Original Research Article

An efficient synthesis of 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol: A key intermediate in Fenspiride HCl synthesis

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Abstract

The article confers a scalable manufacturing process of Fenspiride HCl. 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol is the main building block in Fenspiride HCl synthesis. The reported reagents for 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol synthesis are costly, explosive, highly toxic, produce hazardous waste, and also need to be handled with most care. The paper introduces aqueous ammonia as an alternate reagent in Fenspiride HCl and used in 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol synthesis. The new green chemistry aspect makes the process environment-friendly and cheaper. It also eliminates toxic, sensitive, and hazardous reagents and makes the process safe on uncomplicated on bulk scale production.

The high pure Fenspiride HCl is obtained by following this process and meets the ICH limits with good yield.

Key words: - Antitussives, Endotoxamia treatment, aq. Ammonia, Fenspiride HCl, commercial viable, ICH limits, Active pharmaceutical ingredient.

Introduction

Fenspiride {8-(2-phenylethyl)-1-oxa-3, 8-diazaspiro [4, 5] decan- 2-oneHCl} (1) is an oxazolidinone spiro compound and used for respiratory diseases treatment [1]. It has antitussives properties and is mainly used in the treatment of acute and chronic inflammatory diseases of ENT organs and respiratory, as well as it also widely in the maintenance treatment of asthma [2]. It is also been used for the treatment of allergy within otolaryngology system and respiratory tracts, respiratory manifestations of measles, flu, and symptomatic therapy of whooping cough [3,4] and has a potential benefit in endotoxemia treatment [5].

In the detailed literature survey for Fenspiride HCl (1), we found that limited literature available for the synthesis of Fenspiride HCl (1) which includes, use of several hazardous reagents and is difficult to handle on the bulk scale manufacturing.

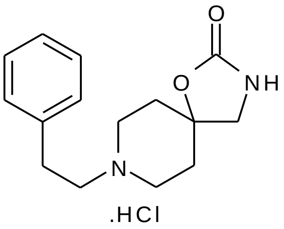

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Figure 1: Structure of Fenspiride HCl

Although it is a very old drug, a detailed review of the literature revealed that there are very few processes available for the synthesis of Fenspiride hydrochloride (1).

Initially, Gilbert et al. (2) [6] reported the synthesis of (1), starting with 1- phenethyl-4-hydroxy-4-aminomethylpiperidine (4) [prepared according to the British Patent No. 1100281, from piperidone (2) via cyanohydrin (3) and subsequent reduction] (Scheme1). Cyclization of 4 was affected with ethyl carbonate under reflux at 80 °C in the presence of freshly prepared sodium methoxide. They also reported an alternative synthesis starting from spiro (4,5) decane derivative (5) and coupling with Bromo derivative (6) (Scheme 1) [7].

Later, Ida Taccone reported the synthesis of Fenspiride [8], starting from N-substituted-4 piperidone (2), which was reacted in an appropriate solvent or solvent mixture with an alpha halogen ester in the presence of activated zinc. The resulting beta-hydroxy ester (7) was then reacted with an excess of hydrazine to afford beta-hydroxy hydrazide (8) which was then subjected to a Curtius transposition [9] with excess nitrous acid (Scheme 2, route I) to afford fenspiride.

Somanathan et al. [10] reported an alternative synthesis (Scheme 2, route II) by starting with N-(2-phenylethyl)-4-piperidone (2) which was treated with trimethylsilylcyanide in the presence of ZnI_2, followed by LAH reduction to arrive at intermediate 4. Finally, cyclization of aminol 4 using triphosgene afforded Fenspiride HCl (1).

Pramanik et.al [11] reported the synthesis (Scheme 4) starting from N-(2-phenylethyl)-4-piperidone (2) which was undergoes for nitro aldol condensation with nitro methane in presence of potassium carbonate, followed by zinc reduction to get intermediate 4. Finally, BOC anhydride is used for cyclization to arrive at Fenspiride HCl (1). It is reported that Nitroalkanes [12] have peculiar properties and to be handled with extreme care. Specifically while using nitro methane with strong base special care to taken to avoid the alkali metal salt formation, which is very shock-sensitive and may undergo the explosion in dry condition.

