Stereoselective Synthesis of New Chiral $N$-Tertiary Tetrasubstituted $\beta$-Enamino Ester Piperidines through an Ammonia-Catalyzed Process

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SUPPORTING INFORMATION

Table of Contents

S2 General information
S2 Isomerization of compound ($E$)-5
S2 Preparation and characterization data of compound 7a
S3 Preparation of 2a from 5
S5-S30 $^1$H and $^{13}$C NMR spectra of compounds 11a-d, 6a-d, 2a-d and 7a.
**General information:**

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from sodium/ benzophenone ketyl immediately prior to use. CH₂Cl₂ was distilled from calcium hydride. All reactions were carried out under argon. ¹H NMR spectra were recorded at 250 MHz and ¹³C NMR at 62.5 MHz. Chemical shifts (δ) were expressed in ppm relative to TMS at δ = 0 for ¹H and to CDCl₃ at δ = 77.1 for ¹³C and coupling constants (J) in Hertz.

**Isomerization of [1-(1(S)-phenylethyl)-piperidin-2-ylidene]acetic acid methyl ester ((E)-5).** To a solution of compound (E)-5 (89 mg, 3.42 mmol) in dry MeOH (10 mL) was added AcCl (0.25 mL, 3.5 mmol). After stirring for 15 min, the reaction mixture was concentrated in vacuo and dissolved in a 7 N methanolic solution of ammonia (10 mL) under argon. After 15 min stirring at room temperature, the solution was concentrated in vacuo and the solid residue dissolved in anhydrous THF (10 mL) under argon. This solution was canulated over a suspension of NaH (128 mg, 5.13 mmol) in THF (10 mL). After stirring for 20 min., the reaction mixture was filtered and the solid residue washed with CH₂Cl₂. The combined organic layer was concentrated in vacuo to give 90 mg of a 1:1 mixture of (E)-5 and (Z)-5. Characteristic signals for (Z)-5 (from a mixture): ¹H NMR (CDCl₃) δ 1.33 (d, J = 6.5 Hz, 3H), 2.07 (t, J = 7.25 Hz, 2H), 2.35-2.55 (m, 2H), 3.59 (s, 3H), 3.72 (q, J = 6.5 Hz, 1H), 4.49 (s, 1H); ¹³C NMR (CDCl₃) δ 24.3, 25.6, 29.5, 30.2, 36.0, 47.2, 58.3, 82.7, 126.4, 127.3, 128.3, 145.6, 163.8, 170.6.

**2-[1-(1(S)-Phenylethyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-propionic acid methyl ester** (7a). A solution of 5 (530mg, 2 mmol) in methyl iodide (10 mL) was refluxed for 48 h. The
reaction mixture was concentrated in vacuo to give iminium ion 1a as a solid which was washed with Et₂O (3×20 mL) and identified as a 70:30 mixture of isomers by NMR. Treatment with K₂CO₃: saturated aqueous solution of K₂CO₃ (15 mL) was added to iminium 1a and the aqueous layer was extracted with CHCl₃ (4×10 mL). The combined organic layer was washed with brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo to give a 75:25 mixture of compound 7a (70:30 mixture of diastereoisomers) and 6a according to NMR (470 mg overall). This mixture was not further purified due to the instability of 7a.

Treatment with NaH: a suspension of intermediate iminium ion 1a in THF (5 mL) was transferred via canula on a suspension of NaH (120 mg, 3 mmol) in THF (6 mL). After 5 min stirring, the mixture was filtrated and concentrated in vacuo to give crude compounds 7a and 6a (530 mg overall) as an oil.

Treatment with NEt₃: to solution of iminium ion 1a in MeOH was added NEt₃ (3 mmol). The reaction mixture was concentrated in vacuo and Et₂O was added. After filtration, the solvent was removed to give crude compound 7a and 6a (500 mg overall).

From a mixture of the two isomers along with 6a: ¹H NMR (CDCl₃) δ 1.25-1.56 (m, 8H), 1.98-2.05 (m, 2H), 2.68-2.83 (m, 2H), 3.38-3.51 (m, 1H), 3.69 (s, 3H), 4.59 and 4.65 (2t, J = 4Hz, 1H), 4.68-4.76 (m, 1H), 7.22-7.38 (m, 5H); ¹³C NMR (CDCl₃) δ 15.8, 16.2, 16.6 and 17.3, 21.8 and 22.0, 22.9 and 23.7, 42.3 and 42.5, 43.1 and 43.4, 51.8, 54.2 and 54.3, 99.4 and 100.2, 126.4, 126.8, 127.1, 127.2, 128.0, 128.3, 142.8, 143.0 and 143.4, 175.2 and 175.4.

**Preparation of compound 2a from 5.**

A solution of 5 (1g, 3.86 mmol) in MeI (10 mL) was refluxed for 48 h. The reaction mixture was concentrated in vacuo and the residue was washed with Et₂O (3×20 mL) to afford intermediate iminium 1a. The latter was dissolved in a 7 N methanolic solution of ammonia (10 mL) under argon. After 15 min stirring at room temperature, the solution was
concentrated in vacuo and the solid residue dissolved in anhydrous THF (10 mL) under argon. This solution was canulated over a suspension of NaH (232 mg, 5.8 mmol) in THF (10 mL). After stirring for 20 min., the reaction mixture was filtered and the solid residue washed with THF. The combined organic layer was concentrated in vacuo and the residue was purified by bulb-to-bulb distillation (200°C, 0.1 mm Hg) to give the expected product 2a as colorless oil (937 mg) in 89% yield.