Improved Preparation of *N*-Propargyl-2-(5-benzyloxyindolyl)methylamine [a]

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An improved synthetic sequence for the synthesis of *N*-propargyl-2-(5-benzyloxyindolyl)methylamine (**1**) is described.

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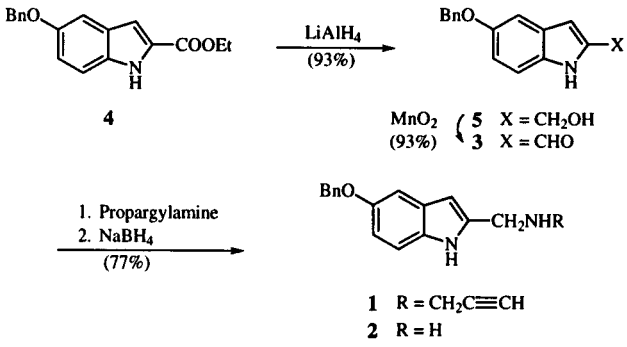
In 1991 Fernández-Alvarez and co-workers described the synthesis and biological evaluation of a series of *N*-acetylenic and allenic derivatives of 2-(5-benzyloxyindolyl)-methylamines [1]. They showed that most of these compounds were potent, but not selective, inhibitors of monoamine oxidase A and B [2].

A recent renewed interest in our laboratory in these results has focussed our synthetic effort on one of these compounds, namely *N*-propargyl-2-(5-benzyloxyindolyl)-methylamine (**1**) [3]. Previous synthesis of this and related molecules relied on the *N*-propargylation of the parent primary amine **2**; this protocol gave the desired compound in low chemical yield (~30%) and produced secondary by-products, the *N*,*N*'-dialkylated material; a tedious separation by chromatography was neccessary and, in addition, no complete reaction was observed [1]. This situation made impractical the scale-up of this reaction as desired. Obviously, an improved methodology was in order, and in this communication we report a new and improved preparation of the title compound **1**.

Scheme 1



This approach is based on the reductive amination [4] of the carbonyl intermediate **3** (see Scheme 1). This compound was simply prepared by lithium aluminum hydride reduction of the known ethyl 2-(5-benzyloxyindole)carboxylate (**4**) [5] followed by mild oxidation with manganese dioxide. With this compound in hand we attacked the key step. After extensive experimentation, conditions were found for a clean and high yielding reaction. Aldehyde **3** was stirred at room temperature, for 24 hours, with an excess of commercial propargylamine and the crude reaction mixture was reduced with sodium borohydride at 0° followed by warming to room temperature. The indole **1** was obtained in 77% yield, after simple filtration on a silica gel column. The spectroscopic data and comparison with an authentic sample [1] proved the identity of our sample.

EXPERIMENTAL

Reactions were monitored by tlc using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by uv (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% ethanol. Anhydrous sodium sulfate was used to dry organic solutions during workups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as eluent. The ^{1}H spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as the internal standard.

2-(5-Benzyloxyindole)carboxyaldehyde (**3**).

Ethyl 2-(5-benzyloxyindole)carboxylate (**4**) [5] (10 g, 0.035 mole) was suspended in dry tetrahydrofuran (200 ml) and treated with lithium aluminium hydride (8 g, 0.21 mole, 6 equivalents) at reflux for 4 hours; after 2 hours at room temperature, the flask was cooled at 0° and the excess of lithium aluminum hydride destroyed by careful addition of water. The solid was removed by filtration and washed with tetrahydrofuran several times. The solvent was evaporated and the residue dissolved in ethyl ether, dried and evaporated to give alcohol **5** as a yellow solid which recrystallization from benzene had mp 106°, 7 g, 93% yield, which was oxidized without further analysis as follows. Compound **5** (3 g, 0.011 mole), dissolved in dry tetrahydrofuran (150 ml) was treated with manganese dioxide (12.5 g, 0.14 mole, 12.7 equivalents) and sodium chloride (2.5 g). The suspension was stirred rapidly for 90 hours at room temperature. After this period a saturated aqueous solution of sodium chloride (25 ml) was added and the mixture stirred for 2 hours. After filtration over Celite, the solvent was removed to give a solid that was recrystallized from benzene, 2.35 g, 93% yield, mp 180-181°; ir (potassium bromide): υ 3320 (NH), 1650 (COH), 1525, 1455, 1185 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.80 (s, 1H, CHO),

9.17 (br s, 1H, NH), 7.50-7.15 (m, 9H, aromatic), 5.10 (s, 2H, OCH_2).

Anal. Calcd. for $C_{16}H_{13}NO_2$ (251.28): C, 76.49; H, 5.17; N, 5.57. Found: C, 76.25; H, 5.40; N, 5.65.

N-Propargyl-2-(5-benzyloxyindolyl)methylamine (**1**).

Compound **3** (243 mg, 0.96 mmole), dissolved in tetrahydrofuran (6 ml), was treated with propargylamine (0.33 ml, 4.8 mmoles, 5 equivalents), powdered molecular sieves 4 A (500 mg) and stirred at room temperature for 24 hours. The mixture was filtered, washed with tetrahydrofuran several times and evaporated. The crude was dissolved in methanol (7 ml), cooled to 0° and treated with sodium borohydride (38 mg, 1 mmole, 1.1 equivalents); the flask was warmed at room temperature and after 30 minutes the reaction was completed as shown by tlc analysis. The solvent was evaporated and the residue dissolved in ethyl acetate, washed with brine, dried, filtered and evaporated. The crude residue was chromatographed through a short silica gel column, eluting with hexane:ethyl acetate/1:1, to give indole **1**, (mp 176, 214 mg, 77% yield, whose behavior by tlc in different solvents and spectroscopic data were identical to those described in literature [1].

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[a] This paper is dedicated with respect to the memory of Professor Eldiberto Manuel Fernández Alvarez.

REFERENCES AND NOTES

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