Synthesis of 2-Amino-3-benzyl-5-(p-hydroxyphenyl)pyrazine

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2-Amino-3-benzyl-5-(p-hydroxyphenyl)pyrazine (2), a precursor of Watasenia preluciferin (coelenterazine) (1), is widely distributed in marine bioluminescent animals. It was prepared from p-hydroxyphenylglyoxal aldoxime (5) in two steps: by condensation with α-aminophenylpropiononitrile in the presence of TiCl₄ in pyridine, followed by reduction of the resulting N-oxide (6) with Zn–AcOH in CH₂Cl₂ and produced 2, with an 89% overall yield. This procedure was linked with the facile one-step preluciferin synthesis reported in the previous paper. Thus, Watasenia preluciferin (1), frequently required for various chemiluminescent and bioluminescent studies, was conveniently synthesized in three steps from 5, with a 56% overall yield, overcoming the difficulty of obtaining it from natural sources.

Key words 2-aminopyrazine derivative; precursor; Watasenia preluciferin; bioluminescent compound

Experimental

Melting points are uncorrected. ¹H-NMR spectra were recorded on a JEOL A-600 (600 MHz) spectrometer with trimethylsilane (TMS) as internal standard.

2-Amino-3-benzyl-5-(p-hydroxyphenyl)pyrazine-1-oxide (6) To a cold solution (−5 °C) of p-hydroxyphenylglyoxal aldoxime (5) (330 mg, 2 mmol) and α-aminophenylpropiononitrile hydrochloride (5) (463 mg, 2.4 mmol) in pyridine (8 ml) was added TiCl₄ (1.89 g, 10 mmol) drop-wise with vigorous stirring. The mixture was warmed gradually to 20 °C. On completion of the reaction (ca. 30 min, judging from TLC, MeOH–CH₂Cl₂; 1 : 10), the mixture was poured into ice-water, 10% HCl (40 ml) was added to the mixture and the separated precipitate was taken up in AcOEt. The AcOEt layer was washed with water and dried over Na₂SO₄. Removal of the solvent left a crystalline solid which was washed with ether to afford 6 (551 mg, 94%), mp 230 °C (decomp). This product was sufficiently pure for further use. A small sample was recrystallized from MeOH to give pale yellow needles, mp 230–233 °C (decomp). ¹H-NMR (DMSO-d₆, δ): 0.47 (2H, s), 6.80 (2H, d, J = 8.4 Hz), 6.95 (2H, s), 7.20 (1H, t, J = 7.6 Hz), 7.30 (2H, t, J = 7.6 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.56 (2H, d, J = 7.6 Hz), 8.65 (1H, s), 9.69 (1H, brs). Anal. Calcd for C₁₀H₆N₃O₂: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.68; H, 5.23; N, 14.36.

2-Amino-3-benzyl-5-(p-hydroxyphenyl)pyrazine (2) To a solution of 6 (293 mg, 1 mmol) in MeOH–CH₂Cl₂; 1 : 30 (60 ml) was added Zn powder (586 mg) and AcOH (0.18 ml, 3 mmol). After being refluxed for 20 min with vigorous stirring, the mixture was filtered and the filtrate was diluted with AcOEt. The system was then washed with H₂O and 10% NaHCO₃, dried over Na₂SO₄ and evaporated to dryness under reduced pressure. Silica gel column chromatography (MeOH–CH₂Cl₂; 1 : 30) of the residue gave a crystalline solid which was crystallized from ether-hexane to give 2-aminopyrazine (2) (263 mg, 95%) as pale yellow prisms, mp 217–219 °C. ¹H-NMR (DMSO-d₆, δ): 0.47 (2H, s), 6.80 (2H, d, J = 8.4 Hz), 6.95 (2H, s), 7.20 (1H, t, J = 7.6 Hz), 7.30 (2H, t, J = 7.6 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.56 (2H, d, J = 7.6 Hz), 8.72 (2H, d, J = 8.8 Hz), 8.28 (1H, s), 9.51 (1H, brs). Anal. Calcd for C₁₀H₆N₃O₂: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.77; H, 5.51; N, 15.20.

Fig. 1
Acknowledgment

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References and Notes

4) Kishi Y., Tanino H., Goto T., Tetrahedron Lett., 27, 2747—2748 (1972). Overall yield of 2 from 3 in three steps was 57.6%.
9) This compound was submitted to the facile one-step cyclization reported in the previous paper. That is, a mixture of 2 and excess p-hydroxyphenylpyruvic acid (7 equiv.) was heated in dioxane at 130 °C under gentle refluxing. After 30 min, the solvent was then allowed to evaporate almost to dryness at 140 °C. The resultant dark resinous residue was purified by chromatographic work to give 1 in 63% yield.