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Synthetic methodology and structure activity relationship study of N-[1-(2-phenylethyl)-piperidin-4-yl]-propionamides

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ABSTRACT

N-[1-(2-Phenylethyl)-piperidin-4-yl]-propionamide (fentanyl) is the prototype of the 4-anilidopiperidine class of synthetic opioid analgesics. This study was aimed to review the best method of synthesis and to determine the Structure-Activity-Relationship (SAR) of fentanyl analogs. The best method of synthesis of fentanyl is the method described in International Application No.: PCT/IN2009/000159. The advantages are as followed- simple, high yielding, cost effective, eco-friendly, environmentally safe, industrially feasible, does not require stringent process conditions, sophisticated infrastructure and specially skilled personnel. The objective of SAR studies is to discover compounds with adequate potency, greater selectivity and with enhanced pharmacokinetic properties in comparison to existing drugs.

Key words: Opiod analgesics, N-[1-(2-Phenylethyl)-piperidin-4-yl]-propionamide, Method of Synthesis, Structure-Activity-Relationship.

INTRODUCTION

Piperidines are important class of heterocyclic compounds of which 4-anilidopiperidine derivatives in which a nitrogen atom has been inserted between piperidine & aromatic ring represent a particular class of mu-agonist characterized by very high analgesic potency relatively short duration of action & good overall safety margin during surgical anesthesia.

The basic anilide N-[1-(2-Phenylethyl)-piperidin-4-yl]-propionamide (Fig.1) is the prototype of this class of analgesic. It is about 50-100 times more potent than morphine and is characterized

by a rapid onset of analgesia and a relatively short duration of action [1-3]. From its pharmacological action, it appeared to be capable of forming a complex with stereospecific receptor postulated for analgesic action.

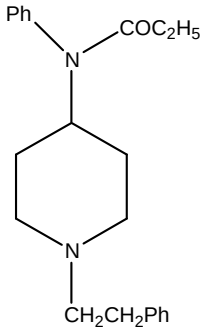


Fig. 1 Fentanyl

N-[1-(2-Phenylethyl)-Piperidin-4-yl]-Propionamide (Fentanyl) is a synthetic primary μ- opioid agonist & a potent narcotic analgesic with a rapid onset & short duration of action [1]. Fentanyl was first synthesized by Dr. Paul Janssen in 1960 following the medical inception of pethidine several years earlier. Fentanyl is extensively used for anesthesia & analgesia in operating rooms & intensive care units. It is often administered in combination with benzodiazepine to produce procedural sedation for endoscopy, cardiac catheterization & oral surgery. Fentanyl is often used in cancer therapy & other chronic pain management due to its effectiveness in relieving pain. However, there is increasing number of reports of respiratory depression events since late 1970s [2]

Analogues of N-[1-(2-Phenylethyl)-Piperidin-4-yl]-Propionamide (Fentanyl)

A very large number of fentanyl analogs have been synthesized since 1963. The corresponding pharmacological data have been published and the structure-activity relationship established. The pharmaceutical industry has developed several analogues of fentanyl:

- Alfentanyl (trade name **Alfenta**), an ultra-short acting (5–10 minutes) analgesic. Its potency is 1/4 the potency of fentanyl and around 1/3 of the duration of action, but with an onset of effects, it is 4 times faster than fentanyl [4-5]. However, alfentanyl has been used frequently in clinical practice [6].
- Sufentanyl (trade name **Sufenta**), a potent analgesic (5 to 10 times more potent than fentanyl) for use in heart surgery. It is approximately 5 to 10 times more potent than fentanyl. It has a rapid onset and recovery is considered to be more rapid than with fentanyl [4-6].
- Remifentanyl (trade name **Ultiva**), currently the shortest acting opioid, has the benefit of rapid offset, even after prolonged infusions. It is approximately as potent as fentanyl [7]. It has a more rapid onset of analgesia than fentanyl or sufentanyl and an ultrashort duration of action [6].
- Carfentanyl (trade name **Wildnil**) is an analogue of fentanyl with an analgesic potency 10,000 times that of morphine and is used in veterinary practice to immobilize certain large animals such as elephants. [8]
- Lofentanyl is an analogue of fentanyl, with potency slightly greater than Carfentanyl with a remarkably long duration of action, though not with clinical significance [9-10].

Like other μ agonists, all these drugs suffer from serious adverse effects including respiratory depression, muscle rigidity, nausea, sedation and with prolonged use, tolerance and addiction [6]. Several other compounds are still under extensive evaluation in animals nowadays, while some of them are proposed as useful tools for studying the opioid receptors [11-15].

