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Fentanyl Synthesis Using *N*-BOC-4-Piperidinone

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Fentanyl was synthesized using commercially available *N*-BOC-4-piperidinone as the starting material. The process methodology is reported with experimental details, which avoided standard purification techniques. Fentanyl free base, fentanyl HCl, and fentanyl citrate were synthesized with acceptable yields and high purity.

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PREFACE

The work described in this report was authorized under Defense Threat Reduction Agency (DTRA; Fort Belvoir, VA) project number CB10678. The work was started in November 2019 and completed in January 2021.

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FENTANYL SYNTHESIS USING *N*-BOC-4-PIPERIDINONE

1. INTRODUCTION

The synthesis of fentanyl is centered on elaboration of a piperidine ring core structure. Fentanyl has a relatively simple chemical structure (Figure 1).

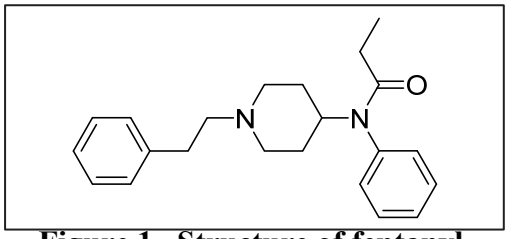


Figure 1. Structure of fentanyl.

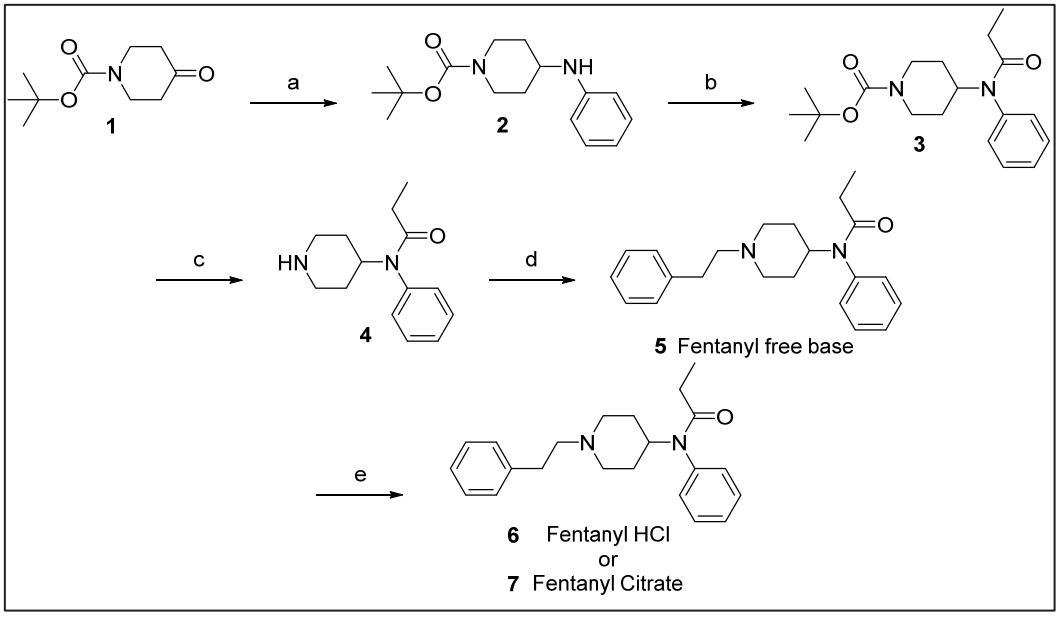
Previous work examined the Raman spectral characterization of fentanyl salts for route attribution.[1] The fentanyl salts analyzed were generated using five distinct synthetic routes. Three of these routes appeared in the open literature.[2-4] Another synthetic route examined in the previous work employed commercially available *N*-BOC-4-piperidinone **1** as the starting material. This route has not been published in the open literature. *N*-BOC-4-piperidinone **1** has been reported being used in the synthesis of a fluorinated fentanyl analog in the patent literature.[5] Also, the synthesis of cyclopropylfentanyl urinary metabolites used *N*-BOC-4-piperidinone **1** as the starting material and used the same methodology with some reagent differences.[6] Similar chemistry was also found in the synthesis of fentanyl haptens in vaccine research.[7]

Herein, the synthesis of fentanyl using *N*-BOC-4-piperidinone **1** as the starting material is reported with experimental details. Standard purification techniques (column chromatography and recrystallization) were not employed in the production of any of the intermediates or fentanyl free base. Purification techniques were only performed for the purposes of spectral analysis when needed. The most common salts found are the hydrochloride or citrate salt. These fentanyl salts were prepared and isolated by precipitation then filtration and were not recrystallized prior to analysis.

