Reduce the solvent and effluent generation during the synthesis of 3, 5-Dimethyl-4-Nitropyridine-N-Oxide.

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Abstract
The present invention belongs to the synthetic preparation of 3,5-dimethyl-4-nitropyridine-N-oxide. The method comprises in a two steps. First step is oxidation of 3,5-Dimethyl pyridine by using hydrogen peroxide. Adding a catalyst in the first step is reduces the quantity of acetic acid which is very useful during the scale up. It reduces waste generation. The second step is nitration by using sulfuric acid and nitric acid. The synthesis method of the 3, 5-dimethyl-4-nitropyridine-N-oxide carried out without isolation of 3, 5-Dimethyl pyridine N-Oxide. It reduces the organic waste as well as improves the reaction yield. The final compound was characterized by NMR, Mass spectra and elemental analysis.

Keywords: -Oxidation, Nitration, Synthesis, Characterization, Effluent, Solvent, Omeprazole, Proton NMR, carbon NMR spectroscopy and Mass spectroscopy

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Introduction

This inversion is relates to a method for reducing effluent generation during 3,5-dimethyl-4-nitropyridine-N-oxide synthesis. 3,5-Dimethyl-4-nitropyridine-N-oxide is a useful pharmaceutical intermediate to synthesize omeprazole and other organic compounds [1]. At present, the compound 3,5-dimethyl-4-nitropyridine-N-oxide can be produced by 3,5-Lutidine[1-17].

First step is oxidation of 3, 5-Lutidine by using acetic acid and hydrogen peroxide. There were some attempt to produced 3, 5- Dimethyl pyridine N-oxide from 3,5-Lutidine. For example US patent 4620008 [1] ,US patent 6245913 B1 [2]and Journal of Visualized Experiments [7] discloses a process for preparing 3,5- Dimethyl pyridine N-oxide wherein the oxidation of the 3,5-Lutidine is carried out with 6 to 10 equivalent moles of acetic acid.

In all above mentioned process, a large quantity of base was used to neutralize excess acetic acid and large quantity of effluent generated which is an unfavorable condition for industrial production. To avoid this circumstances oxidation of 3,5-Lutidine carried out in the presence of metal oxide such as tungsten, molybdenum to reduce acetic acid during oxidation[15,16]. The disadvantage by using such a type of catalyst is the high price and loss after the reaction. This can lead to environmental hazard. Also some parts of catalyst can be carry forward to the organic phase during extraction of 3,5-Dimethylpyridine N-oxide and effect on the quality of 3,5-Dimethyl pyridine N-oxide. In some of the cases cross-linked polystyrene resin catalyst with a quaternary ammonium salt group and the active material anion is phosphate, tungstate and/or phosphor tungstate catalyst was used [14]. This catalyst is commercially not available and needs to be prepared.

In the literature reported by patent CN101648910A.and CN101648910B product was extracted in dichloromethane after oxidation and dry the organic phase by magnesium sulphate [3,8].

Amey Palava, IN201821026750 shows a method for making 3,5-Dimethyl pyridine N-oxide by oxidation of 3,5-Lutidine with m-chloroperbenzoic acid [4,5].This procedure has disadvantage of generation of m-chlorobenzoic acid as a byproduct. Similarly as per patent EP369208 A1 per acetic acid was used as an oxidant [8]. There are two major disadvantages to use of per acid.

1) Use of per acid leads to generation of organic or inorganic acid as a byproduct.
2) The other disadvantage by using m-chloroperbenzoic acid and per benzoic acid is higher price.

There are some trials to making 3,5-Dimethylpyridine N-oxide by using inorganic oxidant like sodium hypo chloride, sodium per borate [17]. This leads to generation of metal salt as a byproduct.

According to patent CN114805193, titanium-silicon molecular sieve was used to abstract water during oxidation [13] but it is difficult to remove water from the titanium-silicon molecular sieve and loss of titanium-silicon molecular sieve after the reaction can lead to environmental hazard.
Generally 3,5-dimethyl pyridine N-oxide prepared by oxidant such as hydrogen peroxide, m-chloroperoxybenzoic acid or per acetic acid. Among them hydrogen peroxide is the most suitable oxidant in the presence of acetic acid. The purpose of this inversion to overcome above mentioned problem related to industrial process. The present invention is to prepare 3,5-Dimethylpyridine-N-oxide with minimum use of solvent and without neutralization. This can lead to minimum waste generation. The preparation of second step 3,5-Dimethyl 4-Nitro pyridine-N-oxide without isolation of Step-1.