All the above-described methods are associated with several shortcomings for large-scale production owing to its huge annual consumption, i.e. involving highly toxic cyanide reaction, use of hazardous reagents like LAH, sodium metal, use of Class-I solvent like benzene and highly flammable diethyl ether, low yield, etc.

In an effort to avoid all these limitations, earlier a commercial scale process was developed by our team [13] (Scheme 3). Piperidone 2 on Corey−Chaykovsky [14] epoxide formation using trimethyl sulfoxonium iodide in

DMSO in the presence of sodium hydroxide as base resulted in epoxide 10 in good yield. In situ epoxide opening using sodium azide in DMSO at 45−50 °C afforded azido intermediate (11). Reduction of azide (11) was best affected under hydrogenation conditions using hydrazine hydrate under heating to arrive at amine (4). The final oxazolidone formation was accomplished using carbonyl diimidazole (CDI) under basic medium to arrive at fenspiride free base (12) followed by salt formation using HCl-EtOAc which provided the target molecule fenspiride HCl with high HPLC purity (>99.7%) complying with ICH guidelines. The above process is being used for the commercial manufacturing of fenspiride on 40−50 kg scale. Even though the yield in each step is reasonable to high and produces high quality API, the process owns the risk/safety factor associated with the use of NaN3 along with the effluent treatment after reaction, the process could not be scaled up.

Scheme-1

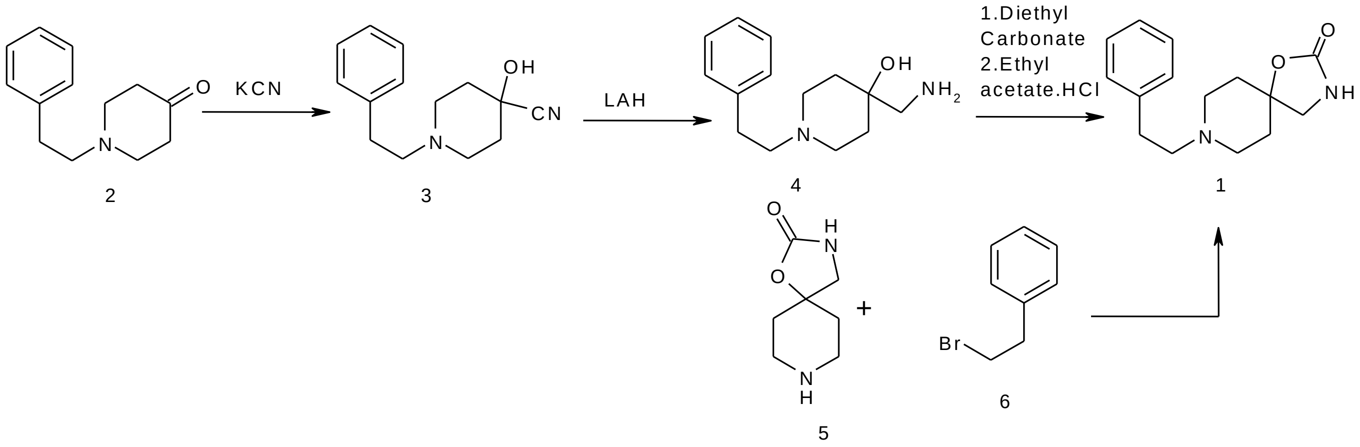


Figure 2: Synthesis scheme 1.

