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# An Improved Scalable Process for Synthesis of Piperidin-4-yl-carbamates

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An efficient route for the synthesis of methyl piperidine-4-yl-carbamate *para*-toluene sulfonate salt has been developed. The synthesis involves the reductive amination of 1-benzylpiperidin-4-one with ammonia using Raney-Ni as a catalyst followed by de-protection of benzyl group and finally by making its salt. The advantage of this methodology includes use of easily available commercial raw materials and shorter reaction times with high yields makes this process most viable for large scale manufacturing methyl piperidine-4-yl-carbamate salts.

**Keywords: 1-Benzylpiperidin-4-one, Raney-Ni, *p*-Toluene sulfonate, JAK inhibitor, Serotonin receptors.**

## INTRODUCTION

Nitrogen containing heterocyclic compounds having basic nature is of much potential use in biological importance. The design of newer strategies for the synthesis is an important area of research in organic chemistry. Piperdinyl compounds and its salts and solvates have greater importance in the organic chemistry for making and designing in many drugs. The compounds with much biological importance in the research and development attained a much focus for the generation of new piperidinyl compounds and large number of compounds has been synthesized.

The new synthetic compound served as a building block for the JAK (Janus Kinase) JAK1, JAK2 and JAK3 family inhibitor activity [1,2]. Tyrosine kinase is an enzyme that specially phosphorylates tyrosine residues of proteins and plays an important role in intracellular signal transduction system involved in a wide range of biological functions such as cell survival, differentiation, proliferation, secretion doing. By binding cytokines to cytokine receptors, JAK is phosphorylated and phosphorylates the tyrosine residues of the receptor.

Piperidine derivatives have been associated with much valuable biological activity such as HIV-mediated diseases and as serotonin receptor agents [3]. There is a tremendous use in the inhibiting an activity in the monoamine receptor. This invention relates with pharmacokinetic properties for the treatment of symptoms, diseases and disorders associated with monoamine receptors, including serotonin receptors.

The commercial activity of the above API's (Fig. 1) which has a great activity of inhibition and exhibited good results in $IC_{50}$ values. The piperidine ring is a structural feature of many alkaloids and drug candidates and there were many of piperidine compounds mentioned in clinical and preclinical studies. Several piperidine subunits display important biological properties like antiviral, antidepressant effects, cytotoxic activity and antimalarial activity. The synthetic apporach is shown in the below schematic representation having a multi beneficial in drug skelton.

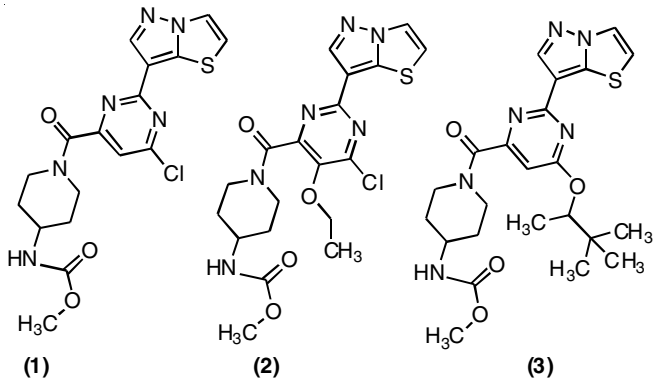



Fig. 1. Commercial API's containing piperidine-4-yl)carbamates moieties

## EXPERIMENTAL

Commercially available raw materials were used without purification. Melting points and boiling points measured with an electronic melting apparatus and were not corrected. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded in $CDCl_3$ as solvent on a 400 MHz Bruker spectrometer using tetramethylsilane

(TMS) as an internal standard and Deuterium exchange was also recorded. Chemical shifts were calculated in terms of "ppm". The high-resolution mass spectrum (HRMS) was also recorded.

