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PROCESS OPTIMIZATION AND GREEN CHEMISTRY APPROACH DURING SYNTHESIS AND CHARACTERIZATION OF 2-CHLOROMETHYL-3,5-DIMETHYL-4-METHOXY PYRIDINE HYDROCHLORIDE

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ABSTRACT

The present invention is related to the synthetic preparation of 2-chloromethyl-3,5 Dimethyl-4-methoxy pyridine hydrochloride by using a greener chemistry approach and process optimization. The method consists of three steps. The first step is the methoxylation of 3,5- Dimethyl-4-nitropyridine-1-oxide by using sodium hydroxide and methanol to obtain 3,5 Dimethyl-4-methoxypyridine-1-oxide. The second step is methylation followed by hydroxylation of 3,5 Dimethyl-4-methoxypyridine-1-oxide by using dimethyl sulfate, Ammonium persulphate, hydrogen peroxide, and water to obtain 2-hydroxymethyl -3,5-dimethyl -4-methoxy pyridine. The third step is chlorination of 2-hydroxymethyl-3,5-dimethyl- 4-methoxy pyridine to obtain 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride. The synthesis method of the 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride was carried out without isolation of the first and second steps. It improves productivity and reduces the use of solvents. Mass spectra, Nuclear Magnetic Resonance, and C, H, N, and O elemental analysis characterized 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride product.

Keywords: Synthesis, Characterization, Omeprazole, Nuclear Magnetic Resonance Spectroscopy, Mass Spectroscopy, Green Chemistry, Process Optimization.

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INTRODUCTION

This invention is related to a method for preparing 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride compound. 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride is a useful pharmaceutical intermediate to synthesize omeprazole and other organic compounds. Omeprazole is mainly used to reduce the amount of acid in the stomach. It is widely used to treat heartburn indigestion and acid reflux. It is also taken to prevent and treat stomach ulcers. Omeprazole is used together with clindamycin or amoxicillin to kill helicobacter pylori. Omeprazole is a type of medicine called a proton pump inhibitor (PPI). 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride is a key intermediate for the preparation of omeprazole. The compound 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride can be produced from 3,5-dimethyl-2-hydroxymethyl-4-methoxypyridine. There are several ways to produce 3,5-dimethyl-2-hydroxymethyl-4-methoxypyridine. The Taiwanese group published the procedure of pyrone, pyridone, and pyridine derivatives and it can be converted to 3,5-dimethyl-2-hydroxymethyl-4-methoxypyridine[1]. There are two disadvantages to this process. It consists of a large number of steps and low availability of raw materials. These two factors affect the product yield. According to the US patent 5,616,713, the process for preparing 2-hydroxymethyl-3,5-dimethyl- 4-methoxy pyridine consists of five steps[2]. It can be produced from 2-methyl-1-penten-1-alkoxy- 3-one. The first step is the acylation of 2-methyl-1-penten-1-alkoxy-3-one to obtain 2-alkoxycarbonyl-3,5-dimethyl-4-pyrone. The second step is the Ammonolysis of 2-alkoxycarbonyl-3,5-dimethyl-4-pyrone to obtain 2-alkoxycarbonyl-3,5-dimethyl-4(1H)-pyridone. Third step is halogenations of 2-alkoxycarbonyl-3,5-dimethyl-4(1H)-pyridone to obtain 2-alkoxycarbonyl-4-halo-3,5-dimethylpyridine;Fourth step is methoxylation of 2-alkoxycarbonyl-4-halo-3,5-dimethylpyridine to obtain 2-methoxycarbonyl-3,5-