Scheme-2

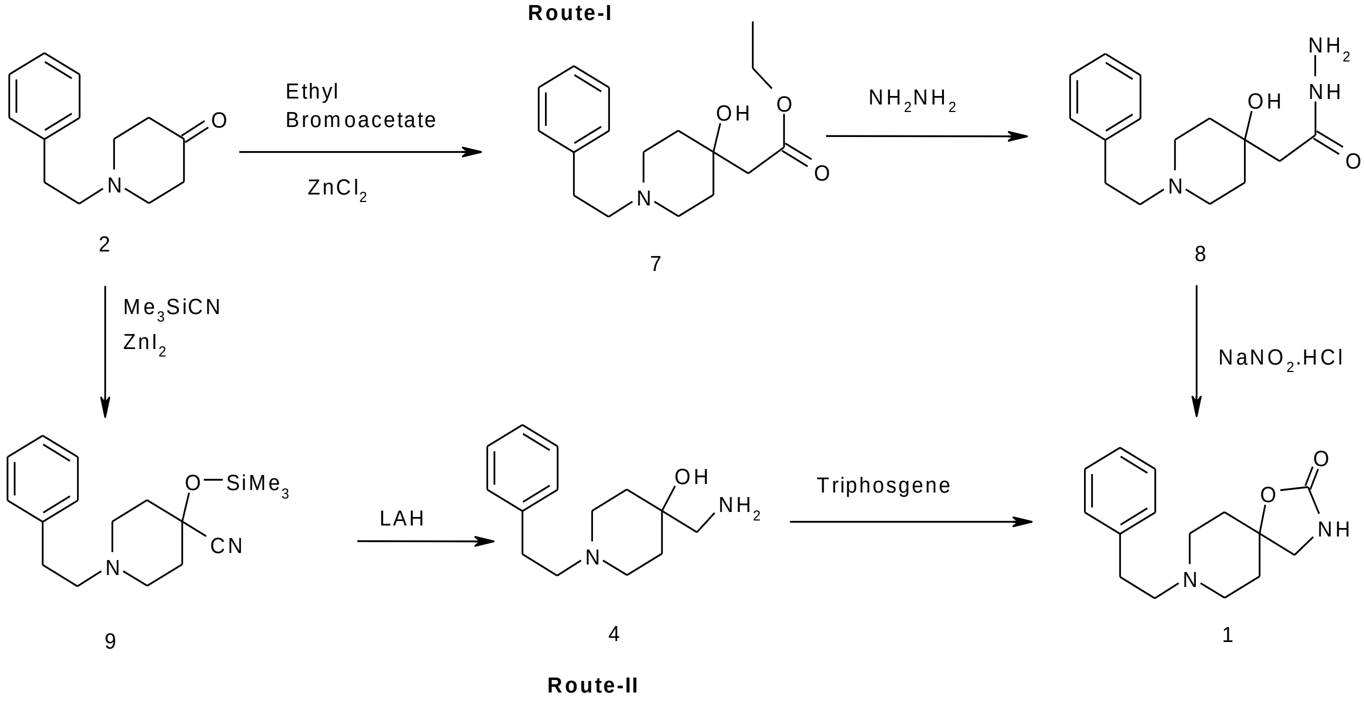


Figure 3: Synthesis scheme 2.