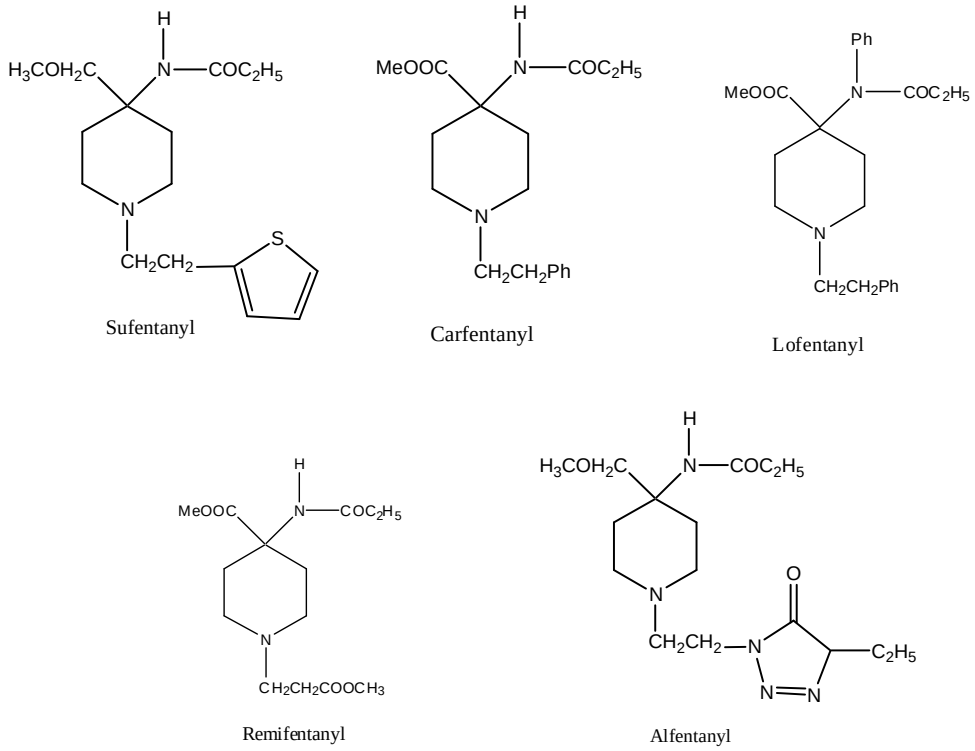


Fig. 2 Analogs of Fentanyl

Structure Activity Relationship of 4-anilidopiperidines:

The objective of SAR studies is to discover compounds with adequate potency, greater selectivity and with enhanced pharmacokinetic properties in comparison to existing drugs. The development of novel opioids as research tools is almost equally important. They serve as probes for 3D structures of binding domains of opioid receptors, which are presently only poorly understood [16]. The establishment of detailed SAR, in combination with conformation analysis of the ligands, is an important approach to studying receptors [17-19]. Isotopically labeled fentanyl derivatives have been employed in opioid receptor studies, both *in vitro* and *in vivo* [20-22]. For example, positron emission tomography, (PET), with 11C labeled carfentanyl, has been used in healthy volunteers to observe the opioid receptor distribution in the body organs and other receptor properties [23-24]. Furthermore, novel opioid ligands are indispensable in studies of pain transmission mechanisms [25-26].

1) Effects of ortho fluorination of the anilido functionality: initial structural modification of the basic 4-anilidopiperidine was to vary the N-acyl moiety & to substitute on the anilido phenyl ring.

a) Replacement of the propionamide group of fentanyl with a methoxyacetamide or 2-methoxypropionamide did not diminish efficacy of analgesia.
b) Enhancing the bulk at this area of the molecule by extending or branching of the alkoxy

chain generally abolished activity.

c) Introduction of a para substituent in the anilido phenyl group of fentanyl decreases analgesic activity, with fluorine substituent causing the least shift.

d) Absence of either the cis juxtaposition between the substituents at carbon 3 &4 or the ortho fluorine resulted in complete loss of activity.

e) The presence of an ortho fluorine on the aromatic ring of the amide group enhanced potency.

2) In the 4-(heteroanilido) piperidines the insertion of one or two carbon chain between the phenyl & nitrogen of the anilido group of the fentanyl provide more potent compound which provide shorter duration of anesthesia.

3) In aryl & 4-heteroaryl piperidines the most potent analgesic had a phenethyl and a 2 or 3-thienylethyl substituent at the piperidino nitrogen & that an ortho-flourine on the anilido phenyl enhanced analgesic activity while a chlorine diminishes analgesia.

a) Direct attachment of heteroaryl ring to the piperidine ring resulted in compounds having improved potency relative to fentanyl.

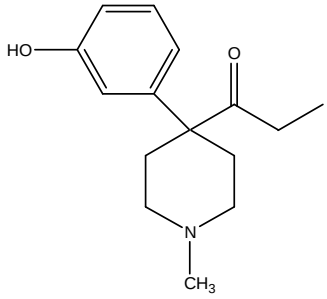
4) In the heterocyclyalkylation at the piperidine nitrogen compounds bearing certain five membered rings are more potent than six membered rings.

a) When azolinone ring were fused to a benzene ring, potent analgesia was detected, but was reduced when an additional C=O or an internal heteroatom was introduced.

b) Optimal pharmacological accommodation was seen with those compounds in which heterocycles were fused to only one benzene ring & an ethyl connector attached to a nitrogen, which was situated between the benzene ring & a C=O group

5) Both esters and reverse esters at the 4-position are active, as are the simple ketones. Propyl is the optimal chain length {excluding the ester oxygen}.