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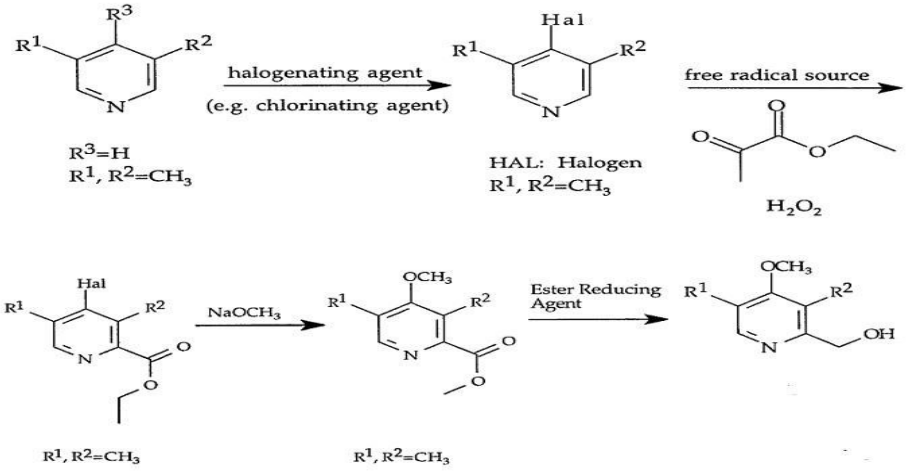
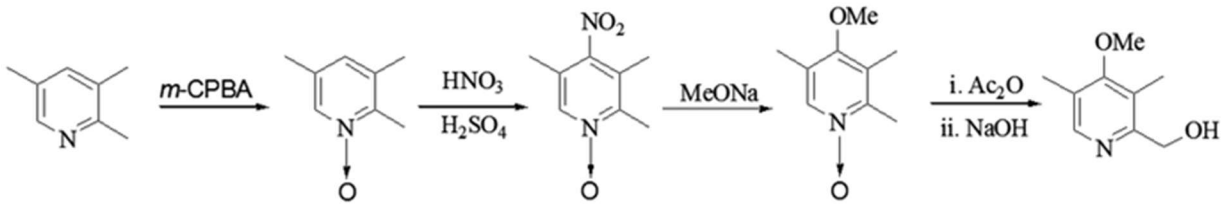
dimethyl-4-methoxy pyridine. The fifth step is reducing 2-methoxy carbonyl-3,5-dimethyl-4-methoxypyridine to obtain 3,5-dimethyl-2-hydroxymethyl-4-methoxy pyridine. This process consists of a large number of steps, poor yield, and low availability of raw materials. In 1997 Zoghbi Michel and Chen Liquin described the process of 3,5-dimethyl-2-hydroxymethyl -4-methoxypyridine[3] It consists of five steps. The first step is chlorination of 3,5-Lutidine by using Thionyl chloride to obtain 4-Chloro-3,5-dimethylpyridine hydrochloride. After the neutralized product is converted into 4-chloro-3,5-dimethylpyridine, the Second step is the reaction of 4-chloro-3,5-dimethylpyridine with Ethyl pyruvate to obtain 2-Pyridinecarboxylic acid, 4-chloro-3,5-dimethyl-, ethyl ester. The third step is the methoxylation of 2-Pyridinecarboxylic acid, 4-chloro-3,5-dimethyl, ethyl ester to obtain Pyridine carboxylic acid 3,5-dimethyl-4-methoxy- methyl ester. The fourth step is the reduction of Pyridine carboxylic acid 3,5-dimethyl-4-methoxy- methyl ester to obtain 3,5-dimethyl-2-hydroxymethyl -4-methoxypyridine. The fifth step is chlorination of 3,5-dimethyl-2-hydroxymethyl-4-methoxypyridine to obtain 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride. The reaction scheme-1 of each step is as per given below:



Scheme-1

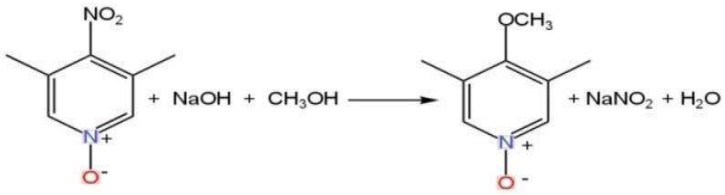
Brandstrom *et al.*[4] US4620008, Senn-Bilfinger Joerg[5] US4472409, Dharmpal[6] US5670526, European Patent Publication No. 0103553, Canadian Letters Patent 1,234,118, United States Patents 4,544,750 and 4,620,008 described the process of preparing 3,5-dimethyl-2-hydroxymethyl-4-methoxypyridine. The starting material 2,3,5- trimethyl pyridine can be obtained by methylation of 3,5-dimethyl pyridine. The process of 2-chloromethyl-3,5-Dimethyl-4-methoxy pyridine hydrochloride consists of five steps including the first step oxidation of 2,3,5-trimethyl pyridine to obtain 2,3,5-trimethylpyridine-1-oxide. The second step is the nitration of 2,3,5-trimethylpyridine-1-oxide to obtain 2,3,5-trimethyl-4-nitropyridine-1-oxide. The third step is the methoxylation of 2,3,5-trimethyl-4-nitropyridine-1-oxide to obtain 2,3,5-trimethyl-4-methoxy pyridine-1-oxide. The fourth step is acetylation and hydrolysis of 2,3,5-trimethyl-4-methoxy pyridine-1-oxide to obtain 3,5-dimethyl-2-hydroxymethyl-4-methoxypyridine.[2,6,7,8] The fifth step is the chlorination of 3,5-dimethyl-2-hydroxymethyl-4-methoxypyridine to obtain 2-chloromethyl-3,5-Dimethyl-4-methoxy pyridine hydrochloride. The reaction scheme-2 of each step is as per given below:



Scheme-2

Acetic anhydride was used in Scheme-1 and Scheme-2. Acetic anhydride is banned in many countries because it is used as the major precursor for the production of heroin and is also used in the manufacture of improvised explosive devices (IEDs). Therefore these two route schemes 1 and 2 are not suitable for commercial production. According to the Chinese patent CN114805193, all three steps are isolated So

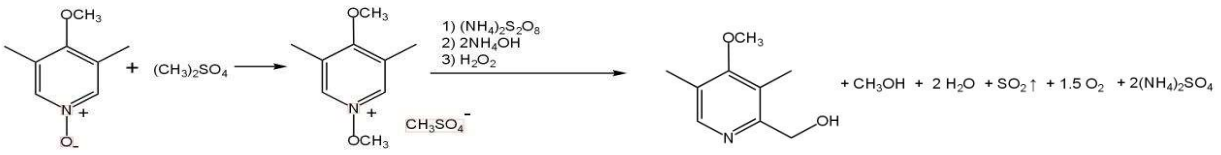
solvent and energy consumption is high by adopting this process. Brandstrom *et al.* disclosed the process of preparing 3,5-dimethyl-2-hydroxymethyl-4-methoxypyridine from 3,5-Lutidine. The starting material 3,5-Dimethyl-4-Nitro pyridine-N-oxide can be prepared from 3,5-Dimethyl pyridine.[7-23] There are disadvantages to using this process. The first one is the large number of solvents and reagents used. The second one is the large amount of effluent generation and the third one is the high energy consumed. The objective of the present invention is to optimize reaction conditions, process parameters, and green chemistry approach to the synthesis of omeprazole intermediate 2-chloromethyl-3,5-dimethyl- 4-methoxypyridine hydrochloride. In the pharmaceutical sector process development and process optimization is necessary. To function on a large scale, the operation should be simple, safe, and straightforward. Today, green chemistry is a common concept in process chemistry. Green chemistry deals with the process that conserves energy, minimizing the use of solvents and reagents during the process. By adopting these approaches, we can contribute to a greener and more sustainable future. The present invention conserves the energy, minimizing the use of solvent and reagent during the synthesis of 2-chloromethyl-3,5-dimethyl-4-methoxypyridine hydrochloride. The new invention method is more economical for preparing 2-chloromethyl-3,5-dimethyl- 4-methoxypyridine hydrochloride. There are three steps to produce 2-chloromethyl-3,5-dimethyl-4-methoxypyridine hydrochloride. The first step reaction scheme for preparing 3,5-Dimethyl-4-methoxypyridine-1-oxide from 3,5-Dimethyl-4-Nitropyridine-1-oxide as per below Scheme-3.