Scheme-3

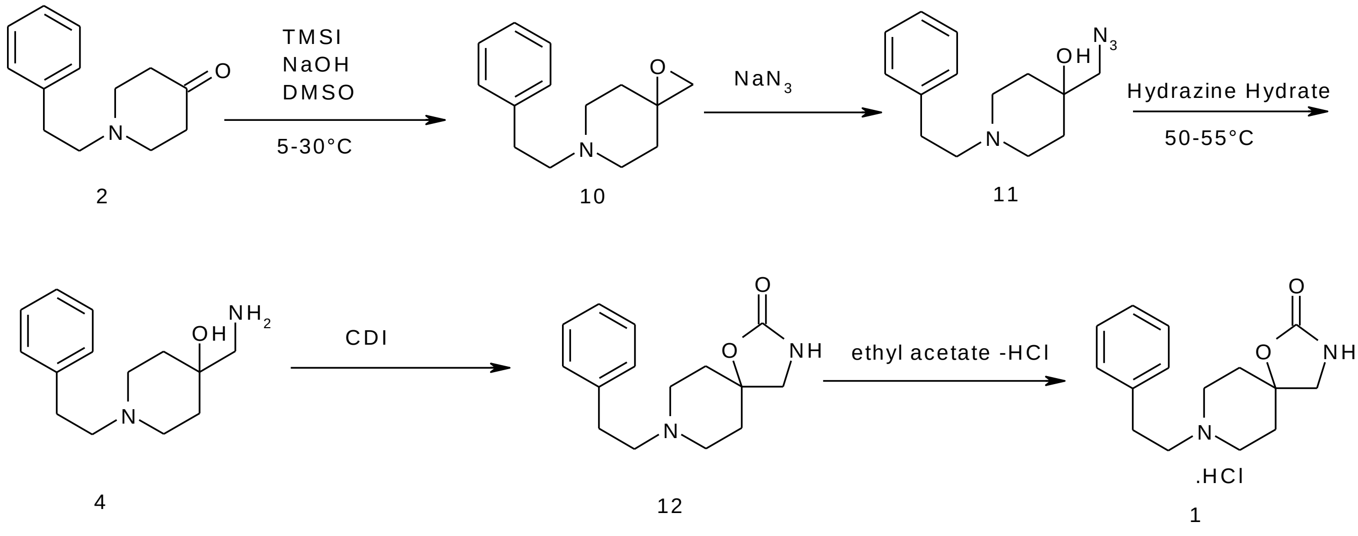


Figure 4: Synthesis scheme 3.

Scheme -4

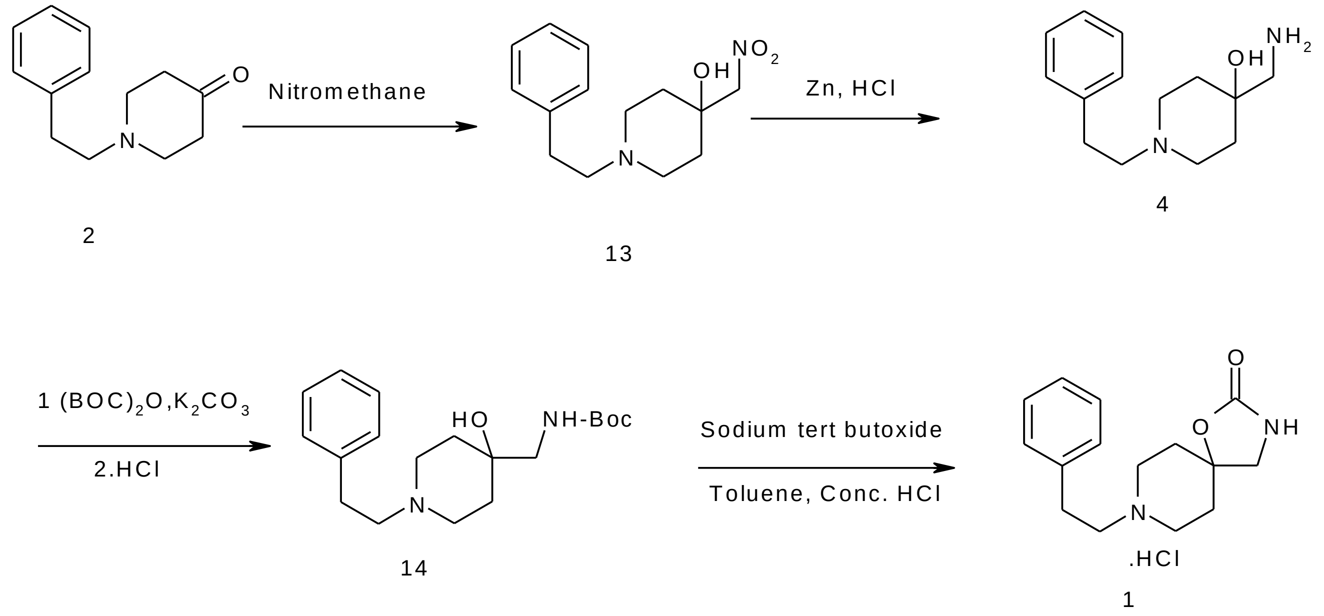


Figure 5: Synthesis scheme 4.

Experimental Section

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufaturers.^{1}HNMR spectra and ^{13}C NMR $CDCl_3$ and DMSO-d_6 and mass spectra were determined on an API-2000LCMS mass spectrometer from Biosystems.