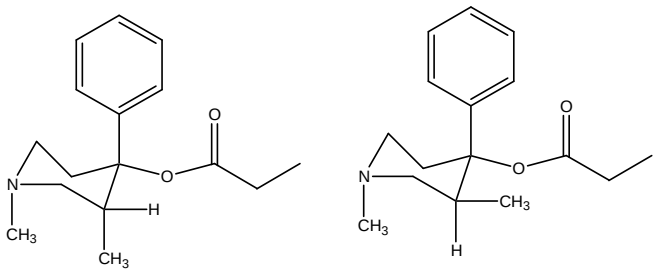
6) The phenyl ring at the 4-position is necessary for activity, and must be able to assume the axial position. Addition of m-OH group will enhance activity, such analogues are called bemidones.



Ketobemidone

Fig.3 Example of Bemidone

7) If a reverse ester is combined with a 3-methyl, the analogues are known as prodines. The methyl group may cause enantiomeric recognition by the opioid receptor.



trans = alpha-prodine cis-beta-prodine

Fig.4 Cis-trans isomer of prodine

8) The nitrogen substituent is a methyl in most cases. A phenethyl or its equivalent will increase activity. It is not possible to confer antagonist activity with a nitrogen substituent such as allyl.
9) Substitution by either ethyl or phenyl moiety on the propioanilide group generally decreases activity, on the contrary, an o- methoxy substituent appears to increase opiate receptor binding slightly.
10) The cis- (+) – methyl analogue has been found to be 6684 times as potent as morphine but a methyl group in the 2- position or 2, 5 dimethylation leads to significant reduction in analgesic activity.
11) When the piperidine derivative is either contracted to a 3-anilido piperidine derivative or expanded to a 4-anilido perhydroazepine derivative, activity is again decreased.
12) The analgesic activity of the 4-anilido piperidines is greatly enhanced by the presence of substituent in the 4-position of piperidine ring.
13) Substitution of a methoxy methyl group at the 4-position of the piperidine ring leads to a compound possessing 10,000 times the potency of morphine in rats.
14) Introduction of alkoxy carbonyl or oxo-alkyl substituents in the 4-position also enhances activity.
15) A conformationally constrained derivative in which phenyl is constrained in the beta-orientation is inactive but in conformationally constrained tropane analogs of fentanyl the beta-analogs, in which the anilido group is equatorial, is more potent than the alpha-isomer in which the propioanilido moiety is pseudoequatorial.

Structure Activity Relationship of N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl] – propanamide:

1. Introduction of a methyl group in position 3 of the piperidine ring may dramatically enhance the analgesic activity, depending on the relative and the absolute stereochemistry [27, 28]. Also, replacing 3-methyl with an allyl or a propyl group significantly reduces overall potency [29, 30]
2. The presence of an alkyl group substituent in position 3 of the piperidine ring generally decreases or completely inhibits the analgesic activity compared to fentanyl. However, with increasing voluminosity of the alkyl group, the potency decreases rapidly [31].
3. The antinociceptive potency of fentanyl analogs substituted in the position 3 of the piperidine ring is independent of the nature of the substituent group, *i.e*., it is influenced by the steric factor only.
4. The relative *cis*/*trans* stereochemistry is important since the *cis* isomers are 1.5-6 times more active than the *trans* isomers. [45, 50]

5. It was observed that the optimum length in case of anilido side chain of the N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide derivatives is the propionanilide. Replacement of the propionyl group of anilido side chain with either acetyl or benzoyl group decreases the activity.
6. Replacement of the propionamide with 2- or 3- fumaramide resulted in the compounds with antagonist activity against morphine induced analgesia & respiratory depression.
7. The conformational studies have revealed the fact that the anilido moiety adopts an equatorial conformation.
8. The size of the piperidine ring also plays an important role in determining the analgesic activity.
9. Introduction of a methyl group at the C-3 of the piperidine ring gave chiral analogues. The (+)-cis- methoxy N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide was found to be 100 times more potent whereas, corresponding racemic trans isomer was approximately as active as N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide.
10. Compounds in which the anilido phenyl ring had an ortho-substituent, the trans isomers were found to be more potent then cis- isomers.
11. Effect of other structural variations in the anilido part like ring closure between the ortho position & the piperidine ring or in the propionyl chain & the replacement of the N atom by a tetrahedral C-atom on the analgesic activity has also been carried out to obtain better understanding of the structural features governing the opiate receptors interaction of N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide like analgesia.

