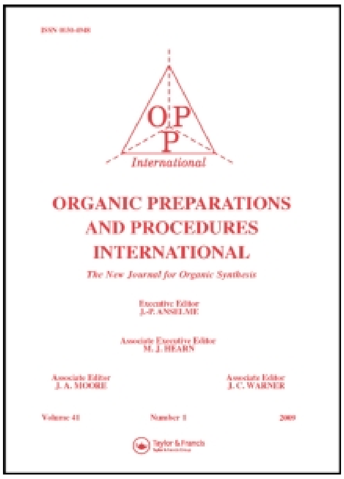

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Kamat, Vijayendra P. and Kirtany, Janardan K.(1994) 'A SIMPLE AND SHORT SYNTHESIS OF 2(2'-AMINOBENZYLAMINO)BENZYL ALCOHOL, A CONSTITUENT OF *JUSTICIA GENDARUSSA* BURM LEAVES', Organic Preparations and Procedures International, 26: 4, 494 — 497

To link to this Article: DOI: 10.1080/00304949409458047

URL: http://dx.doi.org/10.1080/00304949409458047

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A SIMPLE AND SHORT SYNTHESIS OF 2-(2'-AMINOBENZYLAMINO)BENZYL ALCOHOL, A CONSTITUENT OF *JUSTICIA GENDARUSSA* BURM LEAVES

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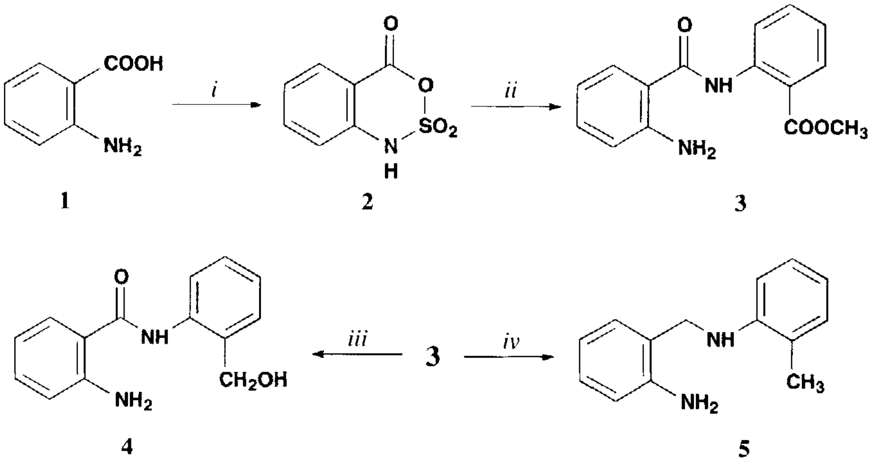
The isolation and characterization of some simple aromatic amines from the leaves of *Justicia gendarussa* Burm known for their medicinal value has been described by Chakravarty *et al.*[1] Structure **9** which was assigned to one of the amines based on spectral data was confirmed by a multistep synthesis starting from *o*-toluidine. We sought to prepare the amine **9** by a simpler and shorter route and our results are presented herein.

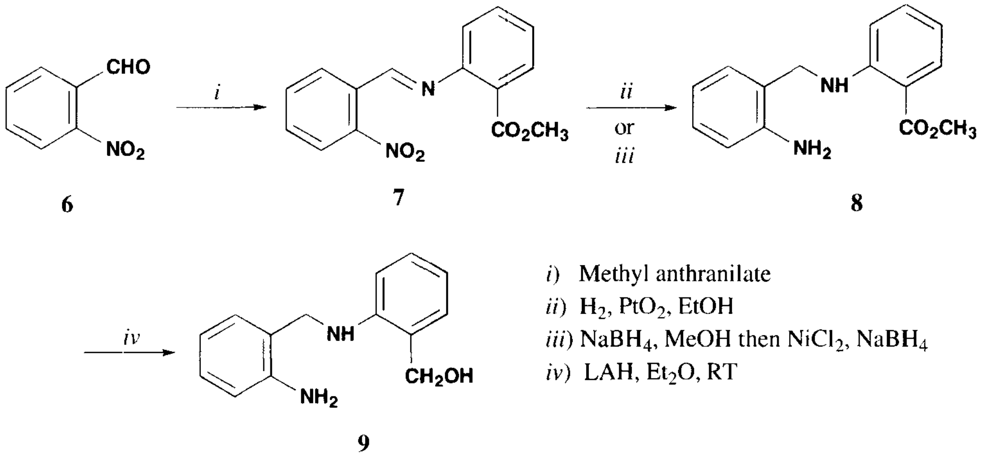
Our initial approach (Scheme 1) consisted of reaction of methyl anthranilate with sulfinamide anhydride (**2**, obtained by heating anthranilic acid (**5**) with thionyl chloride in dry benzene under reflux)[2] to give **3**, which was expected to furnish the amine **9** on reduction with LAH. When reduction of **3** was carried out with LAH in THF at room temperature for 24 hrs, only carbomethoxy group was converted to primary alcohol to yield **4**; the amide carbonyl remained unaffected. Under a



