A convenient one pot synthesis of fentanyl

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Fentanyl, N-(1-phenethyl-4-piperidyl) propionanilide, was prepared by performing three successive one pot reactions at room temparature.

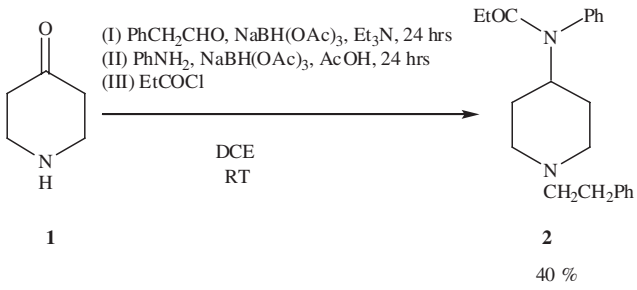
Keywords: fentanyl, one pot, three step, reductive amination, sodium triacetoxyborohydride

Opiate agonists play a significant role in the short and long term alleviation of pain as well as in various fields of biomedical research.[1-2] Among the three types of agonists, relatively specific for μ, κ and δ receptors respectively, μ agonists are therapeutically the most significant. 4-Anilidopiperidines[3,4] represents a particular class of μ agonists which are characterised by a high analgesic potency, relatively short duration of action and a good overall safety margin during surgical anesthesia. Fentanyl [N-(1-phenethyl-4-piperidyl) propionanilide] is a prototype of this series.[5,6] It is about 50–100 times more potent than morphine in humans with a fast onset and short duration of action. It acts in the central nervous system to relieve pain and is widely used in surgical anesthesia as the citrate salt at doses ranging from 2 to 50 μg / kg.[7] The low molecular weight, high potency and lipid solubility of fentanyl make it suitable for delivery via transdermal therapeutic system (TTS).[8]

Various methods for the synthesis of fentanyl have appeared in the literature.[9-11] All of these methods however, require multiple steps and lengthy refluxing reaction conditions. The isolation and purification of the intermediate compounds is tedious and leads to increased time and energy consumption and reduction in overall yield. Herein, we report a straightforward one pot synthesis of fentanyl that involves tandem reductive alkylation and amination reactions in presence of sodium triacetoxyborohydride (STAB) followed by N-acylation reaction (Scheme 1). Sodium triacetoxyborohydride is mainly used for the selective reduction of aldehydes,[12] stereocontrolled reduction of β-hydroxyketones to β-antidiols[13] and the reductive alkylation/amination of the amines.[14] Our approach takes advantage of the mild reducing power of sodium triacetoxyborohydride. To preferentially reduce imines to amines in the presence of aldehyde and ketones.

The starting compound in the proposed scheme is 4-piperidone monohydrochloride **1** which is a bifunctional molecule containing keto and sec-amino functional groups. In the first step, the sec-amino group of this precursor was reductively alkylated with phenylacetaldehyde (1 equiv) in presence of sodium triacetoxyborohydride (1.4 equiv) to generate 1-(2-phenethyl)-4-piperidone. Under these reaction conditions, the ketonic function of the reactant remained intact due to the chemoselectivity of the reagent. No reduction of the aldehyde to the alcohol was observed. After completion of the step I, aniline (1 equiv) with additional amount of sodium triacetoxyborohydride (1.4 equiv) was added to the reaction mixture for reductive amination of keto group of 1-(2-phenethyl)-4-piperidone. Glacial acetic acid (2 equiv) was also added in the second step to accelerate the reductive amination of the keto group. After completion of step II, 4-anilino-N-phenethylpiperidine was converted to fentanyl **2** by dropwise addition of propionyl chloride to the reaction mixture in the final step.

Isolation and purification of the fentanyl from the above reaction mixture was done by the following procedure.



1 **2**

40 %

Scheme 1

After the completion of the reaction, the reaction mixture was diluted with dichloromethane. It was then washed with aqueous sodium hydroxide solution followed by water. The product was purified by shaking organic phase with 2 N HCl which converted all the basic compounds along with desired product in to their hydrochloride salts. The organic phase was separated and washed well with water. The non-polar fentanyl hydrochloride remained in the dichloromethane layer. Concentration of the organic phase gave crude fentanyl hydrochloride, which was recrystallised from acetone to give the pure salt as white powder. On treatment with 20% sodium hydroxide, fentanyl was obtained as colourless crystalline compound, m.p. 82–83 °C (lit[3] 83–84 °C) and characterised by its spectral data.

In conclusion, we describe a convenient and efficient one pot synthesis of fentanyl hydrochloride. This method is very simple and efficient. The whole reaction takes place under mild conditions and at room temperature. By performing three successive one pot reactions, separation and purification of the intermediates were excluded, thereby increasing the overall yield. This method can also be used for the synthesis of fentanyl analogues.

Experimental

To a stirred suspension of 4-piperidone monohydrochloride (15.36 g, 0.1 mol) in dichloroethane (450 ml), triethylamine (27.87 ml, 0.2 mol) and phenylacetaldehyde (11.17 ml, 0.1 mol) were added and stirred for half an hour at room temperature under N_2. Thereafter sodium triacetoxyborohydride (30 g, 0.14 mol) was added to the reaction mixture with continuous stirring. Reaction mixture was further stirred for 24 h. Aniline (9.12 ml, 0.1 mol), acetic acid (11.53 ml, 0.2 mol) and sodium triacetoxyborohydride (30 g, 0.14 mol) were then added and again stirred for 24 h. Propionyl chloride (26.16 ml, 0.3 mol) was then added dropwise and the mixture was stirred for 2 h. The reaction mixture was then diluted with dichloromethane and washed with 4% aqueous sodium hydroxide solution followed by water. The organic phase was then shaken with 2N HCl. The organic layer was separated and the aqueous layer was extracted with DCM. Combined organic phase was dried over sodium sulfate and concentrated to give crude HCl salt of fentanyl. Crude product was recrystallised with acetone to give white powder of fentanyl hydrochloride. The salt was treated with 20% NaOH to give fentanyl which was recrystallised from petroleum ether (60–80°), 13.44 g (40 %), m.p. 82–83 °C.

IR (KBr): 1657 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.99 (t, 3H, -CH_3), 1.3–1.4 (m, 2H, Ph-CH_2), 1.7–1.8 (m, 2H, -N-CH_2), 1.85 (q, 2H,), 2.05–2.15

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(m, 2H), 2.45 (dd, 2H), 2.65 (dd, 2H), 2.9–3.0 (m, 2H), 4.58–4.67 (m, 1H), 7.00–7.35 (m, 10 × Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 9.58, 22.57, 28.49, 30.56, 33.82, 52.14, 53.08, 60.46, 125.98, 128.21, 128.34, 128.59, 129.24, 130.41, 138.85, 140.24, 173.50.

EIMS (*m/z*): 336 [M^+, $C_{22}H_{28}N_2O$], 245, 202, 189, 146 (100), 132, 105, 96, 91, 77, 70, 57, 42.

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