A Review on Synthesis of Nicotine

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Abstract **- Nicotine, is the principal Alkaloid of tobacco plant. An alkaloid is one of a group of nitrogenous organic compounds that have marked physiological effects on humans. Nicotine occurs throughout the tobacco plant in the leaves. The compound constitutes about 5% of the plant by weight. The tobacco plant (*Nicotiana tabacum*) and the compound are named for Jean Nicot, a French ambassador, who sent tobacco seeds to Paris. Crude nicotine the compound was obtained in purified form in 1828, the right molecular formula was developed in 1843, and the first laboratory synthesis was reported in 1904. Nicotine is one of the fluid alkaloids. In its pure state it is a colourless, odourless liquid with an oily consistency, but when exposed to light or air, it acquires a brown colour and gives off a strong odour of tobacco. The present review is focused on the synthesis of nicotine by various methods. It is synthesized by three methods namely Iodine-Mediated Hofmann–Loffler Reaction, methylation and reduction.**

Index Terms **- Iodination, Methylation, Nicotine, Psychoactive, Reduction, Vermifuge.**

I.INTRODUCTION

Nicotine is the most addictive ingredient in the tobacco used in cigarettes, cigars, and snuff. In its psychoactive effects, nicotine is a unique substance with a biphasic effect; when inhaled in short puffs it has a stimulant effect[2], but when smoked in deep drags it can produce euphoria effect[3]. This is why smoking can feel energize at some times and can seem to stop stressful stimuli at others. *Nicotine is also an addictive drug*,[2] though, and smokers characteristically show a very high tendency to sicken after having successfully stopped smoking for a time. When ingested in larger doses, nicotine is a *highly noxious poison* that causes vomiting and nausea, headaches, stomach pains, and, in acute cases, convulsions, paralysis, and death[3,5]. Nicotine is commercially found from tobacco leaves and is used as an insecticide and as a veterinary vermifuge[10]. Nitric acid or other oxidizing agents turn it to nicotinic acid, or niacin, which is used as a food supplement.

Biological Source-Nicotine is a naturally synthesized alkaloid obtains from leaves of tobacco plant *Nicotiana tabacum.* [1]

Family- Nightshade

Uses- Nicotine is widely used recreationally as a stimulant and anxiolytic as a pharmaceutical drug.

Structure-

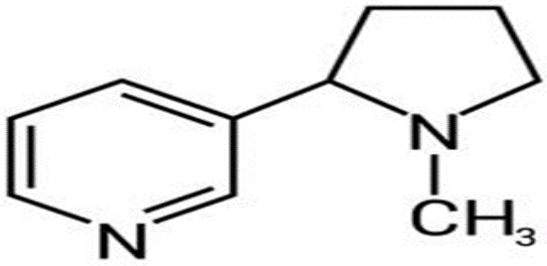


Fig 2: Structure of nicotine[4]

Chemical Formula- $C_{10}H_{14}N_2$

Molecular Weight- 162.23

IUPAC name- S-3-(1-Methyl-2-pyrrolidinyl)pyridine

II.COMMERCIAL APPLICATIONS

1. Medical- Nicotine is used to help treat addiction to or dependence on smoking cigarettes. Quitting smoking directly can cause one to experience many severe effects and longing called withdrawal symptoms[3]. Products that deliver low doses of nicotine are sometimes used to ease the quitting process and manage withdrawal symptoms. This treatment is called nicotine replacement therapy. Nicotine replacement therapy products contain less nicotine than cigarettes, and they do not contain many of the unhealthy chemicals typically found in cigarettes. Nicotine replacement can arise in the form of patches, gum, lozenges, inhalers, and nasal sprays. Large smokers may be medically control to use a combination of NRT products.

When used consistently, NRT increases a person's chances of successfully smoking by 50-70% [6].

2. Pesticide- In the natural habitat, nicotine defends tobacco plants from herbivores. Nicotine has been used as an insecticide for longer times, although its use this way has seriously dwindled. In 2014, the Environmental Protection Agency prohibits nicotine pesticides from being vend commercially in the United States. Nicotine pesticides are also banned in countries under the European Union. Instead, chemicals called neonicotinoids are used in many pesticide products. Neonicotinoids are obtain from nicotine and are chemically close to nicotine. Digression from plant protection, they are also worn for tick and flea control for pests[5].

