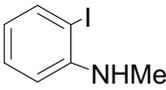
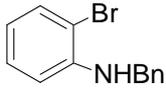
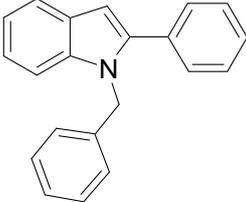
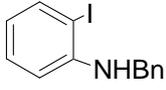
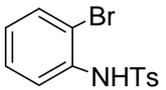
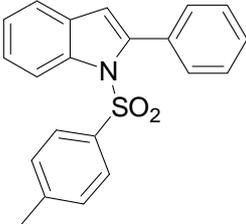
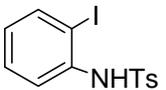
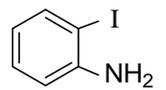
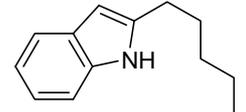


Table 1. Synthesis of 2-substituted indoles by Pd-catalyzed heteroannulation with phenylacetylene.

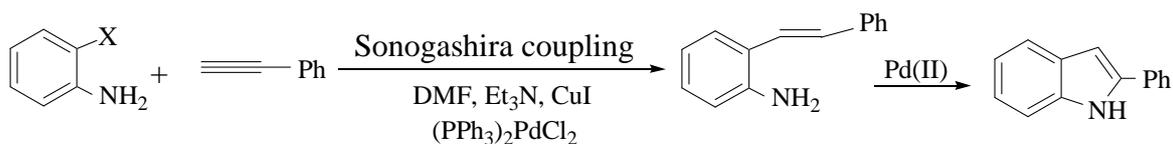
Entry	Aryl halide	Product	Yield%
1			72
2		"	69
3		"	78
4		"	75

Table 1. Cont.

Entry	Aryl halide	Product	Yield%
5			82
6		"	80
7			74
8		"	76
9			68
10		"	70
11			68

When we tried to use tetrahydropyranyl propargyl ether or propargyl bromide instead of phenylacetylene, these reactions did not give any products. We also tried to use 1-heptyne instead of phenylacetylene, but the reaction did not give any of the desired 2-alkylindole derivative under our standard mild conditions. We then examined this reaction under more forcing conditions. After 24 hrs at reflux the reaction went to completion and 2-pentyl-1H-indole was obtained in 68% yield.

Scheme 2.



The mechanism of the reaction is illustrated in Scheme 2. Most probably a two step process occurs: first a standard Sonogashira coupling and then the known Pd (II) catalyzed intermolecular cyclization of the nucleophilic nitrogen moiety onto the triple bond, followed by proton abstraction.

Conclusions

In summary, we have demonstrated that indoles can be synthesized from anilines and phenylacetylene in the presence of a palladium catalyst in an organic medium in moderate to good yields. Pd(PPh₃)₂Cl₂ exhibits high reactivity in the heteroannulation of *o*-haloanilines and phenylacetylene. This method provides a convenient new route to various heteroannulation products in a one-pot reaction. We believe this process combined with an amine exchange reaction can be successfully applied for the synthesis of other N-heterocycles. We also consider the preparation of Pd(PPh₃)₂Cl₂ (this work) to be more economical and simpler than other recently published procedures (for example, Pd-NaY Zeolite [13]).

Experimental

General

All products are known and their physical and spectroscopic data were compared with the reported values. GC–MS analyses were performed on an Agilent system consisting of a GC–MS model 5973 network mass selective detector and a model 6890 GC. IR spectra were obtained with a Buck Scientific model 500 spectrometer. ¹H-NMR spectra were recorded on a Bruker 90 MHz FT-NMR .

Preparation of Pd(PPh₃)₂Cl₂

Following the general procedure of Heck [15], to a solution of palladium (II) chloride (0.05 mol, 8.85 g) and LiCl (0.1 mol, 4.25 g) in dry methanol (80 mL) was added triphenylphosphine (0.11 mol, 27.5 g). The resulting reddish brown reaction mixture was heated in a water bath (temp. 80 °C) until a yellow and nearly insoluble solid formed. The reaction mixture was cooled to ambient temperature and the yellow product (32.7 g, 93%) collected by vacuum filtration washed with methanol (25 mL) and dried overnight in a desiccator prior to use.