Scheme-3

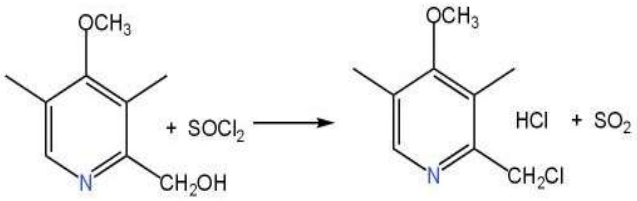
According to Brandstrom *et al.* reaction was taken in the presence of a methanol solvent. After the reaction was completed, the mass was neutralized by Conc. Hydrochloric acid So excess sodium methoxide is converted into methanol and sodium chloride. The mixture of methanol and water was distilled. After the distillation, methylene dichloride was added in residue to the dissolved product and salt sodium chloride remained in solid form. Filter the mass to remove the sodium chloride salt. The filtrate evaporated. The product remains in residue. Add the petroleum ether and isolate the product by filtration technique.[4] The purpose of the present invention is to process optimization and reduce the use of solvents. The above-mentioned invention is achieved through the mass being neutralized by sulphuric acid instead of conc. Hydrochloric acid. The excess sodium methoxide is converted into methanol and sodium sulfate. Add dry salt sodium sulfate which is the byproduct of this step if required. The role of adding dry sodium sulfate is to absorb the water which is generated during the reaction. After adding the salt, filter the mass to remove the salt and use the filtrate mass in the next step without isolation. The benefit of using sulphuric acid is it does not contain water so salt remains in solid form after the neutralization. There are three major benefits from the present invention. First, we get moisture-free methanol which is recycled without purification. Second, the new invention method does not require petroleum ether for purification and methylene dichloride solvent for extraction. Ether easily explodes, posing a safety hazard, and the high cost of solvents is not convenient for production. Third, the new invention avoids extraction, methanol purification, methylene dichloride distillation, and product filtration which saves great energy consumption. The second step reaction scheme for preparing 3,5-Dimethyl-4-methoxy-2-hydroxy methyl pyridine from 3,5-Dimethyl-4-methoxypyridine-1-oxide as per below scheme-4.

According to US4620008 patent 3,5-Dimethyl-4-methoxypyridine-1-oxide was dissolved in methanol. Dimethyl sulfate was added dropwise. pH is adjusted by adding 10 M NaOH and reflux for one hour. Add a second lot of Dimethyl sulfate and reflux for one hour and thirty minutes. The reaction mass was stirred overnight at room temperature to prepare 3,5-Dimethyl-4-methoxypyridine-1-methoxy dimethyl sulfate salt. Thereafter reaction mass was heated to reflux and slowly added Ammonium persulphate. After the addition, the mass was refluxed for one hour and thirty minutes and stirred overnight at room temperature. After reaction completion add methanol to precipitate salt.



Scheme-4

filter the salt and evaporate methanol from the filtrate mass. The remaining mass was adjusted to pH 10 using a caustic solution. After the pH was adjusted the product was extracted by methylene dichloride. The organic layer was dried by using sodium sulfate evaporation and dry yielding 3,5-Dimethyl-4-methoxy-2-hydroxy methyl pyridine[4]. In the above process, the time cycle is approximately thirty hours and the methanol quantity is very high. The new invention process reduces the time cycle and quantity of methanol to half. In the above process caustic solution is used for neutralization so the mixture of sodium sulfate and ammonium sulfate is generated as a waste. By applying the new invention process Ammonium sulfate is generated as a byproduct which is recycled and salable. The new invention process also avoids salt filtration and product isolation. The third step of the reaction scheme for preparing 2-chloromethyl-3,5-Dimethyl-4-methoxy- pyridine hydrochloride from 3,5-Dimethyl-4-methoxy-2-hydroxy methyl pyridine as per the below scheme-5.



Scheme-5

According to the US2005038076A1 patent 2-hydroxymethyl-3,5-Dimethyl-4-Methoxy pyridine was isolated while by using a new invention approach 2-hydroxymethyl-3,5-Dimethyl-4-Methoxy pyridine used without isolation which saves energy consumption and prevent solvent loss. The new invention process also improves the yield.

EXPERIMENTAL

Material and Methods

The starting material is 3,5-Dimethyl-4-nitropyridine-1-oxide prepared by using 3,5-Lutidine. The first step is the oxidation of 3,5-Lutidine by using hydrogen peroxide and acetic acid to obtain 3,5-dimethyl pyridine-N-oxide and the second step is nitration by using sulphuric and nitric acid to obtain 3,5-dimethyl-4-Nitro pyridine-N-oxide.[23] Sodium hydroxide, Methanol, Ammonium persulphate, sulphuric acid, hydrogen peroxide, Dimethyl sulfate, and toluene were distributed by Loba chemical. TLC plates, Thionyl chloride, Methylene dichloride, Ammonia solution, Isopropyl alcohol hydrochloric acid solution, and Isopropyl alcohol were purchased from Merck. All the chemicals were of LR grades.