Example 1 : Preparation of 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (4)

6-(2-phenylethyl)-1-oxa-6-azaspiro [2.5] octane (10)(150 g), was dissolved in methanol (750ml) and gradually added to the 10-15°C precooled aqueous ammonia (3000 ml) with continued stirring. The reaction was stirred for 3 hrs. at 15°C to 30°C.The reaction progress was monitored by HPLC for the complete conversion of6-(2-phenylethyl)-1-oxa-6-azaspiro [2.5] octane to 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (4). On the confirmation of unreacted compound (10) below 5%, the reaction mixture was subjected for concentration to arrive at 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (4)

Yield: 130g

Purity: 94.75%

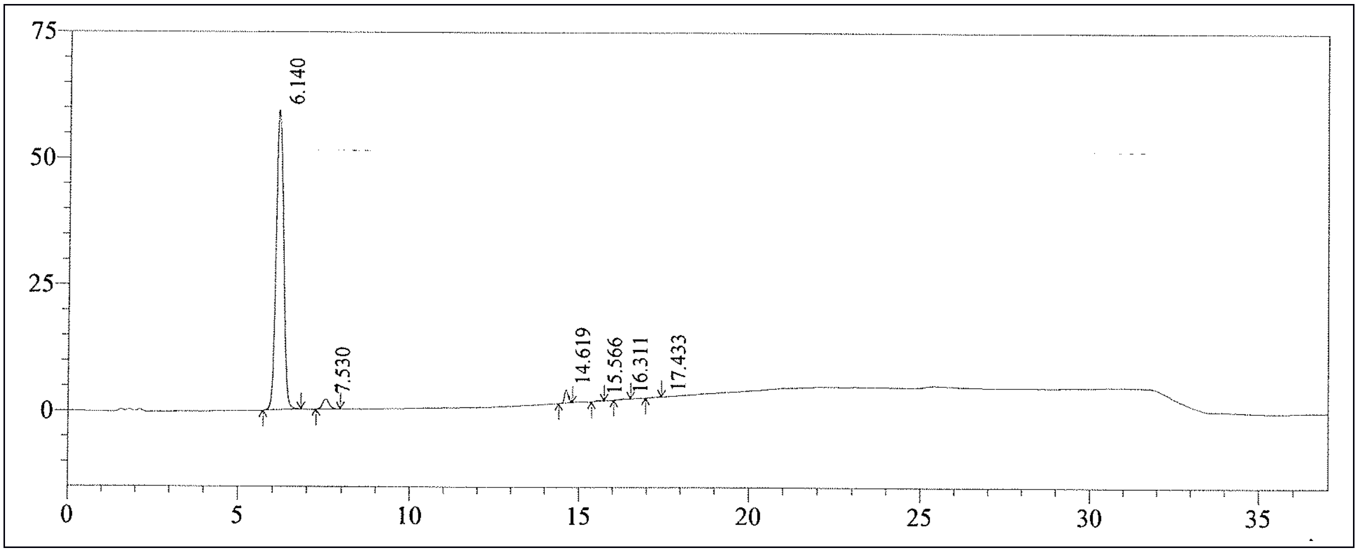


Figure 6: 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (4) related substances by HPLC

^{1}H NMR (CDCl3): δ 1.59-1.62 (m, 4H, NH_2, 2(CH_2)), 2.35(brs, 3H, 2H, CH_2), 2.43-2.51 (m, 2H, CH_2),2.64-2.68(m, 4H, 2(CH_2)),2.78-286 (m,4H,2(CH_2)) 7.17-7.30 (m 5H, Ar-H).

Infrared spectroscopy:3293 –OH stretch,2940 –C-H, aliphatic stretch, 1317 –C-N stretch,1111 –C-O stretch; **Mass M/Z:** $(M+H)^+$ 235.2.

Example 2: Preparation of 4-tertiary-butoxy aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (14)

Compound (4) (100), obtained in Example 1, was mixed with Sodium hydroxide (59.0 g) and the mixture was cooled between 20^0C and 30^0C. Di-tertiary butyl dicarbonate (214.4 g) in methanol (300 ml) was then gradually added to it with continued stirring. The resulting mixture was stirred at 25°C to 35°C till the completion of reaction as monitored by HPLC.

After completion of the reaction, water was added to the stirred reaction mass, followed by the addition of toluene with continued stirring. Separation and concentration of the organic layer provided 4-tertiary-butoxy aminomethyl-1-(2-phenylethyl)-piperidin-4-ol which was diluted with dichloromethane (500ml). The organic layer was separated and concentrated to give 4-tert.butoxyaminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (14).

