Nature of Invention: Chemical molecule and synthesis route

Applicant: Petro Protons Pvt Ltd.

Inventors: Names in the order of contribution (highest contributor's name will be first. Author's must be listed under the R&D division)

Narottam Kumar Pankaj - 210652

Rohit Kumar - 210873

Nitin Babu - 210677

Bhanupratap - 210263

Chemical Formula: $C_6H_6N_2O$

Chemical Name: Niacinamide

Chemical synthesis routes:

According to the process of the invention for preparing nicotinamide, In the first stage:

(a) 2-methyl-1,5-diaminopentane in the gas phase at 300° to 400° C. and at 0 to 10 bar gauge pressure is converted into 3-methylpiperidine by passing it over a catalyst containing as the active component at least one oxide of Al and/or Si, having at the surface a ratio of acid centers to basic centers of more than 2 and having a specific surface area of more than 40 $m^{2/}$ g, and, immediately afterwards, the 3-methylpiperidine is passed at 220° to 400° C. over a dehydrogenation catalyst and is converted into 3-picoline,
then in the second stage:
(b) 3-picoline is, in the presence of ammonia and an oxygen-containing gas, passed at 280° to 400° C. over an ammonoxidation catalyst comprising the oxides of vanadium, titanium, zirconium and molybdenum in a molar ratio of V_2O_5 to TiO_2 to ZrO_2 of from 1:1:2, respectively, to 1:12:25, respectively, and having an MoO_3 content, based on the V_2O_5, of from 0.54 percent by weight to 2.6 percent by weight,
and, finally, in the third stage:

(c) the resultant 3-cyanopyridine is converted by means of microorganisms of the genus Rhodococcus into the end product.

A process for the preparation of 3-methylpyridine (that is, 3-picoline), wherein, first, 3-methylpiperidine is prepared from 2-methyl-1,5-diaminopentane in the gas phase at 300° to 400° C. and at 0 to 10 bar above atmospheric by passing the starting material over a catalyst which contains, as the active component, at least one oxide of Al and/or Si, which has a ratio between acid and basic centers on the surface of greater than 2 and has a specific surface area of greater than 40 m2 /g, and the resultant 3-methylpiperidine is subsequently passed over a dehydrogenation catalyst, preferably at 220° to 400° C. The dehydrogenation catalyst used is a noble metal, such as, palladium or platinum, on a support. The dehydrogenation catalyst preferably is palladium on an amorphous silicon/aluminum oxide which has been prepared by ion exchange with a soluble palladium complex.

The term "oxides of Al and/or Si" is taken to mean the individual oxides, such as Al2 O3, mixed oxides of Al2 O3/ SiO2 and crystallized compounds thereof, such as aluminum silicates, in particular zeolites. It is important that they have a predominantly acidic character and a specific surface area of greater than 40 m2 g. The acidic character arises from the ratio between acidic and basic centers on

the surface, which must, in accordance with the invention, be greater than 2. The acidic centers are determined analytically by irreversible adsorption of NH3 at 80° C., and the basic centers by irreversible adsorption of CO2 at 80° C. Preferred catalysts for the novel process are activated Al2 O3, mixed oxides of Al2 O3/ SiO2, or zeolites. Zeolites are crystalline natural or synthetic aluminum silicates which have a highly ordered structure with a rigid three-dimensional network of SiO4 and AlO4 tetrahedra connected by common oxygen atoms. The ratio between the number of Si and Al atoms and oxygen is 1:2. The electrovalence of the aluminum-containing tetrahedra is compensated by inclusion of cations in the crystal, for example, alkali metal or hydrogen ions. Cation exchange is possible. The spaces between the tetrahedra are occupied by water molecules before dehydration by drying or calcination.

If the zeolite, owing to its preparation method, is not in the catalytically active, acidic H form, but instead, for example, in the Na form, it can be converted fully or partially into the desired H form by ion exchange, for example with ammonium ions, followed by calcination or by treatment with acids.

The catalysts are preferably employed as fixed-bed catalysts, and the starting material is expediently passed through the catalyst using hydrogen or an inert gas, such as nitrogen, as carrier gas.

The reaction temperature is set at 300° to 400° C., preferably at 305° to 375° C. The pressure is 0 to 10 bar, preferably 0 to 5 bar, above atmospheric.

A measure of the flow rate over catalysts is the mass hourly space velocity (MHSV). In the present case, an MHSV of 2.1 to 4.2 g of starting material per g of catalyst and per hour is advantageously maintained. The vapor-form starting material can be diluted, preferably with N2 or H2.

