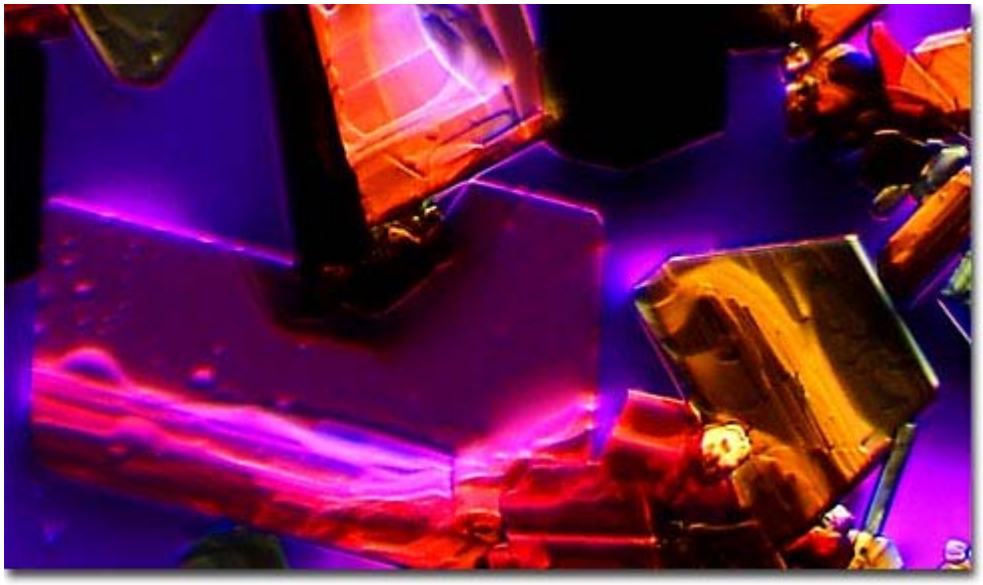
Synthesis of Fentanyl

by *Siegfried*



1. Introduction

I'm french speaking organic chemist so excuse my rusty english [*most things corrected by me - Rhodium*].

Fentanyl and its analogs are among of the most powerful opiate agonists, but their synthesis are often hard. Here is a synthesis of Fentanyl which can be easily adapted for the other analogs (Para-Fluoro-Fentanyl, Alpha-Methyl-Fentanyl).

This procedure is not theoretic and have been tested and improved many times over. This synthesis is conducted at room temperature so you don't need any special apparatus.

Fentanyl is a very interesting component for underground chemistry because one gram of pure fentanyl is equivalent of 100gr of very good street heroin.

2. Principle

The precursor used is N-Phenethyl-Piperidone (NPP) which can be easily synthesized from Piperidone and Phenethyl-Tosylate or Phenethyl-Bromide through a simple SN2 mechanism.

The NPP is reacting with Aniline giving the Imine derivative which is reduced to the

4-Anilino-N-Phenethyl-Piperidine (4-ANPP).

The 4-ANPP is then reacted with Propionyl Chloride giving Fentanyl which is then purified.

3. Procedure

a) **Synthesis of the Imine derivative of NPP**

10 mmole of NPP is dissolved in a minimal volume of Aniline (about 5-6 ml), then 1 gr of 4A Molecular Sieves is added.

The mix is really gently stirred (so that the Molecular Sieves aren't destroyed by the agitation) with a magnetic stirrer for about 24 H at room temperature.

The conversion have repeatedly been calculated with MS and is more than 99%, so the next phase can be conducted without any purification.

b) **Synthesis of the ANPP**

The reaction mixture from (a) is filtered from the Molecular Sieves which are rinsed with 2*2ml THF, the filtrate and washings are poured into a 50 ml flask, whereupon 20 ml dry Methanol is added, and the mix is stirred.

About 1-1.5gr of Sodium Borohydride is very slowly added to the mixture at room temperature, and the mix is stirred for about 2 h. The conversion into ANPP is checked with any method and if not completely reduced, add slowly another 0.5gr $NaBH_4$ and stir for one more hour.

When the conversion into ANPP is complete (more than 95%), evaporate the Methanol and the THF under vacuum.

After the evaporation there is a mass formed from the Aniline, the excess $NaBH_4$ and the ANPP complexed with borane.

Pour 50 ml of water into the flask, then destroy the complex by the slow addition of a small quantity of concentrated HCl (35%) until the pH is about 1, then the mix is well stirred for another hour. Now 50ml of a saturated NaCl solution is added to the mixture, and after about 10 min, a solid mass precipitate.

Separate the solid from the liquid with a filtration and keep the solid (this is ANPP hydrochloride) after washing it with a little saturated NaCl solution.

Add another 50ml of saturated NaCl solution and place the mix in the fridge (at about 2 deg C) and wait 2-3 h. If there is more precipitate, filter the solution and add the solid to the first crop. The solid mass is ANPP which must be treated.

Dissolve the solid in about 60ml water and 2N NaOH until the pH reaches 12.5, then extract with 3*15ml CH2Cl2. Wash the CH2Cl2 phase with 5 ml water, and evaporate the solvent in vacuum. The residue is an oily yellow-orange liquid which spontaneously crystallizes, this is the ANPP which is pure enough for the next step.