Yield: 150g

Example 3 : Preparation of Fenspiride (1)

Sodium tertiary butoxide (47.3g) was gradually added to a mixture of toluene (800 ml) and compound (14)(145g), obtained in example 2, with stirring and the reaction mass heated between 95°C and 110°C, till completion of the reaction, as monitored by HPLC. The reaction mass was cooled and concentrated under reduced pressure, followed by the addition of water and filtration.

Ethyl acetate and water were then added to the solid obtained after filtration and heated between 35°C and 45°C. Organic layer separation followed by concentration gave a residue. Gradual addition of ethyl acetate to the residue separated out Fenspiride base, which was filtered after cooling. The wet cake was optionally washed with ethyl acetate and dried under a vacuum.

Fenspiride base (120 g) dissolved in dichloromethane (720 ml) at room temperature and 10% solution of hydrogen chloride in ethyl acetate (360 ml) is gradually added to the solution at room temperature. After completion of the reaction, as monitored by TLC, the reaction mass is concentrated, and ethyl acetate is added to the residue. Filtration and drying of the resulting solid yields Fenspiride hydrochloride (1).

Yield: 110g

Purity: 99.9%

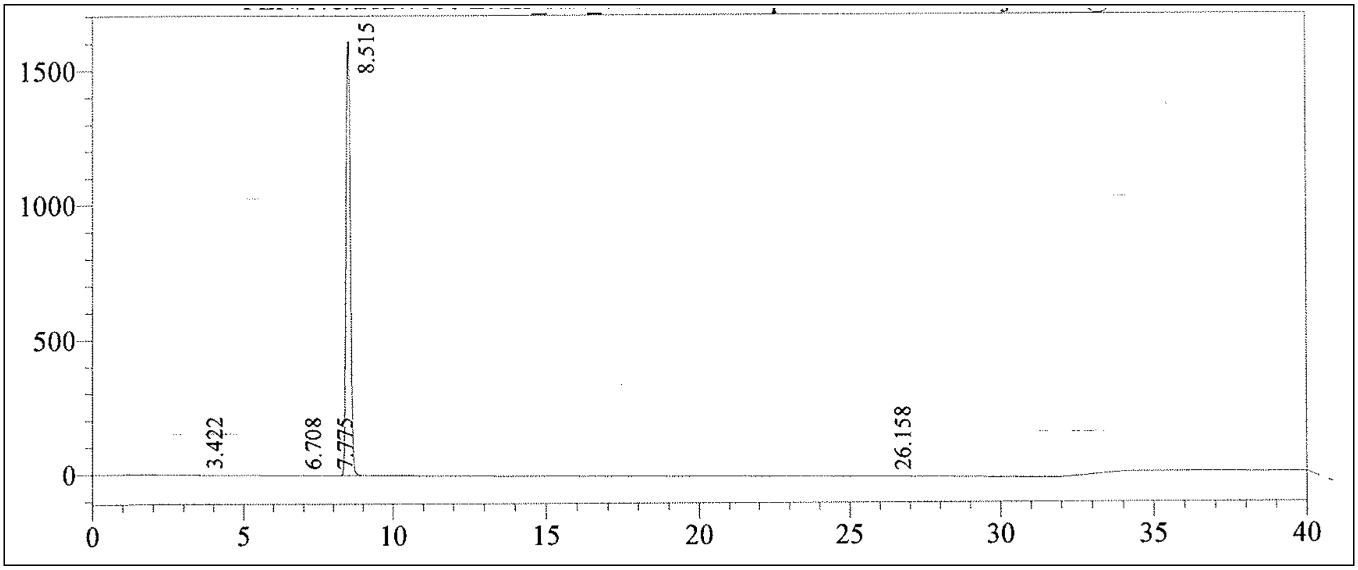


Figure 7: Fenspiride HCl (1) related substances by HPLC

^{1}H NMR (DMSO D6): δ 2.07-2.21 (m, 4H, 2(CH_2)), 3.05-3.15 (m, 4H, 2(CH_2)), 3.28-3.56 (m, 6H, 3(CH_2)), 7.23-7.36(m, 5H, Ar-H), 7.69-7.272 (2S 1H, NH_2), 11.13 & 11.23(2brs 1H, HCl).