2. CHEMISTRY

The synthesis of fentanyl HCl **6** and fentanyl citrate **7** is shown in Figure 2. The route was performed in triplicate. Preparation of intermediate **2** was accomplished through reductive amination with *N*-BOC-4-piperidinone **1**, aniline, and sodium triacetoxyborohydride (STAB). Intermediate **3** was prepared via acylation with propionyl chloride in the presence of diisopropylethylamine. Amine **4** was produced, after some experimentation, through BOC deprotection of the piperidinone ring nitrogen using 4M HCl in 1,4 dioxane. Alkylation of intermediate **4** was done to provide fentanyl free base **5**. Fentanyl HCl **6** was formed through use of 6.4M methanolic HCl in diethyl ether/isopropanol. Fentanyl citrate **7** was formed through use of citric acid in isopropanol.

The methodology used in the reductive amination to form intermediate **2**, the propionylation step to generate compound **3**, and the alkylation forming fentanyl free base **5** employed synthetic methodology reported in 2014 for fentanyl synthesis.[2] This Valdez methodology, which used phenylethylpiperidonone as an intermediate, was found to be compatible with the BOC protecting group. BOC deprotection of compound **3** to amine **4** has been reported utilizing trifluoroacetic acid.[6] Herein, the use of 4M HCl dioxane solution proved to be a better system for this deprotection. It should be noted that similar STAB based reductive aminations with aniline and *N*-BOC-4-piperidinone **1** for the synthesis of intermediate **2** from have been reported.[6, 8] Alternative methods for the same transformation have employed sodium cyanoborohydride reductive amination with aniline,[9] and acid catalyzed palladium hydrogenative reductive amination with aniline.[7] Phosphorous based reductive cross coupling,[10] and a zinc based reductive coupling[11] have also been used to generate intermediate **2** from compound **1**.



a) Sodium triacetoxyborohydride, acetic acid, aniline, 1,2 dichloroethane. b) Propionyl chloride, dichloromethane. c) 4M HCl, 1,4 dioxane. d)(2-bromoethyl)benzene, cesium carbonate, acetonitrile. f) Hydrochloric or citric acid, solvent.

Figure 2. Synthetic route to fentanyl salts using *N*-BOC-4-piperidinone 1.

3. EXPERIMENTAL PROCEDURES

3.1 Instrumentation

Flash chromatography was performed on a Buchi Reveleris X2 semiautomatic purification system. NMR data were obtained on a JEOL 400 MHz spectrometer, and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. UPLC-HRMS analysis was accomplished using a Waters Acquity UPLC Synapt G2-S equipped with an electrospray ionization (ESI) interface.

3.2 *tert*-Butyl 4-(phenylamino)piperidine-1-carboxylate 2

N-BOC-4-piperidinone **1** (2.00 g, 10.04 mmol), aniline (1.03 g, 11.04 mmol) and acetic acid (0.60 g, 10.04 mmol) were dissolved in 13 mL dichloromethane and cooled in an ice bath. STAB (3.19 g, 15.06 mmol) was added portion wise. The mixture was stirred and allowed to come to room temperature for 16 h. The mixture was diluted with 15 mL of aqueous 2M NaOH and was stirred for 1h. The mixture was transferred to a separatory funnel, shaken and the organic solution was removed. The aqueous solution was extracted two times with dichloromethane. The combined organic solution was dried with sodium sulfate, filtered through Celite, and the volatiles were evaporated to provide 2.89 g of compound **2** as a solid which was taken to the next step without further purification. An analytical sample was prepared by flash chromatography with gradient elution using 1:1 hexane/dichloromethane to dichloromethane to 95:5 dichloromethane/acetone. 1H-NMR (400 MHz, CHLOROFORM-D) δ 7.16 (t, 2H, J = 7.9 Hz), 6.68 (t, 1H, J = 7.3 Hz), 6.59 (d, 2H, J = 7.8 Hz), 4.03 (br s, 2H), 3.49-3.38 (m, 2H), 2.91 (t, 2H, J = 12.0 Hz), 2.02 (br d, 2H, J = 11.9 Hz), 1.45 (s, 9H), 1.36-1.26 (m, 2H). 13C-NMR (101 MHz, CHLOROFORM-D) δ 154.9, 146.8, 129.5, 117.6, 113.4, 79.7, 50.2, 42.8, 32.5, 28.5.