i) $SOCl_2$, PhH, Δ *ii*) Methyl anthranilate *iii*) LAH, THF, RT *iv*) LAH, Et_2O, RT

Scheme 1

different set of conditions (LAH, Et_2O, room temperature, 20 days), both the amide carbonyl and carbomethoxy group of **3** were reduced, the latter completely to the methyl to furnish **5**. These difficulties led us to seek an alternate route shown in Scheme 2.



i) Methyl anthranilate
ii) H_2, PtO_2, EtOH
iii) $NaBH_4$, MeOH then $NiCl_2$, $NaBH_4$
iv) LAH, Et_2O, RT

Scheme 2

The Schiff's base **7**, obtained by condensation of *o*-nitrobenzaldehyde (**6**) with methyl anthranilate, was converted to **8** by catalytic hydrogenation or by reduction with $NaBH_4$ in MeOH[3] followed by $NiCl_2$•6 $H_2O/NaBH_4$;[4] in the latter method, the first reagent reduced the imine to amine while the second one effected reduction of nitro group to the amino group. Finally, LAH reduction of **8** gave the title amine **9**, whose mp. and spectral data agreed well with those reported in the literature;[1] **5** was isolated as a minor product. In summary, we have accomplished a simple and short synthesis of 2-(2'-aminobenzylamino)benzyl alcohol (**9**) starting from easily available starting materials.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were obtained on a Shimadzu IR 435 spectrophotometer while PMR spectra were recorded on a JEOL FX-90 spectrometer with TMS as an internal standard. The silica gel (mesh 60-120) was used for column chromatography.

Preparation of 3.- A mixture of anthranilic acid (1.5 g, 11 mmol) and thionyl chloride (8.5 mL, 116 mmol) in dry benzene (25 mL) was refluxed for 2 hrs. The solvent was removed under reduced pressure and to the viscous oily residue, a solution of methyl anthranilate (1.65 g, 11 mmol) in dry benzene (25 mL) was added over a period of five minutes with stirring. The mixture was stirred at room temperature for 48 hrs, then poured in cold water and the organic layer was separated, washed with 10% $NaHCO_3$ solution, water and dried (Na_2SO_4). Evaporation of solvent followed by chromatography of the brown semi-solid residue over silica gel (100 g) using petroleum ether-ether (4:1) furnished 2.54 g (86%) of **3**, mp. 128°; IR (Nujol): 3490, 3380, 3350, 1695, 1670, 1580, 1532, 745 cm^{-1}. PMR ($CDCl_3$): δ 4.0 (s, 3H), 6.59-7.65 (m, 6H), 8.05 (dd, 1H, J = 8 and 2Hz), 8.823 (dd, 1H, J = 8 and 2Hz).

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.18; N, 10.37. Found: C, 66.44 ; H, 5.19 ; N, 10.49

LAH Reduction of 3 to 4.- A solution of **3** (0.200 g, 7.4 mmol) in anhydrous tetrahydrofuran (15 mL) was added to a slurry of lithium aluminum hydride (0.025 g) in dry THF (10 mL) with stirring over a period of 10 minutes. The reaction mixture was stirred overnight at room temperature. Excess reducing agent was decomposed by moist ether followed by careful addition of water. The organic layer was then filtered through a bed of Celite. Removal of solvent furnished a semi-solid purified through column chromatography over silica gel (8 g) using hexane-ethyl acetate (8:2) to give 0.163 g (91%) of the product, mp. 145°; IR (Nujol): 3450-3290 (broad), 1650, 765, 750 cm^{-1}. PMR (DMSO-d_6): δ 4.78 (d, 2H, J = 5.3 Hz), 5.7 (d, 1H, J = 5.3 Hz, exchangeable with D_2O), 6.3 (br s, 2H, exchangeable with D_2O), 6.53-7.764 (m, 7H), 8.12 (dd, 1H, J = 8 & 2Hz), 10.13 (br s, 1H, exchangeable with D_2O).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.78 ; N, 11.57. Found: C, 69.43; H, 5.75; N, 11.55