^{13}C NMR (DMSO D6): 29.36 (CH_2), 29.64 (CH_2) 31.40 & 32.23 (CH_2), 47.75 (CH_2), 47.93(CH_2), 48.33 & 49.66 (CH_2), 54.77&56.22 (CH_2), 76.16& 77.50(C), 126.77 (CH), 128.68 4(CH), 137.21 (C), 157.29 & 157.38 (CO),

Infrared spectroscopy: 3210 –NH stretch, 3167 –C-H aromatic stretch, 1748 -C=O stretch, 1254 –C-N stretch, 1076 –C-O stretch;

Mass M/Z: $(M+H)^+$ 261.3.

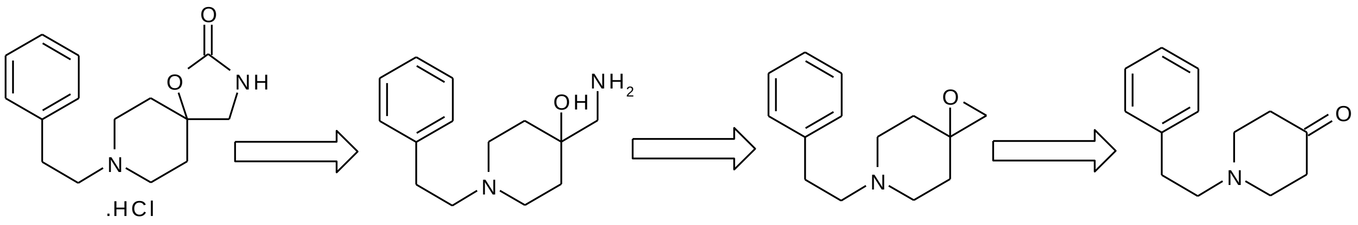
CHN analysis: - %C (61.19%), % H (6.96%), %N (9.47%)

Results and discussion

The available literature on Fenspiride hydrochloride gives numerous methods of preparation that are full of hazardous reagents. As part of our ongoing efforts toward developing an efficient, commercially viable process of generic drugs, we decided to look for a better process involving simpler reagents/reaction conditions that result in hazard less manufacturing of Fenspiride. To meet our requirement, it is needed to enhance the batch size and exclude the hazardous reagent from the process

Amino alcohol intermediate - (4) synthesis involves the hazardous reagents, hence we focused on the amino alcohol intermediate - (4) synthesis. Specifically, we decided to eliminate the use of reagents like LAH, NaN_3, and Hydrazine from the synthesis. To make the hazard-free manufacturing of Fenspiride HCl, we came up with a strategy from pyridone – (2) via epoxide- (10) which could be easily converted to the critical/penultimate amino alcohol intermediate - (4) and subsequently Fenspiride HCl.

Scheme-5:- Retrosynthetic presentation of the proposed route.



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4

10

2

Figure 8: Synthesis scheme 5.