Second step is nitration of 3,5-Dimethyl pyridine N-oxide by using Nitric acid and sulphuric acid. Oxygen attached to the pyridine nitrogen can improve nitration ability at 2 & 4-position because conjugative effects of oxygen negative charge in the pyridine ring by the conjugation effect. The role of sulphuric acid in the nitration process as a catalyst and dehydration. In the nitration process water is generated as a byproduct. The rate of reaction becomes slow in the presence of water.
According to patent number US 4620008nitration was carried out by using large quantity of sulphuric acid and nitric acid [1, 2, 8]. Due to use of a high quantity of nitric and sulphuric acid, large quantity of base required to neutralize it. This leads to high quantity of effluent generated in Step-2.Also large amount of solvent used in the second step to extract product [1, 6].
EP369208A1 patent discloses a process of nitration was carried out in the present of solvent which reduce the productivity as well as use of solvent increase to product cost [8]

According to patent CN104557693A potassium sulphate was used for nitration [10]. The disadvantage of this process is one additional step required to prepared potassium sulphate. Potassium sulphate was prepared by the reaction of potassium hydroxide with sulphuric acid.

The present inversion is directed to use of sulphuric acid less than equivalent mole of 3,5-dimethyl pyridine N-oxide and isolation of product without neutralization. The another object of this inversion to avoid solvent during the preparation of 3, 5-Dimethyl-4-Nitropyridinr N-oxide from 3,5-dimethyl pyridine N-oxide.

This method is simple, easy handling and meets industrial production. The second step is product 3,5-Dimethyl-4-Nitropyridine-N-oxide
characterized by LC MS, NMR and Elemental analysis.

Therefore, it is an object of this invention to overcome above mention drawbacks in particular the disadvantage of large amount of effluent generation and solvent used.

MATERIALS AND METHODS:

Materials

3,5 Lutidine was purchased from Nikiva Pharma. Hydrogen peroxide and Ammonium sulphate were distributed by SD Fine chemical. TLC plates, Methanol, Acetic acid, Sulphuric acid and Nitric acid were purchased from Merck. All the chemicals were of LR grades.

METHODS

3,5-Lutidine was reacted with hydrogen peroxide and acetic acid in presence of ammonium sulphate to produce 3,5-Dimethyl pyridine N-oxide. Later remove the excess water and acetic acid from product by distillation. This product was used for nitration without purification. After the nitration reaction mass quench in to the cool water. The product 3,5-Dimethyl 4-Nitro pyridine N-oxide was filter and washed with water. In this method round bottom flask was used.

The product 3,5-Dimethyl 4-Nitro pyridine N-oxide was characterized by NMR, LC MS and C,H,N and O analyzer.