LAH Reduction of 3 to 5.- Compound **3** (0.250 g, 9.2 mmol) was reduced with LAH (0.030 g) in dry ether (15 mL) by stirring at room temperature for 20 days and worked up as usual followed by column chromatography over silica gel (10 g) using hexane-ether (9:1), furnished **5** as a crystalline substance 0.188 g (96%), mp. 101°; IR (CCl_4): 3450, 3350 cm^{-1}. PMR ($CDCl_3$): δ 2.12 (s, 3H), 3.44 (br s, 3H), 4.249 (s, 2H), 6.64-7.256 (m, 8H).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.24; H, 7.54; N, 13.20. Found: C, 79.14; H, 7.84; N, 13.17

Schiff's Base 7 and Its Reduction to 8.- A mixture of **6** (1.0 g, 6.6 mmol) and methyl anthranilate (1.0 g, 6.6 mmol) was heated on steam bath for 30 minutes and dry benzene (100 mL) was added to it. The reaction mixture was refluxed overnight using Dean-Stark water separator. The excess benzene was removed by distillation to give 1.8 g (96%) of **7** as a yellow oil. This was used as such for next reaction.

To a solution of **7** (0.940g, 3.3 mmol) in absolute methanol (6 mL) was added $NaBH_4$ (0.456 g, 12 mmol) slowly and portionwise. The reaction mixture was stirred overnight at room temperature. A solution of nickelous chloride hexahydrate (1.566 g, 6.6 mmol) in absolute methanol (20 mL) was added in one portion followed by $NaBH_4$ (0.500 g, 13 mmol) in portions with cooling (5°) and stirring over a period of 30 minutes; stirring was continued for 3 hrs at room temperature. After removal of methanol by distillation, the black precipitate was dissolved in 10% HCl and the acid solution was made basic to pH 8 by the addition of conc. NH_4OH, extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with water and dried (Na_2SO_4). Evaporation of solvent followed by chromatography over silica gel (50 g) using ether-petroleum ether (3:7) gave 0.694 g (82%) of **8**, mp. 105°; IR (CCl_4): 3450, 3350, 1690, 1515 cm^{-1}. PMR ($CDCl_3$):δ 3.82 (s, 3H), 4.313 (s, 2H), 6.54-6.85 (m, 4H), 7.04-7.46 (m, 3H), 7.915 (dd, 1H, J = 8 & 2 Hz); MS: *m/z* 256 (M^+), 151, 119, 106 (base peak).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.31; H, 6.25; N, 10.93. Found: C, 70.66; H, 6.12; N, 11.08

Hydrogenation of 7 to 8.- A solution of **7** (0.200 g, 7 mmol) in absolute ethanol (10 mL) was hydrogenated in presence of platinum oxide (0.050 g) at room temperature in a Parr hydrogenation apparatus (pressure 2 atm.). The catalyst was filtered off and the filtrate was concentrated to yield 0.170 g

(97%) of **8**, mp. 105°, identical with the product obtained earlier.

2-(2'-aminobenzylamino)benzyl Alcohol (9).- A solution of **8** (0.250 g, 0.97 mmol) in dry ether (15 mL) was added to a slurry of LAH (0.050 g) in anhydrous ether (10 mL) with stirring over a period of 10 minutes. The reaction mixture was stirred overnight at room temperature. Excess LAH was decomposed by careful addition of moist ether followed by drops of water till a granular precipitate was formed. The ethereal layer was filtered through a bed of Celite. Removal of solvent followed by column chromatography over silica gel (10 g) using hexane-ether (9:1) gave 0.032 g (15.6%) of **5**, mp.101° as a minor product. Continued elution with hexane-ether (1:1) furnished 0.170 g (77%) of **9**, mp. 132°, lit.[1] mp. 131°; IR ($CHCl_3$): 3600, 3400,3350 cm^{-1}. PMR ($CDCl_3$): δ 3.4 (br s, 4H), 4.24 (s, 2H), 4.61 (s, 2H), 6.631-7.35 (m, 8H).

Acknowledgement.- The authors thank Dr. Masaaki Miyashita, Faculty of Pharmaceutical Sciences, Nagasaki University, Japan and Prof. K. M. Madyastha, I.I.Sc., Bangalore, India, for spectral measurements, Prof. R. S. Mali for helpful discussion and Prof. S. K. Paknikar for encouragement.

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