General Procedure

3,5-Dimethyl-4-Nitropyridine-1-oxide was reacted with sodium hydroxide and methanol to produce 3,5-Dimethyl-4-methoxypyridine-1-oxide. Later excess sodium methoxide was neutralized by using sulphuric acid to produce sodium sulfate and methanol as byproducts. Filter the mass to remove the sodium sulfate salt. Filtrate contains methanol and 3,5-Dimethyl-4-methoxypyridine-1-oxide. Methylation and Hydroxylation of filtrate mass carried out without isolation of 3,5-Dimethyl-4-methoxy pyridine -1-oxide. Methylation was carried out in the presence of dimethyl sulfate and Hydroxylation was carried out in the presence of Ammonium persulphate, hydrogen peroxide, Ammonium sulfate, and water. After the hydroxylation, product 3,5-Dimethyl-4-methoxy-2-hydroxymethyl pyridine was extracted in toluene and a certain portion of toluene was distilled off to increase productivity. Chlorination of residual mass without isolation of 3,5-Dimethyl-4-methoxy-2-hydroxymethyl pyridine. Chlorination was carried out by using Thionyl chloride. Sulfur dioxide gas was generated during chlorination. Finally, filter the mass and purify

the 2-chloromethyl-3,5-dimethyl-4-methoxy-pyridine hydrochloride in an isopropyl alcohol hydrochloric acid solution.

Detection Method

The product 3,5-Dimethyl 4-Nitro pyridine N-oxide was characterized by Nuclear Magnetic Resonance, Mass spectra, and C, H, N, and O analysis.

Synthesis of 3,5-Dimethyl-4-methoxypyridine-1-oxide (Scheme-3)

833 ml dry methanol and 77.4 gm sodium hydroxide were charged to the round bottom flask at 25-35 ^{0}C. The resulting solution was slowly heated to reflux temperature. Reflux the resulting mass till no solid is observed in mass. 450 ml mass was distilled off to remove water that was generated during the reaction. The residual mass containing sodium methoxide solution is filled in a liquid additional funnel. In another round bottom flask charged 500 ml methanol and 250.0 gm 3,5-Dimethyl-4-Nitro pyridine 1-oxide. Stir the mass for 15 minutes. The resulting solution was slowly heated to 60-62 ^{0}C. Slowly add sodium methoxide solution dropwise within two hours at 60-65 ^{0}C. Cook the mass for two hours at 60-65 ^{0}C. The reaction completion was controlled by thin-layer chromatography (TLC). The mass is cooked for a further two hours in case 3,5-Dimethyl-4-Nitro pyridine 1-oxide is unreacted. After the complete reaction, the mass was cooled to 0-5 ^{0}C. Slowly add sulphuric acid to adjust pH around 8. Filter the mass to remove the salt. Give two times 100 ml methanol wash. Take this filtrate for the next step.

Synthesis of 3,5-dimethyl-4-methoxy-2-hydroxymethyl-pyridine (Scheme-4)

