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Short Communication

Palladium-catalyzed synthesis of indoles via intramolecular Heck reaction

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ABSTRACT

Highly effective Pd-catalyzed synthesis of indoles from 2-halo-anilines and allyl bromides via intramolecular Heck reaction in the presence of $P(OPh)_3$ as the ligand is described.

1. Introduction

The intramolecular Heck reaction has provided an extremely useful approach to construct carbocyclic and heterocyclic ring systems [1–11], including indoles and their derivatives. Indoles are widely distributed in nature and often exhibit powerful bioactivity, and the typical examples include the important neurotransmitter serotonin and the anti-tumor drug indirubin [12–14]. Intramolecular Heck reaction of 2-halo-*N*-allylaniline derivatives, known as Mori–Ban indole synthesis [15–17], was first disclosed by Mori and Ban in 1977 for a substrate bearing an ester moiety on the allylic terminus [18]. Shortly after their report, Hegedus and co-workers reported the reaction using simple *N*-allyl derivatives [19]. Since then, this type of intramolecular Heck reaction has been studied by several researchers including Larock and Babu [20], Li [3], and Hiemstra et al. [21]. However, such a synthetic route to indoles is still limited due to the modest yields. For example, Holmes and Carroll found that Pd-catalyzed intramolecular Heck reaction could be performed in $ScCO_2$ and the desired indole was obtained with only 37% yield [22]. In order to acquire better result, very high temperature (140 °C) was employed for the intramolecular Heck reaction using Pd/*N*-heterocyclic carbene (NHC) catalytic system [23]. Therefore, we aimed to develop a new and practical procedure for the synthesis of indole-compounds. Here, we report the Pd-catalyzed synthesis of indoles from 2-halo-*N*-allylaniline under lower temperature in the presence of a commercially available ligand.

2. Experimental

All reactions were carried out under air. Various anilines and allyl bromides were purchased from Aldrich, Acros or Alfa. Flash column chromatography was performed using silica gel (100–200 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200–300 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were recorded in $CDCl_3$ on a Varian Inova-400 NMR spectrometer (400 MHz) or Varian Inova-300 NMR spectrometer (300 MHz) with TMS as an internal reference. Products were characterized by comparison of ^1H NMR, ^{13}C NMR MS, TOF-MS data in the literatures.

2.1. General procedure for the synthesis of 2-halo-N-allylanilines

A mixture of 2-haloanilines (0.36 mmol), allyl bromide (0.3 mmol), K_2CO_3 (2 equiv), and DMF (2 mL) in a Schlenk tube was stirred under air at 90 °C for the desired time until complete consumption of starting material as monitored by TLC. After the mixture was poured into water, extracted with ethyl acetate, dried by anhydrous Na_2SO_4, then filtered and evaporated under vacuum, the residue was purified by flash column chromatography (petroleum ether or petroleum ether/ethyl acetate) to afford the corresponding coupling products.

2.2. General procedure for the synthesis of 2-halo-N,N-allylanilines

A mixture of 2-haloanilines (0.3 mmol), allyl bromide (0.72 mmol), t-BuOK (3 equiv), and DMSO (2 mL) in a Schlenk tube was stirred under air at 70 °C for the desired time until complete consumption of

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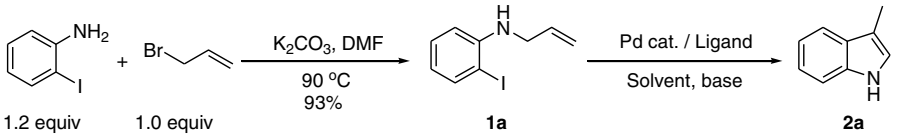

