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Preparation of the 4-Hydroxytryptamine Scaffold via Palladium-Catalyzed Cyclization: A Practical and Versatile Synthesis of Psilocin

Nicholas Gathergood[†,‡] **and Peter J. Scammells***[,†]

Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia, and School of Biological and Chemical Sciences, Deakin University, Geelong, Victoria 3217, Australia

peter.scammells@vcp.monash.edu.au

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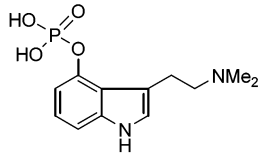
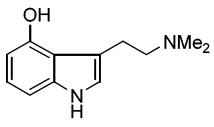
ABSTRACT

The 4-hydroxytryptamine scaffold of psilocin was successfully prepared via palladium-catalyzed cyclization of protected *N-tert*-butoxycarbonyl-2-iodo-3-methoxyaniline and an appropriately substituted silyl acetylene. Removal of the protecting groups afforded psilocin in good yield.

4-Substituted indoles are an important class of alkaloids that exhibit a wide range of activity.[1] Psilocybin **1** and its metabolite, psilocin **2**, are reported to enter the central nervous system through the gastrointestinal tract and cause powerful psychotomimetic effects.[2] There have been considerable studies into the effects of substitution on the 4-hydroxytryptamine scaffold.[3]



Psilocybin **1**



Psilocin **2**

To facilitate the development of an improved methodology for the analysis of psilocin, our aim was to develop an economical and efficient synthesis of psilocin for use as a reference standard.

Methods for the preparation of indoles substituted in the 3 position can be split into two categories. Either the desired indole core is formed (e.g., 4-hydroxyindole) and then modified at the 3 position or the appropriate *ortho*-haloaniline structure is coupled with a silylated alkyne, directly giving an indole product substituted at the 3 position. Synthesis of 4-hydroxyindoles from indole via 4-iodoindoles using thallium acetate has been reported by Somei et al.,[4] and this route has been used to prepare psilocin.[5] A synthesis of

[†] Monash University.
[‡] Deakin University.

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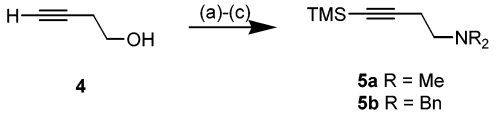
psilocin and psilocybin from 4-benzyloxyindole was reported by Nichols and Frescas;[6] however, the cost of this starting material is considerable.[7] The 4-hydroxyindole ring structure has also been formed in a two-step process by the palladium-catalyzed cross-coupling of *ortho*-iodoanilines and (trimethylsilyl)acetylene, followed by a cyclization in the presence of potassium *tert*-butoxide.[8] This method, however, is not amenable to the direct preparation of the desired indole framework present in tryptamine. An example of a palladium-catalyzed cyclization reaction of *ortho*-vinylanilines to yield indoles has also been reported.[9]

Palladium-catalyzed cyclization of iodo-aromatics with unsaturated fragments to yield indole products substituted at the 3 position has been reported.[10] Ujjainwalla and Warner describe the synthesis of 5-, 6-, and 7-azaindoles derivatives via palladium-catalyzed heteroannulation of 4-(triethylsilyl)-3-butyn-1-ol and aminopyridines (e.g., 2-amino-3-iodopyridine).[11] Recently, triethylsilylalkynes were reacted with *ortho*-iodoanilines to give substituted tryptophan analogues.[12,13] Sakagami and Ogasawara[14] reported the preparation of psilocin in six steps from *N*-*tert*-butoxycarbonyl-2-iodo-3-methoxyaniline **3**.

