

Total Synthesis of Sufentanil

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Sufentanil, a potent anilidopiperidine analgesic, was synthesized from a simple thiophenylethylamine via six step sequence. The key parts of this synthesis involved an efficient construction of thiophenylethylpiperidone by aminomethano desilylation-cyclization followed by Swern oxidation and a direct regioselective *N*-nucleophilic spiral epoxide cleavage with aniline promoted by Lewis acids.

Key words : Total Synthesis, Sufentanil, Analgesics, Piperidine, Oxirane

INTRODUCTION

Sufentanil (**1**), a well-known analgesic characterized by high potency, a rapid onset, and short duration of action, belongs to a series of the 4-propionanilidopiperidines which represents a class of morphine-like analgesics (Janssen *et al.*, 1968). The extensive synthetic studies focused on 4-anilidopiperidine and its structural analogues (Borne *et al.*, 1984) have recently been carried out, although few synthetic studies on sufentanil have been reported. More recently, a series of work on the syntheses of sufentanil and its structural analogues have been carried out in our laboratory in conjunction with development of the novel analgesic agents. We have also reported an ideal synthetic route to *N*-arylpiperidines as a part of our successful results (Suh *et al.*, 1997) and we herein describe a total synthesis of sufentanil in full detail.

MATERIALS AND METHODS

Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. *N,N*-dimethylformamide and dimethyl sulfoxide were distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves under argon. Dichloromethane, triethylamine, benzene, toluene, and pyridine were freshly dist-

illed from calcium hydride. Nitromethane was distilled and stored over calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade and distilled. Reaction flasks were oven dried at 120°C. Air and moisture sensitive reactions were performed under an argon atmosphere.

Flash column chromatography was performed using silica gel 60(230-400 mesh, Merck) with indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). Melting points were measured on a Buchi melting point apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Mass spectra obtained with VG Trio-2 GC-MS instrument. ¹H and ¹³C NMR spectra were recorded on either a JEOL JNM-GCX 400 or JEOL JNM-LA 300 spectrometer as solutions in deuteriochloroform(CDCl₃). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent (CHCl₃). ¹H-NMR data are reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonance), number of protons and coupling constant in hertz (Hz).

4-Hydroxy-1-(2-thiophenethyl)piperidine (7)

A heterogenous mixture of allyltrimethylsilane (2.0 mL, 12.6 mmol), water (2.8 ml), thiophenylethylammonium trifluoroacetate (2.02 g, 8.4 mmol) and 37% aqueous formaldehyde (1.87 ml, 23.1 mmol) in water was stirred at 58°C for 24 hours. Water was added and then the reaction mixture was alkalized with 1N NaOH and extracted with CH₂Cl₂. The organic extracts were washed with brine, dried over anhydrous MgSO₄ and evaporated.

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The residue was purified by column chromatography (MeOH : CHCl₃ = 1 : 10) to give a piperidine (0.77 g, 43.3%) as a white solid. IR (neat) cm⁻¹ 3280; ¹H-NMR (CDCl₃, 400MHz) δ 7.15 (d, 1 H, *J* = 4.8 Hz), 6.94 (dd, 1 H, *J* = 4.8, 3.2 Hz), 3.75 (qin, 1 H, *J* = 4.4 Hz) 3.05 (t, 2 H, *J* = 7.6 Hz), 2.89-2.85 (m, 2 H), 2.69 (t, 2 H, *J* = 4.2 Hz), 2.26 (t, 2 H, *J* = 9.6 Hz), 1.97-1.93 (m, 2 H), 1.73-1.61 (m, 4 H); LRMS (EI) *m/e* 221 (M⁺)

1-(2-Thiophenethyl)-4-piperidone (8)

Oxalyl chloride (0.44 ml, 5.17 mmol) dissolved in CH₂Cl₂ (12 ml) was placed in a flask under nitrogen. The flask was cooled to -78°C and DMSO (0.73 ml) in CH₂Cl₂ (2.15 ml) was added dropwise for about 5 min. Stirring was continued at -78°C for an additional 10 min followed by addition of the alcohol **7** (575 mg, 2.72 mmol) in CH₂Cl₂ (2 ml) for about 5 min. After additional 15 min with stirring, triethylamine (2.88ml, 20.7mmol) was added for about 5 min with stirring and then the reaction mixture was allowed to warm to room temperature. Water (12 ml) was added and the aqueous layer was reextracted with CH₂Cl₂ (50 ml). The combined organic layers were washed with brine, and dried over anhydrous MgSO₄. The filtered solution was concentrated and the residue was purified by column chromatography to give a ketone (556 mg, 98%) as a white solid. IR (neat) cm⁻¹ 1718; ¹H-NMR (CDCl₃, 400 MHz) δ 7.08 (d, 1 H, *J* = 5.2 Hz), 6.87 (dd, 1 H, *J* = 5.2, 3.6 Hz), 6.78 (d, 1 H, *J* = 3.3 Hz), 2.99 (t, 2 H, *J* = 7.6 Hz), 2.76 (t, 4 H, *J* = 6.5 Hz), 2.42 (t, 4 H, *J* = 5.6 Hz); LRMS (EI) *m/e* 209 (M⁺)