3.3 *tert*-Butyl 4-(N-phenylpropionamido)piperidine-1-carboxylate 3

Compound **2** (1.06 g, 3.84 mmol) and diisopropylethylamine (0.99 g, 7.67 mmol) were dissolved in 33 mL dichloromethane and cooled in an ice bath. Propionyl chloride (0.71 g, 7.67 mmol) was added dropwise. The mixture was stirred and allowed to come to room temperature for 16 h. The mixture was diluted with 15 mL of water and was stirred for 1h. The mixture was transferred to a separatory funnel, shaken and the organic solution was removed. The aqueous solution was extracted two times with dichloromethane. The combined organic solutions were extracted with saturated aqueous sodium bicarbonate then with saturated aqueous sodium chloride. The organic solution was dried with sodium sulfate, filtered, and the volatiles were evaporated to provide 1.41 g of compound **3** as a solid which was taken to the next step without further purification. An analytical sample was prepared by flash chromatography with gradient elution using 1:1 hexane/dichloromethane to dichloromethane to 96:4 dichloromethane/acetone. 1H-NMR (400 MHz, CHLOROFORM-D) δ 7.42-7.37 (m, 3H), 7.06-7.04 (m, 2H), 4.76 (tt, 1H, J = 12.2, 3.6 Hz), 4.09 (br s, 2H), 2.78 (t, 2H, J = 12.1 Hz), 1.91 (q, 2H, J = 7.4 Hz), 1.75 (d, 2H, J = 12.3 Hz), 1.37 (s, 9H), 1.24-1.13 (m, 2H), 1.00 (t, 3H, J = 7.4 Hz). 13C-NMR (101 MHz, CHLOROFORM-D) δ 173.6, 154.7, 138.8, 130.4, 129.5, 128.5, 79.6, 52.3, 43.3, 30.6, 28.6, 28.4, 9.7.

3.4 Fentanyl free base 5

Compound **3** (1.00 g, 3.01 mmol) was dissolved in 25 mL 1,4 dioxane. 4M aqueous HCl (25 mL) was added and the solution was stirred at room temperature for 4 h. The solution was taken to pH=8 by the addition of 2M aqueous NaOH. The solution was extracted three times with dichloromethane. The combined organic extracts was dried with sodium sulfate, filtered, and the volatiles were evaporated to provide N-phenyl-N-(piperidin-4-yl)propionamide **4** as a brown oil. Compound **4**, 2-bromoethyl benzene (0.59 g, 3.16 mmol), and cesium carbonate (1.18 g, 3.61 mmol) were mixed with 10 mL of acetonitrile and stirred in an 80 °C oil bath for 16 h. The mixture was allowed to cool to room temperature, then water and

dichloromethane were added. The organic layer was separated, and the aqueous mixture was extracted two times with dichloromethane. The combined organic extracts were dried with sodium sulfate, filtered, and the volatiles were evaporated to provide 0.943 g of fentanyl free base **5** as a solid. 1H-NMR (400 MHz, CHLOROFORM-D) δ 7.40-7.06 (m, 10H), 4.68 (tt, 1H, J = 12.1, 3.8 Hz), 3.01-2.98 (m, 2H), 2.74-2.70 (m, 2H), 2.55-2.51 (m, 2H), 2.15 (t, 2H, J = 11.5 Hz), 1.91 (q, 2H, J = 7.5 Hz), 1.81-1.178 (m, 2H), 1.43 (m, 2H), 1.00 (t, 3H, J = 7.4 Hz). 13C-NMR (101 MHz, CHLOROFORM-D) δ 173.7, 140.3, 138.9, 130.5, 129.4, 128.7, 128.5, 128.4, 126.1, 60.6, 53.2, 52.2, 33.9, 30.6, 28.6, 9.7.