We now report a short preparation of psilocin, avoiding the use of thallium salts, from inexpensive starting materials that we believe is convenient for synthetic and analytical chemists. Our approach is a concise, convergent synthesis of psilocin from *N*-*tert*-butoxycarbonyl-2-iodo-3-methoxyaniline **3** in three steps. The key step is the formation of the indole core via a palladium-catalyzed cyclization. The two fragments required for the cyclization are **3** and alkyne **5a**. Compound **3** was prepared from Boc-protected 3-methoxyaniline, via directed lithiation[15] and iodination.[16]

The preparation of **5a** from 3-butyn-1-ol **4** has been previously reported;[13] however, no experimental procedure or characterization data was included in this patent. Tosylation, substitution with *N*,*N*-dimethylamine,[17] and treatment with *n*-butyllithium, trimethylsilyl chloride gave the required

Scheme 1. Synthesis of Silyl Acetylene Precursors[a]



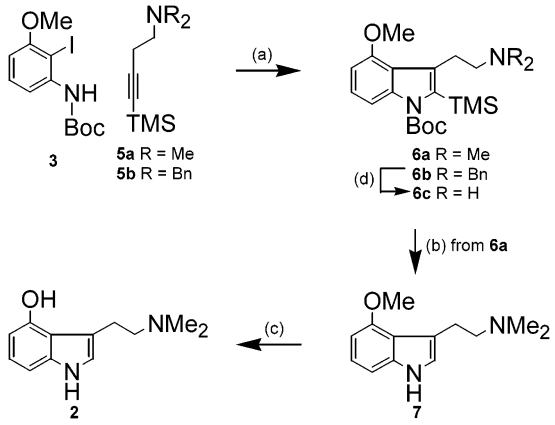
4 **5a** R = Me, **5b** R = Bn

[a] Reagents and conditions: (a) TsCl, NEt_3, CH_2Cl_2; (b) $HNMe_2$ (40 wt % solution in water), rt, 16 h or $HNBn_2$, MeOH, reflux, 48 h; (c) *n*-BuLi, Et_2O, −10 °C and then TMSCl. Yield of **5a** = 88%, **5b** = 56% (both from **4**).

alkyne in good yield (Scheme 1). Compound **5b** was prepared analogously using *N*,*N*-dibenzylamine.

The key palladium-catalyzed cyclization step (Scheme 2) was attempted under a variety of conditions, and the best

Scheme 2. Synthesis of Psilocin[a]



3 **5a** R = Me, **5b** R = Bn; **6a** R = Me, **6b** R = Bn, **6c** R = H; **2**; **7**

[a] Reagents and conditions: (a) $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), NEt_4Cl (1 equiv), *i*-Pr_2EtN (3 equiv), DMF, 80 °C (yield of **6a** = 69%, **6b** = 77%); (b) neat TFA, 25 °C, 3 h (yield of **7** = 58%); (c) BBr_3, CH_2Cl_2, from −78 to 25 °C (yield of **2** = 61%); (d) 20% $Pd(OH)_2$/C, 40 psi H_2 (yield of **6c** = 83%).

results were obtained using $Pd(OAc)_2$, triphenylphosphine, tetraethylammonium chloride, and *N*,*N*-diisopropylethylamine in DMF at 80 °C for 48 h.[18] When tri-2-furylphosphine was used in place of triphenylphosphine, a significantly lower yield of the desired indole was obtained (32%). Although LiCl has been reported to improve the regioselectivity, reproducibility, and yield of such cyclizations,[11] the use of LiCl and Na_2CO_3 in this case gave slightly inferior results.

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(16) Preparation of 14 g of **3** was performed in our laboratories using standard glassware.

(17) This substitution reaction was accomplished successfully using an aqueous solution of *N*,*N*-dimethylamine with no formation of 3-butyn-1-ol detected by NMR. Previous methods have used *N*,*N*-dimethylamine as a gas or dissolved in an organic solvent; both of these sources of *N*,*N*-dimethylamine are considerably more expensive or inconvenient to use.

(18) A dry flask was charged with 1-*tert*-butoxycarbonyl-2-iodo-3-methoxyaniline (3.21 g, 9.16 mmol, 1 equiv), 4-(trimethylsilyl)-3-butyn-1-dimethylamine (3.10 g, 18.3 mmol, 2 equiv), palladium(II) acetate (420 mg, 1.84 mmol, 0.2 equiv), triphenylphosphine (960 mg, 3.68 mmol, 0.4 equiv), tetraethylammonium chloride (1.52 g, 9.12 mmol, 1 equiv), diisopropylethylamine (3.54 g, 4.8 mL, 27.4 mmol, 3 equiv), and DMF (65 mL) under a nitrogen flush and heated to 80 °C for 48 h. After the mixture was cooled, DMF and volatiles were removed by rotary evaporation and then ethyl acetate (50 mL) and water (50 mL) were added to the residue. The aqueous phase was extracted with ethyl acetate (3 × 25 mL); the organic phase was washed with 5% $NaHCO_3$ (25 mL) and brine (25 mL), and solvents were removed by rotary evaporation. The crude was purified by column chromatography (SiO_2, 90:10:1 $CHCl_3$/CH_3OH/NH_4OH) to give the title compound as a light brown oil in 69% yield (2.45 g, 6.3 mmol).