3-Methylpiperidine can be converted into 3-picoline by known dehydrogenation processes. The 3-methylpiperidine stream produced by the process of the invention can be passed directly over a dehydrogenation catalyst, so that the dehydrogenation takes place immediately after the cyclization. This is possible because the 3-methylpiperidine is produced in unusually high purity and in particular now contains virtually no MPDA, which has been found greatly to impair the activity of dehydrogenation catalysts.

The dehydrogenation catalysts used are preferably noble metals, such as, for example, Pd or Pt, on a support. Particularly advantageous dehydrogenation catalysts have been found to be those obtainable from amorphous silicon aluminum oxides by ion exchange with soluble palladium complexes, such as Pd(NH3)4 !Cl2. The amorphous silicon aluminum oxides are advantageously first dewatered and charged with ammonia. The ion exchange with the soluble palladium complex can take place by suspension of the amorphous oxide in a solution of the complex. Alternatively, a solution of the complex can be passed through a packing of the amorphous oxide, but, in contrast to the former method, uniform loading can only be achieved by complete exchange.

The above methods also allow palladium contents of up to 5 percent by weight or more to be achieved in one step using relatively dilute solutions, for example, 0.01 mol/l of Pd(NH3)4 !Cl2.

The reaction temperature during the dehydrogenation is preferably 220° to 400° C. In one embodiment, the cyclization catalyst is applied directly to the dehydrogenation catalyst bed, and the 2-methyl-1,5-diaminopentane is passed in from above. In a preferred embodiment, the catalysts are introduced into separate reactors. This allows independent temperature control and, if desired, independent catalyst regeneration.

The 3-picoline obtained can, without intermediate purification, be fed directly to the ammonoxidation stage. However, it is preferably subjected to, for example, an intermediate purification by distillation, which has a positive effect on the catalyst life in the next (second) stage.

The ammonoxidation in the second stage is the subject-matter of (a) PCT Published Application WO 95/32055 (PCT/EP 95/0 1945) and (b) U.S. patent application Ser. No. 08/732,343. U.S. patent application Ser. No 08/732,343, applicants: SEMBAEV et at., entitled: "Catalytic Composition For The Oxidative Ammonolysis Of Alkylpyridines", filed on the same date as this application, is commonly owned with this application. The pertinent portions of U.S. patent application Ser. No. 08/732,343 are incorporated herein by reference.

U.S. patent application Ser. No. 08/732,343 discloses a catalyst composition of the oxides of vanadium, titanium, zirconium and molybdenum, for use in the oxidative ammonolysis of alkylpyridines, for example, 3-methylpyridine to the corresponding 3-cyanopyridine.

As the ammonoxidation catalyst, preference is given to using a catalyst composition comprising the oxides of vanadium, titanium, zirconium and molybdenum in a molar ratio of V2 O5 to TiO2 to ZrO2 of from 1:3:4, respectively, to 1:8:16, respectively, and having a MoO3 content, based on V2 O5, of from 0.54 percent by weight to 1.20 percent by weight. The preparation of the catalyst is comprehensively described in the above-mentioned PCT application PCT/EP 95/01945.

As the oxygen-containing gas, preference is given to using air since air has the advantage that the oxygen is already diluted with inert gases. However, the partial pressure of oxygen can be further regulated by mixing in inert gas such as nitrogen or oxygen-free process gases obtained by recycling.

The reactants 3-picoline, ammonia and oxygen-containing gas (calculated as O2) are advantageously passed in gas form and in a molar ratio of from 1:1:1.5, respectively, to 1:8.5:60, respectively, at 280° to 400° C., preferably 310° to 380° C., over the catalyst. The preferred molar composition of the feed gas is 3-picoline, ammonia and oxygen-containing gas (calculated as O2) in a ratio of from 1:1:1.5, respectively, to 1:4:25, respectively.

Water can have a favorable influence on the activity of the catalyst and is advantageously passed over the catalyst in a molar ratio of water to 3-picoline of up to, and including, 5:1, respectively, and preferably about 1.5:1, respectively.

In this second stage, yields of 3-cyanopyridine of up to 99 percent are achieved at a space velocity over the catalyst of from 50 to 150 (gl--1 h-1) of 3-picoline. The catalyst life is likewise extraordinarily high and is at least one year.

As compared with the prior art, the present ammonoxidation process, as a constituent part of the process of the invention, made it possible to develop a process which satisfies all of the criteria of an industrial reaction.