3.5 Fentanyl HCl 6

Fentanyl free base **5** (0.38 g, 1.12 mmol)) was taken up in 3 mL diethyl ether/1.0 mL of isopropanol and agitated. 6.4M HCl-methanol (0.36 mL) was added. The mixture stood at room for 1 h and then was refrigerated for 16 h. The precipitated solids were filtered and then washed with diethyl ether. The solids were air dried to provide 0.28 g of the fentanyl HCl **6**. 1H-NMR (400 MHz, METHANOL-D4) δ 7.53-7.47 (m, 3H), 7.32-7.21 (m, 7H), 4.84-4.76 (m, 1H), 3.64 (d, 2H, J = 12.6 Hz), 3.29-3.24 (m, 2H), 3.20-3.13 (m, 2H), 2.99-2.95 (m, 2H), 2.12 (d, 2H, J = 13.7 Hz), 1.97 (q, 5H, J = 7.5 Hz), 1.68 (dq, 2H, J = 12.8, 3.2 Hz), 0.97 (t, 7H, J = 7.4 Hz). 13C-NMR (101 MHz, METHANOL-D4) δ 174.8, 138.0, 136.1, 130.1, 129.7, 128.9, 128.7, 128.4, 127.0, 57.6, 52.0, 49.8, 30.1, 28.0, 27.7, 8.5. HRMS: *m/z* calculated for $C_{22}H_{29}N_2O$ $[M + H]^+$ 337.2280, found 337.2285.

3.6 Fentanyl citrate 7

Fentanyl free base **5** (0.44 g, 1.30 mmol)) was taken up in 1.5 mL of warm isopropanol. Citric acid (0.26 g, 1.36 mmol) was dissolved in 1.0 mL of warm isopropanol and then added dropwise to the free base solution. The citric acid vial was rinsed with 0.5 mL of warm isopropanol and added to the solution. The mixture was allowed to cool to room temperature and was refrigerated for 16 h. The precipitated solids were filtered and then washed with cold isopropanol then diethyl ether. The solids were air dried to provide 0.42 g of the fentanyl citrate 7. 1H-NMR (400 MHz, METHANOL-D4) δ 7.51-7.43 (m, 3H), 7.30-7.19 (m, 7H), 4.80-4.73 (m, 1H), 3.58 (d, 2H, J = 12.3 Hz), 3.20-3.16 (m, 2H), 3.08-3.02 (m, 2H), 2.97-2.93 (m, 2H), 2.70 (dd, 4H, J = 29.7, 15.3 Hz), 2.06 (d, 2H, J = 13.3 Hz), 1.96 (q, 2H, J = 7.5 Hz), 1.74-1.64 (m, 3H), 0.97 (t, 3H, J = 7.4 Hz). 13C-NMR (101 MHz, METHANOL-D4) δ 177.9, 174.8, 173.5, 138.1, 136.6, 130.1, 129.6, 128.9, 128.6, 128.5, 126.8, 72.8, 57.6, 51.8, 50.1, 43.3, 30.2, 28.0, 27.7, 8.5. HRMS: *m/z* calculated for $C_{22}H_{29}N_2O$ $[M + H]^+$ 337.2280, found 337.2283.

3.7 Mass spectral purity analysis

The purities of the precipitated fentanyl salts were determined by UPLC-HRMS analysis via TargetLynx™ software by comparison with a commercially available fentanyl standard (Cerilliant, F-002-1ML).[1] The experimentally calculated concentration of fentanyl free base in salt samples was then compared to the expected fentanyl free base concentration for the purity analysis. Three independent samples were analyzed for each test sample. The average purities for three runs were 94.7% for fentanyl HCl **6** and 94.8% for fentanyl citrate **7**.

4. CONCLUSION

The synthesis of fentanyl HCl **6** and fentanyl citrate **7** was accomplished in triplicate starting with commercially available *N*-BOC-4-piperidinone **1**. The procedures were described in detail and efficiently generated fentanyl salts with reproducible yields and high purities. This was accomplished without the use of flash chromatography and recrystallization as purification techniques

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ACRONYMS AND ABBREVIATIONS

BOC	*tert*-butyloxycarbonyl
STAB	sodium triacetoxyborohydride
NMR	nuclear magnetic resonance
UPLC	Ultra-performance liquid chromatography$
HRMS	high resolution mass spectrometry
ppm	parts per million
MHz	megahertz

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