In all cases, several byproducts were present in the crude reaction mixture (apparent by TLC and ^{1}H NMR) and column chromatography was required to obtain pure **6a**. One plausible route for the formation of these byproducts is the cyclization of the dimethylamino group on the activated vinylic−palladium bond. Although **6a** was stable to purification by column chromatography, the byproducts decomposed, making their identification difficult.

To complete the synthesis of psilocin, the Boc and trimethylsilyl groups of **6a** were cleaved by treatment with neat TFA to afford **7** in good yield. *O*-Demethylation using boron tribromide[13,19] yielded psilocin **2**.

To further explore the versatility of the palladium cyclization and increase the degree of derivatization of the route presented, we studied the effect of preparing alkynes with more sterically hindered amino fragments. Compound **6b** was prepared in the same manner as **6a**. We were pleased to find that the Pd cyclization of **3** with **5b** gave a clean reaction to **6b** in 77% yield. This suggests that the undesired cyclization of the terminal amine is inhibited by the steric bulk of the two benzyl groups.

Confirmation of the regiochemistry of the palladium-catalyzed cyclization between the dibenzylamino-substituted alkyne **5b** and **3** was established by X-ray crystallography. Figure 1 (below) clearly shows that the tryptamine scaffold has been prepared and that the extra steric bulk of the benzyl groups on the nitrogen has not inverted the regiochemistry of the cyclization. Psilocin prepared by the route shown in Scheme 2 exhibited NMR data that was in agreement with the literature,[14] thus proving the regiochemistry of the palladium-catalyzed cyclization of **5a** and **3**.

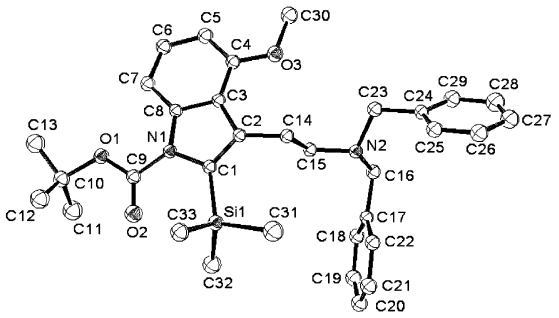

Figure 1. ORTEP of indole **6b** (hydrogen omitted for clarity).

Modification of the alkyl groups in serotonin and related compounds to alter the activity of these compounds has been an active field of research.[3] Compound **6b** is also a versatile intermediate for the preparation of analogues of psilocin with modified amine substituents. The *N*-benzyl groups of **6b** were removed by catalytic hydrogenation to give **6c** in good yield. Compound **6c** is amenable to conversion to psilocin analogues with modified side chains. For example, reductive alkylation of the terminal amino group of 4-benzyloxytryptamine has been successfully completed by Yamada et al.[5]

In conclusion, the carbon framework for psilocin can be formed by the palladium-catalyzed cyclization of **3** with **5a**. Removal of the protecting groups leads to the target in good yield. Using **5b** in the cyclization step increased the yield and generated a cleaner reaction. The benzyl-protected amino group of **6b** can then be selectively deprotected. This leads to the useful intermediate **6c**, which can be reductively alkylated to a series of secondary and tertiary amines. This approach has the flexibility to allow a short synthesis of amino analogues by incorporation of the desired amine via the alkyne fragment or by modification of a late-stage intermediate. New methodology for analysis of psilocin and its analogues will be reported in due course.

Acknowledgment. The authors thank Mr. Gary Fallon for the crystal structure of compound **6b** and the Australian Research Council for financial support.

Supporting Information Available: Spectroscopic data for psilocin **2** and X-ray data for the indole **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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