Scheme 1

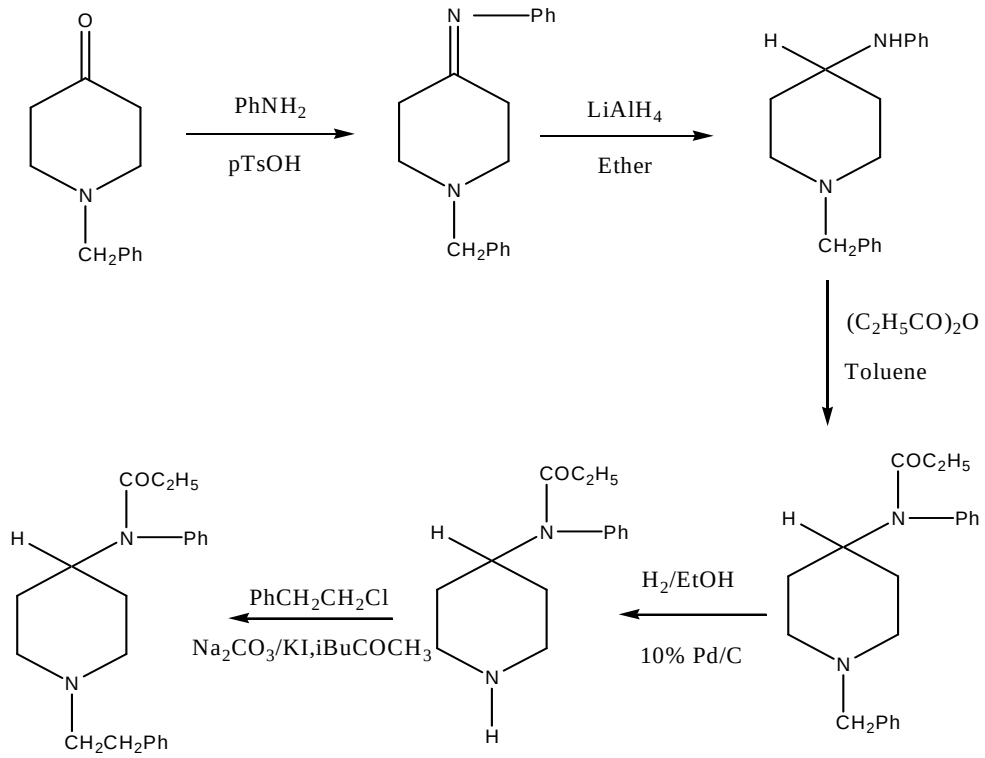


Fig. 5 Synthetic Scheme Followed by Janssen et al

12. The addition of a polar carbon substituent like $–COOCH_3$ & $-CH_2OCH_3$ at C-4 position of

the piperidine ring enhanced the potency. For example, Carfentanyl was found to be 27 fold more active than N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide & 7800 times more than morphine.

13. Combinations of a heterocyclic substituent on the piperidine chain & a polar carbon group at C-4 of the piperidine ring yielded clinically useful drugs "Sufentanyl & Alfentanyl"

14. Incorporation of an ester functionality into piperidino substituent gave Remifentanyl which was 30-fold more potent than Alfentanyl with rapid onset & offset of action.

Method of Synthesis of N-Phenyl-N-[1-(2-Phenylethyl)-Piperidin-4-yl]-Propanamide:

Janssen et al [32-34] first synthesized N-Phenyl-N-[1-(2-Phenylethyl)-piperidin-4-yl]-propanamide, one of the most potent synthetic narcotic analgesics in 1964 (Scheme 1) describes their synthetic route.

Comments:

1. The main disadvantage associated with this process is a multi-step, hence requires more time and over all appreciably reduced yield. It also requires stringent operating conditions such as reflux temperature in all five steps thus making the process energy extensive, which in turn makes the process uneconomical.

2. The other drawback is that every process step makes use of organic solvent requiring removal of these solvents, which not only adds to the overall cost of the process but also makes the process environmentally unsound and unsafe.

3. Further steps (i), (ii), (iii), & (v) being moisture sensitive requires additional infrastructure and precautions, which is undesirable for large scale production.

4. Lithium aluminium hydride in step (ii) reacts violently with water and liberates hydrogen, which is likely to cause the material ignite. Thus, for large scale production, use of lithium aluminium hydride in step (ii) is undesirable from safety and environmental point of view.