The overall yield of ANPP is about 50-80%. The main loss of yield is during the purification process because the separation process between the excess of Aniline and ANPP is not optimized. There are perhaps some solutions to this, which will be discussed in the optimization and discussion section.

c) **Conversion of ANPP to Fentanyl**

10mmols of ANPP are dissolved in about 8 ml of Pyridine with stirring, and then 12 mmoles of Propionyl Chloride is added dropwise to the reaction mixture at room temperature. The reaction is

exothermic and the Propionyl Chloride must be carefully added, so that the temperature doesn't rise over 60 deg C. You don't need a cooling bath, the temperature should be controlled with the addition rate of Propionyl Chloride and must stay between 30 and 60 deg C during the addition.

When all the Propionyl Chloride is added, the reaction mixture is stirred for about one hour at room temperature.

Check the conversion with any method and if not complete, add another 1 mmol of Propionyl Chloride. Normally the conversion should be complete after the first operation but if there is too much Aniline you need more Propionyl Chloride.

The reaction mix is then poured into 80 ml water with stirring, and conc HCl (about 35%) is added dropwise until the pH falls below 1.5. This operation can be done with another procedure as follows: Prepare 80 ml of 2N HCl and simply pour the reaction mix into this solution. This results in the pyridine and the fentanyl turns into their respective hydrochlorides. The solution is then leaved with stirring for about 30min. The Pyridine HCl is not soluble in CH2Cl2, while the nonpolar Fentanyl HCl is. Extract the solution with 3*20ml of CH2Cl2, then wash the organic phase with 2*10ml saturated NaCl solution.

The solvent is evaporated under vacuum, and a yellow mass is formed which consists of Fentanyl hydrochloride with a small quantity of Propionanilide as an impurity. 10-15ml Acetone is now added, and a white powder forms, which is Fentanyl HCl. Filter the solid and wash it with a small quantity (2*3ml) of acetone.

The Fentanyl HCl is now pure enough for use (>99.5%). The yield in this step is over 90%!

If not pure enough (it was never the

case for me) you can purify it by recrystallisation from hot acetone.

d) **Preparation of synthetic white Heroin for street use**

The pure Fentanyl can not be used as is, because it's much, much too strong and MUST be diluted, else there will be a lot of overdoses!

The following procedure gives a white heroin which is the same as very good (30%) street heroin.

100mg of Fentanyl. HCl is dissolved in 2ml of Methanol. Weigh up 10g of Lactose and warm it at about 60-70 deg C into a large dish with a hotplate. Add the methanolic solution of Fentanyl dropwise at regular intervals into the warm Lactose for a good pre-mix . Wait until all the Methanol is evaporated and mix the Lactose-Fentanyl thoroughly. This is crucial because if this is not thoroughly mixed, there will be a part of the Lactose without Fentanyl and part of the Lactose with too much Fentanyl, possibly causing dramatic overdoses!

Now you have a very high quality of street white Heroin.

This type of Heroin was used and sold during a year, and the feedback of the consumers was very good. The consumers were very happy and didn't want the usual brown Heroin anymore. So be careful, some people (The Mafia and other dealers) will perhaps turn very jealous!

Remember that with 1gr of pure Fentanyl HCl you can make 100gr of very high quality Heroin!

DON'T USE and DON'T SELL pure Fentanyl HCl, this is a very toxic material which can cause many overdoses if not diluted!

e) **Optimization and discussion**

The overall yield of this synthesis is about 50-80% and the main loss of product is during the purification of ANPP in step (b).

There are perhaps other alternatives for the separation of Aniline and ANPP (recrystallisation, distillation). I think a good solution is extracting the Aniline and ANPP together and separate them with the evaporation of Aniline under vacuum, then recrystallize the ANPP in a suitable solvent.

Para-Fluoro-Fentanyl can be synthetised with this procedure using Para-Fluoro- Aniline instead of plain Aniline, but the purification process must be adapted.

The very powerful Alpha-Methyl-Fentanyl can also be synthetised with this method using N-(2-Phenylpropyl)-Piperidinone which can be synthetised from 1-Phenyl- 2-Bromopropane and Piperidinone or other methods. The 1-Phenyl-2-Bromopropane is used in the underground manufacture of Amphetamine, and the procedure of the synthesis of this compound can be easily adapted for the creation of N-(2-Phenylpropyl)-Piperidinone or the NPP (N-Phenethyl-Piperidinone).

Fentanyl is a very good and powerful opiate but there are some remarks:

- Fentanyl is very addicting , much more than simple Heroin, the regular users of this synthetic white Heroin I described was really strongly addicted.

- The risk of overdose is really large, even with the dilution I described before, so test your stuff before selling it!

- The duration of the

effects is a little shorter than with normal Heroin.

Related texts:

N-Phenethyl-4-piperidone

N-alkylation of 4-piperidone can be done in PTC conditions - and no need to isolate your piperidone as free base. Add to one liter of acetonitrile 3 mole finely powdered potassium carbonate, then add 10 g of PTC catalyst - TBAB or TEBA, or just polyethylene glycol-400. Stir this suspension 15 min at 50-60°C, and then add in little portions your 4-piperidone hydrochloride, watching that the CO2 evolution wasn't too vigorous. Stir another hour at 50-60°C, and then add dropwise phenethylbromide, and stir 15-20 h at mild reflux. Then cool, and filter off inorganic salts - if filtration goes too slowly, add to suspension some (30-40 ml) saturated sodium sulphate solution, this makes the sticky precipitate granular and filterable. Yield almost quantitative (trust me), and no distillation needed - as result you have slightly yellow solid with mp 60°C.

Future Opioids
Actiq ('perc-a-pop') : the fentanyl lollipop