Experiment

Synthesis of 3,5-Dimethyl-pyridine N-Oxide

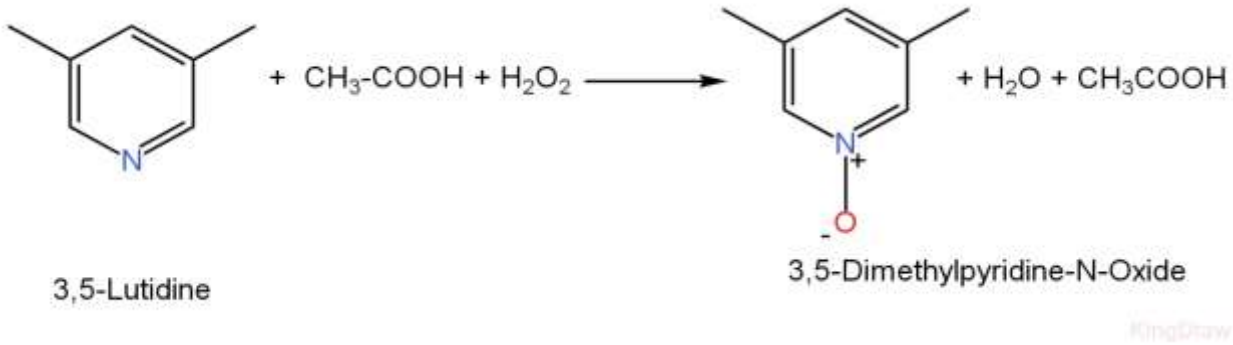
65 gm Acetic acid and 200 gm 3,5-Lutidine were charged to the round bottom flask at 25-35^{0}C. The resulting solution stirred for 5 minutes. Add 6 gm 33% Ammonium sulphate solution of water into the flask followed by 20 ML methanol. The resulting mass was stirred for 10 minutes and heated with stirring up to 50-55^{0}C. Add slowly 200 gm 35% hydrogen peroxide solution at 50-55^{0}C within an hour. Slowly apply heating to reach reaction mass temperature 80-85^{0}C. After reaching the temperature react for 12 hours at 80-85^{0}C. The reactions completion was controlled by thin-layer chromatography (TLC) which is coated with silica gel 60 F_{254} plates from Merck Co., India and 3,5- Lutidine and 3,5-Dimethyl pyridine N-oxide were detected by exposure to UV light. Reaction was cook for 2 hours in case of unreacted 3,5-Lutidine observed on TLC plate. After completed the reaction, The mass was cool to 50^{0}C. The water, methanol, acetic acid and hydrogen peroxide were distilled out from the mass under reduced pressure 755-760 mm Hg at a temperature up to100^{0}C. The mass was concentrated at 755-760 mm Hg vacuum and dry run at 100^{0}C temperature for 30 minutes.

Synthesis of 3,5-Dimethyl-4-Nitropyridine N-Oxide

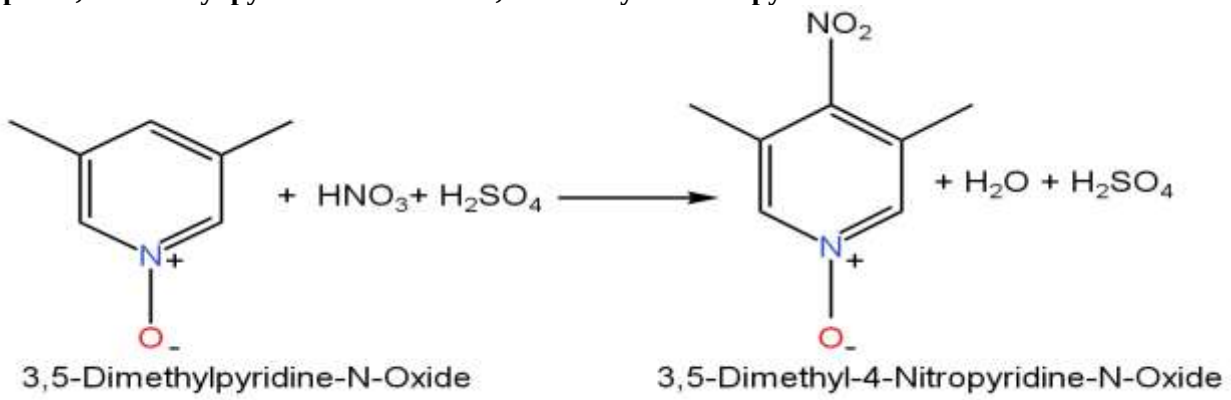
3,5-Dimethyl-pyridine N-Oxide was used in next step without isolation. The mass was cool to 25-30^{0}C. The addition of 840 gm sulphuric acid was carried out at 25-30^{0}C. After that drop by drop addition of nitric acid at 25-30^{0}C. Then the mass was slowly heated to 95-100^{0}C.The mass was cooked for 12 hours at 95-100^{0}C. The reaction was monitored by TLC. The 1200 ML of water was charged in other round bottom flask. The water was cool to 5 ^{0}C. The reaction mass was quenched into the water slowly and stirred for 1 hour. The mass was filtered and washed with 120 ML DM water. The cake was dried under vacuum. After drying weight of 3,5-Dimethyl 4-Nitro pyridine N-oxide was observed 224 gm (Yield-72%). The melting point of the product was observed 176 ^{0}C. The color of the product was light yellow. The identity of the product was confirmed by proton NMR, Elemental analysis and MS spectra.