4-Anilinomethyl-4-hydroxy-1-(2-thiophenethyl)piperidine(10) and 2-Anilino-1-(2-thiophenethyl)-4-piperidyl-methanol (11)

Aniline (0.16 ml, 1.76 mmol) and triethyloxonium tetrafluoroborate (0.44 ml of 1 M sol'n in CH₂Cl₂, 0.44 mmol) was added to the oxirane **9** (196 mg, 0.88 mmol) in CH₂Cl₂ (8 ml) at -78°C. The mixture was stirred at -78°C for 6 hrs. After quenching with water, the solution was alkaliified with 1N NaOH and extracted with CH₂Cl₂ (20 ml). The organic layers were dried over anhydrous MgSO₄ and evaporated. The residue was purified by column chromatography to give piperidyl-methanol **11** (19.7 mg, 6.2%), and hydroxypiperidine **10** (15.5 mg, 4.8%).

Spectral data of 10

IR (neat) cm⁻¹ 3353, 3501; ¹H-NMR (CDCl₃, 400 MHz) δ 7.14 (d, 1 H, *J* = 4.0 Hz), 7.19 (t, 2 H, *J* = 8.0 Hz), 6.93 (dd, 1 H, *J* = 4.8, 4.0 Hz), 6.84 (d, 1 H, *J* = 3.6 Hz), 6.75 (dd, 1 H, *J* = 0.8, 3.6 Hz), 6.72 (dd, 2 H, *J* = 0.8, 5.6 Hz), 3.95 (brs, 1 H), 3.15 (s, 1 H), 3.06 (t, 2 H, *J* = 8.0 Hz), 2.79 (t, 2 H, *J* = 7.6 Hz), 2.23 (t, 2 H, *J* = 8.0 Hz), 2.49 (dt, 2 H, *J* = 3.6, 10.4 Hz), 1.83-1.68 (m, 4 H); EIMS *m/e* 316 (M⁺)

Spectral data of 11

IR (neat) cm⁻¹ 3401; ¹H-NMR (CDCl₃, 400 MHz) δ 7.13 (t, 2 H, *J* = 8.0 Hz), 7.06 (d, 1 H, *J* = 4.8 Hz), 6.85 (t, 1 H, *J* = 4.8 Hz), 6.79 (t, 2 H, *J* = 7.2 Hz), 6.73 (d, 2 H, *J* = 7.2 Hz), 3.58 (s, 2 H), 2.95 (t, 2 H, *J* = 8.0 Hz), 2.65-2.58 (m, 4 H), 2.31 (t, 2 H, *J* = 8.0 Hz), 1.90 (dm, 2 H, *J* = 13.6 Hz), 1.65 (dm, 2 H, *J* = 13.6Hz); LRMS (EI) *m/e* 316 (M⁺)

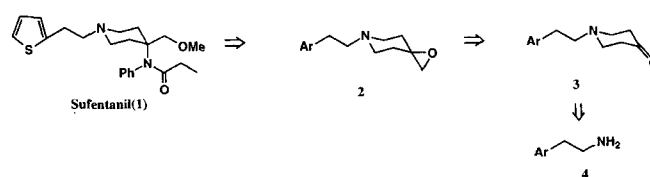
N-[4-Methoxymethyl-1-(2-thiophenethyl)]-4-piperidyl-N-phenylpropanamide(Sufentanil) (1)

A mixture of piperidylamine **12** (1.4mg, 0.004mmol) and propionic anhydride (1.2ml, 0.009mol) was refluxed with stirring for 19hrs. Cooled to 0°C, the mixture was alkaliified with NH₄OH and extracted with CH₂Cl₂. The organic layers were dried over MgSO₄ and evaporated. The residue was chromatographed to give a sufentanil (0.8mg, 50%). IR (neat) cm⁻¹ 1654; ¹H-NMR (CDCl₃, 400MHz) 7.30-7.38 (m, 5H), 7.13 (d, 1H, *J* = 4.9Hz), 6.92 (dd, 1H, *J* = 4.9, 3.4Hz), 6.80 (d, 1H, *J* = 3.4Hz), 4.09 (s, 2H), 3.45 (s, 2H), 2.91-2.98 (m, 2H), 2.68-2.71 (m, 2H), 2.61-2.68 (m, 2H), 2.23-2.29 (m, 4H), 1.70-1.79 (m, 2H), 1.85 (q, 2H, *J* = 7.3Hz), 0.96 (t, 3H, *J* = 7.3Hz); EIMS *m/e* 387 (M⁺)