General procedure for the synthesis of 2-substituted-1H-indoles with Pd(PPh₃)₂Cl₂

A mixture of the appropriate 2-arylhalide (0.75 mmol), Pd(PPh₃)₂Cl₂ (0.0175 g, 0.025 mmol), CuI (0.01 g, 0.055 mmol), triethylamine (0.202 g, 0.278 mL, 2 mmol) and phenylacetylene (0.153 g, 1.5 mmol) were stirred in DMF (5 mL) at room temperature for 24 h. Upon completion of the reaction, the reaction mixture was diluted with saturated aqueous ammonium chloride and the product was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. The reaction mixture was filtered and concentrated. The product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent. The 2-phenyl-1H-indole was obtained in 69–78% yields (Table 1, entries 1–4). Mp 189–190 °C; ¹H-NMR (CDCl₃) 8.34 (s, br, 1H), 7.62 (m, 3H), 7.42–7.27 (m, 4H), 7.20–7.09 (m, 2H), 6.80 (s, 1H).

Synthesis of 1-methyl-2-phenylindole; (Table 1, entries 5, 6)

N-Methyl-2-bromo(iodo)aniline [15] [0.139 (0.175) g, 0.75 mmol], Pd(PPh₃)₂Cl₂ (0.0175 g, 0.025 mmol), CuI (0.01 g, 0.055 mmol), triethylamine (0.202 g, 0.278 mL, 2 mmol), phenylacetylene (0.153 g, 1.5 mmol) and DMF (5 mL) were mixed at room temperature for 8 h. The progress of the reaction was monitored by TLC. Upon completion of the reaction the mixture was diluted with saturated aqueous ammonium chloride and the product was extracted with ethyl acetate. The organic layer was dried over MgSO₄ and filtered. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate to afford 1-methyl-2-phenyl indole as a brown solid. Mp. 110-112°C; ¹H-NMR (CDCl₃) 7.38 (m, 2H), 7.32 (m, 2H), 7.22 (m, 1H), 7.2 (m, 4H), 6.5 (s, 1H), 3.56 (s, 3H).

Synthesis of 1-benzyl-2-phenylindole (Table 1, entries 7, 8)

Pd(PPh₃)₂Cl₂ (0.0175 g, 0.025 mmol), *N*-benzyl-2-bromo(iodo)aniline [15] [0.197 (0.232) g, 0.75 mmol], CuI (0.01 g, 0.055 mmol), triethylamine (0.202 g, 0.278 mL, 2 mmol), phenylacetylene (0.153 g, 1.5 mmol) and DMF (5 mL) were placed in a sealed tube at room temperature for 12 h. Upon completion of reaction, the reaction mixture was worked up and purified as described above. 1-Benzyl-2-phenylindole was obtained in 74 (76%) yield. Mp. 95-99°C; ¹H-NMR (CDCl₃) 7.6-7.07 (m, 14H), 6.4 (s, 1H), 5.1 (s, 2H).

Synthesis of 2-phenyl-1-(toluene-4-sulfonyl)indole (Table 1, entries 9, 10)

Pd(PPh₃)₂Cl₂ (0.0175 g, 0.025 mmol), *N*-tosyl-2-bromo(iodo)aniline [16] [0.222 (0.257) g, 0.75 mmol], CuI (0.01 g, 0.055 mmol), triethylamine (0.202 g, 0.278 mL, 2 mmol), phenylacetylene (0.153 g, 1.5 mmol) and DMF (5 mL) were placed in a sealed tube at room temperature for 12 h. As above, 2-phenyl-1-(toluene-4-sulfonyl)indole was obtained in 68 (70)% yield. Brown solid; Mp. 75-99°C; ¹H-NMR (CDCl₃) 7.81-7.0 (m, 13H), 6.4 (s, 1H), 2.35 (s, 2H).

Synthesis of 2-pentyl-1H-indole (Table 1, entry 11)

Pd(PPh₃)₂Cl₂ (0.0175 g, 0.025 mmol), 2-iodoaniline (0.164 g, 0.75 mmol), CuI (0.01g, 0.055 mmol), triethylamine (0.202 g, 0.278 mL, 2 mmol), 1-heptyne (0.144 g, 1.5 mmol) and DMF (5 mL) were heated under reflux conditions for 24 h. After workup as described above, 2-pentyl-1H-indole was obtained in 68 % yield. Brown oil; ¹H-NMR (CDCl₃) 7.81-7.0 (m, 4H), 6.4 (s, 1H), 2.65 (t, 2H), 1.6-1.45(m, 6H), 1.05(t, 3H).

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