In 2018, the European Commission prohibited the public use of neonicotinoids pesticide due to public health concerns and possible threats to bees. In the U.S. many pesticides containing neonicotinoids have been prohibited, and some restrictions apply to the use of others still permitted, for the same reasons as the European prohibit.

Risk-

- Nicotine contributes to the development of emphysema- a type of chronic obstructive pulmonary disease- in smokers[6].
- It's potentially carcinogenic. Chronic nicotine use had been associate to lung cancers, gastrointestinal cancer, pancreatic cancer, and breast cancer[6].
- Nicotine use is linked with peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD).
- Nicotine use high risk of hypertension and cardiovascular diseases.
- Nicotine use during pregnancy increases the likelihood of complications and adverse outcomes like miscarriages and stillbirth

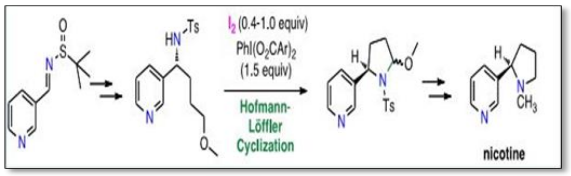
III.METHODS OF SYNTHESIS

- Synthesis of Nicotine via an Iodine-Mediated Hofmann–Loffler Reaction.[7]
- Synthesis of nicotine by using Methylation.[8]
- Synthesis of nicotine by using the reduction.[9]

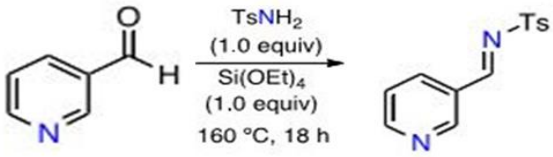
1. Synthesis of Nicotine via an Iodine-Mediated Hofmann–Loffler Reaction.

Introduction- in the Hofmann−Loffler reaction has been developed that enables the first enantioselective synthesis of nicotine based on this synthetic methodology. The outcome of the free pyridine core on the tangled electrophilic iodine reagents was explored. The final synthesis run under average reaction conditions that tolerate the free pyridine core. The similar synthetic order is also applicable to a number of derivatives with higher substituted pyridine cores, including bipyridine derivatives.[7]

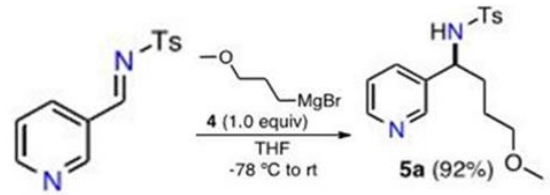
Common Reaction-



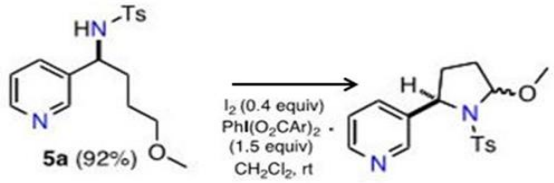
Step 1: Genesis of 3-pyridinyl N-tosylaldimine from pyridine3-carboxaldehyde.



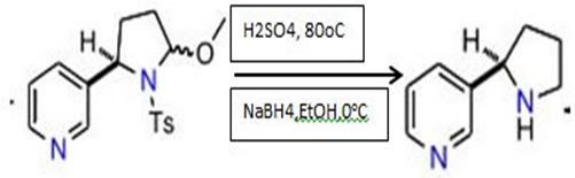
Step 2: Formation of amide from 1, 2-alkylation with the required Grignard reagent.



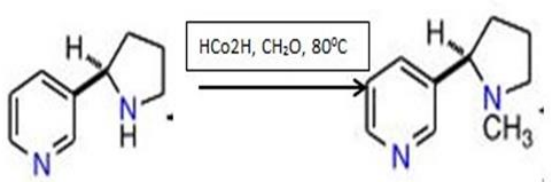
Step 3: Formation of hemiaminal derivative



Step 4: Formation of pyrrolidine.



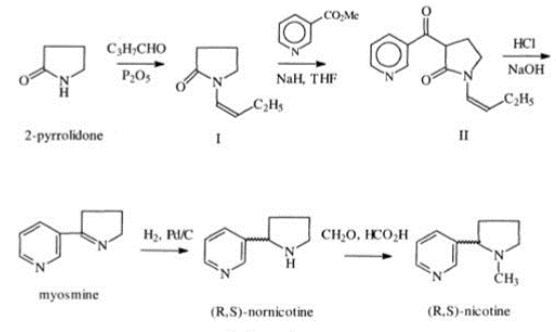
Step 5: Formation of Nicotine.