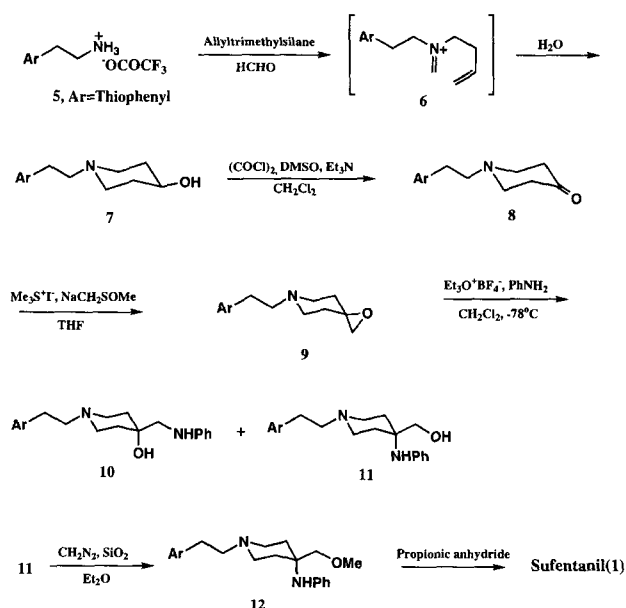
RESULTS AND DISCUSSION

Our synthetic approach shown in Scheme 1 involved an efficient construction of the piperidone skeleton via sequential aminomethano desilylation-cyclization and oxidation of the resulting hydroxypiperidine. The *N*-arylalkylpiperidone **3** was also directly converted to the spiroepoxypiperidine **2** as a second potential intermediate which reacted with aniline to afford 4-anilino-piperidine along with 4-anilinomethylpiperidine as its regioisomer.

The intramolecular Mannich type cyclization as a key step of our synthesis was conducted, as outlined in Scheme 2, by a reaction of trifluoroacetic acid salt of the starting thiophenethylamine **5** with 1.1 equivalent of allyltrimethylsilane and 2.3 equivalent of 37% aqueous formaldehyde (Grieco and Fobare 1986, and Larson et al., 1986). The resulting 4-hydroxythiophenethylpiperidine **7** was oxidized to piperidone **8** by the introduction of epoxide moiety. It should be noted that only Swern oxidation was effective for oxidation of



Scheme 1. Retrosynthetic scheme



Scheme 2. Synthetic scheme

hydroxypiperidine (Omura and Swern, 1978).

The one step conversion of thiophenylethylpiperidone **8** to the spiroepoxide **9** as a second potential intermediate was achieved by dimethylsulfonium ylide treatment as shown in Scheme 2. The variety of reaction conditions for regioselective ring opening of the epoxide at more substituted carbon by aniline were examined. Triethyloxonium tetrafluoroborate ($\text{Et}_3\text{O}^+\text{BF}_4^-$) as Lewis acid in methylene chloride below -78°C turned out to be the best choice for the highest regioselectivity (1.8 : 1) in favor of **11**. Usage of other Lewis acids afforded the regioisomer **10** as a predominant product or only byproducts by retro-Mannich type reaction. Although the regioselectivity and yields are not satisfactory yet, the direct introduction of aniline nucleophile to spiroepoxide at more substituted carbon enables the two step conversion of the arylalkylpiperidone to the highly advanced sufentanil intermediate. Methylation of piperidylmethanol (**11**) was achieved by an initial reaction with diazomethane (Ohno *et al.*, 1979). Finally, the synthesis was completed by the known acylation of anilino-piperidine **12** with propionic anhydride (Borum and Wiley, 1948) to afford the desired product which was identical in all aspects to the authentic sufentanil.

In conclusion, the total synthesis of sufentanil was accomplished by only six step reaction sequence. The

key features of this synthesis include the efficient construction of thiophenethylpiperidine skeleton from thiophenethylamine and the regioselective ring opening of spiroepoxide at more substituted carbon by *N*-nucleophile. This methodology is applicable to the efficient syntheses of other anilino-piperidine analgesics and their structural analogues.

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