Scheme 2

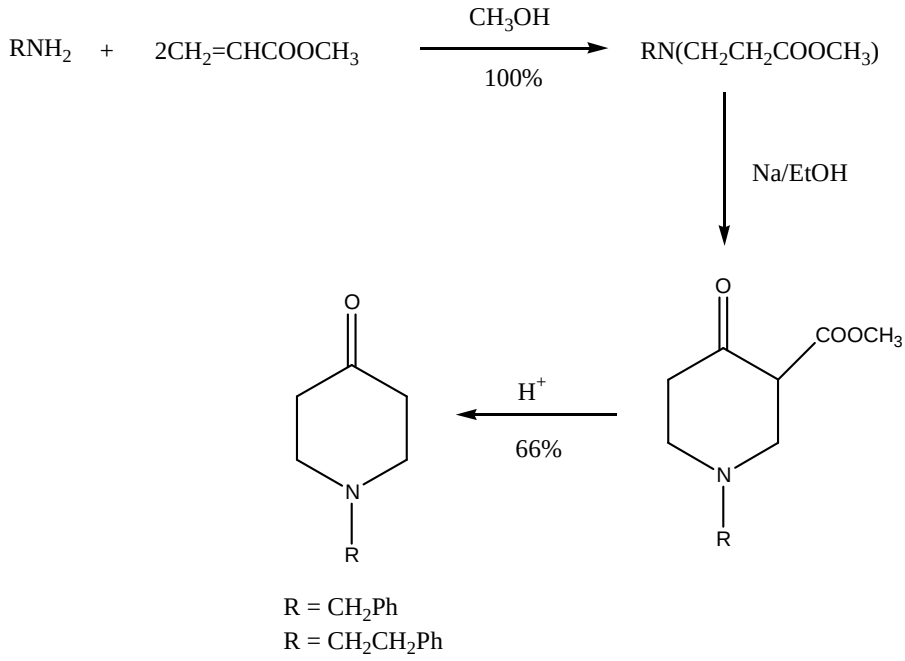
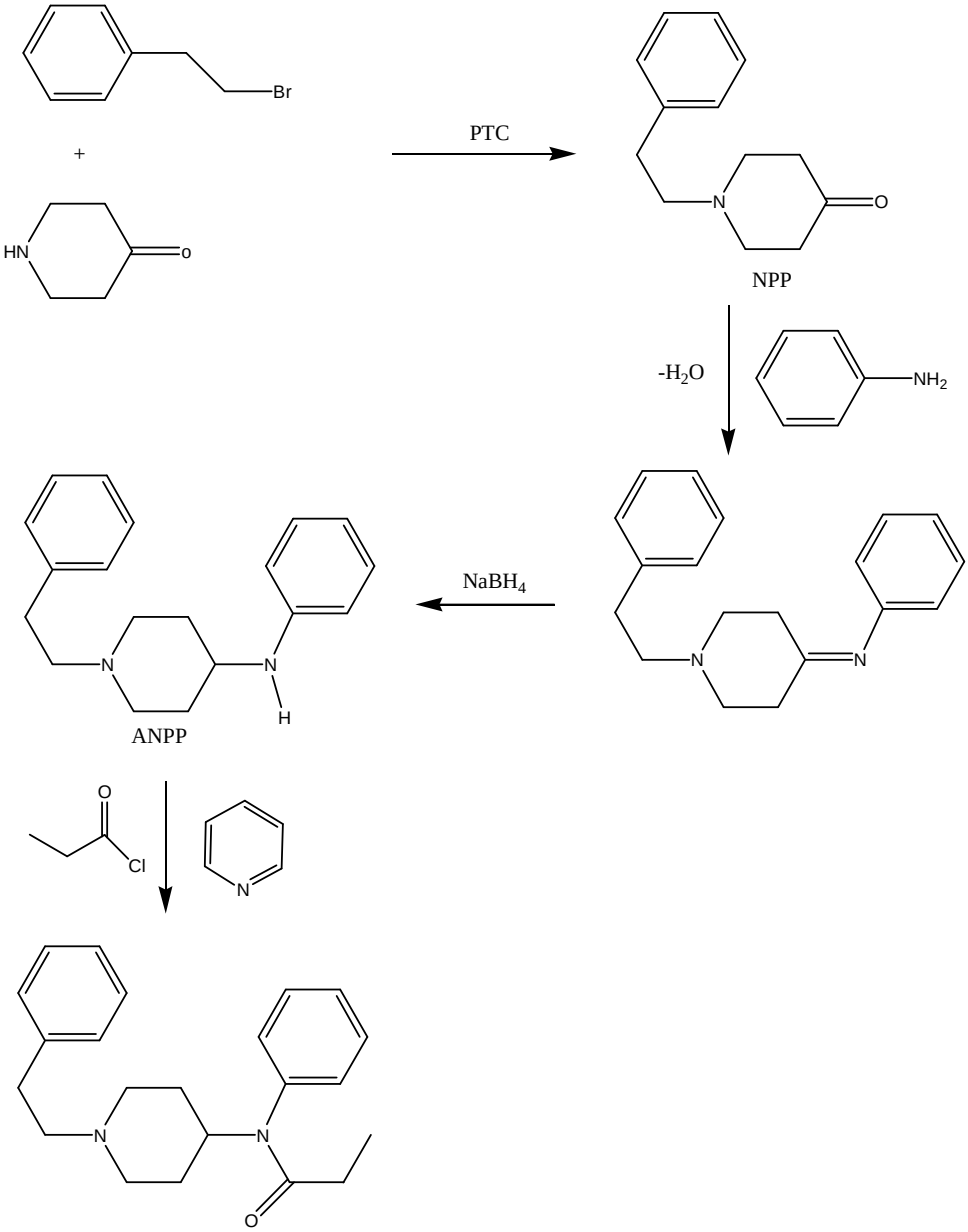


