

Communications

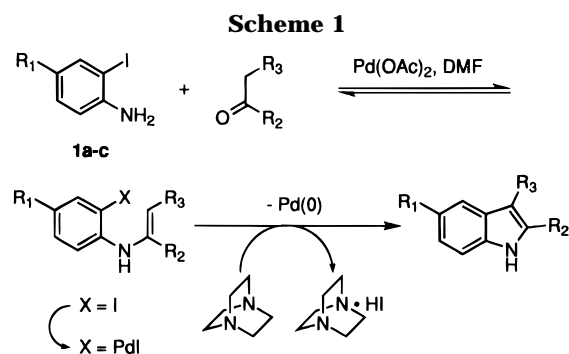
Syntheses of Indoles *via* a Palladium-Catalyzed Annulation between Iodoanilines and Ketones

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The indole nucleus is a common and important feature of a variety of natural products and medicinal agents.¹ The traditional approach for preparing the indole nucleus is the Fischer indole reaction.² As this reaction has shortcomings, the palladium-catalyzed coupling of *o*-haloanilines is becoming an excellent alternative.³ A combination of such a palladium-catalyzed reaction with ketones and aldehydes would be a tremendously straightforward approach⁴ (Scheme 1). Herein, we wish to disclose a new and efficient method for indole synthesis using a palladium-catalyzed annulation between *o*-iodoanilines and ketones.



The reaction would necessarily proceed by enamine formation⁴ followed by an intramolecular Heck reaction⁵ (Scheme 1). In our search for the appropriate reaction conditions, we found that an amine base was critical to the successful coupling. However, in the palladium-catalyzed coupling of the iodoaniline **1c** ($\text{R}_1 = 1\text{-(1,2,4-triazolyl)methyl}$)⁶ and cyclohexanone with diisopropyl-

Table 1. Coupling Reaction of Iodoanilines and Ketones

Entry	Iodoaniline	Ketone	Indole	Yield, %
1	1c	cyclopentanone		53
2	1a, 1b ($\text{R}_1 = \text{CN}$)	cyclohexanone		77 61
3	1c	cycloheptanone		72
4	1c	2-methyl-cyclohexanone		68
5	1a	3-methyl-cyclohexanone		65; 8
6	1a			55
7	1a			78
8	1a			55
9	1a	5 α -cholestanone		79
10	1a	pyruvic acid		82
11	1a			64

(1) (a) Saxton, J. E. *Indoles*; Wiley-Interscience: New York, 1983; Part 4. (b) Saxton, J. E. *Nat. Prod. Rep.* **1994**, 493; **1995**, 387. (c) Ihara, M.; Fukumoto, K. *Nat. Prod. Rep.* **1995**, 277.

(2) For reviews on the Fischer indole reaction, see: (a) Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1993**, 25, 607. (c) Gribble, G. W. *Contemp. Org. Synth.* **1994**, 1, 1 and references cited therein.

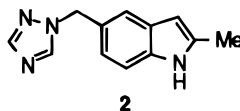
(3) (a) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, 45, 2709. (b) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Jpn.* **1986**, 59, 927. (c) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, 28, 5291. (d) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, 113, 6689. (e) Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, 60, 482. (f) Desarbre, E.; Merour, J.-Y. *Tetrahedron Lett.* **1996**, 37, 43 and references cited therein.

(4) For examples of couplings with 1,3-dicarbonyl systems, see: (a) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, 45, 2938–2942. (b) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215. (c) Koerber-Ple, K.; Massiot, G. *Synlett* **1994**, 759.

(5) For reviews of the Heck reaction, see: (a) Heck, R. F. *Org. React.* **1982**, 27, 345. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 2379. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, 28, 2.

amine as base the byproduct 2-methylindole **2** (~9%) was generated. The formation of the byproduct is a result of the ability of palladium to oxidize the amine,⁷ generating Pd(0) and the imine/enamine of isopropylamine and acetone. Transamination with **1c** and Heck coupling provided **2**

(6) The iodoaniline is a precursor to the 5HT_{1D} agonist, *rizatriptan*. (a) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Reamer, R. A.; Verhoeven, T. R.; Reider, P. J.; Cottrell, I. F.; Houghton, P. G. *Tetrahedron Lett.* **1994**, 35, 6981. (b) Street, L. J.; Baker, R.; Davey,



In order to obtain a reaction free of amine-derived byproducts, an amine that would not be oxidized by palladium was required. Applying Bredt's rule,⁸ quinuclidine or DABCO should resist oxidation to the imine. Direct coupling of *o*-iodoaniline (**1a**) with cyclohexanone in the presence of 5 mol % Pd(OAc)₂ and 3 equiv of DABCO as base successfully afforded the tetrahydrocarbazole **4a** in 77% yield with no other major impurities (Table 1). The use of DMF as solvent is crucial to the success of the reaction; other solvents, such as acetonitrile and toluene were ineffective.

This is the first example of a palladium-catalyzed coupling of a simple ketone and an iodoaniline to prepare an indole. Although 1,3-dicarbonyl systems have been coupled to indoles,⁴ the reported reaction conditions did not provide any coupling with cyclohexanone. In addition, it was necessary to preform the β -enaminone.

