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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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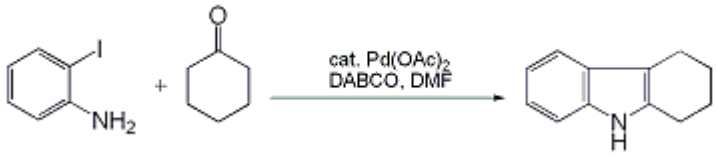
INDOLE SYNTHESIS BY Pd-CATALYZED ANNULATION OF KETONES WITH o-IODOANILINE: 1,2,3,4-TETRAHYDROCARBAZOLE

[1H-Carbazole, 2,3,4,9-tetrahydro-]



Submitted by Cheng-yi Chen and Robert D. Larsen[1] .
Checked by Adam Charnley and Steven Wolff.

1. Procedure

To a 100-mL, two-necked flask, is added a mixture of cyclohexanone (5.9 g, 60 mmol) , o-iodoaniline (4.4 g, 20 mmol) , and 1,4-diazabicyclo[2.2.2]octane (DABCO) (6.7 g, 60 mmol) in N,N-dimethylformamide (DMF) (60 mL). The mixture is degassed three times via nitrogen/vacuum, followed by the addition of palladium acetate ($Pd(OAc)_2$) (2.24 mg, 0.1 mmol) (Note 1). The mixture is degassed twice and heated at 105°C for 3 hr or until completion of the reaction (Note 2). The reaction mixture is cooled to room temperature and partitioned between isopropyl acetate (150 mL) and water (50 mL). The organic layer is separated, washed with brine (50 mL), and concentrated under vacuum to dryness. The residue is chromatographed on 50 g of silica gel using 700 mL of ethyl acetate-heptane (1:6) as the eluent to give 2.22 g of 1,2,3,4-tetrahydrocarbazole (65%) as a pale brown solid (Note 3).

2. Notes

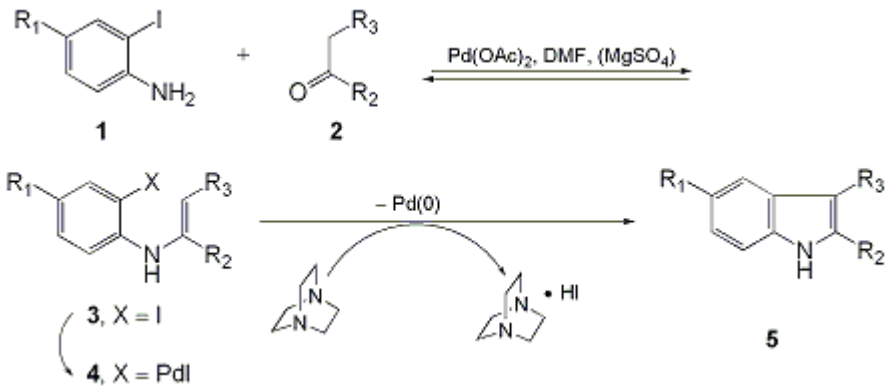
1. Both cyclohexanone and o-iodoaniline were purchased from Lancaster Synthesis and used directly in the reaction without further purification.
2. The reaction generally takes 3-5 hr to complete and is monitored by TLC (R_f = 0.50, SiO_2, eluted with EtOAc - heptane, 1:4).
3. The product is fully characterized: mp 116-118°C; IR (neat) cm^{-1}: 3401, 2928, 2848, 1470, 1305, 1235, 739 ; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.86-1.99 (br m, 4 H), 2.74 (br t, 4 H, J = 6), 7.08-7.71 (br m, 2 H), 7.29 (m, 1 H), 7.49 (m, 1 H), 7.64 (br s, 1 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.05, 22.20, 22.32, 22.42, 108.98, 109.61, 116.81, 118.12, 119.96, 126.82, 133.30, 134.66 . Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 82.87; H, 7.53; N, 7.84.

