

Total Synthesis of Fentanyl

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Fentanyl of a potent anilidopiperidine analgesic has been synthesized from a simple phenylethylamine by four step sequence. The key part of this synthesis involves an efficient construction of phenylethylpiperidone skeleton via aminomethano desilylation-cyclization followed by Swern oxidation.

Key words : Fentanyl, Anagesics, Piperidine, Aminomethano desilylton-cyclization

INTRODUCTION

Fentanyl (**1**), a well-known anagesic characterized by high potency, a rapid onset, and short duration of action belongs to a series of the 4-propionanilidopiperidines which represent a class of morphine-like anagesics (Janssen *et al.*, 1968). In conjunction with development of novel anagesic agents, a series of work on the syntheses of fentanyl (Lednicer *et al.*, 1977) and its structural analogues (Borne *et al.*, 1984) have recently been carried out in our laboratory. More recently, we have also reported the excellent synthetic route to *N*-arylalkylpiperidines as a part of our successful results (Suh *et al.*, 1997) and we herein report a total synthesis of fentanyl as a full paper in detail.

MATERIALS AND METHODS

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

performed using silica gel 60 (230-400 mesh, Merck) with indicated solvents. Thin-layer chromatography was performed using 0.25mm silica gel plates (Merck). Melting points were measured on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with JASCO DIP-1000 digital polarimeter at ambient temperature using 100mm cell of 2 mL capacity. 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), coupling constant in hertz (Hz), and number of protons.

4-Hydroxy-1-(2-phenylethyl)piperidine (**2**)

A heterogeneous mixture of allyltrimethylsilane (1.87 ml, 25 mmol), water (2.9 ml), phenylethylammonium trifluoroacetate (2.35 g, 10 mmol) and 37% aqueous formaldehyde (1.87 ml) in water was stirred at 5°C for 48 hours. Water was added and then the reaction mixture was alkalinized with 1N NaOH and extracted with CH₂Cl₂. The organic extracts were washed with brine, dried over anhydrous MgSO₄ and evaporated to give white solid. The solid was recrystallized (EtOAc: *n*-Hexane) to give 1.30 g (63%) of white crystal. IR (KBr) cm⁻¹ 3160; ¹H NMR (CDCl₃, 400 MHz) δ 7.39-7.21 (m, 5H), 3.78-3.73 (m, 1H), 2.90-2.81 (m, 4H), 2.68-2.60 (m, 2H), 2.28-2.23 (m, 2H), 1.99-1.94 (m, 2H), 1.76-1.61(m, 2H); EIMS *m/z* 204 (M⁺-H), 114.

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1-(2-Phenylethyl)-4-piperidone (6)

Oxalyl chloride (0.19 ml, 2.2 mmol) dissolved in CH_2Cl_2 (5 ml) was placed in a flask under nitrogen. The flask was cooled to -78°C and DMSO (0.34 ml, 4.8 mmol) in CH_2Cl_2 (1 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 **3** (404 mg, 2 mmol) in CH_2Cl_2 (2 ml) for about 5 min. After additional 15 min stirring, triethylamine (1.39 ml, 10 mmol) was added for about 5 min with stirring and then the reaction mixture was allowed to warm to room temperature. Water (15 ml) was added and the aqueous layer was reextracted with CH_2Cl_2 (50 ml). The organic layers were combined, washed with brine, and dried over anhydrous MgSO_4 . The filtered solution was concentrated and the residue was purified by column chromatography (EtOAc:*n*-Hexane=2:1 with 0.5 v/v % NH_4OH) to give white solid (335 mg, 84%) IR (KBr) cm^{-1} 1720; ^1H NMR (CDCl_3 , 400 MHz) δ 7.29-7.18 (m, 5H), 2.84-2.68 (m, 8H), 2.47-2.44 (m, 4H); EIMS m/z 203 (M^+), 112.

4-anilino-1-(2-phenylethyl)piperidine (7)

A mixture of ketone **6** (100 mg, 0.49 mmol), aniline (45 mg, 0.49 mmol) and a catalytic amount of *p*-toluenesulfonic acid in toluene was stirred at reflux with removal of water by a Dean-Stark trap for 44 hours. The reaction mixture was cooled and solvent was evaporated.