Fig. 6 Synthetic Scheme Followed by Zee et al

5. The diethyl ether used is highly inflammable low boiling organic solvent posing fire hazards that requires special fire safety measures particularly in up scaling of the process.
6. Similarly the palladium charcoal used in hydrogenation/debenzylation increases the cost of the process.
7. The effluent stream of the subject process is likely to impair the environment.
8. The process as reported in literature is energy extensive, cost extensive, time consuming, requires sophisticated infrastructure to maintain stringent operating conditions, requires specially trained skilled personnel, likely to impair ecosystem & environment and unfit for large scale production, i.e. industrially and commercially unviable.



N-(1-Phenethyl-piperidin-4-yl)-*N*-phenyl-propionamide

Fig. 7 Synthetic Scheme Followed by Siegfried

Zee et al [36-38] synthesized the starting material from Phenethylamine, and methyl acrylate in methanol via the intermediate diester, the hydrolysis of which yielded the desired 4-piperidone, (Scheme 2) then reductive amination of desired 4-piperidone with aniline using Na/EtOH as the reducing agent was done followed by acylation with propionyl anhydride in toluene to give 93% of N-Phenyl-N-[1-(2-Phenylethyl)-piperidin-4-yl]-propanamide

Siegfried reported the synthesis of N-Phenyl-N-[1-(2-Phenylethyl)-piperidin-4-yl]propanamide using N-phenethyl piperidone (NPP) as the precursor. The NPP reactswith aniline giving the imine derivative which is reduced to 4-Anilino-N-Phenethylpiperidine (4-ANPP) which then reacts with propionyl chloride giving Fentanyl.

The overall yield of this synthesis is about 50-80% & the main loss of material occurs during purification of ANPP in step B

Polish patent No. 72,416 [37] describes a process for the preparation of N-Phenyl-N-[1-(2-Phenylethyl)-piperidin-4-yl]-propanamide also comprises of following five steps:

- Condensation of 2-phenylethylaminewith methyl or ethyl acrylate to get N,N-bis-(2-Carbalkoxyethyl)-phenylethylamine,
- Cyclising the said amine in presence of sodium methoxide (alkoxide) to give 1 - (2-phenylethyl) piρeridine-4-one,
- Condensing the said l-(2-phenylethyl) piperidine-4-one with aniline to give l-(2-phenylethyl) piperidinylidene aniline, followed by
- Reduction by employing lithium aluminium hydride, and subsequently
- Acylating to procure N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide

Comments

1. It employs moisture sensitive sodium methoxide and lithium aluminium hydride
2. It involves five steps and thus inherits the draw backs associated therewith.
3. This process is cost extensive, unsafe to environment, requires special operational conditions and thus unfeasible for industrial and commercial applications.

CRDEC [39-40] developed method which involves the Strecker synthesis with aniline, KCN, and AcOH in 2-propanol gave excellent yield of alpha aminonitrile which undergoes Reductive decyanation with $NaBH_4$ in 2-PrOH resulting in compound with 85-90% yield. These two steps can be carried out in one pot without the isolation. Thus, this process represents a considerable improvement over the others

Suh et al [41] reported a four step method for the synthesis of N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide starting from $PhCH_2CH_2NH_3^{+-}O_2CCF_3$. The key step of this method involved the efficient construction of the phenethyl piperidone skeleton via aminomethano-desilylation-cyclization followed by swern oxidation.

Gupta et al [42] have reported a one pot synthesis of N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide which involves three consecutive reactions in a single reaction vessel. Though this method provided an attractive synthetic route, it was not found suitable for the scale up synthesis of N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide because of low yield of product.