2. Synthesis of nicotine by using N-Methylation[8,11]

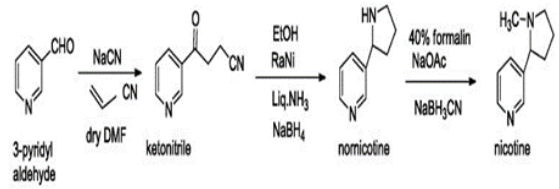
- Intro- A process for (R, S)-nicotine is described. Condensation of 1-(but-1-enyl) pyrrolidin-2-one with nicotinic acid ester gave 1-(but-1-enyl)-3-nicotinoylpyrrolidin-2one which on treatment with an acid and a base gave myosamine. Myosamine was converted to (R, S)-nicotine by reduction followed by N-methylation.
- The most convenient way to prepare (R, S)-nicotine is through myosamine. Myosamine is hydrogenated to (R, S)-nornicotine, which on N-methylation[11] gives (R, S)-nicotine.[8]

General Reaction- [8,11]



3. Synthesis of nicotine by using the reduction.[9]

Intro- the formation of nicotine from 3-pyraldyaldehyde using a step by step method.the process having following steps- Stetter reaction, Reduction cyclisation and methylation.



Accordingly, present reduction reaction provides a process for the preparation of racemic nicotine comprising the steps of

i. Combination of 3-pyridylaldehyde and acrylonitrile in present of dimethylformamide and sodium cyanide using Stetter reaction at a temperature in the range of 30-40°C to get the ketonitrile.

ii. reducing the ketonitrile as obtained in step (i) in presence of reducing reagent in alcoholic solvent followed by cyclisation to obtain nornicotine;

iii. Methylating of nor-nicotine as synthesized in step (ii) using sodium acetate, formalin and sodium cyanoborohydride in H_2O come after by purification by column chromatography to obtain the pure racemic nicotine. Voluntary isolating and purifying intermediate compounds obtained in step (i) and (ii).[9]

IV. ADVANTAGES OF NICOTINE SYNTHESIS BY USING THE REDUCTION PROCESS

1. The present process serves as a highly efficient and scalable production method for the synthesis of racemic nicotine.
2. The advantage of the present invention is that the process could be operated in one pot or step-wise method.
3. Another benefit of the present discovery is the employment of simpler reaction parameters.
4. Isolation and/or purification of the products are straightforward.
5. This is an attractive and economic method for the production of racemic nicotine.
6. The racemic nicotine could be easily put through to set on by adopting the find methods to obtain optically pure nicotine.

V. CONCLUSION

Afterward the enantioselective synthesis is too costly on an industrial scale, synthesis of (R, S)-nicotine followed by resolution and acemization of unwanted (R, S)-nicotine was explored. The resolution of (R, S)-nicotine is found in the writings. Aceto et al. have set on racemic nicotine using d-tartaric acid. DeTraglia and Tometsko have set on (R, S) nicotine using Pseudomonas putida cultures. Racemization of (S)-nicotine is also found in the writings. The present inventors have developed a new and efficient process for the synthesis of (R,S)-nicotine. Simultaneously with the familiar methods for its resolution and racemization of the unwanted isomer, this process supplied an attractive and economical method for the production of synthetic (S)-nicotine. It will be an different natural nicotine, which has several drawbacks as mentioned above.Within the general

quest to streamline amination chemistry, the direct conversion of C−H bonds into C−N bonds has come across paramount interest from the synthetic body.1,2 The Hofmann−Loffler reaction[1] represents a unique radical-based methodology to form nitrogenated saturated heterocycles such as pyrrolidines from the corresponding acyclic N-halogenated precursors.3−5 For the cases of non-symmetrical heterocycles, retrosynthetic analysis of a given target compound provides two alternative C−N bond disconnections. Nicotine is a natural alkaloid occurring naturally in the leaves of the tobacco plant and, to a lesser extent, from other members of the nightshade plant family. Nicotine has excitatory or debilitating effects on ganglia of the vegetative nervous system. Its pathogenesis importance is heavily connected to causes deriving from smoking excesses.

CONFLICTS OF INTEREST

The authors do not have any conflict of interest to declare.

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