

SYNTHESIS OF (2*S*, 5*S*)-2, 5-BIS(PHENYLMETHYL)PIPERAZINE BY THE
REDUCTION WITH SODIUM BOROHYDRIDE USING TITANIUM TETRACHLORIDE

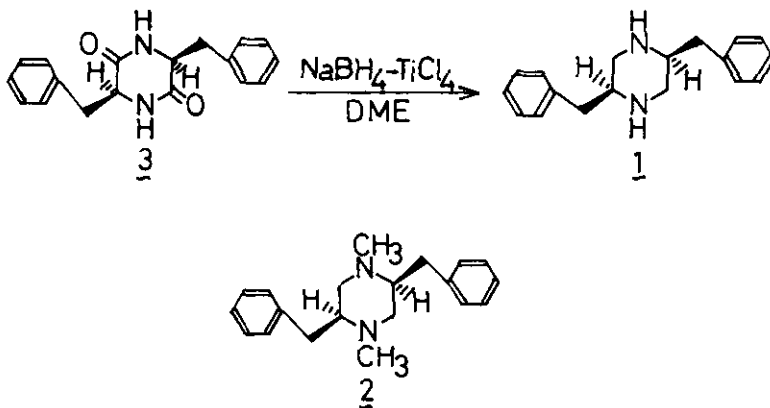
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Abstract—Optically active piperazine **1** is synthesized in relatively high yield by the reduction of *cyclo*-L-Phe-L-Phe with sodium borohydride-titanium tetrachloride.

During our continuing study on asymmetric synthesis,¹ optically active (2*S*, 5*S*)-2, 5-bis(phenylmethyl)piperazine (**1**) is required. Compound **1** also constitutes the main structure of the naturally occurring alkaloid (**2**) isolated from *Zanthoxylum arborescens*.²

Reduction of the corresponding diketopiperazine (*cyclo*-L-Phe-L-Phe, **3**) may be one of the shortest way to synthesize **1**. However **3** has very poor solubility in organic solvents, and the yield of its reduction to **1** with lithium aluminum hydride³ is only



moderate. Jung and Rohloff very recently reported the reductions of chiral diketopiperazines with borane-tetrahydrofuran (BH₃-THF).⁴ However, the yield of **1** from **3** is low (35%). This prompted us to report our result on the synthesis of **1**. We found that sodium borohydride (NaBH₄) reduction of **3** using titanium tetrachloride (TiCl₄)⁵ in refluxing dimethoxyethane (DME) affords **1** in relatively high yield (78%).⁶

Experimental procedure is as follows: **3** was prepared according to the literature procedure.⁷ A suspension of **3** (2.85g, 9.7 mmol) and NaBH₄ (2.48g, 64 mmol) in DME (100 ml) was cooled in an ice-bath, and was added TiCl₄ (6.07g, 32 mmol). The mixture was refluxed, and NaBH₄ (0.498g, 13 mmol) and TiCl₄ (1.25g, 7 mmol) were further added 3 times respectively every 12 h. Then the reaction was quenched by adding H₂O. The insoluble precipitate was filtered off. The filtrate was made basic with 28% aq. NH₃, and was extracted with CH₂Cl₂. The extract was dried over anhydrous Na₂SO₄. Organic solvent was evaporated and the residue was stirred overnight in 6M HCl and MeOH to hydrolyze completely. After the evaporation of MeOH, the mixture was made alkaline with 1M aq. NaOH. The mixture was extracted with CH₂Cl₂ and the extract was dried over anhydrous Na₂SO₄, evaporated and was treated with 2.8M methanolic HCl in Et₂O. Dihydrochloride of **1** was obtained in 78% yield as crystals, m.p. 230-232°C (decomp.), $[\alpha]_D^{25} -29.78^\circ$ (c 2.653, H₂O). {lit.³ $[\alpha]_D^{20} -29.66^\circ$ (c 2.705, H₂O)}. ¹H-NMR as free **1** (CCl₄, ppm) δ 1.33 (2H, s, NH), 2.80-2.87 (10H, m), 7.20 (10H, s); IR as free **1** (neat): 3300, 3050, 3020, 2920, 2700, 1603, 1498, 1455, 1313, 1305, 1225, 1190, 1130, 1080, 1030, 990, 800, 742, 702 cm⁻¹; Anal. as salt of 3,6-dinitrophthalic acid. Anal. Calcd. for C₂₆H₂₆O₈N₄: C, 59.76; H, 5.02; N, 10.72. Found: C, 59.61; H, 5.01; N, 10.76.

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6. Reaction time is 48 h. For the shorter reaction time of 20 and 33 h, yields of 1 were 54 and 66% respectively. On the other hand, LiAlH_4 reduction of 2 which had been reacted with triethyloxonium tetrafluoroborate gave 1 in only 26% yield.
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