

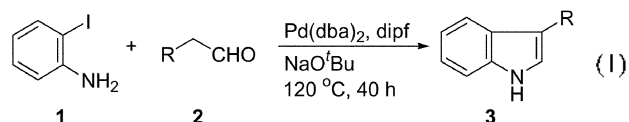
Communications

Palladium-Catalyzed Synthesis of 3-Substituted Indoles
from 2-Iodoaniline and AldehydesChan Sik Cho,^{*,†} Hyung Sup Shim, Heung-Jin Choi, Tae-Jeong Kim, and Sang Chul Shim^{*}^{*}Research Institute of Industrial Technology, Kyungpook National University, Daegu 702-701, Korea
[†]Department of Applied Chemistry, College of Engineering, Kyungpook National University, Daegu 702-701, Korea
Received January 26, 2004**Key Words :** Aldehydes. Annulation, 2-Iodoaniline. Palladium catalyst, 3-Substituted indoles

It is known that many indole containing compounds exhibit a wide spectrum of pharmacological and biological activities. Thus, besides conventional named routes, homogeneous transition metal-catalyzed synthetic methods have also been developed as alternative methods for the construction of indole framework because of the wide availability of substrates.¹ We have also reported on ruthenium-catalyzed synthesis of indoles *via* an alkanol group transfer from alkanolamines to anilines (amine exchange reaction)² and ring-opening of epoxides by anilines.³ In connection with this report, palladium-catalyzed direct or step-by-step annulation of 2-haloanilines with carbonyl compounds such as ketones,⁴ 1,3-diketones⁵ and α -keto esters⁶ also give access to a variety of indoles.⁷ However, in contrast to the annulation with such carbonyl compounds, there is no precedent on the similar annulation of 2-haloanilines with aldehydes leading to indoles. Under these circumstances, herein we report on palladium-catalyzed synthesis of 3-substituted indoles from 2-iodoaniline and aldehydes.

Based on our recent report on palladium-catalyzed synthesis of indoles from 2-iodoaniline (**1**) and ketones,^{4b} several annulations between **1** and octanal (**2a**) are attempted (Eq. 1 and Table 1).⁸ Treatment of equimolar amounts of **1** and **2a** in the presence of a catalytic amount of Pd(dba)₂ (dba = dibenzylideneacetone) and 1,1'-bis(di-*iso*-propylphosphino)ferrocene (dipf) along with NaO^tBu in DMF at 120 °C for 40 h afforded 3-hexylindole (**3a**) in 35% yield (25% for 20 h). A slight increase in the yield of **3a** was observed with the

molar ratio of [**2a**]/[**1**] = 2 (44% yield; 31% for 20 h). The addition of molecular sieves, 4A as dehydrating agent did not give any significant change under the employed conditions and lower reaction temperature (80 °C) resulted in a lower yield of **3a** (24% for 20 h). Among examined solvents (for 20 h) DMF was revealed to be the solvent of choice (23% in MeCN; 12% in dioxane; 10% in toluene).

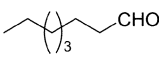
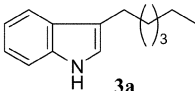
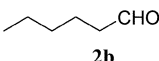
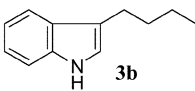
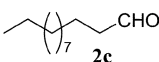
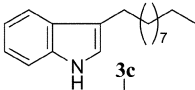
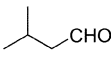
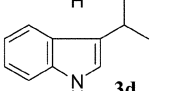
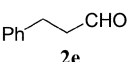
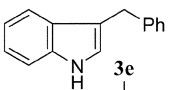
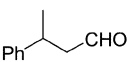
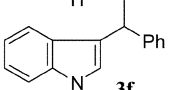
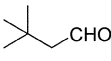
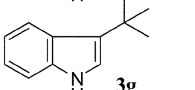


From the reaction of **1** with an array of aldehydes **2** under the controlled reaction conditions, the corresponding 3-substituted indoles were formed in moderate yields, and several representative results are summarized in Table 1. Aldehydes (**2a-2c**) which have aliphatic straight chain were similarly cyclized with **1** irrespective of chain length (runs 1-3). The reaction proceeds likewise with aldehyde **2d** which has a branched chain to give the corresponding indole **3d** (run 4). With β -phenyl substituted aldehydes (**2e** and **2f**) the product yield was generally higher than that when other examined aldehydes were used (runs 5 and 6). However, the reaction between **1** and 3,3-dimethylbutyraldehyde (**2g**) resulted in a very complicated unidentifiable mixture without the formation of indole **3g** (run 7).