The resultant 3-cyanopyridine can be fed to the biohydrolysis in the form of an aqueous solution, either directly or after a work-up step, e.g., a crystallization, extraction or distillation. A preferred work-up comprises countercurrent extraction of the 3-cyanopyridine with toluene, for example, and subsequent vacuum distillation. The solvent used, e.g., toluene, can be completely recycled.

The biohydrolysis of 3-cyanopyridine as substrate to give nicotinamide is advantageously carried out using microorganisms of the species Rhodococcas rhodochrous, Rhodococcus sp. S - 6 or Rhodococas equi, preferably using microorganisms of the species Rhodococcus sp. S - 6 (FERM BP-687), Rhodococas rhodochrous J1 (FERM BP-1478) or Rhodococcus equi TG328 (FERM BP-3791). In particular, the reaction is carried out by means of microorganisms of the species Rhodococcus rhodochrous (FERM BP-1478). The three species mentioned above were deposited by Nitto Chemical Industry Co., Ltd. in the Fermentation Research Institute, Agency of Industrial Science & Technology, Ministry of International Trade and Industry, Japan, according to the rules of the Budapest Treaty. The FERM BP-numbers are the official deposit numbers. The microorganisms of the species Rhodococcus sp. S - 6, Rhoclococcus rhodochrous J1 and Rhodococcus equi TG328 are microorganisms described in the literature. Rhodocoous rhodochrous J1(FERM BP-1478) is

comprehensively described in (a) European Published Patent Application No. B 307,926, and (b) U.S. Pat. No. 5,334,519, Rhodococcus sp. S - 6 (FERM BP-687) in (a) European Published Patent Application No. A 0,188,316 and (b) U.S. Pat. No. 5,179,014, and and Rhodococcus equi TG328 (FERM BP-379 1) in U.S. Pat. No. 5,258,305.

The pertinent portions of U.S. Pat. No. 5,179,014 are incorporated herein by reference. U.S. Pat. No. 5,179,014 discloses and described Rhodococcus sp. S - 6, and its morphology, growth state in various culture media (30° C.), physiological characteristics and chemical composition of cells.

The pertinent portions of U.S. Pat. No. 5,334,519 are incorporated herein by reference. U.S. Pat. No. 5,334,519 discloses and describes Rhodococcus rhodochrous sp. J - 1, and its morphology.

The pertinent portions of U.S. Pat. No. 5,258,305 are incorporated herein by reference. U.S. Pat. No. 5,258,305 discloses and describes Rhodococcus equi TG328, and its morphology, growth on culture media (at 30° C.) and physiological properties.

Likewise suitable for the process are the functionally equivalent variants and routants of these microorganisms. For the purposes of the present invention, "functionally equivalent variants and mutants" are microorganisms which have essentially the same properties and functions as the original microorganisms. Such variants and mutants can arise by chance, for example, by means of UV irradiation.

The microorganisms are usually cultured (grown) and the effective enzymes induced prior to the actual biotransformation as described in European Published Patent Application No. B 307,928. The biotransformation is preferably carried out using, as is customary in the art, immobilized microorganism cells.

The biotransformation is advantageously carried out in a pH range of from 6 to 10, preferably in a pH range of from 6.5 to 8.5. The pH is here advantageously set using a suitable phosphate buffer.

The biotransformation can be carried out at a temperature of from 5° to 50° C., preferably from 15° to 30° C.

Preferably, the biohydrolysis of the 3-cyanopyridine, which is advantageously present in aqueous solution in a concentration of from 5 to 30 percent by weight, is carried out in a reactor cascade comprising from 2 to 5 connected stirred reactors which each contain the biocatalyst. Particular preference is given to using cascades comprising 3 or 4 stirred vessels. The 3-cyanaopyridine content of the aqueous solution particularly preferably fluctuates between 10 and 20 percent by weight.

After a residence time of from 5 to 30 hours, the nicotinamide can be isolated from the product stream, for example, by crystallization. Preferably, the reaction solution is purified over activated carbon or a polystyrene resin (e.g., Amberlite) and the nicotinamide is isolated from the aqueous phase in a conventional manner.

The conversion in the biohydrolysis is virtually quantitative and gives a nicotinamide having a purity of over 99.5 percent.

Some other methods of preparations :-

2-Methylglutaronitrile, a byproduct of adiponitrile production, is converted to 2-methyl-1,5-diaminopentane. Cyclic hydrogenation gives 3-methylpiperidine.