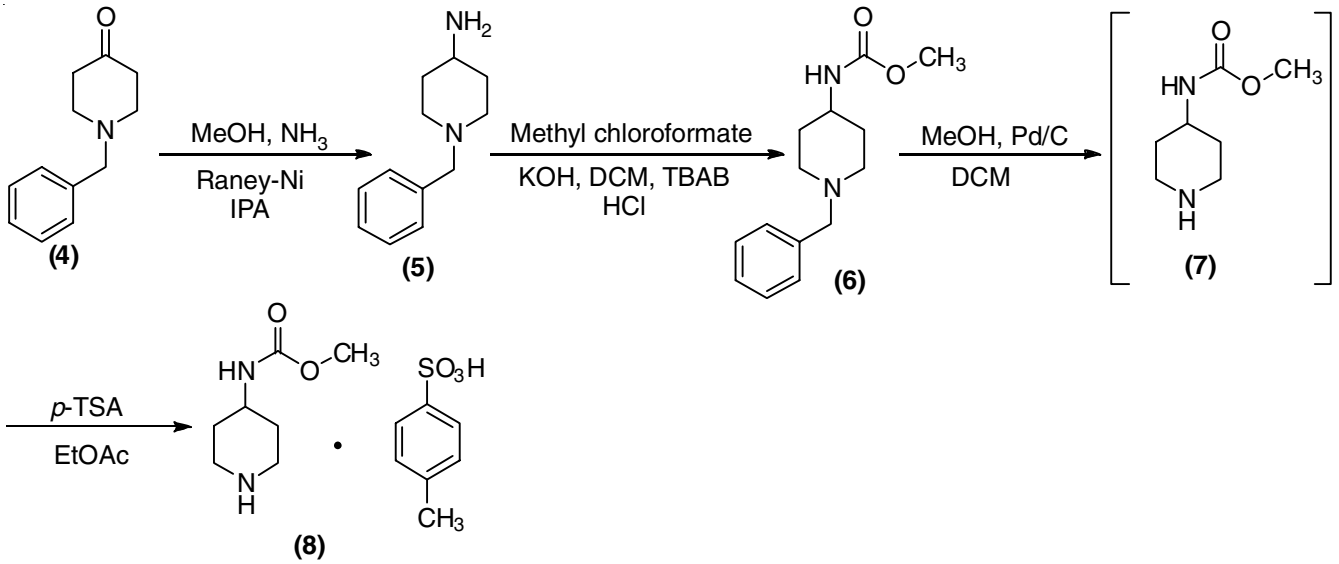
**Synthesis of 1-benzylpiperidin-4-amine (5):** Charge 1-benzylpiperidin-4-one (5 kg) (**4**) into pressure reactor at 25-35 °C and charge methanol (2 vol) to it. Stir the reaction mixture for 10-15 min in a pressure reactor at 25-35 °C. Charge Raney-Ni (10 %) into pressure reactor at 25-35 °C. Apply 0.5 kg nitrogen gas and stir the reaction mixture for 5 min. Release the nitrogen gas and apply 0.5 kg of hydrogen gas pressure and stir the reaction mixture for 5 min. Release the hydrogen gas and Pass ammonia gas to the above mass at below 10 °C. Raise the temperature to 25-35 °C and purge hydrogen gas 2-3 kg pressure. Pass hydrogen gas and monitor the completion of reaction by gas chromatography. Distilled out the reaction mixture with methanol at 100 °C. Cooled the reaction mixture to room temperature and charge isopropanol (1 vol). The reaction mixture was neutralized with conc. HCl at pH 1.0-2.0 at room temperature. Refluxed the reaction mixture and raise the temperature to 75-80 °C for 30 min. Added isopropanol to mass and check the material formation. Cooled the reaction mixture to 10 °C and maintained for 30 min. Filtered and washed with water and chilled isopropanol. Charge the wet cake and adjust the pH with 13.0-13.5 by using caustic-lye solution. Added toluene to the above filtered cake and stirred for 30 min. Separate the aqueous and organic layers. Washed the aqueous layer with toluene and combined organic layers with liq. ammonia. Stirred for 15 min and separate product layer. Distilled out toluene and pale yellow oily liquid with 99.60 % purity is obtained. Yield 90 % (4.52 kg), boiling point: 281.2 ± 29.0 °C at 760 torr.; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.27-7.16 (m, 5H), 3.42 (s, 2H), 2.77-2.74 (d, 2H), 2.60-2.53 (m, 1H), 1.98-1.92 (m, 2H), 1.79-1.68 (d, 2H), 1.37-1.28 (m, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$): δ 137.9, 128.3, 127.4, 126.2, 62.3, 51.7, 45.0, 35.2.

**Synthesis of methyl 1-benzylpiperidin-4-yl-carbamate (6):** Charge dichloromethane into glass reactor at 25-35 °C and charge the above obtained 1-benzyl piperidine-4-amine (4.52 kg) (**5**). Cool the reaction mixture to 5-15 °C. Add slowly potassium hydroxide (1.2 eq) in water solution to the glass reactor at 5-15 °C. Charge *tert*-butyl ammonium bromide (TBAB) (0.1 %) to the above cooling reaction mixture and maintain for 30 min. Add slowly methylchloroformate (1.0 eq) *i.e.* (1.1 kg) solution at 5-15 °C for 2 h. Dissolve methyl chloroformate in dichloromethane 1 vol). Maintain the reaction mixture for 2-3 h at 5-15 °C. Monitor the reaction progress by TLC. After competition of the reaction raise the temperature to 25-35 °C. Add water to the reaction mixture and stir for 15 min. Separate the reaction mixture and wash the organic layer with water. The organic layer was charged into glass reactor and adjust the pH with conc. HCl (0.45 v) at 25-35 °C (pH 1.0-2.0) and stir for 30 min separate the aqueous layer and organic layer. Wash the aqueous layer with dichloromethane and take aqueous layer and adjust pH with potassium hydroxide (pH 8.0-9.0) and stir for 2-2.5 h at 25-35 °C. Dry the material at 50-60 °C for 8-10 h to obtain the product as off-white powder with 99.82 % purity. Yield 92 % (5.03 kg), melting point: 80 ± 3 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.27-7.19 (m, 5H), 3.61 (s, 3H), 3.50 (s, 1H), 3.45 (s, 2H), 2.77-2.74 (s, 2H), 2.09-2.03 (s, 2H), 1.89-1.86 (s, 2H), 1.46-1.36 (m, 2 H); $^{13}$C NMR (400 MHz, $CDCl_3$): δ 156.19, 138.29, 129.03, 128.15, 126.97, 62.99, 52.11, 51.85, 48.12, 32.47.

