

Synthesis of Indole Derivatives from 2-Bromoanilines by a Palladium-assisted Reaction

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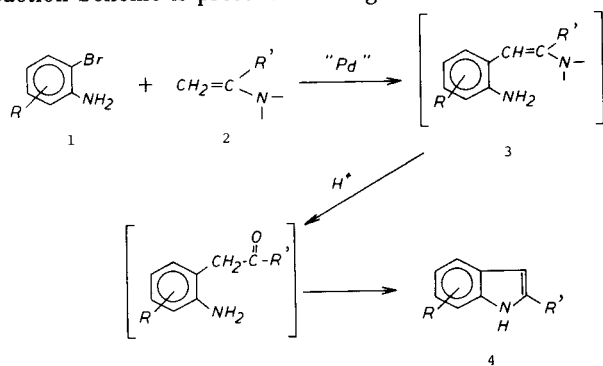
In the presence of palladium(II) acetate, 2-bromoanilines readily react with enamines such as *N*-vinylpyrrolidone or α -piperidinostyrene to produce indole derivatives.

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The search for an efficient synthesis of indoles has been a problem for nearly a century in organic synthesis. However, methods involving electrophilic ring closures, such as the Fischer or Bischler Synthesis, are generally not applicable to indoles containing only an electron-withdrawing group [1]. Hegedus *et al.* [2] have recently reported the synthesis of indoles from *o*-allylanilines, and from 2-ethenyylaniline *p*-toluenesulfoanilides by a palladium-catalyzed cyclization reaction. We have also described an efficient synthesis of indoles based on a variety of palladium-catalyzed reactions of *o*-bromoanilines [3]. We wish herein to report the development of a palladium-assisted reaction for the preparation of indoles containing an electron-withdrawing group from readily obtainable *o*-bromoanilines and enamines. The overall reaction Scheme is presented in Figure 1.

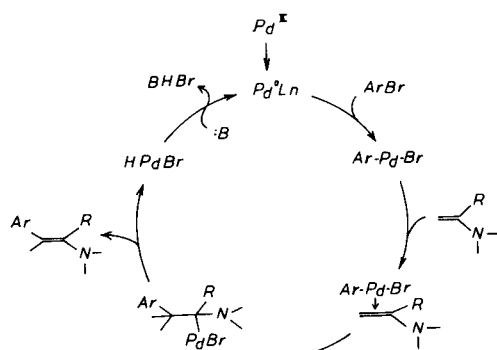
The arylation with aryl bromides or iodides of some of the alkenes has been reported previously by Heck [4]. In the presence of palladium(II) acetate, tri-*o*-tolylphosphine and triethylamine, the starting *o*-bromoanilines **1** undergo palladium-assisted substitution with enamines such as *N*-vinylpyrrolidone (**2a**) and α -piperidinostyrene (**2b**), to form the *o*-ethenyylanilines **3**, which are in turn cyclized to the indoles **4** in the presence of the dilute aqueous acid. While the palladium-assisted substitution of **1** with enol ethers and enol esters, such as ethyl vinyl ether and vinyl acetate, were unsuccessful.

Yields and melting points for all products are given in Table 1. The reaction of **1** to **3** is thought to proceed by oxidative addition of aromatic halide **1** to the palladium(0) complex, followed by intermolecular olefin insertion and β -hydride elimination (Scheme 1).



1 a : R = H	4 a : R = R' = H
1 b : R = 4-CH ₃	4 b : R = 5-CH ₃ , R' = H
1 c : R = 4-Cl	4 c : R = 5-Cl, R' = H
1 d : R = 4-NO ₂	4 d : R = 5-NO ₂ , R' = H
1 e : R = 5-OCH ₃	4 e : R = 6-OCH ₃ , R' = H
1 f : R = 3-COOCH ₃	4 f : R = 4-COOCH ₃ , R' = H
1 g : R = 5-COOCH ₃	4 g : R = 6-COOCH ₃ , R' = H
	4 h : R = H, R' = Ph
	4 i : R = 5-CH ₃ , R' = Ph
	4 j : R = 5-Cl, R' = Ph
	4 k : R = 5-NO ₂ , R' = Ph
	4 l : R = 6-OCH ₃ , R' = Ph
	4 m : R = 4-COOCH ₃ , R' = Ph

Figure 1



Scheme 1

EXPERIMENTAL

All melting points are uncorrected.

General Procedure for the Palladium-catalyzed Reaction of *o*-Bromoanilines **1** to indoles **4**.

A mixture of **1** (14.9 mmoles), palladium(II) acetate (0.167 g, 0.745 mmole), tri-*o*-tolylphosphine (0.906 g, 2.98 mmoles), triethylamine (1.88 g, 18.6 mmoles) and enamine (**2a** or **2b**) (17.5 mmoles) in acetonitrile (20

Table 1

The Palladium-assisted Reaction of 2-Bromoanilines **1** with Enamines **2**

2-Bromoaniline	Enamine	Product	Yield (%)	Mp °C
1a	2a	4a	56	51-53 lit 52-53 [a]
1b	2a	4b	48	58-60 lit 58-59 [b]
1c	2a	4c	43	69-71 lit 71-72 [c]
1d	2a	4d	52	134-135 lit 134-136 [d]
1e	2a	4e	46	89-91 lit 88-90 [e]
1f	2a	4f	55	64-65 lit 64-65 [f]
1g	2a	4g	40	78-80 lit 80-80.5 [g]
1a	2b	4h	46	185-187 lit 186-188 [h]
1b	2b	4i	40	210-212 lit 213 [i]
1c	2b	4j	38	189-190 lit 191 [j]
1d	2b	4k	46	200-202 lit 201-203 [k]
1e	2b	4l	35	168-170 [l]
1f	2b	4m	41	125-126 [m]

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6.96-7.68 (m, 9H, Ar-H + NH). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}$: C, 80.69; H, 5.87; N, 6.27; M, 223. Found: C, 80.60; H, 5.81; N, 6.20; M^+ , 223. [m] Colorless crystals; ir (potassium bromide): 3325 (NH), 1690 (ester), 1600, 1500, 795, 760, 750, 690 cm^{-1} (benzene ring); $^1\text{H-nmr}$ (deuteriochloroform): δ 3.99 (s, 3H, $-\text{COOCH}_3$), 7.16-7.70 (m, 7H, Ar-H), 7.83 (d, 1H, $\text{C}_5\text{-H}$), 8.77 (br-s, 1H, $-\text{NH}$). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.47; H, 5.22; N, 5.57; M, 251. Found: C, 76.37; H, 5.06; N, 5.48; M^+ , 251.

ml) was heated in a sealed tube flushed with nitrogen at 100° for 20 hours. After cooling and separation of the resulting palladium black, the solvent was removed under reduced pressure. The remaining residue was stirred with 10% hydrochloric acid (30 ml) in ethanol (30 ml) at room temperature for 24 hours. After the solvent was distilled off *in vacuo*, the remaining aqueous solution was neutralized with saturated sodium hydrogencarbonate solution and extracted with ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography using silica gel and hexane-benzene (2:1).

The structures of the products were verified by elemental analyses, by their $^1\text{H-nmr}$ and ir spectra, and by comparison with an authentic sample. The results are presented in Table 1.

REFERENCES AND NOTES

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