Dehydrogenation yields 3-methylpyridine, which is then ammoxidated and partly hydrolyzed to nicotinamide.
Blum R; Vitamins, 11. Niacin (Nicotinic Acid and Nicotinamide). Ullmann's Encyclopedia of Industrial Chemistry 7th ed. (1999-2018). NY, NY: John Wiley & Sons. Online Posting Date: April 14, 2015

In a multitubular reactor 3-methylpyridine, air, ammonia, and hydrogen react at ca. 350 °C and moderate pressure to give 3-cyanopyridine. Heterogeneous catalysts containing oxides of antimony, vanadium, and titanium, antimony, vanadium, and uranium or antimony-vanadium-titanium catalyst are highly effective. For instance, with a vanadium, titanium, zirconium, molybdenum catalyst, a reactor temperature of 340 °C, and a molar feed ratio of 3-methylpyridine:ammonia: oxygen of 1:1.3:40 yields 95% of 3-cyanopyridine. 3-Cyanopyridine is converted to nicotinamide by alkaline hydrolysis. This reaction has the advantage that saponification to the amide is fast compared to total hydrolysis to nicotinic acid. The hydrolysis to the amide is normally carried out with catalytic amounts of bases, mainly sodium hydroxide, at 130-150 °C.
Blum R; Vitamins, 11. Niacin (Nicotinic Acid and Nicotinamide). Ullmann's Encyclopedia of Industrial Chemistry 7th ed. (1999-2018). NY, NY: John Wiley & Sons. Online Posting Date: April 14, 2015

In the Lonza process, 3-cyanopyridine is converted to nicotinamide by means of an immobilized microorganism of the genus Rhodococcus. Heterogeneous catalysts are also mentioned. A copper-chromium oxide catalyst, manganese dioxide, or manganese dioxide with chromium-nickel oxide, chromium-cobalt oxide, or manganese dioxide with titanium-silicon dioxide give good yields of nicotinamide.
Blum R; Vitamins, 11. Niacin (Nicotinic Acid and Nicotinamide). Ullmann's Encyclopedia of Industrial Chemistry 7th ed. (1999-2018). NY, NY: John Wiley & Sons. Online Posting Date: April 14, 2015

Nicotinic acid is melted and reacted with ammonia gas to yield nicotinamide. The reaction is catalyzed by the presence of ammonium salts. After distillation, nicotinamide is dissolved in water, purified by the addition of activated carbon, filtered, recrystallized and centrifuged. The nicotinamide contained in the mother liquor is reclaimed by a special recovery operation. The wet pure nicotinamide filter cake is dried under vacuum in a rotary vacuum drier.
OECD; Screening Information Data Set (SIDS) Inital Assessment Report for SIDS Initial Assessment Meeting (SIAM) 15, 3-Pyridinecarboxamide (Nicotinamide) (98-92-0) p.7 (October 2002). Available from, as of June 4, 2018: https://www.inchem.org/pages/sids.html

A buffered solution of 3-cyanopyridine in water is hydrolyzed to nicotinamide in the presence of a catalyst. The resulting solution is purified over activated carbon, filtered and then concentrated in a evaporator. The concentrated nicotinamide solution is dried under vacuum.
OECD; Screening Information Data Set (SIDS) Inital Assessment Report for SIDS Initial Assessment Meeting (SIAM) 15, 3-Pyridinecarboxamide (Nicotinamide) (98-92-0) p.7 (October 2002). Available from, as of June 4, 2018: https://www.inchem.org/pages/sids.html

Preparation from 3-cyanopyridine: E.J.Gasson, D.J. Hadley, United States of America patent 2904552 (1959 to Distillers). Alternately prepared by passing ammonia gas into molten nicotinic acid: A. Truchan, J.B. Davidson, United States of America patent 2993051 (1961 to Cowles Chem.).

References: https://patents.google.com/patent/US5719045A/en
https://pubchem.ncbi.nlm.nih.gov/source/hsdb/1237#section=Methods-of-Manufacturing-(Complete)

List the contributions of each author:

- **Rajat Phogat (Author 1)** carried out the literature search and found the reaction steps, and product yield. He also found necessary separation steps to achieve desired product purity.

Sign the pdf and upload.

Name	Roll No	Signature
CEO Name– **Atharva Deshmukh**	210231	
First author Name **Rajat Phogat**	210814	
Second author Name (if any)		
Third author Name (if any)		
Fourth author Name (if any)		
Fifth author Name, Roll No & signature (if any)		
Sixth author Name (if any)		