**Synthesis of methyl-piperidin-4-yl, carbamate.*p*-TSA salt (8):** Charge methanol (5 vol) into pressure reactor and charge methyl 1-benzylpiperidin-4yl-carbamate (5.03 kg) (6) at 25-35 °C. Add slowly (0.15 t) of 5 % wet Pd/C into pressure reactor. Purge 0.1 kg of nitrogen into the reaction mixture and stirred for 5 min. Release the nitrogen gas and pass 0.1 kg of hydrogen gas to the reaction mixture and stirred for another 5 min. Release the hydrogen gas and purge fresh hydrogen gas for 5-6 kg pressure. Heat the reaction mixture to 50-55 °C for 2-3 h. Monitor the completion of reaction by TLC. If TLC complies cool the reaction mixture to 25-35 °C then release hydrogen gas. Filter the reaction mixture through hyflo-bed under nitrogen atmosphere and wash with methanol (1 vol). From filtrate, distilled out methanol completely under vacuum at below 50 °C. Codistilled with dichloromethane vacuum at below 50 °C and check methanol content (limit is below 5 %) by gas chromatography to obtain the crude product **7**. Charge the obtained product to glass line reactor and charge ethyl acetate (125 L) and stir for15-30 min at 25-35 °C. Cool the reaction mixture to 15-20 °C. Dissolve *p*-TSA (4.32 kg) in ethyl acetate (40 L) and add slowly to the above mixture and adjust pH 1-2 over a period of 2-2.5 h at 15-20 °C. Maintain the reaction mixture for 2 h and filter, wash with ethyl acetate (1 vol) and suck dry for 1 h. Dry the material under vacuum for 6-10 h at 40 °C. Check LOD and moisture content (limit is 2 %) if LOD and MC passing unload the material. Obtain the title compound as white colour powder to off-white colour powder with 99.82 % purity. Yield 95 % (6.4 kg), melting point: 162-164 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.87 (bs, 1H), 7.70-7.68 (d, 2H), 7.15-7.14 (d, 2H), 5.54 (bs, 1H), 3.62(s, 1H), 3.57 (s, 3H), 3.39-3.36 (t, 2H), 2.92-2.87 (t, 2H), 2.35(s, 3H), 1.96 (m, 2H), 1.77-1.68 (m, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$): δ 156.28, 141.36, 140.70, 129.00, 125.66, 51.90, 45.32, 42.78, 28.33, 21.20. HRMS (ES+ve) calcd. for $C_{14}H_{22}N_2O_2S$ $[M+Na]^+$ cal. 330.12, found: 353.2.

## RESULTS AND DISCUSSION

After the literature scouting for the synthesis of piperidin-4-yl-carbamates, we have developed an efficient scalable process with the economically benign, commercially available raw materials. As shown in **Scheme-I**, reductive amination reaction of commercially available 1-benzylpiperidin-4-one (**4**) [4-13] and ammonia in presence of methanol and isoproponal solvent catalyzed by Raney-Ni reduction [21-23] resulting an intermediate of 1-benzylpiperidine-4-amine (**5**) [14-16] as a pale yellow oily liquid with an isolated yield of 90 %. The reaction of 1-benzylpiperidin-4-amine (**5**) with methyl chloroformate by using potassium hydroxide as base, tetrabutylammonium broimde (TBAB) as phase transfer catalyst in dichloromethane, hexane and with water as solvents at a room temperature gave carbamate product (**6**) as an off-white powder with 92 % yield. Deprotection *i.e.*, de-benzylation of carbamate intermediate **6** with Pd/C in methanol dichloro-




**Scheme-I:** Synthesis of N-piperidin-4-yl-carbamic ester salts with Raney-Ni catalyzed

methane furnished methyl piperidin-4-yl-carbamate (**7**) [17,18] which can be taken for salt formation with *p*-TSA in ethyl acetate yields a stable compound methyl piperidin-4-yl-carbamate.*p*-TSA salt (**8**) as a white colour solid with 90 % yield.

## Conclusion

A new convenient and efficient process is developed for the synthesis of methyl piperidin-4-yl-carbamate.*p*-TSA salt. By this route one can easily manufacture in large scale batches by using the economically low cost chemicals. The method provides preparation of many active pharma ingredients.

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