Waste Disposal Information

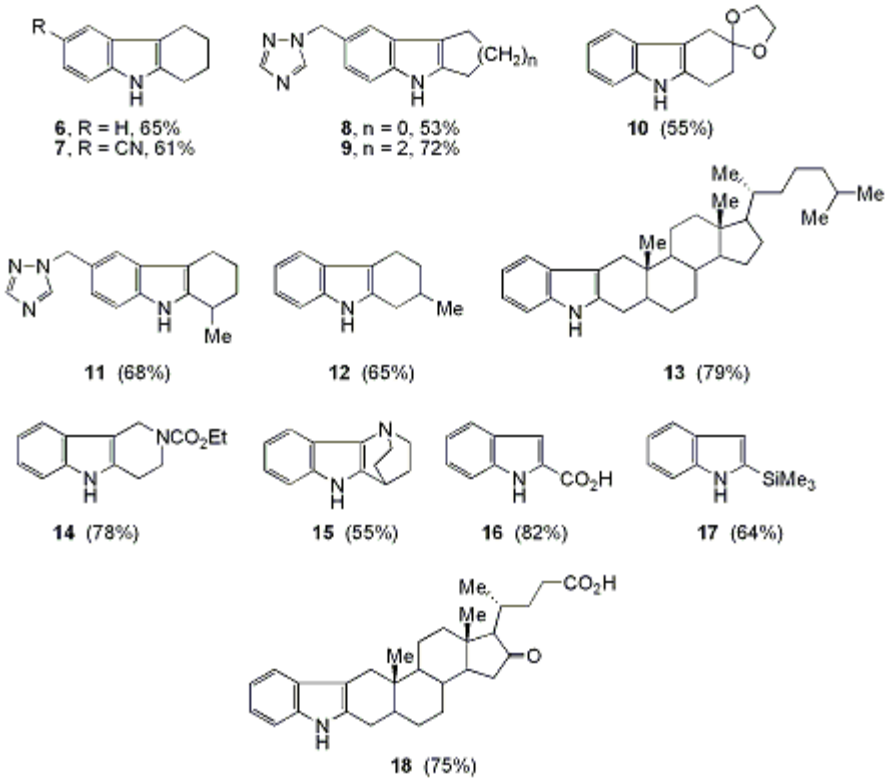
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The indole nucleus is a common and important feature of a variety of natural products and medicinal agents.[2] The traditional approach for preparing the indole nucleus is the Fischer indole reaction.[3] As this reaction has shortcomings, the palladium-catalyzed coupling of ortho-haloanilines is becoming an excellent alternative.[4] Recently, the submitters disclosed a new and efficient method for indole synthesis using a palladium-catalyzed annulation between o-iodoanilines and ketones (Scheme 1).[5]



As illustrated in Chart 1, this reaction is applicable to a variety of o-iodoanilines and cyclic ketones to prepare the desired indoles in good yields. The coupling reaction is highly regioselective.[6] For example, condensation of o-iodoaniline **1**, R=1-(1,2,4-triazolyl)methyl, with 2-methylcyclohexanone gave tetrahydrocarbazole **11** in 68% yield. Reaction of 3-methylcyclohexanone with o-iodoaniline formed tetrahydrocarbazole **12** predominantly. The reaction is also compatible with cyclopentanone and cycloheptanone (compounds **8** and **9**). The reaction tolerates a variety of functional groups, especially the acid-sensitive ketal (**10**), carbamate (**14**), or the benzyl triazole[7] (**8**, **9** and **11**). These compounds, which would be unstable under the conditions of the traditional Fischer indole reaction,[8] were conveniently synthesized using this method. The structurally interesting indole **15** was prepared from 3-quinuclidinone hydrochloride (1.0 equiv) in 55% yield. The interesting coupling of the indole nucleus onto a steroid was also achieved with 5α-cholestanone (1.0 equiv) affording **13** exclusively in 79% yield. Pyruvic acid and acetyl silane were also acceptable substrates, used to prepare indoles **16** and **17** in 82% and 64% yield respectively. Overall, the simple procedure, mild reaction conditions, and availability of the starting materials render this method a valuable addition to indole chemistry.



The high regioselectivity of these reactions follows the same pattern as those of 2- and 3-substituted cyclohexanones when converted to enamines.[9] Apparently, $A^{1,2}$ and $A^{1,3}$ strain in the transition state controls the regiochemistry. The additive magnesium sulfate ($MgSO_4$), presumably acting as a

dehydrating agent, was found to promote the annulation (for compounds **7**, **8**, **11**, **13**, **15** and **17**), indicating that the formation of the imine or enamine intermediate is critical to the reaction. The annulation of dehydrocholic acid and o-iodoaniline clearly demonstrated the high efficiency of this reaction as both excellent chemoselectivity and regioselectivity were observed (**18**). The coupling reaction led to the unique combination of indole and steroid moieties into one interesting molecule.

References and Notes

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6. For a recent example of a regioselective Fischer indole reaction mediated by organoaluminum amides, see: Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Org. Chem*. **1993**, *58*, 7638.
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8. A Fischer indole reaction in pyridine has been reported: Welch, W. M. *Synthesis* **1977**, 645.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

o-Iodoaniline:
Aniline, o-iodo- (8);
Benzenamine, 2-iodo- (9); (615-43-0)

1,2,3,4-Tetrahydrocarbazole:
Carbazole, 1,2,3,4-tetrahydro- (8);
1H-Carbazole, 2,3,4,9-tetrahydro- (9); (942-01-8)

Cyclohexanone (8,9); (108-94-1)

1,4-Diazabicyclo[2.2.2]octane: DABCO (8,9); (280-57-9)

N,N-Dimethylformamide: CANCER SUSPECT AGENT:
Formamide, N,N-dimethyl- (8,9); (68-12-2)

Palladium acetate:
Acetic acid, palladium(2+) salt (8,9); (3375-31-3)