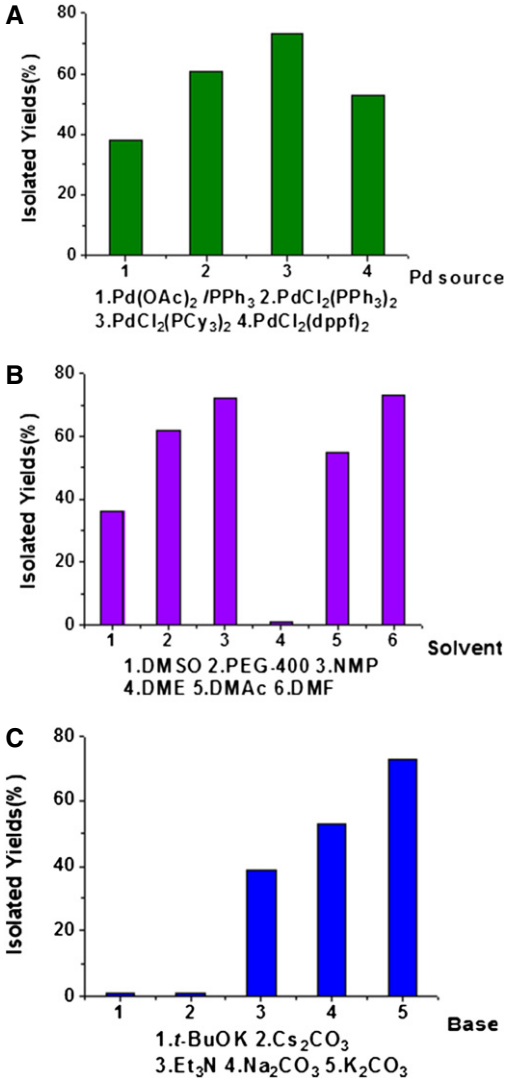

Scheme 1. Primary optimization study for the synthesis of indole (**2a**).

Table 1
Screening various catalytic conditions for cyclization of **1a** to prepare **2a**[a].

Entry	Pd cat. (mol%)	L (mol%)	Yield (%)[b]
1	$PdCl_2(PCy_3)_2$ (2)	–	73
2[c]	$PdCl_2(PCy_3)_2$ (2)	–	71
3	$PdCl_2(PCy_3)_2$ (4)	–	76
4[d]	$PdCl_2(PCy_3)_2$ (2)	–	74
5[d]	$PdCl_2(PCy_3)_2$ (4)	–	84
6[d]	$PdCl_2$ (4)	PCy_3 (4)	79
7[d]	$PdCl_2$ (4)	PCy_3 (8)	86
8[d]	$PdCl_2$ (4)	PCy_3 (12)	70
9[d]	$PdCl_2(PCy_3)_2$ (4)	PCy_3 (5)	Trace
10[d]	$PdCl_2(PCy_3)_2$ (4)	PPh_3 (4)	77
11[d]	$PdCl_2(PCy_3)_2$ (4)	$P(OPh)_3$ (4)	99
12[d]	$PdCl_2(PCy_3)_2$ (2)	$P(OPh)_3$ (2)	75

[a] Catalytic conditions: 2-Iodo-*N*-allylaniline (0.3 mmol), K_2CO_3 (2 equiv), DMF (2 mL), 90 °C, 24 h, air.
[b] Isolated yield based on 2-iodo-*N*-allylaniline.
[c] 110 °C.
[d] 4 equiv of K_2CO_3.

starting material as monitored by TLC. After the mixture was poured into water, extracted with ethyl acetate, dried by anhydrous Na_2SO_4, then filtered and evaporated under vacuum, the residue was purified by flash column chromatography (petroleum ether or petroleum ether/ethyl acetate) to afford the corresponding coupling products.

2.3. General procedure for palladium-catalyzed synthesis of indoles via intramolecular Heck reaction

A mixture of 2-halo-*N*-allylaniline or 2-halo-*N*,*N*-allylaniline (0.3 mmol), $PdCl_2(PCy_3)_2$ (4 mol%), $P(OPh)_3$ (4 mol%), K_2CO_3 (4 equiv), DMF (2 mL), in a Schlenk tube was stirred under air at 90 °C for 24 h. After the mixture was poured into water, extracted with ethyl acetate, dried by anhydrous Na_2SO_4, then filtered and evaporated under vacuum, the residue was purified by flash column chromatography (petroleum ether or petroleum ether/ethyl acetate) to afford the corresponding coupling products. For the characterization of the desired products please see supporting materials.