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Facile Two-Step Synthesis of 2-(2′-Aminobenzylamino)benzyl Alcohol, a Naturally Occurring Amine from Justicia gendarussa

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FACILE TWO-STEP SYNTHESIS OF 2-(2′-AMINOBENZYLAMINO)BENZYL ALCOHOL, A NATURALLY OCCURRING AMINE FROM *JUSTICIA GENDARUSSA*

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Abstract : A very simple and preparatively efficient two-step synthesis of the title compound **1**, a basic constituent of the Indian medicinal plant *Justicia gendarussa* is accomplished via reductive alkylation of 2-aminobenzyl alcohol using zinc chloride and zinc borohydride.

2-(2′-Aminobenzylamino)benzyl alcohol **1** has recently been isolated[1] along with some other simple amines from the leaves of *Justicia gendarussa* (Acanthaceae) which is known for its therapeutic applications[2] in the treatment of odema of beriberi, rheumatism and cardiac asthma in the traditional Indian system of medicine. Apart from the amine **1**, β-sitosterol, a very common plant sterol with no related medicinal activity has so far been isolated[3] from this plant. Its chemical structure proposed on the basis of spectroscopic studies has been confirmed[1] by a multistep synthesis that affords the amine in less than 2% overall yield. The development of a shorter, high-yielding route for **1** that would make this molecule more readily available to the interested investigators is a desirable objective.

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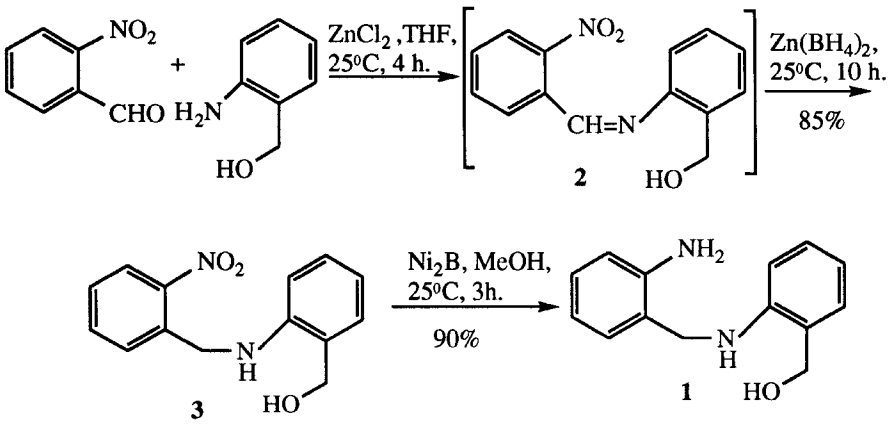

Scheme

As part of our interest in the development of mild and safe reagent systems for reductive amination reactions,[4] we have recently described[5] the novel use of zinc chloride and zinc borohydride in the reductive aminations of formaldehyde. The present paper describes a very simple and effective two-step synthesis of **1** utilizing the reductive amination of 2-nitrobenzaldehyde with 2-aminobenzyl alcohol in the presence of zinc chloride and zinc borohydride as the key step.

A mixture of 2-aminobenzyl alcohol (1 mol equiv.), 2-nitrobenzaldehyde (1.2 mol equiv.) and zinc chloride (1.5 mol equiv.) in anhydrous THF was stirred at room temperature for 4 h. The reducing agent, zinc borohydride (1 mol equiv.) which was prepared from zinc chloride (1 mol equiv.) and sodium borohydride (2 mol equiv.) was then added and the resulting mixture was further stirred for 10 h. The pure nitroamine **3** was isolated in 85% yield by simple extraction of the organic part with hydrochloric acid (1 N). Zinc chloride was possibly functioning as a mild Lewis acid catalyst as well as an excellent water scavanger to produce the

intermediate imine **2** which was then reduced by zinc borohydride. Reduction of the nitro group in **3** was accomplished in almost quantitative yield using nickel boride[6] to afford 2-(2´-aminobenzylamino)benzyl alcohol **1** whose spectral data and mp were in agreement with those reported in the literature.[1]

In conclusion, an expedient high-yielding synthesis of the title amine **1** is developed via reductive amination of 2-nitrobenzaldehyde with 2-aminobenzyl alcohol using zinc chloride and zinc borohydride.

Experimental

All melting points are uncorrected. ^{1}H NMR spectra were scanned on a 60 MHz EM 360 spectrometer of Varian Associates and a 300 MHz Brucker AC-300 spectrometer in $CDCl_3$ solutions with Me_4Si as an internal reference. IR spectra were recorded on a perkin-Elmer 298 spectrometer. Thin layer chromatography was done on precoated silica gel plates. THF was freshly distilled over LAH before use.

Nitroamine 3 : A mixture of 2-nitrobenzaldehyde (0.91g, 6 mmol), 2-aminobenzyl alcohol (0.62g, 5 mmol) and zinc chloride (1.02g, 7.5 mmol) in anhydrous THF (20 mL) was stirred at room temperature under dry atmosphere for 4 h. A solution of zinc borohydride[5] (5 mmol) in anhydrous THF was then added and stirring was continued for a further period of 10 h. The reaction mixture was then poured into aqueous ammonia (20 mL, 2N), the contents were stirred for 10 min. and the organic part was extracted with Et_2O (50 mLx3). The combined organic solution was next extracted with hydrochloric acid (1 N, 2x10 mL) to separate the neutral materials. The acidic aqueous solution was then made alkaline by slow addition of 10% aqueous NaOH (pH=10) and extracted with Et_2O (50mLx3). The combined Et_2O extracts were dried (K_2CO_3) and concentrated *in vacuo* to give a yellow oil which on flash chromatography over silica gel yielded 1.1g (85%) of pure nitroamine **3**,

ν_{max}/ cm^{-1} 3380, 3060,2921, 2857, 1633, 1601, 1518, 1505, 1460, 1338 and 1300; δ_H 4.72 (s, 2H), 4.78 (s, 2H), 6.43 (d, J = 8 Hz, 1H), 6.67 (t, J = 7.3 Hz, 1H), 7.09 (t, J = 7.4 Hz, 2H), 7.4 (t, J = 8 Hz, 1H), 7.54 (t, J= 7.4 Hz, 1H), 7.64 (d, J = 8 Hz, 1H) and 8.06 (d, J = 8 Hz, 1H). (Found: C, 65.22; H, 5.32; N, 10.62, $C_{14}H_{14}N_2O_3$ requires C, 65.11; H, 5.46; N, 10.85%).

2-(2´-aminobenzylamino)benzyl alcohol 1 : Nickel boride (0.63g), prepared from nickel acetate tetrahydrate and sodium borohydride according to the reported procedure[6] was added to a solution of the nitroamine **3** (0.52g, 2 mmol) in methanol (20 mL) at room temperature. The mixture was stirred for 3 h and quenched with hydrochloric acid (15 mL, 1N). The acidic solution was next made alkaline (pH = 10) by addition of aqueous ammonia (2 N) to afford a suspension which was extracted with Et_2O (50 mLx3). The combined organic extracts were dried and concentrated under reduced pressure. The residue that solidified on cooling was recrystallised from a mixture of hexanes and Et_2O to furnish 0.41g (90 %) of **1** as a white solid, mp 130°C (lit.[1] 131°C); δ_H 4.26 (s, 2H), 4.64 (s, 2H), 6.69 - 6.78 (m, 3H), 6.83 (d, J = 7.8 Hz, 1H), 7.09 - 7.2 (m, 3H) and 7.27 (t, J = 7.8 Hz, 1H).

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