Indoles from *o*-Haloanilines: Syntheses of Tryptamines and Tryptophols *via* Regioselective Hydroformylation of Functionalized Anilines

Yong Dong* and Carl A. Busacca

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877

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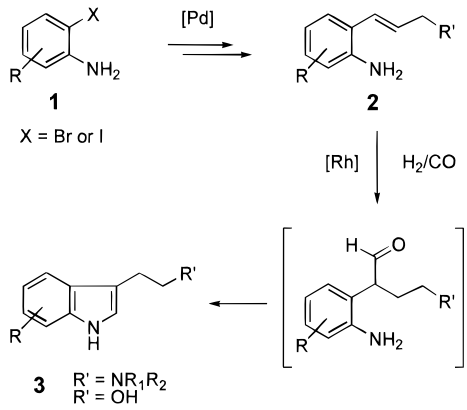
The indole ring has long been a popular synthetic target for chemists. As in most well-investigated areas, synthesis of indole and its derivatives has flourished into a rich field with many excellent methodologies.[1] We report here a new synthesis of indoles from *o*-haloanilines by a sequence of two transition-metal catalyzed reactions. We believe this method provides a useful access to the substituted tryptamines[2] and tryptophols,[3] which are common structural units in many indole alkaloids[4] and possess important pharmacological properties of their own.[5]

Having successfully synthesized 4-aryl-2,3-dihydropyrroles *via* Pd-catalyzed arylation of *N*-tosylallylamine and the subsequent Rh-catalyzed hydroformylation of Heck adducts,[6] we reasoned that if there were an *o*-amino group in the styrene-type Heck adduct, the ensuing regioselective hydroformylation of these functionalized anilines **2** may be followed by cyclization and dehydration to afford the corresponding tryptamines or tryptophols **3** (Scheme 1).

To test this observation, aniline **2a** was first obtained from iodoaniline **1a** and *N*-tosylallylamine under a typical Heck condition [5 mol % $Pd(OAc)_2$, 10 mol % $(o\text{-Tol})_3P$, TEA, CH_3CN, refluxing].[7] Much to our delight, tryptamine **3a**[8] was formed smoothly in 58% yield from the hydroformylation of **2a** [H_2/CO (1:1), 300 psi, 5 mol % $HRh(CO)(PPh_3)_3$, Ph_3P, $PhCH_3$, 70 °C, 70 h]. No hydrogenation product, or hydroxypyrrolidine (a possible cyclization product from NHTs of the side chain) was detected in the crude ^1H NMR spectra, and only traces of an aldehyde were observed. *N*,*N*-di-Boc-allylamine was used next for ease of deprotection. The results are summarized in Table 1. At this point, conditions for the Heck reaction and hydroformylation are not fully optimized.[9] The functional groups in anilines **2d**−**j**, included CH_3, CF_3, OCH_3, Br, Cl, F, which survived unscathed under the hydroformylation condition. Consequently, tryptamines **3d**−**j** were modified with functionalities at C5, C6,[10a] and C7.[10b] Starting material was recovered (ca. 80%) when aniline **2c** having an *o*-CH_3 was subjected to the above hydroformylation condition. Thus, the efforts to synthesize C4-substituted tryptamine met with no success.[11] Tryptophol **3k** was formed exclusively in 73% yield from aniline **2k**, which was the reduction product of methyl *o*-aminocinnamate (61%, iBu_2AlH, THF, −78 °C). This cinnamate in turn was a Heck adduct (91% yield) derived from iodoaniline **1a** and methyl acrylate.

Scheme 1



In summary, we have developed the first indole synthesis from the hydroformylation of functionalized anilines. By utilization of readily available *o*-haloanilines, syn gas, allylamine or methyl acrylate, and by combination of two common catalytic transformations, the overall result is the facile construction of indoles with an aminoethyl or hydroxyethyl side chain at C-3. We expect that this approach is also applicable to introduce other different C3 side chains. This new method requires only catalytic amounts of palladium and rhodium complexes. In ad-

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(11) Attempted olefination of di-*ortho*-substituted bromides such as 2,6-dinitrobromobenzene, 2,6-diaminobromobenzene, 2-amino-6-nitrobromobenzene, and the triflate of 2-bromo-3-nitrophenol all failed. Thus, only aniline **2c** was studied for the synthesis of C4-substituted tryptamine.

S0022-3263(97)01179-1 CCC: $14.00

Table 1. Tryptamines and Tryptophol from Hydroformylation of Functionalized Anilines

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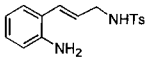
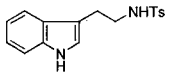
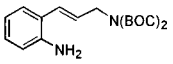
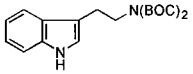
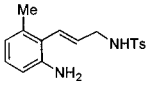
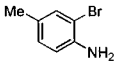
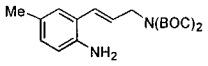
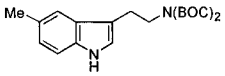
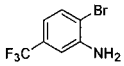
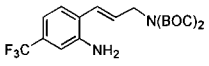
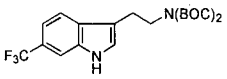
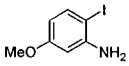
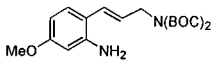
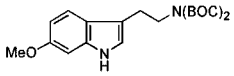
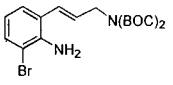
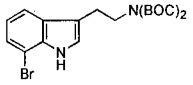
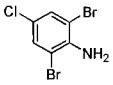
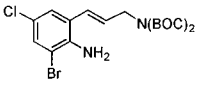
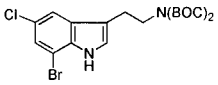
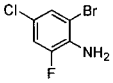
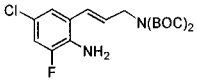
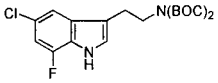
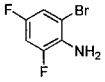
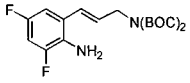
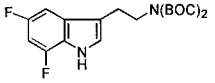
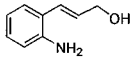
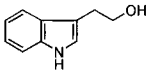
a			71		58
b	**1a**		73		69
c			48		
d			50		60
e			78		58
f			56		32
g			50		60
h			52		54
i			72		56
j			69		62
k	**1a**		56		73

dition, it renders a short reaction sequence in which tryptamines and tryptophols are generated in two to three steps from the appropriate *o*-haloanilines. The resulting indoles are prepared without the necessity of protections of the indole nitrogen and hydroxy group of tryptophol. The halo-substituted tryptamines in particular should prove to be valuable intermediates for further derivatization.

Supporting Information Available: Experimental procedures and spectral data for all new compounds (7 pages).

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