In summary, we have demonstrated that 2-iodoaniline is cyclized with various aldehydes under Pd(dba)₂/1,1'-bis(di-*iso*-propylphosphino)ferrocene/NaO^tBu/DMF to give the corresponding 3-substituted indoles in moderate yields. The present reaction is a straightforward synthetic method of

^{*}Co-corresponding authors: Chan Sik Cho (cscho@knu.ac.kr), Sang Chul Shim (scshim@knu.ac.kr)

Table 1. Palladium-catalyzed synthesis of indoles **3** from 2-iodoaniline (**1**) and aldehydes **2**^a

Run	Aldehydes 2	Indoles 3	Yield (%)
1	 2a	 3a	44
2	 2b	 3b	48
3	 2c	 3c	40
4	 2d	 3d	40
5	 2e	 3e	58
6	 2f	 3f	53
7	 2g	 3g	0

^aReaction conditions: **1** (1 mmol), **2** (2 mmol), Pd(dba)₂ (0.05 mmol), dppf (0.06 mmol), NaO^tBu (2.2 mmol), DMF (10 mL), 120 °C, for 40 h.

indoles from readily available 2-iodoaniline and aldehydes.

Typical experimental procedure is as follows. A mixture of **1** (0.219 g, 1 mmol), hexanal (**2b**) (0.200 g, 2 mmol), Pd(dba)₂ (0.029 g, 0.05 mmol), 1,1'-bis(di-*iso*-propylphosphino)ferrocene (0.025 g, 0.06 mmol), and NaO^tBu (0.211 g, 2.2 mmol) in DMF (10 mL) was placed in a 50 mL pressure vessel. After the system was flushed with argon, the mixture was allowed to react at 120 °C for 40 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate-chloroform mixture) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (ethyl acetate/hexane mixture = 1/5) to give 3-butylindole (**3b**) (0.083 g, 48%). The compounds prepared by the above procedure were characterized spectroscopically.⁹

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- 3-Butylindole (3a)**.¹⁰ Yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 0.94 (t, *J* = 7.0 Hz, 3H), 1.37-1.46 (m, 2H), 1.65-1.73 (m, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 6.92 (d, *J* = 2.0 Hz, 1H), 7.08-7.12 (m, 1H), 7.15-7.21 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.80 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.0, 22.7, 24.8, 32.3, 111.0, 117.1, 119.0 (✓), 121.0, 121.8, 127.6, 136.3.
- 3-Hexylindole (3b)**.¹¹ Pale yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.30-1.42 (m, 6H), 1.67-1.74 (m, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 7.09-7.12 (m, 1H), 7.16-7.20 (m, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.90 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.5, 23.1, 25.6, 29.7, 30.5, 32.2, 111.4, 117.6, 119.4 (✓), 121.4, 122.2, 128.0, 136.7.
- 3-Decylindole (3c)**.¹¹ Yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 0.87-0.90 (m, 3H), 1.26-1.40 (m, 14H), 1.66-1.73 (m, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 2.0 Hz, 1H), 7.08-7.12 (m, 1H), 7.15-7.19 (m, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.69 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.1, 22.7, 25.2, 29.4, 29.6, 29.7, 30.2, 31.9, 111.0, 117.1, 119.0, 121.0, 121.7, 127.6, 136.3, several peaks are eclipsed.
- 3-Isopropylindole (3d)**.¹² Light yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 1.36 (dd, *J* = 7.0 and 1.5 Hz, 6H), 3.16-3.27 (m, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 7.09-7.13 (m, 1H), 7.16-7.20 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.84 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 23.3, 25.4, 111.1, 119.0, 119.2, 119.4, 121.8, 124.0, 126.7, 136.5.
- 3-Benzylindole (3e)**.¹³ Solid (hexane); mp 103-106 °C (lit. 105-106 °C); ¹H NMR (400 MHz, CDCl₃): δ 4.08 (s, 2H), 6.79 (s, 1H), 7.04-7.08 (m, 1H), 7.14-7.20 (m, 2H), 7.23-7.27 (m, 5H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.71 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 32.1, 111.6, 116.2, 119.6, 119.8, 122.5, 122.9, 126.4, 127.9, 128.8, 129.2, 136.9, 141.7.
- 3-(1-Phenylethyl)indole (3f)**.¹⁴ Viscous brown oil; ¹H NMR (400 MHz, CDCl₃): δ 1.66 (d, *J* = 7.0 Hz, 3H), 4.33 (q, *J* = 7.0 Hz, 1H), 6.85 (d, *J* = 1.5 Hz, 1H), 6.95-6.99 (m, 1H), 7.09-7.16 (m, 2H), 7.21-7.28 (m, 5H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.69 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 35.8, 110.0, 118.1, 118.6, 120.1, 120.2, 120.8, 124.8, 125.7, 126.4, 127.2, 135.5, 145.8.
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