The generality of this reaction was investigated.⁹ The desired indoles were readily prepared in 52–82% yields from iodoanilines **1a**–**1c**¹⁰ and cyclic ketones (Table 1). In addition to the coupling of cyclohexanones (entries 2, 4, and 5), the reaction is also compatible with cyclopentanone¹¹ and cycloheptanone (entries 1 and 3). The coupling reaction is highly regioselective. For instance,

W. B.; Guiblin, A. R.; Jelley, R.; Reeve, A. J.; Routledge, H.; Sternfeld, F.; Watt, A. P.; Beer, M. S.; Middlemiss, D. N.; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J.; Sohal, B.; Graham, M. I.; Matassa, V. G. *J. Med. Chem.* **1995**, *38*, 1799.

(7) For the oxidation of amines with Pd(OAc)₂, see: (a) McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J.; Stephenson, D. K. *J. Chem. Res. Synop.* **1984**, 360. (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (c) Clark, F. R. S.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 121.

(8) For a review of Bredt's rule, see: Shea, K. J. *Tetrahedron* **1980**, *36*, 1683.

(9) A typical procedure follows: A mixture of iodoaniline (**1a**) (2.19 g, 10 mmol), cyclohexanone (2.94 g, 30 mmol, 3 equiv), DABCO (3.36 g, 30 mmol, 3 equiv), and Pd(OAc)₂ (112 mg, 0.5 mmol, 5 mol %) in dry DMF (30 mL) was degassed *via* vacuum/nitrogen purges and heated to 105 °C. The mixture was heated at 105 °C for 3 h or until the reaction was complete (usually <12 h). The reaction mixture was cooled to room temperature and partitioned between isopropyl acetate (150 mL) and water (50 mL). The organic layer was separated, washed with brine (50 mL), and concentrated under vacuum to dryness. The residue was chromatographed and crystallized from isopropyl acetate–heptane to give 1.32 g of tetrahydrocarbazole **4** (77%) as an off-white solid: mp 119–120 °C (lit. mp 118–120 °C: Rogers, C. U.; Corson, B. B. *Organic Synthesis*; Wiley: New York, 1967; Collect. Vol. IV, p 884). The ketone charge ranged from 1 to 3 equiv.

(10) Iodoaniline **1a** is commercially available from Aldrich. Iodoanilines **1b** and **1c** were prepared from the corresponding anilines using ICl–CaCO₃ in methanol following the procedure in ref 6 in 86% and 92% yield, respectively.

condensation of iodoaniline **1c** with 2-methylcyclohexanone gave 2-methyltetrahydrocarbazole **6** in 68% yield (entry 4). Reaction of 3-methylcyclohexanone with iodoaniline formed carbazole **7** predominantly (7/8; 8:1) (entry 5).

The reaction tolerates a variety of functional groups, especially the acid-sensitive acetal (entry 6), carbamate (entry 7), or benzyl triazole^{6a} (entries 1, 3, and 4). These intermediates, which would be unstable under the conditions of the traditional Fischer indole reaction, were conveniently synthesized using this method. The structurally interesting indole **11** was prepared from 3-quinuclidinone hydrochloride (1.0 equiv) in 55% yield (entry 8). The coupling of the indole nucleus onto a steroid was also achieved with 5 α -cholestanone (1.0 equiv), affording **12** exclusively in 79% yield (entry 9).

The coupling of acyclic ketones is not as effective. For example, only a 30% yield of **2** with excess acetone was obtained. However, the coupling was quite successful with pyruvic acid and acetylsilane (entries 10 and 11). With pyruvic acid, **1a** coupled efficiently to give 2-indolecarboxylic acid (**13**) in 82% yield. Coupling of acetylsilane gave a 2:1 mixture of 2-(trimethylsilyl)indole **14** and indole (**15**) in a combined 64% yield. Evidently, the reaction conditions cause some desilylation. Either the carboxy¹² or silyl group^{6a} can be removed providing an entry into 2-unsubstituted indoles.

Though most reactions proceeded efficiently in DMF at 105 °C, the additive MgSO₄ (1.5 equiv), presumably acting as a dehydrating agent, was found to promote the annulation in the more sluggish cases (entries 1, 2b, 4, 8, and 11).

In summary, we have discovered and demonstrated a new and efficient method for the synthesis of indoles from carbonyl compounds. In conjunction with the use of alkynes in the palladium-catalyzed indolization,^{5,6a} the coupling of cyclic ketones widens the spectrum of indoles that can be prepared by this means. The simple procedure, mild reaction conditions, and availability of the starting materials render this method a valuable addition to indole chemistry.

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Supporting Information Available: Experimental procedure for the annulation of iodoaniline **1a** and cyclohexanone, and spectral data for compounds **3**–**12** (3 pages).

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(11) The coupling reaction reported by Kibayashi^{4a} failed with cyclopentanedione.

(12) Jones, G. B.; Chapman, B. J. *J. Org. Chem.* **1993**, *58*, 5558.