Category

Synthesis of Heterocycles

Key words

indoles

rhodium catalysis

oxidative coupling

D. R. STUART, M. BERTRAND-LAPERLE, K. M. N. BURGESS, K. FAGNOU* (UNIVERSITY OF OTTAWA, CANADA)

Indole Synthesis via Rhodium Catalyzed Oxidative Coupling of Acetanilides and Internal Alkynes
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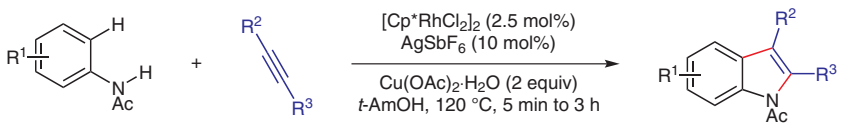
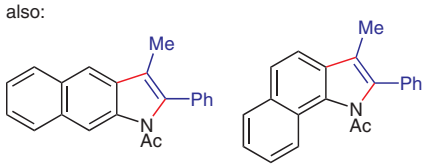
Synthesis of Indoles via Oxidative Coupling of Acetanilides with Acetylenes



1 **2** **3**
47–82%
16 examples

R^1 = 4-OMe, 5-OMe, 3,5-di-OMe, 4-F, 4-Cl, 4-CO_2Me, 6-Me
R^2 = Me, *n*-Pr, *n*-Hex, Ph
R^3 = *n*-Pr, *n*-Hex, Ph, thiophen-2-yl, *N*-tosylindol-5-yl

also:



Significance: Reported here is the rapid synthesis of indoles **3** via the rhodium-catalyzed oxidative coupling of acetanilides **1** and internal alkynes **2**. Extensive optimization with regard to the catalyst, additives and solvent led to the preferred conditions detailed above. Both electron-rich and -deficient acetanilides participate well in the reaction. Substrates bearing an *ortho*-substituent are also tolerated. When a *meta*-substituent is present, cyclization is directed to the least sterically hindered position. Experiments to probe the reaction mechanism using deuterated substrates and solvents suggest that initial rhodation on the aniline occurs at both *ortho*-positions, and that only the least hindered regioisomer undergoes cyclization to give the observed regioselectivity. Removal of the acetyl group was achieved in >90% yield in all cases on standard treatment with KOH or K_2CO_3 in MeOH–CH_2Cl_2.

Comment: Indoles are ubiquitous in nature and are present in many drug compounds (see Book below). Aside from classical methods, transition-metal-catalyzed reactions have, within the last decade, become recognized as powerful tools for the synthesis of indoles (G. Zeni, R. C. Larock *Chem. Rev.* **2004**, *104*, 2285). However, these methods typically rely on a preactivated substrate in the form of an aryl halide, adding cost and reducing the number of readily available starting materials. The current method takes advantage of a C–H activation event to provide indoles from simple and inexpensive anilines. The substrate scope with regard to aryl substitution was adequately studied but the acetylene scope is somewhat limited at this stage. Extension to functionalized acetylenes would be advantageous for further synthetic manipulation.

Book: J. A. Joule, In *Science of Synthesis*, Vol. 10; J. Thomas, Ed.; Georg Thieme Verlag: Stuttgart, New York, **2000**, 361-593.

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