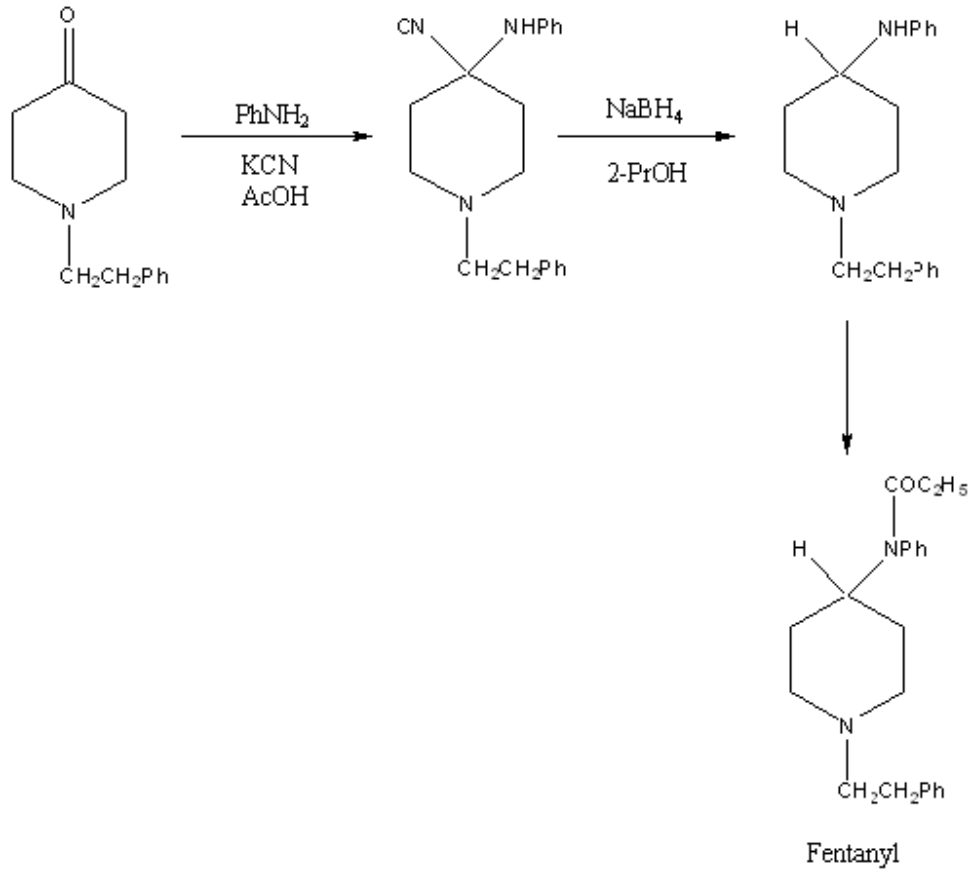


Fig. 8 Synthetic Scheme Followed at CRDEC

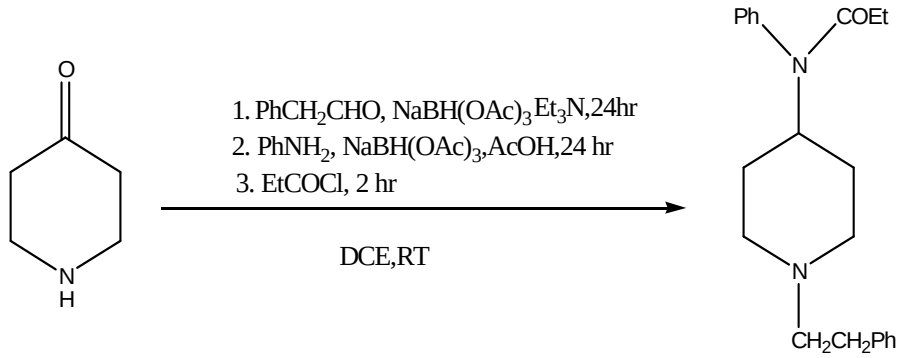


Fig. 9 Synthetic Scheme Followed by Gupta et al

The Indian application No.2554/DEL/2004 [43] from DRDO discloses a method comprising:

- Refluxing 4-piperidonehydrochloride monohydrate with phenethyl bromide in acetonitrile in presence of potassium carbonate and tetra butyl ammonium bromide (TBAB) to give NPP (N- phenethyl-4-piperidone)
- Reacting NPP with aniline in presence of zinc & carboxylic acid preferably acetic acid to give ANPP, then reacting with propionyl chloride to get N-phenyl-N-[1-(2-phenylethyl) piperidin-4-yl] propanamide.

Advantages:
(a) Reducing number of steps from five to three.
(b) Employing all readily available indigenously available reactants.
(c) Eliminating employing moisture sensitive (sodium methoxide), fire hazard reagents (lithium metal hydride) and highly flammable low boiling solvent.
Disadvantages:
(a) The process is low yielding.
(b) Polymerization of 4-piperidone hydrochloride monohydrate reactant takes place in step (i), which results in increased load on effluent.
(c) Using organic solvent as a reaction medium and removal of organic solvent is necessary this adds to the cost as well as makes the process environmentally unsafe/unsound.
(d) Requirement of anhydrous condition

International Application No.: PCT/IN2009/000159 [43] provides a method for the preparation of N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide Comprising:

- Reacting 4-piperidone hydrochloride (NPP) with aniline in presence of reducing environment to produce 4-anilinopiperidine (4- ANPP).