3,5-Dimethyl-4-methoxy pyridine 1-oxide was used in the next step without isolation. Charge filtrate mass in a round bottom flask. 90 gm Dimethyl sulfate was added dropwise within 15 minutes at 40-60 ^{0}C and adjusted the pH of 5.0 by using ammonium hydroxide. The mass was stirred for 15 minutes and then refluxed for one hour. Further 91.0 gm Dimethyl sulfate was added dropwise within 15 minutes at 40-60 ^{0}C and adjusted the pH of 2.8-3.2 by using ammonium hydroxide. The mass was stirred for 15 minutes and then refluxed for two hours. Cool the reaction mass to room temperature. 282.2 gm water was charged into the round bottom flask. The mixture was heated to 60-65 ^{0}C. 83.3 gm ammonium sulfate was dissolved into 168 ml water and this solution was added to the round bottom flask dropwise. The mixture was heated to 70-75 ^{0}C. After reaching temperature 23.8 gm 30% hydrogen peroxide was added dropwise within 15 minutes. The mixture was stirred for thirty minutes. 38.1 gm ammonium persulfate was dissolved into 76 ml water and this solution was added dropwise to the round bottom flask within one hour at 65-75 ^{0}C. The mixture was stirred for one hour at 65-70 ^{0}C. After one hour of cooking, the Mass was cooled to 35-40 ^{0}C, and the pH was adjusted to a pH of 2.8-3.2 by using ammonium hydroxide. The mixture was heated to 65-70 ^{0}C and stirred for 90 minutes then Mass was cooled to 35-40 ^{0}C and the pH was adjusted to the pH of 2.8-3.2 by using ammonium hydroxide. The addition of Ammonium per sulfate, cooking, pH adjustment, and further cooking was carried out four times. The mixture was stirred for twelve hours at 65-70 ^{0}C. The reaction completion was controlled by thin-layer chromatography (TLC). The mass is cooked for a further two hours in case the starting material is unreacted. Mass was cooled to 35-40 ^{0}C and pH was adjusted to the pH 2.8-3.2 by using ammonium hydroxide. If starting material 3, 5-Dimethyl- 4-methoxy pyridine 1-oxide is unreacted; the mass is cooked for a further two hours. After the complete reaction, methanol was evaporated under a vacuum below 60 ^{0}C. The mass was cooled to 30-35 ^{0}C. The pH of the reaction mass was adjusted to 9 by adding 32% caustic lye. Toluene (1.1 liters) was added and the mixture stirred vigorously for thirty minutes. The organic layer was separated. The extraction procedure was repeated with 250 ml of toluene followed by 150 ml of toluene, and the combined toluene was extracted with 450 ml of water. The upper organic layer was charged into the round bottom flask. 11.8 gm of activated carbon was added. The mixture was stirred for thirty minutes and filtered through the hyflo bed. The hyflo bed was washed with two times 100 ml toluene. The filtrate evaporated up to 40% volume till the density of residue was 0.89 gm/ml. The remaining mass is used in the next step without isolation.

Synthesis of 2-chloromethyl-3,5-dimethyl-4-methoxypyridine hydrochloride (Scheme-5)

The mixture of 3,5-dimethyl-4-methoxy-2-hydroxymethyl- pyridine and toluene was charged into the round bottom flask. The mass was cooled to -5 ^{0}C. The Thionyl chloride (181.0 gm) was added dropwise to the round bottom flask. After the addition, the temperature slowly increases up to 10-15 ^{0}C. The reaction

mixture was stirred for thirty minutes then the temperature slowly increased to 30-35 ^{0}C. The reaction mixture was stirred for four hours. The reaction completion was controlled by Thin-layer chromatography (TLC) which is coated with silica gel 60 F254 plates from Merck Co., India the mass was cooked for two hours at 30-35 ^{0}C in case 3,5-dimethyl-4-methoxy- 2-hydroxymethyl- pyridine remains unreacted. After the complete reaction, toluene was distilled off below 30 ^{0}C under a 740-755 mm Hg vacuum. The vacuum was applied for one hour at 30 ^{0}C. After releasing the vacuum 300 ml of toluene was charged into the round bottom flask. The reaction mass cooled to 20-25 ^{0}C. The reaction mixture was stirred for thirty minutes. The mass was filtered and washed with 60 ml toluene. The cake was sucked dry for thirty minutes. The cake was charged in the round bottom flask. 5% 120 ml Isopropyl alcohol hydrochloride solution was charged into the round bottom flask. The mass was stirred for thirty minutes at 30-35 ^{0}C and 10-15 ^{0}C for one hour. The product was filtered and washed with 3 times 25 ml chilled isopropyl alcohol.

RESULTS AND DISCUSSION

Characterization of the 2-chloromethyl-3,5-dimethyl-4-methoxypyridine hydrochloride as per below.

Mass Spectra

Theoretical Value Mol. Wt -185.7 gm/mol
Practical Value- 186.00 gm/mol

C, H, N, O Elemental Analysis

Theoretical Value: C-48.20%, H-6.62%, N-7.54%, O-8.61%
Practical Value: C-48.47%, H-6.01%, N-6.36%, O-8.66%.