Scheme-6

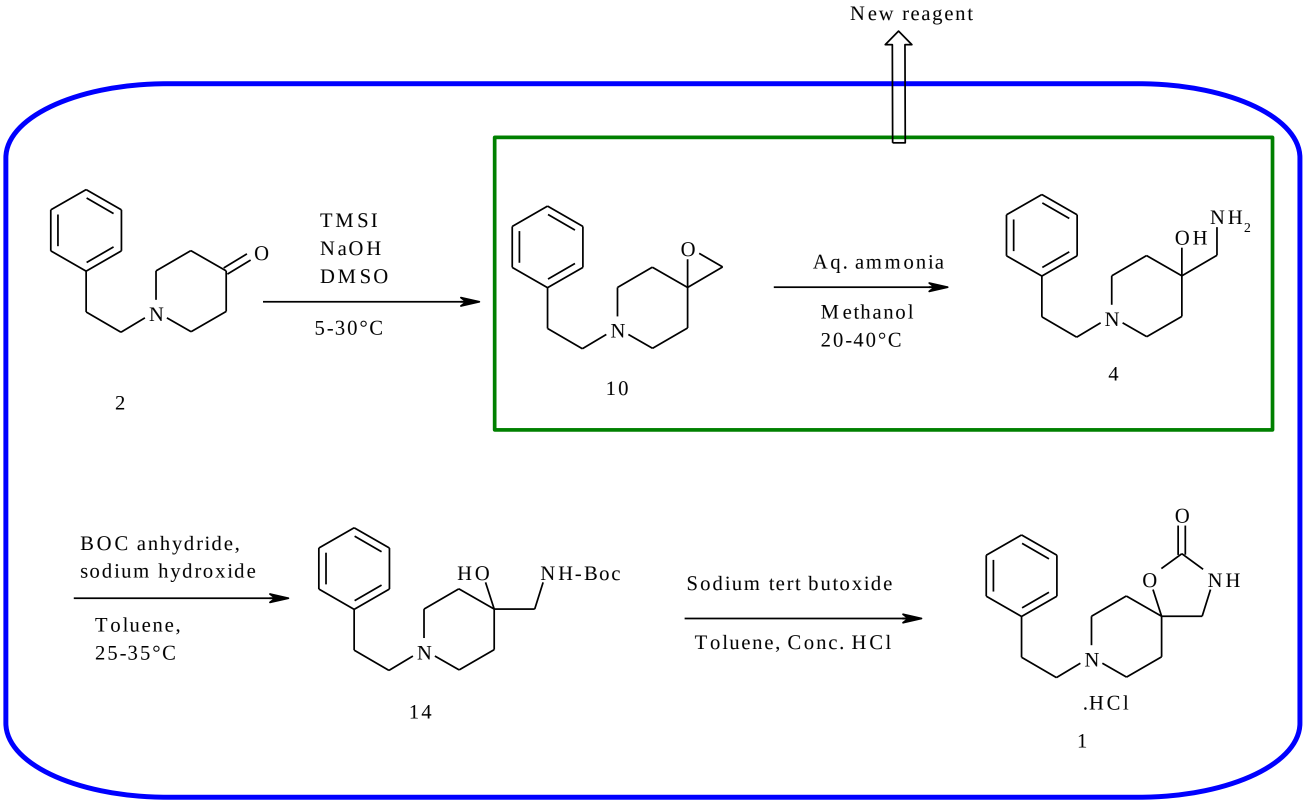

Figure 9: Synthesis scheme 6.

Starting with compound 2, on base promoted reaction with trimethyl sulphoxonium iodide provided epoxide derivative (10) with good quality and yield (Scheme 6). Using this route, we manufactured the epoxide derivative (10) on 150 kg scale

The reaction mainly involves the epoxide ring opening by aqueous ammonia and which yields in the C-N bond formation. Pursuant, to our retrosynthetic strategy, epoxide ring opening of compound (10) with the aqueous ammonia was affected with the mild condition using aq ammonia as a base and reagent in methanol at room temperature to furnish the critical intermediate- (4) with excellent yield and purity (scheme no 6).later we protected the amine -4 as its BOC derivative. The BOC-protection was attempted the cyclisation (isoxazolidone formation) of intermediate (14) under basic conditions, which would directly provide us the desired Fenspiride free base and subsequently HCl salt (1).

CONCLUSION

In conclusion, we developed a new process for the large scale manufacturing of Fenspiride hydrochloride involving simple process reagents/conditions. The article describes the synthesis of 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol using aq. ammonia as a new reagent in the synthesis. Which abolish the reagents, sodium azide, KCN, LAH nitromethane, hydrazine from the process and make the process simple and robust. The advanced process avoids the use of explosive reagents like nitromethane, and lethal reagents like palladium, zinc, which was used in the earlier synthetic routes of intermediate-4. The new synthesis makes the process cost-effective and commercially viable. Considering the operational simplicity on an industrial scale, all the chemicals and reagents which are used in the present route are very easy to handle on large-scale application.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ASSOCIATED CONTENT

Supporting Information:

Spectral Copies of IR, ESI-MS, ^{1}H NMR, ^{13}C NMR and Elemental analysis of compound 4 ,1. This material is available after references

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