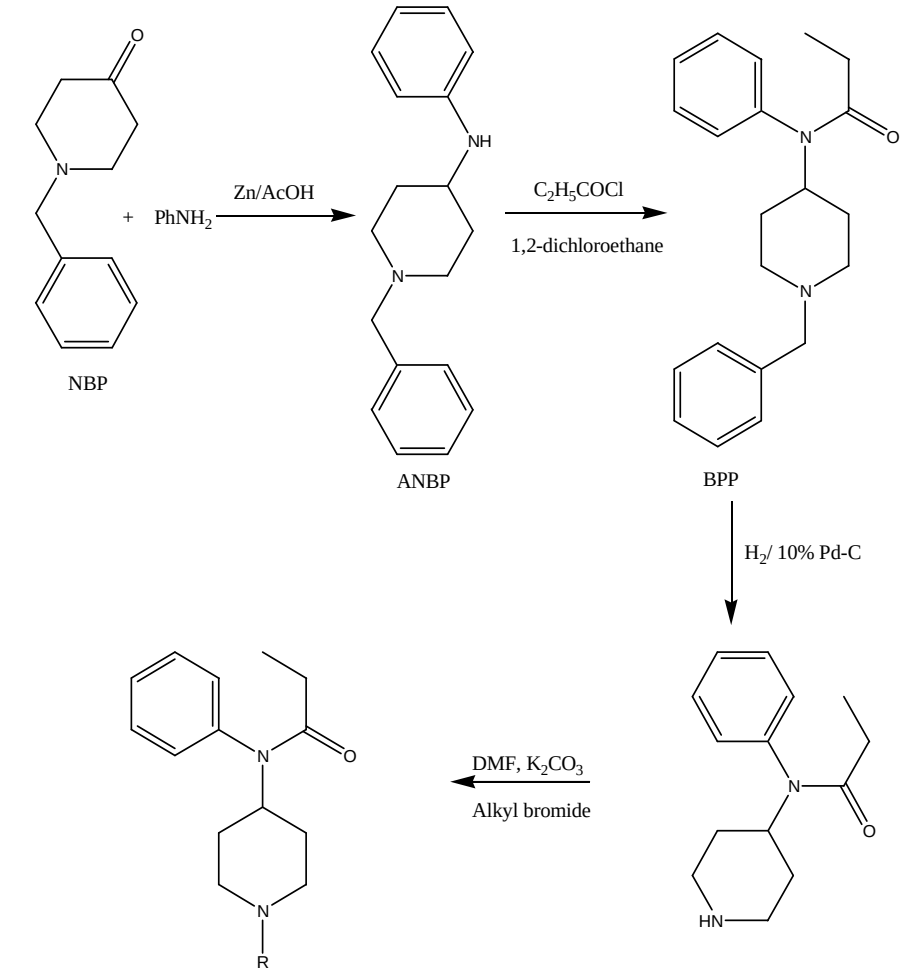


Fig. 10 Synthetic Scheme as per International Application No.: PCT/IN2009/000159

- Alkylating / reacting the 4- ANPP as obtained from step (a) with phenethyl halide under reflux conditions in highly alkaline medium to give 4-anilino-N-phenethylpiperidine.
- Converting the said 4-anilino-N-phenethylpiperidine to N-Phenyl-N-[1-(2-phenylethyl)-piperidin-4-yl]-propanamide by reacting with propionyl chloride in presence of halogenated hydrocarbons then isolating N-Phenyl-N-[1-(2-phenylethyl) piperidin-4-yl]-propanamide by solvent extraction and purified by crystallization from petroleum ether (60-80 °C).

Comments

This method is better than all above described methods because the process yield is more than 60%. This process does not require organic solvents as the reaction medium thereby making the process cost effective as well as eco-friendly.

This invention also avoids using hazardous reagents such as sodium borohydrate, sodium methoxide, lithium aluminium hydride, inflammable low boiling solvents, ether using different starting material, high cost reagents such as palladium charcoal avoiding polymerization of reagents, directing process in a predetermined manner thereby making process environmently safe, sound & beneficial. This process avoids employing sodium borohydride & eliminates exothermic reaction resulting in making process economical.

This invention particularly relates a method that is simple, high yielding, cost effective, eco-friendly, environmentally safe, industrially feasible, does not require stringent process conditions, sophisticated infrastructure and specially skilled personnel.

CONCLUSION

It could be concluded by comparing the Pros and cons of all the above described methods that the best method of synthesis of fentanyl is as described in International Application No.: PCT/IN2009/000159 owing to its process yield more than 60%, absence of organic solvents as the reaction medium thereby making the process cost effective as well as eco-friendly. Also, it avoids the use of hazardous reagents such as sodium borohydrate, sodium methoxide, lithium aluminium hydride, inflammable low boiling solvents, ether using different starting material, high cost reagents such as palladium charcoal avoiding polymerization of reagents, directing process in a predetermined manner thereby making process environmently safe, sound & beneficial. The S.A.R study will help in discovering new compounds with adequate potency, greater selectivity and with enhanced pharmacokinetic properties in comparison to existing drugs.

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