Reaction Scheme

Step-1: 3,5-Lutidine to 3,5-Dimethyl pyridine N-oxide



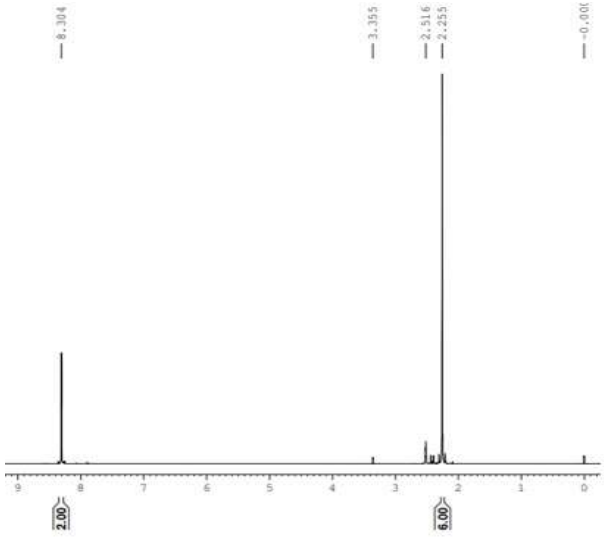
Step-2: 3,5-Dimethyl pyridine N-oxide to 3,5-Dimethyl-4-Nitro pyridine N-oxide



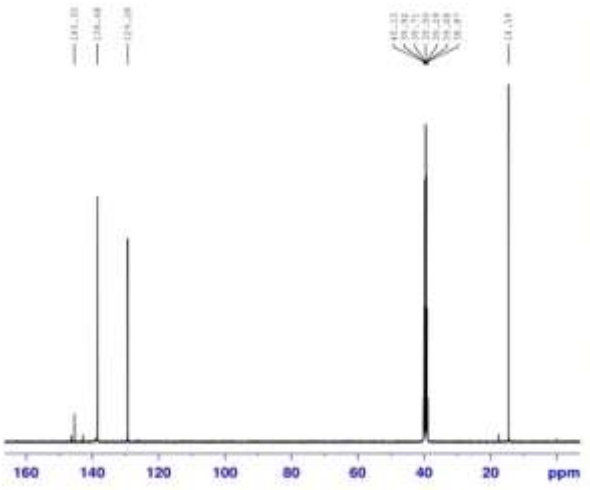
4. Spectral Data

3,5-Dimethyl-4-Nitropyridine-N-oxide:

^{1}H NMR (400 MHz, DMSO-d6) δ value: 2.25 (S, 6H), 8.3 (S, 2H)



^{13}C (400 MHz, DMSO-d6) δ value: 38.87-40.13 (two CH_3 group), 129.28 (Carbon attached to CH3), 138.48 (Carbon near to Nitrogen), 145.35 (Carbon attached to NO_2)



Mass: Observed (m/z) 168.22, calculated (m/z) 168.15;

Elemental Analysis (%): Observed C-50.17; H-4.77; N-16.86

Calculated: - C-50.00; H-4.79; N-16.66

Results and Discussion

In this study We synthesized 3,5-Dimethyl-4-Nitropyridine N-oxide with minimum quantity of reagents and solvents. This leads to process environment friendly. The quality of product

determine by NMR, Elemental analyzer and mass spectra. This analysis data clearly matches with the theoretical calculated value.

Conclusion

We developed an efficient method for the synthesis of 3,5-Dimethyl-4-Nitropyridine N-oxide. It is characterized by different analytical techniques. This synthesis method is simple, environment friendly, higher yield, low cost and process applicable at industrial scale up. We used 3,5-Dimethyl pyridine N-oxide without isolation for step-2. This reduces effluent as well as solvent. The final compound isolate without the use of solvent and neutralization also reduces effluent as well as solvent.

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