The resulting crude imine was dissolved in absolute ethanol (5 ml) and NaBH_4 (43 mg, 1.1 mmol) was added in a small portion. The mixture was stirred at 50°C for 14 hours and then quenched by addition of water. The mixture was diluted with CH_2Cl_2 and the organic layer was washed with water and brine, dried over anhydrous MgSO_4 , evaporated and chromatographed (MeOH: CH_2Cl_2 :acetone=1:30:20) to give white solid (85 mg, 62%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.24-6.53 (m, 10H) 3.45 (bs, 1H), 3.29-3.23 (m, 1H), 2.91-2.54 (m, 6H), 2.18-1.40 (m, 6H); EIMS m/z 280 (M^+), 189

Alternative method for 7

PtO_2 was added to the imine in absolute ethanol and hydrogenated under hydrogen balloon. The reaction mixture was filtered through a celite bed, concentrated and chromatographed by the same procedure as above to give white solid.

N-(1-Phenylethyl-4-piperidyl)propionanilide (Fentanyl, 1)

To a toluene (20 ml) solution of piperidine **7** (100 mg, 0.36 mmol) was added 51 μl of propionic anhydride and the reaction mixture was stirred at reflux for 30 hours. After addition of water (20 ml), the mixture was alkalinized with *c*- NH_4OH and extracted with CH_2Cl_2 .

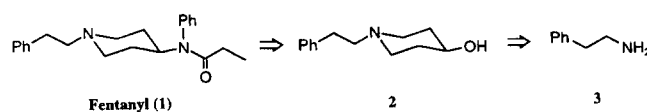
The organic layer was washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated to give 120 mg (100%) of white solide. IR (KBr) cm^{-1} 1650; ^1H NMR (CDCl_3 , 400 MHz) δ 7.47-7.12 (m, 10H), 4.76-4.72 (m, 1H), 1.98 (q, 2H, $J=7.2$ Hz), 1.07 (t, 3H, $J=7.2$ Hz).

RESULTS AND DISCUSSION

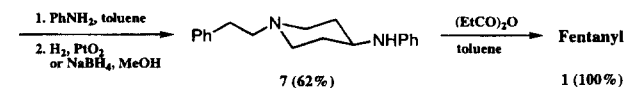
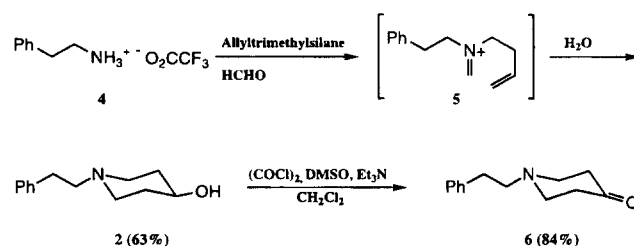
Our synthetic approach shown in scheme 1 involves an efficient construction of the piperidone skeleton *via* sequential aminomethano desilylation cyclization and oxidation of the resulting hydroxypiperidine (**2**) followed by introduction of propionanilide side chain.

The intramolecular Mannich type cyclization as a key step of our synthesis was conducted as outlined in scheme 1 by reaction of trifluoroacetic acid salt **4** of the starting phenylethylamine with 1.1 equivalent of allyltrimethylsilane and 2.3 equivalent of 37% aqueous formaldehyde (Grieco *et al.*, 1986, and Larson *et al.*, 1986). The resulting 4-hydroxy-phenylethylpiperidine **2** was oxidized to piperidone **6** for the introduction of aniline moiety. It should be noted that only Swern oxidation (Omura *et al.*, 1978) was effective for oxidation of hydroxypiperidine **2**. Reductive amination of piperidone **6** was achieved by an initial reaction with aniline and then NaBH_4 reduction. Finally, the synthesis was completed by the known acylation (Lendica *et al.*, 1977) of anilinpiperidine **7** with propionic anhydride to afford the desired product which was identical in all aspects with the authentic fentanyl.

In conclusion, the total synthesis of fentanyl was accomplished by only four step reaction sequence. The key feature of this synthesis includes the efficient construction of phenylethylpiperidine skeleton from phenyl-



Scheme 1.



Scheme 2.

ethylamine. Further synthetic applications of this route to the other anilidopiperidine analgesics and their analogues are in progress.

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