Proton NMR Spectra

^{1}H Proton NMR δ value- 8.66 (1H singlet, pyridine ring hydrogen), 5.16 (2H singlet, -CH_2 Cl), 4.04 (3H singlet, -OCH_3), 2.3 (3H singlet, -CH_3), 2.5 (3H singlet, -CH_3).

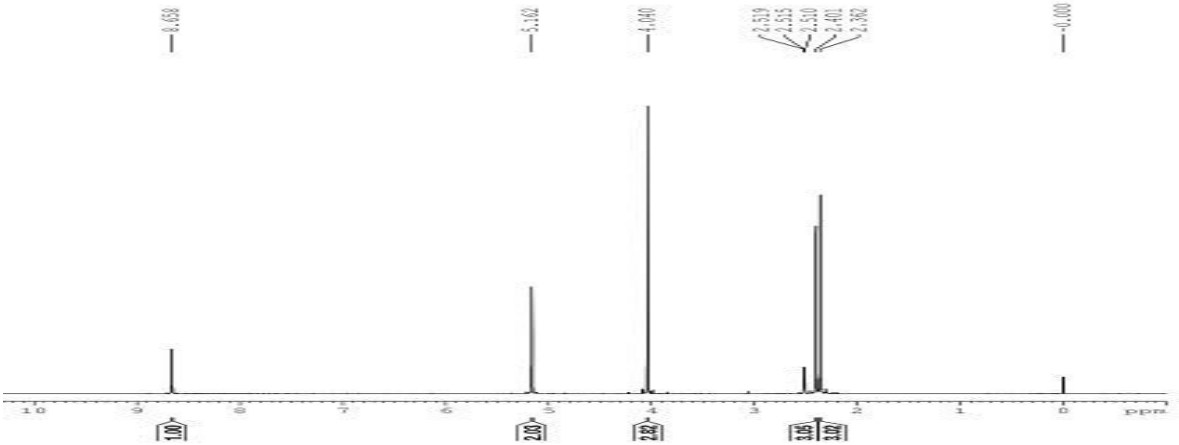


Fig.-1: Proton NMR Spectra of 2-chloromethyl-3,5-dimethyl-4-methoxypyridine Hydrochloride in Dimethyl sulphoxide –d6

Carbon NMR Spectra

^{13}C NMR δ value- 169.94, 148.84, 142.13, 128.96, 61.19, 40, 13.88, 10.83. In this study, we synthesized 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride with a minimum quantity of reagents and solvents. This leads to process environment friendly. The quality of the product is determined by NMR, Elemental analysis, and mass spectra. This analysis data clearly matches the theoretically calculated value. This indicates that the synthesis compound 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride is good in quality.

CONCLUSION

We developed an efficient method for the synthesis of 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine hydrochloride. It is characterized by different analytical techniques. This synthesis method is simple, environment-friendly, higher yield, low cost, and is process applicable at industrial scale-up. We used 3,5-

dimethyl pyridine N-oxide, 3,5-dimethyl-4-methoxy pyridine N-oxide, and 3,5-dimethyl -4-methoxy-2-hydroxymethyl- pyridine without isolation. This reduces effluent as well as solvent.

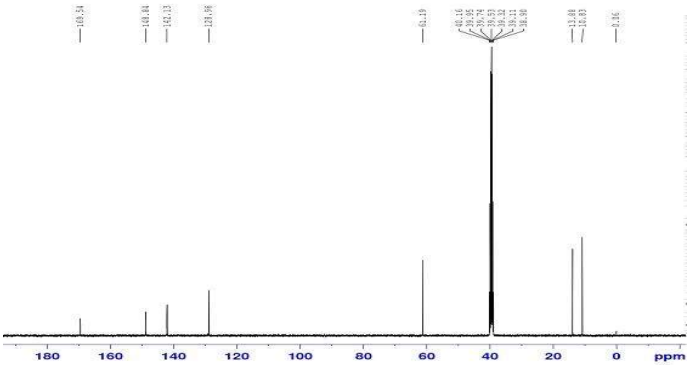


Fig.-2: Carbon NMR Spectra of 2-chloromethyl-3,5-dimethyl-4-methoxypyridine Hydrochloride in Dimethyl Sulphoxide-d6

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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